A Cohort Study of Thiazolidinediones and Fractures in Older Adults with Diabetes

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Context: Thiazolidenediones (TZDs) are selective ligands of peroxisome-proliferator-activated receptor-γ and have been shown to reduce bone mineral density. Recent results from several randomized controlled trials find an increased risk of fracture with TZDs compared with other oral antidiabetic agents.

Objective: The aim of the study was to determine the association between TZD use and fracture risk among older adults with diabetes.

Design: We conducted a cohort study.

Participants: Medicare beneficiaries with at least one diagnosis of diabetes initiating monotherapy for an oral hypoglycemic agent participated in the study.

Main Outcome: We measured the incidence of fracture within the cohort.

Results: Among the 20,964 patients with diabetes eligible for this study, 686 (3.3%) experienced a fracture during the median follow-up of approximately 10 months. Although not statistically significant, patients using only a TZD were more likely to experience a fracture than those using metformin (adjusted relative risk, 1.31; 95% confidence interval, 0.98–1.77; $P = 0.071$) or a sulfonylurea (adjusted relative risk, 1.21; 95% confidence interval, 0.94–1.55; $P = 0.12$). Each individual TZD was associated with an increased risk, with confidence intervals overlapping unity, compared with both metformin and sulfonylureas. The adjusted risk of any fracture associated with TZD use compared with metformin was elevated for non-insulin-using patients, women and men. If TZD use is associated with fractures, the number needed for one excess fracture when comparing TZD users to sulfonylurea users was 200, and the number was 111 when comparing TZDs with metformin.

Conclusions: As has been found with other analyses, our data suggest that TZDs may be associated with an increased risk of fractures compared with oral sulfonylureas and metformin. **(*J Clin Endocrinol Metab* 94: 2792–2798, 2009)**

Thiazolidinediones (TZDs) are selective ligands of the peroxisome-proliferator-activated receptor (PPAR) γ. Despite early concerns raised by the observed hepatotoxicity associated with troglitazone, these agents are used widely for treating diabetes because of their ability to improve end-organ sensitivity to the effects of insulin. Interest in the use of these agents has grown because evidence accumulates regarding their potential role in reducing triglycerides and improving high-density lipoprotein levels (1).

The effects of the TZDs on the PPAR system are widespread, including interacting with PPAR α, β, δ, and γ. The effects of TZDs have already been described on the liver, skeletal muscle, adipose tissue, and endovasculature (2). These nonselective effects on the PPAR system likely underlie the known fluid reten-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2008-2157 Received October 3, 2008. Accepted May 18, 2009.
First Published Online May 26, 2009

Abbreviations: CI, Confidence interval; PPAR, peroxisome-proliferator-activated receptor; RR, relative risk; TZD, thiazolidinedione.

tion associated with TZDs, and effects on PPAR-γ likely underlie the effect of these agents on bone.

Several reports have raised concerns about possible negative effects of PPAR agonists on bone density (3–5). A randomized controlled trial among healthy postmenopausal women found that rosiglitazone use over 14 wk was associated with a significant reduction in hip bone density compared with placebo (6). This information was followed by two recent MedWatch warnings from the U.S. Food and Drug Administration (FDA) that the manufacturers of rosiglitazone and pioglitazone reported an increased risk of fracture in separate randomized controlled trials (7, 8). The trial involving rosiglitazone compared this agent with metformin or glyburide, all as monotherapies. Since the original MedWatch report, the fracture endpoints from the ADOPT trial were formally published, and the risk of fracture appears to reside with women and not men (9). Another recently published trial comparing pioglitazone with glimepiride also found a significant increase in fractures among the TZD arm (10). One nested case-control study on this topic has been published and found an association between TZDs and fractures (11). This study did not present information about the number needed to harm, a useful metric for clinicians. Most prior studies were not conducted in older adults, a group at high risk of fractures and diabetes.

Although prior reports suggest that TZDs may have important effects on bones, physicians and patients are faced with several important clinical questions when deciding between available oral antidiabetic agents:

- Are the fracture risks of a magnitude to be clinically significant (primary)?
- Are the fracture risks similar across both rosiglitazone and pioglitazone (secondary)?
- Are the risks restricted to specific patient subgroups (secondary)?
- And are the risks observed at all anatomic sites (secondary)?

To examine these questions, we studied a large Medicare cohort from one U.S. state with linked pharmacy claims data. The presence of potential confounders was assessed in a large national Medicare survey.

Subjects and Methods

Design

We conducted a cohort study among a cohort of Medicare beneficiaries with diabetes. From this cohort of adults over 65 yr of age, patients with hip, humerus, wrist, or spine fracture were identified as fracture events. Oral hypoglycemic use was defined based on pharmacy information, and only patients without any use of a given category of oral hypoglycemic agents in the prior 180 d were considered for these analyses. The risks of fracture associated with TZD monotherapy were compared with sulfonylurea and metformin monotherapy. Hazard ratios were calculated in Cox proportional hazards models, adjusting for potential confounders. Potential confounders not well ascertained in Medicare data were assessed in a separate survey of Medicare beneficiaries.

Study cohort and follow-up

Medicare beneficiaries from one U.S. state were selected for study if they were also enrolled in state-run pharmacy benefits programs for low-income elderly. The study period spanned the period from 1997–2005. Patients with at least one diagnosis of diabetes who had been consistent users of the Medicare and drug benefits services were eligible for inclusion. Consistent use was defined as at least one health care encounter and one prescription filling in each of the two 6-month periods before cohort entry. Eligible patients were required to have a diagnosis of diabetes in the 180 d before initiating one of the oral hypoglycemic agents of interest. From this group of eligible patients, we defined three patient cohorts initiating treatment with a TZD, sulfonylurea, or metformin. For the TZD cohort, patients could not have filled a prescription for a glitazone in the prior 180 d.

At the first filling of a glitazone prescription after 180 d without, patients entered the study cohort (index date). Patients must have then filled a second prescription for an oral hypoglycemic agent within the first 90 d. Follow-up for endpoints began after these 90 d. Parallel definitions were used to define initiators of sulfonylureas and metformin. Cohort follow-up ended at the first of any of the following events: death, loss of eligibility for Medicare or the drug benefit program, 180 d after the last dosage of oral hypoglycemic agent, or end of follow-up (December 31, 2005).

This work was approved by the Human Research Committee at Partners HealthCare. Data use agreements are in place with Medicare and the state pharmacy benefits programs that supplied information for the study database.

Fracture outcomes

We used fracture definitions for hip, humerus, and wrist fracture based on previously validated algorithms (12). These involve combinations of diagnoses and procedures specific for a given fracture but cannot identify low-energy from high-energy trauma. Spine fracture was defined by at least two diagnoses of spine fracture, with one diagnosis after an imaging procedure of the spine. Fractures at these four anatomic sites were grouped together in a composite ("any") fracture endpoint. Analyses on the composite outcome did not allow the same person to contribute two fractures in that patients were censored at the first outcome. As noted below, follow-up for fracture outcomes began 90 d after the index date.

Exposures of interest

The putative relationship between TZDs and fractures is through their effect on bone metabolism. Prior work has shown that rosiglitazone may affect bone mineral density within several months (6). Therefore, we created a 90-d lag period after the first prescription (index date) during which fractures were very unlikely to be associated with use of TZDs. Fracture endpoints during the first 90 d were not attributed to the exposures of interest. Moreover, we extended the exposure period 180 d after the last available oral hypoglycemic of interest to account for any sustained effects of TZDs on bone metabolism. Thirty- and 90-d extension periods were also considered in sensitivity analyses.

Utilization was determined based on pharmacy records, including name of agent, date of prescription filling, and the number of tablets. Troglitazone was included as part of the glitazone group before it was removed from the U.S. market. Secondary analyses broke out each glitazone separately. Only monotherapy of each oral hypoglycemic agent was included as an exposure of interest. Patients were censored if they began a second oral hypoglycemic agent from another category. This allowed us to observe the effects of monotherapy *vs.* trying to discern the influence of a given agent in the context of combination therapy. Insulin use was relatively uncommon and was considered a covariate in adjusted models.

In secondary analyses, we explored the effect of duration of oral hypoglycemic use and fracture risk. Three mutually exclusive time periods of drug use were defined: 91–365 d after the index date (short-term use); 365–730 d after the index date (medium-term use); and more than 730 d after the index date (long-term use).

Covariates

All covariates were defined in the 180 d before cohort entry using diagnosis and procedure codes from health care utilization data. These included sociodemographic, diabetes-related, osteoporosis-related, and health care utilization variables. Age, gender, and race were the sociodemographic variables considered. Diabetes-related factors consisted of: the use of insulin; diagnoses of peripheral neuropathy, end-stage renal disease, retinopathy, and diabetic gastroparesis; diabetes-related hospitalizations; and number of visits for diabetes. Covariates associated with osteoporosis or fractures included: a history of a fracture; the diagnosis of osteoporosis, rheumatoid arthritis, or hyperparathyroidism; an emergency room visit for a fall; and use of oral steroids or agents for osteoporosis (alendronate, calcitonin, etidronate, ibandronate, estrogen replacement therapy, raloxifene, risedronate, and teriparatide). Congestive heart failure hospitalizations were also considered because of TZD contraindication in such patients. In addition, all models were adjusted for the year of the index date.

Several important covariates are unmeasured in the main study database, including height and weight, general health status, vision and hearing impairment, difficulty walking, and tobacco use. Because these variables could possibly confound the relationship between oral antidiabetic agents and fractures, we assessed their distribution in the Medicare Current Beneficiary Survey (13). This large representative national survey recruits 10,000 Medicare beneficiaries annually to answer a range of standardized questions (including current medication use) administered in the home by trained assessors. We examined data from the survey for 1999–2002.

Statistical analyses

The characteristics of patients in each exposure group were compared. Fracture rates were calculated for each exposure group at each anatomic site. To adjust for potential confounders, we estimated the relative risk (RR) and 95% confidence interval (CI) using multivariable Cox proportional hazards models. All variables considered as possible covariates were included in adjusted models (Table 1). Entry and exit dates for the cohort are noted above in *Study cohort and follow-up*. Two sets of models were examined, one with sulfonylurea users as the reference group and another with metformin users as the reference group. Separate models were examined for the composite endpoint (hip, humerus, wrist, or spine fracture) and then for each anatomic site. Because the definition in health care utilization data of incident spine fracture is likely less accurate, we removed this fracture type from the composite endpoint in sensitivity analyses. Additional analyses focused only on the patients without concurrent insulin use as well as men and women separately.

To assess the sensitivity of the multivariable outcome models with respect to control for confounding, we separately estimated the propen-

TABLE 1. Characteristics of study population in 6 months prior to the index date

Patient variables	TZD monotherapy (n = 2,347)	Sulfonylurea monotherapy (n = 13,709)	Metformin monotherapy (n = 4,235)
Sociodemographic			
Age (yr)	77 ± 7	78 ± 7[c]	76 ± 7[c]
Gender, female	1,793 (76)	10,326 (75)	3,344 (79)[b]
Race, white	2,161 (92)	12,764 (93)	3,911 (92)
Diabetes-related			
Renal disease	58 (2)	253 (2)[b]	34 (1)[c]
Retinopathy	82 (3)	422 (3)	109 (3)[b]
Peripheral neuropathy	155 (7)	766 (6)	199 (5)[c]
Hospitalizations for diabetes	108 (5)	723 (5)	164 (4)
Physician visits for diabetes	4 ± 4	4 ± 4[c]	4 ± 3[c]
Insulin use	210 (9)	494 (4)[c]	161 (4)[c]
Osteoporosis-related			
Osteoporosis diagnosis	171 (7)	863 (6)	367 (9)
Prior fracture	22 (1)	150 (1)	32 (1)
Fall	80 (3)	530 (4)	153 (4)
Hyperparathyroid	18 (0.8)	60 (0.4)[b]	12 (0.3)[c]
Rheumatoid arthritis	50 (2)	340 (2)	94 (2)
Oral glucocorticoid use	193 (8)	964 (7)[b]	290 (7)[b]
Osteoporosis medication[a]	291 (12)	1223 (9)[c]	577 (13)
Other health care-related items			
Physician visits for nondiabetes	5 ± 4	5 ± 4[c]	5 ± 4
Comorbidity index score	3 ± 2	3 ± 2	2 ± 2[c]
No. of different medications	8 ± 4	8 ± 4[c]	7 ± 4[c]
Congestive heart failure	145 (6)	1038 (8)[b]	148 (3)[c]

Data are expressed as number (%) or mean ± SD.

[a] Osteoporosis medications include bisphosphonates, calcitonin, raloxifene, teriparatide, and estrogen replacement therapy.

[b,c] *P* value compared with TZDs: [b] $P < 0.05$; [c] $P < 0.01$.

sity for glitazone use compared with metformin use as well as the propensity for glitazone use compared with sulfonylurea. Both propensity scores were estimated in logistic regression and used the same covariates described above with the exception of insulin use. Insulin use was not included in these models because it was strongly associated with glitazone use. Thus, including it in the estimation of the propensity score resulted in considerable nonoverlap of the propensity score distributions for glitazone users compared with both metformin and sulfonylurea users. We used the estimated propensity score in two different ways to control for confounding in the Cox proportional hazards models: 1) we included four dummy variables to adjust for propensity score quintiles; and 2) we matched a single metformin or sulfonylurea user to each glitazone user based on the propensity score using a greedy matching algorithm (14). The baseline covariates in the propensity-matched cohorts were compared. Because insulin was not included in the propensity score, all propensity models were additionally controlled for insulin use.

Finally, we conducted sensitivity analyses to examine whether unmeasured confounders might explain the results (15). Data from a large survey of different Medicare beneficiaries was used to assess the prevalence of potential confounders among participants reporting monotherapy with each oral antidiabetic. For potential confounders found to be differentially distributed across oral antidiabetic agents, we assessed how strong the relationship would need to be between confounder and fracture endpoint to explain the apparent RR calculated in the main analyses.

For each comparison, the Cox proportional hazard curve was visually inspected to rule out violations of the proportional hazard assumption. We included both calendar year of study entry and age at study entry as fixed covariates. Because of the short follow-up period, we refrained from updating calendar year and age. All cohort analyses are presented and were conducted using SAS Statistical Software (SAS Institute Inc., Cary, NC).

Results

We identified 4.4 million Medicare beneficiaries from Pennsylvania concurrently eligible for a state-run drug benefit program who filled at least one oral hypoglycemic agent between 1997 and 2005. Four percent (n = 188,592) had no evidence of filling an oral hypoglycemic from the same category during the prior 180 d, and the majority of these patients had a diagnosis of diabetes (ICD-9-CM 250.XX) in the prior 180 d (n = 116,732). Some of these patients did not meet health care system use requirements (n = 29,969) and were excluded. As well, to follow a group of patients on monotherapy, we excluded patients who were concurrent users of another hypoglycemic agent (n = 44,663) or who filled more than one oral hypoglycemic agent on their index date (n = 3,945). Moreover, patients were required to receive at least two dispensings of their index oral hypoglycemic agent (n = 33,080) and survive for at least 90 d after they filled their index treatment. The final cohort comprised 20,964 patients. The median follow-up time between cohort entry and the date of censoring was 306 d and differed between exposure groups: TZDs, 234 d; metformin, 290 d; sulfonylureas, 333 d; other drugs, 219 d. (Because cohort entry began 90 d after the start of an oral hypoglycemic agent, the above median days on drug do not include the first 90 d; thus, the median time of drug use is 90 d longer than what is stated above). Time on medication for each exposure group was as follows: TZD—1–365 d, 63%; 366–730 d, 20%; and >730 d, 17%; metformin—1–365 d, 56%; 366–730 d, 21%; and >730 d, 23%; and sulfonylurea—1–365 d, 52%; 366–730 d, 22%; and >730 d, 25%.

The mean age of this Medicare population was 78 yr; three fourths were female and 92% were Caucasian. This reflects the characteristics of the population our study cohort was drawn from. The baseline characteristics were similar across the four exposure groups (Table 1). Potentially important differences in baseline characteristics were observed in insulin and osteoporosis medication use, as well as congestive heart failure.

During the study follow-up period, 686 (3.3%) of the study cohort experienced any fracture. As illustrated in Table 2, the composite fracture rate was higher among patients using TZDs (28.7 per 1,000 person-years) than sulfonylureas (23.7 per 1,000 person-years) and metformin (19.7 per 1,000 person-years). This pattern was seen across all anatomic sites, except at the hip where the rate among sulfonylurea users (10.0 per 1,000 person-years) was slightly higher than glitazone users (9.1 per 1,000 person-years). The fracture rates for women using TZDs were higher than those for women using sulfonylureas or metformin. The number needed for one excess fracture ("number needed to harm") when comparing TZD users to sulfonylureas was 200. When comparing TZDs with metformin, the number need to harm was 111.

The RRs of fracture associated with glitazone monotherapy use were calculated compared with metformin and sulfonylurea monotherapy. The RR for the composite fracture endpoint for glitazone use appeared higher when compared with metformin monotherapy (RR, 1.31; 95% CI, 0.98–1.77; $P = 0.071$) than sulfonylurea monotherapy (RR, 1.21; 95% CI, 0.94–1.55; $P =$

TABLE 2. Exposure to oral hypoglycemic medications and fracture rates, overall and by gender

Oral hypoglycemic monotherapy	Total no. in the cohort	Fracture site														
		Composite			Hip			Humerus			Wrist			Spine		
		Events	Person years	Rate	Events	Person years	Rate	Events	Person years	Rate	Events	Person years	Rate	Events	Person years	Rate
TZDs	2,347	74	2,577	28.7	24	2626	9.1	14	2,616	5.4	18	2,608	6.9	21	2,615	8.0
Women	1,793	65	1,983	32.8	19	2,032	9.4	14	2,022	6.9	18	2,013	8.9	17	2,021	8.4
Men	554	[a]	594	15.2	[a]	594	8.4	[a]	595	0	[a]	595	0	[a]	594	6.7
Sulfonylureas	13,709	480	20,283	23.7	207	20,616	10.0	87	20,620	4.2	120	20,558	5.8	106	20,599	5.1
Women	10,326	415	15,746	26.4	179	16,046	11.1	78	16,047	4.9	110	10,326	6.9	83	16,044	5.2
Men	3,383	65	4,536	14.3	28	4,570	6.1	[a]	4,573	2.0	[a]	4,572	2.2	23	4,555	5.0
Metformin	4,235	110	5,594	19.7	28	5,677	4.9	25	5,671	4.4	28	5,654	5.0	37	5,661	6.5
Women	3,344	101	4,604	21.9	25	4,683	5.3	21	4,680	4.5	28	4,660	6.0	35	4,667	7.5
Men	891	[a]	991	9.1	[a]	994	3.0	[a]	991	4.0	[a]	994	0	[a]	994	2.0

Fracture rates are per 1,000 person-years.

[a] Cell sizes smaller than 11 are not allowed to be reported because of privacy concerns raised by the Center for Medicare and Medicaid Services.

TABLE 3. Adjusted RR of composite fracture endpoint for TZD users

Sensitivity analysis	RR (95% CI)
Metformin (reference)	
Fully adjusted[a]	1.31 (0.98–1.77)
Insulin, no	1.32 (0.97–1.79)
Women	1.31 (0.96–1.80)
Men	1.41 (0.55–3.59)
Excluding spine fracture	1.46 (1.02–2.08)
Propensity adjusted[b]	1.31 (0.96–1.80)
Propensity matched[c]	1.32 (0.93–1.87)
Sulfonylureas (reference)	
Fully adjusted[a]	1.21 (0.94–1.55)
Insulin, no	1.18 (0.91–1.53)
Women	1.23 (0.94–1.60)
Men	1.08 (0.53–2.19)
Excluding spine fracture	1.19 (0.89–1.59)
Propensity adjusted[b]	1.17 (0.90–1.52)
Propensity matched[c]	1.41 (1.01–1.96)

[a] Fully adjusted models include all variables listed in Table 1, as well as all monotherapy exposures.

[b] Propensity-adjusted models include indicator terms for the quintile of propensity score and insulin use.

[c] Propensity-matched models include insulin covariate.

0.12). Although not statistically significant, the RRs for TZD use were elevated in adjusted models across several sites studied (compared with metformin): hip fracture RR, 1.44 (95% CI, 0.89- 2.32); humerus fracture RR, 1.15 (95% CI, 0.60–2.23); wrist fracture RR, 1.38 (95% CI, 0.76–2.50); and spine fracture RR, 1.18 (95% CI, 0.72–1.95). Similar RRs were observed in sensitivity analyses restricted to non-insulin users, men and women separately, and when spine fracture was dropped from the composite endpoint (Table 3). Furthermore, the propensity-matched analysis in which the covariates are extremely well balanced (see Appendix I, published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org) gave the largest RR estimates (Table 3).

Secondary analyses examined the risks associated with monotherapy of each glitazone separately (Table 4). Although not statistically significant, each individual glitazone was associated with an increased risk compared with both metformin and sulfonylureas, the risk with troglitazone being higher than with the other agents. We did not observe a relevant trend toward increasing RR of fracture with longer duration of glitazone use

TABLE 4. Adjusted RR of composite fracture endpoint for individual TZDs

	RR (95% CI)
Metformin (reference)	
Pioglitazone	1.39 (0.95–2.03)
Rosiglitazone	1.15 (0.75–1.75)
Troglitazone[a]	1.61 (0.86–3.01)
Sulfonylureas (reference)	
Pioglitazone	1.28 (1.09–2.95)
Rosiglitazone	1.06 (0.72–1.56)
Troglitazone[a]	1.48 (0.81–2.71)

Adjusted models included all variables noted in Table 1.

[a] No longer marketed.

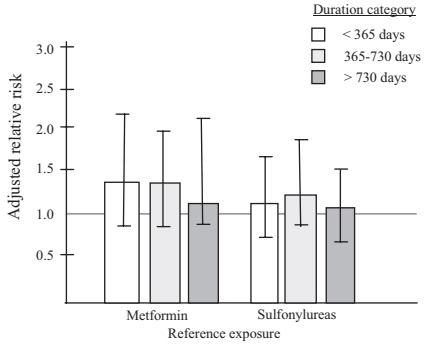

FIG. 1. RR of fracture associated with different duration of glitazone use among a cohort of diabetics initiating use of oral antidiabetic agents. Three mutually exclusive time periods of drug use were defined: 91–365 d after the index date (short-term use); 365–730 d after the index date (medium-term use); and more than 730 d after the index date (long-term use).

(Fig. 1). There were also no important differences in hazard ratios when the exposure extension periods were reduced to 90 or 30 d.

To assess whether these findings may be due to unmeasured confounding bias, we examined the distribution of unmeasured patient characteristics in a large survey of different Medicare beneficiaries (Table 5). There were several substantial differences in survey responses. Most importantly, glitazone users were more likely to report fair or poor general health (53%) compared with users of metformin (43%) or sulfonylureas (40%). The sensitivity analyses found that even if one assumes a 2-fold increase in fracture risk associated with fair or poor health, the RR of fracture comparing TZDs to metformin would be reduced from 1.31 (what was observed) to 1.20. A similar analysis comparing TZDs with sulfonylureas, where we observed a RR of 1.21, found that the actual risk would be 1.15.

Discussion

In a group of older diabetic patients, there was a suggestion of an elevated risk of fracture associated with glitazone use compared with other oral antidiabetic agents. Although the RRs we observed in this older adult population appear small, the absolute differences in fracture rate are large and potentially clinically meaningful. For example, glitazone users experienced nine more events per 1,000 patient-years (28.7 *vs.* 19.7) than metformin users for the composite fracture outcome. This translates into 111 patients treated with a TZD compared with metformin for one excess fracture, *i.e.* the number needed to harm. These results were similar across anatomic sites and important patient subgroups. The magnitude of RR differed slightly between TZDs, but the estimate of risk with individual agents was not precise.

The possible elevation in risk we observed is consistent with findings from randomized controlled trials recently described in FDA MedWatch reports as well as several recently published studies and a meta-analysis (7–10, 16). These data prompted label changes and letters to be sent to doctors about a possible risk of fracture associated with both available TZDs—pioglitazone and rosiglitazone. However, these data largely reported on rates for any fracture, not specific anatomic sites. Little data were

TABLE 5. Survey results of Medicare beneficiaries who use oral hypoglycemic agents as monotherapy

	TZDs (n = 188)	Sulfonylureas (n = 1284)	Metformin (n = 439)	Other (n = 42)
General health, fair or poor	100 (53)	509 (40)	190 (43)	16 (38)
Vision, none or limited vision	21 (11)	139 (11)	56 (13)	8 (19)
Hearing, deaf or very limited	20 (11)	104 (8)	29 (7)	3 (7)
Height (inches)	65 ± 5	65 ± 5	65 ± 4	64 ± 4
Weight (pounds)	193 ± 48	178 ± 40	186 ± 45	178 ± 47
Current tobacco use	17 (15)	140 (17)	46 (18)	5 (28)
Walking two blocks, unable or with a lot of difficulty	101 (54)	558 (43)	181 (41)	24 (57)
Falls in last year, yes/no	24 (23)	107 (23)	49 (29)	3 (19)

Data are expressed as number (%) or mean ± SD.

given about subgroups, such as men. Trial results suggest that much of the fracture risk resides in women (10, 16), however a prior observational study found that the risk of fractures was observed in men and women (11). Moreover, because the different TZDs were not all included in the same study, comparison across agents was difficult. The current report adds to an emerging literature that consistently finds that TZDs associate with fracture (9–11, 16). Our results find a smaller RR than some prior reports (11, 16). This may be attributed to the fact that older frail populations, such as our study cohort, have many competing risks for fracture. Thus, any one factor has a small impact on the RR but may translate into substantial absolute risks. Another important issue with our cohort study is the relatively short median exposure, approximately 11 months. In other studies, fracture risk among TZD users only became statistically significantly elevated after more than 2 yr of TZD exposure; however, the curves begin to diverge after 1 yr (9). We did not observe a trend toward greater risk with longer exposure. However, the risk associated with relatively brief use of TZDs likely represents the skeletal toxicity of these agents in a vulnerable population.

The current analyses have some important limitations. First, treatment assignment is nonrandom in typical practice databases, such as the one we used. Although the utilization patterns we observe reflect actual use of oral antidiabetic agents, there are potential confounders that could introduce bias. Our findings were robust, reflecting an elevated risk with TZDs in unadjusted, adjusted, and subgroup analyses. However, an unmeasured factor in the main study database, such as poor health, could have influenced both prescribing patterns and fractures. We checked for this potential in a large Medicare survey and found some imbalance. Sensitivity analyses suggest that these measured imbalances may explain a portion of the results but are unlikely to fully explain the increased risk of fracture with TZDs. Second, we relied on prescription filling patterns to determine patient exposures. This utilization data may not reflect what patients actually use on a daily basis, but it is likely one of the best sources of medication information in typical practice (17). Furthermore, the study database does not include the use of calcium and vitamin D supplements. Third, we did not confirm the presence of a given fracture by inspecting x-ray data. Our algorithms for defining fractures have been examined and found to be strongly predictive of fracture in prior research (12). However, the spine fracture endpoint has undergone less rigorous evaluation to date and is less able to distinguish between prevalence and incident fractures (18). We performed sensitivity analyses removing spine fracture from the composite endpoint; the results were not meaningfully different. Fourth, the study population was older adults with low incomes. These patients are generally more at risk of fractures from many causes, and competing risk factors can act to reduce the estimate of RRs (19). Similar studies should be repeated in younger patients with diverse socioeconomic status. Fifth, some of our analyses were underpowered. Sixth, some of the patient initiating oral hypoglycemics may have used these agents previous to our 6-month baseline observation period. Finally, several relevant clinical details were not available in the study database, including type of diabetes, bone mineral density, and bone metabolism markers.

This study has important strengths. It demonstrates the ability of pharmacoepidemiology to complement information gathered in randomized controlled trials. Although larger and more detailed observational studies can be designed and executed, the current study used existing data to support findings from randomized controlled trials (7–10). Our results were consistent across analytic method and strengthened in the propensity-matched analysis. The findings were relatively consistent across anatomic sites but did not demonstrate a clear duration effect. These analyses extend the current understanding of the relationship between TZDs and fracture by including relevant subgroup and duration analyses.

The recent Institutes of Medicine report on drug safety in the United States suggests that timely postmarketing surveillance needs to be a central activity of the FDA (20). In the case of the TZDs, data were accumulating about their potential effects on bones as early as 2002. The manufacturers sent warning letters to doctors after several large randomized controlled trials found a potential risk. It is possible that the earlier data should have prompted some communication about possible risks and more expeditious studies including fracture endpoints.

In conclusion, this study suggests an elevated risk of fracture associated with TZDs compared with other oral antidiabetic agents. The risk with TZDs was present at multiple anatomic sites, among relevant patient subgroups, and was of a potentially clinically significant magnitude. There are basic science data supporting a link between TZDs and a reduction in bone mineral density (5). Moreover, preliminary results from the FDA's Med-

Watch program raise concerns about the risk of fracture associated with TZDs (7, 8). Although many of our results do not reach statistical significance, the multitude of oral hypoglycemics to choose from suggests that fracture risk should be factored into the prescribing decision when considering TZDs. These agents are contraindicated in patients with congestive heart failure, and it may be prudent to limit the use of TZDs in patients at risk of fracture.

Acknowledgments

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Disclosure Summary: There was no specific support for this project. D.H.S. receives salary support from the National Institutes of Health (NIH) (AR 047782, AG027066, and AR055989), the Arthritis Foundation, the Engalitcheff Arthritis Outcomes Initiative, and Millenium. He has received salary support in the past 3 yr from research grants to Brigham and Women's Hospital from Pfizer, Merck, Savient, and GlaxoSmithKline. S.M.C. received support from the Canadian Institutes of Health Research through a postdoctoral fellowship. T.S. receives investigator-initiated research funding from the NIH (AG023178) and salary support from unrestricted research grants from pharmaceutical companies to the Brigham and Women's Hospital. N.K.C., R.L., and C.C. have no disclosures.

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