Health and economic effects of adding nateglinide to metformin to achieve dual control of glycosylated hemoglobin and postprandial glucose levels in a model of Type 2 diabetes mellitus

Salas M, Ward A, Caro J

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
Combination therapy with nateglinide and metformin was compared with metformin monotherapy for the treatment of Type 2 diabetes mellitus.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with Type 2 diabetes mellitus. Baseline characteristics (gender, race, age distributions) and risk factors (serum cholesterol level, smoking status, body mass index, systolic blood pressure) were assigned in the cohort on the basis of the observed distributions of these factors among incidence cases of diagnosed Type 2 diabetes mellitus in the USA.

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

Dates to which data relate
The effectiveness data were derived from literature published from 1984 to 2001. The costs were generally derived from 1997 to 2000 data. The exception was the costs associated with blindness, which were based on a 1992 study. All the costs were uplifted to 2000 prices.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of completed studies.

Modelling
A model was used to simulate the long-term microvascular and macrovascular complications that might occur in a cohort of 10,000 patients with Type 2 diabetes mellitus, who had been treated with nateglinide plus metformin or metformin alone. The mean accumulated costs, the mean frequency of diabetes-related complications, and the mean survival times were then estimated. Each cycle of the model lasted for one year and the duration of the model was 30 years. Microvascular complications included nephropathy, retinopathy and neuropathy-related complications (all further analysed in various levels of severity). Macrovascular complications consisted of myocardial infarction and stroke. All of the patients were allowed to accumulate complications for the time horizon of 30 years, unless death occurred.
earlier. To make the model more realistic, a pre-comparison period of 5 years was added before the start of the model. During this period complications were potentially developing, so that patients entered the model with varying degrees of microvascular or macrovascular disease. No costs were calculated for the pre-comparison period.

Outcomes assessed in the review
The outcomes assessed in the review were:

- the initial glycosylated haemoglobin (HbA1c) and postprandial glucose (PPG) levels at the beginning of the model period;
- the annual upward drift of HbA1c during treatment with oral agents;
- the decrease in HbA1c and PPG blood levels achieved by treatment with nateglinide-metformin or metformin alone; and
- the rates of developing any of the diabetes-related complications (microvascular and macrovascular disease) described in the model, including the risk of death.

Study designs and other criteria for inclusion in the review
Not reported.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Approximately 14 primary studies were included in the review.

Methods of combining primary studies
Most of the effectiveness results were not combined. In the case of risk of death, two methods were used based on different studies, and the greatest estimated risk was selected.

Investigation of differences between primary studies
Not reported.

Results of the review
The mean baseline level of HbA1c was 8.4%. This level was used to determine the assignment of a corresponding PPG level by reference to a joint distribution for these two measures.

The annual upward drift of HbA1c during treatment with oral agents was 0.15%.

The mean decrease in HbA1c level after treatment was 1.48% for nateglinide-metformin and 0.81% for metformin.
alone.

The mean decrease in PPG level after treatment was 2.30 g/dL for nateglinide-metformin and 0.90 g/dL for metformin alone.

The complication rates were not presented in the paper. However, it was reported that these related to HbA1c (regarding microvascular disease) and PPG (regarding macrovascular disease) levels, as well as other baseline characteristics and risk factors assigned to the study population (i.e. age, gender, systolic blood pressure, serum total cholesterol, body mass index, and smoking status).

**Methods used to derive estimates of effectiveness**
The authors made some assumptions concerning the input data for the model.

**Estimates of effectiveness and key assumptions**
Some complication rates were adopted from the literature on diabetes, based on the assumption that they applied to Type 2 diabetes mellitus. A major assumption of the model was that the upward drift in HbA1c levels with combination therapy would not be as rapid as that seen with metformin monotherapy, although an estimate of the annual drift rate for combination therapy was not provided. Another key assumption was that the PPG level predicted the risk of macrovascular disease.

**Measure of benefits used in the economic analysis**
The outcome measure used in the economic analysis was the number of life-years gained (LYG). This measure was discounted at an annual rate of 3%.

**Direct costs**
The study perspective was not stated. However, all the direct medical costs associated with the management of Type 2 diabetes mellitus and its complications were estimated. The costs of routine care included physician visits (also annual ophthalmology and dietician visits), laboratory tests, home monitoring and supplies. The costs of complications included acute care (initial management in the inpatient or outpatient setting) and subsequent care, which comprised sub-acute inpatient care (rehabilitation, skilled and intermediate care nursing facilities, chronic hospitals), home health care, outpatient therapy, physician visits, and diagnostic and therapeutic procedures.

The quantities and the unit costs were not reported separately. Five all-payer databases were used to derive estimates for the use of inpatient care. Outpatient services were estimated from government and other published reports, ambulatory care and emergency room databases, practice guidelines, and surveys. Physician visit and laboratory test costs were determined from 2000 Medicare fee schedules. The mean total costs per patient were derived using modelling. Cost-to-charge ratios were used. All the costs were expressed in 2000 prices. Discounting was carried out at an annual rate of 3%, which was appropriate since the costs were incurred during 30 years.

**Statistical analysis of costs**
The costs were treated deterministically. No statistical analysis of the costs was performed.

**Indirect Costs**
The indirect costs were not included in the analysis.

**Currency**
US dollars ($).
Sensitivity analysis

One-way sensitivity analyses were conducted on key model inputs to assess their impact on the results. The inputs varied were:

- the duration of disease before the start of the model (10 years), which was translated to a higher proportion of complications at baseline;
- the baseline HbA1c level (7.9 - 9.4%);
- the costs of diabetes-related complications (+/- 20%);
- the annual upward drift of HbA1c level (no drift in combination therapy; no drift in both therapies); and
- the discount rate (0 - 5%).

The results were also estimated separately for different age categories and both genders. No justification for the ranges selected was given.

Estimated benefits used in the economic analysis

The undiscounted average survival (LYG) was 14.02 years per patient for nateglinide-metformin, and 13.69 years per patient for metformin alone. The undiscounted difference in survival was 0.33 years per patient, favouring the combination therapy. The discounted average survival was 10.76 years per patient for combination therapy, and 10.55 years per patient for metformin monotherapy. The discounted difference in survival was 0.21 years per patient. The duration of the model was 30 years.

Cost results

The discounted mean total cost per patient was $52,342 for nateglinide-metformin, and $43,504 for metformin monotherapy (discount rate 3%). Thus, combination therapy incurred an additional cost of $8,838 per patient. The undiscounted cost results were not reported. The costs were calculated for a period of 30 years.

Synthesis of costs and benefits

An incremental cost-effectiveness ratio (ICER) was calculated, by combining the estimated differences in costs and benefits. In order to estimate confidence intervals (CIs) around the ICER, parametric bootstrap analyses were conducted by the multiple-simulation method with 250 samples.

The ICER of adding nateglinide to metformin was $27,131 per undiscounted LYG (95% CI: 23,710 - 28,577), or $43,024 per discounted LYG (95% CI: 37,285 - 45,193).

The sensitivity analysis showed that the results were relatively resistant to gender and the cost of complications. However, the results were sensitive to discount rate. Increasing the discounting to 5% changed the ICER by 11%. Higher initial HbA1c levels led to a better result with combination therapy. For example, an initial level of 9.4% resulted in an ICER of $25,612. Longer disease duration favoured combination therapy. In addition, if combination therapy reduced the upward drift of HbA1c over time, the ICER was estimated to fall below $10,000.

Authors' conclusions

Combination therapy with nateglinide and metformin provided good value for money compared with metformin alone. The increased drug-treatment costs were expected to be partially offset by long-term savings resulting from the reduced rate of complications.

CRD COMMENTARY - Selection of comparators

Although no explicit justification was given for the comparator used, it appears to have reflected routine practice.
which, nevertheless, had been demonstrated to fail to sustain control of blood glucose levels over time. You should decide whether the comparator represents current practice in your own setting.

Validity of estimate of measure of effectiveness
It was not stated that a systematic review of the literature had been undertaken. Most of the estimates derived from the available literature were not combined. The impact of differences between the primary studies when estimating effectiveness was not discussed. Given the level of reporting on how the estimates used as model inputs were identified and collated, it was difficult to assess their validity.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. The model used was appropriate for this purpose because it simulated the course of potential complications occurring in the study population in the long run, using probabilities related to the baseline population characteristics and risk factors.

Validity of estimate of costs
The study perspective was not stated. However, the costs consisted of health service costs associated with the routine care of Type 2 diabetes mellitus and the management of subsequent long-term complications. Thus, if the perspective was that of the health service provider, all the relevant categories of costs were included in the analysis. The costs and the quantities were not reported separately. A sensitivity analysis of the complication costs was conducted, but no justification was given for the ranges used. Cost-to-charge ratios were used in the study. Discounting was carried out, which was appropriate since the costs were incurred during 30 years. The year to which the prices referred was stated, which will aid any future reflation exercises.

Other issues
The authors made appropriate comparisons of their findings with those of other studies. The issue of the generalisability of the results to other settings was not addressed. The authors implied that key assumptions related to the upward drift of HbA1c levels over time, and the use of PPG level as predictor of risk of macrovascular disease, constituted limitations of the study. In addition, they acknowledged that their model did not consider dose adjustments, price changes, decreases in compliance, or changes in treatment regimens. Nevertheless, the study results were adequately reported and the conclusions reflected the scope of the analysis.

Implications of the study
Although not explicitly recommended, it can be inferred from the study that a combination of nateglinide and metformin should be considered as a replacement for metformin monotherapy in the management of Type 2 diabetes mellitus, despite the higher drug-treatment costs. The reduction in diabetes-related complications obtained with combination therapy would have a substantial economic effect that would partially offset the treatment costs. In particular, according to the authors, the reduction of macrovascular complications would have an enormous impact on health maintenance organisations, because such complications account for more than half of the costs associated with the inpatient treatment of diabetes-related complications.

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Bibliographic details
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