Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis

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Executive summary

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**Background**

Thrombophilias are heritable [such as factor V Leiden and the prothrombin G20210A mutation (PTG20210A)] or acquired (such as lupus anticoagulant) defects in blood coagulation that lead to a predisposition towards thrombosis. A thrombus is a solid mass of blood constituents that can fragment and block vessels downstream (thromboembolism). Depending on the blood vessel occluded, venous thromboemboli can lead to pulmonary embolism (PE) or, rarely, stroke.

**Objectives**

This review addresses the following question: ‘Is thrombophilia testing following a venous thrombotic event clinically effective and cost-effective in the management of thrombosis compared with no testing for thrombophilia?’

**Methods**

A comprehensive search was undertaken to systematically identify clinical effectiveness and cost-effectiveness literature comparing thrombophilia testing of patients with thrombosis with no testing, and the resulting long-term anticoagulation management and outcomes. A discrete event simulation model was constructed that assessed the cost-effectiveness of changing the standard 3-month duration of warfarin treatment to 10 years, 20 years or lifelong. The model was run for both sexes, using hypothetical cohorts of patients assumed to be 30, 40, 50, 60 and 70 years of age. Separate analyses were conducted for patients in whom the initial venous thromboembolic event (VTE) was a deep vein thrombosis (DVT) and for those in whom the initial VTE was a PE.

**Results**

No trials were identified that met the inclusion criteria for the clinical effectiveness review. A number of papers were identified that investigated the cost-effectiveness of interventions for managing patients who may have thrombophilia, but none was appropriate to use in its published form.

There is a great deal of uncertainty in the cost per quality-adjusted life-year (QALY) of thrombophilia testing, largely because of the wide uncertainty regarding the increased risk of recurrence in patients with each thrombophilia, which is log-normally distributed. Our results are based on the mean cost per QALY taken from probabilistic sensitivity analyses (PSAs), which are generally less than £20,000, but it is noted that the chance of obtaining cost per QALY values greater than £100,000 is not remote. With this caveat thrombophilia testing in patients with PE had an estimated mean cost per QALY of below £20,000 regardless of sex or age. In patients with a previous DVT, thrombophilia testing had an estimated mean cost per QALY of below £20,000 in men aged 69 years or less and in women aged 49 years or less. The estimated duration of warfarin treatment (either lifelong, 20 years, 10 years or no extended treatment) that was most cost-effective is presented for each age, sex, initial VTE event and type of thrombophilia. The results are influenced by the fact that the risk of recurrence is greater in men than in women and by the fact that the frequency of adverse events associated with warfarin treatment increases as patients become older.

Uncertainty around some of the parameters, such as the prevalence of thrombophilia type, was not included within the model and, thus, whilst this is not expected to alter the mean cost per QALY it is expected that the range of cost per QALY values that could be correct is wider than those presented in this report.

**Discussion**

This report focuses on the cost-effectiveness of thrombophilia testing in determining whether the duration of warfarin treatment should be extended. No other anticoagulation therapies or interventions to prevent VTE have been modelled. Additional benefits of knowing the thrombophilia status of a person, such as pregnancy or the use of oral contraceptives or hormone replacement...
therapy, have been excluded as they are outside the remit of the appraisal. For the same reason the costs and disutilities of any adverse effects of undertaking a genetic test, such as counselling or anxiety, have been excluded.

The sensitivity and specificity of tests for specific types of thrombophilia were largely uncertain and we have used 99% for both characteristics. Although this is likely to be relatively accurate for the DNA-based tests such as those for factor V Leiden (FVL) and the prothrombin G20210A mutation (PTG20210A), it is likely to overestimate the accuracy of other tests, meaning that the results produced will be potentially favourable to thrombophilia testing. As the group of patients who are heterozygous for both FVL and PTG20210A are key determinants of the cost-effectiveness ratio, the overall cost per QALY of global testing may not markedly change; however, future research on the likely sensitivity and specificity of the tests for each thrombophilia type is needed.

The results from the PSA show that there is a great deal of uncertainty in the mean incremental cost-effectiveness ratios, primarily because of uncertainties in key input parameters, in particular the increased risks associated with thrombophilia. Reducing these confidence intervals is an area for future research and will allow more accurate assessments of the cost per QALY of thrombophilia testing to be undertaken.

Because of the lack of data on the additional expense of conducting tests for some types of thrombophilia, these have been omitted from the modelling work. If it can be proven that the marginal costs of undertaking these tests are small, the most cost-effective duration of warfarin treatment (3 months, 10 years, 20 years or lifelong) could be approximated from thrombophilia types with similar increased risks of recurrence. Our work additionally estimates which tests may be omitted from the battery of tests, if this is logistically possible, as their outcomes would not alter the management of the patient.

Conclusions

No clinical studies were identified that met the inclusion criteria for the review.

Our mathematical model estimates that undertaking thrombophilia testing on patients with PE has a mean cost per QALY below £20,000 regardless of sex or age, although there is great uncertainty around these values. In patients with a previous DVT, thrombophilia testing has an estimated mean cost per QALY below £20,000 in men aged 69 years or less and in women aged 49 years or less, but again there is great uncertainty in the values.

Publication

The Health Technology Assessment (HTA) Programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’.

The HTA Programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Second, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

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Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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