Will the use of low-molecular-weight heparin (enoxaparin) in patients with acute coronary syndrome save costs in Canada?


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
A low-molecular-weight heparin (LMWH), enoxaparin, was compared with unfractionated heparin for antithrombotic therapy in patients hospitalised with ischaemic heart disease

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients who were hospitalised for unstable angina or non-Q-wave myocardial infarction. The study sample comprised patients who had been recruited onto the ESSENCE project and who were resident in Canada. These patients comprised 40% (n=1259) of the total patient sample who were recruited from The United States, Europe, South America and Canada. Patients were required to have suffered from rest angina within 24 hours of random assignment and to show evidence of underlying ischaemic heart disease (IHD) as manifested by one of three pre-defined criteria: new ST-segment depression 0.1mV or more, transient ST-segment elevation or T-wave changes in at least 2 contiguous leads; documented previous myocardial infarction or coronary revascularisation procedure; or results of non-invasive or invasive testing demonstrating IHD.

Setting
The study was set in secondary care in Canada.

Dates to which data relate
The dates relating to the collection of effectiveness evidence and resources used were not reported. The price year was 1997.

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

Link between effectiveness and cost data
Retrospective costing was carried out on the same sample as that used to collect the effectiveness evidence.

Study sample
Power calculations for the ESSENCE trial were not reported in this paper. Patients who fitted the study inclusion
criteria were enrolled and randomised to receive LMWH or unfractionated heparin. The paper reported inclusion criteria, which indicated that the initial study sample was appropriate for the clinical study question. A total of 3,171 patients were enrolled into the study and of these 1,259 (40%) were Canadian patients (627 in the heparin group and 632 in the LMWH group). The recruitment rate to the study was not reported.

Study design
This was a multi-centre (176) and multi-country (United States, Europe, South America and Canada) randomised controlled trial. The method of randomisation was not reported. Patients were followed-up for one-year. Seventy nine Canadian patients (7%) were lost to follow-up. No blinding method for the assessment of outcomes was reported.

Analysis of effectiveness
The basis for the analysis of the clinical study (intention to treat or treatment completers only) was not stated.

The primary health outcomes used in the analysis were the composite triple end point of death, nonfatal myocardial infarction (MI) (or reinfarction) or recurrent angina at 14 days.

The two groups, heparin and LMWH, were comparable in terms of age, weight, gender, risk factors (family history, smoking, hypertension, raised cholesterol levels and diabetes mellitus), prior cardiac history and electrocardiograph changes. There were no differences between the Canadian sub-sample and the total ESSENCE sample.

Effectiveness results
The cumulative one-year risk of the composite triple end-point (death, MI, or recurrent angina) was 35.7% for the heparin group and 32.0% for the LMWH group, (p<0.02) of the total ESSENCE sample.

Clinical conclusions
The authors reported that the conclusions drawn from ESSENCE were that patients with unstable angina or non-Q-wave MI, initially assigned to receive enoxaparin compared with unfractionated heparin, had a 10% lower relative risk for the composite triple end point of death, MI or recurrent angina.

Modelling
A multivariate regression model, using ordinary least squares, was used to estimate the cost for each component of care measured in the Canadian ESSENCE patients.

A second regression model was used to estimate the cost for each component of care in a community hospital, which was predicted to have lower costs. The results from this model were used in the sensitivity analysis.

A Kaplan-Meier life-table model was used to determine the cumulative risk of revascularisation whilst allowing for patient censoring caused by loss to follow-up.

Measure of benefits used in the economic analysis
No summary measure of benefits was reported and, hence, a cost-consequences analysis was conducted.

Direct costs
Quantities and costs were reported separately. The study included direct costs to the hospital during the initial hospital stay and the one-year follow-up. The costs included were: initial hospital stay (length of stay, time in intensive care, use of diagnostic catheterisation, PTCA, CABG and enoxaparin or heparin and re-hospitalisation (length of stay including intensive care, CABG or PTCA and cardiac catheterisation, and reasons for readmission such as MI, recurrent angina, revascularisation or other reason). An estimate for physician fees for in-patient visits was also included in the cost...
estimates. The unit cost for these visits was based on the maximum allowed for consultations, daily hospital visits and procedures from the Ontario Health Insurance Plan Schedule of Benefits. The estimation of the quantities was based on actual data. The estimation of unit costs was derived using modelling to estimate the cost for each component of hospital care. Hospital and procedure costs were obtained from two hospitals (teaching hospital for the baseline analysis and community hospital for the sensitivity analysis) participating in the Ontario Case Costing Project, which aimed to promote standardised cost accounting and allocation of overhead expenses to patient care areas. Discounting was not carried out because of the short time frame of the study (one year). The dates relating to the measurement of quantity of resources were not reported. The price year was 1997.

**Statistical analysis of costs**
Confidence intervals around the point estimate of cost were estimated using bootstrap techniques.

**Indirect Costs**
Indirect costs were not relevant to the chosen study perspective and were not included.

**Currency**
Canadian dollars (Can$). No currency conversion was reported.

**Sensitivity analysis**
A one-way sensitivity analysis was carried out using the following variables:
- upper 95% confidence intervals (CI) from the cost regression model for all revascularisation procedures;
- lower 95% CI from the cost regression model for all revascularisation procedures;
- estimated costs for the community hospital rather than the teaching hospital used in the baseline analysis.

**Estimated benefits used in the economic analysis**
The reader is referred to the effectiveness results reported above.

**Cost results**
The mean total cost per patient per year in the LMWH group was Can$15,012.

The mean total cost per patient per year in the heparin group was Can$16,497.

The difference between the mean total cost per patient for LMWH and heparin was - Can$1,485 (95% CI: -3,167 to 93, p<0.06).

**Synthesis of costs and benefits**
Estimated costs and benefits were not combined because LMWH was both more effective and less expensive than heparin.

Enoxaparin was cost saving in 97% of the 1000 bootstrap replicates, which indicates that the findings of this study were robust.

In the sensitivity analysis:
- taking the lower 95% CI reduced the cost saving per patient of LMWH to Can$1,447;
taking the upper 95% CI increased the cost saving per patient of LMWH to Can$1,523;

using the community hospital costs reduced the cost saving per patient of LMWH to Can$1075.

**Authors’ conclusions**
The authors concluded that the reduced use and cost of revascularisation procedures and other hospital care more than offset the additional cost of enoxaparin.

**CRD COMMENTARY - Selection of comparators**
The selection of comparators (enoxaparin and unfractionated heparin) was supported by published evidence. You, as a user of this database, should consider whether the type of LMWH (enoxaparin) and doses used reflect current clinical practice in your own setting.

**Validity of estimate of measure of effectiveness**
The measure of effectiveness was based on data from a large multi-centre trial (ESSENCE). The authors did not report the details of the trial design or methods. The patients’ groups were reported to have been comparable at baseline. The study was powered for using a triple end-point outcome although the power calculation was not reported in the paper. The justification and method of combining the three outcomes was not reported in this paper. In particular, the authors did not report the results for each component of the triple outcome measure. If the triple endpoint is a simple addition of the rates at which these events occur, it implies that recurrent angina, myocardial infarction and death are of equal importance and value. It is not clear from the paper whether the endpoint included all episodes of myocardial infarction and recurrent angina or whether it was restricted to severe episodes. Although there were statistically significant differences in the triple endpoint, differences in the rates of a double endpoint (death and myocardial infarction) were not statistically significant. These factors could potentially bias the results of the study and over-estimate the differences found between the interventions.

**Validity of estimate of measure of benefit**
The study appropriately did not include a summary measure of benefit because enoxaparin was found to be more effective than unfractionated heparin.

**Validity of estimate of costs**
The study was not powered to detect a statistical difference in costs. The authors acknowledged this limitation of the study. They also referred to the fact that this was a sub-group analysis from a larger trial. Therefore treatment-related effects on resource use were estimated with lower precision than would have been the case if the total trial sample had been used. However, as the authors noted, the aim of the study was to explore the impact in terms of Canadian health care resources, which would not have been possible if data from the other countries (United States, Europe and South America) had been included. Detailed data on resource use were not collected during the ESSENCE trial and the use of modelling techniques was necessary to estimate the total cost per patient as a function of length of stay. However, this approach reflects a trade-off in study design: more precision on cost estimates versus more time and effort in documenting specific resource use during follow-up over a one-year time period in 3,171 patients.

**Other issues**
Due to the inherent design and approach taken by this study, the results are specific to the Canadian health care setting. The authors caution that it may not be appropriate directly to translate the results of this study to other health care settings.

**Implications of the study**
The authors suggest that economic evidence supports the adoption of enoxaparin in the treatment of unstable angina.
because it is less costly and more effective than unfractionated heparin. The authors caution that the cost estimates have reduced precision because they are derived from a single-country subgroup. However, the size and direction of the risk reductions in resource use are consistent with the results of ESSENCE.

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