Prescribing Trend of Pioglitazone After Safety Warning Release in Korea

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ABSTRACT

OBJECTIVES: This study was conducted to determine the number of pioglitazone users before and after the issue of the pioglitazone safety warning (intervention) by South Korea's Ministry of Food and Drug Safety on June 10, 2011.

STUDY DESIGN: A quasi-experimental interrupted time series study was conducted to examine the number of pioglitazone and other antidiabetic drug users between 2009 and 2015.

METHODS: We used the National Health Insurance Service–National Sample Cohort database to estimate the number of pioglitazone and other antidiabetic drug users between 2009 and 2015. Relative and absolute changes in the number of drug users were calculated with 95% CIs. Monthly numbers of drug users were presented according to the maximum likelihood estimation method, and a segmented regression analysis was performed to evaluate the effect of the intervention. A Durbin-Watson statistic and Dickey-Fuller test were used to assess autocorrelation and seasonality, respectively.

RESULTS: A total of 80,724 patients with diabetes, including 12,249 pioglitazone users, were investigated. The relative change in pioglitazone users was –8.13% (95% CI, –8.41% to –7.86%). The intervention was associated with an immediate decrease of 177 pioglitazone users per 1000 patients with diabetes (P <.05). Without this intervention, the predicted proportion of pioglitazone users would be 90 per 1000 patients with diabetes, which is 1.5-fold higher than the actually observed rate of 60 per 1000 patients with diabetes.

CONCLUSIONS: This intervention led to a moderate decrease in pioglitazone users. Until further evidence is available, caution should be exercised when prescribing pioglitazone to patients with high potential risk of bladder cancer and alternative treatments should be considered.

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Pioglitazone is a drug of the thiazolidinedione (TZD) class used to treat type 2 diabetes.[1] In June 2011, a French study suggested an increased risk of bladder cancer among patients treated with pioglitazone, resulting in the withdrawal of this drug by the French government. A study conducted in the United States reported similar findings.[2] Following these results, the US FDA issued a drug safety communication, followed by warnings from both the European Medicines Agency and the Australian Therapeutic Goods Administration reporting similar concerns. On June 10, 2011, South Korea's Ministry of Food and Drug Safety (MFDS) also released a safety warning (hereafter referred to as "the intervention") stating that pioglitazone should be prescribed with caution.[3]

A pioglitazone withdrawal study in France investigating the impact of pioglitazone's regulatory withdrawal on antidiabetic drug use found no adverse events among patients with diabetes.[4] On the other hand, an Australian and British study on TZD utilization trends reported that safety warnings were associated with decreased use of the respective drugs, rosiglitazone and pioglitazone.[5,6] Furthermore, Taiwan's FDA communicated the possible risks of bladder cancer associated with pioglitazone, and this regulatory action had a positive impact of decreasing the use of pioglitazone among high-risk patients.[7]

The data reported in previous studies had limitations because they were analyzed over a relatively short period of time. Although the withdrawal study in France was conducted from 2010 to 2014, the drug withdrawal took place in January 2011, thus resulting in a prewithdrawal period of only 12 months.[4] This short prewithdrawal period may affect the predicted number of drug users. Another study conducted in Spain examining the effect of rosiglitazone's safety warning analyzed data collected over only 3 years (2006-2008), an even shorter period (safety warnings for rosiglitazone were released throughout 2007 and 2008).[8] With such short observation periods, application of a time lag before or after an intervention may not be feasible. Furthermore, pioglitazone use following the MFDS' safety warning has yet to be evaluated in Korea.

The current study was therefore conducted to explore the proportion of pioglitazone users before and after the intervention between

2009 and 2015. Furthermore, we evaluated the impact of the intervention on pioglitazone use by comparing the use of other antidiabetic drugs. If numbers of both pioglitazone users and users of other antidiabetic drugs decreased, a cause other than our intervention may be behind it. We hypothesized that with the intervention, the proportion of pioglitazone users would decrease and lead to an increase in the proportion of patients using other antidiabetic drugs, indicating that safety warnings are an effective regulatory measure to prevent use and thus potential adverse outcomes.

TAKEAWAY POINTS

- To our knowledge, no study has been conducted in South Korea to evaluate the effect of the pioglitazone safety warning about its risk of bladder cancer that was released by South Korea's Ministry of Food and Drug Safety on June 10, 2011.
- For pioglitazone, the relative change in the proportion of drug users per 1000 patients with diabetes was –8.13% (95% CI, –8.41% to –7.86%) and the absolute change was –1.04 (95% CI, –1.40 to –0.68) percentage points per 1000 patients with diabetes.
- The pioglitazone safety warning was associated with an immediate decrease of 177 pioglitazone users per 1000 patients with diabetes whereas, if the intervention had not been implemented, the proportion of pioglitazone users would have shown an increasing trend.

METHODS

Data

This study was conducted using the nationwide population-based National Health Insurance Service–National Sample Cohort (NHIS-NSC) database, which includes approximately 1 million individuals randomly selected from almost the entire Korean population, using national claims data from January 1, 2009, to December 31, 2015 (described in detail elsewhere).[9] The NHIS-NSC database contains anonymized patient codes along with sociodemographic characteristics; medical care history; medical care institution types; *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnosis codes; and drug prescription information (generic name, prescription date, duration, and dosage).

Study Design

The interrupted time series (ITS) study design, a type of quasi-experimental research, is widely used when evaluating the effectiveness of population-level health interventions implemented at a clearly defined point in time.[10] The design generally involves constructing a time series of population-level rates for a particular quality improvement focus and statistically testing for variations in the outcome rate in the time periods before and after implementation of an intervention designed to alter the outcome.[11] A segmented regression approach was used with an autoregressive integrated moving average approach to test the effect of the intervention on the outcome of interest by using an appropriately defined impact model, as there was no remaining residual autocorrelation.[10,11]

Study Subjects

Study subjects included all patients found in the NHIS-NSC database 18 years or older with a diagnosis of diabetes (*ICD-10* codes E10-E14), in both inpatient and outpatient settings, who were prescribed any antidiabetic drug between January 2009 and December 2015. The periods before (January 1, 2009, to June 10, 2011) and after (June 11, 2011, to December 31, 2015) the intervention were defined as shown in **eAppendix A** (eAppendices available at **ajmc.com**).

Definition of Exposure and Outcome

Exposure was defined as "before" or "after," relative to the intervention. The proportion of antidiabetic drug users was defined as the number of antidiabetic drug users divided by the total number of patients with diabetes. Use of the study drug, pioglitazone (anatomical therapeutic chemical classification system code, A10BG03), was compared with use of other antidiabetic drugs (comparators), which were classified as (1) rosiglitazone (A10BG02), (2) sulfonylurea derivatives (A10BB) and metformin (A10BA02), (3) dipeptidyl peptidase-4 (DPP-4) inhibitors (A10BH) and glucagon-like peptide-1 (GLP-1) analogues (A10BJ), and (4) insulin analogues (A10A). Metformin, the preferred initial treatment of diabetes, and sulfonylurea, which is used for second-line therapy together with metformin, were grouped because these 2 drug classes are regarded as the most cost-effective and widely prescribed treatment for diabetes.[12] Additionally, because both DPP-4 inhibitors and GLP-1 analogues are incretin-based drugs with similar mechanisms of action, they were grouped together as well.[13]

Potential Confounders

Demographic variables, such as age and gender, were identified from the database. With regard to medical institution type (ie, institutions that patients visited for diabetes-related healthcare services), the following classification was applied: tertiary hospitals (≥500 beds), general hospitals (30-499 beds), and clinics (<30 beds). With regard to comorbidities, those with a history of ischemic heart disease (*ICD-10* codes I24 and I25), myocardial infarction (I21), ischemic stroke (I63), hypertension (I10-I15), and cancer (C00-D49) were assessed in the whole study period (ie, the periods before and after the intervention).

Statistical Analysis

Age, gender, medical institution type, and comorbidities were presented as frequencies and proportions. The absolute standardized difference (aSD) was calculated for all categorical variables. The absolute change in drug users was calculated as the difference between the proportions before and after the intervention, whereas the relative change (%) was calculated by dividing the absolute change by the proportion of users before the intervention. 95% CIs were calculated for both absolute and relative changes. To estimate the impact of the intervention, the proportion of monthly antidiabetic

drug users was analyzed via ordinary least-squares regression and maximum likelihood estimation.

A segmented regression model was designed using data available for 30 months prior to the intervention. Using preintervention data, the monthly rates over time were projected to predict what would have occurred without the intervention. The dependent variable was the proportion of antidiabetic drug users per 1000 patients with diabetes. Independent variables included time (months), intervention indicator, and time after the intervention (months). The intervention indicator variable was set as a dichotomous variable: 0 (before) or 1 (after). Time after the intervention was a continuous variable representing the number of months after the intervention and was set to 0 for all months prior to the intervention. The equation used for the regression model is as follows[10,11]:

$$Y = B_0 + B_1 \times Time + B_2 \times Intervention + B_3 \times Time\ after\ intervention + e$$

The estimates for "intervention" and "time after intervention" are the main coefficients of interest from the segmented regression analysis, with the former measuring the level of change immediately after the intervention and the latter measuring the trend after the intervention. The assumption of autocorrelation for time-series data was assessed via Durbin-Watson statistics, and seasonality or stationarity was assessed using an augmented Dickey-Fuller test.[14,15] In addition, the numbers of incident and prevalent pioglitazone users per 1000 patients with diabetes were calculated to compare and contrast their trends. Incident pioglitazone users were defined as those having no prescription for pioglitazone within the previous 12 months of the first occurrence of pioglitazone use. Prevalent pioglitazone users were defined as those having a prescription for pioglitazone in each respective month, regardless of their past use. To test the sensitivity and robustness of the study results, a 3-month lag was applied both before and after the intervention.

All statistical analyses were performed using the SAS Enterprise Guide statistical application program provided by the NHIS (release 9.71; SAS Institute Inc; Cary, North Carolina) and accessed through a virtual machine system. A 2-tailed P value <.05 or aSD <0.1 was considered statistically significant.

RESULTS

We identified a total of 80,724 patients with diabetes between 2009 and 2015. Among these, 12,249 (15.17%) were pioglitazone users, with men representing a higher proportion of both patients with diabetes and pioglitazone users. There were no statistically significant differences in age before or after the intervention for both groups (aSD >0.1), whereas there were statistically significant differences in medical institutions for only patients with diabetes and in comorbidities for both groups (aSD < 0.1) (**Table 1**). Proportions of women, patients aged 50 to 59 years, patients aged 70 to 79 years, and visitors to primary care clinics who used pioglitazone decreased after the intervention, with relative changes of –3.74%, –7.13%, –37.85%, and –7.91%, respectively (**eAppendix B**).

In the preintervention period, the proportion of pioglitazone users was 12.77%, and this decreased to 11.73% after the intervention, resulting in relative and absolute changes of –8.13% and –1.04 percentage points, respectively. However, proportions of patients using sulfonylurea and metformin, DPP-4 inhibitors and GLP-1 analogues, and insulin analogues all showed an increase after the intervention, with use of DPP-4 inhibitors and GLP-1 analogues increasing the most (relative change, 209.03%) (**Table 2**).

The estimates for "intervention" and "time after intervention" are the main coefficients of interest from the segmented regression analysis. As observed from the "time" estimates, use of all antidiabetic drugs except rosiglitazone showed an increasing trend over the entire study period. The "time after intervention" coefficient showed a decreasing trend for use of pioglitazone, sulfonylurea and metformin, and insulin analogues, although the trend for pioglitazone was not statistically significant. Finally, the coefficient for "intervention" was statistically significant only for pioglitazone, sulfonylurea and metformin, and insulin analogues (P <.05) (**Table 3**). The intervention was associated with an immediate decrease in pioglitazone users of 177 per 1000 patients with diabetes (P <.05), whereas there was a decrease of 448 for DPP-4 inhibitors and GLP-1 analogues.

From 2009 to 2015, proportions of pioglitazone and insulin analogue users showed a decreasing trend (**Figure 1**), although this trend was not as steep as that of rosiglitazone. Without the intervention, the predicted proportion of pioglitazone users was 90 per 1000 patients with diabetes, whereas the actually observed proportion was 60 per 1000 patients with diabetes (**Figure 2**). Likewise, by applying a 3-month lag both before and after the intervention, similar results were observed, indicating robustness in results (**eAppendix C**). The numbers of prevalent and incident pioglitazone users are shown, with the general trend of prevalent users increasing and that of incident users decreasing (**eAppendix D**).

DISCUSSION

The prevalence of diabetes shown in our study is in agreement with the 8.0% reported by the Diabetes Fact Sheet in Korea in 2016.[16] Pioglitazone accounted for 15.2% of all antidiabetic drugs used in Korea in this study. All antidiabetic drugs except rosiglitazone and pioglitazone showed an overall increasing trend of use from 2009 to 2015. After the intervention, the relative change in the proportion of pioglitazone users was –8.13%, with the intervention being associated with an immediate decrease of 177 pioglitazone users per 1000 patients with diabetes. Thus, it can be deduced that safety warnings are effective in decreasing the number of patients using the flagged drug.

Upon release of the pioglitazone safety warning by the MFDS, a moderate decrease in the proportion of pioglitazone users was observed. The proportion of pioglitazone users actually began to decrease a few months prior to the intervention, possibly due to

TABLE 1. Characteristics of Patients With Diabetes and Pioglitazone Users Before and After Issue of the Safety Warning

	Patients With Diabetes n (%)							Pioglitazone Users n (%)						
			Intervention							Intervention				
	Total N = 80,724		Before n = 55,585		After n = 74,887			Total n = 12,249		Before n = 7097		After n = 8784		
Characteristics	n	%	n	%	n	%	aSD	n	%	n	%	n	%	aSD
Gender							0.028							0.032
Male	43,928	54.42	29,790	53.59	40,754	54.42		6816	55.65	3885	54.74	4957	56.43	
Female	36,796	45.58	25,795	46.41	34,133	45.58		5433	44.35	3212	45.26	3827	43.57	
Age in years							0.190							0.176
<50	35,018	43.38	20,779	37.38	33,455	44.67		5603	45.74	2905	40.93	4285	48.78	
50-59	20,375	25.24	14,793	26.61	19,266	25.73		3212	26.22	1960	27.62	2253	25.65	
60-69	18,666	23.12	14,570	26.21	16,963	22.65		2695	22.00	1688	23.78	1840	20.95	
70-79	6,059	7.51	4940	8.89	4825	6.44		696	5.68	507	7.14	390	4.44	
≥80	606	0.75	503	0.90	378	0.50		43	0.35	16	0.23	37	0.42	
Medical institution type							0.033							0.114
Tertiary hospital	34,933	43.27	18,557	33.38	29,058	38.80		2787	22.75	1283	18.08	2134	24.29	
General hospital	40,062	49.63	21,263	38.25	33,059	44.15		3761	30.70	1876	26.43	2625	29.88	
Primary care clinic	58,661	72.67	38,571	69.39	52,669	70.33		8046	65.69	4873	68.66	5554	63.23	
Comorbidities														
Ischemic heart disease	3869	4.79	1821	3.28	2802	3.74	0.025	259	2.11	104	1.47	184	2.09	0.058
Myocardial infarction	1421	1.76	578	1.04	1035	1.38	0.007	48	0.39	17	0.24	35	0.40	0.006
Ischemic stroke	5293	6.56	2664	4.79	3861	5.16	0.006	318	2.60	129	1.82	227	2.58	0.076
Hypertension	48,243	59.76	31,485	56.64	42,679	56.99	0.070	6070	49.56	3522	49.63	4212	47.95	0.097
Cancer	7920	9.81	2960	5.33	5976	7.98	0.026	309	2.52	116	1.63	213	2.42	0.054

aSD indicates absolute standardized difference.

healthcare provider awareness arising from various study results reporting an increased risk of bladder cancer associated with pioglitazone use and precautionary actions prior to the national regulatory body announcement.[2,17] A study conducted in Korea examining the trends of antidiabetic drug use in adult patients with diabetes from 2002 to 2013 showed a trend similar to that reported in our study, with the use of TZDs decreasing steadily from a peak of 13.0% in 2009 to 6.5% in 2013, which was lower than the use in 2002 (7.3%).[18]

Key events associated with pioglitazone between 2009 and 2015 had either a positive or negative influence on its use. Before the intervention, in July 2010, a study reported an increased risk of cardiovascular (CV) disease with rosiglitazone use, leading to the withdrawal of the drug in September 2010.[19] This resulted in a sharp increase in the number of pioglitazone users, as results of previous studies suggested that safety warnings lead to a decrease in the respective drug's use while concurrently prompting an increase in the use of drugs with similar mechanisms.[6,20] This particular trend was observed worldwide, including in Australia, Denmark, France, Germany, the Netherlands, Taiwan, and the United States.[7,20-23] However, around the time of rosiglitazone withdrawal, in August 2010 and April 2011, respectively, 2 studies reported a risk of fracture and bladder cancer associated with the use of pioglitazone, leading to a decrease in pioglitazone use.[2,17]

Following the intervention, the MFDS updated pioglitazone's label to contain information on its increased risk of bladder cancer in November 2011. Since the intervention, there has been a continuous decrease in the proportions of both prevalent and incident pioglitazone users. However in January 2013, following positive results of the PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) clinical trial, which reported the benefits of pioglitazone for patients with diabetes with a history of CV disease,[24] insurance reimbursement was extended to include 30-mg pioglitazone on top of the previously reimbursed 15-mg pioglitazone to lessen the burden of patients with diabetes showing no improvement in blood glucose levels with 15-mg pioglitazone.[2] This resulted in an increase in the proportions of both prevalent and incident pioglitazone users. In addition, in November 2013, health insurance benefit coverage criteria to third-line antidiabetic drugs were extended and a pioglitazone complex was released to the market in the following month.[25,26] The aforementioned events resulted in an increase in pioglitazone users.

Despite the intervention, pioglitazone still accounted for 11.73% of all antidiabetic drugs used in the period after the

TABLE 2. Absolute and Relative Changes in the Number of Pioglitazone Drug Users Compared With Those Using Other Antidiabetic Drugs Before and After Issue of the Pioglitazone Safety Warning

Drug	Drug Users, n (%)		Relative Change in Use, % (95% CI)	Absolute Change in Use, Percentage Points (95% CI)
	Before Intervention	After Intervention		
Total	55,585 (100.00)	74,887 (100.00)		
Pioglitazone	7097 (12.77)	8784 (11.73)	−8.13 (−8.41 to −7.86)	−1.04 (−1.40 to −0.68)
Comparator drugs				
Rosiglitazone	2069 (3.72)	5 (0.01)	−99.82 (−240.10 to −41.50)	−3.72 (−3.87 to −3.56)
Sulfonylurea + metformin	52,365 (94.21)	70,750 (94.48)	0.29 (0.27-0.30)	0.27 (0.01-0.52)
DPP-4 inhibitors + GLP-1 analogues	9610 (17.29)	40,011 (53.43)	209.03 (203.62-214.60)	36.14 (35.66-36.62)
Insulin analogues	16,053 (28.88)	25,696 (34.31)	18.81 (18.37-19.26)	5.43 (4.93-5.94)

DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

TABLE 3. Two-Segment[a] Regression Analysis to Estimate the Interaction Between Intervention and Time of Antidiabetic Drug Users

Antidiabetic Drug			Characteristics					
			Intercept (β0)	Time (β1)	Intervention (β2)	Time After Intervention (β3)	DW Test Statistics	Dickey-Fuller Statistics
Study drug	Pioglitazone	β	1780	14.95	−176.59	−11.42	2.0988	−1.94
		Standard error	204.75	8.78	82.45	11.70	*P* <DW: .5741 *P* >DW: .4259	*P* = .3125
		P	<.0001	.0926	.0353	.3323		
Comparator drugs	Rosiglitazone	β	1069	−35.50	−24.24	35.11	1.8998	−2.05
		Standard error	78.10	3.88	48.20	4.90	*P* <DW: .2501 *P* >DW: .7499	*P* = .2670
		P	<.0001	<.0001	.6165	<.0001		
	Sulfonylurea + metformin	β	26,420	148.99	1015	−62.70	2.1387	−1.97
		Standard error	274.89	15.77	317.83	17.23	*P* <DW: .6197 *P* >DW: .3803	*P* = .2976
		P	<.0001	<.0001	.0020	.0005		
	DPP-4 inhibitors + GLP-1 analogues	β	380.45	133.20	−447.72	164.42	1.8508	1.05
		Standard error	187.34	10.09	184.96	11.85	*P* <DW: .1571 *P* >DW: .8429	*P* = .9968
		P	.0456	<.0001	.0178	<.0001		
	Insulin analogues	β	3174	11.37	47.89	−13.79	1.9146	−7.37
		Standard error	25.58	1.49	30.49	1.58	*P* <DW: .2311 *P* >DW: .7689	*P* <.0001
		P	<.0001	<.0001	.1204	<.0001		

DPP-4 indicates dipeptidyl peptidase-4; DW, Durbin-Watson; GLP-1, glucagon-like peptide-1.

[a]Segment 1: January 1, 2009, to June 10, 2011. Segment 2: June 11, 2011, to December 31, 2015.

intervention (July 2011 to December 2015), showing only a minor absolute reduction of 1.04 percentage points. A study in France showed trends between 2006 and 2013 of pioglitazone and other antidiabetic drug use similar to those shown in our study, with decreased incidence of first-line noninsulin glucose-lowering drugs (especially TZDs), but DPP-4 inhibitors and metformin showing opposite trends to those found in our study.[20] We found no discrepancies regarding the trend of antidiabetic drug use, and the decrease in the proportion of pioglitazone users in Korea was considered a result of the intervention.

Our study showed a significant short-term reduction in the proportion of pioglitazone users after the intervention. Without it, high-risk patients, such as those 65 years or older, men, and those with additional risk factors like having been exposed to aromatic chemicals or smoking, would have been vulnerable to bladder cancer with the use of pioglitazone.[27] However, the intervention prevented such vulnerability implicated with the drug from occurring within this high-risk population, thereby minimizing health risks of these patients. Our study showed that the MFDS safety warning for pioglitazone effectively decreased the proportion of pioglitazone users. This finding was also observed in several past studies evaluating the effectiveness of similar interventions.[5,22,28,29] However, the observed effect is not universal because others have found contrasting results.[8] Nonetheless, in Korea, safety warnings along with the pop-up alert system of drug utilization review have been shown to affect prescribing, thereby reducing the proportion of users of the flagged drugs.[30,31] Thus, further studies are needed to validate the true effectiveness of safety warnings.

Strengths and Limitations

The strengths of our study are that, to the best of our knowledge, this is the first population-based study conducted in Korea to examine the temporal trends in the prevalence of pioglitazone users before and after the safety warning issued in June 2011. In addition, we used the nationally representative NHIS-NSC database, which provided a valuable opportunity to investigate and explore the extent of pioglitazone use and its changes over time in Korea. Notably, the NHIS-NSC database underwent strict systematic stratified random sampling with proportional allocation within each stratum by using the individual's total annual medical expenses as a target variable for sampling, resulting in robust representation of the Korean population.[9]

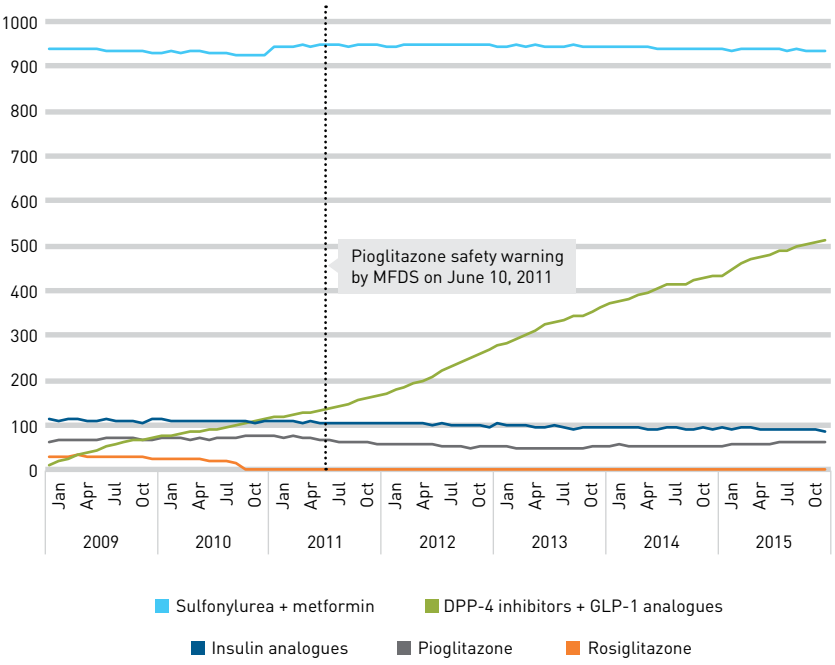
Despite the strengths of this study, the results should be interpreted with caution considering the following limitations. First, the disease codes listed in the NHIS-NSC database may not represent the participant's true disease status, as the codes were created for health insurance claims. Moreover, as this was an ITS study, other interventions besides the intervention of interest may have influenced the number of pioglitazone users. It is therefore difficult to ascertain whether the steady decline in the number of pioglitazone users was either accelerated or slowed by factors other than the intervention of interest (eg, by the release of a new and more effective antidiabetic drug).

CONCLUSIONS

Regulatory actions, such as the pioglitazone safety warning released by the MFDS, have been shown to reduce the likelihood of prescribing the relevant drug. This population-based study demonstrated decreases in the proportion of pioglitazone users compared with the proportions of those using other antidiabetic drugs over time. However, this decreasing trend appeared to have started before the intervention. Those with high potential risk of bladder cancer should be prescribed pioglitazone with caution or should consider alternative treatments.

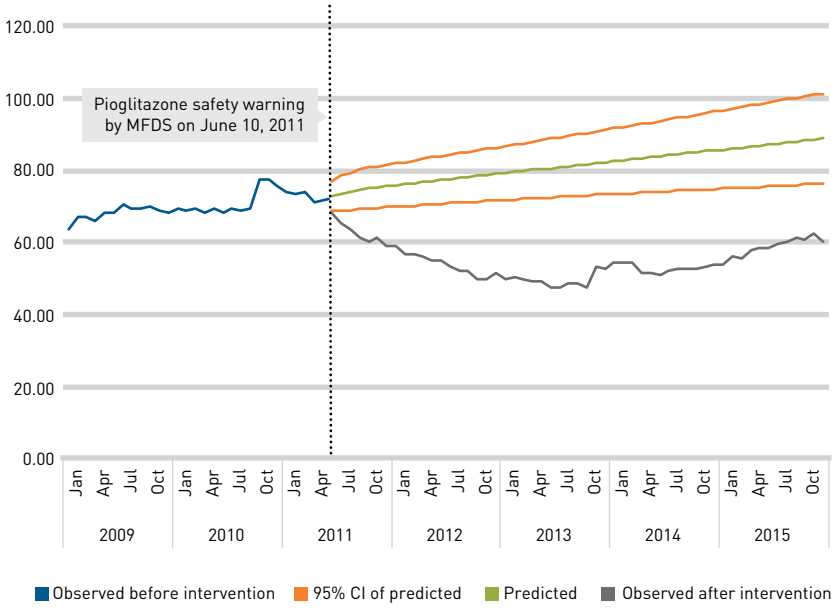
The results of our study are relevant to ongoing research investigating and evaluating the effectiveness of regulatory actions taken by national regulatory bodies. Importantly,

FIGURE 1. Monthly Number of Antidiabetic Drug Users per 1000 Patients With Diabetes Before and After Issue of the Pioglitazone Safety Warning



DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; MFDS, Ministry of Food and Drug Safety.

FIGURE 2. Observed and Predicted Monthly Proportion of Pioglitazone Users Before and After Issue of the Pioglitazone Safety Warning



MFDS indicates Ministry of Food and Drug Safety.

future studies should assess regulatory actions using various study designs, and comparison of their results would allow for conclusions to be drawn regarding the true effectiveness and impact of a regulatory action. ■

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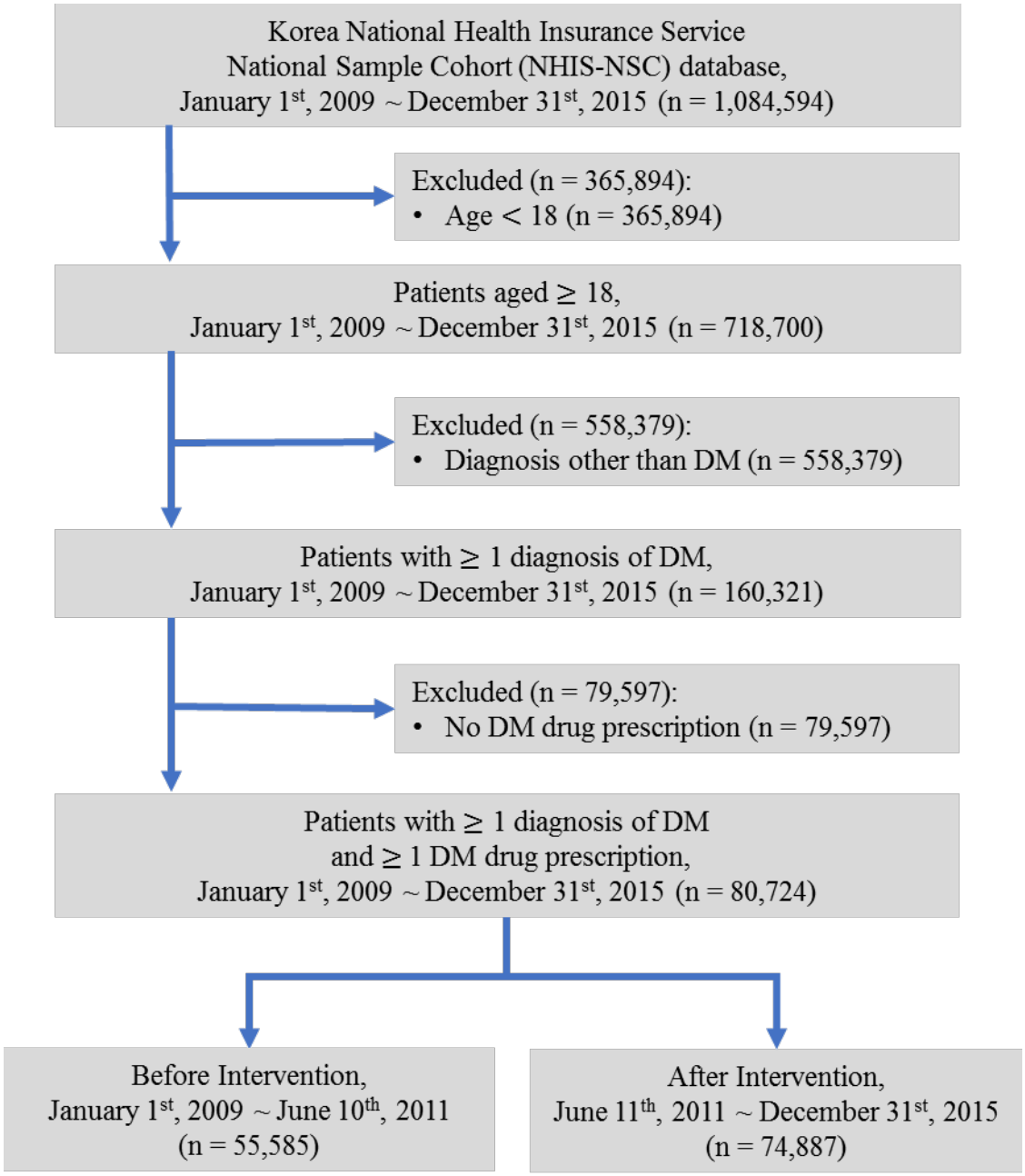
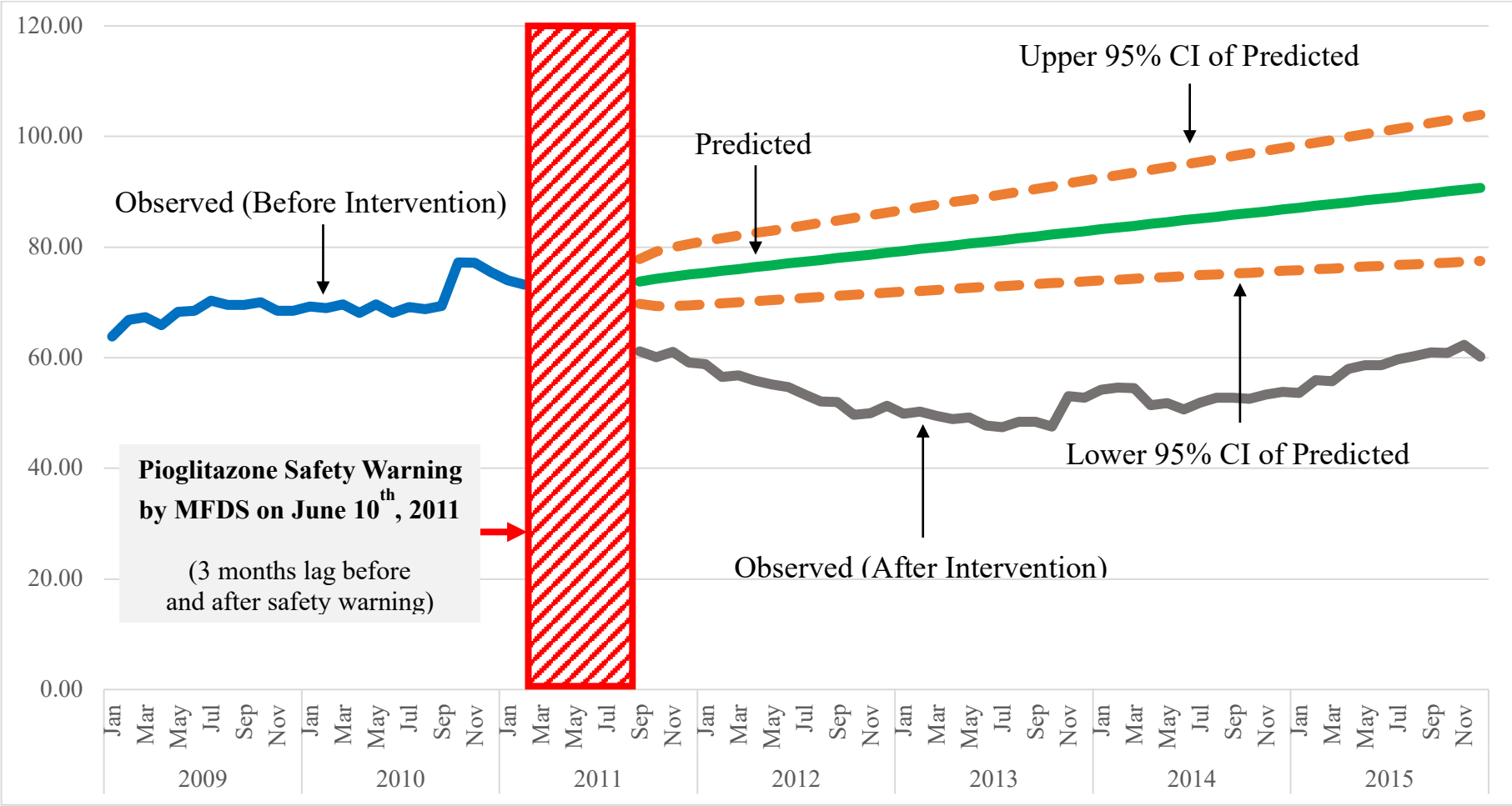
eAppendix A. Study subject selection flow chart showing inclusion and exclusion criteria



eAppendix B. Characteristics of pioglitazone drug users before and after issue of the pioglitazone safety warning

Characteristics	No. of Pioglitazone Users (%)		Relative Change in Use, %	Absolute Change in Use, %
	Before Intervention	After Intervention	(95% CI)	(95% CI)
Total	7,019 (100.00)	8,784 (100.00)		
Sex				
Male	3,885 (54.74)	4,957 (56.43)	3.09 (2.90 to 3.29)	1.69 (0.14 to 3.25)
Female	3,212 (45.26)	3,827 (43.57)	-3.74 (-3.98 to -3.51)	-1.69 (-3.25 to -0.14)
Age (years)				
~ 49	2,905 (40.93)	4,285 (48.78)	19.18 (18.00 to 20.43)	7.85 (6.30 to 9.40)
50 ~ 59	1,960 (27.62)	2,253 (25.65)	-7.13 (-7.65 to -6.64)	-1.97 (-3.35 to -0.58)
60 ~ 69	1,688 (23.78)	1,840 (20.95)	-11.93 (-12.86 to -11.07)	-2.84 (-4.14 to -1.53)
70 ~ 79	507 (7.14)	390 (4.44)	-37.85 (-43.36 to -33.04)	-2.70 (-3.44 to -1.97)
80 ~	16 (0.23)	37 (0.42)	86.84 (48.27 to 156.23)	0.20 (0.02 to 0.37)
Medical Institution Type				
Tertiary hospital	1,283 (18.08)	2,134 (24.29)	34.38 (31.82 to 37.16)	6.22 (4.95 to 7.48)
General hospital	1,876 (26.43)	2,625 (29.88)	13.05 (12.17 to 14.00)	3.45 (2.05 to 4.85)
Primary care clinic	4,873 (68.66)	5,554 (63.23)	-7.91 (-8.46 to -7.41)	-5.43 (-6.91 to -3.96)

eAppendix C. Observed and predicted monthly proportion of pioglitazone users before and after issue of the pioglitazone safety warning with three-month lag both before and after the safety warning



eAppendix D. Incident and prevalent pioglitazone users before and after the pioglitazone safety warning by month from January 2009 to December 2015