Comparison of Pioglitazone and Gliclazide in Sustaining Glycemic Control Over 2 Years in Patients With Type 2 Diabetes

MENG H. TAN, MD1
ARUN BAKSI, FRCP2
BORIS KRAHULEC, MD3
PIOTR KUBULSKI, MD4
ANDRZEJ STANKIEWICZ, MD5

RICHARD URQUHART, MD6
GARETH EDWARDS, BS6
DON JOHNS, PHD1

FOR THE GLAL STUDY GROUP

OBJECTIVE — The hypothesis that pioglitazone treatment is superior to gliclazide treatment in sustaining glycemic control for up to 2 years in patients with type 2 diabetes was tested.

RESEARCH DESIGN AND METHODS — This was a randomized, multicenter, double-blind, double-dummy, parallel-group, 2-year study. Approximately 600 patients from 98 centers participated. Eligible patients had completed a previous 12-month study and consented to continue treatment for a further year. To avoid selection bias, all patients from all centers were included in the primary analysis (a comparison of the time-to-failure distributions of the two groups by using a log-rank test) regardless of whether they continued treatment for a 2nd year. By using repeated-measures ANOVA, time course of least square means of HbA1c and homeostasis model of assessment (HOMA) indexes (HOMA-%S and HOMA-%B) were analyzed.

RESULTS — A greater proportion of patients treated with pioglitazone maintained HbA1c <8% over the 2-year period than those treated with gliclazide. A difference between the Kaplan-Meier curves was apparent as early as week 32 and widened at each time point thereafter, becoming statistically significant from week 52 onward. At week 104, 129 (47.8%) of 270 groups by using a log-rank test) regardless of whether they continued treatment for a 2nd year. By using repeated-measures ANOVA, time course of least square means of HbA1c, and homeostasis model of assessment (HOMA) indexes (HOMA-%S and HOMA-%B) were analyzed.

CONCLUSIONS — Pioglitazone is superior to gliclazide in sustaining glycemic control in patients with type 2 diabetes during the 2nd year of treatment.

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It is possible that the long-term glycemic effect of sulfonylureas and thiazolidinediones are not the same because of the differences in their mechanisms of action. Sulfonylureas stimulate the secretion of insulin by the patient’s pancreatic \( \beta \)-cells and the resultant hyperinsulinemia corrects the hyperglycemia (5). Pioglitazone is a peroxisome proliferator–activated receptor \( \gamma \) agonist that reduces insulin resistance in peripheral organs (enhanced total body glucose disposal) and in the liver (decreased hepatic glucose production) (9).

We tested the hypothesis that pioglitazone, because it reduces insulin resistance, is superior to sulfonylurea in sustaining glycemic control beyond 1 year in patients with type 2 diabetes. This hypothesis was tested by comparing the time to failure to maintain glycemic control (HbA1c <8%) in patients treated with pioglitazone or gliclazide for as long as 2 years. We also report the time course of HbA1c, fasting plasma glucose (FPG), fasting serum insulin (FSI), and homeostasis model assessment (HOMA) for insulin sensitivity (HOMA-%S, an insulin sensitivity surrogate), and for \( \beta \)-cell activity (HOMA-%B, a surrogate for \( \beta \)-cell activity).

**METHODS** — This was a randomized, multicenter, double-blind, double-dummy, parallel-group, 2-year study conducted in Australia, Canada, Finland, Poland, the Slovak Republic, South Africa, and the U.K. in accordance with good clinical practice guidelines and the principles of the Declaration of Helsinki. The institutional review board at each center approved the study protocol. Patients provided written informed consent before participation.

The primary analysis was the time to failure to maintain glycemic control (HbA1c <8%). At the time this study was designed, the American Diabetes Association (10) recommended that additional action was suggested when the patient’s HbA1c was >8%. For this study, we chose this as the failure threshold and not the treatment target. We determined that a sample size of 300 patients per group would provide at least 80% power to detect an 11% survival difference between treatments in the distributions of time to failure to maintain glycemic control with a log-rank test \( (\alpha = 0.05, \text{two sided}) \), assuming a 60% success rate in maintaining glycemic control in the gliclazide group.

Thus, of the original 206 centers from the parent study, a subset of 98 centers, with ~600 patients to satisfy the sample size requirements, was involved in this study (Fig. 1). The 98 centers were selected solely on the basis of the numbers of patients recruited for the parent study. Outcomes of the parent study were not known at the time of the selection of these 98 centers because the parent study was still ongoing. All patients who completed the 1-year parent study at these 98 centers were invited to participate in the extension of the parent study. Those who consented continued treatment for a further year. In the gliclazide group, 34 patients did not consent, and in the pioglitazone group, 22 patients did not consent. To avoid selection bias, all patients from the 98 centers were included in the primary analysis, regardless of whether they continued treatment for a 2nd year. This included 297 patients randomized to gliclazide and 270 patients randomized to pioglitazone at the beginning of the parent study.

The major entry criteria for the parent study were patients with type 2 diabetes inadequately controlled (HbA1c 7.5–11.0%) with diet alone, male and female
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Table 1—Patient characteristics and dispositions

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Pioglitazone group</th>
<th>Gliclazide group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>270</td>
<td>297</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>171 (63.3)</td>
<td>182 (61.3)</td>
</tr>
<tr>
<td>Women</td>
<td>99 (36.7)</td>
<td>115 (38.7)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>253 (93.7)</td>
<td>275 (92.6)</td>
</tr>
<tr>
<td>Others</td>
<td>17 (6.3)</td>
<td>22 (7.4)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 ± 9.8</td>
<td>56 ± 9.9</td>
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<tr>
<td>Duration of diabetes (years)</td>
<td>2.7 ± 3.5</td>
<td>2.9 ± 3.8</td>
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<tr>
<td>Height (m)</td>
<td>1.69 ± 0.09</td>
<td>1.70 ± 0.09</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>91.7 ± 19.9</td>
<td>89.2 ± 18.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32 ± 6.4</td>
<td>31 ± 5.6</td>
</tr>
<tr>
<td>Patient disposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>33 (12.2)</td>
<td>25 (8.4)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>45 (16.7)</td>
<td>86 (29.0)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>6 (2.2)</td>
<td>5 (1.7)</td>
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<tr>
<td>Withdrawal of consent</td>
<td>31 (11.5)</td>
<td>44 (14.8)</td>
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<tr>
<td>Lost to follow up</td>
<td>2 (0.7)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (2.2)</td>
<td>6 (2.0)</td>
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<tr>
<td>Completed study</td>
<td>147 (54.4)</td>
<td>127 (42.8)</td>
</tr>
</tbody>
</table>

Data are means ± SD or n (%).

RESULTS

Patient demographic, baseline characteristics, and disposition

The pioglitazone and gliclazide groups were similar in age, duration of diabetes, height, weight, BMI, ethnicity, and sex distribution (Table 1). Participants were mainly middle-aged, obese, white patients who had diabetes for <3 years at entry into the study. Table 1 also shows the primary reasons for discontinuation from the study in both groups. For the adverse events category, 6 of 33 (18%) patients discontinued in the pioglitazone group, compared with 1 of 25 (4%) in the gliclazide group, because of weight increase. In the gliclazide group, 3 of 25 (12%) discontinued because of headaches compared with none in the pioglitazone group.

Time to failure to maintain glycemic control

The Kaplan-Meier curves for the two groups showed that a greater proportion of patients treated with pioglitazone maintained HbA₁c of <8% over the 2-year period than those treated with gliclazide (Fig. 2). A difference between the curves was apparent as early as week 32 and widened at each time point thereafter, becoming statistically significant from week 52 onwards. At week 104, 129 (47.8%) of 270 pioglitazone-treated patients and 110 (37.0%) of 297 gliclazide-treated patients maintained HbA₁c <8%.

Of the patients with at least one post-baseline measurement of HbA₁c, 111 of 261 (42.5%) pioglitazone-treated patients were <7% at their last visit compared with 81 of 289 (28.0%) gliclazide-treated patients (P < 0.001).
Time course of HbA1c and FPG
Figure 3A shows the time course of least square means for HbA1c for both groups. Both groups had similar baseline HbA1c. Between weeks 4 and 24, gliclazide treatment improved HbA1c more than pioglitazone treatment did. At weeks 32 and 42, there was no difference in the HbA1c between the two groups. From week 52 to 104, pioglitazone treatment improved HbA1c more than gliclazide treatment did. At week 104, the pioglitazone treatment group was much less.

Time course in FSI, HOMA-%S, and HOMA-%B
Figure 4A shows the time course of least square means for FSI for both groups. Both groups had similar baseline FSI. In contrast to gliclazide treatment, which increased FSI, pioglitazone treatment decreased FSI from week 4 to 104. At week 104, the pioglitazone treatment group had lower FSI than the gliclazide treatment group (pioglitazone-gliclazide FSI: −52.9 ± 9.9 pmol/l; 95% confidence limit −72.6 to −33.3).

Figure 4B shows the time course of least square means for HOMA-%S for both groups. Both groups had similar baseline HOMA-%S. In contrast to gliclazide treatment, which decreased HOMA-%S, pioglitazone treatment increased HOMA-%S from week 4 to 104. At week 104, the pioglitazone treatment group had higher HOMA-%S than the gliclazide treatment group (pioglitazone-gliclazide HOMA-%S: 36.2 ± 4.4%; 95% confidence limit 27.5 to 45.0).

Figure 4C shows the time course of least square means for HOMA-%B for both groups. Both groups had similar baseline HOMA-%B. Overall, gliclazide treatment increased HOMA-%B more than pioglitazone treatment did from week 4 to 104. Between weeks 4 and 42, the difference in HOMA-%B between the two groups was substantial. After week 42, the increase in HOMA-%B in the gliclazide treatment group was much less. Hence, between weeks 52 and 104, the difference in HOMA-%B between the two groups was small. At week 104, the gliclazide treatment group had slightly higher HOMA-%B than the pioglitazone treatment group (pioglitazone-gliclazide HOMA-%B: −9.1 ± 3.7%; 95% confidence limit −16.3 to −1.82).

CONCLUSIONS — Several studies reported that sulfonylurea treatment, when compared with thiazolidinedione treatment, had a greater antihyperglycemic effect for as long as 4 months after therapy initiation. This effect was shown when glibenclamide (6) and glimepiride (7) were compared with pioglitazone. However, at week 52, both drugs (glibenclamide or glimepiride versus pioglitazone) showed comparable decreases in HbA1c. This change was also observed when rosiglitazone was compared with glyburide in an open-label study (8). Glyburide resulted in an initially rapid reduction in HbA1c, after which glycemic control deteriorated from week 16 to 52.

There was no difference in HbA1c between the rosiglitazone and glyburide groups at week 52. Similar findings were observed with gliclazide versus pioglitazone after 1 year (11). The present study extends these previous observations by analyzing time-to-treatment failure with pioglitazone and gliclazide over a 2-year treatment period and by describing the concomitant changes in HbA1c, FPG, FSI, HOMA-%S, and HOMA-%B during this period.

These findings support the hypothesis that pioglitazone treatment is superior to gliclazide treatment in sustaining gly-
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Kahn (15) proposed a model for the spectrum of glucose intolerance based on the relationship between insulin sensitivity and insulin secretion. As insulin sensitivity decreases, insulin secretion must proportionally increase to enable the subject to have normal glucose tolerance. If the insulin secretion is not proportionally increased, deterioration of glucose intolerance can occur. An extrapolation of this is that if insulin sensitivity is increased, insulin secretion can decrease proportionally.

HOMA is a widely used clinical tool and provides a method of assessing insulin sensitivity (or insulin resistance) and β-cell activity from basal (fasting) glucose and insulin (16). Whereas pioglitazone treatment increased HOMA-%S, it was decreased by gliclazide treatment (Fig. 3B). The difference in insulin sensitivity between the pioglitazone and gliclazide groups is sustained throughout the 2 years. In contrast, the difference in β-cell activity caused by the pioglitazone and gliclazide was not. In the gliclazide group, the initial rapid increase in HOMA-%B (which reflected the increase in β-cell activity) during the first 16 weeks of treatment (titration period) declined substantially thereafter. In the pioglitazone group, the initial increase in HOMA-%B with pioglitazone treatment was smaller compared with that of gliclazide treatment, but the increase was maintained throughout the 2-year treatment period. These changes in HOMA-%B over time resulted in a large difference between the two groups at week 16 and a smaller difference during the 2nd year (Fig. 4C). The combination of a substantial difference in HOMA-%S and a small difference in HOMA-%B from week 52 to 104 may partially explain the difference between the two treatments in glycemic control during this period.

The relative contributions of insulin-stimulated glucose uptake and basal hepatic insulin sensitivity to surrogate measures of insulin sensitivity were recently described by Tripathy et al. (17). The M value of glucose clamp studies correlated with HOMA-IR in subjects with normal glucose tolerance and in patients with type 2 diabetes. However, there was no such correlation in subjects with either impaired fasting glucose (IFG) alone or IFG/impaired glucose tolerance (IGT). The HOMA-IR correlated with hepatic insulin sensitivity in patients with type 2 diabetes and in subjects with IFG/IGT. The authors concluded that these discrep-
ancies develop as a result of a nonparallel deterioration of the variables included in the calculation with worsening glucose tolerance.

Groop et al. (4) reported that hepatic overproduction of glucose combined with impaired peripheral glucose metabolism accounted for 43.4% of their cases. Miyazaki et al. (9) reported that pioglitazone treatment in patients with type 2 diabetes, receiving monotherapy or combination pioglitazone and sulfonylurea therapy, decreased their hepatic glucose production and increased their total body glucose disposal. Recently, Bajaj et al. (18) showed that pioglitazone monotherapy decreased hepatic glucose production and increased whole-body glucose disposal. The decrease in hepatic glucose production was negatively correlated with the increase in plasma adiponectin concentration and positively with the reduction in hepatic fat content in these patients. The increase in whole-body glucose disposal was positively correlated with the increase in plasma adiponectin concentration. Whether the enhancement of insulin sensitivity in the pioglitazone group enabled it to have a more sustained glycemic effect than did gliclazide group that improved the hyperglycemia via hyperinsulinemia remains to be established.

Other causes may contribute to the differences in sustaining glycemic improvement in patients with type 2 diabetes treated with drugs (4). Among patient-related factors, BMI and age at diagnosis may play a role. Patients with type 2 diabetes with lower BMI at diagnosis have been considered to eventually require insulin, and this has been shown for sulfonylurea “secondary failure” (19). In the present study, the BMIs of the two groups were comparable and therefore not a factor. Others have reported that the age at diagnosis may influence the duration of successful sulfonylurea therapy (20). In the present study, the mean ages of the patients were similar in both groups. Because the duration of diabetes can affect secondary failure with OAM therapy (21) or progression of type 2 diabetes, the proportion of patients who fail to maintain HbA1c <8% at different diabetes durations may vary. In this study, the mean duration of diabetes (~3 years) for the participants was similar in both groups. Different sulfonylureas have different secondary failure rates: gliclazide 7%, glibenclamide 17.9%, and glipizide 25.6% (22). The difference between pioglitazone and other sulfonylureas in maintaining a glycemic target is not established.

In closing, results of this study show that pioglitazone is superior to gliclazide in sustaining glycemic control in patients with type 2 diabetes during the 2nd year of treatment. The combination of a substantial difference in HOMA-%S and a small difference in HOMA-%B from week 52 to 104 may explain the difference between the two treatments in glycemic control over time. Whether enhanced insulin sensitivity in the pioglitazone group promoted a more sustained glycemic effect than did gliclazide (which decreased hyperglycemia via hyperinsulinemia) remains to be established.

**Figure 4**—Time courses of FSI, HOMA-%S, and HOMA-%B during the 2-year treatment period. Time courses of FSI (A), HOMA-%S (B), and HOMA-%B (C) are shown. Data are presented as least square means ± SE.
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