

# 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 child-bearing 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 consistently



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 consistently 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-degree 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.

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