Testing for factor V Leiden in patients with pulmonary or venous thromboembolism: a cost-effectiveness analysis
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Three strategies for the management of patients who had just suffered their first episode of venous thromboembolism (VTE) were examined. The strategies were:

standard anticoagulant therapy for 6 months without testing (no test and treat);
testing for factor V Leiden mutation and treating patients with positive results for 3 years (test and treat for 3 years);
testing for factor V Leiden mutation and lifetime treatment of those identified as carriers (test and treat for life).

Type of intervention
Screening, secondary prevention, and treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with a first venous thromboembolic event.

Setting
The setting was secondary care. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness evidence came from studies published between 1973 and 2001. The dates for the resource use data were not explicitly reported. The price year was 1999.

Source of effectiveness data
The effectiveness evidence was derived from a review of completed studies and authors' assumptions.

Modelling
A Markov state transition decision model was constructed to assess the costs and benefits of the alternative strategies in a hypothetical 35-year-old woman who had suffered her first episode of VTE. The structure of the tree and all health states were reported in the paper. The time horizon of the model was lifetime. The length of each cycle was not reported.
Outcomes assessed in the review
The outcomes estimated were:

the prevalence of factor V Leiden (at different initial ages);

the sensitivity and specificity of activated protein C resistance;

the rate of recurrent VTE in patients with or without factor V Leiden, with vena caval filter, or VTE;

the efficacy of anticoagulation therapy;

the efficacy of venal caval filter in preventing pulmonary embolism (PE);

the rates of death and permanent sequelae with deep venous thrombosis (DVT) or with PE;

the rate of major bleeding on warfarin;

the relative risk (RR) of major bleeding during the first month of warfarin therapy; and

the rates of death or permanent sequelae with major bleeding event.

Also estimated were:

the utility values associated with long-term morbidities (i.e. "well while receiving warfarin", permanent bleeding sequelae, and permanent post-phlebitic syndrome); and

the age-adjusted annual excess mortality with permanent bleeding sequelae.

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature was conducted. The design of some of the primary studies was reported, although for most of them no description was provided.

Sources searched to identify primary studies
The primary studies were identified using MEDLINE and the bibliographies of selected articles.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Thirty studies were included in the review.

Methods of combining primary studies
Not stated.

Investigation of differences between primary studies
Not stated.
Results of the review
The overall prevalence of factor V Leiden was 0.21; 0.23 for age younger than 45 years, 0.19 for age at least 45 years, 0.11 for age at least 70 years, and 0.40 in selected patients at risk for thrombophilia.

The sensitivity of activated protein C resistance was 84% and the specificity was 72%.

For the rate of recurrent VTE in patients with factor V Leiden, the RR in the first month was 5.2, the average rate was 0.074/year, the rate of idiopathic VTE was 0.126/year, and the rate of precipitated VTE was 0.055/year.

In patients without factor V Leiden, the RR after the first month was 8.9 and the average rate was 0.023/year.

In patients with vena caval filter, the RR was 1.87.

In patients with VTE, the probability of DVT was 0.75 and the probability of PE was 0.25.

The efficacy of anticoagulation therapy ranged from 0.66 to 0.95.

The efficacy of venal caval filter in preventing PE was 0.90.

With DVT, the rate of death was 0.03 and the rate of permanent sequelae was 0.17.

With PE, the rate of death was 0.21.

The rate of major bleeding while on warfarin was 0.011/year.

The RR of major bleeding during the first month of warfarin therapy was 10.

With a major bleeding event, the rate of death was 0.23 and the rate of permanent sequelae was 0.08.

The utility value was 0.99 for "well while receiving warfarin", 0.6 for permanent bleeding sequelae, and 0.95 for permanent post-phlebitic syndrome.

The age-adjusted annual excess mortality with permanent bleeding sequelae was 0.08.

The utility value associated with death was 0.

Methods used to derive estimates of effectiveness
The authors made some assumptions that were used not only to derive estimates of effectiveness, but also to define the model structure and options for treatment patterns.

Estimates of effectiveness and key assumptions
The authors' main assumption was that the sensitivity and specificity of the polymerase chain reaction (PCR) analysis were 100%. Since all false-positive test results were identified with follow-up PCR testing, this testing sequence had a sensitivity of 84% and a specificity of 100%. All other detailed assumptions were reported.

Measure of benefits used in the economic analysis
The summary benefit measure used was the quality-adjusted life-years (QALYs). These were derived from the decision model, combining data on survival and utility weights. An annual discount rate of 3% was applied, and discounted or undiscounted results were reported. The sources from which the utility data were derived were not given.

Direct costs
An annual discount rate of 3% was applied as lifetime costs were estimated. The unit costs and the quantities of resources used were not presented separately for all items. Micro-costing data were not provided. The health services included in the economic evaluation were hospitalisations, ambulatory care and testing. Hospitalisations were due to intracerebral haemorrhage, gastrointestinal bleed, DVT, PE and filter placement. Ambulatory care covered warfarin therapy and monitoring, non-anticoagulated patient with post-phlebitic syndrome, otherwise well patient, and patient with neurologic deficit following intracranial haemorrhage. Testing consisted of activated protein C resistance and PCR test for factor V Leiden mutation. The cost/resource boundary of the third-party payer appears to have been adopted. The costs were mainly derived from Medicare sources and other published studies. Resource use was obtained from published data and authors' assumptions. The price year was 1999. All the costs were inflated using the medical component of the Consumer Price Index.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not considered, even though the authors stated that a societal perspective was adopted.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were conducted to address the issue of variability in the data. Two alternative scenarios were considered. In the modified base-case it was assumed that, after the first 3 years, the risk of recurrent VTE in patients with factor V Leiden became the same as those without the mutation. In the constant rate scenario, a persistent risk of recurrent VTE at 7.3% per year was considered.

Under the constant rate scenario, the model inputs varied included the risk of major haemorrhage, the efficacy of anticoagulation therapy, disease prevalence, the rate of recurrent VTE in patients with factor V Leiden, and age. Also varied were the sensitivity of testing for activated protein C resistance, the efficacy of vena caval filter in preventing PE, and the discount rate.

Other specific case scenarios were also considered, where sets of inputs were varied simultaneously. The ranges of values used in the sensitivity analysis were presumably derived from the literature. No changes in cost inputs were performed.

**Estimated benefits used in the economic analysis**
Under base-case assumptions (risk of recurrent VTE at 16% for the first 3 years and then 0% thereafter), the discounted QALYs were 23.18 with test and treat for 3 years, 23.03 for no test and treat, and 22.94 for test and treat for life.

In the modified base-case, the discounted QALYs were 23.00 with test and treat for 3 years, 22.90 for no test and treat, and 22.91 for test and treat for life.

In the constant rate case, the discounted QALYs were 22.82 with test and treat for 3 years, 22.81 for no test and treat, and 22.89 for test and treat for life.

**Cost results**
Under base-case assumptions, the discounted costs were $9,676 with test and treat for 3 years, $10,392 for no test and treat, and $13,179 for test and treat for life.
In the modified base-case, the discounted costs were $11,210 with test and treat for 3 years, $11,513 for no test and treat, and $13,404 for test and treat for life.

In the constant rate case, the discounted costs were $12,599 with test and treat for 3 years, $12,260 for no test and treat, and $13,597 for test and treat for life.

**Synthesis of costs and benefits**

An incremental analysis was conducted to combine the costs and benefits of the alternative strategies.

In the base-case and modified base-case, the test and treat for 3 years strategy was both more effective and less costly than the other strategies, thus it was dominant.

In the constant rate scenario, no test and treat was as effective as, but less costly, than test and treat for 3 years. The incremental cost per QALY with test and treat for life over no test and treat was $16,823.

The most striking results of the sensitivity analysis under the constant rate scenario were as follows:

- beyond an annual bleeding rate of 1.6%, the cost per QALY of testing and treating for life exceeded the threshold of $50,000, while at rates greater than 1.9% per year, not testing was dominant (in the base-case, the annual bleeding rate was estimated to be 1.1%);

- testing and treating for life was the preferred strategy unless the efficacy of anticoagulation dropped below 62% and not testing became dominant;

- for a population of patients with a very low prevalence of factor V Leiden, the cost per QALY of testing and treating for life exceeded the recommended threshold;

- at rates of recurrent VTE lower than 4.5% per year, not testing dominated testing and treating for life, while in patients with a clear precipitant, the incremental cost per QALY was very high;

- the cost per QALY of testing and treating for life was also above the recommended threshold for women older than 67 years and men older than 71 years.

Variations in other model inputs did not change substantially the results of the base-case analysis.

**Authors' conclusions**

The strategy of test and treat for 3 years dominated the alternative strategies for the management of patients who had experienced their first episode of VTE. However, under an alternative scenario, the option of testing and treating for life had a reasonable cost-effectiveness ratio. Therefore, the results of the analysis were highly dependent upon the main assumption about the time-dependent risk of recurrent venous thromboembolism (VTE) in survivors of a first episode of VTE.

**CRD COMMENTARY - Selection of comparators**

The choice of the comparators appears to have been appropriate as it reflected the possible testing and treatment patterns for the sample of patients considered in the study. You should decide whether they are valid alternatives in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness evidence came from data mainly derived from published studies. A review of the literature was undertaken, but it does not appear to have been systematic. Limited information on the design, characteristics and patient samples of the primary studies was reported. In addition, the methods used to extract and combine the primary estimates were not described. Some assumptions were also made in the decision model. This introduced some
uncertainty into the analysis of the effectiveness. However, the authors performed extensive sensitivity analyses to address this issue, thus enhancing the robustness of the results of the analysis.

Validity of estimate of measure of benefit
The summary benefit measure (QALYs) was appropriate since the disease considered in the study had a strong impact on both quality of life and survival. Discounting was applied, as recommended in the USA, but the undiscounted results were also reported. The impact of variations in the discount rate was investigated in the sensitivity analysis. However, the sources used to assess the quality weights were not given and the issue of variation in the utility gains was not addressed. The use of QALYs permits comparisons to be made with the benefits of other health care interventions.

Validity of estimate of costs
The authors stated that a societal perspective was adopted in the study but the indirect costs, which would have been relevant to this perspective, were not included in the cost analysis. The unit costs were provided in macro-categories since Medicare reimbursement rates were used for most items. The information on resource use was sparse and was not reported satisfactorily. Several assumptions were also made, but these were not investigated in the sensitivity analysis. Overall, the cost analysis was specific to the study setting. The price year was reported, which makes reflation exercises in other settings possible. The costs were treated deterministically since no statistical test was conducted. No sensitivity analyses of the costs were conducted.

Other issues
The authors compared their findings with those from a completed study. Specifically, the authors replicated their study using the assumptions used in the published studies and found that their results would not have changed dramatically, as testing and treating for 3 years remained the preferred strategy, although with a minimal margin. However, the issue of the generalisability of the study results to other settings was not addressed explicitly and sensitivity analyses were not conducted on the cost estimates. This will have affected the external validity of the analysis. Also, all the sensitivity analyses were performed on the constant rate scenario and not on the base-case. The study referred to the population of patients with factor V Leiden who were heterozygotes and this was reflected in the conclusions of the analysis.

Implications of the study
The study results suggested that testing strategies are more cost-effective than no testing. However, the optimal duration of anticoagulation therapy depends on the risk of recurrent VTE over time. In particular, lifelong therapy is unlikely to be cost-effective for:

- a patient population with a very low prevalence of factor V Leiden;
- those with a lower risk for recurrent VTE (e.g. patients with a clear precipitant); or
- patients with risk factors for bleeding while receiving anticoagulant therapy (e.g. those older than 70, with a history of gastrointestinal bleeding and intracerebral haemorrhage, and renal or hepatic insufficiency).

Therefore, lifelong therapy should be limited to patients with no obvious precipitant for VTE, who are at low risk of bleeding complications from oral anticoagulant therapy. This issue should be investigated further in future studies.

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Bibliographic details
Other publications of related interest


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MeSH
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