Low-molecular-weight heparin, bemiparin, in the outpatient treatment and secondary prophylaxis of venous thromboembolism in standard clinical practice: the ESFERA study

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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 with venous thromboembolism (VTE) were treated as outpatients or inpatients according to doctors' criteria, and all received subcutaneous bemiparin (Hibor; 115 IU/kg) once daily for 7 to 10 days, followed by subcutaneous bemiparin (an oral vitamin K antagonist (VKA) or other) once daily for 3 months according to investigators' criteria. In the primary analysis, outpatient and inpatient cohorts were compared. In the secondary analysis, secondary prophylaxis cohorts were compared (long-term bemiparin versus bemiparin followed by VKA).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Patients with an acute VTE event who were over 18 years old were included in the study. Patients were excluded if they were hypersensitive to heparin or other pig-derived substances, had a history of documented or suspected immune-mediated heparin-induced thrombocytopaenia (HIT), had an active haemorrhage, had a high risk of bleeding, or severe impairment of liver and pancreas. Further criteria for exclusion were injuries or surgery on the central nervous system, eyes or ears in the last 2 months, intravascular coagulation attributable to HIT, acute or subacute endocarditis, follow-up not possible, pregnancy, end-stage disease or life expectancy of less than 3 months, and participation in another study in the previous month.

Setting
The setting was secondary care and community care. The economic study was carried out in Spain.

Dates to which data relate
The effectiveness and resource use data were from 2002 to 2005. The price year was 2004.

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

Link between effectiveness and cost data
The same patients provided both the cost and the effectiveness data. The costing was carried out prospectively.

Study sample
No power calculations were reported. The study sample consisted of all patients meeting the inclusion criteria under the care of the medical centres involved in the study. Of the 601 patients initially recruited to the study, 18 did not have sufficient outcome data. Data from 583 patients were analysed, of which 434 (74.4%) were initially treated as outpatients and 149 (25.6%) as inpatients. In terms of long-term treatment, 279 patients who continued with bemiparin for 98 days. Of these, 219 had initially been outpatients and 60 had initially been inpatients. Of the 116 patients who switched to VKA after initially being on bemiparin, 85 had initially been outpatients and 31 had initially been inpatients.

**Study design**
This was a multi-centre, prospective, non-randomised study in standard clinical practice, in which patients were allocated to receive inpatient or outpatient treatment as a result of clinical judgement. Similarly, patients were selected for the type of long-term treatment on the basis of "standard clinical practice". A total of 176 patients were lost to follow-up.

**Analysis of effectiveness**
The analysis of the outpatient or inpatient question was conducted on an intention to treat basis, while the analysis of the long-term bemiparin or VKA treatment question was based in treatment completers only. Mean age and sex were comparable in the outpatient and inpatient cohorts and also in the bemiparin and VKA long-term groups. The inpatient group had a higher rate of proximal deep vein thrombosis (DVT), concomitant pulmonary embolism (PE) and a history of cancer, congestive heart failure or cerebral-vascular disease. There were a higher proportion of males in the VKA group, the distribution of DVT between distal and proximal was different, and a higher percentage of the patients who continued with bemiparin had more than two risk factors.

The primary health outcome used in the analysis was any adverse event. This was defined as any of the following negative health outcomes: PE, recurrent DVT, major bleeding, minor bleeding, thrombocytopaenia, death related to VTE or bleeding, and deaths from other causes.

**Effectiveness results**
When the inpatient and outpatient groups were compared, the differences in health outcomes were not statistically significant at the 5% level.

When the two kinds of long-term treatment were compared, patients who continued with bemiparin had an overall rate of adverse events of 2.9% compared with 9.5% for those who received VKA, (p=0.007).

The rate of major bleeding was 0.4% in the bemiparin group and 1.7% in the VKA group, (p=0.047).

The rate of minor bleeding was 1.8% in the bemiparin group and 6.0% in the VKA group, (p=0.032).

The rate of thrombocytopaenia was 0.4% in the bemiparin group and 2.6% in the VKA group, (p=0.048).

**Clinical conclusions**
The authors concluded that the outpatient and inpatient groups were similar in terms of the health outcomes. Patients assigned to long-term treatment with bemiparin had better outcomes than those who were assigned to long-term treatment with VKA.

**Measure of benefits used in the economic analysis**
No summary measure of benefit was produced since the authors carried out a cost-consequences analysis.

**Direct costs**
No discounting was carried out as the costs were incurred during less than 2 years. The unit costs and total costs were given. The unit costs were given for the initial visit, the different diagnostic procedures (echo-Doppler, venogram, V/P lung scan, helical computed tomography, pulmonary angiogram), one hospital day, an inpatient medical visit, an inpatient nursing day, the different drug dosages, INR/aPTT monitoring per test, an outpatient medical visit, emergency evaluation, and each kind of complication (including cost per death). The estimation of the costs was based on actual data. The resource data came from the study, while the unit cost data came from different published sources and the Spanish Medicare Reimbursement Rate. The price year was 2004.

Statistical analysis of costs
For statistical analysis of cost comparisons between the different cohorts, both the t-test (assuming an underlying normal distribution of data), and a nonparametric Wilcoxon rank sum test (which has no underlying distribution assumptions) were used. The reported p-values were for a two-tailed test statistic. No p-values were reported in cases where sample sizes were not large enough for a meaningful measure of difference. Statistical analyses were performed using the statistical software package SPSS for Windows (SPSS version 13.0, Chicago, IL, USA).

Indirect Costs
No indirect costs were estimated as the perspective was that of the National health System.

Currency
Euros (EUR).

Sensitivity analysis
The effect of increasing or decreasing each unit cost by 50% was estimated.

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

Cost results
For primary and secondary pharmacoeconomic analyses, the costs were estimated after 98 days (median observation period).

For the first study question about inpatient versus outpatient treatment

For the first study question about inpatient versus outpatient treatment, acute phase costs were estimated for the assessable patients for the acute phase in both cohorts (n=583; outpatient 434, inpatient 149), and long-term phase costs were estimated after excluding 176 patients with missing data for long-term treatment (118 patients were excluded in the outpatient cohort for long-term treatment phase and 58 patients excluded in the inpatient cohort for long-term treatment phase).

For the secondary pharmacoeconomic analysis (BEM/BEM versus BEM/VKA) acute phase costs were estimated for the assessable patients for acute phase in both cohorts (n=395; BEM/BEM 279, BEM/VKA 116), and long-term phase cost were estimated in the same population, since the 395 patients included in the secondary pharmacoeconomic analysis were assessable for long-term phase.

The cost per patient was EUR 1,206 in the outpatient group and EUR 5,191 in the inpatient group, (p<0.001). The sensitivity analysis showed that inpatients costs were always significantly greater than outpatient costs.

For the second study question about long-term treatment, the costs per patient were EUR 3,616 in the bemiparin group and EUR 3,831 in the VKA group, (p=0.412).
The sensitivity analysis showed that, in most cases, the long-term bemiparin group had lower costs; the cost-differences were never statistically significant. The costs of adverse events were taken into consideration.

**Synthesis of costs and benefits**
The costs and benefits were not combined as the study was a cost-consequences analysis.

**Authors' conclusions**
Outpatient treatment for the initial treatment phase was cheaper and resulted in similar health outcomes as inpatient treatment for venous thromboembolism (VTE). The second treatment phase with bemiparin resulted in lower rates of major and minor bleeding and other adverse events than treatment with vitamin K antagonists (VKA), with similar effectiveness and costs.

**CRD COMMENTARY - Selection of comparators**
The choice of the comparator in the first study question, initial inpatient treatment for patients with acute VTE, was implicitly justified by it representing current practice in some settings. The choice of the comparator in the second study question, VKA for the long-term treatment of patients with acute VTE, was implicitly justified by it often representing current practice. You should decide if the comparators represent current practice in your own setting.

**Validity of estimate of measure of effectiveness**
The source of the effectiveness data was a single study. The study design, a prospective cohort study (non-randomised), has some limitations in terms of the study's hypothesis. Patients were not randomly assigned to the different treatment options in either of the two studies, and this introduces the possibility of selection bias and confounding. However, the study sample appears to have been representative of the study population.

The patient groups were shown to be comparable with respect to age and sex, but there were significant differences in some demographic characteristics. The incidence of recurrent VTE was very low in all cohorts and it is arguable that the authors were not able to make multivariate analyses to analyse a possible influence of baseline characteristics on the effectiveness results.

**Validity of estimate of measure of benefit**
The authors did not derive a summary measure of health benefit. In effect, they carried out a cost-consequences analysis. The comments in the 'Validity of estimate of measure of effectiveness' field (above) therefore apply.

**Validity of estimate of costs**
From the cost perspective adopted (i.e. the health system), all the relevant categories of costs appear to have been included. The unit costs and the total costs were reported separately for several cost components, but the quantities were not reported separately. The resource use quantities were taken from the study, while the prices were taken from published sources. No statistical, sensitivity or any other kind of analysis of the quantities was performed. A sensitivity analysis of the prices was conducted. Discounting was unnecessary as all the prices were incurred during one year. The price year was given, which would facilitate reflation exercises in other time periods.

**Other issues**
The authors made appropriate comparisons of their study with the findings of other studies. The pharmacoeconomic results for long-term treatment cohorts were similar to those obtained in a previous randomised clinical trial (Gomez-Outes et al, 2006, see 'Other Publications of Related Interest' below for bibliographic details), with bemiparin being cost-neutral to VKA in the long-term treatment. The issue of the generalisability to other settings was not addressed. The authors did not present their results selectively. The study results and conclusions should be interpreted in the setting of normal clinical practice in Spain.
**Implications of the study**
Outpatient management of VTE with bemiparin in selected patients results in significant cost-savings compared to inpatient treatment, while maintaining effectiveness and safety. Bemiparin may be a safer and cost-neutral alternative to VKA for long-term treatment of VTE. The authors acknowledge the need for randomised controlled trials to investigate the questions that they aimed to answer in their study.

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**Other publications of related interest**

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