Testing for inherited thrombophilia and consequences for antithrombotic prophylaxis in patients with venous thromboembolism and their relatives

A review of the Guidelines from Scientific Societies and Working Groups

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Summary
The clinical penetrance of venous thromboembolism (VTE) susceptibility genes is variable, being lower in heterozygous carriers of factor V Leiden and prothrombin 20210A (mild thrombophilia), and higher in the rare carriers of deficiencies of antithrombin, protein C or S, and those with multiple or homozygous abnormalities (high-risk thrombophilia). The absolute risk of VTE is low, and the utility of laboratory investigation for inherited thrombophilia in patients with VTE and their asymptomatic relatives has been largely debated, leading to the production of several Guidelines from Scientific Societies and Working Groups. The risk for VTE largely depends on the family history of VTE. Therefore, indiscriminate search for carriers is of no utility, and targeted screening is potentially more fruitful. In patients with VTE inherited thrombophilia is not scored as a determinant of recurrence, playing a minor role in the decision of prolonging anticoagulation; indeed, a few guidelines consider testing worthwhile to identify carriers of high-risk thrombophilia, particularly those with a family history of VTE. The identification of the asymptomatic carrier relatives of the probands with VTE and thrombophilia could reduce cases of provoked VTE, offering them primary antithrombotic prophylaxis during risk situations. In most guidelines, this is considered justified only for relatives of probands with a deficiency of natural anticoagulants or multiple abnormalities. Counselling the asymptomatic female relatives of individuals with VTE and/or thrombophilia before pregnancy or the prescription of hormonal treatments should be administered with consideration of the risk driven by the type of thrombophilia and the family history of VTE.

Keywords
Inherited thrombophilia, guidelines, venous thromboembolism, laboratory investigation, familial investigation

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Introduction

Venous thromboembolism (VTE) susceptibility genes are present in 5-10% of the general population and in at least 40% of patients with VTE (1, 2). An association with VTE has been firmly established for antithrombin (AT), protein C (PC), and protein S (PS) deficiencies, as well as for factor V Leiden (FVL) and prothrombin (PT) 20210A (1-7). There is consistent evidence for a risk gradient for VTE, which is higher in carriers of AT, PC, and PS deficiencies and those who are homozygous or carriers of multiple abnormalities (high-risk thrombophilia) and moderate in heterozygous carriers of FVL or PT20210A (mild thrombophilia) (1-7). Accordingly, the search of the aforementioned inherited abnormalities is the only panel recommended for the laboratory investigation of inherited thrombophilias (8-12). However, many experts consider testing for thrombophilia to be of little utility in the clinical management of the large majority of patients with VTE (5, 12-15). The association of inherited thrombophilia with arterial thrombosis or obstetric complications has been reported to be weaker and equivocal, such that laboratory investigation in this setting is generally not warranted or should be conducted only in selected patients (5, 10, 12, 16, 17).

Despite such limitations, testing for inherited thrombophilia is common in clinical practice. A partial survey carried out in 2007 in Italy (60 million inhabitants) recorded approximately 22,000 tests for FVL and 20,000 tests for PT20210A (18). In 2007 in Australia (20 million inhabitants), 20,378 genetic tests for FVL were recorded (19). In current practice, the reason for testing for inherited thrombophilia is VTE in 42% of evaluated patients, arterial thrombosis in 15-23%, and an obstetric complication in 13-17% (20,21). Asymptomatic individuals account for 12-16% of testing because there is a known history of thrombophilia in a relative or there is a positive family history of VTE (19-21). Despite the unanimous recommendation against indiscriminate screening (5, 9-12), a number of women are tested prior to the prescription of oral contraceptives (OCs) or hormone replacement therapy (HRT)

or before planning a pregnancy; in a survey conducted in a tertiary hospital, 15% of the young women tested for FVL were referred before prescribing oral contraception (22). However, the main reason for testing is laboratory investigation in patients with VTE and their relatives, accounting for more than half of all tests performed. In the present narrative review, we focused on the guidelines and consensus statements produced by Scientific Societies and *ad hoc* Working Groups on this issue; we searched documents in peer-reviewed journals listed in PUBMED, using as key words the relevant MeSH terms and other pertinent terms. The principal terms used were "diagnosis" or "screening" and "hereditary" or "inherited" "thrombophilia", "prevention" or "prophylaxis" and "venous thrombosis" or "venous thromboembolism", "pregnancy", and "practice" or "consensus" or "evidence-based" "guidelines". The electronic search was supplemented by a manual search of reference lists and recent reviews. For analysis we included only papers in English language published between 2005 and 2012, and only those in which the guideline development was produced by either national or international Scientific Societies and/or *ad hoc* Working Groups based on a systematic review of the literature or consensus expert opinion. Accordingly, we excluded review papers, editorials, or commentaries produced by single distinguished opinion leaders and co-workers. We analysed in detail a total of 18 documents published since 2005, which addressed the issue of testing for inherited thrombophilia specifically (n=6, references [9-14]), or in the frame of a guideline concerning primary or secondary prevention of venous thromboembolism in the general population or in women planning pregnancy or hormonal treatments; we included only the most recently updated version of each document. Moreover, the current knowledge in this field has been summarised.

Testing for inherited thrombophilia in patients with VTE and consequences for secondary antithrombotic prophylaxis

In patients with VTE, diagnostic algorithms for inherited thrombophilia preferentially target young individuals (i.e. aged less than 40-50 years), those with recurrent events, and those with a strong family history of VTE (23). Although in carriers of FVL or PT20210A (mild thrombophilia), advanced age itself can be a risk factor for developing unprovoked VTE (24, 25), in case series of unselected patients with VTE, an age <50 years remains significantly associated with a positive result for thrombophilia (26). However, regardless of the diagnostic yield, the recommendation for testing for inherited thrombophilia should be linked with a tailored management of positive patients, such as a prolongation of anticoagulant prophylaxis of recurrent events.

After a first VTE, the duration of secondary prophylaxis using anti-vitamin K agents (international normalized ratio [INR] target 2.0 to 3.0), or using novel oral anticoagulants in the future, should be established by weighing the risk of a major haemorrhagic complication against the risk of a novel unprovoked VTE event. The cumulative risk of recurrent VTE is as high as 40% after 10 years from the first event (27); however, it is low in patients having had VTE in association with circumstantial risk factors (surgery, trauma, pregnancy and puerperium, use of OCs) and maximal in patients with a first unprovoked VTE (27-30). The prediction of recurrence should allow the selection patient candidates for long-term (indefinite) anticoagulation. Unfortunately, the factors associated with a clinically relevant increase in risk of recurrence are not fully understood, and the complexity of interactions and differences in study methodologies generates discrepancies of results and uncertainty in decision making for thromboprophylaxis (31). However, the final likelihood of recurrence is viewed as resultant of the clinical circumstances of the first event (provoked or unprovoked), the features of early treatment, and the patient characteristics, such as male sex, young age, thrombophilic abnormalities, laboratory global phenotypes (e.g. D-dimer assay), and clinical global phenotypes (e.g. vein recanalisation) (15, 32, 33).

Inherited thrombophilia is considered to play a minor role in this setting, and it is not scored as determinant for the risk of recurrence (32, 33). In fact, inherited thrombophilia has been reported to have little impact on the risk of recurrence in prospective studies (29, 30). As expected, in such investigations the most represented abnormalities are FVL and PT20210A (mild thrombophilia), which are present in nearly one third of patients with VTE. Studies specifically aimed to investigate the risk of recurrence in carriers of either mutations gave conflicting results. The risk of recurrent VTE among heterozygous carriers of either FVL or PT20210A has been recently revised by at least three meta-analyses (34-36). One estimated that patients with a first VTE and FVL or PT20210A have significant 1.4-fold and 1.7-fold increases in the risk of recurrence, respectively (34). In a second meta-analysis restricted to prospective studies, the risk of recurrent VTE conferred by heterozygous FVL was increased by 1.4-fold, whereas the risk found among heterozygotes for PT20210A was lower (35). A more recent systematic review found that heterozygosity for FVL was associated with a 1.6-fold increase in risk for recurrent VTE in probands, whereas heterozygosity for PT20210A was not predictive of recurrence (36). However, the magnitude of the risk is modest, and the haemorrhagic risk related to the indication for long-term anticoagulation could be not justified in the majority of cases. Moreover, in a large retrospective case-control study, laboratory investigation for inherited thrombophilia in patients with a first VTE did not reduce the incidence of recurrence (37). Anyhow the value of laboratory investigation for the outcome of recurrence should be investigated in a trial in which the participants tested for thrombophilia should have predetermined consequences, such as a prolongation of the duration of anticoagulant treatment or a higher intensity of anticoagulation; such a trial has never been performed (38). Nevertheless, in a prospective cohort of 599 patient with a first VTE, the presence of inherited thrombophilia was associated with a 1.8-fold increase in risk for recurrence, and in patients with inherited thrombophilia measurement of D-dimer identified a subset with low risk of recurrence (4.2% after 1.4 years of follow-up in the presence of normal D-dimer levels), and a subset with high risk of recurrence (27.1% in the presence of altered

D-dimer levels, with a hazard ratio of 8.3-fold in comparison with the subset with low risk) (39). Those findings suggest that thrombophilia cannot be considered as a whole and that further efforts are needed to clarify the role of mild thrombophilia in the interaction with other predictors of recurrent VTE and to identify subsets of patients at higher risk for recurrence.

Recent recommendations do not consider patients with AT, PC, or PS deficiency or multiple gene alterations (high-risk thrombophilia) different from all the other patients with inherited thrombophilia regarding the duration of anticoagulant treatment (12, 15). However, it can be expected that the risk of recurrent VTE for the rare patients with a deficiency of a natural anticoagulant AT, PC, or PS is difficult to determine in most studies because it is diluted by the weak effect of the much more frequent polymorphisms FVL and PT20210A. In older family studies the rate of recurrent VTE was higher in carriers of PC or PS deficiency in comparison with their non-carrier relatives (40-42). In a prospective cohort of unselected patients, those with an AT deficiency had a 2.6-fold increase in risk for recurrence, yet the result is likely not significant due to the small number of cases (29). In a retrospective controlled investigation, AT deficiency was associated with a significant 1.9-fold increase in risk for recurrence in the absence of anticoagulation in comparison with patients with no thrombophilia; deficiencies of PC or PS were associated with a lower risk of recurrence (1.4-fold) (43). Moreover, in probands and their deficient relatives belonging to the EPCOT prospective cohort the incidence of recurrent VTE was 10.5% per patient-year in patients with AT deficiency and 3.5% per patient-year in carriers of FVL (44). In a retrospective investigation on proband patients with a deficiency of natural anticoagulants and their deficient relatives, the incidence of recurrent VTE was confirmed to be high, resulting in 7.7% per patient-year (10% for AT deficiency, 6% for PC deficiency, and 8.4% for PS deficiency) (45).

There is convincing evidence that patients with multiple defects are more prone to recurrent VTE (46-49). A retrospective study demonstrated that homozygotes for FVL showed a higher risk for recurrent VTE than heterozygotes (50). In a systematic review, homozygosity for FVL was associated with a 2.6-fold increased risk for recurrent VTE (36). In conclusion, although the quality of the evidence in this area is low and does not allow firm recommendations, patients with AT deficiency, homozygosity for FVL, multiple defects, and perhaps PC or PS deficiency could be more prone to recurrence and therefore potential candidates for long-term oral anticoagulation after a first unprovoked VTE. This has been accepted by an International Consensus Statement in 2005 (9) and, more recently, by the French consensus guideline on testing for thrombophilia in VTE (11), which recommend laboratory investigations in patients with VTE occurred at young age and/or in those with unprovoked events. It should be underlined that the conditions listed above are present in a not-negligible portion of patients with VTE, being identifiable in at least 10%. Nevertheless, the British and American guidelines do not consider routine testing to be justified among patients with VTE (12-15). A possible exception could be testing patients with a family history of VTE (12, 14), particularly testing targeting patients with a deficiency of natural anticoagulants and if anticoagulant treatment is to be discontinued (14). The detailed recommendations of the published guidelines of Scientific Societies and international Working Groups are summarised in ▶Table 1.

A special situation is the occurrence of rare thromboses in unusual sites such as the cerebral or splanchnic veins; in this setting, up to half of the patients carry inherited thrombophilia (51). The optimal duration of anticoagulant treatment after a first event is unknown, but international guidelines recommend indefinite anticoagulation in the presence of persistent risk factors (e.g. high-risk thrombophilia) for patients with cerebral vein thrombosis (52, 53) or patients with extrahepatic portal vein obstruction (54), and laboratory investigation is warranted. However, the British guidelines warn that decision making regarding duration of anticoagulant therapy after venous thrombosis at an unusual site based on the results of testing for thrombophilia is not evidence based (12, 55); nevertheless, continued anticoagulation in patients with cerebral vein thrombosis and deficiency of AT, PC or PS is suggested by some experts (55).

Whether inherited thrombophilia increases the risk of VTE in patients with cancer is controversial, with cancer being such a strong risk factor that can obscure the role of other predictors of VTE. Nevertheless, in some reports it seems that FVL and PT20210A can increase the risk of VTE in patients with cancer (56, 57). Special groups of patients with malignancy and inherited thrombophilia who are at higher risk of VTE in comparison with non-carrier cancer patients are those with central venous catheters (58) or those with acute lymphoblastic leukaemia (ALL) who are treated with L-asparaginase (59). However, so far knowledge of inherited thrombophilia status is not considered in the strategies of prophylaxis and treatment of VTE in cancer patients (60), and there is only limited experience on thrombophilia-driven prophylaxis with low-molecular-weight heparin (LMWH) in children with ALL (61).

Testing for inherited thrombophilia in asymptomatic individuals and consequences for primary antithrombotic prophylaxis

VTE is a common complex disease and is the result of gene-gene and gene-environment interactions. Unfortunately, a simple model due to the presence or absence of two dichotomous factors (high-risk alleles and exposure to an environmental risk factor) is not reliable in most cases. This is due to the incomplete clinical penetrance of genotypes because not all carriers develop VTE during their lifetime as well as to the varying severity and age of onset of the disease. Moreover, the onset of the disease is modulated by gene-gene interactions, which are obscure in the large majority of cases, and by multiple effects of various environmental risk factors, acting on the genotype in an additive or synergistic manner. The above limitations render the indiscriminate genetic testing of populations for VTE-susceptibility genes of little or null clinical utility and unlikely to compete for resources with other medical

Table 1: Guidelines for testing for inherited thrombophilia in patients with venous thromboembolism, in patients with recurrence, in the relatives of individuals with inherited thrombophilia, and in the general population. VTE: venous thromboembolism; DVT: deep venous thrombosis; AT: antithrombin; PC: protein C; PS: protein S; FVL: factor V Leiden; PT20210A: prothrombin 20210A.

	Value of testing to determine the reason for VTE	Value of testing for the prediction of recurrence after unprovoked VTE	Value of testing for the prediction of VTE and prescription of antithrombotic prophylaxis in asymptomatic relatives	Value of testing for the prediction of VTE and the prescription of antithrombotic prophylaxis in the general population
International Consensus Statement, 2005 (9)	Yes, in all patients (except those with a single provoked VTE > 50 years)	Yes (testing for deficiency of AT, PC, PS, homozygosity, and double heterozygosity for FVL and PT20210A)	Yes (in particular females of childbearing age)	No
French Consensus Guideline, 2009 (11)	Yes, in patients with a single unprovoked proximal DVT and/or PE < 60 years, in patients with recurrent proximal DVT and/or PE, and in patients with recurrent unprovoked distal DVT < 60 years)	Yes (testing for deficiency of AT, PC, PS, homozygosity, and double heterozygosity for FVL and PT20210A)	Yes (possible exception for relatives of probands who are isolated heterozygotes for FVL and PT20210A)	No
British Committee for Standards in Haematology, 2010 (12)	No (possible exception for those with a strong family history of unprovoked recurrent VTE)	No (possible exception for those with a strong family history of unprovoked recurrent VTE)	No (possible exception for relatives of probands with deficiency of AT, PC, PS)	No
Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, 2011 (13)	No (analysis limited to FVL and PT20210A)	No (analysis limited to FVL and PT20210A)	No (analysis limited to FVL and PT20210A)	Not analysed
National Institute for Health and Clinical Excellence (NICE), 2012 (14)	Yes, in patients with unprovoked VTE and with a first-degree relative with VTE < 50 years (testing for deficiency of AT, PC, PS)	Yes, in patients with a first-degree relative with VTE < 50 years if anticoagulation treatment is to be discontinued (testing for deficiency of AT, PC, PS)	No (possible exception for females of childbearing age who are first-degree relatives of patients with VTE and known thrombophilia and are planning oral contraception or pregnancy)	Not analysed
American College of Chest Physicians (ACCP) Guidelines, 2012 (15)	Not analysed	No (limited utility in selected patients as part of an overall risk/benefit evaluation of indefinite anticoagulation)	Not analysed	Not analysed

interventions (62). Universal screening before exposure to environmental risk circumstances, such as OCs intake or pregnancy has also been estimated not to be cost-effective (62-64). Moreover, individuals labelled as carriers by random screening could experience insurance discrimination or feel undue anxiety, receiving no real benefit in terms of prevention. In conclusion, general population screening is discouraged because of the doubtful utility and potential detrimental effect on carriers (65-67).

Targeted screening of the siblings of index patients with VTE is clearly more fruitful than screening the general population, with a diagnostic yield of 50%, because such traits are genetically dominant. The primary argument for screening the asymptomatic relatives of patients with thrombophilia is the possibility of reducing the occurrence of provoked VTE, by offering advice concerning primary antithrombotic prevention during situations that could potentially lead to VTE and that are not usually covered with prophylaxis (e.g. low-risk surgery or pregnancy and puerperium), and counselling carrier females about the use of hormone therapy. However, this type of counselling should be weighed against potential detrimental effects on carriers, such as emotional burden due to an overestimated perception of risk (68-71).

The presence of a family history of VTE may be a way to engage in the targeted identification of carrier relatives who may be at higher risk. In fact, a family history of VTE has been consistenly

reported to be a risk factor for VTE independent of the presence of known thrombophilic abnormalities (73-78). Moreover, the carriers of thrombophilia with a family history of VTE have been reported to be more prone to VTE than those without (75, 79, 80).

Several family studies have investigated the risk for VTE among relatives of individuals with inherited thrombophilia (reviewed in [80]). In both prospective and retrospective studies, the incidence of VTE among relatives was higher in carriers of an AT, PC, or PS deficiency, with a range of 0.36% to 4.0% per individual-year. The highest incidence was consistenly observed among carriers of an AT deficiency, with 1.0% to 4.0% per individual-year. In studies using unaffected relatives as the reference group, the risk for VTE among carriers of an AT, PC, or PS deficiency was 4- to 30-fold greater than that in non-carriers. However, a lower incidence of VTE was reported among the relative carriers of FVL and PT20210A, consisting of 0.19% to 0.58% per individual-year for FVL, and 0.11% to 0.37% per individual-year for PT20210A. The low absolute incidence of VTE reported in relatives of patients with FVL or PT20210A has prompted many experts to consider familial screening for inherited thrombophilia to be unwarranted in this setting because it is without high clinical utility (68, 71). This is debated, and some guidelines consider familial screening justified only for relatives of probands with high-risk thrombophilia, i.e. AT, PC, or PS deficiency (11, 12) or multiple abnormalities (11) (►Table 1). However, among the relatives of probands with mild thrombophilia (isolated heterozygotes for FVL and PT20210A), it should be considered that some asymptomatic individuals could be carriers of multiple abnormalities and, therefore, could receive a benefit from diagnosis (80).

Gender-related recommendations in patients with VTE and in relatives of patients with VTE and inherited thrombophilia

Pregnant women with a previous history of unprovoked or oestrogen-related or pregnancy-related or recurrent VTE should be offered antenatal antithrombotic prophylaxis with LMWH independently of the presence of thrombophilia (10, 12, 81-86). Similar considerations can be applied to the prescription of oestrogen-containing OCs or oral HRT to women with a previous VTE, which is considered in both cases an unacceptable health risk independently of the presence of thrombophilia (87, 88).

In contrast, women with a previous VTE provoked by a major transient risk factor such as surgery or major trauma would not typically require antenatal prophylaxis in the absence of other risk factors (10, 12, 82-86). Laboratory investigation for thrombophilia is warranted in women with a previous provoked VTE because this will influence patient management and decisions regarding antenatal thromboprophylaxis (10-12, 82, 84, 86).

Finally, all women with previous VTE should be offered antithrombotic prophylaxis for six weeks after delivery, independently of the circumstances of the first VTE (9-12, 81-86).

In most guidelines special attention is given to asymptomatic women of childbearing age, particularly in the presence of a family history of VTE and/or a familial AT, PC, PS deficiency, homozygosity for FVL or PT20210A, or double heterozygosity for FVL and PT20210A (9-12, 14, 81-86). In general, the recommendations for antepartum and postpartum prophylaxis and the recommendations concerning the use of OCs or HRT for asymptomatic women with thrombophilia are of low-grade evidence. The main recommendations concerning antithrombotic prophylaxis offered to asymptomatic women with inherited thrombophilia during pregnancy and after delivery are reported in ►Table 2.

Antenatal clinical surveillance is unanimously suggested in heterozygotes for FVL or PT20210A, due to the low rate of first antepartum VTE. In them, LMWH should be considered in the presence of additional risk factors (e.g. family history of VTE, immobility, obesity, age >35 years, gross varicose veins) (9, 10, 81, 82, 86). Antenatal LMWH prophylaxis is recommended even in the absence of additional risk factors in carriers of AT deficiency and in homozygous FVL or PT20210A or carriers of multiple thrombophilia abnormalities (9, 10, 81-84). Some guidelines suggest antenatal LMWH prophylaxis in women with a PC or PS deficiency (9, 10), whereas others judge to be sufficient clinical surveillance in the absence of additional risk factors (81-84, 86).

After delivery, LMWH prophylaxis is recommended for six weeks in carriers of AT deficiency, homozygous FVL or PT20210A or multiple abnormalities (9, 10, 82-84, 86). Asymptomatic women with PC or PS deficiency or heterozygous FVL or PT20210A should receive LMWH prophylaxis after delivery for at least seven days (82) or for six weeks in all cases (9, 10, 83, 86) or only in cases with additional risk factors (82, 84).

Some guidelines vary recommendations depending of the family history of VTE: in contrast to the aforementioned recommendations, the American College of Chest Physicians (ACCP) 2012 guidelines suggest antenatal clinical surveillance in almost all asymptomatic women with inherited thrombophilia, considering antenatal LMWH prophylaxis only for homozygotes for FVL or PT20210A with a family history of VTE. LMWH for six weeks after delivery is considered for homozygotes for FVL or PT20210A regardless of the family history and for women with the other inherited thrombophilias only in the case of a family history of VTE; in such cases (except women with a PC or PS deficiency), anti-vitamin K agents targeted at INR 2.0 to 3.0 are also suggested (85). In one recent guideline antenatal prophylaxis is suggested for asymptomatic women with high-risk thrombophilia (including AT deficiency) only in the presence of a family history of VTE (86).

A family history of unprovoked VTE in a first-dregree relative with unknown thrombophilia is a relative contraindication for oestrogen-containing OCs or oral HRT; conversely, transdermal HRT does not appear to increase the risk of VTE, and therefore, thrombophilia testing has been declared unnecessary in both cases (11, 12, 14, 87, 88). Nevertheless, testing for inherited thrombophilia before the prescription of oestrogen-containing OCs may help for counselling selected women who are relatives of a symptomatic carrier of high-risk thrombophilia (deficiency of natural anticoagulants, multiple or homozygous abnormalities) (9, 11, 12, 87).

Table 2: Guidelines for prophylaxis during pregnancy and puerperium in asymptomatic women with inherited thrombophilia. § antithrombotic prophylaxis is recommended only if family history of VTE or other risk factors are present. ¶ antithrombotic prophylaxis is recommended only if family history of VTE is present. ‡ antithrombotic prophylaxis is recommended only if other risk factors are present. LMWH: low-molecular-weight heparin; other abbreviations as in Table 1.

	Antenatal prophylaxis with LMWH	Postpartum prophylaxis with LMWH for 6 weeks
International Consensus Statement, 2005 (9)	AT or PC or PS deficiency Heterozygous FVL or PT20210A § Multiple abnormalities or homozygotes	AT or PC or PS deficiency Heterozygous FVL or PT20210A Multiple abnormalities and homozygotes
Pregnancy and Thrombosis Working Group, 2007 (81)	AT deficiency PC or PS deficiency § Heterozygous FVL or PT20210A § Multiple abnormalities or homozygotes	The consensus panel did not make a formal recommendation.
Italian Society for Haemostasis and Thrombosis (SISET), 2009 (10)	AT or PC or PS deficiency Heterozygous FVL or PT20210A § Multiple abnormalities or homozygotes	AT or PC or PS deficiency Heterozygous FVL or PT20210A Multiple abnormalities or homozygotes
Royal College of Obstetricians and Gynaecologists (RCOG), 2009 (82)	AT deficiency PC or PS deficiency § Heterozygous FVL or PT20210A § Multiple abnormalities or homozygotes	AT deficiency PC or PS deficiency § Heterozygous FVL or PT20210A § Multiple abnormalities or homozygotes In women with a PC or PS deficiency or heterozygous for FVL or PT20210A without family history of VTE or other risk factors, duration of prophylaxis can be 7 days.
Scottish Intercollegiate Guidelines Network (SIGN), 2010 (83)	AT deficiency PC or PS deficiency ¶ Heterozygous FVL or PT20210A ¶ Multiple abnormalities Homozygous FVL	AT or PC or PS deficiency Heterozygous FVL or PT20210A Multiple abnormalities or homozygotes
American College of Obstetricians and Gynecologists (ACOG), 2011 (84)	AT deficiency PC or PS deficiency Heterozygous FVL or PT20210A Multiple abnormalities or homozygotes In women with a PC or PS deficiency or heterozygous for FVL or PT20210A surveillance without anticoagulation can be an alternative	AT deficiency PC or PS deficiency § Heterozygous FVL or PT20210A § Multiple abnormalities or homozygotes
American College of Chest Physicians (ACCP) Guidelines, 2012 (85)	Homozygous FVL or PT20210A ¶	AT or PC or PS deficiency ¶ Heterozygous FVL or PT20210A ¶ Multiple abnormalities ¶ Homozygous FVL or PT20210A Anti-vitamin K agents (INR 2.0 to 3.0) can be an alternative (except for women with a PC or PS deficiency)
Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) and Australasian Society of Thrombosis and Haemostasis (ASTH), 2012 (86)	AT deficiency § PC or PS deficiency § Heterozygous FVL or PT20210A ‡ Multiple abnormalities § Homozygous FVL §	AT or PC or PS deficiency Heterozygous FVL or PT20210A Multiple abnormalities Homozygous FVL

On the other hand, if the index case is a carrier of mild thrombophilia with isolated heterozygous FVL or PT20210A the indication for a family study is weaker and should be considered on a case-by-case basis (11).

As previously stated, family history of VTE is a consistent risk factor of VTE, being associated with a two- to three-fold increased risk of VTE (73-78); however, it should be kept in mind that sensitivity of family history (presence of disease in relatives of the informant) is less accurate than specificity (absence of disease), and that accuracy is higher for information related to first-degree relatives than more distant relatives (89). Therefore, caution should be employed in decision making exclusively based on

family history of VTE irrespective of the individual genotype (high-risk or mild thrombophilia).

Conclusions

The majority of the recommendations concerning inherited thrombophilia are based on low-quality evidence or on experts' opinions. Due to the relative or absolute rarity of the different types of thrombophilia, it is unlikely that randomised controlled studies will explore the impact of different treatment strategies in carriers, either those with previous VTE or asymptomatic individuals. However, this should be accepted as a well-known limitation of the investigation of rare diseases, and evidence-based methodology can help to minimise bias and maximise accuracy of new data, utilising all the associated information available from different sources, which is the underlying principle of evidence-based medicine (90).

There is consistent evidence of an inverse gradient between the rarity of the type of inherited thrombophilia and the clinical penetrance, with the risk for VTE higher in carriers of a deficiency of natural anticoagulants and those who are homozygous or carriers of multiple abnormalities and moderate in heterozygotes for mild thrombophilia (i.e. FVL or PT20210A). In patients who have experienced a first VTE, the clinical circumstances of the event and the laboratory global phenotypes (such as the D-dimer level) add further information to furnish adequate counselling for discontinuing or prolonging antithrombotic secondary prophylaxis. The susceptibility to VTE is modulated by the presence or the absence of a family history of VTE, which is likely due to other unknown co-segregating genes. This is an important clue, in addition to the carrier status of the so-called high-risk or mild thrombophilia, to properly address primary antithrombotic prophylaxis in asymptomatic individuals, particularly women of childbearing age.

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Conflicts of interest

None declared.

References

1. De Stefano V, Rossi E, Paciaroni K, et al. Screening for inherited thrombophilia: indications and therapeutic implications. Haematologica 2002; 87: 1095-1108.
2. De Stefano V. Inherited thrombophilia and life-time risk of venous thromboembolism: is the burden reducible ? J Thromb Haemost 2004; 2: 1522-1525.
3. Vossen CY, Conard J, Fontcuberta J, et al. Familial thrombophilia and life-time risk of venous thrombosis. J Thromb Haemost 2004; 2: 1526-1532.
4. Vossen CY, Conard J, Fontcuberta J, et al. Risk of a first venous thrombotic event in carriers of a familial thrombophilic defect. The European Prospective Cohort on Thrombophilia (EPCOT). J Thromb Haemost 2005; 3: 459-464.
5. Middeldorp S, van Hylckama Vlieg A. Does thrombophilia testing help in the clinical management of patients? Br J Haematol 2008; 143: 321-335.
6. Makris M. Thrombophilia: grading the risk. Blood 2009; 113: 5038-5039
7. Lijfering WM, Brouwer JL, Veeger NJ, et al. Selective testing for thrombophilia in patients with first venous thrombosis: results from a retrospective family cohort study on absolute thrombotic risk for currently known thrombophilic defects in 2479 relatives. Blood 2009; 113: 5314-5322.
8. Carraro P; European Communities Confederation of Clinical Chemistry and Laboratory Medicine, Working Group on Guidelines for Investigation of Disease. Guidelines for the laboratory investigation of inherited thrombophilias. Recommendations for the first level clinical laboratories. Clin Chem Lab Med 2003; 41: 382-391.
9. European Genetics Foundation; Cardiovascular Disease Educational and Research Trust; International Union of Angiology; Mediterranean League on Thromboembolism, Nicolaides AN, Breddin HK, Carpenter P, et al. Thrombophilia and venous thromboembolism. International consensus statement. Guidelines according to scientific evidence. Int Angiol 2005; 24: 1-26.
10. Lussana F, Dentali F, Abbate R, et al.; Italian Society for Haemostasis and Thrombosis. Screening for thrombophilia and antithrombotic prophylaxis in pregnancy: Guidelines of the Italian Society for Haemostasis and Thrombosis (SISET). Thromb Res 2009; 124: e19-25.
11. Pernod G, Biron-Andreani C, Morange PE,et al.; French group on haemostasis and thrombosis; French Society of vascular medicine. Recommendations on testing for thrombophilia in venous thromboembolic disease: a French consensus guideline. J Mal Vasc 2009; 34: 156-203.
12. Baglin T, Gray E, Greaves M, et al.; British Committee for Standards in Haematology. Clinical guidelines for testing for heritable thrombophilia. Br J Haematol 2010; 149: 209-220.
13. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: routine testing for Factor Leiden (R506Q) and prothrombin (20210G>A) mutations in adults with a history of idiopathic venous thromboembolism and their adult family members. Genet Med 2011;13: 67-76.
14. NICE. Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. Clinical guideline 144. London: National Institute for Health and Clinical Excellence, 2012.
15. Kearon C, Akl EA, Comerota AJ, et al.; American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141 (2 Suppl): e419S-94S.
16. de Moerloose P, Boehlen F. Inherited thrombophilia in arterial disease: a selective review. Semin Hematol 2007; 44: 106-113.
17. Royal College of Obstetricians and Gynaecologists. The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage. Green-top Guideline No. 17, 2011; Available at www.rcog.org.uk.
18. Dallapiccola B, Agolini E, Morena A, et al. Censimento 2007 delle attività delle strutture di genetica medica in Italia. Analysis 2009; 4/5: 207-232.
19. Suthers, G. Report of the Australian Genetic Testing Survey 2006. Royal College of Pathologists of Australasia, 2009. Available at www.rcpa.edu.au/static/File/Asset library/public documents/Media Releases/AustralianGeneSurvey2006.pdf.
20. Coppens M, van Mourik JA, Eckmann CM, et al. Current practise of testing for inherited thrombophilia. J Thromb Haemost 2007; 5: 1979-1981.
21. Laberge AM, Psaty BM, Hindorff LA, et al. Use of Factor V Leiden genetic testing in practice and impact on management. Genet Med 2009; 11: 750-756.
22. Gartner V, Weber M, Eichinger S. The emotional impact of genetic testing and aspects of counseling prior to prescription of OC. Contraception 2008; 78: 392-398.
23. Seligsohn U, Lubetsky A. Genetic susceptibility to venous thrombosis. N Engl J Med 2001; 344: 1222-1231.
24. Ridker PM, Glynn RJ, Miletich JP, et al. Age-specific incidence rates of venous thromboembolism among heterozygous carriers of factor V Leiden mutation. Ann Intern Med 1997; 126: 528-531.
25. De Stefano V, Rossi E, Paciaroni K, et al. Different circumstances of the first venous thromboembolism among younger or older heterozygous carriers of the G20210A polymorphism in the prothrombin gene. Haematologica 2003; 88: 61-66.
26. Roldan V, Lecumberri R, Muñoz-Torrero JF, et al.; RIETE Investigators. Thrombophilia testing in patients with venous thromboembolism. Findings from the RIETE registry. Thromb Res 2009; 124: 174-177.
27. Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal

deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica 2007; 92: 199-205.
28. Hansson PO, Sorbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. Arch Intern Med 2000; 160: 769-774.
29. Baglin T, Luddington R, Brown K, et al. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet 2003; 362: 523-526.
30. Christiansen SC, Cannegieter SC, Koster T, et al. Thrombophilia, clinical factors, and recurrent venous thrombotic events. J Am Med Assoc 2005; 293: 2352-2361.
31. Simioni P. Risk of recurrent venous thromboembolism and thrombophilia: does discrepancy make complexity or vice versa ? J Thromb Haemost 2003; 1: 16-18.
32. Baglin T. Using the laboratory to predict recurrent venous thrombosis. Int J Lab Hematol 2011; 33: 333-342.
33. Tosetto A, Iorio A, Marcucci M, et al. Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH). J Thromb Haemost 2012; 10: 1019-1025.
34. Ho WK, Hankey GJ, Quinlan DJ, et al. Risk of recurrent venous thromboembolism in patients with common thrombophilia: a systematic review. Arch Intern Med 2006, 166: 729-736.
35. Marchiori A, Mosena L, Prins MH, et al. The risk of recurrent venous thromboembolism among heterozygous carriers of factor V Leiden or prothrombin G20210A mutation. A systematic review of prospective studies. Haematologica 2007; 92: 1107-1114.
36. Segal JB, Brotman DJ, Necochea AJ, et al. Predictive value of factor V Leiden and prothrombin G20210A in adults with venous thromboembolism and in family members of those with a mutation: a systematic review. J Am Med Assoc 2009; 301: 2472-2485.
37. Coppens M, Reijnders JH, Middeldorp S, et al. Testing for inherited thrombophilia does not reduce recurrence of venous thrombosis. J Thromb Haemost 2008; 6, 1474-1477.
38. Cohn DM, Vansenne F, de Borgie CA, et al. Thrombophilia testing for prevention of recurrent venous thromboembolism. Cochrane Database Syst Rev 2012; 12: CD007069.
39. Palareti G, Legnani C, Cosmi B, et al. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation 2003; 108: 313-318.
40. Allaart CF, Poort SR, Rosendaal FR, et al. Increased risk of venous thrombosis in carriers of hereditary protein C deficiency defect. Lancet 1993; 341: 134-138.
41. Engesser L, Broekmans AW, Briët E, et al. Hereditary protein S deficiency: clinical manifestations. Ann Intern Med 1987; 106: 677-682.
42. Zöller B, Berntsdotter A, García de Frutos P, et al. Resistance to activated protein C as an additional genetic risk factor in hereditary deficiency of protein S. Blood 1995; 85: 3518-3523.
43. De Stefano V, Simioni P, Rossi E, et al. The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C, and protein S. Haematologica 2006; 91: 695-698.
44. Vossen CY, Walker ID, Svensson P, et al. Recurrence rate after a first venous thrombosis in patients with familial thrombophilia. Arterioscler Thromb Vasc Biol 2005; 25: 1992-1997.
45. Brouwer JL, Lijfering WM, Ten Kate MK, et al. High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C or antithrombin. Thromb Haemost 2009; 101: 93-99.
46. De Stefano V, Martinelli I, Mannucci PM, et al. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med 1999; 341: 801-806.
47. Margaglione M, D'Andrea G, Colaizzo D, et al. Coexistence of factor V Leiden and Factor II A20210 mutations and recurrent venous thromboembolism. Thromb Haemost 1999; 82: 1583-1587.
48. Nowak-Gottl U, Junker R, Kreuz W, et al.; Childhood Thrombophilia Study Group. Risk of recurrent venous thrombosis in children with combined prothrombotic risk factors. Blood 2001; 97: 858-862.
49. Meinardi JR, Middeldorp S, de Kam PJ, et al. The incidence of recurrent venous thromboembolism in carriers of factor V Leiden is related to concomitant thrombophilic disorders. Br J Haematol 2002; 116: 625-631.
50. The Procare Group. Is recurrent venous thromboembolism more frequent in homozygous patients for the factor V Leiden mutation than in heterozygous patients? Blood Coagul Fibrinolysis 2003; 14: 523-529.
51. Martinelli I, De Stefano V. Rare thromboses of cerebral, splanchnic and upper-extremity veins. A narrative review. Thromb Haemost 2010; 103: 1136-1144.
52. Einhäupl K, Stam J, Bousser MG, et al.; European Federation of Neurological Societies. EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients. Eur J Neurol 2010; 17: 1229-1235.
53. Ageno W, Dentali F, Squizzato A, et al. Evidence and clinical judgment: treatment of cerebral vein thrombosis. Thromb Haemost 2010; 103: 1109-1115.
54. DeLeve LD, Valla DC, Garcia-Tsao G; American Association for the Study Liver Diseases. Vascular disorders of the liver. Hepatology 2009; 49: 1729-1764.
55. Tait C, Baglin T, Watson H, et al.; British Committee for Standards in Haematology. Guidelines on the investigation and management of venous thrombosis at unusual sites. Br J Haematol 2012; 159: 28-38.
56. Decousus H, Moulin N, Quenet S, et al. Trombophilia and risk of venous thrombosis in patients with cancer. Thromb Res 2007; 120 (Suppl 2): S51-61.
57. Horowitz N, Brenner B. Thrombophilia and cancer. Pathophysiol Haemost Thromb 2008; 36: 131-136.
58. Dentali F, Gianni M, Agnelli G, et al. Association between inherited thrombophilic abnormalities and central venous catheter thrombosis in patients with cancer: a meta-analysis. J Thromb Haemost 2008; 6: 70-75.
59. Caruso V, Iacoviello L, Di Castelnuovo A, et al. Thrombotic complications in childhood acute lymphoblastic leukemia: a meta-analysis of 17 prospective studies comprising 1752 pediatric patients. Blood 2006; 108: 2216-2222.
60. Farge D, Debourdeau P, Beckers M, et al. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. J Thromb Haemost 2013; 11: 56-70.
61. Harlev D, Zaidman I, Sarig G, et al. Prophylactic therapy with enoxaparin in children with acute lymphoblastic leukemia and inherited thrombophilia during L-asparaginase treatment. Thromb Res 2010; 126: 93-97.
62. Wu O, Robertson L, Twaddle S, et al.; Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. Screening for thrombophilia in high-risk situations: a meta-analysis and cost-effectiveness analysis. Br J Haematol 2005;131: 80-90.
63. Vandenbroucke JP, van der Meer FJM, Helmerhorst FM, et al. Factor V Leiden: should we screen oral contraceptive users and pregnant women? Br Med J 1996; 313: 1127-1130.
64. Clark P, Twaddle S, Walker ID, et al. Cost-effectiveness of screening for the factor V Leiden mutation in pregnant women. Lancet 2002; 359: 1919-1920.
65. Grody WW, Griffin JH, Taylor AK, et al.; ACMG Factor V Leiden Working Group. American College of Medical Genetics consensus statement on factor V Leiden mutation testing. Genet Med 2001; 3: 139-148.
66. Recommendations of the European Society of Human Genetics. Provision of genetic services in Europe: current practices and issues. Eur J Hum Genet 2003; 11 (Suppl 2): S2-S4.
67. Recommendations of the European Society of Human Genetics. Population genetic screening programmes: technical, social and ethical issues. Eur J Hum Genet 2003; 11 (Suppl 2): S5-S7
68. Green D. Genetic hypercoagulability: screening should be an informed choice. Blood 2001; 98: 20.
69. Mannucci PM. Genetic hypercoagulability: prevention suggests testing family members. Blood 2001; 98: 21–22.
70. Martinelli I. Pros and cons of thrombophilia testing: pros. J Thromb Haemost 2003; 1: 410-411.
71. Machin SJ. Pros and cons of thrombophilia testing: cons. J Thromb Haemost 2003; 1: 412-413.
72. Bank I, Scavenius MP, Büller HR, et al. Social aspects of genetic testing for factor V Leiden mutation in healthy individuals and their importance for daily practice. Thromb Res 2004; 113: 7-12.
73. Tosetto A, Frezzato M, Rodeghiero F. Prevalence and risk factors of non-fatal venous thromboembolism in the active population of the VITA Project. J Thromb Haemost 2003; 1: 1724-1729.
74. Noboa S, Le Gal G, Lacut K, et al.; EDITH Collaborative Study Group. Family history as a risk factor for venous thromboembolism. Thromb Res 2008; 122: 624-629.
75. Bezemer ID, van der Meer FJ, Eikenboom JC, et al. The value of family history as a risk indicator for venous thrombosis. Arch Intern Med 2009; 169: 610-615.

76. Zöller B, Li X, Sundquist J, et al. Parental history and venous thromboembolism: a nationwide study of age-specific and sex-specific familial risks in Sweden. J Thromb Haemost 2011; 9: 64-70.
77. Sørensen HT, Riis AH, Diaz LJ, et al. Familial risk of venous thromboembolism: a nationwide cohort study. J Thromb Haemost 2011; 9: 320-324.
78. Zöller B, Ohlsson H, Sundquist J, et al. Familial risk of venous thromboembolism in first-, second- and third-degree relatives: a nationwide family study in Sweden. Thromb Haemost 2013; 109: 458-463.
79. Lensen RP, Bertina RM, de Ronde H, et al. Venous thrombotic risk in family members of unselected individuals with factor V Leiden. Thromb Haemost 2000; 83: 817-821.
80. Rossi E, Ciminello A, Za T, et al. In families with inherited thrombophilia the risk of venous thromboembolism is dependent on the clinical phenotype of the proband. Thromb Haemost 2011; 106: 646–654.
81. Duhl AJ, Paidas MJ, Ural SH, et al.; Pregnancy and Thrombosis Working Group. Antithrombotic therapy and pregnancy: consensus report and recommendations for prevention and treatment of venous thromboembolism and adverse pregnancy outcomes. Am J Obstet Gynecol 2007; 197: 457.e1-21.
82. Royal College of Obstetricians and Gynaecologists. Thrombosis and embolism during pregnancy and the puerperium. Reducing the risk. Green-top Guideline No. 37a, 2009. Available at www.rcog.org.uk.
83. Scottish Intercollegiate Guidelines Network. Prevention and management of venous thromboembolism. A national clinical guideline. SIGN publication no. 122, 2010. Available at www.sign.ac.uk.
84. Lockwood C, Wendel G; Committee on Practice Bulletins— Obstetrics. Practice bulletin no. 124: inherited thrombophilias in pregnancy. Obstet Gynecol 2011; 118: 730-740.
85. Bates SM, Greer IA, Middeldorp S, et al.; American College of Chest Physicians. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl): e691S-736S.
86. McLintock C, Brighton T, Chunilal S, et al.; Councils of the Society of Obstetric Medicine of Australia and New Zealand; Australasian Society of Thrombosis and Haemostasis. Recommendations for the prevention of pregnancy-associated venous thromboembolism. Aust N Z J Obstet Gynaecol 2012; 52: 3-13.
87. Royal College of Obstetricians and Gynaecologists. Venous thromboembolism and hormonal contraception. Green-top Guideline No. 40, 2010. Available at www.rcog.org.uk.
88. Royal College of Obstetricians and Gynaecologists. Venous thromboembolism and hormone replacement therapy. Green-top Guideline No. 11, 2011. Available at www.rcog.org.uk.
89. Wilson BJ, Qureshi N, Santaguida P, et al. Systematic review: family history in risk assessment for common diseases. Ann Intern Med 2009; 151: 878-885.
90. Behera M, Kumar A, Soares HP, et al. Evidence-based medicine for rare diseases: implications for data interpretation and clinical trial design. Cancer Control 2007; 14: 160-166.