Thiazolidinediones and Fractures in Men and Women

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Background: Clinical trials and meta-analyses have found that rosiglitazone maleate, a thiazolidinedione that is prescribed for type 2 diabetes mellitus, increases the risk of fractures in women. The association between the use of thiazolidinediones and fractures in men and women is not adequately understood.

Methods: We conducted a prospective cohort study. The primary outcome was peripheral fractures in men and women who were exposed to thiazolidinediones compared with sulfonylureas. We studied 84 339 patients from British Columbia, Canada, who began treatment with a thiazolidinedione or a sulfonylurea. The association between the use of thiazolidinediones and fractures was examined using multivariate-adjusted Cox models.

Results: The mean age of the patients in the study was 59 years, and 43% were women. In this cohort, treatment with a thiazolidinedione was associated with a 28% increased risk of peripheral fractures compared with treatment with a sulfonylurea (hazard ratio [HR], 1.28; 95% confidence interval [CI], 1.10-1.48). The use of pioglitazone hydrochloride was associated with an increased risk of peripheral fracture of 77% in women (HR, 1.76; 95% CI 1.32-2.38). Compared with exposure to sulfonylureas, exposure to pioglitazone was associated with more peripheral fractures in men (HR, 1.61; 95% CI 1.18-2.20), but we did not observe a similar association with exposure to rosiglitazone (HR, 1.00; 95% CI, 0.75-1.34).

Conclusions: Both men and women who take thiazolidinediones could be at increased risk of fractures. Pioglitazone may be more strongly associated with fractures than rosiglitazone. Larger observational studies are needed, and fracture data from clinical trials need to be fully published so that fracture risks can be known with greater certainty.

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FRACTURES ARE A MAJOR CAUSE of morbidity and mortality,[1] resulting in substantial health care and social costs.[2,3] Patients with type 2 diabetes, despite having greater bone density,[4,5] appear to be at higher risk of fractures[6-10] and falls.[11] Factors associated with type 2 diabetes or its treatment could increase fracture risk.[12] Although it has been argued that the use of drugs to control diabetes may reduce the association between diabetes and fractures,[10] a recent meta-analysis of randomized trials of the peroxisome proliferator-activated receptor γ agonists (thiazolidinediones)—rosiglitazone maleate (Avandia) and pioglitazone hydrochloride (Actos)—concluded that the use of those drugs more than doubled the risk of fractures in women but did not increase the risk of fractures in men.[13]

Observational studies have also shown associations between the use of thiazolidinediones and fractures. A study of the general practice research database of the United Kingdom found an increased relative risk of fracture associated with exposure to rosiglitazone and pioglitazone.[14] Another observational study concluded that treatment with a thiazolidinedione, but not metformin, was associated with a higher incidence of fractures.[15] One possible interpretation of that study is that the negative effect of treatment with thiazolidinediones could be the result of a specific action on bone metabolism, and, indeed, human studies have demonstrated that the use of thiazolidinediones can decrease bone formation and accelerate bone loss.[16-21]

Diabetes is a growing problem in North America,[22] and more understanding of the benefits and harms associated with pharmacological treatments is needed. Treatments prescribed should be those that have been proved to reduce morbidity and mortality, not just to reduce blood glucose levels. The main issue is an assumption that oral hypoglycemic drugs can only provide benefit; ie, all glucose lowering must be good. The effect of oral hypoglycemic drugs on bone has not historically been part of treatment decisions. A recent meta-analysis of fractures made an important contribution.[13] However, rosiglitazone and pio-

glitazone were combined in that analysis, and only 1 large trial of each drug was available to study an association in men. A single trial contributed two-thirds of the patients who were receiving treatment with pioglitazone, and fracture data from that trial remain unpublished and were instead drawn from the manufacturer's US product information.[13] More data are therefore needed because pioglitazone and rosiglitazone may have different risks and because the trials may have included too few events to detect all important associations.

In a large population-based study in the province of British Columbia (BC), Canada, we explored the association between exposure to thiazolidinediones and sulfonylureas and risk of fracture. British Columbia provided a unique opportunity to contribute more data on fractures in patients treated with thiazolidinediones because, since late 1995, it has maintained a comprehensive PharmaNet database of prescriptions dispensed at all community pharmacies to its large and stable population of 4.3 million persons.

METHODS

DATA

The study received ethics approval from the University of British Columbia (UBC CREB No. H02-70020). The BC Ministry of Health approved the data access. The PharmaNet database contains all prescriptions that have been dispensed at community pharmacies in BC since January 1996. Prescriptions were linked by unique personal health numbers to provincewide BC Ministry of Health databases for hospitalizations, medical services, and medical services registration. Data on hospitalizations were collected by the Canadian Institute for Health Information, which collects hospital data for all Canadian provinces, including Ontario, where the data have been evaluated for accuracy.[23] The completeness of similar databases in other North American jurisdictions has been studied,[23-27] but we are unaware of any such analyses in BC.

SOURCE POPULATION

The source population included all residents of BC at any time between January 1998 and December 2007 who were also registered for provincial medical coverage according to the BC Ministry of Health client registry file. Federally insured patients (aboriginals, prisoners, and military personnel) were excluded from the source population because we did not have permission to use those data. The patients who were excluded represented approximately 4% of the provincial population. The source population numbered 4.2 million in 2007.

EXPOSURE AND COHORT

The study period was January 1, 1998, to December 31, 2007. We evaluated exposure to the thiazolidinediones (rosiglitazone and pioglitazone) and the sulfonylureas (acetohexamide, chlorpropamide, gliclazide, glimepiride, glyburide, and tolbutamide). Troglitazone was not marketed in Canada. We extracted all prescriptions for those drugs between January 1, 1996, and December 31, 2007. We assembled a cohort of patients from the source population who were incident users of a sulfonylurea or a thiazolidinedione between January 1, 1998 and December 31, 2007. Initiation was defined as a pharmacy dispensing for a sulfonylurea or a thiazolidinedione without another dispensing for those drugs or insulin in the previous 730 days. Approximately 80% of patients who were receiving oral hypoglycemic drugs in BC received metformin first. We selected sulfonylureas for a comparator instead of metformin because sulfonylureas, like thiazolidinediones, are usually prescribed as second-line drug therapy; therefore, patients using a sulfonylurea were expected to be more comparable to patients who were using thiazolidinedione in the duration and progression of their diabetes. We excluded patients who, in the previous 730 days, received a sulfonylurea, a thiazolidinedione, or insulin; had a fracture (*International Classification of Diseases, Ninth Revision* [*ICD-9*], codes 800, 804-807.6, and 808-829) or gestational diabetes (*ICD-9* code 648.8) recorded in a medical services claim or hospital record; or were admitted to a long-term care facility.

Table 1. Fracture Category Definitions

Fracture Category	*ICD-9* Code
Peripheral fracture	
Upper limb	
Hand (metacarpal)	815.x-817.x
Humerus	812.x
Clavicle	810.x
Radius, ulna	813.x
Wrist (carpal)	814.x
Upper limb (general)	818.x, 819.x
Lower limb	
Hip	820.x
Foot	825.x, 826.x
Ankle	824.x
Femur	821.x
Tibia, fibula	823.x
Patella	822.x
Lower limb (general)	827.x, 828.x
Spine	805.x, 806.x
Other	
Skull/face	800.x-804.x
Ribs, sternum, larynx, trachea	807.0-807.6
Pelvis, trunk	808.x, 809.x
Scapula	811.x
Unspecified fracture	829.x

Abbreviation: *ICD-9, International Classification of Diseases, Ninth Revision.*

FRACTURE OUTCOMES

We extracted data on health services use for patients who were diagnosed as having a fracture that was recorded in either the medical services or the hospitalization database. We studied the occurrence of peripheral fractures (*ICD-9* codes 810 and 812-828) and fractures of any kind (*ICD-9* codes 800, 804-807.6, and 808-829) in women and men who had been exposed to thiazolidinediones compared with sulfonylureas. Fracture sites that were included in the analysis are shown in **Table 1**. Cohort members were selected as fracture cases after initiation of treatment with a thiazolidinedione or a sulfonylurea and until the earliest date of the occurrence of the fracture outcome or until December 31, 2007. Patients were followed up until death, until they emigrated from BC, until they became nonadherent to drug treatment (no further prescriptions 60 days after the end of a drug dispensing), or unless they crossed over to the other treatment arm.

COHORT ANALYSIS

We used Cox proportional hazards models to estimate adjusted hazard ratios (HRs) for patients receiving thiazolidinediones com-

pared with patients receiving sulfonylureas. We estimated HRs related to 3 contrasts with sulfonylurea exposure: rosiglitazone, pioglitazone, and either rosiglitazone or pioglitazone. Exposures and outcomes were modeled as binary indicator variables. The HRs were adjusted for potential confounders: age (in 10-year categories), sex, family income, and index year of treatment initiation. The following covariates were included if recorded within 5 years of the treatment initiation: congestive heart failure (hospitalization for *ICD-9* code 425 or 428 or a physician visit for the same plus a prescription for furosemide); ischemic stroke (hospitalization for *ICD-9* code 433, 434, or 436); transient ischemic attack (hospitalization for *ICD-9* code 435); angina (*ICD-9* code 411 or 413); prior acute myocardial infarction (*ICD-9* code 410 or 412); prior hypertension (hospitalization or 2 physician visits within 365 days for *ICD-9* codes 401-405); peripheral vascular disease (hospitalization or physician visit for *ICD-9* code 443); renal disease (*ICD-9* codes 584-586 or 403-404); liver disease (*ICD-9* codes 0706, 0709, 456.0-456.2, 570-572.8, or 573.3-573.9); osteoarthritis (*ICD-9* code 715); and bone mineral density testing. The following covariates were measured and adjusted for within 1 year of treatment initiation: Romano comorbidity score (meant to adjust for confounding by concomitant illnesses by assigning weights to a patient's *ICD-9* diagnosis and then summing those weights into a single score)[28] and exposure to metformin, nitrates, bisphosphonates, digoxin, spironolactone, β-blockers, calcium channel blockers, clopidogrel, cyclooxygenase-2 inhibitors, benzodiazepines, and oral steroids. Finally, we estimated the number needed to treat or harm with thiazolidinediones using the survival function for the sulfonylurea controls and the HR for thiazolidinedione exposure from our Cox models according to the following equation: $\mathrm{NNT/H} = 1/[\mathrm{Sc}(t)\text{-}\mathrm{Sc}(t)^h]$, where NNT/H is the number needed to treat or harm; $\mathrm{Sc}(t)$ is the survival probability in the controls at time t; and h is the thiazolidinedione treatment HR.[29]

We conducted our study according to an analytical protocol that we drafted before the analysis. The original protocol required all cohort members to be prior users of metformin. We later dropped this requirement to increase statistical power after finding that baseline characteristics were the same regardless of that restriction. We adjusted for prior metformin use in the analyses instead, even though it was not associated with fracture risk in our cohort. The decision to estimate the number needed to harm was also made after most of the analyses were completed.

RESULTS

There were 127 581 patients from the source population who began treatment with a sulfonylurea or a thiazolidinedione between January 1, 1998, and December 31, 2007. Of those, 84 339 remained eligible for cohort entry after patients were excluded who (1) received insulin (n = 8097), a drug from the other comparator group (n = 29 662), or other antidiabetic medications (acarbose, glucagon, and repaglinide) (n = 5684); (2) had a fracture (n = 5017) or gestational diabetes (n = 177); or (3) were admitted to a long-term care facility (n = 2107) in the previous 2 years. Overall, 43 242 patients were excluded. The characteristics of the cohort patients are shown in **Table 2**. The average age of the patients in the study was 59 years, and patients in the thiazolidinedione group were 3.8 years younger on average than those in the sulfonylurea group ($P < .001$). Forty-three percent of the patients were women, and, for the 77% of patients with available income data, the average family income was approximately $45 000 Canadian dollars. The average duration of use was 460 days for the thiazolidinedione group and 534 days for the sulfonylurea group. A higher proportion of the sulfonylurea group had renal disease, prior coronary heart disease (myocardial infarction, angina, or congestive heart failure), and coronary interventions. A greater proportion of the thiazolidinedione group than the sulfonylurea group had past use of metformin, antihypertensive agents (except calcium channel blockers and spironolactone), and statins. A lower proportion of the thiazolidinedione group had past use of nonsteroidal anti-inflammatory drugs, digoxin, benzodiazepines, bisphosphonates, and steroids. The baseline characteristics of the patients in the rosiglitazone group and those in the pioglitazone group were similar.

We identified 2214 fractures in the cohorts during follow-up (**Table 3**). The average time to occurrence of any fracture event in the sulfonylurea, rosiglitazone, and pioglitazone cohorts was 1.71, 1.66, and 1.44 patient-years, respectively. Seventy-six percent of fractures were peripheral fractures, and most of the remaining 24% occurred in the spine (8%). However, a greater proportion of fractures occurred at peripheral sites in the pioglitazone group (85%) than in the sulfonylurea group (75%; *P* value for difference, .03). The proportions of spinal fractures were similar between exposure categories, but one-third as many hip fractures occurred in the thiazolidinedione group (0.1 per 100 patient-years) compared with the sulfonylurea group (0.3 per 100 patient-years).

The HRs from our Cox proportional hazards models are shown in **Table 4**. There was a statistically significant 28% higher incidence of peripheral fractures in men and women exposed to thiazolidinediones compared with sulfonylureas (Table 4: adjusted HR, 1.28; 95% confidence interval [CI], 1.10-1.48). When exposure to each thiazolidinedione was estimated separately, pioglitazone was associated with a significant increase in peripheral fractures in women compared with sulfonylureas (adjusted HR, 1.77; 95% CI, 1.32-2.38), but rosiglitazone was not (adjusted HR, 1.17; 95% CI, 0.91-1.50). In men, the association between thiazolidinedione exposure and peripheral fracture was not significantly different compared with sulfonylureas (adjusted HR, 1.20; 95% CI, 0.96-1.50). However, a subgroup analysis showed a statistically significant increase in men treated with pioglitazone compared with sulfonylureas (adjusted HR, 1.61; 95% CI, 1.18-2.20), but the CIs for pioglitazone compared with sulfonylureas and for rosiglitazone compared with sulfonylureas overlapped. The association between rosiglitazone treatment and peripheral fractures was not significantly different from that of treatment with sulfonylureas in either women or men. Compared with sulfonylureas in a combined analysis of men and women, there was a significant increase in peripheral fractures and fractures of any kind in the pioglitazone and combined thiazolidinedione groups but not in the rosiglitazone group. Estimates in the combined sex analysis were comparable to, though somewhat lower in magnitude than, the results observed in women only.

We also estimated treatment effects by category of duration of therapy (<1 year, 1-2 years, and ≥2 years). The HR estimates tended to increase with duration of treatment, but the CIs overlapped across categories. The results of Wald tests for the joint hypothesis of no linear association between categories of exposure duration were mostly nonsignificant except for all fractures in women receiv-

Table 2. Baseline Characteristics of Study Patients by Exposure to Thiazolidinediones or Sulfonylureas in British Columbia (1998-2007)[a]

Variable	Sulfonylurea (n=73 863)	Any Thiazolidinedione (n=10 476)	Pioglitazone Hydrochloride (n=3596)	Rosiglitazone Maleate (n=6880)
Age, mean (SD), y	60 (13)	56 (13)	57 (13)	56 (13)
Women	31 485 (43)	4445 (42)	1527 (42)	2918 (42)
Income quintile[b]				
1 (Lowest)	18 219 (25)	1341 (13)	451 (13)	890 (13)
2	18 745 (25)	2560 (24)	894 (25)	1666 (24)
3	10 663 (14)	2397 (23)	814 (23)	1583 (23)
4	4736 (6)	1480 (14)	527 (15)	953 (14)
5 (Highest)	3462 (5)	1223 (12)	415 (12)	808 (12)
Unknown	18 040 (24)	1475 (14)	496 (14)	980 (14)
Romano comorbidity score, mean (SD)[c]	1.34 (1.3)	1.24 (1.0)	1.20 (0.9)	1.25 (1.1)
Diabetes duration, mean (SD), y	4.0 (4.0)	4.6 (4.0)	4.7 (4.2)	4.6 (4.0)
Medical history				
Renal disease	1323 (1.8)	60 (0.6)	19 (0.5)	41 (0.6)
Acute myocardial infarction[d]	4656 (6.3)	383 (3.7)	117 (3.3)	266 (3.9)
Angina[d]	17 467 (23.6)	2095 (20.0)	719 (20.0)	1376 (20.0)
Congestive heart failure[d]	10 470 (14.2)	895 (8.5)	286 (8.0)	609 (8.9)
Coronary artery bypass graft[d]	1244 (1.7)	116 (1.1)	32 (0.9)	84 (1.2)
Coronary catheterization[d]	4820 (6.5)	553 (5.3)	180 (5.0)	373 (5.4)
PTCA[d]	1716 (2.3)	244 (2.3)	83 (2.3)	161 (2.3)
Bone density test	1081 (1.5)	239 (2.3)	98 (2.7)	141 (2.0)
Drug use in past year[e]				
Metformin	37 427 (50.7)	6856 (65.4)	2294 (63.8)	4562 (66.3)
ACE inhibitor	23 319 (31.6)	3890 (37.1)	1326 (36.9)	2564 (37.3)
Nitrate	5181 (7.0)	449 (4.3)	161 (4.5)	288 (4.2)
NSAIDs	16 655 (22.5)	2272 (21.7)	804 (22.4)	1468 (21.3)
β-Blockers	35 446 (48)	6099 (58.2)	2078 (57.8)	4021 (58.4)
Thiazide diuretics	14 553 (19.7)	2651 (25.3)	975 (27.1)	1676 (24.4)
Digoxin	3466 (4.7)	210 (2.0)	61 (1.7)	149 (2.2)
Spironolactone	1886 (2.6)	236 (2.3)	72 (2.0)	164 (2.4)
Statins	18 999 (25.7)	3823 (36.5)	1343 (37.3)	2480 (36.0)
Calcium channel blockers	11 456 (15.5)	1409 (13.4)	510 (14.2)	899 (13.1)
ACE/ARB	27 667 (37.5)	4902 (46.8)	1733 (48.2)	3169 (46.1)
Clopidogrel	1507 (2.0)	221 (2.1)	80 (2.2)	141 (2.0)
Coxib NSAIDs	3397 (4.6)	793 (7.6)	286 (8.0)	507 (7.4)
Non-Coxib NSAIDs	14 373 (19.5)	1677 (16.0)	593 (16.5)	1084 (15.8)
Benzodiazepine	10 147 (13.7)	1142 (10.9)	407 (11.3)	735 (10.7)
Bisphosphonate	2027 (2.7)	223 (2.1)	90 (2.5)	133 (1.9)
Oral steroid	13 705 (18.6)	1600 (15.3)	521 (14.5)	1079 (15.7)
Inhaled steroid	4091 (5.5)	427 (4.1)	135 (3.8)	292 (4.2)
No. of drugs prescribed, mean (SD)	6.3 (5.2)	6.5 (4.6)	6.5 (4.6)	6.5 (4.6)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; Coxib, cyclooxygenase-2 inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; PTCA, percutaneous transluminal coronary angioplasty.

[a] Values are expressed as number (percentage) unless otherwise indicated.

[b] Net family income in Canadian dollars from the most recent income tax return (1 Canadian dollar approximately equal to 0.85 US dollar).

[c] Romano comorbidity score calculated using data from 1 year before the index date.

[d] History within 5 years before the index date.

[e] Dispensing of drug within 365 days of the index date.

ing rosiglitazone ($P=.03$) and men and women combined receiving rosiglitazone ($P=.04$). The **Figure** shows the number needed to harm for patients prescribed thiazolidinediones instead of sulfonylureas assuming a constant HR of 1.28 for peripheral fractures and all fractures. Eighty-six patients would need to be treated with a thiazolidinedione for 3 years to produce 1 additional peripheral fracture.

COMMENT

This study provides further data that treatment with thiazolidinediones is associated with an increased risk of fracture compared with treatment with sulfonylureas in women, and it provides new data that pioglitazone exposure might increase the risk of peripheral fractures and all fractures relative to treatment with a sulfonylurea in men. Subgroup analyses of each thiazolidinedione suggested that pioglitazone was more strongly associated with fractures than rosiglitazone in our multivariate models. However, the CIs from the subgroup analyses for pioglitazone and rosiglitazone overlapped, which prevents us from making a strong conclusion that the 2 drugs have different fracture risks. The association between pioglitazone and fractures in men must therefore be viewed as a basis for further research rather than as a definitive result.

Table 3. Fractures in Patients With Type 2 Diabetes Treated With Thiazolidinediones or Sulfonylureas in British Columbia (1998-2007)

Group and Fracture Type	Sulfonyluryea			Thiazolidinedione			Rosiglitazone Maleate			Pioglitazone Hydrochloride		
	Follow-up, Patient-Years	Events (n=73 863)	Rate, ×100 Patient-Years	Follow-up, Patient-Years	Events (n=10 476)	Rate, ×100 Patient-Years	Follow-up, Patient-Years	Events (n=6880)	Rate, ×100 Patient-Years	Follow-up, Patient-Years	Events (n=3596)	Rate, ×100 Patient-Years
Men and women												
Peripheral	94 387	1448	1.5	13 402	225	1.7	8721	127	1.5	4395	95	2.2
All	93 814	1920	2.0	13 301	294	2.2	8644	177	2.0	4375	112	2.6
Upper limb	95 392	726	0.8	13 540	118	0.9	8811	59	0.7	4441	58	1.3
Lower limb	95 420	788	0.8	13 534	118	0.9	8780	74	0.8	4466	42	0.9
Spine	96 366	162	0.2	13 667	21	0.2	8865	13	0.1	4512	8	0.2
Hand (metacarpal)	96 233	195	0.2	13 647	36	0.3	8856	20	0.2	4501	16	0.4
Humerus	96 295	164	0.2	13 656	24	0.2	8865	13	0.1	4501	11	0.2
Hip	96 231	275	0.3	13 672	14	0.1	8868	11	0.1	4514	3	0.1
Foot	96 264	170	0.2	13 634	40	0.3	8849	23	0.3	4496	15	0.3
Men												
Peripheral	54 194	610	1.1	7914	100	1.3	5096	54	1.1	2654	45	1.7
All	53 889	869	1.6	7866	134	1.7	5057	78	1.5	2647	53	2.0
Upper limb	54 593	303	0.6	7970	55	0.7	5130	28	0.5	2675	27	1.0
Lower limb	54 600	329	0.6	7982	48	0.6	5126	28	0.5	2691	19	0.7
Spine	54 969	62	0.1	8029	9	0.1	5153	6	0.1	2712	3	0.1
Hand (metacarpal)	54 836	123	0.2	8018	20	0.2	5148	11	0.2	2706	9	0.3
Humerus	54 968	49	0.1	8021	11	0.1	5152	7	0.1	2705	4	0.1
Hip	54 935	105	0.2	8036	5	0.1	5159	3	0.1	2712	2	0.1
Foot	54 945	66	0.1	8023	16	0.2	5155	6	0.1	2704	9	0.3
Women												
Peripheral	40 193	838	2.1	5488	125	2.3	3625	73	2.0	1741	50	2.9
All	39 925	1051	2.6	5435	160	2.9	3588	99	2.8	1729	59	3.4
Upper limb	40 798	423	1.0	5571	63	1.1	3681	31	0.8	1766	31	1.8
Lower limb	40 820	459	1.1	5552	70	1.3	3654	46	1.3	1775	23	1.3
Spine	41 398	100	0.2	5638	12	0.2	3712	7	0.2	1800	5	0.3
Hand (metacarpal)	41 396	72	0.2	5629	16	0.3	3709	9	0.2	1795	7	0.4
Humerus	41 327	115	0.3	5635	13	0.2	3712	6	0.2	1797	7	0.4
Hip	41 296	170	0.4	5637	9	0.2	3709	8	0.2	1802	1	0.1
Foot	41 319	104	0.3	5610	24	0.4	3694	17	0.5	1792	6	0.3

Consistent with the ADOPT trial,[30-32] our data did not show an increased risk of fractures in men who were receiving rosiglitazone, and a recent meta-analysis also showed no change in risk of fractures in men treated with thiazolidinediones.[13] A comparison with those data warrants more discussion. There were 5 randomized trials with sex-specific data included in the meta-analysis. Three of the 5 trials included 15% of patients and only 3 fractures in men. The other 2 trials accounted for 85% of patients and the remaining fractures. One of those large trials was the ADOPT study of rosiglitazone,[30] and the other was the PROactive trial of pioglitazone.[33] An estimate of fractures in men from the ADOPT trial of approximately 1.1 fractures per 100 patient-years in younger men who were receiving glyburide was somewhat lower than our estimate of 1.6 in our control patients. Neither our study nor the trial showed a significant change in fracture risk in men who were receiving rosiglitazone. The fracture data from the PROactive study have not been published.[13] Fractures in the male control patients in that trial, which we estimated to be approximately 0.75 per 100 patient-years based on data from the meta-analysis and trial, were half the rate of 1.6 per 100 patient-years in the sulfonylurea-treated control patients in our study (Table 2). Fractures were not significantly increased in men in the PROactive trial, but it is difficult for us to contemplate the discordance between our results and the trial without fully published data from the trial.

Our estimates for pioglitazone exposure and fractures in females were lower but within the CIs reported in the meta-analysis and in each of the 2 largest trials that it included. In contrast to our sulfonylurea control group, and relevant to results in both men and women, the trials in the meta-analysis included control patients who received placebo, metformin, or glyburide. The same results should not necessarily be expected unless it can be assumed that all of those treatments have the same association with fractures.

From Table 3, it is clear that most nonperipheral fractures in our female cohort members who received pioglitazone occurred in the spine, which could indicate an association between pioglitazone and spinal fractures, but more research is needed, and a strong conclusion cannot be drawn from this observation. Hip fractures were more frequent in the sulfonylurea group. This outcome may have been influenced by residual confounding by age (the sulfonylurea group was somewhat older), but the paucity of hip fractures also prevents a definitive statement.

The chemical structures of rosiglitazone and pioglitazone are similar, but the doses required to achieve a

Table 4. Hazard Ratios (HRs) for Fractures Associated With Treatment With Thiazolidinediones or Sulfonylureas in Patients With Type 2 Diabetes Mellitus in British Columbia (1998-2007)

Group and Fracture Type	Thiazolidinedione				Pioglitazone Hydrochloride				Rosiglitazone Maleate			
	Crude HR	*P* Value[a]	Adjusted HR[b] (95% CI)	*P* Value[a]	Crude HR	*P* Value[a]	Adjusted HR[b] (95% CI)	*P* Value[a]	Crude HR	*P* Value[a]	Adjusted HR[b] (95% CI)	*P* Value[a]
Men and women												
Peripheral												
Exposure duration, y												
Any	1.09	.21	1.28 (1.10-1.48)	.001	1.41	.001	1.68 (1.36-2.08)	<.001	0.95	.56	1.09 (0.91-1.32)	.34
<1	0.98	.87	1.14 (0.92-1.42)	.22	1.34	.06	1.58 (1.16-2.14)	.004	0.82	.16	0.95 (0.72-1.25)	.72
1-<2	1.12	.45	1.31 (0.97-1.77)	.07	1.26	.33	1.51 (0.94-2.40)	.09	1.06	.75	1.23 (0.85-1.77)	.27
>2	1.26	.06	1.48 (1.15-1.90)	.002	1.65	.007	2.01 (1.39-2.91)	<.001	1.08	.62	1.25 (0.90-1.73)	.19
All												
Exposure duration, y												
Any	1.08	.22	1.28 (1.12-1.45)	<.001	1.25	.021	1.51 (1.25-1.84)	<.001	1.00	1.00	1.17 (1.00-1.37)	.053
<1	0.94	.54	1.12 (0.92-1.35)	.25	1.26	.09	1.51 (1.15-1.98)	.003	0.80	.07	0.94 (0.74-1.20)	.617
1-<2	1.11	.44	1.31 (1.01-1.70)	.04	1.08	.73	1.31 (0.85-2.02)	.22	1.13	.42	1.33 (0.98-1.81)	.071
>2	1.31	.01	1.55 (1.24-1.93)	<.001	1.38	.07	1.69 (1.19-2.42)	.004	1.27	.08	1.47 (1.12-1.93)	.006
Men												
Peripheral												
Exposure duration, y												
Any	1.13	.28	1.20 (0.96-1.50)	.10	1.51	.008	1.61 (1.18-2.20)	.003	0.94	.67	1.00 (0.75-1.34)	.98
<1	1.09	.56	1.17 (0.86-1.58)	.32	1.50	.06	1.61 (1.05-2.47)	.03	0.90	.60	0.96 (0.64-1.43)	.83
1-<2	1.13	.61	1.21 (0.75-1.93)	.44	1.30	.48	1.39 (0.67-2.85)	.37	1.09	.78	1.15 (0.65-2.05)	.63
>2	1.18	.40	1.26 (0.85-1.88)	.25	1.68	.06	1.79 (1.03-3.10)	.04	0.91	.75	0.98 (0.57-1.69)	.94
All												
Exposure duration, y												
Any	1.06	.53	1.15 (0.95-1.40)	.14	1.25	.12	1.36 (1.03-1.81)	.033	0.96	.72	1.04 (0.82-1.32)	.73
<1	1.00	.97	1.09 (0.84-1.42)	.52	1.31	.16	1.44 (0.99-2.11)	.06	0.85	.34	0.93 (0.66-1.30)	.67
1-<2	1.07	.75	1.16 (0.77-1.74)	.48	0.92	.81	1.00 (0.49-2.04)	>.99	1.18	.48	1.28 (0.80-2.04)	.30
>2	1.18	.34	1.27 (0.91-1.79)	.16	1.38	.21	1.49 (0.89-2.48)	.13	1.00	>.99	1.08 (0.69-1.70)	.72
Women												
Peripheral												
Exposure duration, y												
Any	1.09	.36	1.34 (1.10-1.64)	.004	1.38	.03	1.77 (1.32-2.38)	<.001	0.97	.77	1.17 (0.91-1.50)	.22
<1	0.91	.51	1.12 (0.83-1.51)	.48	1.23	.35	1.56 (1.01-2.41)	.04	0.76	.17	0.94 (0.63-1.38)	.74
1-<2	1.14	.49	1.41 (0.96-2.07)	.08	1.28	.43	1.64 (0.89-3.03)	.12	1.06	.80	1.29 (0.80-2.08)	.29
>2	1.37	.06	1.67 (1.21-2.32)	.002	1.75	.03	2.29 (1.39-3.77)	.001	1.22	.33	1.46 (0.97-2.19)	.07
All												
Exposure duration, y												
Any	1.12	.18	1.40 (1.18-1.67)	<.001	1.30	.05	1.70 (1.30-2.23)	<.001	1.05	.64	1.29 (1.04-1.59)	.02
<1	0.91	.46	1.14 (0.87-1.49)	.35	1.24	.28	1.61 (1.09-2.36)	.02	0.76	.12	0.94 (0.67-1.33)	.74
1-<2	1.16	.38	1.46 (1.04-2.04)	.03	1.25	.42	1.64 (0.95-2.82)	.07	1.12	.60	1.38 (0.91-2.07)	.13
>2	1.47	.008	1.82 (1.36-2.44)	<.001	1.47	.13	1.95 (1.19-3.20)	.008	1.52	.02	1.82 (1.29-2.56)	.001

Abbreviations: CI, confidence interval.

[a] The *P* values are from the Cox proportional hazards regression models.

[b] The HRs were adjusted for age, sex, family income, and the following within 5 years of the index date: angina, hypertension, acute myocardial infarction, congestive heart failure, ischemic stroke, transient ischemic attack, hypertension, peripheral vascular disease, renal disease, liver disease, osteoarthritis, and bone mineral density testing. The following covariates were measured and adjusted for within 1 year of treatment initiation: Romano comorbidity score, exposure to nitrates, bisphosphonates, digoxin, spironolactone, β-blockers, calcium channel blockers, clopidogrel, cyclooxygenase-2 inhibitors, benzodiazepines, and oral steroids.

similar reduction in blood glucose levels are higher for pioglitazone than for rosiglitazone (15-45 mg compared with 2-8 mg). A direct comparison of the 2 drugs regarding bone formation and loss in peripheral areas of the body is not yet available, but published data from randomized trials have shown that reductions in body mass index (measured at the lumbar and femoral neck) are similar between the moderate dose of pioglitazone given to premenopausal women in a 16-week trial[19] and the highest dose of rosiglitazone given to postmenopausal women in a 14-week trial.[20] Those trials showed a decrease of 1.5% to 1.7% in body mass index over 3½ to 4 months, respectively. While those data do not provide a definitive link between greater fracture risk in patients using pioglitazone than in patients using rosiglitazone, they may be viewed as being compatible with the hypothesis that the use of pioglitazone could weaken bones more than the use of rosiglitazone for equivalent reductions in blood glucose levels. There are also data showing that the use of thiazolidinediones is associated with heart failure[34] and that heart failure is associated with fractures,[35] but a meta-analysis of thiazolidinediones did not find evidence of heterogeneous heart failure risks among patients who were receiving thiazolidinediones.[34]

A significant strength of this study was the use of the BC PharmaNet database, which captured all thiazolidinediones dispensed at community pharmacies regardless of payer. The comprehensiveness of the provincial

drug database is valuable because observational studies that capture drug exposure only for persons with insurance coverage or who satisfy prior authorization criteria can cause some exposed patients to be misclassified as nonexposed in a way that is associated with the outcome. The effect of even a modest amount of exposure misclassification could change effect estimates substantially.[36] If our analysis was limited to prescriptions paid by the province, then we would have classified as exposed only 31% of the provincial patients who were being treated with thiazolidinedione.

Our study had limitations that merit discussion. The accuracy of fracture diagnoses in the BC databases is unknown. Our study period ended before there were warnings of a possible fracture association; therefore, ascertainment bias for diagnosing fractures was unlikely to have occurred between thiazolidinediones and sulfonylureas. As with most population-based outcomes studies of prescription drugs, our study was susceptible to channeling bias, which is a type of confounding by indication where marketing leads to sicker patients being more likely to be early users of new drugs. The expected direction of such a bias is to increase the association between thiazolidinedione exposure and fracture. We cannot say whether our study was more influenced by such forces than other epidemiological studies of the thiazolidinediones, but our HRs (Table 4) increased after multivariate adjustment, which suggests that the true effects were underestimated.

The thiazolidinedione and the sulfonylurea groups were different in their prior use of metformin at baseline (65% thiazolidinedione and 51% sulfonylurea). Although our models included indicator variables for prior metformin use, it did not appear to be an important confounder as it was not strongly predictive of fractures (51% prior use in fracture patients and 54% in nonfracture patients). Patients were allowed to enter the cohort in January 1998 even though thiazolidinediones were not used in BC before March 1999. That amount of time was not a confounder of fracture risk, and we allowed patients who were using sulfonylurea to enter the cohort starting in 1998 to increase statistical power. However, we verified that limiting our data to 1999 or later produced the same point estimates. We adjusted for age to attenuate potential confounding, and while most confounding by age should have been removed, some residual confounding within age groups could have remained. Because the patients who were using sulfonylureas were older than those using thiazolidinedione, residual confounding by age could have biased our HRs lower.

We analyzed the data in 3 categories of exposure duration (<1 year, 1-2 years, and ≥2 years). Our estimates in the first year of exposure were attenuated toward the null in women, which was expected because a drug effect on fractures would be expected to occur gradually. Estimates were not attenuated in men who were treated with pioglitazone for up to 1 year, a result that could suggest that pioglitazone has a relatively rapid harmful effect in men or, alternatively, that there was severe unknown confounding in our analysis. However, the rosiglitazone and the pioglitazone groups were very similar in observed baseline characteristics (Table 2), and a strong confounder would need to be more influential for pioglitazone than rosiglitazone, which seems implausible. Working in the opposite direction was the limitation that average exposure time in our thiazolidinedione group was less than 1.5 years, which probably attenuated our estimates for combined treatment durations (the "any" category of exposure in Table 4) downward.

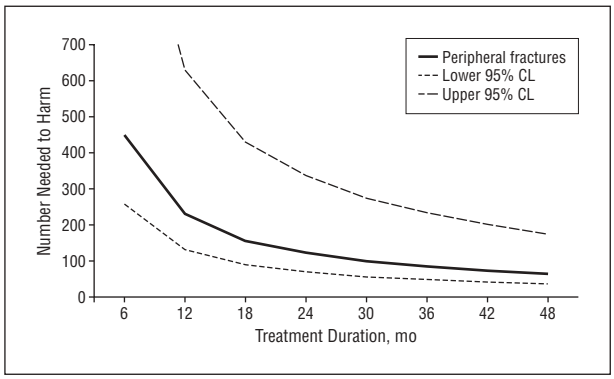

Figure. Number needed to harm for fractures in men and women in British Columbia who are prescribed a thiazolidinedione instead of a sulfonylurea. The upper 95% confidence limit (CL) for the number needed to harm was 1228 at 6 months.

Our findings suggest that both men and women are at increased risk of fracture as a result of exposure to thiazolidinediones and that pioglitazone treatment may be more strongly associated with fractures than rosiglitazone treatment. Prescribers of these medications should therefore not assume that fracture risk is confined to women who take rosiglitazone. Larger observational studies are needed so that fracture risks with pioglitazone and rosiglitazone treatment can be known with greater certainty and so that specific fracture sites such as the hip can be studied with adequate precision. Future studies should also ideally adjust for potential confounders, such as body mass index and physical activity, that we lacked in our analysis. Fracture data from clinical trials also need to be fully published. There is insufficient clinical trial evidence to show that treatment with thiazolidinediones provides clinical benefits beyond glycemic control, and in the absence of mitigating clinical benefits, mounting evidence of harm should discourage physicians from prescribing those drugs.

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Administrative, technical, and material support: Carney. *Study supervision:* Dormuth and Carney. *Clinical expertise:* Wright.

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