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Diagnosis and management of heritable thrombophilias

Peter MacCallum,^{1,2} Louise Bowles,² David Keeling³

¹Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, UK

²Department of Haematology, Barts Health NHS Trust, London, UK

³Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals, Oxford, UK

Correspondence to: P MacCallum p.k.maccallum@qmul.ac.uk

Cite this as: *BMJ* 2014;349:g4387 doi: 10.1136/bmj.g4387

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The term thrombophilia refers to an abnormality of blood coagulation that increases the risk of thrombosis. Such abnormalities represent one component of the triad (along with stasis and abnormalities of the vessel wall) put forward by Virchow in the 19th century to explain why thrombosis occurs.

Thrombophilic abnormalities may be heritable (the topic of this review) or acquired, although both genetic and environmental factors influence activity within the coagulation system and may interact to provoke thrombotic events.¹ Clinicians in primary and secondary care may need to counsel or manage asymptomatic people or patients with venous thromboembolism (VTE) who have either a family history of venous thrombosis or a known heritable thrombophilia. The purpose of this review is to help clinicians decide whether to test for a thrombophilic tendency, what tests to request if testing is to be done, and how to interpret and act on the results.

What are the types of heritable thrombophilias?

In clinical practice the heritable factors predisposing to venous (but not arterial) thrombosis that are most widely assessed are: genetic deficiencies of the naturally occurring anticoagulants (antithrombin, protein C, and protein S) and “gain of function” genetic polymorphisms (factor V Leiden and the prothrombin gene mutation). Several other heritable factors have also shown associations with first or recurrent episodes of VTE, including non-O blood group, sickle cell disorders, and rare mutations within the haemostatic system, but these are not generally included in testing for heritable thrombophilia and are outside the scope of this review. The antiphospholipid syndrome is also not included, because it is an acquired rather than a heritable thrombophilic disorder.^{2,3}

Whereas deficiencies of natural anticoagulants were once thought to be rare abnormalities found in selected families with a strong history of venous thrombosis, the two most recently identified thrombophilias (factor V Leiden and the prothrombin gene mutation) are common within the population as a whole.^{4,5} Further studies have suggested that overall the heritable thrombophilias are modest predictors of a first

SOURCES AND SELECTION CRITERIA

We searched PubMed and the Cochrane Collaboration for recent systematic reviews and meta-analyses on thrombophilia and its epidemiology, pathophysiology, and management. We supplemented these with recent largely UK based national guidelines and with further references obtained through PubMed and through personal archives of references. Evidence on the management of symptomatic or asymptomatic people with heritable thrombophilia is weak and largely based on extrapolation from observational studies.

episode of VTE and have a limited role in the prediction of recurrent events. As such, they are now considered to have limited clinical utility in most common situations, and this has been recognised in recent national guidelines.^{5,6}

How common are heritable thrombophilias and how do they affect the risk of thrombosis?

Most heritable thrombophilias are heterozygous defects. The table summarises their approximate prevalence and relative risks.

Gain of function polymorphisms

Factor V Leiden

The most common heritable thrombophilia within the UK population and identified in clinical practice is factor V Leiden. As a result, knowledge about the epidemiology of factor V Leiden is greater than for the other heritable thrombophilias. The prevalence varies considerably according to ethnic origin. Within white populations of European origin, the prevalence is approximately 3-7% and even higher in some areas, such as southern Sweden.^{7,8} To explain the relatively high prevalence within these populations it has been suggested that the heterozygous state may confer a survival advantage, possibly because of reduced bleeding with childbirth or trauma; however, this is unconfirmed. A similar prevalence is also seen in populations of the Mediterranean and Middle East. In contrast, factor V Leiden is essentially not found in South East Asia, Japan, and sub-Saharan Africa, or in indigenous Australian populations. The predicted prevalence of people homozygous for factor V Leiden in European populations would be around 1 in 1600.

The factor V Leiden polymorphism is a mis-sense mutation. The result of this mutation is that activated factor V, a clotting factor, is inactivated around 10-fold more slowly than normal by activated protein C (so called APC resistance) and this leads to increased thrombin generation. The molecular basis of this activated protein C resistance laboratory phenotype was initially identified by investigators from Leiden University in the Netherlands.⁹

Compared with non-carriers, heterozygous carriers of factor V Leiden have a threefold to fivefold increased risk of

SUMMARY POINTS

Heritable thrombophilias increase the risk of venous thromboembolism (VTE) and are present in about 5% of the population, but most carriers never experience a deep vein thrombosis or pulmonary embolism

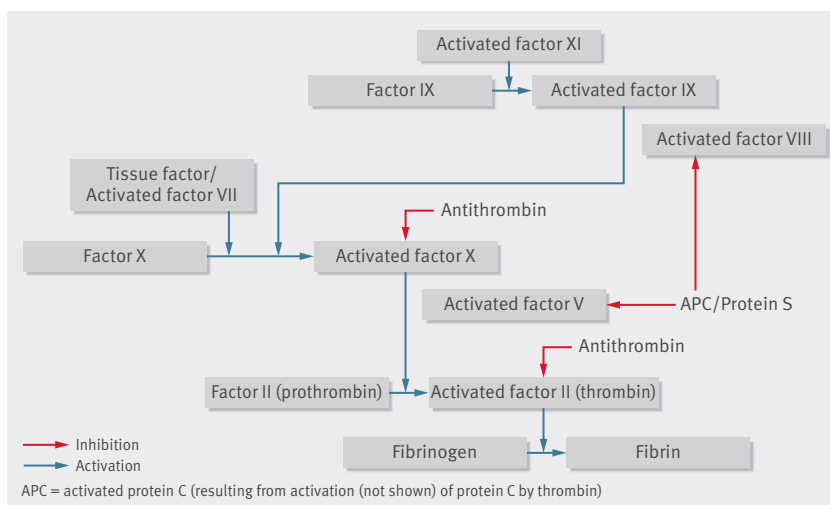
Diagnosis of heritable thrombophilia does not affect acute management and rarely affects the long term management of VTE

Testing for heritable thrombophilias should not be offered to people with deep vein thrombosis or pulmonary embolism without agreement of how and why the result would alter management

Since a family history of VTE is itself a risk factor for VTE, testing for heritable thrombophilias in asymptomatic people with a family history of deep vein thrombosis or pulmonary embolism is rarely required, and the finding of a negative test result may provide false reassurance

Approximate relative risks and prevalences within UK population for different heritable thrombophilias

Thrombophilic disorders	Relative risk	Prevalence (%) in population
Factor V Leiden, heterozygous	3-5	4
Factor V Leiden, homozygous	10	0.05
Prothrombin gene mutation, heterozygous	2-4	1.5
Double heterozygosity for factor V Leiden and prothrombin gene mutation	5	0.05
Antithrombin deficiency (type 1)	10-20	0.02
Protein C deficiency	5-15	0.3
Protein S deficiency	Uncertain	0.1



Outline of coagulation system, highlighting role of inhibitors

VTE throughout life.¹⁰⁻¹² The absolute risk, however, is low, with only 5% of such people developing an episode of VTE by age 65 years.^{13 14} This is a reflection of the background risk of VTE within the population as a whole, which is age dependent but on average affects 1 per 1000 people each year. Approximately 20% of patients with a first unprovoked episode of VTE are heterozygous carriers of factor V Leiden. For reasons that remain unexplained, factor V Leiden seems to be a stronger risk factor for deep vein thrombosis than for pulmonary embolism.¹⁵ Those who are homozygous for factor V Leiden are at a 10-fold or greater risk of VTE than non-carriers.¹⁰⁻¹² However, because such people are uncommon within the population, they do not contribute substantially to the overall burden of VTE.

Interactions have been found with other risk factors for VTE, in particular combined hormonal contraceptives, hormone replacement therapy, and pregnancy. For example, data from a case-control study suggested that the risk of deep vein thrombosis in users of combined hormonal contraceptives was increased fourfold compared with non-users and that the risk associated with combined hormonal contraceptive use in heterozygous carriers of factor V Leiden was multiplicative, resulting in an approximately 30-fold increased risk compared with non-users who did not carry the factor V Leiden gene.¹⁶ Increased risks have also been observed in studies of hormone replacement therapy.¹⁷ However, the absolute (as opposed to relative) risk of VTE while taking combined hormonal contraceptives in the 5% of the population who carry the factor V Leiden gene remains too small (about 15-30 per 10000 women each year) to justify widespread screening.^{18 19}

Prothrombin gene mutation

The prothrombin gene mutation is the second most commonly identified heritable thrombophilia, with around 1-2% of white populations of European origin being heterozygous carriers. The mutation is associated with a twofold to fourfold increased risk of VTE throughout life, slightly less overall than the risk associated with factor V Leiden.^{11 12 20-22} It is present in around 5% of people with a first unprovoked episode of VTE. Prothrombin levels are increased by about 30% in heterozygotes and 70% in homozygotes.

Deficiencies of naturally occurring anticoagulants

The figure shows the roles of the naturally occurring anticoagulants.

Antithrombin deficiency

Heterozygous mutations of the gene for antithrombin, previously called antithrombin III, result in antithrombin deficiency leading to reduced inhibition of factor Xa and thrombin and therefore increased thrombin generation and activity. Two major types of antithrombin deficiency occur: type I (a quantitative defect with reduced production of a normal molecule) and type II (a qualitative defect in which the molecule itself is abnormal). Type II antithrombin deficiency can be subdivided according to the site of the molecular defect: heparin binding site (which carries a lower risk of thrombosis), reactive site, or both. In clinical practice it is difficult to distinguish between the subtypes of type II antithrombin deficiency, and specialist advice should be considered.

Type I antithrombin deficiency is rare (0.02% of the population) and homozygous mutations are incompatible with life.²³ The degree of increased risk of VTE associated with heterozygous antithrombin deficiency remains the subject of debate. This reflects in part on the low prevalence of antithrombin deficiency within the population and therefore the uncertainties around any estimates. Different study designs (for example, case-control versus family cohort) have reached different conclusions, with estimated relative risks varying from similar to those of factor V Leiden to risks that are around fivefold higher.²⁴⁻²⁶ The absolute risk of a first episode of VTE in previously asymptomatic people with antithrombin deficiency in families in whom a proband with VTE is antithrombin deficient has been estimated at around 2% yearly.^{26 27} An antithrombin concentrate is available and some advocate its use in certain high risk patients with antithrombin deficiency and previous VTE who are undergoing procedures where anticoagulation has to be withheld; such situations are rare and expert advice should be sought.

Protein C and protein S deficiency

Protein C and protein S are vitamin K dependent glycoproteins. Heritable deficiencies of either lead to impaired inactivation of factor Va and factor VIIIa and thereby increased thrombin generation. Protein C deficiency is classified into type I (quantitative) and type II (qualitative) defects, although unlike with antithrombin deficiency the thrombotic risk between the different types does not differ. Similarly, type I and type II abnormalities of protein S exist, although type II is rare. A type III deficiency characterised by a normal level of total protein S but a reduced level of the free active pro-

tein has been described and probably represents defective production (type I deficiency) not recognised with the less sensitive assay for total protein S (which therefore incorrectly suggests a normal result).⁴

About 0.3% of the population has protein C deficiency.²⁸ Estimates for risk of VTE associated with protein C deficiency vary from those that are similar to factor V Leiden to those that are closer to antithrombin deficiency. Unlike antithrombin deficiency, homozygous protein C deficiency, although rare, is compatible with life, typically presenting with neonatal purpura fulminans or cerebral vein thrombosis.²³

The prevalence of protein S deficiency is uncertain but is probably around 0.1%.²⁸ The risk of VTE associated with protein S deficiency is uncertain: family studies have suggested risks similar in size to those observed in protein C deficiency,^{26 27} but population studies suggest a lower risk.²⁹

Double heterozygosity

It is possible for more than one thrombophilic tendency to be inherited. This is most commonly seen in people who are heterozygous for both factor V Leiden and the prothrombin gene mutation. Although such people may have a higher risk of VTE than those who are heterozygous for one gene only,²² a recent meta-analysis found the risk to be similar to that of factor V Leiden alone.¹²

What is the importance of family history?

An important point in estimating risks associated with heritable thrombophilias in asymptomatic patients is that the absolute risk depends not only on the identified thrombophilia but also on whether or not the patient has a family history of VTE, which is itself a risk factor for VTE.³⁰⁻³² In families with thrombophilia, those without the familial thrombophilia still have a higher risk of VTE than the general population.³³ This suggests the presence of additional heritable or acquired risk factors in such families even though these cannot currently be easily identified. It also seems likely that heritable or envi-

ronmental factors may be protective against VTE, but these are mostly unclear at this time.

How are heritable thrombophilias diagnosed?

Testing for heritable thrombophilia involves a range of complex coagulation based tests along with genetic testing (box); testing is expensive and the results can be affected by preanalytical variables. Interpretation of results can be challenging and often requires expertise in conjunction with relevant clinical details.

Testing for thrombophilia during the acute phase of a thrombotic event should be avoided as several factors may influence test results acutely and the presence of a heritable thrombophilia does not affect the initial management of VTE. Knowledge of which drugs are being taken at the time of testing is important. Heparin can lower antithrombin levels and warfarin will result in a decrease in levels of vitamin K dependent proteins such as protein C and protein S. Additionally, protein S levels are lowered by hormonal preparations containing oestrogen. The background medical condition of patients can also affect coagulation tests. In disseminated intravascular coagulation and liver disease the levels of natural anticoagulants decrease, and in pregnancy, secondary to the oestrogen effect, protein S levels decrease. Antithrombin levels may decrease in nephrotic syndrome as the protein is leaked in the urine. Neonates have low levels of antithrombin and protein C and protein S and these usually reach normal adult values by 3-6 months, although protein C can take until adolescence to reach normal values.

The “thrombophilia screen” for heritable disorders that clinicians request usually involves measurement of antithrombin, protein C, and protein S levels, and testing for the factor V Leiden and prothrombin gene mutations. Including a prothrombin time and an activated partial thromboplastin time helps to identify those who are taking anticoagulants at the time of testing, thus aiding the interpretation of results (box).

In general, functional assays are used for the assessment of antithrombin and protein C. A chromogenic protein C test is preferable to a clotting based assay. Protein S can be assessed with an antigenic test measuring free protein S, or with a functional assay. Testing for activated protein C resistance may be used in some laboratories to screen for factor V Leiden, but as confirmatory genotyping is essential most do genetic tests for this and the prothrombin gene mutation. For the coagulation based tests, a confirmatory second sample is obligatory if the result of initial testing is abnormal (box).

It should be noted that most patients with values below the traditional lower limit of the reference range (by definition those with levels lower than 2 standard deviations below the mean, that is 1 in 40 patients) will not have an inherited deficiency of the natural anticoagulants.^{29 34} Using this cut-off to dichotomise patients may not be sensible; some studies have shown a gradation of risk with levels,³⁵ whereas another study showed that, for example, protein S deficiency does not seem to be a risk factor for VTE unless levels are very low (<0.10th percentile free protein S).²⁹

When should heritable thrombophilias be looked for?

Venous thromboembolism

Clinicians may wish to screen patients who have VTE and their asymptomatic relatives for heritable thrombophilia

Standard tests (“thrombophilia screen”) for heritable thrombophilias, and common acquired causes of abnormalities

Prothrombin time

Prolonged in disseminated intravascular coagulation, liver disease, and warfarin treatment

Activated partial thromboplastin time

Prolonged in disseminated intravascular coagulation, liver disease, lupus anticoagulant and heparin treatment

Antithrombin activity

Low levels in disseminated intravascular coagulation, liver disease, and nephrotic syndrome, or heparin or L-asparaginase treatment

Protein C activity (chromogenic)

Low levels in disseminated intravascular coagulation, liver disease, and warfarin treatment

Free protein S antigen

Low levels in disseminated intravascular coagulation, liver disease, with acute phase reaction, pregnancy, and warfarin or hormones containing oestrogen treatment

Factor V Leiden genotype

Unaffected by clinical condition or drugs

Prothrombin gene mutation

Unaffected by clinical condition or drugs

for one of two reasons. Firstly, to offer long term rather than short term anticoagulation to the index case, and, secondly, to identify asymptomatic relatives at increased risk of VTE so that an intervention not suitable for all relatives can be used to reduce their individual risk of VTE. However, are these considerations justified?

Management of the index case

Risk factors for recurrence

For the index case an increased risk of recurrence is predicted by a persisting risk factor (for example, active cancer) or an unprovoked event.³⁶⁻³⁸ The risk of recurrence is increased after a first unprovoked episode of VTE if the patient is male³⁹⁻⁴¹ and/or the D-dimer level is increased after completing anticoagulation,⁴⁰⁻⁴² and the identification of such risk factors makes a stronger case for long term anticoagulation for secondary prevention. A family history of thrombosis does not increase the risk of recurrence,⁴³ and prospective cohort studies have shown that heritable thrombophilia does not usefully predict recurrence.^{44 45} A systematic review looking at the two most common heritable thrombophilias found that the odds ratio for recurrence in association with heterozygosity for factor V Leiden was 1.56 (95% confidence interval 1.14 to 2.12) and with heterozygosity for the prothrombin gene mutation was 1.45 (0.96 to 2.21).⁴⁶ These increases in risk are not thought of sufficient size to justify long term anticoagulation if such treatment would not otherwise have been given. It has been suggested that combined defects carry a higher risk of recurrence, but patients who are homozygous for factor V Leiden or the prothrombin gene mutation or double heterozygous carriers of factor V Leiden and the prothrombin gene mutation do not seem to have a high risk of recurrence.^{46 47} Deficiencies of antithrombin, protein C, or protein S are often described as high risk thrombophilias.²⁶ The risk of recurrence had been claimed to be high in studies of families prone to thrombosis,⁴⁸ but in patients who are not selected from such families the relative risk of recurrence seems to be <2.^{44 45 49} One recent study in patients with unprovoked VTE suggested that antithrombin deficiency was associated with a twofold increase in the risk of recurrence after stopping anticoagulation⁵⁰; this requires confirmation. No randomised trials have assessed the benefit of testing for heritable thrombophilias on the risk of recurrent VTE.⁵¹ Additionally, heritable thrombophilias do not predict the risk of either the post-thrombotic syndrome after a deep vein thrombosis or mortality.^{52 53}

The observation that heritable thrombophilias are weaker risk factors for recurrent rather than first VTE events to some seems counterintuitive. The simplest explanation is that in the setting of first episodes the comparison is between those who have had events and those who have not and, as expected, identifiable thrombophilias are found more commonly in the former than in the latter. In contrast, in the setting of recurrences, the comparison is between those who have a detectable heritable thrombophilia and those who are likely to have a thrombophilic tendency (to cause the VTE in the first place) that cannot be easily identified with current laboratory tests.

Duration of anticoagulation

Heritable thrombophilias would seem to have only a minor role in the duration of anticoagulant treatment.⁵⁴ Recent British guidelines^{5 6} are against indiscriminate testing of patients

presenting with VTE and suggest testing should be considered only in selected patients such as those with unprovoked events and a family history of thrombosis who are planning to stop anticoagulation.

A separate situation is seen in venous thrombosis in unusual sites. Here there are even fewer data and although some suggest that the presence of heritable thrombophilia should result in a longer course of anticoagulation,⁵⁵ there is no good evidence base for such recommendations.⁵⁶

Pregnancy and contraception

Combined hormonal contraceptives are contraindicated in women with a previous episode of VTE,⁵⁷ and this is unaffected by the presence or absence of a heritable thrombophilia. However, the levonorgestrel releasing intrauterine device and low dose oral progestogen preparations seem to be safe.⁵⁸ In the context of pregnancy, all women with a previous episode of VTE will be offered thromboprophylaxis for six weeks post partum.^{59 60} Women with a history of unprovoked or oestrogen provoked VTE will also be offered antenatal thromboprophylaxis.^{59 60} Those with a previous event provoked by a minor transient risk factor would not routinely have antenatal thromboprophylaxis, but they should then be tested for a thrombophilic tendency as a positive test result may change this decision.⁶⁰ The presence or absence of a heritable thrombophilia does not affect the dose of low molecular weight heparin used for thromboprophylaxis in pregnancy, with the exception of women with antithrombin deficiency, where guidelines from the Royal College of Obstetricians and Gynaecologists recommend higher (intermediate or treatment) doses, although the equivalent North American guidelines do not draw this distinction.^{59 60}

Management of asymptomatic relatives

As long term anticoagulation of asymptomatic relatives with thrombophilia is not recommended, the only concern is with the possibility of trying to prevent provoked episodes of VTE in relatives. Testing implies that relatives with thrombophilia might be given thromboprophylaxis, or more prolonged prophylaxis, in high risk situations when it would be withheld from relatives without thrombophilia. A family history of VTE is itself a risk factor for VTE,³⁰⁻³² even when heritable thrombophilias cannot be found.³² It therefore seems reasonable to offer thromboprophylaxis in high risk situations to all first degree relatives of patients with VTE and not to withhold this on the basis of a negative thrombophilia screen result. Since the finding of a heritable thrombophilia generally has little impact on the management of asymptomatic relatives, guidelines from the National Institute for Health and Care Excellence recommend against routinely offering thrombophilia testing to first degree relatives of people with a history of deep vein thrombosis or pulmonary embolism and thrombophilia.⁶ Testing might, however, be considered in individual situations such as asymptomatic relatives in families with a high clinical penetrance of VTE.

Pregnancy, contraception, and hormone replacement therapy

Specific problems are associated with contraception and pregnancy in female relatives of childbearing age, and hormone replacement therapy in older women. According to

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

National Institute for Health and Care Excellence. 2012 (www.nice.org.uk/nicemedia/live/13767/59711/59711.pdf)—venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing

Baglin T, Gray E, Greaves M, Hunt BJ, Keeling D, Machin S, et al. Clinical guidelines for testing for heritable thrombophilia. *Br J Haematol* 2010;149:209-20 (<http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2009.08022.x/pdf>)—national specialty guidelines on testing for heritable thrombophilia

Medicines and Healthcare products Regulatory Agency. 2014 (www.mhra.gov.uk/home/groups/pl-p/documents/websitesresources/con391267.pdf)—information on combined hormonal contraception

Royal College of Obstetricians and Gynaecologists. 2009 (www.rcog.org.uk/files/rcog-corp/GTG37aReducingRiskThrombosis.pdf)—discussion on reducing the risk of thrombosis and embolism during pregnancy and the puerperium

Resource for patients

NHS Choices. Thrombophilia. (www.nhs.uk/conditions/thrombophilia/Pages/Thrombophilia.aspx)—information for patients about thrombophilia

a recent European review, combined hormonal contraceptives are estimated to increase the annual risk of VTE from 2 in 10 000 women to approximately 5-10 in 10 000 women (depending on the preparation).⁶¹ The risks seem to be higher in women with heritable thrombophilias from thrombosis prone families and have been estimated at 0.2% per year for the prothrombin gene mutation and 0.5% per year for factor V Leiden, and up to 4% per year for women with deficiencies of antithrombin, protein C, or protein S.⁵⁸ The recent checklist for prescribers issued by the Medicines and Healthcare products Regulatory Agency after review of combined hormonal contraceptives by the European Medicines Agency states that combined hormonal contraceptives should not be prescribed if women have a predisposition for a blood clotting disorder, and the suitability of a combined hormonal contraceptive should be discussed with women if a close relative (parent or sibling) has had a thromboembolic event at a young age (<50 years).⁵⁷ Since women with a history of VTE in a first degree relative before 50 years of age should consider an alternative form of contraception to combined hormonal contraception, thrombophilia testing generally has little role. The exception might be where a high risk thrombophilia (deficiency of a naturally occurring anticoagulant or homozygosity or double heterozygosity for defects) is identified in the symptomatic relative, when its absence in women might allow combined oral contraceptives to be considered. For the most part, however, while the finding of a heritable thrombophilia would mean that combined hormonal contraceptives should not be prescribed, the absence of a detectable tendency for thrombophilia in the setting of a family history of VTE would not provide sufficient reassurance to enable combined hormonal contraceptives to be prescribed without discussion of the risks and alternatives.

Women with a history of unprovoked VTE in a first degree relative should not use oral hormone replacement therapy, but if it is considered essential they can be offered transdermal therapy, which seems not to carry a clinically significant risk of VTE.^{5 62-64}

Pregnant women, or women planning a pregnancy, who have a first degree relative with unprovoked or oestrogen

TIPS FOR NON-SPECIALISTS

The duration of anticoagulation for a first episode of venous thromboembolism (VTE) is determined by factors other than heritable thrombophilia

A family history of VTE is a risk factor for VTE even in the absence of a detectable heritable thrombophilia

Alternatives to combined hormonal contraceptives should be considered in women with a first degree family member with a thromboembolic event before the age of 50 years

Do not routinely offer testing for heritable thrombophilia to first degree relatives of people with a history of VTE and thrombophilia

Testing for heritable thrombophilias during or in advance of pregnancy may be reasonable in asymptomatic women with a family history of VTE

Individuals considering testing for heritable thrombophilias should be counselled in advance about the benefits and disadvantages of such testing

Interpretation of the results of thrombophilia testing may require expertise in the strengths and weaknesses of laboratory assays

associated VTE should be assessed for their risk of pregnancy associated venous thrombosis. This should include a thrombophilia screen, as the Royal College of Obstetricians and Gynaecologists guidelines suggest antenatal thromboprophylaxis if such women have antithrombin deficiency or homozygosity or double heterozygosity for heritable thrombophilia,⁶⁰ although North American guidelines⁵⁹ would only recommend antenatal thromboprophylaxis in the presence of homozygosity for factor V Leiden or the prothrombin gene mutation. Postpartum thromboprophylaxis should be considered in all women with a family history of VTE and a known thrombophilia,^{59 60} particularly if there are additional risk factors. **Arterial disease**

Statistically significant but not clinically important associations have been described between coronary disease and factor V Leiden and the prothrombin gene mutation.⁶⁵ Although an association with heritable thrombophilias is plausible since venous and arterial disease are linked,⁶⁶ the role heritable thrombophilias play in arterial disease is likely to be small compared with traditional risk factors for arterial disease. Additionally, evidence is lacking to support any change in primary or secondary prevention measures if a heritable thrombophilic defect is detected, including in the setting of stroke in patients with a patent foramen ovale.⁶⁷ British guidelines recommend that testing for heritable thrombophilia is not indicated in arterial disease.⁵ The possible role of thrombophilic abnormalities in neonatal stroke and its management is outside the scope of this article.

We thank Siobhan Williams for assistance in the original design of the figure. Contributors: All authors contributed to writing the manuscript and take responsibility for its integrity. PM is guarantor.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: PM has received speaker fees from Boehringer Ingelheim and Bayer, advisory board fees from Daiichi Sankyo, and travel and accommodation costs for meetings from Leo Pharmaceuticals, Boehringer Ingelheim, and Daiichi Sankyo. LB has received travel and accommodation expenses for meetings from Leo Pharmaceuticals and Bayer. DK has received speaker fees from Boehringer Ingelheim, advisory board fees from Bayer and Daiichi Sankyo, and travel and accommodation costs from Bayer.

Provenance and peer review: Commissioned; externally peer reviewed.

References are in the version on thebmj.com.