보건학석사 학위논문

Prescribing Trend of Pioglitazone after Safety Warning Release in South Korea

식품의약품안전처의 안전성서한 발표 후 피오글리타존의 처방 양상변화

2018년 8월

서울대학교 보건대학원

보건학과 보건학전공

정 한 얼

Abstract

Prescribing Trend of Pioglitazone after Safety Warning Release in South Korea

Han Eol Jeong

Epidemiology Major

Department of Public Health Science

Graduate School of Public Health

Seoul National University

Introduction : On June 10th, 2011, South Korea's Ministry of Food and Drug Safety (MFDS) issued a safety warning which reported an increased risk of bladder cancer among those prescribed with pioglitazone. Hence, this study was conducted to quantify the prevalence of pioglitazone users before and after the safety warning.

Methods : To estimate the proportion of pioglitazone and other antidiabetic drugs by using an interrupted time series design between January 1st, 2009 and December 31st, 2015 in South Korea using the

National Health Insurance Service-National Sample Cohort database. Study drugs were pioglitazone and other antidiabetic drugs such as, rosiglitazone, sulfonylurea + metformin, dipeptidyl peptidase (DPP)-4 inhibitors + glucagon-like peptide (GLP)-1 analogues, and insulin analogues. Relative and absolute change in drug users were estimated with 95% confidence intervals (CI). To estimate the impact of the intervention, the monthly number of pioglitazone and antidiabetic drug users among total diabetes mellitus (DM) patients were presented by applying ordinary least-squares regression and maximum likelihood estimation. A segmented regression approach was utilized to analyze the interrupted time series design by testing the effect of an intervention on the outcome of interest using an appropriately defined impact model. The assumption of autocorrelation for time-series data was assessed using Durbin-Watson (DW) statistics and seasonality or stationarity was assessed using the Dickey-Fuller (DF) unit root test.

Results : From our study period, there were a total of 80,724 DM patients and amongst them, 12,249 were pioglitazone users (15.17%). The relative change after the intervention for pioglitazone was -8.13 (95% CI: -8.41 to -7.86) and its absolute change was -1.04 (95% CI: -1.40 to -0.68). The relative change was -99.82 (95% CI: -240.10 to -41.50) for

rosiglitazone, 0.29 (95% CI: 0.27 to 0.30) for sulfonylurea + metformin, 209.03 (95% CI: 203.62 to 214.60) for DPP-4 inhibitors + GLP-1 analogues, and 18.81 (95% CI: 18.37 to 19.26) for insulin analogues. The MFDS safety warning for pioglitazone was associated with an immediate 177 decrease of pioglitazone users ($p<0.05$). For pioglitazone's "Time" trend, no autocorrelation was present (DW: 2.0988, p<DW: 0.5741, p>DW: 0.4259) whereas stationarity was present (DF Unit Root: -1.94, $p>0.05$). If the intervention had not been implemented, the proportion of pioglitazone users would have shown a continuous increasing trend, eventually reaching a proportion of 90 per 1,000 DM patients, which is approximately 50% greater than the proportion at December 31st, 2015.

Conclusions : The safety warning on pioglitazone led to a moderate decrease in pioglitazone users amongst DM patients. Despite the decrease, pioglitazone is still widely prescribed to DM patients, stressing the need to develop and implement strategies to assess and enhance drug safety.

Keywords: Pioglitazone, Diabetes Mellitus, Safety Warning, Interrupted Time Series, Ministry of Food and Drug Safety

Student Number: 2016-22593

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I. Introduction

1.1Background

Pioglitazone (brand name, Actos), a prescription drug of the thiazolidinedione (TZD) class, is an anti-hyperglycemic agent that, when insulin resistance is present, increases hepatic and peripheral insulin sensitivity, resulting in the inhibition of hepatic gluconeogenesis and increase of both peripheral and splanchnic glucose uptake (John Waugh, 2006). In short, it is a drug used to treat type 2 diabetes mellitus (T2DM). TZDs were first introduced in the late 1990s and were quickly accounted for over 30% of office-based T2DM prescriptions (Cohen, Rabbani, Shah, & Alexander, 2010). To date, pioglitazone is the only TZD still commonly used worldwide upon the discontinuation of troglitazone and restricted use of rosiglitazone (Avandia), with lobeglitazone (Duvie) approved and utilized in recent years only in South Korea (Korea) (Lewis et al., 2015). Restricted use of rosiglitazone was taken place, as result from a meta-analysis of 42 randomized clinical trials found a 43% increased risk of myocardial infarction and also an insignificant 64% risk in cardiovascular (CV) deaths associated with the use of rosiglitazone (Steven E. Nissen, 2007).

However, in June 2011, a study done in France suggested an increased risk of bladder cancer among patients that were treated with pioglitazone for over a year. This finding eventually resulted in the French Agency for the Safety of Health Products (AFSSAPS) to withdraw the drug from the market along with a warning announcement regarding its safety issues (AFSSAPS, 2010). Another study conducted in the United States (US) also proposed similar findings, reporting a possible increased risk of bladder cancer in patients prescribed with pioglitazone for two years or more, when compared to that of those who were not (Lewis et al., 2011). Following these results, the US Food and Drug Administration (FDA) issued a drug safety communication on the potential increased risk of bladder cancer in patients who took pioglitazone for longer than a year (FDA, 2011), followed by warnings from both the European Medicines Agency (EMA) (Agency, 2011) and the Australian Therapeutic Goods Administration (TGA) (Administration, 2013), alarming parallel concerns with the FDA. Upon release of these safety warnings from multiple nations fore mentioned, on June 10th, 2011, Korea's Ministry of Food and Drug Safety (MFDS) released a safety warning announcement (hereby, intervention) of their own, stating that pioglitazone (first released in Korea on January 16th, 2001) should be prescribed with caution and informed physicians and

pharmacists with relevant information and guidelines (MFDS, 2011).

A French study on the impact of pioglitazone's regulatory withdrawal on antidiabetic drug use and health in diabetic patients found the accompaniment of significant alterations in the utilization of some antidiabetics along with no adverse impact of pioglitazone withdrawal on either hospitalization or death rates of T2DM patients (Pariente et al., 2017). Likewise, an Australian study on the utilization trends of two TZDs, rosiglitazone and pioglitazone, before and after the issue of their respective safety warnings found that safety warnings were associated with a decrease in the utilization of both drugs but only minor effects were seen after the bladder cancer warnings on pioglitazone utilization (Suvimol Niyomnaitham, 2014). Furthermore, a study conducted in Spain found that although CV warnings affected mainly rosiglitazone and not pioglitazone, rosiglitazone was more utilized than pioglitazone up until the very end of 2008. This trend was not only found in Spain alone, but a similar pattern was also observed in a fellow European nation, the United Kingdom (UK) (Leal et al., 2013). On the contrary, a rather contrasting result was found in the US, as rosiglitazone was less utilized than pioglitazone commencing from the first month upon the release of the CV safety warning of rosiglitazone (Carracedo-Martinez & Pia-Morandeira, 2016). Equally, another study done in the UK found

that the pattern of TZD prescriptions changed after May 2007, which was after the launch of the US FDA safety alert. This then led to a dramatic decrease in rosiglitazone use, followed by suspension by the European Union in 2010 (Leal et al., 2013). Moreover, according to Taiwanese study results, the Taiwan FDA regulatory actions for pioglitazone communicated possible risks of bladder cancer. In turn, the safety warning had an impact on the use of pioglitazone and the quality use of the drug among high-risk patients (Hsu, Ross-Degnan, Wagner, Zhang, & Lu, 2015).

Nonetheless, despite results from previous studies, these studies analyzed data either for a relatively short period of time or the number of study participants were limited, leaving room for bias. A pioglitazone withdrawal study done in France had a time period set from January 2010 to December 2014, where the drug withdrawal took place in January 2011. This setting resulted in only 12 monthly observations to be made for the pre-withdrawal period, which is quite limited for an interrupted time-series study to be conducted (Pariente et al., 2017). Moreover, a Spanish study analyzed data for only two years from January 2006 to December 2008, an even shorter period, where the interventions were as follows: health warnings throughout 2007 and January 2008. Not only was the study period too short, the number of study subjects were limited

as well, with only 386,484 participants (Carracedo-Martinez & Pia-Morandeira, 2016). Above all, the use of pioglitazone following the announcement of MFDS's safety warning have not yet been described in Korea.

1.2 Purpose

This study was conducted to explore and quantify the prevalence of pioglitazone users before and after the intervention on June 10th, 2011, from January 2009 to December 2015, a study period of seven years. Furthermore, we evaluated the impact of the intervention not only on pioglitazone but also other antidiabetic drugs.

1.3 Hypotheses

To provide the scientific evidence throughout the study, two hypotheses were proposed as below:

First, upon announcement of the pioglitazone safety warning by the Korean MFDS, the number of pioglitazone users will decrease.

Second, safety warning is an effective national regulatory intervention to prevent incident adverse outcomes.

II. Methods

2.1 Data

This study was conducted using the nationwide population-based National Health Insurance Service-National Sample Cohort (NHIS-NSC) database, composed of approximately one million people that were randomly extracted from almost the entire Korean population of 50 million, by using national claims data from January 1st, 2009 to December 31st, 2015. Systematic stratified random sampling with proportional allocation within each stratum was conducted for the NHIS-NSC database, using the individual's total annual medical expenses as a target variable for sampling. Furthermore, the NHIS-NSC database contains representative population-based cohort data, which is a major strength as it ensures its applicability in research. Likewise, the data is large-scale, extensive and stable as it is constructed based on nationwide health insurance data generated by the government or public institutions' involvement. The NHIS-NSC database, accessible by those in need through the National Health Insurance Sharing Service (NHISS), contains anonymized patient codes along with sociodemographic

characteristics, medical care history (medical treatment and health examination), medical care institution types, *International Statistical Classification of Diseases and Related Health Problems 10th Edition, Clinical Modification* (ICD-10-CM) diagnosis codes and drug prescription information, including their generic name, prescription date, duration and dosage (Lee., Lee., Park., Shin., & Kim., 2017).

2.2 Study Design

The interrupted time series (ITS) study design, a type of quasi-experimental research, is the strongest design of its type, widely used when evaluating the effectiveness of population-level health interventions that have been implemented at a clearly defined point in time (Lopez Bernal, Cummins, & Gasparrini, 2016). The ITS design is particularly useful when randomized research is not feasible or reckoned unethical for various reasons. The design generally involves constructing a time series of population-level rates for a particular quality improvement focus and statistically testing for a variation in the outcome rate in the time periods before and after implementation of an intervention designed to alter the outcome (Penfold & Zhang, 2013).

A segmented regression approach was utilized to analyze the ITS design by testing the effect of an intervention on the outcome of interest using an appropriately defined impact model. Methodological considerations specific to ITS analysis include the following: possible time-varying confounders (seasonal trends, concurrent events to the intervention) and potential autocorrelation of data (Lopez Bernal et al., 2016). Major strengths of the ITS include controlling for secular trends,

evaluating outcomes using population-level data, representation of clear graphical results, conducting stratified analyses with ease, and evaluating both intended and unintended consequences of interventions. On the contrary, limitations are, the need of a minimum of eight time periods both before and after an intervention in order to evaluate changes statistically, difficulty in analyzing the independent impact of separate components of a program that are implemented close together in time, and finally the existence of a suitable control population (Penfold & Zhang, 2013).

2.3 Study Subjects

Study subjects consisted of all those aged 18 and above and had a diagnosis of DM (ICD-10-CM: E10 - E14) at least once, in either an inpatient or outpatient setting, and also a prescription of an antidiabetic drug between January 1st, 2009 and December 31st, 2015. The period before (January 2009 – May 2011) and after (June 2011 – December 2015) the implementation of intervention (June 2011), was set as shown (Figure 1). Those younger than 18 were excluded from the study (Figure 2).

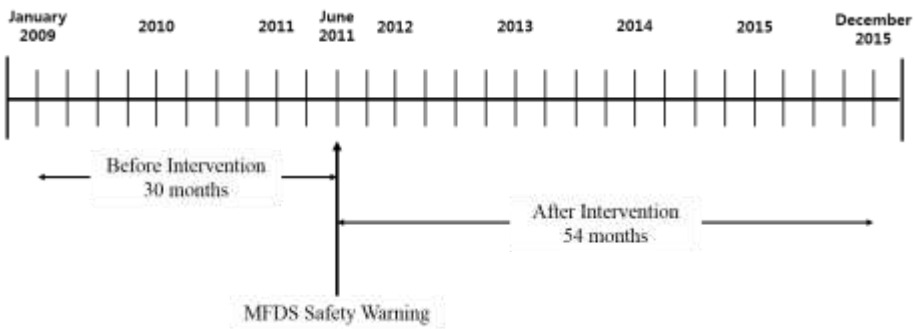

Figure 1. Study Period from January 2009 to December 2015

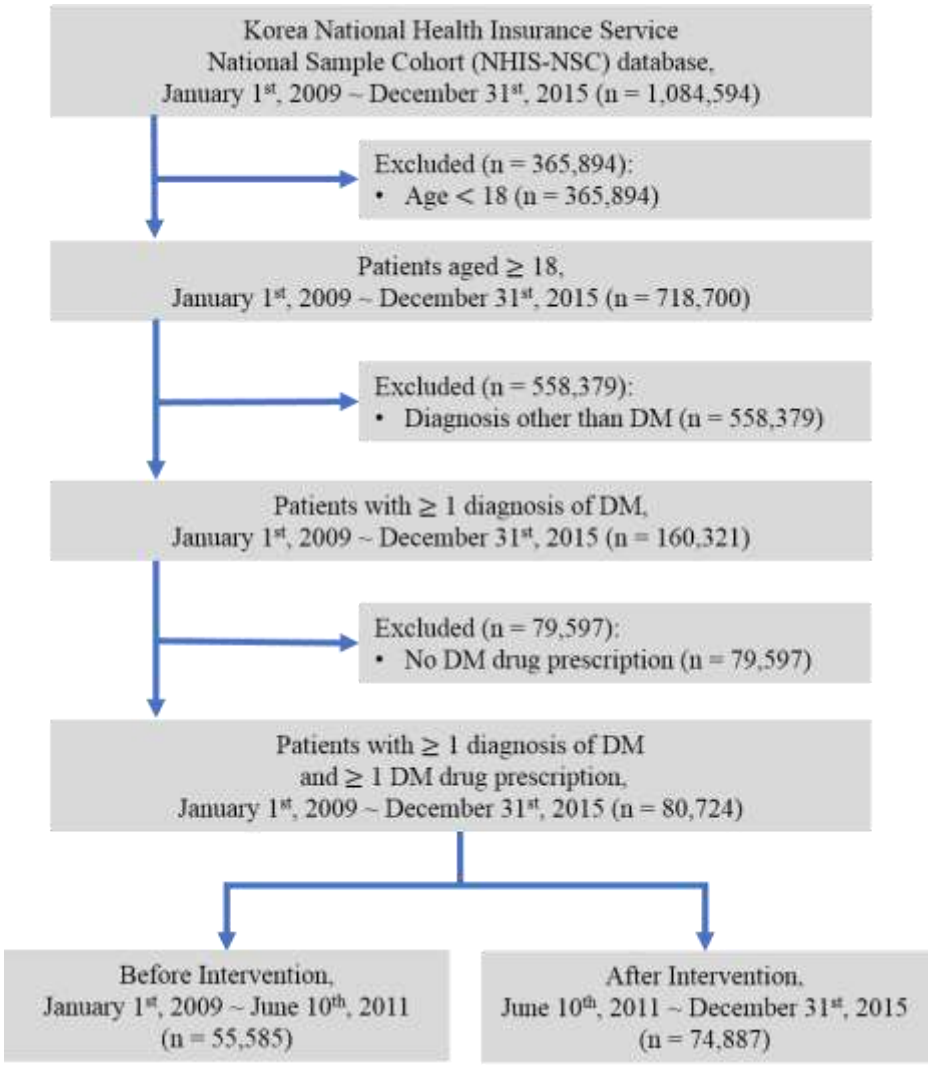

Figure 2. Study subject selection flow and inclusion and exclusion criteria

2.4 Definition of Exposure and Outcome

The exposure was set according to the intervention, as either before or after. Users of antidiabetic drugs were defined as the proportion of each antidiabetic drug user divided by the total number of DM patients, calculated on a monthly basis. Pioglitazone (World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system code, A10BG03) users, along with other types of antidiabetics (A10) were classified into four mutually exclusive categories, rosiglitazone (A10BG02) users, sulfonylurea derivatives (A10BB) and metformin (A10BA02) users, dipeptidyl peptidase-4 (DPP-4) inhibitor (A10BH) and glucagon-like peptide-1 (GLP-1) analogues (A10BJ) users, and insulin analogues (A10A) users, which the latter four were considered as comparator antidiabetic drugs to pioglitazone.

2.5 Covariates

Demographic variables such as age and gender were identified and extracted from the database. Age was categorized into five groups, < 50 years, 50 ~ 59 years, 60 ~ 69 years, 70 ~ 79 years and ≥ 80 years. As for medical institution types, the following criteria was used: tertiary hospitals (≥ 500 beds), general hospitals (30 - 499 beds), and clinics (< 30 beds). For comorbidities, those with a history of ischemic heart disease (ICD-10-CM: I24, I25), myocardial infarction (ICD-10-CM: I21), ischemic stroke (ICD-10-CM: I63), hypertension (ICD-10-CM: I10 - I15) and cancer (ICD-10-CM: C00 – D49) in equivalent months as the month of drug prescriptions were used.

2.6 Statistical Analysis

Age, gender, medical institution types and comorbidities of DM patients and pioglitazone users were presented as frequencies and proportions. The proportion of antidiabetic drugs users in DM patients were calculated as the number of antidiabetic drug users over total DM patients for periods before and after the intervention. The absolute standardized difference (aSD) was calculated for all categorical variables. The absolute change in users was calculated as the change between the proportions before and after the intervention. As for the relative change in users, it was calculated as dividing the absolute change by the proportion of before the intervention. 95% confidence intervals (CIs) were calculated for both absolute and relative changes.

In order to estimate the impact of the intervention, the monthly number of pioglitazone and antidiabetic drug users among total DM patients were presented by applying ordinary least-squares regression and maximum likelihood estimation. A segmented regression model was used where the regression model was estimated using the 30 months of available data preceding the intervention. Using pre-intervention's 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 or pioglitazone users per 1000 DM patients. Independent variables included time (in months), intervention indicator for January 2009 – December 2015, and time after intervention (in months) for June 2011 – December 2015. The intervention indicator variable was set as a dichotomous variable, where it was either '0' (before) or '1' (after). The time after intervention was a continuous variable representing the number of months after the onset of the intervention (June 2011) and was set to '0'for all months prior to the intervention. The regression model was as the following (Jandoc, Burden, Mamdani, Levesque, & Cadarette, 2015; Lopez Bernal et al., 2016; Penfold & Zhang, 2013):

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

The assumption of autocorrelation for time-series data was assessed using Durbin-Watson (DW) statistics and seasonality or stationarity was assessed using the augmented Dickey-Fuller (ADF) unit root test as below (Anaby et al., 2014). For the DW statistics, where e_t represents the residual associated with the observation at time *t*, where *T* represents the number of observations, if DW is calculated to be 2, it can be inferred that there is no autocorrelation present, in which the DW statistics lies

between 0 and 4. It is generally regarded that when the DW statistics is less than 1.0, there may be cause for serious autocorrelation (DW > 2 infers negative correlation and DW < 2 infers positive autocorrelation). Two *p*-values are computed from the DW statistics where, $p <$ DW tests for positive autocorrelation and $p >$ DW tests for the counterpart, negative autocorrelation. A *p*-value of 0.5 or greater for both *p*-values indicate that autocorrelation is not present and thus, correction for autocorrelation is not needed (Bhargava, 1982).

$$\mathrm{DW} = \frac{\sum_{t=2}^{\mathrm{T}}(e_t - e_{t-1})^2}{\sum_{t=1}^{\mathrm{T}} e_t^2}$$

As for the ADF procedure, it is used to test the null hypothesis of whether the times series has a unit root within the autoregressive model polynomial. The ADF statistic is a negative number in which, the more negative the value, stronger the null hypothesis is rejected. The null hypothesis ($\hat{\gamma} = 0$) is that a unit root is present in a time series sample whereas the alternative hypothesis ($\hat{\gamma} < 0$) is stationarity. To test for a unit root, the equation below is used, along with the ADF equation. Unlike the DW test, for the ADF statistics, if the *p*-value is less than 0.5, then the null hypothesis can be rejected, accepting the alternative hypothesis, which is that the time series data is stationary (Greene, 1997).

$$\Delta y_t = \delta y_{t-1} + u_t$$

$$DF_{\mathrm{T}} = \frac{\hat{\gamma}}{SE\,(\hat{\gamma})}$$

All statistical analyses were performed using SAS Enterprise Guide statistical application program provided by the NHIS and accessed through a virtual machine system (Release 9.71, SAS Institute Inc., Cary, NC, US). A two-tailed value of $p < 0.05$ or aSD < 0.10 were considered to be statistically significant. The study protocol was approved by the Institutional Review Board of Seoul National University (IRB No. E1711/003-005) and obtaining informed consent from the study population was waived by the board.

III. Results

3.1 Diabetes patients and pioglitazone user's characteristics

We identified a total of 80,724 DM patients between January 1st, 2009 and December 31st, 2015 and among them, 12,249 (15.17%) were pioglitazone users, with males representing a higher proportion of 54.42% and 55.65%, for both DM patients and pioglitazone users, respectively. There were no statistically significant differences between the age proportion before and after the intervention for both DM patients and pioglitazone users (aSD < 0.10). As for DM patients, those in below 50 comprised the most with 35,018 patients (43.38%), which was also the case for pioglitazone users with 5,603 patients (45.74%). For both DM patients and pioglitazone users, primary care clinic was the dominant medical institution type with 58,661 (72.67%) and 8,046 (65.69%), respectively. Notably, the number of patients for all comorbidities increased after the intervention, with cancer showing the greatest increase from 5.33% to 7.98% for DM patients and 1.63% to 2.42% for pioglitazone users (Table 1).

Table 1. DM patients and pioglitazone user's characteristics before and after the safety warning

Characteristics	DM Patients N (%)							Pioglitazone Users N (%)						
	Total		Intervention				aSD†	Total		Intervention				aSD†
			Before		After					Before		After		
	N = 80,724		N = 55,585		N = 74,887			N = 12,249		N = 7,097		N = 8,784		
	N	%	N	%	N	%		N	%	N	%	N	%	
Gender							0.028							0.032
Male	43,928	54.42	29,790	53.59	40,754	54.42		6,816	55.65	3,885	54.74	4,957	56.43	
Female	36,796	45.58	25,795	46.41	34,133	45.58		5,433	44.35	3,212	45.26	3,827	43.57	
Age (years)							0.190							0.176
~ 49	35,018	43.38	20,779	37.38	33,455	44.67		5,603	45.74	2,905	40.93	4,285	48.78	
50 ~ 59	20,375	25.24	14,793	26.61	19,266	25.73		3,212	26.22	1,960	27.62	2,253	25.65	
60 ~ 69	18,666	23.12	14,570	26.21	16,963	22.65		2,695	22.00	1,688	23.78	1,840	20.95	
70 ~ 79	6,059	7.51	4,940	8.89	4,825	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	

†aSD: absolute standardized difference

*aSD ≤ 0.1

Table 1. DM patients and pioglitazone user's characteristics before and after the safety warning (cont'd)

Characteristics	DM Patients N (%)							Pioglitazone Users N (%)						
	Total		Intervention				aSD†	Total		Intervention				aSD†
			Before		After					Before		After		
	N = 80,724		N = 55,585		N = 74,887			N = 12,249		N = 7,097		N = 8,784		
	N	%	N	%	N	%		N	%	N	%	N	%	
Medical Institution Type							0.033							0.114
Tertiary Hospital	34,933	43.27	18,557	33.38	29,058	38.80		2,787	22.75	1,283	18.08	2,134	24.29	
General Hospital	40,062	49.63	21,263	38.25	33,059	44.15		3,761	30.70	1,876	26.43	2,625	29.88	
Primary Care Clinic	58,661	72.67	38,571	69.39	52,669	70.33		8,046	65.69	4,873	68.66	5,554	63.23	
Comorbidities														
Ischemic Heart Disease	3,869	4.79	1,821	3.28	2,802	3.74	0.025	259	2.11	104	1.47	184	2.09	0.058
Myocardial Infarction	1,421	1.76	578	1.04	1,035	1.38	0.007	48	0.39	17	0.24	35	0.40	0.006
Ischemic Stroke	5,293	6.56	2,664	4.79	3,861	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	6,070	49.56	3,522	49.63	4,212	47.95	0.097
Cancer	7,920	9.81	2,960	5.33	5,976	7.98	0.026	309	2.52	116	1.63	213	2.42	0.054

†aSD: absolute standardized difference

*aSD ≤ 0.1

3.2 Monthly number of antidiabetic drug users before and after the pioglitazone safety warning

For the entire study period of seven years, from 2009 to 2015, users of DPP-4 inhibitors + GLP-1 analogues showed an overall rising trend whereas rosiglitazone users showed a clear declining trend, dropping to zero eventually around September 2010, with insulin analogues showing either a very slight increase or rather constant trend. As for users of pioglitazone, insulin analogues, they both generally showed a decreasing trend, although not as steep as rosiglitazone. In case of sulfonylurea + metformin users, over time, number of users were more or less similar showing a plateau trend (Figure 3 and 4).

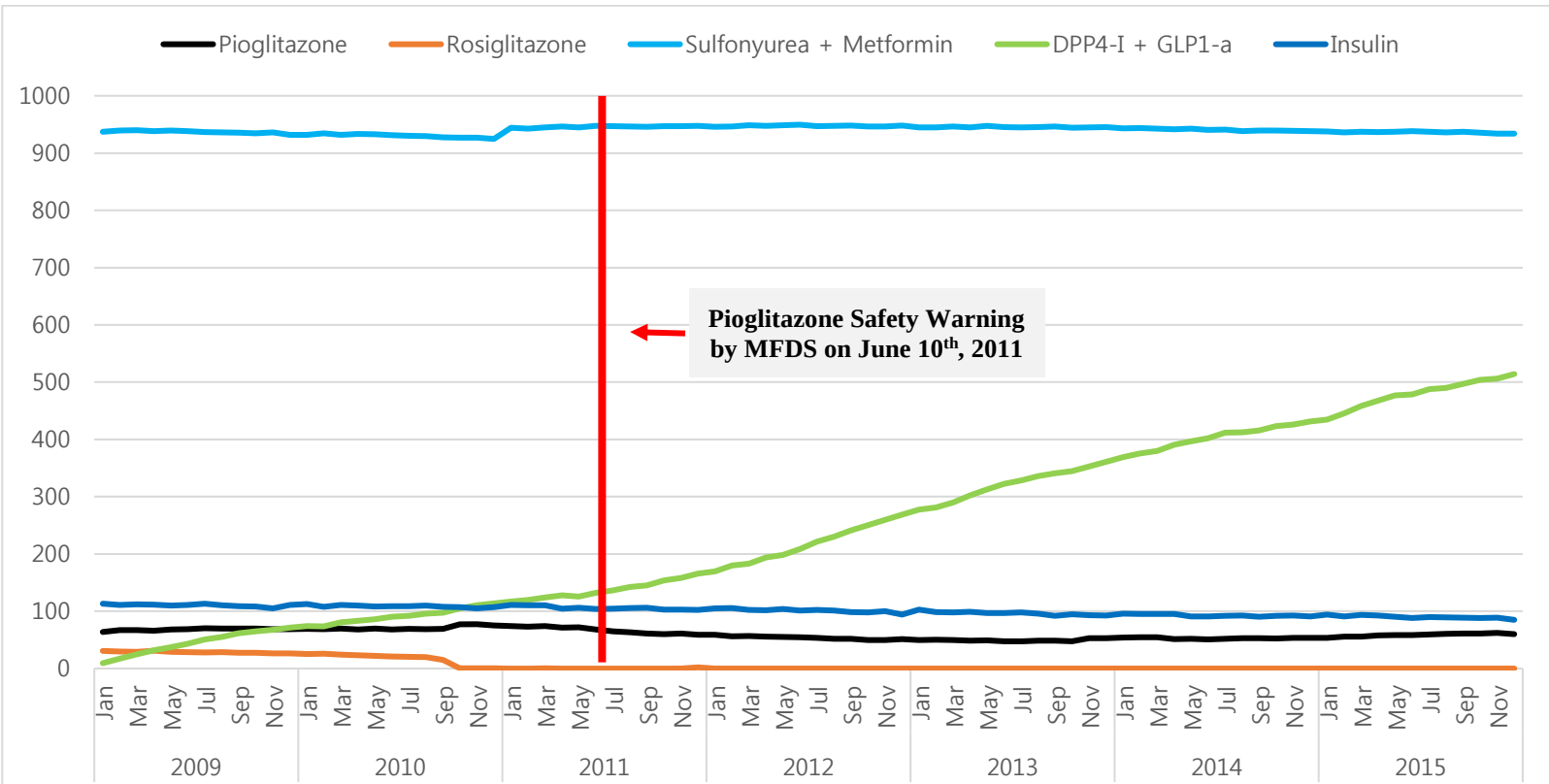

Figure 3. Monthly number of antidiabetic drug users per 1,000 DM patients before and after the pioglitazone safety warning

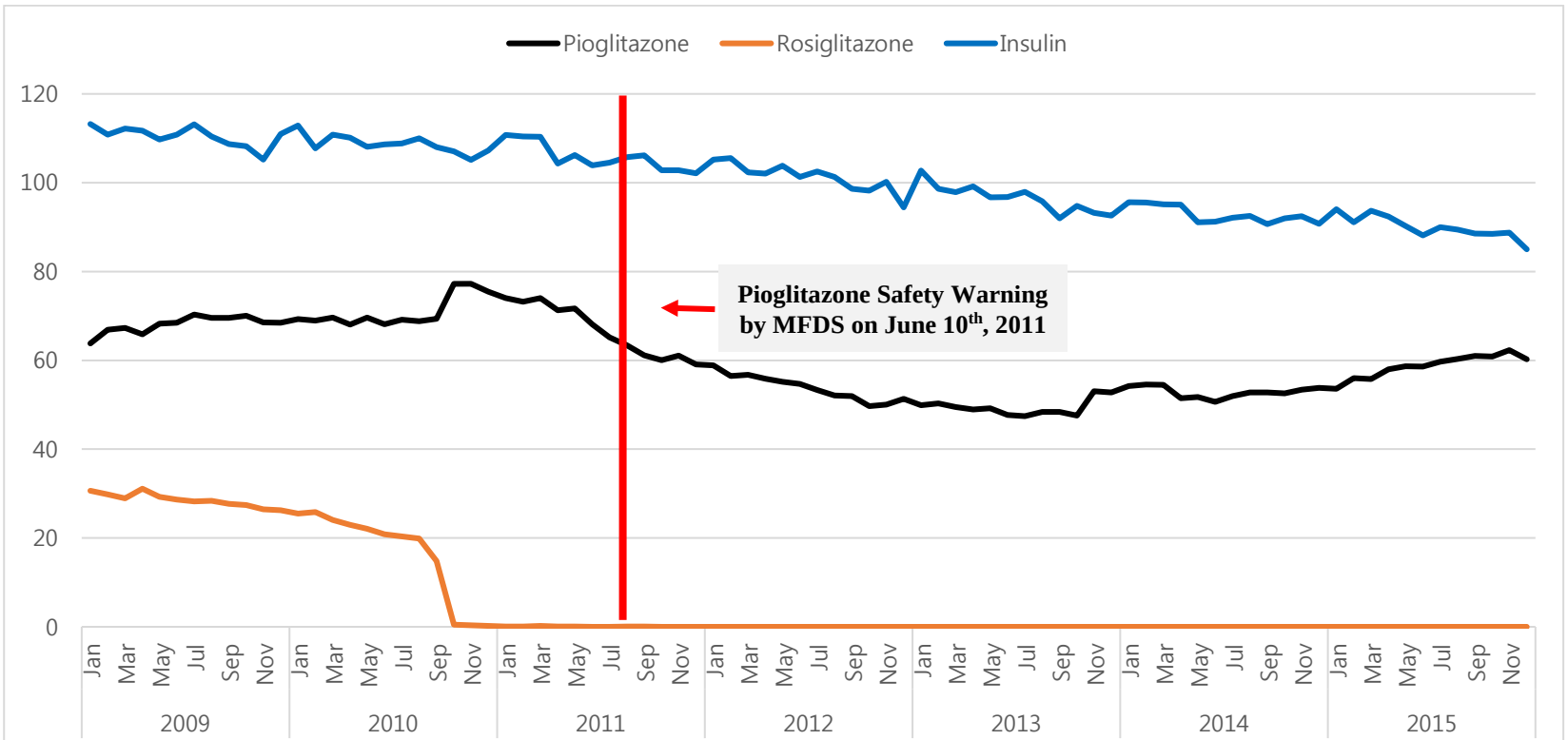

Figure 4. Monthly number of pioglitazone, rosiglitazone and insulin analogues users per 1,000 DM patients before and after the pioglitazone safety warning

3.3 Switching between pioglitazone and antidiabetic drug users from January 2009 to December 2015

Figures 5 to 8 show the monthly number of drug switching between pioglitazone and other antidiabetic drug users from January 2009 to December 2015. In all four figures, the black line represents the incident number of pioglitazone users and the blue and red lines represent the number of antidiabetic drug to pioglitazone switch users and number of pioglitazone to antidiabetic drug switch users, respectively. A point to note is that antidiabetic drugs are commonly used as a combination treatment rather than single treatment.

Around October 2010, the point in time when rosiglitazone, a drug of the TZD class, was withdrawn from the market due it increasing risk of CV diseases, the number of drug users switching from rosiglitazone to pioglitazone surged quite dramatically, reflecting the sudden sharp peak of the blue line, which shows the number of rosiglitazone->pioglitazone drug switchers (Figure 5).

From May 2011 to September 2012, there has been a significant number of drug users switching from pioglitazone to sulfonylurea + metformin, which is turn reflected in the number of incident pioglitazone

users, as it also shows a similar trend (Figure 6). As for the switch between pioglitazone and DPP4-inhibitor + GLP-1 analogues, a steady switch from one to another is observed over time, with a major increase in pioglitazone to DPP-4 inhibitor and GLP-1 analogues users October 2013 contributing to the respective increase in incident pioglitazone users (Figure 7). The number drug switch among pioglitazone and insulin users was rather stable, contributing minimally to the incident number of pioglitazone users (Figure 8).

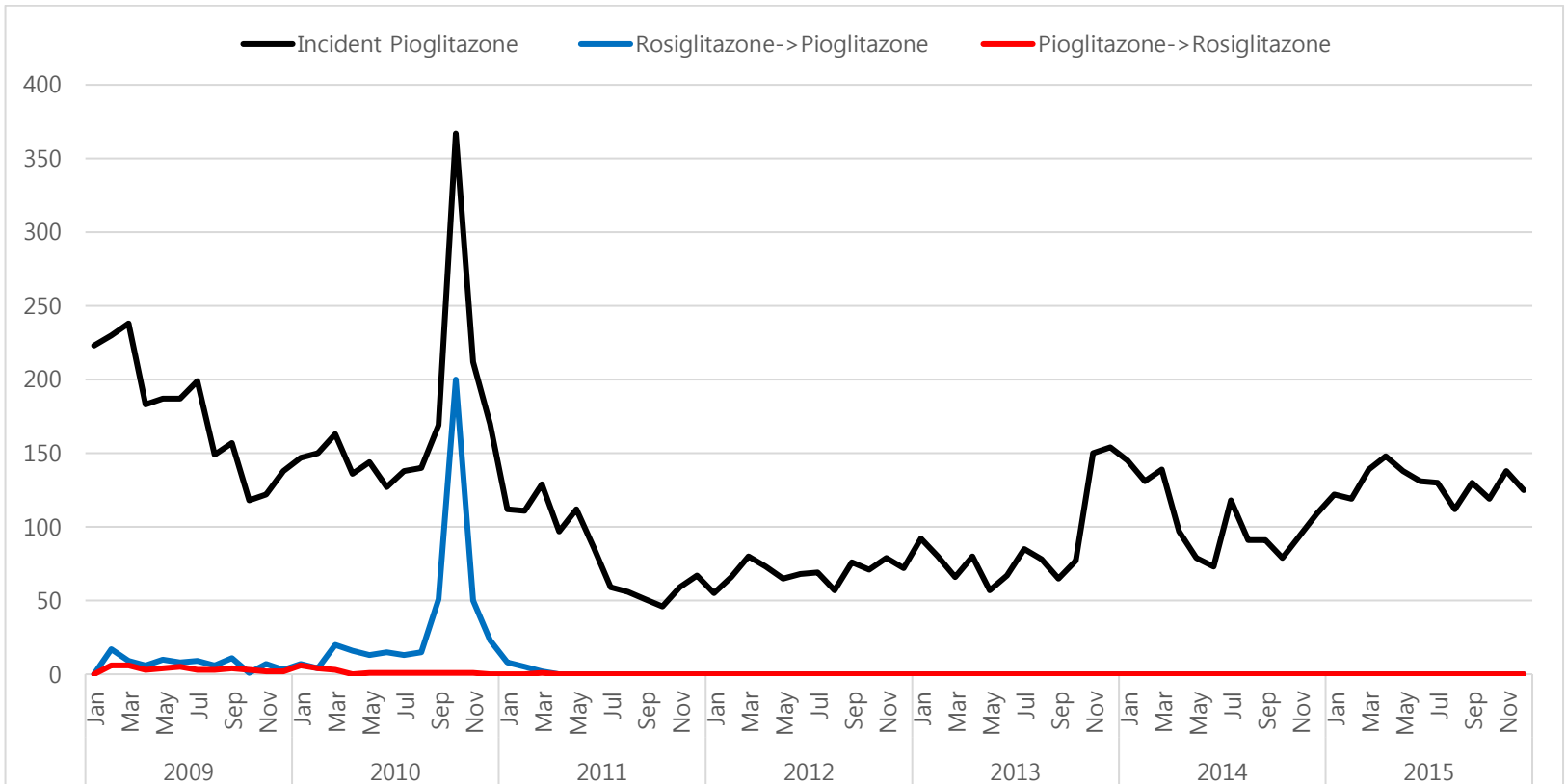

Figure 5. Monthly number of drug switching between pioglitazone and rosiglitazone users from January 2009 to December 2015

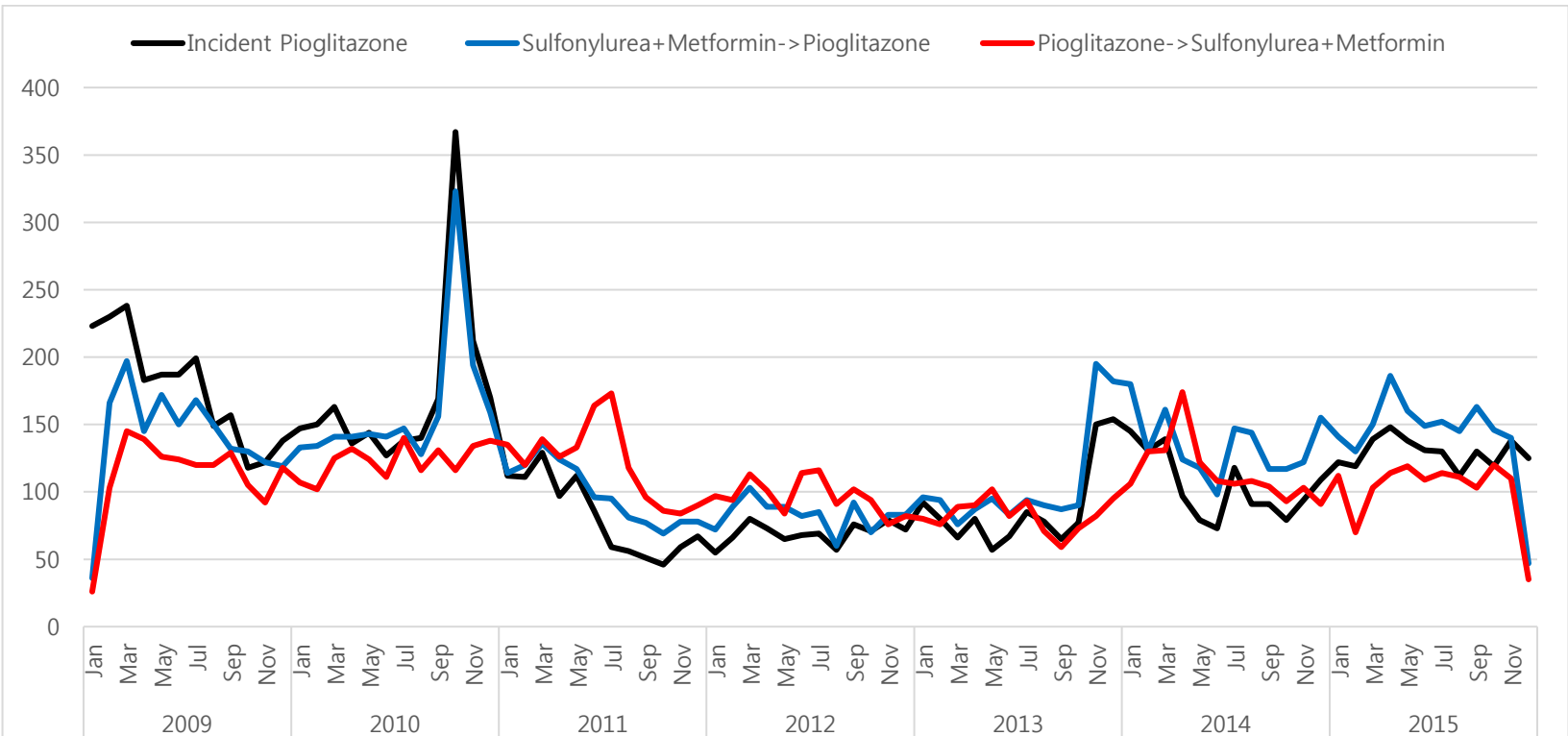

Figure 6. Monthly number of drug switching between pioglitazone and sulfonylurea + metformin users from January 2009 to December 2015

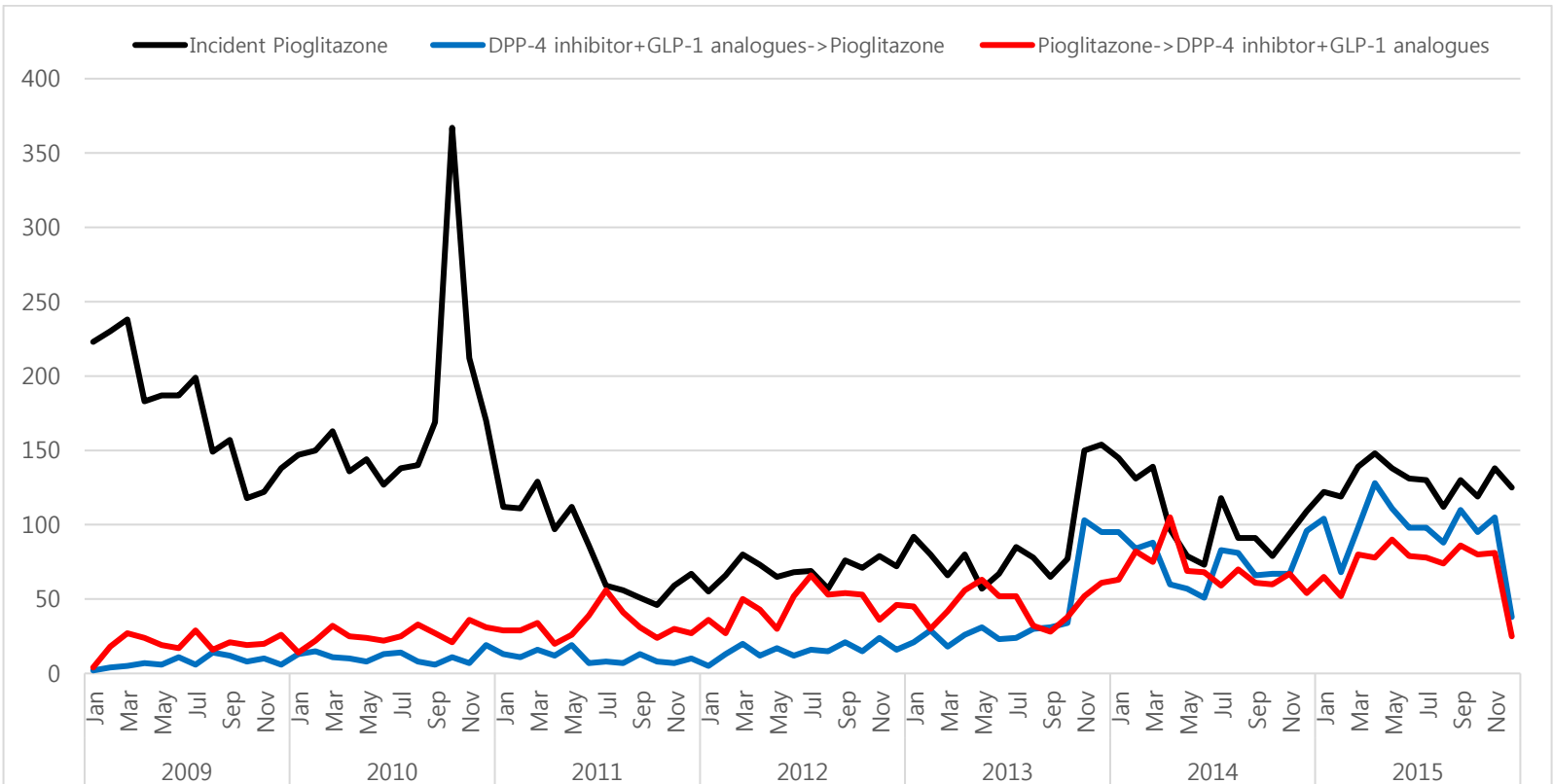

Figure 7. Monthly number of drug switching between pioglitazone and DPP-4 inhibitors + GLP-1 analogues users from January 2009 and December 2015

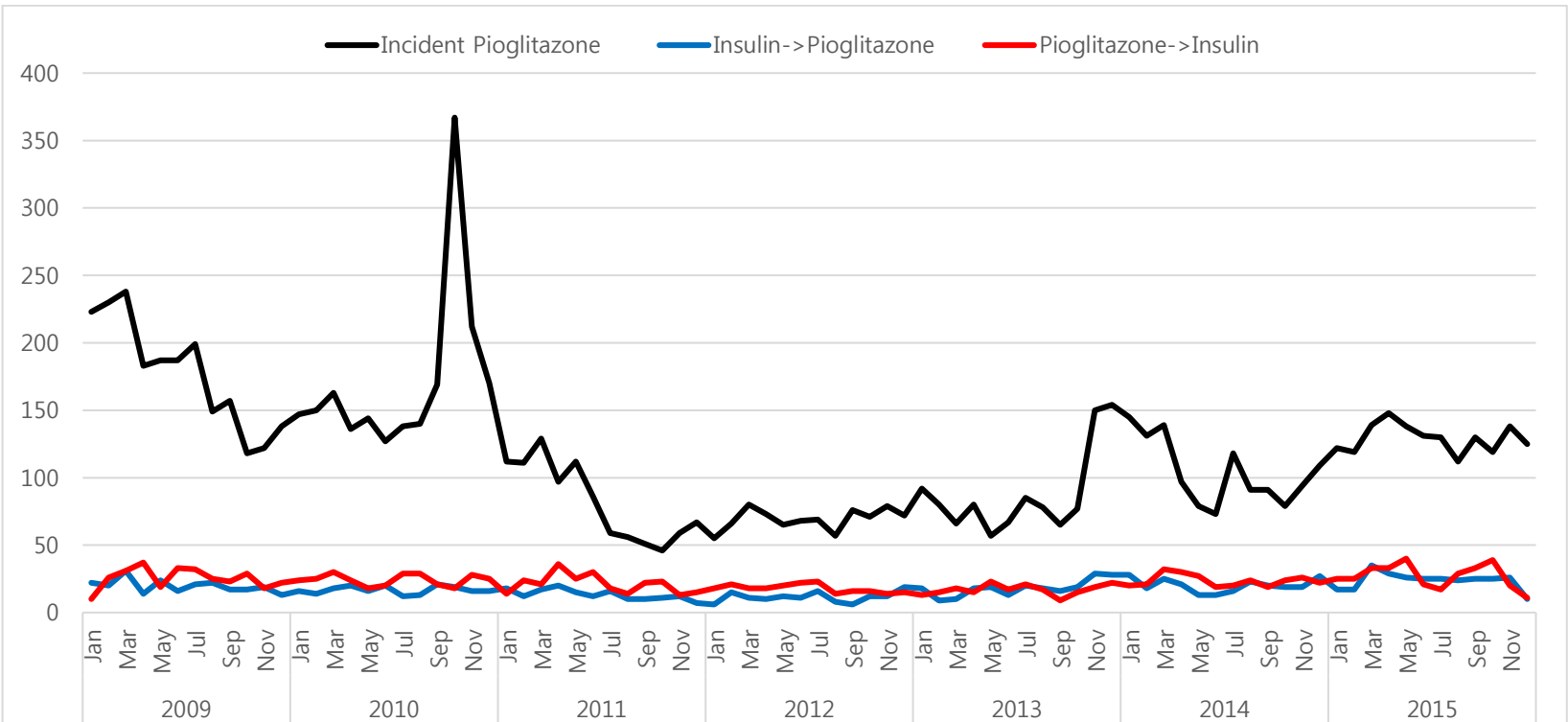

Figure 8. Monthly number of drug switching between pioglitazone and insulin-analogues users from January 2009 and December 2015

3.4 Absolute and relative change in pioglitazone drug users compared with other antidiabetic drugs

During the pre-intervention period of 30 months, the percentage of pioglitazone users was 12.77%, whereas for the 54 months after the intervention, it decreased to 11.73%, resulting in relative and absolute change as follows: -8.13 (95% CI: -8.41 to -7.86) and -1.04 (95% CI: -1.40 to -0.68). Rosiglitazone, another drug of the TZD class showed reductions in both relative and absolute changes after the intervention. However, for the remaining three comparator antidiabetic drugs, sulfonylurea + metformin, DPP-4 inhibitor + GLP-1 analogues, and insulin analogues, they all showed an increase in proportion after the intervention, with DPP-4 inhibitor + GLP-1 analogues increasing the most with a relative change of 209.03 (95% CI: 203.62 to 214.60) and absolute change of 36.14 (95% CI: 35.66 to 36.62) (Table 2).

Table 2. Absolute and relative change in pioglitazone drug users compared with other antidiabetic drugs before and after pioglitazone safety warning

Drug	No. of Drug Users (%)		Relative Change in Use, %	Absolute Change in Use, %
	Before Intervention	After Intervention	(95% CI)	(95% CI)
Total	55,585 (100.00)	74,887 (100.00)		
Pioglitazone	7,097 (12.77)	8,784 (11.73)	-8.13 (-8.41 to -7.86)	-1.04 (-1.40 to -0.68)
Comparator Drugs				
Rosiglitazone	2,069 (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 to 0.30)	0.27 (0.01 to 0.52)
DPP-4 inhibitor + GLP-1 analogues	9,610 (17.29)	40,011 (53.43)	209.03 (203.62 to 214.60)	36.14 (35.66 to 36.62)
Insulin analogues	16,053 (28.88)	25,696 (34.31)	18.81 (18.37 to 19.26)	5.43 (4.93 to 5.94)

3.5 Segmented regression analysis to estimate interaction between intervention and time of antidiabetic drug users (2 segments)

The parameter estimates for "Intervention" and "Time after Intervention" from the segmented regression analysis results are the main coefficients of interest. As the parameter for "Time" controls for the overall secular trend in rates, that is usually treated as a nuisance variable, its effect should be omitted in order to estimate the true impact of the intervention. Rates of initiation over the entire time period of seven years were trending upwards for all antidiabetic drugs except rosiglitazone to a statistically significant degree ($p<0.05$), besides pioglitazone ($p\geq0.05$). The "Time after Intervention" coefficient, which measures the trend after intervention, for pioglitazone, sulfonylurea + metformin, and insulin analogues users showed a decreasing trend whilst rosiglitazone and DPP-4 inhibitors + GLP-1 analogues users showed an opposite, upward trend after the intervention, where the "Time after Intervention" coefficients were all statistically significant (p-value for trend change < 0.05) except for pioglitazone users (p-value for trend change ≥ 0.05). Finally, the coefficient for "Intervention", which measures the level change right

after the intervention, was statistically significant for only pioglitazone, sulfonylurea + metformin, and insulin analogues ($p<0.05$). The safety warning for pioglitazone, released by the MFDS was associated with an immediate 177 decrease of pioglitazone users ($p<0.05$). For pioglitazone's "Time" trend, no autocorrelation was present (DW: 2.0988; $p<$DW: 0.5741, $p>$DW: 0.4259) whereas seasonality or stationarity was present (DF Unit Root: -1.94; $p\geq0.05$) (Table 3).

Table 3. Segmented regression analysis to estimate interaction between intervention and time of antidiabetic drug users (2 segments*)

Antidiabetic Drug			Characteristics					
			Intercept ($\beta 0$)	**Time ($\beta 1$)**	**Intervention ($\beta 2$)**	**Time after Intervention ($\beta 3$)**	**Durbin-Watson Test Statistics**	**Dickey-Fuller Unit Root Statistics**
Study Drug	Pioglitazone	Beta	1,780	14.95	-176.59	-11.42	2.0988	-1.94
		Standard Error	204.75	8.78	82.45	11.70	p<DW: 0.5741 p>DW: 0.4259	p<τ: 0.3125
		p-value	<0.0001	0.0926	0.0353	0.3323		
Comparators Drugs	Rosiglitazone	Beta	1,069	-35.50	-24.24	35.11	1.8998	-2.05
		Standard Error	78.10	3.88	48.20	4.90	p<DW: 0.2501 p>DW: 0.7499	p<τ: 02670.
		p-value	<0.0001	<0.0001	0.6165	<0.0001		
	Sulfonylurea + Metformin	Beta	26,420	148.99	1015	-62.70	2.1387	-1.97
		Standard Error	274.89	15.77	317.83	17.23	p<DW: 0.6197 p>DW: 0.3803	p<τ: 02976.
		p-value	<0.0001	<0.0001	0.0020	0.0005		

*Segment 1: Jan 2009 – Jun 2011, Segment 2: Jun 2011 – Dec 2015

Table 3. Segmented regression analysis to estimate interaction between intervention and time of antidiabetic drug users (2 segments*, cont'd)

Antidiabetic Drug			Characteristics					
			Intercept ($\beta 0$)	**Time ($\beta 1$)**	**Intervention ($\beta 2$)**	**Time after Intervention ($\beta 3$)**	**Durbin-Watson Test Statistics**	**Dickey-Fuller Unit Root Statistics**
Study Drug	Pioglitazone	Beta	1,780	14.95	-176.59	-11.42	2.0988	-1.94
		Standard Error	204.75	8.78	82.45	11.70	p<DW: 0.5741 p>DW: 0.4259	p<τ: 0.3125
		p-value	<0.0001	0.0926	0.0353	0.3323		
Comparators Drugs	DPP-4 inhibitor + GLP-1 analogues	Beta	380.45	133.20	-447.72	164.42	1.8508	1.05
		Standard Error	187.34	10.09	184.96	11.85	p<DW: 0.1571 p>DW: 0.8429	p<τ: 0.9968
		p-value	0.0456	<0.0001	0.0178	<0.0001		
	Insulin analogues	Beta	3,174	11.37	47.89	-13.79	1.9146	-7.37
		Standard Error	25.58	1.49	30.49	1.58	p<DW: 0.2311 p>DW: 0.7689	p<τ: <0.0001
		p-value	<0.0001	<0.0001	0.1204	<0.0001		

*Segment 1: Jan 2009 – Jun 2011, Segment 2: Jun 2011 – Dec 2015

3.6 Segmented regression analysis to estimate interaction between intervention and time of pioglitazone users (3 segments)

Upon reviewing the time series trend of pioglitazone drug users (Figure 3-1), segments were divided into three, which were as follows: Segment A: Jan 2009 to Jun 2011 and Jun 2011 to Nov 2013; Segment B: Jun 2011 to Nov 2013 and Nov 2013 to Dec 2015. In November 2013, a health insurance benefit coverage criteria expansion of 3rd line antidiabetic agents was put into action along with the release of a pioglitazone complex drug on the market in the following month. Looking at the ITS segmented regression analysis results of Segment A, the overall time trend was increasing to a statistically significant degree (p<0.05), whereas, that of Segment B was the opposite with an overall time trend that was decreasing (p<0.05). However, as for the "Time after Intervention" coefficient, Segment A showed an increasing trend after the intervention (p-value for trend change < 0.05) with Segment B showing the contrary (p-value for trend change < 0.05). Lastly, the level change right after the intervention was statistically significant for only Segment A showing an instantaneous 282 decrease of pioglitazone users

(p<0.05). In both Segments A and B's "Time" trend, there were no autocorrelation present (Segment A: DW: 1.7328; p<DW: 0.0745, p>DW: 0.9255; Segment B: DW: 2.1575; p<DW: 0.5837, p>DW: 0.4163) whereas stationarity was not present (Segment A: DF Unit Root: -1.78; p≥0.05; Segment B: DF Unit Root: -0.88; p≥0.05) (Table 4).

Table 4. Segmented regression analysis to estimate interaction between intervention and time of pioglitazone drug users (3 segments)

			Characteristics					
			Intercept ($\beta 0$)	**Time ($\beta 1$)**	**Intervention ($\beta 2$)**	**Time after Intervention ($\beta 3$)**	**Durbin-Watson Test Statistics**	**Dickey-Fuller Unit Root Statistics**
Pioglitazone	Segment A*	Beta	1,863	18.95	-282.31	-34.75	1.7328	-1.78
		Standard Error	29.50	1.72	40.69	2.43	p<DW: 0.0745 p>DW: 0.9255	p<τ: 0.3878
		p-value	<0.0001	<0.0001	<0.0001	<0.0001		
	Segment B**	Beta	2,148	-16.74	85.16	39.19	2.1575	-0.88
		Standard Error	44.28	2.59	54.36	3.99	p<DW: 0.5837 p>DW: 0.4163	p<τ: 0.7863
		p-value	<0.0001	<0.0001	0.1235	<0.0001		

*Segment A: Jan 2009 – Jun 2011 and Jun 2011 – Nov 2013
**Segment B: Jun 2011 – Nov 2013 and Nov 2013 – Dec 2015

3.7 Pioglitazone drug user's characteristics before and after the pioglitazone safety warning

Female pioglitazone users, or those in their 50s or 70s and visitors of primary care clinics, showed a decrease in proportion when the intervention was implemented with relative and absolute changes being the following: -3.74 (95% CI: -3.98 to -3.51) and -1.69 (95% CI: -3.25 to -0.14), -7.13 (95% CI: -7.65 to -6.64) and -1.97 (95% CI: -3.35 to -0.58), -37.85 (95% CI: -43.36 to -33.04) and -2.70 (95% CI: -3.44 to -1.97), and finally, -7.91 (95% CI: -8.46 to -7.41) and -5.43 (95% CI: -6.91 to -3.96), respectively. On the contrary, a large increase in both relative and absolute change were seen for those in younger than 50 and visitors of tertiary hospitals with 19.18 (95% CI: 18.00 to 20.43) and 7.85 (95% CI: 6.30 to 9.40), and 34.38 (95% CI: 31.82 to 37.16) and 6.22 (95% CI: 4.95 to 7.48), respectively (Table 5).

Table 5. Pioglitazone drug user's characteristics before and after 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)

3.8 Observed and predicted monthly proportion of pioglitazone users

If the pioglitazone safety warning intervention released by the MFDS had not been implemented, the proportion of pioglitazone users per 1000 DM patients would have shown a continuous increasing trend, eventually reaching a proportion of approximately 90 per 1,000 DM patients, which is approximately 50% greater than the proportion at December 31st, 2015. Moreover, the time trend of prevalent pioglitazone users per 1,000 DM patients show that no seasonality can be observed, as there are regular patterns to be observed (Figure 4). Likewise, by setting the intervention time point to either April 2011, the first article published reporting an increased risk of bladder cancer with the use of pioglitazone (Lewis et al., 2011), or applying a three months lag period to both before and after the MFDS intervention, similar results were observed to that of the original MFDS intervention in June 2011 (Figure 9 to 11)

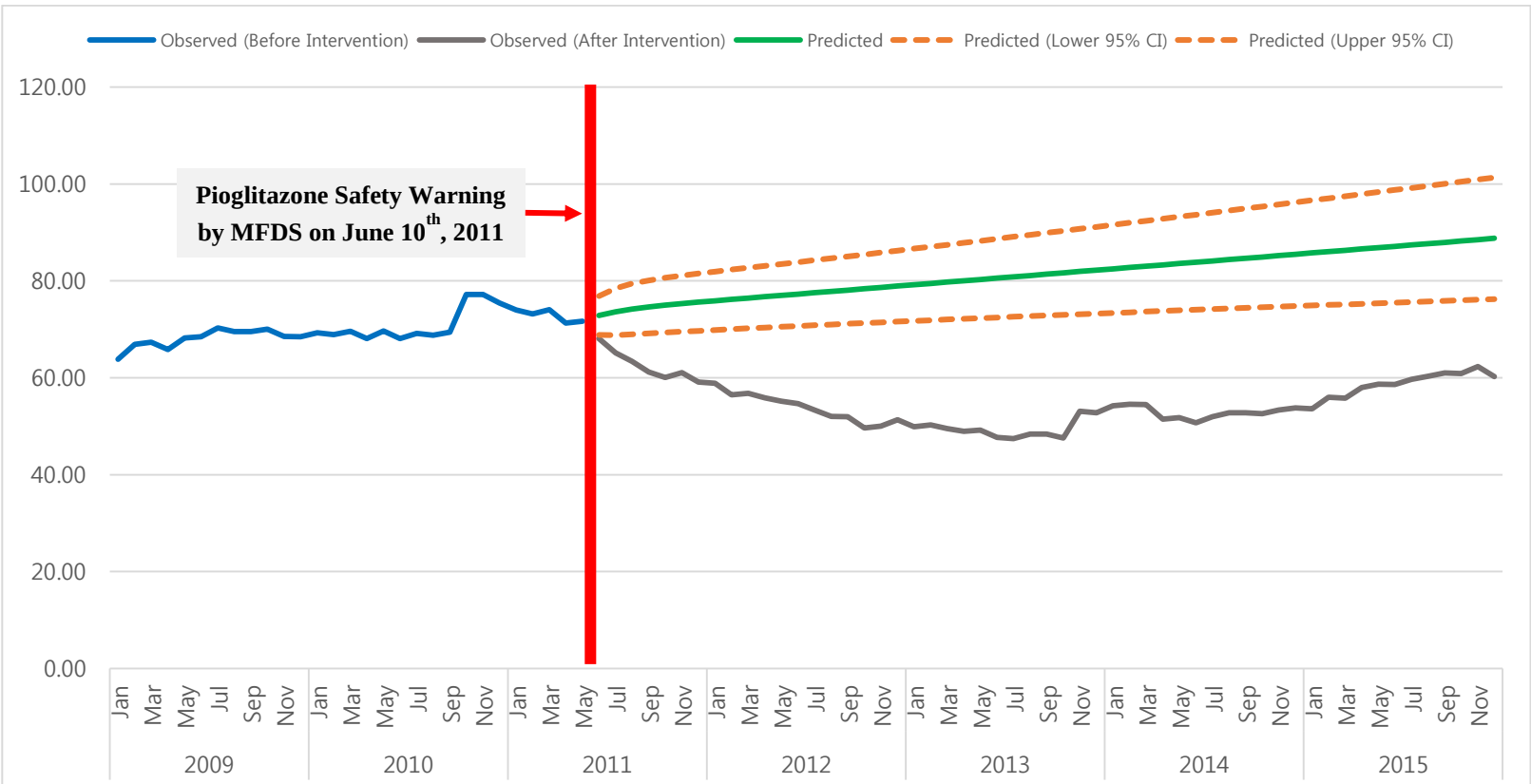

Figure 9. Observed and predicted monthly proportion of pioglitazone users before and after the pioglitazone safety warning

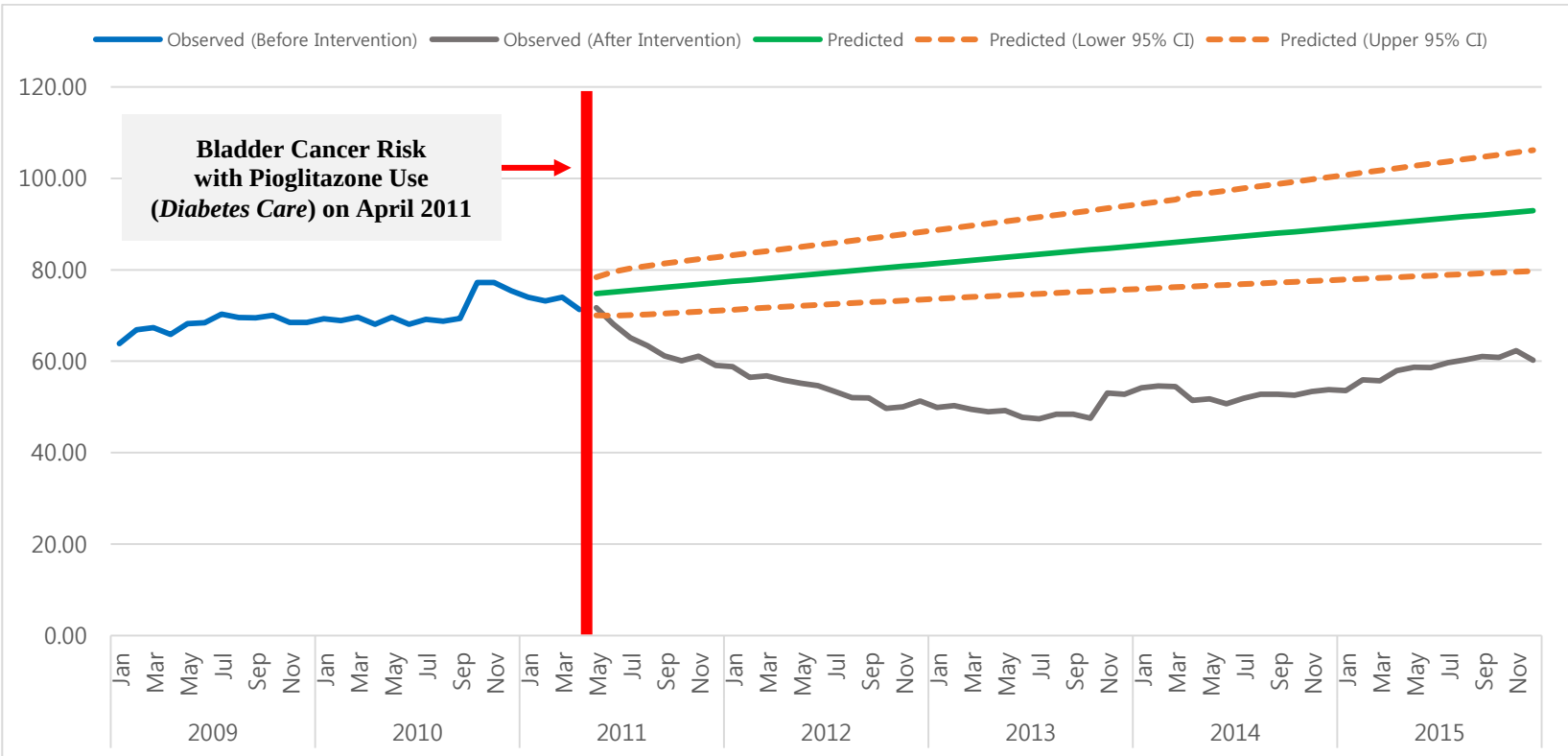

Figure 10. Observed and predicted monthly proportion of pioglitazone users before and after the research article reporting an increased risk of bladder cancer with use of pioglitazone

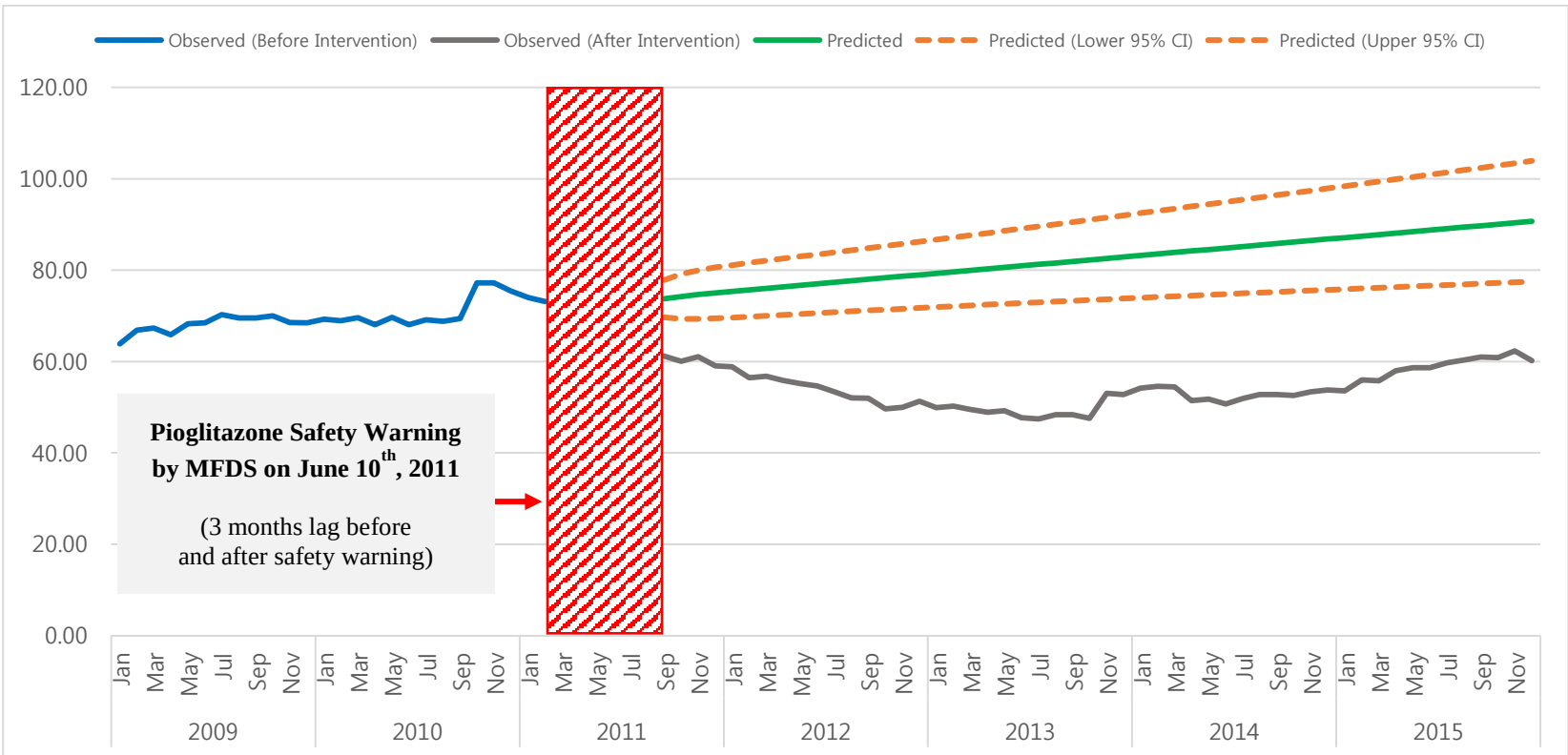

Figure 11. Observed and predicted monthly proportion of pioglitazone users before and after the pioglitazone safety warning with three months lag both before and after the safety warning

3.9 Incident and prevalent pioglitazone users before and after the pioglitazone safety warning from January 2009 to December 2015

The number of prevalent and incident users of pioglitazone for the study period are shown, with the general trend of the prevalent users being an increase whilst incident users are decreasing. Key events that took place throughout the study period, with respect to pioglitazone, are also shown, that are supported with possible explanations to the rises and falls in the incident users of pioglitazone (Figure 12).

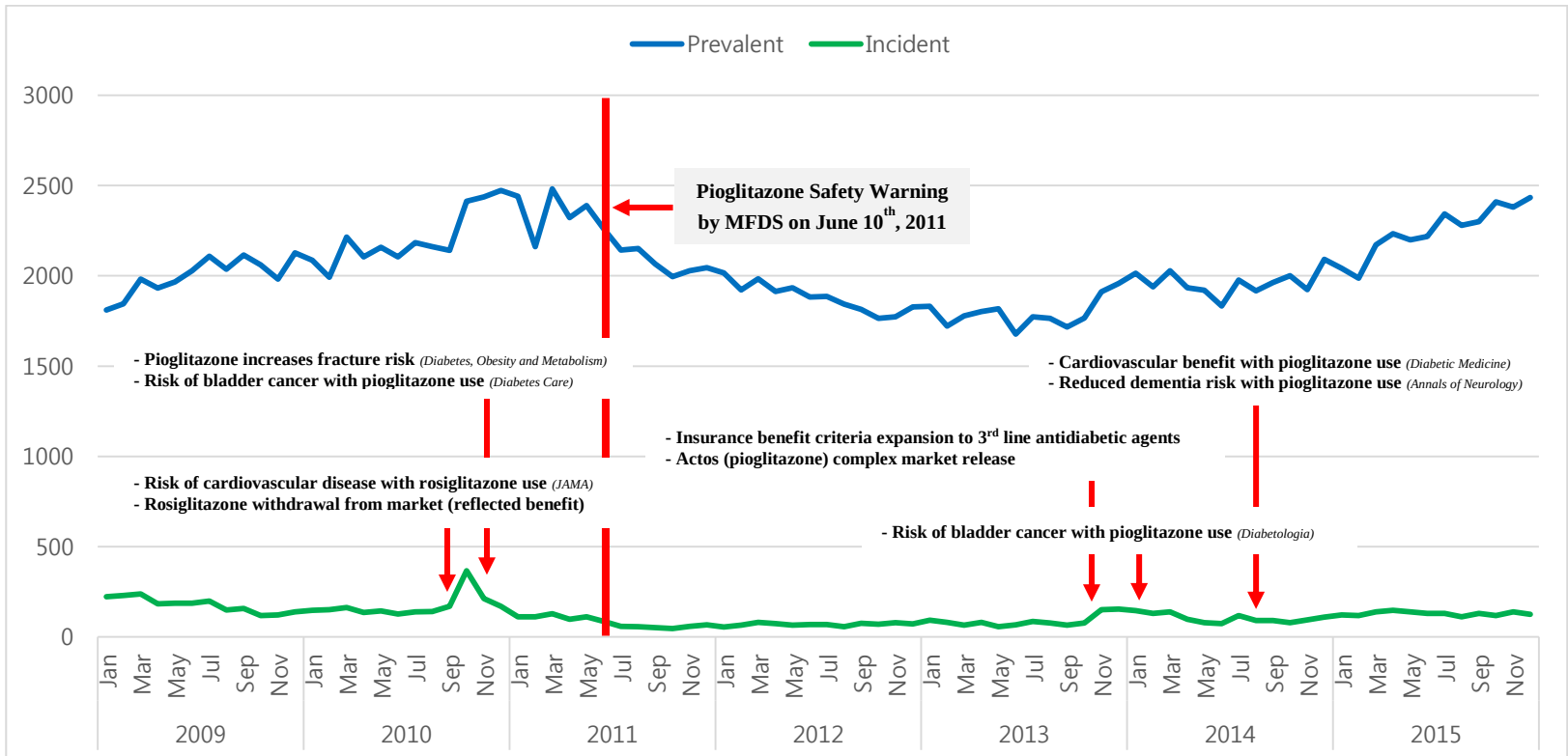

Figure 12. Incident and prevalent pioglitazone users before and after the pioglitazone safety warning by month from January 2009 to December 2015

IV. Discussion and Conclusion

4.1 Discussion

The results of our study show that the prevalence of T2DM was approximately 7.44%, which was in agreement with the prevalence of 8.0%, reported by the International Congress of Diabetes and Metabolism's Diabetes Fact Sheet in Korea 2016 (Metabolism, 2016). Moreover, pioglitazone accounted for 16.03% of all DM drugs in Korea from 2009 to 2015 and amongst all DM drugs, excluding rosiglitazone and pioglitazone, had an overall increasing trend, whether small or large, while insulin analogues showed more of a plateau trend. Among the antidiabetics of interest in our study, pioglitazone and rosiglitazone are both drugs of the TZD class. These two fore mentioned drugs are the only antidiabetic drugs available for use against insulin resistance, as it provides continuous and definite hypoglycemic effects and also increasing the pancreas's beta cell's functions and insulin sensitivity, according to the Korean Diabetes Association. Moreover, sulfonylurea, the oldest antidiabetic drug, and metformin function as antidiabetics as stimulating the release of insulin from the pancreas and inhibiting the production of glucose in the liver, respectively. DPP-4 inhibitors, a novel

drug in the diabetes market, controls insulin by inhibiting the DPP-4 enzyme, giving rise to lowered risk of hypoglycemia and control of blood glucose levels after meals (Eoh, 2013a).

Upon release of the pioglitazone safety warning on June 10th, 2011, by the MFDS, a moderate decrease in the number pioglitazone users after the intervention was seen. It was also observed that the number of pioglitazone users actually began to decrease a few months prior to the intervention. According to results from a study conducted in Korea on the trend of antidiabetic drug use in adult T2DM patients from 2002 to 2013, they found similar trends to that of ours, where the use of DPP-4 inhibitors increased remarkably after its release in late 2008 and the use of antidiabetic agents and their costs have been increasing steadily as well (Ko. et al., 2016).

There were various key events that were associated with pioglitazone between 2009 and 2015, which in turn, had either a positive or negative influence or impact on the number of pioglitazone users. Before the intervention (January 2009 to May 2011), on July 2010, a study result published in the *Journal of the American Medical Association (JAMA)*, reported an increased risk of CV disease with the use of another TZD drug, rosiglitazone, which eventually led to the withdrawal of the drug, Avandia, from the market on September 2010 (Graham. et al., 2010; Park, 2010). This in turn resulted in another sharp rise in the number of

pioglitazone users. This particular trend was also observed in multiple nations worldwide, such as, Australia, Denmark, France, Germany, Netherlands, Taiwan and the US (Arnaud, Bezin, Begaud, Pariente, & Salvo, 2017; Hostenkamp, Fischer, & Borch-Johnsen, 2016; Hsu, Cheng, et al., 2015; Niyomnaitham., Page., Caze., Whitfield., & Smith., 2014; Rikje Ruiter, 2012; Starner., Schafer., Heaton., & Gleason., 2008). However, around the time of withdrawal of rosiglitazone, in August 2010 and April 2011, various studies have reported a risk of fracture and bladder cancer with the use of pioglitazone, leading to a dramatic decrease in pioglitazone users (Aubert., Herrera., W, Haffner., & Pendergrass., 2010; Lewis et al., 2011).

Following the MFDS intervention in June 2011, the MFDS has updated the label information of pioglitazone to contain information regarding the increased risk of bladder cancer with its use in November 2011 (S.-J. Lee, 2011; T.-S. Lee, 2011). Ever since the MFDS intervention, there has been a continuous decrease in both prevalent and incident users of pioglitazone until 2013, where in January, insurance reimbursement was extended to pioglitazone of 30mg, on top of the currently reimbursed 15mg (Eoh, 2013b). In addition, ten months later in November 2013, there was a health insurance benefit coverage criteria expansion of 3rd line antidiabetic agents and in the following month, a pioglitazone complex was released on the market (H. Lee, 2013; J. Lee,

2013). These aforementioned three events let to a sudden increase of pioglitazone users. Previous research also showed that drug safety warnings led to a decrease in the respective drug's utilization whilst showing an increase in drugs with similar biological or chemical mechanisms (Arnaud et al., 2017; Leal et al., 2013). Despite positive news, another study result reporting a risk of bladder cancer with pioglitazone use in just a month later, resulted in a drop of users, regressing back to levels equivalent to that of October 2013 (Levin et al., 2015). Nevertheless, within a year's time, novel research findings have reported that, with the use of pioglitazone, there were CV benefits and furthermore, reduced risk of dementia on December 2014 and August 2015, respectively (Heneka., Fink., & Doblhammer., 2015; Ryder, 2015).

Regardless of the intervention, pioglitazone still accounted for 11.73% of all antidiabetic drugs after the intervention, showing only a minor absolute reduction of 1.04%, from 12.77%, the proportion prior to the intervention. Study results from several nations showed similar results and trends to that of ours, for both pioglitazone and other comparator antidiabetic drugs. For instance, a study conducted in France reported a decreased incidence of first-line non-insulin glucose lowering drugs, especially, TZDs, from 2006 to 2013, whilst DPP-4 inhibitors and metformin showed the converse (Arnaud et al., 2017). Compared to UK study results, which reported a prevalence of TZDs to be around 5.0% in

2008 (Leal et al., 2013), the prevalence of pioglitazone was around 15.0%, almost triple in proportion.

In sum, this study revealed that there was a significant reduction in the number of pioglitazone users after the release of a safety warning concerned with an increased risk of bladder cancer with the use of pioglitazone. Without the intervention, pioglitazone users would have steadily increased but rather, the intervention halted this potential increase and led to a continuous decrease, with minor but non-negligible bumps and dips along the way. Through this study, the safety warning intervention was found to be effective in successfully decreasing the number of people using the warned drug, which would have eventually led to a decrease in the incidence of adverse outcomes or side effects from drug utilization. To confirm whether the above-mentioned is true, further studies would need to be done, but if true, this would alleviate the population's disease burden and increase the population's quality of life, with respect to health, as a whole.

Strengths of our study are that, to the best of our knowledge, this is the first population-based study to be done in Korea, to examine the temporal trends in the prevalence of pioglitazone users before and after its safety warning in June 2011. In addition, we utilized a 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. Especially, 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 (Lee. et al., 2017).

In spite of the many strengths the study had, the results should be interpreted with caution as the following limitations are existent. First, the number of drug users should not be interpreted as the actual, real-world use among DM patients as non-compliance may lead to an overestimation of drug use. Second, the disease codes listed in the NHIS-NSC database may not represent the participant's true disease status as the code was created in order to claim health insurance serviced to participants. Moreover, as a limitation of an ITS study design, other interventions besides our intervention of interest (pioglitazone safety warning), may have influenced the number of pioglitazone users. This was because, it was difficult to distinguish if the steady decline in pioglitazone users was either accelerated or declined to other reasons besides our intervention of interest, for example release of a new and more effective antidiabetic drug.

4.2 Conclusion

A regulatory action, in our case, the pioglitazone safety warning released by the Korean MFDS, has the potential to reduce the likelihood of prescribing a warned drug to DM patients. This population-based study demonstrated decreases in the number of users of pioglitazone compared with other antidiabetic drugs over time. However, the descending trend appeared to have been well underway even before the implementation of the regulatory action. Despite the decreases, pioglitazone is still widely prescribed to DM patients, stressing the need to develop and implement strategies to assess and enhance drug safety for all DM patients.

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Abstract in Korean

국문초록

식품의약품안전처의 안전성서한 발표 후 피오글리타존의 처방 양상변화

정한얼
보건학과 역학전공
서울대학교 보건대학원

연구 배경 : 프랑스 건강제품위생안전청(AFSSAPS)은 방광암 위험 유발의 사유로 당뇨병 치료제 피오글리타존 함유 제제의 사용 중지를 결정했다. 본 정보는 AFSSAPS의 요청에 따라 국립질병보험금고에서 실시한 연구결과, 동 제제로 치료받은 환자들에게 방광암 위험성이 증가함에 따른 시판허가위원회의 안전성 및 유효성에 대한 부정적 평가에 따른 것으로, 피오글리타존 함유 제제 처방 금지를 권고했다고 밝혔다. 이에 따라 대한민국 식품의약품안전처(식약처)는 2011년 6월 10일 피오글리타존 함유 제제에 대한 의약품안전성

서한(안전성서한)을 발표했다. 본 연구는 기술적 역학 연구로서, 식약처의 안전성서한 발표 전후로 피오글리타존 복용자 수를 단절적 시계열 연구 설계 방법론을 활용하여 파악하고자 한다.

연구 방법 : 연구기간인 2009년 1월 1일부터 2015년 12월 31일 사이에 대한민국에서의 피오글리타존과 타 당뇨병 치료제 약물 복용자의 빈도 및 분율을 파악하기 위해 건강보험공단의 표본코호트 자료를 활용하여 단절적 시계열 연구를 진행하였다. 피오글리타존을 관심 약물로, 타 당뇨병 치료제 약물(로시글리타존, 설포닐유레아, 메트포민, DPP-4 억제제, GLP-1 유사체, 인슐린)을 비교 약물로 선정하였다. 안전성서한 발표 전후로 약물 복용자 분율의 상대적 및 절대적 차이와 각각의 95% 신뢰구간(95% CI)을 산출하였다. 안전성서한의 영향을 파악하기 위해 최소제곱추정법과 최대우도추정을 통해 피오글리타존과 타 당뇨병 치료제 약물 복용자의 당뇨환자 빈도 및 분율을 월별로 산출하였다. 단절적 시계열 연구 설계에서 안전성서한이 결과변수에 미치는 영향을 파악하기 위해 구간회귀분석 방법에 적절한 모델을 적용하였다. 시계열 데이터의 자기상관성과 계절성의 유무는 더빈-왓슨 (DW) 통계량과 딕키-풀러 (DF) 통계량을 사용해 검증했다.

연구 결과 : 총 80,724 명의 당뇨병 환자가 연구기간에 포함되었으며, 이 중, 피오글리타존 복용자는 12,249 명(15.17%)이었다. 식약처의 피오글리타존 안전성서한 발표 후, 피오글리타존 복용자 분율의 상대적 차이는 −8.13% (95% CI: −8.41%, −7.86%)이었으며, 절대적 차이는 −1.04% (95% CI: −1.40%, −0.68%)이었다. 로시글리타존, 설포닐유레아, 메트포민, DPP−4 억제제, GLP−1 유사체, 그리고 인슐린 복용자 분율의 상대적 차이는 다음과 같았다: −99.82% (95% CI: −240.10%, −41.50%), 0.29% (95% CI: 0.27%, 0.30%), 209.03% (95% CI: 203.62%, 214.60%), 18.81% (95% CI: 18.37%, 19.26%). 안전성서한 발표와 피오글리타존 복용자 수 감소 간 유의한 연관성을 보였다($p<0.05$). 피오글리타존의 시간에 따른 추세의 자기상관성은 존재하지 않았지만(DW: 2.0988, $p<$DW: 0.5741, $p>$DW: 0.4259), 계절성은 존재했다 (DF Unit Root: −1.94, $p>0.05$). 만약 식약처의 안전성서한이 발표되지 않았다면 피오글리타존의 복용자 수는 꾸준한 상승세가 관찰 됐을 것이며, 2015 년 12 월 31 일 기준으로 1,000 명의 당뇨병 환자 중 실제로 관찰된 60 명보다 약 1.5 배인 90 명의 피오글리타존 복용자가 존재했을 것이다.

결론 : 식약처의 피오글리타존 복용에 따른 방광암 위험 안전성서한 발표 직후 당뇨병 환자 중 피오글리타존 복용자의 분율이 감소

됐음을 확인했다. 안전성서한 발표로 인해 단기적으로 피오글리타존 복용 감소 추세를 보였지만, 시간이 지날수록 단기적 감소 추세를 보이기 전인 안전성서한 발표 이전의 상태를 회복했다. 즉, 식약처의 안전성서한으로 인해 단기적 감소 효과는 있었지만, 본 연구 결과에서 관찰된 복용자 분율의 감소에도 불구하고 피오글리타존은 여전히 높은 비율로 당뇨병 환자들에게 처방되고 있어, 대한민국 국민의 건강 및 약물 복용으로 인한 부작용 등 안전성을 강화하기 위해 식약처, 건강보험공단, 건강보험심사평가원 간의 긴밀한 협조가 필요하다.

주요어 : 피오글리타존, 당뇨병, 안전성서한, 단절적 시계열 연구, 식품의약품안전처

학 번 : 2016-22593