Economic assessment of low-molecular-weight heparin (enoxaparin) versus unfractionated heparin in acute coronary syndrome patients: results from the ESSENCE randomized trial


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 (enoxaparin) administered in a dose of 1mg of enoxaparin per kg of body weight twice daily for between 48 hours and 8 days (together with oral aspirin) as antithrombotic therapy for patients with acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Men and non-pregnant women, aged at least 18 years, with underlying ischemic heart disease and with recent onset of angina at rest lasting at least 10 minutes.

Setting
Hospital. The economic analysis was performed in the USA.

Dates to which data relate
Effectiveness and resource use data were derived from patients enrolled for the clinical trial between October 1994 and May 1996. The price year was 1995.

Source of effectiveness data
Effectiveness data were based on a single study.

Link between effectiveness and cost data
Costing was prospectively performed on a subset (those treated in the USA) of the sample used in the effectiveness study.

Study sample
Power calculations were not reported to have been used to determine the sample size. A total of 3,171 patients were enrolled between October 1994 and May 1996. 1,259 patients were enrolled in Canada, 936 in the USA, 710 in Europe and 266 in South America. There were 1,607 in the intervention group with a mean (median) age of 63 (64) years and 1,564 in the comparator group with a mean (median) age of 64 (65) years.
Study design
This was a prospective randomised double blinded controlled trial. The study was multi-centred with 176 centres in 10 countries (Canada, the USA, South America and Europe). Follow-up was for 30 days. Patients were randomly assigned to the 2 groups but the method of randomisation was not reported. At least 1 dose of the study drug was administered to 98% of the sample and treatment was prematurely discontinued in 367 patients (11.6% of the sample). 207 of these (13.2%) were in the control group and 160 (10.0%) were in the intervention group. Blinding was achieved by giving all patients a subcutaneous injection at 12 hourly intervals, either of the study drug or a placebo, and an intravenous bolus and continuous infusion of either the study drug or a placebo. Dummy adjustments were also administered to aid in blinding. Diagnosis of outcomes was by predetermined protocols. The end points of the study were verified by a committee who were blinded to the treatments given. The median duration of therapy for both treatment groups was 2.6 days (2.3 days for US patients).

Analysis of effectiveness
The analysis was based on intention to treat. The primary outcome was the composite triple endpoint of death, myocardial infarction (or reinfarction), and recurrent angina by 14 days follow-up. A secondary outcome was the same endpoint at 48 hours and 30 days follow-up. The 3 outcomes were also recorded individually. The incidence of major and minor haemorrhage (an adverse effect of treatment) was also recorded. Groups were statistically comparable in terms of age, weight, sex, family history, smoking and other risk factors and previous cardiac history. Comparisons of the two study groups with adjustment for differences in country of origin were performed using a logistic-regression model.

Effectiveness results
At 14 days the composite outcome of death, myocardial infarction or recurrent angina had occurred in 309 patients (19.8%) in the unfractionated heparin group and in 266 (16.6%) of the enoxaparin group. This was a statistically significant difference (p=0.019, odds ratio 0.80, 95% CI: 0.67 - 0.96). At 48 hours, differences were not significant. Death, myocardial infarction or recurrent angina had occurred in 115 (7.4%) in the control and 99 (6.2%) in the intervention group, (p=0.18, OR 0.83, 95% CI: 0.62 - 1.09). At 30 days there was a statistically significant difference. Death, myocardial infarction or recurrent angina had occurred in 364 (23.3%) of the control group and 318 (19.8%) of the intervention group (p=0.016, odds ratio 0.81, 95% CI: 0.68 - 0.96). There was no significant difference between groups in serious haemorrhagic complications at 30 days although there was a difference in minor haemorrhages. 107 (7.0%) suffered major haemorrhage in the control group and 102 (6.5%) in the intervention group (p=0.57). 110 (7.2%) suffered minor haemorrhage in the control group and 188 (11.9%) in the intervention group (p<0.001).

Clinical conclusions
Enoxaparin plus aspirin was more effective than unfractionated heparin plus aspirin in reducing the incidence of ischemic events in patients with unstable angina at the expense of an increase of minor bleeding but not of major haemorrhagic events.

Measure of benefits used in the economic analysis
The benefit measure was the reduction of the composite outcome of death, myocardial infarction or recurrent angina after 30 days.

Direct costs
Costs were not discounted due to the short time frame of the study. Quantities and costs were analysed separately. Cost analysis was based on a subset of study patients (936) who were treated in the USA. Complete hospital billing data covering the 30 day follow-up period was available for 655 patients. For these patients hospital charges were converted to hospital costs by using the department level correction factors contained in each hospital's annual Medicare Cost Report. Physicians' fees for the 1995 Medicare fee schedule were used and covered the following services: daily follow-up in both the intensive care unit and non-ICU, cardiac catheterization, coronary angioplasty and coronary bypass surgery.
Drugs were provided free in the trial and were therefore estimated separately. Enoxaparin at a cost of $0.38 per mg and at a twice daily dose of 1 mg/kg of body weight for a mean treatment duration of 2.25 days was estimated at a mean of $155.

Heparin therapy would include the cost of the drug plus the rental cost of the infusion pump, laboratory costs for aPTT determinations and nursing and physician time. In calculating costs for this study medical personnel labour costs were not included. Unit costs for the disposable costs of heparin therapy were obtained from the Duke Transition One Cost Accounting System and the Duke Medical Center Pharmacy. The mean cost of a course of heparin therapy was estimated at $80.

The remaining US patients without billing records consisted of 117 for whom data was unavailable and 151 treated at hospitals which did not produce bills. Costs for these patients were estimated by using a resource-based regression model, developed in the study for patients with cost data, with medical resource use data from case report forms. Hospital billing charges for follow-up admissions were imputed in a similar manner. Costs were imputed to the non-US patients using the same procedure as described above. The cost analysis did not cover the costs of inpatient consultations and outpatient follow-up care (except for cardiac catheterisation).

**Statistical analysis of costs**

Cost were given as the mean plus or minus the standard deviation, and in medians. The Wilcoxon rank sum test (for continuous variables) or the chi-square test (for discrete variables) were employed to test differences in costs. A bootstrap analysis of 200 samples from the US cohort was performed. The mean cost difference by intention to treat was calculated for each sample and a cumulative distribution of the results of the mean difference in initial hospitalisation costs between groups in 200 bootstrap samples was given. A multi variable linear regression model was used to estimate hospital costs for some of the US patients and for the non-US patients.

**Indirect Costs**

Not considered.

**Currency**

US dollars ($).

**Sensitivity analysis**

A sensitivity analysis was carried out to test whether treatment related resource patterns differed between patients inside and outside the USA. The cost regression model was used to impute US costs for all non-US patients, and medical costs for the overall study cohort were compared.

**Estimated benefits used in the economic analysis**

At 30 days only 19.8% of enoxaparin patients had suffered death, myocardial infarction or recurrent angina compared with 23.3% of heparin patients, (p=0.016).

**Cost results**

Over the time of the initial hospitalisation the total medical costs (hospital, physician and drug) were not significantly different: $11,875 for enoxaparin and $12,620 for heparin, a difference of $763, (p=0.18). However, by the end of 30 days the difference in costs was $1,172, (p=0.04). The total costs over 30 days for enoxaparin were $13,185 (+/- $14,151) and for heparin were $14,357 (+/- $12,171).

**Synthesis of costs and benefits**

No synthesis of costs and benefits was carried out as the intervention was the dominant strategy.
Authors' conclusions
In patients with acute coronary syndrome, low-molecular-weight heparin (enoxaparin) both improved important clinical outcomes and saved money relative to therapy with standard unfractionated heparin.

CRD COMMENTARY - Selection of comparators
A justification was given for the choice of the comparator (unfractionated heparin). It was defined as the standard care in the context in question. You, as a database user, should consider whether this is a widely used health technology in your own setting.

Validity of estimate of measure of benefit
The estimate of benefit is likely to be internally valid given the randomized approach adopted in the effectiveness analysis.

Validity of estimate of costs
Quantities were reported separately from costs and adequate details of the methods of cost estimation were given. Basing costs on hospital bills converted to costs via Medicare correction factors is less reliable than measuring costs directly.

Other issues
The authors' conclusions seemed to be justified. The issue of generalisability to other settings or countries was addressed by performing sensitivity analysis and appropriate comparisons were made with other studies.

Implications of the study
The limited follow-up of the original trial (30 days) leaves open the question of whether the observed clinical and economic benefits would be preserved over a longer time span. If the ESSENCE results are confirmed by the on-going TIMI 11b Trial, the two trials together will undoubtedly establish enoxaparin as the new standard of care for this disorder.

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