Cost-effectiveness of testing for hypercoagulability and effects on treatment strategies in patients with deep vein thrombosis  
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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  
Various combinations of testing and non-testing for hypercoagulable conditions and duration of anticoagulation therapy (12, 18, 24 or 36 months) were compared in patients with idiopathic deep vein thrombosis (DVT). The testing strategies included Russell Viper Venom assays, and tests for anticardiolipin antibody, antithrombin III, Protein C and S levels plus genetic testing for factor V Leiden, prothrombin and dihydrofolate reductase. The base-case comprised anticoagulation therapy for 6 months followed by clinical observation.

Type of intervention  
Screening and treatment.

Economic study type  
Cost-utility analysis.

Study population  
The hypothetical cohort of patients comprised adults with suspected idiopathic DVT (DVT without a known inciting cause). In the base-case analysis the patient was 40 years of age. This age was chosen because hypercoagulable disorders causing the condition are more prevalent in younger patients.

Setting  
The setting was not reported, but it was likely to have been secondary care given the nature of the tests. The economic analysis was carried out in the USA.

Dates to which data relate  
The effectiveness data were collected from a review of studies carried out between 1990 and 2001. The resource use and cost data were collected from a review of studies carried out between 1997 and 1999.

Source of effectiveness data  
The effectiveness data were derived from a non-systematic review of completed studies and authors’ assumptions.

Modelling  
A Markov model was used to simulate transitions between several health states. The health states considered were well, anticoagulated, recurrent thrombosis, postphlebitic syndrome, bleeding complications due to therapy, thrombosis while anticoagulated, or death from thrombosis, bleeding complications or natural causes. The time horizon was 12, 18, 24, 36 months or lifetime. The cycle length was 1 year.
Outcomes assessed in the review
An ad hoc review of the literature was undertaken to identify the following model parameters:

- prevalence of hypercoagulable state;
- the annual relative risk of thrombosis in patients with hypercoagulable states versus unaffected patients;
- the age-dependent relative risk; test characteristics of screening panel;
- the baseline risk of recurrent thrombosis in unaffected patients;
- the risk of permanent postphlebitic syndrome following DVT;
- the risk of pulmonary embolus with thrombosis;
- the risk of permanent sequelae following a major bleeding episode;
- the relative risk of recurrent thrombosis with anticoagulation;
- bleeding complications; and
- mortality.

Study designs and other criteria for inclusion in the review
The review was ad hoc and there were no inclusion criteria.

Sources searched to identify primary studies
Not reported.

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

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

Number of primary studies included
Twenty-two primary studies were included in the review as sources of effectiveness evidence. The types of study included were not reported.

Methods of combining primary studies
A narrative method was adopted for combining the results of the primary studies. The range of results among the included studies was used for the sensitivity analysis.

Investigation of differences between primary studies
Not reported.

Results of the review
The following probabilities and risk estimates for effectiveness data were reported for the base-case:
the risk of permanent postphlebitic syndrome following DVT was 17% per occurrence (range: 13 - 22);
the risk of pulmonary embolus with thrombosis was 20% per occurrence (range: 10 - 30);
the risk of permanent sequelae following a major bleeding episode was 17% per occurrence (range: 12 - 21);
the relative risk of recurrent thrombosis with anticoagulation was 0.05 (range: 0.01 - 0.10);
bleeding complications in year 1 were 7.7% (range: 5.8 - 9.6) for minor bleeding and 3.8% (range: 2.9 - 4.8) for major nonfatal bleeding;
bleeding complications in subsequent years were 6.1% per year (range: 4.6 - 7.6) for minor bleeding and 2.4% per year (range: 1 - 3) for major nonfatal bleeding;
mortality was 15% per occurrence (range: 5 - 25) after pulmonary embolus, 14.3% per occurrence (range: 8 - 20) after major bleeding, and life table for age-related.

Although not part of the model parameters, the authors found that hypercoagulable disorders were present in at least 5% of the patients. In addition, those who had a relative risk 1.25 times that of unaffected patients should be included in a test panel.

Methods used to derive estimates of effectiveness
The authors made assumptions to derive estimates of effectiveness.

Estimates of effectiveness and key assumptions
Authors’ assumptions were reported in connection with baseline rates of recurrent thrombosis. In particular, the authors assumed that the baseline risk of pulmonary embolism did not differ between affected and unaffected patients.

The authors also assumed that the sensitivity and specificity of the screening panel were both 99%.

Measure of benefits used in the economic analysis
The measure of benefit used was the quality-adjusted life-years (QALYs). Health state utilities were taken from the literature (partially using automated computer interviews). Time preference was used to value the utilities. The benefits were discounted at an annual rate of 3%.

Direct costs
Relevant hospital and patient (transportation) costs appear to have been included in the analysis. The resource use and cost data were taken from the literature and reported separately. The cost data were derived from studies conducted between 1997 and 1999. The costs were converted to year 2000 US dollars, using a 3% rate of annual inflation. It was unclear whether the cost of 6 months' anticoagulation therapy, which was received by all patients, was excluded from the analysis. The authors stated that the costs were discounted at the rate of 3% per annum in order to reflect patient time preference.

Statistical analysis of costs
Descriptive statistics were reported for the costs, using annual or average values and ranges.

Indirect Costs
There were no reported indirect costs.
Currency
US dollars ($).

Sensitivity analysis
Parameter uncertainty (probabilities, costs and QALY weights) was investigated using a sensitivity analysis to extrapolate from the primary data sources. The analysis was conducted using ranges suggested in the literature, or by subtracting 25% from the base-case estimates. The specific areas investigated included lifelong costs of care following a major complication, complication rates, and test sensitivity and specificity. Also, the age-related costs of testing and anticoagulation treatment, and mortality from pulmonary embolus and from recurrent thrombosis. One- and two-way sensitivity analyses were conducted to determine how variations in relative risk and prevalence affected the choice of test for a hypercoagulability panel.

Estimated benefits used in the economic analysis
The incremental benefit of testing, followed by anticoagulation treatment of positives for 24 months, was 0.07 QALYs in comparison with no test and treat for 24 months. All other strategies were dominated (i.e. they were more costly and less effective).

Cost results
The incremental cost of testing, followed by anticoagulation treatment of positives for 24 months, was $730 in comparison with no test and treat for 24 months.

Synthesis of costs and benefits
The costs and benefits were combined as the costs per QALY. An incremental cost-effectiveness analysis was conducted.

Several strategies were excluded on the basis of comparisons of overall and marginal cost-effectiveness, following which two were deemed cost-effective.

The first strategy (testing, followed by 24 months' treatment) was associated with lifetime costs of $54,820 and a quality-adjusted life expectancy of 23.76 QALYs. This had an incremental cost-effectiveness of $11,100 per QALY over a strategy of 24 months' treatment without testing ($54,100 lifetime costs with a quality-adjusted life expectancy of 23.70 QALYs).

When the data were tested using higher short-term recurrence rates than in the base-case, a strategy of no testing with 36 months' treatment for all patients had the lowest cost ($54,740) and highest quality-adjusted life expectancy (20.67 QALYs).

Further analysis indicated 18 months' treatment as a preferred option. The authors reported that the sensitivity analysis did not invalidate any of the key findings.

Authors' conclusions
Testing for most hypercoagulable disorders in patients with idiopathic deep vein thrombosis (DVT) was cost-effective. Two years of initial treatment is cost-effective in affected patients and with most disorders, except in those at highest risk of recurrent thrombosis. The replacement of testing with 18 months or more of treatment is preferable if the recurrence rates are high in the years after the initial thrombosis.

CRD COMMENTARY - Selection of comparators
The justification for the choice of the base-case comparator was that it represented usual care. The variation in duration of therapy was justified by the risk of complications. You should decide if these represent valid comparators.
Validity of estimate of measure of effectiveness
There was no evidence that a systematic review of the literature was undertaken. Although this is common practice with models, it does not always ensure that the best data available are used in the model. The authors made assumptions to derive estimates of effectiveness, and no justification for these were provided. Uncertainty was investigated through sensitivity analyses.

Validity of estimate of measure of benefit
The measure of benefit used was the health utility (QALYs) measured over a lifetime. The utilities were obtained from the literature, although the methods used to determine them were not reported.

Validity of estimate of costs
The authors stated that a societal perspective had been used. However, the indirect costs were not reported and only patient transportation costs were considered. Consequently, the perspective appears to have been that of the health service. Costs relevant to a health service perspective appear to have been included. It was unclear whether the cost of initial anticoagulation therapy (6 months) was included in the analysis. However, as this was common to both groups, it was unlikely to have affected the authors' conclusions. The costs and the quantities were reported separately and the price year was reported. Therefore, the analysis is potentially reproducible in other settings. The resource quantities were taken from the literature, but no justification for the studies chosen was given. In addition, the fact that there was no reported sensitivity analysis of the quantities introduces uncertainty into the results. The costs were taken from published sources and the sensitivity analysis was appropriate to test the robustness of the estimates used. Currency conversions were performed. The authors justified discounting at 3% per annum to reflect patient time preference. This appears to have been appropriate given the clinical condition.

Other issues
The authors compared their findings with those from other studies, observing that others had considered only single hypercoagulable disorders using various model structures and assumptions. There was insufficient information on the characteristics of the hypothetical cohort to determine whether the findings of this study were generalisable to other patient populations or settings. The authors referred to several limitations. For example, the broad range of values used for relative risk and prevalence of disorders, which limits the application of findings (to the use of thresholds) in practice. The fact that the costs of minor complications were based on inpatient diagnosis-related groups (owing to the lack of information on the costs of "minor events") may also limit the generalisability of results. The model did not evaluate the possible rise in recurrent thrombosis due to nonadherence to therapy, although the sensitivity analysis did not reveal that this (along with thresholds for anticoagulation efficacy or complication rate) would invalidate the results. Finally, the authors pointed out that, as the cost-effectiveness model was based on a population-level perspective, this potentially limits the generalisability of the findings to individual patients.

Implications of the study
The authors suggested that the findings of this study will provide clinicians with guidance on the testing of hypercoagulable disorders. They also suggested that future research should prospectively evaluate these findings in clinical practice.

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