Management of acute proximal deep vein thrombosis: pharmacoeconomic evaluation of outpatient treatment with enoxaparin vs inpatient treatment with unfractionated heparin

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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
Subcutaneous low-molecular-weight heparin (LMWH; enoxaparin), administered primarily at home, was compared with intravenous (IV) unfractionated heparin (UFH) administered in the hospital for the treatment of acute proximal deep vein thrombosis (DVT). Both treatments were followed by warfarin therapy.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with acute proximal DVT, as diagnosed by duplex ultrasonography. The inclusion and exclusion criteria were adapted from the Canadian RCT. Some additional criteria were applied, which reflected treatment protocols used by the HMO outpatient DVT treatment programme. The inclusion criteria specified persons aged over 18 years with acute, proximal lower-extremity DVT, as diagnosed by duplex ultrasonography, and oral anticoagulation treatment planned for at least 3 months at an intended target international normalised ratio (INR) of 2.0 to 3.0.

The exclusion criteria were extensive:
platelet count of less 100,000;
the presence of active bleeding or haemorrhage from any source;
history of gastrointestinal bleed in the last 6 months;
history of heparin hypersensitivity or heparin-induced thrombocytopenia;
underlying liver disorder (INR greater than 1.5);
familial bleed disorder;
pregnant or lactating woman;
severe hypertension (systolic blood pressure greater than 220 mmHg and/or diastolic blood pressure greater than 120 mmHg);
renal insufficiency (serum creatinine greater than 2.5mg/dL);
catheter-associated DVT;
clinically unstable pulmonary embolus;

morbid obesity (absolute weight greater than 150 kg;

underlying congenital or acquired hypercoaguable state;

c-o-morbidity possibly increasing the risk of home treatment (e.g. congestive heart failure, chronic obstructive pulmonary disorder, diabetes, cancer, recent myocardial infarction or stroke, or any other condition increasing risk to the patient treated at home versus in the hospital);

other condition possibly increasing the risk of home treatment (e.g. no phone, unsuitable home environment, or lack of social support).

**Setting**
The study setting was secondary care. The outpatient-based treatment was primarily conducted in the home. The economic study was conducted in the USA.

**Dates to which data relate**
For the inpatient (UFH) group, the effectiveness data, resource use data and prices referred to 1995 to 1996. For the outpatient (enoxaparin) group, the corresponding data related to 1997 to 1998.

**Source of effectiveness data**
The effectiveness data were derived from a single study.

**Link between effectiveness and cost data**
The costing was undertaken on the same patient sample as that used in the effectiveness study. The cost data were collected retrospectively, from medical records and administrative data.

**Study sample**
The study did not report whether any power calculations, either prospective or retrospective, were performed. The study sample was selected retrospectively among eligible patients who had been treated for DVT in one HMO. All DVT patients who received UFH in hospital between 1995 and 1996, and all DVT patients who were treated with enoxaparin as outpatients between 1997 and 1998 were identified. These constituted the initial pool of potentially eligible patients.

The total number of patients identified was 354. After the inclusion and exclusion criteria were applied, 225 patients were disqualified. The patients were disqualified because the DVT was not proximal (n=46), not acute (n=44), not lower extremity (n=9), or the DVT documentation was insufficient (n=5). Other reasons were a documented, disqualifying co-morbid condition or inappropriate target INR level (n=42), heparin therapy had been initiated for a condition other than DVT (n=61), and in the 1997 to 1998 group, patients who had not received heparin at least partially on an outpatient basis (n=18). The final study groups comprised 64 patients in the UFH group and 65 in the enoxaparin group. There was no evidence that the study sample was appropriate for the clinical study question.

**Study design**
The study was a retrospective, comparative study with historical cohort that was conducted in one HMO. The effectiveness and cost data were derived from medical records and administrative data, which medical record reviewers examined. All discrepancies were resolved in a data cleaning process. The data referred to the time period of one "episode of care". This consisted of an initiation phase, beginning on the first day of heparin treatment and ending on the last day of heparin treatment, and a maintenance phase during which the patients received warfarin. Warfarin therapy started on the day after the last heparin treatment, and lasted for 90 days. No lack of data for this follow-up
period was reported.

**Analysis of effectiveness**

Patients in the initial enoxaparin pool (1997 to 1998) who did not receive outpatient therapy, at least partially, were excluded from the study. However, the enoxaparin group included patients who were treated entirely on an outpatient basis, patients who received initial therapy in the hospital and then switched to outpatient therapy, and patients who started outpatient therapy but were hospitalised at some point during the course of treatment. It was not clear, in all cases, why some patients in the enoxaparin group were treated partially as inpatients. This reason for switching between interventions may have biased the effectiveness results. On the other hand, all patients in the UFH group were hospitalised for the full course of UFH administration since, at the time of their treatment, there was no choice of switching to outpatient administration of enoxaparin.

The primary health outcomes used in the analysis were:

- death from thromboembolic causes,
- recurrent DVT (confirmed by Doppler duplex ultrasound),
- recurrent pulmonary embolism, and
- major bleed during the heparin or warfarin phase.

Major bleed was defined as retroperitoneal bleeding, intracranial bleeding, a drop in haemoglobin of greater than 2 g/dL, or bleeding necessitating transfusion of 2 units of packed red blood cells. The two groups of patients seem to have been comparable in their age and gender. However, no statistical analysis of the baseline characteristics was presented. No further adjustments for confounding factors were performed.

**Effectiveness results**

There were no deaths from thromboembolic causes within any of the groups during the study period.

Three primary clinical events (3 episodes of recurrent DVT) occurred in the UFH group (4.7% of patients) versus two events (one episode of recurrent DVT and one episode of major bleeding in heparin period) in the enoxaparin group (3% of patients). The difference was not statistically significant, (p=0.67).

No significant difference was shown in the number of recurrent venous thromboembolism events, (p=0.36), or bleeding events, (p=1.0), between the two groups.

**Clinical conclusions**

Home care with enoxaparin was equally effective and safe as hospital administration of UFH, for patients with acute proximal DVT.

**Measure of benefits used in the economic analysis**

The authors demonstrated that the primary clinical outcomes assessed were equal between the two groups (no statistically significant difference was found). Thus, the economic analysis was based on cost-differences only (i.e. a cost-minimisation analysis).

**Direct costs**

The perspective of the study was that of an HMO in the USA. It was stated that all the medical resources and costs recorded during the episode of care were included in the analysis, and that no attempt was made to exclude non-DVT costs. The costs were calculated for inpatient care, outpatient care, home health care, pharmacy and hospice, for both initiation phase and maintenance phase. The costs of inpatient care covered the hospital facility, including UFH.
administration and professional fees. Outpatient care covered ambulatory care, diagnostic and laboratory procedures, professional fees and outpatient surgery. Pharmacy costs were for enoxaparin, warfarin and other prescription drugs.

The quantities and the costs were not reported separately. The costs were estimated using actual data on resource use and unit costs, as derived from the administrative database of the HMO. Discounting was not carried out, which was appropriate since the costs were incurred in less than one year. The quantities and prices referred to 1995 to 1996 for the UFH group, and to 1997 to 1998 for the enoxaparin group. The authors stated that, although they did not adjust the costs to the same price year, this did not affect the results since the total costs for the UFH group were shown to be higher in the first place. If the total UFH costs were adjusted for inflation, they would be even higher than the total enoxaparin costs.

**Statistical analysis of costs**
The costs were based on stochastic data. For each treatment group, the mean costs, along with 95% confidence intervals (CIs), were presented for each of the two phases of care and for the total episode of care. The difference between the two group means was assessed using Student’s t-test and confirmed with a bootstrap bias-corrected 95% CI. The association between treatment group and total cost of care was examined further using multiple regression analysis.

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

**Currency**
US dollars ($).

**Sensitivity analysis**
No sensitivity analysis was carried out.

**Estimated benefits used in the economic analysis**
There was no statistically significant difference in the benefits between the two groups. See the 'Effectiveness Results' section.

**Cost results**
The mean total episode of care cost was $9,347 (+/- 8,469) for the enoxaparin group and $11,930 (+/- 10,892) for the UFH group.

The mean difference in cost was -$2,583 favouring the enoxaparin group, (p=0.1349; bootstrap-adjusted CI: -6,147 - +650).

It was stated that these results were confirmed in a multiple regression analysis controlling for age and gender, although the data relating to this analysis were not shown.

The predicted cost-savings with enoxaparin ranged from $2,894 to $3,534 for the mean age male (61.9 years) and female (64.0 years) patients, respectively, (p=0.01).

**Synthesis of costs and benefits**
Not applicable. The difference in benefits between the two interventions was shown not to be statistically significant. The difference in costs also proved to be non statistically significant. Thus, the costs and benefits were not combined.
Authors' conclusions
The results of the study were remarkably similar to those of the Canadian randomised controlled trial (RCT). The study showed that the outpatient treatment of deep vein thrombosis (DVT) with enoxaparin in a routine clinical practice setting of a US health maintenance organisation (HMO) was safe and efficacious. It also reduced the costs in comparison with standard inpatient therapy using intravenous (IV) unfractionated heparin (UFH).

CRD COMMENTARY - Selection of comparators
The choice of the comparator was explicitly justified. The comparator was chosen because it represented standard practice for the treatment of DVT. You should decide whether it represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The estimates of effectiveness outcomes were derived from a retrospective comparative study, based on medical records and administrative data. This study design may have introduced biases into the analysis, such as selection bias and information bias. Moreover, a number of patients in the enoxaparin group were partially treated as inpatients, for reasons not fully explained, and this may have affected the results. The large number of inclusion and exclusion criteria significantly limited the size of study sample. Consequently, it may have not been representative of the study population. The patient groups were shown to be comparable in the analysis for basic characteristics such as age and gender. However, no results of the statistical analysis were provided to show the comparability of groups and to account for potential biases and confounders. The authors noted that, due to the large time span during which the outcomes were assessed, factors other than the study intervention may have affected the results of the analysis. These issues tend to limit the internal validity of the analysis.

Validity of estimate of measure of benefit
The statistical analysis showed that the study outcomes were not significantly different between the two interventions. In effect, a cost-minimisation analysis was conducted.

Validity of estimate of costs
The study perspective was that of an HMO in the USA. All relevant costs were included in the analysis. The quantities and the costs were not reported separately, which limits the possibility of replicating the study in other settings. Further, the costs were grouped in gross categories and a detailed breakdown of the economic items was not provided. A statistical analysis of the costs was performed. Due to the nature of the setting (HMO), the costs were likely to reflect, up to a point, resource use. The dates to which the prices referred were reported and were different for the two groups. However, since the costs of the enoxaparin group, which were more recent, were lower, the authors felt that there was no need to adjust the costs of the UFH group to the same price year, as this would only increase the difference in costs between the two groups. The cost estimates were specific to the study setting and sensitivity analyses were not performed.

Other issues
The authors made appropriate comparisons of their results with those of other studies. The issue of the generalisability of the results to other settings was addressed. The study results were adequately reported. The authors considered the study design to be a limitation, as it was likely to introduce biases into the analysis. Their conclusion was that enoxaparin reduced costs in comparison with UFH. However, the analysis showed that, although enoxaparin treatment was less costly than UFH, this difference was not statistically significant. Nevertheless, the authors' conclusions reflected, in general, the scope of the analysis.

Implications of the study
The authors calculated the total costs related to treating DVT with IV UFH in the USA in 1997. They estimated that a shift of 50% of patients to the enoxaparin regimen could potentially have saved over $150 million in direct medical expenditure. They express the opinion that a protocol that would permit more extensive treatment of DVT on an
outpatient basis than that described in the study (which allowed for partial inpatient treatment in the enoxaparin group), might realise greater savings than those reported.

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