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RISK FACTORS ASSOCIATED WITH DEEP-VEIN THROMBOSIS AND ITS IMPORTANCE ON THE DIAGNOSIS

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ABSTRACT

Venous thromboembolism is a serious disorder due to potential complications, such as pulmonary embolism and the post-thrombotic syndrome. Inherited determinants of venous thromboembolism are only partially known, but considerable progress has been made in the understanding of risk factors for the disease. In particular, the development of molecular biology techniques allowed an identification of two additional causes of inherited thrombophilia: factor V Leiden and the prothrombin G20210A mutation. The understanding of the interaction of these genetic risk factors with acquired risk factors for thrombosis have provided a new approach of patients in risk.

On the other hand, the new noninvasives technologies have contributed to simplify the diagnostic of deep-vein thrombosis. However, phlebography continues to be the standard test for comparison with new diagnostic tests. Clinical models combining clinical diagnosis with noninvasive testing have been developed in order to improve the diagnostic approach in patients with suspected deep-vein thrombosis.

Key-words: Venous thromboembolism, pulmonary embolism, deep-venous thrombosis, thrombophilia.

RESUMO

As potenciais complicações do tromboembolismo venoso, nomeadamente, o embolismo pulmonar e a síndroma pós-trombótica, conferem-lhe particular relevância na patologia vascular. As componentes genéticas do tromboembolismo venoso são só parcialmente conhecidas, embora substancial progresso tenha sido alcançado na identificação e compreensão dos factores de risco. Por exemplo, o desenvolvimento das técnicas de biologia molecular permitiu a identificação de mais duas causas de trombofilia: o factor V de Leiden e a mutação G20210A da protrombina. O conhecimento da interacção destes factores de risco genéticos com os factores de risco adquiridos tem proporcionado uma nova abordagem dos doentes em risco de trombose.

Por outro lado, as novas técnicas não-invasivas têm contribuído para simplificar o diagnóstico da trombose venosa profunda. Contudo, a flebografia continua a ser o meio de diagnóstico padrão de comparação com as novas abordagens diagnósticas. Têm sido desenvolvidos modelos clínicos associando o diagnóstico clínico com as técnicas não-invasivas com o objectivo de melhorar a abordagem diagnóstica dos doentes com suspeita de trombose venosa profunda.

Palavras-chave: Tromboembolismo venoso, embolismo pulmonar, trombose venosa profunda, trombofilia.

INTRODUCTION

Venous thromboembolism is a major cause of morbidity and death among hospitalised patients. Each year venous thrombosis occurs in about one in 1,000 people in developed countries (i,ii). This disorder commonly manifests as deep vein thrombosis of the leg, or, if embolisation occurs, as pulmonary embolism (PE).

Major complications of venous thrombosis are a disabling post-thrombotic syndrome and acute death from a PE that occur in 20% and 1-2% of patients, respectively (iii).

The incidence of thrombosis increase sharply with age, from 1 per 100,000 people per year in childhood to nearly 1 % per year in old age (iv). Thrombosis manifests itself as a multicausal disease in children and in adults.

In the rare event of thrombosis in children, several acquired and genetic risk factors are usually present simultaneously. In 25-30 % of children with thrombosis, deficiencies of protein C, protein S, or antithrombin have been reported, but thrombosis did not develop until other risk factors were present, such as intravenous lines or major illness (v).

In adults, thrombosis is also a multicausal disease since many risk factors occur together in one individual, such as factor V Leiden, prothrombin 20210A, high concentrations of factor VIII, and hyperhomocysteinaemia. In women, acquired risk factors related with sex condition, such as pregnancy, puerperium, use of oral contraceptives or postmenopausal estrogens, can contribute to the development of thrombosis. The association of the thrombophilic defects with

these acquired risk factors deserve special consideration for the management of venous thrombosis in women.

This review focuses on the main risk factors associated with venous thrombosis, particularly deep-vein thrombosis (DVT), and its importance on the diagnosis of this situation.

Epidemiology

At least 30 cases of DVT identifiable by phlebography can be expected among 100 patients who have undergone general surgical operations of moderate severity if they are not given perioperative antithrombotic prophylaxis. Most postoperative thrombi arise in the calves, especially in soleal sinuses or in large veins draining the gastrocnemius muscles, but thrombi can also originate in more proximal veins. Isolated calf thrombi are often asymptomatic. If untreated, 20 to 30 % may extend into the larger, more proximal veins, an event that accounts for most clinically important pulmonary emboli and virtually all fatal ones. Among these 100 patients, four cases of pulmonary emboli will be recognised and one or two of them may be fatal (vi).

Therefore, PE and DVT should be considered as part of the same pathological process. In one study, nearly 40% of patients who had DVT but no symptoms of PE showed evidence of PE on lung scanning (vii). Conversely, in a study of patients with PE, 29 % had abnormalities on ultrasonographic studies of leg veins (viii). Deep venous thrombosis could not be detected in the majority of patients with PE probably because the thrombus had embolized before noninvasive evaluation of the legs was conducted or because compression ultrasonography is insensitive and does not identify small, residual clots (ix).

In a retrospective survey of a defined community, Anderson et al. (1) found an average annual incidence of 48 initial cases and 36 recurrent cases of DVT (86% confirmed objectively) plus 23 cases of pulmonary emboli per 100,000 population (54% confirmed objectively). Extrapolation from their data yields an estimated total of 170,000 initial episodes and 90,000 recurrent episodes of venous thromboembolism in the United States each year. Due to underdiagnosis, the true incidence is probably higher, perhaps 600,000 cases per year. Venous thromboembolism was observed to be more common in men; for each 10-year increase in age, the incidence doubled.

Pulmonary embolism is the leading cause of maternal death in the UK and in the United States, where, from 1979 to 1986, 2726 pregnancy-associated deaths were reported (x).

The improvement of diagnostic methods made possible to verify the association of many proposed risk factors with venous thromboembolism. The recognition of such risk factors help to identify high-risk patients who might benefit from prophylactic antithrombotic therapy.

Risk Factors

In 1856, Virchow postulated three main causes of venous thrombosis: stasis of the blood, changes in the vessel wall and hypercoagulability. Nowadays, in

the approach and in evaluation of hypercoagulability both genetic and acquired risk factors should be considered.

Genetic risk factors

Concerning genetic risk factors, several abnormalities in the clotting system predisposing to venous thrombosis have been identified (Table I). Thrombophilia is a term used to describe an inherited tendency towards venous thromboembolism.

Deficiency of the anticoagulant antithrombin (previously known as antithrombin III) was the first inherited risk factor for venous thromboembolism discovered in 1965 by Egeberg (xi) In the 1980's, protein C deficiency (xii) and protein S deficiency (xiii) were described in familial thrombophilia.

More recently, a resistance to activated protein C^{*}, the most potent endogenous anticoagulant, was described. This was shown to be caused by a mutation in clotting factor V, factor V Leiden (xiv). Normally factor V is inactivated by an initial cleavage of the peptide bond on the carboxyl side of arginine 506 followed by a second cleavage at arginine 306. The mutant factor V is inactivated by cleavage at arginine 306, but this cleavage is ten fold slower without prior cleavage at position 506. Thus the factor V Leiden mutation leads to the phenomenon of resistance to the anticoagulant activity of activated protein C. A point mutation (the substitution of adenine for guanine) in the gene coding for coagulation factor V was described which is responsible for activated protein C resistance (xv). Glutamine replaces arginine at position 506, thereby making activated factor V more difficult for activated protein C to cleave and inactivate (Fig. 1).

Resistance to this protein is considered to be present in individuals where a challenge with activated protein C prolongs less the partial-thrombo-plastin time in plasma than in control subjects (xvi). This resistance appears to be inherited as an autosomal dominant trait (xvii). The mutation appeared to be most common in Europe and it is virtually absent in Africa and Asia xviii. In the United States, the frequency of the factor V Leiden mutation is 5.2% among white women, 2.0% among Hispanic women, and 1.2% among black women (xix).

Factor V Leiden is found in 20% of all cases of deep vein thrombosis. In cases of DVT where there is a family history it is found in 50% and it is found in 60% of pregnancy associated thrombosis. The increased risk of thrombosis that it confers has been estimated from *The Leiden Thrombophilia Study*. The odds ratio for thrombosis was 8 for heterozygotes and 80 for homozygotes (xx) (if factor V Leiden is found in 5% of a population then approximately 1 in 1,600 of the population will be homozygotes).

Of major importance is the interaction of factor V Leiden with other risk factors for thrombosis. It had previously been noted that many kindreds with

inherited defects in the natural anticoagulants (protein C, protein S, antithrombin) had variable thrombotic tendencies. Those with a high incidence of thrombosis may well also have had the common factor V Leiden mutation in the family. Factor V Leiden has been shown to present an additional risk factor in hereditary protein S deficiency (xxi), protein C deficiency (xxii) and antithrombin deficiency (xxiii). In the latter case both defective genes can be on the same chromosome (chromosome 1) and the two risk factors can be inherited together in successive generations.

The oral contraceptive agents (xxiv) and the pregnancy (xxv) increase the frequency of activated protein C resistance even in women without the factor V Leiden mutation. Women with factor V Leiden who use oral contraceptive agents show an estimated 35-fold increase in the risk of venous thromboembolism, as compared with women without the mutation (xxvi). It has been hypothesised that the reported increased risk of PE associated with third-generation oral contraceptive agents results from these agents being more likely to cause resistance to activated protein C than second-generation oral contraceptive agents (xxvii).

Other abnormalities that lead to excesses in the procoagulant system have been described. A mutation in the 3'-untranslated region of the prothrombin gene (guanine to adenine at position 20210, PT20210A) is associated with increased risk of thrombosis (xxviii).

Similarly, high concentrations of clotting factor VIII are related to increased risk of thrombosis, which has been estimated by a factor of about 1.6. Concentrations of factor VIII are determined mostly by blood group, which accounts for the old observation of a relation between non-O group and risk of thrombosis (xxix).

Plasma hyperhomocysteinemia is an abnormality that has been associated with an increase of two to three times risk of deep venous thrombosis in case-control studies from Padua, Italy (xxx), and the Netherlands (xxxi). Hyperhomocysteinemia can result from both genetic and acquired factors. Mutations of cystathionine β-synthase or methylene tetrahydrofolate reductase (MTHFR) lead to increased concentrations of homocysteine. Most individuals with hyperhomocysteinemia, however, do not carry either genetic variant, but have impaired methionine metabolism, so the hyperhomocysteinemia is caused by insufficient dietary intake of folic acid and vitamins B_6 or B_{12} (xxxii).

Acquired risk factors

Acquired risk factors for thrombosis include immobilisation, trauma, surgery, lupus anticoagulant, malignant disease, pregnancy, puerperium, and female hormones.

- Immobilisation increase risk of DVT in paralysed limbs of patients with stroke as well as in the legs of patients with paraplegia (6).

- Major abdominal surgery (general, vascular, urologic, gynecologic), major orthopedic surgery, neurosurgery, and surgery for multiples injuries are high risk factor of DVT (xxxiii). On the other hand, minor, brief, and uncomplicated surgeries, such as transurethral or transvaginal (xxxiv), arthroscopy of knee (xxxv) present low risk.

Surgery predisposes patients to PE, even as late as one month postoperatively. In a study in Malmo, Sweden (xxxvi), 25% of the cases of PE occurred between the 15th and 30th post-surgery days and 15% were detected more than 30 days post-surgery. In a Swiss study (xxxvii), PE after discharge occurred a median of 18 days postoperatively and led to an overall increase of 30% in the rate of postoperative PE.

Epidural analgesia can significantly reduce the incidence of DVT and PE after emergency hip surgery, elective hip replacement, and other operations on the lower limbs and pelvis (xxxviii). Meta-analysis has confirmed the reduction of the occurrence of DVT when regional anesthesia is used instead of general anesthesia (xxxix).

- Many patients with systemic lupus erythematosus present antiphospholipid autoantibodies (lupus anticoagulant and anticardiolipin), which are associated with arterial and venous thrombosis, recurrent pregnancy loss, and thrombocytopenia. Furthermore, patients can present without rheumatic or connective disorders, but with antiphospholipid antibodies and a clinical syndrome manifesting as venous thromboembolic disease (DVT is the most common manifestation in veins), arterial thromboembolic disease (stroke due a cerebral infarction is a prominent manifestation), sterile endocarditis with embolism and miscarriage. This clinical syndrome is called primary antiphospholipid syndrome (xl). Although there is no conclusive evidence of a causal relationship between these antibodies and thrombosis and miscarriage, these antibodies are useful markers for the antiphospholipid syndrome. The identification of the syndrome is clinically important because of the risk of recurrent thrombosis and the need for antithrombotic therapy in many cases (xli). In a case-control study, the lupus anticoagulant was detected in 8.5% of the 59 patients who had deep venous thrombosis confirmed by contrast venography but in none of the 117 with no abnormalities on venography (xlii).
- Neoplastic cells can generate thrombin or synthesize various procoagulants (xliii). Occasionally, previously unsuspected cancer has been identified in patients with newly diagnosed venous thrombosis (xliv).
- Most users of oral contraceptives take second-generation formulations that contain norgestrel, levonorgestrel, or norgestrienone as the progesterone and low-dose estrogen (<50 µg). The risk of PE among users of these oral contraceptives is about three times the risk among nonusers. Third-generation oral contraceptives contain desogestrel, gestodene, or norgestimate as the progesterone in combination with low-dose estrogen. These newly formulated oral contraceptives attenuate the androgenic side effects of acne and hirsutism. Several research groups have reported that the risk of venous thromboembolism among women taking third-

generation formulations is double the risk among those taking second-generation formulations (xlv,xlvi,xlvii,xlviii,xlix,l), but this observation is not universally accepted (li).

- Hormone-replacement therapy (HRT) doubles the risk of venous thromboembolism. Interestingly, the risk is higher nearby the start of therapy than after long-term use (lii,liii). As is true for oral-contraceptive therapy, current but not prior use of HRT places women at increased risk.
- Previous DVT increases the risk of recurrence of this disorder two to threefold (1). In a very recent case-control study it was reported that prior superficial vein thrombosis is an independent risk factor (odds ratio, 9.4) for deep vein thrombosis or pulmonary thrombosis during pregnancy or postpartum (liv).

  Superficial varicose veins that are not the consequence of a previous venous thrombosis are not, by themselves, risk factors for deep venous thrombosis (lv).

Risk estimates

The impact of a risk factor is a function of its prevalence and relative risk. Table I shows the prevalence of various risk factors among white people in the general population of developed countries and among patients with venous thrombosis (3).

Deficiencies of protein C, protein S, and antithrombin are rare, even among patients with thrombosis, which makes the risk is not easy to assess. A fair estimate seems to be that all the deficiencies increase the risk of deep vein thrombosis by about ten-fold (lvi).

The other four abnormalities associated with venous thrombosis are more common in the general population. Factor V Leiden occurs in 20% of patients with venous thrombosis and seems to be a risk factor of much the same strength as the deficiencies of coagulation inhibitors, increasing the risk by about eight-fold among heterozygous carriers (20). G20210A prothrombin-gene seems to be a mild risk factor, increasing the risk by two-fold to three-fold (28).

Double heterozygous carriers of both the factor V Leiden and the prothrombin gene mutations are at high thrombotic risk. The magnitude of the risk of venous thrombosis in pregnant women with the two referred severe thrombophilic conditions has been estimated in a multicenter retrospective family study (lvii). The relative risk of pregnancy-related venous thrombosis was 41.3 for homozygous and 9.2 for double heterozygous carriers. The increased risk of venous thrombosis was particularly high during the postpartum period.

The prevalence of high concentrations of factor VIII and hyperhomocysteinaemia depend on the cut-off values that are applied. Patients with factor VIII concentrations that exceed 1500 IU/L (150% of normal) show a six-fold increased risk of thrombosis compared with those below 1000 IU/L (29). People with concentrations of homocysteine higher than 18.5 μmol/L have

a 2.5-fold increased risk of thrombosis compared with patients whose concentrations are below 18.5 μmol/L (31).

Women with deficiencies of protein C, protein S, or antithrombin, present enhanced and synergistic risk of venous thrombosis in pregnancy and puerperium (lviii), and during use of oral contraceptives (lix).

On the other hand, factor V Leiden was more common in women with thrombosis during pregnancy than in the general population (lx). In the same way, a synergistic effect for factor V Leiden and use of oral contraceptives was observed. Thus, the estimated baseline risk of thrombosis for non-carriers who do not use oral contraceptives, was 0.8 per 10,000 people per year, and 3.0 for users (relative risk 3.8). The annual risk for women with factor V Leiden who did not use oral contraceptives was 5.7 per 10,000 people (relative risk 6.9), while for oral contraceptives users was 28.5 (relative risk 34.7) (lxi).

For cerebral sinus thrombosis, increased risk of thrombosis has been reported for thrombophilic defects. The combination of protein C deficiency, factor V Leiden, or prothrombin 20210A, and the use of oral contraceptive led to a 30-fold to 150-fold increased risk, compared with women who did not use oral contraceptives and did not have such defect (lxii,lxiii).

Diagnosis

Approximately 75 % of patients who present with suspected venous thrombosis or PE do not have these conditions (lxiv,lxv). The diagnosis of DVT relies heavily on the use of objective tests when it is suspected, because clinical diagnosis alone is inaccurate, and untreated patients with venous thromboembolism can have fatal PE. Even among the fraction of patients with DVT who have symptoms in the lower extremities, less than one third present with the classic syndrome of calf discomfort, edema, venous distension, and pain on forced dorsiflexion of the foot (Homans's sign). When symptoms are initially attributed to DVT, reassessment by objective methods shows that this attribution is correct only less than 50% of the cases (lxvi).

The differential diagnosis of DVT includes many afflictions of the knee or calf that cause a painful, swollen leg, such as musculoskeletal causes, impaired venous or lymphatic flow, or popliteal inflammatory cysts (Baker's cysts). Thus, a diagnosis based on suspicions on clinical grounds must be confirmed by a sensitive and specific diagnostic test (Table II).

At one time, scanning with [^{125}I]-labeled fibrinogen was widely used for the objective confirmation of the diagnosis of DVT. However, the test has serious flaws, including low sensitivity for venous thrombi above the midthigh. This point is moot, since [^{125}I]-labeled fibrinogen has been withdrawn from the market due to of transmission of infectious agents by the transfusion of blood products.

The standard diagnostic test for DVT of the lower extremities is ascending phlebography performed according to the method of Rabinov and Paulin (lxvii). Phlebography can detect both distal thrombi (in the calf veins, a common site of inception of DVT) and proximal thrombi (in the popliteal, femoral, and iliac veins), which are the source of most large pulmonary emboli. Regrettably, phlebography has uncomfortable side effects, including contrast medium-

induced thrombosis of peripheral veins in 2 to 3% of patients, a particularly unwelcome complication in patients who would otherwise not require treatment for DVT (lxviii). The new iso-osmolar non-ionic contrast agents have not confirmed the anticipated superiority of over ionic contrast agents for phlebography with respect to thrombotic side effects (lxix).

Other objective diagnostic methods include impedance plethysmography and various forms of real-time B-mode ultrasonography, most of which are more sensitive for the detection of proximal than distal thrombosis. With impedance plethysmography, one measures the electrical impedance between two electrodes wrapped around the calf. Venous obstruction proximal to the electrodes decreases the impedance as the leg becomes engorged with blood, an electrical conductor, and delays the characteristic increase in calf impedance when a thigh tourniquet is deflated.

However, the sensitivity of impedance plethysmography for proximal thrombi in symptomatic patients was found to be far less than previously reported (lxx). When used as a screening test in asymptomatic patients at high risk for DVT, impedance plethysmography lacks sensitivity, because sizeable thrombi can be overlooked if they are not totally occlusive. Then, again, the method lacks specificity, since any process causing venous obstruction in the pelvis (e.g., enlarged lymph nodes or pregnancy) can be interpreted on the plethysmogram as a venous thrombus. Impedance plethysmography seems best suited for the identification of proximal thrombi in symptomatic patients whose condition can be monitored by repeated examinations.

The introduction of real-time B-mode ultrasonography has provided a promising alternative to impedance plethysmography, with a sensitivity for proximal thrombi that approaches 100% in patients with symptomatic DVT (lxxi). The most sensitive finding is failure of the vein to collapse under gentle external pressure, so-called compression ultrasonography (lxxii). In symptomatic outpatients with suspected DVT, serial compression ultrasonography had a positive predictive value of 94%, superior to the positive predictive value of 83% for serial impedance plethysmography (64). Compression ultrasonography of the femoral and popliteal veins and calf trifurcation is highly sensitive (sensitivity, >90%) for detecting proximal-vein thrombosis (in the popliteal or femoral vein), but this technique is less sensitive (sensitivity, approximately 50%) for detecting calf-vein thrombosis (65). This method is preferred for patients with suspected DVT because it is less invasive than venography, the reference standard, and more accurate than impedance plethysmography (lxxiii). Provided that compression ultrasonography present low sensitivity for calf-vein thrombosis, the diagnosis should be sought by performing venography in patients with normal results on compression ultrasonography, but only in cases in which care may be changed by the results (for example, in patients with previous venous thrombosis or persistent symptoms) because treatment of this thrombosis is controversial (lxxiv). When calf-vein thrombi are detected by this approach, the patient should receive anticoagulant therapy.

In duplex scanning, real-time B-mode ultrasonography is supplemented by Doppler flow-detection ultrasonic imaging, which allows detection of blood flow in any vessel seen. In symptomatic patients with proximal DVT the overall sensitivity was 93%, with a specificity of 98% lxxv. The sensitivity of duplex scanning for the detection of distal thrombi is far less satisfactory due to poor

visualisation of the calf veins. Greater accuracy for colour Doppler ultrasonography is claimed but may only be achievable in technically uncompromised studies (lxxvi).

Real-time B-mode ultrasonography, like impedance plethysmography, is less satisfactory for screening asymptomatic patients at high risk of DVT.

Computer-assisted tomography can detect thrombosed veins in the abdomen and pelvis and is considered superior to conventional phlebography in visualising the great veins, identifying intraluminal thrombi, distinguishing new thrombi from older ones, and delineating adjacent abnormalities (e.g., extrinsic compression of the vein) (lxxvii).

For magnetic resonance venography, 100% sensitivity and over 96% specificity are reported for the diagnosis of proximal DVT. Because of its high cost and limited availability, magnetic resonance venography is not suitable for the routine diagnosis of DVT but may be helpful in exceptional cases, such as those in which the fine anatomical detail that can be shown with this method may provide decisive information relevant to the choice of therapy.

In a nutshell, the definitive objective diagnostic test for both symptomatic and asymptomatic DVT continues to be phlebography, although has several inconvenients like being invasive, can be painful, is associated with allergic and other side effects, and it is not available in all centres. Noninvasives tests such as venous ultrasonography and impedance plethysmography can replace venography in patients with clinical suspected DVT, but are limited by the requirement for serial testing if the initial is normal and by falsely abnormal results in 6% (ultrasonography) to 17% (impedance plethysmography) of patients (64). Furthermore, most symptomatic patients do not present venous thrombosis and so serial testing is often unnecessary.

In order to enhance the accuracy of clinical assessment of DVT, Wells et al. 6^5 have developed a clinical model to stratify symptomatic patients with suspected DVT into low, moderate, or high probability for DVT before diagnostic testing (i.e., pre-test probability). With this clinical model (Table III), the need for serial tests in patients in whom the results of initial ultrasonography are normal can be reduced. The diagnostic process can be improved and simplified by combining clinical diagnosis with noninvasive testing through that categorisation defined by pre-test probability. In this study, a low pre-test probability and normal results on ultrasonography (which occurred in 47% of patients) reliably excluded the presence of venous thrombosis.

Based on this clinical model Well et al. (65) have suggested a diagnostic approach in patients with suspected DVT (Fig. 2).

Wells et al. have described in another study (lxxviii) a second strategy with the same aim: to reduce the need for serial tests in patients in whom the results of initial noninvasive testing are normal. They have measured concentrations of plasma d-dimer, a product of plasmin digestion of mature cross-linked fibrin, which is increased in patients with venous thrombosis or pulmonary emboli (lxxix). In that study it was shown that a normal plasma d-dimer value and normal results on impedance plethysmography at presentation (which occurred in 58% of patients) also reliably excluded venous thrombosis. However, one should be aware that d-dimer enzyme-linked immunosorbent assay (ELISA) lacks specificity and levels of d-dimer are also elevated in patients with

myocardial infarction, pneumonia, heart failure, or cancer and in those who have undergone surgery (79). Therefore, d-dimer ELISA is best suited for patients who present to the emergency department or a physician's office without other systemic illnesses (lxxx).

Both Wells' studies suggest that the diagnosis of venous thrombosis can be excluded without further testing in patients whose ultrasonography or impedance-plethysmography results are normal and who have either a low pretest probability or a normal plasma d-dimer value (74).

Diagnosing recurrent venous thrombosis is often difficult because objective test results can be abnormal as a result of previous disease. Recurrence is diagnosed when venography or ultrasonography shows new abnormalities or when the results of impedance plethysmography are abnormal (lxxxi).

CONCLUSIONS

Venous thrombosis is a multifactorial disease. Prevention of first events and recurrences of venous thromboembolism can be optimised only through the knowledge of the main risk factors, their effect, and their interaction with environmental factors. Multiple interactions between genetic and environmental factors contribute to the development of the disease. Currently, six or seven genetic risk factors for venous thrombosis are identified.

The association of the thrombophilic defects, such as factor V Leiden, prothrombin 20210A, high concentrations of factor VIII, with acquired risk factors deserve special consideration for the management of venous thrombosis. For example, pregnancy and oral contraceptives can display a synergistic effect with genetic risk factors for the contribution to the development of thrombosis.

However, put together these genetic defects can explain the clustering of thrombotic events in only a small subset of families with thrombophilia. As to the identification of new genetic risk factors for thrombosis, we seem to have arrived at the end of a practicable road with the classical approach of thrombophilia, which usually starts with the study of the association of hemostatic phenotypes and thrombotic risk. At the same time we have undertaken various genetic approaches aiming at identifying polymorphisms/mu-tations causing thrombotic risk. The odds for finding remaining common genetic risk factors for venous thrombosis during the next ten years may be predicted to be fairly high (lxxxii).

The definitive objective diagnostic test for both symptomatic and asymptomatic DVT continues to be the phlebography. Noninvasive tests such as venous ultrasonography and impedance plethysmography can replace venography in patients with clinical suspected DVT, but are limited by the requirement for serial testing if the initial is normal and by falsely abnormal results. The diagnostic process can be improved and simplified by combining clinical diagnosis with noninvasive testing through that categorisation defined by pre-test probability.

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TABLE I – Prevalence of risk factors for thrombosis[3]

RISK FACTOR	% GENERAL POPULATION	% PATIENTS WITH THROMBOSIS
Protein C deficiency	0.2-0.4	3
Protein S deficiency	Not known	1-2
Antithrombin deficiency	0.02	1
1actor V Leiden	5	20
G20210A prothrombin-gene	2	6
High concentration of factor VIII (>1500 IU/L)	11	25
Hyperhomocysteinaemia (>18.5 µmol/L)	5	10

TABLE II – Tests used in the diagnosis of deep-vein thrombosis (DVT)[6]

TEST	SYMPROMATIC DVT†		ASYMPTOMATIC DVT*		ANATOMIC AREA	COMMENT
	Sensitivity	*Specificity*	*Sensitivity*	*Specificity*		
	percent					
Phlebography	Standard for comparison		Standard for comparison		Pelvis, thigh, popliteal area, calf	Invasive, provides equivocal results in cases of recurrent DVT; not easily repeated
Impedance plethysmography	83#	95	22	98	Thigh, popliteal area	For provisional diagnosis of primary or recurrent proximal DVT; insentive to calf thrombi and to nonocclusive proximal thrombi
Ultrasonografhy	97	97	59	98	Thigh, popliteal area	Most sensitive confirmatory test for symptomatic DVT
Real-time B-mode or duplex						
Doppler flow velocity	88	88	–	–	Thigh, popliteal area	Can be used on limbs in traction or plaster; interpretation is subjective, requires skill
Magnet	96	100	–	–	Inferi	Can distinguish

ic resonance venography		or vena cava, pelvis, thigh	between acute and chronic occlusion; can identify associated abnormalities; noninvasive; expensive; limited avai-lability

† Testing is mostly used to verify clinical suspicion of DVT

* Testing is mostly used to screen high-risk patients

\# Data for sensibility according Heijboer et al[64]

TABLE III – Clinical model for predicting pre-test probability for deep-vein thrombosis[65]

CHECK LIST

Major points
Active cancer (treatment ongoing or within previous 6 months or palliative)*
Paralysis, paresis, or recent plaster immobilisation of the lower extremities
Recently bedridden >3 days and/or major surgery within 4 weeks
Localised tenderness along the distribution of the deep venous system
Thigh and calf swollen (should be measured)
Calf swelling 3 cm > symptomless side (measured 10 cm below tibial tuberosity)
Strong family history of DVT (≥2 first degree relatives with history of DVT)
Minor points
History of recent trauma (≤60 days) to the symptomatic leg
Pitting oedema: symptomatic leg only
Dilated superficial veins (non-varicose) in symptomatic leg only
Hospitalisation within previous 6 months
Erythema

CLINICAL PROBABILITY

High
≤ 3 major points and no alternative diagnosis
≤ 2 major points and ≤ 2 minor points + no alternative diagnosis
Low
1 major point + ≤ 2 minor points + performed alternative diagnosis
1 major point + ≤ 1 minor points + no alternative diagnosis
0 major point + ≤ 3 minor points + performed alternative diagnosis
0 major point + ≤ 2 minor points + no alternative diagnosis
Moderate
All other combinations

* Active cancer did not include non-melanomatous skin cancer; deep-vein tenderness had to be elicited either in the calf or thigh in the anatomical distribution of the deep venous system

Fig. 1 – The factor V Leiden mutation. The G (guanine) to A (adenine) point mutation results in the arginine at the protein C cleavage site being replaced by glutamine

Fig. 2 – Diagnostic approach patients with clinically suspected deep-vein thrombosis (DVT) (adapted from Wells et al[65]). PTP: pre-test probability

* Activated protein C is a serine protease which acts as a natural anticoagulant by inactivating factor V and VIII

Factor V Leiden

505	506	507
Arg	Arg	Gly
AGG	cG_A	GGA

AGG	CA_A	GGA
Arg	GIn	Gly