Intensive lifestyle changes of metformin in patients with impaired glucose tolerance: modelling the long-term health economic implications of the Diabetes Prevention Program in Australia, France, Germany, Switzerland, and the United Kingdom


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
Three strategies used in the Diabetes Prevention Program (DPP) for treating patients with impaired glucose tolerance (IGT) were compared. The three strategies were intensive lifestyle changes (ILC), standard lifestyle advice plus metformin (850 mg twice daily), or standard lifestyle advice plus placebo. Further details about the DPP interventions can be found elsewhere (Diabetes Prevention Program Research Group, see 'Other Publications of Related Interest' for bibliographic details).

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The simulated cohort of patients in this analysis was constructed to resemble the study population of the DPP. The mean age was 50.6 years, the mean body weight was 94.2 kg, the mean body mass index (BMI) was 34.0 kg/m², and 32.2% were men.

Setting
The setting was primary care. The economic evaluation was carried out for Australia, France, Germany, Switzerland and the UK.

Dates to which data relate
The studies providing the effectiveness evidence dated from 1992 to 2003, while those providing cost data dated from 2000 to 2003. The price year was 2002.

Source of effectiveness data
The evidence was derived from a review or synthesis of completed studies and estimates based on expert opinion.

Modelling
A Markov (state transition) decision model was used. Three health states were used, IGT, Type 2 diabetes mellitus (DM) and deceased. Simulated patients initially had IGT and progressed at differing rates to Type 2 DM, depending on the treatment received. State-specific annual mortality rates for IGT or DM were used. The incidence rates of Type 2 DM for each treatment arm in the DPP were used to calculate annual transition probabilities from IGT to Type 2 DM through modelling. The time horizon was a patient's lifetime. The key assumptions made in the model were as follows.
In the base-case scenario, the duration of effect of metformin and ILC would not persist beyond the 3-year trial period, and the costs of implementing the intervention would also be aggregated only during that period. Also, patients who experienced side effects would consult the general practitioner and incur the corresponding costs.

In each country the three treatment arms would be implemented in a primary care setting.

**Outcomes assessed in the review**

The parameters used in the model included:

- the incidence rates of Type 2 DM for each treatment arm; and
- the age- and gender-dependent, country-specific probabilities of death associated with IGT or Type 2 DM, adjusted using relative risks (RRs) for all-cause mortality for patients with IGT versus normoglycaemic patients.

The model also considered gastrointestinal and musculoskeletal symptoms, and metformin tolerability rate, as side effects of treatment.

**Study designs and other criteria for inclusion in the review**

No inclusion criteria for a review of any of the parameters were reported. However, the study designs used by the authors included randomised clinical trials and a systematic analysis of individual primary studies of varying designs. Mostly, the study was based on the results of the DPP trial (Diabetes Prevention Program Research Group, see 'Other Publications of Related Interest' for bibliographic details).

**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**

The authors reported that 50 primary studies provided effectiveness evidence.

**Methods of combining primary studies**

A narrative method was used to combine the studies.

**Investigation of differences between primary studies**

Not reported.

**Results of the review**

The annual rate (per 100 person-years) of conversion from IGT to Type 2 DM was 11.0 in the control arm, 7.8 in the metformin arm, and 4.8 in the ILC treatment arm.

General mortality was considered by country, age and gender, and was based on mortality tables.
The RR of all-cause mortality in IGT compared with normoglycaemia was 1.37 (95% confidence interval, CI: 1.05 - 1.79).

The RR of all-cause mortality was 1.76 (95% CI: 1.17 - 2.66) for undiagnosed Type 2 DM, and 2.26 (95% CI: 1.78 - 2.87) for diagnosed Type 2 DM, all being compared with normoglycaemia.

The annual probabilities of dying were not reported.

There were 30.7 gastrointestinal events per 100 patient-years in the control arm, 77.8 in the metformin arm, and 12.9 in the ILC treatment.

There were 21.1 musculoskeletal events per 100 patient-years in the control arm, 20.0 in the metformin arm, and 24.1 in the ILC treatment arm.

**Methods used to derive estimates of effectiveness**
The authors also made assumptions in their study.

**Estimates of effectiveness and key assumptions**
The time from onset to diagnosis of DM was considered about 8 years. Patients with a duration of DM of less than 8 years were considered undiagnosed, while those with a duration of DM of at least 8 years were considered diagnosed.

**Measure of benefits used in the economic analysis**
Several outcomes were evaluated in the economic analysis. More specifically, the number of years free of DM and life expectancy for each treatment arm.

**Direct costs**
Direct medical costs were included for the appropriate country-specific setting. These included the cost of implementing the DPP, the cost of IGT and Type 2 DM, and the cost of treating side effects. The total lifetime costs per patient were calculated for each treatment arm. The costs of metformin were taken from published sources, with the costs weighted by the market share of the various brands or generic metformin. The total medical costs for Type 2 DM were derived from published sources. These were global costs and included medications, consultations, diagnostics and treatment for complications. The authors calculated the total medical cost of IGT to be 46% of that for patients with Type 2 DM. The resource quantities and the costs could be calculated separately for the DPP (the number of review sessions and consultation, and total cost were given), but not for the treatment of side effects. Discounting was appropriately performed. In the base-case analysis, discount rates of 5% were used for both the costs and clinical outcomes. In the UK, the costs and life expectancy were discounted at annual rates of 6% and 1.5%, respectively. Most of the quantities and costs were analysed separately. The price year was 2002.

Due to space constraints associated with the 'Currency' field, the exchange rates are reported here. The exchange rates in November 2002 were as follows: Euro 1.4209 = 1.00 UK pound sterling ();

Euro 0.5611 = 1.00 Australian dollar (Aus$); and

Euro 0.6624 = 1 Swiss franc (Sfr).

Exchange rates for French francs and German marks were not reported.

**Statistical analysis of costs**
No statistical analysis of the costs was reported.
Indirect Costs
The indirect costs were not included in the analysis.

Currency
Euros (Euro). Please see 'Direct Costs' for exchange rates.

Sensitivity analysis
Extensive sensitivity analyses were performed to identify variables with important impacts on the outcomes, and also to test variations in assumptions. A one-way sensitivity analysis was performed on the total costs and life expectancy by varying each individual probability and cost variable by +/- 10% while holding other variables constant. The value of those variables with the greatest influence on outcomes at which the conclusion would change was also assessed (rank order stability assessment). The reported ranges for the sensitivity analyses were derived from confidence intervals, data from published literature and authors' assumptions. In addition, as efficacy was shown to be different in age and BMI sub-groups, sub-group analyses on baseline age (30 or 65) or BMI (less than 30 or at least 35) were performed.

Estimated benefits used in the economic analysis
In the base-case analysis, assuming only within-trial effects of the interventions, both ILC and metformin increased the number of years free of DM and improved life expectancy. ILC led to greater improvements in life expectancy.

The mean number of years free of DM was 8.14 for the control arm, 9.94 for ILC and 9.02 for metformin.

Delayed onset of Type 2 DM led to mean improvements in non-discounted life expectancy of 0.22 years for ILC versus control, and 0.11 years for metformin versus control. Discounted mean improvements in life expectancy were 0.09 and 0.04 years, respectively.

Cost results
The total lifetime costs for each country and treatment arm were as follows.

Germany: control Euro 33,547, ILC Euro 32,963, metformin Euro 33,282.
UK: control Euro 17,632, ILC Euro 18,653, metformin Euro 18,010.

Compared with control, metformin and ILC resulted in cost-savings in all countries except the UK, where a small increase in costs of Euro 1,021 versus control was seen for the ILC treatment arm, and Euro 378 versus control for the metformin treatment arm.

Synthesis of costs and benefits
In the base-case analysis, assuming only within-trial effects of the interventions, both ILC and metformin were either cost-saving or highly cost-effective in comparison with the control in all countries.

Incremental cost-effectiveness ratios were calculated in terms of the costs per life-year gained when comparisons between the treatment arms revealed increased life expectancy as well as increased costs. Compared with the control, metformin and ILC resulted in cost-savings in all countries except the UK. The incremental cost-effectiveness ratios were Euro 6,381 and Euro 5,400 per life-year gained, respectively, for ILC and metformin versus control. These results fall into the range considered very attractive by international standards.
The results of the sub-group analysis showed that metformin had a better impact on costs and improvement in life expectancy than ILC in younger and more obese patients.

A one-way sensitivity analysis of the ILC treatment arm showed that the RR for all-cause mortality for IGT versus normoglycaemia had the greatest impact on life expectancy.

The annual costs of Type 2 DM had the greatest impact on the total lifetime costs per patient. Variation in the annual costs of metformin had only a minor overall impact on the total lifetime costs per patient in this treatment arm.

**Authors’ conclusions**

Based on probabilities from the Diabetes Prevention Program (DPP) and published data, incorporation of the DPP interventions into clinical practice in five developed countries was projected to lead to an increase in diabetes mellitus (DM)-free years of life, improvements in life expectancy, and either cost-savings or minor increases in costs compared with standard lifestyle advice in a population with impaired glucose tolerance (IGT).

**CRD COMMENTARY - Selection of comparators**

The authors gave a justification for the comparators. Recent data suggested that IGT is commonly considered to represent a pre-diabetic state, which confers an increased risk of developing Type 2 DM along with its associated costly complications. Also, interventions targeted at individuals with IGT provide an opportunity to delay or prevent the onset of Type 2 DM. You should judge whether other comparators or other drugs could also be relevant in your setting.

**Validity of estimate of measure of effectiveness**

The authors did not state that a systematic review of the literature had been undertaken. Although this is a common practice with models, it does not always ensure that the best data available are used in the model. The authors used data from the available studies selectively. One cannot be sure that all the relevant literature was identified, although the estimates of effectiveness were derived credibly from the studies that were identified. The evidence on effectiveness and treatment side effects was derived from randomised clinical trials, which represent an adequate source for the estimation of effectiveness. The authors also used experts’ opinions and their own assumptions, which were justified with reference to the medical literature. The estimates were investigated by sensitivity analyses using ranges derived from confidence intervals, data from published literature, and authors' assumptions.

**Validity of estimate of measure of benefit**

The estimation of benefits was modelled. The Markov model used was appropriate for this purpose, as it included all potential health states associated with DM and enabled benefits to be calculated over the lifetime of the patients. Life expectancy as a measure of benefit only permits partial cross health technology comparisons since quality of life is not taken into consideration. Sensitivity analyses were conducted and the ranges selected were derived from confidence intervals and published literature.

**Validity of estimate of costs**

The authors reported that the costs were estimated from the perspective of a third-party reimbursement payer, thus the indirect costs were appropriately not included. Although some costs could have been omitted from the analysis (e.g. telephone calls, business overheads and educational materials), these were unlikely to have affected the authors’ conclusions as they were underestimating the intervention costs. There was some separation of the resource quantities and the unit costs in the analysis, and this enhances the generalisability of the results to other settings.

To estimate the total direct costs, the authors considered the medical costs and the drug acquisition cost. Although they were taken from published sources, the variation among the different countries in relation to the use of resources might have affected the authors’ conclusions, especially since the cost of Type 2 DM was considered globally. However, sensitivity analyses of the costs were conducted to test the robustness of the results. The ranges were selected on the basis of authors’ assumptions, which limits the relevance of the results of the sensitivity analysis.
Discounting was appropriately carried out. The rates used for clinical and cost outcomes were equal in all but the UK, where a different recommendation exists. The price year was reported, which will aid any future reflation exercise.

Other issues
The authors made appropriate comparisons of their findings with those of other studies. The issue of generalisability was addressed by considering the population and setting selected. The results of the analysis were adequately reported and the authors' conclusions reflected the scope of the analysis.

The authors reported several limitations for this type of cost-effectiveness study, some of which follow. First, data from a carefully controlled clinical trial in one country were translated to routine clinical practice in another. Second, only a primary care setting was assumed for the implementation of the DPP interventions. Third, the variation by country did not adequately reflect country-specific practice patterns. Fourth, there are concerns about application across diverse racial and ethnic groups. Fifth, the DPP focused on overweight patients and prevention is unlikely to be equally cost-effective in lower risk populations. Finally, there was no attempt to disaggregate the costs for the states of IGT or global costs of Type 2 DM management and complications. Some other types of costs were excluded and this may have led to an underestimation of the costs of implementing the DPP interventions.

Implications of the study
The authors made further suggestions following the results of their study. For instance, financial constraints should not prevent the implementation of DM prevention programmes. Future studies (from both the clinical and health economic points of view) should focus on direct comparisons of the effectiveness and cost-effectiveness of various intensive lifestyle and dietary programmes, and on different pharmaceutical regimens to identify the most efficient DM prevention strategy among the increasing number of possible interventions available. An online version of the model will allow cost-effectiveness analysis of the DPP in other settings, including developing countries, to support decision-makers in their efforts to implement efficient methods for the prevention of this disease.

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Other publications of related interest


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