

# Rosiglitazone Prior Authorization Safety Policy: A Cohort Study

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## ABSTRACT

**BACKGROUND:** Prior authorizations (PA) are intended to promote safe and cost-effective medication use. Unwanted outcomes may occur, however, such as a patient forgoing drug therapy after a PA. The label for rosiglitazone was revised in November 2007 to include the warning of contraindicated use with nitrates or insulin, creating an opportunity for a PA directed at safe use.

**OBJECTIVE:** To evaluate antidiabetic drug utilization after the implementation of an electronic PA that denied a claim for rosiglitazone if the patient had a history of either insulin or nitrate supply in the previous 60 days.

**METHODS:** This quasi-experimental study used pharmacy claims for 1.4 million commercially insured members who were exposed to a rosiglitazone PA beginning on January 1, 2009, compared with a group of approximately 2 million commercially insured members who did not have this safety PA intervention. Continuously enrolled members were identified who had a rejected (intervention group) or paid (comparison group) claim for rosiglitazone during the period from January 1, 2009, through June 30, 2009. Pharmacy claims were assessed for the presence of nitrates, insulin, rosiglitazone, other antidiabetic therapy, or no antidiabetic therapy supply on days 30, 60, 90, and 180 after the rejected/paid claim. A time-series analysis using rosiglitazone claims for all health plan members from January 2008 through December 2009 was used to evaluate the impact of the PA on rosiglitazone utilization overall.

**RESULTS:** At 30 days, there were 134 patients (60.4% of 222) in the comparison group with concurrent supply of rosiglitazone with insulin and/or nitrates versus 4 patients (2.4% of 168,  $P < 0.001$ ) in the PA intervention group, and the utilization rate remained significantly higher at 180 days in the comparison group (37.8%,  $n = 84$ ) versus the PA group (2.4%,  $n = 4$ ,  $P < 0.001$ ). Beginning at 60 days, there was no significant difference in the percentage of members with no antidiabetic therapy in the comparison and PA intervention groups (9.9% vs. 15.5%, respectively,  $P = 0.133$ ), and the rates remained similar through 180 days (15.3% vs. 13.7%, respectively,  $P = 0.760$ ). The PA was associated with an absolute decrease of 5.1 average monthly rosiglitazone claims per day per million members ( $P < 0.001$ ).

**CONCLUSIONS:** This PA, intended to reduce known cardiovascular event risks among health plan members with type 2 diabetes, was associated with a significant reduction in concurrent use of rosiglitazone with nitrates or insulin.

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## What is already known about this subject

- A 2010 systematic review of 9 studies assessing pharmacy benefit policies reported that prior authorization (PA) consistently reduced nonpreferred agent utilization and expenditures; however, it was unclear in these studies whether patients were impacted positively or negatively.
- Warning of contraindicated use of rosiglitazone with nitrates or insulin was added to the product label in November 2007. In February 2010, the FDA required updates to the rosiglitazone prescribing information describing the cardiovascular risks and restricting the indications for rosiglitazone to patients already on rosiglitazone or patients who are unable to control their glucose with other antidiabetic medications and not able to use pioglitazone.

## What this study adds

- Implementation of a safety PA was associated with a reduction in the prevalence of concurrent rosiglitazone and nitrate or insulin therapy by more than 15-fold at 6 months follow-up (2.4% vs. 37.8% in the comparison group).
- At 30 days follow-up, the PA intervention group was more likely than the comparison group to have no supply of any antidiabetic therapy (10.1% vs. 0%, respectively); however, the difference became nonsignificant at 60 days and remained nonsignificant through 180 days of follow-up.
- The rosiglitazone safety PA also appeared to impact rosiglitazone utilization overall in the intervention health plan as evidenced by the 13.5% decrease in the predicted average number of rosiglitazone claims per day per million members in a time series analysis, while the comparison health plan experienced no significant change in utilization during the post-intervention time period.

Health insurers or self-insured employers implement prior authorization (PA) policies that require prescribers to obtain prior approval from the health plan or pharmacy benefit management (PBM) company for prescription medication reimbursement in order to promote safe and cost-effective medication use.<sup>1,2</sup> Patients and providers may perceive a PA as a barrier limiting access and potentially resulting in decreased medication use.<sup>1</sup> In 2011, 76% of 274 employers surveyed by the Pharmacy Benefit Management Institute reported using PA as one of their utilization management tools.<sup>3</sup> A 2010 systematic review of 9 studies assessing pharmacy benefit policies reported that PA policies consistently

**TABLE 1** GPI Codes to Identify Drug Therapy

| GPI Codes <sup>a</sup>               | Drug/Class Description            |
|--------------------------------------|-----------------------------------|
| 2710                                 | Insulin products                  |
| 3210                                 | Nitrates                          |
| 27607060<br>2799780260<br>2799800260 | Rosiglitazone-containing products |
| 27607050<br>2799780240<br>2799800240 | Pioglitazone-containing products  |
| 2725<br>279925<br>279950<br>279970   | Biguanides                        |
| 2715                                 | Amylin agonists                   |
| 2717                                 | Glucagon-like peptide-1 agonists  |
| 2720                                 | Sulfonylureas                     |
| 2723<br>2728                         | Glinides                          |
| 2750                                 | Alpha-glucosidase inhibitors      |
| 2755                                 | Dipeptidyl peptidase-4 inhibitors |

<sup>a</sup>Numbers indicate all GPI codes starting with these values.

GPI=Generic Product Identifier (Medi-Span, Indianapolis, IN).

reduced nonpreferred agent utilization and expenditures; however, it was unclear in these studies whether patients were impacted positively or negatively.<sup>4</sup> The PA policies evaluated in the systematic review,<sup>5-13</sup> and the studies of PA policies published after the review, consistently focus on the populations with high pharmacy spending.<sup>14-18</sup> For example, Zhang et al. reported in 2009 the results of a PA policy among Medicaid and Medicare enrollees affecting second-generation antipsychotics and anticonvulsant medication.<sup>7</sup> After an 8-month policy period and 6-month follow-up period, there was a modest reduction in total pharmacy costs of about \$27 per patient, yet treatment discontinuation rates were more than twice as high than in the pre-policy period.<sup>7</sup> Overall, the use of preferred agents or the number of patients switching to preferred agents did not increase. Another PA program evaluated by Buckley et al. (2010) focused on reducing costs by limiting access to palivizumab according to criteria established by the American Academy of Pediatrics.<sup>18</sup> The drug cost avoidance was estimated at more than \$2.4 million (348 infants times \$6,950 palivizumab cost per episode) over 3 years, with no significant differences in the rates of respiratory syncytial virus-related hospitalizations in the PA-approved versus PA-denied groups.

PA policies focused on improving safety are less common. Ideally, using administrative medical claims data, a safety PA policy would identify individuals with certain medical conditions that are contraindicated for the drug. However, since integrated medical and pharmacy claims are not readily available to most health care providers, a more practical approach is to rely solely on pharmacy claims.

Rosiglitazone, a thiazolidinedione used for the management

of type 2 diabetes, has been known to exacerbate congestive heart failure in post-marketing surveillance, and since November 2007, the prescribing information for rosiglitazone specifically recommends against use in combination with nitrates or insulin due to increased risk of myocardial ischemic events.<sup>19</sup> Over the last several years, data have continued to emerge surrounding the cardiovascular safety of rosiglitazone. In February 2010, the U.S. Food and Drug Administration (FDA) required updates to rosiglitazone prescribing information describing the cardiovascular risks and restricting indications to patients already on rosiglitazone or patients who are unable to control their glucose with other antidiabetic medications and not able to use pioglitazone. The Risk Evaluation and Mitigation Strategies (REMS) program to limit rosiglitazone availability was approved by the FDA and implemented on November 17, 2011.<sup>20</sup> The rosiglitazone prescribing information along with emerging safety data offer an opportunity to identify individuals who may be using insulin and/or nitrates and improve their cardiovascular safety through a PA requirement before authorizing rosiglitazone reimbursement.

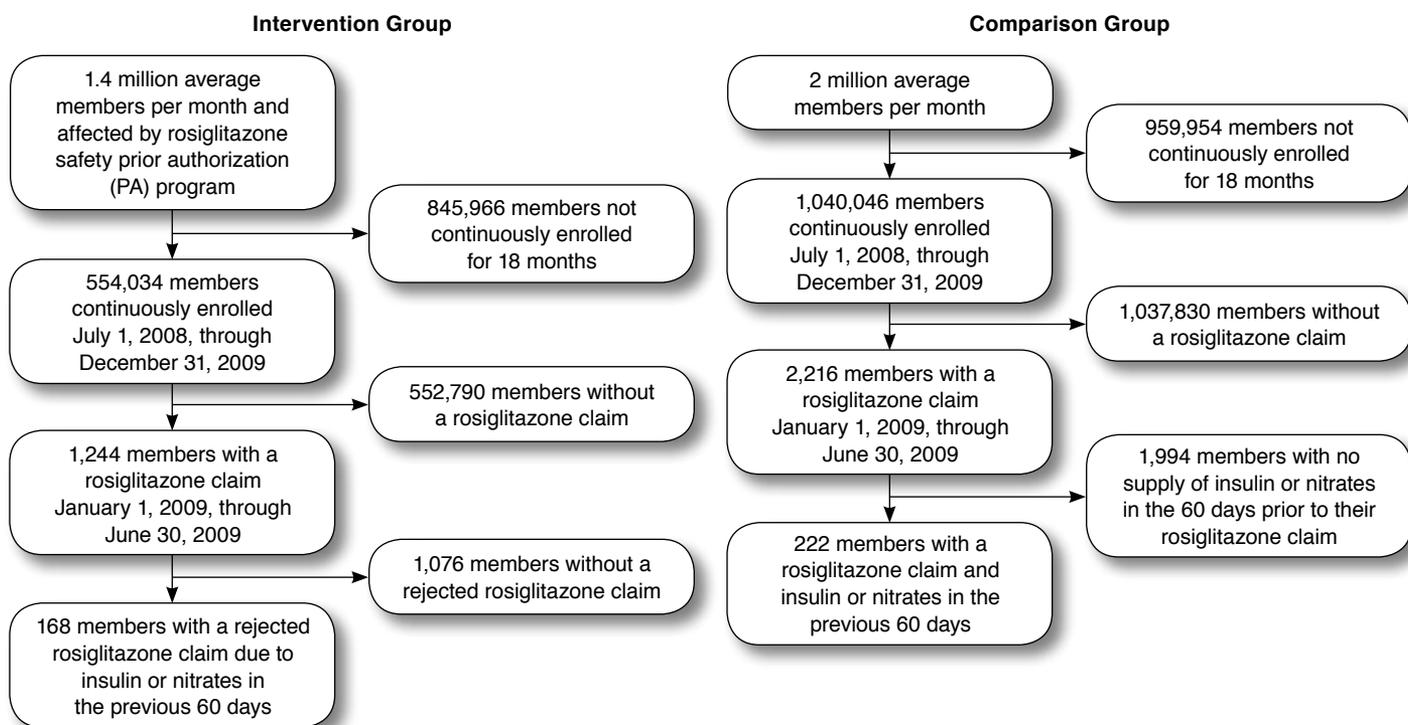
While a PA policy intended to improve safety seems ideal, unwanted outcomes may occur. For example, when faced with the PA reimbursement denial, a patient may decide to forgo all diabetes medication treatment. The objective of our study was to evaluate members' medication utilization following the implementation of a rosiglitazone safety PA policy compared with a group of rosiglitazone utilizers unexposed to the PA policy. This evaluation of a rosiglitazone safety PA policy included an assessment of both the perceived benefit in reduction of concurrent rosiglitazone and insulin or nitrate use and the potential harm caused by individuals forgoing all antidiabetic medication. In addition, we sought to explore the impact of a rosiglitazone safety PA policy on utilization within the entire health plan.

## Methods

The study employed a quasi-experimental concurrent design using retrospective administrative pharmacy claims data from a commercial BlueCross BlueShield (BCBS) plan in the southern United States. This health plan has an average of 1.4 million members per month and implemented a rosiglitazone safety PA policy on January 1, 2009. The safety PA policy used a real-time electronic edit that denied rosiglitazone coverage if the member's pharmacy claims history showed the presence of an insulin or nitrate drug supply during the 60 days prior to the rosiglitazone claim. A prescriber could appeal the rejection by submitting written documentation to the health plan and requesting coverage for the member.

All pharmacy claims were identified using the assigned Generic Product Identifier (GPI, Medi-Span, Indianapolis, IN; Table 1). A comparison group was identified from a different commercially insured BCBS population in the central United States

**FIGURE 1** Flow of Members in Intervention and Comparison Groups



with an average of 2 million members per month that did not implement the rosiglitazone safety PA. For both the intervention and comparison groups, members were required to be continuously enrolled from July 1, 2008, through December 31, 2009.

Each patient's earliest rejected (for the intervention group) and paid (for the comparison group) pharmacy claim for rosiglitazone or a rosiglitazone combination product, determined using GPI codes, was identified during January 1, 2009, through June 30, 2009, and defined as the index claim. Patient characteristics, including average age and gender, were collected. To assess the persistence of concurrent rosiglitazone and insulin or nitrate use as well as lack of antidiabetic medication following the index claim, pharmacy claims were queried at 4 different time points following the index claim: 30 days, 60 days, 90 days, and 180 days for the presence of drug supply for insulin, nitrates, rosiglitazone, or any other antidiabetic agent. For evaluation of presence of drug supply, we created an end date for each claim (i.e., fill date plus days supply on the claim). Post-index drug supply at each time point was reported in the following hierarchical order: rosiglitazone and nitrates or insulin, rosiglitazone (without nitrates or insulin), other antidiabetic agent (insulin or any other antidiabetic agent with exception of rosiglitazone), and no supply of any antidiabetic therapy.

Statistical testing was performed using the Student's t-test for continuous data and Fischer's Exact test for categorical data, SAS version 9.2 (Cary, NC). All *P* values were 2-sided with an *a priori* alpha of 0.05.

An overall rosiglitazone claims trend analysis was performed in both the intervention and comparison health plan populations. All paid rosiglitazone claims were collected from January 1, 2008, through December 31, 2009. Utilization was reported as the monthly average claims per day per million members. Claims were weighted as 30-day supplies. For example, a claim with a 90-day supply counted as 3 claims distributed as 1 claim per month over 3 months. The intervention group's rosiglitazone trend line was analyzed for an impact of the safety edit PA using an interrupted time-series analysis with autoregressive errors via the SAS autoreg procedure. This analytic technique allows for strong observational analysis of a policy change's causal effect because it can assess the trend line for an abrupt change (change in level) at the policy change implementation date and trend after the implementation date while accounting for the pre-implementation trend.<sup>21</sup> Further strengthening the findings was utilization of a separate time-series analysis for the comparison population and assessment of the Durbin-Watson statistic to test for autocorrelation of time in the regression model.

**TABLE 2** Patient Characteristics

|   | Intervention<br>(n = 168) | Comparison<br>(n = 222) | P<br>Value |
|---|---------------------------|-------------------------|------------|
| Age, mean [standard deviation]  | 56 [8.1]                  | 55 [7.8]                | 0.123      |
| Males % (n)   | 67.3 (113)                | 66.7 (148)              | 0.914      |
| No rosiglitazone supply in 60 days prior to index claim <sup>a</sup> % (n)            | 17.9 (30)                 | 21.2 (47)               | 0.443      |
| No supply of any antidiabetic drug in 60 days prior to index claim <sup>a</sup> % (n) | 1.2 (2)                   | 0.5 (1)                 | 0.580      |
| <b>Insulin and/or nitrate supply in 60 days prior to index claim<sup>a</sup></b>      |                           |                         |            |
| Insulin and nitrate supply % (n)  | 3.6 (6)                   | 2.3 (5)                 | 0.541      |
| Insulin-only supply % (n)   | 82.1 (138)                | 86.0 (191)              | 0.326      |
| Nitrate-only supply % (n)   | 14.3 (24)                 | 11.7 (26)               | 0.450      |

<sup>a</sup>Index claim was the first rosiglitazone claim identified in the period from January 1, 2009, through June 30, 2009.

Both interrupted time series analyses were performed by creating a new dataset and 3 new variables. The primary independent variables in the analysis were time, indicating time in months from the start of the pharmacy claims period through the follow-up period (1 through 24); a dummy variable for the intervention indicating whether a month was before (coded 0) or after (coded 1) the intervention date; and the time after the intervention, which was 0 before the intervention and 1 through 12 following the intervention.

## Results

Figure 1 shows analysis flow for the intervention and comparison health plans. Of the 554,034 continuously enrolled members in the intervention group, 1,244 (2.2 per 1,000 members) had a rosiglitazone paid or safety PA-denied index claim between January 1, 2009, and June 30, 2009. The prevalence of members with an index denied rosiglitazone claim was 168 (13.5%) of the 1,244 members with a rosiglitazone submitted claim. Thus, the intervention analyzable group included 168 members with an index denied rosiglitazone claim. As shown in Table 2, the member characteristics and reasons for the denied index rosiglitazone claim were a recent insulin supply in 138 (82.1%) members, nitrate supply among 24 (14.3%) members, or a supply of both insulin and nitrates in 6 (3.6%) members. Of the 1,040,046 members continuously enrolled in the comparison group, 2,216 members (2.1 per 1,000) had a paid rosiglitazone claim between January 1, 2009, and June 30, 2009. If the safety PA policy had been active, 222 (10.0%) of the 2,216 members would have had a denied rosiglitazone claim unless the prescriber successfully appealed: recent supply of insulin 191 (86.0%) members, nitrate supply 26 (11.7%) members, or both insulin and nitrate supply in 5 (2.3%) members. There was no significant difference in baseline characteristics between the 2 groups.

Table 3 shows 30, 60, 90, and 180 days follow-up preva-

lence of members with a rosiglitazone and insulin and/or nitrate supply, rosiglitazone without insulin or nitrates, antidiabetic medication other than rosiglitazone, or no supply of any antidiabetic medication. At 30 days, 17 patients (10.1%, 95% confidence interval [CI]=6.3%-15.7%) in the intervention group had no supply of antidiabetic medication versus no patients (0%) in the comparison group ( $P < 0.001$ ). At 60 days, there was no significant difference in the proportion of patients without any antidiabetic medication in the intervention and comparison groups (15.5% [95% CI=10.7%-21.8%] vs. 9.9% [95% CI=6.6%-14.6%], respectively;  $P = 0.133$ ), and proportions remained similar at 180 days ( $P = 0.760$ , Table 3).

At 30 days, the prevalence of rosiglitazone concurrent supply with insulin and/or nitrates was 25.2 (95% CI=10.8-74.7) times higher in the comparison group (60.4%) compared with the intervention group (2.4%,  $P < 0.001$ ). The between-group differences in the prevalence of rosiglitazone concurrent supply with insulin and/or nitrates remained significant ( $P < 0.001$ ) at 60 and 90 days, and at the 180-day measurement point, the prevalence was 15.8 (95% CI=5.1-61.6) times higher in the comparison group (37.8% [95% CI=31.7%-44.4%]) than in the intervention group (2.4% [95% CI=0.7%-6.2%]). The difference between the intervention and comparison groups was 35.4 percentage points (95% CI=28.7-42.2,  $P < 0.001$ ).

The 2-year rosiglitazone monthly average claims per day per million members time series trend analysis is shown in Figure 2. During the 2 years in the intervention health plan, 4,893 members had 43,705 weighted 30-day claims for rosiglitazone with an average of 59.4 monthly claims per day per million members in January 2008, decreasing by 45.1% to 32.6 at the end of the analysis period in December 2009. Implementation of the PA policy, beginning in January 2009, appears to interrupt the trend line creating 2 segments. As shown in Table 4, the utilization drop in January 2009 associated with the PA implementation was significant (coefficient = -5.1821,  $P < 0.001$ ).

Using the parameter estimates from Table 4, the predicted average claims per day per million members at the end of the analysis period (December 2009) was estimated using 2 separate mathematical equations, one with the PA and another without. The difference between the results of the 2 equations provides the estimated impact of the PA for December 2009 in the intervention health plan. Predicted mean values with and without the PA intervention were 31.66 and 36.72 claims per day per million members, respectively, or an absolute decrease of 5.1 average monthly claims per day per million members (13.5%,  $P < 0.001$ ) associated with the PA. The Durbin-Watson statistic for the final model was 2.40 ( $P = 0.159$ ), indicating no autocorrelation.

In the comparison health plan, a total of 6,462 members had 56,858 weighted 30-day claims for rosiglitazone between January 1, 2008, and December 31, 2009. Average monthly claims per day per million members started at 49.1 in January

**TABLE 3** Medication Utilization in the Intervention<sup>a</sup> and Comparison Groups in the 180 Days After the Index Date

| Medication Supply <sup>b</sup>         | 30 Days                    |                          |         | 60 Days                    |                          |         | 90 Days                    |                          |         | 180 Days                   |                          |         |
|--|----------------------------|--------------------------|---------|----------------------------|--------------------------|---------|----------------------------|--------------------------|---------|----------------------------|--------------------------|---------|
|  | % (n) Intervention n = 168 | % (n) Comparison n = 222 | P Value | % (n) Intervention n = 168 | % (n) Comparison n = 222 | P Value | % (n) Intervention n = 168 | % (n) Comparison n = 222 | P Value | % (n) Intervention n = 168 | % (n) Comparison n = 222 | P Value |
| Rosiglitazone plus insulin/nitrates    | 2.4 (4)                    | 60.4 (134)               | <0.001  | 3.0 (5)                    | 48.2 (107)               | <0.001  | 2.4 (4)                    | 69.5 (121)               | <0.001  | 2.4 (4)                    | 37.8 (84)                | <0.001  |
| Rosiglitazone (no insulin or nitrates) | 3.6 (6)                    | 39.6 (88)                | <0.001  | 2.4 (4)                    | 26.6 (59)                | <0.001  | 2.4 (4)                    | 23.9 (53)                | <0.001  | 5.4 (9)                    | 21.6 (48)                | <0.001  |
| Other antidiabetic drug                | 83.9 (141)                 | 0                        | <0.001  | 79.2 (133)                 | 15.3 (34)                | <0.001  | 84.5 (142)                 | 14.0 (31)                | <0.001  | 78.6 (132)                 | 25.2 (56)                | <0.001  |
| No supply of any antidiabetic drug     | 10.1 (17)                  | 0                        | <0.001  | 15.5 (26)                  | 9.9 (22)                 | 0.133   | 10.7 (18)                  | 7.7 (17)                 | 0.386   | 13.7 (23)                  | 15.3 (34)                | 0.760   |

<sup>a</sup>Rosiglitazone safety PA policy denied coverage for rosiglitazone when the member had evidence of an insulin or nitrate supply in the prior 60 days. The comparison group was identified by application of the safety PA criteria; however, the policy was not active and the rosiglitazone claim was paid.

<sup>b</sup>Classified in hierarchical order: rosiglitazone supply plus insulin/nitrates, rosiglitazone without insulin/nitrates, other antidiabetic drug supply (insulin or any other antidiabetic drug with exception of rosiglitazone), no supply of any antidiabetic drug. Not all columns sum to 100.0% due to rounding. PA = prior authorization.

2008 and decreased by 22.2% to 38.2 in December 2009 (Figure 2). The comparison health plan did not experience a January 2009 drop in utilization ( $P=0.626$ ) or a significant change in trend of monthly average claims per day per million members associated with the intervention date ( $P=0.824$ ).

**Discussion**

In January 2009, a consensus group from the American Diabetes Association and European Association for the Study of Diabetes unanimously advised against the use of rosiglitazone because of the presence of other options for diabetes treatment.<sup>22</sup> Even after cardiovascular concerns with rosiglitazone were publicized in 2007, we found that concurrent nitrate or insulin use did not appear to decrease within a large commercially insured population.<sup>23</sup>

The present study found that at 180 days of follow-up, a rosiglitazone safety PA policy was associated with a 15.8-fold lower prevalence of concurrent insulin and/or nitrate therapy, 2.4% in the intervention group compared with 37.8% in a concurrent nonrandomized group not subject to the safety PA. A potential harm of the PA policy was that at 30 days follow-up, intervention group patients were significantly more likely than comparison group patients to have no supply of any antidiabetic therapy (10.1 percentage point difference); however, there was no significant difference between the groups at the 60-day follow-up point and through 180 days. The rosiglitazone safety PA policy also appeared to affect rosiglitazone utilization globally within the intervention health plan as evidenced by the significant 13.5% decrease in average rosiglitazone claims per day per million members in December 2009, while the comparison health plan did not experience a change in January 2009 or a change in trend after the PA.

**TABLE 4** Parameter Estimates, Standard Errors, and P Values from Interrupted Time-Series Regression Models Predicting Average Monthly Rosiglitazone Claims Per Million Members in the Safety PA Intervention and Comparison Health Plans

| Variable   | Estimate | Standard Error | t-statistic | P Value |
|--|----------|----------------|-------------|---------|
| <b>Intervention Health Plan</b>                        |          |                |             |         |
| Intercept  | 60.5665  | 0.7195         | 84.17       | <0.001  |
| Time in months from start of study period <sup>a</sup> | -0.9959  | 0.0978         | -10.19      | <0.001  |
| Post-intervention date <sup>b</sup>                    | -5.1821  | 0.9596         | -5.40       | <0.001  |
| Time after the intervention date <sup>a,c</sup>        | 0.0196   | 0.1383         | 0.14        | 0.889   |
| <b>Comparison Health Plan</b>                          |          |                |             |         |
| Intercept  | 49.6626  | 0.6739         | 73.70       | <0.001  |
| Time in months from start of study period <sup>a</sup> | -0.5152  | 0.0916         | -5.63       | <0.001  |
| Post-intervention date <sup>b</sup>                    | 0.4448   | 0.8987         | 0.49        | 0.626   |
| Time after the intervention date <sup>a,c</sup>        | -0.0292  | 0.1295         | -0.23       | 0.824   |

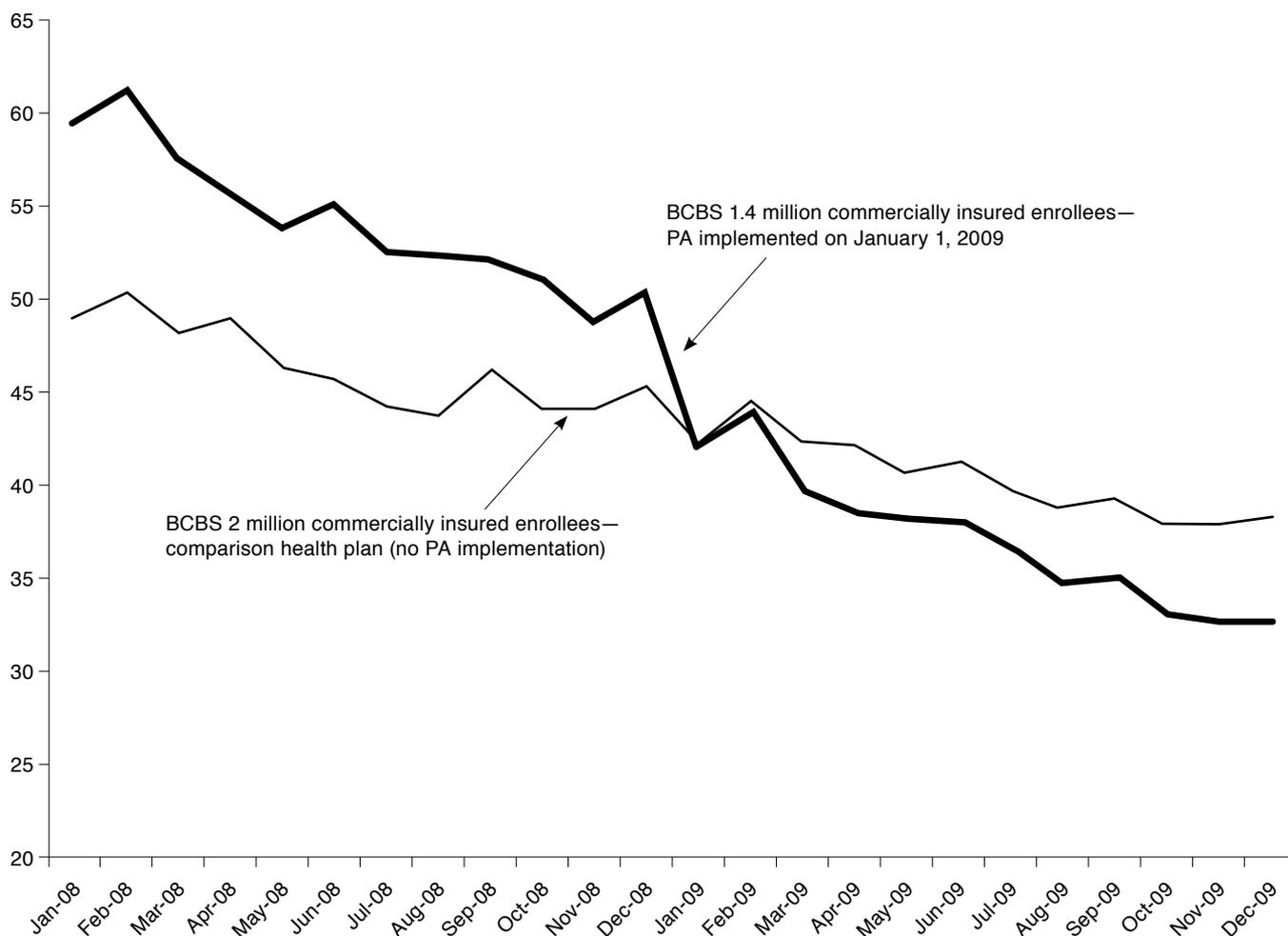
<sup>a</sup>Monthly utilization trend change.

<sup>b</sup>Coded 0 prior to January 2009, 1 thereafter.

<sup>c</sup>Coded 0 prior to January 2009, 1-12 thereafter.

PA = prior authorization.

As described in the recent systematic review by Ostini et al. (2012), there is a paucity of research assessing methods to cease prescribing even when the prescribed regimen can be unsafe.<sup>24</sup> The authors of the systematic review identified 12 high-quality studies, of which none evaluated a PA policy.<sup>24</sup> The present study, which assessed a PA policy implemented to improve medication safety through avoidance of documented

**FIGURE 2** Rosiglitazone Monthly Average Paid Claims Per Day Per Million Members for 2008 and 2009

BCBS = BlueCross Blue Shield; PA = prior authorization.

unsafe concurrent drug use, found a significant decrease in unsafe use of rosiglitazone. These results are consistent with those of a study evaluating the impact of rosiglitazone coverage status, defined as requiring a PA or not, on the safety of prescribing in state Medicaid programs. Ross et al. (2012) reported that Medicaid programs that continued to provide coverage of rosiglitazone as a preferred drug without a PA requirement had prescribing rates that were 3 to 5 times higher compared with programs with a PA requirement.<sup>25</sup>

Rosiglitazone prescribing information (PI) on cardiovascular event rates from 42 clinical trials with an average 6-month study duration was used to estimate the impact of the PA.<sup>19</sup> The current study found at 180 days the difference between intervention and comparison groups with concurrent rosiglitazone and insulin or nitrates was 35.4 percentage points, translating

to 59 individuals not exposed to concurrent insulin or nitrate therapy in the intervention group. Using the baseline nitrate and insulin utilization patterns from Table 2, without the policy, 11 (17.9% of 59) intervention group individuals would have been exposed to concurrent rosiglitazone and nitrates, and 48 individuals (82.1% of 59) would have been exposed to concurrent rosiglitazone and insulin. As stated in the PI, rosiglitazone users receiving nitrates for known coronary heart disease had a 6.14 percentage point higher cardiovascular event rate compared with non-nitrate users.<sup>19</sup> Applying the cardiovascular event rate to the 11 non-nitrate rosiglitazone utilizers translates to 1 event forecast to have been avoided. Using the same logic for the 48 noninsulin rosiglitazone utilizers, an additional 1 event is forecast to have been avoided (PI cardiovascular event rate 1.41%).<sup>19</sup> In summary, the adjusted reduction in concurrent

rosiglitazone and insulin or nitrate use was associated with 59 fewer individuals exposed to unsafe concurrent therapy, and potentially 2 cardiovascular events were avoided.

The reduction in unsafe rosiglitazone use did not occur without potential harm. This study found that 17 individuals (10.1%) in the PA intervention group had no antidiabetic therapy at 30 days. These individuals could potentially have experienced hyperglycemia adverse events such as polydipsia, polyphagia, and polyuria. Short-term hyperglycemia is generally not life-threatening with the exception of hyperosmolar hyperglycemic syndrome.<sup>26</sup> It is unknown if medical complications occurred at a higher rate in the safety PA policy group. In addition, medical care encounters and associated expenditures may have occurred at a higher rate in the PA policy group as a result of the rosiglitazone claim denial or the subgroup without antidiabetic therapy.

PA studies assessing the impact on medical resources after PA denial have been performed for a number of drug classes including proton pump inhibitors, cyclooxygenase (COX)-2 nonsteroidal anti-inflammatory drugs, antidepressants, second generation antipsychotics, pregabalin, and palivizumab.<sup>5,6,11,12,17,18,27</sup> These studies have found no increase in medical utilization or costs among individuals denied drug coverage. A commonality of these studies was the nonacuity of the condition for which the medication is generally used. A PA policy for the use of clopidogrel in acute myocardial infarction found improved cardiovascular outcomes when the PA was removed.<sup>28</sup> However, the clopidogrel study's validity has been questioned because of several features of the research methodology including data access and confounding.<sup>29</sup>

The current PA process can be viewed as time consuming and cumbersome, although keeping patient safety at the forefront can drive creative ways to improve the system. Integrated medical and pharmacy claims data could be used to identify those patients at increased cardiovascular risk from rosiglitazone. In addition, using a clinical rules engine by applying a "SmartPA" could allow real-time claims processing and decrease administrative burden for prescribers and pharmacists.<sup>30</sup> Further investigation of PA policy impact on medical outcomes is necessary.

As measured by segmented regression analysis, rosiglitazone utilization decreased significantly (13.5%) in an intervention population over a 24-month time period. The rosiglitazone claims utilization decrease is consistent with the 13.5% safety PA coverage denial rate of individuals attempting to submit a rosiglitazone claim during the 6 months after PA policy implementation. In addition, this decrease is consistent with decreases in utilization reported in other PA policy studies that have ranged from 5% to 58%<sup>7,10,14,17,31-33</sup> with the exception of an apparent outlier of an 83% decrease in nonpreferred antihypertensives in a Michigan Medicaid population.<sup>32</sup>

### Limitations

The foremost limitation of this study is its quasi-experimental design comparing 2 commercially insured populations without randomization. Although the group characteristics were similar at baseline, claims analyses are limited in their ability to account for many possible differences among individuals and prescribers. Second, the primary internal validity concern regarding the findings of an interrupted time series analysis is the possibility of changes that may have occurred at the same time as the policy change. However, the formulary placement for antidiabetic agents was unchanged in the intervention and comparison groups during the period of this study in 2008 and 2009, and the member cost share for antidiabetic medications in the intervention health plan increased by 7.2% (\$18.14 in 2008 and \$19.44 in 2009) while the comparison health plan increase was 3.1% (\$18.43 in 2008 and \$19.01 in 2009).

Third, prescribers may have instructed patients to discontinue their insulin or nitrate therapy prior to continuing or initiating their rosiglitazone. It is also possible that individuals paid cash or obtained samples of rosiglitazone and continued their rosiglitazone in combination with insulin or nitrates, resulting in an overestimate of the positive outcome from this PA intervention. Fourth, we may have overestimated the prevalence of patients without antidiabetic therapy due to the use of physician samples or cash payment for rosiglitazone or other antidiabetic therapy.

Fifth, the study is limited in the assessment of the effects on the health care system as prescribers and pharmacists expend time addressing the denied claim, including possibly submitting a medical exception request or providing alternate pharmacotherapy. Sixth, the generalizability of our study findings is limited to continuously enrolled commercially insured individuals in the South during 2008 and 2009 utilizing rosiglitazone. However, based on data from 2008 and 2009, geographic variation and rosiglitazone utilization were similar across the United States.<sup>34</sup> Most importantly, the projected number of cardiovascular events avoided was calculated based on previous research. This study did not assess actual medical events, medical utilization, or medical costs, which all could be increased as a result of denied rosiglitazone coverage.

### Conclusions

Our study findings support the use of a PA to promote safe prescribing as evidenced by the potential cardiovascular event risk avoidance. The safety PA policy was associated with a reduction in the prevalence of concurrent rosiglitazone and nitrate or insulin therapy by more than 15-fold at 6 months follow-up. The study findings suggest a potential risk of 10.1% of individuals going without antidiabetic therapy at 30 days after the rosiglitazone claim denial; however, the prevalence of individuals without antidiabetic therapy became similar in the PA and comparison groups by 60 days and remained similar

at 6 months of follow-up. Given the potential cardiovascular event risk and prevalence of concurrent rosiglitazone and insulin or nitrate therapy, determining the risk versus benefit of a safety PA policy implementation is necessary.

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## DISCLOSURES

This study was performed without external funding, and the authors report no financial or other potential conflicts of interest related to the subject of this article. Starnier and Gleason conceived and designed the study with the assistance of Fenrick and Coleman. Starnier collected the data with assistance of Fenrick and Coleman. Starnier and Gleason interpreted the data. Starnier and Gleason wrote the manuscript with the assistance of Wickersham. All 5 authors contributed to revision of the manuscript.

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