

Pioglitazone HCl (ACTOS)
KPNC 4th Interim Report, Cohort Study of Pioglitazone and Bladder Cancer
(Study No. 01-03-TL-OPI-524)
FDA Advice / Information request for sensitivity analysis and other analyses

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This report presents supplementary analysis to the 4th interim analysis of our ongoing study of the relative risk of bladder cancer with Actos (pioglitazone), as specified in the Request Advice/Information request made by the FDA dated 30 August 2011. The requested supplementary analyses presented in this report are:

1. A sensitivity analysis to assess change of cohort entry criteria to minimize left censoring of exposure.
2. Duration analysis for other antidiabetic medications.
3. To investigate effect modification of the pioglitazone association by age and sex.
4. To analyze the pioglitazone association by cancer stage.

Supplementary analyses on the potential confounding and/or detection bias related to the use of screening for proteinuria and use of urinalyses are incomplete at the time of this report and will be reported in the final report.

A sensitivity analysis to assess change of cohort entry criteria to minimize left censoring of exposure

The sensitivity analysis requested by the FDA entailed altering the inclusion and exclusion criteria. The original inclusion criteria were:

- all patients who are in the KPNC Diabetes Registry and who are age 40 or older as of January 1, 1997;
- all additional KPNC Diabetes Registry members who reach age 40 at any point before December 31, 2002;
- patients age 40 or older who enroll in KPNC between January 1, 1997 and December 31, 2002 and who are identified as having diabetes;
- all KPNC members age 40 or older who develop diabetes during this time period.

Follow-up for bladder cancer began for each person when they become eligible (ie, on January 1, 1997, or a subsequent date when they are first identified as having diabetes and being 40 years of age).

The exclusion criteria were: age < 40 years, a diagnosis of bladder cancer recorded in the KPNC cancer registry prior to initiation of observation or within 6 months of entry into KPNC, patients without prescription benefits at the time of entry into the cohort, and those with a gap of more than four months in prescription or membership benefits where the gap started within the first four months of entering the cohort.

The inclusion criteria for this new sensitivity analysis are:

- all patients who are in the KPNC Diabetes Registry and who are age 40 or older as of January 1, 1997;
- all additional KPNC Diabetes Registry members who reach age 40 at any point before December 31, 2009 and who have been enrolled in KPNC since January 1, 1997 without a gap in membership;

- all KPNC members age 40 or older who are newly diagnosed with diabetes between January 1, 1997 and December 31, 2009. The definition of newly diagnosed diabetes requires that the patient be a KPNC member for more than 2 years before being identified as having diabetes according to the registry criteria.

Follow-up and exclusion criteria for the sensitivity analysis are the same as for the original cohort.

Using these new inclusion criteria, we repeated the primary analyses of the 4th interim analysis, examining the relative risk of pioglitazone exposure using the primary definition of exposure, the cumulative dose and duration analyses, the tests for interaction with sex and smoking, and the analysis of stage of disease at diagnosis. The results are summarized in Tables 1 through 9.

The size of the cohort increased from 193,099 with 33,416 exposed to pioglitazone to 221,180 with 27,262 exposed to pioglitazone (Table 1). The reduction in the number exposed to pioglitazone despite the increase in the overall sample size is explained by the new requirement for continuous membership since 1997 (Figure 1 and Figure 2). In the original cohort, among the 33,416 patients treated with pioglitazone, there were 8,799 (26%) who entered the cohort after January 1, 1997 and had less than 2 years of follow-up in KPNC prior to cohort entry who were treated with pioglitazone (Table 2). By design, no patients met these criteria in the modified cohort. Patient characteristics were generally similar using the original and modified inclusion criteria (Table 1). There were fewer missing data at baseline in the modified cohort for race/ethnicity, renal function at baseline, hemoglobin A1c, duration of diabetes, and income. The prevalence of complications of diabetes among patients treated with pioglitazone was similar between the original and modified cohort; the prevalence of the complications among patients not treated with pioglitazone was lower in the modified cohort than in the original cohort.

The median time from cohort entry to the first exposure to pioglitazone was now 5.9 years. The median follow-up after the first exposure to pioglitazone was 4.4 years. The median total follow-up time for patients never exposed to pioglitazone was 5.2 years.

To further assess for the possibility of left censoring (i.e., missing pioglitazone exposure prior to the start of follow-up), we determined the number of patients who received a pioglitazone prescription within 4.5 months of cohort entry. A prescription soon after cohort entry suggests that a patient might also have been using pioglitazone prior to cohort entry. There were 2,392 (7%) and 360 (1%) patients in the original and the modified cohorts, respectively with a pioglitazone prescription soon after cohort entry. It is not known whether or not these patients used pioglitazone prior to cohort entry, although it is certainly possible.

The proportions of patients who received a prescription within 4.5 months of cohort entry were substantially higher for use of other oral hypoglycemic drugs and insulin (Table 2). 76% of pioglitazone-treated patients had a prescription for another oral antidiabetic drug and 12% for insulin soon after cohort entry. In the modified cohort, these proportions were still high (68% and 11% among pioglitazone-treated, respectively). Thus, it seems reasonable to assume that there was unmeasured use of these medications prior to cohort entry. This is addressed in an analysis of patients with newly diagnosed diabetes that is described later in this report and in Table 10.

In general, there were no substantive differences between the results of the original analyses and the analyses using the modified inclusion criteria. The fully adjusted hazard ratio (HR) for ever exposure to pioglitazone was 1.07 (95% CI 0.87 – 1.30) in the original analysis and 1.01 (95% CI 0.81 – 1.27) in the modified cohort (Table 5). Similarly, for the longest duration of therapy category, more than 4 years, the fully adjusted HR was 1.30 (95% CI 0.91 – 1.86) in the original analysis and 1.26 (95% CI 0.84 – 1.88) in the modified cohort. The fully adjusted models used the same covariates as in the 3rd interim and 4th interim reports. Time updating variables, such as diabetic complications, were not included in the models.

In the modified cohort, we were not able to include the category of papillary urethral neoplasm of low malignant potential (PUNLMP), because we only utilized the categorizations in the cancer registry (Table 9). PUNLMP was only identifiable from medical chart abstraction completed as part of the nested case-control study, data which were not employed in this cohort analysis. However, the proportion of bladder cancers among pioglitazone treated patients that were regional stage or distant were similar: 5% vs. 6% in the original and modified cohorts, respectively.

Duration analysis for other antidiabetic medications

The FDA also requested duration analyses for other diabetes medications. Because each of the other medications were utilized prior to the start of the study window, and given that each of the other medications is often used prior to TZDs, it likely there was substantial left censoring of use of other antidiabetic drugs in the full cohort. We therefore limited this analysis to patients who were diagnosed with diabetes after they registered with KPNC (incident sub-cohort), thereby allowing for complete records of all diabetes medications dispensed to the patients. The definition of newly diagnosed with diabetes required that the patient was a member of KPNC for a minimum of 2 years before the first diabetes diagnosis and this diagnosis occurred after January 1, 1997. Although initially proposed to use patients diagnosed with diabetes as early as January 1, 1994, when the pharmacy records were online at all KPNC pharmacies, we elected to limit this to those diagnosed after January 1, 1997 to be consistent with our primary analysis. We have completed these analyses for duration of therapy with pioglitazone, metformin, sulfonylureas, and insulin. Among the 59,070 patients who met the inclusion criteria, there were 8,710 patients treated with pioglitazone, 32,726 treated with metformin, 38,708 treated with sulfonylureas, and 9,861 treated with insulin. In analyses adjusted for age, sex, race, smoking, and calendar year of cohort entry, we observed no increase in the incidence of bladder cancer with ever exposure to pioglitazone [0.68 (0.42-1.10)] or any of the other medication groups (Table 10). Likewise, we did not observe an increase in the incidence of bladder cancer with more than 4 years duration of therapy with pioglitazone [0.66 (0.21-2.09)], metformin [0.94 (0.65-1.37)], or sulfonylureas [0.76 (0.55-1.05)] (Table 10). However, because of the small sample size, particularly in the group with greater than 4 years of therapy, the confidence intervals were very wide. For example, there were only 3 patients with pioglitazone treatment of more than 4 years duration who were diagnosed with bladder cancer and the resultant confidence intervals ranged from 0.21 to 2.09. In contrast to the oral hypoglycemic medications, the incidence of bladder cancer appeared to increase with longer duration of insulin therapy (HR 2.00, 95% CI 0.93 - 4.29) (Table 10).

To further address the potential impact of this finding on our previously observed association an increased risk of bladder cancer among patients with longer duration of therapy with pioglitazone, we conducted three additional analyses:

1. Adjusted for the variables in the initial analysis plus each of the other three diabetes therapies where the other therapy is treated as a time updating variable for never versus ever exposed.
2. Adjusted for model 1 variables plus each of the other three diabetes therapies where the other therapy is treated as a time updating variable using the duration categories of never exposed, less than 1.5 years, 1.5 to 4.0 years, and more than 4 years.
3. Adjusted for model 1 variables with follow-up censored at the time of initiation of insulin.

The results of the additional analysis were generally similar (Table 10). When we censored follow-up at the time of initiation of insulin, the hazard ratio for more than 4 years of pioglitazone was 0.95 (95% CI 0.30-2.99). Because of the wide confidence intervals, however, we urge caution against over interpreting all of the results presented in Table 10.

Effect modification of the pioglitazone association by age and sex

The FDA requested that we perform sex-stratified analysis within 10-year age categories (Table 11). It is noteworthy that there were several strata with small numbers, which prevented computation of a hazard ratio and confidence intervals. As such, the results should be viewed with caution. As requested by the FDA, we also conducted an additional analysis with a dichotomous age definition. These results are presented in Table 12. Although the confidence intervals are tighter in this analysis than in the analysis using 10-year age categories, caution is again necessary when interpreting these results.

Pioglitazone association by cancer stage

The FDA requested analyses that excluded in situ cancer from the outcome and analyses that excluded in situ and local stage cancer from the outcome. Using the original cohort, we completed the analysis that excluded in situ stage cancer from the outcome. This analysis also excluded those with an unknown stage from the outcome definition. Patients with in situ, PUNLMP, or unknown disease stage were censored at the time of their bladder cancer diagnosis. In the fully adjusted model, the hazard ratios for the longest duration and highest cumulative dose exposure were greater than that in the primary analysis, although none were statistically significant. The fully adjusted hazard ratio (95% CI) was 1.17 (0.88-1.55) for ever exposure to pioglitazone, 1.48 (0.85-2.55) for initiation of pioglitazone 6.5 years prior or longer, 1.60 (0.99-2.59) for more than 4 years of pioglitazone exposure, and 1.49 (0.95-2.33) for more than 35,000 mg of total dose (Table 13).

Because there were only 7 pioglitazone-exposed patients with regional or distant stage cancer, we did not complete the analysis limiting the outcome to only regional or distant stage bladder cancer.

Additional results requested by the FDA

Additional results requested by the FDA included the fully adjusted hazard ratios for all variables included in the fully adjusted primary analysis from the original cohort. These data are provided in Table 14. These data confirm expected positive associations with bladder cancer for increasing

age, male sex, Caucasian race, and smoking. No association was observed for diabetes duration and risk of bladder cancer or for exposure to any of the other categories of diabetes medications.

Additional analyses planned and promised in the Fourth Interim Analysis Report from 24 May 2012

As promised, we tested for an interaction by sex and smoking in the test for trend analysis. None of the tests for interaction were statistically significant at a threshold of $p < 0.1$ (see revised [Table 6](#)).

Results that are pending at the time of this report

We are actively exploring the issue of whether disproportionate use of testing for proteinuria may have confounded the results or led to a detection bias. We have designed a series of analyses to explore this issue and anticipate having these completed for inclusion in the final report.

Comments on the results of these supplemental analyses

In general, the sensitivity analysis using the alternative cohort inclusion and exclusion criteria resulted in very similar results as the primary analysis (HR [95% CI]: 1.07 [0.87, 1.30] vs. 1.01 [0.81, 1.27]). This suggests that the inclusion of new members to the KPNC plan after 1997 for whom there could be missing data on pioglitazone use prior to cohort entry did not appreciably bias the results. There was a slightly larger cohort but fewer pioglitazone exposed patients and particularly a reduction in the number of patients with long-term exposure. The result was slightly wider confidence intervals than in our primary analyses, reflecting lower statistical power. This likely resulted from the smaller number of pioglitazone-treated patients and fewer with long duration of exposure despite the larger overall sample size. We note that the patients in the sensitivity analysis are likely to have missing data on exposure to other diabetes medications prior to cohort entry.

The analysis limited to newly diagnosed patients (incident sub-cohort) did not observe an association or exposure-response relationship between pioglitazone use and risk of bladder cancer. For more than 4 years of pioglitazone use, the risk of bladder cancer was 0.66 [95% CI: 0.21, 2.09]. It is important to consider reasons why the results of this analysis differ from that of the full cohort. This new analysis included only newly diagnosed patients while the full cohort included incident and prevalent diabetes. The advantage of an incident cohort analysis is that it assures that there is complete data on use of all anti-diabetic medications and that all patients have comparable duration of diabetes. The major limitation is the reduced statistical power given the much smaller sample size. The difference in the results could reflect reduced precision due to decreased sample size in the incident sub-cohort, or alternatively inadequate adjustment for confounding by insulin or other medication exposures in the full cohort, or to different duration of diabetes in the full cohort and incident sub-cohort. If the latter were true, it would imply that either there is an interaction between pioglitazone exposure and diabetes duration or that duration of diabetes has been incompletely controlled for in the full cohort. Further analysis of the incident sub-cohort at the final 10-yr follow-up should have improved statistical power and may provide further insight into the differences between the full cohort and the incident sub-cohort.

The possible association of long duration of insulin use and bladder cancer in the duration analysis is worthy of consideration. Because pioglitazone is sometimes used as an insulin sparing

agent and at other times in combination with insulin, future studies directly comparing pioglitazone to insulin while adjusting for diabetes duration would be informative. Likewise, studies that excluded patients treated with insulin, as we have done in this subgroup analysis (Table 10, Model 4) could be informative.

Summary

In response to requests by the FDA, we have provided a number of additional data items for review. The hazard ratios for the covariates included in the primary analysis are consistent with the known epidemiology of bladder cancer. The age- and sex-stratified analyses are more difficult to interpret because of the small number of subjects per stratum. This is evident by the markedly increased width of the confidence intervals surrounding the point estimates.

The analysis excluding in situ cancers and papillary neoplasms of uncertain malignant potential resulted in slightly higher hazard ratios than the primary analysis, although these were not statistically significant. Likewise, the test for trend was not significant in these analyses.

Figure 1 Flow Diagram of the Original Cohort Entry Criteria

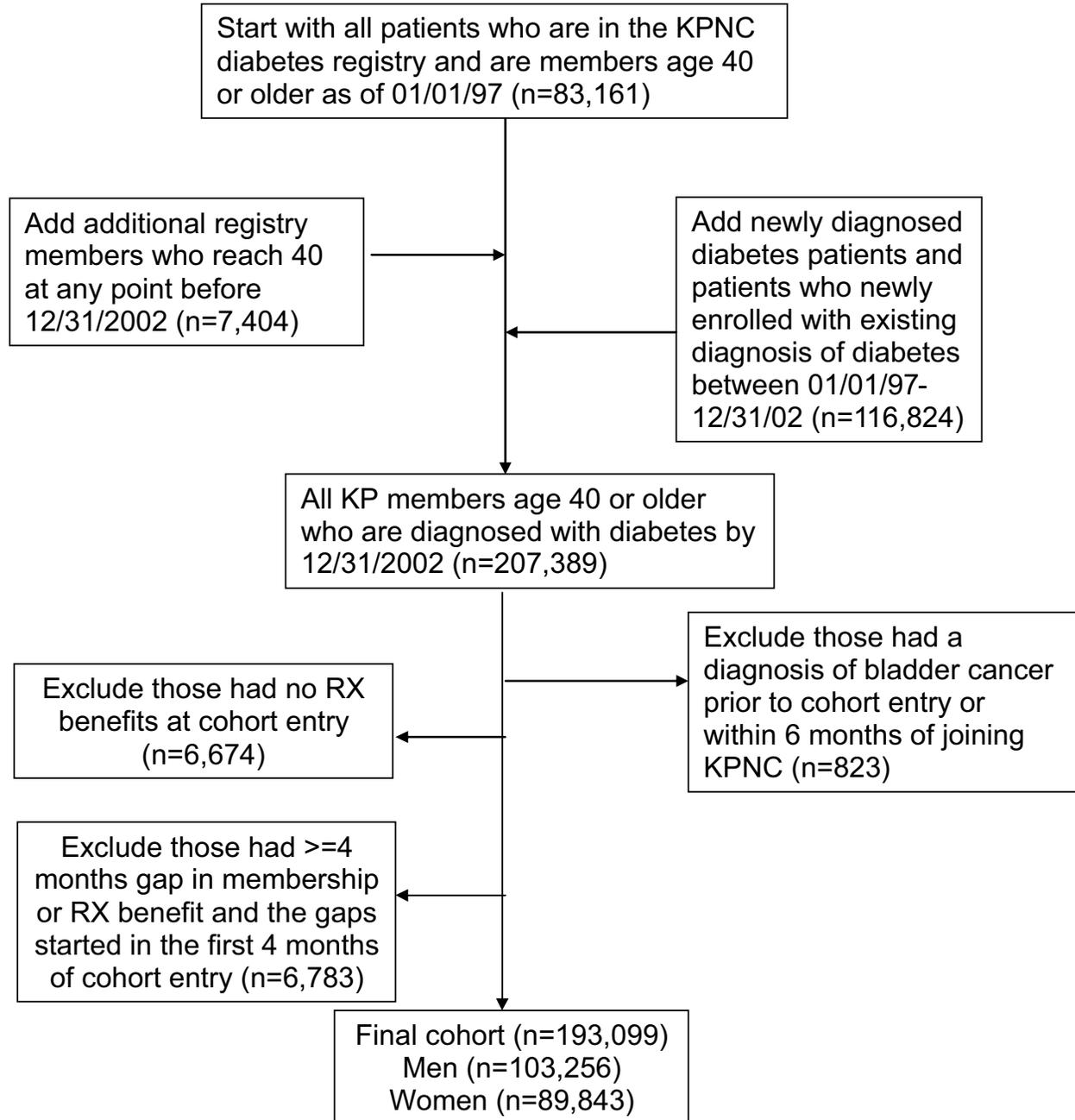


Figure 2 Flow Diagram of the Modified Cohort Entry Criteria

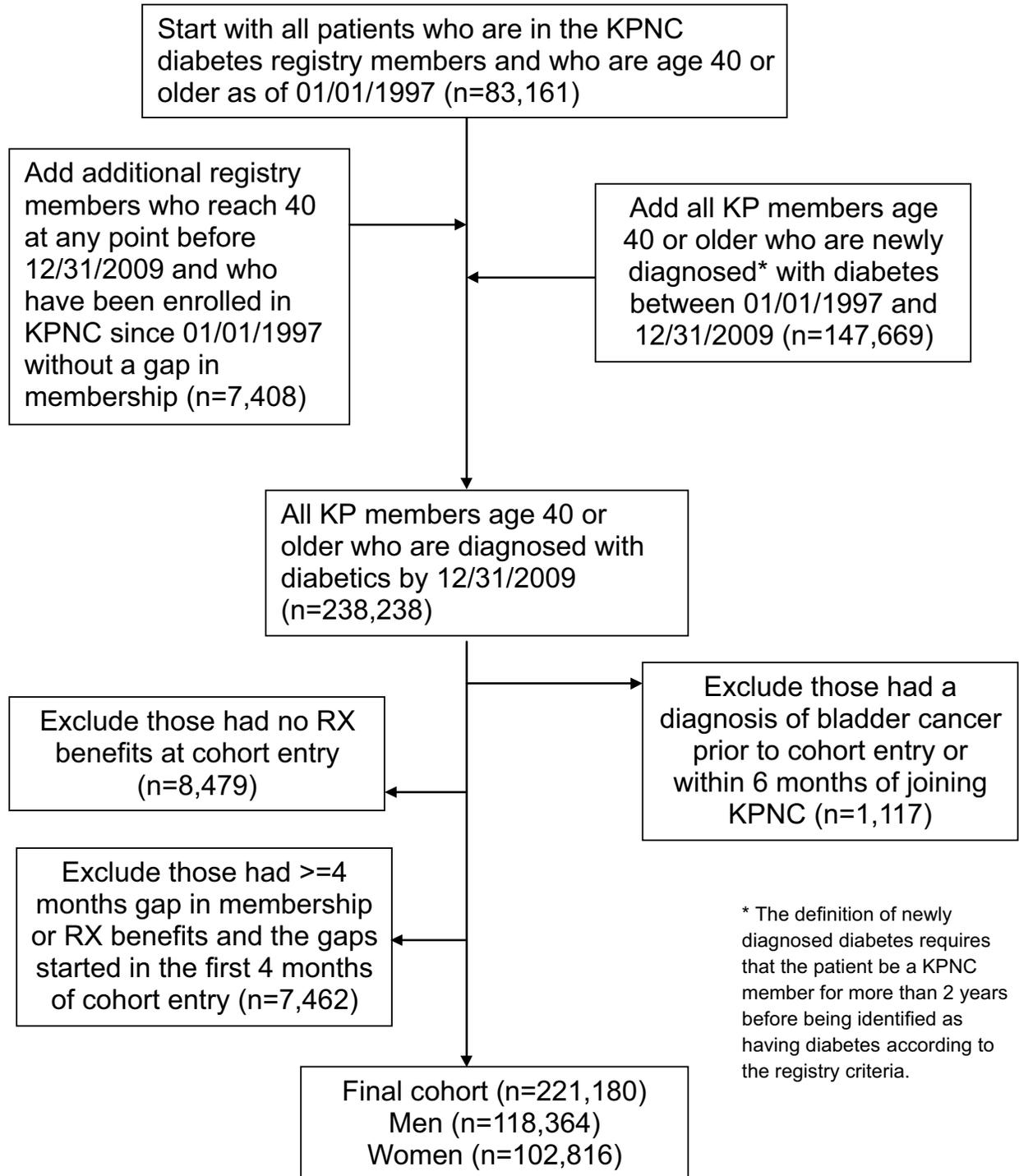


Table 1 Demographics of the Study Cohort According to Pioglitazone Treatment at any Time During Follow-up^s

	Original Cohort		Modified Cohort	
	Pioglitazone treated (n=33,416)	No pioglitazone treatment (n=159,683)	Pioglitazone treated (n=27,262)	No pioglitazone treatment (n=193,918)
Age at baseline				
40-49 years	9,729 (29.1%)	35,335 (22.1%)	8,074 (29.6%)	41,399 (21.3%)
50-59 years	11,066 (33.1%)	40,841 (25.6%)	9,397 (34.5%)	54,373 (28.0%)
60-69 years	8,573 (25.7%)	41,916 (26.2%)	6,809 (25.0%)	50,955 (26.3%)
70 years and older	4,048 (12.1%)	41,591 (26.0%)	2,982 (10.9%)	47,191 (24.3%)
Female sex	15,586 (46.6%)	74,257 (46.5%)	12,761 (46.8%)	90,045 (46.4%)
Race/Ethnicity				
White	17,203 (51.5%)	83,425 (52.2%)	14,264 (52.3%)	101,864 (52.5%)
Black	3,426 (10.3%)	17,270 (10.8%)	3,087 (11.3%)	20,611 (10.6%)
Asian	4,914 (14.7%)	20,423 (12.8%)	4,159 (15.3%)	27,444 (14.2%)
Hispanic	4,466 (13.4%)	17,012 (10.7%)	3,535 (13.0%)	23,984 (12.4%)
Other	1,951 (5.8%)	9,083 (5.7%)	1,614 (5.9%)	10,837 (5.6%)
Missing	1,456 (4.4%)	12,470 (7.8%)	603 (2.2%)	9,178 (4.7%)
Current smoker	6,851 (20.5%)	27,746 (17.4%)	5,512 (20.2%)	30,130 (15.5%)
Renal function at baseline				
Normal creatinine	25,844 (77.3%)	123,209 (77.2%)	22,528 (82.6%)	165,183 (85.2%)
Elevated creatinine*	1,334 (4.0%)	13,907 (8.7%)	1,158 (4.2%)	14,737 (7.6%)
Missing	6,238 (18.7%)	22,567 (14.1%)	3,576 (13.1%)	13,998 (7.2%)
Congestive heart failure at baseline	999 (3.0%)	11,008 (6.9%)	911 (3.3%)	14,769 (7.6%)
Income				
Low [†]	15,985 (47.8%)	80,698 (50.5%)	13,878 (50.9%)	102,590 (52.9%)
High	14,268 (42.7%)	64,690 (40.5%)	12,502 (45.9%)	84,748 (43.7%)
Missing	3,163 (9.5%)	14,295 (9.0%)	882 (3.2%)	6,580 (3.4%)
Baseline HbA1c				
Median (IQ Range)	8.4% (7.1-10.4)	7.5% (6.7-9.4)	8.4% (7.1-10.4)	7.2% (6.5-9.1)
<7%	5,646 (16.9%)	45,634 (28.6%)	5,000 (18.3%)	69,120 (35.6%)
7-7.9%	6,116 (18.3%)	30,856 (19.3%)	5,195 (19.1%)	36,023 (18.6%)
8-8.9%	4,295 (12.9%)	16,686 (10.4%)	3,611 (13.2%)	17,667 (9.1%)
9-9.9%	3,259 (9.8%)	11,244 (7.0%)	2,792 (10.2%)	12,489 (6.4%)
≥10%	8,023 (24.0%)	27,324 (17.1%)	6,937 (25.4%)	30,734 (15.8%)
Missing	6,077 (18.2%)	27,939 (17.5%)	3,727 (13.7%)	27,885 (14.4%)
Newly diagnosed with DM at the start of follow-up [#]	16,905 (50.6%)	92,521 (57.9%)	10,947 (40.2%)	127,123 (65.6%)
Diabetes duration at baseline				
Median (years, IQ Range)	1 (0-4)	0 (0-4)	1 (0-5)	0 (0-2)
0-4 years	19,961 (59.7%)	100,318 (62.8%)	18,454 (67.7%)	153,549 (79.2%)
5-9 years	3,108 (9.3%)	9,546 (6.0%)	3,169 (11.6%)	10,010 (5.2%)
10 or more years	3,068 (9.2%)	17,320 (10.8%)	3,109 (11.4%)	17,714 (9.1%)
Missing	7,279 (21.8%)	32,499 (20.4%)	2,530 (9.3%)	12,645 (6.5%)

Footnotes are on last table page.

Table 1 Demographics of the Study Cohort According to Pioglitazone Treatment at any Time During Follow-up[§] (continued)

	Original Cohort		Modified Cohort	
	Pioglitazone treated (n=33,416)	No pioglitazone treatment (n=159,683)	Pioglitazone treated (n=27,262)	No pioglitazone treatment (n=193,918)
Other cancer prior to baseline	1,032 (3.1%)	8,484 (5.3%)	1,079 (4.0%)	13,326 (6.9%)
Other diabetes medications [‡]				
Other TZDs	2,792 (8.4%)	2,446 (1.5%)	2,244 (8.2%)	2,004 (1.0%)
Metformin	28,084 (84.0%)	71,861 (45.0%)	22,624 (83.0%)	79,428 (41.0%)
Sulfonylureas	29,767 (89.1%)	96,518 (60.4%)	24,062 (88.3%)	88,634 (45.7%)
Other oral hypoglycemic drugs	1,945 (5.8%)	2,119 (1.3%)	1,516 (5.6%)	1,716 (0.9%)
Insulin	16,049 (48.0%)	44,673 (28.0%)	12,680 (46.5%)	39,625 (20.4%)
Statin Use	29,457 (88.2%)	92,863 (58.2%)	24,579 (90.2%)	128,635 (66.3%)
ACE inhibitors or ARB	30,678 (91.8%)	110,114 (69.0%)	25,241 (92.6%)	136,573 (70.4%)
BPH medications [†]	4,531 (25.4%) ^μ	15,881 (18.6%) ^μ	3,742 (25.8%) ^μ	18,969 (18.3%) ^μ
Urinary Incontinence	2,103 (6.3%)	7,626 (4.8%)	1,733 (6.4%)	6,654 (3.4%)
UTI/Pyelonephritis	10,878 (32.6%)	44,385 (27.8%)	8,738 (32.1%)	39,379 (20.3%)
Urolithiasis	2,449 (7.3%)	7,353 (4.6%)	2,067 (7.6%)	7,016 (3.6%)
Other Bladder conditions ^Σ	10,611 (31.8%)	38,628 (24.2%)	8,610 (31.6%)	34,385 (17.7%)
PSA Testing	16,180 (90.8%) ^μ	60,384 (70.7%) ^μ	13,315 (91.8%) ^μ	76,314 (73.5%) ^μ
Diabetes complications ^β	31,437 (94.1%)	131,101 (82.1%)	25,491 (93.5%)	138,374 (71.4%)
Diabetic retinopathy	16,647 (49.8%)	49,277 (30.9%)	13,271 (48.7%)	42,040 (21.7%)
Peripheral neuropathy [∞]	23,888 (71.5%)	84,379 (52.8%)	19,311 (70.8%)	77,126 (39.8%)
Proteinuria ^Ω	24,822 (74.3%)	92,096 (57.7%)	20,374 (74.7%)	100,228 (51.7%)
Microalbuminuria	24,312 (72.8%)	87,325 (54.7%)	20,017 (73.4%)	95,758 (49.4%)
Macroalbuminuria	10,821 (32.4%)	36,179 (22.7%)	8,812 (32.3%)	35,531 (18.3%)
Diabetic nephropathy ^π	7,898 (23.6%)	31,398 (19.7%)	6,484 (23.8%)	30,531 (15.7%)
Coronary artery disease	15,216 (45.5%)	69,035 (43.2%)	12,211 (44.8%)	64,961 (33.5%)

[§] All variables are at any time during follow-up except for some baseline variables noted. All comparisons have p-values <0.01 except female sex (**original cohort** p=0.64; **modified cohort** p=0.25).

* Creatinine ≥1.4 mg/dL for women and ≥1.5 mg/dL for men.

‡ Low income defined as median household income in census block below the cohort average (**original cohort** \$59,000; **modified cohort** \$60,000).

The variable used to define new diabetes differed in the primary and sensitivity analyses. In analysis of the **original cohort**, new diabetes includes patients newly entering the diabetes registry, either because they were newly diagnosed patients or who newly enrolled in Kaiser Permanente with an existing diagnosis of diabetes mellitus. In the analyses of the **modified cohort** the definition of newly diagnosed diabetes requires that the patient be a KPNC member for more than 2 years before being identified as having diabetes according to the registry criteria.

‡ Includes use of any other diabetes medications during follow-up.

† BPH medications to treat benign prostatic hypertrophy.

^μ Number and percentage among males.

^Σ Other bladder conditions include hematuria, retention, urgency, neurogenic bladder, catheter and other bladder/urethral symptoms.

^β Diabetes complications include diabetic retinopathy, peripheral neuropathy, proteinuria, diabetic nephropathy or coronary artery disease.

[∞] Includes diabetic neuropathy, foot ulcer, or amputation.

^Ω Includes microalbuminuria or macroalbuminuria.

^π Creatinine ≥2.0 mg/dL for both men and women.

Table 2 Comparison of When Patients Entered the KPNC Diabetes Registry and Medication Use Within 4.5 Months (145 Days) of Cohort Entry

	Original cohort entry criteria		Modified cohort entry criteria	
	Pioglitazone treated	No pioglitazone treatment	Pioglitazone treated	No pioglitazone treatment
Cohort size	33,416	159,683	27,262	193,918
Diabetes Status				
Entered into KPNC Diabetes Registry prior to January 1, 1997	15,907 (47.6%)	65,105 (40.8%)	15,919 (58.4%)	64,511 (33.3%)
Newly entered into KPNC Diabetes Registry after January 1, 1997 and with at least 2 years of KPNC membership at cohort entry	8,710 (26.1%)	50,360 (31.5%)	11,343 (41.6%)	129,407 (66.7%)
Newly entered into KPNC Diabetes Registry after January 1, 1997 and less than 2 years of KPNC membership at cohort entry	8,799 (26.3%)	44,218 (27.7%)	0	0
Pioglitazone use within 4.5 months of cohort entry*	2,392 (7.2%)	0	360 (1.3%)	0
Other oral anti-diabetic drug use within 4.5 months of cohort entry*	25,531 (76.4%)	92,908 (58.2%)	18,463 (67.7%)	68,528 (35.3%)
Insulin use within 4.5 months of cohort entry*	3,955 (11.8%)	23,897 (15.0%)	2,951 (10.8%)	19,190 (9.9%)

* 1 or more prescription within 4.5 months of cohort entry.

Table 3 Pioglitazone Exposures as of the End of Follow-up

Category	ORIGINAL COHORT	MODIFIED COHORT
Ever exposed, n	33,416	27,262
Time since starting pioglitazone (median, range)	4.8 yr (0.2-11.3)	4.6 yr (0.2-11.3)
Less than 3.5 years (n, %)	10,916 (32.7%)	9,831 (36.1%)
3.5-6.5 years (n, %)	11,372 (34.0%)	8,744 (32.1%)
More than 6.5 years (n, %)	11,128 (33.3%)	8,687 (31.9%)
Duration of therapy (median, range)	2.6 yr (0.2-11.2)	2.4 yr (0.2-11.2)
Less than 1.5 years (n, %)	10,755 (32.2%)	10,063 (36.9%)
1.5-4.0 years (n, %)	12,277 (36.7%)	8,942 (32.8%)
More than 4 years (n, %)	10,384 (31.1%)	8,257 (30.3%)
Cumulative dose, mg (median, range)	21,900 mg (450-257,190)	19,980 mg (450-257,190)
1 – 13000 mg (n, %)	11,176 (33.4%)	10,209 (37.4%)
13001 – 35000 mg (n, %)	10,723 (32.1%)	8,089 (29.7%)
>35000 mg (n, %)	11,517 (34.5%)	8,964 (32.9%)

Table 4 Incidence Rate and Relative Hazard of Bladder Cancer with Pioglitazone Exposure in the Modified Cohort

	Cases of bladder cancer	Person-years of follow-up time	Bladder cancer incidence rate (per 100,000 person-years)	Unadjusted (HR, 95% CI)	Adjusted for age, sex and year of cohort entry (HR, 95% CI)	Adjusted for age, sex, year of cohort entry and smoking (HR, 95% CI)	Fully adjusted [†] (HR, 95% CI)
Unexposed to pioglitazone	1,015	1,356,978	74.8 (70.2-79.4)	Reference	Reference	Reference	Reference
Ever exposed to pioglitazone	105	129,849	80.9 (65.4-96.3)	1.03 (0.84-1.27)	1.03 (0.82-1.29)*	1.03 (0.82-1.29)*	1.01 (0.81-1.27)
Time since starting pioglitazone							
Less than 3.5 years	52	77,051	67.5 (49.1-85.8)	0.86 (0.65-1.14)	0.97 (0.73-1.29)	0.97 (0.73-1.29)	0.91 (0.68-1.21)
3.5-6.5 years	31	38,122	81.3 (52.7-109.9)	1.04 (0.72-1.49)	1.09 (0.76-1.58)	1.09 (0.76-1.58)	0.99 (0.68-1.44)
More than 6.5 years	22	19,773	111.3 (64.8-157.8)	1.41 (0.91-2.17)	1.39 (0.89-2.16)	1.39 (0.89-2.17)	1.19 (0.75-1.88)
Test for trend					P=0.25		P=0.56
Duration of therapy							
Less than 1.5 years	35	63,342	55.3 (36.9-73.6)	0.71 (0.51-1.00)	0.81 (0.58-1.15)	0.81 (0.58-1.14)	0.75 (0.53-1.06)
1.5-4.0 years	42	46,839	89.7 (62.6-116.8)	1.14 (0.83-1.55)	1.20 (0.87-1.66)	1.20 (0.87-1.66)	1.10 (0.79-1.52)
More than 4 years	28	24,737	113.2 (71.3-155.1)	1.43 (0.98-2.10)	1.42 (0.96-2.10)	1.42 (0.96-2.11)	1.26 (0.84-1.88)
Test for trend					P=0.12		P=0.47
Cumulative dose							
1-13000 mg	41	61,870	66.3 (46.0-86.6)	0.85 (0.62-1.17)	0.97 (0.70-1.33)	0.97 (0.70-1.33)	0.90 (0.65-1.25)
13001-35000 mg	30	41,249	72.7 (46.7-98.8)	0.92 (0.64-1.33)	0.96 (0.66-1.39)	0.96 (0.66-1.40)	0.89 (0.61-1.29)
>35000 mg	34	31,798	106.9 (71.0-142.9)	1.35 (0.96-1.91)	1.39 (0.97-1.99)	1.39 (0.97-1.99)	1.21 (0.84-1.76)
Test for trend					P=0.23		P=0.77

[†]Fully adjusted refers to inclusion of all potential confounders in the statistical model from the last report plus year of cohort entry: age, sex, race/ethnicity, other diabetes medications, smoking, other bladder conditions, median household income, congestive heart failure, cancer other than bladder cancer, renal insufficiency, HbA1c and the interaction with new diagnosis of diabetes, duration of diabetes, and year of cohort entry.

*Also adjusted for use of other diabetes medication.

Table 5 Incidence Rate and Relative Hazard of Bladder Cancer with Pioglitazone Exposure

	ORIGINAL COHORT				MODIFIED COHORT			
	Cases of bladder cancer	Person-years of follow-up time	Bladder cancer incidence rate (per 100,000 person-years)	Fully adjusted [†] (HR, 95% CI)	Cases of bladder cancer	Person-years of follow-up time	Bladder cancer incidence rate (per 100,000 person-years)	Fully adjusted [†] (HR, 95% CI)
Unexposed to pioglitazone	952	1,311,069	72.6 (68.0 – 77.2)	Reference	1,015	1,356,978	74.8 (70.2-79.4)	Reference
Ever exposed to pioglitazone	137	166,556	82.3 (68.5 – 96.0)	1.07 (0.87-1.30)	105	129,849	80.9 (65.4-96.3)	1.01 (0.81-1.27)
Time since starting pioglitazone								
Less than 3.5 years	67	99,058	67.6 (51.4 – 83.8)	0.96 (0.74-1.24)	52	77,051	67.5 (49.1-85.8)	0.91 (0.68-1.21)
3.5-6.5 years	43	48,955	87.8 (61.6 – 114.1)	1.07 (0.77-1.48)	31	38,122	81.3 (52.7-109.9)	0.99 (0.68-1.44)
More than 6.5 years	27	24,718	109.2 (68.0 – 150.4)	1.19 (0.78-1.80)	22	19,773	111.3 (64.8-157.8)	1.19 (0.75-1.88)
Test for trend				P=0.53				P=0.56
Duration of therapy								
Less than 1.5 years	46	84,199	54.7 (38.9 – 70.4)	0.78 (0.57-1.05)	35	63,342	55.3 (36.9-73.6)	0.75 (0.53-1.06)
1.5-4.0 years	56	61,223	91.5 (67.5 – 115.4)	1.15 (0.87-1.53)	42	46,839	89.7 (62.6-116.8)	1.10 (0.79-1.52)
More than 4 years	35	30,537	114.6 (76.6 – 152.6)	1.30 (0.91-1.86)	28	24,737	113.2 (71.3-155.1)	1.26 (0.84-1.88)
Test for trend				P=0.24				P=0.47

Footnotes are on last table page.

Table 5 Incidence Rate and Relative Hazard of Bladder Cancer with Pioglitazone Exposure (continued)

	ORIGINAL COHORT				MODIFIED COHORT			
	Cases of bladder cancer	Person-years of follow-up time	Bladder cancer incidence rate (per 100,000 person-years)	Fully adjusted† (HR, 95% CI)	Cases of bladder cancer	Person-years of follow-up time	Bladder cancer incidence rate (per 100,000 person-years)	Fully adjusted† (HR, 95% CI)
Cumulative dose								
1-13000 mg	50	79,833	62.6 (45.3-80.0)	0.89 (0.67-1.20)	41	61,870	66.3 (46.0-86.6)	0.90 (0.65-1.25)
13001-35000 mg	43	55,326	77.7 (54.5 – 101.0)	0.98 (0.71-1.35)	30	41,249	72.7 (46.7-98.8)	0.89 (0.61-1.29)
>35000 mg	44	41,115	107.0 (75.4-138.6)	1.25 (0.91-1.74)	34	31,798	106.9 (71.0-142.9)	1.21 (0.84-1.76)
Test for trend				P=0.45				P=0.77

†Fully adjusted refers to inclusion of age, sex, race/ethnicity, other diabetes medications, smoking, other bladder conditions, median household income, congestive heart failure, cancer other than bladder cancer, renal insufficiency, HbA1c and the interaction with new diagnosis of diabetes, duration of diabetes, and year of cohort entry.

*Also adjusted for use of other diabetes medication.

Table 6 Revised for Original Cohort

Results of age, sex, and calendar year of cohort entry adjusted models stratified by sex and smoking status. Revised to include test for trend results interaction p values.

	Men	Women	Smokers	Non-smokers
Person-years of follow-up time unexposed to pioglitazone	687,083	623,986	251,567	1,059,503
Person-years of follow-up time ever exposed to pioglitazone	87,161	79,395	34,209	132,347
Cases of bladder cancer among pioglitazone unexposed	797	155	225	727
Cases of bladder cancer among pioglitazone exposed	112	25	33	104
	HR, 95% CI	HR, 95% CI	HR, 95% CI	HR, 95% CI
Ever exposed to pioglitazone	1.02 (0.82-1.27)	1.33 (0.83-2.12)	0.91 (0.61-1.36)	1.12 (0.89-1.41)
Interaction p value		0.35		0.79
Time since starting pioglitazone*				
Less than 3.5 years	0.96 (0.73-1.27)	1.05 (0.57-1.96)	0.85 (0.51-1.43)	1.02 (0.77-1.36)
3.5-6.5 years	1.16 (0.82-1.62)	0.96 (0.42-2.20)	1.00 (0.54-1.87)	1.17 (0.81-1.68)
More than 6.5 years	1.12 (0.70-1.80)	2.09 (0.98-4.46)	0.96 (0.41-2.22)	1.43 (0.91-2.26)
Test for trend [†]		0.08		0.24
Interaction p values [†]		0.19		0.84
Duration of therapy*				
Less than 1.5 years	0.70 (0.49-0.99)	1.31 (0.74-2.32)	0.64 (0.34-1.21)	0.86 (0.61-1.21)
1.5-4.0 years	1.24 (0.92-1.67)	0.96 (0.44-2.06)	1.10 (0.64-1.87)	1.23 (0.89-1.70)
More than 4 years	1.41 (0.96-2.06)	1.29 (0.52-3.22)	1.12 (0.54-2.33)	1.49 (1.00-2.22)
Test for trend [†]		0.34		0.14
Interaction p values [†]		0.74		0.93
Cumulative dose*				
1 – 13000 mg	0.78 (0.55-1.09)	1.55 (0.90-2.66)	0.73 (0.40-1.35)	0.98 (0.71-1.36)
13001 – 35000 mg	1.04 (0.74-1.45)	0.87 (0.38-1.98)	1.19 (0.68-2.06)	0.94 (0.65-1.38)
>35000 mg	1.43 (1.03-1.99)	0.86 (0.31-2.36)	0.82 (0.40-1.68)	1.56 (1.10-2.21)
Test for trend [†]		0.67		0.19
Interaction p values [†]		0.94		0.72

* Reference group is unexposed to pioglitazone.

[†] Test for trend combines two strata. Interaction p values are for the interaction between the exposure and sex or smoking in the test for trend analysis.

Table 7 Modified Cohort

Results of age, sex, and calendar year of cohort entry adjusted models stratified by sex and smoking status.

	Men	Women	Smokers	Non-smokers
Person-years of follow-up time unexposed to pioglitazone	716,325	640,653	239,878	1,117,100
Person-years of follow-up time ever exposed to pioglitazone	67,669	62,180	26,913	102,936
Cases of bladder cancer among pioglitazone unexposed	854	161	215	800
Cases of bladder cancer among pioglitazone exposed	83	22	26	79
	HR, 95% CI	HR, 95% CI	HR, 95% CI	HR, 95% CI
Ever exposed to pioglitazone	0.94 (0.73-1.20)	1.61 (0.97-2.69)	0.83 (0.53-1.29)	1.11 (0.85-1.44)
Interaction p value	0.12		0.99	
Time since starting pioglitazone*				
Less than 3.5 years	0.89 (0.64-1.22)	1.46 (0.78-2.75)	0.84 (0.47-1.48)	1.01 (0.73-1.41)
3.5-6.5 years	1.11 (0.74-1.65)	1.00 (0.36-2.76)	0.76 (0.35-1.65)	1.23 (0.81-1.88)
More than 6.5 years	1.11 (0.65-1.89)	2.95 (1.29-6.72)	1.17 (0.50-2.74)	1.47 (0.87-2.47)
Test for trend [†]	0.04		0.34	
Interaction p values [†]	0.10		0.88	
Duration of therapy*				
Less than 1.5 years	0.66 (0.44-1.00)	1.62 (0.86-3.04)	0.70 (0.36-1.39)	0.84 (0.57-1.26)
1.5-4.0 years	1.16 (0.82-1.64)	1.46 (0.67-3.20)	1.00 (0.54-1.87)	1.28 (0.88-1.86)
More than 4 years	1.39 (0.91-2.12)	1.60 (0.57-4.47)	0.98 (0.42-2.25)	1.61 (1.03-2.51)
Test for trend [†]	0.12		0.16	
Interaction p values [†]	0.36		0.97	
Cumulative dose*				
1 – 13000 mg	0.76 (0.52-1.12)	2.04 (1.16-3.61)	0.79 (0.42-1.51)	1.02 (0.71-1.48)
13001 – 35000 mg	0.93 (0.62-1.40)	1.13 (0.45-2.81)	1.07 (0.56-2.05)	0.91 (0.58-1.44)
>35000 mg	1.44 (0.99-2.09)	1.02 (0.32-3.27)	0.74 (0.32-1.70)	1.68 (1.13-2.50)
Test for trend [†]	0.38		0.25	
Interaction p values [†]	0.68		0.84	

* Reference group is unexposed to pioglitazone

[†] Test for trend combines two strata. Interaction p values are for the interaction between the exposure and sex or smoking in the test for trend analysis.

Table 8 Results of Age, Sex, and Calendar Year of Cohort Entry Adjusted Models Stratified by Sex and Smoking Status

	Men	Women	Smokers	Non-smokers
	HR, 95% CI	HR, 95% CI	HR, 95% CI	HR, 95% CI
Time since starting pioglitazone*				
Less than 3.5 years				
Original Cohort	0.96 (0.73-1.27)	1.05 (0.57-1.96)	0.85 (0.51-1.43)	1.02 (0.77-1.36)
Modified Cohort	0.89 (0.64-1.22)	1.46 (0.78-2.75)	0.84 (0.47-1.48)	1.01 (0.73-1.41)
3.5-6.5 years				
Original Cohort	1.16 (0.82-1.62)	0.96 (0.42-2.20)	1.00 (0.54-1.87)	1.17 (0.81-1.68)
Modified Cohort	1.11 (0.74-1.65)	1.00 (0.36-2.76)	0.76 (0.35-1.65)	1.23 (0.81-1.88)
More than 6.5 years				
Original Cohort	1.12 (0.70-1.80)	2.09 (0.98-4.46)	0.96 (0.41-2.22)	1.43 (0.91-2.26)
Modified Cohort	1.11 (0.65-1.89)	2.95 (1.29-6.72)	1.17 (0.50-2.74)	1.47 (0.87-2.47)
Duration of therapy*				
Less than 1.5 years				
Original Cohort	0.70 (0.49-0.99)	1.31 (0.74-2.32)	0.64 (0.34-1.21)	0.86 (0.61-1.21)
Modified Cohort	0.66 (0.44-1.00)	1.62 (0.86-3.04)	0.70 (0.36-1.39)	0.84 (0.57-1.26)
1.5-4.0 years				
Original Cohort	1.24 (0.92-1.67)	0.96 (0.44-2.06)	1.10 (0.64-1.87)	1.23 (0.89-1.70)
Modified Cohort	1.16 (0.82-1.64)	1.46 (0.67-3.20)	1.00 (0.54-1.87)	1.28 (0.88-1.86)
More than 4 years				
Original Cohort	1.41 (0.96-2.06)	1.29 (0.52-3.22)	1.12 (0.54-2.33)	1.49 (1.00-2.22)
Modified Cohort	1.39 (0.91-2.12)	1.60 (0.57-4.47)	0.98 (0.42-2.25)	1.61 (1.03-2.51)
Cumulative dose*				
1 – 13000 mg				
Original Cohort	0.78 (0.55-1.09)	1.55 (0.90-2.66)	0.73 (0.40-1.35)	0.98 (0.71-1.36)
Modified Cohort	0.76 (0.52-1.12)	2.04 (1.16-3.61)	0.79 (0.42-1.51)	1.02 (0.71-1.48)
13001 – 35000 mg				
Original Cohort	1.04 (0.74-1.45)	0.87 (0.38-1.98)	1.19 (0.68-2.06)	0.94 (0.65-1.38)
Modified Cohort	0.93 (0.62-1.40)	1.13 (0.45-2.81)	1.07 (0.56-2.05)	0.91 (0.58-1.44)
>35000 mg				
Original Cohort	1.43 (1.03-1.99)	0.86 (0.31-2.36)	0.82 (0.40-1.68)	1.56 (1.10-2.21)
Modified Cohort	1.44 (0.99-2.09)	1.02 (0.32-3.27)	0.74 (0.32-1.70)	1.68 (1.13-2.50)

* Reference group is unexposed to pioglitazone.

Table 9 Cancer Stage by Exposure Status

Cancer stage	ORIGINAL COHORT		MODIFIED COHORT	
	Pioglitazone treated (n=137 cases)	No pioglitazone treatment (n=952 cases)	Pioglitazone treated (n=105 cases)	No pioglitazone treatment (n=1,015 cases)
PUNLMP*	1 (1%)	7 (1%)	N/A [†]	N/A [†]
In situ	65 (47%)	467 (49%)	52 (49%)	499 (49%)
Local	61 (45%)	363 (38%)	45 (43%)	381 (38%)
Regional	6 (4%)	58 (6%)	5 (5%)	72 (7%)
Distant	1 (1%)	28 (3%)	1 (1%)	32 (3%)
Undetermined	3 (2%)	29 (3%)	2 (2%)	31 (3%)

* Papillary urethral neoplasm of low malignant potential.

[†]Not available because this analysis includes patients for whom chart review has not been completed.

Table 10 Analysis of Duration of Other Diabetes Therapies Among the 59,070 Patients Who Were Newly Diagnosed[§] with Diabetes During 1997-2002

	Pioglitazone HR (95% CI)	Metformin HR (95% CI)	Sulfonylureas HR (95% CI)	Insulin HR (95% CI)
N exposed	8,710	32,726	38,708	9,861
N exposed cases/ N exposed by end of follow- up				
Duration of therapy				
Less than 1.5 years	8/2,813	32/5,994	52/7,694	12/4,493
1.5-4.0 years	8/3,506	51/9,489	61/10,283	7/3,404
More than 4 years	3/2,391	42/17,243	69/20,731	7/1,964
Model 1				
Ever/Never Exposed	0.68 (0.42-1.10)	0.96 (0.75-1.23)	0.95 (0.75-1.19)	0.99 (0.66-1.49)
Duration of therapy				
Never exposed	Reference	Reference	Reference	Reference
Less than 1.5 years	0.59 (0.29-1.19)	0.76 (0.52-1.11)	0.98 (0.71-1.34)	0.76 (0.43-1.36)
1.5-4.0 years	0.73 (0.36-1.48)	1.03 (0.75-1.42)	0.97 (0.71-1.31)	0.87 (0.41-1.86)
More than 4 years	0.66 (0.21-2.09)	0.94 (0.65-1.37)	0.76 (0.55-1.05)	2.00 (0.93-4.29)
Model 2				
Duration of therapy				
Never exposed	Reference	Reference	Reference	Reference
Less than 1.5 years	0.59 (0.29-1.20)	0.78 (0.53-1.13)	0.98 (0.71-1.35)	0.80 (0.45-1.44)
1.5-4.0 years	0.73 (0.36-1.50)	1.06 (0.76-1.46)	0.98 (0.72-1.33)	0.92 (0.43-1.98)
More than 4 years	0.66 (0.21-2.09)	0.99 (0.68-1.44)	0.79 (0.57-1.10)	2.05 (0.95-4.40)
Model 3				
Duration of therapy				
Never exposed	Reference	Reference	Reference	Reference
Less than 1.5 years	0.62 (0.30-1.27)	0.78 (0.54-1.14)	0.99 (0.72-1.36)	0.83 (0.46-1.49)
1.5-4.0 years	0.79 (0.38-1.63)	1.09 (0.79-1.50)	1.00 (0.74-1.35)	0.96 (0.45-2.05)
More than 4 years	0.70 (0.22-2.22)	1.01 (0.69-1.47)	0.82 (0.59-1.14)	2.08 (0.97-4.48)
Model 4				
Duration of therapy				
Never exposed	Reference	Reference	Reference	N/A
Less than 1.5 years	0.68 (0.32-1.45)	0.77 (0.52-1.15)	0.99 (0.72-1.38)	N/A
1.5-4.0 years	0.98 (0.48-2.00)	1.09 (0.78-1.52)	0.88 (0.64-1.22)	N/A
More than 4 years	0.95 (0.30-2.99)	0.96 (0.65-1.44)	0.76 (0.54-1.07)	N/A

[§] The definition of newly diagnosed with diabetes required that the patient was a member of KPNC for a minimum of 2 years before the first diabetes diagnosis.

Model 1 - Results of age, sex, race, smoking and calendar year of cohort entry adjusted models.

Model 2- Adjusted for model 1 variables plus each of the other three diabetes therapies where the other therapy is treated as a time updating variable for never versus ever exposed.

Model 3 – Adjusted for model 1 variables plus each of the other three diabetes therapies where the other therapy is treated as a time updating variable using the duration categories of never exposed, less than 1.5 years, 1.5 to 4.0 years, and more than 4 years.

Model 4 - Adjusted for model 1 variables with follow-up censored at the time of initiation of insulin.

N/A – Not applicable.

Table 11 Sex-stratified Analysis Within 10-Year Age Categories, Original Cohort Entry Criteria

	Age 40-49		Age 50-59	
	Men	Women	Men	Women
	HR, 95% CI	HR, 95% CI	HR, 95% CI	HR, 95% CI
Ever exposed to pioglitazone	0.55 (0.14-2.10)	1.55 (0.22-11.1)	0.75 (0.45-1.27)	1.03 (0.35-3.00)
Interaction p value	0.22		0.45	
Time since starting pioglitazone*				
Less than 3.5 years	0.81 (0.19-3.52)	NA	0.82 (0.42-1.57)	0.91 (0.21-3.97)
3.5-6.5 years	NA	NA	0.69 (0.27-1.73)	1.30 (0.29-5.89)
More than 6.5 years	1.50 (0.17-13.5)	2.83 (0.46-17.2)	1.13 (0.44-2.94)	0.85 (0.10-7.01)
Interaction p values [†]	0.05		0.48	
Duration of therapy*				
Less than 1.5 years	0.52 (0.07-3.91)	1.52 (0.16-14.6)	0.63 (0.27-1.43)	0.47 (0.06-3.57)
1.5-4.0 years	1.21 (0.27-5.44)	NA	0.68 (0.29-1.56)	1.76 (0.50-6.21)
More than 4 years	NA	1.56 (0.16-15.0)	1.42 (0.66-3.05)	0.86 (0.11-6.87)
Interaction p values [†]	0.17		0.48	
Cumulative dose*				
1 – 13000 mg	0.55 (0.07-4.19)	1.61 (0.17-15.5)	0.77 (0.35-1.66)	0.99 (0.23-4.33)
13001 – 35000 mg	0.72 (0.09-5.53)	NA	0.52 (0.19-1.43)	0.64 (0.08-4.91)
>35000 mg	0.79 (0.10-6.46)	1.36 (0.14-13.1)	1.20 (0.58-2.45)	1.42 (0.31-6.55)
Interaction p values [†]	0.23		0.47	

Footnotes are on last table page.

Table 11 Sex-stratified Analysis Within 10-Year Age Categories, Original Cohort Entry Criteria (continued)

	Age 60-69		Age 70+	
	Men	Women	Men	Women
	HR, 95% CI	HR, 95% CI	HR, 95% CI	HR, 95% CI
Ever exposed to pioglitazone	1.16 (0.85-1.57)	1.50 (0.73-3.09)	1.02 (0.68-1.54)	1.20 (0.52-2.75)
Interaction p value	0.78		0.72	
Time since starting pioglitazone*				
Less than 3.5 years	1.07 (0.73-1.57)	1.64 (0.74-3.65)	0.91 (0.54-1.53)	0.58 (0.14-2.37)
3.5-6.5 years	1.45 (0.93-2.24)	0.79 (0.19-3.33)	1.09 (0.55-2.14)	1.05 (0.25-4.35)
More than 6.5 years	0.90 (0.43-1.86)	1.28 (0.30-5.55)	1.38 (0.55-3.45)	3.15 (0.93-10.7)
Interaction p values [†]	0.98		0.34	
Duration of therapy*				
Less than 1.5 years	0.63 (0.37-1.08)	1.28 (0.50-3.23)	0.86 (0.48-1.54)	1.80 (0.78-4.16)
1.5-4.0 years	1.55 (1.05-2.28)	0.99 (0.31-3.23)	1.09 (0.59-2.00)	0.46 (0.06-3.30)
More than 4 years	1.51 (0.89-2.55)	2.07 (0.62-6.94)	1.26 (0.55-2.86)	NA
Interaction p values [†]	0.94		0.60	
Cumulative dose*				
1 – 13000 mg	0.76 (0.46-1.26)	1.55 (0.66-3.65)	0.83 (0.45-1.52)	1.86 (0.80-4.30)
13001 – 35000 mg	1.32 (0.86-2.03)	1.42 (0.51-4.00)	0.94 (0.48-1.85)	0.46 (0.06-3.31)
>35000 mg	1.51 (0.95-2.38)	0.55 (0.07-4.04)	1.49 (0.76-2.93)	NA
Interaction p values [†]	0.69		0.53	

* Reference group is unexposed to pioglitazone; models adjusted for year of cohort entry.

[†] Interaction p values are for the interaction between the exposure and sex or smoking in the test for trend analysis.

Table 12 Sex-stratified and Age-stratified (<60 Or >=60) Analysis, Original Cohort Entry Criteria

	Age <60		Age >=60	
	Men	Women	Men	Women
	HR, 95% CI	HR, 95% CI	HR, 95% CI	HR, 95% CI
Ever exposed to pioglitazone	0.71 (0.44-1.16)	1.09 (0.43-2.75)	1.09 (0.85-1.39)	1.30 (0.76-2.24)
Interaction p value	0.24		0.74	
Time since starting pioglitazone*				
Less than 3.5 years	0.80 (0.44-1.46)	0.69 (0.16-2.97)	0.96 (0.71-1.31)	1.08 (0.55-2.13)
3.5-6.5 years	0.58 (0.23-1.46)	0.91 (0.21-4.02)	1.28 (0.89-1.84)	0.84 (0.30-2.29)
More than 6.5 years	1.19 (0.50-2.86)	1.71 (0.46-6.32)	1.00 (0.57-1.77)	1.87 (0.73-4.78)
Interaction p values†	0.10		0.59	
Duration of therapy*				
Less than 1.5 years	0.59 (0.28-1.28)	0.69 (0.16-2.98)	0.69 (0.46-1.02)	1.40 (0.75-2.62)
1.5-4.0 years	0.75 (0.36-1.56)	1.24 (0.36-4.25)	1.33 (0.96-1.83)	0.70 (0.26-1.92)
More than 4 years	1.22 (0.57-2.61)	1.13 (0.25-5.07)	1.37 (0.88-2.13)	1.11 (0.34-3.55)
Interaction p values†	0.23		0.71	
Cumulative dose*				
1 – 13000 mg	0.72 (0.35-1.48)	1.09 (0.32-3.71)	0.75 (0.51-1.11)	1.56 (0.86-2.84)
13001 – 35000 mg	0.55 (0.22-1.35)	0.45 (0.06-3.41)	1.14 (0.79-1.63)	0.93 (0.38-2.29)
>35000 mg	1.13 (0.58-2.23)	1.40 (0.40-4.92)	1.43 (0.98-2.09)	0.30 (0.04-2.20)
Interaction p values†	0.26		0.43	

* Reference group is unexposed to pioglitazone; models adjusted for year of cohort entry.

† Interaction p values are for the interaction between the exposure and sex or smoking in the test for trend analysis.

Table 13 Analysis of the Original Cohort But Limiting the Outcome to Local, Regional, or Distant Stage Tumors

	Cases of bladder cancer	Person-years of follow-up time	Bladder cancer incidence rate (per 100,000 person-years)	Fully adjusted [†] (HR, 95% CI)
Unexposed to pioglitazone	449	1,311,069	34.2	Reference
Ever exposed to pioglitazone	68	166,556	40.8	1.17 (0.88-1.55)
Time since starting pioglitazone				
Less than 3.5 years	26	99,058	26.2	0.84 (0.56-1.27)
3.5-6.5 years	26	48,955	53.1	1.47 (0.96-2.25)
More than 6.5 years	16	24,718	64.7	1.48 (0.85-2.55)
Test for trend				0.10
Duration of therapy				
Less than 1.5 years	24	84,199	28.5	0.91 (0.59-1.39)
1.5-4.0 years	24	61,223	39.2	1.09 (0.71-1.68)
More than 4 years	20	30,537	65.5	1.60 (0.99-2.59)
Test for trend				0.15
Cumulative dose				
1 – 13000 mg	27	79,833	33.8	1.08 (0.72-1.61)
13001 – 35000 mg	17	55,326	30.7	0.85 (0.52-1.41)
>35000 mg	24	41,115	58.4	1.49 (0.95-2.33)
Test for trend				0.29

[†]Fully adjusted refers to inclusion of all potential confounders in the statistical model from the last report plus year of cohort entry: age, sex, race/ethnicity, other diabetes medications, smoking, other bladder conditions, median household income, congestive heart failure, cancer other than bladder cancer, renal insufficiency, HbA1c and the interaction with new diagnosis of diabetes, duration of diabetes, and year of cohort entry.

Table 14 Hazard ratios and Confidence Intervals for All Variables Included in the Analysis of Ever Exposure to Pioglitazone in the Original Cohort Entry Criteria

All covariates	Fully Adjusted HR (95% CI)
Diabetes Medications	
Pioglitazone	1.07 (0.87-1.30)
Other TZDs	1.12 (0.78-1.60)
Metformin	1.05 (0.91-1.22)
Insulin	1.12 (0.94-1.33)
Sulfonylureas	1.11 (0.92-1.34)
Other oral hypoglycemic agents	1.03 (0.64-1.65)
Never treated with any diabetes medications	1.11 (0.87-1.42)
Received at least one prescription for a diabetes medication but never met the definition of exposure	0.96 (0.66-1.40)
Male sex	4.69 (3.99-5.51)
Age	
Age 40-49	reference
Age 50-59	4.51 (3.00-6.80)
Age 60-69	13.0 (8.81-19.3)
Age >=70	20.2 (13.6-30.0)
Cohort Entry	
Entered cohort in 1997	reference
Entered cohort in 1998	0.85 (0.62-1.16)
Entered cohort in 1999	0.92 (0.69-1.24)
Entered cohort in 2000	0.80 (0.59-1.10)
Entered cohort in 2001	0.65 (0.48-0.88)
Entered cohort in 2002	0.66 (0.48-0.92)
Race	
Caucasian	reference
Black	0.52 (0.41-0.66)
Asian	0.40 (0.31-0.52)
Hispanic	0.42 (0.33-0.55)
Other Race	0.70 (0.54-0.92)
Smoking Before Censor Date	1.51 (1.31-1.74)
Any Bladder Conditions on or Prior to Baseline	0.95 (0.79-1.14)
Income	
Median Household Income Above Average (\$59K)	0.96 (0.85-1.08)
Income Census Data Missing	0.89 (0.67-1.17)
Congestive Heart Failure Prior to or on Baseline	1.13 (0.89-1.43)
Had Cancer Other than Bladder Cancer Prior to Baseline	1.18 (0.94-1.48)

Table 14 Hazard ratios and Confidence Intervals for All Variables Included in the Analysis of Ever Exposure to Pioglitazone in the Original Cohort Entry Criteria t (continued)

All covariates	Fully Adjusted HR (95% CI)
Serum Creatinine	
Abnormal at Baseline	1.16 (0.94-1.44)
Missing at Baseline	1.06 (0.87-1.28)
Baseline HbA1c	
<7	Reference
7-7.9	0.85 (0.67-1.09)
8-8.9	1.01 (0.77-1.33)
9-9.9	0.87 (0.62-1.22)
>=10	0.99 (0.75-1.31)
Missing	0.73 (0.55-0.99)
Newly Diagnosed Diabetic	
	1.23 (0.91-1.68)
Interaction Term	
HbA1c 7-7.9 and Newly Diagnosed Diabetic	0.86 (0.61-1.21)
HbA1c 8-8.9 and Newly Diagnosed Diabetic	0.79 (0.52-1.21)
HbA1c 9-9.9 and Newly Diagnosed Diabetic	0.95 (0.57-1.58)
HbA1c >=10 and Newly Diagnosed Diabetic	0.72 (0.49-1.06)
HbA1C Missing and Newly Diagnosed Diabetic	0.91 (0.61-1.35)
Diabetes Duration	
<5 Years	reference
5-9 Years	1.13 (0.90-1.43)
10+ Years	1.06 (0.86-1.31)
Missing	0.95 (0.79-1.15)