Long-term cost-effectiveness of pioglitazone versus placebo in addition to existing diabetes treatment: a US analysis based on PROactive
Valentine WJ, Tucker D, Palmer AJ, Minshall ME, Foos V, Silberman C

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
This study investigated the costs and clinical outcomes of treating patients with pioglitazone in addition to their existing medications for type 2 diabetes with macrovascular complications. The authors concluded that pioglitazone demonstrated clinically superior and cost-effective outcomes compared with placebo. The methods were comprehensive, valid, and mostly transparent and the authors’ conclusions appear to be in line with the objective and reliable.

Type of economic evaluation
Cost-effectiveness analysis, cost-utility analysis

Study objective
The aim was to assess the costs and health effects of pioglitazone, in the secondary prevention of cardiovascular events, for high-risk patients with established type 2 diabetes. The study population was adults, with a mean age of 62 years; 66% were male and they had a mean duration of diabetes of 10 years and were receiving anti-diabetic treatment.

Interventions
Pioglitazone was compared with placebo for patients with long-term type 2 diabetes, who were already on anti-diabetic treatment and were at high risk of experiencing cardiovascular events. Pioglitazone is an oral anti-diabetic drug with blood-glucose lowering properties and beneficial effects on triglyceride and high-density lipoprotein levels.

Location/setting
USA/primary care.

Methods
Analytical approach:
A simulation model that combined a series of inter-linking Markov sub-models was used. The data were derived primarily from a multi-centre clinical trial called the Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROactive) trial (Dormandy, et al. 2005, see ‘Other Publications of Related Interest’ below for bibliographic details). The time horizon was the patient's lifetime, with a maximum of 35 years. The authors reported that the study was carried out from the US third-party payer (Medicare) perspective.

Effectiveness data:
The clinical data for the first three years were derived from the prospective, multi-centre, double-blind randomised clinical trial (Dormandy, et al. 2005). The primary clinical outcomes included cardiovascular event rates, relative risks of events (beyond the trial period), and all-cause and cardiovascular mortalities. The sample size in the PROactive trial was 5,238 patients and the intervention group had a mean exposure to pioglitazone of 30.4 months. The event rates for subsequent years (year four onwards) were calculated by applying a relative risk adjustment to each additional life-year gained, so that the risk of events increased with a patient's age.

Monetary benefit and utility valuations:
The health-state utilities were derived from quality-of-life data reported in the Cost of Diabetes in Europe – Type II study (Bagust, et al. 2005, see ‘Other Publications of Related Interest’ below for bibliographic details), using the European Quality of life (EQ-5D) questionnaire.
Measure of benefit:
The measures of benefit were life-years saved (LYS) and quality-adjusted life-years (QALYs) gained and these were discounted at an annual rate of 3%.

Cost data:
The included direct medical resources were medications, patient management or monitoring, event occurrences, treatment, and follow-up. Resource quantities were collected during the PROactive trial and, after the trial ended, published sources were used for quantities and costs. The costs were discounted at an annual rate of 3%, reported in 2005 US dollars ($) and, when necessary, adjusted to 2005 prices using the US Consumer Price Index.

Analysis of uncertainty:
Probabilistic methods were used to assess the uncertainty in the incremental cost-utility ratios. One-way sensitivity analysis was used to assess variation in the key estimates, such as time horizons between five and 20 years, discount rates, clinical effectiveness, and the utilities. The results were illustrated in a cost-effectiveness acceptability curve.

Results
Both the discounted and undiscounted results were presented.

The mean discounted costs were $272,694 (SD 6,795) for the pioglitazone group and $265,390 (SD 6,617) for placebo group over the lifetime. The mean discounted QALYs were 8.92 for pioglitazone and 8.75 for placebo. The mean LYS were 12.0 for pioglitazone and 11.8 for placebo. The incremental cost for pioglitazone over placebo was $7,305 and the incremental QALYs were 0.17 or 62 days.

The incremental cost per QALY was $44,105 and the cost per LYS was $30,792.

The incremental cost per QALY was shown to be sensitive to the time horizon (a five-year horizon altered the ratio to $831,601) and assumptions on the duration of benefits. At a willingness-to-pay threshold of $50,000 per QALY, there was a 55% probability that pioglitazone would be cost-effective over placebo.

Authors' conclusions
The authors concluded that pioglitazone added to the usual anti-diabetic treatment for high-risk macrovascular disease, in patients with type 2 diabetes, was likely to be cost-effective.

CRD commentary
Interventions:
A brief description of pioglitazone was provided, but more information on dose, frequency, administration, and compliance should be available in the original trial publication (Dormandy, et al. 2005). The reader should decide if pioglitazone is a feasible option in their own setting.

Effectiveness/benefits:
The effectiveness data were based on a large, rigorous, randomised controlled multi-centre trial, which is likely to have produced high-quality minimally-biased estimates. Further information on the randomisation, event rates, statistical approach, and quality of the clinical findings should be available in the main PROactive publication (Dormandy, et al. 2005). The utility values were measured using the widely accepted EQ-5D questionnaire (Bagust, et al. 2005).

Costs:
Details of the costing methods were reported and each event or state cost and additional follow-up costs were presented, alongside their source. The daily costs of cardiovascular medication, patient management costs, and complication costs were also presented. A few author assumptions were necessary, but these were clearly documented.

Analysis and results:
The authors adapted a well validated, interactive, internet based, simulation model. Some details were presented, particularly for the modifications, but the full details were reported by Palmer, et al. (2004, see 'Other Publications of Related Interest' below for bibliographic details). The simulated cohort was based on the study population and the
baseline characteristics, including socio-demographics, risk factors, and the complication profile, were clearly stated. The model inputs and the base-case results were clearly reported. The sensitivity analysis was extensive and used appropriate methods, but only selected results were reported.

Concluding remarks:
The economic evaluation methods were comprehensive, valid, and mostly transparent. The authors’ conclusions appear to be in line with the objective and reliable.

Funding
Supported by a grant from Takeda Global Research and Development, Inc, Deerfield, IL, USA.

Bibliographic details

PubMedID
18657104

DOI
10.1111/j.1524-4733.2008.00403.x

Original Paper URL
http://onlinelibrary.wiley.com/journal/120847948/abstract

Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Computer Simulation; Cost-Benefit Analysis; Diabetes Complications /economics /prevention & control; Diabetes Mellitus, Type 2 /drug therapy /economics; Drug Therapy, Combination; Female; Humans; Hypoglycemic Agents /economics /therapeutic use; Life Expectancy; Male; Middle Aged; Quality-Adjusted Life Years; Thiazolidinediones /economics /therapeutic use; United States

AccessionNumber
22009100672

Date bibliographic record published
07/04/2009

Date abstract record published
19/05/2010