Cost-effectiveness of low-molecular-weight heparin in the treatment of proximal 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
Low-molecular-weight heparin (LMWH) was used to treat patients with proximal deep venous thrombosis. The comparator was unfractionated heparin (UH) which was the standard treatment. No ‘do nothing’ option was considered. For both health technologies, treatment was administered for six days, although exact doses were not specified.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population consisted of 1,000 hypothetical patients who had proximal deep venous thrombosis.

Setting
The study setting was an acute care facility. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were taken from studies published between 1980 and 1999 (most of which were published during the 1990s). The cost data were taken from 11 studies, published between 1988 and 1997 (most of which were published during the mid-1990s). The price year was 1996.

Source of effectiveness data
Effectiveness data were derived from a review/synthesis of the literature.

Modelling
A decision model was developed in order to determine the most cost-effective method of treating deep venous thrombosis. A cohort of 1,000 patients were initially given the options of either: treat with UH; treat with LMWH; or selective treatment with UH or LMWH (depending upon whether or not the patient was a candidate for outpatient treatment: UH if no, LMWH if yes). Probabilities were then used to determine the success of treatment, including the possibility of complications and a three month follow up period (where recurrences were possible).

Outcomes assessed in the review
The parameters of the model included the probability of: recurrent thromboembolism within three months; the occurrence of pulmonary embolism during heparin treatment; heparin related complications; mortality; duration of
therapy; duration of therapy in hospital; day of occurrence of complication; relative risk of recurrent thrombosis following a complication; eligibility for outpatient treatment with LMWH; patients never hospitalised; and the various costs of treatments.

**Study designs and other criteria for inclusion in the review**
Clinical and observational studies were used in order to determine the values of the model's parameters.

**Sources searched to identify primary studies**
Not stated.

**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**
26 studies were used as sources of effectiveness data.

**Methods of combining primary studies**
Primary studies were combined using the narrative method.

**Investigation of differences between primary studies**
Not stated.

**Results of the review**
The estimates of the parameters included in the model were the probability of:

- recurrent thromboembolism within three months, UH = 6% (range: 2.9% - 9.6%), LMWH = 4.4% (range: 0% - 6.9%);
- the occurrence of pulmonary embolism during heparin treatment, UH = 0.6% (range: 0.4% - 1.9%), LMWH = 0.6% (no values given);
- heparin related complications - major bleed UH = 4% (range: 0% - 15%), LMWH = 1.6% (range: 0% - 15%);
- heparin related complications - heparin induced thrombocytopenia UH = 1% (range: 1% - 3%), LMWH = 0% ('less than 1%');
- mortality from pulmonary embolism 5% (range: 1.5% - 21%), from heparin induced thrombocytopenia 5% ('less than 50%'), from bleed 0.1% (no values given), from recurrent thromboembolism 8.8% (no values given);
- duration of therapy 6 days (range: 5.5 - 6.5);
- duration of LMWH therapy in hospital 2.5 days (no values given);
- day of occurrence of complication 4th day (no values given);
- relative risk of recurrent thrombosis following a complication 1.5 ('less than 37');
eligibility for outpatient treatment with LMWH 40% (range: 35% - 70%); and
patients never hospitalised LMWH strategy 30% (range: 36% - 48%(sic)).

Measure of benefits used in the economic analysis
The major outcomes reported in the study were recurrent cases of thromboembolism avoided and deaths avoided.

Direct costs
No discounting was performed on costs, since the time frame of the study was three months. Direct costs included the medical costs associated with the treatment of the initial episode of deep venous thrombosis, major bleed, heparin induced thrombocytopenia, pulmonary embolism, and recurrent thromboembolism. The expected cost was derived, using the model described above. All costs were reported in 1996 US dollars by applying the exchange rate for foreign currency, and then adjusting for inflation by using the Consumer Price Index for medical care. The cost data were taken from 11 published studies. Only those costs that were expected to differ between treatments were used. Details of the breakdown of costs were provided in the study's appendix.

Indirect Costs
No indirect costs such as 'time off work' were included in the study.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analysis was performed on all parameters within the model. One way, two way and a best and worse case analysis were all performed. The ranges tested were as follows: the probability of:

- recurrent thromboembolism within three months: UH base case = 6% (sensitivity analysis, 4% - 8%), LMWH = 4.4% (3.2% - 6.1%);

- the occurrence of pulmonary embolism during heparin treatment: UH = 0.6% (0.5% - 1%), LMWH = 0.6% (0.4% - 1.2%);

- heparin related complications - major bleed: UH = 4% (3% - 8%), LMWH = 1.6% (0.6% - 7.2%);

- heparin related complications - heparin induced thrombocytopenia: UH = 1% (0% - 2%), LMWH = 0% (0% - 2%);

- mortality from pulmonary embolism 5% (1% - 20%), from heparin induced thrombocytopenia 5% (0% - 50%), from bleed 0.1% (0% - 5%), from recurrent thromboembolism 8.8% (5% - 14%);

- duration of therapy 6 days (5 - 10);

- duration of LMWH therapy in hospital 2.5 days (1 - 10);

- day of occurrence of complication 4th day (3rd - 7th);

- relative risk of recurrent thrombosis following a complication 1.5 (1 - 10);

- eligibility for outpatient treatment with LMWH 40% (0% - 70%); and

- patients never hospitalised LMWH strategy 30% (0% - 50%).
Estimated benefits used in the economic analysis
Per 1,000 patients, the results were as follows:

UH for all: 61.43 cases of recurrent thromboembolism, 6.2 deaths (0.8 during index case, 5.4 during follow up);
LMWH for all: 44.74 cases of recurrent thromboembolism, 4.2 deaths (0.3 during index case, 3.9 during follow up);
'Selective UH/LMWH': 54.76 cases of recurrent thromboembolism, 5.4 deaths (0.6 during index case, 4.8 during follow up).

The length of the follow up was three months.

Cost results
Over a three month period, the total expected costs for 1,000 patients were as follows:

UH for all: $3,203,329 ($3,040,187 during index case, $163,142 during follow up);
LMWH for all: $2,892,564 ($2,775,095 during index case, $117,469 during follow up);
'Selective UH/LMWH': $2,795,742 ($2,662,779 during index case, $132,963 during follow up).

No discounting was performed, since the time frame was three months.

Synthesis of costs and benefits
Incremental cost-effectiveness of each of the three strategies was measured. The UH strategy was dominated by both the LMWH and Selective UH/LMWH strategies (that is, it was both more costly and less effective). When LMWH and Selective UH/LMWH were compared, LMWH resulted in 10 fewer cases of recurrent thromboembolism and 1.2 fewer deaths, but was $96,822 more expensive. In the sensitivity analysis, LMWH always resulted in lower costs than UH unless the proportion of eligible patients for home treatment was less than 14% (the base case was 40%) or LMWH patients were hospitalised for more than 6.5 days (base case was 2.5 days). LMWH always resulted in higher costs than the Selective LMWH/UH strategy, unless the cost of UH rose to more than $3,018 (the base case value was $2,376). LMWH always resulted in fewer deaths and recurrent thromboembolism than both the UH and Selective LMWH/UH strategies.

Authors’ conclusions
The Selective UH/LMWH strategy was the least costly option, but the LMWH for all strategy was the most effective. The incremental benefit of 10 fewer cases of recurrent thromboembolism and 1.2 fewer deaths must be compared against the incremental cost of $96,822 in order to select the most cost-effective alternative.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of comparator was clear. No 'do nothing' alternative was considered. This study, unlike previous studies, considered an option whereby, if the patient could be treated at home, then LMWH was an option, but if not, then UH should be used.

Validity of estimate of measure of effectiveness
The estimates used in the model were appropriately derived from the literature and tested over plausible ranges in the sensitivity analyses. Although there was no reporting of a systematic review, the validity of the estimates is likely to be high.

Validity of estimate of measure of benefit
The benefits measured in the study were mortality and recurrent thromboembolism, which were derived through the modelling process. No other measures of effectiveness were measured as benefits (i.e., time spent in treatment). Small side effects were not included in the benefits. A good range of sensitivity analyses was performed.

**Validity of estimate of costs**
Indirect costs such as time off work were not included in the study, which was appropriate for the chosen perspective.

**Other issues**
The authors indicated findings of dominance as well as incremental cost-effectiveness, and, in general, their reporting was very clear and comprehensive. The authors did however point out the atypical nature of the subjects used in trials (which formed the basis of their estimates) as well as variations in treatment compared with real life practices. These may hinder the validity of the results of modelling exercises. Comparisons with other studies were made and the issue of generalisability was addressed and enhanced through the sensitivity analyses performed. The limitations of the study and the assumptions made were both well covered in the discussion section of the paper.

**Implications of the study**
LMWH is recommended for treatment of patients with deep venous thrombosis, in whom pulmonary embolism was not suspected. For patients requiring hospitalisation however, intravenous UH was an alternative option.

**Source of funding**
None stated.

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