Testing strategies for diagnosing lupus anticoagulant: decision analysis

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 testing strategies for the detection of lupus anticoagulant (LA) were considered. The testing strategies were different combinations of three tests:

- a prolonged activated partial thromboplastin time (aPTT) assay prolonged with negative mixing studies and a platelet neutralisation procedures (PNP) assay that suggested the presence of LA;
- dilute Russell viper venom times (dRVVT) assays; and
- tissue thromboplastin inhibition (TTI) assay.

Type of intervention
Diagnosis.

Economic study type
Cost-utility analysis.

Study population
The study population comprised three patient populations:

- patients with systemic lupus erythematosus (SLE), with or without antiphospholipid syndrome;
- patients in a high-risk obstetrics clinic because of recurrent foetal loss, or patients with prior deep venous thrombosis (DVT); and
- healthy people without known coagulopathy (with a prolonged aPTT on screening).

Setting
The setting was secondary or tertiary care. The economic analysis was carried out in Baltimore (MD), USA.

Dates to which data relate
The effectiveness data were gathered from studies published between 1983 and 2000. The resource data were gathered from studies published between 1996 and 1999. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from published studies and discussion with experts.

Modelling
Three decision analytic models were created to simulate the costs and the health outcomes assigned to each strategy in the three patient populations.

The seven health states defined were well, major bleed, myocardial infarction (MI), DVT, foetal loss, stroke and death. Three health states were related to the intervention. These were well, major haemorrhage related to anticoagulation, and death.

The model was based on several assumptions (see below). The time horizon was 1 year.

**Outcomes assessed in the review**
The outcomes assessed in the review and used as model inputs were:

- the prevalence of LA in the three populations,
- the rates of adverse events,
- the sensitivity and specificity of each strategy, and
- the utilities assigned to each health state.

**Study designs and other criteria for inclusion in the review**
Not reported.

Studies were retrieved if they reported adverse outcomes in any of the three populations, in a way that permitted annual incidences to be calculated.

**Sources searched to identify primary studies**
Different sources were used to identify the primary studies. More specifically, a search of MEDLINE using PubMed and a review of current textbooks of rheumatology and haematology.

**Criteria used to ensure the validity of primary studies**
Not specified.

**Methods used to judge relevance and validity, and for extracting data**
One rheumatologist reviewed the probabilities to see whether they approximated the incidences seen in her practice.

**Number of primary studies included**
Approximately 28 studies were included in the review.

**Methods of combining primary studies**
The results of the individual primary studies were combined using a narrative method.

**Investigation of differences between primary studies**
The authors did not investigate any differences between the primary studies.

**Results of the review**
The prevalence of LA was 3% in healthy people.
The prevalence of LA was 35% in patients with SLE.

The prevalence of LA was 8% in patients with recurrent abortions and 9% in patients with thromboses.

The incidence of DVT was 0.95% in the general population with LA, 4.3% in patients with SLE, and 5.0% in patients in a high-risk obstetrics clinic.

The incidence of stroke was 1.1% in the general population with LA, and 2.3% in patients with SLE and patients in a high-risk obstetrics clinic.

The incidence of foetal loss was 0.6% in the general population with LA, 0.8% in patients with SLE, and 2.0% (patients not anticoagulated), or 0.9% (patient anticoagulated) in a high-risk obstetrics clinic.

The incidence of MI was 0.48% in the general population with LA, and 0.7% in patients with SLE and patients in a high-risk obstetrics clinic.

The incidence of major non-cerebral bleed was 0.5% in the general population with LA, and 2% (patients not anticoagulated) or 1.0% (patient anticoagulated) in SLE clinics and a high-risk obstetrics clinic.

The incidence of death was 0.1% in the general population with LA, and 0.15% in patients with SLE and patients in a high-risk obstetrics clinic.

Methods used to derive estimates of effectiveness

The authors made several assumptions to estimate the outcomes. It appears that estimates were based on authors' opinion and discussion with experts.

Estimates of effectiveness and key assumptions
Asymptomatic people were assumed not to be anticoagulated even after a positive test for LA.

Patients from a general clinic who did not test positive for LA were assumed to have a negligible risk of adverse events.

Patients undergoing evaluation because of clotting or recurrent spontaneous abortion were assumed to be anticoagulated for the entire year, regardless of the presence or absence of LA upon testing.

Patients with prior thrombosis and no LA were assumed to be at negligible risk for recurrent events while they were on an anticoagulant.

The utilities were assumed to be the same for each population.

Measure of benefits used in the economic analysis
The authors used utility assessment as a means to gauge whether the least costly strategies were likely to be acceptable to patients. The utility values were derived from the literature. Therefore, the authors evaluated whether any strategy could be expected to be of greater utility to a patient than another. The sensitivities and specificities of each strategy were also calculated in the model.

Direct costs
The hospital costs were evaluated. The costs items included were those associated with the testing strategy (including the technologist's cost) and those incurred from adverse events resulting from misdiagnosis or from treatment. Fixed costs, such as equipment costs, were not included because they were fairly constant across the strategies. The testing costs were estimated on the basis of overhead and reagent costs from one tertiary care institution. The foetal loss costs were estimated from institutional charges, and from Medicare reimbursement for dilatation and curettage. All of the other costs were derived from the literature. The authors assumed that patients with a positive diagnosis did not incur...
substantially more costs from more frequent visits, as patients with SLE were seen on a regular schedule regardless of the presence of LA. The costs were assumed to be the same across models. The unit costs and the quantities of resources were reported separately. The price year was not reported. The costs were not discounted, which was appropriate as they were incurred during less than 2 years.

**Statistical analysis of costs**
No statistical analysis of the costs was performed.

**Indirect Costs**
The indirect costs were not included.

**Currency**
US dollars ($).

**Sensitivity analysis**
One-way sensitivity analyses were performed on all parameter values, using ranges derived from the literature. Parameters to which the model was sensitive, and those variables thought to be particularly clinically relevant, were tested in two- and three-way sensitivity analyses.

**Estimated benefits used in the economic analysis**
The utility associated with each strategy was not reported.

In the models of patients with prolonged aPTT, or with thrombosis or foetal loss, the path with the greatest utility was "not testing and assuming no patient had LA".

In the model of patients with SLE, the strategy with the highest utility was that of "using TTI followed by dRVVT and confirmatory dRVVT".

The results were robust to changes in the utility values.

**Cost results**
The total costs were not reported. The least costly strategy in healthy people with prolonged aPTT, or with thrombosis or foetal loss, was "not testing" for LA, assuming that the patients did not have LA. The models were robust to all variables, except the prevalence in the first model and the probability of LA in the second.

The least costly strategy in patients with SLE was "not testing" for LA, assuming that the patients did not have LA. The next least expensive strategy was that involving the use of TTI alone, which was preferred in many of the sensitivity analyses performed. This model was sensitive to many variables. More specifically, the cost of stroke, cost of DVT, cost of MI, cost of a major bleed, the hourly cost of a technician, the probability of a major bleed, the probability of LA, the probability of adverse events with therapy, and the sensitivity of the TTI test.

**Synthesis of costs and benefits**
The costs and benefits were not combined.

**Authors' conclusions**
The optimal path in healthy people with prolonged activated partial thromboplastin time (aPTT), or with thrombosis or foetal loss, was "not testing" for lupus anticoagulant (LA). In the model of patients with systemic lupus erythematosus
(SLE), the strategy with the highest utility (using tissue thromboplastin inhibitor, TTI) was not the least expensive strategy (not testing).

**CRD COMMENTARY - Selection of comparators**

The rationale for the choice of the comparators was clear. They represented possible testing strategies for the detection of LA. You should decide whether they represent approaches currently used in your own setting.

**Validity of estimate of measure of effectiveness**

A review of the literature was undertaken. However, it was not evident that it was done systematically. The source searched to identify the primary studies was reported. The criteria used to ensure the validity of the primary studies were not reported, nor were the methods used to judge the relevance and validity of the data. In addition, there was little discussion of the quality of the retrieved studies, thus making it difficult to comment on the quality of the efficacy estimates. However, the impact of differences between the primary studies and the relevance of the assumptions made on estimates were assessed in sensitivity analyses. These analyses improved both the internal validity and the generalisability of the study by demonstrating the robustness of the results to changes in the base-case estimates.

**Validity of estimate of measure of benefit**

The estimate of benefits was modelled. The utility weights were derived from the literature, but the authors did not report whether the studies reported utility values derived from patients’ preferences or from experts’ opinion. This fact hinders the interpretation of the utility measurements. Discounting was not relevant and, appropriately, was not performed. The total utility assessment for each model was not reported, thus making it difficult for the reader to understand the results. The authors provided no justification for the time horizon (one year).

**Validity of estimate of costs**

All the categories of costs relevant to the perspective adopted (hospital) appear to have been included in the analysis. Fixed costs were not included, but their exclusion was justified on the grounds that they were fairly constant across the strategies. Details of the unit costs and sources of resources were reported, but not the quantities of resources, which may limit the generalisability of the economic analysis to other settings. The price year was not reported and this prevents reflation exercises. Discounting was not relevant, as the follow-up considered in the analysis was no longer than one year, and was not performed. A sensitivity analysis on the costs was performed to account for variability in the cost estimates.

**Other issues**

The authors did not make appropriate comparisons of their results with those from other published studies. They also did not address the issue of the generalisability of the study results to other settings. The results were not reported selectively and the conclusions reflected the scope of the study. The authors highlighted some limitations of their study. These focused on the absence of a diagnostic standard to which the strategies could be compared and the limited quality of the estimates used in the study. Sensitivity analyses were performed to account for variability in the cost or effectiveness data. Consequently, the external validity of the study may be high.

**Implications of the study**

The authors recommended that clinicians’ strategies for detecting LA may need modification. They also suggested that prospective trials are needed to test the diagnostic approaches that they have identified as being most cost-effective, in appropriate patient populations.

**Source of funding**

None stated.
Bibliographic details

PubMedID
12111765

DOI
10.1002/ajh.10115

Indexing Status
Subject indexing assigned by NLM

MeSH
Abortion, Spontaneous /immunology; Autoantibodies /blood; Costs and Cost Analysis; Decision Trees; Humans; Lupus Coagulation Inhibitor /blood; Lupus Erythematosus, Systemic /immunology; Partial Thromboplastin Time; Prothrombin Time; Sensitivity and Specificity; Thromboplastin /antagonists & inhibitors; Thrombosis /immunology

AccessionNumber
22002001174

Date bibliographic record published
31/08/2005

Date abstract record published
31/08/2005