The cost-effectiveness of fondaparinux compared with enoxaparin as prophylaxis against thromboembolism following major orthopedic surgery

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 the selective anti-thrombotic fondaparinux (2.5 mg once daily) and the low molecular weight heparin enoxaparin (40 mg once daily) for the prevention of venous thromboembolism (VTE), either deep-vein thrombosis (DVT) or pulmonary embolism (PE).

Type of intervention
Other: Prophylaxis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients undergoing THR, TKR or HFS. A combined cohort comprised the relative proportions of patients undergoing these procedures in England and Wales during the year 2000/2001, that is, THR (28%), TKR (25%) and HFS (47%).

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

Dates to which data relate
The effectiveness data were gathered from studies published between 1982 and 2002. The resource data were gathered from two sources published in 2001. The price data came from the years 2000, 2001 and 2002. No common price year was quoted.

Source of effectiveness data
The effectiveness data were derived from a review of the literature.

Modelling
A decision analytic model was constructed to simulate the transition of hypothetical patient cohorts between health states. Microsoft Excel software was used. Patients received 7 days of therapy and were followed for different time periods. More specifically, at discharge, at day 30, at day 90, at year 1 and at year 5.

Outcomes assessed in the review
The outcomes assessed were:
the probabilities of early and late DVT for the three orthopaedic procedures;
the probabilities of clinical DVT or PE following early and late DVT;
the risk of recurrent VTE;
the risk of post-thrombotic syndrome from clinical VTE or from sub-clinical DVT;
the false-positive rate of DVT and PE;
the probability of prophylaxis-related major bleeding;
the probability of major bleeding related to the treatment of clinical DVT or PE;
the risk of death following PE, major bleeding or recurrent VTE; and
the natural mortality rate.

Study designs and other criteria for inclusion in the review
The review does not appear to have been a systematic review of the literature. However, the authors reported the study designs of the primary studies included in the review. The primary studies were large randomised trials, clinical trials conforming to UK practice, a large cohort study, a long-term follow-up study, a long-term prospective cohort study, or retrospective studies.

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
About 30 studies were included in the analysis.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
The authors investigated some differences between the studies, for example the dose regimen. However, they did not investigate how these differences affected the estimate of the effectiveness of the technology.

Results of the review
There were too many parameters to report in this abstract. The reader is referred to the original paper.

Methods used to derive estimates of effectiveness

The authors made several assumptions to estimate the outcomes.

**Estimates of effectiveness and key assumptions**
The probabilities of clinical VTE were estimated by assuming that the ratios of sub-clinical DVT that become symptomatic were similar to that seen for enoxaparin.

The authors assumed that the probability of late DVT for patients receiving fondaparinux was the same as for enoxaparin.

The risk of post-thrombotic syndrome was assumed to begin at day 91 (chronic phase), with different estimates depending on whether the patient had initially developed a clinical VTE or had a sub-clinical DVT.

Rates of unconfirmed DVT or PE were assumed not to differ by type of procedure or prophylaxis.

**Measure of benefits used in the economic analysis**
The specific measures of benefits were the number of clinical VTE events averted and VTE-related deaths averted for each of the surgical cohort at different time periods. The benefits were not discounted.

**Direct costs**
The cost boundary was the health service. The direct costs estimated were the costs of drugs (including acquisition, administration and monitoring), laboratory tests, VTE treatment and adverse events. The resource quantities were derived from a detailed survey of six hospitals and from the literature, and were verified by an expert panel of clinicians. The unit costs were obtained from national published sources and from a survey of 16 hospital trusts. No common price year was reported. The unit costs per course or per episode were reported. The resource quantities and the costs were reported separately. A discount rate of 6% was applied since the costs were incurred during more than 2 years.

**Statistical analysis of costs**
No statistical analysis on the costs was performed.

**Indirect Costs**
The indirect costs were not included.

**Currency**
UK pounds sterling (§).

**Sensitivity analysis**
One-way sensitivity analyses were conducted to evaluate the impact of changes in key parameters. Five scenario analyses were conducted to test the impact of altering differences between fondaparinux and enoxaparin in major bleeding and early DVT.

**Estimated benefits used in the economic analysis**
The total number of clinical VTE per 1,000 procedures at discharge was 9.4 with fondaparinux and 20.4 with enoxaparin. The total number of VTE-related deaths was 1.8 with fondaparinux and 3.7 with enoxaparin.

The total number of clinical VTE at day 30 was 20.6 with fondaparinux and 35.6 with enoxaparin. The total number of VTE-related deaths was 2.7 with fondaparinux and 5.1 with enoxaparin.
The total number of clinical VTE at day 90 was 31.4 with fondaparinux and 49.9 with enoxaparin. The total number of VTE-related deaths was 3.7 with fondaparinux and 6.8 with enoxaparin.

The total number of clinical VTE at year 1 was 31.9 with fondaparinux and 50.8 with enoxaparin. The total number of VTE-related deaths was 3.8 with fondaparinux and 6.9 with enoxaparin.

The total number of clinical VTE at year 5 was 33.4 with fondaparinux and 53.4 with enoxaparin. The total number of VTE-related deaths was 3.9 with fondaparinux and 7.1 with enoxaparin.

After 5 years, fondaparinux was expected to produce 20.0 fewer clinical VTE and 3.2 fewer VTE-related deaths per 1,000 procedures.

The greatest absolute benefit was observed in patients undergoing HFS, where fondaparinux was expected to produce 23.2 fewer clinical VTE events and 5.9 fewer VTE-related deaths per 1,000 procedures after 5 years.

**Cost results**
During the inpatient period, the costs with fondaparinux (101 per patient) were higher than the costs with enoxaparin (95 per patient). The difference was -6.

Fondaparinux was cost-neutral between discharge and day 30 (130 in both fondaparinux and enoxaparin cohorts). Fondaparinux was cost-saving beyond this period: 160 (fondaparinux) versus 164 (enoxaparin) at day 90, 167 versus 174 at year 1 and 219 versus 246 at year 5.

The cost-savings were greatest in patients undergoing TKR (38 per patient). For THR and HFS, the cost-savings were 17 and 29, respectively.

Changes in the key parameters in the model did not alter the overall results.

Fondaparinux would cease to be cost-saving at its full price if the price of enoxaparin was lower by more than 50% (i.e. less than 2.13 per day).

Fondaparinux would also cease to be cost-saving in the THR and TKR cohorts if the rate of late DVT with fondaparinux were increased by 50% over enoxaparin.

**Synthesis of costs and benefits**
The authors did not report any synthesis of the costs and benefits, as fondaparinux was both more effective and less costly after day 90 than enoxaparin.

**Authors’ conclusions**
Compared with enoxaparin, fondaparinux is more effective and reduces costs to the health care system. Fondaparinux is, therefore, a cost-effective and dominant strategy in patients undergoing major orthopaedic surgery in the UK.

**CRD COMMENTARY - Selection of comparators**
Enoxaparin was chosen as the comparator because it was the most commonly prescribed low molecular weight heparin by UK orthopaedic surgeons. You should consider whether this type of care is similar to that offered in your own setting.

**Validity of estimate of measure of effectiveness**
The authors reported that either randomised trials, long-term prospective cohort studies, or retrospective studies were used as primary studies. There was no evidence that a systematic review of the literature was conducted. The differences between the primary studies were investigated, but were not explained, and the validity of the studies was
not analysed. The estimates were varied in the sensitivity analysis and the rationale for the ranges over which they were varied was provided.

**Validity of estimate of measure of benefit**
The estimation of benefits was modelled. The decision analysis model used to derive the measure of health benefit was appropriate.

**Validity of estimate of costs**
The authors reported that they adopted the UK NHS perspective and, as such, all relevant direct costs were included. Health resource use was derived from actual data. The cost estimates were not specific to the study setting and sensitivity analyses of the costs were performed. The ranges of which the estimates were varied were reported in detail and justifications for them were provided. Discounting was performed. The resource quantities and the costs were reported separately. However, no common price year was reported, which hinders the transferability of the results to other settings.

**Other issues**
The authors did not compare their findings with those from other studies. They also did not specifically address the generalisability of the results to other settings. The authors highlighted some limitations of their study. For example, the number of assumptions, uncertainty concerning the incidence of post-thrombotic syndrome, and the non inclusion of indirect costs. The authors do not appear to have reported the results selectively.

**Implications of the study**
The authors recommended that, at current prices, fondaparinux would be the strategy in the UK for prophylaxis following major orthopaedic surgery. The economic benefits of using fondaparinux for a longer duration (longer than 7 days) will be addressed in future studies.

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