Cost effectiveness of thromboprophylaxis with a low-molecular-weight heparin versus unfractionated heparin in acutely ill medical inpatients

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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
Three prophylactic strategies for the prevention of venous thromboembolism (VTE) were compared in acutely ill medical inpatients. Strategy 1 was enoxaparin, a low molecular weight heparin (LMWH), at a dose of 40 mg/day. Strategy 2 was unfractionated heparin (UFH) at a dose of 5,000 IU twice daily. Strategy 3 was no prophylaxis.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised 10,000 hypothetical general medical patients who were acutely ill, such as those hospitalised for congestive heart failure, chronic obstructive pulmonary disease, or acute infections.

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

Dates to which data relate
The effectiveness evidence dated from 1960 to 2001, and resource use and costs from 1999 to 2001. The price year was 2001.

Source of effectiveness data
The effectiveness data were derived from a review of completed studies.

Modelling
A simple decision tree with a 30-day time horizon was used, starting at hospital admission. The model incorporated which thromboprophylaxis regimen was administered, drug-related adverse events (e.g. haemorrhage and heparin-induced thrombocytopenia), and VTEs and deaths. It also reflected the uncertainties in the clinical diagnosis of deep venous thrombosis (DVT).

Outcomes assessed in the review
The parameters obtained from the review included:

the efficacy and safety of prophylaxis;
the consequences of adverse events;

the efficacy and safety of treatment for DVT;

the efficacy and safety of treatment for pulmonary embolism (PE);

the natural history of DVT or PE and acute illness; and

clinical diagnosis and other diagnostic test operating characteristics for DVT and PE.

Study designs and other criteria for inclusion in the review
No specific criteria were reported. The study designs included randomised controlled trials (RCTs) and meta-analyses for efficacy data, and a wider range of designs for adverse effect data and test operating characteristics (which were the same in all arms).

Sources searched to identify primary studies
The sources searched were not specifically reported, although the authors stated they were unable to find another RCT similar to the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial (Samama et al., 1999, see 'Other Publications of Related Interest' below for bibliographic details).

Criteria used to ensure the validity of primary studies
Not stated.

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

Number of primary studies included
Thirty-six articles were included in the review.

Methods of combining primary studies
Many of the studies were not combined. The authors stated that where multiple data sources were used, the estimates were combined across studies by direct pooling.

Investigation of differences between primary studies
The authors justified their selection of a single study for estimating the efficiency of enoxaparin versus placebo. It was the only published placebo-controlled trial of an LMWH that enrolled general medical patients, administered a dose of enoxaparin consistent with current recommendations, and diagnosed DVT using venography. For the efficacy of UFH, the authors used data from a meta-analysis of trials that compared LMWH with UFH in medical patients.

Results of the review
What follows is a selection of baseline parameters for LMWH, UFH and no prophylaxis.

Efficacy and safety of prophylaxis:

the probability of DVT was 0.055 with LMWH, 0.066 with UFH, and 0.142 with no prophylaxis;

the probability of bleeding was 0.031 with LMWH, 0.058 with UFH, and 0.020 with no prophylaxis; and
the probability of heparin-induced thrombocytopenia was 0.001 with LMWH, 0.01 with UFH, and 0.000 with no prophylaxis.

Consequences of adverse events:

the probability that the bleed is major was 0.185 for all;

the probability of death from a major bleed was 0.148 for all;

the probability of symptomatic heparin-induced thrombocytopenia given heparin-induced thrombocytopenia was 0.543 for all; and

the probability of death from symptomatic heparin-induced thrombocytopenia was 0.098 for all.

All of the parameters related to the efficacy and safety of DVT and PE therapy, natural history, and diagnostic test operating characteristics were equal across the three comparators.

Methods used to derive estimates of effectiveness
The authors made some assumptions on the basis of relevant literature.

Estimates of effectiveness and key assumptions
The probability of death in these patients was assumed to be 0.10, which is consistent with clinical trials carried out on acutely ill medical patients.

Measure of benefits used in the economic analysis
The measure of benefits used was deaths averted.

Direct costs
The cost categories included were study medications and ancillary resources, laboratory procedures, hospital inpatient days, physician inpatient visits, and physician office or outpatient visits. Some costs after 30 days were included if they were incurred as a direct consequence of events within the first 30 days (e.g. 6 months of warfarin therapy following DVT). The quantities were reported. These were based on published sources from 2001, as well as authors’ assumptions, and then estimated through modelling. Discounting was, appropriately, not considered as the time horizon was shorter than two years. All the costs were measured in 2001 US dollars and were reflated, where necessary, to 2001 using the medical care component of the Consumer Price Index.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
One- and two-way sensitivity analyses were performed for key parameters of natural history, safety and efficacy. Also, to evaluate the effect of alternative assumptions on the model outcomes. A sub-group analysis was conducted on
patients from the MEDENOX trial with heart failure, respiratory disease, or infectious disease.

**Estimated benefits used in the economic analysis**
The risk attributable to DVT, PE and attributable deaths was lowest among LMWH patients (532, 106, 37, respectively), intermediate with UFH (616, 122, 53), and highest with no prophylaxis (1,392, 277, 81).

Compared with no thromboprophylaxis, LMWH is expected to prevent 860 cases of DVT, 171 cases of PE, and 44 deaths. UFH is expected to prevent 776 cases of DVT, 155 cases of PE, and 28 deaths.

The total number of deaths was 1,037 with LMWH, 1,053 with UFH, and 1,081 with no prophylaxis.

**Cost results**
The total costs for this hypothetical cohort of 10,000 patients (including thromboprophylaxis, adverse events, and diagnosis and management of DVT and PE) were $3,105,000 for no prophylaxis, $3,502,000 for LMWH, and $3,772,000 for UFH.

The incremental cost of LMWH versus no prophylaxis was $397,000, whilst that of UFH versus LMWH was $270,000.

**Synthesis of costs and benefits**
Compared with no prophylaxis, LMWH with enoxaparin was the more cost-effective strategy, at a cost of $9,100 per death averted. UFH was dominated by LMWH, which was both less costly and more effective in preventing deaths. The results were similar for the three sub-groups of patients (heart failure, respiratory disease, or infectious disease) and the cost per death averted with LMWH was even more favourable (range: $1,400 - $6,700).

The model was robust to variations in the competing risk of death, the assumed risk of progression from DVT to PE with and without treatment, and the probability of death due to treated or untreated PE. The model was more sensitive to changes in the risk of DVT. When it was reduced by half, the cost per death averted for enoxaparin versus no prophylaxis increased to $56,300. The model was also more sensitive to the risk of bleeding ($14,000 per death averted if high bleed risk).

Enoxaparin dominated UFH in all scenarios, even when assuming equal efficacy or equal rates of haemorrhages. If both equal efficacy and equal rates of haemorrhage were assumed, UFH was no longer dominated by enoxaparin, and enoxaparin had an incremental cost-effectiveness of $43,256 per death averted. Up to a per dose price of $37.42 (versus the base-case of $24.46), the cost per death averted with enoxaparin was lower than that with UFH.

**Authors’ conclusions**
Thromboprophylaxis with enoxaparin, a low molecular weight heparin (LMWH), represents a cost-effective use of health care resources in acutely ill medical inpatients. In addition, it dominates thromboprophylaxis with unfractionated heparin (UFH).

**CRD COMMENTARY - Selection of comparators**
The authors clearly justified the selection of the comparators, although the choice of enoxaparin instead of other available LMWH was not so clearly stated. You should decide if the chosen comparators are relevant in your setting.

**Validity of estimate of measure of effectiveness**
Although a detailed description of the search strategy and sources to develop the model was not given, the authors adequately referenced all parameters used to model effectiveness. The authors used the evidence selectively from pertinent studies to estimate enoxaparin efficacy (one RCT) or UFH efficacy (a meta-analysis of UFH versus LMWH), although it was unclear why they did not use the latter source for all efficacy data. Given the lack of reporting of the
review and model development, it was difficult to ascertain if the best available evidence was used to inform this study.

**Validity of estimate of measure of benefit**
The measure of benefit used in the economic analysis was deaths averted. It was obtained from the model. A utility measure such as quality-adjusted life-years would have enabled better comparisons with other health interventions.

**Validity of estimate of costs**
All the relevant cost categories were included in the analysis for the stated perspective. For example, study medications and ancillary resources, laboratory procedures, hospital inpatient days, physician inpatient visits, and physician office or outpatient visits on account of treatment as well as adverse effects. Although the time horizon of the study was 30 days, some relevant costs for medium-term treatment (i.e. warfarin therapy) were adequately considered. The quantities and the costs were reported separately, which will aid extrapolation of the study results to other settings. Discounting was not necessary because of the short time horizon of the study. The cost data were reported and appropriately reflated when necessary, thus aiding future reflation exercises. The authors used standard sources for estimating the costs, and acknowledged that they were uncertain about their reflection of the true costs.

**Other issues**
The authors adequately compared their results with other health economic studies published in the literature. They also acknowledged several limitations of their study. First, the necessary simplification and combination of multiple data sources of different designs and populations inherent to most models. Second, the short time horizon considered. Third, the heterogeneity of the patient population. Finally, the risk function assumed which could not be verified.

**Implications of the study**
The authors reported that their conclusions would have been probably similar from a societal perspective. This study and many others on the topic generally exclude women of childbearing potential, patients with recent strokes, and those requiring chronic anticoagulation, so extrapolation to these groups is not warranted.

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**Other publications of related interest**

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