Chapter 6

Evaluation of the Long-term Durability and Glycemic Control of FPG and HbA1c for Pioglitazone in Japanese Patients with Type 2 Diabetes

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Abstract

Aim: Application of a model-based approach to evaluate long term durability and glycemic control of pioglitazone in comparison to other oral glucose-lowering drugs in Japanese type 2 diabetes mellitus (T2DM) patients.

Methods: Japanese T2DM patients were enrolled in a prospective, randomized, open-label, blinded-endpoint study and received pioglitazone ± other oral glucose-lowering drugs (excluding another thiazolidinedione (TZD)) (n=293) or oral glucose-lowering drugs excluding TZD (n=294). Treatment was adjusted to achieve HbA1c<6.9% and samples for FPG and HbA1c were collected over 2.5-4 years. A simultaneous cascading indirect response model structure was applied to describe the time course of FPG and HbA1c. HbA1c levels were described using both an FPG-dependent and an FPG-independent function. To account for titration, drug effects for both treatment groups were implemented using a time dependent Emax model.

Results: Pioglitazone was superior in both time to maximum effect and the magnitude of reduction achieved in FPG and HbA1c. Greater reduction (2-fold) in FPG was observed with pioglitazone compared to the control group. Maximum drug effect for FPG was predicted to occur earlier (11 months) for pioglitazone than the control group (14 months). The simulated additional reduction in FPG and HbA1c achieved with pioglitazone was predicted to be maintained beyond the currently observed study duration.

Conclusion: Pioglitazone was found to result in improved glycemic control and durability compared to control treatment. This model-based approach enabled the quantification of differences in FPG and HbA1c for both treatment groups and simulation to evaluate longer term durability on FPG and HbA1c.

Introduction

The prevalence of diabetes in Japan has been increasing over the past two decades, primarily driven by lifestyle changes [1,2]. There will be an estimated number of diabetes cases in Japan of 8.9 million by the year 2030, following the same trend as other Asian countries [3]. Epidemiological studies have established that hyperglycemia is a significant risk factor for the development of cardiovascular disease (CVD) [4,5]. Japanese type 2 diabetes mellitus (T2DM) subjects have been shown to have a three-fold higher risk for CVD than non-diabetic subjects and the Ministry of Health, Labour and Welfare in Japan has now identified diabetes as a healthcare priority [1].

Current guidelines in Japan recommend achieving a target HbA1c <7.0% to inhibit the progress of and prevent the onset of macrovascular disease [6]. There are currently seven groups of oral agents currently used in Japan: Sulfonylurea drugs, fast-acting insulin secretion stimulators (glinides), biguanides, thiazolidines (TZD), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, and sodium glucose cotransporter-2 inhibitors [7]. However there are differences in the usage patterns compared to North America and Europe [1]. Furthermore the underling pathology of T2DM was found to be different between Japanese and Caucasian subjects [8,9]. In comparison to Caucasians, Japanese are unable to compensate insulin resistance with increased insulin secretion to the same extent. A recent study identified body composition as the major determinant for these pathophysiological differences between Japanese and Caucasian T2DM subjects [9]. As a result of differences in glycemic targets and in the pathophysiological features of diabetes, treatment guidelines in Japan differ from those in Western countries [7].

T2DM is a slowly progressing disease and glycemic deterioration is predominantly due to insulin resistance and beta-cell failure [10]. Currently there are no available therapies that can completely stop the progressive loss of glycemic control, although different therapies can delay the extent of this loss by different degrees [11]. To evaluate this further, determination of a coefficient of failure (which is the slope obtained by performing regression analysis) was proposed as an approach to assess beta-cell failure from any index of glycaemia [12]. Further extension of this approach can be undertaken using pharmacokinetic-pharmacodynamic

models developed to characterize the time course of drug effects. The advantage of implementing a model based approach being the key characterization of the relationship between treatment and the physiology of the disease over time [13]. Traditional approaches such as last observation carried forward result in a collapse in the time dimension of the data and therefore disregard the actual trajectory of change in disease status over time [14]. As a result of this, crucial information on disease progression over time is ignored and short-term hypoglycemic effects of a treatment are combined with its longer term effects on the disease.

In contrast however, a model based approach is applied to describe and explain changes in disease status as a function of time and drug therapy. In Caucasian T2DM patients these approaches have been widely applied to discriminate between standard of care and new therapies, assessing alternative treatment strategies and by using meta-analysis to evaluate the current competitive landscape for anti-diabetic therapy [15-18]. Furthermore the regulatory authorities advocate the application of these model based approaches with a particular focus on understanding exposure response relationships [19,20].

Up until now, no model based approach in Japanese T2DM patients has been undertaken on mid to long-term data. Therefore this analysis represents to our knowledge, the first model based approach to evaluate the drug specific effects in Japanese T2DM patients for pioglitazone in combination with other oral glucose lowering drugs as compared to oral glucose-lowering drugs alone simultaneously on FPG and HbA1c. The aim of this analysis is to further enhance our understanding of the treatment and time course effects on FPG and HbA1c whilst the development of a model will enable the simulation for both groups to compare the longer term glycemic durability.

Methods

Subjects and Data Collection

The data used in this analysis are from a multicenter, prospective, randomized, open-label, blinded-endpoint (PROBE) study that was designed to assess the glycemic effects of pioglitazone and their impact on cardiovascular outcomes in Japanese patients with type 2 diabetes over a period of 2.5–4 years. Patients received pioglitazone and other oral

glucose-lowering drugs (excluding another TZD) (n=293) or oral glucose-lowering drugs excluding TZD (n=294). Treatment was adjusted to achieve HbA1c<6.9%. The primary results of this study have already been described in detail elsewhere [21,22].

Population Data Analysis

During the study HbA1c was collected every 12 weeks and FPG was collected every 24 weeks. The baseline characteristics are described in Table 1. The changes in FPG and HbA1c levels over time were described using a simultaneous, cascading indirect response model structure, similar to the approach previously described in Caucasian patients [14,23]. HbA1c (%) data were collected using the Japanese Diabetes Society values and then converted to the National Glycohemoglobin Standardization Program (NGSP) values [24].

Disease progression submodel for FPG and HbA1c

The model was parameterized in terms of a zero order production rate for FPG (KinG) and a first-order rate constant for the removal of FPG (KoutG). Changes in HbA1c were initially modelled as secondary changes dependent on FPG, with a first order rate constant (KinH) for production and a first order HbA1c degradation rate constant, KoutH for disappearance. The description of HbA1c production also included the use of a power function on FPG^{γ} [15,25]. Disease progression for FPG was implemented as a proportional increase in the FPG level with a slope (FPGDP), relative to the baseline at study start. A number of different models for disease progression were explored including exponential and log-linear, however these were not found to be superior.

The overall model structure is described below in equations 1-3.

$$KinGDP = (BSLG * KinG) * (1 + FPGDP * TIME) \quad \text{EQ(1)}$$

$$\frac{dFPG}{dt} = KinGDP - KoutG \cdot (1 + DEF) \cdot FPG \quad \text{EQ(2)}$$

$$\frac{dHbA1c}{dt} = FPGind + KinH \cdot FPG^{\lambda} - KoutH \cdot HbA1c \quad \text{EQ(3)}$$

During model development, it was noted that the changes in HbA1c over time could not be fully described by the changes observed in FPG alone. Furthermore, there were differences observed in the rate of change over time between FPG and HbA1c following graphical inspection of the data. This is consistent with previous reports and is likely to result from the co-contribution and input of non-fasting glucose since HbA1c is a measure of average glucose comprising of both fasting and postprandial hyperglycemia [26,27]. A separate FPG-independent effect to describe the source of changes in HbA1c was therefore included which resulted in significantly improved model diagnostics and fit. This FPG independent input was described using a zero order rate constant (KinZ) and a linear time dependent parameter (DPind) included in the following equation:

$$FPGind = KinZ * (1 + DPind * TIME) \qquad \text{EQ(4)}$$

Drug effect Model

The drug effect (DEF) on FPG was incorporated using an Emax model driven by TIME, where Emax is the maximal effect of overall exposure to FPG-lowering drugs. ET50 is the time required for titration to half of the maximal exposure. For both treatment groups DEF was implemented as a stimulatory effect on KoutG. The Emax model approach was applied to account for the titration of anti-diabetic medication in the early phase of the study. This information could not be directly included in the analysis at the individual patient level due to the way in which time was recorded in the case report form for the titration schemes. To account for titration-related dose changes in both patient populations the drug effect was described with the following approach:

$$DEF = Emax \cdot TIME/ET50 + TIME \qquad EQ(5)$$

ET50 in the pioglitazone group was estimated with a value close to 0 and with low precision. This is likely to result from the maximum effect of titration being achieved for drugs in the pioglitazone group by the time of first FPG sample collection at 3 months. As a result, this parameter was fixed to zero for all remaining model development without any loss in goodness-of-fit.

Subjects who entered the trial were already receiving anti-diabetic medication, the details of which are shown in Table 1. However the assumption was used that these subjects were indeed at steady state on their baseline medication when they entered the trial. Further refinements to the model to account for this additional background therapy at the individual patient level did not result in any improvements in model diagnostics.

Table 1. Baseline characteristics

Characteristics	Pioglitazone Group (n=293)	Control Group (n=294)
Age (years)[a]	58.0 (35.0 – 74.0)	58.0 (37.0 – 74.0)
Sex (male:female)	184:109	181:113
Body weight (kg)[a]	69.0 (45.0 – 107.0)	68.0 (44.0 – 116.0)
BMI (kg/m^2)[a]	26.5 (18.5 – 37.3)	26.2 (19.0 – 42.6)
FPG baseline (mg/dL)[a]	153.0 (77.0 – 304.0)	157.0 (81.0 – 371.0)
HbA1c baseline (%)[a]	7.9 (6.9 – 11.4)	7.6 (6.9 – 11.8)
Number of non-TZD mediations at baseline[a]	1 (0 – 4)	2 (0 – 4)
Non-TZD diabetic medication at baseline by type		
Sulphonylureas (%)	73.0	81.6
alpha-Glucosidase inhibitors (%)	35.8	55.8
Biganides (%)	42.6	67.7
Rapid-acting insulin secretagogue drugs (%)	6.5	12.9
Number of non-TZD diabetic medications at baseline		
0 (%)	10.6	1.4
1(%)	42.0	37.1
2 (%)	39.2	46.9
>=3 (%)	8.2	14.6

[a]Median and range

Data Analysis

All analyses were performed using the nonlinear mixed effects modeling approach in NONMEM (version 7, release 1; Icon Development Solutions, Ellicott City, Maryland). The first-order conditional estimation method with interaction (ADVAN6, TOL=5) was used. Statistical analysis was performed in S-Plus (version 8.1 Professional, TIBCO Software Inc.).

Simulations of FPG and HbA1c were performed in Berkeley Madonna version 8.3.13 (Macey & Oster, University of California, Berkeley).

Inter-individual Variability and Residual Error

Inter-individual variability (IIV) on FPG baseline and EMAX was explored assuming a log normal distribution of the individual parameter estimates. However IIV on the baseline for HbA1c was evaluated using a Box-Cox transformation model to account for skewness observed in the individual data, likely resulting from inclusion criteria based on HbA1c>6.9% [25,28]. IIV on FPGDP was described by an additive random effect. Residual variability was included using a proportional model and the correlation between IIV on baselines was included using the OMEGA BLOCK option.

Covariate Analysis

Potential covariates at baseline included age, sex, weight, BMI, number of non-TZD medications, type of non-TZD medication and baseline FPG and HbA1c. These were evaluated in the model using a forward inclusion and backward elimination procedure [29]. Before performing the covariate analysis the most appropriate distribution of the covariates was evaluated.

Model Qualification

The visual predictive check (VPC) was used to evaluate the ability of the final model to predict both the central tendency and the variability of FPG and HbA1c (median and 90th prediction interval) [30]. The stability of the model was tested by using 100 bootstrap replicates of the original dataset. To further inform model validation ETA shrinkage for the random effects was estimated [31].

Model Selection

No further improvement in the model was considered by a change in objective function of less than 10.8 ($P \leq 0.001$) for each additional degree of freedom (=extra parameter). In addition graphical analysis enabled assessment of bias and the biologically plausibility of the parameter estimates was evaluated.

Evaluation of the treatment effects on glycemic markers

Based on observed data the % of subjects achieving a HbA1c<7.0% and the mean HbA1c values at 2.5 years (the minimum study duration for all subjects) were estimated and compared for both treatment groups.

Observed change from baseline in HOMA-IR was calculated and a two-sample t-test was used to compare the mean values of change from baseline in HOMA-IR at each visit between treatment groups. To further explore the predictability of the model, change from baseline in HOMA-IR was recalculated using the model predicted FPG values.

To explore the influence of drug effects on the time course for pioglitazone and the control group the median FPG and HbA1c time profiles were simulated.

Results

The results presented here were based on the simultaneous analysis of FPG and HbA1c data in 587 T2DM subjects with median treatment duration of 3.14 years (maximum 3.9 years). Results of the VPC are shown in Figure 1a and 1b and indicate adequate precision and accuracy of the model. The results for the model parameters are specified in Table 2 along with their bootstrap estimate. All model parameters could be obtained with adequate precision, and all parameters fall within the 95% CI's. Estimated shrinkage for all random effect parameters was low (< 21%). Additional diagnostics are provided in Supplemental Figures S1-S4.

Figure 1. (a) Visual predictive check for observed and predicted FPG data.

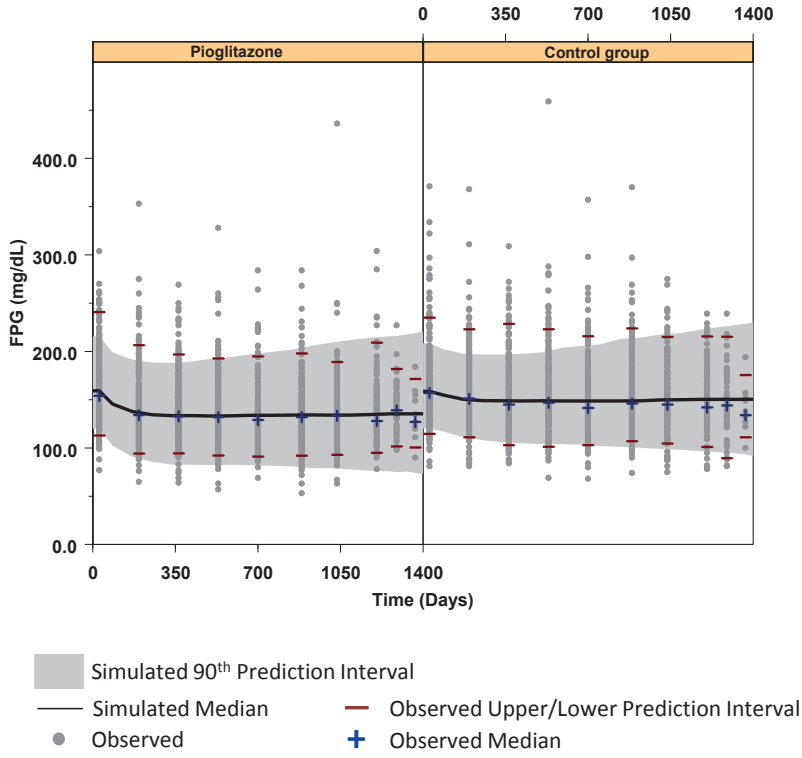


Figure 1. (b) Visual predictive check for observed and predicted HbA1c data.

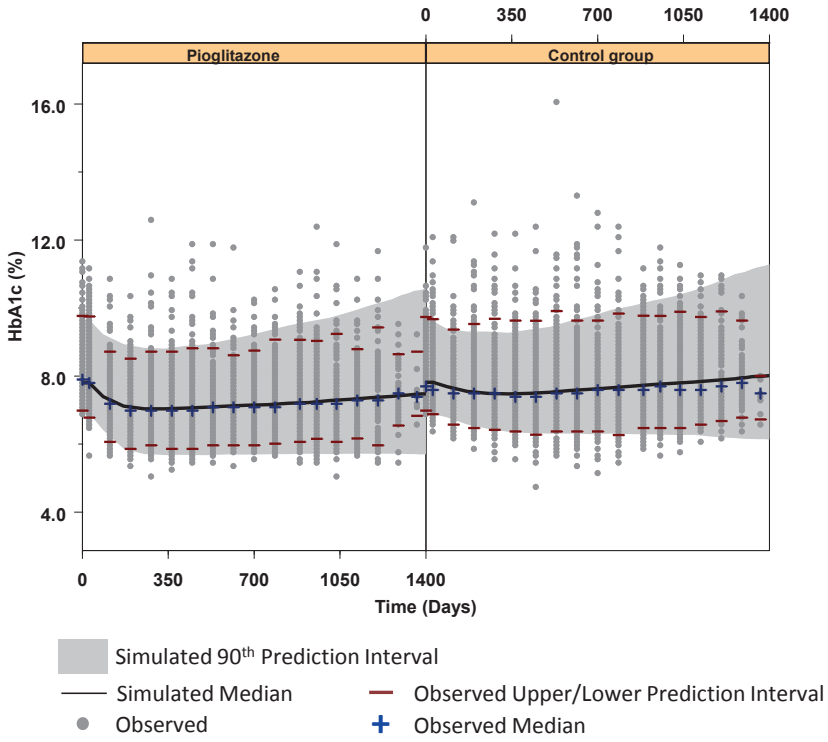


Table 2. Summary of parameter estimates for the final model including bootstrap estimates

Parameter	Model Estimate (CV%)	Mean Bootstrap Estimate (95% CI)[a]
	Fixed effects	
BSL FPG (Females) (mg/dL)	156.0 (1.1)	155.7 (152.5-158.9)
KoutG ($days^{-1}$)	0.0089 (11.4)	0.0089 (0.0073-0.011)
BSL HbA1c (%)	7.83 (0.5)	7.83 (7.75-7.91)
Box Cox	3.28 (14.8)	3.28 (2.27-4.29)
KoutH ($days^{-1}$)	0.072 (13.1)	0.071 (0.051-0.116)
Emax Piogliazone (%)	17.3 (8.3)	17.5 (14.4-20.5)
Emax Control (%)	8.4 (14.8)	8.5 (5.7-11.2)
ET50 Pioglitazone (days)	0 FIX	0 FIX
ET50 Control (days)	49.2 (46.3)	49.0 (-0.9-100.8)
KinZT ($days^{-1}$)	0.28 (16.9)	0.29 (0.17-0.41)
FPGDP ($years^{-1}$)	0.017 (28.3)	0.016 (0.006-0.027)
DPind ($years^{-1}$)	0.03 (14.8)	0.03 (0.006-0.06)
Gamma	1.91 (21.8)	1.84 (1.0-2.7)
Gender on FPG BSL	0.05 (22.9)	0.05 (0.03-0.08)
	Random effects: inter-individual variability (IIV)	
ω^2 BSL FPG	0.03 (7.2)	0.03 (0.023-0.033)
ω^2 BSL HbA1c	0.01 (8.5)	0.01 (0.008-0.011)
ω^2 FPGDP	0.004 (19.7)	0.003 (0.002-0.005)
ω^2 Emax	0.75 (11.8)	0.74 (0.57-0.90)
Correlation (ω^2 BSL HbA1c, ω^2 BSL FPG)	0.01 (10.0)	0.01 (0.009-0.013)
	Random effects: residual error	
Residual error FPG (%)	14.4 (4.6)	14.4 (13.7-15.1)
Residual error HbA1c (%)	5.8 (5.1)	5.8 (5.4-6.1)

[a] During conduct of the bootstrap, 97.0 % of runs minimized successfully.

CV, coefficient of variation; CI, confidence interval; BSL FPG, baseline for fasting plasma glucose; KoutG, first-order rate for fasting plasma glucose; BSL HbA1c, baseline for glycosylated hemoglobin; KoutH, first-order rate constant for glycosylated hemoglobin; Emax, is the maximal effect of overall exposure to FPG-lowering drugs; FPGDP, disease progression rate for FPG; DPind disease progression rate for FPG-independent input; KinZT, zero order rate constant for FPG-independent input; ET50, the time required for titration to half of the maximal exposure; ω^2, inter individual variability.

During the study period (2.5-4 years), 90 subjects (9% Pioglitazone, 6% control group) discontinued before 2.5 years. This was based on a number of criteria including: adverse

event, voluntary withdrawal or major protocol deviation. Patient discontinuation may possibly influence model parameters when caused by selective drop-out of certain subpopulations of patients. This may be due to lack of efficacy, occurrence of side effects, and/or compliance. To exclude this, models were run using all the data and excluding the drop-out subjects. All model parameters were compared by including and excluding these discontinued subjects. Only a slight difference was observed in the FPG disease progression rate parameter (FPGDP) 0.017 $year^{-1}$ (with all subjects) and 0.016 $year^{-1}$ (excluding discontinued subjects). This result showed only a very minor influence of these subjects was observed on the FPG profile and due to the low observed drop out in the study further model development including drop-out was not performed.

Drug effect model

Differences in the effect due to maximum drug exposure (EMAX) on FPG were observed between the two treatment groups. The model derived Emax values for pioglitazone and the control group were 17% and 8%, respectively. Resulting in approximately 2-fold greater reduction in FPG for pioglitazone as compared to the control treatment (median maximum simulated change from baseline in FPG was -21 mg/dL compared to -9 mg/dL for pioglitazone and the control group, respectively). An ET50 value of 49 days for the control group indicated that half the maximum exposure level of drugs affecting FPG was achieved in approximately 2 months. However for the pioglitazone group, ET50 was fixed at 0 indicating that apparent steady state for the titration of treatment for FPG occurs earlier than the control group. Based on simulation, the resulting maximum drug effect for FPG was achieved at approximately 14 and 11 months for the control and pioglitazone groups, respectively.

Disease progression was parameterized as a proportional increase over time relative to the FPG baseline. The model predicted increases over time were estimated at approximately 2 mg/dL (95% CI 0.9 – 3.5)/per year for FPG and 0.2 % (95% CI 0.15 – 0.25)/per year for HbA1c (Figure 2a and 2b). A second contribution to HbA1c production was described using an additional FPG- independent input (DPind); this FPG-independent input was estimated to contribute an additional 0.03% to the increase in HbA1c per year. Simulated FPG and HbA1c

median values over time for pioglitazone are shown simultaneously in Figure 2c. As shown in the simulation the additional FPG-independent input to HbA1c results in differences in the rate of change over time between FPG and HbA1c.

Figure 2. (a) Simulated FPG time profiles for pioglitazone and control group over 5 years

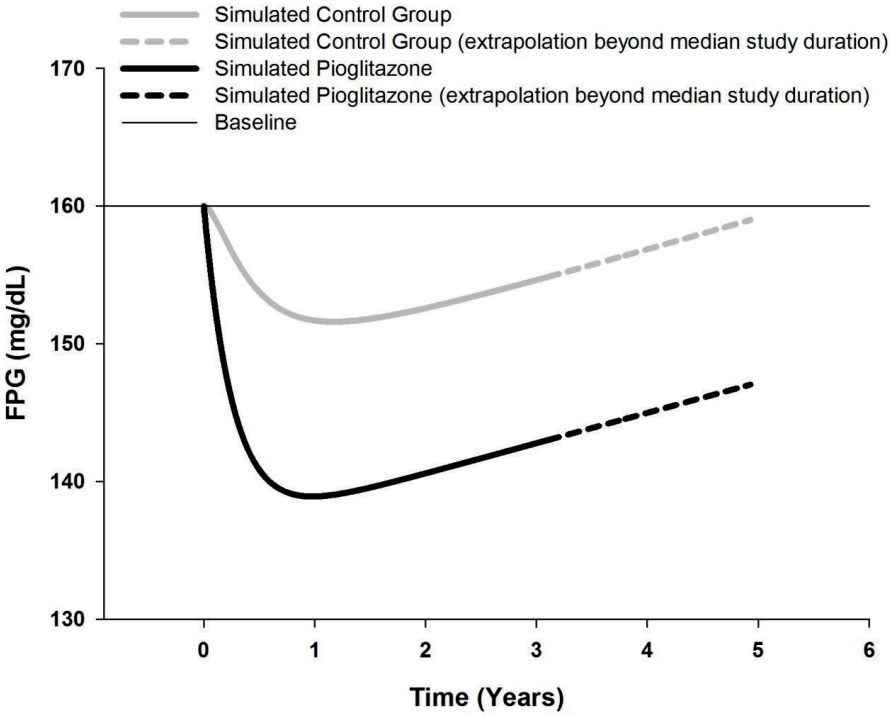


Figure 2. (b) Simulated HbA1c time profiles for pioglitazone and control group over 5 years

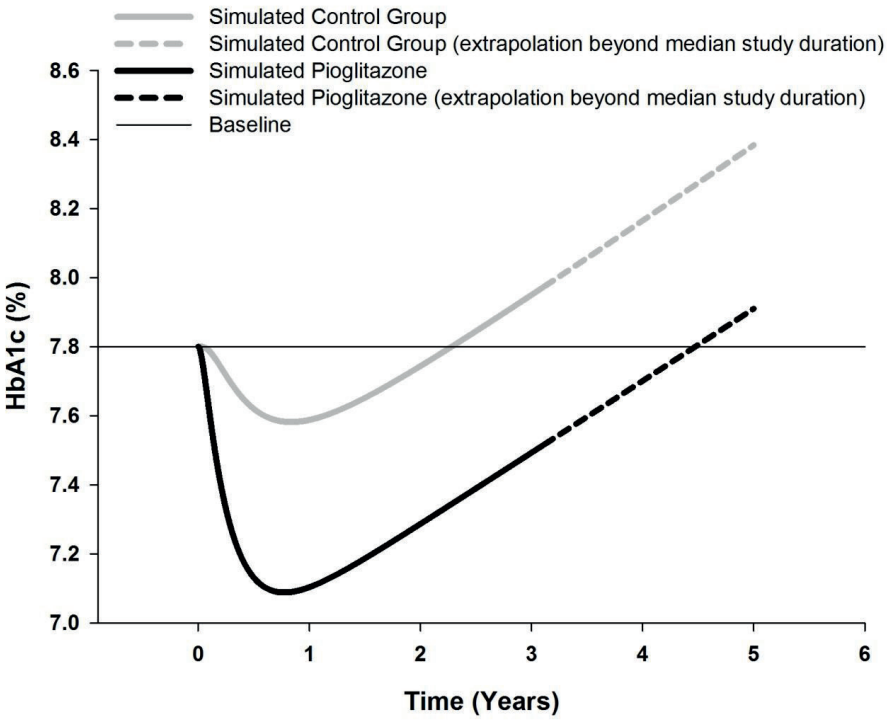
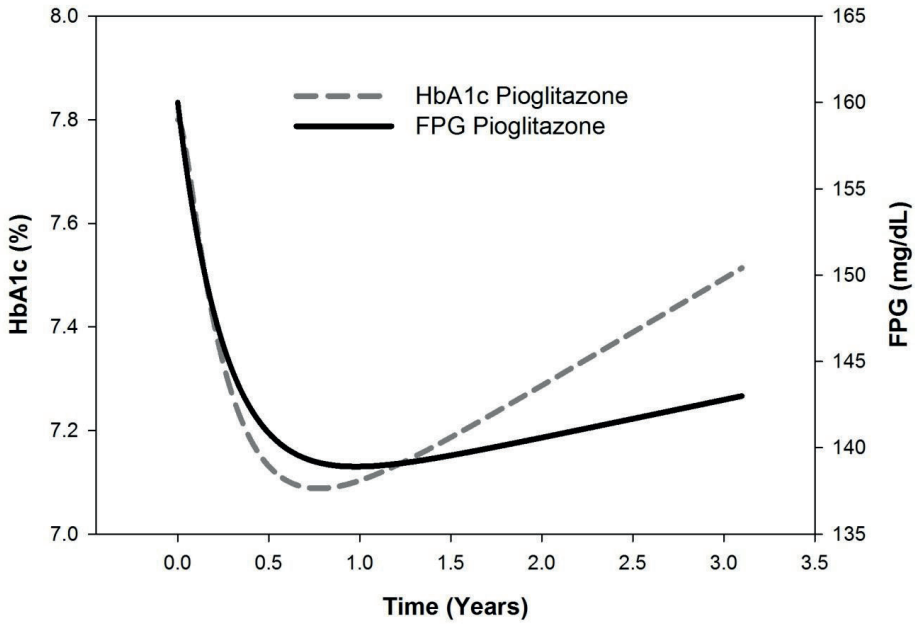


Figure 2. (c) Simulated comparison of FPG and HbA1c time profiles for pioglitazone



No differences in the apparent disease progression rates (FPGDP or DPind) between treatments could be identified from the model predicted post-hoc parameters.

Evaluation of the treatment effects on glycemic markers

Model-based simulation results

Glycemic durability was evaluated using the model optimized parameters to simulate the median FPG and HbA1c time profiles over a 5 year period (Figure 2a and 2b). Median FPG in the control group was predicted to almost return to baseline levels (160 mg/dL) 5 years after starting treatment, however at 5 years in the pioglitazone group predicted FPG levels were still considerably lower (147 mg/dL) (Figure 2a). The duration of time required for median HbA1c levels to return to baseline (HbA1c=7.8%) was approximately 2.1 years in the control group and approximately 4.5 years for the pioglitazone group, for the typical patient

in this population (Figure 2b). The differences between pioglitazone and the control group in simulated FPG and HbA1c median values was approximately 13 mg/dL and 0.5%, respectively at 5 years.

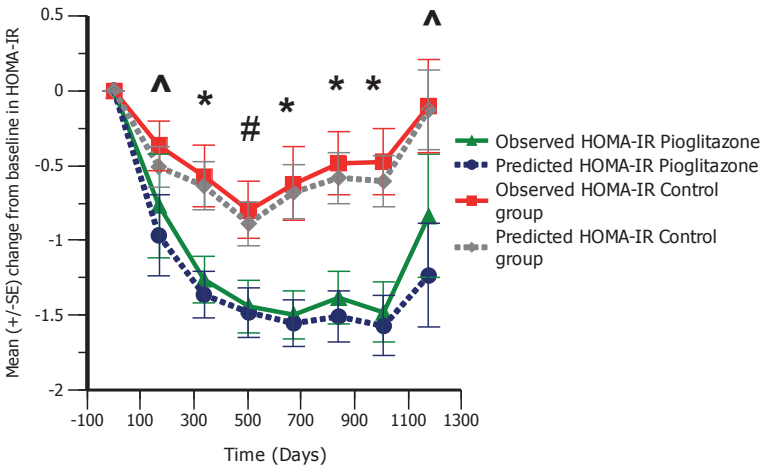
Observed data analysis

At 2.5 years (the minimum study duration for all subjects), 34% of the patients in the pioglitazone group had an observed HbA1c level <7.0%, as compared to only 18% in the control group. Mean observed HbA1c values at 2.5 years were 7.3% and 7.8% ($p<0.001$) for the pioglitazone and control groups, respectively.

This is comparable to data observed in Caucasians when pioglitazone was added to metformin, at 2 years 31% of patients had an HbA1c<7.0% [32].

Figure 3a shows the observed and predicted change from baseline in HOMA-IR by treatment group. A statistically significant difference ($p<0.05$) from the control group for pioglitazone in observed HOMA-IR was maintained from 168 days until the last visit. The observed and predicted change from baseline HOMA-IR values are compared graphically (Figure 3a). Observed and predicted values are in close agreement, confirming the good predictability of the model.

Figure 3. (a) Observed and predicted change from baseline in HOMA-IR over the study duration. (not significant = ^) (# = p<0.05) (*= p<0.01).



Covariate Analysis

Following the covariate analysis, only one relationship was identified as significant. Male subjects were found to have a slightly (5%) higher BSLG than female subjects. These differences in FPG levels by gender have been previously reported in Japanese subjects [33].

Discussion

Here we present the first application of a model based approach to evaluate drug and disease effects in Japanese T2DM patients over a 2.5-4 year treatment period. Our analysis enabled the determination of disease progression rates in Japanese treatment experienced T2DM patients for both FPG and HbA1c and a comparison of the drug effects between treatment groups. Stronger drug effects (2-fold greater) could be identified for pioglitazone as compared to the control group. Furthermore these effects could be maintained over a longer period, indicating that pioglitazone in combination with other oral glucose lowering drugs in Japanese T2DM patients can result in improved glycemic durability.

Greater reductions in both FPG and HbA1c data were observed in the pioglitazone group. Data in Caucasian subjects evaluating the treatment effects of pioglitazone in combination with other glucose lowering drugs have also shown favorable glycemic results in both short and long term studies [34]. When comparing gliclazide or metformin alone with pioglitazone given as add-on therapy improved and sustained glycemic control was maintained over a 2 year study period [32]. In a longer term study, glycemic durability over 3.5 years in Caucasian subjects for Pioglitazone in combination with metformin revealed significant benefits in glycemic control compared with glibenclamide [35]. Furthermore reductions in HOMA-IR were also maintained out to 3.5 years in the same study. Indicating that pioglitazone through lowering the burden of insulin resistance could lead to increased protection of the beta-cells [35].

A difference in the rate of change over time between FPG and HbA1c was identified. These differences were accounted for in the model using a separate FPG-independent and time-dependent effect on HbA1c. Studies have shown that mean plasma glucose (the arithmetic mean of FPG and PPG) correlates better with HbA1c than FPG alone [26,16]. It is therefore hypothesized that the different rates of change observed between FPG and HbA1c are due primarily to the input related to PPG. To demonstrate the magnitude of this FPG-independent contribution, the HbA1c time profile is simulated with and without the hypothesized contribution of PPG (Figure S5). An absolute difference of approximately 1% in HbA1c is observed between the HbA1c simulation dependent only on FPG and the

simulation dependent on FPG and PPG. Recent publications have reported that PPG has an absolute contribution of approximately 1.3-1.6 % to overall HbA1c levels [36]. Treatments which specifically target PPG have also shown reductions in HbA1c in the region of 1-1.5% [36]. Based on these studies the estimated absolute contribution of PPG to HbA1c is between 1%-1.6%. This is consistent with our findings and therefore supports the hypothesis that PPG is the main driver for the differences we observed between the rate of change over time in FPG and HbA1c.

The model enabled the quantification and evaluation of apparent disease progression rates for FPG and HbA1c. Although no differences could be identified in the underlying disease progression rate that is estimated here in either FPG or HbA1c between groups, pioglitazone is shown to maintain glycemic control over a longer duration whilst reducing insulin resistance. As predicted form its mechanism of action, pioglitazone maintains a statistically significant decrease in HOMA-IR until the last visit compared to the control group (Figure 3a). A clinically meaningful difference in HbA1c [37], between the two groups at 5 years was also predicted in the current study. The difference between pioglitazone and the control group in the simulated FPG and HbA1c median values was predicted as approximately 13 mg/dL and 0.5%, respectively at 5 years. Apparent disease progression rates in this trial are lower than those reported in the UKPDS study in Caucasian subjects determined using the coefficient of failure [12], however comparison to other studies maybe confounded by both the baseline characteristics, the combination of different glycemic treatments and titration schemes and ethnic background. Therefore, a model based approach that combines glycemic data from Caucasian and Japanese T2DM patients simultaneously, should be performed to elucidate any differences in disease progression rates while considering the other covariates affecting clinical response.

There are several limitations of our current model analysis. Due to study limitations no individual dose titration data could be included in the analysis and no pharmacokinetic data was collected for any of the treatments, in addition any long term simulation is based only on trial data with a median duration of 3.1 years. Each of these factors contribute to a certain degree of uncertainly in our extrapolations beyond the actual study duration.

In summary, the application of a model based approach quantified differences in FPG and HbA1c for both treatment groups and enabled simulation to evaluate the longer term durability on FPG and HbA1c data for both pioglitazone and the control group. Based on this result pioglitazone when given in combination with other oral glucose lowering drugs in Japanese T2DM patients was found to result in improved glycemic control and durability as compared to oral glucose lowering treatment alone.

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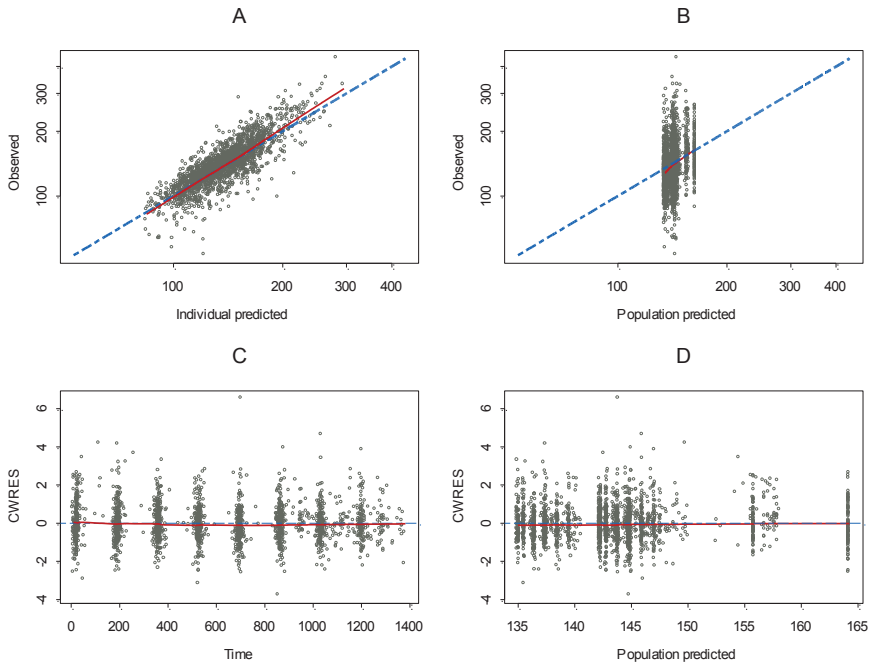
Supplemental Appendix

Figure S1. Diagnostic plots of FPG for pioglitazone



A: Observations vs. individual fitted values

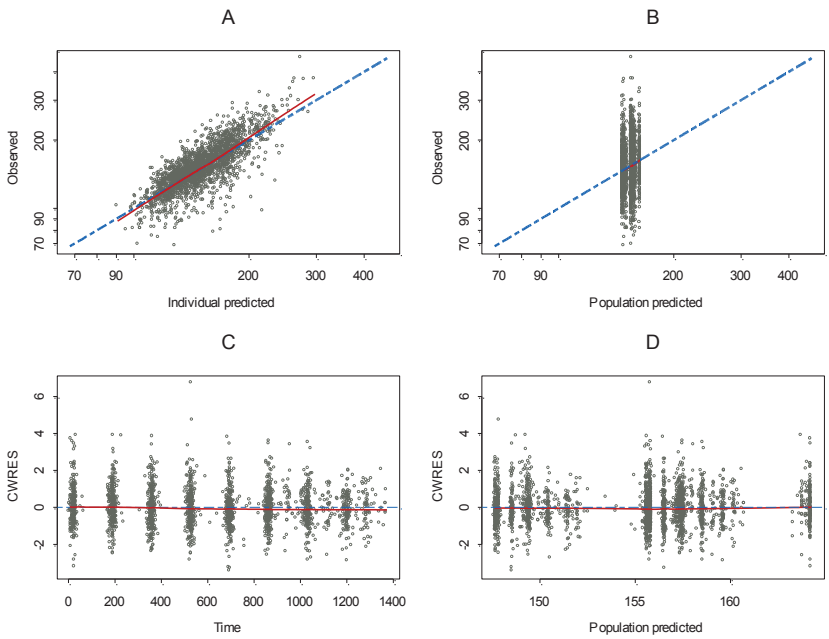
B: Observations vs. population fitted values

C: Conditional weighted residuals vs. time

D: Conditional weighted residuals vs. population fitted values

Dashed line: line of identity (A and B) or line indicating 0 (C and D)

Figure S2. Diagnostic plots of FPG for control group



A: Observations vs. individual fitted values

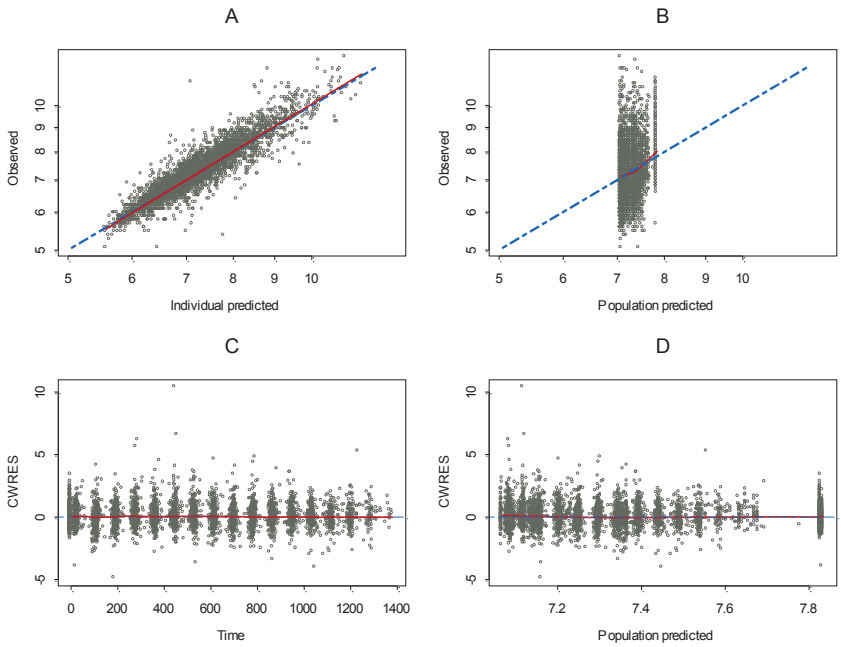
B: Observations vs. population fitted values

C: Conditional weighted residuals vs. time

D: Conditional weighted residuals vs. population fitted values

Dashed line: line of identity (A and B) or line indicating 0 (C and D)

Figure S3. Diagnostic plots of HbA1c for pioglitazone



A: Observations vs. individual fitted values

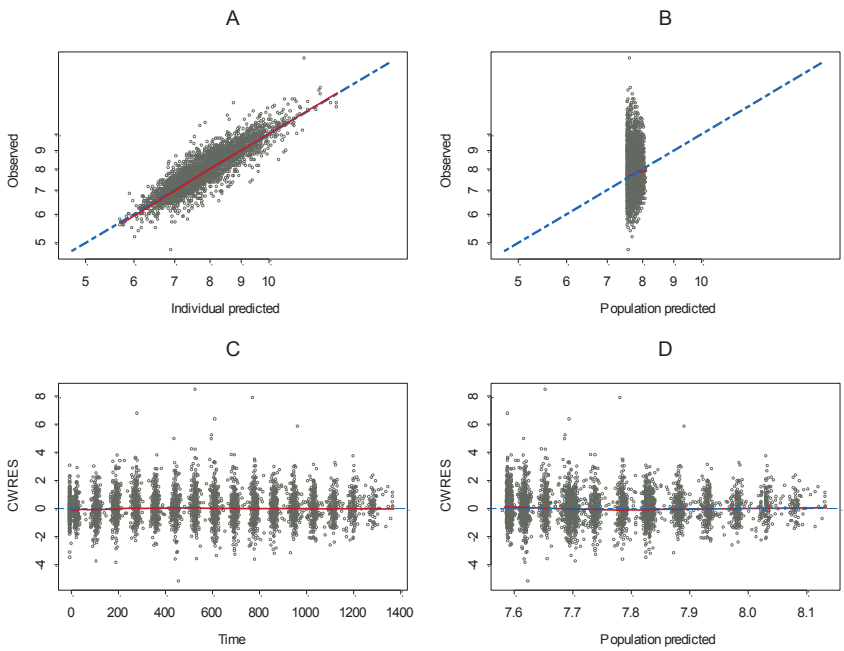
B: Observations vs. population fitted values

C: Conditional weighted residuals vs. time

D: Conditional weighted residuals vs. population fitted values

Dashed line: line of identity (A and B) or line indicating 0 (C and D)

Figure S4. Diagnostic plots of HbA1c for control group



A: Observations vs. individual fitted values

B: Observations vs. population fitted values

C: Conditional weighted residuals vs. time

D: Conditional weighted residuals vs. population fitted values

Dashed line: line of identity (A and B) or line indicating 0 (C and D)

Figure S5. Observed (dot), individual predicted (IPRED) and the population prediction (PRED) for the FPG time profile of typical representative subjects

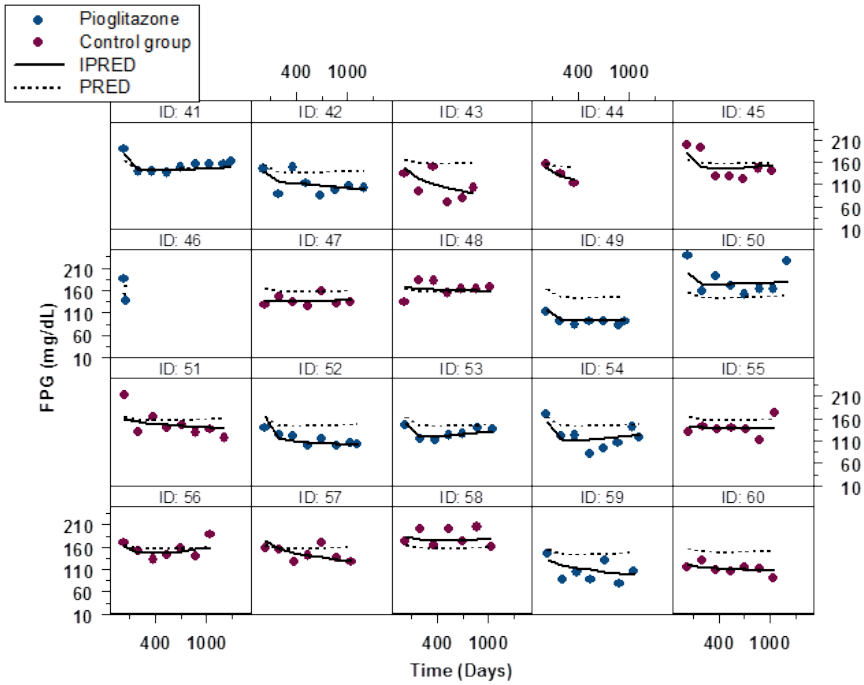


Figure S6. Observed (dot), individual predicted (IPRED) and the population prediction (PRED) for the HbA1c time profile of typical representative subjects

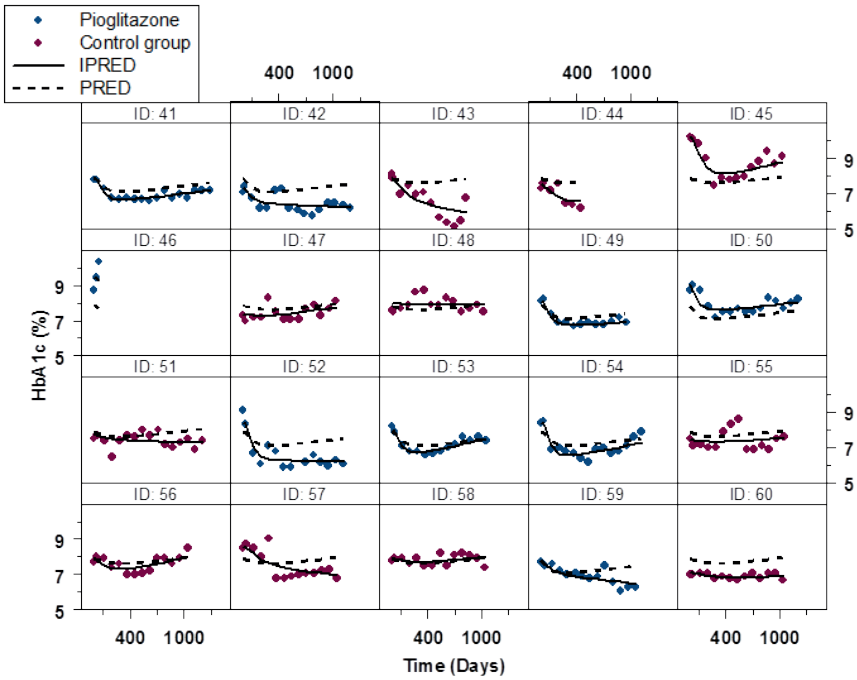


Figure S7. Simulated Pioglitazone HbA1c time profile for HbA1c dependent on FPG only and HbA1c dependent on both FPG and PPG