M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 1, 2010

FROM: David J. Graham, MD, MPH
Associate Director for Science and Medicine
Office of Surveillance and Epidemiology

TO: Gerald Dal Pan, MD, MHS
Director
Office of Surveillance and Epidemiology

SUBJECT: Analysis of Medicare thiazolidinedione study data by date of birth

Background

We recently completed an observational cohort study comparing cardiovascular and mortality risks in elderly Medicare patients initiating therapy with a thiazolidinedione (TZD) in which use of rosiglitazone was compared with pioglitazone. We found that rosiglitazone increased the risk of hospitalized stroke, hospitalized heart failure (HF), all-cause mortality (death), and the composite end points of acute myocardial infarction (AMI) or death; AMI, stroke, or death; and AMI, stroke, HF, or death. The two cohorts were virtually identical with respect to over 60 different baseline variables and there was essentially no difference between unadjusted and adjusted hazard ratios. This study was fully documented in a study report prepared for the July 2010 advisory committee meeting on cardiovascular risk with rosiglitazone and was also published in a peer-reviewed journal (JAMA 2010; 304(4):411-18; published online ahead of print (doi:10.1001/jama.2010.920)).

Concerns were raised about whether there might be irregularities or "noise" in the dataset that were creating spurious associations. We were asked to conduct an analysis that compared patients with even birth-dates to those with odd birth-dates for the occurrence of our study end points. The reasoning behind this particular comparison was that even or odd birth-dates should not be associated with the occurrence of a study end point or with exposure to one TZD or the other.

Methods

Detailed methods relating to TZD cohort formation, follow-up, and censoring criteria are described in the advisory committee meeting briefing document. For the current analysis, each member of the TZD cohort (n=227 571) was assigned a Stata birth-date, with January 1, 1960 assigned a value of 0, and each more remote or recent date assigned a negative or positive number representing the number of days a given birth-date was either before or after January 1, 1960. Patients were then sorted into even- and odd-numbered cohorts.

Baseline covariates were tabulated and compared using standardized mean differences (SMD), where a difference of 0.1 standard deviations or less is considered negligible. Hazard ratios were estimated

using Cox proportional hazards regression with 95% confidence intervals. Unadjusted estimates and estimates adjusted for all study covariates were calculated using Stata v.11 (Stata Corp, College Station, Texas).

Results

There were 227 571 patients in the analysis, with 113 992 (50.1%) having an even-numbered birth-date and 113 579 (49.9%) having an odd-numbered birth-date (SMD=0.004). The birth-date cohorts were virtually identical with respect to the distribution of the 68 different covariates listed in our advisory committee briefing package. For 65 of these variables, the standardized mean difference between birth date cohorts was less than 0.01 standard deviations. For the remaining 3 variables, the SMD was 0.011 for kidney failure, 0.015 for race/ethnicity = "white," and 0.013 for race/ethnicity = "black." For cardiovascular-related variables, the differences were generally less than 0.005 standard deviations (table 1). Of note, differences of 0.1 standard deviations or less are considered negligible.

Table 1. Selected baseline characteristics (%) in TZD-treated patients with an even or odd birth-date and standardized mean difference between birth-date cohorts.

	Even birth-date (n=113 992)	Odd birth-date (n=113 579)	Std mean diff
Female	59.8	59.9	0.001
Age=65-69	28.9	29.1	0.005
Rosiglitazone	29.7	29.7	0.002
Charlson score=0	75.4	75.3	0.003
Medication use			
ACE inhibitors/ARBs	66.9	67.2	0.005
β-blockers	42.6	42.7	0.003
Calcium channel blockers	32.7	32.9	0.004
Digoxin	7.0	6.9	0.004
Loop diuretics	21.5	21.5	0.001
Nitrates	10.6	10.6	0.000
Insulin	13.8	13.7	0.004
Statins	58.7	58.7	0.001
Medical conditions			
Acute myocardial infarction	1.0	1.1	0.002
Heart failure	6.3	6.3	0.000
Stroke	1.2	1.2	0.004

Cox proportional hazards regression showed no increase or decrease in risk for any of the individual or composite cardiovascular end points among TZD-users with an even birth-date compared with those having an odd birth-date (table 2). Of note, adjustment for over 60 covariates did not change the hazard ratios by more than ± 0.01.

Table 2. Hazard ratios (95% CI) of acute myocardial infarction, stroke, heart failure, all-cause mortality, and composite cardiovascular endpoints in TZD-treated patients treated with even or odd birth dates (n=227571). Reference = odd birth date.

Endpoint	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio[†] (95% CI)
Acute myocardial infarction	0.95 (0.86-1.04)	0.94 (0.86-1.03)
Stroke	1.04 (0.92-1.17)	1.04 (0.92-1.17)
Heart failure	1.05 (0.98-1.12)	1.04 (0.97-1.11)
All-cause mortality	1.01 (0.94-1.10)	1.00 (0.93-1.08)
AMI or death	0.99 (0.93-1.05)	0.98 (0.92-1.04)
AMI, stroke, or death	0.99 (0.94-1.05)	0.98 (0.93-1.04)
AMI, stroke, heart failure, or death	1.01 (0.97-1.06)	1.00 (0.96-1.05)

[†] Cox proportional hazards model stratified by prior endpoint and cancer and adjusted for variables in tables 1-3 of FDA study report included in July 2010 advisory committee briefing package.

Similar results were obtained when analyses were restricted to patients entering the TZD cohort either prior to or after publication of the Nissen and Wolski meta-analysis on May 21, 2007 (N Engl J Med 2007; 356(24):2457-71).

Conclusions

Birth-date was not associated with any of the study end points examined in our Medicare study of cardiovascular and mortality risks in elderly patients treated with rosiglitazone compared with pioglitazone. This analysis provides no basis to suggest that the original study findings were biased or due to irregularities or “noise” in the data.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21071	SUPPL-35	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID J GRAHAM
09/13/2010