Fondaparinux sodium compared with enoxaparin sodium: a cost-effectiveness analysis

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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 (FON), at a dose of 2.5 mg/day, for the prophylaxis of venous thromboembolism (VTE) after major orthopaedic surgery. FON was given postoperatively for 7 days.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients undergoing major orthopaedic surgery such as hip fracture surgery (HFS), total hip replacement (THR) and total knee replacement (TKR).

Setting
The setting was a hospital. The economic study was carried out in Norway.

Dates to which data relate
The effectiveness data were derived from studies published between 1982 and 2002. The resource use data were based on a database of surgery performed between 1999 and 2001. The price year was 2003.

Source of effectiveness data
The effectiveness data were obtained from a synthesis of published studies.

Modelling
A deterministic decision tree model was used to assess the cost-effectiveness of FON versus ENO as prophylactic treatment after major orthopaedic surgery. Patients could or could not develop VTE (including DVT and PE) during initial hospitalisation, which could be clinically apparent (symptomatic VTE) or remain asymptomatic. DVT was detected by clinical diagnosis. Patients who were wrongly suspected of having a DVT were also considered in the model. Patients with confirmed DVT did not receive treatment but remained at risk of long-term complications (recurrences or post-thrombotic syndrome). Patients with undetected DVT were at risk of long-term complications and some of them would develop PE. A similar pattern applied to those who developed PE. The model also considered the risk of major haemorrhage during either prophylaxis or the treatment of DVT or PE, and the risk of fatality, whether PE-related or not. Multiple time horizons were considered from surgery up to 5 years thereafter, although data were presented only at discharge and days 30 and 90. A simplified version of the decision tree was illustrated.
Outcomes assessed in the review
The outcomes estimated from the literature were the probabilities of the following events:

- early DVT (from inpatient to discharge),
- clinical DVT,
- clinical PE,
- late DVT (from discharge to day 30),
- subsequent clinical DVT and clinical PE,
- recurrent VTE (5 years),
- post-thrombotic syndrome for clinical VTE and for sub-clinical DVT,
- suspected but unconfirmed DVT,
- suspected but unconfirmed PE,
- major bleeding (both prophylaxis-related or treatment-related), and
- death (following PE or following major bleeding).

All these probabilities were estimated for FON and ENO separately for patients undergoing TKR, THR or HFS.

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature was undertaken to identify the primary studies. The clinical inputs came from several sources, such as clinical trials, cohort studies, retrospective studies and other published sources. No other details of the primary studies were given.

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
Twenty-three primary studies provided the clinical data.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.
Results of the review

In case of early disease (inpatient to discharge), the probabilities of DVT were 0.1249 (FON) and 0.2715 (ENO) for TKR, 0.0397 (FON) and 0.0863 (ENO) for THR, and 0.0864 (FON) and 0.1878 (ENO) for HFS.

The probabilities of clinical DVT were 0.0111 (FON) and 0.0242 (ENO) for TKR, 0.0078 (FON) and 0.0170 (ENO) for THR, and 0.0133 (FON) and 0.02894 (ENO) for HFS.

The probabilities of clinical PE were 0.0047 (FON) and 0.0103 (ENO) for TKR, 0.0044 (FON) and 0.0097 (ENO) for THR, and 0.0075 (FON) and 0.0164 (ENO) for HFS.

In case of late disease (from discharge to day 30), the probabilities of DVT with FON and ENO were 0.1256 with both drugs for TKR, and 0.1932 with both drugs for THR and for HFS.

The probabilities of clinical DVT were 0.0037 (FON) and 0.0031 (ENO) for TKR, 0.0106 (FON) and 0.0101 (ENO) for THR, and 0.0192 (FON) and 0.0171 (ENO) for HFS.

The probabilities of clinical PE were 0.0019 (FON) and 0.0016 (ENO) for TKR, 0.0013 with both drugs for THR, and 0.0024 (FON) and 0.0021 (ENO) for HFS.

The probability of recurrent VTE was 0.0451 with both drugs and all types of surgeries.

The probability of post-thrombotic syndrome for clinical VTE was 0.28 with both drugs and all types of surgeries.

The probability of post-thrombotic syndrome for sub-clinical DVT was 0.1168 with both drugs and all types of surgeries.

The probability of suspected but unconfirmed DVT was 0.1 with both drugs and all types of surgeries.

The probability of suspected but unconfirmed PE was 0.02 with both drugs and all types of surgeries.

The probability of prophylaxis-related major bleeding was 0.028 with FON and 0.026 with ENO for all type of surgeries

The probability of treatment-related major bleeding was 0.0224.

The probability of death following PE was 0.145 with both drugs for TKR and THR, and 0.682 with both drugs for HFS, while the probability of death following major bleeding was 0.0063 with both drugs and all types of surgeries.

Measure of benefits used in the economic analysis

Three summary benefit measures were used in the economic analysis. These were clinical DVT cases, clinical PE cases, and VTE-related deaths. All benefits were estimated using a modelling approach.

Direct costs

The perspective of the study was that of the Norwegian health care system. The analysis included the costs associated with VTE management, which comprised the costs of prophylaxis, confirmation, and treatment of clinical VTE before and after hospital discharge, physician visits, and diagnostic tests for the assessment of suspected but unconfirmed VTE, bleeding and post-thrombotic syndrome. The unit costs were presented separately from the resource quantities for some items, while other costs were presented as macro-categories.

Data on hospital stay were derived from the Norwegian National Register of Hospital Patients, which included 51,555 adult patients who underwent TKR, THR or HFS over the years 1999 - 2001, after excluding patients with multiple traumas affecting more than one organ system. This database also provided the proportion of patients undergoing the three types of surgery (10.7% TKR, 40.1% THR and 49.2% HFS). Dosages of prophylactic medications were based on
European practice and costs were derived from wholesale prices. Other quantities of resources were based on authors’ opinions and costs came from the Norwegian Diagnosis-Related Group (DRG) system, the Norwegian Ministry of Health and National Insurance Services. The cost of treating post-thrombotic syndrome was derived from a Swedish study. Discounting was relevant as the long-term costs were assessed, and an annual discount rate of 3% was applied. The price year was 2003.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not taken into account.

**Currency**
Norwegian kroner (NOK). The average exchange rate from NOK to US dollars ($) in 2003 was $1 = NOK 7.08.

**Sensitivity analysis**
Univariate sensitivity analyses were carried out to assess the robustness of the base-case results, in terms of the cost-effectiveness ratios, to variations in key clinical and economic inputs. Specifically, variations were carried out on the discount rate, the price of study medications, and risks of early and late DVT with FON relative to ENO. Alternative values were based on published confidence intervals or were set by the authors.

**Estimated benefits used in the economic analysis**
Fewer clinical DVT cases, clinical PE cases, and VTE-related deaths were observed with FON in comparison with ENO, regardless of the type of surgery and the time horizon of the analysis. For example, the expected number of clinical DVT cases per 10,000 patients for the three types of surgery combined (on the basis of percentage of patients undertaking surgeries in the Norwegian cohort) was:

- 40 with FON and 87 with ENO (difference -47) during the inpatient stay,
- 153 and 245 (difference -92) up to 30 days, and
- 244 and 357 (difference -113) up to 90 days.

Similar trends were observed for longer time horizons and the other benefit measures. FON was always more effective in preventing DVT and PE cases and VTE-related death.

**Cost results**
In general, the costs associated with FON were higher than those associated with ENO (excluding the cost of hospitalisation due to VTE events). For example, the total costs per patients for the three surgeries combined were:

- NOK 1,709 with FON and NOK 1,360 with ENO (difference NOK 349) during the inpatient stay,
- NOK 2,203 and NOK 2,056 (difference NOK 147) up to 30 days, and
- NOK 2,584 and NOK 2,539 (difference NOK 45) up to 90 days.

In general, the longer the time horizon, the greater the cost-savings associated with FON.

**Synthesis of costs and benefits**
Several incremental cost-effectiveness ratios (ICERs) were calculated to combine the costs and benefits of the two prophylactic treatments. The ICER varied depending on the time horizon (the longer the time horizon, the more cost-effective the FON strategy).

For example, the incremental cost per avoided DVT event with FON over ENO after TKR (considering the avoided hospitalisation costs due to DVT events) was NOK 17,114 at discharge, while FON was dominant at 30 and 90 days after discharge.

The incremental cost per avoided PE after TKR was NOK 70,465 at discharge, NOK 14,512 at 30 days, and NOK 147 at 90 days.

The incremental cost per avoided VTE after TKR was NOK 53,195 at discharge, while FON was dominant at 30 and 90 days after discharge.

The net cost per death avoided after TKR was NOK 242,500 at discharge, NOK 141,429 at 30 days, and NOK 89,412 at 90 days.

Similar results were found for THR. FON was generally dominant after 30 days when DVT, PE or VTE events were used as the benefit measure, while the incremental cost per death avoided decreased with longer follow-up. However, FON was more cost-effective (often dominant) in the case of HFS, probably due to the higher mortality rate for PE following this type of surgery. The authors stated that FON was always dominant at the 5-year follow-up, although the data were not presented.

The results of the sensitivity analysis suggested that, in general, the base-case ICERs were robust. The price difference between the two drugs was the key cost determinant.

Authors' conclusions
Fondaparinux sodium (FON), used to prevent the incidence of venous thromboembolism (VTE), was a cost-effective treatment in short follow-up periods for hip fracture surgery (HFS). For extended follow-up periods (i.e. 5 years), FON was also cost-effective for total knee replacement (TKR) and total hip replacement (THR).

CRD COMMENTARY - Selection of comparators
The authors provided a justification for the choice of the comparators, which were appropriate for the study question. FON represented a new anti-thrombotic agent for prophylaxis of VTE after major orthopaedic surgery, while ENO represented standard care in Norway. Dosages were also reported. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a synthesis of completed studies which, given that no details of the methods or conduct of a systematic review of the literature were provided, may have been identified selectively. The authors gave some information on the characteristics of the primary studies, which were of different designs (e.g. clinical trials, cohort studies and epidemiological studies). However, details of the study populations were not provided. Similarly, the methods used to extract and combine the primary estimates were not reported, and the issue of homogeneity amongst the primary studies was not addressed. However, the effectiveness of FON in preventing VTE came from clinical trials or from a meta-analysis of these trials, which strengthens the internal validity of the study. On the other hand, it appears that no head-to-head studies were available, thus the analysis was probably based on an indirect comparison.

Validity of estimate of measure of benefit
The summary benefit measures were specific to the disease considered in the study. They would be difficult to compare with the benefits of other health care interventions. The impact of the treatments on quality of life was not investigated. Mortality was also included as a final benefit measure, which enables comparisons with other diseases.
Validity of estimate of costs
The perspective of the economic study was that of the Norwegian health care system. Typical Norwegian sources were used to derive the costs. The unit costs were reported for some items, although other costs were presented as macro-categories because of the Norwegian hospital accounting system. Appropriate exchange rates were reported. Discounting was appropriately applied and the impact of changing the discount rate was investigated. The price year was reported, which will simplify reflation exercises in other time periods. While the cost estimates were specific to the study setting, the impact of using alternative cost estimates was investigated in the sensitivity analysis. Resource consumption was derived from Norwegian hospital statistics, which are likely to be an accurate reflection of treatment patterns in the authors' country. This was one of the main strengths of the cost analysis.

Other issues
The authors stated that their main findings were consistent with those observed in previous studies that had applied the same model to country-specific patient data and costs. The issue of the generalisability of the study results to other settings was not addressed and limited sensitivity analyses were carried out. Therefore, caution should be exercised when extrapolating the results of the study to other settings. The authors noted that the main limitation of the study was the use of a modelling approach, rather than a clinical trial with Norwegian patients, to assess the cost-effectiveness of the two drugs. In general, the main limitation of the analysis would appear to be the lack of details of the data synthesis and the poor analysis of the uncertainty around key parameters.

Implications of the study
The study results suggested that FON is more effective than ENO for the prophylaxis of VTE and that it becomes cost-saving over time.

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None stated.

Bibliographic details

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Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Anticoagulants /economics /therapeutic use; Arthroplasty, Replacement, Hip /adverse effects /methods /statistics & numerical data; Arthroplasty, Replacement, Knee /adverse effects /methods /statistics & numerical data; Cost-