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

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Abstract

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

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Objectives: To assess whether thrombophilia testing following a venous thrombotic event is clinically effective and cost-effective in the management of thrombosis compared with no testing for thrombophilia.
Data sources: Major electronic databases were searched from September to November 2006.
Review methods: A systematic review of the clinical effectiveness and cost-effectiveness literature was undertaken according to standard methods. A discrete event simulation model was constructed to assess the cost-effectiveness of changing the standard 3-month duration of warfarin treatment to 10 years, 20 years or lifelong.
Results: No clinical studies were identified that met the inclusion criteria for the systematic review. Further literature searches and clinical opinion were therefore used to inform the cost-effectiveness analysis. Thrombophilia testing in patients with pulmonary embolism (PE) had an estimated mean cost per quality-adjusted life-year (QALY) of below £20,000 regardless of sex or age. In patients with a previous deep vein thrombosis (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 (lifelong, 20 years, 10 years or no extended treatment) that was most cost-effective is presented for each age, sex, initial venous thromboembolism (VTE) event and type of thrombophilia.
Conclusions: In terms of determining the duration of anticoagulation management, scenarios were found in which the cost per QALY of thrombophilia testing was below £20,000. However, these results are subject to great uncertainty, largely because of lack of knowledge about the increased risk of recurrence with each type of thrombophilia. Results are influenced by the fact that men have a greater risk of recurrence than women and by the fact that the frequency of adverse events associated with warfarin treatment increases with age. Further research, for example on the likely sensitivity and specificity of the tests for specific types of thrombophilia, is needed to reduce the uncertainty associated with these results. Studies comparing patients with VTE tested for thrombophilia with those whose risk assessment was based on personal and family history of thrombosis would also be beneficial.

Contents

Glossary and list of abbreviations

Glossary

Anticoagulation therapy Medication that prevents formation of blood clots in blood vessels or prevents existing clots from growing

Antiphospholipid antibodies Anticardiolipin antibodies and lupus anticoagulant

Antithrombin deficiency A reduction in the quantity of normal antithrombin protein or production of abnormal protein

Dysfibrinogenaemia Fibrinogen abnormalities

Factor V Leiden A point mutation in the gene for clotting factor V

Heterozygous Having two different alleles of a gene for a particular trait (e.g. an individual who is heterozygous for factor V Leiden has one gene with the factor V Leiden mutation and one normal copy of the gene)

Homozygous Having two identical alleles of a gene for a particular trait (e.g. an individual who is homozygous for factor V Leiden has both genes with the factor V Leiden mutation)

Hyperhomocysteinaemia Elevated levels of homocysteine

Idiopathic venous thromboembolism Venous thromboembolism of no known cause, which is not linked to known risk factors. Alternatively may be referred to as spontaneous or unprovoked

Index venous thromboembolism First venous thromboembolic event

Protein C deficiency A reduction in the quantity of normal protein C or production of abnormal protein C

Protein S deficiency A reduction in the quantity of normal protein S or production of abnormal protein S

Prothrombin G20210A mutation Mutation by a G to A transition at nucleotide position 20210 in the prothrombin gene

Prothrombotic Predisposition to thrombosis

Thrombophilia A heritable (genetic) or acquired defect in blood coagulation that leads to a predisposition towards thrombosis

Transient risk factors Factors that increase the risk of thromboembolism for a time-limited period

Unselected venous thromboembolism Venous thromboembolism that may include those that have been provoked by known risk factors, for example surgery

List of abbreviations

CI	confidence interval
APC	activated protein C
AT	antithrombin
CEAC	cost-effectiveness acceptability curve
DES	discrete event simulation
DVT	deep vein thrombosis
FVL	factor V Leiden
HR	hazard ratio
HRQoL	health-related quality of life
INR	international normalised ratio
MAICER	maximum acceptable incremental cost-effectiveness ratio
OR	odds ratio
PC	protein C
PE	pulmonary embolism
PS	proteins
PTG20210A	prothrombin G20210A mutation
PTS	post-thrombotic syndrome
PSA	probabilistic sensitivity analysis
PS	protein S
QALY(s)	quality-adjusted life-year(s)
RR	relative risk
RRR	relative risk reduction
SEM	standard error of the mean
VTE	venous thromboembolism

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

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.

Chapter 1
Background

Description of the health problem

Thrombophilia

Thrombophilia is a heritable (genetic) or acquired defect in blood coagulation that leads 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. Venous thrombosis often occurs in normal vessels, with the majority of venous thrombi forming in the deep veins of the leg (deep vein thrombosis, DVT).

Physiological blood coagulation is complex and is mediated through the interaction of numerous plasma proteins. These circulate in an inactive form to prevent unwanted clot formation, but when activated contribute to a potent cascade of interactions culminating in the generation of thrombin. The initiating event is interaction of factor VII/VIIa with tissue factor. Tissue factor is present in most cells and is made available as a result of injury. When factor VIIa binds to tissue factor this initiates the coagulation cascade, in which factors IX and X are activated. Through activated factors IX and X, in the presence of activated factors VIII and V, thrombin is generated from prothrombin (factor II). Thrombin converts factor I (fibrinogen) to insoluble fibrin, the principal component of thrombus. Thrombin also acts as a catalyst to its own formation by feedback activation of factors VIII and V. In addition, thrombin recruits platelets and promotes cross-linking of fibrin strands through activation of factor XIII.

There is a regulatory system to prevent uncontrolled coagulation. Tissue factor pathway inhibitor inhibits the early events. Antithrombin inhibits thrombin as well as activated factors IX, X and XI. When thrombin binds to thrombomodulin it is redirected to an anticoagulant role through activation of protein C. Activated protein C, together with the free form of protein S that acts as a cofactor for protein C, inactivates factors Va and VIIIa. Finally, a parallel system controls the generation of plasmin, the principal enzyme capable of lysis of fibrin.[1–6]

Thrombophilia can be genetic, acquired or mixed (due to a mixture of genetic and environmental factors). Heritable (genetic) thrombophilia is caused most commonly by mutations in the genes for coagulation factors II and V. Acquired thrombophilia refers to conditions in which individuals without genetic defects in coagulation factors are at increased risk of thrombosis, for example those with lupus anticoagulant or anticardiolipin antibodies. Examples of mixed-type thrombophilias are elevation of factor VIII or homocysteine levels. Malignancy can lead to an increased risk of thrombosis. Transient risk factors for thrombosis are conditions in which individuals are temporarily at increased risk of thrombosis, for example pregnancy, oestrogen therapy from combined oral contraceptives or hormone replacement therapy, obesity, fractures and major surgery. There is an increased risk of thrombosis with increasing age.[7]

Factor V Leiden (FVL) and the prothrombin G20210A mutation (PTG20210A) are genetic thrombophilias associated with increased procoagulant (promoting coagulation) activity. The FVL mutation is a point mutation in the gene for clotting factor V (1691G-A). Activated protein C (APC) is one of the major inhibitors of the coagulation system. An impairment in plasma anticoagulant response to APC is known as APC resistance. FVL is the most frequent cause, although not the only cause, of inheritable APC resistance. PTG20210A is a mutation of the prothrombin gene that is associated with elevated plasma prothrombin levels. In the general population the prevalence of FVL heterozygosity is 1–15%,[8] of FVL homozygosity is 0.02–0.05%[9] and of PTG20210A is 2–5%.[8] The prevalence of FVL and PTG20210A is higher in Caucasian populations than in African or Asian populations.[10] Compared with people without the mutation there is an increased risk of experiencing VTE of 3–8 times for heterozygous carriers of FVL, 80 times for homozygous carriers of FVL and 3 times for carriers of PTG20210A.[11]

Antithrombin (AT), protein C (PC) and protein S (PS) are physiological anticoagulants and a deficiency of any of these can be heritable. AT inhibits thrombin and also some activated clotting factors. AT deficiency can be caused by either a reduction in the quantity of normal AT protein or production of abnormal protein. PC, when activated, is a major inhibitor of the coagulation system. PC deficiency can be caused by either a lower level of PC or less functional PC. PS is a cofactor for APC. PS deficiency can be caused by reduced production of PS, a defect in PS or reduced availability of PS. In the general population the prevalence of AT deficiency is 0.02–0.04%,[9] of PC deficiency is 0.2–0.4%[9] and of PS deficiency is 0.003–2%.[11,12] The low prevalence of these deficiencies makes it more difficult to accurately assess the relative risk (RR) of VTE, but estimates suggest an increased risk of first VTE compared with people without the deficiency of 19–50 times for individuals with AT deficiency,[11,13] 6.5–15 times for PC deficiency,[11,12] and 5–10 times for PS deficiency,[11,12] although this risk had been estimated to be 32 times as high by a retrospective study.[13]

Antiphospholipid antibodies, that is anticardiolipin antibodies and lupus anticoagulant, are forms of acquired thrombophilia. The mix of genes and environmental factors can cause elevated levels of homocysteine, fibrinogen or clotting factors VIII, IX and XI. Sufficiently elevated levels of these can increase the risk of VTE. The prevalence of hyperhomocysteinaemia (levels > 18.5 µmol/l) in the general population is 5–7%,[12] that of elevated factor VIII (> 150 IU/dl) is 11%,[8] of elevated factor IX (> 129 IU/dl) is 3%[8] and of elevated factor XI (> 120.8 IU/dl) is 10%.[8] Dysfibrinogenaemia is rare in the general population.[11]

It is possible to have more than one type of thrombophilia. Most types of thrombophilia are considered neither necessary nor sufficient cause for thrombosis. Individuals can have thrombophilia without experiencing a thrombotic event. Thrombosis can occur in people without thrombophilia.

Venous thrombosis

The estimated annual incidence of VTE (not restricted to patients with thrombophilia) is 1 in 1000 individuals in the general population.[14] The incidence is higher in older age groups than in younger age groups.[7]

VTE can be associated with, for example, pregnancy, oestrogen therapy, fractures and major surgery. When there is no known cause, VTE is referred to as idiopathic. Within a group of VTE patients it is estimated that approximately 30–50%[10,15] will have a known form of heritable thrombophilia, depending on the population.

A higher prevalence of some types of thrombophilia has been found in patients with venous thrombosis than in the general population, although there is considerable variation in reported prevalence rates according to study/population. The prevalence rates of thrombophilia in unselected (including idiopathic and non-idiopathic) patients with VTE are shown in *Table 1*.

Venous thrombosis is an important cause of morbidity and mortality; approximately 90% of PEs are caused by dislodged fragments from asymptomatic DVTs.[19] PE can be fatal. Estimates of mortality rates vary widely, from 2.3%, based on patients enrolled in clinical studies, to 28%, based on a cohort study.[20] Post-thrombotic syndrome (PTS) is a long-term complication of DVT. Approximately 30–50%[21,22] of DVT patients may suffer post-thrombotic symptoms in the long term. These symptoms include pain, swelling and venous ulceration of the affected leg. The risk of developing PTS has not been found to be affected by thrombophilia, as shown for FVL, PTG20210A or elevated factor VIII.[23]

In the UK approximately 500,000 patients are being prescribed oral anticoagulants.[24]

TABLE 1 *Prevalence of thrombophilia in unselected VTE patients*

Thrombophilia	Prevalence in VTE patients (%)
FVL heterozygous	10–50[8]
FVL homozygous	1.5[9]
PTG20210A heterozygous	5–18[9]
AT deficiency	0.5[16]–3[8]
PC deficiency	3–5[8]
PS deficiency	1–5[8]
Hyperhomocysteinaemia	5.7–35[9]
Dysfibrinogenaemia	0.8[17]
Elevated factor VIII	10–25[9]
Elevated factor IX	7.5[8]
Elevated factor XI	19[8]
Anticardiolipin antibodies	2.7[18]
Lupus anticoagulant	2.7[18]

Anticoagulants suppress the synthesis of clotting factors in the blood and therefore prolong the time it takes for the blood to clot. Warfarin is the most commonly prescribed anticoagulant, but other oral anticoagulants include acenocoumarol and phenindione.[24] Warfarin interferes with the vitamin K-dependent synthesis of factors II, VII, IX and X, and also affects proteins C and S.[25] The dose of warfarin prescribed is determined by the international normalised ratio (INR), which is a measure of coagulability. Patients on oral anticoagulants need to be monitored regularly, with INR testing. The INR is derived from measurements of the time that it takes for a sample of the patient's blood to clot, for example an INR of 2 means that the blood takes twice as long as normal to clot. Usual practice is to give a large initial loading dose of warfarin and adjust the daily dose according to the INR results from blood samples taken over the following days. Because there is a delay before the onset of the clinical effects of warfarin, in the initial stages of treatment, heparin is often given concomitantly as it has an immediate effect. Once the patient has achieved the target INR, the patient continues treatment with a maintenance dose of warfarin. The patient must undergo periodic blood tests to ensure that the target INR is maintained. Monitoring is time-consuming for patients and clinicians. The dose of warfarin is adjusted to maintain the INR within a target therapeutic range, which is determined by the indication for treatment. The recommended target INR for VTE is 2.5.[26]

The benefits of anticoagulation in terms of a reduction in the risk of thromboembolic events must be balanced against the increased risk of haemorrhage. While taking oral anticoagulants long term there is an annual risk of haemorrhage of approximately 1–15%, with the risk increasing with higher INR.[24] The risk of haemorrhage is not affected by the presence of thrombophilia.[27,28]

Current service provision

The National Screening Committee, considering screening women for heritable thrombophilia, concluded that there was no evidence to support routine screening of women of childbearing age, those about to be prescribed oestrogen preparations or those with a family history of thrombophilia.[29] A recent Health Technology Assessment report found that thrombophilia screening was not indicated in patients undergoing major orthopaedic surgery, nor in women during pregnancy or prior to prescribing oestrogen.[30] This report suggests that selective testing based on a history of VTE may be more cost-effective than universal screening.[30]

Thrombophilia testing can be conducted by specialist laboratories, although some hospitals perform some tests on site. Thrombophilia testing is not currently restricted to patients with thrombosis. Asymptomatic relatives of patients with thrombophilia may be tested. Testing may follow recurrent miscarriage, other obstetric conditions or certain neurological symptoms.[31]

For first episode of VTE in non-pregnant, non-surgical patients, the British Committee for Standards in Haematology (BCSH) recommends oral anticoagulant prophylaxis producing an INR of 2.5 for 3 months for patients with DVT or PE, or at least 6 months for patients with idiopathic VTE.[26] The same recommendation applies to those with a diagnosis of heritable thrombophilia.[17] Recurrent idiopathic VTE requires consideration of indefinite anticoagulation, whether or not a patient is diagnosed with heritable thrombophilia.[17]

Some randomised controlled trials of anticoagulation therapy duration or intensity have illustrated the similarity in reaction to anticoagulation between VTE whether or not heritable thrombophilia was diagnosed. The PREVENT trial compared placebo with low-intensity warfarin in idiopathic VTE.[32] The risk reduction for recurrence of VTE for warfarin versus placebo was similar for those with or without FVL or PTG20210A.[32] The WODIT trial compared 3 months of warfarin therapy with 12 months of warfarin therapy in patients with idiopathic VTE.[33] There was a borderline significant higher risk of recurrence of VTE in thrombophilia for patients on 3 months of warfarin, accounted for by patients with the acquired thrombophilias hyperhomocysteinaemia and antiphospholipid antibodies and not by the heritable thrombophilias FVL, PTG20210A, and antithrombin, protein C or protein S deficiencies.[33] The ELATE trial compared low-intensity with normal-intensity warfarin in idiopathic VTE.[28] Recurrence rates of VTE did not differ according to whether or not patients had FVL or PTG20210A.[28] The THRIVE III trial, comparing ximelagatran to placebo, studied VTE that was not restricted to idiopathic events.[34] It found no significant interactions between treatment group and thrombophilia (FVL, PTG20210A, antithrombin, protein C or protein S deficiencies, or cardiolipin antibodies).[35] Overall,

thrombophilia does not seem to alter the efficacy of anticoagulation therapy.

A diagnosis of thrombophilia may affect advice given on transient risk factors, for example oestrogen therapy, or may influence decisions about targeted thromboprophylaxis in high-risk situations such as surgery.

Description of technology under assessment

Thrombophilia testing refers to a panel of tests that are performed on individuals who are believed to be at high risk of thrombosis. A blood sample is taken and a panel of diagnostic tests are performed to detect deficiencies in blood coagulation.

Diagnostic tests that may be predictive for an increased risk of venous thrombosis include those for factor V Leiden, prothrombin G20210A, clotting factors and the physiological anticoagulants antithrombin, protein C and protein S. Examples of CE marked indications for use are shown in Appendix 1 (CE marking is a declaration by the manufacturer that the product meets all of the appropriate provisions of the relevant legislation implementing certain European directives).

Thrombophilia testing may follow thrombosis, recurrent miscarriage, other obstetric conditions or certain neurological symptoms. For this review we consider thrombophilia testing following thrombosis, and focus on testing as a means of identifying those who may benefit from a prolonged course of anticoagulant therapy to prevent thrombosis.

Informed consent from the patient should precede testing. When thrombophilia testing follows thrombosis the test should not be performed during the acute phase and should be delayed until at least 1 month after completion of anticoagulation.[33] Some thrombophilia tests are influenced by post-thrombotic state and anticoagulation therapy.[33] Tests should not be conducted during pregnancy or oestrogen therapy.[33] If testing while on anticoagulants is unavoidable, this necessitates repeat testing at a later date. Abnormal tests should be confirmed by testing on fresh blood samples. The Royal College of Physicians of Edinburgh recommends that thrombophilia testing is supervised by experienced haematologists informed of relevant factors that may influence test results in each individual.[36]

Genetic tests for FVL and PTG20210A are considered robust. Significant difficulties are encountered in the accurate diagnosis and classification of deficiencies of natural anticoagulants.[17] Errors may occur in testing, making quality assurance important.[37]

Thrombophilia testing can be conducted by specialist laboratories, although some hospitals perform some tests on site. Different departments use different panels of tests in a thrombophilia screen. The BCSH recommends that thrombophilia testing is restricted to expert haemostasis units.[31] The Royal College of Physicians of Edinburgh recommends that molecular testing be carried out in a central laboratory but that coagulometers in hospitals are adequate for thrombophilia tests and avoid frozen plasma samples being transported, which is costly and may disadvantage sample stability.[36]

In 1999, UK National External Quality Assessment Scheme (NEQAS) Blood Coagulation surveyed UK laboratories and determined that a minimum of 37,800 thrombophilia screens were performed across the UK in that year (Dr I. Jennings, Scientific Programme Manager, UK NEQAS Blood Coagulation, personal communication). In the UK, 25,000 tests for APC resistance were conducted within 12 months in 1996/7.[38]

Sources of requests for tests vary according to laboratory. Data from one hospital coagulation department found 2700 requests for thrombophilia testing annually, most frequently (45%) from regional hospitals, with other requests from inpatients (16%), haematology clinics (10%), other outpatient clinics (12%), general practice (8%) and obstetrics (9%).[39] Some requests (11%) were not appropriately timed as patients were on oral anticoagulation therapy.[39] Only 17% of these tests had abnormal results, most of which were detected by the haematology clinic on the basis of family history of VTE.[39] The Royal College of Nursing (RCN) recommends that requests for thrombophilia testing should be made only by health-care professionals trained to understand the implications and usefulness of testing.[40]

Chapter 2

Definition of the decision problem

Decision problem

The intervention for this review was thrombophilia tests performed on individuals with venous thrombosis, including the resulting anticoagulation management.

The comparator for this review was individuals with thrombosis who are not subject to thrombophilia testing, and their anticoagulation management.

The review originally aimed to discover whether anticoagulation management is altered according to thrombophilia test results, and the effect on subsequent thrombotic event rates. The review also aimed to investigate adverse events resulting from anticoagulation management, specifically rates of haemorrhage, and effect on health-related quality of life (HRQoL). It was found that anticoagulation management is not generally altered according to diagnosis of thrombophilia and so the focus of the review was to assess the cost-effectiveness of thrombophilia testing in determining the duration of warfarin treatment following a VTE.

Overall aims and objectives of assessment

Objectives

The 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 not testing for thrombophilia?'

Areas outside the scope of this appraisal

Screening of individuals exposed to conditions that are transient risk factors (e.g. major surgery and pregnancy) has been excluded from the scope of this appraisal, as have pregnancy outcomes. Case finding by testing of asymptomatic individuals with a family history of thrombophilia or thrombosis but no personal history of thrombosis is also outside the scope of this review. These are important issues but it was not feasible to appraise all of these within a single technology assessment report.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

Identification of studies

A comprehensive search was undertaken to systematically identify clinical effectiveness literature concerning thrombophilia testing of patients with thrombosis and the resulting long-term anticoagulation management. The search strategy comprised searching of electronic databases, scrutiny of bibliographies of retrieved papers and contact with the project advisory group to identify key papers.

Searches of electronic databases were not restricted by language, publication date or publication type. Searches included arterial as well as venous thrombotic events as the review initially aimed to investigate these. Searches were conducted between September and November 2006. The MEDLINE search strategy is shown in Appendix 2 and was adapted for use on the other databases. The following electronic databases were searched from inception: MEDLINE (Ovid), CINAHL, EMBASE, PreMEDLINE, Cochrane Library including the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register (CENTRAL), DARE, NHS EED and HTA databases, Science Citation Index (SCI), National Research Register (NRR), Current Controlled Trials, BIOSIS, Centre for Reviews and Dissemination (ongoing reviews database), Research Findings Register, Web of Science.

Inclusion criteria

Population

- Individuals with venous thrombosis. Thrombotic events had to be confirmed by objective testing. Thromboses were included whether first event or recurrent episode. The following subgroups were to be considered: smoking status; sex; age at first event; site of first thrombosis.

Intervention

- Thrombophilia testing using a panel of diagnostic tests and the resulting anticoagulation management. Any panel of diagnostic tests for thrombophilia was considered. Examples of thrombophilia tests include those for factor V Leiden, prothrombin G20210A, APC resistance, protein C, protein S and antithrombin levels, antiphospholipid antibodies and homocysteine levels, dysfibrinogenaemia, and levels of factor VIII, factor IX and factor XI. Anticoagulation management comprised any prescription of anticoagulants and follow-up of the patient.

Comparator

- Current standard care, that is risk assessment based on personal and family history of thrombosis, and the resulting long-term anticoagulation management.

Outcomes

- Venous thrombotic events (including fatal events) including DVT, PE, venous stroke.
- Mortality (death from any cause).
- Adverse effects of anticoagulation treatment (e.g. haemorrhage).
- Health-related quality of life.
- Anticoagulation management measures, including whether or not an anticoagulant is prescribed, frequency of INR testing, INR target, duration of anticoagulant prescription, duration of follow-up of patient.

Study types

- According to the accepted hierarchy of evidence, randomised controlled trials and meta-analyses from systematic reviews were searched initially as they provide the most authoritative forms of evidence. Data were not available from these types of study and so the search was broadened to include non-randomised controlled trials and cohort and case–control studies.

Exclusion criteria

- Publications in languages other than English.
- Thrombophilia tests conducted while patient was taking warfarin.
- Thrombosis in pregnancy or pregnancy complications associated with thrombophilia.
- Thrombosis related to temporary risk factors, including major surgery or oestrogen therapy.

- Case finding by testing individuals with a family history of thrombosis or thrombophilia but no personal experience of thrombosis.

Based on the above inclusion/exclusion criteria, study selection was made by one reviewer.

Data extraction, critical appraisal and data synthesis

It had been planned for one reviewer to extract data using a standardised form, with no blinding to authors or journal, for the purpose of providing a narrative account of trial quality for the reader. Planned quality assessment was with criteria based on those proposed by the NHS Centre for Reviews and Dissemination for randomised controlled trials, or using the Downs and Black checklist for randomised and non-randomised studies if other study types had been accepted into the review.

The lack of data made any kind of data synthesis impossible. It had been planned that prespecified outcomes would be tabulated and discussed within a descriptive synthesis, or, if statistical synthesis had been appropriate, meta-analysis would have been conducted using fixed- and random-effect models.

Results

Following removal of duplicates the search yielded 10,341 citations. Of these, 38 were database citations of ongoing studies, all of which were excluded by title.

Of the remaining 10,303 published articles 10,185 were rejected from titles and abstracts. A total of 118 articles were accepted by title search, many of which did not have abstracts available. Of these retrieved papers none met the inclusion criteria for intervention and comparator for the review; that is there were no comparisons available of patients tested for thrombophilia with patients whose risk assessment was based on a personal and family history of thrombosis. This is illustrated in the flow diagram (*Figure 1*).

Discussion

There were no studies available comparing patients tested for thrombophilia with patients whose risk assessment was based on a personal and family history of thrombosis. Thus, there were no studies meeting the inclusion criteria that could have provided data on any of the outcomes for which data were sought. Therefore clinical data for the cost-effectiveness model were not obtained from this clinical effectiveness systematic review. It may be that studies of this kind have not been conducted because thrombophilia testing is not routine after a first thrombotic event or because thrombophilia diagnosis does not alter anticoagulation management. A potential limitation of the search was that it excluded publications in languages other than English.

Methods for finding clinical data for the cost-effectiveness model

Given the lack of data from the systematic review of clinical effectiveness it was agreed with NICE that the cost-effectiveness model would consider the cost-effectiveness of thrombophilia testing in determining the duration of warfarin treatment following a VTE, and that data for the parameters to build the cost-effectiveness model would be derived not from a systematic literature review of all model parameters but from references identified

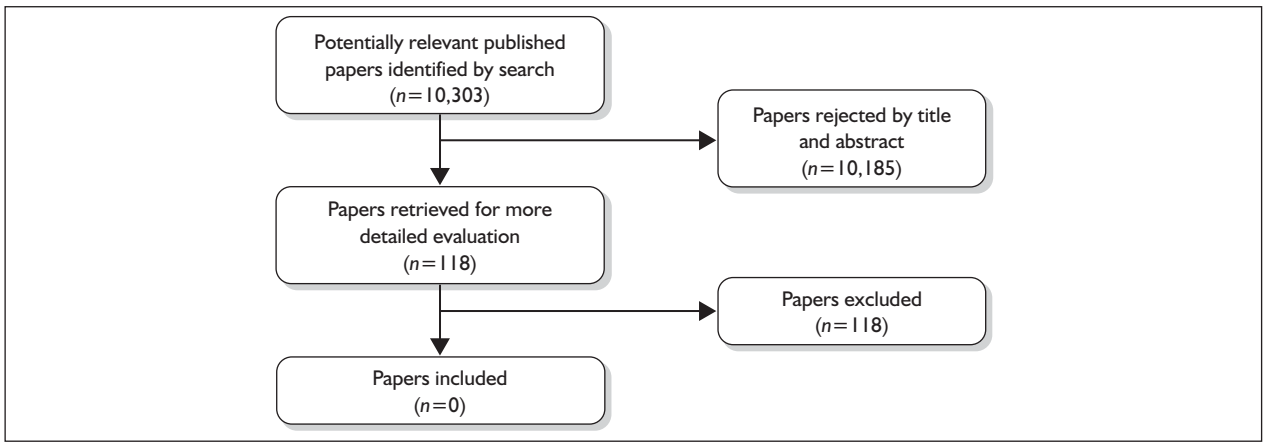

FIGURE 1 *Flow diagram of study selection.*

from the extensive literature searches conducted (see Methods for reviewing effectiveness) and recommendations from the clinical advisory group.

Clinical data for the cost-effectiveness model

Prevalence

The prevalence of thrombophilias in patients with venous thrombosis was taken from the prevalence in unselected patients, as data restricted to idiopathic thrombosis were not identified. The prevalence rates of thrombophilia in unselected VTE patients (idiopathic and non-idiopathic VTE) are shown in *Table 1*.

Recurrence rate following VTE in patients without thrombophilia

For patients without prothrombotic abnormalities (FVL, PTG20210A, AT, PC or PS deficiency, hyperhomocysteinaemia, hyperfibrinogenaemia, or elevated factor VIII, IX or XI), the recurrence rate following first idiopathic VTE was found to be 32.4 per 1000 patient-years [95% confidence interval (CI) 19.2–51.2 per 1000 patient-years] with a mean follow-up of 7.3 years.[41]

Relative risk of recurrence in thrombophilia

Following a venous thrombotic event, the risk of VTE recurrence after discontinuation of anticoagulants may be higher for patients with some types of thrombophilia than for those without. The relative risk (RR) of recurrence following idiopathic VTE was sought for each form of thrombophilia (*Table 2*) but was not available for all types of thrombophilia. The RR of recurrence following unselected (including idiopathic and non-idiopathic) VTE was sought to allow conversion of the RRs in unselected VTE to risks for idiopathic VTE (*Table 3*).

TABLE 2 *Relative risk of recurrence following idiopathic VTE for patients with thrombophilia compared with those without thrombophilia after discontinuation of anticoagulation*

Type of thrombophilia	Relative risk (95% CI)
Heterozygous for FVL	1.0 (0.5–2.0)[42]
Heterozygous for PTG20210A	1.48[43]
Heterozygous for both FVL and PTG20210A[a]	5.4 (2.0–14.1)[42]
Lupus anticoagulant	6.8 (1.5–31)[18]
Anticardiolipin antibody	2.3 (0.5–11)[18]
Hyperhomocysteinaemia	2.7[44]
Elevated factor VIII	5.43[b]/6.21[45c]
Elevated factor IX	3.06[46]
Elevated factor XI	2.1[46]

a With reference to heterozygous FVL.
b Chromogenic factor VIII.
c Clotting factor VIII.

TABLE 3 *Relative risk of recurrence following unselected VTE for patients with thrombophilia compared with those without thrombophilia after discontinuation of anticoagulation*

Type of thrombophilia	Relative risk (95% CI)
Heterozygous for FVL	1.46[47]
Homozygous for FVL[a]	2.26 (0.93–5.46)[48]
Heterozygous for PTG20210A	1.73[47]
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	1.44 (1.02–2.01)[49]

a With reference to non-carriers or heterozygous FVL.

In idiopathic DVT, a retrospective cohort study found no increased risk of recurrence for heterozygous FVL based on 43 patients with recurrence (RR 1.0; 95% CI 0.5–2.0).[42] A recent meta-analysis looking at heterozygous FVL pooled 10 studies of VTE recurrence following first episode of VTE in 3104 patients.[47] Patients were unselected apart from the exclusion of malignancy. The meta-analysis found an increased odds of recurrence for patients with FVL [odds ratio (OR) 1.41; 95% CI 1.14–1.75], which resulted in a RR of 1.46.[47] A prospective study found that the odds of recurrence in homozygous FVL, with reference to non-carriers or heterozygous FVL, was 4.1 (95% CI 0.97–15.5), which resulted in a RR of 2.3.[48]

In idiopathic DVT, a retrospective cohort study found that patients heterozygous for PTG20210A had no significant difference in hazard from patients without the abnormality, based on 41 patients with recurrence [hazard ratio (HR) 1.5; 95% CI 0.7–3.1; RR 1.5].[43] A recent meta-analysis looking at PTG20210A pooled nine studies of VTE recurrence following first episode of VTE in 2903 patients.[47] Patients were unselected apart from the exclusion of malignancy. The meta-analysis found an increased odds of recurrence for patients heterozygous for PTG20210A (OR 1.72; 95% CI 1.27–2.31).[47]

In idiopathic VTE, a retrospective cohort study found that patients heterozygous for both FVL and PTG20210A had an increased risk of recurrence (RR 5.4; 95% CI 2.0–14.1) with reference to patients heterozygous for FVL, based on 17 patients with recurrence.[42]

In unselected (including idiopathic and non-idiopathic) VTE, the presence of AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants was associated with a RR of recurrence of 1.44 (95% CI 1.02–2.01).[49] An anticoagulant study found that lupus anticoagulant was associated with an increased risk of recurrence following idiopathic VTE (RR 6.8; 95% CI 1.5–31), and that the RR for anticardiolipin antibodies did not reach significance (RR 2.3; 95% CI 0.5–11).[18]

In idiopathic VTE, hyperhomocysteinaemia had an increased risk of recurrence (RR 2.7; 95% CI 1.3–5.8).[44] Data were not found that indicated the RR of recurrence for patients with dysfibrinogenaemia. A prospective study found that elevated factor VIII was associated with a RR of VTE recurrence of 5.43 (chromogenic factor VIII) or 6.21 (clotting factor VIII) following first idiopathic VTE.[45] This study found lower rates of recurrence and lower RRs, 2.62 for chromogenic factor VIII and 1.72 for clotting factor VIII, for patients with non-idiopathic VTE.[45] A prospective study in idiopathic VTE found an increased risk of recurrence (RR 3.06; 95% CI 1.29–7.28) in patients with elevated factor IX.[46] This study also found a RR of recurrence of 2.14 (95% CI 1.01–4.58) in patients with elevated factor XI.[46]

There may be a higher risk of recurrence in men than in women.[50] This may be explained by women whose first VTE event was related to pregnancy or oestrogen therapy[51] and so would not apply in idiopathic thrombosis. However, this explanation is not supported in all studies,[52] and a higher risk of recurrence in men than women following idiopathic VTE has been found.[41]

Chapter 4

Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

A systematic review of the cost-effectiveness literature was undertaken using the search terms provided in Appendix 2. The search identified 2499 citations, of which 2492 were rejected from titles and abstracts. A total of seven articles were therefore retrieved; however, none was directly relevant to the question we were asked to evaluate. We have given the reasons why each paper was insufficient in Appendix 3.

Independent economic assessment

Methods

Although no literature was found concerning thrombophilia testing of patients with thrombosis and the resulting long-term anticoagulation management, enough data were found on the increased risk of VTE associated with each thrombophilia type, the prevalence of thrombophilia, the efficacy of warfarin, the risks of haemorrhage associated with warfarin, the outcomes of VTE and haemorrhages, and the costs and utilities to be able to provide cost-effectiveness analyses. No data have been found within a UK context on the benefits of treatment compared with the risks of warfarin coupled to costs and utility. Our analysis may provide clinicians with an evidence-based approach within which to evaluate the period of warfarin treatment to be provided.

Modelling structure

An individual patient-based discrete event simulation (DES) model was constructed in Simul8© (Simul8 Corporation). The rationale for this approach is that it provides more flexibility than a cohort model as the history of the patient can be incorporated. This allows risks that are dependent on time since an event, such as the risk of a haemorrhage being greater in the initial months of warfarin treatment or the risks of VTE being highest immediately after a VTE, to be considered. Thus, a more accurate determination of the costs and quality-adjusted life-years (QALYs) associated with each treatment option is possible. Additionally, the cohort approach relies on an arbitrary definition of cycle duration, which is not needed within the DES model. Note that the only intervention evaluated to prevent recurrence of a VTE is warfarin.

The model simulates the experiences of hypothetical patients who have just suffered an index DVT or index non-fatal PE. The events that can occur are an additional VTE, a warfarin-induced haemorrhage or death due to a non-VTE-related cause (which can be reached from any non-absorbing state). Each outcome is associated with a cost and utility impact that, because of the individual patient modelling structure, can be incorporated into future time periods. At the resolution of a non-fatal event the time to the next event is simulated. This continues until all patients are in an absorbing state (fatal PE, fatal haemorrhage or death through non-VTE-related causes). A representation of the model is given in *Figure 2*.

In accordance with clinical advice, lifelong warfarin therapy would be prescribed following a subsequent VTE event. If a patient sustained a haemorrhage, warfarin treatment would be discontinued but would be restarted following a subsequent VTE if the patient had not bled intracranially.

Because of the differential rate of recurrence between men and women, the differential ratio of PE and DVT in those whose initial VTE was a DVT and in those in whom it was a PE, and the increased rates of haemorrhage as a patient becomes older, a large number of analyses were conducted.

Population of the model

The literature retrieved from the cost-effectiveness review was used to identify sources for the economic model that were not covered within the review of clinical effectiveness or the increased risk of recurrence associated with thrombophilia. The source used for populating the parameters within the model and the rationale for using this value are provided in the accompanying text.

Population start age and life expectancy

Hypothetical cohorts of men aged 30, 40, 50, 60 and 70 years were simulated. Life expectancies

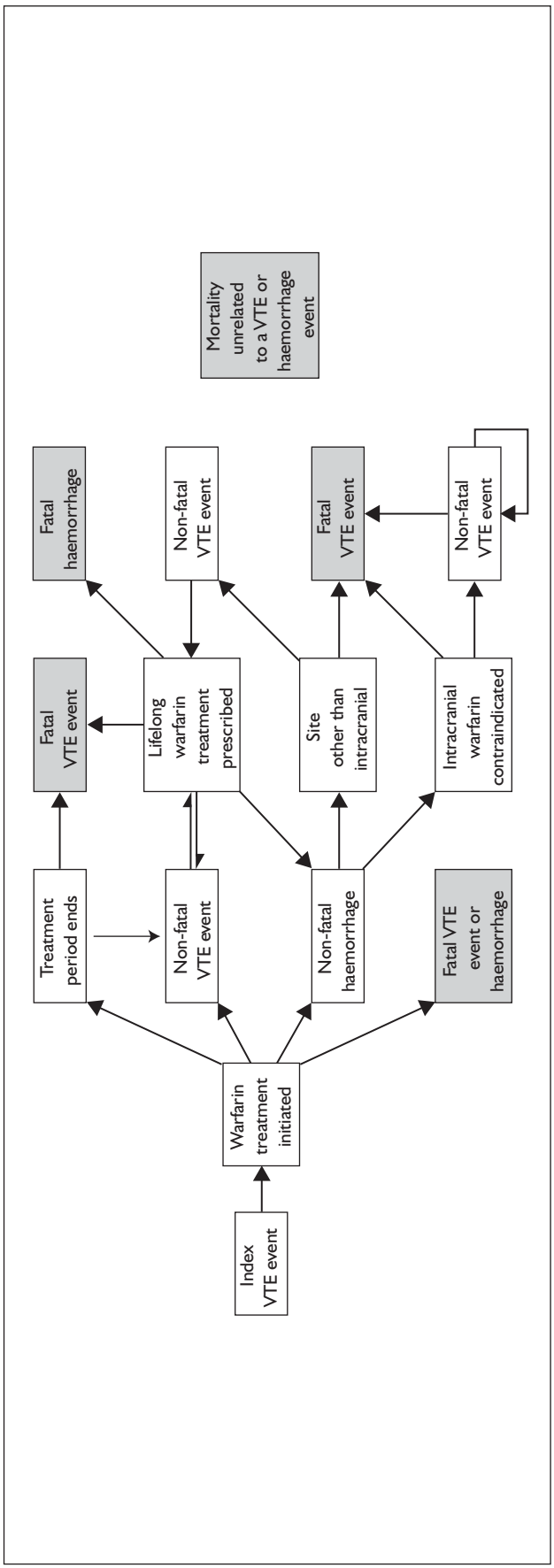

FIGURE 2 *A flow diagram representation of the mathematical model. Shaded cells represent absorbing states. The state of mortality unrelated to a VTE or haemorrhage event can be reached from any non-absorbing state. The arrows are omitted for clarity.*

have been obtained from interim life tables published by the Office for National Statistics.[53] We have assumed that a previous DVT or non-fatal PE will not affect life expectancy except through VTE or a haemorrhage, events that are explicitly modelled. The life expectancy and starting utility associated with age are given in *Table 4*. The underlying utility for patients aged 30 and 40 years is not provided and has been assumed to increase in a fairly linear manner with respect to the values for 50 and 70 years.

Risk of recurrent VTE

To accurately assess the implications of increased risks associated with thrombophilia, the recurrence rates of VTE associated with patients without thrombophilia must be known. The most appropriate data found come from Christiansen *et al.*,[41] who followed up an untreated cohort of patients without FVL mutation, PTG20210A, anticoagulation deficiency, elevated levels of factors VII, IX and XI, hyperfibrinogenaemia or hyperhomocysteinaemia. The Christiansen *et al.* data may include patients with lupus anticoagulant and anticardiolipin antibodies and could thus overestimate the risk for non-thrombophilic patients. The rate of recurrence of VTE for these patients was 3.24 per 100 patient-years, which we have assumed to be applicable regardless of whether the patient had previously sustained a DVT or a PE. Although this paper discusses correcting results for the age of the patient, no data were presented that showed how rates change according to age of the patient, and we have assumed that the probability of recurrence is independent of age, although data[7] show that the risk of an initial VTE increases as a person ages. The likely effect of an increased risk of recurrence as a patient ages has been included in the discussion.

It is reported that men have an increased HR of 2.7 (95% CI 1.8–4.2).[41] This value has been combined with the percentage of males within the study to calculate that the risk of recurrence for males would be 5.1 per 100 patient-years, with the corresponding value for females 1.9 per 100 patient-years.

The data from Christiansen *et al.*[41] show a non-significant decrease in risk with time since VTE, which may then increase beyond 6 years of follow-up. Smaller studies by Prins *et al.*,[55] Kearon *et al.*[18] and Simioni *et al.*[56] all suggest that the risk might be increased in the initial 3 months following a short course of warfarin treatment. The data available are insufficient and too heterogeneous to conclusively determine whether the risks are higher in this period, and we do not dismiss the notion that 6 months of warfarin treatment may be as appropriate as 3 months of treatment. This decision is, however, largely independent of any known thrombophilic status and has been excluded from our analyses. We have assumed that 3 months of treatment is the standard course of treatment but note that the decision on whether to provide lifelong treatment or not will be equally valid if the initial course of treatment is for 6 months.

Data were not found related to the increased probability of subsequent VTE in the high-risk period immediately following a VTE in patients who did not receive warfarin, either because the VTE was undetected or because of a previous intracranial haemorrhage. In the absence of better data we have assumed that for a patient who does not receive warfarin treatment following a VTE there is a 20% probability of a recurrent VTE in the next 6 months, which is independent of gender. This risk is double that which has been estimated to occur in patients who have taken a course of warfarin following a VTE,[57] with the magnitude of the increase tempered in the expectation that the VTEs that remain undetected will be less severe and less likely to recur. This value is altered in the sensitivity analyses. Beyond this time period the risks of recurrent VTE in patients not receiving

TABLE 4 *The life expectancy and starting utility associated with age*

Age (years)	Life expectancy (years)[53]	Starting utility[54]
30	47.75	0.950[a]
40	38.24	0.900[a]
50	29.04	0.850
60	20.49	0.829
70	13.09	0.727

a Author-estimated values.

warfarin taken from Christiansen *et al*. have been used.[41]

The increased risk of VTE due to thrombophilia

Some forms of thrombophilia may increase the risk of recurrent VTE, with the RR being dependent upon the cause of the condition. Because of the scarcity of data received regarding the marginal costs of individual tests, we have assumed the cost characteristics of the thrombophilia tests as detailed in Wu *et al.*,[30] i.e. tests for FVL, PTG20210A, AT deficiency, PC deficiency, PS deficiency, lupus anticoagulants and anticardiolipin antibodies. Thus, only these types of thrombophilia are included within our modelling. Ideally we require data on the increased risks of recurrent idiopathic VTE, and these data, where available, are summarised in *Table 5*; however, where data are available only for unselected (including idiopathic and non-idiopathic) VTE, these are given in *Table 6*. These tables also provide estimates of the prevalence of the thrombophilia in patients with VTE. It is assumed that these prevalences are independent of age, sex and previous VTE event; however, no data were found to support or refute this assumption.

We have to convert the RR in unselected VTE to risks for idiopathic VTE. To do this we need to use a thrombophilia that has data for both idiopathic and unselected VTE to estimate a relationship between the two groups. These data are available for heterozygous FVL, which has a RR of 1.0 in idiopathic and 1.46 in unselected VTE. These values are 1.48 and 1.73, respectively, for heterozygous PTG20210A. As unselected VTE includes provoked VTEs, such as those that occur in surgical patients, which are less likely to spontaneously recur, the RRs are higher in patients with unselected VTE than in those with idiopathic VTE. We have arbitrarily assumed that the RR of 2.6 for unselected VTE in patients homozygous for FVL compared with non-carriers or patients heterozygous for FVL would be reduced to 2.0 for idiopathic VTE in patients homozygous for FVL compared with non-carriers or patients heterozygous for FVL. Similarly we have assumed that the RR of idiopathic VTE for patients with AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants is 1.25, reduced from 1.44 when compared with unselected VTE. The risks for patients with AT deficiency, PC deficiency or PS deficiency may be overestimated if the lupus-like anticoagulants have a similar RR to lupus anticoagulant, and the RR may indeed be 1. We have modelled using the value of 1.25 but have commented on the difference in treatment between patients with AT deficiency, PC deficiency or PS deficiency and those who are FVL heterozygous, which has an estimated RR of 1.

Efficacy of warfarin treatment in preventing VTE

Warfarin reduces the risk of subsequent VTE. We do not make comment on the quantity of warfarin

TABLE 5 *The relative risk of recurrence following idiopathic VTE for thrombophilic people compared with people without thrombophilia*

Type of thrombophilia	Relative risk (95% CI)	Prevalence (%)
Heterozygous for FVL	1.0 (0.5–2.0)[42]	10–50[8]
Heterozygous for PTG20210A	1.48 (0.84–2.62)[47]	5–18[9]
Heterozygous for both FVL and PTG20210A[a]	5.4 (2.0–14.1)[42]	3.45[8,9]
Lupus anticoagulant	6.8 (1.5–31)[18]	3[18]
Anticardiolipin antibody	2.3 (0.5–11)[18]	3[18]

a With reference to heterozygous FVL.

TABLE 6 *The relative risk of unselected VTE for thrombophilic people compared with people without thrombophilia*

Type of thrombophilia	Relative risk (95% CI)	Prevalence (%)
Homozygous for FVL[a]	2.26 (0.93–5.46)[48]	1.5[9]
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	1.44 (1.02–2.01)[49]	13[49]

a With reference to non-carriers or heterozygous FVL.

prescribed to a patient and have assumed that this decision is made by the clinician. The exact relative risk reduction (RRR) in recurrent VTE is not known, with estimates ranging from 90% to 95%. These are given in *Table 7*, with a decision made to use 95% as our mean estimate. It is assumed that this RRR is applicable throughout the duration of warfarin treatment and that this effect is instantly removed following the cessation of warfarin treatment.

The outcomes following a recurrent VTE

The outcome following a VTE is dependent on whether or not the person receives warfarin treatment on the detection of the VTE.[59] Because of scarce data we have assumed that the effect of warfarin on the VTE is independent of whether the patient has a course of warfarin prescribed following the VTE or remains on lifelong warfarin. A person with a VTE will not receive warfarin if the VTE remains undetected or if there has been a history of intracranial haemorrhage. We have assumed that the sensitivity of clinical tests in detecting a VTE is 95% as this value is representative of current detection methods for DVT and it is assumed that patients with a previous VTE will receive more sensitive tests before a decision to prescribe lifelong warfarin is taken.[60] We have assumed that this value is also applicable for the detection of PE. It was further assumed that all patients with a non-fatal VTE will see a clinician and be referred for testing.

The outcome of a VTE is additionally dependent on whether the previous VTE manifested in a DVT or a PE.[61] Among patients with a previous PE, 81.1% of VTE resulted in PE, whereas for patients with a previous DVT 78.6% of VTE resulted in DVT. The fatality rates were also markedly different, with 26.4% of VTE resulting in death after a previous PE, compared with 7.6% after a DVT.[61]

The probability of a fatal, or non-fatal, PE following a recurrent VTE for a patient on warfarin after a VTE has been taken from Douketis *et al.*[61] Following a subsequent DVT there were 19 fatalities in 250 VTE events (7.6%), and there were 19 fatalities in 72 events (26.4%) following a subsequent PE. The probability of a VTE that is a DVT resulting in PTS for patients receiving warfarin has been taken from Goodacre *et al.*[59]

Data on patients with a VTE who do not receive warfarin are by definition scarce, as these are patients in whom the VTE has been unidentified or who have sustained an intracranial haemorrhage. The probability of a fatal, or non-fatal, PE or PTS in patients who remain untreated following a DVT has been taken from Goodacre *et al*.[59] Data on patients with a PE who do not receive warfarin treatment were not found and had to be estimated by the authors. Data from Goodacre *et al.*[59] showed that the probability of a VTE progressing to a PE was 10 percentage points higher in those who do not receive warfarin treatment (68.6% DVT and 31.4% PE) than in those who receive warfarin treatment (78.6% DVT and 21.4% PE). We have assumed that this increase in PE without treatment is also applicable following a PE. We further assume that two-thirds of PEs are fatal compared with the one-third observed in treated patients. These assumptions are tested in sensitivity analyses.

For all outcomes following a VTE it is assumed that any cost and disutility associated with the event occur immediately.

These assumptions result in the risks provided in *Tables 8* and *9*.

Risk of haemorrhage due to warfarin use

The rate of haemorrhage is greater in the initial months of anticoagulation therapy,[62,63] which may be due to factors that predispose the patient to haemorrhage,[63] a patient initially being prescribed too great a dose of anticoagulant whilst the optimal level is determined,[63] or co-prescribed medication.[64] During the initiation period the INR of the patient is closely monitored,[64] resulting in

TABLE 7 *The efficacy of warfarin in preventing VTE*

Publication	RRR of warfarin in preventing VTE (95% CI or reported range)
Prins *et al.*[55]	0.900
Marchetti *et al.*[58]	0.950 (0.65–1.00)
Kearon *et al.*[18]	0.950 (0.63–0.99)

TABLE 8 *The outcome of a recurrent VTE in patients who have had a previous DVT but not a previous PE related to whether the person receives warfarin treatment*

	Treated (%)	Untreated (%)
Fatal PE	7.60	20.93
Non-fatal PE	13.80	10.47
PTS	4.22	29.21
Resolved VTE	74.38	39.39

For sources see accompanying text.

TABLE 9 *The outcome of a recurrent VTE in patients who have had a previous PE related to whether the person receives warfarin treatment*

	Treated (%)	Untreated (%)
Fatal PE	26.40	60.73
Non-fatal PE	54.70	30.37
PTS	1.01	3.31
Resolved VTE	17.89	5.59

For sources see accompanying text.

higher resource use. The rates of haemorrhage adopted in the model within the initial 3-month period have been calculated from Linkins *et al.*[62] and are presented in *Table 10*. It is assumed that there is no risk of haemorrhage following the withdrawal of warfarin therapy.

For longer-term risks of haemorrhage associated with warfarin use we have used data from Prins *et al*.[55] as this study has related the risks of haemorrhage to age, with the rates increasing as a patient ages. The risks used beyond the initial 3-month period by age are presented in *Table 11*. The proportion of haemorrhages that are fatal, non-fatal and intracranial, and non-fatal and non-intracranial have been set to the proportions of long-term events reported in Linkins *et al.*[62]

Warfarin treatment is withdrawn from any patient experiencing a haemorrhage requiring medical intervention. On clinical advice we have assumed that, when warfarin has been discontinued because of a haemorrhage and the patient experiences a subsequent VTE, warfarin would be reinstated provided that the haemorrhage was not intracranial.

Sensitivity and specificity of thrombophilia testing

Auerbach *et al.*[65] assumed that the sensitivity and specificity of thrombophilia testing were 99%, figures that are similar to those provided by a manufacturer for the accuracy of a FVL test (Roche Diagnostic, 30 January 2007, personal communication). To analyse specificity the following assumptions were made: that 50% of the idiopathic VTE population were non-thrombophilic (as may be the case from *Tables 10* and *11*); that, of those misdiagnosed, the proportion of false positives by thrombophilia type would be equal to their corresponding proportion in a population with an idiopathic VTE. Results are shown assuming 100% sensitivity and specificity and with the base-case values of 99% so that the magnitude of the change in results when sensitivity and specificity are changed can be gauged. Such high values are likely in DNA-based tests such as those for FVL or PTG20210A[66] but are likely to be overestimates for tests for other types of thrombophilia; however, values were not found for individual thrombophilia types. It is noted that, where thrombophilia testing has been suggested to be cost-effective, these results are driven by those patients with lupus anticoagulant or who are heterozygous for both FVL and PTG20210A. Although the estimate of 99% for both sensitivity and specificity is likely to be relatively accurate for FVL and PTG20210A, if the true sensitivity and specificity of the tests for detecting patients with lupus anticoagulant were markedly lower than 99%, the cost-effectiveness ratios for thrombophilia testing produced in this report will be favourable to thrombophilia testing.

Costs of VTE-related events

Costs have been extracted from standard literature sources[67–69] where available. When these costs are not readily available for a specific event we have used data from the literature updating to 2005–6 prices using the inflation indices in Curtis and Netten.[68] The summarised costs used in the model are presented in *Table 12*, with detailed calculations given in Appendix 5.

Utility

The utility multipliers for the VTE-related health states are presented in *Table 13*.

Utility scores are combined multiplicatively within the model so that a patient receiving warfarin after sustaining a non-fatal PE would have a utility

TABLE 10 *The rates of haemorrhage associated with the initial 3 months of warfarin treatment*[62]

Haemorrhage location/type	Absolute rate in the initial 3 months of treatment with warfarin
Fatal haemorrhage	0.0034
Non-fatal intracranial haemorrhage	0.0009
Non-fatal non-intracranial haemorrhage	0.0175

TABLE 11 *The annual rates of haemorrhage associated with warfarin treatment after the initial 3-month period*

Haemorrhage location/type	Patient age (years)				
	Less than 40	40–49	50–59	60–69	Over 69
All haemorrhages	0.0060	0.0100	0.0150	0.0220	0.0320
Fatal haemorrhage	0.0014	0.0009	0.0014	0.0051	0.0074
Non-fatal intracranial haemorrhage	0.0008	0.0011	0.0017	0.0028	0.0041
Non-fatal non-intracranial haemorrhage	0.0038	0.0080	0.0119	0.0141	0.0205

For sources see accompanying text.

TABLE 12 *Cost of VTE-related events (all costs are in 2005–6 prices)*

Description of variable	Mean value (£)	Source
Treatment of a resolving deep vein thrombosis	183.46	See Appendix 5
Warfarin treatment		
Cost of warfarin, first quarter	538.48	See Appendix 5
Cost of warfarin, subsequent quarters	211.38	See Appendix 5
Cost of treating post-thrombotic syndrome	3284.70	See Appendix 5
Cost of treating a fatal pulmonary embolism	1803.86	NHS reference costs[69]
Cost of treating a non-fatal pulmonary embolism	1390.54	NHS reference costs[69]
Cost of treating a fatal haemorrhage	6792.65	Sandercock *et al.*[70]
Cost of treating a non-fatal intracranial haemorrhage		
Initial one-off cost	5774.78	See Appendix 5
Ongoing cost per year	4798.19	See Appendix 5
Cost of treating a non-fatal non-intracranial haemorrhage	736.93	NHS reference costs[69]
Cost of thrombophilia test that detects FVL, PTG20210A, AT deficiency, PC deficiency, PS deficiency, lupus anticoagulants and anticardiolipin antibodies	70.60	Wu *et al.*[30]

TABLE 13 *Utility multipliers for VTE-related heath states*

Health state	Utility multiplier	Chosen sources
Post DVT receiving warfarin	0.987	Gage *et al.*[71]
Post DVT not receiving warfarin	1.000	Assumption
PTS	0.977	O'Meara *et al.*[72]
Non-fatal PE	0.940	Goodacre *et al.*[59]
Non-fatal intracranial haemorrhage	0.290	O'Meara *et al.*[72]
Non-fatal non-intracranial haemorrhage	0.997	Goodacre *et al.*[59]

multiplier of 0.931 (0.990×0.940). This value is then multiplied by the average utility for patients at the specified age as reported by Kind *et al.*[54] and presented in *Table 4*.

The utility for a patient who has recovered from a DVT without any adverse effect and is no longer receiving warfarin could not be determined from the literature. The assumption made is that this patient has recovered to the utility associated with people of that age within the general population as reported by Kind *et al.*[54]

Another reported utility multiplier for PTS was 0.995.[58] However, we chose to use the value of O'Meara *et al*.[72] because it was the value assumed to be most appropriate by the authors in the recent review of diagnostic tests for detecting DVT[59] and because the effect assumed in the former paper was so negligible.

Discount rates

The discount rates for both the costs and QALYs were set at 3.5% per annum in accordance with published guidelines.[73]

Results

Methodology for calculating cost-effectiveness ratios

In evaluating the cost-effectiveness of introducing any testing policy the resultant outcome is that either all patients or no patients receive the test. It needs to be emphasised that, even in a situation in which testing is not cost-effective, this may not be the optimal decision on an individual basis, as there may be patients who would have received different care if their thrombophilic status were able to be determined without cost. However, once all of the costs of tests to find such patients are incorporated the decision will be cost-effective from a societal perspective.

To estimate the cost-effectiveness of any screening programme the initial step is to calculate the increased costs and QALYs associated with any change in treatment of individuals that occurs as a result of information obtained from the screening test, whilst excluding the costs of the test. As an example, the cost per QALY of extending the warfarin treatment period to 10 years, 20 years or lifelong is calculated for women aged 50 years with a previous DVT who are known to have lupus anticoagulant. These costs per QALY are provided and the most cost-effective duration highlighted in the results. This procedure will be repeated for each classification of thrombophilia investigated (FVL, PTG20210A, AT deficiency, PC deficiency, PS deficiency, lupus anticoagulants and anticardiolipin antibodies), allowing the most cost-effective duration of warfarin treatment (3 months, 10 years, 20 years or lifelong) to be determined. The incremental costs and QALYs of moving to the most cost-effective period of warfarin treatment are calculated for each thrombophilia. These are summated to find the total costs incurred and total QALYs accrued associated with a change in treatment. The total costs and total QALYs gained associated with changes in treatment duration must be cost-effective for the following logic: changes in the recommended treatment period are by definition cost-effective as otherwise the patient would remain on the standard duration of warfarin, which affects neither costs nor QALYs. The addition of costs and QALYs that are all associated with cost-effectiveness can produce only an overall cost-effectiveness ratio.

However, the costs of identification need to be incorporated because, using the same example, thrombophilia testing must be undertaken in all women aged 50 years with a previous DVT to identify those in whom changes in treatment duration are cost-effective. The estimated costs of performing the tests in all women aged 50 with a previous DVT, with a repeat test if a thrombophilia that could be treated cost-effectively is found, as opposed to all thrombophilic patients, as reported by Wu *et al.*,[30] would then be added to the summated costs incurred through changes in warfarin treatment period. This total cost is then divided by the total QALYs accrued through changes in warfarin treatment period to find the cost per QALY of undertaking thrombophilia testing in females aged 50 with a previous DVT. This is not necessarily cost-effective because when few patients may benefit from changes in treatment the relative costs of undertaking thrombophilia testing may result in a high cost per QALY. This calculation in performed for both sexes at initial VTE ages of 30, 40, 50, 60 and 70 years and for both those whose initial VTE was a DVT and those whose initial VTE was a PE.

To undertake these analyses, the maximum acceptable incremental cost-effectiveness ratio (MAICER) must be estimated so that it can be ascertained for which thrombophilia changes in the warfarin treatment period are cost-effective. For example, if the cost per QALY of moving to a warfarin treatment period of 10 years was £25,000 (costing £2500 and accruing 0.1 QALYs) and the MAICER was £30,000, then changing to a 10-year treatment period would be cost-effective, allowing

some benefits to be gained from the thrombophilia test conducted on this individual. If, however, the MAICER was £20,000, the patient would remain on the standard 3 months of warfarin and the money spent on conducting this test would not influence clinical management and no benefits would be gained from conducting the test. Thus, calculating the cost-effectiveness of a screening programme is predicated on assuming a given MAICER.

In accordance with NICE guidelines[73] we have assumed primarily that the MAICER is £20,000 per QALY. However, sensitivity analyses have been conducted showing the results that would be achieved if it was viewed that there were additional factors associated with thrombophilia testing that would warrant an increase in the MAICER to £30,000.

Deterministic results using 20,000 hypothetical patients and the mid-point estimate for each parameter were calculated for all combinations of age (30, 40, 50, 60 or 70 years), sex (male or female), previous VTE (DVT or PE) and duration of warfarin treatment (3 months, 10 years, 20 years or lifetime). These results are presented in the next section.

When probabilistic sensitivity analyses (PSAs) were undertaken, it became evident that the deterministic results were systematically smaller (i.e. more beneficial to testing) than those when PSA were conducted. This was primarily due to parameters such as the increased risk of VTE associated with thrombophilia type, the efficacy of warfarin at reducing VTE, the underlying risk of recurrent VTE, the outcome following a VTE and a number of disutilities contained within the model being non-normally distributed. To reduce computational time it was decided that PSA would be conducted only on those combinations for which the mean costs per QALY from the deterministic analyses were below £20,000.

Deterministic analyses conducted using the mean value for each parameter

For brevity this scenario will henceforth be termed a 'mid-point analysis'. The results from the mid-point analyses assuming a MAICER of £20,000 are summarised in *Tables 14–17*. The detailed analyses that are combined to form these tables are provided in Appendix 4. Additional data showing the results from the mid-point analyses assuming a MAICER of £30,000 are summarised in *Tables 18–21*.

These tables include the cost per QALY, with thrombophilia testing assumed to be 99% sensitive and specific. As few data were found on the costs of undertaking a thrombophilia test, apart from those reported in Wu *et al.*,[30] analyses were undertaken to calculate the price of thrombophilia testing at which the cost per QALY rose above a specific MAICER. This allows some indication of the likely cost per QALY if new data on the costs of undertaking thrombophilia testing become available.

We provide an example to aid understanding of the data, which is summarised in *Table 14*. This example looks at men with a previous DVT and assumes a threshold of £20,000 per QALY. For such patients the mid-point analyses estimate that it is cost-effective to undertake thrombophilia testing at all ages as the costs per QALY are below £20,000 at all ages. The mid-point analyses estimate that the following durations of warfarin treatment are the most cost-effective for patients aged 30–39 years: patients with all types of thrombophilia should receive more than 3 months of treatment; patients who have lupus anticoagulant or who are heterozygous for both FVL and PTG20210A should receive lifelong treatment; patients with anticardiolipin antibodies, who are homozygous for FVL or who are heterozygous for PTG20210A should receive 20 years of treatment; patients who are deficient in either AT, PC or PS or who are heterozygous for FVL should receive 10 years of treatment. The mid-point analyses estimate that, for patients aged 70 years or over, extended duration of warfarin treatment should be provided only if a patient is shown to have lupus anticoagulant or is heterozygous for both FVL and PTG20210A, in which case the treatment period should be 10 years.

Note that we have assumed that the standard treatment is 3 months of warfarin, which was used to determine the cost-effectiveness of thrombophilia testing. If the standard management is significantly different, for example lifelong treatment being routine for all patients with an initial PE, then the results could also be significantly different, as thrombophilia testing would not be recommended in *Table 16* for men aged 30–39 years as the management of the patient would not alter. We did not investigate this because alternative management strategies, if they exist, were not sufficiently detailed and we assumed that clinicians would tend to be risk averse when prescribing medications with potentially fatal side effects.

TABLE 14 *Cost per QALY of thrombophilia testing for men with a previous idiopathic DVT assuming that treatment is provided when the cost per QALY is below £20,000*

Type of thrombophilia	**Patient age (years)**				
	30	**40**	**50**	**60**	**70**
Lupus anticoagulant					
FVL and PTG20210A (both heterozygous)					
Anticardiolipin antibody					
FVL homozygous					
PTG20210A heterozygous					
Deficiency in either AT, PC or PS					
FVL heterozygous					
Cost per QALY of thrombophilia testing[a]	£10,740	£9894	£9194	£10,239	£16,641
Cost per QALY of thrombophilia testing[b]	£10,804	£10,135	£9,502	£10,665	£17,377
Cost of thrombophilia testing per individual at which the cost per QALY becomes > £20,000[b]	£1700	£950	£600	£350	£150

a Assuming 100% sensitivity and specificity.
b Assuming 99% sensitivity and specificity.

TABLE 15 *Cost per QALY of thrombophilia testing for women with a previous idiopathic DVT assuming that treatment is provided when the cost per QALY is below £20,000*

Type of thrombophilia	Patient age (years)					Key
	30	40	50	60	70	
Lupus anticoagulant						Lifelong treatment
FVL and PTG20210A (both heterozygous)						20 years' treatment
Anticardiolipin antibody						
FVL homozygous						10 years' treatment
PTG20210A heterozygous						
Deficiency in either AT, PC or PS						3 months' treatment
FVL heterozygous						
Cost per QALY of thrombophilia testing[a]	£9329	£14,384	£20,746	N/A	N/A	
Cost per QALY of thrombophilia testing[b]	£9656	£14,986	£21,755	N/A	N/A	
Cost of thrombophilia testing per individual at which the cost per QALY becomes > £20,000[b]	£500	£250	£50	N/A	N/A	

a Assuming 100% sensitivity and specificity.
b Assuming 99% sensitivity and specificity.

TABLE 16 *Cost per QALY of thrombophilia testing for men with a previous idiopathic PE assuming that treatment is provided when the cost per QALY is below £20,000*

Type of thrombophilia	Patient age (years)				
	30	40	50	60	70
Lupus anticoagulant					
FVL and PTG20210A (both heterozygous)					
Anticardiolipin antibody					
FVL homozygous					
PTG20210A heterozygous					
Deficiency in either AT, PC or PS					
FVL heterozygous					
Cost per QALY of thrombophilia testing[a]	£5682	£6137	£7620	£9494	£9635
Cost per QALY of thrombophilia testing[b]	£5683	£6158	£7627	£9516	£9877
Cost of thrombophilia testing per individual at which the cost per QALY becomes > £20,000[b]	£11,200	£7850	£4950	£2250	£950

a Assuming 100% sensitivity and specificity.
b Assuming 99% sensitivity and specificity.

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TABLE 17 *Cost per QALY of thrombophilia testing for women with a previous idiopathic PE assuming that treatment is provided when the cost per QALY is below £20,000*

Type of thrombophilia	Patient age (years) 30	40	50	60	70
Lupus anticoagulant					
FVL and PTG20210A (both heterozygous)					
Anticardiolipin antibody					
FVL homozygous					
PTG20210A heterozygous					
Deficiency in either AT, PC or PS					
FVL heterozygous					
Cost per QALY of thrombophilia testing[a]	£10,366	£9590	£7447	£8544	£10,782
Cost per QALY of thrombophilia testing[b]	£10,415	£9766	£7663	£8783	£11,147
Cost of thrombophilia testing per individual at which the cost per QALY becomes > £20,000[b]	£2650	£1950	£1400	£850	£400

a Assuming 100% sensitivity and specificity.
b Assuming 99% sensitivity and specificity.

TABLE 18 *Cost per QALY of thrombophilia testing for men with a previous idiopathic DVT assuming that treatment is provided when the cost per QALY is below £30,000*

Type of thrombophilia	Patient age (years)				
	30	40	50	60	70
Lupus anticoagulant					
FVL and PTG20210A (both heterozygous)					
Anticardiolipin antibody					
FVL homozygous					
PTG20210A heterozygous					
Deficiency in either AT, PC or PS					
FVL heterozygous					
Cost per QALY of thrombophilia testing[a]	£11,411	£12,016	£14,307	£11,802	£16,641
Cost per QALY of thrombophilia testing[b]	£11,487	£12,326	£14,842	£12,330	£17,371
Cost of thrombophilia testing per individual at which the cost per QALY becomes > £30,000[b]	£3500	£1800	£950	£650	£250

a Assuming 100% sensitivity and specificity.
b Assuming 99% sensitivity and specificity.

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TABLE 19 *Cost per QALY of thrombophilia testing for women with a previous idiopathic DVT assuming that treatment is provided when the cost per QALY is below £30,000*

Type of thrombophilia	Patient age (years)					Key
	30	40	50	60	70	
Lupus anticoagulant						Lifelong treatment
FVL and PTG20210A (both heterozygous)						20 years' treatment
Anticardiolipin antibody						
FVL homozygous						10 years' treatment
PTG20210A heterozygous						
Deficiency in either AT, PC or PS						3 months' treatment
FVL heterozygous						
Cost per QALY of thrombophilia testing[a]	£12,755	£14,384	£20,884	£41,321	N/A	
Cost per QALY of thrombophilia testing[b]	£13,066	£14,839	£21,687	£42,680	N/A	
Cost of thrombophilia testing per individual at which the cost per QALY becomes > £30,000[b]	£1000	£550	£250	£50	N/A	

a Assuming 100% sensitivity and specificity.
b Assuming 99% sensitivity and specificity.

TABLE 20 *Cost per QALY of thrombophilia testing for men with a previous idiopathic PE assuming that treatment is provided when the cost per QALY is below £30,000*

Type of thrombophilia	Patient age (years)				
	30	40	50	60	70
Lupus anticoagulant					
FVL and PTG20210A (both heterozygous)					
Anticardiolipin antibody					
FVL homozygous					
PTG20210A heterozygous					
Deficiency in either AT, PC or PS					
FVL heterozygous					
Cost per QALY of thrombophilia testing[a]	£5682	£6935	£7620	£10,066	£13,030
Cost per QALY of thrombophilia testing[b]	£5683	£6935	£7627	£10,105	£13,310
Cost of thrombophilia testing per individual at which the cost per QALY becomes > £30,000[b]	£18,850	£13,450	£8900	£4450	£1750

a Assuming 100% sensitivity and specificity.
b Assuming 99% sensitivity and specificity.

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TABLE 21 *Cost per QALY of thrombophilia testing for women with a previous idiopathic PE assuming that treatment is provided when the cost per QALY is below £30,000*

Type of thrombophilia	Patient age (years) 30	40	50	60	70
Lupus anticoagulant					
FVL and PTG20210A (both heterozygous)					
Anticardiolipin antibody					
FVL homozygous					
PTG20210A heterozygous					
Deficiency in either AT, PC or PS					
FVL heterozygous					
Cost per QALY of thrombophilia testing[a]	£11,143	£13,974	£10,817	£9247	£10,782
Cost per QALY of thrombophilia testing[b]	£11,200	£14,058	£11,073	£9482	£11,124
Cost of thrombophilia testing per individual at which the cost per QALY becomes > £30,000[b]	£5450	£3250	£2350	£1500	£700

a Assuming 100% sensitivity and specificity.
b Assuming 99% sensitivity and specificity.

Additionally, we have assumed that all tests will be run as a complete battery for logistical reasons. If it is possible to easily omit tests from the battery then *Tables 14–21* provide information on which tests can be excluded. For example, in *Table 14* it is seen that management for men aged 70 years or over would be changed only in patients who have lupus anticoagulant or who are heterozygous for both FVL and PTG20210A. Tests that do not report on these characteristics could be omitted to reduce expenditure.

Furthermore, some thrombophilia types have not been included in these analyses, for example elevation of factor VIII, because of uncertainties in the marginal costs of performing tests for them. This thrombophilia has an increased risk of recurrence that is very similar to that of being heterozygous for both FVL and PTG20210A. If a test for factor VIII was inexpensive, then this could be added to the results and the management strategy approximated by the results for being heterozygous for both FVL and PTG20210A. Similar approximations can be made for all of the remaining omitted thrombophilia types.

Note that it is uncommon for the treatment duration for patients with AT deficiency, PC deficiency or PS deficiency to be different from that for patients who are heterozygous for FVL. Thus, should the RR of recurrence for the former group of patients have been overestimated, this rarely affects the management strategy.

Univariate sensitivity analyses

In general, univariate sensitivity analyses are of limited value as they fail to account for interactions between variables within the model and have limited interpretability. As such, extensive univariate sensitivity analyses were not undertaken. The results from PSAs, described in the following section, are preferable as, by simultaneously varying the values for all uncertain parameters, any non-linearity within the model will be incorporated into the estimation of mean cost per QALY.[74]

Some parameters, however, do not lend themselves to PSA as they are characteristics of the starting population and therefore two univariate sensitivity analyses were conducted: the first regarding the number of patients with a previous DVT who had sustained PTS; the second on the distribution of outcomes for patients who remain untreated following a VTE. When analyses were conducted assuming that all patients with a history of a DVT had sustained PTS, the results did not markedly change. This is because of the small residual disutility associated with PTS, which was assumed to be represented by a multiplier of 0.977 (*Table 13*).

Because of the scarcity of data, the distribution of events in patients untreated with warfarin following a VTE is uncertain and assumptions were needed to populate the base-case analyses. Sensitivity analyses have been carried out with the very conservative assumption that patients who remain untreated following a VTE have the same outcomes as patients who are treated. This did not markedly affect the results of the base-case analyses, mainly because of the relatively small number of people who were assumed to not receive treatment, namely those patients who had previously suffered an intracranial haemorrhage whilst on warfarin or those who were not on lifelong warfarin who sustained a VTE that was undetected.

Our threshold analyses have been conducted with respect to the costs of thrombophilia testing. The costs of tests whilst still remaining under a MAICER of £30,000 per QALY have been given in *Tables 14–21*.

A post-hoc analysis of the relationship between the sampled value for the increased risk of recurrence and the costs and QALYs accrued within the PSA was undertaken as it was believed that the risk of recurrence would be a key driver of the modelled results. The PSA results for 60-year-old men with lupus anticoagulant and a previous DVT who do not receive extended treatment and the PSA results for 70-year-old women with lupus anticoagulant and a previous PE who do not receive extended treatment were analysed. In all cases the adjusted R^2 coefficient in a linear regression between risk of recurrence and either total costs or total QALYs was greater than 0.5, showing that this variable explained over 50% of the variation in the results, despite the remaining variables also varying. This offers evidence that the risk of recurrence is likely to be the key driver of the modelled results.

Probabilistic sensitivity analyses

PSA was conducted on the parameters included in Appendix 6 using a Monte Carlo methodology as detailed in Claxton *et al*.[74] This approach samples once from the probability distribution for each variable contained within the model to produce a parameter configuration. This process is repeated until a predetermined number of parameter configurations have been sampled. The model is then run using the parameter configuration to

generate the prespecified number of estimates of cost-effectiveness. This is recognized by NICE and is a requirement in the reference case.[73] In our analyses, 100 parameter configurations were generated for each combination of age, sex, previous VTE and thrombophilia type.

For each parameter configuration the model was run simulating 5000 hypothetical patients. The results produced by each parameter configuration were then ranked in order of cost-effectiveness to produce a cost-effectiveness acceptability curve (CEAC),[75] which shows the likelihood of a given intervention having a cost per QALY below a given MAICER. The PSA results shown in *Tables 14–21* have been based on the assumption that thrombophilia testing was both 100% specific and 100% sensitive. The changes in the cost per QALY were the tests assumed to have both sensitivity and specificity of 99% are also shown, and it is noted that the cost per QALY does not markedly change.

The rationale for the groups of patients on which PSAs were conducted was based on those with cost per QALY ratios that are most borderline cost-effective with reference to published guidelines.[73] Thus, we initially analysed women aged 50 years with a previous idiopathic DVT, as the cost per QALY of conducting thrombophilia testing on such patients was approximately £20,000. When it was determined that the PSAs were systematically producing cost per QALY values that were less favourable to thrombophilia testing than the mid-point analyses, we analysed subgroups of patients with cost per QALY ratios below £20,000 until the cost per QALY of thrombophilia testing remained below £20,000 in the PSA.

Women aged 50 years with a previous idiopathic DVT

The CEAC for thrombophilia testing women with a previous idiopathic DVT who are aged 50 years is given in *Figure 3*. This assumes that those who were found to have lupus anticoagulant or who were heterozygous for both FVL and PTG20210A would be treated with the course of warfarin treatment indicated in our mid-point results (10 years for both). It is seen that the median value of cost-effectiveness is dominated, with the mean value calculated as £37,671. This value is markedly higher than the £20,746 estimated in the mid-point analyses, showing that the combination of sampled values produces a non-linear model. The cause of this is the non-normal distributions assigned to key parameters such as the increased risk of a recurrent VTE associated with each type of thrombophilia, the disutility associated with warfarin use and the efficacy of warfarin in preventing VTE.

To explain these results the distributions for the increased risks of recurrence associated with each thrombophilia type must be noted. *Figure 4* shows this for lupus anticoagulant, and a wide uncertainty in the true RR compared with patients without thrombophilia is seen. For women aged 50 years with a previous DVT, with an increased risk of 5.4, as seen for patients who are heterozygous for both FVL and PTG2021A, and analysing the mid-point results, a cost per QALY of £18,034 is seen (*Table 41*), whilst with an increased risk of 2.3, as seen for patients with anticardiolipin antibody, extended warfarin treatment is dominated by the standard treatment period for warfarin (*Table 42*). A value of increased risk of approximately

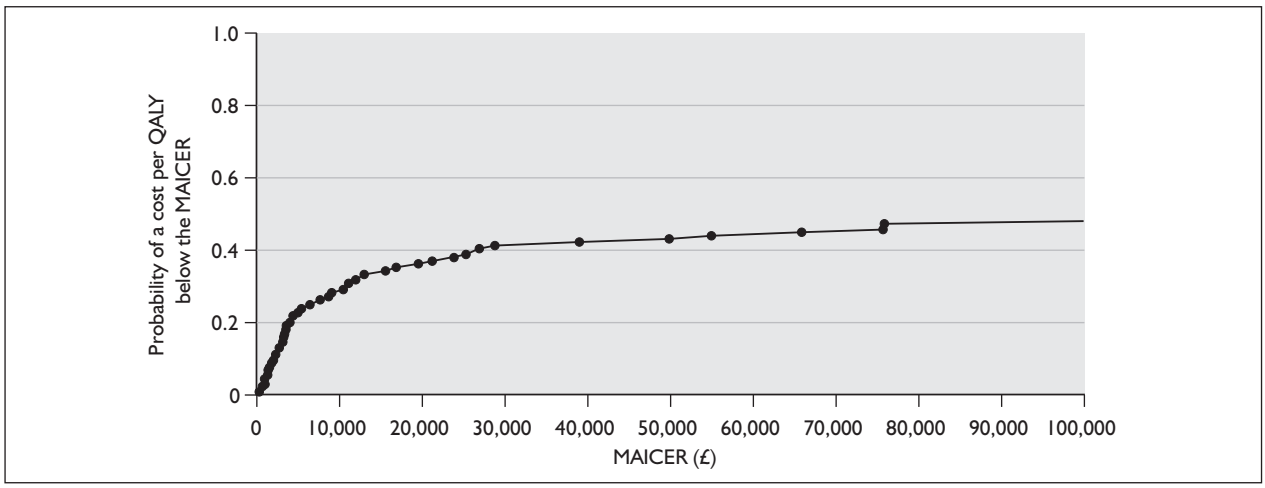


FIGURE 3 *The cost-effectiveness acceptability curve (CEAC) for women aged 50 years with a previous idiopathic DVT, and who have lupus anticoagulant or are heterozygous for both FVL and PTG20210A and who are receiving treatment.*

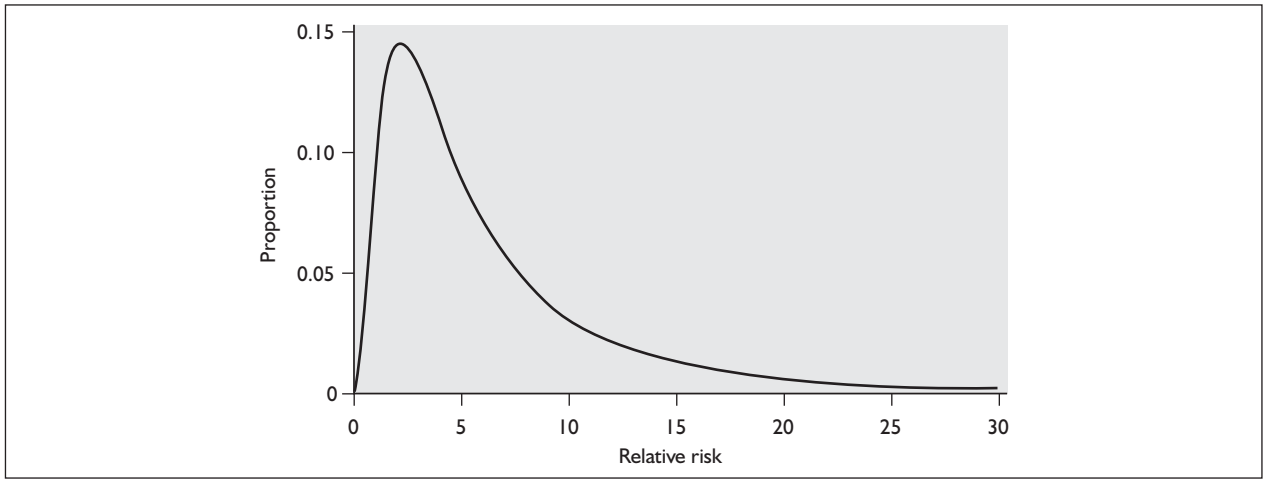


FIGURE 4 *The distribution of increased relative risk associated with lupus anticoagulant.*

5.2 (authors' estimation) would be needed for treatment to have a cost per QALY of £20,000. The mode and median values associated with the distribution for the increased risk associated with lupus anticoagulant (*Figure 4*) are 2.05 and 4.55, respectively, resulting in the majority of simulations having a cost per QALY of more than £20,000 and a sizeable proportion being dominated by the standard course of warfarin. The additional costs associated with thrombophilia testing will also increase the incremental cost-effectiveness of testing at this age.

The effect of the non-normal distributions for the increased risk of thrombophilia becomes less influential as the difference between the mean of the log-normal distribution for lupus anticoagulant and the increased risk required for treatment to be deemed cost-effective becomes greater. This is seen in the additional examples provided.

Further analyses were undertaken assuming that only those women with lupus anticoagulant would receive treatment. This reduced the cost per QALY of thrombophilia testing to a mean of £39,525, with a median value of approximately £75,000, as shown in *Figure 5*. The mean is slightly higher than when patients who are heterozygous for both FVL and PTG20210A are additionally treated. This is because the number of thrombophilia tests undertaken remains relatively constant and no QALYs are gained or costs accrued from treatment of patients who are heterozygous for both FVL and PTG20210A.

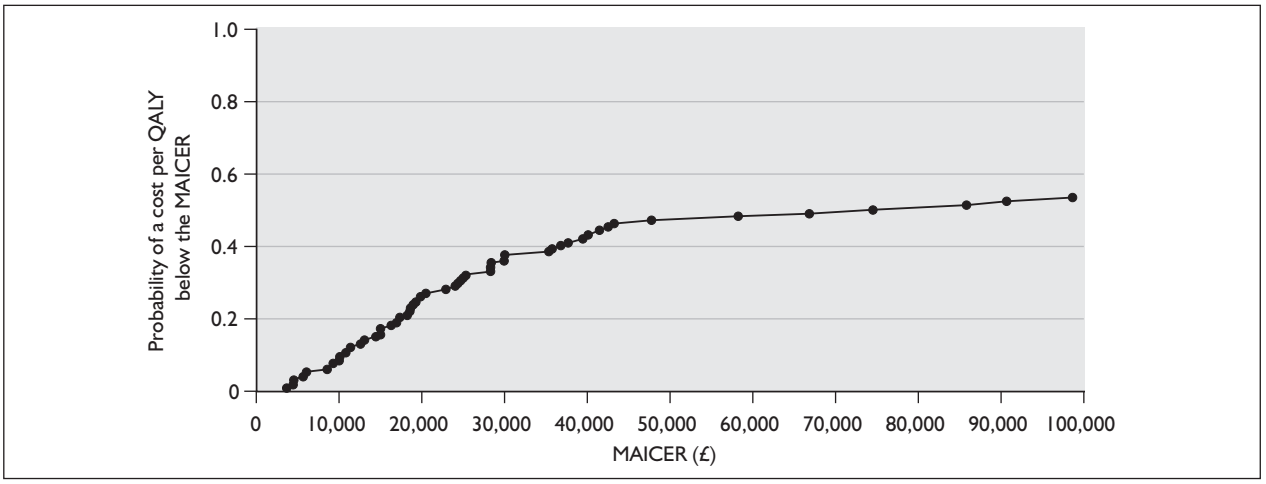


FIGURE 5 *The cost-effectiveness acceptability curve (CEAC) for women aged 50 years with a previous idiopathic DVT, who have lupus anticoagulant and who are receiving treatment.*

Men aged 70 years with a previous idiopathic DVT

The cost per QALY of thrombophilia testing had a mean value of £27,006, with a median value of approximately £30,000, as shown in *Figure 6*. For reference the mean cost per QALY from the mid-point analysis was £16,641 (*Table 14*).

Women aged 40 years with a previous idiopathic DVT

The cost per QALY of thrombophilia testing had a mean value of £18,689, with a median value of approximately £18,000, as shown in *Figure 7*. For reference the mean cost per QALY from the mid-point analysis was £14,384 (*Table 15*).

Men aged 60 years with a previous idiopathic DVT

The cost per QALY of thrombophilia testing had a mean value of £13,516 and a median value of approximately £16,000, as shown in *Figure 8*. For reference the mean cost per QALY from the mid-point analysis was £10,239 (*Table 14*).

Women aged 70 years with a previous idiopathic PE

The cost per QALY of thrombophilia testing had a mean value of £14,692 and a median value of approximately £15,000, as shown in *Figure 9*. For reference the mean cost per QALY from the mid-point analysis was £10,782 (*Table 17*).

Given the PSA results presented above it was assumed that all remaining combinations of age, sex and previous idiopathic VTE that had cost per QALY ratios of below £20,000 in the mid-point analyses would also remain below £20,000 when PSA was conducted.

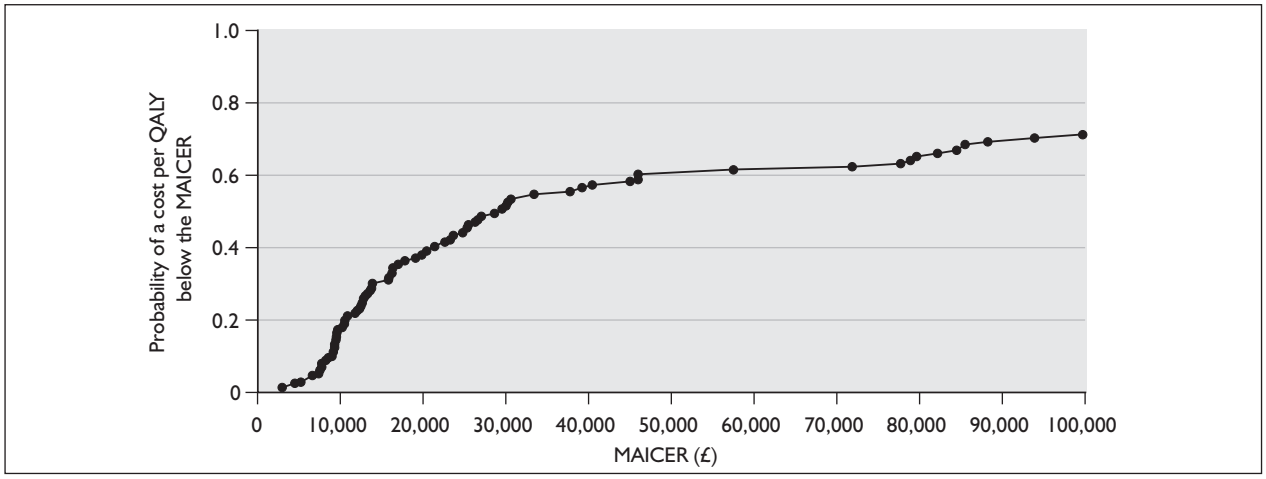


FIGURE 6 *The cost-effectiveness acceptability curve (CEAC) for men aged 70 years with a previous idiopathic DVT, who have lupus anticoagulant or who are heterozygous for both FVL and PTG20210A and who are receiving treatment.*

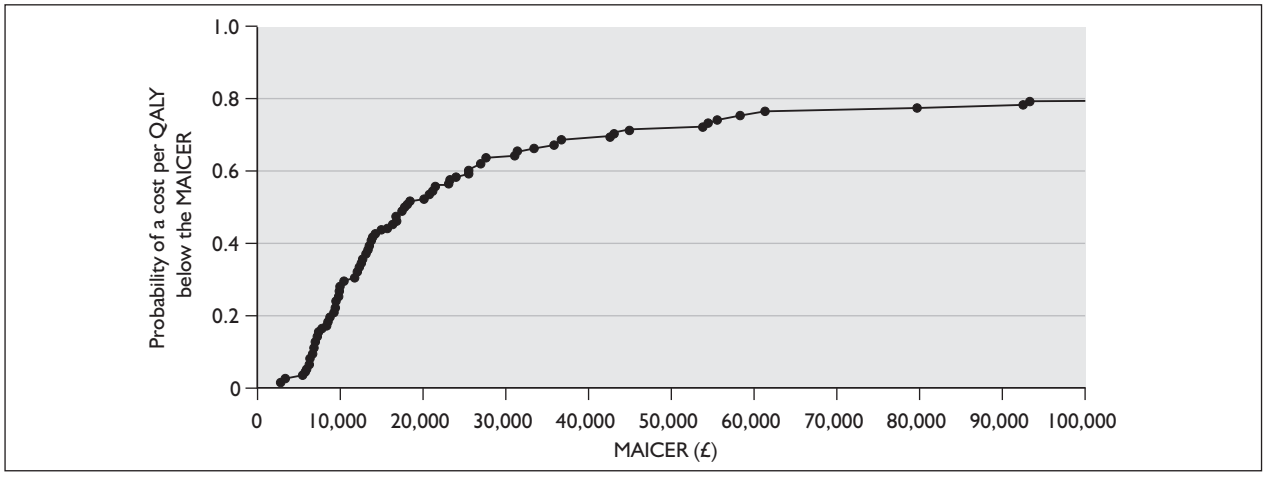


FIGURE 7 *The cost-effectiveness acceptability curve (CEAC) for women aged 40 years with a previous idiopathic DVT, who have lupus anticoagulant or who are heterozygous for both FVL and PTG20210A and who are receiving treatment.*

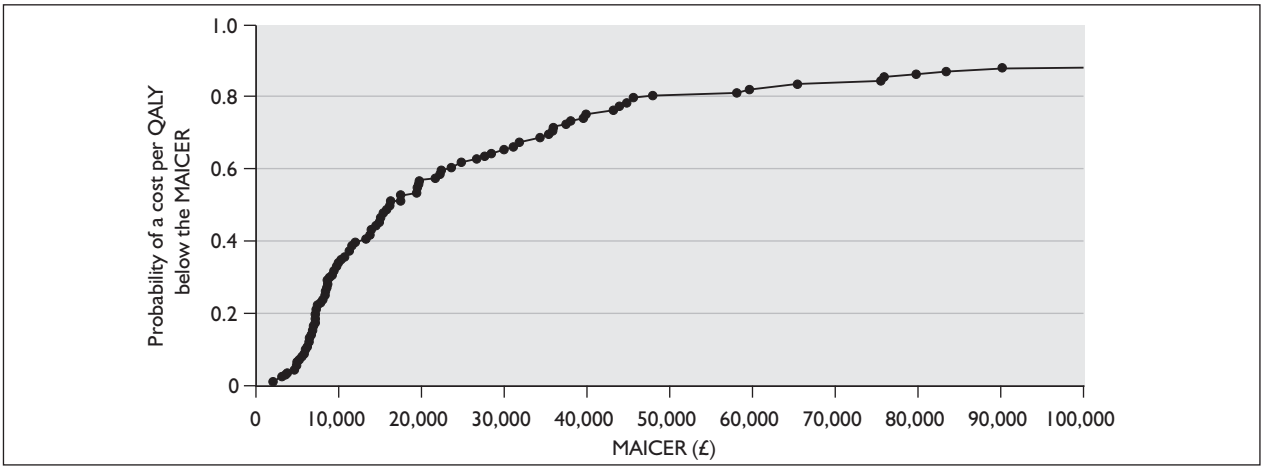


FIGURE 8 *The cost-effectiveness acceptability curve (CEAC) for men aged 60 years with a previous idiopathic DVT, who have lupus anticoagulant or who are heterozygous for both FVL and PTG20210A and who are receiving treatment.*

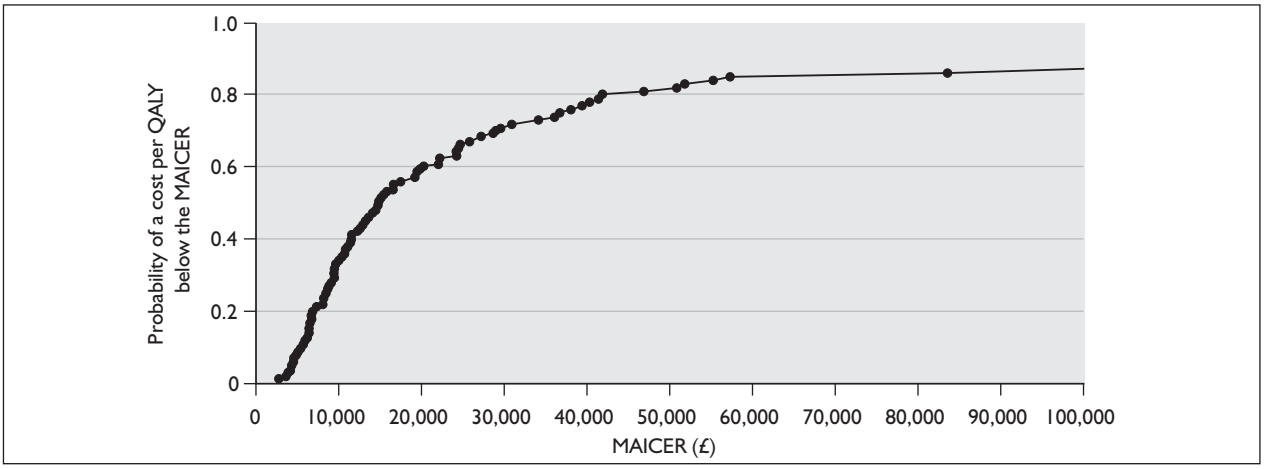


FIGURE 9 *The cost-effectiveness acceptability curve (CEAC) for women aged 70 years with a previous idiopathic PE, who have lupus anticoagulant or who are heterozygous for both FVL and PTG20210A and who are receiving treatment.*

Calculating the cost per QALY ratios from PSA for the thrombophilia type that had the lowest increased risk of recurrence whilst having a cost per QALY of treatment of below £20,000 in the mid-point analyses and for which global thrombophilia testing had a cost per QALY of below £20,000 in the mid-point analyses

Having determined that the cost per QALY ratios provided in the mid-point analyses were systematically lower than the cost per QALY values generated in the PSA, analyses were undertaken on the thrombophilia type that had the lowest increased risk of recurrence whilst having a cost per QALY of treatment of below £20,000 for each age, sex and type of previous idiopathic VTE event, denoted in *Tables 14–21* as the lightest shaded box at each age. Thus, for example, for men aged 50 years with a previous DVT event, being homozygous for FVL had the lowest risk of recurrence whilst remaining under a cost per QALY of £20,000 for treatment (*Table 14*), and PSA was undertaken assuming the treatment durations provided in *Table 14* to calculate a cost per QALY ratio for thrombophilia testing. Only the cost of the repeat thrombophilia test to determine the specific thrombophilia is included in these calculations as it is assumed that the costs of global testing are borne by thrombophilia with greater mean chances of VTE recurrence.

All other thrombophilia types that can be successfully treated at this age, sex and previous VTE combination are assumed to have cost per QALY values that are lower than this figure. These analyses were conducted for all age, sex and previous VTE combinations that were not included in the previous sections on PSA. The cost per QALY values from these analyses are presented in

Tables 22 and *23* for a previous DVT and *Tables 24* and *25* for a previous PE.

Summary of the results

From our analyses it appears that undertaking thrombophilia testing on patients with PE has a mean cost per QALY of below £20,000 regardless of sex or age. It is also estimated that, for men aged 69 years or younger with a previous DVT and for women aged 49 years or younger with a previous DVT, thrombophilia testing has a cost per QALY of below £20,000. Thrombophilia testing is also indicated to be cost-effective in men aged over 70 years with a previous DVT if a MAICER of £30,000 per QALY is employed. These results are influenced by the fact that men have a greater risk of recurrence than women and by the fact that the frequency of adverse events associated with warfarin treatment increases as patients become older.

We have summarised the estimated duration of warfarin treatment for each thrombophilia type for which global thrombophilia testing is cost-effective using a MAICER of £20,000 per QALY in *Tables 26* and *27*. Note however, that these results are subject to a great deal of uncertainty, as discussed in the following section.

Discussion

Our work has enabled an evidence-based assessment of the most cost-effective duration (3 months, 10 years, 20 years or lifelong) of warfarin treatment based upon age, sex and previous VTE type, which may help clinicians decide on the most appropriate treatment length by indicating the scenarios in which our results suggest that thrombophilia testing is cost-effective. However, as depicted in the CEACs presented, there is a great deal of uncertainty in the cost-effectiveness of thrombophilia testing. As the prevalence of each thrombophilia type was not altered within the model the uncertainty around the cost-effectiveness of thrombophilia testing is likely to be greater than that shown. *Figure 7* shows that, even in circumstances in which the expected cost per QALY ratio is below £20,000, there is a sizeable probability (20%) that the cost per QALY exceeds £100,000. This uncertainty is driven primarily by the wide confidence intervals associated with the increased risk of recurrence for each

TABLE 22 *The mean cost per QALY ratios from PSA for the thrombophilia type that had the lowest increased risk of recurrence whilst having a cost per QALY of treatment below £20,000 in the mid-point analyses and for which global thrombophilia testing had a cost per QALY of below £20,000 in the mid-point analyses: men with a previous idiopathic DVT event*

Age (years)	Thrombophilia type	Treatment duration (years)	Mean cost per QALY of treatment (£)
30	FVL heterozygous	10	22,385
40	PTG20210A	10	25,026
50	FVL homozygous	10	23,502
60	Heterozygous for both FVL and PTG20210A	20	13,516
70	Heterozygous for both FVL and PTG20210A	10	20,506

TABLE 23 *The mean cost per QALY ratios from PSA for the thrombophilia type that had the lowest increased risk of recurrence whilst having a cost per QALY of treatment below £20,000 in the mid-point analyses and for which global thrombophilia testing had a cost per QALY of below £20,000 in the mid-point analyses: women with a previous idiopathic DVT event*

Age (years)	Thrombophilia type	Treatment duration (years)	Mean cost per QALY of treatment (£)
30	Heterozygous for both FVL and PTG20210A	20	11,626
40	Heterozygous for both FVL and PTG20210A	20	15,144

Note that the thrombophilia for women aged 50 years with a previous DVT has been omitted because of a cost per QALY of greater than £40,000. See section, Women aged 50 years with a previous idiopathic DVT, p.29, for further explanation.

TABLE 24 *The mean cost per QALY ratios from PSA for the thrombophilia type that had the lowest increased risk of recurrence whilst having a cost per QALY of treatment below £20,000 in the mid-point analyses and for which global thrombophilia testing had a cost per QALY of below £20,000 in the mid-point analyses: men with a previous idiopathic PE event*

Age (years)	Thrombophilia type	Treatment duration (years)	Mean cost per QALY of treatment (£)
30	FVL heterozygous	Lifelong	8396
40	FVL heterozygous	Lifelong	10,898
50	FVL heterozygous	20	12,613
60	FVL heterozygous	10	17,482
70	PTG20210A	10	16,784

TABLE 25 *The mean cost per QALY ratios from PSA for the thrombophilia type that had the lowest increased risk of recurrence whilst having a cost per QALY of treatment below £20,000 in the mid-point analyses and for which global thrombophilia testing had a cost per QALY of below £20,000 in the mid-point analyses: women with a previous idiopathic PE event*

Age (years)	Thrombophilia type	Treatment duration (years)	Mean cost per QALY of treatment (£)
30	FVL heterozygous	10	19,106
40	Deficiency in either AT, PC or PS	10	19,427
50	FVL homozygous	10	14,440
60[a]	Anticardiolipin antibody	10	38,010
70[b]	Anticardiolipin antibody	10	230,335

a Note that the thrombophilia with the next lowest increased risk of recurrence was heterozygous for both FVL and PTG20210A, with a cost per QALY of £6898.
b Note that the thrombophilia with the next lowest increased risk of recurrence was heterozygous for both FVL and PTG20210A, with a cost per QALY of £13,855.

thrombophilia, particularly those with the higher mean RRs, such as lupus anticoagulant and being heterozygous for both FVL and PTG20210A.

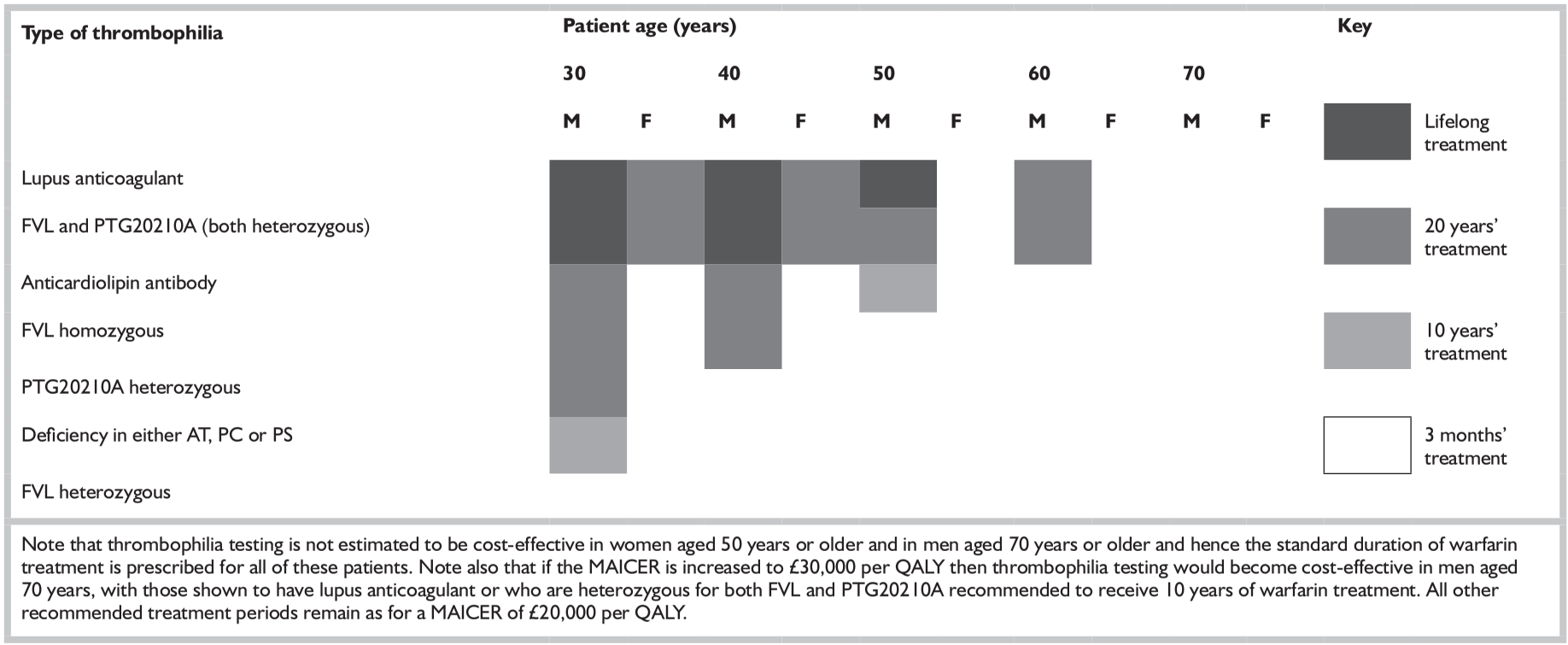
The sensitivity and specificity of tests for each thrombophilia type could not be obtained. In the model we used a sensitivity and specificity of 99%, which are the values reported for DNA tests such as those for FVL or PTG20210A; however, this is likely to overestimate the accuracy of other tests. This will be favourable to thrombophilia testing, particularly if the sensitivity and specificity of the tests for identifying lupus anticoagulant are markedly lower than 99%. This casts further uncertainty around the robustness of the results produced.

We have not considered the extended use of warfarin after an initial VTE event without the diagnosis of thrombophilia. The results for men aged less than 39 years with a previous PE suggest that, using a MAICER of £20,000, patients who are heterozygous for FVL would benefit from extended warfarin treatment (*Table 27*). As the mean RR for these patients compared with patients without thrombophilia is 1, any conclusion on the use of extended warfarin for patients who are heterozygous for FVL would also apply to those patients without thrombophilia. If a MAICER of £30,000 per QALY were adopted then this age limit is estimated to increase to men aged 49 years or less. Further research would need to be conducted to estimate the numbers of people that such a policy would affect.

Our results have been predicated on the assumption that 3 months of treatment is the standard duration of warfarin treatment. Were the standard treatment under certain circumstances to be lifelong, for example in young men with a PE, then our estimate of the cost-effectiveness of thrombophilia testing could markedly change. Such analyses were not conducted as there was no clear guidance on when alternative treatment strategies would be employed, and it was assumed that clinicians would be risk averse when prescribing medications with potentially fatal side effects.

Not all types of thrombophilia have been evaluated in this report, primarily because no information

TABLE 26 *The calculated duration of warfarin treatment by age and sex for people presenting with an idiopathic DVT assuming a MAICER of £20,000 per QALY*



Note that thrombophilia testing is not estimated to be cost-effective in women aged 50 years or older and in men aged 70 years or older and hence the standard duration of warfarin treatment is prescribed for all of these patients. Note also that if the MAICER is increased to £30,000 per QALY then thrombophilia testing would become cost-effective in men aged 70 years, with those shown to have lupus anticoagulant or who are heterozygous for both FVL and PTG20210A recommended to receive 10 years of warfarin treatment. All other recommended treatment periods remain as for a MAICER of £20,000 per QALY.

TABLE 27 *The calculated duration of warfarin treatment by age and sex for people presenting with an idiopathic PE assuming a MAICER of £20,000 per QALY*

Type of thrombophilia	Patient age (years)										Key
	30		40		50		60		70		
	M	F	M	F	M	F	M	F	M	F	
Lupus anticoagulant											Lifelong treatment
FVL and PTG20210A (both heterozygous)											20 years' treatment
Anticardiolipin antibody											10 years' treatment
FVL homozygous											
PTG20210A heterozygous											3 months' treatment
Deficiency in either AT, PC or PS											
FVL heterozygous											

Note that these results remain constant if the MAICER is increased to £30,000 per QALY.

was found on the marginal cost of performing tests for them. If this marginal cost is small then these tests should be considered, with an approximation of the duration of warfarin treatment taken from a thrombophilia with a similar increased risk of recurrence. For instance, factor VIII has not been considered in this report; however, the increased risk of recurrence is very similar to that for patients who are heterozygous for both FVL and PTG20210A (*Table 2*) and the duration of warfarin treatment associated with factor VIII would be assumed to be equal to that in patients who are heterozygous for both FVL and PTG20210A. Were it feasible to include additional tests at a relatively small marginal cost then it is likely that the cost-effectiveness results produced in this report have been unfavourable to thrombophilia testing.

We assumed that the risk of recurrence of VTE was constant with respect to age. There were limited data that indicated that the risk may increase with age. Although we have not explicitly modelled this relationship, it will have the effect of increasing the cost-effectiveness of extended warfarin treatment in the elderly and thus the cost-effectiveness of thrombophilia testing in patients of this age. At the age of 70 years or older only those patients who present with an idiopathic PE are recommended for thrombophilia testing; if there is an increased risk of recurrence associated with increasing age it is possible that thrombophilia testing in men aged 70 years or older who present with a DVT could also become cost-effective. Conversely, if the risk of recurrence is age related, the cost-effectiveness of thrombophilia testing in younger patients would become less favourable.

We have also not investigated the costs saved by omitting tests from the panel of tests in cases in which it is shown that even if the patient were to have a particular thrombophilia then management would not change. For example, analysis of men aged 70 years with a DVT (*Table 18*) suggests that only tests for lupus anticoagulant and FVL and PTG20210A need to be undertaken. We have left the logistics of removing redundant tests, if it is deemed appropriate, for those in the field.

The average population utilities for people aged 30 and 40 years were estimated by the authors, as these were not reported in the source used for utilities. It is possible that these utilities may slightly overestimate the true utilities. If this is the case, the cost–utility ratios predicted for thrombophilia testing at these ages would be slightly favourable to thrombophilia testing as the QALYs lost because of an adverse event or mortality would be lower. It is not expected that this would alter the conclusions produced by the modelling as the cost per QALY ratios at these ages were not bordering on the £20,000 threshold.

Only warfarin has been evaluated as an intervention aimed at reducing recurrent VTE. The cost-effectiveness of other potential interventions is an area for future research.

Chapter 5

Assessment of factors relevant to the NHS and other parties

Patient information

It is important that people receive information about the tests, including why testing is indicated, the nature of the procedure and the time required for testing, as well as the consequences of testing, before deciding whether to consent to testing. Patients undergoing thrombophilia testing should receive advice on the limitations of the tests and the implications of a diagnosis. Trained health professionals should inform patients about thrombophilia testing. Information leaflets may be useful to patients and their families. Anticoagulant or VTE specialists, mainly nurses but also pharmacists, biomedical scientists and doctors, have a role in educating patients about testing and the impact of the results.[39]

Implications of testing

There can be negative implications of testing, such as inappropriate testing causing stress to patients.[40] Patients with negative test results may be given false reassurance. However, a positive diagnosis of thrombophilia may be beneficial to a patient's psychological health by providing an explanation as to why they developed thrombosis.[36] A diagnosis of thrombophilia may influence decisions about targeted thromboprophylaxis in high-risk situations such as surgery or pregnancy, and also may affect advice given on transient risk factors, for example oestrogen therapy.[76]

A diagnosis of heritable thrombophilia may impact on the patient's family. Family members may wish to be tested for thrombophilia. Asymptomatic family members with a positive diagnosis would then be subject to advice and potentially to targeted thromboprophylaxis without having experienced a thrombosis.

Cost implications

Thrombophilia testing is currently conducted for indications other than thrombosis, e.g. recurrent miscarriage. Antiphospholipid antibodies are tested for by other clinicians, e.g. rheumatologists.[31] The numbers of thrombophilia tests undertaken in the population covered in this assessment is not known and thus the impact on total expenditure cannot be accurately estimated.

Chapter 6
Discussion

Statement of principal findings

No trials were identified that studied the clinical effectiveness of thrombophilia testing by comparing a patient population tested for thrombophilias with a population who did not undergo testing.

Our results estimate that undertaking thrombophilia testing on patients with PE may have a mean cost per QALY of below £20,000 regardless of sex or age; however, there is great uncertainty in these values. For men aged 69 years or less with a previous DVT and for women aged 49 years or less with a previous DVT it is estimated that the mean cost per QALY is below £30,000; however, there is also a great deal of uncertainty in these results. Examples exist in which the mean cost per QALY is below £20,000 yet there is a sizeable probability that the cost per QALY could be greater than £100,000. This uncertainty is driven primarily by the wide confidence intervals associated with the increased risk of recurrence for each thrombophilia, particularly those with the higher mean RRs, such as lupus anticoagulant and being heterozygous for both FVL and PTG20210A.

These broad results are influenced by the fact that men have a greater risk of recurrence than women and by the fact that the frequency of adverse events associated with warfarin treatment increases as patients become older.

Strengths and limitations of the assessment

Strengths

There was a comprehensive literature search, which was unlikely to have missed any relevant articles. A mathematical model was constructed that allowed the risks of recurrence to vary by age, sex, previous VTE event and type of thrombophilia. The individual patient approach allowed the increased risks in the period immediately following a VTE to be considered throughout the lifetime of a patient. To our knowledge this is the first model that incorporates these features. If the estimated results from our model are correct then the most cost-effective period of warfarin treatment from those considered can easily be interpreted from two tables, one for patients presenting with an idiopathic DVT and one for those presenting with an idiopathic PE. However, these results come with the caveat that there is a great deal of uncertainty in key parameters, which has resulted in wide confidence intervals for the cost per QALY of thrombophilia testing.

Limitations

The question of whether alterations in anticoagulation management result from thrombophilia testing is flawed as, at the time of writing this report, a change in anticoagulation management is not currently undertaken according to a diagnosis of heritable thrombophilia.[17,26] The data for the model population are limited with wide confidence intervals around many key parameters, which limits the robustness of the cost per QALY ratios. Only warfarin has been evaluated as an intervention to prevent recurrent VTE. We did not undertake systematic reviews for all of the parameters in the model, relying on previous economic evaluations and non-systematic reviews when necessary. It is possible that some relevant data were missed. A paper published after the search dates for this review indicated that there would be little advantage in increasing the duration of oral anticoagulant therapy from 3 to 6 months;[77] however, the paper is not of direct relevance to this review because it excluded patients with known thrombophilia, was not restricted to first events and was not restricted to idiopathic events.

Uncertainties

When possible the modelling work has tried to address the uncertainties associated with evaluating the cost-effectiveness of thrombophilia testing; however, some uncertainties that relate to gaps within the knowledge base still remain. The length of the period following a VTE during which a patient is at high risk is not known, with conflicting results in the literature. The authors have not tried to determine the optimal duration of warfarin treatment following the initial VTE, for example 3 or 6 months, and will leave this to clinicians. Our

work has focused on whether thrombophilia testing followed by extended warfarin treatment, when appropriate, is a cost-effective policy.

The sensitivity and specificity of thrombophilia tests to identify thrombophilia types that are non-genetic were unknown. We have produced results assuming that the sensitivity and specificity were both 100% or 99%; however, if these values were in reality considerably lower than this then the robustness of the results would be weakened.

We have also assumed that the increased risk associated with thrombophilia remains constant over time. Were this risk to attenuate then the benefits associated with longer-term treatment would be overestimated.

We have excluded patients with multiple types of thrombophilia with the exception of patients who are heterozygous for both FVL and PTG20210A. Patients with other combinations of multiple thrombophilia may benefit from extended warfarin treatment, and excluding these patients from our model may be unfavourable to thrombophilia testing. However, the proportion of patients with multiple thrombophilia excluding those who are heterozygous for both FVL and PTG20210A will be small and thus the results are unlikely to change.

The modelling work has excluded any benefit that may be accrued from thrombophilia testing beyond that associated with the duration of warfarin treatment, and thus we have excluded factors such as the management of pregnancy or the prescription of medications such as combined oral contraceptives or hormone replacement therapy for which knowledge of the thrombophilic status of a patient may be advantageous. Conversely, any disutility associated with undertaking genetic tests, such as anxiety or adverse implications of undertaking a genetic test, have been excluded, as have any costs associated with counselling patients shown to have thrombophilia.

We incorporated the sensitivity of clinicians to detect VTE within the model, which was assumed to be 95% for both DVT and PE. These data, together with outcome data for patients who do not receive treatment following a VTE, are uncertain and require further research.

The marked differences between the results produced deterministically using the mean value for each parameter and those produced by PSA show the great deal of uncertainty around key parameters in the model, in particular the wide confidence intervals for the increased risk of recurrence associated with each thrombophilia type. 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.

Areas for future research

The results from the PSA have shown that there is a great deal of uncertainty in the mean incremental cost-effectiveness ratios, primarily because of uncertainties in key input parameters. Future research aimed at reducing the uncertainty around the increased risks of VTE recurrence for each thrombophilia type, the uncertainty in the underlying rate of recurrence following an idiopathic VTE, the haemorrhage rate of those on warfarin, the sensitivity and specificity of tests to identify each thrombophilia type, and the relationship between increased risk, time since the VTE event and the sensitivity and specificity of clinicians to detect a VTE event should be considered. Strengthening this knowledge base would allow more accurate assessments of the cost per QALY of thrombophilia testing to be undertaken. Whether or not gathering such information would be a cost-effective use of resources can be determined using expected value of sample information techniques. Applying such a methodology is a further area for future research.

Evaluating the cost-effectiveness of interventions other than warfarin that reduce the risk of recurrent VTE is also an area for future research.

Chapter 7
Conclusions

No clinical studies were identified that met the inclusion criteria for the review and so the model parameters were searched for from within the literature search and with input from the clinical advisory group. Studies comparing VTE patients tested for thrombophilia with VTE patients whose risk assessment was based on personal and family history of thrombosis would be beneficial.

In terms of determining the duration of anticoagulation management, scenarios were found in which the cost per QALY of thrombophilia testing was below £20,000; however, these results are subject to great uncertainty. Undertaking thrombophilia testing on all patients with a PE was estimated to have a mean cost per QALY below £20,000 regardless of sex or age. In patients with a previous DVT, thrombophilia testing had an estimated mean cost per QALY below £20,000 in men aged 69 years or younger and in women aged 49 years or younger. These results are influenced by the fact that men have a greater risk of recurrence than women and by the fact that the frequency of adverse events associated with warfarin treatment increases with age. Further research is needed to enable the uncertainty associated with these results to be reduced.

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Clinical advisory group

Professor M. Greaves, Head of School of Medicine, University of Aberdeen; Dr T. Baglin, Chairman, Haemostasis and Thrombosis Task Force, British Society for Haematology; Dr I. Jennings, Deputy Manager, UK NEQAS (Blood Coagulation); Dr S. Kitchen, Clinical Scientist, Sheffield Haemophilia and Thrombosis Centre; Dr M. Makris, Reader in Haemostasis and Thrombosis, Royal Hallamshire Hospital, Sheffield.

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Contribution of authors

E.L. Simpson was the review lead and undertook the clinical effectiveness review. M.D. Stevenson and A. Rawdin undertook the cost-effectiveness review. D. Papaioannou conducted the literature searches. Jim Chilcott and Eva Kaltenthaler are guarantors.

About ScHARR

The School of Health and Related Research (ScHARR) is one of the four schools that constitute the Faculty of Medicine at the University of Sheffield. ScHARR brings together a wide range of medical and health-related disciplines including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research and information science. It includes the Sheffield unit of the Trent RDSU, which is funded by NIHR to facilitate high-quality health services research and capacity development.

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the effectiveness and cost-effectiveness of health-care interventions for the NIHR Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute for Health and Clinical Excellence. ScHARR-TAG is part of a wider collaboration of six units from other regions, namely Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Aberdeen Health Technology Assessment Group (Aberdeen HTA Group), University of Aberdeen; Liverpool Reviews and Implementation Group (LRiG), University of Liverpool; Peninsula Technology Assessment Group (PenTAG), University of Exeter; NHS Centre for Reviews and Dissemination, University of York; and West Midlands Health Technology Assessment Collaboration (WMHTAC), University of Birmingham.

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81. AxisShield submission to the National Institute of Health and Clinical Excellence – thrombophilia. 2006.

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Appendix 1

Examples of thrombophilia tests and their CE marked indications for use

Manufacturer	Test	CE marked indication for use
Dade Behring[78]	Protein S Ac	Determination of the functional activity of protein S in plasma for the diagnosis of hereditary or acquired protein S deficiencies
Dade Behring[78]	Berichrom™ Antithrombin III (A)	For the quantitative determination of the functional activity of antithrombin III in plasma on autoanalysers for the diagnosis of diminished antithrombin III synthesis and increased consumption and for monitoring substitution therapy
Dade Behring[78]	Berichrom™ Protein C	For the detection of congenital and acquired protein C deficiency; in conjunction with other methods (antigenic determination, protein C coagulometric method) for the differential diagnosis of different protein C deficiency states; or for the monitoring of substitution therapy with protein C concentrates in congenital protein C deficiency
Dade Behring[78]	ProC Global	For the determination of the anticoagulatory capacity of the protein C system in human plasma and to diagnose hereditary or acquired deficiency states of the protein C system. Used in conjunction with coagulation factor V-deficient plasma, is suitable for the determination of FVL
Dade Behring[78]	Protein C reagent	A coagulation test for the quantitative determination of protein C activity in human plasma
Dade Behring[78]	LA 1 screening reagent/ LA 2 confirmation reagent	Simplified, one-stage, dilute Russell's viper venom time reagents intended to specifically detect lupus anticoagulants (LA), a type of antiphospholipid antibody. Can also be used to study defects in the interactions of clotting factors in the common pathway
Bio-Rad[79]	Anticardiolipin IgA test	An enzyme-linked immunosorbent assay (ELISA) for the semi-quantitative determination of anticardiolipin IgA antibodies in human serum or plasma. For the detection and semi-quantitation of anticardiolipin antibodies in individuals with systemic lupus erythematosus (SLE) and lupus-like disorders (antiphospholipid syndrome). For in vitro diagnostic use
Bio-Rad[79]	Anticardiolipin IgG test	An enzyme-linked immunosorbent assay (ELISA) for the semi-quantitative determination of anticardiolipin IgG antibodies in human serum or plasma. For the detection and semi-quantitation of anticardiolipin antibodies in individuals with systemic lupus erythmatosus (SLE) and lupus-like disorders (antiphospholipid syndrome). For in vitro diagnostic use
Bio-Rad[79]	Homocysteine test	For the quantitative determination of total L-homocysteine in human serum or plasma. The device can assist in the diagnosis and treatment of patients suspected of having hyperhomocysteinaemia and homocystinuria. For in vitro diagnostic use
Bio-Rad[79]	Homocysteine by high-performance liquid chromatography (HPLC)	The Bio-Rad homocysteine by HPLC test is intended for the quantitative determination of homocysteine in human plasma or serum. For in vitro diagnostic use
CDG UK[80]	Homocysteine by HPLC	(CE marked – details not provided)
CDG UK[80]	Homocysteine by enzyme immunoassay (EIA)	(CE marked – details not provided)
CDG UK[80]	Anticardiolipin IgG	(CE marked – details not provided)
CDG UK[80]	Anticardiolipin IgM	(CE marked – details not provided)
CDG UK[80]	Anticardiolipin IgA	(CE marked – details not provided)

Manufacturer	Test	CE marked indication for use
AxisShield[81]	Staclot Protein S	(CE marked – details not provided)
AxisShield[81]	Asserachrom Protein S	(CE marked – details not provided)
AxisShield[81]	Liatest Protein S	(CE marked – details not provided)
AxisShield[81]	Asserachrom Free Protein S	(CE marked – details not provided)
AxisShield[81]	Liatest Free Protein S	(CE marked – details not provided)
AxisShield[81]	Stachrom Protein C	(CE marked – details not provided)
AxisShield[81]	Acticlot aPCR	(CE marked – details not provided)
AxisShield[81]	Liatest AT III Ag	(CE marked – details not provided)
AxisShield[81]	Stachrom AT III	(CE marked – details not provided)
Trinity Biotech[82]	Bioclot® Protein S-300ACT	For the quantitative determination of protein S activity in citrated human plasma using a clotting assay. For in vitro diagnostic use only
Trinity Biotech[82]	Bioclot® Protein C	For the quantitative determination of protein C in human plasma by clotting assay. For in vitro diagnostic use only
Trinity Biotech[81]	Spectrolyse® Antithrombin III	For the quantitative determination of antithrombin III in human plasma by chromogenic assay. For in vitro diagnostic use only
Trinity Biotech[82]	Bioclot® FVa-aPC Resistance	For the determination of resistance to activated protein C in human plasma using a clotting assay. For in vitro diagnostic use only
Instrumentation Laboratory[83]	HemosIL Test™ Liquid Antithrombin	Automated chromogenic assay for the quantitative determination of antithrombin in human citrated plasma on IL Coagulation Systems
Instrumentation Laboratory[83]	HemosIL ProClot	Automated functional clotting protein C assay for the quantitative determination of protein C in human citrated plasma on IL Coagulation Systems
Instrumentation Laboratory[83]	HemosIL Liquid Antithrombin	Automated chromogenic assay for the quantitative determination of antithrombin in human citrated plasma on the ACL Futura/ACL Advance and ACL TOP Systems
Instrumentation Laboratory[83]	HemosIL Free Protein S	Automated latex ligand immunoassay for the quantitative determination of free protein S in human citrated plasma on IL Coagulation Systems
Instrumentation Laboratory[83]	HemosIL Plasminogen	Automated chromogenic assay for the quantitative determination of plasminogen in human citrated plasma on IL Coagulation Systems
Instrumentation Laboratory[83]	HemosIL Homocysteine	Automated latex enhanced immunoassay for the quantitative determination of total L-homocysteine in human citrated plasma on IL Coagulation Systems
Instrumentation Laboratory[83]	IL Test TM Protein C	Automated chromogenic assay for the quantitative determination of protein C in human citrated plasma on IL Coagulation Systems
Instrumentation Laboratory[83]	HemosIL ProS	Automated coagulation functional assay for the quantitative determination of free protein S in human citrated plasma on IL Coagulation Systems
Instrumentation Laboratory[83]	HemosIL Plasmin Inhibitor	Automated chromogenic assay for the quantitative determination of plasmin inhibitor in human citrated plasma on IL Coagulation Systems
Instrumentation Laboratory[83]	HemosIL Factor V Leiden (APC™ Resistance V)	For determination of resistance to activated protein C caused by the factor V:Q506 (factor V Leiden) mutation, in plasma from untreated individuals and from patients on oral anticoagulant or heparin therapy

All above data provided by sponsor submissions to NICE.

Appendix 2

Literature search terms for MEDLINE

Clinical effectiveness

1. clinical trial.pt. (225210)
2. meta$.pt. (11138)
3. review.pt. (683286)
4. exp review literature/(2443)
5. exp clinical trials/(87937)
6. meta-analysis/(4893)
7. exp guidelines/(47776)
8. health planning guidelines/(916)
9. or/1–8 (992360)
10. randomized controlled trials/(36135)
11. controlled clinical trial.pt. (26436)
12. randomized controlled trials/(36135)
13. random allocation/(21037)
14. double blind method/(42876)
15. single blind method/(7621)
16. or/10–15 (128447)
17. clinical trial.pt. (225210)
18. exp clinical trials/(87937)
19. (clin$adj25 trial$).tw. (79059)
20. ((singl$or doubl$or trebl$or tripl$) adj25 (blind$or mask$)).tw. (41776)
21. placebos/(7536)
22. placebo$.tw. (52195)
23. random$.tw. (220009)
24. research design/(23074)
25. or/17–24 (475260)
26. Comparative Study/(560069)
27. exp evaluation studies/(279253)
28. follow-up studies/(157398)
29. prospective studies/(131914)
30. (control$or prospectiv$or volunteer$).tw. (894853)
31. or/26–30 (1600442)
32. 16 or 25 or 31 (1758984)
33. animal/(1390937)
34. human/(3698913)
35. 33 not 34 (936064)
36. 32 not 35 (1425207)
37. exp "Sensitivity and Specificity"/(167664)
38. sensitivity.tw. (151370)
39. specificity.tw. (97754)
40. ((pre-test or pretest) adj probability).tw. (454)
41. post-test probability.tw. (131)
42. predictive value$.tw. (22089)
43. likelihood ratio$.tw. (2584)
44. or/37–43 (331092)
45. exp case-control studies/(222729)
46. case control stud$.mp. (70352)
47. exp cohort studies/(323926)
48. cohort analysis.mp. (796)
49. exp longitudinal studies/(288791)
50. exp prospective studies/(131914)
51. exp follow-up studies/(157398)
52. cohort$.tw. (71183)
53. or/45–52 (523656)
54. meta-analysis/(4893)
55. meta analy$.tw. (12804)
56. metaanaly$.tw. (469)
57. meta analysis.pt. (11138)
58. (systematic adj (review$1 or overview$1)).tw. (8999)
59. exp review literature/(2443)
60. or/54–59 (27802)
61. cochrane.ab. (6521)
62. embase.ab. (4721)
63. (psychlit or psyclit).ab. (655)
64. (psychinfo or psycinfo).ab. (864)
65. (cinahl or cinal).ab. (1773)
66. science citation index.ab. (556)
67. bids.ab. (168)
68. cancerlit.ab. (312)
69. or/61–68 (9349)
70. reference list$.ab. (2752)
71. bibliograph$.ab. (4046)
72. hand-search$.ab. (1317)
73. relevant journals.ab. (222)
74. manual search$.ab. (664)
75. or/70–74 (7994)
76. selection criteria.ab. (6672)
77. data extraction.ab. (2971)
78. 76 or 77 (9084)
79. review.pt. (683286)
80. 78 and 79 (6373)
81. comment.pt. (214279)
82. letter.pt. (259780)
83. editorial.pt. (112306)
84. animal/(1390937)
85. human/(3698913)
86. 84 not (84 and 85) (936064)
87. or/81–83,86 (1328208)
88. 60 or 69 or 75 or 78 (38808)
89. 88 not 87 (35917)
90. 9 or 36 or 44 or 45 or 46 or 53 or 89 (2257794)
91. factor v Leiden.mp. (2486)
92. activated protein c resistance.mp. or exp activated protein c resistance/(1007)
93. apc resistance.mp. (468)
94. exp protein c deficiency/(565)

95. protein c deficienc$.tw. (410)
96. exp protein s deficiency/(591)
97. protein s deficienc$.tw. (549)
98. exp antithrombin III deficiency/(259)
99. anti thrombin deficienc$.tw. (0)
100. antithrombin deficienc$.tw. (200)
101. antiphospholipid antibod$.tw. (2560)
102. antiphospholipid antibodies.mp. or exp Antibodies, Antiphospholipid/(4074)
103. lupus anticoagulant.mp. or exp lupus coagulation inhibitor/(1582)
104. anticardiolipin antibodies.mp. or exp Antibodies, Anticardiolipin/(2015)
105. homocysteine.mp. or exp Homocysteine/(8131)
106. dysfibrinogenaemia.mp. (13)
107. factor VIII.mp. or exp factor VIII/(5055)
108. factor 8.mp. (1036)
109. d-dimer.mp. (2315)
110. factor IX.mp. or exp Factor IX/(1523)
111. factor 9.mp. (323)
112. factor XI.mp. or exp Factor XI/(450)
113. factor 11.mp. (39)
114. dilute russell viper venom time.mp. (33)
115. prothrombin G20210A.mp. (385)
116. MTHFR C677T.mp. (435)
117. kaolin clotting time.mp. (38)
118. or/91–117 (26120)
119. thrombophilia.mp. or exp Thrombophilia/(7295)
120. mass screening.mp. or exp Mass Screening/(43753)
121. screen$.mp. (159255)
122. test$.mp. (765004)
123. exp "diagnostic techniques and procedures"/or diagnostic tests, routine/(1024968)
124. (diagnostic test$and procedure$).mp. (1579)
125. or/120–124 (1629523)
126. 119 and 125 (2335)
127. 118 or 126 (27217)
128. deep vein thrombosis.mp. or exp Venous Thrombosis/(14230)
129. dvt.mp. (2271)
130. pulmonary embolism.mp. or exp Pulmonary Embolism/(9702)
131. pe.mp. (7031)
132. venous thromboembolism.mp. (3551)
133. vte.mp. (1159)
134. stroke.mp. or exp Cerebrovascular Accident/(58898)
135. cva.mp. (563)
136. peripheral vascular disease$.mp. or exp Peripheral Vascular Diseases/(5229)
137. pvd.mp. (511)
138. myocardial infarction.mp. or exp Myocardial Infarction/(50751)
139. mi.mp. (9201)
140. coronary heart disease.mp. or exp Coronary Disease/(62297)
141. chd.mp. (5642)
142. exp Lateral Sinus Thrombosis/or exp Hepatic Vein Thrombosis/or exp Sagittal Sinus Thrombosis/or exp Thrombosis/or exp Coronary Thrombosis/or exp Sinus Thrombosis, Intracranial/or exp Cavernous Sinus Thrombosis/or exp "Intracranial Embolism and Thrombosis"/or exp Carotid Artery Thrombosis/or exp Venous Thrombosis/or exp Intracranial Thrombosis/(37174)
143. exp Embolism/(20440)
144. exp Thromboembolism/(10415)
145. thrombo$.mp. (94723)
146. thromboembolism$.mp. (10235)
147. embol$.mp. (32214)
148. occlu$.mp. (57340)
149. or/128–148 (292284)
150. exp Anticoagulants/(43413)
151. anticoag$.mp. (28066)
152. warfarin.mp. or exp Warfarin/(6252)
153. blood coagulation test$.mp. or exp Blood Coagulation Tests/(6685)
154. or/150–153 (55019)
155. 90 and 127 and 149 and 154 (3411)
156. *Pregnancy Complications/(10779)
157. *Pregnancy Outcome/(5261)
158. *Abortion, Spontaneous/(1519)
159. *Contraceptives, Oral/(1495)
160. *Hormone Replacement Therapy/(2483)
161. *Estrogen Replacement Therapy/(5519)
162. or/156–161 (25911)
163. pregnancy complication$.ti. (141)
164. pregnancy outcome$.ti. (1336)
165. pregnancy loss$.ti. (437)
166. miscarriage$.ti. (644)
167. foet$.ti. (1044)
168. puerperium$.ti. (257)
169. oral contraceptive$.ti. (1781)
170. oral contraception.ti. (125)
171. hormone replacment therap$.ti. (0)
172. oestrogen therap$.ti. (26)
173. estrogen therap$.ti. (209)
174. oestrogen replacement.ti. (60)
175. estrogen replacement.ti. (606)
176. or/163–175 (6620)
177. 162 or 176 (28991)
178. 155 not 177 (4908)

Cost-effectiveness

1. factor v leiden.mp.
2. activated protein c resistance.mp. or exp activated protein c resistance/
3. apc resistance.mp.
4. exp protein c deficiency/

5. protein c deficienc$.tw.
6. exp protein s deficiency/
7. protein s deficienc$.tw.
8. exp antithrombin III deficiency/
9. anti thrombin deficienc$.tw.
10. antithrombin deficienc$.tw.
11. antiphospholipid antibod$.tw.
12. antiphospholipid antibodies.mp. or exp Antibodies, Antiphospholipid/
13. lupus anticoagulant.mp. or exp lupus coagulation inhibitor/
14. anticardiolipin antibodies.mp. or exp Antibodies, Anticardiolipin/
15. homocysteine.mp. or exp Homocysteine/
16. dysfibrinogenaemia.mp.
17. factor VIII.mp. or exp factor VIII/
18. factor 8.mp.
19. d-dimer.mp.
20. factor IX.mp. or exp Factor IX/
21. factor 9.mp.
22. factor XI.mp. or exp Factor XI/
23. factor 11.mp.
24. dilute russell viper venom time.mp.
25. prothrombin G20210A.mp.
26. MTHFR C677T.mp.
27. kaolin clotting time.mp.
28. or/1–27
29. thrombophilia.mp. or exp Thrombophilia/
30. mass screening.mp. or exp Mass Screening/
31. screen$.mp.
32. test$.mp.
33. exp "diagnostic techniques and procedures"/ or diagnostic tests, routine/
34. (diagnostic test$and procedure$).mp.
35. or/30–34
36. 29 and 35
37. 28 or 36
38. deep vein thrombosis.mp. or exp Venous Thrombosis/
39. dvt.mp.
40. pulmonary embolism.mp. or exp Pulmonary Embolism/
41. pe.mp.
42. venous thromboembolism.mp.
43. vte.mp.
44. stroke.mp. or exp Cerebrovascular Accident/
45. cva.mp.
46. peripheral vascular disease$.mp. or exp Peripheral Vascular Diseases/
47. pvd.mp.
48. myocardial infarction.mp. or exp Myocardial Infarction/
49. mi.mp.
50. coronary heart disease.mp. or exp Coronary Disease/
51. chd.mp.
52. exp Lateral Sinus Thrombosis/or exp Hepatic Vein Thrombosis/or exp Sagittal Sinus Thrombosis/or exp Thrombosis/or exp Coronary Thrombosis/or exp Sinus Thrombosis, Intracranial/or exp Cavernous Sinus Thrombosis/or exp "Intracranial Embolism and Thrombosis"/or exp Carotid Artery Thrombosis/or exp Venous Thrombosis/or exp Intracranial Thrombosis/
53. exp Embolism/
54. exp Thromboembolism/
55. thrombo$.mp.
56. thromboembolism$.mp.
57. embol$.mp.
58. occlu$.mp.
59. or/38–58
60. exp Anticoagulants/
61. anticoag$.mp.
62. warfarin.mp. or exp Warfarin/
63. blood coagulation test$.mp. or exp Blood Coagulation Tests/
64. or/60–63
65. *Pregnancy Complications/
66. *Pregnancy Outcome/
67. *Abortion, Spontaneous/
68. *Contraceptives, Oral/
69. *Hormone Replacement Therapy/
70. *Estrogen Replacement Therapy/
71. or/65–70
72. pregnancy complication$.ti.
73. pregnancy outcome$.ti.
74. pregnancy loss$.ti.
75. miscarriage$.ti.
76. foet$.ti.
77. puerperium$.ti.
78. oral contraceptive$.ti.
79. oral contraception.ti.
80. hormone replacment therap$.ti.
81. oestrogen therap$.ti.
82. estrogen therap$.ti.
83. oestrogen replacement.ti.
84. estrogen replacement.ti.
85. or/72–84
86. 71 or 85
87. Economics/
88. exp "Costs and Cost Analysis"/
89. economic value of life/
90. exp economics hospital/
91. exp economics medical/
92. economics nursing/
93. exp models economic/
94. Economics, Pharmaceutical/
95. exp "Fees and Charges"/
96. exp budgets/
97. ec.fs.
98. (cost or costs or costed or costly or costing$).tw.

99. (economic$or pharmacoecomomic$or price$or pricing$).tw.
100. quality adjusted life years/
101. (qaly or qaly$).af.
102. or/87–101
103. 37 and 59 and 64 and 102
104. 103 not 86

Appendix 3

Critique of the retrieved cost-effectiveness papers

We have summarised the cost-effectiveness literature that was retrieved from our systematic review. In this section we have concentrated on key structural differences between the models in the published literature and our mathematical model. We do not explicitly discuss minor differences in the values of common parameters as these will be discussed in the section describing the population of the model. Differences between our model and all of those previously published are contained in the following paragraph, with differences relating to specific papers detailed thereafter.

No paper reviewed employed a model using an individual patient approach. These models could not then increase the risk of subsequent VTE in the period immediately after a VTE and may thus underestimate the number of subsequent DVTs. No published model considered the sensitivity of detection of VTE, which will overestimate the survival of patients with VTE and may also leave patients untreated in the high-risk period immediately following a VTE. Models that explicitly considered haemorrhages did not subdivide these so that warfarin treatment would be reinitiated following a VTE in patients with a previous non-intracranial haemorrhage but not in patients who had suffered an intracranial haemorrhage.

***Auerbach et al.*[65]**
This paper does not give results by gender and the base rate of VTE amongst patients without thrombophilia has been taken from a population that is unselected for cause of VTE and is only known to be without the FVL mutation so may contain all other types of thrombophilia. There also appears to be uncertainty in how the recurrent VTE rates were extracted from the source paper.[84]

***Aujesky et al.*[85]**
This paper calculates the cost-effectiveness of oral anticoagulation strategies after a first VTE but does not distinguish between thrombophilic and non-thrombophilic patients.

***Eckman et al.*[86]**
This paper considers only the cost-effectiveness of testing for patients with the FVL mutation. The results are not divided between men and women and are provided only for patients aged 35 years. The base rate of VTE amongst patients without thrombophilia has been taken from a population that is only known to be without the FVL mutation and so may contain all other types of thrombophilia.

***Marchetti et al.*[58]**
This paper considers the cost-effectiveness of testing for patients with the FVL mutation but no other types of thrombophilia. The population is men with VTE, not just those with idiopathic VTE, aged 60 years. The rates of recurrence of VTE have not been taken from patients without thrombophilia.

***Marchetti et al.*[87]**
This paper considers the cost-effectiveness of testing for patients with both the FVL mutation and PTG20210A but no other types of thrombophilia. The population is men with VTE, not just those with idiopathic VTE, aged 60 years. The rates of recurrence of VTE have not been taken from patients without thrombophilia.

***Keeling et al.*[57]**
This paper does not perform a cost–utility analysis but reports the number of years of treatment needed to avoid a fatal event, divided by age but not by gender. The RRs associated with each type of thrombophilia have not been applied within the model.

***Prins et al.*[55]**
This paper does not perform a cost–utility analysis but reports the number of years of treatment needed to avoid a fatal event, divided by age but not by gender. The RRs associated with each type of thrombophilia have not been applied within the model.

Appendix 4

Detailed results from the mid-point analyses

These results assume that the sensitivity and specificity of thrombophilia testing are 100%.

Men with a previous DVT

The cost per QALY of alternative treatment periods was compared with a standard 3-month treatment period assuming that the thrombophilic status of the patient is known without cost.

The most cost-effective strategy at each age assuming a MAICER of £20,000 is shaded and was established by undertaking incremental analyses (data not shown). No shading denotes that the standard 3-month treatment period is most cost-effective.

TABLE 28 *Lupus anticoagulant*

Length of treatment	Age (years)				
	30	40	50	60	70
10 years	£2397	£3341	£4567	£5525	£9489
20 years	£2865	£3966	£5169	£6723	£11,007
Lifelong	£3707	£4484	£5583	£6791	£11,007

TABLE 29 *FVL heterozygous and PTG20210A*

Length of treatment	Age (years)				
	30	40	50	60	70
10 years	£3011	£4000	£5296	£6946	£12,838
20 years	£3386	£4856	£6343	£8707	£15,776
Lifelong	£4520	£5811	£7331	£8839	£15,776

TABLE 30 *Anticardiolipin antibodies*

Length of treatment	Age (years)				
	30	40	50	60	70
10 years	£5946	£8955	£16,346	£23,201	£115,552
20 years	£7359	£11,147	£18,435	£37,456	£149,434
Lifelong	£11,185	£15,537	£25,356	£36,147	£149,434

TABLE 32 *PTG20210A*

Length of treatment	Age (years)				
	30	40	50	60	70
10 years	£8977	£16,225	£28,990	Dominated	Dominated
20 years	£11,803	£20,750	£43,623	Dominated	Dominated
Lifelong	£20,274	£34,937	£73,822	Dominated	Dominated

TABLE 33 *AT deficiency, PC deficiency, PS deficiency*

Length of treatment	Age (years)				
	30	**40**	**50**	**60**	**70**
10 years	£12,070	£21,510	£48,293	Dominated	Dominated
20 years	£15,331	£30,494	£30,494	Dominated	Dominated
Lifelong	£28,127	£58,641	£58,641	Dominated	Dominated

TABLE 34 *FVL heterozygous*

Length of treatment	Age (years)				
	30	**40**	**50**	**60**	**70**
10 years	£16,571	£35,078	£35,078	Dominated	Dominated
20 years	£21,757	£54,919	Dominated	Dominated	Dominated
Lifelong	£47,817	£213,729	Dominated	Dominated	Dominated

This risk of recurrent thrombosis is the same as for patients without thrombophilia as the relative risk of FVL heterozygous compared with no thrombophilia is 1.

Cost per QALY of thrombophilia testing when the costs of the tests are incorporated

TABLE 35 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for men aged 30 years with a previous DVT*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	Lifelong	5590	1.508
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	Lifelong	6202	1.372
Anticardiolipin antibody	2.7[18]	20 years	5333	0.725
FVL homozygous	1.5[9]	20 years	5553	0.677
PTG20210A heterozygous	5–18[9] (assumed 11.5)	20 years	6308	0.534
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	10 years	3704	0.307
FVL heterozygous	10–50[8] (assumed 30)	10 years	4119	0.249
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			3033	0.293
Cost of tests[b]			116	
Totals			3149	0.293
Cost per QALY of thrombophilia testing			*£10,740*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with thrombophilia who would change the duration of warfarin treatment are retested as in Wu *et al.*[30]
It is seen that introducing thrombophilia testing in men aged 30 years with a previous DVT has a cost per QALY gained of £8670 compared with no thrombophilia testing.

TABLE 36 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for men aged 40 years with a previous DVT*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	Lifelong	4926	1.099
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	Lifelong	5564	0.957
Anticardiolipin antibody	2.7[18]	20 years	5623	0.504
FVL homozygous	1.5[9]	20 years	5941	0.444
PTG20210A heterozygous	5–18[9] (assumed 11.5)	10 years	3727	0.230
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	3 months	–	–
FVL heterozygous	10–50[8] (assumed 30)	3 months	–	–
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			993	0.109
Cost of tests[b]			86	
Totals			1079	0.109
Cost per QALY of thrombophilia testing			*£9894*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with thrombophilia who would change the duration of warfarin treatment are retested as in Wu *et al.*[30]

It is seen that introducing thrombophilia testing in men aged 40 years with a previous DVT has a cost per QALY gained of £9742 compared with no thrombophilia testing.

TABLE 37 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for men aged 50 years with a previous DVT*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	Lifelong	4433	0.794
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	20 years	4872	0.665
Anticardiolipin antibody	2.7[18]	10 years	3359	0.205
FVL homozygous	1.5[9]	10 years	3489	0.224
PTG20210A heterozygous	5–18[9] (assumed 11.5)	3 months	–	–
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	3 months	–	–
FVL heterozygous	10–50[8] (assumed 30)	3 months	–	–
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			400	0.052
Cost of tests[b]			78	
Totals			478	0.052
Cost per QALY of thrombophilia testing			*£9194*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with thrombophilia who would change the duration of warfarin treatment are retested as in Wu *et al.*[30]
It is seen that introducing thrombophilia testing in men aged 50 years with a previous DVT has a cost per QALY gained of £9110 compared with no thrombophilia testing.

TABLE 38 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for men aged 60 years with a previous DVT*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	20 years	3610	0.537
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	20 years	4038	0.464
Anticardiolipin antibody	2.7[18]	3 months	–	–
FVL homozygous	1.5%[9]	3 months	–	–
PTG20210A heterozygous	5–18[9] (assumed 11.5)	3 months	–	–
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	3 months	–	–
FVL heterozygous	10–50[8] (assumed 30)	3 months	–	–
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			236	0.030
Cost of tests[b]			75	
Totals			311	0.030
Cost per QALY of thrombophilia testing			*£10,239*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with thrombophilia who would change the duration of warfarin treatment are retested as in Wu *et al*.[30]
It is seen that introducing thrombophilia testing in men aged 60 years with a previous DVT has a cost per QALY gained of £10,052 compared with no thrombophilia testing.

Women with a previous DVT

The cost per QALY of alternative treatment periods was compared with a standard 3-month treatment period assuming that the thrombophilic status of the patient is known without cost.

The most cost-effective strategy at each age assuming a MAICER of £20,000 is shaded and was established by undertaking incremental analyses (data not shown). No shading denotes that the standard 3-month treatment period is most cost-effective.

TABLE 39 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for men aged 70 years with a previous DVT*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	10 years	2375	0.250
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	10 years	2654	0.207
Anticardiolipin antibody	2.7[18]	3 months	–	–
FVL homozygous	1.5[9]	3 months	–	–
PTG20210A heterozygous	5–18[9] (assumed 11.5)	3 months	–	–
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	3 months	–	–
FVL heterozygous	10–50[8] (assumed 30)	3 months	–	–
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			155	0.014
Cost of tests[b]			75	
Totals			230	0.014
Cost per QALY of thrombophilia testing			*£16,641*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with thrombophilia who would change the duration of warfarin treatment are retested as in Wu *et al.*[30]
It is seen that introducing thrombophilia testing in men aged 70 years with a previous DVT has a cost per QALY gained of £16,259 compared with no thrombophilia testing.

TABLE 40 *Lupus anticoagulant*

	Age (years)				
Length of treatment	**30**	**40**	**50**	**60**	**70**
10 years	£5598	£3095	£12,551	£21,295	£66,880
20 years	£6493	£3439	£15,289	£27,651	£100,287
Lifelong	£9738	£3980	£19,965	£34,239	£100,287

TABLE 41 *FVL heterozygous and PTG20210A heterozygous*

	Age (years)				
Length of treatment	**30**	**40**	**50**	**60**	**70**
10 years	£7238	£11,191	£18,034	£33,032	£480,510
20 years	£8694	£13,446	£21,826	£58,552	Dominated
Lifelong	£13,731	£20,318	£34,062	£61,055	Dominated

TABLE 42 *Anticardiolipin antibodies*

	Age (years)				
Length of treatment	**30**	**40**	**50**	**60**	**70**
10 years	£22,206	£55,466	Dominated	Dominated	Dominated
20 years	£34,151	£129,487	Dominated	Dominated	Dominated
Lifelong	£125,499	Dominated	Dominated	Dominated	Dominated

TABLE 43 *FVL homozygous*

	Age (years)				
Length of treatment	**30**	**40**	**50**	**60**	**70**
10 years	£28,474	£99,290	Dominated	Dominated	Dominated
20 years	£45,678	Dominated	Dominated	Dominated	Dominated
Lifelong	£227,631	Dominated	Dominated	Dominated	Dominated

TABLE 44 *PTG20210A*

	Age (years)				
Length of treatment	**30**	**40**	**50**	**60**	**70**
10 years	£55,979	Dominated	Dominated	Dominated	Dominated
20 years	£326,890	Dominated	Dominated	Dominated	Dominated
Lifelong	Dominated	Dominated	Dominated	Dominated	Dominated

TABLE 45 *One of AT deficiency, PC deficiency or PS deficiency*

	Age (years)				
Length of treatment	**30**	**40**	**50**	**60**	**70**
10 years	£501,798	Dominated	Dominated	Dominated	Dominated
20 years	Dominated	Dominated	Dominated	Dominated	Dominated
Lifelong	Dominated	Dominated	Dominated	Dominated	Dominated

TABLE 46 *FVL heterozygous*

	Age (years)				
Length of treatment	**30**	**40**	**50**	**60**	**70**
10 years	Dominated	Dominated	Dominated	Dominated	Dominated
20 years	Dominated	Dominated	Dominated	Dominated	Dominated
Lifelong	Dominated	Dominated	Dominated	Dominated	Dominated
This risk of recurrent thrombosis is the same as for patients without thrombophilia as the relative risk of FVL heterozygous compared with no thrombophilia is 1.					

Cost per QALY of thrombophilia testing when the costs of the tests are incorporated

TABLE 47 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for women aged 30 years with a previous DVT*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	20 years	5194	0.800
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	20 years	5683	0.654
Anticardiolipin antibody	2.7[18]	3 months	–	–
FVL homozygous	1.5[9]	3 months	–	–
PTG20210A heterozygous	5–18[9] (assumed 11.5)	3 months	–	–
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	3 months	–	–
FVL heterozygous	10–50[8] (assumed 30)	3 months	–	–
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			335	0.044
Cost of tests[b]			75	
Totals			410	0.044
Cost per QALY of thrombophilia testing			*£9329*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with the above thrombophilia are retested as in Wu *et al.*[30]
It is seen that introducing thrombophilia testing in women aged 30 years with a previous DVT has a cost per QALY gained of £9173 compared with no thrombophilia testing.

TABLE 48 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for women aged 40 years with a previous DVT*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	20 years	5570	0.544
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	20 years	6112	0.455
Anticardiolipin antibody	2.7[18]	3 months	–	–
FVL homozygous	1.5[9]	3 months	–	–
PTG20210A heterozygous	5–18[9] (assumed 11.5)	3 months	–	–
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	1–3[49]	3 months	–	–
FVL heterozygous	10–50[8] (assumed 30)	3 months	–	–
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			360	0.030
Cost of tests[b]			75	
Totals			435	0.030
Cost per QALY of thrombophilia testing			*£14,384*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with the above thrombophilia are retested as in Wu *et al.*[30]
It is seen that introducing thrombophilia testing in women aged 40 years with a previous DVT has a cost per QALY gained of £14,159 compared with no thrombophilia testing.

TABLE 49 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for women aged 50 years with a previous DVT*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	10 years	3236	0.258
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	10 years	3567	0.198
Anticardiolipin antibody	2.7[18]	3 months	–	–
FVL homozygous	1.5[9]	3 months	–	–
PTG20210A heterozygous	5–18[9] (assumed 11.5)	3 months	–	–
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	1–3[49]	3 months	–	–
FVL heterozygous	10–50[8] (assumed 30)	3 months	–	–
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			209	0.014
Cost of tests[b]			75	
Totals			284	0.014
Cost per QALY of thrombophilia testing			*£20,746*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with the above thrombophilia are retested as in Wu *et al.*[30]
It is seen that introducing thrombophilia testing in women aged 50 years with a previous DVT has a cost per QALY gained of £20,283 compared with no thrombophilia testing.

TABLE 50 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for women aged 60 years with a previous DVT*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	3 months	–	–
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	3 months	–	–
Anticardiolipin antibody	2.7[18]	3 months	–	–
FVL homozygous	1.5[9]	3 months	–	–
PTG20210A heterozygous	5–18[9] (assumed 11.5)	3 months	–	–
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	3 months	–	–
FVL heterozygous	10–50[8] (assumed 30)	3 months	–	–
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			–	–
Cost of tests[b]			70.6	
Totals			70.6	–
Cost per QALY of thrombophilia testing			*Dominated*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with the above thrombophilia are retested as in Wu *et al.*[30]
It is seen that introducing thrombophilia testing in women aged 60 years with a previous DVT is dominated by no thrombophilia testing.

TABLE 51 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for women aged 70 years with a previous DVT*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	3 months	–	–
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	3 months	–	–
Anticardiolipin antibody	2.7[18]	3 months	–	–
FVL homozygous	1.5[9]	3 months	–	–
PTG20210A heterozygous	5–18[9] (assumed 11.5)	3 months	–	–
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	3 months	–	–
FVL heterozygous	10–50[8] (assumed 30)	3 months	–	–
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			–	–
Cost of tests[b]			70.6	
Totals			70.6	–
Cost per QALY of thrombophilia testing			*Dominated*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with the above thrombophilia are retested as in Wu *et al*.[30]
It is seen that introducing thrombophilia testing in women aged 70 years with a previous DVT is dominated by no thrombophilia testing.

Men with a previous PE

Cost per QALY of alternative treatment periods wascompared with a standard 3-month treatment period assuming that the thrombophilic status of the patient is known without cost.

The most cost-effective strategy at each age assuming a MAICER of £20,000 is shaded and was established by undertaking incremental analyses (data not shown). No shading denotes that the standard 3-month treatment period is most cost-effective.

TABLE 52 *Lupus anticoagulant*

	Age (years)				
Length of treatment	**30**	**40**	**50**	**60**	**70**
10 years	£1551	£1836	£2065	£2319	£3051
20 years	£1685	£1976	£2242	£2494	£3208
Lifelong	£1874	£2089	£2284	£2522	£3208

TABLE 53 *FVL heterozygous and PTG20210A heterozygous*

	Age (years)				
Length of treatment	**30**	**40**	**50**	**60**	**70**
10 years	£1718	£1983	£2294	£2622	£3560
20 years	£1868	£2164	£2494	£2931	£3953
Lifelong	£2129	£2360	£2680	£2967	£3953

TABLE 54 *Anticardiolipin antibodies*

	Age (years)				
Length of treatment	**30**	**40**	**50**	**60**	**70**
10 years	£2690	£3188	£3965	£4991	£8839
20 years	£2960	£3571	£4334	£6377	£10,326
Lifelong	£3601	£4190	£4992	£6468	£10,326

TABLE 55 *FVL homozygous*

	Age (years)				
Length of treatment	**30**	**40**	**50**	**60**	**70**
10 years	£2919	£3633	£4385	£5714	£10,634
20 years	£3235	£4042	£4937	£7507	£12,341
Lifelong	£3954	£4716	£5684	£7556	£12,341

Table 56 *PTG20210A*

	Age (years)				
Length of treatment	**30**	**40**	**50**	**60**	**70**
10 years	£3666	£4465	£5535	£8374	£17,760
20 years	£4076	£5122	£6514	£11,365	£20,730
Lifelong	£5148	£6175	£7761	£11,315	£20,730

Table 57 *One of AT deficiency, PC deficiency or PS deficiency*

	Age (years)				
Length of treatment	**30**	**40**	**50**	**60**	**70**
10 years	£4078	£5425	£7053	£10,598	£23,722
20 years	£4674	£6119	£8344	£14,754	£28,374
Lifelong	£5977	£7500	£9808	£14,938	£28,374

Table 58 *FVL heterozygous*

	Age (years)				
Length of treatment	**30**	**40**	**50**	**60**	**70**
10 years	£5230	£6631	£9191	£16,154	£46,865
20 years	£5941	£7513	£11,031	£22,316	£52,942
Lifelong	£7612	£9583	£13,168	£22,663	£52,942
This risk of recurrent thrombosis is the same as for patients without thrombophilia as the relative risk of FVL heterozygous compared with no thrombophilia is 1.					

Cost per QALY of thrombophilia testing when the costs of the tests are incorporated

TABLE 59 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for men aged 30 years with a previous PE*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	Lifelong	6689	3.568
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	Lifelong	7222	3.392
Anticardiolipin antibody	2.7[18]	Lifelong	9487	2.634
FVL homozygous	1.5[9]	Lifelong	9810	2.481
PTG20210A heterozygous	5–18[9] (assumed 11.5)	Lifelong	10,779	2.094
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	Lifelong	11,355	1.900
FVL heterozygous	10–50[8] (assumed 30)	Lifelong	12,238	1.608
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			7218	1.291
Cost of tests[b]			116	
Totals			7344	1.291
Cost per QALY of thrombophilia testing			*£5682*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with the above thrombophilia are retested as in Wu *et al*.[30]
It is seen that introducing thrombophilia testing in men aged 30 years with a previous PE has a cost per QALY gained of £4550 compared with no testing.

TABLE 60 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for men aged 40 years with a previous PE*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	Lifelong	5895	2.822
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	Lifelong	6387	2.706
Anticardiolipin antibody	2.7[18]	Lifelong	8501	2.029
FVL homozygous	1.5[9]	Lifelong	8927	1.893
PTG20210A heterozygous	5–18[9] (assumed 11.5)	Lifelong	9861	1.597
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	Lifelong	10,471	1.396
FVL heterozygous	10–50[8] (assumed 30)	20 years	7899	1.051
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			5606	0.932
Cost of tests[b]			116	
Totals			5722	0.932
Cost per QALY of thrombophilia testing			*£6137*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with the above thrombophilia are retested as in Wu *et al.*[30]
It is seen that introducing thrombophilia testing in men aged 40 years with a previous PE has a cost per QALY gained of £5394 compared with no testing.

TABLE 61 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for men aged 50 years with a previous PE*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	Lifelong	4988	2.184
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	Lifelong	5494	2.050
Anticardiolipin antibody	2.7[18]	Lifelong	7532	1.509
FVL homozygous	1.5[9]	Lifelong	7864	1.383
PTG20210A heterozygous	5–18[9] (assumed 11.5)	20 years	7156	1.099
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	20 years	7576	0.908
FVL heterozygous	10–50[8] (assumed 30)	20 years	8036	0.728
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			4863	0.635
Cost of tests[b]			116	
Totals			4979	0.635
Cost per QALY of thrombophilia testing			*£7620*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with the above thrombophilia are retested as in Wu *et al.*[30]
It is seen that introducing thrombophilia testing in men aged 50 years with a previous PE has a cost per QALY gained of £5919 compared with no testing.

TABLE 62 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for men aged 60 years with a previous PE*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	20 years	4033	1.617
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	20 years	4430	1.511
Anticardiolipin antibody	2.7[18]	20 years	6257	0.981
FVL homozygous	1.5[9]	20 years	6549	0.872
PTG20210A heterozygous	5–18[9] (assumed 11.5)	10 years	4479	0.648
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	10 years	4787	0.452
FVL heterozygous	10–50[8] (assumed 30)	10 years	5181	0.321
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			3219	0.351
Cost of tests[b]			116	
Totals			3336	0.351
Cost per QALY of thrombophilia testing			*£9494*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with the above thrombophilia are retested as in Wu *et al.*[30]
It is seen that introducing thrombophilia testing in men aged 60 years with a previous PE has a cost per QALY gained of £6978 compared with no testing.

TABLE 63 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for men aged 70 years with a previous PE*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	20 years	3107	0.968
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	20 years	3487	0.882
Anticardiolipin antibody	2.7[18]	10 years	4170	0.472
FVL homozygous	1.5[9]	10 years	4433	0.417
PTG20210A heterozygous	5–18[9] (assumed 11.5)	10 years	4883	0.275
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	3 months	–	–
FVL heterozygous	10–50[8] (assumed 30)	3 months	–	–
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			944	0.107
Cost of tests[b]			86	
Totals			1030	0.107
Cost per QALY of thrombophilia testing			*£9635*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with the above thrombophilia are retested as in Wu *et al.*[30]
It is seen that introducing thrombophilia testing in men aged 70 years with a previous PE has a cost per QALY gained of £9444 compared with no testing.

Women with a previous PE

The cost per QALY of alternative treatment periods was compared with a standard 3-month treatment period assuming that the thrombophilic status of the patient is known without cost.

The most cost-effective strategy at each age assuming a MAICER of £20,000 is shaded and was established by undertaking incremental analyses (data not shown). No shading denotes that the standard 3-month treatment period is most cost-effective.

TABLE 64 *Lupus anticoagulant*

Length of treatment	Age (years)				
	30	40	50	60	70
10 years	£2525	£3095	£3796	£4525	£6876
20 years	£2794	£3439	£4108	£5265	£8202
Lifelong	£3393	£3980	£4688	£5611	£8202

TABLE 65 *FVL heterozygous and PTG20210A heterozygous*

Length of treatment	Age (years)				
	30	40	50	60	70
10 years	£2914	£3598	£4369	£5659	£8981
20 years	£3234	£4023	£4853	£6828	£11,061
Lifelong	£4016	£4800	£5672	£7307	£11,061

TABLE 66 *Anticardiolipin antibodies*

Length of treatment	Age (years)				
	30	40	50	60	70
10 years	£6232	£7868	£10,664	£19,098	£53,897
20 years	£6936	£9096	£12,760	£26,641	£67,191
Lifelong	£9310	£11,921	£16,198	£29,111	£67,191

TABLE 67 *FVL homozygous*

Length of treatment	Age (years)				
	30	40	50	60	70
10 years	£7134	£9188	£13,938	£22,563	£93,161
20 years	£7925	£10,944	£17,284	£36,182	£124,806
Lifelong	£10,592	£14,497	£22,685	£37,948	£124,806

TABLE 68 *PTG20210A*

	Age (years)				
Length of treatment	**30**	**40**	**50**	**60**	**70**
10 years	£9675	£14,943	£23,858	£77,627	Dominated
20 years	£11,595	£18,204	£31,053	£133,981	Dominated
Lifelong	£16,473	£25,310	£45,154	£158,898	Dominated

TABLE 69 *One of AT deficiency, PC deficiency or PS deficiency*

	Age (years)				
Length of treatment	**30**	**40**	**50**	**60**	**70**
10 years	£13,107	£17,297	£37,999	£208,351	Dominated
20 years	£15,416	£23,547	£49,177	£1,900,759	Dominated
Lifelong	£22,311	£33,680	£81,858	Dominated	Dominated

TABLE 70 *FVL heterozygous*

	Age (years)				
Length of treatment	**30**	**40**	**50**	**60**	**70**
10 years	£16,651	£26,950	£92,405	Dominated	Dominated
20 years	£20,736	£42,979	£206,552	Dominated	Dominated
Lifelong	£32,864	£74,214	Dominated	Dominated	Dominated

This risk of recurrent thrombosis is the same as for patients without thrombophilia as the relative risk of FVL heterozygous compared with no thrombophilia is 1.

Cost per QALY of thrombophilia testing when the costs of the tests are incorporated

TABLE 71 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for women aged 30 years with a previous PE*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	Lifelong	9633	2.839
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	Lifelong	10,216	2.544
Anticardiolipin antibody	2.7[18]	20 years	8177	1.179
FVL homozygous	1.5[9]	20 years	8473	1.069
PTG20210A heterozygous	5–18[9] (assumed 11.5)	20 years	9212	0.794
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	10 years	5492	0.419
FVL heterozygous	10–50[8] (assumed 30)	10 years	5712	0.343
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			4444	0.440
Cost of tests[b]			116	
Totals			4561	0.440
Cost per QALY of thrombophilia testing			*£10,366*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with the above thrombophilia are retested as in Wu *et al*.[30]
It is seen that introducing thrombophilia testing in women aged 30 years with a previous PE has a cost per QALY gained of £8362 compared with no testing.

TABLE 72 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for women aged 40 years with a previous PE*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	Lifelong	8783	2.207
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	Lifelong	9402	1.959
Anticardiolipin antibody	2.7[18]	20 years	8428	0.927
FVL homozygous	1.5[9]	20 years	8721	0.797
PTG20210A heterozygous	5–18[9] (assumed 11.5)	10 years	5571	0.373
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	10 years	5624	0.325
FVL heterozygous	10–50[8] (assumed 30)	3 months	–	–
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			2289	0.249
Cost of tests[b]			95	
Totals			2384	0.249
Cost per QALY of thrombophilia testing			*£9590*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with the above thrombophilia are retested as in Wu *et al*.[30]
It is seen that introducing thrombophilia testing in women aged 40 years with a previous PE has a cost per QALY gained of £9428 compared with no testing.

TABLE 73 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for women aged 50 years with a previous PE*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	Lifelong	7661	1.634
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	Lifelong	8407	1.482
Anticardiolipin antibody	2.7[18]	20 years	8544	0.670
FVL homozygous	1.5[9]	10 years	5325	0.382
PTG20210A heterozygous	5–18[9] (assumed 11.5)	3 months	–	–
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	3 months	–	–
FVL heterozygous	10–50[8] (assumed 30)	3 months	–	–
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			805	0.119
Cost of tests[b]			78	
Totals			883	0.119
Cost per QALY of thrombophilia testing			*£7447*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with the above thrombophilia are retested as in Wu *et al*.[30]
It is seen that introducing thrombophilia testing in women aged 50 years with a previous PE has a cost per QALY gained of £7417 compared with no testing.

TABLE 74 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for women aged 60 years with a previous PE*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	20 years	6010	1.142
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	20 years	6602	0.967
Anticardiolipin antibody	2.7[18]	10 years	5384	0.282
FVL homozygous	1.5[9]	3 months	–	–
PTG20210A heterozygous	5–18[9] (assumed 11.5)	3 months	–	–
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	3 months	–	–
FVL heterozygous	10–50[8] (assumed 30)	3 months	–	–
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			534	0.071
Cost of tests[b]			77	
Totals			610	0.071
Cost per QALY of thrombophilia testing			*£8544*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with the above thrombophilia are retested as in Wu *et al*.[30]
It is seen that introducing thrombophilia testing in women aged 60 years with a previous PE has a cost per QALY gained of £8505 compared with no testing.

TABLE 75 *The weighted cost incurred and QALYs gained from the most cost-effective warfarin duration associated with each thrombophilia, for women aged 70 years with a previous PE*

Type of thrombophilia	Estimated prevalence among patients with idiopathic VTE (%)	Most cost-effective treatment duration	Cost per person (£)	QALYs accrued per person
Lupus anticoagulant	2.7[18]	20 years	5340	0.651
FVL heterozygous and PTG20210A heterozygous	3.45; calculated from Franco and Reitsma[8] and Dickey[9]	10 years	4343	0.484
Anticardiolipin antibody	2.7[18]	3 months	–	–
FVL homozygous	1.5[9]	3 months	–	–
PTG20210A heterozygous	5–18[9] (assumed 11.5)	3 months	–	–
AT deficiency, PC deficiency or PS deficiency or lupus-like anticoagulants	13[49]	3 months	–	–
FVL heterozygous	10–50[8] (assumed 30)	3 months	–	–
All patients with idiopathic DVT weighted by thrombophilia prevalence[a]			291	0.034
Cost of tests[b]			75	
Totals			367	0.034
Cost per QALY of thrombophilia testing			*£10,782*	

a These values are obtained by summating the products of prevalence and costs (or QALYs).
b Assuming that patients with the above thrombophilia are retested as in Wu *et al*.[30]
It is seen that introducing thrombophilia testing in women aged 70 years with a previous PE has a cost per QALY gained of £10,636 compared with no testing.

Appendix 5

Additional information on the calculation of costs used within the model

TABLE 76 *Calculation of costs of treating a resolved DVT and of warfarin treatment*

Description of variable	Mean value	Source
Cost of further resolving deep vein thrombosis	£183.46	
Based on:		
Days on heparin	8.6	Boccalon *et al.*[88]
Unit cost per dose of low-molecular-weight heparin	£11.10	BNF[67]
Number of anticoagulant clinic reviews	4	Goodacre *et al.*[59]
Unit cost per anticoagulant clinic review	£22	NHS reference costs[69]
Cost of warfarin, first quarter	£538.48	
Based on:		
Cost of warfarin treatment for one quarter	£4.88	BNF[67]
Number of nursing visits during treatment	17.2	Boccalon *et al.*[88]
Unit cost per nursing visit	£23.00	Curtis and Netten[68]
Number of GP visits during treatment	2	Goodacre *et al.*[59]
Unit cost per GP visit	£69.00	Curtis and Netten[68]
Cost of warfarin, subsequent quarters	£211.38	
Based on:		
Cost of 90 days' warfarin treatment	£4.88	BNF[67]
Number of nursing visits during treatment	6	Assumption
Unit cost per nursing visit	£23.00	Curtis and Netten[68]
Number of GP visits during treatment	1	Assumption
Unit cost per GP visit	£69.00	Curtis and Netten[68]
Implementation cost of warfarin treatment	£327.10	
Ongoing cost of warfarin treatment per year	£847.52	

TABLE 77 *Calculation of costs of treating post-thrombotic syndrome and a non-fatal intracranial haemorrhage*

Description of variable	Mean value	Source
Cost of treating post-thrombotic syndrome	£3284.70	
Based on:		
Unit cost for new vascular surgery outpatient	£163.62	NHS reference costs[69]
Number of follow-up outpatient clinic reviews	31	Goodacre *et al.*[59]
Unit cost for follow-up vascular surgery outpatient	£100.68	NHS reference costs[69]
Cost of treating a non-fatal intracranial haemorrhage		
Initial one-off cost	£5774.78	
Ongoing cost per year	£4798.19	
Based on:		
Treatment of severe haemorrhage, first year	£10572.97	Sandercock *et al.*[70]
Treatment of severe haemorrhage, subsequent years	£4798.19	Sandercock *et al.*[70]

Appendix 6

Mean values and probability distributions for parameters used in the model

TABLE 78 *Probability of events*

Description of variable	Mean value	Probability distribution	Parameters				Initial source
Risk of recurrent VTE in men	0.0507						
Risk of recurrent VTE in women	0.0188						
Based on:							
Baseline risk recurrence	0.0324	Beta	$a = 22.36$		$b = 667.779$		Christiansen *et al.*[41]
Increase in risk recurrence in men	2.7	Log-normal	$m = 0.936$		$s = 0.340$		Christiansen *et al.*[41]
Risk of recurrence in first 6 months	0.20	Uniform	Min = 0.1		Max = 0.3		Assumption
Proportion of:							
Treated DVTs that result in resolving DVT at next VTE	0.7438	Dirichlet	A	B	C	D	Douketis *et al.*[61]
Treated DVTs that result in PTS at next VTE	0.0422	Dirichlet	74.38	4.22	13.8	7.6	Douketis *et al.*[61]
Treated DVTs that result in non-fatal PE at next VTE	0.1380	Dirichlet					Douketis *et al.*[61]
Treated DVTs that result in fatal PE at next VTE	0.0760	Dirichlet					Douketis *et al.*[61]
Untreated DVTs that result in resolving DVT at next VTE	0.3939	Dirichlet	A	B	C	D	Douketis *et al.*[61]
Untreated DVTs that result in PTS at next VTE	0.2921	Dirichlet	39.39	29.21	10.47	20.93	Douketis *et al.*[61]
Untreated DVTs that result in non-fatal PE at next VTE	0.1047	Dirichlet					Douketis *et al.*[61]
Untreated DVTs that result in fatal PE at next VTE	0.2093	Dirichlet					Douketis *et al.*[61]
Treated PEs that result in resolving DVT at next VTE	0.1789	Dirichlet	A	B	C	D	Douketis *et al.*[61]
Treated PEs that result in PTS at next VTE	0.0101	Dirichlet	17.89	1.01	54.7	26.4	Douketis *et al.*[61]
Treated PEs that result in non-fatal PE at next VTE	0.5470	Dirichlet					Douketis *et al.*[61]
Treated PEs that result in fatal PE at next VTE	0.2640	Dirichlet					Douketis *et al.*[61]
Untreated PEs that result in resolving DVT at next VTE	0.0559	Dirichlet	A	B	C	D	Douketis *et al.*[61]
Untreated PEs that result in PTS at next VTE	0.0331	Dirichlet	5.59	3.31	30.37	60.73	Douketis *et al.*[61]
Untreated PEs that result in non-fatal PE at next VTE	0.3037	Dirichlet					Douketis *et al.*[61]
Untreated PEs that result in fatal PE at next VTE	0.6073	Dirichlet					Douketis *et al.*[61]

TABLE 79 *Probability of haemorrhage events associated with warfarin treatment*

Description of variable	Mean value	Probability distribution	Parameters			Initial source
Probability of haemorrhage in initial 3 months of treatment	0.02187	Normal	SE = 0.00145			Linkins *et al.*[62]
Probability of haemorrhage subsequently						
Probability of haemorrhage between the ages of 40 and 49	0.006	Exponential	The ratio of the standard deviation and the mean from Linkins *et al.*[62] was assumed to be applicable to the point estimates presented in Keeling[57]			Keeling[57]
Probability of haemorrhage between the ages of 50 and 59	0.010	Exponential				Keeling[57]
Probability of haemorrhage between the ages of 50 and 59	0.015	Exponential				Keeling[57]
Probability of haemorrhage between the ages of 60 and 69	0.022	Exponential				Keeling[57]
Probability of haemorrhage at age 70 and above	0.032	Exponential				Keeling[57]
Proportion of:						
Haemorrhage in initial 3 months that are fatal	0.15766	Dirichlet	A	B	C	Linkins *et al.*[62]
Haemorrhage in initial 3 months that are non-fatal intracranial	0.04148	Dirichlet	35	9.21	177.79	Linkins *et al.*[62]
Haemorrhage in initial 3 months that are non-fatal, non-intracranial	0.80086	Dirichlet				Linkins *et al.*[62]
Haemorrhage subsequently that are fatal	0.11364	Dirichlet	A	B	C	Linkins *et al.*[62]
Haemorrhage subsequently that are non-fatal intracranial	0.09091	Dirichlet	5	4	35	Linkins *et al.*[62]
Haemorrhage subsequently that are non-fatal, non-intracranial	0.79545	Dirichlet				Linkins *et al.*[62]

TABLE 80 *Costs*

Description of variable	Mean value	Probability distribution	Parameters	Initial source
Costs associated with warfarin therapy				
Implementation of warfarin therapy	£327.10	None		See Appendix 2
Maintenance of warfarin therapy (yearly)	£847.52	None		See Appendix 2
Cost of treating a further resolving deep vein thrombosis, based on:				
Days on heparin	8.6	Log-normal	$m = 2.15$ $s = 0.043$	Boccalon *et al.*[88]
Unit cost per dose of low-molecular-weight heparin	£11.10	None		BNF[67]
Number of anticoagulant clinic reviews	4	None		Curtis and Netten[68]
Unit cost per anticoagulant clinic review	£22.00	None		NHS reference costs[69]
Treating post-thrombotic syndrome				
Unit cost of new vascular surgery outpatient appointment	£163.62	Normal	SEM = £5.67	NHS reference costs[69]
Unit cost of follow-up vascular surgery outpatient reviews	£100.68	Normal	SEM = £3.64	NHS reference costs[69]
Number of follow-up vascular surgery outpatient reviews	31	None		Goodacre *et al.*[59]
Treating a fatal pulmonary embolism				
Standard unit cost	£1,692.99	Normal	SEM = £42.13	NHS reference costs[69]
Excess bed-day charge[a]	£192.11	Normal	SEM = £3.69	NHS reference costs[69]
Treating a non-fatal pulmonary embolism				
Standard unit cost	£1,326.05	Normal	SEM = £30.86	NHS reference costs[69]
Excess bed-day charge[a]	£199.35	Normal	SEM = £3.29	NHS reference costs[69]
Treating a fatal haemorrhage				
Standard unit cost	£6,792.65	Normal	SEM = £169.82	Sandercock *et al.*[70]
Treating a non-fatal intracranial haemorrhage				
Impact cost	£5,774.78	Normal	SEM = £114.37	Sandercock *et al.*[70]
Maintenance cost (yearly)	£4,798.19	Normal	SEM = £119.95	Sandercock *et al.*[70]
Treating a non-fatal non-intracranial haemorrhage				
Standard unit cost	£652.45	Normal	SEM = £17.37	NHS reference costs[69]
Excess bed-day cost[a]	£206.75	Normal	SEM = £3.44	NHS reference costs[69]

a The excess bed-day cost is sampled and then the cost per case is determined before being added to the standard cost.

TABLE 81 *Parameters associated with treatment and diagnosis*

Description of variable	Mean value	Probability distribution	Parameters		Initial source
Efficacy of warfarin	0.95	Beta	$a = 40.777$	$b = 2.146$	Kearon *et al.*[18]
Diagnosis of DVT	0.95	Uniform	Min = 0.93	Max = 0.97	Assumption

TABLE 82 *Utilities*

Description of variable	Mean value	Probability distribution	Parameters		Initial source
Post VTE					
Receiving warfarin	0.987	A beta distribution was fitted to the data from Gage *et al.*[71] ($a = 22.06648$; $b = 0.29064$). Parametric bootstrapping using 70 patients per run was used to determine the values for the PSA			Gage *et al.*[71]
Not receiving warfarin	1	None			Assumption
Adverse events associated with VTE					
Post-thrombotic syndrome	0.977	Beta	$a = 232.64$	$b = 5.48$	O'Meara *et al.*[72]
Non-fatal pulmonary embolism	0.94	Beta	$a = 19.43$	$b = 1.24$	Goodacre *et al.*[59]
Severity of haemorrhage associated with warfarin treatment					
Non-fatal intracranial haemorrhage	0.29	Beta	$a = 8.34$	$b = 20.41$	O'Meara *et al.*[72]
Non-fatal non-intracranial haemorrhage	0.997	Uniform[a]	Min = 0.996	Max = 0.998	Goodacre *et al.*[59]

a Authors' assumption.

TABLE 83 *Prevalence of thrombophilia*

Description of variable	Mean value	Probability distribution	Parameters	Initial source
Factor V Leiden				
Homozygous	0.015	Normal	SD = 0.0038[a]	Dickey[9]
Heterozygous	0.3	Normal	SD = 0.0758[b]	Franco and Reitsma[8]
PTG20210A				
Heterozygous	0.115	Normal	SD = 0.0246[b]	Dickey[9]
Lupus anticoagulant	0.0267	Normal	SD = 0.0132[c]	Kearon *et al.*[18]
Anticardiolipin antibody	0.0270	Normal	SD = 00134[c]	Kearon *et al.*[18]
Antithrombin, protein C or protein S deficiency	0.13	Normal	SD = 0.0328[a]	Prandoni *et al.*[49]

a Assuming that the ratio between the standard deviation and the reported mean is equal to that seen in heterozygous factor V Leiden.
b Assuming that the reported ranges were 99% confidence intervals around the mean, which is the mid-point of the range.
c Calculated from the published data.

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We look forward to hearing from you.

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