Outpatient treatment of venous thromboembolism with low-molecular-weight heparin: an economic evaluation


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 low molecular weight heparin (LMWH) in combination with warfarin for the treatment of patients with deep vein thrombosis (DVT). LMWH administration followed current treatment guidelines. For instance, heparin was discontinued once an international normalised ratio of more than 2.0 was achieved, and oral warfarin was given for 3 to 6 months more, depending on the etiology of the DVT. Several alternatives to LMWH were considered at analysis. These were heparin alone, heparin combined with warfarin, and enoxaparin combined with warfarin.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients experiencing DVT.

Setting
The setting appears to have been a hospital. The economic study was carried out in the USA.

Dates to which data relate
The authors did not report the dates to which the effectiveness and cost data related. The price year was not given.

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

Link between effectiveness and cost data
The costing was undertaken retrospectively on the same sample of the population as that used in the effectiveness analysis.

Study sample
No power calculations to determine the sample size were performed in the planning phase of the study. Patients who had an overnight hospital stay of at least one day with a discharge diagnosis of DVT were considered at analysis. Patients were excluded from the effectiveness analysis if they were not enrolled continuously for 6 months before or 12 months after hospitalisation or their discharge regimen was not consistent with current guidelines. They were also excluded if data on the costs of the treatment were missing, or if the suspected total costs were extremely high (>5
standard deviations over the mean).

In total, 3,466 patients were considered for the effectiveness analysis. There were 1,696 patients in the warfarin only group with a mean age of 53.9 years (standard deviation, SD=13.9); 56.3% were females. Thirteen patients received heparin alone. Their mean age was 50.9 years (SD=10.5) and 38.5% were females. There were 164 patients who received enoxaparin plus warfarin. Their mean age was 47.8 years (SD=13.7) and 53.7% were females. Sixteen patients received heparin plus warfarin. Their mean age was 54.1 years (SD=13.7) and 75% were females. Finally, 1,577 received no discharge therapy. The mean age in this group was 52.9 years (SD=14.9) and 56.6% were females. It is reasonable to assume that the study sample was representative of the study population.

**Study design**
This was a cohort study, which appears to have been multi-centred since the effectiveness data were collected from the PharMetrics Integrated Outcomes database. The authors reported that this database includes data for 37 health plans in the USA. The patients were allocated to the alternative treatment cohorts according to their initial therapy, and not following a randomised allocation. The duration of follow-up was the 12 months after the hospitalisation for the clinical analysis, and the 6 months prior to hospitalisation.

**Analysis of effectiveness**
The basis for the effectiveness analysis was treatment completers only. The primary health outcomes assessed were the average length of stay by age and by plan type, the number (and percentage) of DVT readmissions during the first year after hospitalisation, and the number (and percentage) of patients with readmission for haemorrhage. The authors undertook multiple linear regression analysis to deal with confounding variables around baseline demographics and co-morbidities.

**Effectiveness results**
The average lengths of stay for the various age groups of patients were:

- for warfarin alone, 6.7 (40 or younger), 6.8 (41 to 64), 7.1 (65 or older), and 6.8 days (whole group);
- for heparin alone, 6.0 (40 or younger), 4.7 (41 to 64), 7.0 (65 or older), and 5.1 days (whole group);
- for enoxaparin plus warfarin, 4.6 (40 or younger), 4.1 (41 to 64), 3.2 (65 or older), and 4.2 days (whole group);
- for heparin plus warfarin, 9.0 (40 or younger), 8.8 (41 to 64), 5.7 (65 or older), and 8.3 days (whole group); and
- for no discharge therapy, 7.1 (40 or younger), 7.0 (41 to 64), 8.3 (65 or older), and 7.2 days (whole group).

When compared with enoxaparin plus warfarin, the average lengths of stay were statistically significantly higher for warfarin alone, (p=0.0001), heparin plus warfarin, (p=0.002), and no discharge therapy, (p=0.0001), but not for heparin alone, (p=0.29).

The average lengths of stay for patients managed by a health maintenance organisation (n=1,610), an indemnity organisation (n=662), a preferred provider organisation (n=681) or a point-of-service plan (n=435) were as follows:

- for warfarin alone, 7.05 (health maintenance organisation), 6.08 (indemnity organisation), 6.55 (preferred provider organisation), and 6.94 days (point-of-service plan);
- for heparin alone, 6.50 (health maintenance organisation), 4.00 (indemnity organisation), 5.00 (preferred provider organisation), and 2.00 days (point-of-service plan);
- for enoxaparin plus warfarin, 4.08 (health maintenance organisation), 4.07 (indemnity organisation), 4.59 (preferred provider organisation), and 4.35 days (point-of-service plan);
for heparin plus warfarin, 8.55 (health maintenance organisation), 8.00 (indemnity organisation), 0 (preferred provider organisation), and 7.33 days (point-of-service plan); and

for no discharge therapy, 7.75 (health maintenance organisation), 7.10 (indemnity organisation), 6.65 (preferred provider organisation), and 6.66 days (point-of-service plan).

One hundred and fifty-three patients (9%) in the warfarin alone group experienced a DVT readmission in the first year after hospitalisation. This compared with 3 patients (23.1%) in the heparin alone group, 11 patients (6.7%) in the enoxaparin plus warfarin group, 3 patients (18.8%) in the heparin plus warfarin group, and 154 patients (9.8%) in the no discharge therapy group.

In total, 35 patients (1% over the total) were readmitted to the hospital because of haemorrhage. There were 14 patients in the warfarin only cohort (0.83%), one in the group of patients receiving enoxaparin plus warfarin (0.6%), and 20 in the no discharge therapy cohort (1.27%). The authors reported that no statistically significant differences were found among the cohorts in terms of the rate of readmission for haemorrhage.

Clinical conclusions
Enoxaparin combined with warfarin seemed to be the most effective therapy, as it presented the lowest average length of stay and the lowest DVT readmission rates.

Measure of benefits used in the economic analysis
A cost-consequences analysis was performed. Therefore, no summary measure of health benefit was used in the economic analysis.

Direct costs
The resource quantities were not reported separately from the costs. The direct costs included in the analysis were those of the providers of health care. The authors reported that they included these costs in terms of the payments made to providers for diagnosis of DVT, hospitalisation, readmission, and dispensing of prescriptions. However, they did not state that they were adjusted in order to reflect the opportunity costs. The cost data were obtained from the PharMetrics Integrated Outcomes database and, therefore, were derived from actual data.

The costs of inpatient services were calculated taking into consideration the differences in the length of hospital stay. The authors stated that they took this approach because the costs related not only to DVT, but also to other illnesses and elective surgery. Cost comparisons were only made for those treatments presenting statistically significant differences in the length of stay. The costs were reported for the categories of outpatient, prescriptions and DVT readmission costs. There were also some comparisons for the inpatient costs. The total DVT-related costs were reported in terms of the reduction in the total costs for enoxaparin plus warfarin, compared with the warfarin-alone and the untreated cohorts. Discounting was not carried out, but it was not relevant because the costs were incurred over less than 2 years. The price year was not given.

Statistical analysis of costs
It would appear that Student’s t-tests were performed to compare the costs for the different treatment groups.

Indirect Costs
The indirect costs were not reported.

Currency
US dollars ($).
Sensitivity analysis
No sensitivity analysis was reported.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The one-year outpatient costs (including outpatient and prescription costs) were $986 for warfarin alone, $1,655 for heparin alone, $1,886 for enoxaparin plus warfarin, $582 for heparin plus warfarin, and $705 for untreated patients.

The DVT readmission costs per patient over one year were $715 for warfarin alone, $1,395 for heparin alone, $575 for enoxaparin plus warfarin, $778 for heparin plus warfarin, and $850 for untreated patients.

Patients treated with enoxaparin plus warfarin had lower total DVT-related costs when compared with warfarin alone (by $1,151) and with the untreated cohort (by $1,227).

The pharmacy costs were statistically significantly higher for the enoxaparin plus warfarin cohort, compared with the warfarin-alone cohort (by $319), (p<0.0001), and the untreated cohort (by $405), (p<0.0001).

Synthesis of costs and benefits
Not applicable due to the cost-consequences analysis carried out.

Authors' conclusions
Patients with deep vein thrombosis (DVT) treated with enoxaparin and warfarin as outpatient coagulation therapy, compared with warfarin monotherapy or no anticoagulant agent, were discharged from hospital earlier, had fewer readmissions and had lower total DVT-related costs.

CRD COMMENTARY - Selection of comparators
The comparators used may have been chosen because they represent current practice in the authors' setting, although this was not clearly stated. You should decide if these are widely used health technologies in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were collected retrospectively from a database, which may have resulted in biased results if the information was not correctly recorded. Data from 37 health plans were collected, but it was unclear whether the study sample was representative of the study population because of the inclusion criteria considered at analysis. For example, some patients may have died within the 12-month period considered at analysis, and were excluded due to the inclusion criteria of the study.

A retrospective cohort study was performed. This seems to have been adequate for the type of data used in the analysis since the effectiveness data were collected from a database. The patients were not randomly allocated, but they were assigned to treatment cohorts on the basis of their initial therapy. Therefore, the results may be biased if the patients were receiving different initial therapies according to specific characteristics, which may have adversely affected the comparability of the groups at analysis. Confounding due to differences between the groups in demographics and clinical characteristics may have affected the outcomes, although the authors stated that their multivariate analyses controlled for these differences. However, the effectiveness results were reported by age and plan type, because these variables could act as confounding variables in the results obtained. In addition, there were other risk factors that may have influenced the results and that were not considered at analysis. These included obesity, history of DVT, immobilisation and pregnancy.
The sample size for some of the sub-groups was very small. There was no estimate of effectiveness assessing the health of individuals. Although it was shown that the average length of stay and the DVT readmission rates were shorter for those patients receiving enoxaparin plus warfarin, there was no evidence to show that these patients were better off in terms of health than those in any other treatment group. DVT may cause mortality or situations of morbidity that were not considered at analysis. Therefore, the perspective adopted at analysis (the third-party payer) may have been too restrictive. The dates to which the effectiveness data related were not reported.

All these limitations introduce uncertainty into the reliability of the conclusions. The authors also reported that some patients may not have complied with the treatment given, thus influencing the results obtained.

**Validity of estimate of measure of benefit**
The authors did not derive a summary measure of health benefit. The analysis was therefore categorised as a cost-consequences study.

**Validity of estimate of costs**
All the categories of costs relevant to the perspective adopted appear to have been considered at analysis. The resource quantities and the costs were not reported separately. The authors considered the payments made to the providers, but not the costs of the services provided. Payments may not reflect the opportunity costs of the resources used in the analysis, which weakens the generalisability of the results to other settings. The dates to which the cost data related were not reported, and neither was the price year. These factors also hinder reflation exercises to other settings.

Patients with extremely high costs were excluded from the analysis, which may have biased the results. Cost comparisons were only made for those treatment presenting statistically significant differences in the length of stay. As some groups had very small sample sizes, the study may have had insufficient power to detect differences between some groups in terms of the length of stay. This may have resulted in some relevant comparisons not being considered. The authors reported that some patients may have been treated entirely on an outpatient basis and, therefore, the results of the study would underestimate the cost-savings of outpatient treatment, since those patients who were not hospitalised for at least one day were not included in the effectiveness analysis.

**Other issues**
The authors made comparison of their findings with those from other studies, reporting consistency between them. However, some differences in the amount of cost-savings with LMWH were found. The authors did not address the issue of the generalisability of the results to other settings.

**Implications of the study**
The results of the study show that enoxaparin and warfarin presented favourable results in terms of shorter hospital stay, lower DVT readmission rates and shorter costs. However, these results should be treated with caution due to the limitations highlighted.

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None stated.

**Bibliographic details**

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Other publications of related interest


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