A cost-effectiveness analysis of fondaparinux sodium compared with enoxaparin sodium as prophylaxis against venous thromboembolism: use in patients undergoing major orthopaedic surgery

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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 fondaparinux sodium as prophylaxis against venous thromboembolism (VTE) was investigated. Fondaparinux (Arixtra, Sanofi-Synthelabo) was administered for 7 days at a dose of 2.5 mg once daily. This intervention was compared with enoxaparin (Lovenox, Aventis Pharma), which was administered for 7 days at a dose of 20 mg twice daily as recommended in the USA.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised three distinct cohorts of surgical patients (i.e. hip replacement, knee replacement and hip fracture repair). Cohorts of patients undergoing elective surgery were 65 years of age at the time of surgery, while those undergoing surgery following hip fracture were 80 years of age.

Two analyses were performed in two different study populations. The first analysis involved patients recruited in the published trials of fondaparinux (over 7,000 patients). This analysis used the proportions of patients undergoing each of the three major surgical procedures in these trials. The second analysis was a US Food and Drug Administration (FDA)-approved label analysis for a hypothetical cohort of US patients. Since it took FDA-approved label recommendations into consideration, only patients for whom fondaparinux was initiated 6 to 8 hours post-surgery, and who had a body weight of more than 50 kg and were without severe renal impairment (creatinine clearance >30 mL/minute), were included in the analysis.

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

Dates to which data relate
The effectiveness data were derived from studies published between 1982 and 2002. The price year was 2003.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published literature. The authors made assumptions to supplement data derived from the literature.
Modelling
A decision analysis model was developed to evaluate the clinical outcomes and costs of thromboprophylaxis. The model enabled translation of clinical trial end points (venographic deep-vein thrombosis (DVT)) into end points relevant to routine practice (clinical DVT and pulmonary embolism (PE)) and extrapolated the economic consequences beyond the time horizon of the clinical trial. The model provided for two distinct periods. On was an acute phase, beginning with surgery and ending at 90 days. The other was a chronic phase, ending 5 years after surgery.

Outcomes assessed in the review
The main outcomes assessed in the review were the probabilities of events in total hip replacement, total knee replacement and hip repair fracture with enoxaparin or fondaparinux. These probabilities included:

- the probability of early thrombi in the inpatient period;
- the probability of early clinical DVT;
- the probability of early clinical PE;
- the probability of late thrombi;
- the probability of late clinical DVT;
- the probability of late clinical PE;
- the probability of recurrent VTE; and
- the probability of post-thrombotic syndrome.

The authors also derived the proportions of patients undergoing total knee replacement, hip fracture repair and total hip replacement.

Study designs and other criteria for inclusion in the review
The main probabilities were derived from randomised trials and cohort studies, following recommendations by Sullivan et al. (see ‘Other Publications of Related Interest’ below for bibliographic details). The proportion of patients undergoing each of the three surgical procedures was derived from the fondaparinux trials and from data from the National Hospital Discharge Survey. Data from the fondaparinux trials formed part of the trial-based analysis. Data from the National Survey formed part of the label-based analysis, representing the proportion of surgical procedures undertaken in the USA.

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
Approximately 20 primary studies were used to derive the main probabilities.
Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
The proportion of patients undergoing surgical procedures in the fondaparinux trials was 64% for total hip replacement, 13% for total knee replacement, and 23% for hip fracture repair.

The proportion of patients undergoing surgical procedures in the US was 28% for total hip replacement, 39% for total knee replacement, and 33% for hip fracture repair.

The main transitional probabilities for patients undergoing total hip replacement were as follows.

The probability of early thrombi was 0.0863 with enoxaparin and 0.0473 with fondaparinux.

The probability of early clinical DVT ranged from 0.0029 to 0.0100 with enoxaparin, and from 0.0016 to 0.0022 with fondaparinux, during the first 90 days after the operation.

The probability of early clinical PE ranged from 0.0016 to 0.0057 with enoxaparin, and from 0.0009 and 0.0031 with fondaparinux, during the first 90 days after the operation.

The probability of late thrombi during the first 30 days after discharge for those receiving enoxaparin was 0.1932.

The probability of late clinical DVT was 0.0050 with enoxaparin and 0.0052 with fondaparinux during the first 90 days after discharge.

The probability of late clinical PE was 0.0006 with enoxaparin and 0.0007 with fondaparinux during the first 90 days after discharge.

The probability of recurrent VTE for those receiving enoxaparin ranged from 0.0018 during day 1 to day 30, to 0.0107 during year 2.

The probability of post-thrombotic syndrome following clinical VTE for those receiving enoxaparin was 0.173 during day 91 to day 365, 0.055 during year 2, and 0.0173 for each year during years 3 to 5.

The probability of post-thrombotic syndrome following sub-clinical VTE for those receiving enoxaparin was 0.0722 during day 91 to day 365, 0.055 during year 2, and 0.0072 for each year during years 3 to 5.

The main transitional probabilities for patients undergoing total knee replacement were as follows.

The probability of early thrombi was 0.2715 with enoxaparin and 0.1247 with fondaparinux.

The probability of early clinical DVT ranged from 0.0035 to 0.0116 with enoxaparin, and from 0.0016 to 0.0053 with fondaparinux, during the first 90 days after operation.

The probability of early clinical PE ranged from 0.0015 to 0.0050 with enoxaparin, and from 0.0007 and 0.0023 with fondaparinux, during the first 90 days after operation.

The probability of late thrombi during the first 30 days after discharge for those receiving enoxaparin was 0.1256.

The probability of late clinical DVT was 0.0016 with enoxaparin and 0.0019 with fondaparinux during the first 90 days after discharge.
The probability of late clinical PE was 0.0008 with enoxaparin and 0.0009 with fondaparinux during the first 90 days after discharge.

The probability of recurrent VTE for those receiving enoxaparin ranged from 0.0018 during day 1 to day 30, to 0.01071 during year 2.

The probability of post-thrombotic syndrome following clinical VTE for those receiving enoxaparin was 0.173 during day 91 to day 365, 0.055 during year 2, and 0.0173 for each year during years 3 to 5.

The probability of post-thrombotic syndrome following sub-clinical VTE for those receiving enoxaparin was 0.0722 during day 91 to day 365, 0.055 during year 2, and 0.0072 for each year during years 3 to 5.

The main transitional probabilities for patients undergoing total knee replacement were as follows.

The probability of early thrombi was 0.1878 with enoxaparin and 0.0785 with fondaparinux.

The probability of early clinical DVT ranged from 0.0069 to 0.0151 with enoxaparin, and from 0.0029 to 0.0063 with fondaparinux, during the first 90 days after operation.

The probability of early clinical PE ranged from 0.0039 to 0.0086 with enoxaparin, and from 0.0016 and 0.0036 with fondaparinux, during the first 90 days after operation.

The probability of late thrombi during the first 30 days after discharge for those receiving enoxaparin was 0.1932.

The probability of late clinical DVT was 0.0086 with enoxaparin and 0.0097 with fondaparinux during the first 90 days after discharge.

The probability of late clinical PE was 0.0010 with enoxaparin and 0.0012 with fondaparinux during the first 90 days after discharge.

The probability of recurrent VTE for those receiving enoxaparin ranged from 0.0018 during day 1 to day 30, to 0.0107 during year 2.

The probability of post-thrombotic syndrome following clinical VTE for those receiving enoxaparin was 0.173 during day 91 to day 365, 0.055 during year 2, and 0.0173 for each year during years 3 to 5.

The probability of post-thrombotic syndrome following sub-clinical VTE for those receiving enoxaparin was 0.0722 during day 91 to day 365, 0.055 during year 2, and 0.0072 for each year during years 3 to 5.

Methods used to derive estimates of effectiveness
The authors supplemented the results from the review with their own assumptions. These assumptions were validated by an international advisory board that comprised North American and European physicians, clinical epidemiologists and economists.

Estimates of effectiveness and key assumptions
The authors assumed that:

patients could develop a thrombus either during the period of hospitalisation (early thrombus) or later, between hospital discharge and day 30 (late thrombus);

patients with early or late thrombi could present with clinical VTE prior to day 90, or could remain asymptomatic;

the detection of DVT or PE was based on symptomatic presentations, which was subsequently objectively confirmed;

patients with confirmed VTE underwent treatment and remained at risk of long-term complications;
patients with undetected and untreated DVT were at risk of post-thrombotic syndrome; and fondaparinux had a similar effect to enoxaparin on the risk of occurrence of late thrombi and subsequent clinical events.

**Measure of benefits used in the economic analysis**
The measure of benefit used was the rate of symptomatic thromboembolic events.

**Direct costs**
The direct costs of the health care service were included in the analysis. These comprised:

- prophylaxis costs, which included the acquisition cost of the drug, as well as the administration and monitoring costs of each therapy for 7 days;
- the costs of treating confirmed VTE, which included in-hospital marginal costs or readmission costs, visits to the physician and outpatient clinic, home health visits and drug costs;
- the costs of excluding suspected VTE, which included work-up costs such as testing and physician visits;
- the costs of adverse events such as major bleeding; and
- the costs of treating long-term complications such as acute post-thrombotic syndrome, which included the costs of treating varicose veins, venous ulcer, chronic insufficiency and cellulitis.

The authors reported that minor bleeding costs were not included in the analysis because of the difficulty in obtaining precise estimates and the fact that clinical trials had not shown a difference in this outcome between fondaparinux and enoxaparin. The costs were derived from various sources, such as a database and published US economic evaluations. However, the costs of treating post-thrombotic syndrome were estimated from a Swedish study, owing to the lack of reliable US studies. Discounting was appropriate and, therefore, all costs beyond one year were discounted at a rate of 3%. The study reported the average and marginal costs. All cost parameters were expressed in 2003 prices.

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

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

**Currency**
US dollars ($). The costs derived from the Swedish study were converted from Swedish kroner using average exchange rates and were updated to 2003 price levels.

**Sensitivity analysis**
One-way sensitivity analyses were performed from the day 90 time-point. Baseline assumptions were varied in order to examine the effect of possible variations. Where possible, the reported 95% confidence intervals were used; otherwise the authors added or subtracted 50% to the values to ensure a wide range that would capture any plausible changes in parameters. Changes in selected parameters were performed individually for each of the surgical sub-groups. The parameters tested included:

- the risk difference for the efficacy and safety of fondaparinux relative to enoxaparin;
the risk difference for late events;
the rate of clinical events following hip fracture surgery over elective hip surgery;
the rate of false-positive diagnoses;
event costs; and
the costs of fondaparinux and enoxaparin.

A specific analysis, which assumed the same costs of events across all surgical groups, was also conducted.

Estimated benefits used in the economic analysis
According to the trial-based analysis, fondaparinux prevented 3.7 clinical VTE events per 1,000 patients at hospital discharge when used in place of enoxaparin for any form of major orthopaedic surgery. The number of thromboembolism events prevented increased to 12.1 events at 1 month and 15.1 events at 3 months. At 3 months, this result translated into a number-needed-to-treat (NNT) to avoid an additional clinical VTE event of 66.

Using the US label-based analysis, fondaparinux was found to prevent 5.4 clinical VTE events per 1,000 patients at hospital discharge when used in place of enoxaparin for any form of major orthopaedic surgery. At 3 months, fondaparinux prevented 17.8 clinical VTE events per 1,000 patients (NNT 56).

Cost results
In the trial-based analysis, the cost-savings per patient of using fondaparinux over enoxaparin were -$15 at discharge from hospital (i.e. at discharge from hospital fondaparinux cost $15 more than enoxaparin per patient), $61 at 30 days, $89 at 3 months, and $155 at 5 years following surgery.

In the label-based analysis, the cost-savings per patient of using fondaparinux over enoxaparin were $25 at discharge from hospital, $112 at 30 days, $141 at 3 months, and $234 at 5 years following surgery.

Synthesis of costs and benefits
The costs and benefits were not combined as fondaparinux was found to be more effective and less costly than enoxaparin.

The authors reported that the results of the one-way sensitivity analyses were generally robust to plausible changes in all values tested. The results were also found to be insensitive to changes in the discount rate. Fondaparinux was found to be dominant in all assumptions in both the trial- and label-based analyses, even with the wide variation in the overall main variables.

Authors' conclusions
The study suggested that fondaparinux, when compared with the current standard regimen of enoxaparin for prophylaxis of venous thromboembolism (VTE) in major orthopaedic surgery, improved outcomes and was cost-saving from the perspective of a US health care payer.

CRD COMMENTARY - Selection of comparators
An explicit justification was given for using enoxaparin as the comparator. Enoxaparin was a standard of care recommended by the American College of Chest Physicians and was found to be very cost-effective, or even cost-saving, in comparison with unfractionated heparin and, in most cases, cost-effective in comparison with warfarin. You should decide if this is a widely health technology in your own setting.
Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken to identify relevant research and minimise biases. The authors also omitted to report the sources used to identify all relevant research, and much of the methodology used in the review. However, the authors derived the main probabilities from recent randomised trials and prospective cohort studies, following published recommendations. Such study designs are considered to be the 'gold' standard when comparing health interventions. The authors supplemented data from the literature with their own assumptions. These assumptions, as well as data from the literature, were varied using appropriate ranges in a comprehensive sensitivity analysis. Further, the assumptions were validated by an international advisory board of North American and European physicians, clinical epidemiologists and economists.

Validity of estimate of measure of benefit
The estimate of benefits was modelled. Although the authors used a 5-year time horizon, the model only provided the estimate of benefit (i.e. clinical VTE events prevented) up to day 90.

Validity of estimate of costs
All the categories relevant to the perspective adopted (i.e. US health care payer) were included in the analysis. The authors reported that some minor costs, such as minor bleeding costs, were omitted from the analysis. These omissions are unlikely to have affected the authors' conclusions, as clinical trials found no differences in this outcome between fondaparinux and enoxaparin. The costs and the quantities were not reported separately, which will limit the generalisability of the authors' results. Appropriate sensitivity analyses of the costs were performed, using large ranges. Since the costs were incurred during a 5-year period, future costs were appropriately discounted. The price year was reported, which will aid any possible inflation exercises.

Other issues
The authors reported that other economic analyses had assessed the short-term benefits of prophylaxis against VTE, but had not fully examined its long-term consequences (e.g. recurrences and post-thrombotic syndrome). The issue of generalisability to other settings was partially addressed in the sensitivity analysis. The authors did not report the effectiveness of fondaparinux over 5 years, which was the time horizon of the analysis, concentrating instead on the short-term period only. There were several other limitations to the study. First, the probabilities of clinical outcomes were derived from a wide spread of randomised controlled trials and cohort studies with different designs and goals. Second, an assessment of event rates was difficult because of the limited data for post-thrombotic syndrome. Finally, the study only examined costs related to the health care system and did not address patient-focused issues such as quality of life.

Implications of the study
The authors appear to have recommended the use of fondaparinux in the US health care setting for patients undergoing major orthopaedic surgery.

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