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 study examined the addition of pioglitazone to existing treatments (“add-on” therapy) for patients with Type 2 diabetes and a history of macrovascular disease. Pioglitazone could be given at 15, 30 or 45 mg/day.

Type of intervention
Secondary prevention.

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

Study population
The study population comprised patients with Type 2 diabetes and a history of macrovascular disease who were at high risk of further cardiovascular events. Macrovascular disease was defined as one or more of the following: more than 6-month history of myocardial infarction (MI), coronary artery revascularization, stroke, 3-month history of acute coronary syndrome (ACS), other evidence of coronary artery disease, or peripheral arterial obstructive disease. In the lifetime analysis, the hypothetical patients had baseline characteristics consisting of 66.1% male and a mean age of 61.8 years.

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

Dates to which data relate
The data on clinical outcomes and resources used were derived from a study published in 2004. The price year was 2005.

Link between effectiveness and cost data
The costing was performed prospectively on the same sample of patients as that used in the analysis of effectiveness.

Study sample
A sample of 5,238 patients was enrolled. A total of 2,605 patients were randomly assigned to the pioglitazone arm, while 2,633 were assigned to the usual care arm. Patient demographics were not reported. Other details of the sample selection process were not reported, but readers were referred to the original publication.

Study design
The PROactive study was a double-blind, placebo-controlled trial. The length of follow-up was almost 36 months. At the end of follow-up, clinical data were available for 2,463 patients in the pioglitazone arm and 2,470 in the placebo
arm. Other aspects of the study design were not reported.

Analysis of effectiveness
The primary clinical end point was a composite of all-cause mortality, nonfatal MI, including silent MI; stroke, ACS, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. The secondary outcome measures were time to first event or death from any cause, MI (excluding silent MI) and stroke, changes in cholesterol and triglycerides levels, and rate of progression to long-term insulin therapy. Life expectancy within the trial time horizon was calculated as the area under the survival curves for the pioglitazone and placebo treatment arms. Clinical outcomes were assessed every 6 months, up to 3 years. The analysis of the clinical outcomes was based on intention to treat. The baseline comparability of the study groups was not reported, although patients were likely to be comparable in terms of the clinical and demographic characteristics given the large sample size and the randomisation process.

Effectiveness results
The effectiveness analysis showed that there was a 10% relative risk reduction in the composite outcome for pioglitazone compared with placebo, although this did not reach statistical significance, (p=0.095). However, pioglitazone led to a statistically significant reduction of 16% in the risk of mortality, nonfatal MI and stroke, (p=0.027).

Levels of cholesterols were more favourable in the pioglitazone group.

The number of patients progressing to long-term insulin therapy was reduced by half in the pioglitazone arm.

Clinical conclusions
The effectiveness analysis showed that pioglitazone added to usual care was an effective alternative to conventional therapy in patients with Type 2 diabetes at risk of cardiovascular events.

Modelling
A decision model analysis was used to extrapolate the short-term clinical outcomes of the PROactive Study to a lifetime perspective (35 years). A modified version of the validated Center for Outcomes Research (CORE) Diabetes Model was used and a number of new complication sub-models were developed or modified. Constant risk rates were assumed for almost all inputs in order to project the 36-month clinical data to a long-term horizon. Few other details of the model were given.

Measure of benefits used in the economic analysis
The summary benefit measure used was the number of quality-adjusted life-years (QALYs). These were estimated using the decision model. Utility weights used to calculate QALYs in the base-case were derived from the Cost of Diabetes in Europe-Type 2 study. In particular, disutilities were associated with all main clinical events (e.g. MI, ACS, percutaneous coronary intervention, coronary artery bypass grafting). Life-years (LYs) were also calculated and combined with the costs. The benefits were discounted at an annual rate of 3.5%.

Direct costs
The analysis of the costs was carried out from the perspective of the NHS. The within-trial analysis included pharmacy costs (pioglitazone, other glucose-lowering medication, and cardiovascular medication) and event costs (e.g. MI, ACS, percutaneous coronary intervention, coronary artery bypass graft, stroke, major leg amputation). The long-term model included pharmacy costs, patient management costs (routine practice of screening for retinopathy, nephropathy and non-standard ulcer treatment) and costs of complications (event rates).

Many details of the unit costs and resource quantities were reported and, for most items, the unit costs and the resource
quantities were reported separately. The costs were based on published UK-specific unit costs. Published studies were also used. Wherever possible, diabetes-specific event costs were used. Resource consumption was based on event rates observed in the clinical trial. Discounting was relevant, as the long-term costs were included in the analysis and an annual discount rate of 3.5% was used. The price year was 2005.

**Statistical analysis of costs**
Standard statistical tests were carried out to assess the significance of differences in event rates (e.g. hospitalisations) in the within-trial analysis. The costs were treated stochastically in the long-term analysis.

**Indirect Costs**
Productivity costs were not included in the analysis.

**Currency**
UK pounds sterling (GBP).  

**Sensitivity analysis**
The issue of uncertainty in input parameters was extensively addressed using sensitivity analyses. In the within-trial economic evaluation, a deterministic sensitivity analysis investigated the impact of variations in utility weights (using alternative sources of values), event rates (which were varied by +/- 20%), and cost estimates (which were varied around their 95% confidence interval). Another source of costs (nonselective National Tariff 2006 data for inpatient care) was also used. In the long-term analysis, a second-order Monte Carlo simulation was performed in order to assess uncertainty in the cost-effectiveness results. Some parameter distributions were reported and justified. Cost-effectiveness acceptability curves were then generated. Variations in individual inputs (time horizon, key clinical and economic estimates, duration of treatment, utility values, etc.) were also considered. In particular, great attention was given to different time horizons (5, 10 or 20 years) and different utility weights (taken from the UKPDS group data or the University of Michigan data).

**Estimated benefits used in the economic analysis**
In the within-trial analysis, the expected QALYs were 2.7441 with pioglitazone and 2.7251 with placebo. The difference was 0.0190 QALYs.

In the within-trial analysis, the expected discounted LYs were 2.8075 with pioglitazone and 2.7970 with placebo. The difference was 0.0105 LYs.

In the long-term simulation, the expected QALYs were 8.536 with pioglitazone and 8.384 with placebo. The difference was 0.152 QALYs.

In the long-term simulation, the expected discounted LYs were 11.456 with pioglitazone and 11.237 with placebo. The difference was 0.218 LYs.

**Cost results**
In the within-trial analysis, the expected costs were 6,700 with pioglitazone and 6,598 with placebo (cost-difference 102). Pioglitazone led to savings of 91 over placebo in terms of costs of events. However, pharmacy costs increased by 193.

In the long-term simulation, the expected costs were 67,863 with pioglitazone and 67,244 with placebo (cost-difference 619). The majority of the costs in the long-term analysis were due to complications.
Synthesis of costs and benefits
Incremental cost-utility ratios and cost-effectiveness ratios were calculated to combine the costs and benefits of the alternative treatments.

In the within-trial analysis, the incremental cost per QALY gained with pioglitazone over placebo was 5,396 in the base-case analysis, rising to a maximum of 14,118 in the sensitivity analysis.

The incremental cost per LY gained with pioglitazone was 8,129.

Overall, the sensitivity analysis did not alter the conclusions of the base-case analysis. The greatest determinant of the analysis was the inclusion of a disutility associated with hospital admission for heart failure. Also, a 20% decrease or increase in event rates associated with pioglitazone would result in great variation in cost-effectiveness results (from dominance to an incremental cost per QALY over 30,000).

In the long-term simulation, the incremental cost per QALY gained with pioglitazone over placebo was 4,060, while the incremental cost per LY gained with pioglitazone was 2,835.

The cost-effectiveness acceptability curves showed that, for a willingness-to-pay threshold of 30,000 or 20,000 per QALY there was an 84.3% or 79.5% likelihood, respectively, that pioglitazone would be cost-effective from the perspective of the NHS. The sensitivity analysis suggested that pioglitazone was more cost-effective over the longer time horizon. Variations in other model inputs corroborated the base-case findings.

Authors’ conclusions
The addition of pioglitazone to conventional treatment was a cost-effective treatment for patients with Type 2 diabetes at risk of cardiovascular events both in the short- and long-term timeframe. The results of the analysis were in general robust to variations in both clinical and economic data.

CRD COMMENTARY - Selection of comparators
The choice of the comparator was appropriate as usual care was considered as the basic comparator. Usual care was based on international clinical guidelines for patients with diabetes. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The clinical estimates used in the analysis were derived from a large clinical trial, a study design that usually has a high internal validity. Little information on the design and other aspects of the trial was provided since all details were presented in the primary publication. However, the large sample of patients involved, the double-blind nature of the study, and the appropriate follow-up ensures the robustness of the clinical data.

Validity of estimate of measure of benefit
The choice of LYs and QALYs as summary benefit measures was appropriate as they capture two relevant dimensions of health for patients with diabetes (i.e. survival and quality of life). The source used to derive utility values was reported, but details of the instrument used to derive these estimates were not provided. Alternative sources of values were used in the sensitivity analysis. Discounting was applied in accordance with UK recommendations. Undiscounted life expectancy estimates were also presented.

Validity of estimate of costs
The analysis of the costs was consistent with the perspective adopted in the study. Typical NHS sources were used for most costs. Some estimates reported in other studies were also used. The authors provided extensive information on the cost items, although costs of events were presented as macro-categories. Many details of resource use for the within-trial analysis were provided and cost estimates were varied in the sensitivity analysis. Resource use reflected real-world consumption of health services as it was derived directly from the sample of patients evaluated in the clinical trial. The price year was reported, which will facilitate reflation exercises in other time periods.
Other issues
The authors stated that comparisons with other studies may be difficult because of differences in terms of model inputs and structure, but similar conclusions were found with respect to the results of the analysis. Thus, the findings from other recently published studies were reported and discussed. The use of comprehensive sensitivity analysis enhanced not only the robustness of the modelling exercise, but also the generalisability of the study results to other settings. The authors stated that some conservative assumptions were made in the assessment of utility values associated with treatment. In the evaluation of uncertain input, the analysis was also biased against pioglitazone.

Implications of the study
The study results support the use of pioglitazone in the secondary prevention of cardiovascular events in patients with Type 2 diabetes. The authors pointed out that future studies should provide better estimates of utility values, especially those associated with oedema in patients with Type 2 diabetes.

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Other publications of related interest
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