**Diabetes Care Publish Ahead of Print, published online January 25, 2008**

# Rosiglitazone Associated Fractures in Type 2 Diabetes: An Analysis From ADOPT

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**Running Title:** Rosiglitazone and Fractures in Type 2 Diabetes

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Clinical trial registry number NCT00279045.

Received for publication 30 November 2007 and accepted in revised form 22 January 2008.

Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org.

## ABSTRACT

*Objective*: To examine possible factors associated with the increased risk of fractures observed with rosiglitazone in ADOPT (A Diabetes Outcome Progression Trial).

*Research Design and Methods:* Data from the 1840 women and 2511 men randomized in ADOPT to rosiglitazone, metformin or glyburide for a median of 4.0 years were examined with respect to time to first fracture, rates of occurrence and sites of fractures.

*Results*: In men, fracture rates did not differ between treatment groups. In women, at least one fracture was reported with rosiglitazone in 60 patients (9.3% of patients, 2.74/100 patient years [PY]), metformin in 30 (5.1%, 1.54/100 PY) and glyburide in 21 (3.5%, 1.29/100 PY). The cumulative incidence (95% CI) of fractures in women at five years was 15.1% (11.2, 19.1) with rosiglitazone, 7.3% (4.4, 10.1) with metformin and 7.7% (3.7, 11.7) with glyburide, representing hazard ratios of 1.81 (1.17, 2.80) and 2.13 (1.30, 3.51) for rosiglitazone compared to metformin and glyburide, respectively. The increase in fractures with rosiglitazone occurred in pre- and postmenopausal women, and was predominantly in the lower and upper limb. No particular risk factor underlying the increased fractures in female patients who received rosiglitazone therapy was identified.

*Conclusions:* Further investigation into the risk factors and underlying pathophysiology for the increased fracture rate in women taking rosiglitazone is required to relate them to preclinical data and better understand the clinical implications of and possible interventions for these findings.

Type 2 diabetes is associated with an increased risk of fractures, with the risk increasing with longer duration of disease (1; 2). These fractures affect predominantly the hip, arm and foot (1-5), and occur despite the fact that bone mineral density is either normal or even increased in patients with type 2 diabetes compared to those who are not hyperglycemic (5-7). While the reason for this increased risk is unclear, it has been postulated that in older patients some of the risk may be related to disability and falls (8). In the context of specific diabetes therapy, a recent report from the Health, Aging and Body Composition Study, an observational study, noted that older women with type 2 diabetes who were taking thiazolidinediones experienced increased bone loss compared to controls while no differences were seen in men (9). However, a recent retrospective study suggested a greater loss of bone mineral density in men taking rosiglitazone (10).

A Diabetes Outcome Progression Trial (ADOPT) was a randomized, controlled, clinical trial comparing the effect of the thiazolidinedione rosiglitazone, the biguanide metformin and the sulfonylurea glyburide on glucose control in recently diagnosed (<3 yrs), drug-naïve patients with type 2 diabetes (11). In the study it was shown that treatment with rosiglitazone produced more durable glycemic control than metformin or glyburide as measured by fasting glucose and hemoglobin A1c. This effect resulted from a greater preservation of ß-cell function with rosiglitazone. After unblinding and completion of the prespecified statistical analysis plan, a review of adverse events of special interest uncovered an increase in the number of fractures in women taking rosiglitazone; a brief description of the finding was added as a post-script to the primary manuscript then in press (11). In women we observed an increased occurrence of bone fractures in the upper and lower limbs, but an increase in hip or vertebral fractures was not noted. An increased fracture risk was subsequently reported in women receiving pioglitazone (12), the other thiazolidinedione currently in clinical use. We now report in greater detail the ADOPT findings related to fractures.

## STUDY DESIGN AND METHODS

***Subjects and Study Design.*** ADOPT randomized 4360 individuals with type 2 diabetes who had been diagnosed within three years and were naïve to oral hypoglycemic drugs. Nine of the randomized subjects never received study medication so that 1456 subjects were assigned to rosiglitazone, 1454 to metformin and 1441 to glyburide therapy. The study was carried out in 488 centers in 17 countries in North America and Europe. The protocol was reviewed and approved by institutional review boards for each centre and all subjects gave written, informed consent. The study was registered at ClinicalTrials.gov (number: NCT00279045).

The study protocol has been previously published (13). Briefly, ADOPT was a randomized, double blind, parallel-group trial. Eligible patients with diabetes were 30 to 75 years of age and had a fasting plasma glucose concentration between 126 and 180 mg/dl on lifestyle therapy. Exclusion criteria included clinically significant liver disease, renal impairment, a history of lactic acidosis, unstable or severe angina, known congestive heart failure (CHF, New York Heart Association class I-IV) requiring pharmacological intervention, uncontrolled hypertension, or chronic diseases requiring periodic or intermittent treatment with oral or intravenous corticosteroids, or continuous use of inhaled corticosteroids.

Subjects were randomized to receive double-blind treatment with either rosiglitazone, metformin or glyburide. The

initial daily dose of rosiglitazone was 4 mg, metformin 500 mg and glyburide 2.5 mg, and this was titrated to the maximum effective daily dose (rosiglitazone 4 mg twice daily, metformin 1 g twice daily, and glyburide 7.5 mg twice daily). Forced titration of the dose of medication occurred at each visit when the fasting plasma glucose level was 140 mg/dl or more. The primary outcome was time to monotherapy failure on maximum-tolerated dose of the study drug, which was defined as a fasting plasma glucose >180 mg/dl on two successive occasions or by independent adjudication (11).

***Concomitant Medication Use and Adverse Event Reporting.*** Site investigators recorded all concomitant prescription medication use at baseline and at each clinic visit. Medications were classified using a validated coding system (GSKDrug). Site investigators reported adverse events during the treatment portion of the study and these were categorized using MedDRA. Fractures included any preferred term with the text "fracture" within the higher-level group term of "Bone and Joint Injuries". In the case of fractures, the site of the fractures was as reported to or determined by the investigators with no adjudication or subsequent directed assessment performed as part of the study protocol.

***Methods, Assays and Calculations.*** Fasting blood samples were drawn for measurement of fasting plasma glucose, HbA1c and immunoreactive insulin levels and all assays were performed at a central laboratory (13).

***Statistical Methods.*** The cumulative incidence of time-to-event variables was estimated by the Kaplan-Meier method (14); with withdrawals from study medication right censored. The relative risk (hazard ratio [HR]) was estimated from the Cox Proportional Hazards model (14). These methods allow for differential duration of exposure amongst groups. Treatment comparison of time to first fracture by body site was also based on Cox Proportional Hazards regression, but using Fisher's Exact Test in cases where there were zero counts (i.e. no fractures) in one of the treatment groups.

Wilcoxon rank sum tests were performed to compare baseline variables between groups based on treatment assignment (15). Differences in proportions were tested using the contingency $chi^2$-test and differences in quantitative or ordinal variables using the Kruskal-Wallis test (15).

Cox Proportional hazards models assessed the effect of the updated current values of weight, serum creatinine, hematocrit, calcium, HbA1c and waist circumference as time-dependent covariates on the risk of fractures.

Data are presented as mean±SD unless specified. A two-sided $p \leq 0.05$ was considered statistically significant. Analyses were conducted using SAS® (SAS Institute, Cary, NC).

## RESULTS

***Demographic and Clinical Variables at Baseline and Follow Up.*** Women and men randomized to the three treatment arms were well matched at baseline (Table 1). As anticipated, the majority of women in the study were age >50 years (71%) and postmenopausal by self report (77%). The proportions of patients at baseline using selected categories of medications related to bone health did not differ among the treatment groups within each gender (Table 1), although generally more women than men were using medications associated with better bone health (estrogen containing hormones, calcium supplements, and bisphosphonates).

The median duration of follow-up was 4.0 years for the rosiglitazone and metformin groups and 3.3 years for the glyburide group. The proportions of patients completing the study were 63%, 62% and 56% for the rosiglitazone, metformin and glyburide groups, respectively. Thus, the number of

patient-years of medication exposure was 4953.8 for the rosiglitazone group, 4905.6 for the metformin cohort and 4243.6 for the glyburide group.

***Bone Fractures by Treatment Assignment.*** Of the 4351 treated patients, 200 reported a fracture during the course of the study; 92 (6.3%) among those randomized to rosiglitazone, 59 (4.1%) to metformin, and 49 (3.4%) to glyburide. Accounting for differences in treatment exposure, the incidence of a fracture was 1.86/100 patient years (PY) with rosiglitazone, 1.20/100 PY with metformin and 1.15/100 PY with glyburide. Figure 1A presents the Kaplan-Meier estimated cumulative incidence of a fracture (with 95% confidence interval [CI]), reaching 9.8% (7.7, 11.9) at 5 years with rosiglitazone, 5.6% (4.1, 7.1) with metformin and 5.7% (3.9, 7.6) with glyburide. The Cox Proportional Hazards model estimated HRs (with 95% CI) for risk of fracture with rosiglitazone versus metformin and glyburide were 1.57 (1.13, 2.17, p=0.0073) and 1.61 (1.14, 2.28, p=0.0069), respectively. Interestingly, the increased risk of fracture with rosiglitazone was first apparent after approximately 12 months of therapy.

***Bone Fractures in Men.*** Among the 2511 men, 89 reported a fracture, with no difference among the groups: 32 (4.0%) of those treated with rosiglitazone, 29 (3.4%) with metformin, and 28 (3.4%) with glyburide. The incidence allowing for the period of exposure was 1.16/100 PY with rosiglitazone, 0.98/100 PY with metformin, and 1.07/100 PY with glyburide. Figure 1B presents the Kaplan-Meier estimated cumulative incidence of a fracture, demonstrating no significant difference in risk as estimated from the Cox Proportional Hazards model. Greater detail of the sites of fractures by treatment assignment in men is listed in Table 1 of the Online Appendix.

***Bone Fractures in Women.*** Among the 1840 women, 111 reported a fracture, 60 (9.3%) of those treated with rosiglitazone, 30 (5.1%) with metformin, and 21 (3.5%) with glyburide. The incidence allowing for the period of exposure was 2.74/100 PY with rosiglitazone, 1.54/100 PY with metformin, and 1.29/100 PY with glyburide. The cumulative incidence of a fracture (Figure 1C) reached 15.1% (11.2, 19.1) at 5 years with rosiglitazone, 7.3% (4.4, 10.1) with metformin and 7.7% (3.7, 11.7) with glyburide. The Cox Proportional Hazards model estimated HRs (with 95% CI) for risk of fracture with rosiglitazone versus metformin was 1.81 (1.17, 2.80, p=0.008) and for rosiglitazone versus glyburide was 2.13 (1.30, 3.51, p=0.0029). There was no apparent increased risk of fractures with rosiglitazone over the first 12 months of exposure, the increased risk being manifest beyond 12 months of exposure. Fracture risk did not appear to be related to ethnicity, but numbers in the subgroups were small. Amongst women with a fracture, 11.7% in the rosiglitazone, 16.7% in the metformin and 23.8% in the glyburide groups reported an accidental limb injury or fall within 30 days prior to the fracture. Further, amongst women who reported a fracture, 18.3% on rosiglitazone, 16.7% on metformin, and 14.3% on glyburide reported more than one fracture.

Amongst premenopausal women on rosiglitazone, 6.8% (10/147) reported a fracture versus 3.2% (4/127) on metformin (p=0.1709) and 1.9% (3/156) on glyburide (p=0.0362). Amongst postmenopausal women, 10.0% (50/498) on rosiglitazone, 5.6% (26/463) on metformin and 4.0% (18/449) on glyburide reported a fracture (p=0.0111 for rosiglitazone versus metformin and p=0.0003 versus glyburide).

Table 2 presents demographic, clinical characteristics and selected prior medication use at baseline among women who did and did not report a fracture within each treatment group. Women in the glyburide group who

reported fractures were older at baseline; in the rosiglitazone group, more women who reported a fracture were receiving treatment for hypertension at baseline.

Table 2 of the Online Appendix presents the proportions of selected concomitant medications used by women with a fracture (up until the time of first fracture) and those without a fracture (at any time during the study). There were no clear differences in the patterns of use of estrogen containing hormones, calcium supplements, bisphosphonates, thiazide and loop diuretics, or glucocorticoids between women who did (up until the time of first fracture) or did not report a fracture (at any time during the study) within any treatment group. Greater detail of the proportions of concomitant medications used by women with and without a fracture is listed in Table 2 of the Online Appendix.

Among women in the rosiglitazone group, 5.6% reported a fracture in the lower limb versus 3.1% in the metformin group (p=0.0432), and 1.3% in the glyburide group (p=0.0020), and 3.4% reported a fracture in the upper limb versus 1.7% with metformin (p=0.0753), and 1.5% with glyburide (p=0.1188). There was no difference in the proportion of women who reported a spinal fracture (0.2% with rosiglitazone, 0.2% with metformin and 0.2% with glyburide). When considering selected sites, a difference in the proportion experiencing fractures was observed in the foot (3.4% with rosiglitazone, 1.2% with metformin and 0.7% with glyburide; $p<0.05$ for rosiglitazone compared to metformin and glyburide), humerus (0.8% with rosiglitazone, 0% for the other treatments) and hand (1.2% with rosiglitazone, 0.7% with metformin and 0.2% with glyburide; $p>0.05$ for rosiglitazone compared to metformin and glyburide). Figure 1 of the Online Appendix illustrates the proportion of women in each group who reported a fracture at selected sites with a more detailed description of the sites of fractures by treatment assignment in Table 3 of the Online Appendix.

In time-dependent covariate analyses fit separately within each group, the only effect nominally significant at $p\leq0.05$ was the effect of waist circumference within the glyburide group (HR 1.031 per cm [1.001-1.062, p=0.0402]). However, the effect of this covariate did not differ significantly among treatment groups. None of the other covariates had a significant effect (nominal $p\leq0.05$) on the risk of fractures among women within either group, nor did the covariate effects differ among groups. While changes in weight did not significantly affect the risk of fractures among women within any individual treatment group individually, among all females irrespective of treatment there was an increased risk of fracture with increasing body weight: HR 1.04 per kg (95% CI: 1.01-1.07, p=0.0140). However, accounting for changes in weight over time did not substantially impact the estimated increased risk with rosiglitazone, yielding an adjusted HR for rosiglitazone versus glyburide of 2.06 (1.25-3.42) and a HR of 1.60 (0.99, 2.60) versus metformin, similar to those in the unadjusted analyses.

## DISCUSSION

We found that long-term treatment with the thiazolidinedione rosiglitazone is associated with an approximate doubling of the risk of bone fractures in females with type 2 diabetes compared to those taking metformin or glyburide. This increased risk occurs in both premenopausal and postmenopausal women, manifests after a year of therapy, and does not appear to be due to increased falls or accidental limb injury. However, the majority of events occurred in postmenopausal women, who had a much higher incidence of fractures. The limited body of data in premenopausal women, while not definitive, is consistent with a similar effect. Over five years of follow-up, there

was no increased risk of fracture among men.

Our report highlights the value of large, long-term clinical trials. Most clinical studies involving thiazolidinediones are small and of three to twelve months in duration. Given the observation within ADOPT that the cumulative incidence of fractures did not differ with the three therapies until beyond a year, it is not surprising that this adverse effect had not previously been reported. In fact, until we briefly documented this untoward effect of rosiglitazone in ADOPT (11), an increased risk of fractures with a thiazolidinedione had never been clinically demonstrated. The only suggestion that this could occur had come from an epidemiological study of 69 diabetic women aged 70-79 years who manifested increased bone mineral loss on thiazolidinediones (9). Following our initial publication, it has been reported that another thiazolidinedione, pioglitazone, is also associated with an approximate 70% increase in the risk of fractures in women (12), indicating that this adverse effect is likely a thiazolidinedione class effect.

It is well recognized that diabetes is associated with an increased risk of fractures (1-3; 5), with this being well documented in the Women's Health Initiative. In the latter study, more than 90,000 women were followed for seven years (5). The cohort included some 5% with diabetes, and in these women it was found that diabetes was associated with a 20% increase in the risk of fractures with the frequency of fractures being increased in the spine, hip, and sites in the upper and lower limbs, with the exception of the lower arm, wrist and hand. This increased risk of fractures occurred despite the fact that bone mineral density is increased in patients with diabetes compared to those without the disease (5-7). Furthermore, fractures in patients with diabetes are frequently non-traumatic in nature (16).

What then may be the mechanism responsible for the increased risk of fractures in thiazolidinedione-treated women? This is not fully understood but both animal (17), and more recently human data (10; 18), have demonstrated that thiazolidinedione administration is associated with a reduction in bone mineral density. In humans, this deleterious effect was recently reported to occur in non-diabetic, postmenopausal women who were dosed for 14 weeks and, based on biomarker measurements, resulted from both an acceleration of bone resorption and a reduction in new bone formation (18). These findings are supported by studies in rodents (17) which have, in addition, shown that activation of PPARγ promotes adipocyte rather than osteoblast differentiation from mesenchymal progenitor cells (19-21) and may reduce IGF-1 levels in bone and thereby also decrease osteoblast formation (22). We previously reported that in ADOPT, 5 years after initiating treatment with rosiglitazone, the risk of monotherapy failure was decreased by 32% compared to metformin and by 63% compared to glyburide (11). That fractures were increased in women receiving rosiglitazone despite the agent's greater durability of glucose control suggests that hyperglycemia is not likely a mediator of this deleterious effect of the thiazolidinedione class. Finally, the time-dependent covariate analysis failed to identify any particular risk factor for the increase in fractures with rosiglitazone, and notably this was not related to weight gain.

There are limitations to our findings, but they are unlikely to affect the clinical relevance of the observations. First, fracture reports were not systematically collected or adjudicated and vertebral fractures are often silent, possibly introducing ascertainment bias. Further, the cause and outcome of reported fractures were not systematically followed up. Second, we did not obtain measurements of bone mineral density to assess whether the long-term effect of

rosiglitazone included a loss of bone. Third, as the cohort was relatively young and follow up was for a median of 4.0 years, we cannot exclude the possibility that exposure to medication will not be associated with an increased risk of fractures at other sites later in life.

In summary, we have documented the increased risk of fractures with rosiglitazone relative to metformin or glyburide in women with type 2 diabetes. An increase in fracture risk has also been observed with pioglitazone, and these increases occur in the context of elevated fracture risk among women with type 2 diabetes generally. The mechanism by which these fractures occur is not clear. However, the risk of fracture should be considered in the care of patients with type 2 diabetes, especially female patients, treated with thiazolidinediones, and attention should be given to assessing and maintaining bone health according to current standards of care.

**ACKNOWLEDGMENTS**

ADOPT was overseen by a steering committee comprised of Steven Kahn, Giancarlo Viberti [co-chairs], Steven Haffner, William Herman, Rury Holman, Paul Aftring, Nigel Jones, John Lachin, Colleen O'Neill and Bernard Zinman. The analyses presented here would not have been possible without the effort of the study participants and study staff. The study was supported by funds from GlaxoSmithKline from whom the academic members of the ADOPT Steering Committee received honoraria, consulting fees, and/or grant/research support. Paul Aftring, Mark Heise, Barbara Kravitz and Dahong Yu are employees of GlaxoSmithKline.

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**TABLE 1.** Baseline demographic characteristics, clinical measures and prior medication use in men and women by treatment assignment

| | Women | | | Men | | |
|---|---|---|---|---|---|---|
| | Rosiglitazone (n=645) | Metformin (n=590) | Glyburide (n=605) | Rosiglitazone (n=811) | Metformin (n=864) | |
| Age (yrs) | 56.1±10.2 | 56.7±10.0 | 56.3±10.7 | 56.4±9.9 | 57.0±9.9 | |
| Postmenopausal (n, %) | 498 (77.2) | 463 (78.5) | 449 (74.2) | NA | NA | |
| Time since diagnosis of diabetes (n, %) | | | | | | |
| < 1 year | 275 (42.6) | 281 (47.6) | 278 (46.0) | 375 (46.2) | 392 (45.4) | |
| 1-2 years | 351 (54.4) | 288 (48.8) | 309 (51.1) | 407 (50.2) | 436 (50.5) | |
| > 2 years | 18 (2.8) | 21 (3.6) | 18 (3.0) | 29 (3.6) | 36 (4.2) | |
| Body mass index ($kg/m^2$) | 33.6±7.2 | 33.8±6.8 | 33.8±7.1 | 31.1±6.1 | 31.0±5.2 | |
| Waist circumference (cm) | 103.4±15.3 | 104.4±15.2 | 103.8±16.3 | 106.7±13.9 | 106.4±13.6 | |
| Waist/hip ratio | 0.90±0.09 | 0.91±0.09 | 0.90±0.09 | 0.99±0.07 | 0.98±0.09 | |
| Systolic BP (mm Hg) | 132.2±15.8 | 132.9±15.2 | 132.3±15.1 | 133.65±15.5 | 132.8±15.6 | |
| Diastolic BP (mm Hg) | 79.0±8.8 | 79.3±8.5 | 79.2±8.7 | 80.4±8.5 | 80.0±9.2 | |
| Fasting plasma glucose (mg/dl) | 150.9±23.3 | 150.6±25.6 | 151.9±27.6 | 152.0±27.6 | 151.9±25.6 | |
| HbA1c (%) | 7.37±0.89 | 7.36±0.93 | 7.35±0.88 | 7.36±0.97 | 7.36±0.94 | |
| Fasting insulin (pmol/l) | 154.2±99.1 | 162.6±113.4 | 167.8±132.3 | 146.4±114.9 | 144.5±109.9 | |
| Estrogen containing hormones (n, %) | 125 (19.4) | 137 (23.2) | 114 (18.8) | 1 (0.1) | 1 ( 0.1) | |
| Calcium supplements (n, %) | 41 (6.4) | 52 (8.8) | 40 (6.6) | 11 (1.4) | 15 (1.7) | |
| Bisphosphonates (n, %) | 12 (1.9) | 11 (1.9) | 8 (1.3) | 1 (0.1) | 2 (0.2) | |
| Glucocorticoids (n, %)* | 47 (7.3) | 41 (6.9) | 51 (8.4) | 61 (7.5) | 50 (5.8) | |
| Thiazide diuretics (n, %) | 120 (18.6) | 123 (20.8) | 126 (20.8) | 109 (13.4) | 96 (11.1) | |
| Loop diuretics (n, %) | 20 (3.1) | 27 (4.6) | 23 (3.8) | 9 (1.1) | 18 (2.1) | |

* Includes all routes of administration. For all continuous variables, data are expressed as mean±SD.

**TABLE 2.** Demographic, baseline characteristics and selected prior medications by treatment assignment in women with and without fractures

| | Rosiglitazone | | | Metformin | | | Glyburide | | |
|---|---|---|---|---|---|---|---|---|---|
| | With Fractures (n=60) | Without Fractures (n=585) | P value | With Fractures (n=30) | Without Fractures (n=560) | P value | With Fractures (n=21) | Without Fractures (n=584) | P value |
| Age: ≤50 - ≤60 | 11 (18.3) | 181 (30.9) | 0.065 | 8 (26.7) | 153 (27.3) | 0.954 | 3 (14.3) | 176 (30.1) | 0.012 |
| Age: >50 - ≤60 | 24 (40.0) | 205 (35.0) | | 11 (36.7) | 203 (36.3) | | 5 (23.8) | 197 (33.7) | |
| Age: >60 | 25 (41.7) | 199 (34.0) | | 11 (36.7) | 204 (36.4) | | 13 (61.9) | 211 (36.1) | |
| Race: White | 53 (88.3) | 497 (85.0) | 0.398 | 28 (93.3) | 485 (86.6) | 0.645 | 20 (95.2) | 508 (87.0) | 0.805 |
| Black | 1 (1.7) | 28 (4.8) | | 2 (6.7) | 32 (5.7) | | 1 (4.8) | 38 (6.5) | |
| Asian | 0 (0.0) | 15 (2.6) | | 0 (0.0) | 13 (2.3) | | 0 (0.0) | 12 (2.1) | |
| Hispanic | 5 (8.3) | 42 (7.2) | | 0 (0.0) | 25 (4.5) | | 0 (0.0) | 25 (4.3) | |
| Other | 1 (1.7) | 3 (0.5) | | 0 (0.0) | 5 (0.9) | | 0 (0.0) | 1 (0.2) | |
| Postmenopausal | 50 (83.3) | 448 (76.6) | 0.235 | 26 (86.7) | 437 (78.0) | 0.263 | 18 (85.7) | 431 (73.8) | 0.220 |
| Smoking Status: | 4 (6.7) | 79 (13.5) | 0.132 | 5 (16.7) | 67 (12.0) | 0.443 | 4 (19.0) | 71 (12.2) | 0.347 |
| Alcohol Status: | 17 (28.3) | 173 (29.6) | 0.841 | 11 (36.7) | 143 (25.5) | 0.180 | 9 (42.9) | 163 (27.9) | 0.136 |
| Hypertension Rx: | 40 (66.7) | 306 (52.3) | 0.034 | 12 (40.0) | 325 (58.0) | 0.052 | 10 (47.6) | 336 (57.5) | 0.367 |
| Lipid Rx: | 14 (23.3) | 138 (23.6) | 0.965 | 7 (23.3) | 140 (25.0) | 0.837 | 7 (33.3) | 134 (22.9) | 0.269 |
| Estrogen containing hormones | 13 (21.7) | 112 (19.1) | 0.638 | 5 (16.7) | 132 (23.6) | 0.383 | 5 (23.8) | 109 (18.7) | 0.554 |
| Calcium supplements | 4 (6.7) | 37 (6.3) | 0.918 | 3 (10.0) | 49 (8.8) | 0.814 | 1 (4.8) | 39 (6.7) | 0.728 |
| Vitamin D | 6 (10.0) | 47 (8.0) | 0.598 | 3 (10.0) | 52 (9.3) | 0.896 | 2 (9.5) | 45 (7.7) | 0.760 |
| Bisphosphonates | 1 (1.7) | 11 (1.9) | 0.907 | 1 (3.3) | 10 (1.8) | 0.542 | 0 | 8 (1.4) | 0.589 |
| Glucocorticoids* | 4 (6.7) | 43 (7.4) | 0.846 | 1 (3.3) | 40 (7.1) | 0.424 | 2 (9.5) | 49 (8.4) | 0.854 |
| Statins | 10 (16.7) | 119 (20.3) | 0.498 | 6 (20.0) | 126 (22.5) | 0.749 | 5 (23.8) | 111 (19.0) | 0.583 |
| Thiazide diuretics | 14 (23.3) | 106 (18.1) | 0.323 | 4 (13.3) | 119 (21.3) | 0.298 | 5 (23.8) | 121 (20.7) | 0.732 |

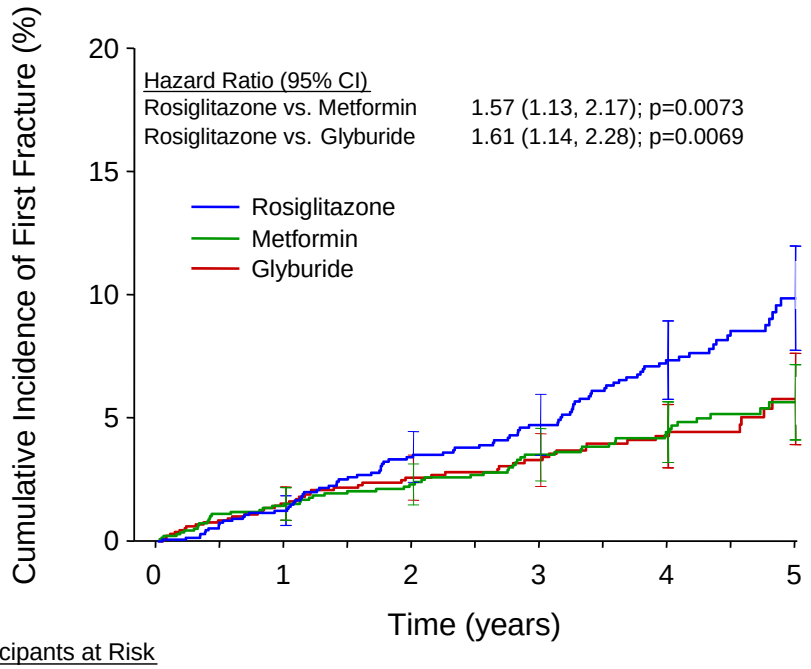
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Loop diuretics | 2 (3.3) | 18 (3.1) | 0.913 | 2 (6.7) | 25 (4.5) | 0.574 | 0 | 23 (3.8) | 0.354 |
| Age (yrs) | 58.7±9.70 | 55.9±10.17 | 0.041 | 57.4±9.73 | 56.6±10.02 | 0.854 | 61.1±9.09 | 56.1±10.76 | 0.029 |
| BMI (kg/m$^2$) | 33.5±6.42 | 33.7±7.23 | 0.936 | 34.1±5.98 | 33.8±6.86 | 0.713 | 32.6±6.77 | 33.8±7.08 | 0.496 |
| HbA1c (%) | 7.49±0.957 | 7.36±0.879 | 0.373 | 7.31±0.821 | 7.36±0.935 | 0.883 | 7.31±1.103 | 7.36±0.872 | 0.644 |
| Fasting plasma glucose (mg/dl) | 152.8±20.35 | 150.7±23.56 | 0.191 | 149.1±23.37 | 150.7±25.75 | 0.686 | 148.3±17.04 | 152.0±27.86 | 0.758 |
| BP: Systolic | 132.1±13.90 | 132.2±15.98 | 0.759 | 131.0±12.94 | 133.0±15.31 | 0.648 | 129.4±13.97 | 132.5±15.17 | 0.497 |
| Diastolic | 78.7±8.04 | 79.1±8.89 | 0.658 | 77.1±7.77 | 79.4±8.49 | 0.160 | 80.5±7.95 | 79.2±8.76 | 0.452 |

* Includes all routes of administration. Data are presented as n (%) and for all continuous variables as mean±SD

## FIGURE LEGEND

**Figure 1A-1C.** Kaplan–Meier estimates of the cumulative incidence of fractures at five years in all patients (A), men (B) and women (C). Fractures were as reported by the clinical site and the hazard ratio (95% confidence intervals) for these events is listed for comparisons by treatment group. Bars represent 95% confidence intervals.

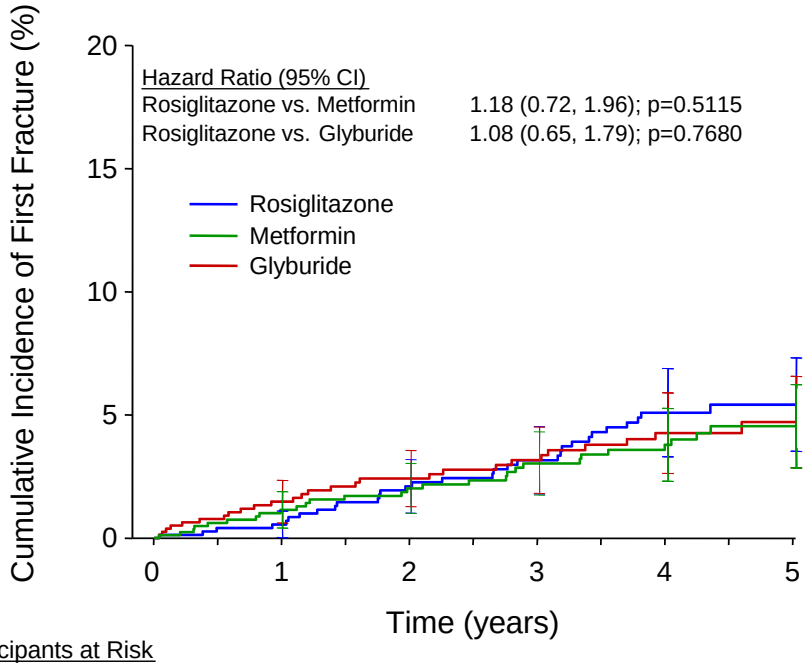
**FIGURE 1A**




Participants at Risk

| | | | | | | |
|---|---|---|---|---|---|---|
| Rosiglitazone | 1456 | 1190 | 1041 | 916 | 757 | 294 |
| Metformin | 1454 | 1186 | 1050 | 917 | 750 | 302 |
| Glibenclamide | 1441 | 1095 | 935 | 760 | 580 | 201 |

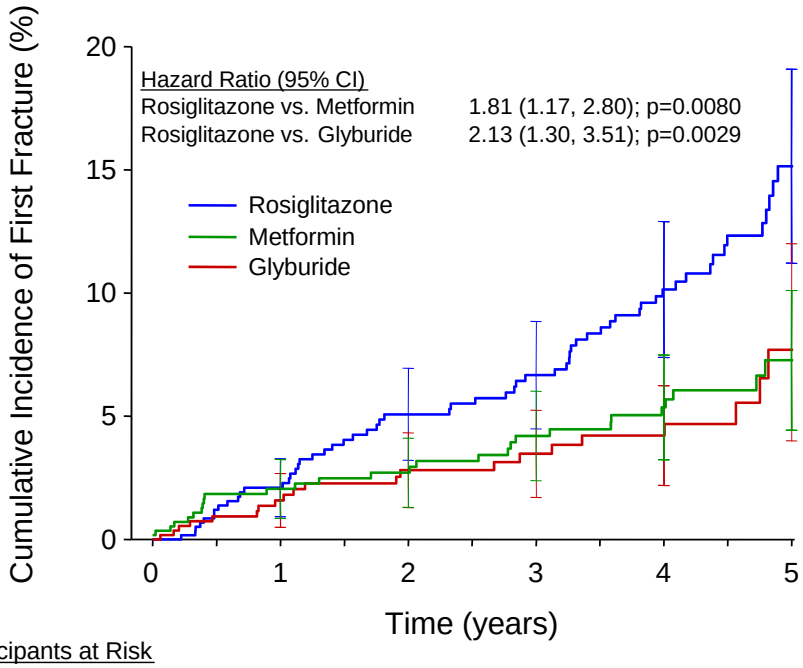
**FIGURE 1B**




Participants at Risk

| | | | | | | |
|---|---|---|---|---|---|---|
| Rosiglitazone | 811 | 676 | 593 | 522 | 432 | 167 |
| Metformin | 864 | 722 | 636 | 551 | 457 | 185 |
| Glibenclamide | 836 | 660 | 574 | 481 | 371 | 134 |

**FIGURE 1C**




Participants at Risk

| | | | | | | |
|---|---|---|---|---|---|---|
| Rosiglitazone | 645 | 514 | 448 | 394 | 325 | 127 |
| Metformin | 590 | 464 | 414 | 366 | 293 | 117 |
| Glibenclamide | 605 | 435 | 361 | 279 | 209 | 67 |