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Continuation or discontinuation of pioglitazone when starting bedtime insulin in patients with poorly controlled type 2 diabetes in an inner-city population

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Abstract

Objective—We studied the impact of continuing versus discontinuing pioglitazone on hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and weight when starting bedtime insulin in patients with poor glycemic control.

Methods—We retrospectively analyzed data from a 13-month randomized control trial on 77 patients with type 2 diabetes mellitus (DM), who despite maximum doses of three oral diabetes medications (metformin, sulfonylurea and pioglitazone) had HbA1C levels above 7.5%. Patients were randomized to either continuing or discontinuing pioglitazone in addition to starting and up-titrating bedtime insulin. HbA1C, FPG, and weight were assessed at baseline, 3 months, 7 months and 13 months with the differences from baseline for the two groups compared at each of the three time points using the Wilcoxon rank sum test.

Results—We found that HbA1c was significantly lower at the 7-month (p=0.01) and 13-month time points (p=0.036) and FPG was significantly lower at all three time points in the group continuing pioglitazone compared with those discontinuing pioglitazone. Continuing pioglitazone resulted in a greater increase in weight at the 3-month (p=0.002), 7-month (P=0.0001) and 13-month (P=0.00003) time points. Patients with the lowest HbA1c (< 8.2%) at baseline were more likely to benefit from continuing pioglitazone than those with higher baseline HbA1c. Patients who started insulin and discontinued pioglitazone had similar HbA1c, FPG and weight at the three time points as at baseline, suggesting that pioglitazone and bedtime insulin has similar glycemic effect in this population.

Conclusions—We conclude that in patients with uncontrolled type 2 DM, continuing pioglitazone while concurrently starting bedtime insulin within a 13-month period led to a significant decrease in both HbA1c and FPG levels compared with those who did not receive pioglitazone; however weight increased during this period.

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Keywords

Type 2 diabetes; thiazolidinedione; metformin; Actos; pioglitazone; sulfonylurea; HbA1c

1. Introduction

Diabetes mellitus (DM) is a chronic disease that leads to both microvascular and macrovascular complications (American Diabetes Association, 2014). Data from the 2014 National Diabetes Fact Sheet showed that in the United States, 29.1 million (9.3%) of the population has DM and the total costs for diagnosed cases in 2012 were $245 billion (Centers for Disease Control and Prevention, 2014). Type 2 DM, which accounts for approximately 90% of patients affected by the disease, is due to both defects in pancreatic β-cell secretion as well as increased insulin resistance. The treatment for type 2 DM includes nutritional counseling and increased physical activity, followed by oral anti-hyperglycemic agents and eventually insulin if glycemia is not controlled adequately (Derosa, 2010). A survey from 2007 to 2012 among US adults diagnosed with type 2 DM demonstrated that 64% of patients met adequate glycemic targets (Cheung et al., 2009).

Medical treatment for type 2 DM usually involves a step-wise, approach with metformin recommended as the initial treatment (Inzucchi et al., 2012). If hyperglycemia persists following metformin treatment, the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) 2012 Position Statement algorithm on antihyperglycemic therapy recommended additional agents, including sulfonylureas, glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, or insulin (Inzucchi et al., 2012). In the Los Angeles County Department of Health services (LAC-DHS), there are approximately 75,000 mostly safety net patients with DM, and a treatment algorithm has been developed for these patients. Following maximum metformin therapy, a sulfonylurea (glimepiride, glyburide or glipizide) is added and its dose is maximized. If the HbA1c is still elevated, pioglitazone (Actos), a thiazolidinedione which has a mechanism of action of activating the peroxisome proliferator-activated-γ receptor (PPARγ) in liver, skeletal muscle, and adipose tissues and therefore reducing resistances of these tissues to insulin (Derosa, 2010), is added. After a maximum dose of pioglitazone (45 mg) is prescribed and the HbA1c is still elevated, the standard protocol in LAC-DHS is to stop pioglitazone and add bedtime NPH insulin, while continuing on metformin and the sulfonylurea agent. The principle behind this regimen, originally called bedtime insulin/daytime sulfonylurea (BIDS) (Yki-Jarvinen et al., 1992), is that the bedtime insulin reduces the morning fasting plasma glucose (FPG), while the oral medications maintain glycemic control throughout the day.

Some advantages of pioglitazone treatment are reductions in HbA1c, FPG as well as in cardiovascular risk and reductions in inflammatory markers, including CRP, tumor necrosis factor-α and interleukin-1 (Zhang, Schwartz, Permana, & Reaven, 2008). Compared with other oral anti-hyperglycemic agents, pioglitazone use is associated with lower incidences of hypoglycemia and improvements in the lipid profile, blood pressure, and carotid intima media thickness (Derosa, 2010). Some of the disadvantages of pioglitazone include edema,

heart failure, weight gain, anemia, increased fracture rate, macular edema, and possible associations with bladder cancer (Colmers, Bowker, Majumdar, & Johnson, 2012; Derosa, 2010). A 3–5% incidence of mild to moderate edema was associated with pioglitazone monotherapy, with the percentage increased when pioglitazone was combined with insulin (Nesto et al., 2004; Parulkar, Pendergrass, Granda-Ayala, Lee, & Fonseca, 2001). An increase in the body weight with the use of pioglitazone occurs due to fluid retention and increased fat mass, and is more severe when pioglitazone is administered in combination with insulin (Derosa, 2010).

Several studies showed that the addition of thiazolidinediones to insulin significantly improved glycemic control of patients with type 2 DM that are not adequately controlled with insulin therapy (Buch et al., 2002; Buse et al., 1998; Mattoo et al., 2005; Miyazaki et al., 2001; Rosenstock et al., 2002; Rubin, Egan, & Schneider, 1999; Strowig, Aviles-Santa, & Raskin, 2002). However, the continuation or discontinuation of pioglitazone with the initiation of night-time insulin has not been studied. With the approval of generic pioglitazone in 2012 and the subsequent reduction in price, studying the use of pioglitazone in combination with insulin is now of greater importance, especially for safety-net clinics in which both cost of medications and convenience for patients (single night-time injection with morning glucose monitoring versus multiple insulin dosing requiring more intense glucose monitoring) become an issue.

In the diabetes clinic at of Martin Luther King, Jr. Multi-Service Ambulatory Care Center (MLK-MACC), now called Martin Luther King, Jr. Outpatient Center (MLK-OC), we noticed that when patients were followed with the above glycemic regimen and had their pioglitazone discontinued upon initiation of bedtime NPH insulin, their glycemic control often did not improve. Thus, the objective of this study was to compare the impact of continuing versus discontinuing pioglitazone when bedtime insulin is started, on HbA1c and FPG outcomes in a predominantly minority safety-net population over a 13-month repeated measure interval. We also assessed weight gain in the two groups, as it is common adverse effect of pioglitazone treatment.

2. Methods

2.1 Design, setting and sample

This study examined patients with type 2 DM with poor glycemic control (HbA1c above 7.4%) from the Diabetes Clinic at MLK-MACC between January 1, 2010 and December 31, 2012; they were randomly assigned (based on whether their medical record number was either even or odd) to either continue or discontinue pioglitazone when starting on bedtime insulin. All patients received their usual diabetes care by their providers (one physician, two nurse practitioners and one physician assistant) throughout the study. Their providers were aware that the patients were in the study and in which arm they were assigned. Patients starting on insulin and continuing on pioglitazone were usually counseled that weight gain and fluid retention may occur although it was not done in a systematic manner. The patients were on the maximum dose of metformin, sulfonylurea (either glimepiride, glyburide or glipizide) and pioglitazone (45 mg given orally every morning) for at least 3 months and had an HbA1c above target (>7.4%) before starting bedtime insulin (Davidson, 2010). Bedtime

NPH insulin was started at a dose of 16 units in patients with a desirable body weight ≥ 120% and 10 units in patients with a desirable body weight < 120%. The dose of insulin was adjusted at each clinic visit between 2–3 weeks initially and 4–6 weeks subsequently (although due to compliance issues, sometimes the dose was adjusted less frequently), based on FPG from patients' self-monitoring of blood glucose (SMBG) results. Patients who did not achieve glycemic control while on bedtime insulin were switched by their provider to twice-a-day insulin, and all data analysis ended at that time. Lifestyle changes were encouraged at each visit, and lifestyle counseling did not change during the study period. Medical records of these patients were retrospectively analyzed and FPG (analyzed in clinic using a Novo Biomedical glucometer), HbA1c (analyzed by a Tosoh G8 HPLC analyzer at the MLK-MACC pathology department), weight, and dose of insulin were assessed at baseline as well at approximately 3, 7, and 13 months afterwards. Insulin dose was only available on some of the patients, and some data including weight, HbA1c and FPG were missing on a small number of subjects. The study was approved by expedited review under 45 CFR 46.110(b)(1) (category 5) by the County of Los Angeles Department of Public Health Institutional Review Board that reviews research projects at LAC-DHS.

2.2 Statistical analyses

The two groups (continuation versus discontinuation of pioglitazone) were compared at each of the three time points using the Wilcoxon rank sum test and corrected using the Bonferroni correction factor. In addition, two-way repeated measures analysis of variance, with the Greenhouse-Geisser correction for lack of circularity of the variance-covariance matrix, was used to evaluate the effect of pioglitazone over time. Adjustment to the significance of group differences based on either type of sulfonylurea used, gender, or language spoken was considered by the use of a linear model incorporating these covariates. For missing data, last value carried forward analysis was used. Data are reported as mean ± SD.

3. Results

3.1 Clinical characteristics of sample

The total number of patients was 77 (mean age, 53.9 ± 7.9 years; 48 women, 29 men) with baseline descriptive statistics for those randomized to the continued (31 patients) and discontinued (46 patients) pioglitazone groups listed in Table 1. There were no statistical differences in baseline parameters.

3.2 Effects of pioglitazone continuation or discontinuation on HbA1c, FPG and weight

The differences for HbA1c, FPG and weight in the continued and discontinued pioglitazone groups at baseline, 3 months, 7 months and 13 months are shown in Fig. 1A, 1B and 1C, respectively. Those in the continued pioglitazone group had a lower HbA1c at 7 and 13 months, a lower FPG at 3 months, 7 months and 13 months and a higher weight at 3 months, 7 months and 13 months. Adjustment for type of sulfonylurea used, gender or primary language did not change the significance of the main outcomes. Fig. 2 shows the average dose of insulin for patients in the two groups at 3 months, 7 months and 13 months with no differences in insulin dosing at each point. Considering the analyses of HbA1c, FPG and weight results over time using the two-way repeated measures analysis of variance, similar

outcomes are seen by considering the group-by-time interaction: reduced HbA1c (p=0.0009), reduced FPG (p=0.001), and increased weight (p=0.004).

Table 2 shows the number of patients that achieved glycemic targets of HbA1c ≤ 7.0% and ≤ 8.0% in both the continued pioglitazone and the discontinued pioglitazone groups. Ten out of 45 patients in the discontinued pioglitazone did not achieve adequate glycemic control on night time only insulin therapy as determined by their provider and subsequently required twice daily insulin, compared with 3/31 in the continued pioglitazone group (chi squared=2.03, p=NS). There were no reports of patients in either group having significant edema or severe hypoglycemia.

3.3 Effects of baseline HbA1c quartiles on HbA1c levels in the continued pioglitazone group compared with the discontinued pioglitazone group

Table 3 depicts the Wilcoxon rank sum test for change from baseline for HbA1c according to baseline quartiles in the continued pioglitazone group compared with the discontinued pioglitazone group. At the 3- and 7-month time points, only those patients with a HbA1c in the lowest quartile at baseline had a difference between the two groups. In contrast, at the 13-month time point, there was a difference between the two groups for the 1st, 3rd and 4th quartiles. Overall this data suggests that the patients with the lowest HbA1c (< 8.2%) at baseline are more likely to benefit from continuing pioglitazone.

4. Discussion

Our main findings are that patients with uncontrolled diabetes who continued pioglitazone when starting bedtime insulin had both lower HbA1c and FPG compared with the group who discontinued pioglitazone. FPG and HbA1c remained elevated in patients assigned to both arms of the study, suggesting that insulin was not up-titrated as aggressively as needed. Because this study was a retrospective analysis of existing charts of patients with diabetes, we can not provide an explanation of why insulin dose was not adjusted more aggressively or why switching to twice daily insulin was not done earlier. However, it is likely that these management decisions occurred equally in both groups. The lower HbA1c and FPG in the group who continued pioglitazone was offset by weight gain in this group (average weight gain 4.0 kg at 13 months) compared with the discontinued pioglitazone (average weight loss of 1.2 kg at 13 months). Thus the advantages and disadvantages of continuing pioglitazone when starting bedtime insulin need to be determined for each patient. It is also noteworthy that in those who started bedtime insulin and discontinued pioglitazone, both FPG and HbA1c were constant, indicating that the glucose-lowering effects of pioglitazone and bedtime insulin are similar. This needs to be confirmed in a larger study, but suggests that the switch from pioglitazone to insulin, which is more labor-intensive to the patient, may not achieve better glycemic control. As we also found that those patients with a HbA1c in the lowest quartile at baseline had more beneficial effects of continuing pioglitazone, our paper suggests that pioglitazone should be continued in those with an HbA1c less than 8.2%. The cost of pioglitazone has been substantially reduced and larger purchasers such as LAC-DHS obtain a substantial discount compared with retail costs. The overall cost of insulin therapy

including the cost of insulin, syringes and glucose strips versus the costs of pioglitazone needs to be assessed for each medical system.

In 2001, a systematic review of the clinical effectiveness of pioglitazone was published (Chilcott, Tappenden, Jones, & Wight, 2001) and cited only one abstract of insulin plus pioglitazone or placebo (Rubin, Egan, & Schneider, 1999). This abstract found that 15 and 30 mg of pioglitazone decreased HbA1c by 0.73% and 1.0%, respectively, over placebo (Rubin, Egan, & Schneider, 1999). The systematic review concluded that pioglitazone was an effective adjunct to either metformin or sulfonylurea, but more studies are needed to address pioglitazone in combination with other antidiabetic agents. We found several additional studies on thiazolidinedione [troglitazone (Buch et al., 2002; Buse et al., 1998; Strowig, Aviles-Santa, & Raskin, 2002), pioglitazone (Berhanu, Perez, & Yu, 2007; Charbonnel et al., 2010; Davidson, Perez, Zhang, & Pioglitazone 343 Study, 2006; Mattoo et al., 2005; Miyazaki et al., 2001; Rosenstock et al., 2002; Yamanouchi, 2010; Yasunari et al., 2011), or rosiglitazone (Raskin et al., 2001) added to insulin regimens in patients with type 2 DM. These studies all found that the addition of pioglitazone to insulin significantly improved glycemic control of patients with type 2 DM who were not adequately controlled with insulin therapy. The duration of most of these studies was for 6-months and edema and body weight gain were the most common adverse effects reported for the combined use of thiazolidinedione and insulin. While these studies importantly show the effectiveness and safety of adding pioglitazone to insulin therapy, they do not directly address the more clinically relevant issue of whether pioglitazone should be stopped when insulin is started. It is common for patients who are treated with triple oral glycemic therapy, including pioglitazone, to have insulin added. However, it is unlikely to have pioglitazone added to those patients on insulin, who, if still hyperglycemic, would have their insulin regimen intensified.

Hsia (Hsia, 2011) used a similar population from the diabetes clinic at our outpatient center, and performed a prospective randomized study comparing a single doses of bedtime NPH, bedtime glargine insulin, or morning glargine insulin in patients on triple oral medications who had their pioglitazone discontinued when they started the study. In each group, the average HbA1c decreased from 9.3% to 7.8% that may reflect that patients in a prospective study are closely monitored by the study coordinator to assure that they come to their appointments and adhere to their medications, conditions that were absent in our retrospective analysis of the actual practice in our diabetes clinic. Dorkham et al. (Dorkhan, Frid, & Groop, 2008) compared the addition of glargine insulin and pioglitazone in patients with type 2 DM on metformin and sulfonylurea and found that the effect of glargine insulin of HbA1c was not significantly different from that of pioglitazone. This is similar to our findings in that HbA1c and FPG were similar before and after the addition of night-time NPH insulin and discontinuation of pioglitazone. Thus, if a single injection of insulin is added and pioglitazone is discontinued in patients with an elevated HbA1c, providers and patients should anticipate that an intensification of insulin therapy may be needed. With the development of new classes of non-insulin medications for type 2 DM including DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors, combination of these drugs with the triple oral regimen of metformin, sulfonylurea and pioglitazone can be used instead of initiating insulin therapy.

4.1 Strengths and limitations

The strengths of our study include addressing an important issue in the step-wise management of patients with type 2 DM, its duration of one-year, the participant population of inner city, mostly-indigent patients, and the real-world setting of the study being carried out during patient care in a diabetes clinic. The weaknesses of the study include the lack of a placebo group, uneven randomization at baseline, lack of aggressive up-titration of insulin to reduce hyperglycemia and its retrospective nature.

5. Conclusions

In conclusion, we found that in patients started on night-time insulin, continuing pioglitazone led to lower HBA1c and FPG, but increased weight gain. Providers and patients need to determine if the glycemic benefits outweigh the detrimental effects on weight.

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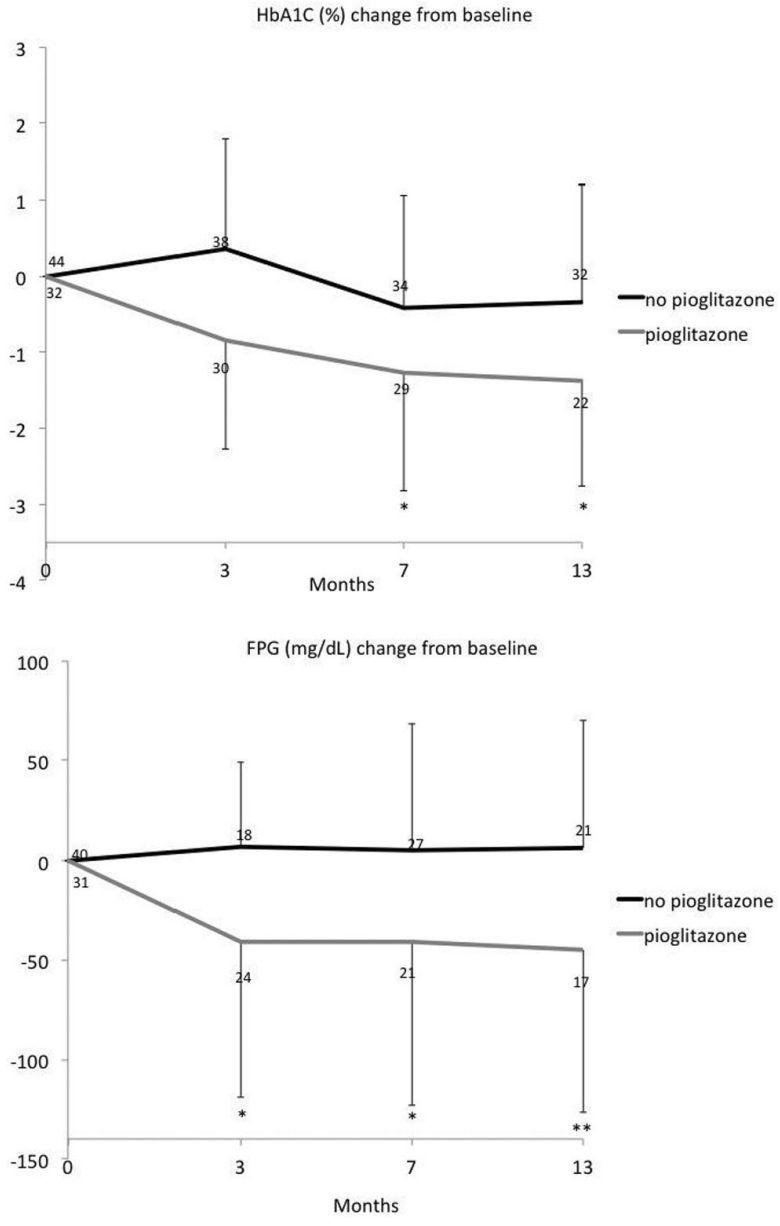

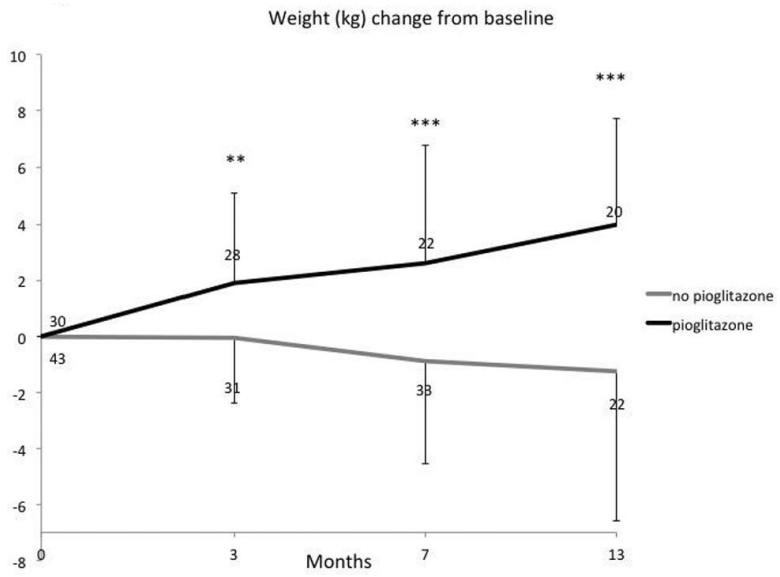

Figure 1.

Change from baseline (mean ± SD) in patients continuing and discontinuing pioglitazone at 3 months, 7 months and 13 months for HbA1c (A), FPG (B) and weight (C). *, $p < 0.05$, **, $p < 0.005$, ***, $p < 0.0005$. Number of subjects analyzed at each time point is given.

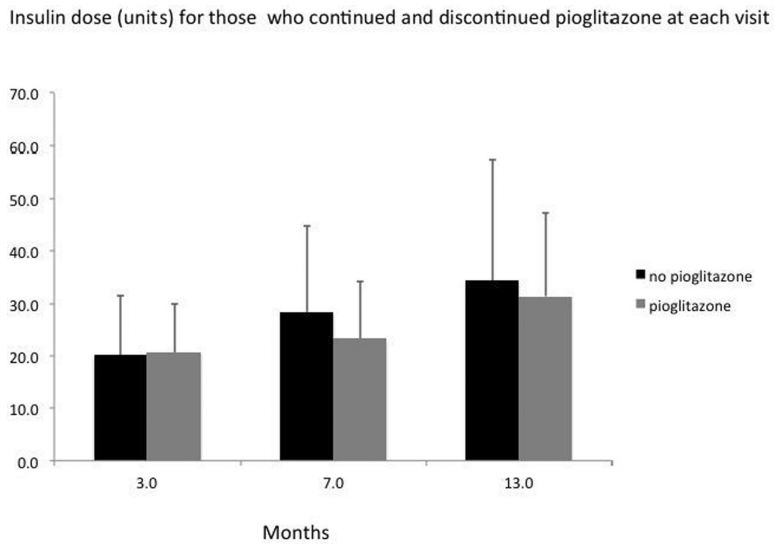

Figure 2.

Mean ± SD insulin dose in those patients continuing and discontinuing pioglitazone at 3 months, 7 months and 13 months. p=NS at all time points.

Table 1

Baseline values of patients who continued and discontinued pioglitazone when starting bedtime insulin.

	Continued Pioglitazone (31)	Discontinued Pioglitazone (46)	p-value
Age *	53.6±7.3	54.0±8.3	0.92
Weight *	82.7±17	84.6±21	0.17
HbAlc(%) *	9.82±1.7	9.29±1.6	0.13
FPG (mg/dL) *	214±71	187±68	0.10
Gender-male	12	17	0.98
Gender-female	20	28	
Language-Spanish	22	32	0.82
Language-English	10	13	
Glimepiride	4	15	0.10
Glyburide	6	8	
Glipizide	22	22	

* Mean±SD

Table 2

Number of patients who continued and discontinued pioglitazone that achieved HbAlc goal out of total number of patients that had HbAlc measured at that time.

	Continued Pioglitazone	Discontinued Pioglitazone	P-value of chi-squared test
3-months			
≤ 7.0%	4/30	2/38	0.24
≤ 8.0%	14/30	16/38	0.71
7-months			
≤ 7.0%	2/29	7/34	0.12
≤ 8.0%	16/29	14/34	0.27
13-months			
≤ 7.0%	2/22	6/32	0.33
≤ 8.0%	13/22	17/32	0.66

Table 3

Wilcoxon rank sum test for change from baseline for HbAlc according to baseline HbAlc quartiles in the continued pioglitazone group compared to the discontinued pioglitazone group.

Time point	HbAlc: 1st quartile (< 8.2%) at baseline	HbAlc: 2nd quartile (8.2% −8.89%) at baseline	HbAlc: 3rd quartile (8.9% −10.59%) at baseline	HbAlc: 4th quartile (> 10.6%) at baseline
3 months	P=0.004	P=0.15	P=0.97	P=0.79
7 months	P=0.009	P=0.22	P=0.19	P=0.36
13 months	P=0.03	P=0.18	P=0.01	P=0.04