Comparative safety of pioglitazone versus clinically meaningful treatment alternatives concerning the risk of bladder cancer in older US adults with type 2 diabetes

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Aims: To compare bladder cancer incidence between patients initiating pioglitazone treatment and patients initiating treatment with dipeptidyl-peptidase-4 inhibitors [DPP-4s] or sulfonylureas.

Methods: We identified Medicare beneficiaries aged >65 years who initiated treatment with pioglitazone (N = 38 700), DPP-4s (N = 82 552) or sulfonylureas (N = 126 104) between 2007 and 2014 after at least 6 months without prescriptions for these drug classes. Patients were followed from second prescription until bladder cancer outcome (2 claims within 60 days) using a 6-month induction/latency period, censoring for treatment change, death or end of 2014. We used propensity score-weighted Cox proportional-hazards models to obtain adjusted hazard ratios (aHR) and their 95% confidence intervals.

Results: Overall mean age of participants was 75 years and 41% were men. Over a median of 1.2 treatment years, 727 beneficiaries developed bladder cancer. Pioglitazone initiators had an increased incidence of bladder cancer (308 vs 204 [DPP-4s] or 231 [sulfonylureas] per 100 000 person-years; aHR, 1.57 [1.23-2.00] vs DPP-4s and 1.32 [1.02-1.70] vs sulfonylureas). The increased risk emerged within the first 2 years of treatment (aHR, 1.63 [1.22-2.17] vs DPP-4s and 1.32 [0.98-1.78] vs sulfonylureas). If treatment was discontinued within the first 2 years, the risk after 2 years post initiation was attenuated (aHR, 0.89 [0.61-1.28]) compared with patients treated for more than 2 years (aHR, 1.45 [0.93-2.26]) both vs DPP-4s. Findings were consistent across secondary and sensitivity analyses.

Conclusions: Pioglitazone was associated with an elevated risk of bladder cancer compared with DPP-4s and sulfonylureas. The elevated risk emerged within the first 2 years of treatment and was attenuated after discontinuing. Pioglitazone's relative effectiveness should be weighed against a small absolute increase in risk of bladder cancer.

KEYWORDS

antidiabetic drug, database research, DPP-IV inhibitor, pharmaco-epidemiology, thiazolidinediones

1 | INTRODUCTION

The safety of pioglitazone has been greatly debated in the literature over the past decade. Before its approval by the Food and Drug Administration (FDA) in 1999, excess bladder tumours were reported in preclinical rat studies.[1] This was thought to be a rat-specific phenomenon[2] until the 3-year PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) published results that revealed excess bladder tumours in humans who were assigned pioglitazone vs placebo (0.5%[N = 14] vs 0.2%[N = 6], respectively) in 2005[3]; thus, it behooved the FDA to request a 10-year safety study. When interim results of the 10-year study revealed an increased risk of

bladder cancer after 2 years (adjusted hazard ratio (aHR), 1.44 [1.03-2.02]),[4] the FDA issued a bladder cancer warning for pioglitazone exposure in excess of 2 years in 2011,[5] a warning that was recently re-issued in December 2016.[6]

Multiple publications that reported no evidence of an increased risk of bladder cancer for pioglitazone followed the initial safety warning,[4,7–14] including the final results of the 10-year study (aHR, 1.06 [0.89-1.26])[4] and a PROactive follow-up study that observed patients for an additional period of 10 years after the trial (risk ratio (RR), 1.05 [0.61-1.79]).[12] Far fewer publications reported an increased risk overall,[15–18] including 3 more recent studies that compared pioglitazone users to non-users of pioglitazone's thiazolidinediones drug class at the time of pioglitazone initiation (aHR, 1.63 [1.22-2.19]),[16] to those who never used pioglitazone (RR, 1.83 [1.10-3.05]),[18] and to those who received placebo (0.6% [n = 12] vs 0.4% [n = 8]) in the Insulin Resistance Intervention after Stroke (IRIS) trial.[17]

Although much has been published on the safety of pioglitazone, explanations for discrepancies in the observed risk of bladder cancer are not satisfactory, rendering the totality of evidence inconclusive.[19] One potential explanation highlighted in this paper is comparator choice. Others include differing data sources, whether or not prevalent users were included, and definition of the risk window. This is the first study to employ the incident user design and a wide range of secondary and sensitivity analyses in a national sample of older US adults to compare the risk of incident bladder cancer among initiators of pioglitazone to that among initiators of clinically meaningful alternatives, dipeptidyl-peptidase-4 inhibitors (DPP-4s) and sulfonylureas, as is recommended for comparative effectiveness research to present the least biased comparison.[20,21]

2 | MATERIALS AND METHODS

2.1 | Data source

We used a 20% random sample of all Medicare beneficiaries with concurrent fee-for-service enrollment in Parts A (inpatient), B (outpatient) and D (pharmacy) during at least 1 month between January 2007 and December 2014. Medicare provides public insurance to over 98% of older US adults, and has information about demographic and enrollment characteristics, diagnoses, procedures and dispensed prescriptions for enrollees.[22]

2.2 | Study population

We included patients aged 66 years or older who had initiated treatment with pioglitazone or an active comparator (DPP-4s [largely sitagliptin and saxagliptin] and sulfonylureas [largely glyburide, glipizide and glimepiride]) with continuous enrollment in Medicare Parts A and B during the year prior to drug initiation (Figure S1, Appendix S1). Incident use required patients to have no prescription claims for the drug classes included in each comparison during the 180-day period prior to the initial claim and to have a second claim for the same drug class within 90 days. The second claim date defined the cohort entry date. Patients who initiated both pioglitazone and the comparator on the same day were excluded because of the inability to differentiate the individual effects of either drug. Patients with a diagnostic claim for bladder cancer or a procedure code for common bladder cancer treatment (bacillus Calmette-Guérin [BCG] immunotherapy, transurethral resection of bladder tumour [TURBT], chemotherapeutic bladder instillation or cystectomy) at any time prior to the cohort entry date were excluded. Because secondary malignancies account for only 1.5% of all bladder tumours,[23] we did not exclude patients with a history of non-bladder malignancies, to maximize power for this rare outcome. Treatment classification for each comparison was determined based on first qualifying treatment per patient during the study period.

2.3 | Outcome

Incident events were defined as at least 2 International Classification of Disease (ICD-9) diagnostic claims for bladder cancer within 60 days, an algorithm previously validated for other solid tumours.[24] We included non-invasive (233.7) in addition to invasive (188.x) claims as the majority of bladder cancers are diagnosed at an early stage.[25] The first claim date defined the event date, assuming this to be closest to the date of actual diagnosis.

2.4 | Follow-up

The primary approach for defining the follow-up period for outcome ascertainment, referred to here as the "as-treated" (AT) approach, started on the cohort entry date and continued until the first occurrence of incident bladder cancer, disenrollment, study end (December 2014) or treatment discontinuation (no subsequent dispensing of initiated drug class within days-supply plus a 90-day grace period). We added an additional 6-month latent period after treatment discontinuation to allow time for disease manifestation and detection. Additional analyses, referred to here as the "initial-treatment" (IT) approach, did not censor for treatment discontinuation, similar to the intent-to-treat model used in randomized controlled trials. We present AT as the primary approach as non-adherence in IT analyses can attenuate results towards the null, potentially masking drug effects on safety outcomes. The first 6 months of follow-up were excluded, regardless of censoring approach, to allow for time between exposure and development of disease (induction period) to reduce the potential for spurious associations attributable to increased medicalization after initiation of a therapy or the possibility of preclinical symptoms of bladder cancer influencing treatment choice (protopathic bias). Latency and induction periods were also varied from 0 to 12 and 0 to 18 months, respectively (Table S1, Appendix S1).

Because the original FDA warning was for exposure in excess of 2 years, follow-up was analysed overall and was stratified at 2 years. We further evaluated the risk of bladder cancer during the time period in excess of 2 years after drug initiation when actual treatment duration was less than 2 years. Only a subset of patients not otherwise censored within 2 years were included in analyses evaluating associations 2 years after drug initiation.

2.5 | Detection procedures

Urologic screening and diagnostic procedures (cytology, dipstick urinalysis, non-dipstick urinalysis, urine function test and cystoscopy) were enumerated at 0 to 6 and 6 to 12 months pre- and post-drug initiation to evaluate whether an increased incidence of bladder cancer could be attributed to earlier and more frequent detection resulting from an increased rate of urologic procedures.

2.6 | Confounding control and statistical analysis

Medicare claims A and B (medical) were available as of January 2006 but Medicare claims D (pharmaceutical) were only available as of January 2007. Therefore, the baseline covariate assessment period prior to drug initiation was 6 months for medications and 12 months for comorbidities and healthcare utilization, thus maximizing use of available data. Descriptive statistics summarized covariates. The incidence rates of crude bladder cancer (first event per patient) were calculated based on the Poisson distribution overall and for each treatment category. We used propensity scores (PS) based on all covariates to control for remaining differences between the compared cohorts. The propensities of initiating pioglitazone vs DPP-4s and pioglitazone vs sulfonylureas were estimated for each patient using 2 separate logistic regression models (1 for each comparison).[26] Standardized morbidity ratio (SMR) weighting that assigned the pioglitazone group a weight of 1 and each comparator group a weight of [PS/(1-PS)][27] was used to standardize the DPP-4s and sulfonylureas comparator covariates to the covariate distribution observed in the pioglitazone group. We report weighted comparison columns that represent pseudo-populations of patients initiating DPP-4s and sulfonylureas with covariate distribution balanced to that of the pioglitazone treatment group, allowing for unconfounded treatment effect estimates.[27,28] We used weighted Kaplan–Meier plots to evaluate the proportional hazards assumption. Weighted Cox proportional hazards models, with treatment as the only independent variable, were used to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) of the incidence of bladder cancer for each comparison, and then for each detection procedure during each time period.

2.7 | Sensitivity analyses

We conducted multiple sensitivity analyses to quantify the robustness of results. First, we assessed robustness of the outcome definition using a more conservative (any claim) (Table S3, Appendix S1) and a more stringent definition (requirement of additional procedure claim for bladder cancer treatment within 3 months of initial diagnosis) (Table S4, Appendix S1) to increase sensitivity and specificity. Second, we evaluated the cohort selection processes separately, excluding patients with each of the following: any cancer diagnosis except non-melanoma skin cancer identified using all available data, as prevalent cancer may also affect outcome (Tables S5 and S6, Appendix S1); no metformin use during baseline, as these patients are treated contrary to guidelines (Table S7, Appendix S1 and Table 3); diagnosis of congestive heart failure (CHF), as treated contrary to FDA warning issued for thiazolidinediones (Tables S8 and S9, Appendix S1); treatment initiation after the FDA bladder cancer warning, as propensity to initiate pioglitazone was likely to change (Tables S10 and S11, Appendix S1), as well as patients in the upper 1% and 2% tails of the PS distribution of each drug group, as trimming those treated contrary to prediction can reduce unmeasured confounding[29] (Tables S12–S15, Appendix S1). Third, we re-estimated the PS, excluding indicator variables for calendar time of drug initiation from the model, as time may be an instrumental variable for pioglitazone treatment rather than a confounder following the bladder cancer warning (Tables S16 and S17, Appendix S1).[30] Fourth, we implemented a range of grace periods for defining treatment discontinuation in the AT analysis from 90 to 45 and 180 days (Table S18, Appendix S1), and we calculated individual grace periods based on the days-supply, double-days-supply and triple-days-supply of the last dispensing (Table S19, Appendix S1). Finally, given the poor sensitivity of claims for identification of smoking status,[31] we conducted an external validation study using data from the 2007 to 2011 Medicare Current Beneficiary Survey (MCBS). We identified new users of all 3 drug classes based on Part D data and present data on smoking and BMI reported during the interview[32] (Table S20, Appendix S1).

All data were analyed using SAS, v9.4. The University of North Carolina at Chapel Hill institutional review board approved this study, which began as a methodological comparison of various study design approaches to a comparison of pioglitazone and DPP-4s. Upon review of the early findings, which suggested a safety concern, a new study protocol was written and registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance electronic register of studies (http://www.encepp.eu, EU PAS Register Number: EUPAS13279).

3 | RESULTS

Distribution of patient characteristics for those initiating treatment with pioglitazone vs DPP-4s (38 700 vs 82 552) and those initiating treatment with pioglitazone vs sulfonylureas (20 075 vs 126 104) is presented in Table 1. Overall, when compared to each respective comparator, those who initiated pioglitazone treatment were more likely to be younger, non-white men, and were less likely to have a smoking-related claim or to have comorbid diagnoses of cancer, chronic obstructive pulmonary disorder (COPD) or CHF. Although differences were present for both comparisons, they were generally more pronounced in the sulfonylureas comparison. Relative to DPP-4s, pioglitazone users were less likely to have a history of use of metformin, insulin or angiotensin receptor blocker, which was reversed when compared to sulfonylureas. After SMR weighting, distribution of the variables presented in Table 1 for the weighted DPP-4s and sulfonylureas pseudo-populations became virtually identical to the pioglitazone group within each respective comparison, indicating no confounding by these variables.

Table 2 shows incidence rates of bladder cancer per 100 000 person-years (representing post-initiation years for the IT and treatment years for the AT analyses) and corresponding HRs (crude and fully adjusted) for initiators of pioglitazone vs DPP-4s or sulfonylureas. Median treatment duration (1.1-1.2 years) was similar in all AT analyses, explained by the frequent treatment changes among patients with type 2 diabetes, while available follow-up in the IT

TABLE 1 Distribution of covariates of patients who initiated treatment with pioglitazone, dipeptidyl-peptidase-4 or sulfonylureas

Variable	PIO[a](N = 38 700) N	%	DPP(N = 82 552) N	%	SMRW DPP[b] %	PIO[a](N = 20 075) N	%	SU(N = 126 104) N	%	SMRW SU[b] %
Demographic characteristics at drug initiation										
Age 66 to <70	10 050	26.0	18 838	22.8	26.1	5316	26.5	29 020	23.0	26.4
Age 70 to <75	11 195	28.9	22 311	27.0	29.0	5832	29.1	33 267	26.4	29.1
Age 75 to <80	8018	20.7	17 356	21.0	20.6	4144	20.6	25 689	20.4	20.7
Age 80 to <85	5495	14.2	12 925	15.7	14.2	2733	13.6	19 616	15.6	13.6
Age >= 85	3942	10.2	11 122	13.5	10.0	2050	10.2	18 512	14.7	10.2
Male	16 280	42.1	31 683	38.4	42.3	8350	41.6	51 459	40.8	41.7
White	27 849	72.0	62 274	75.4	72.6	14 332	71.4	98 793	78.3	71.3
Black	4676	12.1	9165	11.1	11.7	2411	12.0	14 999	11.9	12.0
Other race[c]	6175	16.0	11 113	13.5	15.7	3332	16.6	12 312	9.8	16.7
Drug initiation year: 2007	2384	6.2	1915	2.3	6.1	1138	5.7	4278	3.4	5.7
Drug initiation year: 2008	9515	24.6	7459	9.0	24.5	4511	22.5	17 222	13.7	22.5
Drug initiation year: 2009	8362	21.6	7546	9.1	21.6	3910	19.5	17 293	13.7	19.4
Drug initiation year: 2010	7146	18.5	9084	11.0	18.5	3610	18.0	16 869	13.4	18.0
Drug initiation year: 2011	4279	11.1	12 785	15.5	11.1	2379	11.9	16 635	13.2	11.8
Drug initiation year: 2012	2262	5.8	14 440	17.5	5.9	1392	6.9	16 930	13.4	6.9
Drug initiation year: 2013	2419	6.3	14 876	18.0	6.3	1532	7.6	19 040	15.1	7.6
Drug initiation year: 2014	2333	6.0	14 447	17.5	6.0	1603	8.0	17 837	14.1	8.0
Bladder comorbidities during baseline[d]										
Bladder stones	103	0.3	219	0.3	0.3	52	0.3	386	0.3	0.3
Kidney stones	1231	3.2	3202	3.9	3.2	671	3.3	4577	3.6	3.3
Urinary tract infection	9545	24.7	24 107	29.2	24.6	5176	25.8	35 116	27.8	25.9
Diabetes-related complications during baseline[d]										
Nephropathy	3176	8.2	8628	10.5	8.3	1539	7.7	9414	7.5	7.8
Neuropathy	7437	19.2	19 216	23.3	19.6	3624	18.1	21 696	17.2	18.1
Retinopathy	6593	17.0	14 293	17.3	17.1	2991	14.9	15 060	11.9	14.9
Healthcare utilization or smoking-related encounter during baseline[d]										
Any admission	9954	25.7	25 816	31.3	25.4	5127	25.5	44 433	35.2	25.6
Any long-term admission	1029	2.7	2465	3.0	2.6	537	2.7	4761	3.8	2.7
Any short-term admission	9447	24.4	24 776	30.0	24.2	4879	24.3	42 301	33.5	24.4
Any SNF admission	2940	7.6	8305	10.1	7.5	1547	7.7	15 420	12.2	7.8
Any electrocardiogram	19 935	51.5	49 468	59.9	51.3	10 550	52.6	73 158	58.0	52.5
Any office visit	36 672	94.8	79 327	96.1	95.0	18 970	94.5	117 367	93.1	94.4
Any influenza shot	20 308	52.5	46 497	56.3	53.1	10 657	53.1	66 792	53.0	53.0
Any lipid panel	32 584	84.2	71 134	86.2	84.6	16 795	83.7	98 445	78.1	83.7

(*Continues*)

TABLE 1 (Continued)

Variable	PIO[a](N = 38 700) N	%	DPP(N = 82 552) N	%	SMRW DPP[b] %	PIO[a](N = 20 075) N	%	SU(N = 126 104) N	%	SMRW SU[b] %
Any PSA test (men)	9493	58.3	18 042	56.9	58.4	4946	59.2	26 542	51.6	59.2
Any colonoscopy	3787	9.8	8491	10.3	9.8	2026	10.1	12 453	9.9	10.1
Any mammogram (women)	7583	33.8	17 525	34.5	34.3	4008	34.2	23 445	31.4	34.0
Any Pap smear (women)	3367	8.7	7403	9.0	8.7	1776	8.8	10 324	8.2	8.9
Any blood test	2017	9.0	4417	8.7	9.1	1146	9.8	5565	7.5	9.8
Smoking[e]	3334	8.6	10 533	12.8	8.5	1834	9.1	16 977	13.5	9.2
Other comorbidities during baseline[d]										
Congestive heart failure	6648	17.2	20 971	25.4	17.1	3479	17.3	32 491	25.8	17.3
Chronic kidney disease	5051	13.1	13 402	16.2	13.0	2600	13.0	19 373	15.4	13.0
Connective tissue disease	11 778	30.4	29 046	35.2	30.4	6454	32.1	40 520	32.1	32.2
COPD	6246	16.1	16 169	19.6	16.0	3499	17.4	26 752	21.2	17.4
Depression	5802	15.0	15 189	18.4	14.8	3234	16.1	23 535	18.7	16.1
Gastrointestinal disorders	308	0.8	808	1.0	0.8	196	1.0	1243	1.0	1.0
Infections	16 802	43.4	40 235	48.7	43.3	8989	44.8	58 534	46.4	44.8
Myocardial infarction	319	0.8	1026	1.2	0.8	142	0.7	1630	1.3	0.7
Stroke	4429	11.4	10 804	13.1	11.2	2367	11.8	17 576	13.9	11.8
History of cancer[f]	7489	19.4	19 836	24.0	19.4	4046	20.2	29 856	23.7	20.1
Antidiabetic use during baseline[d]										
DPP						2219	11.1	12 343	9.8	8.7
GLP-1	625	1.6	1202	1.5	2.0	330	1.6	1279	1.0	1.7
Insulin	6474	16.7	15 526	18.8	16.7	4258	21.2	18 544	14.7	21.2
Short-acting insulin	4186	10.8	9537	11.6	10.7	2847	14.2	12 198	9.7	14.2
Long-acting insulin	3901	10.1	10 041	12.2	10.1	2575	12.8	10 915	8.7	12.8
Meglitinides	909	2.3	2557	3.1	2.5	672	3.3	3001	2.4	3.4
Metformin	18 532	47.9	42 485	51.5	48.0	8784	43.8	55 033	43.6	43.8
Sulfonylureas	18 959	49.0	38 750	46.9	49.7					
Other antidiabetic[g]	308	0.80	737	0.89		124	0.62	510	0.40	
Medications during baseline[d]										
ACE inhibitors	14 332	37.0	29 477	35.7	36.9	6476	32.3	42 145	33.4	32.2
Anti-cholesterol drugs	649	1.7	1335	1.6	1.7	352	1.8	2436	1.9	1.7
ARBs	5573	14.4	14 254	17.3	14.5	2979	14.8	16 520	13.1	14.9
Beta-2 antagonists	3095	8.0	7849	9.5	7.9	1704	8.5	12 404	9.8	8.4
Bile acid sequestrants	419	1.1	1311	1.6	1.1	274	1.4	1565	1.2	1.4
Beta-blockers	15 08	40.6	39 780	48.2	40.8	7810	38.9	56 550	44.8	38.8
CAIs	1308	3.4	3060	3.7	3.5	734	3.7	3396	2.7	3.7

(*Continues*)

TABLE 1 (Continued)

Variable	PIO[a](N = 38 700) N	%	DPP(N = 82 552) N	%	SMRW DPP[b] %	PIO[a](N = 20 075) N	%	SU(N = 126 104) N	%	SMRW SU[b] %
Calcium channel blockers	10 863	28.1	25 282	30.6	28.1	5277	26.3	35 605	28.2	26.3
Estrogen	517	1.3	1071	1.3	1.4	296	1.5	1554	1.2	1.5
Fibrates	3225	8.3	6803	8.2	8.6	1556	7.8	8286	6.6	7.8
Glycosides	2018	5.2	5446	6.6	5.2	979	4.9	8787	7.0	4.9
Loop diuretics	7615	19.7	22 028	26.7	19.8	3689	18.4	32 470	25.7	18.4
Niacin	692	1.8	1320	1.6	1.8	399	2.0	1441	1.1	2.0
Non-loop diuretics	12 621	32.6	31 537	38.2	32.8	6054	30.2	47 217	37.4	30.2
Statins	20 500	53.0	41 348	50.1	53.3	10 127	50.4	54 091	42.9	50.4

Abbreviations: ACE, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blockers; CAIs, Carbonic anhydrase inhibitors; COPD, Chronic obstructive pulmonary disease; DPP, dipeptidyl-peptidase-4; GLP-1, glucagon-like peptide-1 receptor agonists; IQR, interquartile range; PIO, pioglitazone; PSA, Prostate-specific antigen; SMRW, Standardized morbidity ratio weighted; SNF, Skilled nursing facility; SU, sulfonylureas.

[a] Number of people initiating PIO differs for each comparison because of exclusions of prior use of drugs included in comparison only.

[b] Distribution of pseudo-population of people initiating SU or DPP treatment, SMR-weighted to the distribution of covariates of those initiating PIO treatment, using the propensity score to balance covariates (and therefore control for confounding). N's not reported.

[c] "Other race" combines the following races as defined by Medicare: Other, Asian, Hispanic or Native American.

[d] The baseline period was the 12 months prior to drug initiation for comorbidities and healthcare utilization, and 6 months prior to drug initiation for medication history.

[e] Smoking was defined using a previously validated algorithm that was a composite of tobacco use diagnosis codes or consultation CPT codes or prescription filled for smoking cessation. Although perfect specificity and PPV, this measure has poor sensitivity (27.9% [95% CI: 16.6%-39.1%] [31]

[f] History of cancer was evaluated during all available data prior to cohort entry.

[g] Other antidiabetic medications included alpha-glucosidase inhibitors, amylin analogs, and sodium-glucose co-transporter 2 (SGLT2) inhibitors. These drugs were not included in the propensity score model as <1% combined in this study population.

analyses was >1 year longer for pioglitazone than for DPP-4s or sulfonylureas because more patients initiated with pioglitazone in the earlier years and with DPP-4s in later years.

Compared to DPP-4s initiators in the AT and IT analyses, pioglitazone initiators had an increased incidence of bladder cancer overall (307.8 vs 204.4 per 100 000 person-years; aHR,1.57 [1.23-2.00] and 244.4 vs 195.7; aHR,1.22 [1.02-1.47], respectively). The increased risk emerged within the first 2 years of treatment (aHR, 1.63 [1.22-2.17] and 1.38 [1.08-1.77]) and remained after 2 years (aHR, 1.45 [0.93-2.26] and 1.08 [0.82-1.41]). If treatment was discontinued within the first 2 years, the risk 2 years post-initiation was attenuated (205.3 vs 200.7; aHR, 0.89 [0.61-1.28]).

Compared to sulfonylureas initiators, pioglitazone initiators had an increased incidence of bladder cancer overall in the AT analysis (306.3 vs 230.5; aHR, 1.32 [1.02-1.70]), but not in the IT analysis (223.5 vs 226.6; aHR, 1.02 [0.84-1.24]). However, this is probably an artifact of longer follow-up available for pioglitazone initiators, as there was some increased risk when follow-up was restricted to 2 years (241.5 vs 232.9; aHR, 1.05 [0.80-1.36]). If treatment was discontinued within the first 2 years, the risk after 2 years post-initiation was attenuated (179.7 vs 240.0; aHR, 0.82 [0.55-1.23]).

HRs that adjusted for age, sex and race were similar to crude HRs (Table S2, Appendix S1). Figure 1 displays Kaplan–Meier curves estimated using Cox proportional hazards models, PS-weighted (standardized to the pioglitazone population) for all variables in Table 1, unless otherwise specified. We identified increasing relative rates of bladder cancer over time associated with pioglitazone for all analyses, except the comparison to sulfonylureas in the IT analysis.

Table S1 and Appendix S1 report the AT results from Table 2 with varied induction and latency periods. When no induction or latency periods were used, aHRs were attenuated for pioglitazone compared to DPP-4s (1.14 [0.90-1.46]) or sulfonylureas (1.13 [0.87-1.46]). For both comparisons, similar results were found when induction was lengthened from 6 to 12 and 18 months. When latency was shortened from 6 to 3 months, aHRs were attenuated for pioglitazone vs DPP-4.

Figure 2, which illustrates the relative rates of detection procedures estimated using Cox proportional hazards models, PS-weighted (standardized to pioglitazone population) for all variables in Table 1, indicates no appreciable differences for 0 to 6 or >6 to 12 months post-initiation. In our external validation study using MCBS data (Table S20), pioglitazone initiators were less likely to have ever been smokers compared to DPP-4 initiators (48.6% vs 56.2%) and sulfonylurea initiators (49.1% vs 60.0%). Pioglitazone initiators were less likely to be obese (BMI ≥ 30 kg/m^2) than were DPP-4 initiators (38.1% vs 54.3%) and sulfonylurea initiators (42.1% vs 42.8%).

Multiple sensitivity analyses identified more pronounced HRs in the AT analyses for pioglitazone compared to DPP-4, and attenuated HRs compared to sulfonylureas. These included use of a more stringent outcome definition (Table S4, Appendix S1) and the sensitive cohorts that excluded patients with the following: prevalent cancer, CHF, treatment contrary to PS in the 1% and 2% tails, and no concurrent metformin use (Table S6, S9, S13, and S15, Appendix S1 and Table 3). Otherwise, sensitivity analyses yielded similar HRs (Tables S3-S19, Appendix S1).

4 | DISCUSSION

In this incident-user, active-comparator study of a national sample of older US adults, we identified a risk of bladder cancer associated with pioglitazone that increased with treatment duration compared to DPP-4s and sulfonylureas, clinical alternatives for the management of type-2 diabetes, which was consistent across a wide range of sensitivity analyses.

Weighted Kaplan–Meier curves revealed an increasing rate of bladder cancer over time, which aligns with results reported for follow-up <1.5, 1.5 to 4 and >4 years by Lewis et al. (aHR, 0.88 [0.68-1.16], 1.03 [0.80-1.33], and 1.16 [0.87, 1.54], respectively),[4] and with results reported for follow-up ≤1, 1 to 2 and >2 years by Azoulay et al. (RR, 0.56 [0.07-4.42), 3.03 [0.63-14.52), and 1.99 [1.14-3.45], respectively),[18] by Tuccori et al. (aHR, 1.33 [0.73-2.40], 1.66 [0.97-2.84], and 1.78 [1.21-2.64], respectively)[16] and by Mackenzie et al. who evaluated both incident-user (aHR, 1.02 [0.81-1.28], 0.95 [0.62-1.44], and 1.24 [0.83-1.84]) and prevalent-user cohorts (aHR, 1.03 [0.93-1.14], 1.14 [0.98-1.31], and 1.16 [1.00-1.35], respectively).[14] Our overall results contradict those that revealed no evidence of increased risk, for multiple reasons including differences in data source, comparator choice, whether or not prevalent users were included, and definition of the risk window.

Data sources and inclusion criteria can create potential sources of selection bias. Three large observational studies assessed the association between pioglitazone and bladder cancer using US data.[4,9,14] Lewis et al. who followed Kaiser Permanente Northern California diabetes registrants aged 40 years or older,[4] and Vallarino et al. who followed United Healthcare beneficiaries aged 45 years or older,[9] used cohorts of employer-based commercially insured individuals, which may under-represent patients at greatest risk of bladder cancer, given that the median age at diagnosis is 73 years.[25] Mackenzie et al. used a cohort of Medicare beneficiaries similar to ours, but found no evidence of increased risk of bladder cancer for users of pioglitazone when compared to all other diabetic therapies.[14]

Our study is the first to compare pioglitazone to DPP-4s, a class of drugs prescribed to patients similar to those using pioglitazone, as demonstrated by the balance of measured covariates prior to adjustment and consistency across crude and adjusted HRs for pioglitazone vs DPP-4s. Sulfonylureas were chosen as an additional comparator, being the most common therapy after metformin during the study period.[33] A composite comparison of DPP-4s or sulfonylureas was considered but not included because combining therapies would mix effects. Comparator choice can strongly influence results, because treatment choices are routinely based on the underlying disease and its severity; confounding by severity threatens study validity when there are major differences in disease severity between those receiving the study drug and the comparator.[20,21] Vallarino et al. found a reduction in risk of bladder cancer with pioglitazone when compared to insulin,[9] which may be a poor comparator choice as insulin differed from pioglitazone during much of the study period in three ways: route of administration (injection vs oral); cost (generally less expensive); and indication (typically indicated for patients with more severe diabetes). Other studies included all non-pioglitazone antidiabetic users as the comparator,[7,10,13–16,18,33,34] combining therapies for patients with varying degrees of diabetes severity into 1 group,

TABLE 2 Bladder cancer incidence among initiators of pioglitazone, dipeptidyl-peptidase-4 or sulfonylureas

Comparison	Drug	Follow-up (Years), Median (IQR)[a]	N[b]	Events	Person-time (Years)	Rate[c]	UnadjustedHR (95% CI)[d]	Fully adjustedHR (95% CI)[e]
As-treated analyses								
Overall								
PIO vs DPP	PIO	1.15 (0.67-2.16)	29 651	147	47 766	307.8	1.50 (1.21-1.86)	1.57 (1.23-2.00)
	DPP	1.11 (0.59-2.12)	61 438	193	94 426	204.4	1 (reference)	1 (reference)
PIO vs SU	PIO	1.11 (0.65-2.09)	15 198	73	23 830	306.3	1.32 (1.02-1.69)	1.32 (1.02-1.70)
	SU	1.24 (0.62-2.45)	97 056	387	167 879	230.5	1 (reference)	1 (reference)
Duration of treatment restricted to 2 years								
PIO vs DPP	PIO	1.15 (0.67-1.97)	29 651	108	36 010	299.9	1.49 (1.16-1.92)	1.63 (1.22-2.17)
	DPP	1.11 (0.59-1.97)	61 438	144	71 869	200.4	1 (reference)	1 (reference)
PIO vs SU	PIO	1.11 (0.65-1.97)	15 198	57	18 125	314.5	1.30 (0.98-1.73)	1.32 (0.98-1.78)
	SU	1.24 (0.62-1.97)	97 056	287	119 458	240.3	1 (reference)	1 (reference)
Duration of treatment after 2 years								
PIO vs DPP	PIO	1.14 (0.47-2.08)	8367	39	11 756	331.7	1.53 (1.00-2.32)	1.45 (0.93-2.26)
	DPP	1.01 (0.41-1.97)	16 894	49	22 557	217.2	1 (reference)	1 (reference)
PIO vs SU	PIO	1.11 (0.46-2.07)	4110	16	5706	280.4	1.37 (0.81-2.32)	1.29 (0.76-2.18)
	SU	1.23 (0.51-2.29)	31 940	100	48 422	206.5	1 (reference)	1 (reference)
Initial treatment analyses								
Overall								
PIO vs DPP	PIO	3.35 (1.52-4.86)	35 512	282	115 379	244.4	1.26 (1.07-1.49)	1.22 (1.02-1.47)
	DPP	1.86 (0.82-3.28)	70 628	308	157 386	195.7	1 (reference)	1 (reference)
PIO vs SU	PIO	3.23 (1.39-4.75)	18 224	128	57 282	223.5	0.99 (0.82-1.20)	1.02 (0.84-1.24)
	SU	2.05 (0.86-3.73)	108 593	594	262 177	226.6	1 (reference)	1 (reference)
Time since treatment initiation restricted to 2 years								
PIO vs DPP	PIO	1.97 (1.52-1.97)	35 512	152	58 351	260.5	1.35 (1.09-1.66)	1.38 (1.08-1.77)
	DPP	1.86 (0.82-1.97)	70 628	194	99 661	194.7	1 (reference)	1 (reference)
PIO vs SU	PIO	1.97 (1.39-1.97)	18 224	71	29 399	241.5	1.04 (0.81-1.34)	1.05 (0.80-1.36)
	SU	1.97 (0.86-1.97)	108 593	364	156 316	232.9	1 (reference)	1 (reference)
Time since treatment initiation after 2 years								
PIO vs DPP	PIO	2.28 (1.28-3.36)	24 488	130	57 028	228.0	1.16 (0.90-1.49)	1.08 (0.82–1.41)
	DPP	1.38 (0.61-2.64)	33 748	114	57 725	197.5	1 (reference)	1 (reference)
PIO vs SU	PIO	2.22 (1.25-3.33)	12 187	57	27 883	204.4	0.93 (0.70-1.24)	0.99 (0.73-1.32)
	SU	1.69 (0.76-2.92)	55 848	230	105 861	217.3	1 (reference)	1 (reference)
Initial treatment analyses - restricted to patients with ≤ 2-year duration of treatment								
Time since treatment initiation after 2 years								
PIO vs DPP	PIO	2.15 (1.22-3.24)	16 121	74	36 042	205.3	1.02 (0.72-1.44)	0.89 (0.61-1.28)
	DPP	1.35 (0.57-2.62)	16 854	57	28 404	200.7	1 (reference)	1 (reference)
PIO vs SU	PIO	2.10 (1.20-3.21)	8077	32	17 807	179.7	0.74 (0.50-1.10)	0.82 (0.55-1.23)
	SU	1.60 (0.70-2.83)	23 908	105	43 745	240.0	1 (reference)	1 (reference)

Abbrevaitions: CI, Confidence Interval; DPP, dipeptidyl-peptidase-4; HR, hazard ratio; IQR, interquartile range; PIO, pioglitazone; SU, sulfonylureas.

[a] Follow-up began on the cohort entry date (second dispensing) and was censored at first occurrence of outcome, death, end of study (December 2014) or end of enrollment. As-treated analyses were additionally censored at treatment discontinuation (no subsequent fill of initiated drug class within days-supply plus a 90-day grace period). A 180-day induction period was imposed, excluding time from the beginning of follow-up. As-treated analyses additionally added a 180-day latency period to the end of follow-up, when possible, prior to death or end of patient data.

[b] Number contributing with at least 180 days of follow-up. Those who initiated PIO differs for each comparison because of exclusions of prior use of drugs included in comparison only.

[c] Incidence rate reported per 100 000 person-years.

[d] Cox proportional hazards models.

[e] Cox proportional hazards models adjusted for all variables in Table 1, except for those excluded within each comparison by incident user design, using propensity-score weighting (standardized to PIO population).

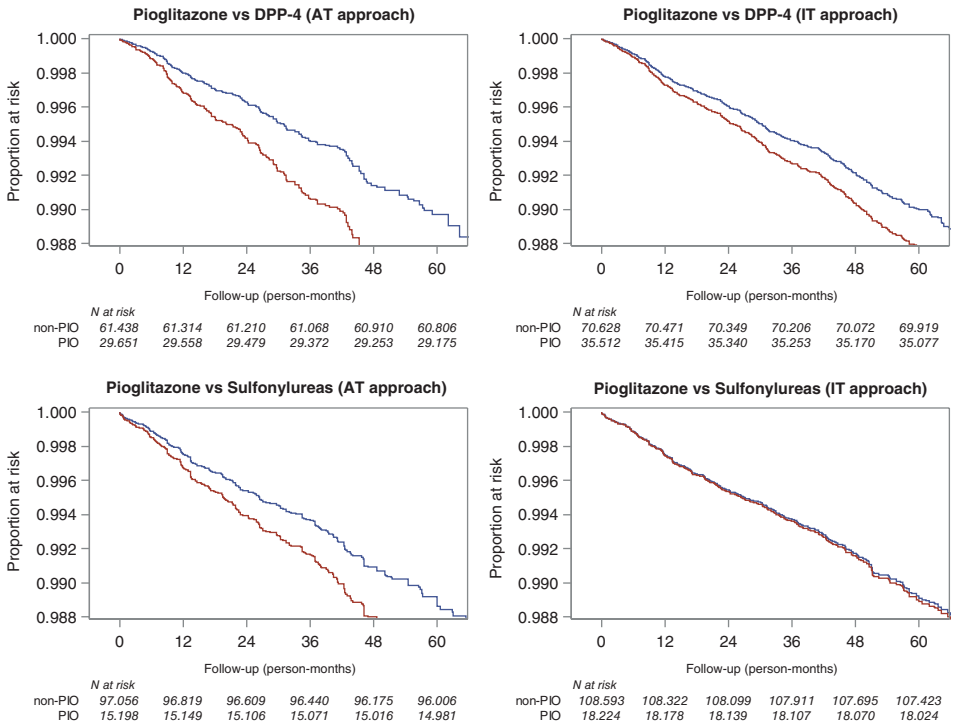

FIGURE 1 Weighted Kaplan–Meier curves identifying participants remaining without bladder cancer throughout follow-up among initiators of pioglitazone (dotted gray line) or active comparator (solid black line; dipeptidyl-peptidase-4 or sulfonylureas) with at least 180 days of follow-up

making it difficult to determine individual treatment effects and increasing the potential for biased estimates.

An active comparator is recommended for comparative effectiveness research, to present the least biased estimates.[20,21] Including untreated patients with diabetes in the comparator[4,13] can threaten validity further as a result of confounding by indication, as these patients may be able to manage their diabetes without medical therapy (eg, diet and exercise). Using claims, we were unable to fully control for 2 known risk factors for bladder cancer, smoking and workplace exposures (ie, industrial chemicals).[25] A smoking algorithm with excellent specificity but poor sensitivity (27.9%)[31] was added, to identify smoking-related claims. Diagnosis of COPD was also included in the PS model as a smoking status proxy. In our external validation study, pioglitazone initiators were less likely to be smokers and to be obese than were comparator drug initiators. Assuming transportability of MCBS to our sample, the increased risk of bladder cancer observed cannot be explained by residual confounding by smoking or BMI, and may actually be an underestimation of the true risk.

Our study has other limitations that should be considered when interpreting results. Bladder cancer was defined using administrative claims without pathological confirmation; thus, misclassification is possible, but unlikely to be differential with respect to treatment choice. We used a previously validated algorithm for identifying solid tumours in administrative claims[24] and varied the definition in sensitivity analyses to confirm similar results. Timing of outcome ascertainment is especially important for cancer outcomes, given the unlikelihood that short-term treatment will have an immediate causal impact. For example, subsequent review of the 11 bladder neoplasms (8 pioglitazone and 3 placebo) reported within the first year of the PROactive study[3] allowed us to conclude that the events could not have been caused by short-term exposure.[12] As the actual risk period relevant for drug-associated cancers is poorly understood, evaluating multiple risk windows, as we did,

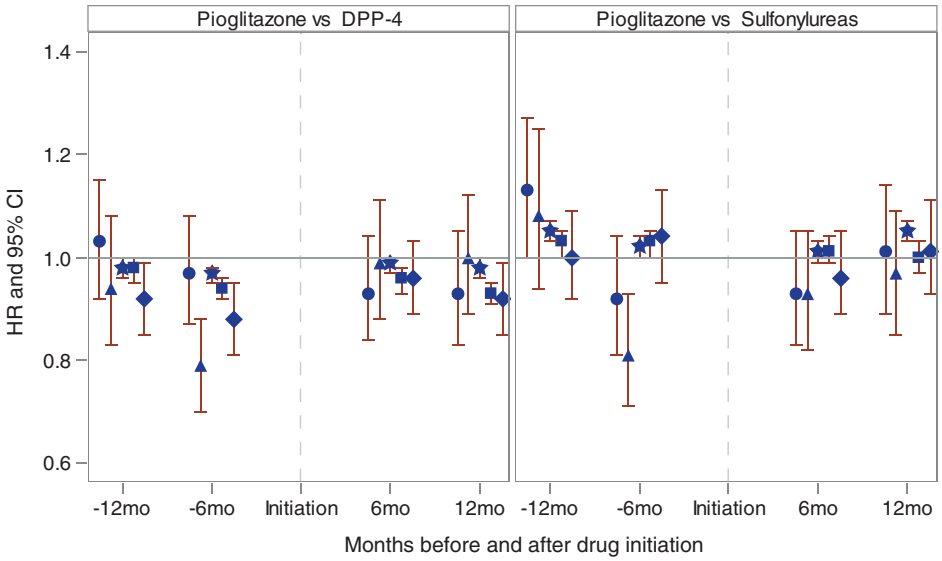

FIGURE 2 Relative rates of bladder cancer-related diagnostic procedures 6 and 12 months before and after initiation of pioglitazone, dipeptidyl-peptidase-4 and sulfonylureas where circle = cystoscopy, triangle = cytology, square = non-dipstick urinalysis, star = dipstick urinalysis, diamond = urine function test

TABLE 3 Exclusion of patients without history of metformin use: incidence of bladder cancer among initiators of pioglitazone, dipeptidyl-peptidase-4 and sulfonylureas

Comparison	Drug	Follow-up (years), Median (IQR)[a]	N[b]	Events	Person-time (years)	Rate[c]	Unadjusted HR (95% CI)[d]	Fully Adjusted HR (95% CI)[e]
As-treated analyses								
Overall								
PIO vs DPP	PIO	1.17 (0.67-2.21)	14 476	75	23 713	316.3	1.75 (1.29-2.38)	1.82 (1.28-2.59)
	DPP	1.14 (0.60-2.17)	32 088	91	50 400	180.6	1 (reference)	1 (reference)
PIO vs SU	PIO	1.17 (0.67-2.17)	6819	27	11 059	244.1	1.18 (0.78-1.77)	1.21 (0.79-1.85)
	SU	1.31 (0.65-2.58)	43 281	161	77 736	207.1	1 (reference)	1 (reference)
Duration of treatment restricted to 2 years								
PIO vs DPP	PIO	1.17 (0.67-1.97)	14 476	53	17 768	298.3	1.69 (1.18-2.43)	1.80 (1.17-2.76)
	DPP	1.14 (0.60-1.97)	32 088	67	38 016	176.2	1 (reference)	1 (reference)
PIO vs SU	PIO	1.17 (0.67-1.97)	6819	18	8315	216.5	1.02 (0.62-1.68)	1.03 (0.62-1.73)
	SU	1.31 (0.65-1.97)	43 281	115	54 678	210.3	1 (reference)	1 (reference)
Duration of treatment after 2 years								
PIO vs DPP	PIO	1.13 (0.47-2.09)	4214	22	5945	370.0	1.91 (1.07-3.41)	1.86 (1.02-3.41)
	DPP	1.03 (0.43-2.00)	9129	24	12 384	193.8	1 (reference)	1 (reference)
PIO vs SU	PIO	1.13 (0.47-2.12)	1942	<11	NR	328.0	1.65 (0.81-3.38)	1.65 (0.81-3.37)
	SU	1.24 (0.51-2.31)	15 159	46	23 058	199.5	1 (reference)	1 (reference)
Initial-treatment analyses								
Overall								
PIO vs DPP	PIO	3.41 (1.57-4.86)	17 081	133	56 079	237.2	1.40 (1.10-1.79)	1.31 (1.00-1.72)
	DPP	1.90 (0.84-3.31)	36 450	140	81 932	170.9	1 (reference)	1 (reference)
PIO vs SU	PIO	3.32 (1.46-4.80)	8022	51	25 684	198.6	1.07 (0.79-1.45)	1.11 (0.81-1.52)
	SU	2.12 (0.91-3.81)	47 590	219	117 202	186.9	1 (reference)	1 (reference)
Time since treatment initiation restricted to 2 years								
PIO vs DPP	PIO	1.97 (1.57-1.97)	17 081	71	28 215	251.6	1.43 (1.05-1.96)	1.38 (0.96-1.99)
	DPP	1.90 (0.84-1.97)	36 450	91	51 710	176.0	1 (reference)	1 (reference)
PIO vs SU	PIO	1.97 (1.46-1.97)	8022	23	13 063	176.1	0.87 (0.56-1.36)	0.88 (0.56-1.38)
	SU	1.97 (0.91-1.97)	47 590	141	69 406	203.2	1 (reference)	1 (reference)
Time since treatment initiation after 2 years								
PIO vs DPP	PIO	2.27 (1.29-3.32)	11 993	62	27 865	222.5	1.37 (0.93-2.00)	1.24 (0.84-1.84)
	DPP	1.39 (0.62-2.65)	17 644	49	30 222	162.1	1 (reference)	1 (reference)
PIO vs SU	PIO	2.21 (1.27-3.29)	5506	28	12 621	221.9	1.34 (0.87-2.06)	1.43 (0.92-2.23)
	SU	1.71 (0.77-2.93)	25 124	78	47 796	163.2	1 (reference)	1 (reference)

Abbreviations: CI, confidence interval; DPP, dipeptidyl-peptidase-4; HR, hazard ratio; IQR, interquartile range; NR, not reportable given number of events <11; PIO, pioglitazone; SU, sulfonylureas.

[a] Follow-up began on the cohort entry date (second dispensing) and was censored at first occurrence of outcome, death, end of study (December 2014) or end of enrollment. As-treated analyses were additionally censored at treatment discontinuation (no subsequent fill of initiated drug class within days-supply plus a 90-day grace period). A 180-day induction period was imposed, excluding time from the beginning of follow-up. As-treated analyses additionally added a 180-day latency period to the end of follow-up, when possible, prior to death or end of patient data.

[b] Number contributing with at least 180 days of follow-up. The number initiating PIO differs for each comparison because of exclusions of prior use of drugs included in comparison only.

[c] Incidence rate reported per 100 000 Person-years.

[d] Cox proportional hazards models.

[e] Cox proportional hazards models adjusted for all variables in Table 1, except for metformin and those excluded within each comparison by incident user design, using propensity-score weighting (standardized to PIO population).

minimizes the potential for protopathic bias or the identification of spurious events following misclassification of the risk period.[35,36] Furthermore, using both IT and AT approaches allowed us to present conservative estimates via the IT approach, in addition to treatment-duration-specific estimates via the AT approach.

Detection bias was another potential concern for this study. Annual urinalysis is recommended for patients with diabetes, given the increased risk of kidney disease.[37,38] Edema, a common side-effect of pioglitazone,[39] may lead to additional urological screening and diagnostic work-up, because it can also be an early sign of kidney disease.[40] Our additional analyses did not reveal evidence of an increased rate of these procedures in pioglitazone initiators compared to DPP-4s or sulfonylureas initiators, which eliminated detection bias as an explanation for our findings.

In summary, we identified an increased risk of bladder cancer associated with pioglitazone treatment, as suggested by some,[15–18]

but disputed by others.[4,7–14] The risk emerged within the first 2 years of treatment and increased over time. Findings from our secondary and sensitivity analyses suggest that these results are unlikely to be explained by differential detection rates, cohort selection, outcome definitions or censoring approaches. It is important to note that relative differences reflected when reporting hazard ratios may distort clinical interpretation, as the crude absolute risk differences were incredibly small, requiring over 1000 person-years of treatment to observe one excess bladder cancer event for pioglitazone compared to DPP-4s or sulfonylureas. Therefore, when considering which diabetic treatment to prescribe, pioglitazone's tolerability and effectiveness in maintaining blood-glucose control relative to clinical alternatives[41] should be weighed against a small absolute increase in risk of bladder cancer. Although rare, bladder cancer is the fifth most common cancer, representing 4.6% of all new cancer cases in the USA.[25] With the continued development and marketing of new antidiabetic medications, evaluation of their safety, using study design and analytic methods that minimize all threats to validity, is increasingly important.

Conflict of interest

E. M. G. is a doctoral student at the University of North Carolina (UNC) at Chapel Hill. She receives a Graduate Research Assistant stipend from the CER Strategic Initiative of UNC's Clinical and Translational Science Award (UL1TR001111). She is also a consulting scientist for Aetion, Inc., a software company that has industry clients, but receives no direct financial benefit from industry clients. J. B. B. is supported by the NIH (UL1TR001111 and R01HL110380). He is an investigator and/or consultant without any direct financial benefit to him under contracts between his employer and the following companies: Amylin Pharmaceuticals, Inc., Andromeda, Astellas, AstraZeneca, Boehringer Ingelheim GmbH & Co. KG, Bristol-Myers Squibb Company, Dance Biopharm, Elcelyx Therapeutics, Inc., Eli Lilly and Company, GI Dynamics, GlaxoSmithKline, Halozyme Therapeutics, F. Hoffmann-La Roche, Ltd., Intarcia Therapeutics, Johnson & Johnson, Lexicon, LipoScience, Macrogenics, Medtronic, Merck, Metavention, Novo Nordisk, Orexigen Therapeutics, Inc., Osiris Therapeutics, Inc., Pfizer, Inc., PhaseBio Pharmaceuticals Inc., Quest Diagnostics, Sanofi, Scion neuroStim, Takeda, ToleRx, vTv Pharmaceuticals. He has stock options and has received payments from PhaseBio. J. L. L. is funded by the UNC Oncology Clinical Translational Research Training Program (5K12CA120780) and receives salary support and research support from the PhRMA Foundation for a Research Starter Award to the Department of Epidemiology, UNC. V.P. receives salary support from investigator-initiated grants from Merck and Amgen and from the Comparative Effectiveness Research (CER) Strategic Initiative, NC TraCS Institute, UNC Clinical and Translational Science Award (UL1TR001111). T. S. receives investigator-initiated research funding and support as Principal Investigator (R01/R56 AG023178) from the National Institute on Aging (NIA), and as Co-Investigator (R01 CA174453; R01 HL118255, R21-HD080214), National Institutes of Health (NIH). He also receives salary support as Director of the Comparative Effectiveness Research (CER) Strategic Initiative, NC TraCS Institute, UNC Clinical and Translational Science Award (UL1TR001111) and as Director of the Center for Pharmacoepidemiology (current members: GlaxoSmithKline, UCB BioSciences, Merck) and research support from pharmaceutical companies (Amgen, AstraZeneca) to the Department of Epidemiology, UNC. He does not accept personal compensation of any kind from any pharmaceutical company. He owns stock in Novartis, Roche, BASF, AstraZeneca and Novo Nordisk.

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Author contributions

E. M. G., J. B. B. and T.S. participated in study conception and design. E. M. G. drafted the manuscript and analysed the data with programming support from V. P. All authors participated in the analysis plan, interpretation of the data, and reviewed and provided comments on the manuscript. E. M. G. is the guarantor of this work. E. M. G. and V. P. had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Cohen SM. Effects of PPARgamma and combined agonists on the urinary tract of rats and other species. *Toxicol Sci*. 2005;87:322–327.
2. Dominick MA, White MR, Sanderson TP, et al. Urothelial carcinogenesis in the urinary bladder of male rats treated with muraglitazar, a PPAR alpha/gamma agonist: evidence for urolithiasis as the inciting event in the mode of action. *Toxicol Pathol*. 2006;34:903–920.
3. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial in macroVascular Events): a randomised controlled trial. *Lancet*. 2005;366:1279–1289.
4. Lewis JD, Habel LA, Quesenberry CP, et al. Pioglitazone use and risk of bladder cancer and other common cancers in persons with diabetes. *JAMA*. 2015;314:265–277.
5. Federal Drug Administration. Actos (pioglitazone): ongoing safety review – potential increased risk of bladder cancer. MedWatch Safety Alerts for Human Medical Products: 2011 Safety Alerts for Human Medical Products. 2011. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm259150.htm. Accessed December 1, 2016.
6. Federal Drug Administration. FDA Drug Safety Communication: Updated FDA review concludes that use of type 2 diabetes medicine pioglitazone may be linked to an increased risk of bladder cancer. 2016. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm519616.htm. Accessed January 10, 2017.
7. Tseng CH. Pioglitazone and bladder cancer: a population-based study of Taiwanese. *Diabetes Care*. 2012;35:278–280.
8. Fujimoto K, Hamamoto Y, Honjo S, et al. Possible link of pioglitazone with bladder cancer in Japanese patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2013;99:e21–e23.
9. Vallarino C, Perez A, Fusco G, et al. Comparing pioglitazone to insulin with respect to cancer, cardiovascular and bone fracture endpoints, using propensity score weights. *Clin Drug Investig*. 2013;33:621–631.
10. Wei L, MacDonald TM, Mackenzie IS. Pioglitazone and bladder cancer: a propensity score matched cohort study. *Br J Clin Pharmacol*. 2013;75:254–259.
11. Kuo HW, Tiao MM, Ho SC, Yang CY. Pioglitazone use and the risk of bladder cancer. *Kaohsiung J Med Sci*. 2014;30:94–97.
12. Erdmann E, Harding S, Lam H, Perez A. Ten-year observational follow-up of PROactive: a randomized cardiovascular outcomes trial

evaluating pioglitazone in type 2 diabetes. *Diabetes Obes Metab*. 2016;18:266–273.
13. Korhonen P, Heintjes EM, Williams R, et al. Pioglitazone use and risk of bladder cancer in patients with type 2 diabetes: retrospective cohort study using datasets from four European countries. *BMJ*. 2016;354:i3903.
14. Mackenzie TA, Zaha R, Smith J, Karagas MR, Morden NE. Diabetes pharmacotherapies and bladder cancer: a medicare epidemiologic study. *Diabetes Ther*. 2016;7:61–73.
15. Neumann A, Weill A, Ricordeau P, Fagot JP, Alla F, Allemand H. Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. *Diabetologia*. 2012;55:1953–1962.
16. Tuccori M, Filion KB, Yin H, OH Y, Platt RW, Azoulay L. Pioglitazone use and risk of bladder cancer: population based cohort study. *BMJ*. 2016;352:i1541.
17. Kernan WN, Viscoli CM, Furie KL, et al. Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med*. 2016;374:1321–1331.
18. Azoulay L, Yin H, Filion KB, et al. The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. *BMJ*. 2012;344:e3645.
19. Hampp C, Pippins J. Pioglitazone and bladder cancer: FDA's assessment. *Pharmacoepidemiol Drug Saf*. 2017;26:117–118.
20. Lund JL, Richardson DB, Sturmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep*. 2015;2:221–228.
21. Velentgas P, Dreyer NA, Nourjah P, Smith SR, Torchia MM. *Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide*. AHRQ Publication No. 12(13)-EHC099. Rockville, MD: Agency for Healthcare Research and Quality; 2013. Available at: https://www.effectivehealthcare.ahrq.gov/ehc/products/440/1166/User-Guide-to-Observational-CER-1-10-13.pdf. Accessed January 10, 2017.
22. Research Data Assistance Center (ResDAC). Strengths and limitations of CMS administrative data in Research. 2012. http://www.resdac.org/resconnect/articles/156. Accessed August 20, 2014.
23. Ishibashi N, Maebayashi T, Aizawa T, et al. Refractory Haematuria resulting from peritoneal dissemination of metastatic gastric cancer: radiation therapy for a nodule infiltrating the urinary bladder. *Urol J*. 2017;14:2982–2984.
24. Setoguchi S, Solomon DH, Glynn RJ, Cook EF, Levin R, Schneeweiss S. Agreement of diagnosis and its date for hematologic malignancies and solid tumors between medicare claims and cancer registry data. *Cancer Causes Control*. 2007;18:561–569.
25. American Cancer Society. Bladder cancer: detailed guide. Last Medical Review: 2/26/2014. 2014.
26. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70:41–55.
27. Sato T, Matsuyama Y. Marginal structural models as a tool for standardization. *Epidemiology*. 2003;14:680–686.
28. Kurth T, Walker AM, Glynn RJ, et al. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. *Am J Epidemiol*. 2006;163:262–270.
29. Sturmer T, Rothman KJ, Avorn J, Glynn RJ. Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution--a simulation study. *Am J Epidemiol*. 2010;172:843–854.
30. Gokhale M, Buse JB, Mack C, Stürmer T. Calendar time as an instrumental variable in assessing the risk of heart failure with antihyperglycemic drugs [abstract]. In: Abstracts of the 32nd International Conference on Pharmacoepidemiology & Therapeutic Risk Management, The Convention Centre Dublin, Dublin, Ireland August 25–28, 2016. Abstract nr 71. *Pharmacoepidemiol Drug Saf*. 2016;suppl 3:3–679.
31. Desai RJ, Solomon DH, Shadick N, Iannaccone C, Kim SC. Identification of smoking using Medicare data--a validation study of claims-based algorithms. *Pharmacoepidemiol Drug Saf*. 2016;25:472–475.
32. Centers for Medicare & Medicaid Services. Appendix A. Technical documentation for the medicare current beneficiary survey. 2003. https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/MCBS/Downloads/OLD/HHC2003appendixA.pdf. Accessed May 4, 2017.
33. Lipska KJ, Yao X, Herrin J, et al. Trends in drug utilization, glycemic control, and rates of severe hypoglycemia, 2006-2013. *Diabetes Care*. 2017;40:468–475.
34. Piccinni C, Motola D, Marchesini G, Poluzzi E. Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. *Diabetes Care*. 2011;34:1369–1371.
35. Rothman KJ. Induction and latent periods. *Am J Epidemiol*. 1981;114:253–259.
36. Chubak J, Boudreau DM, Wirtz HS, McKnight B, Weiss NS. Threats to validity of nonrandomized studies of postdiagnosis exposures on cancer recurrence and survival. *J Natl Cancer Inst*. 2013;105:1456–1462.
37. American Diabetes Association (ADA). Standards of medical care in diabetes--2013. *Diabetes Care*. 2013;36(suppl 1):S11–S66.
38. National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC). Proteinuria (NIH Publication No. 14–4732). 2014. Available at: https://www.niddk.nih.gov/health-information/kidney-disease/chronic-kidney-disease-ckd/tests-diagnosis/albuminuria-albumin-urine#tests. Accessed January 10, 2017.
39. Niemeyer NV, Janney LM. Thiazolidinedione-induced edema. *Pharmacotherapy*. 2002;22:924–929.
40. Lewis JD, Habel L, Quesenberry C, et al. Proteinuria testing among patients with diabetes mellitus is associated with bladder cancer diagnosis: potential for unmeasured confounding in studies of pioglitazone and bladder cancer. *Pharmacoepidemiol Drug Saf*. 2014;23:636–645.
41. Waugh J, Keating GM, Plosker GL, Easthope S, Robinson DM. Pioglitazone: a review of its use in type 2 diabetes mellitus. *Drugs*. 2006;66:85–109.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.