Cost-effectiveness of prolonged out-of-hospital prophylaxis with low-molecular-weight heparin following total hip replacement

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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
Patients who had undergone elective hip replacement were given low molecular weight heparin (LMWH), subcutaneously, for 9 days in hospital and 19 to 23 days after discharge from hospital. The LMWH used was enoxaparin at a dose of 40 mg daily. Bilateral venography was carried out 19 to 23 days after discharge.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population was all patients who had undergone elective hip replacement and were able to return home. The patients had to be older than 39 years old and weigh more than 60 kg. Patients were excluded for a variety of medical characteristics. These included renal insufficiency, hypersensitivity to contrast medium, heparin or LMWH, a past or present risk of haemorrhage, endocarditis, severe liver disease or untreated hypertension, and venous thromboembolism within the preceding 3 months. They were also excluded if they had received treatment with heparin, LMWH, oral anticoagulants or non-steroidal anti-inflammatory drugs within the 5 days before surgery, if they had undergone ipsilateral hip surgery within the preceding 6 months, or if they were pregnant or lactating. Only patients who gave their consent were included.

Setting
The setting was secondary care, a hospital in Sweden. This was followed by outpatient care, which was carried out at the patients' homes and organised by the hospital.

Dates to which data relate
No dates for the effectiveness evidence or the resource evidence were reported. No price year was given. The original effectiveness paper was published in 1996.

Source of effectiveness data
The effectiveness data were derived from a single study published in 1996 (see Other Publications of Related Interest no.1).

Link between effectiveness and cost data
The costing was undertaken on the same patient sample as that used in the effectiveness study. It is unclear whether the costing was carried out prospectively or retrospectively.
Study sample
No power calculations to determine the sample size were reported. Of the 288 patients who were enrolled initially, 262 were randomised. Of the remainder, 8 patients withdrew their consent, the condition of 5 was deteriorating, 4 had violations of the study protocol, 2 had intercurrent events, 1 died, 1 was excluded for administrative reasons, and 5 were not randomised for other reasons. Further details are provided in the original publication (see Other Publications of Related Interest no.1). There were 131 patients randomly allocated to each of the two treatment groups. After randomisation, no patients were excluded from the analysis.

Details of the age, sex composition, body mass index, history of previous thromboembolism, presence of varicose veins and presence of leg ulcers of the two patient groups were given in the original publication (see other Publications of Related Interest no.1). No statistical test on the differences between the two groups was carried out.

The authors did not justify the choice of patient sample with respect to the characteristics of the disease.

Study design
This was a randomised double-blind control trial carried out at one centre (see Other Publications of Related Interest no.1). There was no follow-up after the assessment one month after surgery.

Analysis of effectiveness
The analysis was conducted on an intention to treat basis. The three health outcomes recorded were DVTs detected through phlebography, DVTs detected clinically, and the incidence of PE. The authors stated that the demographic characteristics and prognostic features in the two patient groups were comparable but they did not provide any statistical calculation to back this statement. The numbers were tabulated in the original publication (see Other Publications of Related Interest no.1). The confounding variables given were the body mass index, prior thromboembolism, the presence of varicose veins, and the presence of leg ulcers.

Effectiveness results
Before phlebography was carried out, 2 patients in the standard group and 0 patients in the prolonged group had PEs. Phlebography could be carried out on 233 of the 262 patients in the trial, giving the following results.

The total number of thromboembolisms (including the PEs) was 45 in the standard group and 21 in the prolonged group, (p<0.001). Without phlebography, the following clinical events would have been detected: 7 DVTs and 2 PEs in the standard group, and 2 DVTs in the prolonged group (see Other Publications of Related Interest no.1).

Clinical conclusions
Prophylaxis with LMWH one month after elective hip replacement reduced the incidence of DVT and PE.

Outcomes assessed in the review
The outcomes assessed were the death rate of patients in the standard group as a result of PE, and the life expectancy of patients undergoing hip replacement.

Study designs and other criteria for inclusion in the review
The authors used a clinical trial of enoxaparin versus warfarin and a Swedish national statistics book.

Sources searched to identify primary studies
None reported.
Criteria used to ensure the validity of primary studies
None reported.

Methods used to judge relevance and validity, and for extracting data
None reported.

Number of primary studies included
Two primary studies were included in the review.

Methods of combining primary studies
Not applicable as only one study per parameter estimate was used.

Investigation of differences between primary studies
Not applicable.

Results of the review
The number of deaths avoided was 0.0004 per patient treated.

The average life expectancy (of men and women aged 68 and 69) in Sweden was 15.2 years.

Methods used to derive estimates of effectiveness
The authors made assumptions about the effectiveness.

Estimates of effectiveness and key assumptions
A death rate of 2% was assumed for patients with PE.

A life expectancy of 10 years was assumed.

Measure of benefits used in the economic analysis
The measures of benefits used were the life-years gained and the DVTs avoided.

Direct costs
Discounting was not carried out as it was irrelevant, the costs being incurred during a period of less than one year. The following costs were identified:

the cost of enoxaparin in a 40 mg prepared syringe;

the cost of administering enoxaparin at home in a non-trial setting;

the cost of hospitalisation to treat DVT (cost of one hospital day, the number of hospital days);

the cost of ambulatory treatment for DVT (LMWH, outpatient visits, warfarin treatment); and

the cost of diagnostic tests after clinical symptoms of DVT.

The authors distinguished between the costs incurred in the clinical trial when there was no marginal cost for administering enoxaparin as all patients received an injection, and the costs that would be incurred in a non-trial setting.
if enoxaparin were given as part of the post-operative treatment.

The resource quantities and the unit costs were presented separately. With the exception of the cost of administering enoxaparin at home, these were estimated from actual data. No price year was given. The sources of the prices were not stated. The prices were those that the hospital paid.

**Indirect Costs**
The indirect costs were not included in the analysis.

**Currency**
Swedish kroner (SEK).

**Sensitivity analysis**
The authors investigated the sensitivity of the results to the cost of administering enoxaparin at home. This depended on different assumptions relating to the proportion of patients who can be taught to self-administer enoxaparin before they have been discharged from hospital. The authors also examined the sensitivity of the results in years gained to different assumptions about the death rate caused by PE and the life expectancy of the patients.

Analyses were also conducted to investigate whether the results were sensitive to assumptions about whether the treatment of all DVTs, or only those with clinical symptoms, was the appropriate cost scenario for comparison between the two regimes.

The sensitivity of the results to the kind of treatment that DVT patients would get, ambulatory or in-hospital, was also examined.

**Estimated benefits used in the economic analysis**
The authors considered two scenarios.

For the worst-case scenario, the number of deaths avoided per treated patient was calculated from the clinical trial and the PE death rate (2%) to be 0.0003. Using a life expectancy of 10 years produced 0.003 life-years gained per treated patient.

For the best-case scenario, the number of deaths avoided was taken as 0.0004 and the life expectancy 15.2 years, to produce 0.006 life-years per treated patient (see Other Publications of Related Interest no.2). The number of DVTs avoided in the prolonged group was estimated as 0.1832 per treated patient.

The number of clinical DVTs avoided was estimated as 0.0534 per treated patient.

**Cost results**
The authors gave the cost per patient without taking into account any administrative costs, as the costs of administering enoxaparin after the patients had left hospital was the same as administering placebo.

For the prolonged group (excluding administrative costs), the cost per patient was SEK 596 for prophylaxis plus SEK 2,439 for hospitalisation.

For the standard group (excluding administrative costs), the cost per patient was SEK 312 plus SEK 6,447.

In the actual study, the administrative cost of administering enoxaparin by a research nurse was 6,510 SEK.

The duration of the costs was one month after surgery, adverse incidents during that time period being taken into account.
Synthesis of costs and benefits

Under the assumptions that 50 or 75% of the patients can be taught to self-administer enoxaparin, while in hospital, the prolonged strategy was dominant.

The authors performed a sensitivity analysis on the cost figures, where any cost-savings were deducted from the incremental treatment cost of SEK 2,487.

First, to determine the effect of treating DVT patients as outpatients (in the study they had been treated in hospital). The savings from ambulatory treatment would be SEK 1,374, giving a cost per DVT avoided of SEK 6,075.

Second, to determine the effect of assuming that the real cost-saving of the prolonged strategy in a non-trial setting would be only on clinical DVTs and PEs avoided. The cost-savings would now only be SEK 1,783, giving a cost per clinical DVT avoided of 13,184 SEK.

The cost per life-year gained was calculated (1) under the assumption that 0.003 life-years were gained per patient in the study and the costs were those that would be incurred only if clinical DVTs and PEs were treated. This came to 235,000 SEK per life-year gained. This cost was also calculated under the same assumption as (1) but with the assumption that 0.0006 life-years were gained per patient in the study. This came to 120,000 SEK per life-year gained.

Authors’ conclusions

"The net saving per patient is SEK 3,400, which means that if the administration costs are lower than this, the intervention will be cost-saving."

"The cost for administration should not exceed those for initial patient training at the hospital and one follow-up visit by a district nurse to ensure compliance."

CRD COMMENTARY - Selection of comparators

The comparator, no prophylaxis after leaving hospital, was justified as it has represented standard practice in the past.

Validity of estimate of measure of effectiveness

The analysis used a randomised controlled trial (see Other Publications of Related Interest no.1), which was appropriate for the study question. It also used other published sources. All of the information and analysis has been published already (see Other Publications of Related Interest no.2). The eligibility criteria for inclusion in the trial were age greater than 39 years and weight greater than 60 kg. The exclusion criteria were also described (see ‘Study Population’ section). The baseline characteristics were also given to allow comparison with the study population. The patient groups were described as comparable in the original publication, although no statistical results were given.

Validity of estimate of measure of benefit

The measure of benefit, life-years gained, was modelled using different assumptions relating to the deaths caused by PE and the life expectancy of the patients in the trial. Further details were provided in an earlier publication (see Other Publications of Related Interest no.2). The authors' estimate of 0.003 life-years gained depended largely on an assumption of 10 extra life-years saved for each person's life saved. The authors gave no justification for this assumption.

Validity of estimate of costs

The presentation of the costs was unclear, and consequently it was difficult to follow all of the authors' calculations. The earlier paper (see Other Publications of Related Interest no.2) is of help for gaining a better idea of the cost information. However, from the texts it would appear that all of the relevant categories of direct costs have been included. When the authors explored different scenarios for the administration of enoxaparin at home, they did not take
account of the indirect cost of this for the patients. Also, the price year was not given. However, a breakdown of the total costs was presented.

Other issues
The authors made appropriate comparisons of their results with those from some other studies. However, they did not address the issue of generalisability to other settings. The sensitivity analysis will account to some extent for this issue. As the costs of hospitalisation and administering enoxaparin after discharge are crucial, these are factors that must be considered when assessing generalisability. The authors presented their results selectively, thus requiring the other papers to be read.

Implications of the study
The study presents an economic case for prolonged enoxaparin. The authors show that the economic case depends on the costs of administering enoxaparin. As self-administration reduces these costs dramatically, they recommend that its feasibility should be investigated in a trial.

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Other publications of related interest


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