Neil Graham, Hunaid Rashiq and Beverley J Hunt

Testing for thrombophilia:

clinical update

N Graham, BA, MRCP, Core Medical Trainee (CT1), Hammersmith Hospital, Imperial College Healthcare NHS Trust, London. **H Rashiq**, MB BChir, GP trainer, The Omnia Practice, Birmingham. **BJ Hunt**, FRCP, FRCPath, MD professor of thrombosis & haemostasis, King's College & consultant, Departments of Haematology, Pathology & Rheumatology, Guy's & St Thomas' NHS Foundation Trust, London.

Address for correspondence

Beverley Hunt, Thrombosis & Haemophilia Centre, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH, UK.

E-mail: Beverley.Hunt@gstt.nhs.uk

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BACKGROUND

Thrombophilia describes inherited and acquired prothrombotic states which predispose to venous, but not arterial thromboembolism. The heritable states are of limited clinical significance in primary care and while they may underlie a patient's presentation with deep venous thrombosis (DVT) or pulmonary embolism (PE) of uncertain cause, tests infrequently alter management. Testing patients is not without pitfalls: results are only informative if taken in the right patient at an appropriate time, as explained in recent guidance from the National Institute for Health and Care Excellence (NICE)[1] and described below.

CLINICAL SIGNIFICANCE

The inherited thrombophilias are described in greater detail in Box 1 and largely fall into one of two groups: common low thrombosis-risk states, such as activated protein C resistance (due to the Factor V Leiden mutation) and rarer higher-risk states, including protein C or S deficiency. Due to their rarity, epidemiological data around some of the thrombophilias are poor: guidelines on these from NICE and the British Society for Haematology are largely expert opinion based on limited observational data.[1,2]

The most common acquired thrombophilia state is antiphospholipid antibodies (aPL), which requires positive tests for one or more of three antibodies on two occasions more than 12 weeks apart: lupus anticoagulant, anticardiolipin antibodies, and anti β^2-glycoprotein I antibodies. These are unusual in that they predispose to thrombosis in any vascular bed, so can cause arterial and microvascular events as well as venous thromboembolism (VTE).[3]

Pregnancy, malignancy, and some drugs produce prothrombotic states, that underlie around 20% of cases of VTE,[4] alongside myeloproliferative disease such as polycythaemia rubra vera. Oral and transdermal contraceptives, hormone replacement therapy, and tamoxifen are all associated with an increased risk of VTE, while pregnancy itself causes a hypercoagulable state, in addition to increased venous stasis. More rarely, inflammatory states such as Behçet's disease may underlie thrombosis.

WHEN SHOULD I CONSIDER TESTING FOR THROMBOPHILIA?

As the recent NICE guidelines emphasise, testing should only performed when it is likely to change the patient's management, such as in the risk–benefit analysis of whether to discontinue anticoagulation after a recent VTE.[1]

Meta-analysis of prospective cohort and randomised controlled trials shows a very low risk of recurrent thrombosis in those with 'provoked' VTE, in which case anticoagulation can safely be discontinued after 3 months for distal DVT, and 6 months for proximal DVT or PE.[5]

Conversely, if there is uncertainty in deciding whether to stop anticoagulation after a case of 'unprovoked' VTE (those circumstances where no temporary 'provoking' risk factor such as hospital admission, pregnancy, or use of the combined oral contraceptive is identified), the GP should consider aPL testing for acquired thrombophilia, as no positive family history is required to justify testing.[1]

The presence or absence of VTE in any first-degree relative should be sought and if present, inherited thrombophilia tests are indicated and in keeping with NICE guidance.[1]

Screening for cancer is recommended by NICE in patients with unprovoked VTE, it may underlie 6–10% of all patients with unprovoked VTE. NICE suggests a physical examination, urinalysis, bloods (including full blood count, calcium, and liver function tests), and a chest X-ray should

Box 1. Typical components of a thrombophilia blood panel

Inherited states

Heterozygous Factor V Leiden mutation (FVR506Q)[6]
Mutation in Factor V gene confers resistance to activated protein C and increases thrombosis risk 3–5x

Heterozygous prothrombin 20210 mutation[7]
Elevated prothrombin levels due to mutation increase risk by 2–3x

Heterozygous protein C deficiency[8]
Rare mutations reduce the function or production of protein C, an inhibitor of coagulation together with protein S, increasing thrombosis risk around 3x

Heterozygous protein S deficiency[9]
Rare mutations reducing function or production lead to increased risk of around 10x

Hereditary antithrombin deficiency[10]
Reduced function or production of antithrombin thought to confer high thrombosis risk

Dysfibrinogenaemia
Very rare prothrombotic mutation thought to confer high thrombosis risk

Acquired states

Antiphospholipid antibodies (aPL)[3]
Variable risk of venous or arterial thrombosis due to the presence of any one or a combination of anti-cardiolipin, lupus anticoagulant, or anti β^2-glycoprotein I antibodies. Antiphospholipid syndrome is due to the presence of persistent aPL antibodies and/or certain pregnancy complications

Full blood count, calcium, and liver function tests
Variable risk of thrombosis due to the presence of cancer or myeloproliferative disease

Box 2. Key points

Test selectively: a full panel costs around £300 and tests taken inappropriately may add little, or misinform patient management. Only check for heritable thrombophilia in patients with unprovoked VTE and a positive family history.

Differentiate venous and arterial thrombosis: arterial events such as most ischaemic stroke or myocardial infarction are not affected by heritable thrombophilias, whereas inherited and acquired thrombophilias may contribute to venous thrombosis.

Get the timing right: physiological anticoagulant levels are reduced after acute thrombosis, invalidating test results. If a positive antiphospholipid test is found, it should be repeated 12 weeks later, as the antibody may be transient.

Avoid interfering drugs: anticoagulants interfere with the tests, which should be performed 2 weeks after cessation of vitamin K antagonists, which invalidate protein C and S and lupus anticoagulant assays and 24 hours after low molecular weight heparins are stopped, as these produce a false positive lupus anticoagulant test.

Use the correct blood bottle: all samples should be taken in sodium citrate (blue vacutainers), filling to the line to ensure the correct dilution is attained. Local policies for anticardiolipin tests vary and may require a clot-activated sample with (red top vacutainer), or without gel for serum separation (gold top vacutainer).

Appreciate the limitations: tests will not find abnormalities in all patients with VTE and a strong family history, reflecting the likelihood that some heritable states are yet to be identified, especially in the non-Caucasian population. Therefore, a negative set of investigations does not exclude an inherited prothrombotic tendency and if in doubt, a referral to a thrombosis specialist should be made.

be performed. In those aged ≥40 years with non-diagnostic initial findings, an abdomino-pelvic CT should be offered, alongside a mammogram for women.[1]

WHEN SHOULD I AVOID TESTING FOR THROMBOPHILIA?

Testing for thrombophilia will be uninformative if the patient is taking anticoagulation or has had a recent VTE for both will interfere with the assays. Beyond those patients with unprovoked VTE and a strong family history, there is very limited evidence to support use of the tests (Box 2).

In the risk assessment of women before starting oestrogen-containing oral hormonal therapy, a positive family history of VTE in a first-degree relative is sufficient grounds to avoid the combined oral contraceptive. Thrombophilia testing will not change this decision and should not be performed.[2]

Testing also has a limited role in screening asymptomatic relatives of patients with known thrombophilia. Meta-analysis of prospective cohort studies suggest that testing asymptomatic relatives is not helpful in low risk thrombophilias, while the evidence in high-risk thrombophilias is unclear.[2] In such cases discussion with a thrombosis expert is advised.

CONCLUSION

The increasing availability of thrombophilia tests, particularly for heritable disease, has lead to much inappropriate use, but they rarely inform management. Judicious testing, taking into account the NICE recommendations, and practical advice in Box 2 is fundamental to ensuring meaningful results. In the event of positive, or uncertain results, timely discussion with a thrombosis expert should help to clarify the next stages of management.

Provenance
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