Cost-effectiveness of intense insulin treatment after acute myocardial infarction in patients with diabetes mellitus: results from the DIGAMI 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 use of intense insulin therapy after acute myocardial infarction for patients with diabetes mellitus. The treatment consisted of an insulin-glucose infusion for at least 24 hours, followed by subcutaneous multidose insulin for at least 3 months. The intervention was started by a nurse in the coronary care unit, as soon as possible after the patient's arrival.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness and cost-utility analyses.

Study population
The study population comprised patients with suspected acute myocardial infarction within the preceding 24 hours, who had known diabetes mellitus and a blood glucose level of greater than 11 mmol/L, or a blood glucose level of greater than 11 mmol/L without known diabetes mellitus. Patients were excluded if they were unable to participate for reasons of health, if they refused to participate, if they were resident outside the hospital catchment area, or if they were enrolled in other studies. This information was obtained from the published effectiveness study (see Other Publications of Related Interest).

Setting
The setting was a hospital. The economic study was carried out in 19 centres in Sweden.

Dates to which data relate
The effectiveness and resources use data were collected from 1 January 1990 to 18 December 1993. The price year was 1999.

Source of effectiveness data
The effectiveness evidence was derived from a single study, the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) (see Other Publications of Related Interest). In addition, the authors made assumptions about the effectiveness.

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were performed to determine the sample size. A sample of about 600 patients was required to demonstrate the expected mortality reduction with a 5% significance level and a power of 80%. All patients presenting at the study centres during the period were selected. An initial sample of 1,240 patients was considered eligible for inclusion. However, 620 patients were excluded, mainly because they were incapable (45%) or unwilling to participate in the study (38%). The remaining 620 patients constituted the final sample. Of these, 306 were assigned to the infusion group and 314 to the control group. The mean age in the infusion group was 67 (+/- 9) years and 62% of the patients were male. The mean age in the control group was 68 (+/-9) years and 63% were male. This information was obtained from the published effectiveness study (see Other Publications of Related Interest).

**Study design**
The study was a blind, randomised controlled trial. The methods of randomisation and blinded assessment were not reported. The study was carried out in 19 centres in Sweden. The mean long-term follow-up was 3.4 years (range: 1.6 - 5.6). The loss to follow-up was not reported. These details came from the published effectiveness study (see Other Publications of Related Interest).

**Analysis of effectiveness**
The clinical basis of the effectiveness analysis was not reported. However, it appears that all the patients included in the study were accounted for in the analysis according to allocation (intention to treat). The primary health outcome assessed in the analysis was the mortality rate after one year and 5 years of follow-up. The study groups were reported to be statistically comparable in terms of their age, gender, body mass index, previous disease, type of diabetes, antiemetic or other treatment, and status of smoker. The details were reported in the published effectiveness paper (see Other Publications of Related Interest).

**Effectiveness results**
The mortality rates after one year of follow-up were 19% in the infusion group and 26% in the control group. The mortality rates after 5 years of follow-up were 33% in the infusion group and 44% in the control group. The difference was statistically significant.

**Clinical conclusions**
The effectiveness analysis showed that intense insulin treatment after myocardial infarction could substantially improve long-term survival among patients with diabetes mellitus.

**Methods used to derive estimates of effectiveness**
The authors made several assumptions on the grounds of the medical literature and their opinions. Most of these assumptions were made conservatively, thereby favouring the control group.

**Estimates of effectiveness and key assumptions**
The authors assumed a constant annual mortality risk of 20% for survivors at 5 years. It was also assumed that the annual mortality risk after 5 years would be equal for patients in both groups. Due to a lack of data, the quality of life was assumed to be equal in both groups and the quality weight was 0.70.

**Measure of benefits used in the economic analysis**
The benefit measures used in the economic analysis were the life-years gained, and the quality-adjusted life years (QALYs) gained in the infusion group in comparison with the control group. A 3% discount rate was applied.

**Direct costs**
A 3% discount rate was used since the time horizon of the study was 6 years. The unit costs and the quantities of
resources were reported. The resource/cost boundary reflected the perspective adopted in the analysis. The health services included in the analysis were the drug regimens (insulin-glucose infusion, oral antidiabetics, and subcutaneous insulin), initial hospitalisation (hospital stay, thrombolytic therapy, and pacemakers), and one-year follow-up (hospital stay, percutaneous transluminal coronary angioplasty and coronary artery bypass graft procedures, and outpatient physician visits).

The quantities of resources were estimated using data recorded in the clinical trial and gathered from 1 January 1990 to 18 December 1993. The cost estimates were derived from actual data, such as official Swedish retail prices and the charges at the participating centres. The price year was 1999.

**Statistical analysis of costs**
Statistical analyses of the costs were conducted.

**Indirect Costs**
The indirect costs were discounted at 3% since the costs were incurred over a time period of longer than 2 years. The unit costs and the quantities of resources were reported separately, reflecting the boundary of the patient. The indirect costs included in the analyses were for labour productivity losses and for the future costs occurring during the increased length of life (both health care and non-health care consumption). Working status was estimated as the percentage of full-time work of each patient in the trial. The indirect costs were estimated using actual data, reflecting the average value of labour production of a Swedish worker, and official Swedish statistics published in different years.

**Currency**
The costs were estimated in Swedish kroner (SEK), but were presented in Euros. The exchange rate in June 1999 was Euro 1 = SEK 8.70.

**Sensitivity analysis**
Sensitivity analyses were conducted to take into account the uncertainty around some data estimates:
- the use of different discount rates;
- the quality of life weight;
- annual mortality after 5 years of follow-up;
- similar annual mortality in both treatment groups after 3 or 4 years rather than 5 years;
- the exclusion of future costs;
- the inclusion of health care costs only, or health care costs in 1 year;
- a labour production equal to 0 after the first year of follow-up.

It is presumed that one-way analyses were carried out.

**Estimated benefits used in the economic analysis**
Compared with the control group, the discounted life-years gained in the insulin group were 0.94 and the QALYs were 0.66.

**Cost results**
The quantities of resources consumed were generally similar in the two study groups. Only outpatient physician visits
per patient were statistically greater in the infusion group (6.07) than in the control group (5.02), (p=0.005).

The overall mean cost of insulin was greater in the infusion group than in the control group. Insulin cost Euro 236 (standard deviation, SD=177) in the infusion group versus Euro 176 (SD=107) in the control group, (p< 0.001).

The costs of initial hospitalisation were Euro 5,557 (SD=6,043) in the infusion group and Euro 4,618 (SD=6,836) in the control group, (p=0.068). The costs of one-year follow-up were Euro 4,759 (SD=4,779) in the infusion group and Euro 4,501 (SD=6,972) in the control group, (p=0.833).

The total costs during the first year amounted to Euro 10,411 (SD=9,709) in the infusion group and Euro 9,436 (SD=8,741) in the control group, (p=0.068). The costs of one-year follow-up were Euro 4,759 (SD=4,779) in the infusion group and Euro 4,501 (SD=6,972) in the control group, (p=0.833).

The total indirect costs were Euro 2,383 in the infusion group and Euro 2,358 in the control group, (p=0.961).

**Synthesis of costs and benefits**

The costs and the benefits were combined by performing incremental cost-effectiveness and cost-utility analyses. The incremental cost per life-year saved was Euro 16,900, while the incremental cost per QALY gained was Euro 24,100. Variations in the annual mortality rates, quality of life weight, and discount rate did not affect the incremental cost-effectiveness of the infusion strategy. The exclusion of future costs resulted in incremental costs of Euro 1,000 per life-year gained and Euro 1,500 per QALY gained. If only the health care costs (also in future years) were included, the incremental ratios would be Euro 6,600 and Euro 9,400, respectively. If only the health care costs in the first year of follow-up were included, both of the cost-effectiveness ratios would be equal to those reported when future costs were excluded. Finally, if the labour costs were assumed to be 0 after the first year, the cost-effectiveness ratios would be slightly greater than those estimated in the base-case.

**Authors’ conclusions**

The analysis showed that intense insulin treatment after myocardial infarction was cost-effective in patients with diabetes mellitus, with an additional cost of $16,900 per life-year gained and $24,100 per QALY gained.

**CRD COMMENTARY - Selection of comparators**

The rationale for the choice of the comparator was clear. No intense insulin treatment was chosen because it represented the standard practice in a coronary care unit. You should assess whether it represents a widely used intervention in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness analysis used a blind, randomised clinical trial, which was appropriate to the study question. The internal validity of the analysis was also increased by performing power calculations in the planning phase, to determine the appropriate sample size. Further, the groups were shown to be comparable in terms of several characteristics. Some authors' assumptions were made, mainly to overcome the lack of data, especially in terms of the quality of life.

**Validity of estimate of measure of benefit**

The benefit measures were derived from the effectiveness analyses. Quality-adjusted survival was explicitly calculated to take into account different health statuses during the gained life-expectancy, although the quality weight originated from an assumption by the authors. Both benefit measures were discounted at recommended rates.

**Validity of estimate of costs**

The analysis of the costs reflected the societal perspective adopted in the study. As a consequence, the indirect costs (productivity losses) and the future costs (incurred in the gained life-expectancy) were included in the analysis, in
addition to the direct costs of the treatment. The costs were treated stochastically and extensive sensitivity analyses were conducted. The costs were collected in the Swedish currency, but then reported in Euros. The unit costs and the quantities of resources were reported separately. These issues tend to improve the external validity of the analysis.

**Other issues**

In order to assess whether the intense insulin treatment was acceptable in the Swedish setting, the authors compared their findings with those derived from the sector of road investment (the only sector where the price for a life saved was computed). The cost-benefit ratios per life-year and QALY gained were far below those reported in the road investment sector. As a result, the study intervention appears to have been highly cost-effective.

The issue of the generalisability of the study results to other settings was not explicitly addressed. However, several sensitivity analyses were conducted, especially in terms of the cost data. In addition, the unit costs and the quantities of resources were reported separately, thereby enhancing the external validity of the analysis. It might have been beneficial to have included more effectiveness information in this paper, although it was available elsewhere. Finally, the authors' conclusions were in keeping with the study perspective.

**Implications of the study**

The authors recommend that future studies should focus on specific pathophysiological benefits behind the beneficial effects of the intense insulin treatment observed in the present study.

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**Other publications of related interest**


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