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CLINICAL TRIAL

Remission of hyperglycemia after withdrawal of oral antidiabetic drugs in Japanese patients with early-stage type 2 diabetes

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Keywords
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ABSTRACT

Aims/Introduction: To assess whether intervention with oral antidiabetic drug in Japanese patients with the early stage of type 2 diabetes could provide a significant remission of the disease process.

Materials and Methods: Patients with diabetes duration <5 years were randomized to the lifestyle modification (LFS), pioglitazone (PIO) or sulfonylurea (SU) treatment group. In phase 1 as the on-treatment period and in phase 2 as the off-treatment period, the duration that glycated hemoglobin (HbA1c) was maintained at less than the target was compared among groups.

Results: A total of 278 patients were assigned to LFS (n = 84), PIO (n = 101) and SU (n = 93), and 212 patients completed phase 1. The number of patients that dropped out because of HbA1c elevation was larger in the LFS group, and the duration of HbA1c being maintained at <7.9% was longer in the SU group than the other groups. The duration of HbA1c being maintained at <7.4% in phase 2 was significantly shorter in the SU group than in the other groups. The proportion of patients who achieved HbA1c <6.9% or 6.2% at the end of phase 1 was obviously less in the LFS group than other groups. The duration of HbA1c being maintained at <6.2% in phase 2 was longer in the PIO group than other groups, although not significant statistically. An increase in serum adiponectin and decreases in high-sensitivity C-reactive protein and homeostatic model assessment of insulin resistance were shown in patients treated with PIO, but not LFS and SU, in phase 1, but were canceled in the drug-off phase 2 period.

Conclusions: PIO treatment provided a prolonged remission of hyperglycemia after stopping the dosage in patients with the early stage of type 2 diabetes.

INTRODUCTION

Type 2 diabetes is known to be a chronic, progressive and incurable condition, in which tight management of metabolic imbalance and risk factors to prevent vascular complications is normally required over a long period of time[1,2]. The natural history of the disease is characterized by a progressive decline in β-cell function and an inexorable pathological process that usually progresses despite lifestyle modifications (LFS) and pharmacological interventions[3,4]. It is generally accepted that pharmacological treatment continues on a permanent basis, and the typical course of the disease consists of the sequential intensification of antidiabetic drugs over time[5,6].

In contrast, it was reported that 16% of adults in the USA who once diagnosed as diabetes take no hypoglycemic medications, and the number of clinical studies reporting the remission of type 2 diabetes in certain populations is gradually growing[7–10]. A *post-hoc* analysis from the Action for Health in Diabetes (Look AHEAD) study showed evidence of remission among adults with type 2 diabetes in both the intensive lifestyle management and the diabetes support and education groups[11]. These findings suggested that individuals who returned to normal or near-normal blood glucose levels without pharmacological intervention

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showed biological evidence of remission, including normalization of β-cell function and hepatic insulin sensitivity[12]. Temporary administration of short-term intensive insulin therapy early in the course of type 2 diabetes can also induce a remission wherein many patients subsequently maintain normal glucose levels without any antidiabetic medication for up to 2 years, suggesting that pharmacological intervention could modify, at least for a certain period of time, the natural history of the disease[13]. The most notable examples of the remission of type 2 diabetes are seen in many studies of bariatric surgery, showing that many obese patients with diabetes can actually make a full recovery by surgical treatment[14].

Despite these promising results and the clinical importance of remission, studies to date have focused largely on remission after gastric bypass, which have limited coverage in scope of the target, and little is known if oral antidiabetic medication could modify the natural history of diabetes and/or achieve remission in the general population of type 2 diabetes patients.

Thus, we carried out a multicenter, randomized, open-label, prospective study to examine whether discontinuance of oral antidiabetic agents in the early stage of the disease could provide a remission and/or modify the disease process and progress of atherosclerosis in Japanese patients with type 2 diabetes who received standard care with oral antidiabetic medications excluding bariatric surgery.

METHODS

The present study (PREVENT-J: Pioglitazone and Sulfonylurea Remission from Type 2 Diabetes Mellitus Development and Anti-Atherosclerosis in Japan [University Hospital Medical Information Network Center: ID 000000947]) was a multicenter, prospective, randomized, open-label, blinded end-point study carried out in 25 centers in the west of Japan (Okayama, Hiroshima and Yamaguchi Prefectures). The study was carried out in compliance with the ethical principles for medical research involving human participants, the Declaration of Helsinki, with patients who freely provided informed consent in writing after being fully informed about the study and under the approval of the ethic committee of the Kawasaki Medical School Hospital.

Eligibility criteria

Patients aged 20–70 years were eligible for enrollment if they met the following criteria: diabetes duration <5 years, modestly controlled type 2 diabetes with glycated hemoglobin (HbA1c) <7.9% (63 mmol/mol) for drug-naïve patients or HbA1c <7.4% (54 mmol/mol) for patients receiving monotherapy with either metformin or α-glucosidase inhibitor for at least 8 weeks before randomization.

Patients who met the following criteria were excluded: used antidiabetic agents other than metformin or α-glucosidase inhibitor, including sulfonylurea (SU), pioglitazone (POI), dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 agonist or insulin during 8 weeks before enrollment; a current or past history of heart failure (ejection fraction ≤40% with echocardiogram); serious hepatic dysfunction; serious renal dysfunction; a history of cardiovascular disorders (coronary angioplasty, coronary stent placement, coronary bypass surgery, myocardial infarction, stroke or transient ischemic attack); and a history of adverse events for thiazolidinediones.

Study design

Drug-naïve patients were randomized into groups to receive intensive LFS with nutritional guidance by a managerial dietician, treatment with PIO or SU in addition to conventional diet therapy (1:1:1). Intensive nutritional guidance by a managerial dietician was required for at least 6 months in patients with LFS. In addition, conventional nutritional guidance was carried out whenever they visited the clinic if necessary. Patients receiving monotherapy with either metformin or α-glucosidase inhibitor were randomized to receive add-on medication either with once-daily PIO or SU (1:1). The attending physicians were required to adjust the dose of add-on medications to achieve the target HbA1c level, defined as at least 6.9 and 6.2% to the lowest extent possible. The HbA1c target was determined by a Japanese guideline at the start of the trial. The starting dose of PIO was 15 mg q.d., and the dose could be escalated after confirmation of safety up to 45 mg q.d. for men and 30 mg q.d. for women at the attending physicians' discretion. The type and daily dose of SU were decided arbitrarily, and was allowed to increase up to the maximum dose if necessary. A downward adjustment of dose for safety reasons was also allowed.

The present study consisted of two phases (phase 1 as the on-treatment period and phase 2 as the off-treatment period), and each phase lasts for a maximum of 18 months. Patients were discontinued from the study if their HbA1c exceeded 7.9% in phase 1 and 7.4% in phase 2 in two consecutive outpatient visits. If the patients achieved HbA1c <6.9% at the end of phase 1 (18 months after randomization), those who consented to further assessment were qualified to proceed to phase 2, which again lasts for a maximum of 18 months. At the beginning of phase 2, PIO or SU used in phase 1 was discontinued, and the patients in the LFS group continued the lifestyle intervention. Then, the patients were followed for a maximum of 18 months as long as their HbA1c levels were kept <7.4% (Figure S1).

Anthropometry and laboratory tests

Participants were asked to visit the hospital under fasting conditions monthly or bimonthly throughout the study period for regular checkups including physical examination, vital signs, review of adverse events, HbA1c and plasma glucose level. Other laboratory tests for triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, urine albumin, insulin, proinsulin, high-sensitivity C-reactive protein (hs-CRP), high molecular weight adiponectin (Adiponectin ELISA Kit; Otsuka Pharmaceutical Co., Tokushima, Japan) and urine 8-hydroxydeoxyguanosine were carried out at baseline and the

end of each phase. An oral glucose tolerance test was carried out in patients who optionally consented under overnight fasting at baseline, 18 months and 36 months. Under the 75-g oral glucose tolerance test, plasma glucose and immunoreactive insulin (IRI) levels were measured at 0, 30, 60 and 120 min. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated by the formula: HOMA-IR (mU/L × mg/dL) = ([fasting IRI × fasting glucose]/405). The insulinogenic index represented the ratio of IRI to glucose from 0 to 30 min after glucose loading.

To ensure the safety of the study, patients were checked for their symptoms and signs, and monitored for their renal and hepatic functions based on the results of a blood biochemical test throughout the study period.

End-points

The primary end-points of the study were the duration of HbA1c maintained at <7.9% in phase 1 (Kaplan–Meier method), the duration of HbA1c maintained at <7.4% in phase 2 (Kaplan–Meier method) and changes in the values of atherogenic markers including hs-CRP, high molecular weight adiponectin, and urine 8-hydroxydeoxyguanosine from baseline to 18 and 36 months.

Secondary end-points included: (i) the proportion of patients who achieve HbA1c <6.9% and 6.2% at the end of phase 1; (ii) the duration of HbA1c maintained at <6.2% in phase 2 (Kaplan–Meier method); (iii) development of a cardiovascular event (Kaplan–Meier method); (iv) changes in proinsulin/insulin ratio; and (v) changes in the values of metabolic markers including blood pressure, urine albumin, triglyceride, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol. Safety end-points included incidence of edema, hypoglycemia, changes in the serum levels of hepatic enzymes, as well as standard general safety end-points. The independent evaluation committees assessed end-points and safety on a blinded basis.

Statistical analysis

Demographic data were compared between groups using the χ^2-test for categorical variables, and continuous variables were compared by one-way layout analysis of variance (ANOVA). Comparative tests of laboratory values were carried out by the Wilcoxon rank-sum test (18 months sampling point *vs* baseline or 36 months sampling point). The number of patients that dropped out of the study as a result of HbA1c elevation, >7.9% in phase 1 and >7.4% in phase 2 was assessed by the Kaplan–Meier method and compared with the log–rank test. The durations of HbA1c levels maintained below defined levels in phase 1 and 2 were compared by one-way layout ANOVA.

The durations of HbA1c levels maintained at <7.4% in phase 2 for patients who were discontinued for sustained HbA1c elevation between the PIO group and SU group were compared by the Mann–Whitney *U*-test. Rates of cardiovascular events were compared with the log–rank test for the time to the first event after randomization. Hazard ratios and 95% confidence intervals were estimated with Cox proportional hazard models. Data are presented as mean ± standard error of the mean. In all cases, *P*-values < 0.05 were considered statistically significant.

Study management

The chief investigator and principal investigators of the study are listed in Appendix 1. A steering committee (Appendix 2) was responsible for the study design and scientific execution. An independent efficacy and safety evaluation committee (Appendix 3), consisting of three members blinded to any information related to the group allocations, evaluated each event and classified the results. All investigators and hospitals participating in the present study are listed in Appendix 4.

RESULTS

Disposition of patients

The first patient was enrolled in February 2008 and the last patients visited in August 2013. Of the 290 patients randomized, excluding 12 who agreed to withdrawal immediately, 84 patients were assigned to LFS, 101 to PIO and 93 to SU groups. Overall, 212 patients (73.1%) completed the phase 1 period (58, 80 and 78 in LFS, PIO and SU, respectively). The other 78 patients who failed to complete phase 1 due to severe violation of the protocol, adverse events or lost to follow up were excluded from the efficacy end-point analysis. Gliclazide and glimepiride were mainly used in the SU group, and average daily doses were relatively lower, as shown in Figure 1. The average daily dose of PIO was also low (16.5 mg). A total of 206 patients (97.2%) could maintain their HbA1c <7.9%. A total of 142 out of 206 patients (68.9%) who achieved HbA1c <6.9% at the end of the phase 1 qualified and consented to proceed to the phase 2 observation period (26, 56 and 60 in LFS, PIO and SU, respectively). Of these, 23, 42 and 45 patients in the LFS, PIO and SU group, respectively, completed phase 2 (Figure 1). Patients who could not complete phase 2 were excluded from efficacy end-point analysis.

Patient characteristics

The baseline characteristics of the participants are given in Table 1. Anthropometric and clinical data were not different at baseline between the three study groups (Table 1). Baseline data for HbA1c, fasting plasma glucose, insulin, proinsulin and lipid levels, serum levels of inflammatory markers, and adiponectin levels were comparable in the three groups (Table 1).

Anthropometric and clinical data of the patients who proceeded to phase 2 were not different at baseline between the three study groups, except adiponectin, and fasting IRI and proinsulin levels (Table S1). Anthropometric and clinical data at the end of phase 2 were also not different at baseline between the three study groups (Table S2).

Duration of HbA1c maintained at <7.9% in phase 1

The HbA1c levels in the LFS group did not change over time in the phase 1 period in contrast to a significant decrease in

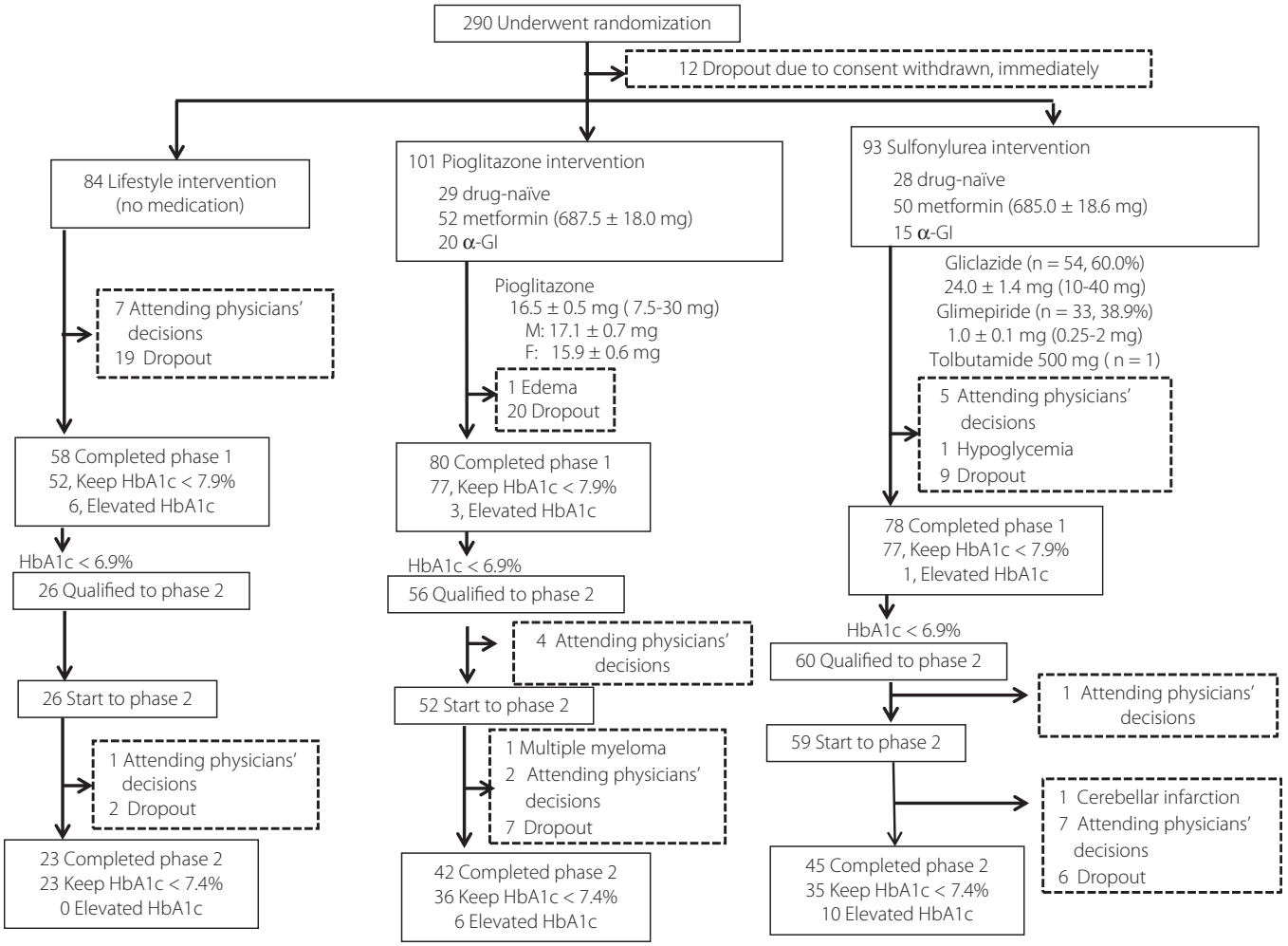

Figure 1 | Patient disposition. α-GI, α-glucosidase inhibitor; HbA1c, glycated hemoglobin.

the other two groups. SU showed the most potent effect in lowering HbA1c throughout this study phase, particularly in the first 6 months.

If the patients completed the entire 18 months by maintaining HbA1c lower than the defined level of 7.9%, the days were counted as 547.5 days. Administration of OADs was more potent in lowering HbA1c for the first 18 months of the treatment period than LFS intervention. Average number of days of duration were 527.6, 530.5 and 545.6 days, respectively, in the LFS, PIO and SU groups (Figure 2a). This was also shown by analysis using the Kaplan–Meier method, showing that the number of patients who dropped out of the study during the phase 1 as a result of HbA1c elevation >7.9% was significantly greater in the LFS group. There were no significant differences between the patients assigned to PIO and SU (Figure 2b).

Duration of HbA1c maintained at <7.4% in phase 2

When phase 2 was started, HbA1c levels did not show any difference between three groups. All patients in the LFS group could maintain their HbA1c at <7.4% during phase 2. In contrast, the number of patients who terminated the study as a result of HbA1c elevation >7.4% gradually increased by discontinuation of OADs. If the patients completed the entire 18 months of phase 2 by maintaining HbA1c levels lower than the defined level of 7.4%, the days were counted as 547.5 days. Data including both the patients who terminated the study as a result of HbA1c elevation during phase 2 and those who completed phase 2 showed that the average number of days of duration were 547.5, 508.1 and 445.5 days in the LFS, PIO and SU groups, respectively (Figure 3a). The proportion of patients who failed to maintain their HbA1c level at <7.4% was significantly larger in the SU discontinuation group than the other two groups. There was no statistical difference between PIO discontinuation and the LFS group (Figure 3b).

In the middle of phase 2, six out of 42 patients (14.3%) in PIO group and 10 out of 45 (22.2%) patients in the SU group reached HbA1c levels ≥7.4%. The duration that HbA1c was maintained at <7.4% in these patients was significantly longer

Table 1 | Baseline characteristics at the beginning of phase 1

	Total	Lifestyle	Pioglitazone	Sufonylurea	
No. participants (male/female)	290 (151/139)	89 (47/42)	102 (55/47)	99 (49/50)	NS
Age (years)	58.7 ± 0.5	58.9 ± 0.8	58.5 ± 0.9	58.8 ± 0.8	NS
Disease duration (years)	3.8 ± 0.2	3.6 ± 0.3	3.6 ± 0.3	4.3 ± 0.3	NS
BMI (kg/m^2)	24.4 ± 0.2	24.2 ± 0.4	24.4 ± 0.4	24.7 ± 0.4	NS
HbA1c (%)	6.94 ± 0.03	6.93 ± 0.05	6.98 ± 0.05	6.91 ± 0.06	NS
FPG (mg/dL)	132.4 ± 1.7	132.2 ± 3.5	130.0 ± 2.2	135.1 ± 3.5	NS
F-IRI (mIU/mL)	9.8 ± 0.7	11.3 ± 2.0	8.8 ± 0.9	9.6 ± 0.9	NS
F-proinsulin (pmol/L)	16.7 ± 0.8	18.0 ± 1.4	15.4 ± 1.0	17.0 ± 1.4	NS
Insulinogenic Index	0.21 ± 0.02	0.29 ± 0.05	0.18 ± 0.02	0.19 ± 0.02	NS
Systolic BP (mmHg)	130.0 ± 0.7	129.7 ± 1.8	129.2 ± 1.9	131.1 ± 1.5	NS
Diastolic BP (mmHg)	75.1± 0.7	75.9 ± 1.1	73.6 ± 1.2	76.0 ± 1.2	NS
HDL-chol (mg/dL)	58.1 ± 1.1	59.4 ± 2.7	58.1 ± 1.5	57.0 ± 1.4	NS
TG (mg/dL)	139.5 ± 5.8	141.2 ± 10.6	126.5 ± 6.8	151.6 ± 12.1	NS
LDL-chol (mg/dL)	117.7 ± 1.8	116.3 ± 3.4	117.6 ± 2.6	119.1 ± 3.5	NS
Urine albumin (mg/g Cr)	41.3 ± 5.8	28.9 ± 4.8	60.7 ± 14.9	37.8 ± 5.0	NS
Adiponectin (μg/mL)	6.3 ± 1.1	4.8 ± 0.3	5.7 ± 0.4	8.3 ± 3.3	NS
hs-CRP (ng/mL)	1,226.9 ± 237.3	809.6 ± 127.9	1,426.5 ± 292.3	1,380.6 ± 607.9	NS
8-OHdG (ng/mL)	10.7 ± 0.4	9.4 ± 0.6	11.0 ± 0.7	11.6 ± 0.7	NS

Data presented as mean ± standard error. Data were from the patients completed that phase 1 (intention-to-treat analysis). 8-OHdG, 8-hydroxydeoxyguanosine; BMI, body mass index; BP, blood pressure; F-IRI, fasting immunoreactive insulin; FPG, fasting plasma glucose; F-proinsulin, fasting, proinsulin; HbA1c, glycated hemoglobin; HDL-chol, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-chol, low-density lipoprotein cholesterol; NS, not significant; TG, triglyceride.

in the PIO group than the SU group (271.7 and 133.6 days, respectively, $P < 0.03$; Figure 3c).

Atherogenic markers

Serum adiponectin levels were significantly increased only in PIO-treated patients, but rather lowered in both the LFS and SU groups. Significant decreases in hs-CRP and HOMA-IR were also observed only in the PIO-treated group. The 8-hydroxydeoxyguanosine levels and the insulinogenic index did not change in the three groups. The proinsulin level was significantly lower in the PIO-treated patients than those in the other two groups at the end of phase 1. The proinsulin-to-insulin ratio was not different among the three groups at the end of phase 1 (Figure S2a).

Adiponectin levels in the PIO group decreased to the same level as shown in other groups by the end of the phase 2 period. The proinsulin levels and the proinsulin/insulin ratio were not different among groups at the end of phase 2 (Figure S2b).

Secondary end-point

The proportion of patients who completed phase 1 and achieved HbA1c <6.9% at the end of phase 1 was lower in the LFS group than those in the PIO and SU groups (46.4, 70 and 77% in LFS, PIO and SU, respectively). Just three of 58 (5.2%), 10 of 80 (12.5%) and 18 of 78 (12.8%) patients could maintain their HbA1c levels at <6.2% at the end of phase 1, and three, six and 15 patients were accepted to enter phase 2. The proportion of patients who could maintain their HbA1c levels at <6.2% throughout the phase 2 period was higher in the PIO group than the other groups, and the average duration of HbA1c being maintained at <6.2% was also longer in the PIO group than the other two groups (256.0, 431.5 and 287.9 days in LFS, PIO and SU groups, respectively), but did not differ statistically among the groups (Figure 4a,b).

The incidence of cardiovascular events was very low throughout the study period, and only one cerebral infarction was observed in the SU group. A significant increase in high-density lipoprotein cholesterol levels was observed in the PIO-treated group. No significant changes in other metabolic markers, such as blood pressure, lipids and the liver function, were observed in all three groups during the study.

The overall frequency of adverse events was quite low in all treatment groups. One edema case in the PIO group and one case with hypoglycemia in the SU group during the phase 1 period were observed. No severe adverse events were reported.

DISCUSSION

To our knowledge, the PREVENT-J study is the first trial to elucidate whether temporary intensive treatment with oral antidiabetic medication could modify the natural history of diabetes and/or achieve remission in patients with type 2 diabetes. In order to secure a longer period of observation, we intended to select the patients who were in the early stage of the disease and modestly controlled with HbA1c <7.9% (63 mmol/mol) for drug-naïve patients, or HbA1c <7.4% (54 mmol/mol) for patients on either metformin or α-glucosidase inhibitor.

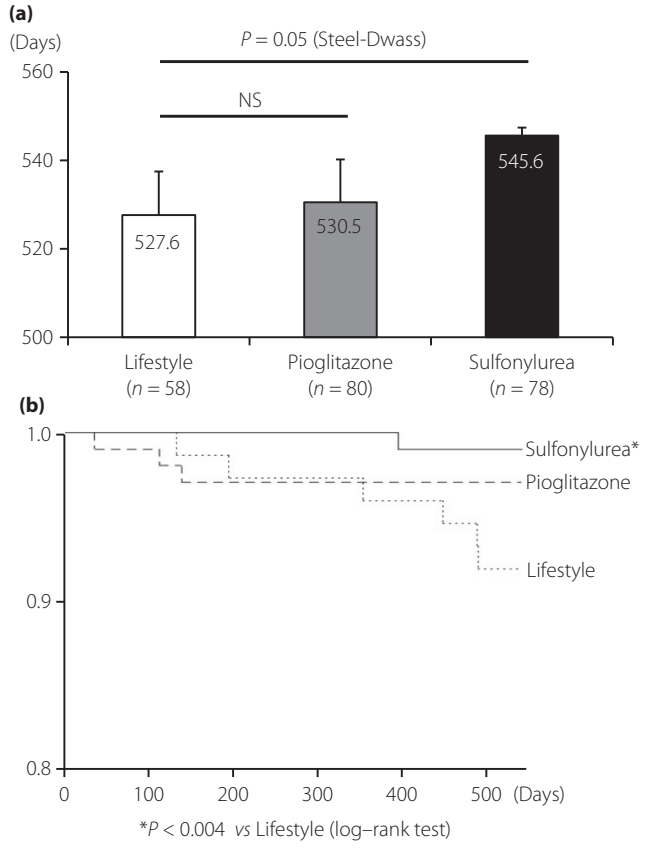

Figure 2 | Glycated hemoglobin <7.9% in the phase 1 period. (a) The duration of glycated hemoglobin being maintained at <7.9% in the phase 1 period as a primary end-point and (b) the proportion of patients that maintained glycated hemoglobin at <7.9% during phase 1 (Kaplan–Meier). NS, not significant.

As expected, the HbA1c reduction in the phase 1 period was significant in both the SU and PIO groups, and was the most prominent in the SU group in the first 6 months. The proportion of patients who achieved HbA1c levels <6.9% was much higher in the SU and PIO groups (75.6 and 70.0%) than the LFS group (44.8%). The rate of interruption as a result of HbA1c elevation (>7.9%) was significantly higher in the LFS intervention group compared with the SU group. Eventually, the duration of HbA1c being maintained at <7.9% as a primary end-point was significantly longer in the SU group than the LFS group. The A Diabetes Outcome Progression Trial study showed that HbA1c levels were lower in patients treated with glyburide than in patients with metformin or rosiglitazone during the first 1.5 years in the trial[6]. The present results also showed that the hypoglycemic effect of SU is more potent in the phase 1 period, as shown in A Diabetes Outcome Progression Trial study.

In contrast, the proportion of patients who could maintain their HbA1c levels at <7.4% in the phase 2 period was significantly reduced in the SU group than other groups, as shown in Figure 3b. As shown in Figure 3a, the duration of HbA1c being maintained at the target 7.4% was not significantly different between the PIO and SU groups, because the majority of patients in both groups could maintain the target HbA1c level. In patients who dropped out as a result of HbA1c elevation, however, the average number of days of maintaining HbA1c levels at <7.4% was much higher in the PIO group compared with the SU group (Figure 3c). Furthermore, the proportion of patients who could keep their HbA1c levels at <6.2% throughout phase 2 was numerically the highest in the PIO group, and the average number of days of maintaining HbA1c levels at <6.2% in patients whose HbA1c reached ≥6.2% in phase 2 was also the highest in the PIO group. These results suggest a better sustainability of PIO for glycemic control, even after the withdrawal of medication.

It is well known that PIO is one of the most effective therapies for improving glucose homeostasis and insulin resistance in type 2 diabetes patients. Actually, a significant effect of PIO has been shown for a relatively better durability in glycemic control (ref. A Diabetes Outcome Progression Trial study)[6] and diabetes prevention in impaired glucose tolerance (ref. Actos Now for the Prevention of Diabetes study)[15]. As a protective effect of PIO on disease progression, a large body of evidence has shown that PIO protects against pancreatic β-cell damage and preserves β-cell function in animal models of diabetes[16,17]. In addition to amelioration of insulin resistance, a preventive effect on β-cell dysfunction might account for a contributing factor of PIO on HbA1c exacerbation in the present study.

A significant increment of proinsulin level, however, was unexpectedly observed after pioglitazone withdrawal (phase 2 period), despite the level not being different from those in the other two groups. A significantly higher level of proinsulin was observed in five out of 36 cases, which pulled above the average in the PIO group. Although the change in proinsulin level seemed to be emphasized because of the lower level at the baseline, the present results suggest that pioglitazone does not always sufficiently preserve the β-cell function under certain conditions. The underlying mechanism of this issue is a future task to be solved.

Interestingly, all of the 23 patients in the LFS group could sustain the target HbA1c level of <7.4% throughout phase 2. This might suggest that LFS intervention is still effective for glycemic control in patients with a relatively early stage of diabetes. However, the absolute proportion of patients who completed phase 1 and achieved the target HbA1c of <7.4% throughout the study period (36 months) was the smallest in the LFS group in comparison with the other two groups (39.6, 45.0 and 44.8% in LFS, PIO and SU, respectively).

In the present study, the new onset of cardiovascular diseases was very low throughout the whole study period, probably because patients with previous cardiovascular diseases were excluded. However, a significant increase in serum adiponectin level, and decreases in hs-CRP and HOMA-IR were shown in patients treated with PIO, but not LFS and SU, in the on-treatment period (phase 1). PIO is known to have a beneficial effect

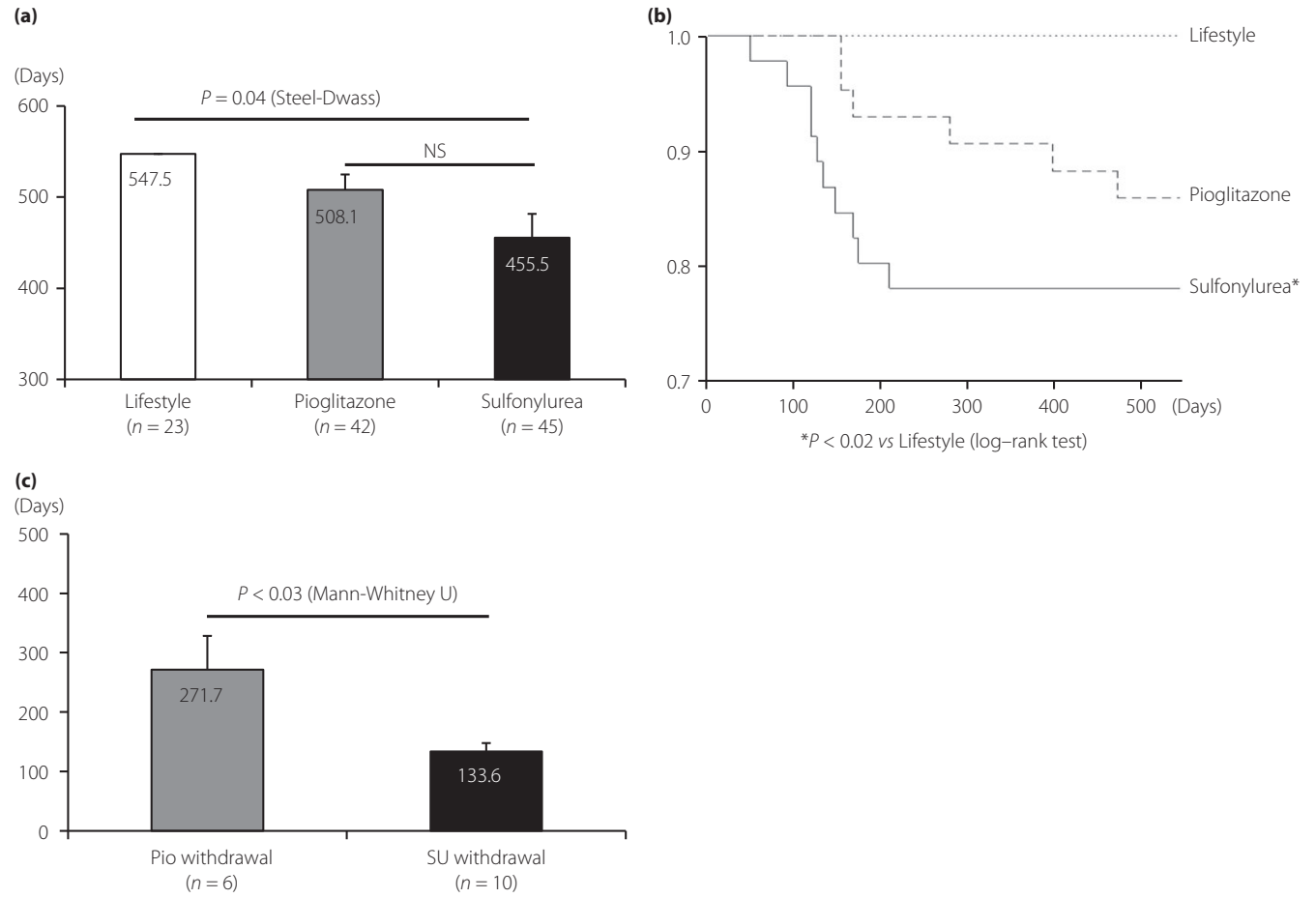

Figure 3 | Glycated hemoglobin (HbA1c) <7.4% in the phase 2 period. (a) The duration of HbA1c being maintained at <7.4% in patients who completed phase 2 as a primary end-point and (b) the proportion of the patients that maintained HbA1c at <7.4% during phase 2 (Kaplan–Meier). The duration of HbA1c being maintained at <7.4% throughout phase 2 was calculated as 547.5 days. (c) The duration of HbA1c being maintained at <7.4% in phase 2 was compared between pioglitazone- and sulfonylurea-treated groups. Data only from the patients who terminated the study in the middle of phase 2 as a result of elevation of HbA1c >7.5% were used. NS, not significant.

on atherogenic markers and progression of cardiovascular risk markers[18–20]. Unfortunately, these effects of PIO were not sustained, and were completely canceled by the end of phase 2. These results might suggest that an action mechanism of PIO on anti-atherosclerosis would be different from that on antihyperglycemic effects.

The present study had a few limitations. First, the study was carried out under the prospective, randomized, open-label, blinded end-point design, thereby some sort of bias might not always be excluded in the assessment of outcomes. Although the independent evaluation committee members assessed end-points blinded to the treatment assignment, open-label treatments might affect the investigators' choice of management in the clinical setting. In fact, daily doses of PIO and SU were relatively lower than usual daily doses, probably due to avoiding its adverse events. The possibility cannot be denied that such behavioral characteristics for prescription might attenuate a clinical efficacy of PIO. Second, the patients who were enrolled in the present study were limited to being in the relatively early stage of diabetes, because the study protocol included the patient group not taking antidiabetic drugs for a longer duration. Thus, the present data might not be always applicable universally in the real world for the treatment of type 2 diabetes patients. It is still unclear whether or not the present results would be able to extrapolate to patients whose diabetic stage is advanced. In addition, the present data do not always show clearly how long the period of PIO treatment would be required to obtain a significant remission of disease without pharmacotherapy. A further study of a larger and longer scale should be necessary to reconfirm the present results.

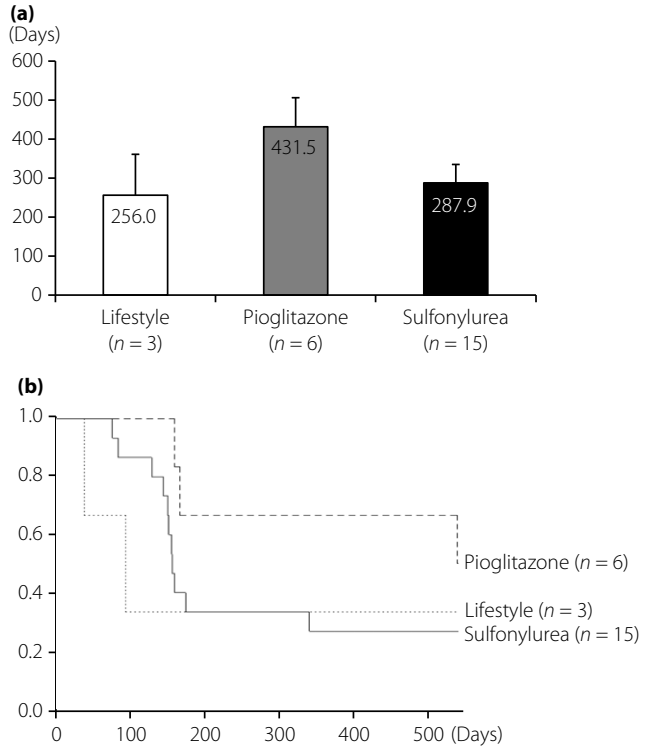

Figure 4 | Glycated hemoglobin (HbA1c) <6.2% in the phase 2 period (*n*, the number of patients that maintained HbA1c <6.2% at the start of the phase 2 period). (a) The duration if HbA1c being maintained at <6.2% in phase 2 as a secondary endpoint and (b) the proportion of the patients that maintained HbA1c <6.2% during phase 2 (Kaplan–Meier).

In conclusion, pharmacological intervention with PIO for 18 months provides a relatively longer remission of hyperglycemia after interruption of medication in type 2 diabetes patients with the early stage of disease.

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DISCLOSURE

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APPENDIX 1

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APPENDIX 2

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Organizer: Yukio Tanizawa, Shigeru Okuya, Kiminori Yamane, Kazushi Ishida.

APPENDIX 3

Efficacy and Safety Evaluation Committee

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 | Study design.
Figure S2 | Atherogenic and metabolic markers. Effects of lifestyle intervention (LS), pioglitazone (PIO) and sulfonylurea (SU) on atherogenic and metabolic markers were compared in (a) phase 1 and in (b) phase 2 (per protocol analysis).
Table S1 | Patient characteristics at the beginning of phase 2 at 18 months of the study. Data were from the patients preceding phase 2 (intention-to-treat analysis).
Table S2 | Patient characteristics at the end of phase 2 at 36 months of the study. Data were from the patients completed phase 2 (ITT analysis).