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Pioglitazone elicits long-term improvements in insulin sensitivity in patients with type 2 diabetes: comparisons with gliclazide-based regimens

Abstract *Aims/hypothesis:* Recent studies have demonstrated that pioglitazone (PIO) has beneficial effects on insulin sensitivity compared with placebo in patients with type 2 diabetes. The effects of PIO and gliclazide (GLIC)-based therapy on insulin sensitivity have not previously been directly compared. This analysis aimed to compare the effects of 52 weeks of treatment with PIO (30–45 mg/day) and GLIC (80–320 mg/day), both titrated to maximum tolerable doses, as monotherapy or in combination with metformin (MET), on insulin sensitivity and lipid parameters known to be related to insulin sensitivity in patients with type 2 diabetes. *Methods:* We performed an analysis of 1,880 patients with inadequately controlled type 2 diabetes (HbA$_1$c 7.5–11.0%) who were participants in two parallel-group, double-blind, double-dummy, randomised, multi-centre, clinical trials. Measures of insulin sensitivity and lipids were assessed. *Results:* The PIO- and GLIC-based regimens produced similar levels of glycaemic control (HbA$_1$c). In both trials, insulin sensitivity as assessed using the homeostasis model assessment was improved in patients receiving PIO, but decreased in those receiving GLIC (mean change, baseline to endpoint: PIO 15.5, GLIC −15.6; $p<0.001$ and PIO+MET 18.9, GLIC+MET −5.3; $p<0.001$). Improvements in the atherogenic index of plasma (mean change: PIO −0.17, GLIC −0.08; $p<0.001$ and PIO+MET −0.17, GLIC+MET −0.02; $p<0.001$), triglycerides (mean change, mmol/l: PIO+MET −0.62, GLIC+MET −0.22; $p<0.001$) and NEFA (mean change, mmol/l: PIO+MET −0.12, GLIC+MET −0.05; $p<0.001$) were greater in PIO-treated patients than in patients receiving GLIC. *Conclusions/interpretation:* The PIO-based regimens resulted in improved insulin sensitivity and more favourable insulin sensitivity-related lipid profiles compared with the GLIC-based regimens. These benefits may be important in the management of cardiovascular risk in patients with type 2 diabetes.

Keywords Gliclazide · Homeostasis model assessment · Insulin resistance · Pioglitazone · Type 2 diabetes

Abbreviations AIP: Atherogenic index of plasma · GLIC: Gliclazide · HOMA: Homeostasis model assessment · MET: Metformin · PIO: Pioglitazone · QUICKI: Quantitative insulin sensitivity check index

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Introduction

Sulphonylureas, such as gliclazide (GLIC), are oral anti-hyperglycaemic medications that are used in patients with type 2 diabetes when dietary and exercise modifications fail to achieve glycaemic targets. Sulphonylureas improve glycaemic control by directly stimulating insulin secretion from pancreatic beta cells [1]. Patients receiving sulphonylureas often achieve an initial improvement in glycaemic control; however, this drug class has been associated with secondary failure and does not directly address insulin resistance as a core defect of type 2 diabetes [2].

Thiazolidinediones, such as pioglitazone (PIO), improve glycaemic control by increasing insulin sensitivity in the liver and peripheral tissues [3]. PIO is an agonist for the peroxisome proliferator-activated receptor-γ, which regulates multiple genes controlling carbohydrate and lipid metabolism [4]. In a recent 52-week head-to-head study, PIO monotherapy produced a reduction in HbA$_1$c similar to that observed with GLIC (1.4–1.5%), while producing significantly greater reductions in fasting plasma glucose,

triglycerides, and HDL cholesterol [5]. In a companion study, the addition of either agent to pre-existing metformin (MET) therapy produced similar decreases in HbA$_1$c (1.2–1.4%) and fasting plasma glucose [6]. PIO is now approved in Europe for glycaemic control in patients with type 2 diabetes, both as monotherapy (in metformin-intolerant patients) and as a component of combination therapy with sulphonylureas or MET.

Insulin resistance and diabetic dyslipidaemia are associated with increased cardiovascular risk [7–11]. Despite similar efficacy with respect to glycaemic control (HbA$_1$c), PIO and GLIC may affect insulin resistance and diabetic dyslipidaemia differently because of their different mechanisms of action. The aim of these analyses was to compare the effects of PIO and GLIC on insulin sensitivity, beta cell activity and selected lipid parameters that are known to modulate insulin sensitivity in adults with type 2 diabetes, so as to extend the findings previously reported by the two clinical trials described above [5, 6].

Materials and methods

Patients and study design The current report describes analyses of the results from two 52-week, randomised, double-blind, double-dummy, multicentre clinical trials. In the monotherapy study [5], 1,250 patients with inadequately controlled type 2 diabetes received either PIO (n=624) or GLIC (n=626). In the combination therapy study [6], 630 patients whose type 2 diabetes was inadequately treated with MET received either PIO+MET (n=317) or GLIC+MET (n=313). Both studies had a 16-week forced dose-titration phase and a 36-week maintenance phase. In both studies, patients were titrated to the maximum tolerated

Fig. 1 Disposition of patients screened. **a** Monotherapy study. **b** Combination therapy study
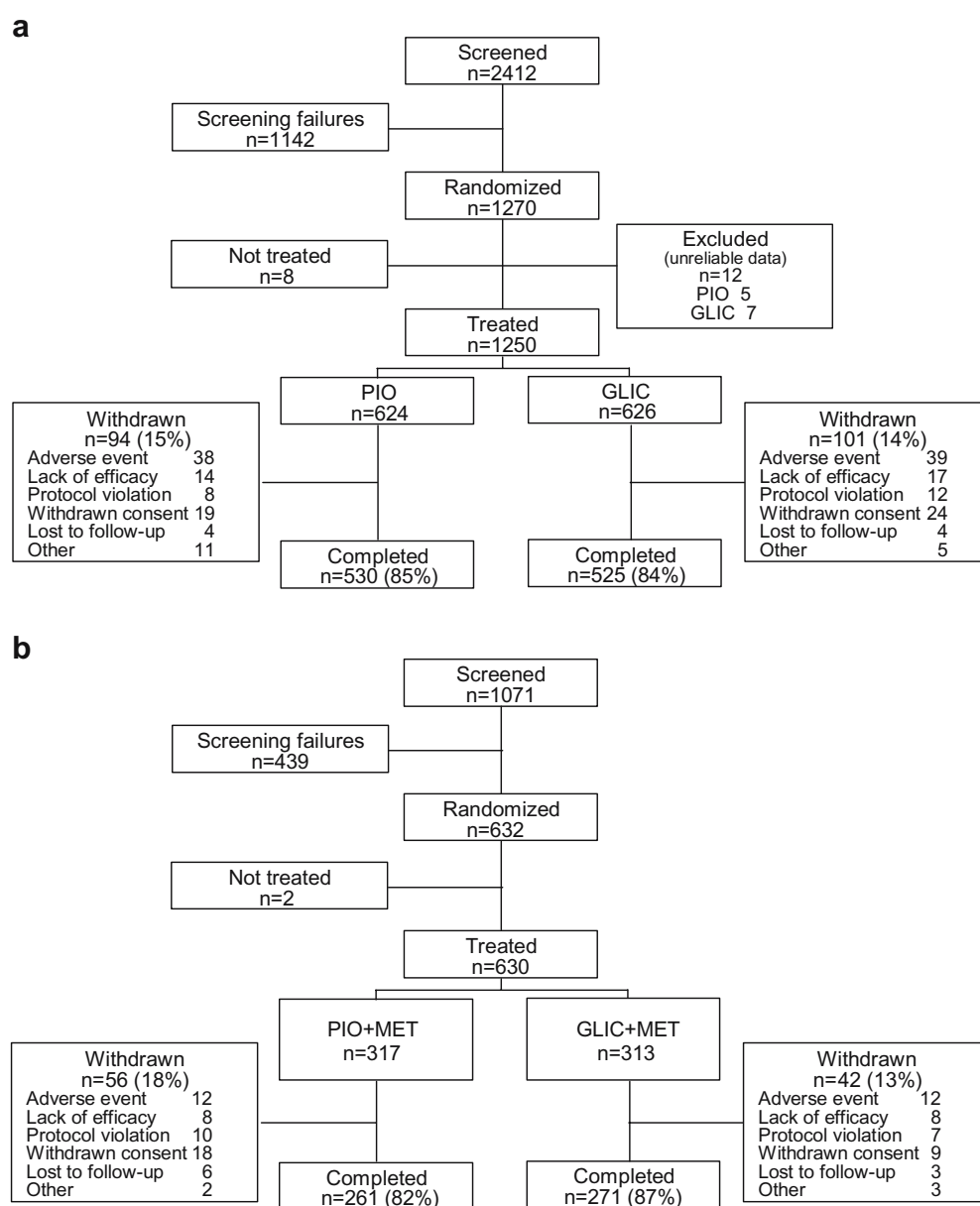
dose, not to exceed 45 mg for PIO or 160 mg twice daily for GLIC. In the combination study, MET was administered at the pre-study dose, which was ≥50% of the maximum recommended dose or the maximum tolerated dose (whichever was lower). The dose of MET remained unchanged throughout the study.

Men and women aged 35–75 years were eligible for the monotherapy study if they had type 2 diabetes that was inadequately treated by diet alone (HbA$_1$c ≥7.5 to ≤11.0%), and were eligible for the MET combination study if they had type 2 diabetes that was inadequately managed (HbA$_1$c ≥7.5 to ≤11.0%) with MET alone (at ≥50% of the maximum recommended dose or at the maximum tolerated dose for ≥3 months). Additional inclusion criteria included stable or worsening glycaemic control over a period of at least 3 months. For the combination study, an additional inclusion criterion indicated that fasting serum C-peptide levels must be ≥0.50 nmol/l (≥1.5 ng/ml). Patients who had previously received glucose-lowering drugs were excluded from the monotherapy study. Previous treatment with insulin, a sulphonylurea or a thiazolidinedione resulted in exclusion from the combination therapy study. Patient disposition for each trial is shown in Fig. 1. The most common reason for screening failure was that a patient's HbA$_1$c value was outside the range specified in the inclusion criteria. A similar proportion of patients in each treatment group (>80%) completed the trial.

The ethics committee for each site approved each study protocol and all patients gave written informed consent prior to study entry. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice of the European Community.

Efficacy measurements The primary endpoint for each trial was HbA$_1$c. Secondary endpoints included fasting plasma glucose, fasting serum insulin and lipids. All data provided in the present analyses were derived from prospectively defined trial endpoints.

Blood samples for assessment of fasting serum insulin and fasting plasma glucose were collected at baseline and Weeks 4, 8, 12, 16, 24, 32, 42 and 52 as previously de-scribed for these trials [5, 6]. The values obtained were used for the calculation of homeostasis model assessment-S (HOMA-%S, which is a surrogate for insulin sensitivity) and HOMA-%B (a surrogate for beta cell activity) [12, 13]. Patients fasted the night prior to blood sampling and did not take their morning dose of study drug until after blood sampling. Values for HOMA-%S and HOMA-%B were calculated using a computer program from the Diabetes Research Laboratories (Oxford, UK) [13]. Values for the quantitative insulin sensitivity check index (QUICKI, another surrogate for insulin sensitivity) were calculated as 1/($\log_{10}$ fasting serum insulin+$\log_{10}$ fasting plasma glucose) [14]. Triglycerides, NEFAs and HDL cholesterol were assessed at baseline and Weeks 8, 16, 24, 32, 42 and 52 as previously described [5, 6]. The atherogenic index of plasma (AIP) was calculated as $\log_{10}$(triglycerides : HDL cholesterol) [15].

Statistical analysis The monotherapy and combination therapy studies were analysed separately. Repeated measures analysis of variance was used to compare the effects of PIO-based therapy with those of GLIC-based therapy. The repeated measures model employed an unstructured covariance matrix and included treatment, time, treatment–time interaction and the baseline value of the dependent variable as independent variables. Treatment and time were fixed effects. Least-squares means from the model were used to estimate the treatment effects at each time point. The least-squares means of the treatment groups were then compared at each time point using the Student's *t*-test. A *p* value of less than 0.05 was considered statistically significant. Results are expressed as means±SD for baseline values and as means±SEM for least-squares means.

Results

Baseline patient characteristics were generally similar for the PIO and GLIC groups in each trial (as previously published [5, 6]) and are provided in Table 1. Each patient population was representative of a type 2 diabetes cohort

Table 1 Baseline clinical characteristics

	PIO (*n*=624)	GLIC (*n*=626)	PIO+MET (*n*=317)	GLIC+MET (*n*=313)
Age (years)	56±9.5	56±9.6	56±9.2	57±9.0
Gender (% male)	61.4%	61.7%	50.8%	49.2%
Duration of diabetes at study start (years)	2.8±3.8	3.0±3.8	5.8±5.1	5.5±5.1
Body weight (kg)	90.7±18.6	88.1±16.9	91.8±16.2	92.7±17.4
BMI (kg/m^2)	31.7±6.0	30.6±5.1	32.6±5.0	32.6±5.8
HbA$_1$c (%)	8.7±1.0	8.7±1.1	8.7±1.0	8.5±0.9
Fasting plasma glucose (mmol/l)	11.1±2.8	11.2±2.9	11.8±3.1	11.3±2.6
Fasting plasma insulin (pmol/l)	104.2±81.9	103.5±114.0	106.3±81.3	104.2±69.9
C-peptide (nmol/l)	1.3±0.5	1.3±0.5	1.2±0.4	1.2±0.4
Triglycerides (mmol/l)	2.6±2.1	2.8±3.2	2.9±1.9	2.8±1.9
NEFA (mmol/l)	0.65±0.26	0.64±0.33	0.73±0.25[a]	0.73±0.26[a]

The data shown are means±SD.
[a] *n*=89

with obesity (as indicated by BMI) and hyperinsulinaemia (based on fasting serum insulin measurements). Patients in the combination study had a longer duration of diabetes. Patients randomised to PIO monotherapy had higher mean body weight and BMI than patients randomised to GLIC monotherapy ($p<0.05$).

Insulin sensitivity assessments At endpoint, the PIO and PIO+MET therapies had increased HOMA-%S relative to baseline values, whereas GLIC and GLIC+MET had decreased HOMA-%S (Fig. 2a, b). In both studies, HOMA-%S was significantly higher in the PIO group than in the corresponding GLIC group at endpoint ($p<0.001$). In the PIO and PIO+MET groups, HOMA-%S had increased to values greater than baseline by Week 4 and remained elevated throughout the duration of the study ($p<0.001$ for all time points). In contrast, both GLIC and GLIC+MET resulted in decreases in HOMA-%S relative to baseline at

Week 4 and thereafter ($p<0.001$ for all time points). In the PIO and PIO+MET groups, increases in QUICKI paralleled those of HOMA-%S; GLIC and GLIC+MET produced smaller increases in QUICKI (Fig. 2c, d). Treatment differences between PIO and GLIC were significantly different for both assessments of insulin sensitivity ($p<0.001$ for monotherapy and combination therapy) at all post-baseline time points.

Assessment of beta cell activity PIO, GLIC, PIO+MET and GLIC+MET all produced significant increases in HOMA-%B (surrogate for beta cell activity) relative to baseline values (Fig. 2e, f). GLIC-based regimens resulted in more rapid and greater increases in HOMA-%B, while patients receiving PIO or PIO+MET experienced more gradual and smaller increases in HOMA-%B. Although HOMA-%B values decreased in the two GLIC groups following the titration period, they remained above baseline values and

Fig. 2 Time courses of HOMA-%S (**a**, **b**), QUICKI (**c**, **d**), and HOMA-%B (**e**, **f**). Data from the monotherapy study are shown in the *column on the left*, while data from the combination study are shown in the *column on the right*. The data points are means±SEM. *$p<0.001$ vs GLIC; †$p<0.001$ vs GLIC+MET. PIO, *filled circles*; GLIC, *open circles*; PIO+MET, *filled inverted triangles*; GLIC+MET, *open inverted triangles*
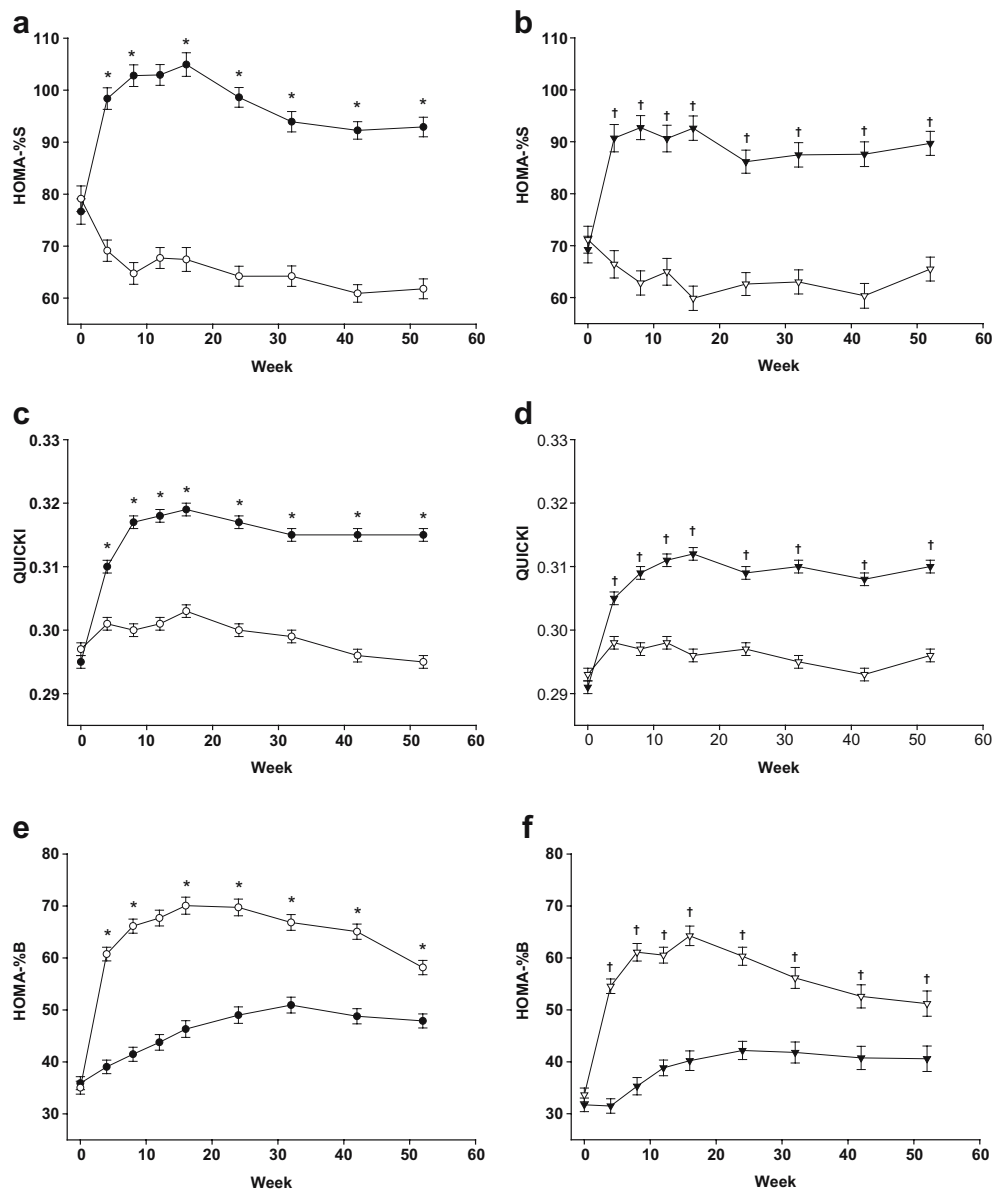
Fig. 3 Time courses of AIP (**a**, **b**) and triglycerides (**c**). Data from the monotherapy study are shown in the *column on the left*, while data from the combination study are shown in the *column on the right*. Time courses of changes in levels of triglycerides during the monotherapy study have been published previously [5]. The data points are means±SEM. *$p<0.001$ vs GLIC; †$p<0.001$ vs GLIC+ MET; ‡$p<0.05$ vs GLIC+MET. PIO, *filled circles*; GLIC, *open circles*; PIO+MET, *filled inverted triangles*; GLIC+MET, *open inverted triangles*
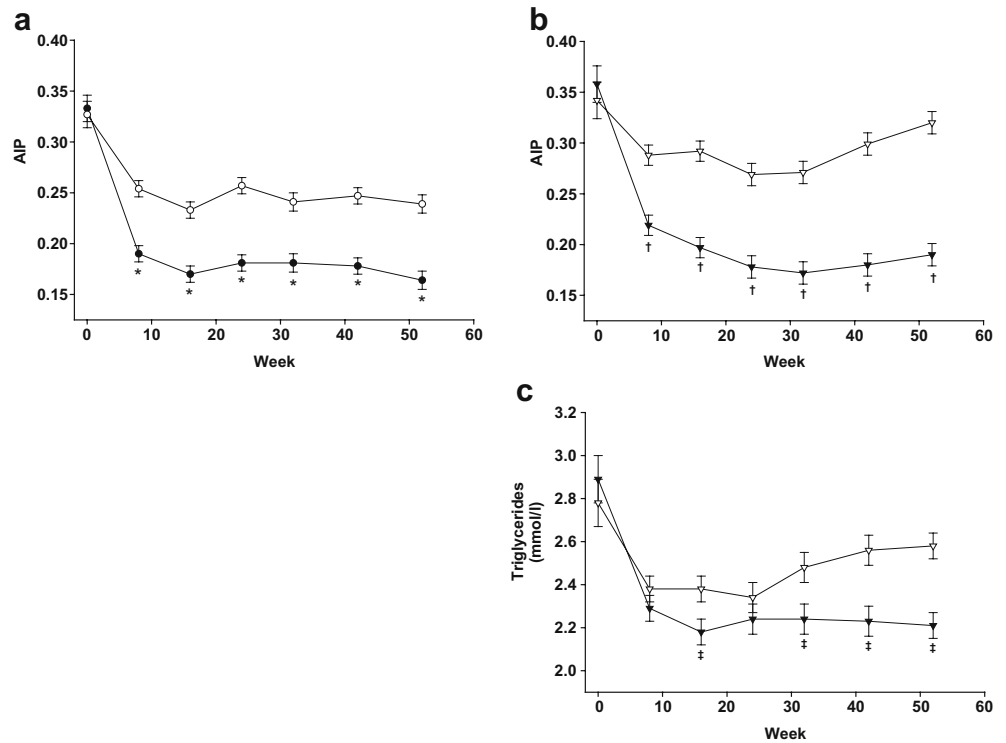
were significantly higher than those in the corresponding PIO group for the duration of the study.

Lipids All four treatment groups demonstrated significantly reduced AIP values relative to baseline from Week 4 through Week 52 ($p<0.001$ for all groups; Fig. 3a, b). The reductions observed in the PIO and PIO+MET groups were significantly greater than those in the corresponding GLIC group at all time points. Time courses for changes in triglycerides and NEFA during the monotherapy study have been reported previously [5]. In the combination study, triglyceride levels were acutely reduced compared with baseline by both therapies (Fig. 3c). Triglyceride levels were significantly lower in the PIO+MET group than in the GLIC+MET group at Week 16 and from Week 26 through Week 52, as triglyceride levels tended to increase toward baseline levels in the GLIC+MET group. Both PIO+MET and GLIC+MET produced significant reductions in NEFA

levels from baseline to endpoint (0.73 mmol/l to 0.61 mmol/l for PIO+MET, $p<0.0001$; 0.73 mmol/l to 0.68 mmol/l for GLIC+MET, $p=0.021$); these reductions were significantly greater in the PIO+MET group (−16.4%) than in the GLIC+MET group (−6.8%, $p=0.044$).

Safety The time course of body weight for each treatment group is shown in Fig. 4. Each regimen resulted in weight gains from baseline to endpoint. Patients receiving PIO were heavier at baseline than those receiving GLIC. By Week 4, body weights were no longer different between the two groups and remained similar until Week 32. At Weeks 42 and 52, patients on PIO had higher body weights than those on GLIC. Patients receiving PIO+MET also gained slightly more weight than those receiving GLIC+MET. Those in the GLIC+MET group were heavier than patients in the PIO+MET group at baseline through Week 16, but not at later time points in the study.

Fig. 4 Time courses of changes in body weight during the monotherapy study (**a**) and the combination study (**b**). The data points are means±SEM. PIO, *filled circles*; GLIC, *open circles*; PIO+MET, *filled inverted triangles*; GLIC+MET, *open inverted triangles*
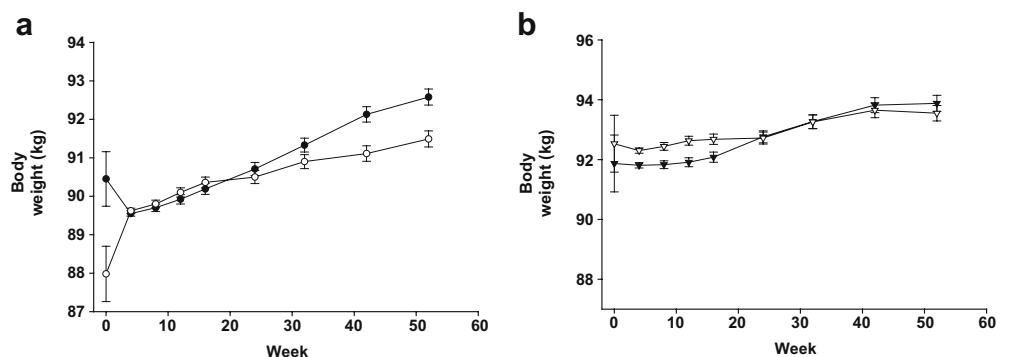
Discussion

PIO and GLIC have been shown to provide similar degrees of glycaemic control (i.e. reductions in HbA$_1$c) when compared as monotherapies and in combination with MET [5, 6]. The present analysis extends previous observations by comparing the effects of these oral antihyperglycaemic medications on insulin sensitivity, insulin secretion activity of the beta cells, and lipid parameters that are associated with insulin sensitivity in adults with type 2 diabetes, with an emphasis on the relative time courses of these changes. We found that PIO-based regimens enhanced insulin sensitivity and produced a more favourable lipid profile compared with GLIC-based monotherapy or combination therapy.

In this analysis, HOMA-%S and QUICKI were employed as surrogates for insulin sensitivity. Due to the large numbers of patients studied in these trials, the use of more sophisticated and invasive measures (e.g. euglycaemic–hyperinsulinaemic clamps, frequently sampled IVGTTs) was not feasible. As measures of insulin sensitivity/resistance, HOMA-%S and QUICKI have both shown strong correlations with euglycaemic–hyperinsulinaemic clamp studies [14, 16–18].

Compared with patients on GLIC, insulin sensitivity was significantly increased at the first point of measurement (Week 4) in patients receiving monotherapy or combination therapy with PIO and remained elevated throughout the duration of the 52-week study. In addition, PIO-based regimens significantly reduced fasting serum insulin levels, C-peptide levels, and 32–33 split pro-insulin levels over the 52-week time course, while GLIC-based regimens were associated with net increases in each of these measures [5]. These data are consistent with previous studies investigating the effects of PIO monotherapy on insulin sensitivity [19, 20], and highlight an important difference between the mechanisms of action of PIO (increasing insulin sensitivity) and GLIC (increasing insulin secretion). This distinction may be important in the long-term care of patients with type 2 diabetes given the association of insulin resistance with the development of cardiovascular complications in this population [8–11].

Patients receiving PIO-based regimens demonstrated more moderate increases in HOMA-%B than those receiving GLIC-based therapies; however, patients in the PIO groups did not exhibit a waning of effect after the titration phase of the study. The use of HOMA-%B in patients treated with secretagogues is acceptable, provided that the measure is interpreted as an assessment of beta cell activity as opposed to beta cell health or pathology [12]. The PIO-based therapies appeared to have beneficial effects on both of the core defects of type 2 diabetes, insulin resistance (as assessed by HOMA-%S and QUICKI) and beta cell activity (as assessed by HOMA-%B). Improving both of these components of insulin homeostasis in concert could be more beneficial than improving either component alone [21].

PIO has previously been found to elicit beneficial lipid-related effects, reducing triglyceride and NEFA levels while raising HDL cholesterol levels [5, 6]. In the present ana-lyses, PIO-based treatments were associated with early reductions in AIP and triglyceride levels; these parameters were decreased to a significantly greater extent in the PIO groups compared with the corresponding GLIC group. Of additional interest are the parallel time courses of improvements in HOMA-%S and favourable alterations in lipids (reductions in AIP, triglycerides and NEFA) observed in the PIO monotherapy and combination therapy groups. These findings are consistent with the established relationship between triglycerides and insulin resistance [22–25]. Moreover, they are in agreement with previous reports that reductions in elevated circulating NEFA levels result in improved insulin sensitivity in patients with type 2 diabetes [26, 27] due to the capacity of NEFA to reduce glucose transport and phosphorylation in human skeletal muscle [28, 29]. As AIP is inversely correlated with HOMA-%S [30], enhanced insulin sensitivity would be expected to be associated with a decreased AIP, as observed in the present analyses.

After 52 weeks of therapy, PIO and PIO+MET were associated with slight, but significant increases in LDL cholesterol levels and substantially greater increases in HDL cholesterol levels compared with GLIC and GLIC+MET, respectively [5, 6]. Consequently, total cholesterol/HDL cholesterol ratios were significantly reduced in both PIO groups. The ratio of total cholesterol : HDL cholesterol was demonstrated to be a useful and simple index of the risk of ischaemic heart disease in men during the Quebec Cardiovascular Study [31]. Similarly, AIP is an independent predictor of angiographically documented coronary artery disease [32]. By inference, a reduction in AIP and/or the total cholesterol : HDL cholesterol ratio may lower overall cardiovascular risk. As AIP is inversely correlated with LDL particle size [15], the reductions in AIP suggest that PIO-based therapy may have caused a shift from small, dense LDL particles to larger, less atherogenic LDL particles, which would also explain the slight increases in LDL cholesterol levels. Consistent with this interpretation, PIO has previously been shown to increase LDL particle size [33].

During the study, mean body weight increased in all treatment groups. Our findings are consistent with previous reports on PIO and sulphonylurea usage [34, 35]. In patients with type 2 diabetes treated with PIO, weight gain and enhancement of insulin sensitivity have been associated with increased subcutaneous fat and simultaneous reductions in visceral abdominal fat [36]. This redistribution of fat may explain the concomitant weight gain and increased insulin sensitivity observed in these patients [34]. Of interest, despite gaining weight when treated with pioglitazone, patients in the present studies exhibited improved glycaemic control, improved insulin sensitivity, decreased triglycerides and increased HDL cholesterol levels.

In the Quebec Cardiovascular Study, which investigated a general population, hyperinsulinaemia in combination with high triglycerides or low HDL cholesterol was associated with an increased risk of cardiovascular disease [37, 38]. By inference, reductions in hyperinsulinaemia and hypertriglyceridaemia and/or increases in HDL cholesterol

should decrease cardiovascular risk. In a Finnish study on people with type 2 diabetes, factor analysis demonstrated that the cluster of increased insulin, elevated triglycerides, reduced HDL cholesterol and high BMI increased the risk of CHD [39]. Insulin resistance, as estimated using HOMA, has also been shown to be an independent predictor of cardiovascular complications in patients with type 2 diabetes [40]. The studies described in this report have demonstrated that, over a 1-year period, the administration of PIO as monotherapy or in combination with MET provided more beneficial outcomes compared with GLIC-based therapies with respect to insulin sensitivity, triglycerides, AIP and NEFA in patients with type 2 diabetes. Given that PIO and GLIC exhibited similar antihyperglycaemic efficacy in terms of HbA$_1$c, these additional beneficial effects of PIO treatment cannot be explained by its glucose-lowering activity alone. The additional benefits associated with PIO-based regimens may potentially be of value in decreasing cardiovascular risk in patients with type 2 diabetes. A study is currently underway to determine whether PIO (versus placebo) reduces cardiovascular morbidity and mortality when used as an adjunct to current therapy in patients with type 2 diabetes [41].

Duality of interest

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