Differences in hypoglycemia event rates and associated cost-consequence in patients initiated on long-acting and intermediate-acting insulin products

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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
Two insulin products for the treatment of patients with Type 1 or Type 2 diabetes were examined. One was the intermediate-acting insulin analogue neutral protamine Hagedorn (NPH), while the other was the long-acting insulin analogue glargine.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with Type 1 or Type 2 diabetes who were newly initiated on one of the study medications (i.e. patients had no prescriptions for glargine or NPH in the 4 months prior to the index date).

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were gathered from July 2000 to August 2002. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was carried out retrospectively on the same sample of patients as that used in the clinical study.

Study sample
Power calculations were not carried out. Eligible patients were identified from an administrative claims database of a south-eastern US managed care plan covering approximately 1.5 million individuals. Only patients who received at least 4 months of continuous index medication without changing to or adding the index medication comparator were included. An overall sample of 1,434 was identified. There were 310 patients (51.9% men) in the glargine group and 1,124 patients (51.3% men) in the NPH group. The mean age of the patients was 49 (+/- 17) years in the glargine group and 55 (+/- 17) years in the NPH group.
Study design
This was a retrospectively cohort study that was carried out at several medical centres covered by the managed care plan. The patients were followed longitudinally post-index date to the discontinuation of index medication, the end of benefit eligibility, or to the end of the study period, whichever occurred first. All patients had a minimum of 4 months of post-index continuous eligibility. The average length of follow-up was 8.6 (+/- 4.5) months. No patient appears to have been lost to the follow-up assessment.

Analysis of effectiveness
All of the patients included in the initial study sample were accounted for in the analysis of effectiveness. The outcome measures used were hypoglycaemia events, the absolute risk difference in hypoglycaemia events, and the number-needed-to-treat (NNT) to avoid one hypoglycaemic event. A regression model was used to examine hypoglycaemia events, with the independent variable being insulin type (NPH or glargine). The covariates included a pre-index count of hypoglycaemia events, age, gender, best (lowest) post-index A1c (glycated haemoglobin), the use of regular insulin, and the use of oral hypoglycaemic agents. The model was run on the sub-cohort of patients who had post-index A1c measurements (n=875).

At baseline, the study groups were well balanced in their gender distribution, but statistically significant differences were observed in terms of:

- age (glargine patients were younger),
- co-morbidities (more NPH patients had hypertension, ischaemic heart disease, congestive heart failure and peripheral vascular disease),
- co-morbidity index (which was higher for NPH patients),
- Type 1 diabetes mellitus (more frequent among glargine patients),
- provider specialty, and
- payer type.

Effectiveness results
In the pre-index period, the number of patients with hypoglycaemia events was 20 (6.5%) in the glargine group and 47 (4.2%) in the NPH group. The number of events per cohort was 31 in the glargine group and 110 in the NPH group. Thus, the mean numbers of events per 100 patients per year were 30 (glargine group) and 29 (NPH group), respectively.

In the post-index period, the number of patients with hypoglycaemia events was 15 (4.8%) in the glargine group and 73 (6.5%) in the NPH group. The number of events per cohort was 22 in the glargine group and 258 in the NPH group. Thus, the mean numbers of events per 100 patients per year were 10 (glargine group) and 31 (NPH group), respectively.

The mean change from the pre- to the post-index in the number of events per 100 patients per year was -20 (95% confidence interval, CI: -3.2 - -36.2) in the glargine group and 2 (95% CI: 20.7 - -17.2) in the NPH group.

The model showed that the NPH group was over three times more likely than the glargine group to be associated with hypoglycaemic events (incident rate ratio 3.18, 95% CI: 1.33 - 7.62).

The hypoglycaemia event rate per 100 patients per year was 7.3% in the glargine group and 18.3% in the NPH group, (p<0.05).

The absolute risk difference in hypoglycaemia events per 100 patients per year was 11 (0.11 per patient per year).

The NNT was 9.
Clinical conclusions
The effectiveness analysis showed that glargine was significantly more effective than NPH in reducing the rate of hypoglycaemic events.

Measure of benefits used in the economic analysis
The health outcomes were left disaggregated and no summary benefit measure was used in the economic analysis. In effect, a cost-consequences analysis was carried out.

Direct costs
Discounting was not relevant since the costs were incurred during less than 2 years. The unit costs were not presented separately from the quantities of resources used. Only resource use associated with concomitant oral antidiabetic medication was reported. The health services included in the economic evaluation were medication and inpatient/outpatient management of a hypoglycaemic event. The cost/resource boundary of the managed care organisation was used. Thus, the costs were defined as the amount paid excluding co-pays and deductibles. The resource use data was estimated from the sample of patients included in the clinical study (July 2000 to August 2002). The costs came from the administrative database of the managed care organisation using medical claims. The price year was not reported.

Statistical analysis of costs
Student's t-test was used to test the statistical significance of differences in the costs between the two groups.

Indirect Costs
The indirect costs were not included in the economic evaluation.

Currency
US dollars ($).

Sensitivity analysis
Two sensitivity analyses were carried out to examine the robustness of base-case estimates of costs to variations in the A1c value or A1c threshold (8% or 9% instead of the base-case value of 7%). The authors set the alternative values.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The mean attributable cost of a hypoglycaemic event was $1,087 (95% CI: 764 - 1,409), of which $472 (95% CI: 270 - 674) were due to outpatient care.

The median attributable cost of a hypoglycaemic event was $332 ($189 due to outpatient care).

The mean cost of medication was $390 (95% CI: 351 - 429) with glargine and $343 (95% CI: 320 - 367) with NPH, (p<0.05).

The mean cost-difference was $47 (95% CI: 2 - 92; p<0.05).

Thus, the extra cost for glargine to prevent one hypoglycaemic event was $423. This was obtained by multiplying the NNT to prevent one hypoglycaemic event (9 patients) by the cost-difference between the two strategies ($47). This
increase in cost associated with glargine treatment to prevent one hypoglycaemic event was lower than the cost of the event itself.

The base-case results were robust to changes investigated in the sensitivity analysis.

**Synthesis of costs and benefits**
A synthesis of the costs and benefits was not relevant since a cost-consequences analysis was performed.

**Authors’ conclusions**
Patients initiated on glargine had a significantly lower hypoglycaemia event rate than those initiated on neutral protamine Hagedorn (NPH). Further, the increase in cost associated with switching patients from NPH to glargine was less than the mean attributable cost of one hypoglycaemic event.

**CRD COMMENTARY - Selection of comparators**
The authors justified the choice of the comparators, which were appropriate for the study question. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness analysis came from a review of the data extracted from a large administrative database, where two cohorts of patients were compared. The use of a randomised and prospective design would have been more appropriate to limit the impact of selection bias and confounding. The study groups were not well balanced at baseline, thus a regression analysis was performed to adjust for such differences. However, the authors stated that no control for race or income was performed. The method used to select the sample of patients was reported and it appears that the patients have been followed for an appropriate period. No loss to follow-up was observed because only patients with complete charts were included in the analysis. The study sample was representative of the study population because individuals were selected from a large database. Further, the evidence came from multiple centres. The sample size was quite big, especially for the NPH group, although no justification was provided for the number of patients involved in the analysis.

**Validity of estimate of measure of benefit**
No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted. Please refer to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

**Validity of estimate of costs**
The analysis included costs consistent with the perspective adopted in the study, although it was restricted to the direct medical costs. A detailed breakdown of the cost items was not provided and the costs were presented as macro-categories. Thus, no information on the unit costs or quantities of resources used was provided. The cost data came from patient claims, and it was unclear whether charges rather than actual costs were used. The dates during which the resources used and costs were gathered were reported, although an explicit price year was not given. Statistical analyses of the costs were carried out, but the cost estimates were specific to the study setting. The authors noted that some insulin products were over-the-counter medications, thus it was difficult to assess them and include them in the cost analysis.

**Other issues**
The authors stated that their findings were consistent with those from two published clinical trials. However, the authors stated that their results might not be transferable to settings different from that considered in the current analysis. Limited sensitivity analyses were performed, which limits the external validity of the study.
Implications of the study
The study results suggested that hypoglycaemia events and their associated therapeutic costs would be reduced by switching from NPH to glargine.

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