Long-term clinical and cost outcomes of treatment with biphasic insulin aspart 30/70 versus insulin glargine in insulin naive type 2 diabetes patients: cost-effectiveness analysis in the UK setting

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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 biphasic insulin aspart 30/70 (BIAsp 30/70), a formulation of 30% soluble insulin aspart and 70% insulin aspart crystallised with protamine in one injection, for the treatment of patients with Type 2 diabetes who have failed oral antidiabetic agents. BIAsp 30/70 was given at a total daily dose of 12 units (6 units twice daily, pre-breakfast and pre-supper).

Type of intervention
Treatment.

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

Study population
The study population comprised a hypothetical cohort of patients with Type 2 diabetes who had failed oral antidiabetic agents. Uncontrolled diabetes was defined as a mean haemoglobin A1c (HbA1c) level of at least 8% on more than 1,000 mg/day metformin alone, or in combination with other oral antidiabetic agents, for at least 3 months.

Setting
The setting was primary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data were derived from studies published between 1994 and 2005. The costs and resource use data were derived from studies published between 1998 and 2004. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Modelling
A published decision model, the CORE Diabetes model, was used to assess the long-term clinical and economic consequences of the two treatments in a hypothetical cohort of naive Type 2 diabetes patients. The model was constructed on a series of sub-models, based on Markov cycles, in order to simulate the most important complications of diabetes (cardiovascular disease, eye disease, hypoglycaemia, nephropathy, neuropathy, foot ulcer, amputation, stroke, ketoacidosis, lactic acidosis and mortality). Each sub-model used a Monte Carlo simulation with time, state, time in state and diabetes type-dependent probabilities. This peer-reviewed model had been extensively validated. The time horizon of the model was 35 years.
Outcomes assessed in the review
The clinical outcomes derived from the literature were:

- the baseline characteristics of the patient population that entered the model (including demographic and clinical factors),
- the baseline rates of complications,
- the proportions of patients taking specific medications or undergoing screening for some complications, and
- treatment effectiveness.

Study designs and other criteria for inclusion in the review
The primary studies used to derive clinical outcomes were presumably identified selectively, as a systematic review does not appear to have been undertaken. Much of the data on the baseline characteristics of the patients and treatment effects were derived from a published 28-week clinical trial enrolling 233 patients (the INITIATE study) randomised to receive BIAsp 30/70 or insulin glargine. Other data were derived from published studies that were not described.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
The internal validity of the INITIATE study was high because of its randomised design. The validity of the other studies was unclear.

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

Number of primary studies included
Six primary studies provided the clinical data used in the decision model.

Methods of combining primary studies
The primary estimates were not combined as each study provided a series of clinical estimates.

Investigation of differences between primary studies
Not reported.

Results of the review
The baseline characteristics of the study population were as follows:

- proportion of men, 54.5%;
- Caucasian origin, 53.2%;
- mean age, 52.45 years;
- mean body mass index (BMI), 31.45 kg/m2;
mean duration of diabetes, 9 years;
mean HbA1c, 9.77%.

The following baseline patient characteristics were considered.

- The rate of hypertensive heart disease was 0%.
- The rate of angina pectoris was 1.72%.
- The rate of myocardial infarction was 2.15%.
- The rate of heart failure was 0.43%.
- The rate of cardiac dysrhythmia was 1.29%.
- The rate of stroke was 0%.
- The rate of peripheral vascular disease was 0.86%.
- The rate of peripheral neuropathy was 23.2%.
- The rates of foot ulcer and amputation were 0.43%.
- The rates of microalbuminuria and gross proteinuria were 4%.
- The rate of background diabetes retinopathy was 8.5%.
- The rate of proliferative diabetic retinopathy was 0%.
- The rate of blindness and low vision was 8.5%.
- The rate of cataract was 4.3%.
- The rate of macular oedema was 0%.

The proportion of patients taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was 20.6%.

The proportion of patients taking statins was 17.8%.

The proportion of patients taking aspirin was 7.7%.

The rates of patients screened for retinopathy, renal disease and foot disease were 63.2%, 60% and 37.3%, respectively.

In terms of the effectiveness of treatment, the change from baseline in HbA1c was -2.79% with BIAsp 30/70 and -2.36% with glargine.

The change from baseline in BMI was +1.88 kg/m2 with BIAsp 30/70 and +1.22 kg/m2 with glargine.

The increase from baseline in total dose of insulin (in units per kg of body weight) was +0.82 with BIAsp 30/70 and +0.55 with glargine.

Transition probabilities were based on the published CORE Diabetes Model and were not reported.

Measure of benefits used in the economic analysis

The summary benefit measures used were the life-years (LYs) and quality-adjusted life-years (QALYs). These were
estimated using the modelling approach. An annual discount rate of 3.5% was applied. The sources of utility adjustments were not described.

**Direct costs**
The analysis took the perspective of the third-party payer. It included the cost categories of treatment of diabetes-specific complications, insulin, aspirin, statins, angiotensin-converting enzyme inhibitors, and screening for retinopathy and nephropathy. The unit costs were not presented separately from the quantities of resources used as most costs were presented as macro-categories. The costs and resource use associated with the treatment of complications were derived from published studies. The drug prices came from average wholesale prices. The price year was 2004 and prices estimated in previous years were updated to 2004 values using the third-party payer composite National Health Service price inflation index. An annual discount rate of 3.5% was used as the costs were incurred during a long timeframe.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
UK pounds sterling (€).

**Sensitivity analysis**
Univariate sensitivity analyses were carried out to assess the robustness of cost-effectiveness and cost-utility ratios to variations in the model inputs, such as the improvement in HbA1c, discount rate, and time horizon (5, 10 and 15 years). Alternative values were set by the authors. A probabilistic sensitivity analysis was also performed, using a Monte Carlo simulation with 1,000 patients run 1,000 times, in order to generate cost-effectiveness acceptability curves.

**Estimated benefits used in the economic analysis**
The expected LYs were 12.07 (+/- 0.16) with BIAsp 30/70 and 11.88 (+/- 0.16) with glargine (difference 0.19 +/- 0.20).

The expected QALYs were 8.46 (+/- 0.11) with BIAsp 30/70 and 8.27 (+/- 0.11) with glargine (difference 0.19 +/- 0.14). The model also showed that BIAsp 30/70 was associated with significantly fewer retinopathy and nephropathy complications than glargine.

**Cost results**
The expected lifetime costs were 36,715 (+/-824) with BIAsp 30/70 and 35,396 (+/-853) with glargine (difference 1,319 +/- 1,083).

The higher treatment costs of BIAsp 30/70 in comparison with insulin glargine (2,296) were partially offset by the reduced cost of complications.

**Synthesis of costs and benefits**
Incremental cost-effectiveness and cost-utility ratios were calculated to combine the costs and benefits of the alternative treatments.
The incremental cost per LY gained with BIAsp 30/70 over glargine was 6,788, while the incremental cost per QALY gained was 6,951.

The sensitivity analysis showed that if BIAsp 30/70 and glargine led to the same reduction in HbA1c (equal effectiveness), then glargine was dominant. Shorter time horizons led to higher cost-effectiveness ratios, making BIAsp 30/70 less attractive. Variation in the discount rates had no substantial impact on the results.

The cost-effectiveness acceptability curve showed that, at a willingness to pay of 30,000 per QALY gained, the probability of BIAsp 30/70 being cost-effective over glargine was 88%.

Authors' conclusions
Biphasic insulin aspart 30/70 (BIAsp 30/70), for the treatment of patients with Type 2 diabetes who have failed oral antidiabetic agents, improved (quality-adjusted) life expectancy in comparison with glargine at a reasonable cost from the perspective of the third-party payer in the UK.

CRD COMMENTARY - Selection of comparators
The authors provided a clear justification for the choice of the comparators, which were appropriately selected given the objective of the study. The dosages of the two medications were reported. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from published sources, although it was unclear whether the studies were identified from a review of the literature. No information on the conduct and method of a review was provided. Details and other characteristics of the primary studies were generally not described, except for the clinical trial used to derive much of the data on the patients and treatment efficacy. This should enforce the internal validity of the study. However, the issue of homogeneity among the trial and other data sources was not addressed. The impact of changes in the key clinical parameter (i.e. treatment effectiveness) was tested in the sensitivity analysis. Transition probabilities among health states were taken directly from the CORE Diabetes Model and were not reported in this study.

Validity of estimate of measure of benefit
QALYs and LYs were appropriate benefit measures because they incorporate the impact of the antidiabetic treatment on both quality of life and survival, which are relevant dimensions of health for the disease examined in the study. Both measures also have the advantage of being comparable with the benefits of other health care interventions. Discounting was applied. No information on the sources of utility adjustments and methods to derive these values was reported.

Validity of estimate of costs
The cost analysis was consistent with the perspective chosen for the study. Most of the costs were presented as macro-categories and were estimated from published studies. Thus, a breakdown of the cost items was not provided, which might limit the possibility of replicating the analysis in other settings. Further, these costs were specific to the study setting and their potential transferability to other contexts was not examined. The authors noted the strengths of using diabetes-specific costs that were higher than those usually associated with non-diabetic patients. The price year was reported, making reflation exercises in other time periods possible. The costs were discounted as recent guidelines suggest. The impact of changing the discount rate was investigated.

Other issues
The authors did not compare their cost-effectiveness results with those from other studies, but pointed out that this was the first long-term pharmacoeconomic study on a biphasic insulin analogue in comparison with a long-acting basal insulin. The issue of the generalisability of the study results to other settings was not explicitly addressed, and the external validity of the analysis was limited. However, the authors addressed the issue of variability and uncertainty in
the model parameters through the use of a probabilistic sensitivity analysis. The authors noted that a further strength of the analysis was the use of a validated decision model. However, the use of data from a single trial to derive treatment effectiveness represented a limitation of the analysis.

Implications of the study
The study results demonstrated that, compared with insulin glargine, the use of BIAsp 30/70 for the treatment of patients with Type 2 diabetes who have failed oral antidiabetic agents represents excellent value for money in the UK setting.

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