

Original Research

Patient factors associated with hemoglobin A1C change with pioglitazone as adjunctive therapy in type 2 Diabetes Mellitus

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ABSTRACT*

Objective: To identify patient factors associated with change in hemoglobin A1C (A1C) with adjunct pioglitazone therapy in routine clinical practice.

Methods: This was a retrospective analysis of adult type 2 diabetes mellitus patients in a health maintenance organization setting who were newly-initiated on pioglitazone between January 2002 and December 2005. Eligible patients were receiving at least one other oral antihyperglycemic medication prior to initiating pioglitazone and maintained a stable dose of pioglitazone for 90 days. Data on eligible patients' characteristics, pharmacy purchases, comorbidities, and A1C measurement 90 days prior to the pioglitazone purchase date (baseline) and 90 days after achieving a stable dose (follow-up) were obtained from electronic records. Multivariate regression modeling was used to assess factors independently associated with: 1) absolute change in A1C, 2) achieving a ≥ 1 percentage point decrease in A1C, and 3) achieving an A1C <7%.

Results: Baseline and follow-up A1Cs were available for 128 patients. At baseline, mean age was 65 years, 38% were female, mean A1C was 8.4%, and 74% had an A1C >8%. At follow-up, the mean A1C change was -1.2 percentage points (interquartile range = -0.4, -2.1), 59% achieved a ≥ 1 unit decrease in A1C, and 44% achieved an A1C <7%. Independent predictors in all models were baseline A1C and time (in days) between baseline and follow-up A1C measurements ($p < 0.05$).

Conclusions: Adjunct pioglitazone therapy in routine clinical practice was associated with clinically meaningful reductions in A1C levels. Patients with higher baseline A1C achieved the greatest absolute reduction in A1C but were less likely to achieve levels <7%.

Keywords: Diabetes Mellitus, Type 2. Thiazolidinediones. Regression Analysis. United States.

VARIABLES ASOCIADAS A CAMBIOS EN LA HEMOGLOBINA A1C EN PACIENTES COM PIOGLITAZONA COMO COADJUVANTE EN DIABETES MELLITUS TIPO 2

RESUMEN

Objetivo: Identificar las variables asociadas a cambios en hemoglobina A1C en pacientes con pioglitazona como tratamiento coadyuvante en la práctica clínica rutinaria.

Métodos: Fue un análisis retrospectivo de pacientes con diabetes tipo 2 entre enero 2002 y diciembre 2005 en una organización sanitaria donde se acababa de iniciar la pioglitazona. Los pacientes elegibles estaban recibiendo al menos otro antidiabético oral antes de comenzar la pioglitazona y mantuvieron una dosis estable de pioglitazona durante 90 días. Se obtuvieron los datos a partir de los registros electrónicos de las características de los pacientes, compras en farmacia, comorbilidades, y medidas de A1C 90 días antes de la compra de la pioglitazona (basal) y 90 días después de alcanzar una dosis estable (seguimiento). Se utilizó un modelo de regresión multivariada para evaluar las variables asociadas independientemente con: 1) el cambio absoluto en A1C, 2) el alcanzar una disminución de $\geq 1\%$ en la A1C, y 3) el alcanzar una A1C <7%.

Resultados: Se dispuso de A1C basales y de seguimiento de 128 pacientes. Al inicio, la media de edad era de 65 años, 38% eran mujeres, la media de A1C era de 8,4% y el 74% tenían una A1C >8%. En el seguimiento, la media de A1C era -1,2% menor (rango intercuartil -0,4; -2,1%), el 59% redujo $\geq 1\%$ la A1C, y el 44% alcanzó una A1C <7%. Los predictores independientes en todos los modelos fueron la A1C basal y el tiempo (en días) entre el inicio y las medidas de seguimiento de A1C ($p > 0,05$).

Conclusiones: La terapia adyuvante con pioglitazona se asoció en la práctica clínica con reducciones significativas de los niveles de A1C. Los pacientes con niveles iniciales de A1C más altos alcanzaron la mayor reducción en valor absoluto de A1C, pero eran los menos probables de alcanzar niveles <7%.

Palabras clave: Diabetes Mellitus, Tipo 2. Tiazolidindionas. Análisis de regresión. Estados Unidos.

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INTRODUCTION

Two landmark trials, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), emphasize the significance of glycemic control in patients with diabetes mellitus.^{1,3} These studies reported that maintaining glycemic control (i.e., hemoglobin A1C [A1C]<7.0%) is necessary to reduce the risk of microvascular and macrovascular complications, including nephropathy, neuropathy, retinopathy, and cardiovascular events, such as myocardial infarction or stroke.¹⁻³ An epidemiological review of the UKPDS revealed that a reduction in A1C of 1 percentage point resulted in a 35% reduction in the microvascular complications (i.e., retinopathy, nephropathy, and neuropathy) of diabetes mellitus type 2 (DM 2).^{1,2} Based largely on the results of these two trials, the American Diabetes Association recommends a target A1C goal of <7% for most patients with diabetes and maintains that glycemic control is fundamental to reducing the microvascular complications of the disease.⁴ In fact, a recent hyperglycemia management consensus algorithm advocates that an A1C≥7 serves as a call to action to optimize therapy.⁵

Thiazolidinedione (TZD) agents, selective agonist of the peroxisome proliferator-activated receptor-gamma subtype (PPARγ), are oral antihyperglycemic agents approved by the Food and Drug Administration (FDA) for use in DM2 as monotherapy or in combination with sulfonylureas, metformin, or insulin.^{6,7} While TZDs have demonstrated efficacy in the reduction of A1C values when used in combination with other oral antihyperglycemic agents in clinical trials,⁸⁻¹¹ limited real-world effectiveness data are available.¹²⁻¹⁶ In addition, few studies have reported on factors associated with change in A1C in clinical practice.^{12,13,17,18} Importantly, knowledge of characteristics of patients who respond to adjunct pioglitazone is narrow. The intent of this study was to evaluate pre-to-post the effectiveness of adjunctive pioglitazone therapy in patients with DM2

and provide additional data regarding the patient characteristics associated with changes in A1C after the addition of pioglitazone to existing oral antihyperglycemic therapy in a diverse, real-world population of patients managed in routine clinical practice.

METHODS

Setting and Design

This was a naturalistic, retrospective, pre-to-post analysis conducted at Kaiser Permanente Colorado, a group model, not-for-profit, health maintenance organization with approximately 450,000 members in the Denver/Boulder metropolitan area, operating 18 regional medical offices. All phases of the study were approved by the Kaiser Permanente Colorado Institutional Review Board.

Patient Population

Active Kaiser Permanente Colorado patients 18 years of age and older who had newly initiated pioglitazone therapy to existing other oral antihyperglycemic medication therapy between January 1, 2002 and December 31, 2005 were eligible for inclusion (Figure 1). A newly-initiated regimen was identified as a pioglitazone prescription purchased from a Kaiser Permanente Colorado pharmacy during the study period with no other pioglitazone prescription purchased in the prior 180 days (to ensure that 90- and 180-day supply mail order prescription purchases were accounted for in this assessment). The first purchase date of the newly-initiated pioglitazone therapy was set as the study index date. Patients were included if they had continuous coverage for a Kaiser Permanente Colorado pharmacy benefit for the 180 days prior to the index date (to ensure comprehensive prescription purchase history) and remained on a single dose of pioglitazone for at least 90 days after initiation of therapy. The study stable date was defined as the date when a patient had remained on a single dose of pioglitazone for 90 days. In addition, patients that had purchased insulin therapy at any time in the 180 days prior to the index date and 180 days after the stable date were excluded.

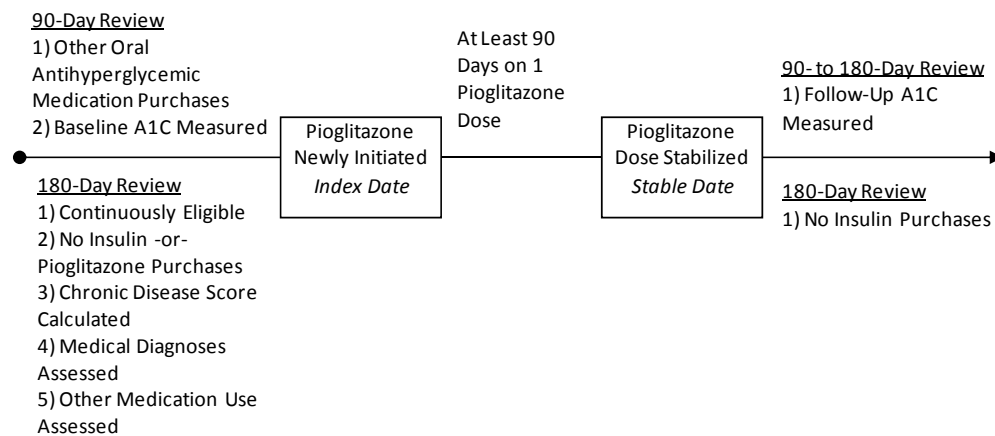


Figure 1. Study Timeline

Data Collection

Data were extracted from integrated electronic medical, pharmacy, and laboratory record databases. Patients' data were linked across databases by their Kaiser Permanente Colorado unique nine digit health record number. Validity of these data sources has been described previously.¹⁹ Pharmacy records were queried using Generic Product Identifier numbers²⁰ to assess medication prescription purchases and purchase dates during the 180 days prior to the index date (these data were required to assess inclusion criteria and calculate a chronic disease score²¹). Patient demographics were extracted from their pharmacy records. Medical records were queried with International Classification of Diseases, Ninth Revision (ICD-9) codes to identify a medical office diagnosis for coronary artery disease, chronic kidney disease, gastroparesis, previous myocardial infarction, neuropathy, retinopathy, and/or previous stroke in the 180 days prior to the index date. Age was calculated as of the index date. The strength of the dose of pioglitazone at the stable date was recorded (stable dose). Electronic laboratory records data were queried to identify the most proximal A1C in the 90 days prior to the index date for the baseline measurement and between 90 and 180 days after the stable date for the follow-up measurement (Figure 1). Patients without both a baseline and follow-up A1C measurement were excluded. Baseline weight was identified from integrated medical records; however, as data were missing in 22% of the included patients, analysis was not undertaken.

Outcomes

The primary outcome was to quantify from baseline to follow-up the absolute change in A1C values after initiation of pioglitazone. Secondary analyses were performed to quantify the proportions of patients achieving a ≥ 1 percentage point decrease in A1C and an A1C $<7\%$ during the follow-up. Additionally, factors (predictors) independently associated with absolute A1C change, achieving a ≥ 1 percentage point decrease in A1C, and achieving an A1C $<7\%$ were identified.

Analysis

Time (in days) between index date and follow-up A1C measurement was calculated. A chronic disease score,^{21,22} a risk adjustor for baseline health status, was calculated for all patients using pharmacy purchase data for the 180 days prior to the index date. Chronic disease scores can range from 0 to 35 with increasing scores indicating an increasing count of chronic diseases under treatment. Use of the chronic disease score allows for the accounting of each patient's chronic disease burden at the time of his/her initiation of pioglitazone. Persistence with oral antihyperglycemic agents at the time of the follow-up A1C was determined based on the medication sold date, days supplied, and quantity dispensed resulting in a day's supply of medication within +/- two weeks of the follow-up A1C measurement date.

Baseline patient characteristics and study outcomes were reported as means and standard deviations for interval- and ratio-level variables (e.g., age, time) and proportions for nominal- and ordinal-level data (e.g., gender, use of other oral antihyperglycemic medications). Interval- and ratio-level variables were assessed for the normality of their distributions. Times were log transformed to normalize their distribution. The paired-sample t-test²³ was used to evaluate the change from baseline in A1C. Independent sample t-tests and chi-square tests of association²³ were used to compare means and proportions between sub-groups (i.e., those that did and did not achieve a 1 percentage point decrease in A1C and a $<7\%$ A1C). To identify predictors of change in A1C, multivariate linear and logistic regression modeling²³ were utilized. Age, gender, daily stable pioglitazone dose (15 mg, 30 mg, and 45 mg), time between index date and follow-up A1C measurements, baseline metformin, glipizide, glyburide, antihyperlipidemic and antihypertensive medications use, chronic disease score, persistence with pioglitazone, retinopathy and neuropathy diagnoses, and baseline A1C measurement were entered into all models. Diagnoses for coronary artery disease, chronic kidney disease, gastroparesis, and previous myocardial infarction, stroke and baseline sulfonylurea use were not entered in the models due to their very low and high prevalence rates, respectively. The baseline A1C values were assessed as a continuous and categorized (i.e., $\leq 8\%$ vs. $>8\%$) variable.

RESULTS

In total, 128 patients were included in the analysis (Figure 2). The mean age was 65 years, 38% were female, 41% were receiving a stable dose of 15 mg pioglitazone, mean A1C was 8.4%, 74% had an A1C $>8\%$ at the time of pioglitazone initiation, and mean chronic disease score was 7 (indicating, on average, a clinically significant chronic disease burden²¹) (Table 1). The mean absolute A1C reduction was 1.2 percentage points (interquartile range= -0.4, -2.1 percentage points, $p<0.001$), 59% achieved a ≥ 1 percentage point decrease in A1C, and 44% achieved an A1C $<7\%$.

In bivariate analysis, patients who achieved a ≥ 1 percentage point decrease in A1C had a higher mean baseline A1C ($p<0.001$) and were less likely to have had a baseline A1C $\leq 8\%$ ($p<0.001$) than patients who did not achieve a ≥ 1 percentage point decrease in A1C. All patients were persistent with their baseline metformin, glyburide, glipizide, and/or sulfonylurea antihyperglycemic prescription medications at the time of their follow-up A1C measurement ($p>0.05$, data not shown). There were no other differences in clinical and demographic characteristics ($p>0.05$) between the groups of patients who were or were not able to achieve an A1C $<7\%$.

Multivariate linear regression analysis revealed two predictors of absolute change in A1C: baseline A1C level (beta-coefficient= -0.831; $p<0.001$) and time between the index date and follow-up A1C measurement date (beta-coefficient=0.528;

p=0.003) (adjusted R²=0.55) (Table 2). The beta-coefficients indicate that when comparing two patients with all other characteristics being equal, the patient with the higher baseline A1C will have a more favorable response to pioglitazone. Conversely, the patient with a greater number of days between the index date and follow-up A1C

measurement date will have a less favorable response to pioglitazone. When categorizing baseline A1C at ≤8% and >8%, patients with an A1C≤8% (beta-coefficient=1.220; p<0.001) were predicted to have a less favorable response to pioglitazone, also (adjusted R²=0.28).

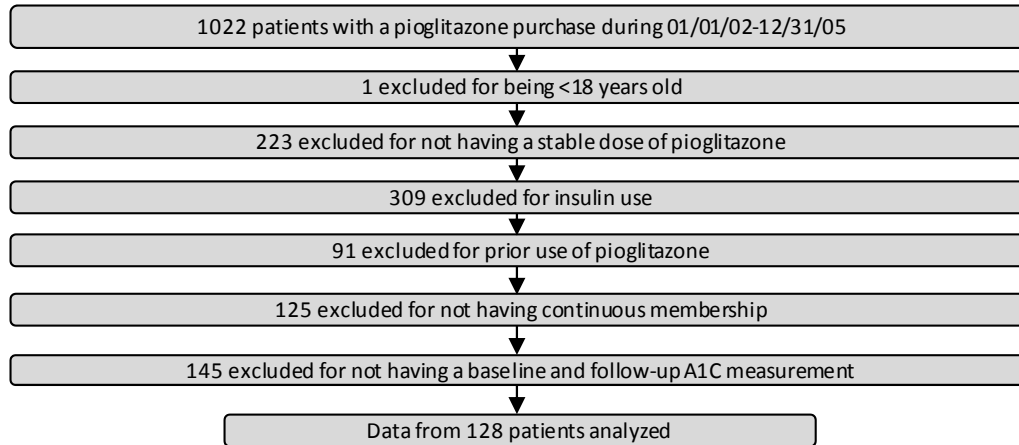


Figure 2: Reasons for and Numbers of Patients Excluded, Included, and Utilized in Analysis

| Characteristic | Overall (n=128) | Achieved ≥1 Percentage Decrease in A1C (n=75) | Achieved <1 Percentage Decrease in A1C (n=53) | P-Value ¹ |
|---|------------------|---|---|----------------------|
| Mean Age ² in Years (SD) | 64.6 (10.5) | 64.5 (10.6) | 64.8 (10.4) | 0.905 |
| Female (%) | 37.5 | 37.3 | 37.7 | 0.963 |
| Mean Baseline A1C % ² (SD) | 8.4 (1.0) | 8.9 (0.9) | 7.7 (0.7) | <0.001 |
| Baseline A1C≤8.0% ² (%) | 35.9 | 14.7 | 66.0 | <0.001 |
| Mean Weight in Kilograms ² (n, SD) | 91.0 (100, 18.3) | 93.1 (59, 18.3) | 87.9 (41, 19.3) | 0.169 |
| Metformin Use ³ (%) | 74.2 | 70.7 | 79.3 | 0.274 |
| Glipizide Use ³ (%) | 37.5 | 42.7 | 30.2 | 0.151 |
| Glyburide Use ³ (%) | 57.8 | 50.7 | 67.9 | 0.052 |
| Sulfonylurea Use ³ (%) | 96.1 | 94.7 | 98.1 | 0.325 |
| Stable Pioglitazone Daily Dose (%) | | | | |
| 15 mg | 41.4 | 42.7 | 39.6 | 0.731 |
| 30 mg | 35.9 | 40.0 | 30.2 | 0.255 |
| ≥45 mg | 22.7 | 17.3 | 30.2 | 0.087 |
| Persistent with Pioglitazone ⁴ (%) | 80.5 | 80.0 | 81.1 | 0.874 |
| Related Medication Use ³ (%) | | | | |
| ACE Inhibitor | 69.5 | 65.3 | 75.5 | 0.220 |
| Beta Blocker | 38.3 | 44.0 | 30.2 | 0.113 |
| Calcium Channel Blocker | 18.0 | 18.7 | 17.0 | 0.807 |
| Thiazide | 32.0 | 34.7 | 28.3 | 0.447 |
| Statin Antihyperlipidemic | 74.2 | 73.3 | 75.5 | 0.785 |
| Non-Statin Antihyperlipidemic | 25.8 | 32.0 | 17.0 | 0.056 |
| Mean Chronic Disease Score (SD) | 7.0 (2.6) | 7.1 (2.9) | 6.9 (2.1) | 0.757 |
| Comorbidity ⁵ (%) | | | | |
| Coronary Artery Disease | 3.9 | 1.3 | 7.6 | 0.074 |
| Chronic Kidney Disease | 4.6 | 2.7 | 0.0 | 0.231 |
| Gastroparesis | 0.0 | 0.0 | 0.0 | 1.000 |
| Previous Myocardial Infarction | 0.0 | 0.0 | 0.0 | 1.000 |
| Neuropathy | 7.0 | 5.3 | 9.4 | 0.371 |
| Retinopathy | 5.5 | 2.7 | 9.4 | 0.097 |
| Previous Stroke | 0.8 | 1.3 | 0.0 | 0.399 |

* Achievement occurred during 90 to 180 days after date of initiation of stable dose
1 – Between cohorts
2 – At time of pioglitazone initiation
3 – As assessed by a purchase for the medication in the 90 days prior to pioglitazone initiation
4 – At the time of the follow-up A1C measurement
5 – As assessed by a medical office diagnosis for the indication in the 180 days prior to pioglitazone initiation

| Table 2. Predictors of Absolute Change in A1C | | | | |
|---|--------------------------------------|---------|---------------------------------------|---------|
| Potential Predictor | Continuous Baseline A1C ¹ | | Categorical Baseline A1C ² | |
| | β-Coefficient | P-Value | β-Coefficient | P-Value |
| Baseline A1C | -0.831 | <0.001 | | |
| ≤ 8% | — | — | 1.220 | <0.001 |
| > 8% | — | — | — | — |
| Age | -0.000 | 0.979 | 0.002 | 0.847 |
| Gender | | | | |
| Female | -0.069 | 0.676 | -0.094 | 0.655 |
| Male | — | — | — | — |
| Log of Days between Index Date and Follow-Up A1C Measurements | 0.528 | 0.026 | 0.573 | 0.010 |
| Metformin Use | | | | |
| Yes | 0.030 | 0.874 | 0.256 | 0.287 |
| No | — | — | — | — |
| Glipizide Use | | | | |
| Yes | 0.224 | 0.382 | 0.041 | 0.900 |
| No | — | — | — | — |
| Glyburide Use | | | | |
| Yes | 0.209 | 0.395 | 0.081 | 0.795 |
| No | — | — | — | — |
| Stable Pioglitazone Daily Dose | | | | |
| 15 mg | 0.225 | 0.391 | 0.382 | 0.254 |
| 30 mg | -0.172 | 0.425 | -0.085 | 0.759 |
| ≥45 mg | — | — | — | — |
| Persistent with Pioglitazone | | | | |
| Yes | -0.101 | 0.603 | -0.243 | 0.329 |
| No | — | — | — | — |
| ACE Inhibitor Use | | | | |
| Yes | 0.133 | 0.537 | 0.015 | 0.955 |
| No | — | — | — | — |
| Beta Blocker Use | | | | |
| Yes | -0.002 | 0.992 | -0.056 | 0.791 |
| No | — | — | — | — |
| Calcium Channel Blocker Use | | | | |
| Yes | 0.104 | 0.573 | -0.043 | 0.854 |
| No | — | — | — | — |
| Thiazide Use | | | | |
| Yes | 0.089 | 0.575 | 0.227 | 0.258 |
| No | — | — | — | — |
| Statin Antihyperlipidemic Use | | | | |
| Yes | 0.173 | 0.358 | 0.195 | 0.417 |
| No | — | — | — | — |
| Non-Statin Antihyperlipidemic Use | | | | |
| Yes | -0.353 | 0.055 | -0.339 | 0.147 |
| No | — | — | — | — |
| Chronic Disease Score | -0.057 | 0.111 | -0.036 | 0.426 |
| Neuropathy | | | | |
| Yes | -0.186 | 0.548 | -0.105 | 0.791 |
| No | — | — | — | — |
| Retinopathy | | | | |
| Yes | -0.138 | 0.697 | 0.115 | 0.797 |
| No | — | — | — | — |

1 – Adjusted R-Square = 0.55
2 – Adjusted R-Square = 0.28

Multivariate logistic regression analysis revealed two predictors of achieving a ≥1 percentage point decrease in A1C: baseline A1C level (odds ratio [OR]=12.84; p<0.001) and time between the index date and follow-up A1C measurement date (OR=0.19; p=0.032) (c-statistic=0.92) (Table 3). When categorizing baseline A1C at ≤8% and >8%, patients with an A1C ≤8% (OR=0.04; p<0.001) were predicted to be less likely to achieve a ≥1 percentage point decrease in A1C (c-statistic=0.88). These odds ratios support the previous model whereby patients with higher baseline A1Cs and longer times between initiation of pioglitazone and follow-up A1C measurements had more and less favorable, respectively, response to pioglitazone.

Multivariate logistic analysis revealed two predictors of achieving an A1C<7%: baseline A1C level (OR=0.64; p=0.038), and time between the index date and follow-up A1C measurement date (OR=0.14; p=0.002) (c-statistic=0.78) (Table 4). When categorizing baseline A1C at ≤8% and >8%, patients with an A1C ≤8% (OR=4.27; p<0.001) were predicted to be more likely to achieve an A1C<7% (c-statistic=0.80). In total, these models indicate that, while patients with higher baseline A1C levels achieve greater absolute decreases in A1C, these patients are less likely to reach an A1C goal of <7%.

| Potential Predictor | Continuous Baseline A1C ¹ | | Categorical Baseline A1C ² | |
|---|--------------------------------------|-------------|---------------------------------------|-------------|
| | Odds Ratio | 95% CI | Odds Ratio | 95% CI |
| Baseline A1C | 12.84 | 4.53, 36.40 | 0.04 | 0.01, 0.14 |
| $\leq 8\%$ | — | — | — | — |
| $> 8\%$ | — | — | — | — |
| Age | 0.99 | 0.94, 1.06 | 0.98 | 0.94, 1.04 |
| Gender | | | | |
| Female | 0.38 | 0.11, 1.36 | 0.68 | 0.23, 1.97 |
| Male | — | — | — | — |
| Log of Days between Index Date and Follow-Up A1C Measurements | 0.19 | 0.04, 0.87 | 0.29 | 0.09, 0.98 |
| Metformin Use | | | | |
| Yes | 2.21 | 0.48, 10.10 | 0.88 | 0.28, 2.80 |
| No | — | — | — | — |
| Glipizide Use | | | | |
| Yes | 0.32 | 0.06, 1.69 | 0.39 | 0.08, 1.94 |
| No | — | — | — | — |
| Glyburide Use | | | | |
| Yes | 0.28 | 0.06, 1.40 | 0.27 | 0.06, 1.23 |
| No | — | — | — | — |
| Stable Pioglitazone Daily Dose | | | | |
| 15 mg | 0.32 | 0.04, 2.59 | 0.43 | 0.08, 2.37 |
| 30 mg | 2.35 | 0.46, 11.88 | 2.19 | 0.54, 8.98 |
| ≥ 45 mg | — | — | — | — |
| Persistent with Pioglitazone | | | | |
| Yes | 0.52 | 0.12, 2.19 | 0.72 | 0.20, 2.57 |
| No | — | — | — | — |
| ACE Inhibitor Use | | | | |
| Yes | 0.29 | 0.06, 1.44 | 0.32 | 0.08, 1.38 |
| No | — | — | — | — |
| Beta Blocker Use | | | | |
| Yes | 1.84 | 0.51, 6.63 | 1.93 | 0.63, 5.91 |
| No | — | — | — | — |
| Calcium Channel Blocker Use | | | | |
| Yes | 1.03 | 0.24, 4.47 | 1.24 | 0.36, 4.30 |
| No | — | — | — | — |
| Thiazide Use | | | | |
| Yes | 0.90 | 0.29, 2.77 | 0.99 | 0.36, 2.78 |
| No | — | — | — | — |
| Statin Antihyperlipidemic Use | | | | |
| Yes | 0.60 | 0.15, 2.38 | 0.82 | 0.26, 2.60 |
| No | — | — | — | — |
| Non-Statin Antihyperlipidemic Use | | | | |
| Yes | 5.15 | 0.98, 24.03 | 3.20 | 0.91, 11.28 |
| No | — | — | — | — |
| Chronic Disease Score | 1.24 | 0.95, 1.61 | 1.17 | 0.91, 1.50 |
| Neuropathy | | | | |
| Yes | 0.17 | 0.02, 1.62 | 0.18 | 0.03, 1.17 |
| No | — | — | — | — |
| Retinopathy | | | | |
| Yes | 0.79 | 0.08, 8.24 | 0.50 | 0.05, 4.29 |
| No | — | — | — | — |

1 – c-statistic = 0.92; 2 – c-statistic = 0.88. CI – Confidence Interval

DISCUSSION

This study provides additional information about the real-world effectiveness of pioglitazone use as adjunctive therapy to other oral antihyperglycemic agents. We found that adding pioglitazone to regimens of other oral antihyperglycemic medication(s) for patients with inadequate glycemic control resulted in clinically significant reductions in A1C but less than half of the patients achieved an A1C $<7\%$ after 90 days of pioglitazone use at a stable dose.

Pioglitazone has a distinct mechanism of action that can provide additional glucose reduction when added to a sulfonylurea and/or metformin.²⁴ According to its package insert, reductions in A1C

of 0.8 to 1.7 percentage points from baseline were obtained when pioglitazone was used in combination with a sulfonylurea or metformin for 24 weeks.⁷ Other studies have revealed mean reductions in A1C of 0.8 to 1.9 percentage points with pioglitazone use.⁸⁻¹³ Specifically, we identified a comparable mean A1C reduction over a similar follow-up time to that reported by Riedel and colleagues (-1.2 percentage points) for patients receiving combination TZD-metformin.¹⁵ Our observed reduction in A1C was also clinically significant given the results of the UKPDS, which reported that for every 1% reduction in A1C, the risk of developing microvascular complications decreases by approximately 35%.^{1,2}

| Potential Predictor | Continuous Baseline A1C ¹ | | Categorical Baseline A1C ² | |
|---|--------------------------------------|-------------|---------------------------------------|-------------|
| | Odds Ratio | 95% CI | Odds Ratio | 95% CI |
| Baseline A1C | 0.64 | 0.42, 0.98 | | |
| ≤ 8% | — | — | 4.27 | 1.63, 11.23 |
| > 8% | | | | |
| Age | 1.01 | 0.96, 1.05 | 1.01 | 0.96, 1.05 |
| Gender | | | | |
| Female | 1.66 | 0.66, 4.19 | 1.81 | 0.69, 4.76 |
| Male | | | | |
| Log of Days between Index Date and Follow-Up A1C Measurements | 0.14 | 0.04, 0.48 | 0.12 | 0.03, 0.43 |
| Metformin Use | | | | |
| Yes | 0.41 | 0.14, 2.00 | 0.44 | 0.15, 1.29 |
| No | | | | |
| Glipizide Use | | | | |
| Yes | 0.86 | 0.21, 3.48 | 0.85 | 0.20, 3.60 |
| No | | | | |
| Glyburide Use | | | | |
| Yes | 0.82 | 0.21, 3.16 | 0.79 | 0.20, 3.21 |
| No | | | | |
| Stable Pioglitazone Daily Dose | | | | |
| 15 mg | 0.44 | 0.10, 1.98 | 0.50 | 0.11, 2.37 |
| 30 mg | 1.75 | 0.50, 6.09 | 2.31 | 0.61, 8.67 |
| ≥45 mg | | | | |
| Persistent with Pioglitazone | | | | |
| Yes | 2.35 | 0.79, 7.05 | 2.28 | 0.75, 6.96 |
| No | | | | |
| ACE Inhibitor Use | | | | |
| Yes | 0.84 | 0.26, 2.69 | 0.77 | 0.23, 2.50 |
| No | | | | |
| Beta Blocker Use | | | | |
| Yes | 1.01 | 0.40, 2.54 | 1.12 | 0.43, 2.90 |
| No | | | | |
| Calcium Channel Blocker Use | | | | |
| Yes | 0.61 | 0.22, 1.67 | 0.58 | 0.21, 1.59 |
| No | | | | |
| Thiazide Use | | | | |
| Yes | 0.74 | 0.31, 1.74 | 0.71 | 0.30, 1.73 |
| No | | | | |
| Statin Antihyperlipidemic Use | | | | |
| Yes | 0.91 | 0.32, 2.64 | 0.90 | 0.30, 2.67 |
| No | | | | |
| Non-Statin Antihyperlipidemic Use | | | | |
| Yes | 2.82 | 0.98, 7.64 | 2.77 | 0.98, 7.66 |
| No | | | | |
| Chronic Disease Score | 1.05 | 0.86, 1.29 | 1.03 | 0.84, 1.26 |
| Neuropathy | | | | |
| Yes | 0.82 | 0.16, 4.24 | 0.90 | 0.16, 5.21 |
| No | | | | |
| Retinopathy | | | | |
| Yes | 1.43 | 0.19, 10.93 | 1.23 | 0.15, 10.20 |
| No | | | | |
| 1 – c-statistic = 0.78 | | | | |
| 2 – c-statistic = 0.80 | | | | |

We found that higher baseline A1C levels were associated with greater change in A1C. Our finding suggests that patients with higher baseline A1C measurements may experience improved glycemic control from the addition of pioglitazone. Conversely, patients with worse glycemic control at baseline were less likely to achieve a goal A1C of <7%; which is the definitive target in diabetes management, more so than is the magnitude of A1C change. Riedel and colleagues similarly identified a higher baseline A1C as a predictor of not achieving A1C goal.¹³ Based on this¹³ and our results, adjunct therapy with pioglitazone appears to lack effectiveness in achieving glycemic control targets, particularly in patients with a baseline

A1C>8%. An additional caveat to consider is that triple oral therapy has not demonstrated cost-effectiveness compared to a regimen of insulin and metformin.²⁵

We found that the greater number of days between the index date and follow-up A1C was associated with a less favorable response to pioglitazone. This suggests that the A1C-lowering ability of pioglitazone may degenerate over time. This is contrary to the results of a recent clinical trial where the antihyperglycemic effect of pioglitazone was sustained over 2 years when used in combination with other oral antihyperglycemic agents such as gliclazide (a sulfonylurea not available in the United

States) or metformin.²⁶ Our results may have varied due to the difference in study settings (e.g., clinical trials incorporate techniques to enhance adherence) and patient populations (e.g., patients were excluded from clinical trials because they had other co-morbid conditions).

Several aspects of our investigation warrant comment. The retrospective nature of our evaluation and lack of a pioglitazone-naïve control group prevented us from assessing causality and regression to the mean; however, we feel that this information is the best available data to describe what occurs in a real-world population of patients with DM2. As this was a naturalistic investigation, we investigated patients started on pioglitazone therapy who received the usual course of care which included the use of other oral antihyperglycemic agents. However, since our findings mirrored those reported in other studies,^{6,8-13} we hypothesize that incorporation of a control group in our investigation would have yielded similar results. Nevertheless, future studies of pioglitazone efficacy should include an adequate control group.

Our data are derived from a limited sample size, and this was attributable to the stringent inclusion criteria we employed to provide a more rigorous assessment of the independent role pioglitazone played in achievement of the outcomes. Such stringent criteria may potentially introduce selection bias (e.g., patients who failed to respond to pioglitazone therapy during the 90 days after initiation were not included) that limits the generalizability of our findings. Inclusion of patients who failed to respond to pioglitazone therapy likely would have provided additional information about the patient population that was prone to fail to achieve an A1C<7% but likely would not have illuminated the patient population that was prone to achieve an A1C<7%.

The suboptimal dosing of adjunct pioglitazone detected in this real-world examination exposes the need for additional reinforcement for prescribers to optimize therapy should they choose to add pioglitazone to existing oral therapy. Additionally, we included a limited amount of variables in the multivariate analysis. Potentially important factors not found in the integrated databases (e.g., race/ethnicity, nutritional assessment, socioeconomic status, health behaviors) may also

be associated with clinically significant differences in A1C change and/or achievement of A1C goals.^{12,13} However, the reported adjusted R² and c-statistics of our models suggest that a substantial proportion of the variance in A1C change and goal achievement was accounted for by our models.

CONCLUSIONS

In this retrospective, naturalistic, pre-to-post evaluation, we found that adjunct pioglitazone therapy was associated with a clinically significant reduction in A1C, particularly in patients with higher baseline A1C measurements, and also an increase in the proportion of patients achieving A1C<7% in those patients with a lower baseline A1C. These findings provide real-world evidence that pioglitazone as adjunct therapy may be associated with improved glycemic control; however, they also suggest that patients requiring greater hyperglycemic control (as shown by higher baseline A1C levels) are less likely to reach treatment targets, thus casting doubt on the clinical utility of pioglitazone therapy in combination with other oral agents. Future naturalistic studies utilizing adequate control groups are needed to confirm the effectiveness of pioglitazone in A1C reduction and maintenance of glycemic goals.

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CONFLICT OF INTEREST

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