Cost-effectiveness of low-molecular-weight heparin for secondary prophylaxis of cancer-related venous thromboembolism

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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 use of low molecular weight heparin (LMWH) versus warfarin for secondary prophylaxis of cancer-related venous thromboembolism (VTE). The study compared subcutaneous LMWH (dalteparin 200 IU/kg during month 1, and 150 IU/kg during months 2 - 6) once daily with warfarin (target international normalised ratio 2.5) for 6 months, overlapping with LMWH for the first 5 days.

Type of intervention
Secondary prevention.

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

Study population
The study population comprised a hypothetical cohort of 65-year-old cancer patients who had experienced a VTE.

Setting
The study setting was secondary care. The economic analysis was conducted in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1982 and 2004. The price year was 2002.

Source of effectiveness data
The effectiveness data were derived from published studies, supplemented with authors’ assumptions.

Modelling
A decision tree was constructed to compare the clinical and economic outcomes of a 6-month course of LMWH or warfarin therapy. The time horizon for the model was patient life expectancy. The model made the following assumptions:

- all patients were at risk of death from any cause;
- patients who developed intracranial bleeding remained disabled for the rest of their lives;
- anticoagulation was permanently discontinued in patients who experienced an intracranial bleeding episode, but transiently interrupted in those who had noncerebral major bleeding;
intracranial bleeding or recurrent thromboembolism prompted the placement of a permanent vena cava filter to prevent pulmonary embolism; and

all patients who survived the first 6 months after the initial venous thromboembolic event were at risk for late complications that included death from any cause and recurrent VTE.

**Outcomes assessed in the review**
The outcomes assessed were:

- patients suffering a nonfatal recurrent VTE;
- patients suffering nonfatal major bleeding;
- patients suffering minor bleeding;
- the frequency of intracranial bleeding;
- the mortality rate from any cause;
- the proportion of VTEs due to deep vein thrombosis;
- the proportion of outpatient treatment for deep vein thrombosis; and
- the proportion of home nursing for LMWH injections.

**Study designs and other criteria for inclusion in the review**
Probabilities for early complications were derived from the CLOT (Comparison of Low Molecular Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer) study, a randomised controlled trial. This was a large clinical trial involving 672 patients with cancer-related VTE. A large meta-analysis of patients receiving anticoagulants for nonspecific VTE was used to estimate the frequency of uncommon complications such as anticoagulation-related intracranial bleeding. In addition, long-term survival was based on a retrospective cohort study of 65-year-old cancer patients with VTE.

**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**
Sixteen studies were included in the review.

**Methods of combining primary studies**
The authors did not describe any methods used to judge the relevance and validity of the data. Ranges were mainly defined by 95% confidence intervals, or estimated by the authors.
Investigation of differences between primary studies
Not reported.

Results of the review
The proportion of patients suffering a nonfatal recurrent VTE was 6.5% (range: 4.1 - 9.7) for LMWH and 13.7% (range: 10.2 - 17.8) for warfarin.

The proportion of patients suffering nonfatal major bleeding was 5.3% (range: 3.2 - 8.3) for LMWH and 3.6% (range: 1.9 - 6.2) for warfarin.

The proportion of patients suffering minor bleeding was 8.3% (range: 5.6 - 11.8) for LMWH and 15.5% (range: 11.8 - 19.9) for warfarin.

The proportion of VTE due to deep vein thrombosis was 69.0% (range: 65.0 - 72.0).

The proportion of outpatient treatment for deep vein thrombosis was 50% (range: 0.0 - 70.0).

The proportion of home nursing for LMWH injections was 20.0% (range: 0.0 - 50.0).

Methods used to derive estimates of effectiveness
The authors made some assumptions in their model, which supplemented the data derived from the literature.

Estimates of effectiveness and key assumptions
The authors assumed that:

- the frequency of intracranial bleeding was the same for the two treatment strategies;
- long-term survival was identical for both treatment strategies; and
- patients with noncerebral major bleeding or recurrent VTE had a 25% increase in 1-year mortality with both treatment strategies compared with patients without these complications.

Measure of benefits used in the economic analysis
The measures of benefits used were the life-years (LYs) and quality-adjusted life-years (QALYs) gained. The authors adjusted life expectancy for quality of life by multiplying the time spent in each health state and its associated health state utility. The health benefits were obtained from the model and were discounted at a rate of 3%.

The utility values were derived from the literature. Decreases in utility because of acute complications were expressed as days of utility lost because of hospitalisation. The authors assumed that patients with deep vein thrombosis who were treated at home had half the disutility of patients who were treated in the hospital.

Direct costs
The costs included in the analysis were those to the health care service and to patients. The health care service costs included hospitalisation, emergency department and physician visits, home nursing, laboratory tests, medical procedures, and drug costs relating to a hospital stay. The hospitalisation and treatment costs were derived from Medicare reimbursement data. The drug costs related to a hospital stay were considered a part of the Medicare
reimbursement; the costs of drugs for ambulatory patients were derived from the 2002 Red Book. Patient costs included were patient transportation expenses for emergency department visits, routine physician visits, anticoagulation monitoring for warfarin therapy, and the costs for patient time based on the average hourly wage of a US non-farm production worker. Since the costs were incurred over the lifetime of the patient, future costs were appropriately discounted at an annual rate of 3%. The study reported the average costs. The price year was 2002.

Statistical analysis of costs
The costs were reported as point estimates (i.e. the data were deterministic).

Indirect Costs
Indirect costs, such as lost wages related to hospitalisation, disability or premature death, were not included following recommendations by the Panel on Cost-Effectiveness in Health and Medicine.

Currency
US dollars ($).

Sensitivity analysis
One-way sensitivity analyses for all variables were conducted. Two-way sensitivity analyses were also conducted on selected variables to assess the effect of varying baseline estimates within clinically plausible ranges on cost-effectiveness. Variables that changed the results for the incremental cost-effectiveness ratio by more than 10% in the one-way sensitivity analysis were selected for probabilistic sensitivity analyses, with parameters varied simultaneously over triangular probability distributions. Values from each probability distribution were randomly selected during each of 10,000 Monte Carlo iterations.

Estimated benefits used in the economic analysis
The estimated LYs gained were 1.442 with LMWH and 1.377 for warfarin. LMWH was associated with a discounted LY gain of 0.066 in comparison with warfarin.

The QALYs gained were 1.097 with LMWH and 1.046 for warfarin. LMWH was associated with a discounted QALY gain of 0.051 in comparison with warfarin.

Cost results
The mean cost per patient treated was $15,329 with LMWH and $7,720 with warfarin. The discounted incremental cost of LMWH was $7,609 in comparison with warfarin.

Overall, 46% of the total costs associated with LMWH were attributable to pharmacy costs.

Synthesis of costs and benefits
The costs and benefits were combined using an incremental cost-effectiveness ratio (i.e. the additional cost per LY gained) and an incremental cost-utility ratio (i.e. the additional cost per QALY gained).

The incremental cost-effectiveness and cost-utility ratios of using LMWH over warfarin were $115,847 per LY gained and $149,865 per QALY gained, respectively.

The one-way sensitivity analysis revealed that the cost-effectiveness was sensitive to several parameters. Specifically, early mortality risks, daily pharmacy costs for LMWH, utilities (treatment with LMWH, cancer, or warfarin), the need for home nursing, and early risks for recurrent VTE and major bleeding. The results of the probabilistic sensitivity analysis showed that warfarin was more cost-effective than LMWH in 97% of cases at a willingness-to-pay threshold of
$50,000/QALY gained and in 72% of iterations at a threshold of $100,000/QALY gained.

**Authors’ conclusions**

Secondary prophylaxis with low molecular weight heparin (LMWH) was more effective than warfarin for venous thromboembolism (VTE). However, owing to the substantial pharmacy costs of extended LMWH prophylaxis in the USA, the treatment was relatively expensive in comparison with warfarin.

**CRD COMMENTARY - Selection of comparators**

A justification was given for the comparator strategy used. Warfarin represented the traditional prophylaxis for cancer-related VTE in the authors' setting. You should decide if the comparator used represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**

The authors did not report that a systematic review of the literature was undertaken to identify all relevant research and minimise biases. They also failed to report much of the methodology undertaken in their review. However, the authors derived the majority of clinical parameters from CLOT (a randomised controlled trial) and from a large meta-analysis. Further, point estimates were reported with ranges which, in some cases, were derived from other published literature. With a few exceptions, the studies in the review were generally all recent and published after 2000. The authors made several assumptions in the model which were explicitly reported. They also conducted numerous sensitivity analyses to test the robustness of their results.

**Validity of estimate of measure of benefit**

The measures of benefit used were the LYS and QALYs. These were derived from a decision tree model. This was appropriate for the study question. The utility values were derived from the literature, but the method used for their derivation was not reported in the current study. The method used to derive disutility values was, however, appropriately reported. Both utility and disutility values were explored in the sensitivity analysis.

**Validity of estimate of costs**

Although the authors reported that a societal perspective was undertaken, they did not include productivity losses or intangible costs. The authors also reported that by not including the costs of adverse consequences and caregiver time spent by family members to administer LMWH injections, the results were biased in favour of LMWH. The costs and the quantities were not reported separately, which will limit the generalisability of the authors' results.

The costs were derived mainly from Medicare reimbursement rates, which might not reflect the true cost of providing a medical service. However, all of the costs were appropriately tested in sensitivity analyses. It would have been more appropriate if the probability distributions employed in the probabilistic sensitivity analysis had no upper or lower bounds (e.g. gamma and beta distributions), rather than using a triangular distribution which has a lower and upper bound and, therefore, might not capture all the uncertainty in an individual parameter.

Since the costs were incurred over the lifetime of the patient, discounting was relevant and was appropriately performed. The price year was reported, which will aid any future inflation exercises.

**Other issues**

The authors made appropriate comparisons of their findings with those from another study, a cost-effectiveness analysis of a 3-month course of enoxaparin versus warfarin in patients with thromboembolism. This other study found enoxaparin to be cost-effective, but that cost-effectiveness decreased when the duration of treatment was extended to 6 months. The generalisability to other settings was addressed in the authors’ extensive sensitivity analyses. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis.
The authors reported a number of further limitations to their study. First, they did not include any chronic complications of VTE. Second, they implicitly assumed that all LMWH preparations were equally safe and effective as dalteparin. Third, the model was mainly based on data from cancer patients with a relatively high performance status, thus the generalisability of their results to patients with lower performance is less certain. Finally, some of the outcome probabilities could not be reliably estimated from clinical trials and had to be derived from other data sources.

Implications of the study
The authors reported that if LMWH was less costly, as in other countries or when substantial discounts are available in the USA, long-term LMWH prophylaxis is more reasonable economically. They also highlighted the need for long-term studies on health outcomes of various anticoagulant strategies in a large population of cancer patients with VTE.

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Other publications of related interest


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