Long-term cost-effectiveness of low molecular weight heparin versus unfractionated heparin for the prophylaxis of venous thromboembolism in elective hip replacement

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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) prophylaxis against venous thromboembolism. The comparator technology was unfractionated heparin (UH).

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
A hypothetical population of 67 year-old patients undergoing elective hip replacement surgery.

Setting
The study setting was hospital. The economic study was carried out in Pavia, Italy.

Dates to which data relate
Evidence of effectiveness was derived from studies published between January 1982 and January 1998. Resource use and cost data were based on the authors' own assumptions and published data (date not reported). However, costs incurred due to post-thrombophlebitic syndrome, major bleeding and strokes, were derived from studies published between 1993 and 1997. Prices were reported in 1998 US dollars ($), having been converted from Italian Lira (L).

Source of effectiveness data
The effectiveness data were derived from a review of previously completed studies, discussion with clinical experts and a survey of citations from the reviewed articles.

Modelling
A decision tree was used to model the clinical outcomes and costs incurred between the initiation of prophylaxis and death for 1,000 patients.

Outcomes assessed in the review
The outcomes assessed in the review were the incidences of:

- deep vein thrombosis (DVT),
pulmonary embolism (PE: fatal and non-fatal),
bleeding (fatal and non-fatal),
strokes,
post-phlebography DVT,
post-thrombophlebitis syndrome and
quality-of-life adjusting factors.
Also assessed were:
The sensitivity and specificity of the diagnostic tests and clinical symptoms,
incidences of false-positive DVT and PE rates, and
the rate of phlebography performance.

Study designs and other criteria for inclusion in the review
Meta-analyses, randomised trials, observational studies and reviews and books containing trial reports published between January 1982 and January 1998 were included in the review. Only English-language publications were included.

Sources searched to identify primary studies
A computerised literature search was conducted to identify the studies, although the authors do not report the databases or search engine(s) used. Surveying citations in the reviewed articles identified other studies.

Criteria used to ensure the validity of primary studies
The authors ranked the quality of evidence by favouring meta-analytical data over randomised trials, observational studies, reviews and books, in that order. More detailed criteria were not reported.

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

Number of primary studies included
27 studies were included in the review.

Methods of combining primary studies
For each parameter of effectiveness, the best available evidence, as judged by the authors, was included as the baseline value.

Investigation of differences between primary studies
The authors noted a difference in prophylaxis regimens between the data sources used in the estimation of effectiveness during the inpatient and post-discharge periods. No further investigations were reported.

Results of the review
The effectiveness of LMWH prophylaxis on DVT, for dose durations of two weeks and four weeks, was 47% (range: 40% - 54%) and 66% (range: 60% - 70%) respectively. The effectiveness of UH prophylaxis on DVT, for dose durations of two weeks and four weeks, was 34% (range: 30% - 40%) and 50% (range: 45% - 55%), respectively.

The effectiveness of LMWH prophylaxis on PE, for dose durations of two weeks and four weeks, was 60% (range: 50% - 70%) and 90% (range: 80% - 95%) respectively. The effectiveness of UH prophylaxis on PE, for dose durations of two weeks and four weeks, was 10% (range: 8% - 12%) and 15% (range: 12% - 18%), respectively.

The rate of major bleeding for two-week prophylaxis with LMWH or UH, was 1.8% (range: 1.6% - 2%) and 2.6% (range: 2.4% - 2.8%), respectively.

Quality-adjusting factors for severe post-thrombophlebitis syndrome and haemorrhagic stroke were 95% (range: 90% - 100%) and 50% (range: 30% - 60%), respectively. Mild and moderate post-thrombophlebitis syndrome did not affect quality of life.

The authors also provided details of the rates of post-operative venous thromboembolic disease and characteristics of diagnostic tools.

**Methods used to derive estimates of effectiveness**

The authors' own assumptions were used to estimate the effectiveness of some parameters.

**Estimates of effectiveness and key assumptions**

The authors assumed that:

the incidence of post-thrombophlebitic syndrome was similar for treated and untreated patients,

the specificity of venography was 100%,

the rate of phlebography performance was 25%.

**Measure of benefits used in the economic analysis**

Quality-adjusted life years (QALYs) was the outcome measure used in the economic analysis. The valuation of health states was based on previously published studies. Benefits were discounted at an annual rate of 3%.

**Direct costs**

Direct costs included in the analysis were the cost of drugs, nurse time required for administration of prophylaxes within the hospital and at home, laboratory and diagnostic tests, work units for the administration of tests and general ward care, and the costs of treating each of the clinical outcomes in the model. Drug quantities were based on assumed dosages and their cost was estimated using the market price, with a 50% downwards adjustment for inpatients. Nursing time was assumed to be ten minutes per dose and this cost was estimated from local billings. Test costs were estimated from Italian and French relative value scales, with costs of work units estimated from local administrative data. Duration of stay for the treatment of DVT or PE was estimated from local survey data assuming equivalent treatment if the condition developed in pre- or post-discharge periods. An episode of PE was assumed to incur a short stay (of unspecified length) at the intensive care unit, in addition. Costs of post-thrombophlebitis syndrome, major bleeding and stroke were taken from the literature. The price year was 1998. Direct costs were discounted at an annual rate of 3%. The economic analysis was carried out from a societal perspective.

**Indirect Costs**

Indirect costs included in the analysis were those of patients' absence from work arising from late complications of DVT. This cost was based on an assumed annual income of $25,000 (1998 price year) and was discounted at an annual rate of 3%.
Currency
Costs were reported in US dollars ($), being converted from Italian Lira (L). The source and date of the conversion rate was not reported.

Sensitivity analysis
A sensitivity analysis was carried out on clinical event rates, drug effectiveness, and overall costs of prophylaxes, tests and treatments. The areas of uncertainty investigated were generalisability of results (with regard to age-adjusted population life expectancy), variability in data, and the authors' assumptions. The range over which the continuous variables were tested represents either the confidence interval of the meta-analyses, the observed range of published data, or else a 20% interval around the baseline value. One-way simple sensitivity analysis was used.

Estimated benefits used in the economic analysis
Benefits of both LMWH and UH were estimated as QALYs accrued over the patient's expected lifetime. The side-effects of prophylaxis, tests and treatment were not considered. The discounted QALYs accrued per patient were 13.40 (LMWH) and 13.33 (UH).

Cost results
The total discounted cost per patient was $2,208 (LMWH prophylaxis) and $2,283 (UH prophylaxis). The costs in Italian Lira were not reported. The incremental cost saving per patient for prophylaxis with LMWH, as compared to UH, was $78. This included the costs of adverse clinical events and follow-on costs incurred over the patient's remaining lifetime.

Synthesis of costs and benefits
The authors reported the incremental cost saving and incremental QALYs but did not combine the two into an incremental cost-effectiveness ratio. Prophylaxis with LMWH produces an incremental benefit of 25 days quality-adjusted life expectancy and an incremental cost-saving of $78 per patient when compared to prophylaxis with UH. Hence, LMWH is a dominant strategy.

Incremental quality-adjusted life expectancy decreased linearly from 58 to 14 days when age was reduced from 80 to 50 years.

When post-thrombophlebitic syndrome was assumed to occur in all patients following a clinically asymptomatic and untreated DVT and never in patients following a symptomatic and treated DVT, the cost saving from LMWH more than tripled.

The cost saving from LMWH became zero when the market price of the prophylaxis reached $140.

Extended four-week prophylaxis with LMWH dominated both four-week and two-week prophylaxis with UH.

Authors' conclusions
Prophylaxis with LMWH is a dominant strategy, since it leads to fewer costs and an improvement in quality-adjusted life expectancy when compared to UH.

CRD COMMENTARY - Selection of comparators
A justification was given for the comparator, namely that UH was the closest competitor to LMWH.

Validity of estimate of measure of effectiveness
The authors stated that a systematic review of the literature had been undertaken. The conduct of the review was not reported clearly enough for it to be possible to ascertain whether all biases were minimised. Baseline estimates of parameters were derived from the best evidence available, although the authors did not report exactly how this was judged. The range of effectiveness estimates in the literature constituted the range to be tested in the sensitivity analysis. The estimate of effectiveness was derived credibly from the primary studies.

**Validity of estimate of measure of benefit**

Quality-adjusting factors were obtained from the literature and estimated using modelling techniques. This choice of estimate was justified.

**Validity of estimate of costs**

All categories of cost relevant to the perspective adopted were included in the analysis. Costs and quantities were reported separately. A sensitivity analysis of dosage and diagnostic testing strategies was conducted. A sensitivity analysis of prices was conducted. The authors reported the price year but not the source of the currency conversion rate. Costs apply to the authors' setting and should be transferred with caution.

**Other issues**

The authors made appropriate comparisons of their findings with those from other studies and addressed the issue of generalisability to other settings. The authors did not present their results selectively. The authors modelled a base-case in which patients were 67 years of age, and this was reflected in their conclusions. The authors reported a number of further limitations to their study, namely that they did not account for instrumental surveillance of post-surgical inpatients, diagnostic testing and treatment of a rare post-embolic complication, or the side-effects of heparin. However, the authors stated that the latter two omissions bias the model against LMWH.

**Implications of the study**

The authors believe that their findings should strengthen European recommendations to use LMWH prophylaxis in elective hip replacement.

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None stated

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**Other publications of related interest**


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