Value of quantitative D-dimer assays in identifying pulmonary embolism: implications from a sequential decision model
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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
The study examined the use of the quantitative D-dimer assay in evaluating patients for suspected pulmonary embolism (PE).

Type of intervention
Diagnosis.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients presenting to an urban emergency department with suspected PE.

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

Dates to which data relate
The effectiveness data related to 1975 to 2004. The resource use and cost data related to 1999 to 2003. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a review of published studies and authors' opinions.

Modelling
A sequential decision model was developed to assess the cost-effectiveness of the 60 different diagnostic strategies for the evaluation of patients with suspected PE. The model assumed that a patient with suspected PE was given an initial clinical evaluation during which their risk category was assessed in terms of their Wells score. Next, the decision to order a test was made, and if this was the D-dimer assay, the clinician decided which cut-off value would trigger an imaging test. If a VQ scan were chosen then the cut-off value for the VQ scan was chosen for when anticoagulation and hospitalisation for PE was initiated. Finally, treatment was determined by the results of the imaging tests. The model had a lifetime horizon. The model used an average age of presentation of 55 years and an average remaining lifetime of 25 years.

Outcomes assessed in the review
The outcomes assessed included:
the incidence of deep vein thrombosis (DVT) for patients with known and suspected PE,
the mortality rates,
the distribution of patients between high, moderate and low Wells categories, and
the incidence of PE within each category.

The performance of the D-dimer assay was assessed according to tested cut-off values. The performance of the other diagnostic imaging tests (e.g. VQ, CVT, CUS and CTP) was also assessed.

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

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
The review includes at least 32 studies for effectiveness and natural history parameters.

Methods of combining primary studies
The primary studies were combined using a narrative method. The final estimates for the model parameters were based on authors’ assumptions where more than one primary source was available.

Investigation of differences between primary studies
Not reported.

Results of the review
The sensitivity of the D-dimer assay for PE varied between 0.99998 and 0.79997 for cut-off values between 200 and 800 ng/mL. The specificity across those same cut-off values varied from 0.08312 to 0.76085.

The sensitivity of CVT for DVT was set at 0.8 and the specificity at 0.98.

The sensitivity of CUS for DVT was set at 0.93 and the specificity at 0.98.

The sensitivity of CTP for DVT was set at 0.9 and the specificity at 0.8.

Methods used to derive estimates of effectiveness
A fitted gamma distribution was used to predict the sensitivity and specificity of the D-dimer assay for PE for the cut-off values of 200, 650 and 800 ng/mL. The sensitivity and specificity of three further cut-off values for the D-dimer assay were modelled by fitting a gamma distribution to the results of studies that evaluated cut-offs of 350 and 500
ng/mL.

**Estimates of effectiveness and key assumptions**
It was assumed that the pre-test probability of PE for high and moderate Wells patients did not vary with suspicion of DVT.

**Measure of benefits used in the economic analysis**
The study estimated quality-adjusted life-years (QALYS) as the measure of benefits used in the economic analysis. The authors did not specify the method by which quality adjustments were derived in the primary studies. They reported that, where published quality adjustment values were not available for particular clinical states in the model, they made use of quality adjustments for an “approximately equivalent” state. The health benefits were discounted at an annual rate of 3%.

**Direct costs**
The study included the direct hospital costs of diagnosis, treatment and liability payments. The cost data were derived from the literature, Medicare data and national malpractice databases. The prices were based primarily on Medicare tariffs. Discounting was applied appropriately at an annual rate of 3%. The study reported the unit costs separately. The paper did not provide the cost results for every diagnostic strategy evaluated. The price year was not reported.

**Statistical analysis of costs**
Since sampled data were not available for the costs, statistical analysis was not possible.

**Indirect Costs**
The authors reported that the indirect costs were captured in the analysis throughout the time of workup (i.e. the result of increased nursing and physician care associated with different workups). The unit costs were reported separately, based on authors’ estimations. The price year was not reported.

**Currency**
US dollars ($).

**Sensitivity analysis**
The authors conducted several one-way and multi-way sensitivity analyses to investigate variability in all parameters used in the model.

**Estimated benefits used in the economic analysis**
The authors did not report the total QALYs obtained for each of the 60 diagnostic strategies evaluated. The QALY-maximising strategy for patients in all Well pre-test categories was estimated to be CTA with no D-dimer assay.

**Cost results**
The authors did not report the total costs estimated for each of the 60 diagnostic strategies evaluated.

The cost-minimising strategy for patients in the Wells pre-test categories of "high; DVT suspected", "high; no DVT suspected", "moderate; DVT suspected" and "moderate; no DVT suspected" was estimated to be CUS-CTP, with D-dimer assay with cut-off 350 ng/mL.

The cost-minimising strategy for patients in the Wells pre-test category of "low" was estimated to be CUS-CTP, with D-
dimer assay with cut-off 650 ng/mL.

**Synthesis of costs and benefits**
The costs and benefits were synthesised to estimate incremental cost-effectiveness ratios in terms of the cost per QALY gained by moving from the cost-minimising strategy to the QALY-maximising strategy. The incremental cost-effectiveness ratio was:

- $11,937 for patients in the Well pre-test category of "high; DVT suspected";
- $6,334 for patients in the Wells pre-test category of "high; no DVT suspected";
- $53,250 for patients in the Wells pre-test category of "moderate; DVT suspected";
- $6,232 for patients in the Wells pre-test category of "moderate; no DVT suspected"; and
- $9,088 for patients in the Wells pre-test category of "low".

A discount rate of 3% per annum was applied to the costs and QALYs.

**Authors' conclusions**
Computed tomography angiogram (CTA) without D-dimer assay was cost-effective in all cases studied, except cases of extreme parameter estimates for patients in the Wells pre-test category "moderate; deep vein thrombosis (DVT) suspected".

**CRD COMMENTARY - Selection of comparators**
The authors evaluated a wide range of diagnostic strategies in patients with suspected PE. They compared the introduction of the D-dimer assay to a range of strategies that included those used in current practice in the study setting. You should decide whether the diagnostic strategies investigated are relevant in your own setting.

**Validity of estimate of measure of effectiveness**
The estimate of effectiveness was derived from a review of published studies and authors' assumptions. The authors did not state whether a systematic review of the literature had been undertaken. They used data from the available studies selectively and did not consider the impact of differences between the primary studies when estimating effectiveness. The authors justified their use of a parametric method to estimate the performance of the D-dimer assay with reference to the fact that there was an absence of full data from the assay's manufacturer. The estimates were investigated in several one-way and multi-way sensitivity analyses.

**Validity of estimate of measure of benefit**
The estimation of benefits was modelled using a sequential decision model. The method used to derive the quality adjustment values used to calculate the QALYs was not described in detail.

**Validity of estimate of costs**
The authors did not specify a perspective for the analysis. They reported that the indirect costs were included. However, the estimation of indirect costs did not reflect the true productivity cost of diagnostic strategies. Those costs would seem to represent additional medical costs associated with the intervention. Therefore, the perspective adopted in the study remained unclear. The authors appear to have incorporated only hospital costs from the perspective of a third-party payer in the form of Medicare. The costs and the quantities were not reported separately for all cost categories, thus it will not be easy to rework the analysis for other settings. However, the authors carried out extensive sensitivity analyses to investigate the robustness of the results to changes in the base-case estimates. Discounting was appropriately reported. However, the price year was not reported and this will present an obstacle to future inflation exercises.
Other issues
The authors compared the results of their study with those from economic evaluations in the same diagnostic area. The issue of generalisability to other patient groups was not addressed. The authors did not present their results in full, but this might have been due to the large number of diagnostic strategies evaluated. The authors’ conclusions reflected the scope of their analysis. The authors acknowledged one major limitation to their study, namely the use of a model and data from the literature.

Implications of the study
The authors suggest that the analysis can be refined when the results of an ongoing prospective study become available.

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