Pioglitazone and Bladder Cancer
A population-based study of Taiwanese

CHIN-HSIAO TSENG, MD, PHD

OBJECTIVE—The association between pioglitazone and bladder cancer has not been investigated in Asians. We aimed to investigate this association.

RESEARCH DESIGN AND METHODS—A total of 1,000,000 individuals were randomly sampled from the National Health Insurance database, and incident cases of bladder cancer during the period from 1 January 2006 to 31 December 2009 were analyzed among 54,928 patients with type 2 diabetes and without previous bladder cancer.

RESULTS—Among 165 incident case subjects, 10 (0.39%) were ever users and 155 (0.30%) were never users of pioglitazone (adjusted hazard ratio in full model 1.305 [95% CI 0.661–2.576]). All bladder cancer in ever users occurred within a duration of therapy <24 months, suggesting an early effect of pioglitazone on bladder cancer or late use of pioglitazone in high-risk patients.

CONCLUSIONS—The association between pioglitazone and bladder cancer was not significant. However, confirmation of this finding is required because of the possible lack of statistical power owing to the small number of events.

Clinical trials have suggested an association between pioglitazone and bladder cancer (1,2). A reporting system indicated an odds ratio of 4.30 (95% CI 2.82–6.52) (3), and an analysis of the Kaiser Permanente Northern California (KPNC) registry found a 40–50% higher risk for duration of use >2 years and cumulative dose >28,000 mg (4). This association was evaluated here using databases from the Bureau of National Health Insurance (NHI) in Taiwan.

RESEARCH DESIGN AND METHODS—Reimbursement records from 1996 through 2009 were retrieved from a random sample of 1,000,000 individuals in NHI databases in 2000 (5–8). The diagnostic codes, based on the ICD-9, were 250.1–250.9 for diabetes and 188 for bladder cancer.

The entry date of 1 January 2006 was selected because it was midway between the start of pioglitazone marketing in Taiwan (2002) and the end date of the databases (2009) and provided a maximum exposure of 4 years and a maximum follow-up of 4 years. After excluding individuals who died or had diabetes or bladder cancer before entry, those with type 1 diabetes, and those not using oral antidiabetes medication or insulin, 54,928 patients with type 2 diabetes were recruited.

Age, diabetes duration, comorbidities, and other covariates were determined as a status/diagnosis before entry (6). Bladder cancer was defined as incident cases from January 2006 through December 2009.

Patients prescribed pioglitazone before entry were defined as ever users; never users were those who had never used pioglitazone. The KPNC dose-responsive parameters (4) were used, namely, 1) time since starting pioglitazone: <18, 18–36, and >36 months; 2) therapy duration: <12, 12–24, and >24 months; and 3) cumulative dose: 1–10,500, 10,501–28,000, and >28,000 mg.

Statistical analyses
Incidence of bladder cancer and 95% CIs were calculated (9). Cox regression was used to calculate hazard ratios (HRs). Three sets of confounders were adjusted for: 1) age and sex; 2) variables significantly predictive of bladder cancer in a previous study (for not overfitting [10], i.e., age, sex, diabetes duration, urinary tract disease (ICD-9 590–599), nephropathy (580–589), chronic obstructive pulmonary disease (490–496), statin use, and region of residence (6); and 3) full model, i.e., age, sex, diabetes duration, nephropathy, urinary tract disease, hypertension (401–405), chronic obstructive pulmonary disease, cerebrovascular disease (430–438), ischemic heart disease (410–414), peripheral arterial disease (250.7, 785.4, 443.81, and 440–448), eye disease (270.2–272.4), heart failure (398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, and 428), rosiglitazone, sulfonylurea, meglitinide, metformin, acarbose, insulin, statin, fibrate, ACE inhibitor/anagliptin receptor blocker, calcium channel blocker, region of residence, occupation, and other cancer before baseline (140–208, excluding 188). A P value <0.05 was considered statistically significant.

RESULTS—Among 2,545 ever users and 52,383 never users, there were 10 (0.39%) and 155 (0.30%) incident cases, respectively. Because no users with a duration of therapy >24 months or a cumulative dose >28,000 mg developed bladder cancer, HRs were estimated for duration of therapy <12 and ≥12 months versus never users and for a cumulative dose of 1–10,500 and ≥10,500 mg versus never users. Table 1 shows case numbers and incidences of bladder cancer and HRs for different pioglitazone categories. No HRs were significant.

CONCLUSIONS—An insignificant 30% increase in overall risk was observed in the full model (Table 1), which is a result similar to those of the KPNC study (4); however, the HR was attenuated in...
Table 1 — Incidence rates and HRs for bladder cancer associated with pioglitazone use

| Time since starting | All Ever users | Never users |
|---------------------|---------------|-------------|
| d, months           | HR (95% CI)   | HR (95% CI) |
| 0                  | 1.03 (0.99-1.07) | 1.00 (1.00-1.00) |
| 1                  | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 2                  | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 3                  | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 4                  | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 5                  | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 6                  | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 7                  | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 8                  | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 9                  | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 10                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 11                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 12                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 13                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 14                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 15                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 16                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 17                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 18                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 19                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 20                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 21                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 22                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 23                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 24                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 25                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 26                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 27                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 28                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 29                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |
| 30                 | 1.04 (1.01-1.08) | 1.00 (1.00-1.00) |

Note: The table shows the incidence rates and hazard ratios (HRs) for bladder cancer associated with the use of pioglitazone, adjusted for previously identified risk factors. The data are presented as person-years of observation per 100,000 person-years. The HRs are calculated using a Cox proportional hazards model.
as biochemical data, obesity, smoking, lifestyle, diet, occupational exposure, and genetic parameters. In addition, the underpowered analyses require confirmation.

In summary, there was an insignificant 30% overall increase in bladder cancer risk among pioglitazone users. However, all bladder cancer occurred within 2 years of the start of therapy and no patients with a cumulative dose >28,000 mg developed bladder cancer, which suggests an early effect of pioglitazone on bladder cancer or late pioglitazone use in patients with a high risk of bladder cancer.

Acknowledgments—This study was based on data from the NHI Research Database provided by the Bureau of NHI and the Department of Health, managed by National Health Research Institutes (reg. number 99274).

No potential conflicts of interest relevant to this article were reported.

C.-H.T. collected and analyzed the data, wrote the manuscript, and is the guarantor of the article.

References
1. Dormandy JA, Charbonnel B, Eckland DJ, et al., PROactive investigators. 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
2. Dormandy J, Bhattacharya M, van Troostenburg de Bruyn AR, PROactive investigators. Safety and tolerability of pioglitazone in high-risk patients with type 2 diabetes: an overview of data from PROactive. Drug Saf 2009;32:187–202
3. 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
4. Lewis JD, Ferrara A, Peng T, et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. Diabetes Care 2011;34:916–922
5. Tseng CH, Chong CK, Tseng CP, Chan TT. Age-related risk of mortality from bladder cancer in diabetic patients: a 12-year follow-up of a national cohort in Taiwan. Ann Med 2009;41:371–379
6. Tseng CH. Diabetes and risk of bladder cancer: a study using the National Health Insurance database in Taiwan. Diabetologia 2011;54:2009–2015
7. Tseng CH. Diabetes and risk of prostate cancer: a study using the National Health Insurance. Diabetes Care 2011;34:616–621
8. Tseng CH. Diabetes and non-Hodgkin’s lymphoma: analyses of prevalence and annual incidence in 2005 using the National Health Insurance database in Taiwan. Ann Oncol. 15 July 2011 [Epub ahead of print]
9. Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). Am J Epidemiol 1990;131:373–375
10. Núñez E, Steyerberg EW, Núñez J. Regression modeling strategies. Rev Esp Cardiol 2011;64:501–507 [in Spanish]
11. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009;52:1766–1777
12. Decensi A, Puntoni M, Goodwin P, et al. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. Cancer Prev Res (Phila) 2010;3:1451–1461
13. Yang X, Chan JC. Comment: analyses using time-dependent pioglitazone usage in Cox models may lead to wrong conclusions about its association with cancer. Diabetes Care 2011;34:e136; author reply 137
14. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–2471