A randomized controlled clinical trial to evaluate the efficacy, safety, cost-effectiveness and effect on PAI-1 levels of the three low-molecular-weight heparins: enoxaparin, nadroparin and dalteparin - the ESCAPE-END 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
The study considered three low molecular weight heparins (LMWHs) for the treatment of unstable angina. These were enoxaparin (1 mg/kg twice daily), dalteparin (120 IU/kg twice daily) and nadroparin (86 anti-Xa/kg twice daily for 3 days). The treatment regimen also included aspirin (100 to 165 mg/day), clopidogrel (75 mg/day) and other anti-anginal medications (e.g. nitrates, beta-blockers and lipid-lowering agents). Antidiabetic drugs were also given if indicated.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adults (aged 18 years or older) who presented to the emergency department with either previously diagnosed ischaemic heart disease or a first attack of unstable angina (according to Braunwald's classification). Patients who had had a thromboembolic event or myocardial infarction in the past 3 months were excluded from the study, as were those with a history of haemorrhagic stroke, contraindications to anticoagulant therapy, or hypersensitivity to aspirin or LMWHs. Treatment with anticoagulants in the previous month, renal or hepatic dysfunction, pacemakers, fever, diastolic blood pressure greater than 110 mmHg, systolic blood pressure less than 90 mmHg, reduced haemoglobin levels (less than 12.5 mg for males or less than 11.0 mg for females) and inability to give informed consent were also exclusion criteria.

Setting
The clinical setting of this study was secondary or tertiary inpatient care. The geographical setting of the economic study was not explicitly stated, but it appears to have been India.

Dates to which data relate
The clinical effectiveness and resource use data related to March 2002 to September 2004. No price year was reported.

Link between effectiveness and cost data
The resource use data were taken from the same patient sample that provided the clinical effectiveness data. It was unclear whether the costing was carried out prospectively or retrospectively.

Study sample
Sample size calculations were performed in the planning stage of the study. The sample size was designed to give an
80% power to detect a difference of 30% in efficacy. Patients who met the inclusion criteria appear to have been recruited consecutively from the emergency department. Of the 226 patients screened for inclusion in the study, 52 did not meet the eligibility criteria and 24 refused to participate. Therefore, a total of 150 patients were included in the study, with 50 patients being allocated to each group.

**Study design**
The study was a single-centred, randomised controlled trial. The patients included in the study were randomised to one of the three groups using computer-generated random numbers. The paper reported that the study had blinded end points. The patients were followed up for 30 days. In total, 5 patients were lost to follow-up (2 in the enoxaparin group, 2 in the nadroparin group and 1 in the dalteparin group.

**Analysis of effectiveness**
The primary health outcomes assessed were cardiac death, recurrent angina, myocardial infarction and need for intervention. A composite of the individual end points was also assessed. Silent ischaemia (defined as ischaemic evidence on electrocardiogram without chest pain), major and minor bleeding, abdominal pain, thrombocytopenia and allergic reactions were also assessed. In addition, a sub-group of 20 patients in each group was selected for PAI-1 measurements; 20 stable angina patients were randomly selected from the cardiology outpatient department as a control. The three patient groups were shown to be comparable in terms of their demographic characteristics, medication on joining the study, electrocardiogram changes and family history. The analysis was performed on an intention to treat basis.

**Effectiveness results**
After 30 days, the composite endpoint of cardiac death, myocardial infarction, recurrent angina and need for intervention had been reached by 12 patients (24%) in the enoxaparin group, 15 patients (30%) in the nadroparin group and 14 patients (28%) in the dalteparin group, (p=0.526).

There was no statistically significant difference between the three groups when each of these end points was considered individually, or in the percentage of patients with silent ischaemia.

No patient experienced major bleeding, thrombocytopenia or allergic reaction.

There was no statistically significant difference in the percentage of patients who had minor bleeds (10% in the enoxaparin group, 14% in the nadroparin group, 12% in the dalteparin group; p=0.586), or who had abdominal pain (5% in the enoxaparin group, 6% in the nadroparin group, 6% in the dalteparin group; p=0.765).

Although there was a significant decline from baseline after 3 days' treatment, no statistically significant difference was observed in PAI-1 levels between the three groups.

**Clinical conclusions**
The authors concluded that there was no statistically significant difference in the efficacy of enoxaparin, dalteparin and nadroparin in the treatment of unstable angina.

**Measure of benefits used in the economic analysis**
In the base-case analysis, no summary benefit measure was used in the economic evaluation; since the authors concluded that the effectiveness results were similar between groups, a cost-minimisation analysis was conducted. In an alternate scenario, the authors used the difference in the composite end point between groups (enoxaparin versus nadroparin, enoxaparin versus dalteparin, and dalteparin versus nadroparin) as the measure of benefits.

**Direct costs**
The direct costs of the health care payer were included in this study. Such costs covered the drugs, ward stay, coronary care unit stay, laboratory tests, thrombolysis, intervention, travel and hospital stay. The resource use data were taken from the same patient sample that provided the clinical effectiveness data, but it was unclear how this information was collected. The sources of the unit costs were not reported in the paper. No breakdown of resource use and unit costs was provided, but a breakdown of costs by category was given. The price year was not reported.

Statistical analysis of costs
The cost data were expressed as a mean value with standard deviation (SD). No statistical test was reported.

Indirect Costs
The study identified lost productivity costs. However, the source of the unit costs was not reported and no breakdown of lost productivity and costs was provided. No price year was reported.

Currency
US dollars ($).

Sensitivity analysis
No statistical or sensitivity analyses were undertaken to assess uncertainty.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section. The difference in the composite end point between groups was not reported but could be derived from the data in table 2 in the original paper.

Cost results
The total cost was $868.60 (SD=966.60) in the enoxaparin group, $540.20 (SD=729.30) in the nadroparin group and $800.50 (SD=924.20) in the dalteparin group, (p=0.678).

Synthesis of costs and benefits
Although health outcomes and costs were similar between the three groups, the authors combined the costs and effectiveness using an incremental cost-effectiveness ratio (ICER) in group comparisons.

The ICER was $54.72 for enoxaparin versus nadroparin, $34.06 for enoxaparin versus dalteparin and $119.91 for dalteparin versus nadroparin.

Authors' conclusions
There was no difference in the efficacy and total costs of enoxaparin, nadroparin and dalteparin in the treatment of unstable angina.

CRD COMMENTARY - Selection of comparators
This study compared three LMWHs (enoxaparin, nadroparin and dalteparin) for the treatment of unstable angina. They were chosen because they reflect current practice in the authors' setting. You should consider how these options compare with usual practice in your own setting before applying the results of this study.

Validity of estimate of measure of effectiveness
The measures of clinical effectiveness were taken from a randomised controlled trial. The method of randomisation,
blinding, length of study and loss to follow-up were all reported in the paper, and these suggest that the internal validity of the study is good. Sample size calculations were performed in the planning stage of the study. However, the authors acknowledged that their assumptions about the expected difference in efficacy between the three drugs might have been too high, thus a larger sample size might have been required to detect a statistically significant difference. The authors did not compare the characteristics of their sample with the wider patient population with unstable angina. It is therefore not possible to comment on whether the sample was representative. The statistical analysis was appropriate and was performed on an intention to treat basis.

**Validity of estimate of measure of benefit**

In the base-case analysis, no summary measure of health benefit was used in the economic analysis. In effect, a cost-minimisation study was performed since the authors concluded that the effectiveness results were similar between groups. In an alternative scenario, the difference in the composite end point between groups (enoxaparin versus nadroparin, enoxaparin versus dalteparin, and dalteparin versus nadroparin) was used as the measure of benefits.

**Validity of estimate of costs**

The paper did not explicitly state the economic perspective of the study but, as the study included costs due to lost productivity, it can be assumed that a societal perspective was adopted. The study identified the direct costs of the health care payer and lost productivity, but did not consider any direct costs incurred by the patient. However, this omission is unlikely to have altered the study findings. The source of the unit costs was not included in the paper and neither statistical nor sensitivity analyses were undertaken to assess uncertainty around the cost data. These factors reduce the generalisability of the study findings. Discounting was not performed, but it was not necessary given the short follow-up period. No price year was reported, which will hinder any future reflation exercises.

**Other issues**

The authors do not appear to have presented their results selectively and their conclusion reflected the scope of their analysis. They compared their findings with similar studies and discussed possible reasons for any differences. The authors did not consider whether their findings could be generalised to other settings or how cost data may vary in other settings. The authors did not report any limitations other than those reported in the sections above.

**Implications of the study**

The authors did not make any recommendations for further research or changes to practice.

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