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GUIDELINE

Thrombophilia testing: A British Society for Haematology guideline

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METHODOLOGY

This guideline was compiled according to the BSH process at [https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org. A literature search was carried out using the terms given in Appendix S1 until April 2021.

Review of the manuscript

Review of the manuscript was performed by the BSH Haemostasis and Thrombosis Task Force, the BSH Guidelines Committee and the sounding board of BSH. It was also placed on the members section of the BSH website for comment. It has also been reviewed by Royal College of Obstetricians and Gynaecologists, Royal College of Paediatrics and Child Health, Royal College of Physicians and Thrombosis UK, a patient-centred charity dedicated to promoting awareness, research and care of thrombosis; these organisations do not necessarily approve or endorse the contents.

INTRODUCTION

This guideline updates and widens the scope of the previous British Society for Haematology (BSH) Clinical guidelines for testing for heritable thrombophilia[1] to include both heritable and acquired thrombophilia.

Abbreviations: aCL, anticardiolipin antibodies; anti-β2GPI, anti-β2-glycoprotein-I antibodies; APS, antiphospholipid syndrome; AT, antithrombin; BCS, Budd–Chiari syndrome; BSH, British Society for Haematology; CAPS, catastrophic antiphospholipid syndrome; CVADs, central venous access devices; CVC, central venous catheter; CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; *CALR*, calreticulin gene; CVST, cerebral venous sinus thrombosis; DOACs, direct oral anticoagulants; GEL, Genomics England Limited; GWAS, genome wide association study; ET, essential thrombocythaemia; FBC, full blood count; FVL, factor V Leiden; FGA, fibrinogen-alpha; FGB, fibrinogen-beta; FGG, fibrinogen-gamma; LA, lupus anticoagulant; MVT, mesenteric vein thrombosis; MPN, myeloproliferative neoplasms; MTHFR, methylenetetrahydrofolate reductase; NICE, National Institue for Health and Excellence; PNH, paroxysmal nocturnal haemoglobinuria; PFO, patent foramen ovale; PCR, polymerase chain reaction; PVT, portal vein thrombosis; PMF, primary myelofibrosis; ZPI, protein Z-dependent protease inhibitor; PC, protein C; PS, protein S; RVO, retinal vein occlusion; RCPCH, Royal College of Paediatrics and Child Health; *SERPINIC*, serine protease inhibitor 1C; SVT, splanchnic vein thrombosis; TFPI, tissue factor pathway inhibitor; NICE, The National Institute for Health and Care Excellence; VTE, venous thromboembolism.

The term thrombophilia is generally used to describe hereditary and/or acquired conditions associated with an increased predisposition to thrombosis. Heritable thrombophilia refers to genetic disorders of specific haemostatic proteins. These guidelines focus only on the factors that are identified from laboratory testing and therefore exclude disorders such as cancer, inflammatory conditions and obesity that are associated with thrombosis through multiple mechanisms.

The most clearly defined heritable thrombophilias are the factor V Leiden (*FVL*) variant (*F5* G1691A), the prothrombin gene variant *(F2* G20210A), protein C (PC) deficiency, protein S (PS) deficiency, and antithrombin (AT) deficiency.[2] Important acquired thrombophilias include the antiphospholipid syndrome (APS), paroxysmal nocturnal haemoglobinuria (PNH), myeloproliferative neoplasms (MPN) and the presence of a *JAK2* mutation in the absence of an MPN phenotype. Pregnancy is a hypercoagulable state due partly to physiological changes in both the coagulation and fibrinolytic systems. Heritable and acquired thrombophilias can interact to further increase the risk of thrombosis, for example during pregnancy and the puerperium. As there is evidence that some thrombophilias may be associated with pregnancy failure and complications, testing for this purpose is included.

THROMBOPHILIA TRAITS: CLINICAL SIGNIFICANCE AND MEASUREMENT OR ASSESSMENT OF DEFECTS

Procoagulant factors and risk of thrombosis

Elevated levels of procoagulant factors may increase the risk of thrombosis but the relationship is not straightforward. First, part of the variance is genetic, and therefore lifelong, but some is acquired so that comorbidities such as obesity or inflammation confound the estimate of effect. Second, some factors, most notably factor V (FV), have anticoagulant effects that counterbalance a procoagulant effect from their elevation.

A meta-analysis of 12 genome-wide association studies (GWAS) for venous thromboembolism (VTE) identified variants in *F2, F5, F11,* and *FGG* (encoding fibrinogen gamma chain) linked to thrombosis as well as non-O alleles of *ABO* which mediate their effect via elevation of von Willebrand factor (VWF) and secondarily factor VIII (FVIII).[3] This approach does not detect rare variants with functional effects increasing thrombotic risk as reported in factor IX (*F9*), factor II (*F2*) and fibrinogen-alpha (*FGA*), fibrinogen-beta (*FGB*), and *FGG*.[4–6] However, the relevance of these genetic variants to routine clinical practice is not clear at present.

A phenotypic analysis was carried out as part of the Multiple Environmental and Genetic Assessment (MEGA) case–control study of VTE. After adjustment for age and sex, levels of factors II, X, IX, XI, VIII and fibrinogen all showed a positive association with risk of thrombosis. After additional correction for FVIII levels, only FIX and FXI retained significance with odds ratios (ORs) for levels >95th centile of 1.8 (95% confidence interval [CI]: 1.1–2.9) and 1.8 (1.1–3.0), respectively. In contrast, the OR for FVIII>95th centile was 16.0 (9.7–26.3) after correction for age, sex, and all the other coagulation factors.[7] However, because of interacting heritable and acquired influences on FVIII activity, variability in levels over time, and as yet, lack of evidence of a role in the management of individuals with thrombosis or asymptomatic family members, routine testing for FVIII is not currently recommended.

Despite results from animal studies, there remains no genetic or phenotypic[8–10] evidence that variation in FXII is associated with thrombosis in humans.[11] FXIII has a complex relationship with thrombosis due to interactions with other factors and the effects of genetic variants on FXIII activity assays. Genetic studies showed that the Val24Leu variant was associated with a reduced risk of venous thrombosis (OR: 0.85; 95% CI: 0.77–0.95).[12,13]

Recommendations

- Routine testing of coagulation factors to assess the risk of thrombosis is not currently recommended (Grade 2C).

Deficiency of natural anticoagulants and risk of thrombosis

The associations of PC, PS and AT deficiencies with increased risks of VTE are well-established.[14] The degree of deficiency is variable and sensitive to assay type but in general thrombosis risk rises as soon the levels of protein C, S or AT fall below the normal range. In contrast, although tissue factor pathway inhibitor (TFPI), heparin cofactor II, and protein Z-dependent protease inhibitor (ZPI) and its cofactor, protein Z, are also natural anticoagulants, the clinical significance of genotypic or phenotypic variation in these is uncertain and testing for clinical purposes is not recommended.

Guidelines on laboratory aspects of testing for deficiencies of natural anticoagulants have recently been published by the British Society for Haematology[15] and the International Society on Thrombosis and Haemostasis.[16–18]

The risk of a first episode of VTE is increased around 15-fold in heterozygous AT deficiency.[19] Overall, the risks are similar in those with type I and type II defects with the exception of most type II heparin binding defects, which appear to have a 4-fold lower risk.[19] In contrast, homozygous heparin binding site defects appear to be associated with a high thrombotic risk.[20] Further differences within antithrombin subtypes have also been observed.[21] However, data on differences in risk between and within different subtypes are limited, and findings vary according to study design, the

population being studied (family or non-family members), and whether all or only unprovoked venous thrombotic events were included in the analysis.

In those with heterozygous PC or PS deficiency, the risk of a first episode of VTE is increased around 5–7-fold.[19,22,23] There are no clinically useful differences in thrombotic risk between type I and type II PC deficiency[15] and no clear evidence of a difference in risk between different subtypes of PS deficiency. These risks for heterozygous PC and PS deficiency are similar to or greater than those associated with *FVL* variant or *F2* G20210A variant, but deficiencies of the natural anticoagulants are much less common (population prevalence of <0.5% for each deficiency), at least in those of European origin, and contribute relatively little to the population burden of VTE.

Deficiencies of physiological anticoagulants interact with acquired risks and a transient provoking factor is present in approximately 50% of episodes of VTE in genetically predisposed individuals.[24,25] Since deficiencies of these natural anticoagulants are caused by multiple different genetic variants, clinical laboratory assessment is generally based on measurement of plasma activities or concentrations rather than molecular analysis.[15] Acquired causes of deficiencies (Table 1) should always be considered before testing and when interpreting results as, if present, it may not be possible to reliably diagnose a heritable deficiency. Acquired problems include warfarin and the potential assay-dependent impact of direct oral anticoagulants (DOACs).[15] When the decision has been made to test for deficiencies of physiological anticoagulants, this should be performed only after 3 months of anticoagulation for acute thrombosis, as there is uncertainty over the validity of the results obtained earlier, leading to repeat testing and increased costs, and with there being no evidence that it influences acute management.

Genomics England have made a panel available for "thrombophilia with a likely monogenic cause." The criteria for using this panel are[26]:

- Clinical features indicative of a likely monogenic venous thrombophilia as assessed by a consultant haematologist or clinical geneticist.
- Testing should typically be targeted at those with venous thromboembolic disease at less than 40 years of age, either spontaneous or associated with weak environmental risk factors and which is also present in at least one first degree relative.
- Testing should only be used where it will impact clinical management.

Identification of patients who fulfil these criteria is at the discretion of the responsible haematologist or clinical geneticist. The panel (R97) currently comprises 15 genes and includes *SERPIN1C, PROS1* and *PROC* as well as *F2, F5* and the fibrinogen genes but some of the genes have an uncertain relationship to risk of thrombosis.[27,28]

Recommendations

- Genetic testing to identify causative variants responsible for phenotypically identified deficiencies of AT, PC, PS should be performed when the results will influence management (Grade 2B).
- Testing for deficiencies of physiological anticoagulants should be performed only after 3 months of anticoagulation for acute thrombosis (Grade 2B).

TABLE 1 Factors commonly affecting measurement of protein C, protein S and antithrombin

Protein C activity Chromogenic assay	Protein S Free protein S antigen	Antithrombin activity Chromogenic assay
Physiological reduction	Physiological reduction	Physiological reduction
Neonates and children (different normal range from adults)	Neonates (Different normal range from adults)	Neonates (Different normal range from adults)
	Pregnancy and puerperium	Late pregnancy, early postpartum[a]
Other causes of reduction	Other causes of reduction	Other causes of reduction
Vitamin K antagonists (e.g., warfarin)	Vitamin K antagonists (e.g., warfarin)	Liver disease
Vitamin K deficiency	Vitamin K deficiency	Disseminated intravascular coagulation
Liver disease	Liver disease	Nephrotic syndrome
Disseminated intravascular coagulation	Nephrotic syndrome	Severe sepsis
Severe sepsis	Disseminated intravascular coagulation	Recent thrombosis
Artefactual increase	Severe sepsis	Heparin therapy
DOACs or heparin if using clotting-based assay	Recent thrombosis	L-asparaginase therapy
Artefactual decrease	Oral oestrogen therapy (e.g., combined oral contraceptive pill or hormone therapy)	Artefactual increase
Factor V Leiden if using clotting-based assay	Acute phase response	DOACs:
	Sickle cell disease	Xa inhibitors – if using Xa-based assay
	Artefactual increase	Thrombin inhibitors – if using thrombin-based assay
	DOACs or heparin if using clotting-based assay.	
	Artefactual decrease	
	Factor V Leiden if using clotting-based assay	

Abbreviation: DOAC, direct acting oral anticoagulant.

[a]James et al. 2014.[176]

FV Leiden, prothrombin gene variant and other genetic variants (except AT, PC and PS deficiency) and risk of thrombosis

The *FVL* and *F2* G20210A variants are the most commonly tested genetic variants predisposing to VTE.[29] These are detected using polymerase chain reaction (PCR)-based methods. Their prevalence varies in populations of different ethnicity. For example, heterozygosity for *FVL* is present in about 5% of individuals of European descent but is rare or absent in peoples from sub-Saharan Africa, East Asia and indigenous populations of the Americas and Australia. Similarly, heterozygosity for the prothrombin gene variant is present in 1%–2% of Europeans and is rare or absent in other ethnic populations.[30]

The *FVL* variant abolishes a cleavage site for activated PC in factor V increasing procoagulant activity. The prothrombin gene variant is a point mutation (G20210A) in the 3′ untranslated region of the gene[31] causing increased levels of prothrombin.[32] These variants result in increased relative risks for first venous thrombosis of 5- and 3-fold, respectively.[33]

A large number of variants in other genes with a wide range of prevalences have been reported to confer an increased risk of thrombosis. These include variants of methylenetetrahydrofolate reductase (*MTHFR*), *SERPINE1* (encoding plasminogen activator inhibitor type 1) (PAI-1) and factor XIII as well as variants linked to the quantitative changes in procoagulant factors discussed above.[28] However, either their association with thrombosis is not convincingly consistent or their effect is too small to alter management and they should not be included in thrombophilia panels at present. Although it has been shown that multiple variants present in an individual can combine to identify a significant risk of recurrence,[34] this requires validation and we do not yet know how and when to introduce this oligogenic model into practice.

Recommendations

- Genetic testing to predict a first episode of venous thrombosis is not recommended (Grade 2B).

Acquired genetic traits and risk of thrombosis

Paroxysmal nocturnal haemoglobinuria (PNH) and myeloproliferative neoplasms (MPN) are acquired genetic traits that increase the risk of thrombosis. PNH is an acquired clonal stem cell disorder characterised by the expansion of a population of blood cells deficient in glycosylphosphatidylinositol anchored proteins (GPI-AP) due to *PIGA* gene mutation resulting in a deficiency or absence of all GPI-anchored proteins including CD55 and CD59 on the cell surface. Absence of CD59 leads to chronic complement activation resulting in the classical clinical features of intravascular haemolysis and thrombosis.[35] Up to 10% of patients with PNH will present with thrombosis. The neutrophil clone size correlates best with thrombosis risk and patients with a clone of over 50% have a cumulative 10-year incidence of thrombosis of 34.5% compared to 5.3% in those with a clone of <50%.

MPNs are characterised by clonal expansion of an abnormal haematopoietic stem/progenitor cell and include polycythaemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). MPN or presence of a clone characterised by a *JAK2* mutation in the absence of an MPN phenotype are associated with arterial and venous thromboses.[36]

The thromboses associated with PNH and MPN can occur anywhere in the venous or arterial systems but particularly in unusual sites for example, splanchnic vein thrombosis (SVT) (which includes portal vein (PVT), mesenteric vein (MVT) and splenic vein thrombosis, and the Budd–Chiari syndrome (BCS)) and cerebral venous sinus thrombosis (CVST).[37,38] In MPN, thrombosis often precedes disease recognition. Molecular abnormalities, primarily the V617F mutation in *JAK2* exon 14, are found in 95% of PV (and an exon 12 mutation in most remaining patients) and in 60%–70% of ET and PMF patients.[39] Isolated *JAK2* mutations occur in approximately 0.1%–0.2% of the general population without an MPN phenotype and in 2.9%–5.6% of patients with CVST with no MPN phenotype[40] (Table 2). A proportion of patients positive for *JAK2* mutation with normal full blood count at presentation progressed into MPN during follow-up.[41] Mutations of *MPL* exon 10 are present in about 5% of those with ET or PMF.[42–44] In patients without *JAK2* or *MPL* mutations, 67%–71% of those with ET and 56%–88% of those with PMF are positive for a calreticulin gene (*CALR*) mutation.[45] In a study by Rumi et al. of 1235 consecutive patients diagnosed with ET or PV, the incidence of thrombosis associated with *JAK2*-mutated patients with ET and PV was similar; 7.1 and 10.5% respectively and was four times that of patients with ET and the *CALR* mutation (2.8%). The incidences of thrombosis associated with the *JAK2* exon 12 and *MPL* mutations are not well documented due to the small number of patients with these mutations.

Testing for *JAK2, CALR, MPL* variants in peripheral blood is sensitive and bone marrow samples are not required.[39] Detailed guidance on assays used for detection of *JAK2* mutations is available in separate guidelines.[46] Diagnosis of

TABLE 2 Studies investigating patients presenting with cerebral venous sinus thrombosis and *JAK2* mutation but normal full blood count

Study	CVST number	*JAK2* mutated and full blood normal count *n* (%)
De Stefano et al.[93]	45	2 (4.8%)
Shetty et al.[94]	70	2 (2.9%)
Passamonti et al.[41]	152	4 (2.6%)
Lamy et al.[95]	125	7 (5.6%)

Abbreviation: CVST, cerebral venous sinus thrombosis.

PNH is based on flow cytometric analysis using antibodies directed against GPI-AP.[47]

Recommendations

- We suggest testing for PNH in patients with thrombosis at unusual sites and abnormal haematological parameters (i.e., cytopenia and abnormal red cell indices) or evidence of haemolysis (i.e., raised lactate dehydrogenase, bilirubin and reticulocyte count) (Grade 2C).
- We recommend testing for MPN panel (including *JAK2* V617F, JAK2 exon 12, CALR, *MPL* mutation analysis) in patients with thrombosis at unusual sites and with full blood count abnormalities suggestive of a myeloproliferative neoplasm (Grade 1C).
- We suggest testing for *JAK2* mutation in patients with splanchnic vein thrombosis or CVST in the absence of clear provoking factors and a normal FBC (Grade 2C).

Acquired non-genetic traits

Antiphospholipid syndrome

The diagnosis of APS is dependent on the presence of at least one clinical feature (thrombosis or pregnancy morbidity) and at least one laboratory feature of antiphospholipid antibodies (aPL) which include lupus anticoagulant (LA), immunoglobulin (Ig) G or IgM anticardiolipin antibodies (aCL) or anti-β2-glycoprotein-I (anti-β2GPI) antibodies).[48] The aPL need to be persistent, that is, present on two or more occasions at least 12 weeks apart.[49] Of the three tests, a positive LA appears to be the most strongly associated with recurrent thrombosis, but individuals who are positive for all three assays ("triple positives") have the highest thrombotic risk.[50–52] Although the BSH guidelines (2012) on the investigation and management of antiphospholipid syndrome stated that in patients with thrombosis, measuring IgM antibodies does not add useful information,[53] both IgG and IgM aCL and anti-β2GPI are part of the international consensus on laboratory diagnostic criteria for APS.[49] There is increasing evidence that IgM anticardiolipin and anti-β2GPI antibodies have a pathogenic role in patients with APS.[54–57]

In patients with thrombotic APS, uncertainties remain as to the recurrence risk in patients with an initial unprovoked, compared to provoked, VTE and in those with venous compared to an initial arterial thrombosis.[58] There is increasing evidence that the recurrence risk of VTE provoked by minor risk factors is similar to that with unprovoked VTE.[59,60] Therefore, such patients may also benefit from extended anticoagulation therapy as in those with unprovoked VTE. As the presence of antiphospholipid antibodies may alter management including choice of antithrombotic therapy in these patients, it may be reasonable to test for antiphospholipid antibodies.

Catastrophic APS (CAPS) is a rare, but potentially fatal, variant of APS characterised by sudden onset of extensive microvascular thrombosis at multiple sites leading to multiorgan failure.[61] CAPS tends to occur usually in patients with triple positive APS. Recommendations on the timing of, and indications for, antiphospholipid antibody testing following venous or arterial thrombosis are provided in the Addendum to British Society for Haematology Guidelines on Investigation and Management of Antiphospholipid Syndrome (2020).[62]

In asymptomatic individuals with triple positive antiphospholipid antibodies (mostly identified because of a prolonged activated partial thromboplastin time or presence of an autoimmune disorder), the incidence of first thrombotic events (which were equally distributed between venous and arterial thrombosis) was estimated to be 5% per year.[52] Lower incidences of thrombosis of 1% and 0.5% annually respectively have been described in asymptomatic single antibody positive individuals and in women with the obstetric antiphospholipid syndrome.[63,64]

Recommendations

- Screening for antiphospholipid antibodies is recommended following unprovoked VTE because this may alter management including choice of antithrombotic therapy (Grade 1B).
- Screening for antiphospholipid antibodies is suggested in patients with VTE provoked by a minor risk factor as this may alter management including choice of antithrombotic therapy (Grade 2C).
- Patients with acute multiple thrombotic events and evidence of organ failure suggestive of CAPS should be tested for antiphospholipid antibodies (Grade 1A).
- As APS is an acquired thrombophilia, screening for antiphospholipid antibodies is not recommended in family members of patients with thrombosis (Grade 1A).

General guidelines on the role of thrombophilia testing

In situations where the clinical utility of testing is not clear, testing is clearly not mandatory (clinical utility is defined as the ability of a test to improve clinical outcome). It is important that patients are counselled in advance of any decision on whether or not to undertake testing. This should include discussion of the aims of testing and how it might alter management decisions.

What is the utility of identifying a heritable thrombophilic trait in a patient who has had a venous thrombotic event in modifying their future management or the management of asymptomatic family members?

The relative risk of thrombophilic traits for recurrent VTE is less than that for a first episode of thrombosis because the comparator group is different. Moreover, the

risk is managed differently, and no clinical trials have been undertaken. There are conflicting data on the association of *FVL* and *F2* G20210A variants with risk of recurrence in the overall population of patients with VTE.[33,65] Observational data suggest that *FVL* Leiden but not *F2* G20210A is associated with an increased risk of recurrence.[33,65] However, in a study with of 354 consecutive patients aged ≥65 years with a first unprovoked VTE, 9.0% of patients had *FVL* and 3.7% had a *F2* G20210A variant.[66] After adjustment for age, sex, and periods of anticoagulation as a time-varying covariate, at 3-year follow up neither the *FVL* (HR 0.98; 95% CI: 0.35–2.77) nor the *F2* G20210A mutation (HR 1.15; 95% CI: 0.25–5.19) was associated with recurrent venous thromboembolism compared to controls.[66]

Patients with natural anticoagulant deficiencies were excluded from prospective studies from which predictive models for recurrent VTE after completion of treatment for a first event were derived.[67] A meta-analysis of individuals with AT deficiency concluded the odds of recurrence were increased 2-4-fold with an absolute annual recurrence risk without long-term anticoagulant therapy of 8.8% (95% CI: 4.6–14.1) for AT-deficient and 4.3% (95% CI: 1.5–7.9) for non-AT-deficient VTE patients.[19] A further cohort study in which AT was measured in percentage points on only one occasion found the odds of recurrent VTE were increased 3.7-fold (95% CI: 1.4–9.9) in those with AT activity <70% (fifth centile 87%) and 1.5-fold (95% CI: 1.0–2.3) in those with AT activities of 70%–87%.[68]

In a prospective study of familial thrombophilia, the annual risk of recurrent VTE in patients who did not receive long-term anticoagulant treatment was 5.1% (95% CI: 2.5–9.4) in those with PC deficiency and 6.5% (95% CI: 2.8–11.8%) in those with PS deficiency.[69] In a meta-analysis, the odds of recurrent VTE were increased 2.9-fold (95% CI: 1.4–6.0) in PC deficient patients and 2.5-fold (95% CI: 0.9–7.2) in those with PS deficiency (25). At 10 years, the rates of recurrence were 31, 43 and 41% among patients with FXI activity <34th centile, between the 34th and 67th centiles, or >67th centile, respectively.[70] Patients with the highest factor VIII level category (>200 iu/dL^{-1}) had a hazard ratio for recurrence of 3.4; (95% CI: 2.2–5.3) compared to those with FVIII ≤100 iu/dL^{-1}.[71] In absolute terms this corresponded to a recurrence rate of 5% per annum compared to 1.4% per annum.

Although these effects are significant, their utility is limited. Clinical history, in conjunction with simple tests such as D-dimer in selected patients, can identify those whose risk of recurrence is high enough to warrant long-term anticoagulation and which is not lowered significantly by the absence of a thrombophilic trait. These factors also identify patients with low risk of recurrence not requiring long-term anticoagulation, even in the presence of heritable thrombophilic traits.[72–75]

There is no evidence that the presence of heritable thrombophilia influences the intensity, choice or the monitoring of anticoagulant therapy when treating thrombosis except potentially in those with AT deficiency.[76] In AT deficiency, diagnosis makes specific treatment (antithrombin concentrate) available,[77] which can be valuable and can also facilitate interpretation of laboratory monitoring of heparin. Nonetheless, this is a rare disorder and so routine testing is not advised in the absence of a strong family history (defined as two or more first-degree relatives with VTE).[78]

For patients with a strong personal and/or family history of thrombosis in the absence of a clear risk factor, genetic analysis via Genomics England Limited (GEL) is available as noted above and should be combined with phenotypic testing where available. The likelihood of detecting a genetic trait increases with the strength of the family history.[26]

The major heritable thrombophilic traits follow Mendelian inheritance albeit with variable penetrance. Levels of FVIII and FXI have clear genetic components but also significant acquired modifiers so the likelihood of relatives being affected is less certain. Identification of a heritable trait in a family member does not indicate a risk of thrombosis high enough to warrant anticoagulation and does not alter most thromboprophylaxis regimens. However, some guidelines include knowledge of heritable thrombophilic traits in their risk assessment schemes with a consequent impact on management.[79] Absence of that trait in a family member significantly reduces their risk of thrombosis but does not return it to normal and the utility of testing will depend on their personal circumstances and the circumstances of the proband's VTE event.[80,81] Overall, the recurrence risk for VTE is determined by the clinical situation (e.g., provoked vs. unprovoked) along with non-Mendelian risk factors (e.g., body mass index and age) rather than the inherited thrombophilia panel. Therefore, when a patient is known to have a heritable thrombophilic trait, it may be reasonable to consider selective testing of first-degree relatives when this will alter their management choices, for example, highly penetrant deficiencies of PC, PS or AT deficiency in a woman of childbearing age. Routine screening for *FVL* is not required in women with a first degree relative with *FVL* but no history of thrombosis (i.e., mother or siblings) prior to starting combined oral contraceptive pills or oestrogen replacement therapy.[82,83] However, the influence of family history of thrombosis, thrombophilia testing and risk of thrombosis related oestrogen-progesterone content of therapies should be discussed with all women to determine whether they will alter their therapy choices and should be documented clearly.

Recommendations

- Testing for heritable thrombophilic traits after a venous thrombotic event is not recommended as a routine to guide management decisions (Grade 2B).
- We do not recommend offering routine thrombophilia testing to first-degree relatives of people with a history of VTE (Grade 2B).

- We suggest selective testing of asymptomatic first-degree relatives of probands with protein C, protein S and antithrombin deficiency where this may influence the management and life choices depending on personal circumstances (Grade 2B).
- Genetic testing for variants in genes (e.g., *MTHFR*, *SERPINE1* variants (PAI-1plasma level)) without a clinically significant link to thrombosis is not recommended (Grade 2C).

Thrombosis in unusual sites

Investigation and management of thrombosis at unusual sites are discussed in another BSH Guideline.[84] For thrombosis at unusual sites, which often involves local or systemic conditions triggering the event, testing for thrombophilia should be reserved for selected patients with unexplained events. The association of MPN and PNH with thrombosis at unusual sites, especially SVT which includes portal, mesenteric, splenic vein thrombosis and the Budd-Chiari syndrome, has been demonstrated in many studies[85,86] and these disorders should be tested for in the absence of a clear reason for the SVT, such as abdominal sepsis, cancer or cirrhosis. Analysis of data from pooled incidence-cases found that in 19% of patients, splanchnic vein (hepatic, mesenteric, portal, splenic, inferior vena cava) thrombosis preceded the diagnosis of PNH.[87] For the remaining patients, visceral thrombosis occurred at a median of 5 years (range, 0–24) after diagnosis. Diagnosis of PNH and MPN is important because these diseases have specific treatments in addition to anticoagulation to prevent recurrent thrombosis.

In a systematic review and meta-analysis of nine small observational studies to assess the prevalence of heritable thrombophilia in patients with PVT and BCS (total 4 studies), the pooled prevalence of AT, PC, and PS deficiencies were 3.9, 5.6, and 2.6% in PVT, and 2.3, 3.8, and 3.0% in BCS, respectively. Only three studies compared the prevalence of heritable thrombophilia between PVT patients and healthy individuals. The pooled odds ratios of heritable AT, PC and PS deficiencies for PVT were 8.89 (95% CI: 2.34–33.72, $p = 0.0011$), 17.63 (95% CI: 1.97–158.21, $p = 0.0032$), and 8.00 (95% CI: 1.61–39.86, $p = 0.011$), respectively.[88] These studies are only for the first thrombotic event and the risk of recurrent events associated with heritable thrombophilia and thrombosis at unusual sites is not well established but seems to be low. Therefore, the value of testing for heritable thrombophilia is unknown and testing should be considered only if the thrombotic event occurs in the absence of a clear risk factor for the index event at a young age (median ~46 years).[88]

CVST is a rare entity accounting for <1% of all strokes.[89] The majority (85%) of CVST patients will have an identifiable risk factor, the most common of which are oestrogen-containing oral contraceptive use and pregnancy.[90] Other rare causes that can contribute to CVST include APS, vasculitis, MPN, PNH, chronic inflammatory disorders, and local factors such as infection, malignancy, trauma or surgery.[90] CVST is reported in 2%–8% of patients with PNH[91,92] and around 3.8% of patients with MPN.[93] Around 2.6%–5.6% of patients diagnosed with CVST are found to have a *JAK2* mutation with normal full blood count at presentation[41,94–96] (Table 2). CVST are reported in 2% to 8% of patients with PNH.[90,97–99] However, it is not clear how many of these patients had a normal full blood count at presentation with CVST.

Several studies have shown the presence of aPL increases the risk of thrombosis at unusual sites such as SVT and CVST.[100,101] As the type and duration of anticoagulation are affected by the presence of antiphospholipid antibodies, testing for these antibodies is recommended in an updated BSH guideline.[62] In the absence of a clear risk factor, patients with CVST may need long-term anticoagulation and routine testing for heritable thrombophilia is not required.

There is no evidence to suggest an association of heritable thrombophilia with retinal vein occlusion (RVO). The pathogenic role of antiphospholipid antibodies in RVO is uncertain. A meta-analysis of 11 studies showed that presence of antiphospholipid antibodies was significantly associated with incidence of RVO (OR = 5.18, 95% CI: 3.37, 7.95).[102] A more recent study that included 331 consecutive patients with RVO and 281 controls, also showed that antiphospholipid antibodies were more prevalent in RVO-patients than in controls (33, 10% vs. 12, 4.3%; OR 2.47; 95% CI: 1.25–4.88; $p = 0.009$) with RVO-APS patients having more frequently lupus anticoagulant or triple positive antiphospholipid antibody than controls.[103] Testing for aPL may be considered in patients without local risk factors and no other explanation for RVO such as diabetes, hypertension, and hpercholesterolaemia as those with persistently positive aPL would be considered for anticoagulation.

Recommendations

- We do not recommend testing for heritable thrombophilia in patients with thrombosis if the only indication is thrombosis at an unusual site because the association is weak, and management would not be changed by their presence (Grade 2B).
- We recommend testing with MPN panel in patients with thrombosis at unusual sites with full blood count abnormalities suggestive of a myeloproliferative neoplasm (Grade 1C).
- We suggest genetic testing with *JAK2* mutation in patients with splanchnic vein thrombosis or CVST in the absence of clear provoking factors and a normal FBC (Grade 2C).
- We recommend testing for antiphospholipid antibodies in patients with thrombosis at unusual sites in the absence of clear provoking factors as the type and duration of anticoagulation are affected by the presence of these antibodies (Grade 1A).

- We suggest considering testing for PNH in patients with thrombosis at unusual sites and abnormal haematological parameters (i.e. cytopenia and abnormal red cell indices) or evidence of haemolysis (i.e. raised lactate dehydrogenase, bilirubin and retics count) (Grade 2C).
- Testing for antiphospholipid antibodies may be considered in patients with RVO in the absence of any other risk factors associated with RVO (Grade 2C).

Arterial thrombosis except stroke (i.e., myocardial infarction, cardiac thrombosis and peripheral vascular thrombosis)

There is conflicting evidence with respect to the presence and the strength of associations between *FVL* and *F2* G20210A variant and arterial thrombosis. Although some observational studies demonstrated a moderate increased risk of myocardial infarction (MI) in patients with *FVL* or *F2* G20210A variants, this has not been reproduced in others. Table S1 summarises meta-analyses on the association of the *FVL* and/ or *F2*G20210A polymorphism with MI. These variants are common in the European population and will be found in many patients with cardiovascular disease. Whether their presence reflects a causal role for cardiovascular events is not known and is difficult to determine from these meta-analyses. When statistically significant associations have been found, these have been too modest to be of clinical significance and there are no clinical trials to suggest that management should be influenced as a result of the presence of these variants.

Because heritable deficiencies of AT, PC and PS are rare, observational studies with sufficient statistical power to assess potential associations with risk of arterial thrombosis are lacking. Overall, there is no evidence to support an association between heritable thrombophilia and arterial thrombosis in adults and no evidence that it affects management. Therefore, testing for heritable thrombophilia is not recommended in patients with arterial thrombosis.

Acquired thrombophilia such as APS, PNH and MPN increase the risk of both venous and arterial thrombosis including myocardial infarction. Arterial thrombosis accounts for 60%–70% of thrombotic events related to MPNs.[104] Testing for antiphospholipid antibodies, MPN and PNH should be considered in patients with arterial thrombosis in the absence of other vascular risk factors or significant atherosclerosis, especially in younger patients and in those with an abnormal full blood count (for MPN and PNH), as this may have a significant impact on management.

The association of APS or antiphospholipid antibodies with atherosclerosis is a matter of debate due to the small numbers of patients studied, and the fact that traditional risk factors for atherosclerosis may coexist. The prevalence of APS ranges from 1.7% to 6%, and that of antiphospholipid antibodies alone reaches 14%, among patients with peripheral vascular disease (PVD) as defined by clinical outcomes. The prevalence of asymptomatic atherosclerosis, defined in terms of plaques on ultrasonography, reaches 15% in patients with APS compared to 9% in SLE patients and 3% in normal controls.[105,106]

Recommendations

- Testing for heritable thrombophilia is not recommended in patients with arterial thrombosis as the association between heritable thrombophilia and arterial thrombosis in adults is weak and does not alter the management (Grade 1B).
- We recommend testing for antiphospholipid antibodies in patients with arterial thrombosis in the absence of other vascular risk factors (Grade 1B).
- In patients with arterial thrombosis and relevant abnormal blood parameters consider testing with an MPN panel and for PNH (Grade 2C).

Ischaemic stroke—all types except cerebral venous sinus thrombosis

The diagnostic yield of thrombophilia screening in arterial ischaemic stroke remains controversial despite a number of case–control, single centre cohort and stroke registry studies.[107–110] Unnecessary thrombophilia testing can result in significant costs and an identified thrombophilia may not necessarily be the cause of stroke and can lead potential inappropriate use of long term anticoagulants.

Table S2 summarises the studies assessing the risk of stroke associated with acquired and heritable thrombophilia. Heritable disorders of young stroke such as Fabry disease and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) are not primarily associated with hypercoagulability and are not discussed in this guideline. In a review of case control studies in 2010, PC, PS and AT deficiency, *FVL* and *F2* G20210A did not show a clear relationship with young stroke.[107] However, in a systematic review of 68 studies that included 11 916 stroke patients from 1993 to 2017, there was a small but statistically significant association with unexplained arterial ischaemic stroke particularly in young patients, except for AT deficiency (which did not reach statistical significance). The authors acknowledged this was not evidence of a causal relationship nor evidence for impact on clinical outcomes.[111] Of 1900 stroke patients in 2015–17, 190 (10%) underwent thrombophilia testing, 137 (72%) had at least one positive result, most commonly elevated factor VIII or homocysteine and low PS, but importantly these findings only changed management in 4 patients (0.2% of the overall patients tested for thrombophilia).[110] However, testing was performed in the acute phase when functional assays would have not been reflective of baseline. Similarly, a retrospective review of 752 tests in 82 stroke patients yielded 56 positive tests in

42 patients but thrombophilia was confirmed in only three patients, and management changed in only one.[112]

An audit of acute post-stroke thrombophilia testing highlighted the high cost and low yield. Of 143 stroke/transient ischaemic attack (TIA) patients, 31% had at least one positive test result, most commonly elevated factor VIII activity (18%) or low PS activity (11%). Both are subject to acute phase effects. Testing altered clinical management in only 1%.[113] Therefore, finding these thrombophilia traits would most often not alter choice of therapy (antiplatelet treatment vs. anticoagulation) for secondary prevention.

The role of thrombophilia testing stratified by stroke aetiology is unclear with conflicting reports on prevalence of heritable thrombophilias in patients with stroke and patent foramen ovale (PFO). There is currently no clear evidence to suggest an additional benefit of thrombophilia testing in patients with PFO.[114–116]

JAK2-positive myeloproliferative neoplasms have been implicated in arterial thrombosis. Early detection of MPN is important because specific treatment is available to prevent recurrence. In 2011 an international collaborative study identified 891 patients with ET and after a median follow up of 6.2 years 9% had experienced arterial thrombosis. Male gender, age >60 years, thrombosis history, smoking history, hypertension, diabetes and presence of *JAK2* V617F were predictors.[117] The *JAK2* V617F variant may be present, even when the full blood count is normal. Thrombosis in larger cerebral arteries causing stroke complicates PV in 10%–20% of patients[118,119] and the reported incidence of stroke/TIA in phlebotomy-treated patients (60–65 years) with PV was around 4%–5%/year.[118,120]

Antiphospholipid antibodies represent an independent risk factor in the first year after stroke[121] with a high risk of recurrence despite anticoagulation treatment. Large, controlled, intervention trials in APS are limited. In a retrospective study of 1900 patients with ischaemic stroke, at least one assay for aPL was positive in 1.6%, which remained positive in only one patient after 12 weeks. Testing for antiphospholipid syndrome was incomplete in 23%, most frequently due to the omission of anti-β2GPI antibodies.[110] A systematic review of 5217 stroke patients and matched controls from 43 studies investigated the presence of antiphospholipid antibodies in young patients (<50 years) with stroke.[122] Overall, 17.2% of patients with stroke and 11.7% with transient ischaemic attack (TIA) had antiphospholipid antibodies. Thirteen out of 15 studies (86.6%) reported significant associations between aPL and the cerebrovascular events with a cumulative OR of 5.48 (95% CI: 4.42 to 6.79).[122]

Recommendations

- Testing for heritable thrombophilia is not recommended in patients with stroke, regardless of age (Grade 1A).
- Testing for antiphospholipid antibodies should be considered in young (<50 years of age) patients in the absence of identifiable risk factors for cardiovascular disease because this may alter management including choice of antithrombotic therapy (Grade 1A).
- In patients with stroke, an abnormal full blood count should prompt consideration for testing with an MPN panel and for PNH (Grade 2C).
- The presence of a PFO in patients with a stroke is not an indication for thrombophilia testing (Grade 2C).

Paediatric thrombosis, neonatal thrombosis, purpura fulminans and stroke in children

The reported incidence of VTE in children is 0.07 to 0.14 per 10 000 children per annum.[123–125] In hospitalised children, the rate is increased 100- to 1000-fold, to ≥58 per 10 000 admissions.[126] The most common age groups for VTE are neonates and teenagers. More than 90% of paediatric patients with VTE have more than one risk factor, with central venous access devices (CVADs) being the most common single risk factor, accounting for over 90% of neonatal VTE and over 50% of paediatric VTE.[123,127]

The role of testing for heritable thrombophilia in neonatal VTE is not clear.[128] A systematic review analysed 13 publications from 2008 to 2014, evaluating the role of heritable thrombophilia in neonatal VTE. The authors concluded that neonatal VTE is multifactorial and clinical risk factors play a greater role than heritable thrombophilia, particularly in CVAD associated VTE.[129] In an earlier study, the overall prevalence of heritable thrombophilia in neonates with VTE was no different than that of the healthy population, concluding that screening neonates with VTE for heritable thrombophilia was not necessary.[130] In contrast, in another study of CVAD-related VTE, 15 of 18 infants with VTE had at least one heritable thrombophilia.[131] In an Italian registry of neonatal VTE, a heritable thrombophilia was found in 33% of infants with an "early-onset" VTE (VTE in the first day of life).[132] While heritable thrombophilia appears to be present in some neonates with VTE, both central venous catheter (CVC)-related and not, the role of heritable thrombophilia testing in neonates with VTE does not currently appear to influence the type or duration of treatment.[129]

In contrast, some physicians are of the opinion that thrombophilia testing should be considered in neonates and children if there is a family history (one or more first-degree relatives with VTE),[78] unprovoked and recurrent VTE, or arterial thrombosis (early stroke and myocardial infarction <45 years, in particular when no triggering factor is present).[31,130,133,134]

As for adults, the identified heritable thrombophilic defects include PS deficiency, PC deficiency, AT deficiency, *FVL* and the *F2* G20210A.[31,130,133] The heritable thrombophilias that may confer serious thrombotic risks in children are homozygous type 2 AT deficiency and homozygous or combined heterozygous deficiency of PC, PS or AT.[135] *FVL* or *F2* G20210A states represent "low-risk" thrombophilias.[31,134] PC and PS deficiency can occur in homozygous, heterozygous or compound

heterozygous forms, and a severe deficiency of these proteins has been linked with neonatal purpura fulminans.[136,137] Testing for PC and PS in cases of purpura fulminans is recommended as appropriate replacement therapy (PC concentrate or fresh frozen plasma in case of PS deficeiency) can be initiated for treatment and prevention of further VTE. In cases of severe AT deficiency, replacement of AT with AT concentrate is required to prevent further thrombosis and to facilitate appropriate anticoagulant effect of heparin.

APS is rare in children. About 30% of children born to mothers with aPL passively acquire these autoantibodies; however, the occurrence of thrombosis seems extremely rare in these neonates.[138,139] Nonetheless, extensive unexplained thrombosis in children could be due to CAPS and testing for antiphospholipid antibodies should be considered.

As in adults, testing for methylenetetrahydrofolate reductase (*MTHFR*) mutations and homocysteine levels should not be included in thrombophilia panels,[140,141] unless features of homocystinuria are present.

Management of Stroke in Children, published in May 2017 by the Royal College of Paediatrics and Child Health (RCPCH), in collaboration with NICE and the Stroke Association, concluded that current clinical practice in the UK for genetic thrombophilia testing varies widely, both between centres and between groups of healthcare professionals. The RCPCH expert panel were unable to reach a consensus on the clinical necessity for genetic thrombophilia testing in a child with stroke. Testing is expensive and identification of heritable thrombophilia may have implications for future children. The clinical relevance of heritable thrombophilia in childhood stroke remains contentious and does not mandate altered management, and identification of a heritable thrombophilic tendency may generate disproportionate concern. In the absence of consensus, this area remains open for individual clinical discretion.[142]

Recommendations

- Neonates and children with purpura fulminans should be tested urgently for protein C and S deficiency (Grade 1B).
- Thrombophilia screening is not routinely recommended for neonatal stroke (Grade 2B).
- In neonates with multiple unexplained thrombosis, especially with clinical evidence suggestive of CAPS, testing for antiphospholipid antibodies and heritable thrombophilia should be considered (Grade 2D).

Thrombophilia testing in relation to pregnancy

Pregnancy is an acquired hypercoagulable state. The incidence of VTE in pregnancy or the puerperium is around 1 in 1000,[143–145] a 5- to 10-fold increase in relation to an age-matched non-pregnant female population. This rises further in the first 6 weeks postpartum to a 20- to 80-fold increase in risk.[146,147] Venous thrombosis remains the leading direct cause of death in pregnant or recently pregnant women in the UK and Ireland.[148]

Arterial thrombosis in pregnancy is rare with an incidence quoted as 1 per 4000 pregnancies.[149] Nevertheless, it is more common than in age-matched non-pregnant controls.

Prior to testing for thrombophilia, women should be counselled regarding the implications for themselves, and family members, of a positive or negative result. When testing is performed, it is preferable that this is done before pregnancy.

As in other settings, testing should only be considered if it is going to influence management. Therefore, in women who have had a previous unprovoked or oestrogen provoked (oral contraceptive pill, in vitro fertilisation, or pregnancy) VTE, routine thrombophilia testing is not indicated as they will require thromboprophylaxis throughout pregnancy and the puerperium.

There is no evidence to support screening of asymptomatic women with a family history of thrombosis in the absence of a known heritable thrombophilia. In women with a first degree relative with PC, PS or AT deficiency identification of these abnormalities may affect management. However, these are rare and universal screening for these deficiencies is not justified by current evidence. Testing for AT is required when there is evidence of heparin resistance where individuals fail to achieve a specified anticoagulation level despite the use of what is considered to be an adequate dose of heparin based on weight and renal function.[150]

A recent systematic review and meta-analysis[151] estimated the absolute risks of a first episode of VTE in pregnancy with different heritable thrombophilias. The authors concluded that based on having a higher absolute risk of VTE, women with AT, PC or PS deficiency or with homozygous *FVL* should be considered for thromboprophylaxis in pregnancy and the puerperium. Women with heterozygous *FVL*, heterozygous *F2* G20210A, or heterozygosity for both *FVL* and *F2* G20210A should generally not be prescribed thromboprophylaxis on the basis of thrombophilia and family history alone. Other than for heterozygous *FVL*, the data were insufficient to allow further estimation of risk during the antenatal and postpartum periods separately in the presence or absence of a family history, and confidence intervals were wide. The greatest absolute risk was seen with antithrombin deficiency, and a subsequent large retrospective cohort study of women with type I antithrombin deficiency similarly found a high risk even in the absence of a family history.[152]

Arterial thrombosis is rare in pregnancy but given the association of APS with both arterial and venous thrombotic events in this demographic, testing for antiphospholipid antibodies should be considered, ideally prior to pregnancy. It is possible to have a marked variation in the level of antiphospholipid antibodies during pregnancy and if aPL testing is performed during the pregnancy, results should be interpreted with caution as negative or positive results during pregnancy do not exclude or confirm a diagnosis of APS.[153–155] Testing should be performed at least

6 weeks after the end of pregnancy and repeated 12 weeks from the first test to confirm the positive results.

Recommendations

- Testing for antithrombin deficiency may be considered in pregnant women with a known family history of this deficiency or evidence of heparin resistance (Grade 2C).
- In women with a history of unprovoked VTE, testing for antiphospholipid antibodies should be performed outside pregnancy (Grade 2B).

Thrombophilia testing in relation to pregnancy morbidity

A number of mostly retrospective cohort studies have found weak associations between heritable thrombophilia and placentally-mediated pregnancy complications such as gestational hypertension and pre-eclampsia;[156,157] intrauterine growth restriction (IUGR) and placental abruption;[158] recurrent first-trimester pregnancy loss[159] and stillbirth,[160] however the published literature is inconsistent. Moreover, several meta-analyses have failed to demonstrate a benefit of low molecular weight heparin (LMWH) and/or aspirin to improve pregnancy outcomes.[161–164] Therefore, guidelines from, for example, the American College of Obstetricians and Gynaecologists recommend against testing for heritable thrombophilia in women with previous adverse pregnancy outcomes.[164]

Acquired thrombophilia does appear to be associated with placenta-mediated pregnancy complications,[165] specifically antiphospholipid antibodies and late fetal loss; lupus anticoagulant with pre-eclampsia, IUGR and late fetal loss;[166–168] anti-β2GPI and recurrent miscarriage.[168] Further, miscarriage, stillbirth and neonatal death were shown to be more common in APS women who had had a previous thrombosis compared to APS women who had not. Poorer outcome was also associated with triple positive antibodies.[169]

In women with previous thrombosis and triple positive APS, treatment with LMWH and aspirin is associated with improved pregnancy outcomes.[170] However, in women with APS and a history of previous early (after 20 weeks gestation) onset pre-eclampsia, LMWH did not appear to confer an additional benefit over aspirin alone.[171] The administration of LMWH to women with APLs and recurrent miscarriage appears to confer a benefit in reducing early pregnancy loss without influencing late obstetric complications.[172,173] Similar to lack of evidence related to the significance of *MTHFR, SERPINE1 variants* and PAI-1 plasma levels in predicting the risk of thrombosis, there is no role of testing these in women with pregnancy morbidities.[174,175]

Taken together the evidence for the benefit of screening women with previous adverse pregnancy outcomes is limited to screening for antiphospholipid antibodies.

Recommendations

- We recommend against heritable thrombophilia screening in women with pregnancy complications, such as recurrent miscarriage or adverse pregnancy outcomes (Grade 2B).
- For women with recurrent or late pregnancy loss, screening for antiphospholipid antibodies can be considered as the results aid risk stratification and treatment decisions (Grade 2B).
- Antiphospholipid antibody testing should be avoided during pregnancy as the results may not be reliable (Grade 2B).

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CONFLICT OF INTERESTS

The BSH paid the expenses incurred during the writing of this guidance. All authors have made a full declaration of interests to the BSH and Task Force Chairs which may be viewed on request. None of the authors have any relevant conflicts of interest to declare.

REVIEW PROCESS

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every three years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (www.b-s-h.org.uk/guidelines).

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REFERENCES

1. Baglin T, Gray E, Greaves M, et al. Clinical guidelines for testing for heritable thrombophilia. Br J Haematol. 2010;149(2):209–20.
2. Arachchillage DRJ, Makris M. Inherited Thrombophilia and Pregnancy Complications: Should We Test? Semin Thromb Hemost. 2019;45(1):50–60.
3. Germain M, Chasman DI, de Haan H, et al. Meta-analysis of 65,734 individuals identifies TSPAN15 and SLC44A2 as two susceptibility loci for venous thromboembolism. Am J Hum Genet. 2015;96(4):532–42.
4. Simioni P, Tormene D, Tognin G, et al. X-Linked Thrombophilia with a Mutant Factor IX (Factor IX Padua). N Engl J Med. 2009;361(17):1671–5.
5. Girolami A, Ferrari S, Cosi E, Girolami B, Lombardi AM. Congenital prothrombin defects: they are not only associated with bleeding but also with thrombosis: a new classification is needed. Hematology. 2018;23(2):105–10.
6. Casini A, de Moerloose P, Neerman-Arbez M. Clinical features and management of congenital fibrinogen deficiencies. Semin Thromb Hemost. 2016;42(04):366–74.
7. Rietveld IM, Lijfering WM, le Cessie S, et al. High levels of coagulation factors and venous thrombosis risk: strongest association for factor VIII and von Willebrand factor. J Thromb Haemost. 2019;17(1):99–109.
8. Johnson CY, Tuite A, Morange PE, Tregouet DA, Gagnon F. The factor XII -4C>T variant and risk of common thrombotic disorders: a HuGE review and meta-analysis of evidence from observational studies. Am J Epidemiol. 2011;173(2):136–44.
9. Koster T, Rosendaal FR, Briet E, Vandenbroucke JP. John Hageman's factor and deep-vein thrombosis: leiden thrombophilia study. Br J Haematol. 1994;87(2):422–4.
10. Siegerink B, Rosendaal FR, Algra A. Antigen levels of coagulation factor XII, coagulation factor XI and prekallikrein, and the risk of myocardial infarction and ischemic stroke in young women. J Thromb Haemost. 2014;12(5):606–13.
11. Key NS. Epidemiologic and clinical data linking factors XI and XII to thrombosis. Hematology. 2014;2014(1):66–70.
12. Wells PS, Anderson JL, Scarvelis DK, Doucette SP, Gagnon F. Factor XIII Val34Leu variant is protective against venous thromboembolism: a HuGE review and meta-analysis. Am J Epidemiol. 2006;164(2):101–9.
13. Byrnes JR, Wolberg AS. Newly-recognized roles of factor XIII in thrombosis. Semin Thromb Hemost. 2016;42(04):445–54.
14. Middeldorp S. Inherited thrombophilia: a double-edged sword. Hematol Am Soc Hematol Educ Program. 2016;2016(1):1–9.
15. Baker P, Platton S, Gibson C, et al. Guidelines on the laboratory aspects of assays used in haemostasis and thrombosis. Br J Haematol. 2020;191(3):347–62.
16. Van Cott EM, Orlando C, Moore GW, Cooper PC, Meijer P, Marlar R. Recommendations for clinical laboratory testing for antithrombin deficiency; communication from the SSC of the ISTH. J Thromb Haemost. 2020;18(1):17–22.
17. Cooper PC, Pavlova A, Moore GW, Hickey KP, Marlar RA. Recommendations for clinical laboratory testing for protein C deficiency, for the subcommittee on plasma coagulation inhibitors of the ISTH. J Thromb Haemost. 2020;18(2):271–7.
18. Marlar RA, Gausman JN, Tsuda H, Rollins-Raval MA, Brinkman HJM. Recommendations for clinical laboratory testing for protein S deficiency: communication from the SSC committee plasma coagulation inhibitors of the ISTH. J Thromb Haemost. 2021;19(1):68–74.
19. Croles FN, Borjas-Howard J, Nasserinejad K, Leebeek FWG, Meijer K. Risk of venous thrombosis in antithrombin deficiency: a systematic review and bayesian meta-analysis. Semin Thromb Hemost. 2018;44(4):315–26.
20. Gindele R, Selmeczi A, Oláh Z, et al. Clinical and laboratory characteristics of antithrombin deficiencies: a large cohort study from a single diagnostic center. Thromb Res. 2017;160:119–28.
21. Alhenc-Gelas M, Plu-Bureau G, Hugon-Rodin J, Picard V, Horellou MH. Thrombotic risk according to SERPINC1 genotype in a large cohort of subjects with antithrombin inherited deficiency. Thromb Haemost. 2017;117(6):1040–51.
22. Luxembourg B, Pavlova A, Geisen C, et al. Impact of the type of SERPINC1 mutation and subtype of antithrombin deficiency on the thrombotic phenotype in hereditary antithrombin deficiency. Thromb Haemost. 2014;111(2):249–57.
23. Di Minno MN, Ambrosino P, Ageno W, Rosendaal F, Di Minno G, Dentali F. Natural anticoagulants deficiency and the risk of venous thromboembolism: a meta-analysis of observational studies. Thromb Res. 2015;135(5):923–32.
24. 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(3):459–64.
25. Mahmoodi BK, Brouwer JL, Ten Kate MK, et al. A prospective cohort study on the absolute risks of venous thromboembolism and predictive value of screening asymptomatic relatives of patients with hereditary deficiencies of protein S, protein C or antithrombin. J Thromb Haemost. 2010;8(6):1193–200.
26. https://www.england.nhs.uk/wp-content/uploads/2018/08/rare-and-inherited-disease-eligibility-criteria-v2.pdf Accessed on 16th Nov 2021.
27. https://nhsgms-panelapp.genomicsengland.co.uk/panels/516/v1.2 Accessed on 20th Nov 2021.
28. Trégouët DA, Morange PE. What is currently known about the genetics of venous thromboembolism at the dawn of next generation sequencing technologies. Br J Haematol. 2018;180(3):335–45.
29. Campello E, Spiezia L, Simioni P. Diagnosis and management of factor V Leiden. Expert Rev Hematol. 2016;9(12):1139–49.
30. Saemundsson Y, Sveinsdottir SV, Svantesson H, Svensson PJ. Homozygous factor V Leiden and double heterozygosity for factor V Leiden and prothrombin mutation. J Thromb Thrombolysis. 2013;36(3):324–31.
31. van Ommen CH, Nowak-Göttl U. Inherited thrombophilia in pediatric venous thromboembolic disease: why and who to test. Front Pediatr. 2017;5:50.
32. Young G, Manco-Johnson M, Gill JC, et al. Clinical manifestations of the prothrombin G20210A mutation in children: a pediatric coagulation consortium study. J Thromb Haemost. 2003;1(5):958–62.
33. Ho WK, Hankey GJ, Quinlan DJ, Eikelboom JW. Risk of recurrent venous thromboembolism in patients with common thrombophilia: a systematic review. Arch Intern Med. 2006;166(7):729–36.
34. van Hylckama VA, Flinterman LE, Bare LA, et al. Genetic variations associated with recurrent venous thrombosis. Circ Cardiovasc Genet. 2014;7(6):806–13.
35. Kelly RJ, Höchsmann B, Szer J, et al. Eculizumab in pregnant patients with paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2015;373(11):1032–9.
36. Landolfi R, Di Gennaro L, Falanga A. Thrombosis in myeloproliferative disorders: pathogenetic facts and speculation. Leukemia. 2008;22(11):2020–8.
37. Arachchillage DR, Laffan M. Pathogenesis and management of thrombotic disease in myeloproliferative neoplasms. Semin Thromb Hemost. 2019;45(6):604–11.
38. Hillmen P, Muus P, Dührsen U, et al. Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. Blood. 2007;110(12):4123–8.
39. McMullin MF, Harrison CN, Ali S, et al. A guideline for the diagnosis and management of polycythaemia vera. A British Society for Haematology Guideline. Br J Haematol. 2019;184(2):176–91.

40. Lauw MN, Bus EW, van Wulfften Palthe AF, et al. Relevance of the JAK2V617F mutation in patients with deep vein thrombosis of the leg. Ann Hematol. 2012;91(1):103–7.
41. Passamonti SM, Biguzzi E, Cazzola M, et al. The JAK2 V617F mutation in patients with cerebral venous thrombosis. J Thromb Haemost. 2012;10(6):998–1003.
42. James C, Ugo V, Casadevall N, Constantinescu SN, Vainchenker W. A JAK2 mutation in myeloproliferative disorders: pathogenesis and therapeutic and scientific prospects. Trends Mol Med. 2005;11(12):546–54.
43. Scott LM, Tong W, Levine RL, et al. JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. N Engl J Med. 2007;356(5):459–68.
44. Rumi E, Pietra D, Ferretti V, et al. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. Blood. 2014;123(10):1544–51.
45. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013;369(25):2379–90.
46. Bench AJ, White HE, Foroni L, et al. Molecular diagnosis of the myeloproliferative neoplasms: UK guidelines for the detection of JAK2 V617F and other relevant mutations. Br J Haematol. 2013;160(1):25–34.
47. Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood. 2005;106(12):3699–709.
48. Arachchillage DRJ, Laffan M. Pathogenesis and management of antiphospholipid syndrome. Br J Haematol. 2017;178(2):181–95.
49. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4(2):295–306.
50. Garcia D, Akl EA, Carr R, Kearon C. Antiphospholipid antibodies and the risk of recurrence after a first episode of venous thromboembolism: a systematic review. Blood. 2013;122(5):817–24.
51. Pengo V, Biasiolo A, Pegoraro C, Cucchini U, Noventa F, Iliceto S. Antibody profiles for the diagnosis of antiphospholipid syndrome. Thromb Haemost. 2005;93(6):1147–52.
52. Pengo V, Ruffatti A, Legnani C, et al. Incidence of a first thromboembolic event in asymptomatic carriers of high-risk antiphospholipid antibody profile: a multicenter prospective study. Blood. 2011;118(17):4714–8.
53. Keeling D, Mackie I, Moore GW, Greer IA, Greaves M. Guidelines on the investigation and management of antiphospholipid syndrome. Br J Haematol. 2012;157(1):47–58.
54. Gardiner C, Hills J, Machin SJ, Cohen H. Diagnosis of antiphospholipid syndrome in routine clinical practice. Lupus. 2013;22(1):18–25.
55. Locht H, Wiik A. IgG and IgM isotypes of anti-cardiolipin and anti-beta2-glycoprotein i antibodies reflect different forms of recent thrombo-embolic events. Clin Rheumatol. 2006;25(2):246–50.
56. Urbanski G, Yelnik CM, Maillard H, et al. Antiphospholipid syndrome with isolated isotype M anticardiolipin and/or anti-B2GPI antibody is associated with stroke. Stroke. 2018;49(11):2770–2.
57. Kelchtermans H, Pelkmans L, de Laat B, Devreese KM. IgG/IgM antiphospholipid antibodies present in the classification criteria for the antiphospholipid syndrome: a critical review of their association with thrombosis. J Thromb Haemost. 2016;14(8):1530–48.
58. Ortel TL, Meleth S, Catellier D, et al. Recurrent thrombosis in patients with antiphospholipid antibodies and an initial venous or arterial thromboembolic event: a systematic review and meta-analysis. J Thromb Haemost. 2020;18(9):2274–86.
59. Schindewolf M, Weitz JI. Broadening the categories of patients eligible for extended venous thromboembolism treatment. Thromb Haemost. 2020;120(1):14–26.
60. Prins MH, Lensing AWA, Prandoni P, et al. Risk of recurrent venous thromboembolism according to baseline risk factor profiles. Blood Adv. 2018;2(7):788–96.
61. Cervera R, Rodríguez-Pintó I, Colafrancesco S, et al. 14th international congress on antiphospholipid antibodies task force report on catastrophic antiphospholipid syndrome. Autoimmun Rev. 2014;13(7):699–707.
62. Arachchillage DRJ, Gomez K, Alikhan R, Anderson JAM, Lester W, Laffan M. Addendum to British Society for Haematology guidelines on investigation and Management of Antiphospholipid syndrome, 2012 (Br. J. Haematol. 2012; 157: 47-58): use of direct acting oral anticoagulants. Br J Haematol. 2020;189(2):212–5.
63. Ruffatti A, Del Ross T, Ciprian M, et al. Risk factors for a first thrombotic event in antiphospholipid antibody carriers: a prospective multicentre follow-up study. Ann Rheum Dis. 2011;70(6):1083–6.
64. Tonello M, Calligaro A, Favaro M, et al. The first thrombotic event in purely obstetric antiphospholipid syndrome patients and in antiphospholipid antibody carriers: comparison of incidence and characteristics. Arch Gynecol Obstet. 2021;303(2):455–61.
65. 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. JAMA. 2009;301(23):2472–85.
66. Méan M, Limacher A, Stalder O, et al. Do factor V leiden and prothrombin G20210A mutations predict recurrent venous thromboembolism in older patients? Am J Med 2017; 130(10): 1220.e17-e22.
67. Ensor J, Riley RD, Moore D, Snell KI, Bayliss S, Fitzmaurice D. Systematic review of prognostic models for recurrent venous thromboembolism (VTE) post-treatment of first unprovoked VTE. BMJ Open. 2016;6(5):e011190.
68. Sokol J, Timp JF, le Cessie S, et al. Mild antithrombin deficiency and risk of recurrent venous thromboembolism: results from the MEGA follow-up study. J Thromb Haemost. 2018;16(4):680–8.
69. 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(9):1992–7.
70. Kyrle PA, Eischer L, Sinkovec H, Eichinger S. Factor XI and recurrent venous thrombosis: an observational cohort study. J Thromb Haemost. 2019;17(5):782–6.
71. Timp JF, Lijfering WM, Flinterman LE, et al. Predictive value of factor VIII levels for recurrent venous thrombosis: results from the MEGA follow-up study. J Thromb Haemost. 2015;13(10):1823–32.
72. 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(3):313–8.
73. Boutitie F, Pinede L, Schulman S, et al. Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials. BMJ. 2011;342:d3036.
74. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet. 2003;362(9383):523–6.
75. Venous thromboembolic diseases: diagnosis matt. https://www.nice.org.uk/guidance/ng158. 2020, Accessed on 18th Jan 2021.
76. Kearon C. Influence of hereditary or acquired thrombophilias on the treatment of venous thromboembolism. Curr Opin Hematol. 2012;19(5):363–70.
77. Egan RJ, Nicholls J, Walker S, Mellor K, Young WT, Stechman MJ. Routine coagulation screening is an unnecessary step prior to ERCP in patients without biochemical evidence of jaundice: a cross-centre study. Int J Surg. 2014;12(11):1216–20.
78. van Sluis GL, Söhne M, El Kheir DY, Tanck MW, Gerdes VE, Büller HR. Family history and inherited thrombophilia. J Thromb Haemost. 2006;4(10):2182–7.
79. https://www.gov.uk/drug-safety-update/combined-hormonal-contraceptives-and-venous-thromboembolism-reviewconfirms-risk-is-small Accessed on 18th Sep 2021.

80. Couturaud F, Kearon C. Predictors of thrombosis in relatives of patients with venous thromboembolism. Curr Opin Pulm Med. 2010;16(5):453–8.
81. Lijfering WM, Brouwer J-LP, Veeger NJGM, 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(21):5314–22.
82. van Vlijmen EF, Wiewel-Verschueren S, Monster TB, Meijer K. Combined oral contraceptives, thrombophilia and the risk of venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost. 2016;14(7):1393–403.
83. Coppens M. Contraception in women with hereditary thrombophilic defects. Clin Adv Hematol Oncol. 2015;13(9):566–8.
84. Tait C, Baglin T, Watson H, et al. Guidelines on the investigation and management of venous thrombosis at unusual sites. Br J Haematol. 2012;159(1):28–38.
85. Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. Blood. 2013;121(25):4985–96. quiz 5105.
86. Casini A, Fontana P, Lecompte TP. Thrombotic complications of myeloproliferative neoplasms: risk assessment and risk-guided management. J Thromb Haemost. 2013;11(7):1215–27.
87. Poulou LS, Xila V, Rokas GI, Karianakis G, Bartzoudis D, Ziakas PD. Temporal trends in mortality rates from visceral vein thrombosis in paroxysmal nocturnal haemoglobinuria: an optimistic view. Thromb Haemost. 2008;99(3):642–5.
88. Qi X, De Stefano V, Wang J, et al. Prevalence of inherited antithrombin, protein C, and protein S deficiencies in portal vein system thrombosis and Budd-Chiari syndrome: a systematic review and meta-analysis of observational studies. J Gastroenterol Hepatol. 2013;28(3):432–42.
89. Bousser MG, Ferro JM. Cerebral venous thrombosis: an update. Lancet Neurol. 2007;6(2):162–70.
90. Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke. 2004;35(3):664–70.
91. Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med. 1995;333(19):1253–8.
92. de Latour RP, Mary JY, Salanoubat C, et al. Paroxysmal nocturnal hemoglobinuria: natural history of disease subcategories. Blood. 2008;112(8):3099–106.
93. Dentali F, Ageno W, Rumi E, et al. Cerebral venous thrombosis and myeloproliferative neoplasms: results from two large databases. Thromb Res. 2014;134(1):41–3.
94. De Stefano V, Fiorini A, Rossi E, et al. Incidence of the JAK2 V617F mutation among patients with splanchnic or cerebral venous thrombosis and without overt chronic myeloproliferative disorders. J Thromb Haemost. 2007;5(4):708–14.
95. Shetty S, Kulkarni B, Pai N, Mukundan P, Kasatkar P, Ghosh K. JAK2 mutations across a spectrum of venous thrombosis cases. Am J Clin Pathol. 2010;134(1):82–5.
96. Lamy M, Palazzo P, Agius P, et al. Should we screen for janus kinase 2 V617F mutation in cerebral venous thrombosis? Cerebrovasc Dis. 2017;44(3-4):97–104.
97. Socié G, Mary JY, de Gramont A, et al. Paroxysmal nocturnal haemoglobinuria: long-term follow-up and prognostic factors. French Society of Haematology. Lancet. 1996;348(9027):573–7.
98. Hall C, Richards S, Hillmen P. Primary prophylaxis with warfarin prevents thrombosis in paroxysmal nocturnal hemoglobinuria (PNH). Blood. 2003;102(10):3587–91.
99. Moyo VM, Mukhina GL, Garrett ES, Brodsky RA. Natural history of paroxysmal nocturnal haemoglobinuria using modern diagnostic assays. Br J Haematol. 2004;126(1):133–8.
100. Darwish Murad S, Valla DC, de Groen PC, et al. Pathogenesis and treatment of Budd-Chiari syndrome combined with portal vein thrombosis. Am J Gastroenterol. 2006;101(1):83–90.
101. Dentali F, Crowther M, Ageno W. Thrombophilic abnormalities, oral contraceptives, and risk of cerebral vein thrombosis: a meta-analysis. Blood. 2006;107(7):2766–73.
102. Zhu W, Wu Y, Xu M, et al. Antiphospholipid antibody and risk of retinal vein occlusion: a systematic review and meta-analysis. PLoS One. 2014;10(4):e0122814.
103. Hernández JL, Sanlés I, Pérez-Montes R, et al. Antiphospholipid syndrome and antiphospholipid antibody profile in patients with retinal vein occlusion. Thromb Res. 2020;190:63–8.
104. Michiels JJ, Berneman Z, Gadisseur A, Lam KH, De Raeve H, Schroyens W. Aspirin-responsive, migraine-like transient cerebral and ocular ischemic attacks and erythromelalgia in JAK2-positive essential thrombocythemia and polycythemia vera. Acta Haematol. 2015;133(1):56–63.
105. Vlachoyiannopoulos PG, Samarkos M. Peripheral vascular disease in antiphospholipid syndrome. Thromb Res. 2004;114(5-6):509–19.
106. Shortell CK, Ouriel K, Green RM, Condemi JJ, DeWeese JA. Vascular disease in the antiphospholipid syndrome: a comparison with the patient population with atherosclerosis. J Vasc Surg. 1992;15(1):158–65. discussion 65-6.
107. Morris JG, Singh S, Fisher M. Testing for inherited thrombophilias in arterial stroke: can it cause more harm than good? Stroke. 2010;41(12):2985–90.
108. Hamedani AG, Cole JW, Mitchell BD, Kittner SJ. Meta-analysis of factor V Leiden and ischemic stroke in young adults: the importance of case ascertainment. Stroke. 2010;41(8):1599–603.
109. Pahus SH, Hansen AT, Hvas AM. Thrombophilia testing in young patients with ischemic stroke. Thromb Res. 2016;137:108–12.
110. May J, Lin C, Martin K, Laura J, Taylor MTGR. Thrombophilia testing in hospitalized patients with acute ischemic stroke: an opportunity for hematology input. Blood. 2019;134(Supplement_1):2105.
111. Chiasakul T, DeJesus E, Tong J, et al. Inherited Thrombophilia and the Risk of ArterialIschemic Stroke: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2019;8(19):e012877–927.
112. Apostolidou E. Assessment of unecessary thrombophilia testing in patients 18-60 with acute cryptogenic stroke. Blood. 2019;134:3397.
113. Gavva C, Johnson M, De Simone N, Sarode R. An audit of thrombophilia testing in patients with ischemic stroke or transient ischemic attack: the futility of testing. J Stroke Cerebrovasc Dis. 2018;27(11):3301–5.
114. Hamedani AG, Cole JW, Cheng Y, et al. Factor V leiden and ischemic stroke risk: the Genetics of Early Onset Stroke (GEOS) study. J Stroke Cerebrovasc Dis. 2013;22(4):419–23.
115. Stephan B, Schenk JF, Beye A, Pindur G. Clinical significance of factor V G1691A- and prothrombin G20210A-mutations in cerebral infarction and patent foramen ovale. Appl Cardiopulm Pathophysiol. 2012;16(1):32–6.
116. Lim ST, Murphy SJX, Smith DR, et al. Clinical outcomes and a high prevalence of abnormalities on comprehensive arterial and venous thrombophilia screening in TIA or ischaemic stroke patients with a patent foramen ovale, an inter-atrial septal aneurysm or both. J Neurol Sci. 2017;377:227–33.
117. Carobbio A, Thiele J, Passamonti F, et al. Risk factors for arterial and venous thrombosis in WHO-defined essential thrombocythemia: an international study of 891 patients. Blood. 2011;117(22):5857–9.
118. Pearson TC, Wetherley-Mein G. Vascular occlusive episodes and venous haematocrit in primary proliferative polycythaemia. Lancet. 1978;2(8102):1219–22.
119. Dawson AA, Ogston D. The influence of the platelet count on the incidence of thrombotic and haemorrhagic complications in polycythaemia vera. Postgrad Med J. 1970;46(532):76–8.
120. Tartaglia AP, Goldberg JD, Berk PD, Wasserman LR. Adverse effects of antiaggregating platelet therapy in the treatment of polycythemia vera. Semin Hematol. 1986;23(3):172–6.
121. Gaspersic N, Zaletel M, Kobal J, et al. Stroke and antiphospholipid syndrome-antiphospholipid antibodies are a risk factor for an ischemic cerebrovascular event. Clin Rheumatol. 2019;38(2):379–84.

122. Sciascia S, Sanna G, Khamashta MA, et al. The estimated frequency of antiphospholipid antibodies in young adults with cerebrovascular events: a systematic review. Ann Rheum Dis. 2015;74(11):2028–33.
123. Andrew M, David M, Adams M, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. Blood. 1994;83(5):1251–7.
124. Gibson BES CE, Bolton-Maggs P, Henderson DJ, Lynn R. Thromboembolism in childhood: a prospective 2 year BPSU study in the United Kingdom. February 2001-February 2003. Br J Haematol 2004;1:OC422.
125. van Ommen CH, Heijboer H, Büller HR, Hirasing RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands. J Pediatr. 2001;139(5):676–81.
126. Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. Pediatrics. 2009;124(4):1001–8.
127. Massicotte MP, Dix D, Monagle P, Adams M, Andrew M. Central venous catheter related thrombosis in children: analysis of the Canadian Registry of Venous Thromboembolic Complications. J Pediatr. 1998;133(6):770–6.
128. Saracco P, Parodi E, Fabris C, Cecinati V, Molinari AC, Giordano P. Management and investigation of neonatal thromboembolic events: genetic and acquired risk factors. Thromb Res. 2009;123(6):805–9.
129. Klaassen IL, van Ommen CH, Middeldorp S. Manifestations and clinical impact of pediatric inherited thrombophilia. Blood. 2015;125(7):1073–7.
130. Revel-Vilk S, Chan A, Bauman M, Massicotte P. Prothrombotic conditions in an unselected cohort of children with venous thromboembolic disease. J Thromb Haemost. 2003;1(5):915–21.
131. Nowak-Göttl U, Dübbers A, Kececioglu D, et al. Factor V Leiden, protein C, and lipoprotein (a) in catheter-related thrombosis in childhood: a prospective study. J Pediatr. 1997;131(4):608–12.
132. Saracco P, Bagna R, Gentilomo C, et al. Clinical data of neonatal systemic thrombosis. J Pediatr 2016; 171: 60-6.e1.
133. Young G, Albisetti M, Bonduel M, et al. Impact of inherited thrombophilia on venous thromboembolism in children: a systematic review and meta-analysis of observational studies. Circulation. 2008;118(13):1373–82.
134. Celkan T, Dikme G. Thrombosis in children: which test to whom, when and how much necessary? Turk Pediatri Ars. 2018;53(1):1–9.
135. Kearon C, Akl EA, Comerota AJ, et al. 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–96S.
136. Mosnier LO, Zlokovic BV, Griffin JH. The cytoprotective protein C pathway. Blood. 2007;109(8):3161–72.
137. Kroiss S, Albisetti M. Use of human protein C concentrates in the treatment of patients with severe congenital protein C deficiency. Biologics. 2010;4:51–60.
138. Tincani A, Rebaioli CB, Andreoli L, Lojacono A, Motta M. Neonatal effects of maternal antiphospholipid syndrome. Curr Rheumatol Rep. 2009;11(1):70–6.
139. Soares Rolim AM, Castro M, Santiago MB. Neonatal antiphospholipid syndrome. Lupus. 2006;15(5):301–3.
140. Simone B, De Stefano V, Leoncini E, et al. Risk of venous thromboembolism associated with single and combined effects of Factor V Leiden, Prothrombin 20210A and Methylenetethraydrofolate reductase C677T: a meta-analysis involving over 11,000 cases and 21,000 controls. Eur J Epidemiol. 2013;28(8):621–47.
141. Franchini M, Martinelli I, Mannucci PM. Uncertain thrombophilia markers. Thromb Haemost. 2016;115(1):25–30.
142. https://www.stroke.org.uk/sites/default/files/stroke_in_childhood_clinical_guidelines.pdf Accessed on 12th Oct 2021.
143. Sultan AA, West J, Tata LJ, Fleming KM, Nelson-Piercy C, Grainge MJ. Risk of first venous thromboembolism in and around pregnancy: a population-based cohort study. Br J Haematol. 2012;156(3):366–73.
144. Virkus RA, Løkkegaard EC, Bergholt T, Mogensen U, Langhoff-Roos J, Lidegaard Ø. Venous thromboembolism in pregnant and puerperal women in Denmark 1995-2005. A national cohort study. Thromb Haemost. 2011;106(2):304–9.
145. Liu S, Rouleau J, Joseph KS, et al. Epidemiology of pregnancy-associated venous thromboembolism: a population-based study in Canada. J Obstet Gynaecol Can. 2009;31(7):611–20.
146. James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. Am J Obstet Gynecol. 2006;194(5):1311–5.
147. Jackson E, Curtis KM, Gaffield ME. Risk of venous thromboembolism during the postpartum period: a systematic review. Obstet Gynecol. 2011;117(3):691–703.
148. https://www.npeu.ox.ac.uk/mbrrace-uk/reports Accessed on 16th July 2021.
149. Tate J, Bushnell C. Pregnancy and stroke risk in women. Womens Health (Lond). 2011;7(3):363–74.
150. Levy JH, Connors JM. Heparin resistance - clinical perspectives and management strategies. N Engl J Med. 2021;385(9):826–32.
151. Croles FN, Nasserinejad K, Duvekot JJ, Kruip MJ, Meijer K, Leebeek FW. Pregnancy, thrombophilia, and the risk of a first venous thrombosis: systematic review and bayesian meta-analysis. BMJ. 2017;359:j4452.
152. Abbattista M, Gianniello F, Novembrino C, et al. Risk of pregnancy-related venous thromboembolism and obstetrical complications in women with inherited type I antithrombin deficiency: a retrospective, single-centre, cohort study. Lancet Haematol. 2020;7(4):e320–8.
153. Topping J, Quenby S, Farquharson R, Malia R, Greaves M. Marked variation in antiphospholipid antibodies during pregnancy: relationships to pregnancy outcome. Hum Reprod. 1999;14(1):224–8.
154. Arachchillage DR, Machin SJ, Mackie IJ, Cohen H. Diagnosis and management of non-criteria obstetric antiphospholipid syndrome. Thromb Haemost. 2015;113(1):13–9.
155. Tripodi A, Cohen H, Devreese KMJ. Lupus anticoagulant detection in anticoagulated patients. Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2020;18(7):1569–75.
156. Li Y, Ruan Y. Association of hypertensive disorders of pregnancy risk and factor V Leiden mutation: a meta-analysis. J Obstet Gynaecol Res. 2019;45(7):1303–10.
157. Ahmed NA, Adam I, Elzaki SEG, Awooda HA, Hamdan HZ. Factor-V Leiden G1691A and prothrombin G20210A polymorphisms in Sudanese women with preeclampsia, a case -control study. BMC Med Genet. 2019;20(1):2.
158. Alfirevic Z, Roberts D, Martlew V. How strong is the association between maternal thrombophilia and adverse pregnancy outcome? A systematic review. Eur J Obstet Gynecol Reprod Biol. 2002;101(1):6–14.
159. Sergi C, Al Jishi T, Walker M. Factor V Leiden mutation in women with early recurrent pregnancy loss: a meta-analysis and systematic review of the causal association. Arch Gynecol Obstet. 2015;291(3):671–9.
160. Silver RM, Saade GR, Thorsten V, et al. Factor V Leiden, prothrombin G20210A, and methylene tetrahydrofolate reductase mutations and stillbirth: the Stillbirth Collaborative Research Network. Am J Obstet Gynecol 2016; 215(4): 468.e1-e17.
161. Areia AL, Fonseca E, Areia M, Moura P. Low-molecular-weight heparin plus aspirin versus aspirin alone in pregnant women with hereditary thrombophilia to improve live birth rate: meta-analysis of randomized controlled trials. Arch Gynecol Obstet. 2016;293(1):81–6.
162. Skeith L, Carrier M, Kaaja R, et al. A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia. Blood. 2016;127(13):1650–5.
163. Karadağ C, Akar B, Gönenç G, Aslancan R, Yılmaz N, Çalışkan E. Aspirin, low molecular weight heparin, or both in preventing

pregnancy complications in women with recurrent pregnancy loss and factor V Leiden mutation. J Matern Fetal Neonatal Med. 2020;33(11):1934–9.
164. ACOG Practice Bulletin No. 197: Inherited Thrombophilias in Pregnancy. Obstet Gynecol. 2018;132(1):e18–34.
165. Liu L, Sun D. Pregnancy outcomes in patients with primary antiphospholipid syndrome: A systematic review and meta-analysis. Medicine (Baltimore). 2019;98(20):e15733.
166. Abou-Nassar K, Carrier M, Ramsay T, Rodger MA. The association between antiphospholipid antibodies and placenta mediated complications: a systematic review and meta-analysis. Thromb Res. 2011;128(1):77–85.
167. Alijotas-Reig J, Esteve-Valverde E, Ferrer-Oliveras R, et al. The European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS): A survey of 1000 consecutive cases. Autoimmun Rev. 2019;18(4):406–14.
168. Cervera R, Serrano R, Pons-Estel GJ, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis. 2015;74(6):1011–8.
169. Rezk M, Dawood R, Badr H. Maternal and fetal outcome in women with antiphospholipid syndrome: a three-year observational study. J Matern Fetal Neonatal Med. 2016;29(24):4015–9.
170. Ruffatti A, Salvan E, Del Ross T, et al. Treatment strategies and pregnancy outcomes in antiphospholipid syndrome patients with thrombosis and triple antiphospholipid positivity. A European multicentre retrospective study. Thromb Haemost. 2014;112(4):727–35.
171. van Hoorn ME, Hague WM, van Pampus MG, Bezemer D, de Vries JI. Low-molecular-weight heparin and aspirin in the prevention of recurrent early-onset pre-eclampsia in women with antiphospholipid antibodies: the FRUIT-RCT. Eur J Obstet Gynecol Reprod Biol. 2016;197:168–73.
172. Eid MI, Abdelhafez MS, El-Refaie W, et al. Timing of initiation of low-molecular-weight heparin administration in pregnant women with antiphospholipid syndrome: a randomized clinical trial of efficacy and safety. Int J Womens Health. 2019;11:41–7.
173. Lu C, Liu Y, Jiang HL. Aspirin or heparin or both in the treatment of recurrent spontaneous abortion in women with antiphospholipid antibody syndrome: a meta-analysis of randomized controlled trials. J Matern Fetal Neonatal Med. 2019;32(8):1299–311.
174. Agersnap I, Nissen PH, Hvas AM. The role of plasminogen activator inhibitor type 1 (PAI-1) in placenta-mediated pregnancy complications: a systematic review. Semin Thromb Hemost. 2022. Epub ahead of print. https://doi.org/10.1055/s-0041-1742082
175. Wiwanitkit V. Roles of methylenetetrahydrofolate reductase C677T polymorphism in repeated pregnancy loss. Clin Appl Thromb Hemost. 2005;11(3):343–5.
176. James AH, Rhee E, Thames B, Philipp CS. Characterization of antithrombin levels in pregnancy. Thromb Res. 2014;134(3):648–51.

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