Cost-effectiveness of second-line antihyperglycemic therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin

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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.

CRD summary
The study objective was to determine the cost-effectiveness of alternative second-line interventions added to metformin for the treatment of type 2 diabetes mellitus in patients with inadequate control by metformin alone. The authors concluded that the addition of a sulphonylurea represented the most cost-effective second-line therapy. The quality of the study methods was good, with the methods and results appropriately reported. The authors’ conclusions appear to be valid and appropriate.

Type of economic evaluation
Cost-utility analysis

Study objective
The objective of the study was to determine the cost-effectiveness of alternative second-line interventions added to metformin for treatment of type 2 diabetes mellitus in patients with inadequate control by metformin monotherapy.

Interventions
Eight interventions were compared: metformin monotherapy; metformin plus sulphonylureas; metformin plus meglitinide; metformin plus alpha-glucosidase inhibitor; metformin plus thiazolidinedione; metformin plus dipeptidyl peptidase-4; metformin plus basal insulin; and metformin plus biphasic insulin.

Location/setting
Canada/Primary care.

Methods
Analytical approach:
The previously validated United Kingdom Prospective Diabetes Study Outcomes model (Clarke, et al. 2004, see ‘Other Publications of Related Interest’ for bibliographic details) was used to combine published data. The time horizon was the lifetime of the patients. The authors reported that the perspective adopted was that of a Canadian third-party healthcare payer.

Effectiveness data:
The effectiveness data were from a previously published systematic review and meta-analysis of randomised controlled trials (McIntosh, et al. 2011, see ‘Other Publications of Related Interest’ for bibliographic details). The main clinical effectiveness estimate was the risk of hypoglycaemia. The estimate for mild to moderate risk of hypoglycaemia came from the longest and largest randomised controlled trial included in the systematic review; severe hypoglycaemia risk came from a retrospective observational study.

Monetary benefit and utility valuations:
The utility weights for long-term diabetes complications were from a study on patients with type 2 diabetes in the UK, in which patients were asked to complete the EQ-5D (European quality of life) questionnaire. Authors assumptions were used to estimate the reduction in quality of life due to hypoglycaemia.

Measure of benefit:
The benefit measure used was quality-adjusted life-years (QALYs) gained, which were discounted at an annual rate of
5%.

**Cost data:**
The direct costs were those for insulin treatment, blood glucose strips, and the management of long-term diabetes complications (heart disease, stroke, myocardial infarction, heart failure, amputation, blindness, and renal failure). Costs of managing long-term complications came from the Ontario Ministry of Health and previously published studies. Costs of treatments were from the price of the lowest cost alternative for each drug class. Costs of blood glucose test strips came from a previously published study. All costs were updated to 2009 prices using the Health Component of the Canadian Consumer Price Index and were discounted at an annual rate of 5%. Costs were reported in Canadian Dollars (CAD).

**Analysis of uncertainty:**
A series of one-way and multi-way sensitivity analyses were undertaken. The estimates varied were: clinical effects, costs of treatments, treatment dosage, time horizon, discount rate, use of blood glucose strips, quality of life, event rates of hypoglycaemia, and adverse events. Cost-effectiveness acceptability curves were generated to illustrate the probability of each intervention being cost-effective across a range of cost-effectiveness thresholds.

**Results**
For metformin monotherapy, the average cost per patient was CAD 39,924 and the average QALYs gained were 8.72.

For metformin plus sulphonylureas, the average cost per patient was 40,669 and the average QALYs gained were 8.78.

For metformin plus meglitinide, the average cost per patient was CAD 42,269 and the average QALYs gained were 8.77.

For metformin plus alpha-glucosidase inhibitor, the average cost per patient was CAD 42,797 and the average QALYs gained were 8.78.

For metformin plus thiazolidinedione, the average cost per patient was CAD 46,202 and the average QALYs gained were 8.78.

For metformin plus dipeptidyl peptidase-4, the average cost per patient was CAD 47,191 and the average QALYs gained were 8.78.

For metformin plus basal insulin, the average cost per patient was CAD 47,348 and the average QALYs gained were 8.77.

For metformin plus biphasic insulin, the average cost per patient was CAD 52,367 and the average QALYs gained were 8.78.

Costs and benefits were combined using an incremental cost-utility ratio (the additional cost per QALY gained). When compared with metformin monotherapy, metformin plus sulphonylurea was associated with an incremental cost per QALY gained of CAD 12,757. All other interventions were found to be dominated as they were less effective and more costly.

The authors reported that at a willingness to pay threshold of over CAD 12,000 per QALY gained, metformin plus sulphonylurea was the intervention with the highest probability of being cost-effective.

**Authors' conclusions**
The authors concluded that the addition of a sulphonylurea represented the most cost-effective second-line therapy.

**CRD commentary**

**Interventions:**
The interventions under study were reported adequately. They appeared to be appropriate comparators and appropriately reflected the study setting. However, some interventions were excluded from the study as they were not
approved in Canada; this may mean that the included interventions may not fully reflect other settings.

Effectiveness/benefits:
The effectiveness data came from a published systematic review and meta-analysis of published trials, so it was likely that the best available evidence was included. A brief description of the systematic review was provided along with an outline of the inclusion criteria and evidence synthesis, but insufficient details were given to assess its quality. The benefit measure appeared appropriate as it captured the morbidity and mortality of the patients. QALYs made the results easier to compare with other disease categories. The utility estimates appeared to be appropriate and were adequately described.

Costs:
The study perspective was clearly reported. For the Canadian third-party healthcare payer, all major relevant cost categories and costs appeared to have been included. The sources for the costs were reported adequately and appeared appropriate. The price year, time horizon, discount rate and currency details were all reported.

Analysis and results:
Outcome and cost information were synthesised using a previously-published well-validated model. Adequate details of the model were provided, including a diagram. The results were tested using one-way and multi-way sensitivity analyses plus cost-effectiveness acceptability curves, which were likely to give a good indication of any uncertainty in the results. The results and the sensitivity analysis results were well reported. As main limitations to their study, the authors acknowledged that they assumed that patients had remained on the same therapy indefinitely, which did not reflect the progressive nature of the disease or clinical practice; they also referred to the lesser quality studies used to estimate the clinical benefits of the interventions.

Concluding remarks:
The quality of the study methods was good, with the methods and results appropriately reported. The authors’ conclusions appear to be valid and appropriate.

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