

## Distal Upper and Lower Limb Fractures Associated With Thiazolidinedione Use

Stephen G. Jones, MS; Soyul R. Momin, MS, MBA; Matthew W. Good, MD; Terence K. Shea, PharmD; and Kenneth Patric, MD

In 1997, the US Food and Drug Administration (FDA) approved troglitazone, a member of the thiazolidinedione drug class, for the treatment of type 2 diabetes mellitus. Although troglitazone caused hepatotoxic effects and was removed from the market in 2000, pioglitazone hydrochloride and rosiglitazone maleate, both thiazolidinediones, are still used with success and relative safety. The thiazolidinedione drug class acts on the nuclear transcription factor peroxisome proliferator-activated receptor  $\gamma$  subtype as a selective ligand.<sup>1</sup> Thiazolidinediones increase glucose uptake in peripheral tissues, heighten fatty acid uptake in adipose tissue, and decrease endogenous glucose production by the liver.<sup>2</sup> Although the exact mechanism of action is unknown, patients with diabetes taking a thiazolidinedione experience drops in glycosylated hemoglobin levels by 1 to 1.5 percentage points.<sup>3</sup>

A higher proportion of fractures among patients with type 2 diabetes mellitus is well documented in the recent literature.<sup>4,5</sup> Adjusting for age, sex, smoking status, body mass index, and stroke history, patients with diabetes have an increased risk for fractures compared with patients without diabetes.<sup>6</sup> In addition, recent research suggests that thiazolidinediones may cause bone loss by increasing bone marrow adiposity and decreasing mature osteoblasts.<sup>7,8</sup> These facts raise concerns about the use of the thiazolidinedione drug class among patients already at increased risk for fractures.

The FDA recently released safety alerts concerning drugs in the thiazolidinedione class. Rosiglitazone use was linked to increased fractures of the upper arm, hand, and foot among female patients.<sup>9</sup> Of 645 women in A Diabetes Outcome Progression Trial (ADOPT)<sup>10</sup> taking rosiglitazone, 60 (9.3%) experienced a fracture during the 2-year study period. This proportion of fractures was significantly higher compared with that in female patients randomized to receive metformin hydrochloride or glyburide ( $P < .05$ ). A nonsignificant increased proportion of fractures was found in male patients. In addition, pioglitazone use has been linked to increased rates of distal upper and lower limb fractures among women.<sup>11</sup> In that clinical trial involving 15,599 patients, results showed an increased proportion of fractures for female patients

taking pioglitazone versus a comparator female group receiving placebo or active nonpioglitazone treatment. Most fractures occurred in locations different from those normally associ-

**Objective:** To determine if patients with diabetes mellitus taking a thiazolidinedione experienced higher proportions of distal upper and lower limb fractures compared with those not taking a thiazolidinedione, as recent US Food and Drug Administration safety alerts suggested.

**Study Design:** This 3-year cross-sectional study used medical and pharmacy claims from a large southeastern managed care organization for continuously enrolled members from January 1, 2004, through December 31, 2006.

**Methods:** A total of 29,284 patients with type 2 diabetes mellitus aged 18 to 64 years were allocated to mutually exclusive study groups of thiazolidinedione users versus thiazolidinedione nonusers and thiazolidinedione type (pioglitazone hydrochloride, rosiglitazone maleate, or a combination).  $\chi^2$  Tests were used to determine if fracture proportions for thiazolidinedione users differed from those of thiazolidinedione nonusers and if thiazolidinedione type was significant. Multivariate logistic regression models and backward stepwise elimination algorithms were constructed to evaluate associations of fracture proportions with age, sex, and chronicity of drug use for 7462 members using a thiazolidinedione.

**Results:** The mean (SE) fracture proportions were significantly higher for thiazolidinedione users (5.1% [0.5%]) versus nonusers (4.5% [0.3%]) ( $P = .03$ ). Fracture proportions did not differ by thiazolidinedione type ( $P = .86$ ). Overall, women experienced a higher mean (SE) proportion of fractures compared with men (6.0% [0.4%] vs 3.5% [0.3%]) ( $P < .001$ ), regardless of thiazolidinedione use. On average, the odds of experiencing a fracture for women using a thiazolidinedione increased 2% for every year increase in age.

**Conclusions:** Patients with diabetes using thiazolidinediones, regardless of type, had higher proportions of distal upper and lower limb fractures compared with those not using thiazolidinediones. Fracture proportions were higher among women and increased with age.

(*Am J Manag Care.* 2009;15(8):491-496)

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### Take-Away Points

Using administrative data, we confirmed that more limb fractures occur in patients with diabetes using thiazolidinediones versus those not using this drug class.

- There were no significant differences among patients using pioglitazone hydrochloride versus rosiglitazone maleate.
- Fracture proportions were higher among women and increase with age.
- Fracture proportions for thiazolidinedione users were nonsignificant among men.
- “Time on drug” was nonsignificant in explaining variation in fracture occurrences.

incomplete and are not comparable with those of our commercial line of business, and (2) concentration on a younger population assists the analysis by partially controlling for known associations of age with bone fragility.

Medical and pharmacy claims data were mined for diabetes status

ated with postmenopausal osteoporosis (eg, foot, spine and tailbone, and hip, pelvis, and upper leg). As in ADOPT, a nonsignificant increased proportion of fractures was observed among male patients.

Although the aforementioned clinical trial results indicate a sex predilection for increased risk of fractures, they do not address the influence of age and chronicity of drug use among patients taking thiazolidinediones. In addition, it is unknown if the proportion of fractures differs for patients using pioglitazone versus rosiglitazone or if this phenomenon is simply a drug class effect. To address these concerns, 3 years of relevant medical insurance claims data were examined. The objective of this study was to determine if the proportion of distal upper and lower fractures differs for patients with diabetes using a thiazolidinedione versus those not using a thiazolidinedione. We also examined fracture rates among patients using pioglitazone, rosiglitazone, or a combination to determine if fracture proportions differ within the drug class. Finally, we determined if age, sex, and chronicity of drug use influenced the proportion of fractures among thiazolidinedione users and nonusers.

using McSource ViPS software (version 6.0; McSource ViPS, Inc, Baltimore, MD).<sup>13</sup> Members were identified as having diabetes if any of the following individual conditions were met within a 24-month period: (1) 2 face-to-face encounters on different dates of service in an ambulatory or nonacute inpatient setting with a diagnosis of diabetes, (2) 1 acute inpatient or emergency department encounter with a diagnosis of diabetes, or (3) at least 1 prescription for insulin or an oral hypoglycemic or antihyperglycemic agent in an ambulatory encounter.

We excluded members with chronic corticosteroid use, type 1 diabetes mellitus, or chronic kidney disease (*International Classification of Diseases, Ninth Revision [ICD-9]* codes beginning with 585). Chronic corticosteroid use was defined as having filled a 6-month supply or more of any corticosteroid powder, elixir, capsule, solution, reconstituted solution, suspension, tablet, or syrup during the 3-year study period. A member was determined to have type 1 diabetes mellitus if he or she had a type 1 diabetes mellitus–related episode of care during the study period. After these criteria were applied, 29,284 members with type 2 diabetes mellitus were included in the study. We initially created the following 2 mutually exclusive study groups to determine if members with diabetes taking a thiazolidinedione of any kind experienced a higher proportion of fractures compared with those not taking a thiazolidinedione: (1) thiazolidinedione users (7462 members with diabetes who filled a pioglitazone- or rosiglitazone-containing prescription during the study period) and (2) control subjects with diabetes (21,822 members with diabetes who did not fill a thiazolidinedione prescription of any kind during the study period).

We then parsed the group of thiazolidinedione users into the following 3 mutually exclusive study groups based on the type of thiazolidinedione prescription filled: (1) pioglitazone group (2589 members with diabetes who filled only a pioglitazone-containing prescription during the study period), (2) rosiglitazone group (3908 members with diabetes who filled only a rosiglitazone-containing prescription during the study period), and (3) combination group (965 members with diabetes who filled both a pioglitazone- and rosiglitazone-containing prescription during the study period).

## METHODS

### Participants and Study Groups

A 3-year (January 1, 2004, through December 31, 2006) cross-sectional member sample was established using medical and pharmacy claims data extracted from a large southeastern managed care organization’s commercial line-of-business claims data warehouse. Administrative claims data have been shown to be effective and valuable in related research,<sup>12</sup> as they allow researchers to leverage statistical power through large sample sizes. Member enrollment data were extracted to attribute demographics, including age, sex, and length of enrollment. Age was calculated as the member’s age as of December 31, 2005 (the study period midpoint). Members aged 18 to 64 years within a commercial health plan and continuously enrolled during the study period were included for further analyses. Members older than 64 years were excluded for the following 2 major reasons: (1) a significant number of these members are covered by Medicare, whose data are

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To ensure data accuracy, data validation methods are executed monthly for the entire data warehouse claims information and for McSource ViPS data transfer methods. If any issues arise from these validations, problems are immediately rectified, and corrected data are posted.

### Fracture Identification

Distal upper and lower limb fractures were identified using 3-digit ICD-9 codes 813.x through 817.x (distal upper limb fractures, including radius and ulna, carpal and metacarpal, and phalanges and hand bones) and 823.x through 826.x (distal lower limb fractures, including tibia and fibula, ankle, tarsal and metatarsal, and phalanges and foot bones). A member was considered to have a fracture if any of these codes were included on a medical claim having service dates during the study period. It was our intent to perform tests of proportions across the study groups (fracture vs no fracture) rather than to examine the number of fractures a member may have experienced during the study period.

### Chronicity of Drug Use

Pharmacy claims data were examined for chronicity of drug use by thiazolidinedione type and were represented per 100 days of drug use, where drug possession was derived from the number of supply days. "Supply days" represents the number of days a member's prescription lasts and serves as a proxy for drug use amount over time. The duration of the study period was 1095 days; therefore, the theoretical maximum number of "per 100 days of drug use" (hereafter, time on drug) equaled 10.95.

### Statistical Analysis

Statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, NC) with  $\alpha = .05$ . Values are reported as the mean (SE), and proportions of fractures and odds ratios (ORs) are given with 95% confidence intervals (CIs), where applicable.

**Comparison of Fracture Proportions Across Groups.** To address the specific concerns of the FDA warning and to validate these events in our member population, we constructed a contingency table using a  $\chi^2$  test to determine if the proportion of fractures among members with diabetes using a thiazolidinedione was significantly different from that among those not using a thiazolidinedione. We then tested for significant differences across the 3 thiazolidinedione study groups (pioglitazone, rosiglitazone, and combination). This was done to address our specific hypothesis that the fracture phenomenon is not limited to a single thiazolidinedione type but rather is a drug class effect.

**Age, Sex, and Chronicity of Drug Use.** Multivariate logistic regression models were constructed to evaluate associations of fracture proportions with age, sex, and chronicity of drug use among 7462 members using a thiazolidinedione. We first constructed a fully-fitted model that included all main effects (age, sex, and time on drug) and interaction effects. Once it was determined from our  $\chi^2$  test that fracture proportions did not differ across thiazolidinedione types, this class variable was excluded from the logistic regression modeling. A backward stepwise elimination algorithm was used to remove variables from the fully-fitted model, where  $P > .05$ . If any of the interaction terms were significant, we constructed subsequent logit models to calculate appropriate adjusted ORs. Results for these models are given as ORs with 95% CIs. Model fit was tested by evaluation of the area under the receiver operating characteristic curve, where values range from 0.5 to 1 (with 1 being a perfect model fit), as well as by a Hosmer-Lemeshow goodness-of-fit test,<sup>14</sup> where  $P > .05$  suggests that the fitted model is an adequate model if making future predictions.

## RESULTS

The overall proportion of fractures across all 29,284 members of the study population was 4.7% (1369 fractures)

■ **Table 1.** Summary Information, Including Fracture Proportions for Study Groups

Study Group	No. of Members	%		Mean (SE)	
		Men	Women	Age, y	Fractures, %
<b>Thiazolidinedione users</b>	<b>7462</b>	54.1	45.9	52 (0.1)	5.1 (0.5) <sup>a</sup>
Pioglitazone hydrochloride	2589	55.2	44.8	53 (0.2)	5.1 (0.7)
Rosiglitazone maleate	3908	54.0	46.0	52 (0.1)	5.1 (0.6)
Combination	965	51.5	48.5	51 (0.3)	5.5 (1.3)
<b>Control subjects with diabetes</b>	<b>21,822</b>	51.9	48.1	52 (0.1)	4.5 (0.3)
<b>Overall</b>	<b>29,284</b>	52.5	47.5	52 (0.1)	4.7 (0.2)

<sup>a</sup>Significantly different from control group at  $\alpha = .05$

■ **Table 2.** Multivariate Logistic Regression Models

Variable	Odds Ratio (95% Confidence Interval)	P
Supply days <sup>a</sup>	1.033 (0.99-1.06)	.064
Sex <sup>a</sup>	—	.037
Age-x-sex <sup>b</sup>	—	.002
Age-x-female sex <sup>b</sup>	1.019 (1.005-1.039)	.013
Age-x-male sex <sup>b</sup>	0.98 (0.962-1)	.047

<sup>a</sup>Results from initial backward stepwise elimination algorithm. Odds ratios are only given for supply days because of the significant age-x-sex interaction.

<sup>b</sup>Results from subsequent sex-based models to determine age effect within sex.

(Table 1). The proportion of fractures was significantly higher among patients with diabetes using a thiazolidinedione (5.1% [0.5%]) versus those not using a thiazolidinedione (4.5% [0.3%]) ( $P = .03$ ). Fracture proportions did not differ significantly among pioglitazone, rosiglitazone, or combination drug users ( $P = .86$ ). The mean age and sex distributions were consistent across all study groups. Overall, women experienced a higher proportion of fractures than men (6.0% [0.4%] vs 3.5% [0.3%]) ( $P < .001$ ), regardless of thiazolidinedione use.

The backward stepwise elimination algorithm that considered all variables yielded 2 statistically significant factors in the final regression model of fracture association (sex and age-x-sex interaction). Because the age-x-sex interaction was significant ( $P = .002$ ), this led to the creation of subsequent models to determine the age effect within each sex (Table 2). Therefore, reported  $P$  values and ORs within sex models represent the age effect within each respective model. After removal of members with chronic corticosteroid use and evidence of chronic kidney disease, time on drug was nonsignificant. On average, the odds of experiencing a fracture for women using a thiazolidinedione increased 2% for every year increase in age. Fracture proportions were only marginally significant for men in the sex-based logistic regression models ( $P = .047$ ), and ORs intersected 1 (OR, 0.98; 95% CI, 0.96-1.00), indicating nonsignificance. Hosmer-Lemeshow goodness-of-fit tests revealed that model fit was adequate for all models ( $P > .05$ ).

Fracture locations were captured from claims data using 3-digit prefaced ICD-9 codes. There were 2127 unique member ICD-9 fracture codes recorded across 1369 members who experienced a fracture during the study period. The percentages of fracture locations in descending order were as follows: closed fracture of medial malleolus (24.8%), closed Colles fracture (24.1%), closed fracture of calcaneus (17.2%), closed fracture of unspecified part of fibula (16.3%), closed fracture of unspecified phalanx or phalanges of hand (7.1%), closed fracture of 1 or more phalanges of foot (4.5%), unspecified closed fracture of carpal bone (3.1%), closed fracture of meta-

carpal bones (site unspecified) (2.8%), and multiple closed fractures of hand bones (0.1%).

## DISCUSSION

Our research suggests that patients with diabetes taking a thiazolidinedione, regardless of type or brand, experienced a higher proportion of distal limb fractures compared with those not taking a thiazolidinedione. Clinical implications of this difference (6 persons per 1000) could vary depending on scale. For example, a managed care organization insuring 3 million lives with an 8% diabetes prevalence would result in approximately 1440 additional fracture claims in a given year for thiazolidinedione users versus nonusers.

The odds of having a fracture were 14% higher on average for members using a thiazolidinedione versus members not using a thiazolidinedione. A recent meta-analysis<sup>15</sup> supports the trends found in our study, revealing that patients with diabetes using a thiazolidinedione had a significant risk of fractures compared with control subjects (OR, 1.45; 95% CI, 1.18-1.79) ( $P < .001$ ). Overall fracture proportions for thiazolidinedione users were higher in our study (5.1% [0.5%]) compared with the overall meta-analysis findings (3.0% [0.4%]). This may result from the male-biased populations within the meta-analysis studies (61.4% male) compared with our more uniform male-female distribution (52.5% male), as men are less likely to experience a fracture.<sup>15</sup> The difference in our overall odds (14%) compared with 18% in the meta-analysis may be an artifact of data inclusion, as the meta-analysis included hip fracture sites that were beyond the scope of our study. The findings of our cross-sectional study provide further evidence that FDA warnings were warranted but expand the issue to include both thiazolidinediones (pioglitazone and rosiglitazone) in the drug class and are in accord with recent observations supporting this class effect.<sup>16</sup>

Our data further underscore a sex and age predilection for fracture occurrence and thiazolidinedione use. A significant increase in fracture risk seems to occur particularly among the older female population, as suggested by others.<sup>5,17,18</sup> Overall, fracture proportions experienced in our study correspond to the meta-analysis<sup>15</sup> findings, in which approximately 6% of women and 2% of men using a thiazolidinedione experienced a fracture. Differences in fracture occurrence between women and men using a thiazolidinedione in ADOPT<sup>10</sup> were more pronounced (9.3% and 3.9%, respectively) than in our population (7.0% and 3.6%, respectively). Controlling for age and chronicity of drug use, our study population of older women

with diabetes taking a thiazolidinedione has an additional increased risk of fracture compared with their controls (ie, women with diabetes not taking the drug). The increased fracture risk observed among older women<sup>19-21</sup> was not found among our male population. Our results suggest that men are at no higher risk of fracture, regardless of thiazolidinedione use, and support other evidence suggesting that the risk of fractures significantly increases for women using a thiazolidinedione but not for men.<sup>9,15</sup> Perhaps contributing to this phenomenon is that women are more susceptible to bone fragility and osteoporosis than men.<sup>11,22</sup> In addition, diabetes further augments this risk, especially in women.<sup>4,5</sup> Others have found significance differences within the male population, suggesting an increased fracture risk among men with diabetes taking thiazolidinediones.<sup>16</sup> Our data indicate that chronicity of drug use for members taking a thiazolidinedione did not significantly influence the proportion of fractures. Time on drug was nonsignificant and may need further investigation.

We make no attempts to ascertain cause and effect or mechanism of action associated with fractures. Recent literature suggests that thiazolidinedione use may be related to bone loss, especially in older women with diabetes.<sup>18,19</sup> Pioglitazone therapy may reduce the production of osteoblasts, which may ultimately lead to bone loss.<sup>6-8</sup> The use of such a medication among patients with diabetes, a population known to be at increased risk for fractures, may exacerbate the problem. In addition, patients with diabetes experience falls more often than the general population.<sup>23</sup> Combined with the mean weight gain of 2 to 4 kg in patients taking thiazolidinediones,<sup>3</sup> this relationship may explain the increased incidence of distal extremity fractures in this population. Other evidence supports this hypothesis.<sup>24</sup> Clearly, further research needs to focus on risk factors associated with fractures, diabetes, and thiazolidinedione use.

Limitations of this study include, but are not limited to, the following: we were unable to use claims data to measure actual medication compliance, the study group was restricted to members younger than 65 years, the length of the study was only 3 years, and fracture location was limited to distal upper and lower limb fractures. There was an increased fracture risk among older members; therefore, the more elderly population ( $\geq 65$  years) may be at most risk for fractures if taking a thiazolidinedione medication. Our study period was limited to 3 years, and more time may be needed to demonstrate a cumulative drug effect. We did not incorporate the date when the fracture occurred into our evaluation; therefore, we were testing for associations related to fractures rather than risk modeling (eg, Cox proportional hazards regression model). We were limited to patient stratification based on filled thi-

azolidinedione prescriptions, without the ability to measure actual compliance with the drug. Insulin use was approximately 8% more prevalent among the thiazolidinedione users compared with the nonuser control group. This may suggest that the severity of diabetes is greater for members using a thiazolidinedione and could contribute to fracture proportions. In addition, we controlled only for age and sex to address specific FDA warnings, and it was beyond the scope of this study to control for other potential influencing factors such as comorbidities associated with fractures, medications that predispose patients to falls, body mass index, smoking status, alcohol and dietary intake, physical activity level, family and personal medical history, and postmenopausal hormone therapy.

In conclusion, this study confirms that higher proportions of fractures are associated with patients having diabetes using thiazolidinediones versus those not using thiazolidinediones, especially among older women, as claimed in recent FDA warnings. No significant fracture risk increase is apparent within the male population. Finally, we conclude that no significant differences in fracture proportions exist between members using pioglitazone- versus rosiglitazone-containing products.

**Author Affiliations:** BlueCross and BlueShield of Tennessee (SGJ, SRM, TKS, KP), Chattanooga; and TC Thompson Children's Hospital (MWG), Chattanooga, TN.

**Funding Source:** None reported.

**Author Disclosures:** The authors (SGJ, SRM, MWG, TKS, KP) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

**Authorship Information:** Analysis and interpretation of data (SGJ, SRM, MWG, TKS, KP); drafting of the manuscript (SGJ, SRM, MWG, TKS, KP); and critical revision of the manuscript for important intellectual content (SGJ, SRM, MWG, TKS, KP).

**Address correspondence to:** Stephen G. Jones, MS, BlueCross and BlueShield of Tennessee, 1 Cameron Hill Cr, Bldg 2.1, Chattanooga, TN 37402. E-mail: stephen\_jones@bcbs.com.

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