Effectiveness and cost-effectiveness of thrombolysis in submassive pulmonary embolism
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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
Two treatments for patients with submassive pulmonary embolism (PE) and right ventricular dysfunction (RVD) were studied. The treatments were alteplase plus heparin (thrombolysis) versus heparin alone. Patients treated with heparin alone received an intravenous bolus of 5,000 units of unfractionated heparin followed by an initial infusion of 1,000 units per hour adjusted to maintain an activated partial thromboplastin time of 2.0 to 2.5 times the upper limit of normal. Patients in the alteplase plus heparin treatment group received a 10-mg bolus of alteplase, followed by a 90-mg intravenous infusion over a 2-hour period. After completing the infusion, this group then received unfractionated intravenous heparin in the same manner as the heparin alone group.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of haemodynamically stable patients with submassive PE and RVD. A haemodynamically stable patient was defined as one with a systolic blood pressure higher than 90 mmHg. The analysis was restricted to patients who did not have an absolute contraindication to non-emergent thrombolytic therapy. Absolute contraindications included a recent stroke, major trauma within the preceding 10 days, gastrointestinal bleeding, and major surgery, biopsy, or thrombolytic treatment within the last 7 days. Further absolute contraindications were uncontrolled hypertension, current pregnancy or lactation, and a life expectancy of less than 6 months because of underlying disease.

Setting
The setting was a hospital. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data and some information on resource consumption were derived from studies published between 1992 and 2002. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Modelling
A Markov model was constructed to determine the costs and benefits of the two treatments in a hypothetical cohort of eligible patients. The time horizon of the model was lifetime, and a monthly cycle length was adopted. Patients entered
the Markov process immediately after their response to the initial treatment had been determined. Initial health states included recurrent PE, intracranial haemorrhage (ICH), severe bleeding, minor bleeding and full health. Patients who did not experience a recurrence or complication were considered to be healthy. Patients who experienced ICH were at risk of entering the "disabled" health state. Patients in the "well" health state were at risk of experiencing recurrent PE, and in the case of moving to this health state they were subsequently at risk of experiencing intracerebral haemorrhage, severe noncerebral bleeding and minor bleeding. A schematic representation of the Markov model was provided.

Outcomes assessed in the review
The outcomes assessed were:

- the mortality risk from PE with heparin alone;
- the reduction in mortality (relative risk, RR) for thrombolysis (alteplase plus heparin) versus heparin alone;
- the proportion of patients requiring treatment escalation for heparin alone and RR compared with thrombolysis;
- the percentage of patients with ICH;
- severe and minor bleeding with heparin alone and RR compared to thrombolysis;
- the proportions of patients who received specific interventions (catecholamine infusion for persistent hypotension, endotracheal intubation, embolectomy, or rescue thrombolysis);
- early and late recurrent PE;
- death following recurrent PE;
- death following ICH;
- death following severe bleeding;
- neurological deficits in survivors of ICH;
- the proportion of patients requiring long-term nursing care following ICH; and
- quality of life adjustments associated with PE, ICH, severe bleeding and neurological disability following ICH.

Study designs and other criteria for inclusion in the review
A review of the literature was undertaken to identify the primary studies used to populate the decision model. Inclusion and exclusion criteria were not reported, but only studies in the English language were sought. Treatment effect came from a large randomised clinical trial. Other data came from different sources, some of which were described, such as:

- the Prospective Investigation of Pulmonary Embolism Diagnosis study (for early and late recurrent PE);
- an international, multicentre registry, the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries trial (for probability of disability after ICH), a review of 18 clinical trials (for probability of death after ICH);
- the International Cooperative Pulmonary Embolism Registry (for risk of death after severe bleeding); and

Age-specific utilities for current health were derived from a large, community-based, cohort study of health-related quality of life in adults. The utility of long-term disability following ICH came from a study that used the time trade-off technique in 57 at-risk patients with chronic atrial fibrillation.
Sources searched to identify primary studies
MEDLINE and EMBASE were searched from 1966 to December 2003. The search was then updated in February 2006. Original articles were also checked for relevant references.

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
Fifteen primary studies provided the clinical data.

Methods of combining primary studies
A narrative approach appears to have been used to combine the primary estimates.

Investigation of differences between primary studies
The authors stated that there was some heterogeneity in patient populations between the clinical trial used for treatment effect and other sources of clinical evidence.

Results of the review
The rate of events in patients receiving heparin and the RR associated with alteplase plus heparin over heparin alone were, respectively:

- 2.7% and 1.0 (range: 0.36 to 6.80) for mortality from PE;
- 23% and 0.4 (range: 0.36 to 6.80) for patients requiring treatment escalation;
- 0.4% and 3.0 (range: 1.7 to 5.5) for ICH;
- 1.3% and 4.2 (range: 2.8 to 4.8) for severe bleeding; and
- 4.1% and 2.3 (range: 1.0 to 4.9) for minor bleeding.

Amongst those who required treatment escalation, the proportions of patients receiving specific interventions were:

- 24.0% (range: 19.0 to 30.0) for catecholamine infusion for persistent hypotension;
- 13.0% (range: 9.7 to 17.7) for endotracheal intubation;
- 2.2% (range: 0.1 to 4.8) for embolectomy; and
- 100% for rescue thrombolysis.

The rate of early recurrent PE was 4.0% (range: 2.5 to 6.4) in the first week and 4.3% (range: 2.7 to 6.8) annually after the first week (late recurrent PE).

The rate of death following recurrent PE was 34% (range: 30 to 44).

The rate of death following ICH was 45% (range: 21 to 72).
The rate of death following severe bleeding was 4.9% (range: 2.7 to 8.9).

The rate of neurological deficits in survivors of ICH was 62% (range: 53 to 71).

The proportion of patients requiring long-term nursing care following ICH was 12% (range: 9 to 15).

The quality of life adjustments were:

0.60 (range: 0.20 to 0.80) for PE;

0.12 (range: 0.00 to 0.91) for ICH;

0.76 (range: 0.50 to 0.99) for severe bleeding; and

0.34 (range: 0.00 to 1.00) for neurological disability following ICH.

**Measure of benefits used in the economic analysis**
The summary benefit measures used were the life-years (LYs) and quality-adjusted life-years (QALYs). These were estimated using the modelling approach. The utility weights were derived from the literature. An annual discount rate of 3% was used.

**Direct costs**
The viewpoint of the third-party payer appears to have been used. The categories of costs included in the analysis were those associated with initial hospitalisations (including study drugs), management of recurrent late PE, treatment escalation, minor bleeding, nursing home care for disability after ICH, treatment of complications in patients responding to primary treatment (ICH, recurrent early PE and severe bleeding), and treatment of complications for patients requiring treatment escalation. The unit costs were not presented separately from the quantities of resources used since as most costs were reported as macro-categories. The costs were mainly derived from Medicare reimbursements. The drug costs reflected average wholesale prices. Resource use was based on data derived from the clinical trials providing the clinical evidence or was assumed by the authors. Discounting was relevant, as the long-term costs were evaluated, and an annual rate of 3% was applied. The price year was 2002.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case analysis.

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

**Currency**
US dollars ($).

**Sensitivity analysis**
One-, two- and multi-way sensitivity analyses were carried out to assess the robustness of the study results to variations in the clinical and economic inputs. The inputs were varied using published ranges. A probabilistic sensitivity analysis was also carried out by assigning probabilistic distributions to those model inputs with the greatest impact on cost-effectiveness ratios. Log-normal or beta distributions were assigned to probabilities, while uniform distributions were assigned to costs.

**Estimated benefits used in the economic analysis**
The expected LYs were 10.57 with heparin alone and 10.52 with alteplase plus heparin (difference -0.050).

The expected QALYs were 8.04 with heparin alone and 7.99 with alteplase plus heparin (difference -0.051).

Cost results
The expected costs per patient were $43,281 with heparin alone and $43,936 with alteplase plus heparin (difference $655).

Patients who received treatment with alteplase plus heparin had higher costs for initial treatment ($9,400 versus $6,700) and treatment complications ($1,450 versus $1,100), but these were partly offset by lower costs for treatment escalation ($1,100 versus $3,300).

Future health costs were similar between the two groups ($31,986 versus $32,137).

Synthesis of costs and benefits
An incremental analysis was carried out to combine the costs and benefits of the alternative strategies. Under base-case assumptions, treatment with heparin alone was the dominant option since it was both more effective and less expensive than treatment with alteplase plus heparin.

The one-way sensitivity analysis showed that only when the RR of death from PE following thrombolytic therapy was 0.68 or lower did thrombolysis become more effective and cost less than $50,000 per QALY gained compared with heparin alone. The two-way sensitivity analysis suggested that, in general, the effectiveness and cost-effectiveness of alteplase plus heparin became more favourable as the baseline risk of death from PE increased and the RR of death decreased. The multi-way sensitivity analysis showed that thrombolytic therapy was cost-effective only under specific scenarios. Finally, the probabilistic sensitivity analysis showed that heparin alone was more effective and less costly (dominant) in 23% of all simulations, and it was more effective and cost less than $50,000 per QALY gained in another 44% of simulations. On the other hand, thrombolytic therapy was more effective and cost less than $50,000 per QALY gained in 32% of simulations. The cost-effectiveness acceptability curve indicated that, at a societal willingness-to-pay threshold of $50,000 per QALY gained, there was a 66% probability that heparin alone was cost-effective and a 33% probability that thrombolysis was cost-effective.

Authors’ conclusions
The use of heparin alone for the treatment of haemodynamically stable patients with pulmonary embolism (PE) and right ventricular dysfunction (RVD) was more cost-effective than alteplase plus heparin in the USA. However, the analysis showed that thrombolytic treatment might be cost-effective in sub-groups of patients at high risk of death from PE.

CRD COMMENTARY - Selection of comparators
No explicit justification was provided for the choice of the comparators, although they did reflect the two alternative strategies commonly used to treat haemodynamically stable patients with PE and RVD in the USA. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were obtained from a review of the literature, the methods and conduct of which were partially reported in the technical appendix. The authors did not use specific inclusion or exclusion criteria, with the exception of the selection of English language studies. Most of the details of the primary studies were reported in the technical appendix, where the sources of each model parameter were also described. Treatment efficacy and other data came from clinical trials, the randomised designs of which should have ensured a high internal validity. However, there was limited information on the methods used to combine the primary estimates. The authors noted that there was some heterogeneity in patient populations of the studies included, but did not explicitly address this issue. The sensitivity...
analysis investigated the impact of individual estimates on the results of the analysis.

**Validity of estimate of measure of benefit**
Both benefit measures used in the analysis were appropriate. Specifically, QALYs capture the impact of the interventions on the most relevant dimensions of health (i.e. survival and quality of life). In addition, LYSs and QALYs are comparable with the benefits of other health care interventions. QALYs were calculated using health-related quality of life data, the sources of which were reported in the appendix. Discounting was performed in accordance with economic evaluation guidelines.

**Validity of estimate of costs**
The authors stated that societal costs were included in the analysis, but only direct medical costs relevant to the third-party payer appear to have been considered. The indirect costs were not, therefore, taken into account. The authors justified the exclusion of these costs on the grounds of the risk of double-counting since QALYs (the denominator of the cost-effectiveness ratio) already capture the value of time lost due to the disease. The sources used to derive the costs were explicitly reported and would appear appropriate. Information on the unit costs and quantities of resources used was not provided separately, which might limit the possibility of replicating the analysis in other settings. However, the use of macro-categories of costs reflected the accounting system used in the Medicare programme. Statistical analyses of the costs were performed only in the sensitivity analysis. The price year was reported, which will simplify reflation exercises in other time periods. The sensitivity analysis addressed the issue of uncertainty in the cost estimates extensively.

**Other issues**
The authors did not compare their findings with those from other studies. The issue of the generalisability of the study results to other settings was not explicitly addressed, but the extensive use of sensitivity analysis enhances the external validity of the study. The authors noted some limitations of their analysis, such as the fact that potential mechanisms by which alteplase could improve outcomes over heparin alone were not considered. Similarly, the use of vena cava filters was not modelled. The results of the sensitivity analysis showed a high uncertainty around the base-case results. The study referred to haemodynamically stable patients with PE and RVD and this was reflected in the authors’ conclusions.

**Implications of the study**
The study results did not support the routine use of alteplase plus heparin for the treatment of haemodynamically stable patients with PE and RVD. Future studies should help identify high-risk groups of patients who could benefit from thrombolytic treatment.

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None stated.

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**Other publications of related interest**
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