Testing for thrombophilia:
clinical update

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) 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.

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-β2-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).

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.

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.

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.

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.

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

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be performed. In those aged ≥40 years with non-diagnostic initial findings, an abdomen-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.

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