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-dose unfractionated heparin was compared with low molecular weight heparins (LMWH) for the prophylaxis of deep vein thrombosis (DVT).

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients admitted to hospital medical wards. No further details about the study population were reported.

Setting
The setting was secondary care. The economic study was conducted in the United States.

Dates to which data relate
The effectiveness evidence related to data published between 1986 and 1996. The cost data were derived from studies published between 1993 and 1996. The price year was 1998.

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

Modelling
No details of the model were reported.

Outcomes assessed in the review
The outcomes assessed in the review were the incidences of DVT, proximal DVT, nonfatal pulmonary embolisms (PEs), and major bleeding episodes.

Study designs and other criteria for inclusion in the review
The studies were included if they were randomised, double-blind studies evaluating heparin and/or LMWH as DVT prophylaxis in medical inpatients. The studies had to be published between January 1985 and April 1998. The studies were excluded if they were non-English language papers, were reported as abstracts, or involved patients in medical
intensive care units.

**Sources searched to identify primary studies**
MEDLINE and Current Content were searched for primary studies.

**Criteria used to ensure the validity of primary studies**
The authors searched exclusively for randomised double-blind trials. The identified studies were excluded from the analysis if they did not include data on some of the outcomes of interest, did not identify the LMWH used, or used a LMWH unavailable in the USA. No other criteria to ensure the validity of the primary studies were reported.

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

**Number of primary studies included**
Five primary studies were included in the review, of which two were used in the analysis.

**Methods of combining primary studies**
The incidences of proximal DVT, nonfatal PEs and major bleedings for were pooled for the heparin regimen, 5,000 U every 8 hours. The outcomes for the other regimens were taken from single studies.

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

**Results of the review**
The incidence of total DVT was:

- 4.6% for heparin, 5,000 U every 12 hours for 10 days;
- 1.35% for heparin, 5,000 U every 8 hours for 7 days;
- 4.4% for enoxaparin, 20 mg four times daily for 10 days; and
- 0.23% for enoxaparin, 40 mg four times daily for 7 days.

The incidence of proximal DVT was:

- 0.93% for heparin, 5,000 U every 12 hours;
- 0.43% for heparin, 5,000 U every 8 hours for 7 to 10 days;
- 1.9% for enoxaparin, 20 mg four times daily for 10 days; and
- 0 for enoxaparin, 40 mg four times daily for 7 days.

The incidence of nonfatal PEs was:

- 0 for heparin 5,000 U every 12 hours;
- 0.61% for heparin, 5,000 U every 8 hours for 7 to 10 days;
0.48% for enoxaparin, 20 mg four times daily for 10 days; and
0 for enoxaparin, 40 mg four times daily for 7 days.

The incidence of major bleeding episodes was:
0.93% for heparin 5,000 U every 12 hours;
0.95% for heparin, 5,000 U every 8 hours for 7 to 10 days;
0.48% for enoxaparin, 20 mg four times daily for 10 days; and
0.5% for enoxaparin, 40 mg four times daily for 7 days.

Measure of benefits used in the economic analysis
No summary measure of benefit was used in the economic analysis. A cost-consequences analysis was therefore performed.

Direct costs
The costs and the quantities were not reported separately. The direct costs associated with hospitalisation were included in the analysis. These were the costs for the prophylactic regimens, and the diagnosis and treatment of DVT, nonfatal PE and major bleeding episodes. The direct cost data were derived from published studies. However, the authors did not report how the costs were estimated in the original studies, or whether the cost data represented cost or charge information. It was not reported whether the costs of DVT, PE and major bleeding episodes included the long-term costs of care and disability. The published cost data for the treatment and follow-up of DVT, nonfatal PE and major bleeding episodes were averaged and adjusted to 1998 prices using a rate of 5% per year. The analysis appears to have excluded the long-term costs of disability associated with DVT, nonfatal PE and major bleeding episodes. The timeframe used to estimate the costs was not reported. It was also not reported whether the costs were discounted to present values.

Statistical analysis of costs
A statistical analysis of the costs was not reported.

Indirect Costs
The indirect costs were not included in the evaluation as they were not appropriate to the perspective of the study.

Currency
US dollars ($). No currency conversions were reported.

Sensitivity analysis
A one-way sensitivity analysis was performed to explore the impact of the drug costs, and the incidences of proximal DVT, nonfatal PE and major bleeding.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The total costs for the intervention or the comparators were not reported.
Synthesis of costs and benefits
The estimated costs and benefits were combined using incremental cost-effectiveness ratios. However, no measure of health benefit was defined.

The use of heparin, 5,000 U every 12 hours, for a cohort of 1,000 patients resulted in savings of $11,678.62 when compared with heparin, 5,000 U every 8 hours. The savings were $12,897.06 when compared with enoxaparin, 40 mg daily, and $14,567.86 when compared with enoxaparin, 20 mg daily.

The use of heparin, 5,000 U every 8 hours, for a cohort of 1,000 patients resulted in savings of $10,752.87 when compared with enoxaparin, 40 mg daily, and $14,999.58 when compared with enoxaparin, 20 mg daily.

One sensitivity analysis found that enoxaparin, 40 mg daily, would be the most cost-effective regimen in medical inpatients if it were approximately one-third of its current cost.

Authors’ conclusions
Unfractionated heparin was the most cost-effective agent for routine prophylaxis in medical inpatients at risk of deep vein thrombosis (DVT).

CRD COMMENTARY - Selection of comparators
The authors justified their choice of intervention and comparator by reference to clinical guidelines published in the United States. These guidelines recommended the use of heparin or LMWH for prophylaxis of DVT. You should decide whether heparin is a widely used method of prophylaxis in your own clinical setting.

Validity of estimate of measure of effectiveness
The methods used to identify relevant research and to select the studies for inclusion in the analysis were provided. However, it was unclear whether the review was conducted in a systematic fashion to minimise bias. The authors used the data from the available studies selectively. The effectiveness estimates for LMWH were obtained from single studies. A pooled effectiveness estimate was used for heparin but there were no details of how this pooled figure was calculated. The authors considered the impact of differences in sample size in the discussion section of the paper. However, they did not report the use of a weighting scheme to reflect differences in sample size in the baseline analysis.

Validity of estimate of measure of benefit
The authors did not derive a summary measure of health benefit, although they reported that they had conducted an incremental cost-effectiveness analysis. The lack of a defined measure of health benefit means that the study was, in fact, a costs-consequences analysis.

Validity of estimate of costs
All the categories of cost relevant to the perspective adopted were included in the analysis. The costs and the quantities were not reported separately. The authors did not report the total costs for each intervention. The cost data were derived from studies that considered patients having joint replacement or abdominal surgery. The demographic and clinical characteristics, and associated use of services for this group may be different from those of medical patients. The sensitivity analysis only reported the impact of the cost of enoxaparin, 40 mg, which may limit interpretation of the study’s findings. No currency conversions were reported. The timeframe of the cost analysis and the use of discounting were not reported.

Other issues
The authors did not make appropriate comparisons of their findings with those from other studies, which had assessed
the cost-effectiveness of heparin and LMWH. The issue of generalisability to other settings was not addressed due to inadequate information on the choice of the comparator and the limited sensitivity analysis. The study enrolled medical inpatients at risk of DVT, and this was reflected in the authors' conclusions.

The authors reported a number of limitations to their study but did not consider the impact of these limitations on the results of their analysis. In particular, they discussed the implications of the small sample size for the published study that evaluated heparin, 5,000 U every 12 hours. The authors were also surprised to find that 5,000 U heparin every 12 hours was associated with a zero incidence of nonfatal PE, while the same dose every 8 hours had a 0.61% incidence.

Implications of the study
The authors state that unfractionated heparin appears to be the cost-effective agent for routine pharmacoprophylaxis in medical patients at risk for DVT. They suggest that more randomised double-blind studies with large sample sizes are needed to evaluate agents for DVT prophylaxis in medical inpatients at risk of DVT. These studies should use the most sensitive diagnostic strategies for detecting DVT and nonfatal PEs, and evaluate shorter prophylaxis intervals.

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