

Comparison of Effect of Pioglitazone With Metformin or Sulfonylurea (Monotherapy and Combination Therapy) on Postload Glycemia and Composite Insulin Sensitivity Index During an Oral Glucose Tolerance Test in Patients With Type 2 Diabetes

ANTONIO CERIELLO, MD¹
DON JOHNS, PHD²
MARIO WIDEL, MS²

DAVID J. ECKLAND, PHD, MRCP³
KATHRYN J. GILMORE, MHA²
MENG H. TAN, MD²

OBJECTIVE — Pioglitazone, metformin, and gliclazide lower HbA_{1c} and fasting plasma glucose in patients with type 2 diabetes. We compared the effects of these three drugs, used as monotherapy and in combination, on postload glycemia and composite insulin sensitivity index (CISI) in these patients.

RESEARCH DESIGN AND METHODS — Postload glycemia and CISI were analyzed for 940 patients who had oral glucose tolerance tests (OGTTs) in four multicenter, randomized, double-blind, double-dummy, parallel group clinical trials (pioglitazone versus metformin, pioglitazone versus gliclazide, pioglitazone plus sulfonylurea versus metformin plus sulfonylurea, and pioglitazone plus metformin versus gliclazide plus metformin). Plasma glucose and insulin were determined during the 3-h OGTT performed at baseline and after 1 year of therapy. Incremental area under the curve for glucose was the surrogate for postload glycemia. CISI was calculated using the formula $\{10,000/\sqrt{\text{[(fasting glucose} \times \text{fasting insulin)} \times (\text{mean glucose} \times \text{mean insulin})]}\}$ during the OGTT.

RESULTS — In monotherapy, pioglitazone reduced postload glycemia and enhanced CISI more than metformin and gliclazide. In combination therapy, pioglitazone plus sulfonylurea reduced postload glycemia and increased CISI more than metformin plus sulfonylurea. Pioglitazone plus metformin also decreased postload glycemia and increased CISI more than gliclazide plus metformin.

CONCLUSIONS — Pioglitazone improves postload glycemia and CISI more than metformin or gliclazide when used as monotherapy or in combination therapy in patients with type 2 diabetes.

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From the ¹Department of Pathology and Medicine, Chair of Internal Medicine, University of Udine P. le S. Maria della Misericordia, Udine, Italy; ²Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana; and ³Takeda Europe R&D Centre, London, U.K.

Address correspondence and reprint requests to Dr. Meng H. Tan, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN 46285. E-mail: tan_meng@lilly.com.

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Abbreviations: AIP, atherogenic index of plasma; CISI, composite insulin sensitivity index; FFA, free fatty acid; FPG, fasting plasma glucose; IAUC_G, incremental area under the curve for glucose; IAUC_{INS}, incremental area under the curve for insulin; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Insulin resistance (decreased insulin sensitivity) and relative insulin deficiency are the core defects in type 2 diabetes (1). Traditionally, oral pharmacological therapy in type 2 diabetes has been directed toward improving glycemic control, with or without correcting one or both core defects of the disease. In 1997, a new class of oral antihyperglycemic medication called thiazolidinediones, or peroxisome proliferator-activated receptor- γ agonists, which reduce insulin resistance, was introduced. Currently, pioglitazone and rosiglitazone are two thiazolidinediones available for clinical use. They reduce plasma glucose and insulin in patients with type 2 diabetes, implying a reduction in their insulin resistance (2,3). Miyazaki et al. (4) have shown that pioglitazone increased total body glucose disposal and reduced hepatic glucose production, suggesting that the drug reduces both peripheral and hepatic insulin resistance (or enhanced both peripheral and insulin sensitivity).

The hyperinsulinemic-euglycemic clamp is recognized as the reference method for measuring insulin sensitivity (5). However, the clamp technique is complex, time-consuming, and costly (6) and is not used to assess large groups of patients. Two steady-state surrogates of insulin sensitivity suitable for use with large populations are the homeostasis model assessment of insulin sensitivity (HOMA-%S) and the quantitative insulin sensitivity check index (QUICKI) computed from fasting serum insulin and plasma glucose levels (7–9). They reflect insulin sensitivity mainly in the basal state.

To better reflect peripheral insulin sensitivity that plays a significant role in

glucose disposal in the postprandial state, Matsuda and DeFronzo (10) proposed a composite index of insulin sensitivity (CISI) that is computed from fasting and four postload glucose and insulin levels during an oral glucose tolerance test (OGTT). CISI reflects whole-body insulin sensitivity and correlates with the insulin sensitivity index determined by the hyperinsulinemic-euglycemic clamp technique in subjects with normal glucose tolerance ($r = 0.73$, $P < 0.0001$ [10]; $r = 0.74$, $P < 0.001$ [11]; and $r = 0.84$, $P < 0.001$ [12]) as well as in patients with type 2 diabetes ($r = 0.54$, $P < 0.0001$ [10]; $r = 0.67$, $P < 0.001$ [11]; and $r = 0.68$, $P < 0.001$ [12]).

The effect of pioglitazone (when used as monotherapy) on HOMA-%S and QUICKI in patients with type 2 diabetes has been previously reported (13–15). Its effect compared with placebo on CISI in patients with type 2 diabetes has also been reported (11). The effect of pioglitazone compared with other oral antihyperglycemic medications on CISI in patients with type 2 diabetes has not been reported. We extend previous findings by comparing the effect of pioglitazone with metformin and gliclazide (as monotherapy and in combination therapy) on CISI in patients with type 2 diabetes.

In current practice, most physicians use HbA_{1c} and fasting plasma glucose (FPG) when assessing glycemic control. Recently, there is a great interest in including postprandial glucose in assessing overall glycemic control for several reasons. First, HbA_{1c}, which reflects mean daily blood glucose, is influenced by both fasting and postprandial glucose, and we are in the postprandial state most of the day (16–18). Second, the 2-h postload glucose is a better marker of cardiovascular mortality than FPG (19). Third, there are many possible connections between postprandial events and the development of diabetes complications (20). In view of this, clinical practice guidelines developed by various groups now include target postprandial glucose values (21–24). The first available thiazolidinedione, troglitazone, decreased postprandial glucose in addition to fasting glucose (25). The effect of pioglitazone, compared with metformin or gliclazide, on postload glycemia has been reported (26–28). We now report the effect of pioglitazone compared with metformin and gliclazide in combination therapy on postload glycemia

during an OGTT in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS— Patients were from four multicenter, randomized, double-blind, double-dummy, parallel group clinical trials conducted in several European countries, including Australia, Canada, South Africa, and Israel. The two monotherapy studies compared pioglitazone versus metformin (study A, $n = 1,194$) (28) and pioglitazone versus gliclazide (study B, $n = 1,250$) (27). The two combination therapy studies compared pioglitazone plus sulfonylurea versus metformin plus sulfonylurea (study C, $n = 639$) (29) and pioglitazone plus metformin versus gliclazide plus metformin (study D, $n = 630$) (30).

Major inclusion criteria were HbA_{1c} 7.5–11%, age 35–75 years, inadequately treated type 2 diabetes with diet alone (monotherapy), inadequately treated type 2 diabetes with sulfonylurea or metformin therapy alone (combination studies), stable or worsening glycemic control for at least 3 months, and C-peptide level ≥ 1.5 ng/ml (combination studies only). Major exclusion criteria were previous use of oral antihyperglycemic medications (monotherapy studies); patients with type 1 diabetes or any history of ketoacidosis; history of myocardial infarction, transient ischemic attacks, or stroke in the previous 6 months; and pregnant or breast-feeding women. Other inclusion and exclusion criteria were outlined previously (27–30).

Each study involved a 52-week treatment period consisting of either a 12-week (pioglitazone versus metformin as monotherapy or in combination with sulfonylurea) or 16-week (pioglitazone versus gliclazide as monotherapy or in combination with metformin) forced titration period to a maximum tolerated dose of pioglitazone and the active comparator followed by a corresponding 36- or 40-week maintenance period at this maximum dose. For study C, patients were taking the following sulfonylureas: glibenclamide, gliclazide, glimepiride, glipizide, gliquidone, and tolbutamide. In the metformin plus sulfonylureas group ($n = 95$), 46.3% used glibenclamide, 22.1% used gliclazide, 21.1% used glimepiride, and 10.5% used other sulfonylureas. In the pioglitazone plus sulfonylureas group ($n = 105$), 42.9% used

glibenclamide, 25.7% used gliclazide, 18.1% used glimepiride, and 13.3% used other sulfonylureas. Further details of the study design and methods have been previously reported (27–30). The substudy analysis reported here focuses on patients who underwent OGTTs at selected sites during the four clinical trials. Sites were selected based on their resource capability (facility, staffing, etc.) and the ability to administer the tests to one-third of their patients.

Measurements

OGTTs (using a 75-g oral glucose load) were administered at baseline and at week 52. Blood samples were taken for the determination of plasma glucose and serum insulin at time 0, 30, 60, 90, 120, and 180 min after glucose load. HbA_{1c} and fasting serum lipids (including HDL cholesterol and triglycerides) were also measured (27–30). The atherogenic index of plasma (AIP) was calculated as the logarithm of the triglyceride-to-HDL cholesterol ratio (31). The incremental area under the curve for glucose (IAUC_G) and insulin (IAUC_{INS}) were calculated using the trapezoidal rule.

Insulin sensitivity was evaluated using CISI determined by the formula $\{10,000/\sqrt{[(\text{fasting glucose} \times \text{fasting insulin}) \times (\text{mean glucose} \times \text{mean insulin})]}\}$ during the OGTT (10). Data from 2- and 3-h OGTTs were analyzed for this study. For the 2-h OGTT, three- (0, 60, and 120 min) and five-point (0, 30, 60, 90, and 120 min) values were computed. For the 3-h OGTT, six-point (0, 30, 60, 90, 120, and 180 min) values were used. Because there were no differences in the CISI outcomes between the three methods of calculation, we report the 2-h, five-point CISI values in this article, as originally reported by Matsuda and DeFronzo (10).

Statistical analysis

Data from patients with both baseline and end point OGTT values were analyzed for this substudy. The analysis included the change from baseline to the last value (week 52) for both CISI and IAUC_G of plasma glucose ($\text{mmol} \cdot \text{h}^{-1} \cdot \text{l}^{-1}$) and IAUC_{INS} ($\text{pmol} \cdot \text{h}^{-1} \cdot \text{l}^{-1}$) in the OGTT. Each analysis was a single-slope ANCOVA with a model that included the treatment as a single factor and the baseline value of the dependent variable as a covariate (32). Pearson correlations were

Table 1—Baseline characteristics for OGTT patients

	Study A: PIO vs. MET		Study B: PIO vs. GLIC		Study C: PIO + SU vs. MET + SU		Study D: PIO + MET vs. GLIC + MET	
	PIO	MET	PIO	GLIC	PIO + SU	MET + SU	PIO + MET	GLIC + MET
n	195	187	129	113	105	95	54	62
Age (years)	55.9 ± 9.1	55.6 ± 9.0	55.8 ± 9.3	57.2 ± 9.2	60.4 ± 8.9	61.3 ± 7.5	54.2 ± 8.7	56.4 ± 8.1
BMI (kg/m ²)	30.7 ± 4.4	31.1 ± 4.8	31.8 ± 6.8	30.0 ± 4.6	30.9 ± 4.0	30.4 ± 4.6	33.4 ± 5.4	33.3 ± 6.8
Duration of diabetes (years)	4.2 ± 4.4	4.3 ± 4.1	3.9 ± 4.0	4.4 ± 4.2	8.0 ± 5.8	9.0 ± 6.7	7.4 ± 5.6	7.3 ± 5.4
Sex (F/M)	84/111	83/104	44/85	39/74	43/62	43/52	22/32	24/38

Data are means ± SD. GLIC, gliclazide; MET, metformin; PIO, pioglitazone; SU, sulfonylurea.

performed to determine whether there were associations between CISI and the specified glycemic and lipid parameters.

RESULTS— A total of 940 patients participated in the OGTTs ($n = 382$ in study A, $n = 242$ in study B, $n = 200$ in study C, and $n = 116$ study D). Patients were obese Caucasians diagnosed with type 2 diabetes for ~4 (monotherapy) and 7 (combination therapy) years before enrollment. Approximately 58% of the patients (across all studies) were male (Table 1). Primary efficacy and safety results for the original studies for the total groups have been previously reported (27–30). In this substudy, as in the parent studies, all therapies lowered HbA_{1c} and FPG when compared with their respective baselines (Table 2). Because the changes in serum lipids in the patients who had OGTT reflect those of the total intent-to-treat population, they are not reported here.

Postload glycemia and CISI changes Pioglitazone versus metformin (study A). In this study, there were no differences in the changes in HbA_{1c} and FPG between the pioglitazone and metformin groups. Pioglitazone had a significant reduction from baseline for fasting insulin and pioglitazone lowered fasting insulin significantly more than metformin (Table 2).

The mean IAUC_G and IAUC_{INS} for pioglitazone versus metformin therapy were previously reported (26). The adjusted least squares mean changes from baseline (with baseline as covariate) show that the postload glycemia was reduced more by pioglitazone than by metformin. Change from baseline to end point in IAUC_{INS} was smaller for pioglitazone compared with metformin.

Pioglitazone and metformin both increased CISI versus baseline (Fig. 1A), with pioglitazone increasing CISI more than metformin. There was no significant

correlation between CISI and HbA_{1c} at end point. There was an inverse correlation between weight and CISI ($r = -0.20$, $P < 0.01$), triglycerides and CISI ($r = -0.18$, $P < 0.01$), and AIP and CISI ($r = -0.28$, $P < 0.001$) at end point. There was no significant correlation between CISI and fasting free fatty acids (FFAs).

Pioglitazone versus gliclazide (study B). In this study, pioglitazone and gliclazide reduced HbA_{1c} and FPG from baseline, with no difference between the two groups. There was a significant difference between the two groups in fasting serum insulin (Table 2). Gliclazide increased fasting serum insulin from baseline, while pioglitazone decreased it.

The mean IAUC_G and IAUC_{INS} comparing pioglitazone and gliclazide therapy were previously reported (27). The adjusted least squares mean reduction from baseline indicated that pioglitazone lowered postload glycemia more than glicla-

Table 2—Glycemic parameters for OGTT patients

	Study A: PIO vs. MET		Study B: PIO vs. GLIC		Study C: PIO + SU vs. MET + SU		Study D: PIO + MET vs. GLIC + MET	
	PIO	MET	PIO	GLIC	PIO + SU	MET + SU	PIO + MET	GLIC + MET
n	194*	187	129	113	105	95	54	62
HbA _{1c} (%)								
Baseline	8.71 ± 0.07	8.70 ± 0.07	8.65 ± 0.08	8.46 ± 0.09	8.74 ± 0.09	8.68 ± 0.09	8.46 ± 0.12	8.47 ± 0.11
Change	-1.55 ± 0.064	-1.64 ± 0.065	-1.51 ± 0.070	-1.40 ± 0.075	-1.25 ± 0.097	-1.46 ± 0.102	-1.02 ± 0.137	-1.00 ± 0.128
FPG (mmol/l)								
Baseline	11.00 ± 0.18	11.48 ± 0.18	10.67 ± 0.21	10.40 ± 0.22	11.71 ± 0.23	11.79 ± 0.24	11.36 ± 0.35	11.51 ± 0.33
Change	-2.52 ± 0.145	-2.46 ± 0.148	-2.36 ± 0.156	-1.93 ± 0.167	-2.21 ± 0.259	-2.2 ± 0.272	-1.53 ± 0.330	-1.29 ± 0.308
FSI (pmol/l)								
Baseline	87.65 ± 4.15	94.17 ± 4.23	106.89 ± 8.14	100.20 ± 8.70	88.79 ± 4.72	95.95 ± 4.97	87.94 ± 8.15	99.62 ± 7.61
Change	-12.77 ± 2.40†	-4.59 ± 2.44	-26.39 ± 5.26†	22.81 ± 5.62	-6.52 ± 3.90	-1.92 ± 4.11	-14.04 ± 7.32‡	12.26 ± 6.83

Data are least square means ± SEM. All treatments were significantly different from baseline for HbA_{1c} and FPG, $P < 0.0001$. Only pioglitazone and gliclazide were significantly different from baseline for FSI, $P < 0.0001$. *One patient did not have both baseline and end point efficacy data and was therefore not included in the analysis. † $P < 0.001$, ‡ $P < 0.05$ between treatments. FSI, fasting serum insulin; GLIC, gliclazide; MET, metformin; PIO, pioglitazone; SU, sulfonylurea.

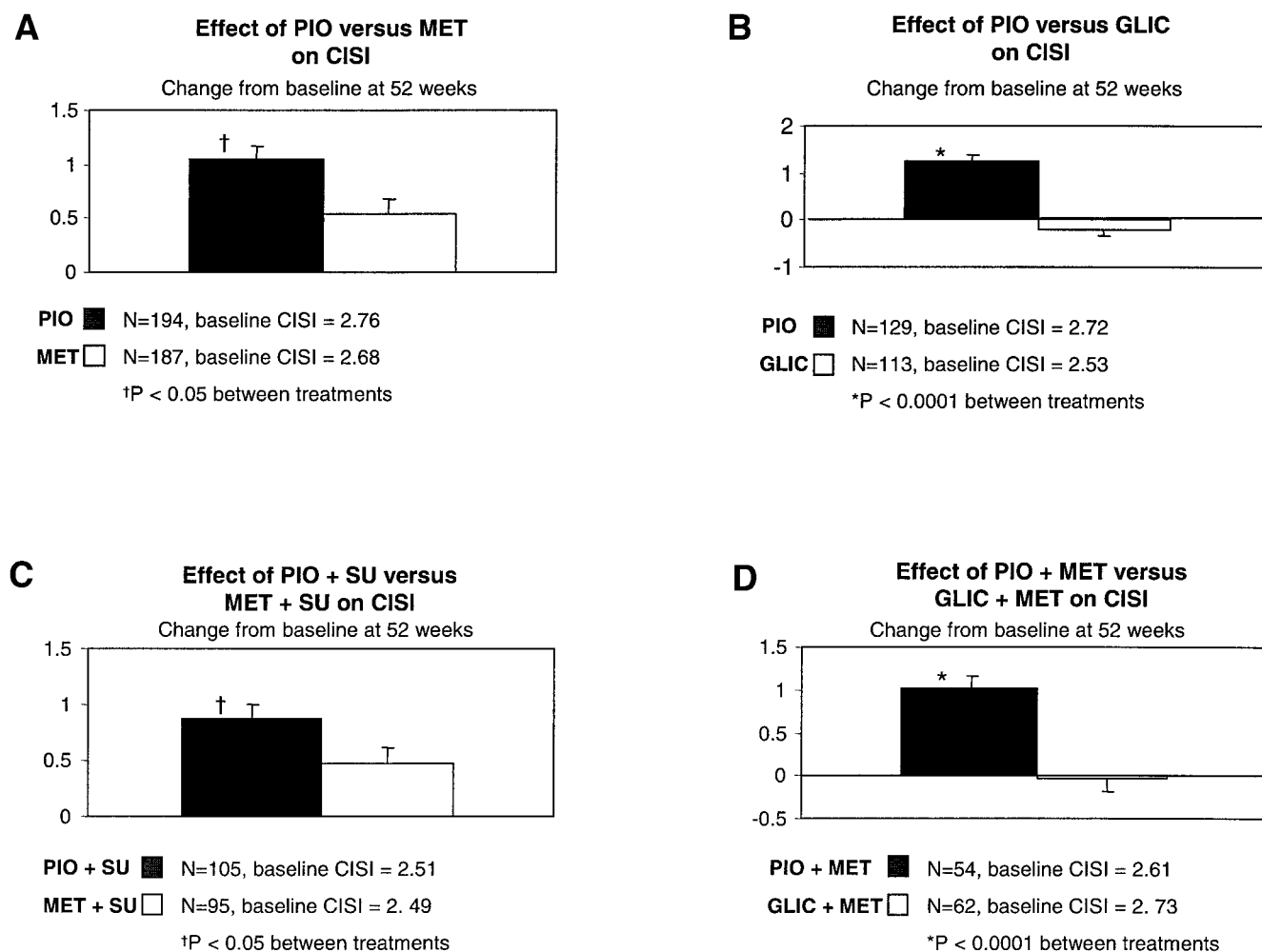


Figure 1—Composite graphs of least square mean changes \pm SEM from baseline to 52 weeks in CISI for monotherapy (A and B) and combination (C and D) studies. GLIC, gliclazide; MET, metformin; PIO, pioglitazone; SU, sulfonylurea.

zide. Gliclazide increased IAUC_{INS} more than pioglitazone.

Pioglitazone therapy increased CISI versus baseline, whereas gliclazide therapy did not. The treatment effect favored pioglitazone (Fig. 1B). There was no significant correlation between CISI and HbA_{1c} at end point. However, there was an inverse correlation between weight and CISI ($r = -0.42, P < 0.001$), triglycerides and CISI ($r = -0.33, P < 0.001$), AIP and CISI ($r = -0.42, P < 0.001$), and fasting FFAs and CISI ($r = -0.18, P = 0.04$) at end point.

Pioglitazone plus sulfonylurea versus metformin plus sulfonylurea (study C). In this study, both groups had comparable reductions in HbA_{1c} and FPG from baseline. The decreases in fasting serum insulin from baseline and between groups were not different (Table 2).

Pioglitazone plus sulfonylurea ther-

apy decreased IAUC_G ($-2.8 \text{ mmol} \cdot \text{h}^{-1} \cdot \text{l}^{-1}$) compared with baseline ($P < 0.001$), whereas metformin plus sulfonylurea therapy did not ($0.0 \text{ mmol} \cdot \text{h}^{-1} \cdot \text{l}^{-1}$). The decrease was greater with pioglitazone plus sulfonylurea than with metformin plus sulfonylurea (difference = -2.8 [95% CI -4.3 to -1.3], $P < 0.001$). There was no difference in the change in IAUC_{INS} between the pioglitazone plus sulfonylurea ($-18.7 \text{ pmol} \cdot \text{h}^{-1} \cdot \text{l}^{-1}$) and metformin plus sulfonylurea ($21.5 \text{ pmol} \cdot \text{h}^{-1} \cdot \text{l}^{-1}$) groups (difference = -40.2 [95% CI -104.0 to 22.9]).

Both pioglitazone plus sulfonylurea and metformin plus sulfonylurea therapy increased CISI from baseline; the increase was greater with the pioglitazone plus sulfonylurea group (Fig. 1C). There was no significant correlation between CISI with HbA_{1c} at end point. There was an inverse correlation between weight and CISI ($r =$

$-0.21, P < 0.05$), triglycerides and CISI ($r = -0.26, P < 0.01$), and AIP and CISI ($r = -0.31, P < 0.01$) at end point. There was no significant correlation between fasting FFAs and CISI.

Pioglitazone plus metformin versus gliclazide plus metformin (study D). In this study, both groups had comparable reductions in HbA_{1c} and FPG from baseline. Although the changes from baseline were not significant, pioglitazone plus metformin decreased fasting serum insulin, while gliclazide plus metformin increased fasting serum insulin. The difference between the two groups was significant (Table 2).

The decrease in IAUC_G was greater with pioglitazone plus metformin than with gliclazide plus metformin (difference = -2.9 [95% CI -4.7 to -1.1]). Pioglitazone and metformin also decreased the IAUC_{INS} ($-43.0 \text{ pmol} \cdot \text{h}^{-1} \cdot$

l^{-1}), whereas gliclazide plus metformin increased it by ($102.6 \text{ pmol} \cdot \text{h}^{-1} \cdot l^{-1}$). The difference between the two treatments was significant (difference = $-145.6 \text{ pmol} \cdot \text{h}^{-1} \cdot l^{-1}$ [95% CI -286.4 to -4.6]).

Pioglitazone plus metformin increased CISI more than gliclazide plus metformin (Fig. 1D). CISI was not correlated with HbA_{1c} at end point. There was an inverse correlation between weight and CISI ($r = -0.45$, $P < 0.001$) at end point. There were no significant correlations between triglycerides, AIP, or FFAs and CISI.

Weight changes

In the pioglitazone versus metformin study, the mean weight change in the pioglitazone group (2.02 kg) was higher than in the metformin group (-2.6 kg). In the pioglitazone versus gliclazide study, there was no difference (pioglitazone group 3.3 kg and gliclazide group 2.7 kg). In the pioglitazone plus sulfonylurea versus metformin plus sulfonylurea study, the mean weight change in the pioglitazone plus sulfonylurea group (2.6 kg) from baseline was different from that of the metformin plus sulfonylurea group (-1.5 kg), whereas in the pioglitazone plus metformin versus gliclazide plus metformin study, there was no difference (pioglitazone plus metformin 1.3 kg and gliclazide plus metformin 0.6 kg).

CONCLUSIONS— Our report compares the effect of pioglitazone with metformin and gliclazide (as monotherapy and combination therapy) on CISI and postload glucose excursion measured during an OGTT in a large number of patients ($n = 940$) with type 2 diabetes. In monotherapy, pioglitazone, metformin, and gliclazide all improve glycemic control (HbA_{1c} and FPG), but their effects on postload glycemia are different. Pioglitazone (mono and combination therapy) consistently reduces IAUC_G with minimal change in IAUC_{INS} . Metformin modestly reduces IAUC_G in monotherapy but not in combination therapy and in both cases is associated with an increase in IAUC_{INS} . Gliclazide does not influence IAUC_G but increases IAUC_{INS} in both mono and combination therapy. Our findings extend those previously reported (26–30).

With the difference in plasma glucose, one would anticipate a difference in HbA_{1c} between the two groups. There are

two possible explanations for why there was no difference in HbA_{1c} between the treatment groups despite a difference in the postload glycemia in this study. First, the two monotherapy studies (studies A and B) were designed to demonstrate noninferiority, and both did (27,28). The two combination studies (studies C and D) were designed to detect a difference of 0.35% in HbA_{1c} , and neither did (the treatments had comparable end points) (29,30). The patients reported in this article represent a subset (patients who had an OGTT) from each of the four studies. One would not expect a different outcome with regard to HbA_{1c} in these subsets from that observed in the full set of each of the studies. Second, it has been reported that despite the differences in postprandial hyperglycemia between patients who were on repaglinide and those on glyburide, the HbA_{1c} of the two groups were similar (33).

HbA_{1c} correlates with mean daily blood glucose. Fasting and morning postload plasma glucose are only part of these daily values. It is possible that the mean daily glycemia was not different between the treatments, while morning postprandial glycemia, as suggested by the postload glucose excursions in the OGTT, was different. Although not a physiological test, the OGTT is accepted as a standardized test to diagnose impaired glucose tolerance and type 2 diabetes. It is also possible that the postprandial blood glucose values after mixed meals differ from the postload glucose values at equivalent time points. Wolever et al. (34) reported a strong correlation between the mean plasma glucose 2 h after the administration of a test meal and the mean 2-h plasma glucose during an OGTT. However, there were nine diabetic subjects who were studied, and their 2-h postmeal blood glucose values were almost 100 mg/dl lower than the 2-h post-glucose load values. Whether pioglitazone, sulfonylurea, and metformin affect postmeal blood glucose and post-glucose load values differently is not known. If they do, this may affect the HbA_{1c} outcome.

We show that pioglitazone, metformin, and gliclazide therapy have different effects on CISI. When compared with baseline, both pioglitazone and metformin increased CISI, with pioglitazone having a greater effect. In contrast, whereas pioglitazone increased CISI, gliclazide did not. In combination therapy,

pioglitazone plus sulfonylurea and metformin plus sulfonylurea both increased CISI from baseline, but the increment was greater with pioglitazone plus sulfonylurea. Similarly, pioglitazone plus metformin increased CISI from baseline, whereas gliclazide plus metformin decreased it.

Sulfonylureas may differ in their effects on insulin secretion. In study C, different sulfonylureas were used in combination with either pioglitazone or metformin. It is, therefore, possible that the CISI may be affected differently in the two groups if the proportions of sulfonylureas used in the two groups were different. As the percentage of patients using the various sulfonylureas is similar in both groups, the different effect of the sulfonylureas on insulin stimulation should be comparable.

The increase in CISI associated with pioglitazone therapy suggests that it enhances whole-body insulin sensitivity in patients with type 2 diabetes. By using the OGTT, we have extended in a large group of patients the findings of Miyazaki et al. (4), who used the hyperinsulinemic-euglycemic clamp technique in a small group of patients ($n = 23$) to show the effect of pioglitazone treatment on whole-body insulin sensitivity. We also extend the findings that pioglitazone therapy, compared with placebo, increased whole-body insulin sensitivity (11).

There was no correlation between HbA_{1c} and CISI. One possible reason is the temporal dissociation between CISI and HbA_{1c} at end point. However, there was a negative correlation between fasting plasma triglycerides and AIP. Hypertriglyceridemia is inversely associated with insulin sensitivity. Recently, it was shown the AIP is inversely correlated with insulin sensitivity (35). Furthermore, in the pioglitazone versus gliclazide treatment study, CISI was negatively correlated with fasting plasma FFA. Elevated plasma FFA is associated with insulin resistance. Usually, when patients with type 2 diabetes gain weight their insulin sensitivity decreases. In our studies, weight gain, as a result of treatment, was negatively correlated with an increase in insulin sensitivity, as measured by CISI. Miyazaki et al. (4,11) reported similar findings in patients with type 2 diabetes.

The relationship between postprandial glycemia and cardiovascular mortality has been reported (19). Possible

metabolic perturbations during the postprandial period that can lead to increased risk for cardiovascular disease have been proposed (20). Controlling postprandial hyperglycemia in patients with type 2 diabetes is associated with a reduction in their carotid intimal thickness (33). In addition, a panel of experts recently concluded that "postprandial hyperglycemia is a risk indicator for micro- and macrovascular complications, not only in patients with type 2 diabetes but also in those with impaired glucose tolerance" (36). The STOP-NIDDM study (37) reported that acarbose reduces cardiovascular outcomes by reducing postload glucose in patients with impaired glucose tolerance. We report here that pioglitazone not only decreased FPG, but also postload glucose.

In closing, pioglitazone reduces postload hyperglycemia while simultaneously improving insulin sensitivity better than metformin and gliclazide in patients with type 2 diabetes. Long-term studies to compare overall improvement in hyperglycemia only versus postprandial hyperglycemia and insulin sensitivity on cardiovascular outcomes in patients with type 2 diabetes would be of great interest. A study is underway to determine whether pioglitazone therapy in patients with type 2 diabetes makes a difference in their cardiovascular outcomes (38).

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