Diabetes Incidence and Glucose Tolerance after Termination of Pioglitazone Therapy: Results from ACT NOW

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Thiazolidinediones have proven efficacy in preventing diabetes in high risk individuals. However, the effect of TZDs on glucose tolerance after cessation of therapy is unclear. We examined the effect of pioglitazone on incidence of diabetes after discontinuing therapy in ACT NOW. 293 subjects (PLACEBO, n=138; PIOGLITAZONE, n=152) completed a median follow up of 11.7 months after study medication was stopped. Diabetes developed in 17/138 (12.3%) PLAC vs. 17/152 PIO (11.2%, p=ns PIO vs PLAC). However, the cumulative incidence of diabetes from start of study medication to end of washout period remained significantly lower in PIO vs PLAC (10.7% vs 22.3%, $p < 0.005$). After therapy was discontinued, 23.0% (35/152) of PIO remained NGT vs 13.8% (19/138) of PLAC (p=0.04). Insulin secretion/insulin resistance (IS/IR) index ($\Delta I_{0-120}/\Delta G_{0-120}$ x MI) was markedly lower in IGT subjects who converted to diabetes during follow up versus those who remained IGT or NGT. The decline in beta-cell function (IS/IR index) was similar in IGT subjects who developed diabetes, irrespective of whether they were treated with PIO or PLAC.

CONCLUSION: (1) the protective effect of PIO on incidence of diabetes attenuates after discontinuation of therapy, (2) cumulative incidence of diabetes in individuals exposed to PIO remained significantly (56%) lower than placebo and a greater number of PIO-treated individuals maintained NGT after median follow-up of 11.4 months; (3) low insulin secretion/insulin resistance index is a strong predictor of future diabetes following PIO discontinuation.

Approximately 30% of adults in the US have impaired glucose tolerance (IGT) (1, 2). The conversion rate of IGT to T2DM varies from 3%–11% per year, and the lifetime risk of T2DM is about 50% (3, 4). Hyperglycemia is the major risk factor for microvascular complications (UKPDS, DCCT), which account for a significant portion of the morbidity and mortality in T2DM. Early detection and treatment would be expected to prevent or delay the onset of these complications. Both lifestyle and pharmacologic interventions, including metformin, thiazolidinediones, and alpha glucosidase inhibitors, have been shown to prevent/delay the progression of IGT to T2DM (5–9). However, it is not clear whether the protective effect of these agents persists after discontinuation of therapy.

Following completion of the Diabetes Prevention Program (DPP) study, subjects were invited to participate in

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Abbreviations:

a lifestyle modification (DPPOS) and followed for 10 years (6, 10). Most subjects in the lifestyle intervention arm regained the lost weight, and the difference in incidence of new diabetes between the lifestyle intervention, metformin, and placebo groups was not significant during the follow-up period (11). However, the cumulative incidence of diabetes remained significantly lower in the group initially treated with lifestyle. In DPP, a group of IGT subjects also received treatment with troglitazone, which was discontinued early because of liver toxicity (12). In troglitazone-treated subjects, a highly significant diabetes preventive effect was observed one year after troglitazone was discontinued (13). Similarly, in TRIPOD women with history of gestational diabetes and who were treated with troglitazone had a lower cumulative incidence of diabetes compared to those treated with placebo one year after discontinuation of treatment (14). In DPP, subjects who reverted to NGT any time during the trial, regardless of the treatment arm, had a lower incidence of diabetes (15). In ADOPT, rosiglitazone had the most durable effect on glycemic control in recently diagnosed T2DM individuals (16). In DREAM 1.6 years after withdrawal of rosiglitazone, the cumulative incidence of diabetes was 39% lower than those treated with placebo (17). These results with thiazolidinediones (12–17) and lifestyle intervention (11, 17) demonstrate a true slowing of the disease, ie, reduced conversion of prediabetes to diabetes, and not a masking of the disease, since there was not a higher rate of new cases of diabetes in the TZD or lifestyle group compared with the placebo group after the therapy was stopped (18).

In ACT NOW pioglitazone reduced the prevalence of T2DM by 72% (5). Herein, we describe the incidence of diabetes and glucose tolerance after cessation of pioglitazone in ACT NOW.

Materials and Methods

Patients and Study Design

The details of recruitment, inclusion and exclusion criteria, study design, and patient characteristics of ACT NOW participants have been published (5). At baseline, 602 IGT subjects received 2-hour OGTT, and plasma samples were obtained every 15 minutes for determination of glucose and insulin concentrations. Participants then were randomized to pioglitazone (30 mg/d) or placebo. One month after randomization, pioglitazone was increased to 45 mg/d. Baseline measurements were repeated at study end (2.4 years after recruitment of last subject), at time of dropout or loss to follow-up (last observation carried forward (LOCF)), or at time of conversion to T2DM. After the closeout visit, pioglitazone and placebo were discontinued and subjects were asked to return for follow-up visits at six month intervals. Of 443 subjects who had closeout visit, 290 (PIO, n = 152 and PLAC, n = 138) returned for at least one six month follow-up visit, had repeat OGTT, and were included in the present analysis. Appropriate informed consent was obtained from all study participants and appropriate treatment of research subjects was carried out.

Measurements. Plasma glucose was measured by glucose oxidase reaction, plasma insulin by radioimmunoassay (RIA) (Diagnostic Products, Los Angeles, CA, USA) (interassay and intra-assay CV 7.1% and 5.1% respectively), and HbA_{1c} with DCA 2000 Analyzer (Bayer, Leverkusen, Germany). Total plasma cholesterol, triglycerides, and HDL cholesterol were measured using enzymatic assay (Stanbio Laboratory, Boerne, TX, USA). LDL-cholesterol was calculated using Friedewald equation.

Calculations. Incremental AUC for plasma glucose and insulin during OGTT was calculated according to trapezoidal rule. The primary stimulus for insulin secretion is the increment in plasma glucose concentration, and insulin section was calculated as the increment in plasma insulin concentration (ΔI) (AUC) divided by the increment in plasma glucose concentration (ΔG) (AUC) from 0 to 120 minutes (ΔI/ΔG). Insulin sensitivity during OGTT was calculated from the Matsuda index (MI). β-cell function was calculated as the insulin secretion (IS)/ insulin resistance (IR) index ($\Delta I_{0-120}/\Delta G_{0-120}$ x (MI) during OGTT. We previously have shown that IS/IR index calculated with $\Delta I_{0-120}/\Delta G_{0-120}$ x MI yields values similar to those calculated with $\Delta Cpep_{0-120}/\Delta G_{0-120}$ (5, 19).

Statistical Analysis. Statistical analyses were performed using SPSS, version 21 (Chicago, IL). Differences between values before and after treatment (within placebo and pioglitazone groups) were analyzed using paired Student's *t* test. Comparisons between placebo and pioglitazone groups were made by independent-samples *t* test (or appropriate nonparametric method) or Chi square, as appropriate. Risk of developing diabetes was analyzed by Cox Proportional Hazard Regression. Comparison between different stages of glucose tolerance was performed using ANOVA with Bonferroni post hoc testing when appropriate. The original sample size calculation (n = 600) was provided in an earlier publication (5). The present study represents a post hoc analysis of subjects who participated in at least one 6-month follow-up visit. Data are presented as mean ± SEM.

Results

Baseline Clinical Characteristics

Of the initial cohort of 602 IGT subjects, 441 individuals received a closeout visit with OGTT, and 290 came for at least the 6 month follow-up visit (Figure 1). Table 1 shows clinical characteristics of the post-treatment follow-up cohort. There were slightly more females in the placebo group. Other clinical, anthropometric, and laboratory parameters were similar in pioglitazone and placebo groups. As expected, at the close out visit, PIO-treated subjects had lower fasting and 2-hour plasma glucose concentrations and there were more individuals with NGT in PIO vs PLAC group.

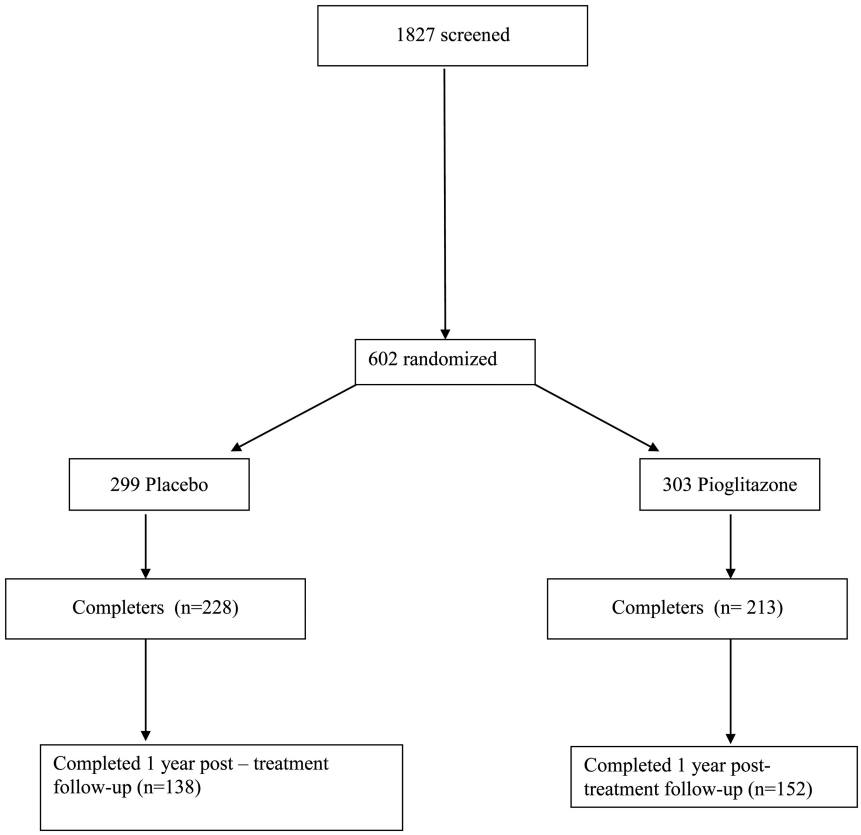

Figure 1. Flow diagram representing number of subjects at time of randomization, at end of active treatment period, and at 11.4 months following cessation of therapy.

Incidence of Diabetes

In ACT NOW, median follow up was 2.4 years and 50 PLAC subjects and 15 PIO subjects developed diabetes (HR = 0.28, $P < .005$). Following cessation of therapy, median follow-up period was 11.4 months in both PIO- and PLAC-treated groups. Diabetes developed in 17/138 (12.3%) in PLAC vs. 17/152 PIO (11.2%) (HR = 0.836; 95% CI 0.421, 1.658, p=ns) (Figure 2B). However, the cumulative incidence of diabetes from time of initial randomization to end of washout period (11.4 months following cessation of therapy) remained significantly lower in PIO vs PLAC (HR = 0.436; 95% CI 0.285–0.668, $P < .005$) (Figure 2A).

Presence of Normal Glucose Tolerance:

11.4 months after therapy was discontinued, 23.0% (35/152) of PIO-treated subjects remained at NGT vs 13.8% (19/138) of PLAC-treated individuals ($P = .04$). Cumulative incidence of NGT (at least once during the entire follow- up) was higher in PIO vs PLAC (101/213 vs 61/228, $P < .05$).

Incidence of Diabetes in Relation to Glucose Tolerance at Time of Therapy Cessation

In PIO group at the end of active treatment (median follow up = 2.4 years), 81 subjects had NGT and 71 had IGT. Of subjects with NGT only 3 (4%) converted to T2DM after 11.4 months vs 13 (24%) who had IGT (HR = 0.176, 95% CI 0.05–0.618, $P = .007$) (Figure 3).

In PLAC group at the end of active treatment, 49 had NGT and 89 had IGT (both $P < .01$ vs PIO). Similarly, the rate of conversion to T2DM was significantly lower in NGT subjects (2/49, 4%) vs IGT subjects (15/89, 17%) (HR = 0.213, 95% CI 0.048–0.96, $P = .04$) after 11.4 months.

Changes in Insulin Sensitivity and Insulin Secretion

After 2.4 years of PIO treatment, both Matsuda index of insulin sensitivity (4.11 ± 0.2 to 8.20 ± 0.4, $P < .005$) and insulin secretion/insulin resistance index (3.30 ± 0.15 to 5.88 ± 0.4, $P < .005$) increased markedly. After 2.4 years of PLAC treatment, there was slight improvement in Matsuda index of insulin sensitivity (4.12 ± 0.2 to 5.51 ± 0.4, $P < .05$; $P < .01$ vs PIO) and insulin secretion/insulin resistance index (3.32 ± 0.3 to 4.31 ± 0.2, $P < .05$; $P < .01$ vs PIO).

11.4 months following discontinuation of therapy, there was no difference in Matsuda index of insulin sensitivity (5.15 ± 0.36 vs 5.23 ± 0.45) or insulin secretion/insulin resistance (IS/IR) index (4.03 ± 0.30 vs 3.83 ± 0.27) between PIO and PLAC groups. However, beta cell function (IS/IR index) in the PIO group was significantly improved compared to baseline (ie, time of randomization).

During the 11.4 month follow up period following therapy cessation, the insulin secretion/insulin resistance index ($\Delta I_{0-120}/\Delta G_{0-120}$ x MI) was markedly lower in IGT subjects who converted to diabetes compared to subjects who remained IGT (1.30 ± 0.1 vs 3.52 ± 0.2, $P < .001$) or NGT (1.31 ± 0.1 vs 5.70 ± 0.4, $P < .001$) (Figure 4). The decline in β-cell function (IS/IR index) was similar in IGT subjects who developed diabetes, irrespective of whether they were treated with PIO or PLAC, while insulin secretion/insulin resistance index improved in subjects who reverted from IGT to NGT irrespective of treatment with PIO or PLAC.

Change in Weight Following Cessation of Therapy

Subjects receiving pioglitazone gained 3.9 kg during active treatment period. Following pioglitazone cessation,

Table 1. Clinical, anthropometric, and laboratory data at the time of entry into the post-treatment follow-up period

	PIOGLITAZONE	PLACEBO
Number	152	138
NGT/IGT	81/71	49/89
Age (years)	54.2 ± 0.7	52 ± 0.7
Weight (kg)	97.1 ± 1.6	95.3 ± 1.7
BMI (kg/m^2)	33.4 ± 0.4	34.1 ± 0.4
Gender (#)		
Male/Female	74/78	59/79
HbA1c (%)	5.5 ± 0.3	5.5 ± 0.3
FPG (mg/dl)	91.8 ± 0.7*	94.4 ± 0.7
2 h PG (mg/dl)	134 ± 2.5*	149 ± 2.6
FPI (mU/liter)	10.1 ± 0.6	10.2 ± 0.5
Total Chol (mg/dl)	170 ± 2	171 ± 7
LDL Chol (mg/dl)	105 ± 2	106 ± 2
Triglyceride (mg/dl)	121 ± 4	120 ± 2
HDL Chol (mg/dl)	40.5 ± 7	40.9 ± 2
SBP (mmHg)	127 ± 1.1	127 ± 0.2
DBP (mmHg)	74 ± 0.6	73 ± 0.1

*$P < 0.05$, pioglitazone *vs.* placebo, BMI = body mass index, FPG = fasting plasma glucose, PG = plasma glucose, SBP and DBP = systolic and diastolic blood pressure, FPI = fasting plasma insulin, Chol = cholesterol

body weight decreased by 1.2 kg. Weight gain during the active treatment period and weight loss following pioglitazone cessation was similar in all age and gender groups and in all glucose tolerance categories. In IGT subjects treated with placebo, no significant changes in body weight were observed during active intervention period and following cessation of therapy.

Discussion

The present results are consistent with previously published results (9, 19, 20) and demonstrate that the effect of pioglitazone on T2DM prevention in high risk IGT subjects wanes after discontinuation of study medication and that the rate of IGT conversion to T2DM 11.4 months after cessation of therapy is similar in pioglitazone- and placebo-treated groups. However, the cumulative incidence of diabetes from time of initial randomization to end of follow-up at 11.4 months (median) remained lower in PIO vs PLAC group (Figure 2). Additionally, a greater number of individuals treated with PIO reverted to NGT compared to PLAC. These findings demonstrate that following discontinuation of pioglitazone disease progression (18) in high risk IGT individuals can be slowed although ultimately (ie, 11.4 months in the present study) the rate of development of diabetes in the PIO-treated group becomes similar to that in the PLAC-treated group.

At the end of the active treatment period in ACT NOW (2.4 years), 58% of PIO subjects reverted to NGT vs 35% of PLAC subjects (5). Ten year follow up of DPP study showed that reversion to NGT at any time during the study was associated with a lower risk of progression to T2DM. In the current study we show that the rate of progression to diabetes following cessation of therapy was only 4% in NGT subjects vs 24% in individuals with IGT. Although the rate of reversion to NGT in both PIO and PLAC groups was similar during the 11.4 months following cessation of therapy, a greater number of subjects achieved normoglycemia with PIO.

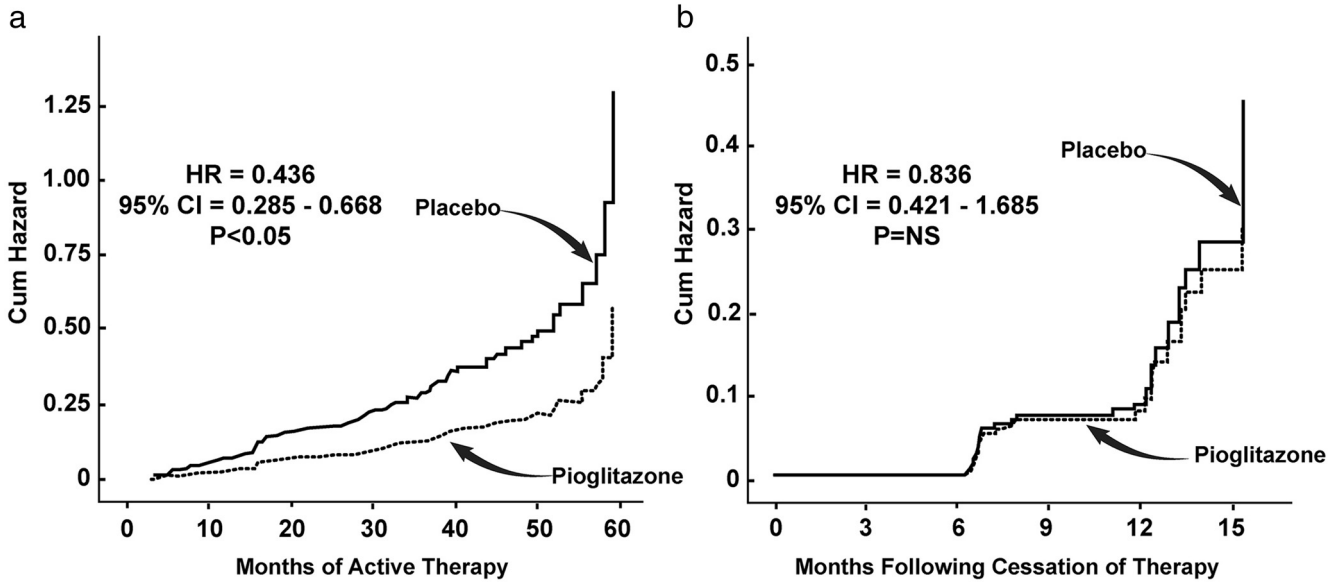

Figure 2. (a) Hazard ratio for the development of diabetes in IGT subjects who participated in the post treatment follow-up period (median = 11.4 months). **(b)** Cumulative hazard ratio (HR) for the development of diabetes in IGT subjects from the time of randomization until the end of post treatment follow-up period.

The effect of PIO to prevent diabetes 11.4 months after discontinuation of study medication in the present study is similar (56% vs 39%) to that observed in DREAM with rosiglitazone (17). The results of the present study are somewhat different from those of the TRIPOD study in which women with a history of gestational diabetes treated with troglitazone had a lower conversion rate to diabetes compared to placebo-treated women 8 months after discontinuation of troglitazone. It is possible that the different study populations, ie, history of gestational diabetes in TRIPOD vs IGT in ACT NOW, or a stronger effect of troglitazone vs pioglitazone on insulin sensitivity could explain this difference between the two studies.

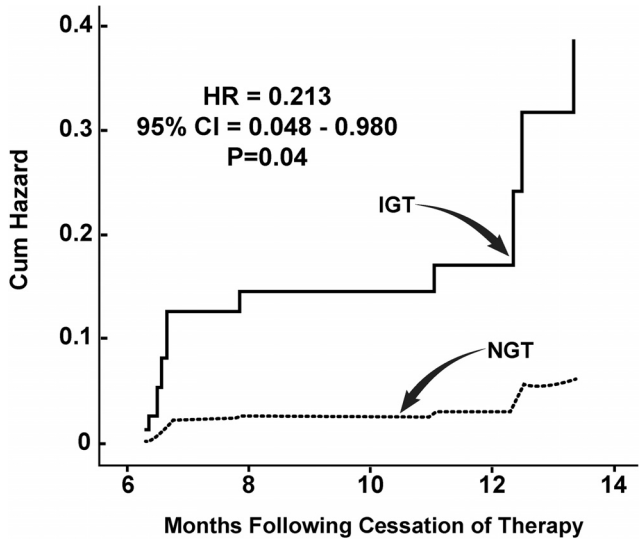

Figure 3. Hazard ratio for the development of diabetes in relation to glucose tolerance status (NGT, IGT) at entry into the post-treatment follow-up period in pioglitazone treated subjects .

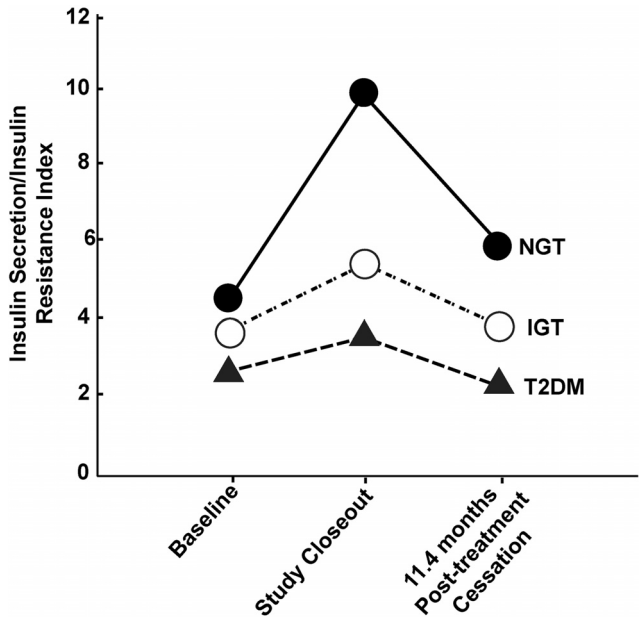

Figure 4. Insulin secretion/insulin resistance index in relation to glucose tolerance status at study end.

PIO therapy was associated with weight gain of 3.9 kg during active treatment period, and there was a modest weight loss of 1.2 kg when medication was stopped. Body weight of individuals treated with PLAC was stable during active treatment period, as well as during post-treatment follow-up. Despite weight gain, PIO was associated with better glycemic control and improved insulin sensitivity and beta cell function. Therefore, weight gain was not associated with any adverse metabolic effects on glucose tolerance, insulin sensitivity, or beta cell function The beneficial effects of PIO, despite weight gain, are mediated by an increase in plasma adiponectin concentration (7, 21), direct effect on insulin sensitivity, and improved beta cell function mediated by PPARγ activation (22, 23) and reversal of lipotoxicity (22, 23).

It can be debated whether pioglitazone prevents or just delays/slows development of diabetes. Regardless, there is a lower cumulative exposure to hyperglycemia in IGT subjects treated with pioglitazone and it is well established that diabetic microvascular complications are related to both the severity and duration of hyperglycemia in type 1 and type 2 diabetes (24, 25). Thus, lower exposure to hyperglycemia is likely to have some protective effect against long-term microvascular complications.

The physiologic mechanisms responsible for IGT conversion to T2DM appear to be similar irrespective of prior treatment. Thus, a decline in beta cell function (IS/IR index) was associated with worsening glycemic control in both PIO and PLAC groups. We previously demonstrated that poor beta cell function at baseline and improved beta cell function in response to therapy were strong predictors of final glucose tolerance status at the end of the active treatment period (19, 26). During active treatment with pioglitazone Matsuda Index of insulin sensitivity also improved significantly (19), while following cessation of pioglitazone therapy insulin sensitivity declined. Thus, pioglitazone not only reduced glycemia, it also improved both core defects present in T2DM (27), while cessation of pioglitazone therapy was associated with deterioration of both beta cell function and insulin sensitivity.

In conclusion, our results support previous observations (12–18) that the effect of TZDs on diabetes prevention is attenuated after discontinuation of study drug, but the cumulative incidence of diabetes remains lower in TZD-treated subjects. The novel observation of the present study is that deterioration of glucose tolerance status following discontinuation of pioglitazone therapy is associated with declines in beta cell function and insulin sensitivity, just as improved beta cell function and insulin sensitivity were strong predictors of IGT reversion to NGT and protection against development of diabetes. The potential success, or failure, of a specific medication is related

to how effectively the therapy corrects the underlying pathophysiologic defects, ie, beta cell dysfunction and insulin resistance.

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