Randomized controlled trial of single-agent glimepiride and pioglitazone in Japanese patients with type 2 diabetes: A comparative study

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ABSTRACT

Aims/Introduction: To compare first-line, single-agent glimepiride and pioglitazone in Japanese patients with type 2 diabetes uncontrolled by diet and exercise with respect to glycemic control, safety and metabolic changes.

Materials and Methods: Patients with previously untreated type 2 diabetes were enrolled in a multicenter, randomized, non-blind, parallel-group trial of glimepiride (0.5–6 mg/day) or pioglitazone (15–45 mg/day) for 6 months.

Results: A total of 191 patients aged 30–75 years were randomized. Similar percentages of patients attained the primary end-point, with glycated hemoglobin < 6.9% at month 6 with glimepiride and pioglitazone, respectively (61.2 vs 56.8%, $P = 0.64$). At month 6, the following significant ($P < 0.05$) intragroup changes in mean plasma lipid concentrations were noted as compared with baseline: total cholesterol decreased from 203.5 to 195.5 mg/dL and low-density lipoprotein (LDL)-cholesterol decreased from 124.5 to 116.3 mg/dL in the glimepiride group, whereas high-density lipoprotein (HDL)-cholesterol increased from 51.6 to 56.0 mg/dL and triglycerides decreased from 167.6 to 143.6 mg/dL in the pioglitazone group. The only symptomatic adverse events were mild-to-moderate in four patients receiving pioglitazone, and constipation in one patient receiving glimepiride. Similar numbers of patients experienced asymptomatic hypoglycemia (<60 mg/dL) in the glimepiride and pioglitazone groups ($n = 7$ and 5, respectively).

Conclusions: There was no statistically significant difference between glimepiride and pioglitazone with respect to glycemic control, and both agents were well tolerated. Glimepiride significantly lowered total cholesterol and LDL-cholesterol, whereas pioglitazone increased HDL-cholesterol. This trial was registered with University Hospital Medical Information Network (UMIN), Japan, UMIN000004582. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2011.00115.x, 2011)

KEY WORDS: Glimepiride, Pioglitazone, Type 2 diabetes mellitus

INTRODUCTION

Consistent with other developed countries, there has been a steady increase in Japan in the number of patients with diabetes. According to the 2007 National Health and Nutrition Survey carried out by the Ministry of Health, Labour and Welfare, the estimated number of persons in Japan strongly suspected of having diabetes (includes those on diabetes treatment) increased to approximately 8.9 million as compared with 6.9 million in 1997 and 7.4 million in 2002[1].

Sulfonylureas are the most frequently used first-line oral anti-diabetic drug class in Japan; they are well suited to the predominant etiology of Japanese diabetic patients; that is, impaired insulin secretion[2]. Long-term follow up (10 years) of patients with type 2 diabetes mellitus enrolled in the United Kingdom Prospective Diabetes Study (UKPDS) showed that, compared with dietary therapy alone, those treated with intensive therapy with either a sulfonylurea or insulin had a significantly reduced relative risk of microvascular disease (24%, $P = 0.001$), myocardial infarction (15%, $P = 0.01$), diabetes-related death (17%, $P = 0.01$) or death from any cause (13%, $P = 0.007$); these benefits were attained despite between-group differences in glycated hemoglobin (HbA_{1c}) being lost after the first year[3]. Although sulfonylureas confer reliable glycemic control, there has been some concern over the risk of hypoglycemia and weight gain[4]. However, the third-generation sulfonylurea, glimepiride, has a relatively low risk of hypoglycemia[5].

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Pioglitazone improves insulin resistance and is the only approved thiazolidinedione in Japan. It is commonly used as a first-line treatment for patients with type 2 diabetes mellitus in Japan. Pioglitazone was expected to reduce cardiovascular event risk[6]. However, concern was raised when another thiazolidinedione, rosiglitazone, was shown to significantly increase the risk of myocardial ischemic events compared with placebo in patients with type 2 diabetes mellitus[7]. A meta-analysis of randomized trials showed that pioglitazone reduced the risk of myocardial ischemic events, although it increased the risk of serious heart failure[8]. In addition to the increase in heart failure, several adverse events have received attention during treatment with pioglitazone, including weight gain, edema[9] and fracture[10].

Various randomized trials have been published that compare glimepiride and pioglitazone in Western patients with type 2 diabetes mellitus[11–15]. There also was a randomized study comparing glimepiride, pioglitazone and metformin in Japanese patients with type 2 diabetes mellitus[16]. Given that the pathophysiology of diabetes might be different in the Japanese population compared with Western populations, further studies are needed in Japanese patients. We therefore carried out a study directly comparing the efficacy and safety of first-line therapy with glimepiride and pioglitazone in drug-naive Japanese patients with type 2 diabetes mellitus, with glycemic control as the primary end-point. We also examined other outcome measures, such as compliance with dietary/exercise therapy and dosage, bodyweight change, and, in particular, lipid changes.

MATERIALS AND METHODS

Patients

Outpatients of either sex with type 2 diabetes mellitus aged 30–75 years who were committed to a stable dietary and exercise regimen for >1 month before randomization were eligible for recruitment. HbA_{1c} had to be 6.9 to <10.4% 1 month before and at randomization, with an absolute HbA_{1c} difference <1% between these measurements. The value for HbA_{1c} (%) is estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula HbA_{1c} (%) = HbA_{1c} (JDS) (%) + 0.4%, considering the relational expression of HbA_{1c} (JDS) (%) measured by the previous Japanese standard substance and measurement methods and HbA_{1c} (NGSP)[17]. Exclusion criteria included: type 1 diabetes mellitus; use of insulin or any oral hypoglycemic agent (including an α-glucosidase inhibitor) in the month before randomization; heart failure or history of heart failure; and any serious intercurrent complication involving the heart, kidney, liver, pancreas or other organs, or hematological condition. All patients had to be sufficiently competent to give consent to participate in the study, and capable of reading, understanding and signing the informed consent form for study participation. The study was approved by the Ethics Committee of the Japan Association for Diabetes Education and Care, and was carried out in accordance with the ethical principles of the Declaration of Helsinki and its subsequent amendments.

Study Design

The present study was a multicenter (33 Japanese centers), randomized, non-blind, parallel-group trial comparing orally administered single-agent glimepiride or pioglitazone (1:1 ratio) for 6 months. Randomization was carried out by a central registration method. Patients continued their stable pre-enrollment dietary and exercise regimen throughout the study.

According to the original trial protocol, patients could receive either glimepiride or gliclazide as the sulfonylurea treatment, but in practice, all selected patients received glimepiride. The starting dose of glimepiride was 0.5 mg/day for patients with $HbA_{1c} \geq 6.9$ to <7.4%, and 1 mg/day for those with $HbA_{1c} \geq 7.4$ to <10.4%. The glimepiride dose could be increased to a maximum of 6 mg/day in order to achieve morning fasting blood glucose of <120 mg/dL. The starting dose of pioglitazone was 15 mg/day, which could be increased to a maximum of 45 and 30 mg/day in men and women, respectively, in order to achieve morning blood glucose of <120 mg/dL. The dosage of glimepiride or pioglitazone could be decreased according to the supervising physician's judgment if morning fasting blood glucose was <80 mg/dL. Drug doses were titrated according to morning fasting blood glucose measured at scheduled clinic visits.

Initiation of any anti-diabetic medication (insulin and blood glucose-lowering drugs) apart from the test drugs and any antihypertensive or antihyperlipidemic drugs was prohibited during the study period. Initiation of any other drugs was discouraged unless absolutely essential, when full details were recorded. Antihypertensive or antihyperlipidemic drugs that had been started >3 months before randomization were allowed, provided the dosage remained unchanged throughout the study; if dose change was essential, the reason and new dose were recorded.

Assessments

Full patient medical history and work-up were obtained 1 month before randomization. Patients attended morning clinical visits at baseline (month 0), at 2 weeks (month 0.5) and each month thereafter (months 1, 2, 3, 4, 5, 6). A general clinical examination of the patient was carried out at months 0, 3 and 6.

Fasting morning blood glucose was measured at each visit. HbA_{1c} was measured at month 0, 3 and 6. Fasting plasma insulin was measured at month 0 and 6. Fasting plasma lipids (total cholesterol, high-density lipoprotein [HDL]-cholesterol, low-density lipoprotein [LDL]-cholesterol and triglycerides) were measured, and bodyweight and blood pressure (BP) were recorded at months 0, 3 and 6. Fasting plasma brain natriuretic peptide (BNP) was measured at months 0 and 6. Fasting plasma insulin and plasma BNP were measured at an independent central laboratory, whereas other measurements were carried out according to routine procedures at each participating center.

Adherence to dietary and exercise therapy was categorized as 'strictly followed', 'sometimes followed' or 'not followed' at each

monthly visit. Adherence to test diabetic drug therapy was determined from returned tablet counts as 'excellent' (90–100% compliance), 'good' (70–89%), 'fair' (50–69%) and poor (<50%).

Adverse events were recorded after indirect questioning and by clinical observation. Their severity was graded as 'mild', 'moderate' or 'severe', and their potential relationship to treatment was graded as 'definite', 'probable', 'possible' or 'none'. Serious adverse events were immediately reported.

End-Points and Statistics

The primary end-point was the percentage of evaluable patients with $HbA_{1c} < 6.9\%$ at the end of the study (month 6) and a secondary end-point was the change in HbA_{1c} at 6 months compared with baseline. Other secondary end-points included changes in fasting plasma glucose, insulin, lipids and BNP, as well as bodyweight and body mass index (BMI) at month 6 compared with baseline. Safety of study medication was also a secondary end-point.

Analyses were carried out using the safety population under the headings 'study population' and 'safety' in the results, whereas analyses under the other headings in the results were carried out using the efficacy population.

Intragroup comparison of data over time vs baseline was analyzed by paired t-test, whereas intergroup comparisons were analyzed by one-way analysis of variance (ANOVA) or χ^2-test. A two-tailed level of significance was accepted for P-values < 0.05. Data are generally presented as mean values standard deviation (SD) or categorical values.

The percentages of patients rated as strictly adherent or sometimes adherent to dietary/exercise therapy and those who had excellent or good adherence to the study anti-diabetic drug therapy were calculated for each month. The median (range)

percentages over the 6-month study treatment period were then calculated.

RESULTS

Study Population

The study was carried out from 1 August 2007 to 28 February 2010. A total of 238 patients were initially screened, of whom 191 were eventually randomized to treatment. Figure 1 shows the disposition of the patients during screening, at randomization, and in the safety and efficacy populations, as well as the reasons for dropout. The safety population included all patients initially randomized to glimepiride ($n = 95$) and pioglitazone ($n = 96$), whereas the efficacy population included 86 patients in the glimepiride group and 91 patients in the pioglitazone group. The baseline demographic and clinical characteristics of the patients in the two groups are shown in Table 1. There were no statistically significant differences in baseline characteristics between the groups, except for mean HDL-cholesterol, which was significantly higher (59.3 ± 23.0 vs 52.8 ± 13.7 mg/dL, $P = 0.024$), and triglycerides, which was significantly lower (129.8 ± 68.4 vs 164.0 ± 112.4 mg/dL, $P = 0.014$), in the group receiving glimepiride.

Glucose Markers

Similar percentages of patients in the glimepiride and pioglitazone groups attained the primary end-point ($HbA_{1c} < 6.9\%$ at month 6): 61.2% (52/85) vs 56.8% (50/88), respectively ($P = 0.64$; Figure 2a). Mean HbA_{1c} was significantly ($P < 0.001$) decreased at months 3 and 6 vs baseline in both the glimepiride and pioglitazone groups (Figure 2b). Mean HbA_{1c} was significantly lower in the glimepiride group as compared with those receiving pioglitazone ($6.9 \pm 0.7\%$ vs $7.3 \pm 1.0\%$; $P = 0.022$) at month 3, but not at month 6 (Figure 2b). There was no
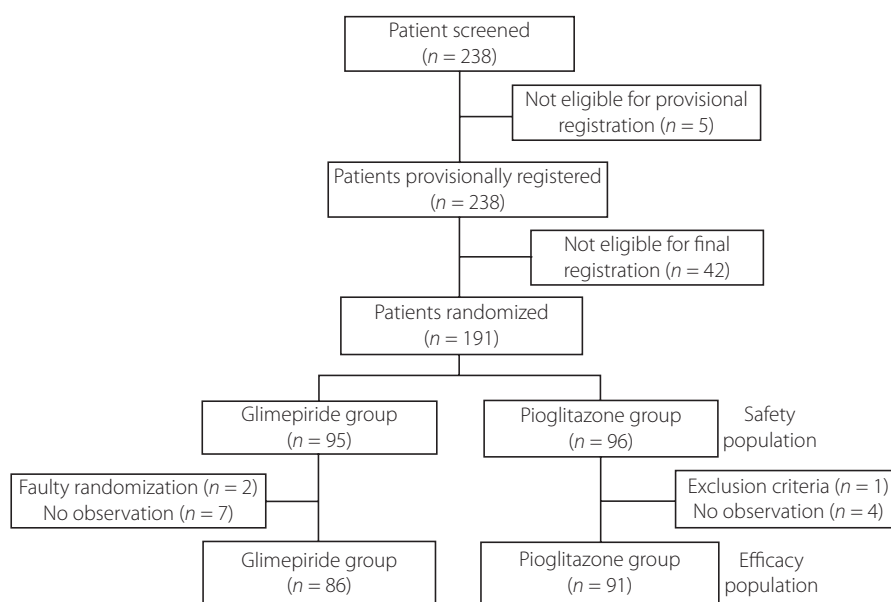

Figure 1 | Patient disposition.

Table 1 | Baseline demographic and clinical characteristics of the study patients

Characteristic	Glimepiride (*n* = 95)	Pioglitazone (*n* = 96)
Sex (male/female)	62/33	65/31
Age (years)	57.7 ± 10.4 (*n* = 95)	56.8 ± 10.3 (*n* = 96)
Body weight (kg)	65.6 ± 12.5 (*n* = 93)	65.5 ± 14.6 (*n* = 92)
Body mass index (kg/m^2)	24.6 ± 3.8 (*n* = 93)	24.5 ± 4.3 (*n* = 92)
Duration of diabetes (years)	6.0 ± 8.2 (*n* = 41)	4.1 ± 4.3 (*n* = 52)
Fasting glucose (mg/dL)	143.1 ± 39.8 (*n* = 90)	145.8 ± 45.6 (*n* = 90)
HbA$_{1c}$ (%)	7.8 ± 0.9 (*n* = 95)	7.8 ± 0.9 (*n* = 95)
Fasting insulin (μU/mL)	8.3 ± 9.4 (*n* = 95)	8.6 ± 12.2 (*n* = 94)
HOMA-β	41.7 ± 71.2 (*n* = 90)	56.9 ± 108.0 (*n* = 89)
HOMA-R	3.0 ± 4.3 (*n* = 90)	2.5 ± 2.6 (*n* = 89)
Total cholesterol (mg/dL)	207.5 ± 39.1 (*n* = 81)	205.5 ± 38.2 (*n* = 87)
LDL-cholesterol (mg/dL)	126.5 ± 36.5 (*n* = 79)	123.2 ± 32.6 (*n* = 79)
HDL-cholesterol (mg/dL)	59.3 ± 23.0 (*n* = 90)*	52.8 ± 13.7 (*n* = 88)*
Triglycerides (mg/dL)	129.8 ± 68.4 (*n* = 91)[†]	164.0 ± 112.4 (*n* = 91)[†]
Brain natriuretic peptide (pg/mL)	27.8 ± 88.2 (*n* = 94)	20.6 ± 39.6 (*n* = 94)

Data are number of patients (categorized data) or mean ± SD (qualitative data). Qualitative data are missing for some patients in treatment groups: numbers with available data are shown in parentheses. These baseline observational data may differ from data used for paired *t*-test analyses.

*High-density lipoprotein (HDL)-cholesterol was significantly different between the groups (*P* = 0.024).

[†]Triglycerides were significantly different between the groups (*P* = 0.014). HbA$_{1c}$, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-β, homeostasis model assessment for β-cell function; HOMA-R, homeostasis model assessment for insulin resistance; LDL, low-density lipoprotein.

significant (*P* = 0.31) difference between the groups in the decrease in mean HbA$_{1c}$ at month 6 vs baseline (Figure 2c).

There were no statistically significant differences between the groups in changes in fasting plasma glucose, fasting insulin, homeostasis model assessment for β-cell function (HOMA-β) and homeostasis model assessment for insulin resistance (HOMA-R) (Figure 3) at month 6 vs baseline. There was a tendency for fasting blood glucose to improve more in the glimepiride group as compared with the pioglitazone group at month 6 vs baseline (−21.2 ± 33.7 vs −12.5 ± 47.7 mg/dL; *P* = 0.17).

Plasma Lipids

Changes in mean plasma lipid concentrations (total cholesterol, HDL-cholesterol, LDL-cholesterol and trigylcerides) at month 6 from baseline are shown in Figure 4 for the treatment groups, which showed significant differences in total cholesterol
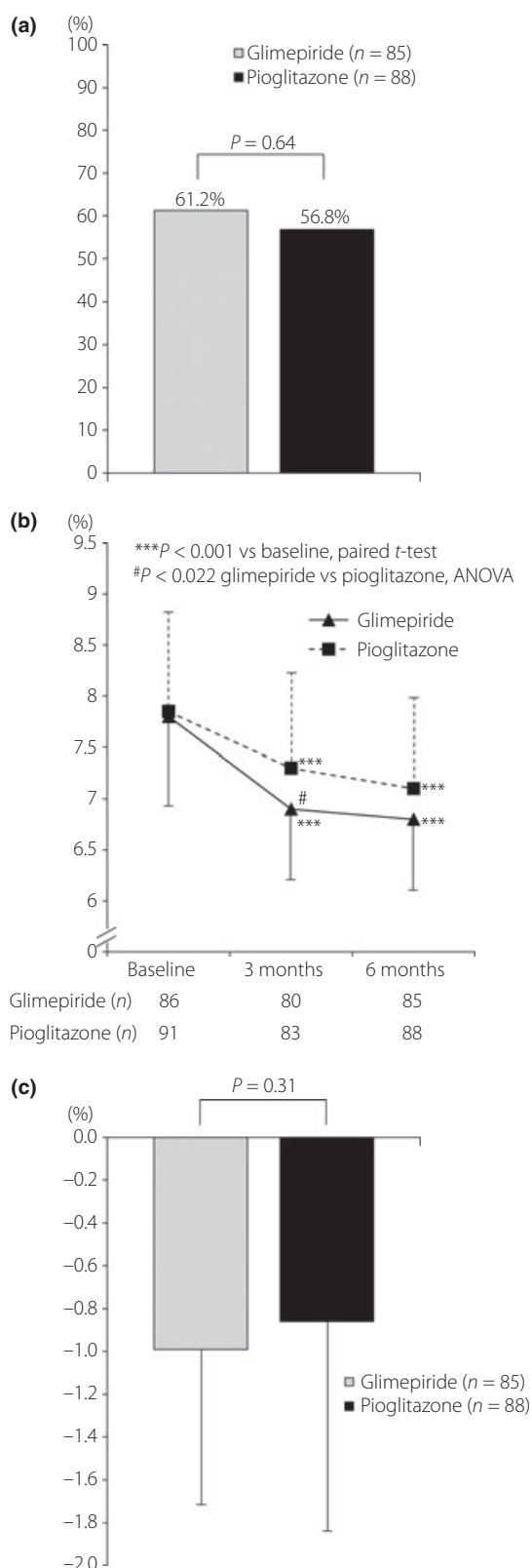

Figure 2 | Glycated hemoglobin (HbA$_{1c}$). (a) Percentage of patients with HbA$_{1c}$ < 6.9% at 6 months. (b) Change in mean (±SD) HbA$_{1c}$ during the study. (c) Change in mean (±SD) HbA$_{1c}$ at month 6 vs baseline.
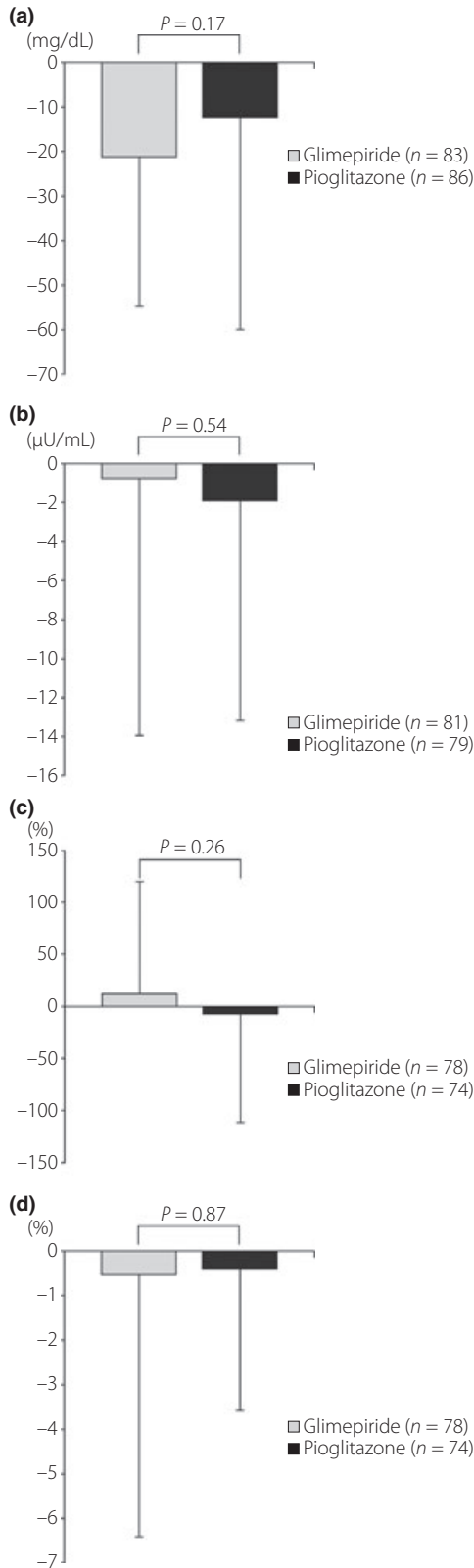
Figure 3 | Change in mean (±SD) fasting (a) glucose, (b) insulin, (c) homeostasis model assessment for β-cell function and (d) homeostasis model assessment for insulin resistance at month 6 vs baseline.
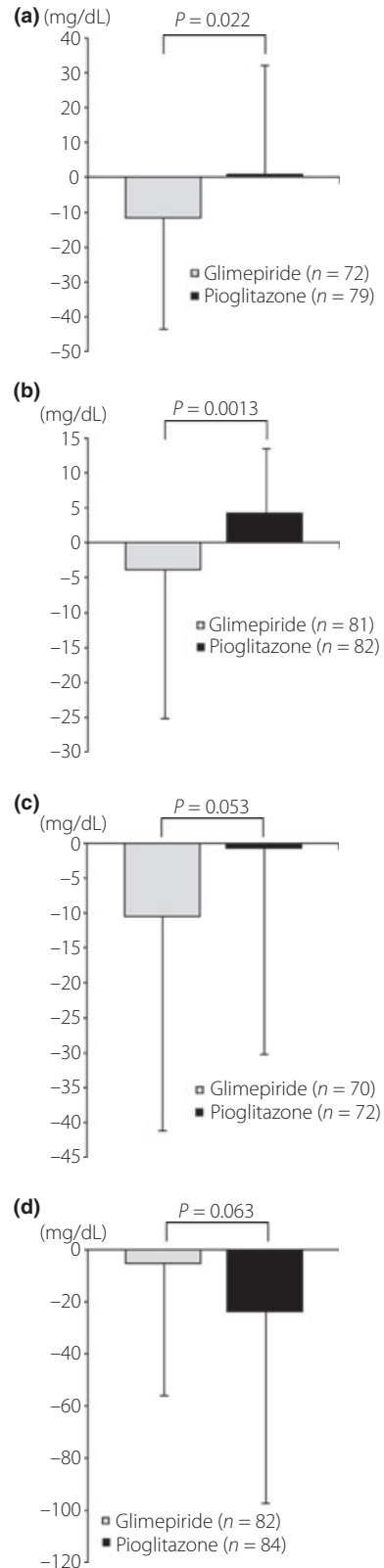
Figure 4 | Change in mean (±SD) fasting (a) total cholesterol, (b) high-density lipoprotein cholesterol, (c) low-density lipoprotein cholesterol and (d) triglycerides at month 6 vs baseline.

(−11.6 ± 32.4 vs 0.8 ± 32.9 mg/dL, P = 0.022) and HDL-cholesterol (−3.9 ± 20.7 vs 4.2 ± 8.7 mg/dL, P = 0.0013) between the glimepiride and pioglitazone groups, respectively. The changes for LDL-cholesterol (−10.5 ± 30.4 vs −0.7 ± 29.7 mg/dL, P = 0.053) and triglycerides (−5.3 ± 49.8 vs −23.8 ± 74.4 mg/dL, P = 0.063) approached significance comparing glimepiride and pioglitazone, respectively. At month 6, the following significant (P < 0.05) intragroup changes in mean plasma lipid concentrations were noted as compared with baseline: total cholesterol decreased from 203.5 ± 37.4 to 195.5 ± 36.0 mg/dL (P = 0.036) and LDL-cholesterol decreased from 124.5 ± 32.8 to 116.3 ± 32.7 mg/dL (P = 0.028) in the glimepiride group, whereas HDL-cholesterol increased from 51.6 ± 13.1 to 56.0 ± 13.7 mg/dL (P < 0.0001) and triglyceride decreased from 167.6 ± 120.2 to 143.6 ± 93.8 mg/dL (P = 0.0079) in the pioglitazone group.

Bodyweight and Body Mass Index
There were no statistically significant intergroup differences for changes in mean bodyweight or BMI at month 6 vs baseline. At month 6, there were significant intragroup increases in bodyweight (from 65.5 ± 15.1 to 66.2 ± 14.4 kg, P = 0.036) and BMI (from 24.5 ± 4.5 to 24.9 ± 4.3 kg/m^2, P = 0.016) compared with baseline for patients in the pioglitazone group. The intragroup changes from baseline to month 6 in the glimepiride group were not statistically significant for bodyweight (from 66.0 ± 12.0 to 66.4 ± 11.7 kg) and BMI (from 24.6 ± 3.6 to 24.8 ± 3.6 kg/m^2).

Brain Natriuretic Peptide
At month 6, the change in mean plasma BNP from baseline (−2.6 ± 37.5 vs 6.0 ± 13.9 mg/dL, P = 0.060) approached significance comparing glimepiride and pioglitazone, respectively. There was a significant intragroup increase in mean BNP (from 17.3 ± 14.6 to 23.3 ± 22.1 pg/mL, P = 0.0003) at month 6 compared with baseline in the pioglitazone group, whereas the change in the glimepiride group was not statistically significant (from 28.6 ± 93.9 to 26.0 ± 62.7 pg/mL).

Adherence to Dietary, Exercise and Anti-diabetic Therapy
Good adherence (strictly adherent or sometimes adherent) to dietary therapy was shown by a median of 89.5% (range 88.2–93.0%) and 91.7% (range 89.3–93.3%) of patients in the glimepiride and pioglitazone groups, respectively. Good adherence to exercise therapy was shown by a median of 86.0% (range 84.9–88.4%) and 83.9% (range 82.2–86.5%) of patients in the glimepiride and pioglitazone groups, respectively. Good adherence (excellent or good) to anti-diabetic medication was shown by a median of 95.9% (range 93.6–97.7%) and 96.5% (range 96.3–98.9%) of patients in the glimepiride and pioglitazone groups, respectively.

Dosage
At month 6, the mean daily drug dosage was 1.51 ± 1.27 mg (range 0.25–6 mg) in the glimepiride group and 23.24 ± 11.40 mg (range 7.5 to −45 mg) in the pioglitazone group. The mean daily glimepiride dosage at month 6 was 1.59 ± 1.33 mg (range 0.25–6 mg) in men and 1.32 ± 1.13 mg (range 0.25–4 mg) in women. The mean daily pioglitazone dosage at month 6 was 25.04 ± 12.52 (range 7.5–45 mg) in men and 19.40 ± 7.37 (range 7.5–30 mg) in women.

Safety
There were no severe or serious adverse events in either group. Seven patients in the glimepiride group and five patients in the pioglitazone group experienced blood glucose concentrations <60 mg/dL, with no statistically significant difference between the groups. The only other adverse events possibly related to treatment were mild or moderate in intensity: four patients with edema in the pioglitazone group and constipation in one patient in the glimepiride group.

DISCUSSION
The present study showed that there was no clear difference between first-line, single-agent glimepiride and pioglitazone therapy in Japanese patients with type 2 diabetes mellitus with respect to glycemic control as determined from the primary end-point, the rate of attaining target HbA$_{1c}$ < 6.9%: 61.2 vs 56.8%, respectively (P = 0.64). However, there was an indication that the onset of action of glimepiride might be faster than that of pioglitazone, because the mean HbA$_{1c}$ was significantly lower in patients receiving glimepiride as compared with those receiving pioglitazone (6.9 ± 0.7% vs 7.3 ± 1.0%; P = 0.022) at month 3, whereas it was comparable in both groups (∼6.9%) at month 6. Previous comparison of glimepiride and pioglitazone in Japanese patients with type 2 diabetes mellitus showed similar results[16]. These patients had higher baseline mean HbA$_{1c}$ (∼10%; JDS) and end-point HbA$_{1c}$ at month 12 (∼7.8%; JDS) than the patients in the present study, although the reduction in mean HbA$_{1c}$ was similar in both treatment groups at end-point, as in the present study. The authors also noted a slower decrease in HbA$_{1c}$ with pioglitazone, with maximal reduction requiring about 6 months. The slower onset of glycemic control with pioglitazone compared with glimepiride has been reported elsewhere[11,13]. We found no statistically significant differences between pioglitazone and glimepiride in the present study for changes in fasting blood glucose, fasting insulin, HOMA-β and HOMA-R at month 6. Other comparative studies of pioglitazone and glimepiride have shown significant reductions in fasting blood glucose and insulin, associated with significant decreases in insulin resistance, with pioglitazone, but not with glimepiride[11,12]. Possible reasons for these inconsistent results might be related to the study duration or the patient background. The study duration in the trial by Tan *et al.*[11] was 52 weeks, which is longer than the present study. The trial by Langenfeld *et al.*[12], which primarily assessed the decrease of carotid intima-media thickness, enrolled more obese subjects (mean BMI 31.8 kg/m^2) than the present trial (mean BMI 24.6 kg/m^2). Further studies that set the reduction of insulin

resistance as the primary end-point are warranted to resolve this possible inconsistency.

With respect to plasma lipid profile, the present study showed that glimepiride significantly decreased total cholesterol and LDL-cholesterol, which is consistent with other studies of Asian[18,19] or Western[12,13] patients. Reports on the effect of glimepiride on HDL-cholesterol in Japanese or Chinese patients have been less consistent, showing either no effect[4,16] or a significant increase[18]. In the present study, glimepiride showed a trend towards decreasing HDL-cholesterol, but this did not reach statistical significance. However, the changes of HDL-cholesterol levels in the glimepiride group were within normal ranges, which suggest that these changes might not be clinically relevant. A possible reason for HDL-cholesterol not increasing in the glimepiride group might be that baseline HDL-cholesterol levels were higher than those of the pioglitazone group. Pioglitazone showed a significant increase in HDL-cholesterol in the present study, which has been the only consistent effect on plasma lipids shown in other studies of pioglitazone in Japanese[20] or Western[12,14,15] patients. Glimepiride has been shown to exert a prophylactic effect on atherosclerosis in cholesterol-fed rabbits[21]. Glimepiride has also been shown to normalize the adverse serum and hepatic lipid profile induced by a simulated Western-like diet in rats, possibly as a result of decreasing very low-density lipoprotein synthesis and increasing LDL catabolism through insulin secretion[22]. Research to elucidate the molecular biological mechanism involved is awaited.

The adherence to diet and exercise regimens was good in the present study, which probably contributed to some degree to the good maintenance of glycemic control and bodyweight. In fact, bodyweight and BMI did not change significantly in the group receiving glimepiride, whereas some concern was raised about possible bodyweight gain during glimepiride therapy in a previous Japanese study[4]. A German study in a general practice setting has shown a BMI-dependent reduction in bodyweight in patients on glimepiride therapy[23]. There was, however, a statistically significant, but relatively minor, increase in bodyweight and BMI in the group receiving pioglitazone. One of the possible reasons for the lack of marked weight gain in each group is that the patients adhered well to the dietary and exercise therapy prescribed by the doctors.

Both glimepiride and pioglitazone were well tolerated in the present study. No severe or serious adverse events were reported. The only symptomatic adverse events possibly related to treatment were mild or moderate in intensity and were limited to edema in the pioglitazone group ($n = 4$) and constipation in the glimepiride group ($n = 1$). Similar numbers of patients experienced asymptomatic hypoglycemia (<60 mg/dL) in the glimepiride and pioglitazone groups ($n = 7$ and 5, respectively).

There were several limitations to the present study, including the relatively small sample size, which limited the power to detect potential differences between the study treatments.

Furthermore, it was essentially an open-label (non-blind) design with the drugs being administered as commercially available drugs. This might have led to an overestimation of adverse events, as both the patients and investigators could have been aware of the known adverse events of the study medications. In addition to adverse events, effectiveness might have been biased as a result of non-blindness, although the primary end-point measurement, HbA_{1c}, is an objective assessment of efficacy unlikely to be affected by subjective bias. In addition, the study background was essentially a real-life situation, in which patients were treated according to normal clinical practice. However, it is possible that dose titration of the study medications might have been insufficient. In fact, the mean daily dose of glimepiride (1.5 mg) at month 6 would appear to be somewhat lower than we would have expected. It is possible that the present study included a higher proportion of patients with milder disease, although a more probable reason for the relatively lower dose might be a result of the background of our patients, who attained comparatively good blood glucose control which, in turn, was related to their excellent adherence to dietary and exercise therapy.

In conclusion, we found that there was no statistically significant difference between glimepiride and pioglitazone with respect to glycemic control as shown by the rate of attaining target $HbA_{1c} < 6.9\%$. Both of these anti-diabetic agents were similarly well tolerated. Weight gain and increased insulin resistance, which have been considered a concern with sulfonylurea therapy, were not observed in the present study. Glimepiride significantly lowered total cholesterol and LDL-cholesterol, whereas pioglitazone increased HDL-cholesterol, which is consistent with previous reports. Based on these findings, it is recommended that when selecting first-line, single-agent drug therapy for patients with type 2 diabetes mellitus, the individual status of the patients, including their adherence to dietary/exercise therapy, dose required, bodyweight, serum lipid profile and general condition, is considered.

ACKNOWLEDGEMENTS

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