Glimepiride versus pioglitazone combination therapy in subjects with type 2 diabetes inadequately controlled on metformin monotherapy: results of a randomized clinical trial

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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 authors studied glimepiride and pioglitazone for the treatment of Type 2 diabetes. Glimepiride was given once daily at a starting dose of 2 mg/day. It was increased over 6 weeks to a maximum dose of 8 mg/day or until the mean of the last three daily self-monitored blood glucose (SMBG) values was less than 120 mg/dL. Pioglitazone was given once daily at a starting dose of 30 mg/day. It was increased over 12 weeks to a maximum dose of 45 mg/day or until the mean of the last three daily SMBG values was greater than 120 mg/dL or the glycosylated haemoglobin (A1C) level was at least 8.0%.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients with Type 2 diabetes inadequately controlled by metformin monotherapy. Patients were included if they were aged between 18 and 79 years, had a diagnosis of diabetes for at least 6 months, and were taking stable doses of metformin or extended-release metformin as their only oral anti-diabetic drug for at least 2 months prior to the study. There were also weight, A1C fasting plasma glucose and C-peptide concentration restrictions. Patients were excluded if they were treated with insulin, thiazolidinediones or sulfonylurea within 3 months of enrolment. They were also excluded if they had a history of substance abuse, severe hypoglycaemia, acute metabolic complications, or clinically significant abnormal baseline laboratory values.

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

Dates to which data relate
The dates when the effectiveness, resource and price data were collected were not reported. Wages were based on 2003 prices.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness study.
Study sample
The study sample comprised 96 patients randomised to and receiving at least one dose of glimepiride and 107 patients randomised to and receiving at least one dose of pioglitazone. There was no report that power calculations were carried out to estimate the influence of chance on the results. Nevertheless, the authors retrospectively commented on the power of the study to detect statistically significant differences. The sample was selected by screening patients with regards to the inclusion and exclusion criteria, but it was unclear whether all those entering the study setting were screened. Following the initial screening, some patients did not complete the trial on account of adverse events, failing to meet the entry criteria, withdrawing consent, treatment failure, protocol violations, lost to follow-up, or other reasons. Eleven patients in the glimepiride group and 15 in the pioglitazone group did not complete the trial.

Study design
This was a 28-week multi-centre, randomised, parallel-group, open-label, forced titration study. Patients received glimepiride plus metformin or pioglitazone plus metformin and were randomised in a 1:1 ratio. The study was based at 51 centres within the USA. There were several reasons for non-completion. Specifically, adverse events (1) and lost to follow-up (4) in the glimepiride group, and adverse events (4), treatment failure (4), protocol violations (2) and lost to follow-up (1) in the pioglitazone group. There was no report of blinding either the patients or physicians.

Analysis of effectiveness
The analysis was conducted on an intention to treat basis for all patients who took at least one dose of their study medication and who had at least one A1C result whilst on treatment. The primary health outcomes were the percentage change in A1C from baseline, the number of patients reaching target levels of A1C, the fasting plasma glucose change from baseline, fasting blood insulin, C-peptide, weight and body mass index change from baseline. The patients in the two groups were compared extensively at baseline. The authors observed no differences in the types and doses of non-diabetic medications and no statistically significant differences in demographic variables, except mean age and age at onset of diabetes.

Effectiveness results
Significant changes were observed in the following outcomes.

The change in fasting blood insulin from baseline was 6.21 (+/- 1.22) microU/mL for glimepiride and -5.18 (+/- 1.15) microU/mL for pioglitazone, (p=0.0001).

The change in C-peptide from baseline was 249.8 (+/- 37.73) pmol/L for glimepiride and -239.8 (+/- 35.47) pmol/L for pioglitazone, (p=0.0001).

Clinical conclusions
The authors concluded that glimepiride and pioglitazone treatments provided similar improvement in glycaemic control with no significant difference between treatment groups, but that glimepiride was associated with a faster improvement in metabolic control.

Measure of benefits used in the economic analysis
The Health Utilities Index Mark 3 (HUI3) (Health Utilities Inc., Hamilton) was used as the summary measure of health outcome. The data were collected via a self-administered questionnaire given to the study participants at randomisation, week 12 and at the end of the study (week 26). The HUI assigns a value of 0 to 1 (perfect health) to eight attributes of health status (vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain).

Direct costs
A perspective for the cost analysis was not reported. The authors did not report aiming to carry out a full cost-effectiveness analysis but to determine resource use and treatment costs. Health care resource use encompassed days of
therapy for study medication, the number of diabetes-related outpatient visits, and the number of hospitalisations. Data were collected from patient diaries and recorded on case report forms. The mean unit costs were reported to have been taken from national average wholesale prices. The dates for the measurement of resource use and a price year were not reported. Discounting was not necessary given the short time horizon of the study.

**Statistical analysis of costs**
The authors estimated confidence intervals (CIs) derived from an analysis of variance model that used treatment centre and interaction between the treatment and centre as independent variables.

**Indirect Costs**
Indirect costs including lost productivity were estimated. This analysis focused on the number of days missed from work and estimated the costs using 2003 wage rates from the Bureau of Labor statistics.

**Currency**
US dollars ($).

**Sensitivity analysis**
No sensitivity analyses were carried out.

**Estimated benefits used in the economic analysis**
For glimepiride, the mean scores for individual attributes ranged from 0.96 to 1.00 at baseline and from 0.95 to 1.00 at end point.

For pioglitazone, the mean scores for individual attributes ranged from 0.95 to 0.99 at baseline and from 0.96 to 1.00 at end point.

The mean changes in total utility score and individual attribute scores were reported to be small for both groups and not to differ significantly between groups. Individual data were not reported.

**Cost results**
The total direct costs for the 26-week time horizon were $577.85 (95% CI: 516.31 to 639.40) for glimepiride and $1,198.64 (95% CI: 1,141.19 to 1,256.09) for pioglitazone, giving a difference of -$620 (95% CI: -704.98 to 536.60).

The total indirect costs were $22.41 (95% CI: -218.39 to 263.21) for glimepiride and $102.17 (95% CI: -122.58 to 326.93) for pioglitazone, giving a difference of -$79.76 (95% CI: -409.15 to 249.63).

**Synthesis of costs and benefits**
The costs and benefits were not combined.

**Authors’ conclusions**
"Patients with type 2 diabetes mellitus with inadequate glycemic control while on metformin monotherapy achieved similar satisfactory glycemic control ... with either add-on glimepiride or pioglitazone."

**CRD COMMENTARY - Selection of comparators**
Following a discussion about the problems associated with monotherapy and the benefits of combination therapy in overcoming these, the authors chose to compare glimepiride and pioglitazone for the treatment of Type 2 diabetes.
Glimepiride was selected as a second-generation sulfonylurea and pioglitazone as an example of a thiazolidinedione. Sulfonylureas and thiazolidinediones were reported to be the most popular combinations with metformin.

**Validity of estimate of measure of effectiveness**
The authors designed a randomised trial that helped reduce systematic differences between patients in the two groups, thus increasing the internal validity of the results. This was demonstrated when a comparison of patients revealed no statistically significant differences. The study sample was noted to be limited in one significant way: the use of fasting C-peptide in the inclusion criteria was noted to potentially bias the patients included towards those with an improved likelihood of benefiting from the technologies of interest. However, this limitation did not necessarily create a bias in favour of one or the other technologies of interest. Appropriate statistical analyses were undertaken to explore potential uncertainties.

**Validity of estimate of measure of benefit**
The summary measure of benefit was observed directly during the clinical trial. This measure of utility gives a summary measure of health that is widely comparable, although the authors did not draw any comparisons with other studies using the HUI3.

**Validity of estimate of costs**
Since a perspective for the cost analysis was not reported, it was not possible to judge whether all the relevant costs were incorporated. However, the inclusion of indirect costs in the analysis suggests the adoption of a societal perspective. The direct costs included an estimate of drug costs, outpatient visits and inpatient visits. However, the authors did not report what elements were included in the latter estimates, so it is unclear whether they incorporated physician and nurse time and hospital overheads. These aspects are important to a societal perspective. The analysis would have benefited from a report of the dates over which resource used was recorded and a price year, as these aspects improve comparability with other studies.

**Other issues**
The authors were able to compare their work with that of others, noting that their results were “in agreement” with previous studies. The issue of generalisability to other settings was not addressed explicitly. However, the inclusion of national average prices makes the cost analysis transferable if other settings can demonstrate comparable resource use, and the authors noted that a larger sample size would increase applicability. The authors do not appear to have reported their results selectively and they assessed the robustness of their work by statistical analysis. The conclusions were an accurate reflection of both the scope of the study and the results presented. Several limitations were noted, for example, the use of fasting C-peptide in the inclusion criteria. The authors also noted the short time horizon and relatively smaller sample size as further potential limitations.

**Implications of the study**
The authors did not make any recommendations for policy or practice following on from their study. They also did not make any suggestions for further work.

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**Bibliographic details**