Intravenous levosimendan treatment is cost-effective compared with dobutamine in severe low-output heart failure: an analysis based on the international LIDO trial

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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 severe low-output heart failure in hospital, were given levosimendan, an intravenous calcium sensitiser (an initial loading dose of 24 micro grams/kg infused over 10 minutes, followed by a continuous infusion of 0.1 micro grams/kg/min for 24 hours) or dobutamine (an initial dose of 5 micro grams/kg/min without a loading dose). Infusion rates of either drug were doubled after 2 hours if the patients had not responded sufficiently. The timing of other cardiovascular medications received by the patients was standardised and the dosage kept constant unless modification was needed for clinical or haemodynamic reasons.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients in hospital because of severe low-output heart failure who were judged to require haemodynamic monitoring and treatment with an intravenous inotropic agent. An extensive list of inclusion/exclusion criteria is given in the parent paper. See "Other Publications of Related Interest" below.

Setting
The setting was secondary care in the following countries: Denmark, Finland, France, Germany, The Netherlands, Norway, Sweden and the UK.

Dates to which data relate
The cost date provided was for the exchange rates, which was 2000. Dates of effectiveness evidence were 1997-1999.

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

Link between effectiveness and cost data
Costing was carried out on the same sample of patients as that used in the effectiveness study. It was not clear whether the costing was done prospectively or retrospectively.

Study sample
Power calculations were carried out and the trial was designed to enrol at least 200 patients so that a three-fold
difference in response rates between the treatment groups could be detected. (See parent paper). Patients were enrolled from 26 centres in 11 countries. Initially 476 patients were screened for eligibility. Of these 273 were excluded according to the inclusion criteria. The remaining 203 patients were randomly allocated to the study groups, leaving 100 assigned to dobutamine and 103 to levosimendan. See 'study design' below for withdrawal/drop-out information.

**Study design**
This was a randomised, double-blind, multicentre, controlled trial conducted in several countries. Randomisation was done by computer and treatment allocation was placed in a sealed envelope only for consultation in the case of emergency. The treatment investigator was blinded to treatment status. To mask the patients, each patient received one active and one placebo infusion and each infusion was identical. Several clinical data were recorded several times within the 24 hours following infusion. Mortality data were recorded after 24 hours of treatment, at 31 and 180 days. One patient (who had been assigned dobutamine) withdrew consent after 24 hours of infusion and was classified as a permanent discontinuation. Ninety-seven patients received dobutamine and 102 received levosimendan. Eighty-seven patients completed 24 hours infusion of dobutamine and 96 completed 24 hours infusion of levosimendan.

**Analysis of effectiveness**
The analysis was based on intention to treat. For this particular study, the following health outcomes were used to evaluate the patients. However, other outcomes such as haemodynamic improvement and adverse events were evaluated in the original study (see "Other Publications of Related Interest' below).

The number of deaths in the first 24 hours, after 31 days and after 180 days.

The number of days alive and out of hospital during 180 days.

The baseline characteristics of patients in the two groups were given in terms of demographics and clinical features. They appeared to be similar but no statistical tests were reported.

**Effectiveness results**
The effectiveness results were as follows:

Three patients in the dobutamine group and no patients in the levosimendan group died during the first 24 hours. After 31 days the figures were 31 and 8 respectively. After 180 days 36 patients in the dobutamine group had died and 27 patients in the levosimendan group had died.

The median number of days alive and out of hospital during the first 180 days was 157 (range: 101 - 173) in the levosimendan group and 133 (range: 43.5 - 169) in the dobutamine group, (p=0.027).

The mean survival over 180 days was 157 +/- 52 days in the levosimendan group and 139 +/-64 days in the dobutamine group, (p<0.01).

Eight (8%) of 103 patients in the levosimendan group died within 31 days compared with 17 (17%) of 100 assigned dobutamine (hazard ratio 0.43 (95% CI: 0.18 - 1.00); p=0.049)

At 6 months, 74% of levosimendan patients and 63% of dobutamine patients were alive, representing a 0.027 years gain in life expectancy for the levosimendan patient.

The risk of death was reduced by 41% in relative terms with levosimendan and the absolute difference in mortality was 11% in favour of levosimendan.

**Clinical conclusions**
Twenty-four hour infusion of levosimendan resulted in longer survival for patients suffering from low-output heart failure included in the trial than a similar infusion of dobutamine.
Modelling
After 180 days of follow-up, patient survival was extrapolated to 3 years on the basis of the results of another trial, the CONSENSUS trial (see "Other Publications of Related Interest" below), which analysed patient outcomes for 10 years after treatment had started. See 'methods used to derive estimates of effectiveness'.

Methods used to derive estimates of effectiveness
After 180 days of follow-up, patient survival was extrapolated to 3 years on the basis of the results of another trial, the CONSENSUS trial (see "Other Publications of Related Interest" below), which analysed patient outcomes for 10 years after treatment had started. It was assumed that a constant proportion of the population surviving 6 months would die each year and that the mean expected additional lifetime was 3 years. Kaplan-Meyer curves were used to calculate gains in life-expectancy resulting from levosimendan.

Estimates of effectiveness and key assumptions
Extrapolating after 180 days using Kaplan Meier methods and the results of the CONSENSUS study, assuming 3 expected additional life-years, levosimendan saved 0.37 life years/patients more than dobutamine.

Measure of benefits used in the economic analysis
Life-years gained was the measure of benefit taken from the effectiveness results. The authors then discounted the annual benefits at a rate of 3% a year.

Direct costs
The cost/resource boundary appeared to be hospital. The following costs were estimated: the drug cost per patient (not clear if this means all drugs or just the drugs being studied), and the hospital cost per patient. The text says that, as levosimendan was not for sale, a hypothetical price was given. Costs for each patient were calculated for a 6-month period, therefore discounting was not relevant. The price of dobutamine was averaged over the different countries in the trial where it is for sale at different prices. Individual country prices were reported. Hospital costs were not broken down into prices and quantities, however the average cost of 2 days in a coronary care unit was given. No price year was given.

Statistical analysis of costs
No statistical analysis of costs was carried out.

Indirect Costs
No indirect costs were calculated.

Currency
Euros (Euro). The conversion rate from local currency was that which prevailed on 15 December 2000.

Sensitivity analysis
Mean survival after 6 months was varied to be 2 and 4 years. The effect of assuming extra costs (both health and non-health costs) resulting from added years of life gained, using the Swedish data, was calculated. The effect of assuming that drugs in vials were used (so that unused drugs in the vials were thrown away) was calculated.

Estimated benefits used in the economic analysis
Using the Kaplan-Meyer method, the CONSENSUS study, and discounting by 3%, patients gained 0.35 years
(equivalent to 128 days) by using levosimendan.

**Cost results**
Total cost per patient in the dobutamine group was Euro 12,769 +/- 12,639 (SD).

Total cost per patient in the levosimendan group was Euro 13,877 +/- 12,327 (SD).

Incremental cost per patient of levosimendan compared to dobutamine was Euro 1,108 euros.

**Synthesis of costs and benefits**
The incremental cost per life year saved was Euro 3,205 when the mean drug price in the different European countries was used.

This incremental cost varied between countries depending on the variation in drug prices, the lowest being Euro 3,091 in France and the highest being Euro 3,331 in the UK.

When the mean survival was hypothesized to be 2 years, the incremental cost per life year had a range of Euro 4,264 to Euro 4,594, and when it was hypothesized to be 4 years the range was Euro 2,444 to Euro 2,634.

When it was assumed that drugs in vials would be used the cost per life year gained increased to a range of Euro 4,008 to Euro 4,245.

When the Swedish data were used incorporating extra societal costs, the cost per life year saved increased to Euro 20,000.

**Authors’ conclusions**
The authors conclude that levosimendan infusion given for 24 hours to patients with low-output heart failure improves health prospects in terms of mortality and morbidity as compared to dobutamine. The cost of this improvement is Euro 3,205 per life year saved which the authors consider to be much less than other widely accepted drug treatments for patients with cardiac problems.

**CRD COMMENTARY - Selection of comparators**
There was no explicit justification for the choice of dobutamine as the comparator treatment for patients with low-output heart failure, but there was an implicit justification that dobutamine was widely used. For an economic analysis, it would have been useful to have included a do nothing or placebo comparator. The authors acknowledged in the parent study that “a meta-analysis of published randomised controlled trials of intravenous inotropic agents found a non-significant trend towards excess mortality compared with placebo”. You, as a user of this database, should decide whether dobutamine represents current practise in your own setting.

**Validity of estimate of measure of effectiveness**
The estimates of effectiveness were based on a randomised clinical trial, which were then extrapolated using the CONSENSUS study. The internal validity of the study was quite high but authors of the parent study noted that perhaps the sample size was too low and there could have been a placebo comparison. Power calculations were not performed to investigate survival rates. However, selection bias should be low due to randomisation. Performance and measurement bias should be low due to double-blinding. Although it would have been better to have data on patients in the trial for longer than 6 months, attrition bias should be low as drop out rates were low.

**Validity of estimate of measure of benefit**
The measure of health benefit used, life years saved, was taken directly from the effectiveness analysis. The authors discounted this measure, which was appropriate given the time frame of the analysis.
Validity of estimate of costs
The cost/resource boundary appeared to be hospital. Costs included drug and hospitalisation costs. The authors acknowledged that the relative cost of levosimendan might have been underestimated as future costs due to extra survival were not calculated. Further, if other societal costs are included, the incremental cost-effectiveness ratio (ICER) of levosimendan over dobutamine increases. Discounting was applied, which was appropriate. However, unit costs were only reported for the drugs, and quantities were not given. This limits the possibility of reproducing the results in other settings, especially as the description of what comprised hospitalisation costs was limited. Country specific costs were provided, which is good for generalisability, and the exchange rate year was given. The authors did perform a sensitivity analysis assuming higher costs after the 6-month follow-up, which increased the cost per life year saved but did not affect the authors' conclusions about the cost-effectiveness of levosimendan.

Other issues
The authors did not report any results on the variability of effectiveness results or hospital costs across countries. This would have been very helpful in decision making in the countries concerned as the generalisability of the results to individual countries has not been addressed. There were no comparisons of the results with other studies. The conclusions reflected the scope of the analysis and results were not reported selectively.

Implications of the study
The authors recommend a larger-scale study with a longer follow-up. Such a study should be accompanied by more detail on the costs and effectiveness results in the different countries. Costs should be broken down in a more transparent manner.

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None stated.

Bibliographic details

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Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Cardiac Output, Low /drug therapy /economics /epidemiology; Cardiotonic Agents /economics /therapeutic use; Cost-Benefit Analysis /economics; Dobutamine /economics /therapeutic use; Double-Blind Method; Europe /epidemiology; Female; Follow-Up Studies; Heart Failure /drug therapy /economics /epidemiology; Humans; Hydrazones /economics /therapeutic use; Infusions, Intravenous; Length of Stay /economics; Life Expectancy; Male; Middle Aged; Patient Admission /economics; Pyridazines /economics /therapeutic use; Randomized Controlled Trials
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