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Effects of safety warnings and risk management plan for Thiazolidinediones in Taiwan[†]

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Abstract

Purpose—To evaluate changes in thiazolidinedione use and quality of prescription following safety warnings for thiazolidinediones and cardiac risk in 2007, Risk Management Plan (RMP) policy for rosiglitazone in 2010, and warning for pioglitazone and bladder cancer risk in 2010 in Taiwan.

Methods—We obtained 2003–2011 claims data from Taiwan’s National Health Insurance Research Database. Using an interrupted time series design and segmented regression, we estimated changes in monthly prescribing rates for thiazolidinediones among all and prevalent diabetes patients with and without cardiovascular disease history (CV history). We also compared time to prescription of thiazolidinediones among new diabetes patients with CV history before and after each regulatory action using survival analysis.

Results—Among prevalent patients with and without CV history, the prescribing rates of rosiglitazone decreased 36.88% and 28.92% after safety warnings in 2007 respectively. Pioglitazone prescriptions increased 13% among patients with CV history, but no changes were detected among patients without CV history. After rosiglitazone’s RMP policy in 2010, large reductions in prescriptions were observed in patients with CV history (–101.67%) and those without CV history (–88.04%). Among new diabetes patients with CV history, cardiac safety warnings in 2007 significantly delayed the prescription of rosiglitazone, but no significant change was found for pioglitazone.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

SUPPORTING INFORMATION

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Conclusions—The Taiwan FDA regulatory actions for thiazolidinediones communicated possible risks of cardiac events and bladder cancer. Different safety regulatory actions had differential impacts on the use of rosiglitazone and pioglitazone and the quality use of these drugs among the high-risk patients.

Keywords

type 2 diabetes; thiazolidinedione; safety warning; risk management plan; Taiwan; pharmacoepidemiology

INTRODUCTION

Thiazolidinediones (TZDs), including rosiglitazone and pioglitazone, have been widely used to treat patients with type 2 diabetes mellitus since 2000.¹⁻³ They are recommended for diabetes with the recognized clinical advantages of achieving and sustaining glycemic control by improving insulin sensitivity.⁴⁻⁶ However, they are second-line treatments and contraindicated in patients with heart failure because of adverse effects of fluid retention and increased risk of heart failure.^{7,8} Conflicting but growing evidence suggests adverse effects of TZDs on the cardiovascular system.^{9,10}

In May 2007, a meta-analysis of 42 randomized clinical trials indicated the association between rosiglitazone use and an increased risk of myocardial infarction.^{9,11,12} The U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) reviewed the potential risk of rosiglitazone based on the available data and found similar results.^{13,14} In response, FDA issued a risk communication to healthcare professionals warning the potential risk of ischemic cardiovascular events in patients taking rosiglitazone,^{15,16} and EMA also communicated to healthcare professionals by press releases.¹⁷⁻²⁰ In August 2007, the FDA required a black box warning on prescribing information for TZDs (rosiglitazone and pioglitazone) regarding their potential to cause or exacerbate heart failure²¹⁻²⁴ despite studies suggesting that pioglitazone has a lower cardiovascular risk.^{25,26} Following FDA's safety warnings for TZDs, Taiwan's Food and Drug Administration (TFDA) also released similar warnings in July 2007.

In September 2010, the FDA reviewed additional data on rosiglitazone, including the final results of the RECORD trial, updated meta-analyses, and a number of observational studies.^{12,25,27-29} Based on these data, the FDA required the manufacturer to undertake a restricted access program under a Risk Evaluation and Mitigation Strategy (REMS), which limits the availability of rosiglitazone.³⁰⁻³² The REMS has several components, including provision of complete risk information to the patient,³³ documentation by the healthcare provider that the information has been received and understood, and enrollment of patients who used rosiglitazone and their physicians and pharmacists.²⁸ In contrast, the EMA suspended the marketing authorization of rosiglitazone in the EU because the benefits of rosiglitazone no longer outweighed the risks.^{7,8,34} TFDA also convened a Drug Safety Assessment Committee meeting and decided to further limit the use of rosiglitazone. In October 2010, the TFDA required manufacturers to implement a Risk Management Plan (RMP) program for rosiglitazone in Taiwan, which is largely similar to that by the FDA.

In 2010, preclinical carcinogenicity studies found bladder tumors in male rats receiving pioglitazone. Additionally, results from two, three-year controlled clinical studies of pioglitazone (the PROactive study^{35,36} and a liver safety study) demonstrated a higher rate of bladder cancer cases in patients with the longest exposure to pioglitazone and in those exposed to the highest cumulative dose of pioglitazone.³⁷⁻⁴¹ In response, the FDA announced the potential increased risk of bladder cancer for pioglitazone in September 2010.^{42,43} Taiwan government also followed FDA's announcement and released a similar safety communication.

Although previous studies^{3,7,16,32,44} have examined the impacts of rosiglitazone's safety warning in 2007 in both the US and the Europe, little is known about how these safety regulatory actions impacted TZD use in Taiwan. Importantly, no studies have examined the effects of the restrict access program for rosiglitazone and the bladder cancer risk warning for pioglitazone in 2010. The aim of this study was to evaluate the impacts of multiple TZD-related warnings on the utilization of both rosiglitazone and pioglitazone in Taiwan.

METHOD

Data source

This study used data from the "Longitudinal Health Insurance dataset," derived from Taiwan's National Health Insurance Research Database (NHIRD). This dataset contains all the original claim data of 1 million beneficiaries randomly sampled in 2000 from ~23 million Taiwan residents registered in the National Health Insurance. The NHIRD includes information from a nationwide, mandatory-enrollment and single-payer healthcare system created in 1995 and this system contracts with 97% of hospitals and clinics throughout the country. The database contains information on patient characteristics (e.g. birth date, gender), prescriptions, procedures, ambulatory care and inpatient care based on International Classification of Diseases, 9th edition (ICD-9) diagnosis codes, and expenditures. Use of the NHIRD for research purpose is exempt from IRB review in Taiwan.

Monthly rolling diabetes cohort

We extracted all patients who had diabetes diagnosis (ICD-9 250.xx) in outpatient visits and had at least one prescription for oral antidiabetic agents between the years 2005 and 2011 from the national, longitudinal cohort dataset. We had data on years 2003–2004 as look-up periods. Date of the first prescription for an antidiabetic agent was defined as the index date for each diabetes patient. For every month, we also calculated the number of prevalent diabetes patients as a denominator population. New patients with diabetes were defined as patients who had no antidiabetic agents within 2 years before the index date; those who did have antidiabetic agents within 2 years before the index date were defined as prevalent patients.

We further divided monthly prevalent patients into (i) those with a history of cardiovascular disease (CV history), defined by ICD-9-CM codes for myocardial infarction, ischemic heart disease, or congestive heart failure (see Appendix in supporting information) in the 2 years before the index date, and (ii) those without CV history. We used these cohorts for our

interrupted time series analyses (described below). Because the warnings communicated the possible cardiovascular risk of TZDs, we anticipated that the warnings may influence prescribing of TZDs to patients with CV history while this should not change among those without CV history. Differences in physician prescribing patterns between patients with and without risk of adverse drug events may reflect quality use of medicines.

New diabetes patient cohort

From the longitudinal cohort dataset, we extracted patients who had the first diabetes diagnosis (ICD-9 250.xx) in outpatient visits and at least one prescription for oral antidiabetic agents between the years 2005 and 2011. Date of the first prescription for an antidiabetic agent for each patient was defined as the index date. We established a new diabetes cohort by extracting all diabetes patients who did not have any diabetes diagnosis in the past 2 years prior to the index date.

To understand patient characteristics before and after the safety regulatory actions, we stratified this cohort into four groups depending on the timing of their index dates: (i) pre-regulatory action of cardiovascular safety warning for TZDs (1 May 2006–30 April 2007), (ii) post-regulatory action of cardiovascular safety warning for TZDs (1 September 2007–31 August 2008), (iii) pre-regulatory action of rosiglitazone's RMP policy/pioglitazone's bladder cancer risk warning (1 September 2009–31 August 2010), and (iv) post-regulatory action of rosiglitazone's RMP policy/pioglitazone's bladder cancer risk warning (1 November 2010–31 October 2011).

We divided new diabetes patients with CV history by time periods for our time to event analyses (described below). To assess effects of the 2007 safety regulatory actions by analyzing the time to first receipt of TZD prescriptions before and after safety regulatory actions, we classified new diabetes patients with CV history identified during the 28 months before (1 January 2005–30 April 2007) and after (1 September 2007–31 December 2009) regulatory actions as pre- and post-regulatory action subgroups. To compare time to first receipt of TZD prescriptions before and after the 2010 safety regulatory actions, new patients with CV history who were diagnosed with diabetes within the 14 months before (1 July 2009–31 August 2010) and after (1 November 2010–31 December 2011) regulatory actions were classified as pre- and post-regulatory action subgroups.

Outcome measures

To examine the impacts of multiple safety regulatory actions regarding TZDs (rosiglitazone and pioglitazone) on use, we used the above “monthly rolling diabetes cohort” and estimated: (i) monthly prescription rate⁴⁵ among all patients with diabetes, calculated by number of TZDs prescription divided by number of total diabetes patient visit per month; and (ii) monthly prescription rate among prevalent patients with/without CV history, which is calculated by number of TZDs prescription divided by number of prevalent diabetes patient visit (with/without CV history) per month.

Furthermore, we used above “new diabetes patient cohort” and evaluated the time to TZD prescription among new diabetes patients with CV history, defined as the number of days from the index date until the date of the first observed TZD prescription.

Statistical analysis

An interrupted time series design,⁴⁶ a strong quasi-experimental method, was used to examine impacts of multiple safety regulatory actions on monthly prescription rates of TZDs among all diabetes patients and among prevalent diabetes patients with/without CV history in the “monthly rolling diabetes cohort”. Based on the timing of multiple safety regulatory actions, we treated these as two distinct interventions: (i) safety warnings for cardiovascular risk (ischemic heart disease for rosiglitazone and congestive heart failure for rosiglitazone and pioglitazone) in May–August 2007, and (ii) RMP policy for rosiglitazone and the warning for pioglitazone and bladder cancer risk in September–October 2010.

We used segmented linear regression models to estimate post-regulatory action changes in both the level and trend of TZD utilization. Using baseline trends, we projected monthly rates over time with the assumption that the baseline trend reflected what would have happened without the safety regulatory actions. The basic model included terms to estimate the baseline level for each outcome (intercept), baseline trend (slope), change in the level immediately after safety regulatory action release, and change in trend post-regulatory action.^{46–48} We controlled for autocorrelations. To identify the most parsimonious models, we used backward elimination and excluded non-significant terms ($P>0.05$). To summarize results in a single metric, we estimated absolute and relative changes (with 95% confidence intervals, CI)⁴⁹ in outcomes at 12 months post-regulatory action compared to projected rates. The interrupted time series design can provide strong evidence of causal effects because it takes into consideration the question of whether an intervention causes abrupt and measurable interruptions in the preexisting trend.^{46–48}

To determine whether the safety regulatory actions affected the quality use of medicines, we used above “new diabetes patient cohort” and survival analysis to examine changes in time to TZD prescription among new diabetes patients with CV history before and after the warnings. Time until TZD prescription was defined as the number of days from the index date until the date of the first observed TZD prescription.^{50,51} Each patient was followed for a maximum of 365 days from the index date until TZD prescription or study end. We used Kaplan–Meier survival curves and Cox regression models. All analyses were carried out with SAS software, Version 9.3 (SAS Institute, Cary, NC).

RESULTS

Characteristics of new diabetes patient cohort

Table 1 (and table in Appendix in supporting information) presents cohort characteristics and utilization of selected medications among new diabetes patient patients within 1 year before and after safety regulatory actions in 2007 and 2010. Overall, there were no apparent changes in major preexisting illnesses (e.g. myocardial infarction, ischemic heart disease, and congestive heart failure) between the two time periods.

Use of TZDs in the baseline period (January 2005–May 2007)

The prescribing rate of rosiglitazone among all diabetes patients gradually decreased from 12.3% in 2005 to 10.6% in 2007, just before the warning for cardiovascular risk (Figure 1).

Use of pioglitazone gradually increased from 3.3% in 2005 to 8.3% in 2007. Figure 2 presents TZD use among prevalent diabetes patients with/without CV history. Use of both rosiglitazone and pioglitazone was similar between patients with and without CV history.

Effects of the 2007 warning for cardiovascular risk on rosiglitazone use

Use of rosiglitazone suddenly dropped to 8% after the warning for cardiovascular risk in 2007 and continued to decline (Figure 1). There was a relative reduction of 31.17% (95% CI: -36.13%, -26.21%) in use of rosiglitazone at one year following the warning compared to expected rates (Table 2A). There were relative reductions of 36.88% (95% CI: -42.17%, -31.58%) and 29.92% (95% CI: -34.36%, -23.48%) in rosiglitazone use among prevalent diabetes patients with and without CV history respectively (Table 2A, Figure 2). Comparing pre- and post-warning new diabetes patients with CV history, time to rosiglitazone prescription increased significantly after the warning (hazard ratio [HR] =0.309; 95% CI: 0.203, 0.472; $p < 0.0001$) (Figure 3).

Effects of the 2007 warning for cardiovascular risk on pioglitazone use

Use of pioglitazone continued to increase following the 2007 warning for cardiovascular risk, and the trend did not change among all diabetes patients (Figure 1). Likewise, there was no change among prevalent diabetes patients without CV history. However, there was a relative increase of 13% (95% CI: -0.25%, 26.26%) in pioglitazone use among prevalent diabetes patients with CV history at one year after the warning (Table 2B, Figure 2). There was no significant change in time to pioglitazone prescription following the 2007 warning (HR=1.326; 95% CI: 0.941, 1.868; $p=0.1063$) (Figure 3).

Effects of the 2010 RMP policy on rosiglitazone use

Between 2007 and the RMP policy on rosiglitazone in 2010, use of rosiglitazone among all patients was very low, and there was a relative reduction of 86.8% (95% CI: -112.64%, -60.97%) at one year following the 2010 RMP (Table 2A). Rosiglitazone was rarely used after the RMP policy; its use decreased by 101.67% (95% CI: -118.69%, -84.66%) and 88.04% (95% CI: -117.03%, -59.05%) among prevalent diabetes patients with and without CV history respectively (Table 2A, Figure 2). There was no significant change in time to rosiglitazone prescription following the RMP policy (Figure 3).

Effects of the 2010 warning for bladder cancer risk on pioglitazone use

The trend in pioglitazone use suddenly decreased following the bladder cancer risk warning in 2010 (Figures 1 and 2). There was a relative reduction of 33.22% (95% CI: -40.78%, -25.67%) in use among all diabetes patients at one year following the bladder cancer risk warning (Table 2B). Use decreased by 25.63% (95% CI: -36.55%, -14.7%) and 31.86% (95% CI: -39.47%, -24.25%) among prevalent diabetes patients with and without CV history respectively (Table 2B, Figure 2).

DISCUSSION

This is the first longitudinal study examining utilization of thiazolidinediones following multiple safety warnings for TZDs released in 2007 and 2010 in Taiwan. Our findings

revealed the impacts of safety regulatory actions on the rates of TZD use and the quality of TZD use by various measures (prescription rate among all and prevalent diabetes patients with/without CV history, as well as time to TZD prescription among new diabetes patients with CV history). For TZDs, after considering both US FDA and EMA regulatory actions, the TFDA generally followed regulatory actions by the US FDA and released similar warnings around the same time. US FDA and EMA safety actions and reviews not only affected medication use in the US and European markets, but likely also affected medication use in Taiwan.

Previous studies indicated that rosiglitazone use decreased markedly after the warning in 2007 while pioglitazone use either remained stable³ or increased slightly^{1,32} in the US. The use of pioglitazone fell after the several warnings in Europe.⁷ Our findings suggested safety warnings led to similar changes in Taiwan. We found that use of rosiglitazone immediately decreased and reductions were sustained in all diabetes patients. However, there was an immediate increase in pioglitazone use in prevalent patients with CV history following the cardiovascular risk safety warnings in 2007, but no changes were detected among those without CV history. The possible reasons are that rosiglitazone was generally recognized to have a significantly higher cardiovascular risk than pioglitazone, even though the safety warning concerning congestive heart failure risk in 2007 targeted both agents.¹² Therefore, reductions in rosiglitazone use with offsetting increases in pioglitazone use might have reflected patients with CV history being switched to pioglitazone; such switch might not have occurred among patients without CV history.

Our study provided the first evidence on the effects of TFDA's Risk Management Plan for rosiglitazone, which is similar to US FDA's Risk Evaluation and Mitigation Strategy for this drug. The overall reduction in rosiglitazone use was likely because of the influence of 2010 RMP requirements and safety reviews by FDA and EMA. The TFDA followed US FDA's decision to apply access restrictions (RMP) to keep rosiglitazone as a treatment option (e.g. for patients who have been unable to achieve glycemic control with other medications) rather than market withdrawal. Despite this, we found that rosiglitazone use reduced substantially among all and prevalent diabetes patients with and without CV history following the policy; subsequent use was extremely low (less than 1%). While reduction in use of rosiglitazone was seen in all diabetes patients regardless of their risk for CV events, the RMP's impact was more pronounced among patients with CV history (−36.88%) than those without CV history (−28.92%). Rosiglitazone was almost never prescribed to new diabetes patients with CV history after the policy.

Our study also was the first to examine effects of the 2010 warning for pioglitazone and bladder cancer risk. This warning appeared to have larger impacts than the cardiovascular risk safety warning in 2007 on pioglitazone use. Declines in pioglitazone use after 2010 may be because of the increasing evidence of potential bladder cancer risk among patients who took high cumulative dose of pioglitazone for long-term, concerns for cancer risk likely influenced pioglitazone use. Another possible explanation is that the effect of RMP for rosiglitazone^{52,53} may have spilled over to pioglitazone despite evidence showing no association between pioglitazone and myocardial infarction or mortality.^{1,23,54} This spillover effect is possible because a recent discrete choice experiment study found that the small

increased risk of bladder cancer did not seem to affect drug choice when evaluated in context of drug benefits and risks,⁵⁵ especially there are effective therapeutic options available for diabetes (e.g. dipeptidyl peptidase-4 inhibitors).

As mentioned above, differences in physician prescribing patterns between patients with and without risk of adverse drug events may reflect quality use of medicines. However, our findings show that changes in use of rosiglitazone and pioglitazone were similar between patients with and without CV history following safety regulatory actions in 2007 and 2010. The possible reasons might include: (i) the availability of other antidiabetic agents apart from TZDs for diabetes treatment; and (ii) additional efforts are required by the RMP before TZD prescription, for example, physician evaluation and checking list and delivering medication guide to patients, which may be barriers for access to TZDs. Hence, while we found that safety regulatory actions reduced TZD use overall, there were no marked improvements in quality use of TZDs, considering patients' risk for CV events. Our findings suggest that regulatory actions may need to be combined with other interventions (e.g. education, updates of clinical guidelines)⁵⁵ to improve/change prescribing patterns.

We anticipated that cardiovascular risk warnings (2007) and RMP policy (2010) would reduce and delay rosiglitazone use among new diabetes patients with CV history; such delays suggest careful prescribing of drugs considering patients' higher risk of drug-related adverse effects in light of the safety warnings. Our findings confirmed these effects following the 2007 cardiovascular risk warning while there were no significant changes after the RMP policy in 2010 (Figure 3), probably because rosiglitazone use was already very low when RMP was implemented. On the other hand, the time to prescription of pioglitazone among new diabetes patients with CV history was not delayed following the 2007 warning (Figure 3), probably because pioglitazone was substituted for rosiglitazone.

There are several limitations of this study. First, this research aimed to explore how multiple safety regulatory actions regarding thiazolidinediones affected drug utilization and prescribing behavior; we did not examine clinical adverse events following safety regulatory actions. This is because patients receiving thiazolidinediones before and after the regulatory actions likely have very different clinical characteristics, which can lead to selection bias if one compares incidences between pre- and post-regulatory actions. Second, we did not examine the specific changes in treatment for individual patients. Further research is needed to determine whether drug switches related to these safety warnings affected medication adherence or real health outcomes, particularly among patients with CV history and those already established on thiazolidinedione therapy. Finally, our analysis was based on claims data, which do not contain patients' biochemical test data, so we could not assess impacts of regulatory actions on clinical outcomes of treatment, such as patients' status of glycemic control (e.g. the score of Hemoglobin A1c [HbA1c Test for Diabetes]). Nevertheless, our longitudinal study using interrupted time series assessed both level and trend changes in thiazolidinedione use in Taiwan is stronger than many studies in this field assessing only changes following the warnings. Our methods and findings should provide a basis for additional research to examine the intended and unintended consequences of regulatory actions to improve drug safety.

CONCLUSION

Overall, the present study examined how multiple safety regulatory actions changed thiazolidinedione utilization and prescribing behavior. Both cardiovascular risk warnings in 2007 and RMP policy in 2010 were associated with substantial reductions in use of rosiglitazone in Taiwan. Especially, the 2007 warnings significantly delayed the prescription of rosiglitazone among patients at risk of cardiovascular events. While the warning regarding potential heart failure risk in 2007 did not reduce pioglitazone use (instead its use increased slightly), a substantial reduction in its use was found after the bladder cancer risk warning in 2010. It is important to examine the consequences of TFDA regulatory actions on medication use and prescribing, and associated health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

- Rosiglitazone use reduced following cardiovascular risk warning (2007) and again after RMP policy (2010), while pioglitazone use decreased only after bladder cancer risk warning (2010).
- The use of rosiglitazone decreased in all prevalent patients following warning (2007). However, pioglitazone use increased in prevalent patients with CV history, but no changes were detected among those without CV history.
- Among new diabetes patients with CV history, cardiovascular risk warning (2007) delayed rosiglitazone use, but it did not delay pioglitazone use.

Figure 1.

Monthly thiazolidinediones prescription rate among all patients with diabetes (based on “monthly rolling diabetes cohort”). *Prescription rate (%) = number of thiazolidinedione prescription / number of diabetes patient visit per month. *diabetes patient visit = outpatient visit with diabetes diagnosis and anti-diabetic medicine prescription. *the baseline period: January 2005–May 2007

Figure 2.

Monthly thiazolidinedione prescription rates among prevalent diabetes patients with/without history of cardiovascular disease (based on “monthly rolling diabetes cohort”). *Prescription rate (%) = number of thiazolidinedione prescription / number of diabetes patient visit per month. *diabetes patient visit = outpatient visit with diabetes diagnosis and anti-diabetic medicine prescription. *the baseline period: January 2005–May 2007

Time to the first TZD prescription	Impact of 2007 Regulatory actions N=4,779	Impact of 2010 Regulatory actions N=2,282
Rosiglitazone	HR=0.309 (0.203-0.472); p<0.0001	HR=0; p=0.9926
Pioglitazone	HR=1.326 (0.941-1.868); p=0.1063

Figure 3.

Time to first receipt of thiazolidinedione prescription among new diabetes patients with history of cardiovascular disease following 2007 and 2010 regulatory actions (based on “new diabetes patient cohort”). *Observation period for 2007 regulatory actions: 28 months pre- (January 2005–April 2007) and post- (September 2007–December 2009) regulatory actions. *Observation period for 2010 regulatory actions: 14 months pre- (July 2009–August 2010) and post- (November 2010–December 2011) regulatory actions

Table 1.
Cohort characteristics of new diabetes patients (based on “new diabetes patient cohort”)

Variables	Cardiovascular safety warning for TZDs			Rosiglitazone-RMP policy/ Pioglitazone-bladder cancer risk warning		
	Pre-regulatory action (2006.5.1–2007.4.30) (N = 4984)	Post-regulatory action (2007.9.1–2008.8.31) (N = 5122)		Pre-regulatory action (2009.9.1–2010.8.31) (N = 5358)	Post-regulatory action (2010.11.1–2011.10.31) (N = 4859)	
	N	%		N	%	N
Female	2238	44.90		2395	44.70	2141
Age, mean (SD)	57 (14)			58 (14)		58 (14)
Charlson comorbidity index score, mean (SD)	2.80 (1.27)			2.78 (1.31)		2.75 (1.34)
≥ 1 hospitalization in the year before index	1080	21.67		1175	21.93	1013
Preexisting illness in one year before index						
Myocardial infarction	41	0.82		63	1.18	57
Ischemic heart disease	732	14.69		822	15.34	667
Congestive heart failure	200	4.01		213	3.98	163
Hypertension	2517	50.50		2857	53.32	2662
Dysrhythmia	301	6.04		367	6.85	279
Renal failure	85	1.71		116	2.16	118
Fracture	20	0.40		26	0.49	26
Cancer	129	2.59		152	2.84	133

* TZDs = thiazolidinediones; RMP = risk management plan.

Table 2. Estimated changes in thiazolidinedione utilization following safety regulatory actions by segmented regression models (based on “monthly rolling diabetes cohort”)

	Intercept	Baseline trend	Level change	Trend change	Relative change		Trend change	Absolute change		Relative change
					(1 year later)	(1 year later)		(1 year later)	(1 year later)	
A. Rosiglitazone										
Effects of cardiac risk safety warnings for thiazolidinedions (2007)										
Effects of RMP policy for rosiglitazone (2010)										
1. Use of rosiglitazone among all patients (including prevalent and new patients) with treated diabetes (number of prescription / number of DM patient visit per month)										
all	0.1239	-0.0007 (-0.0009, -0.0004)	-0.0213 (-0.0263, -0.0163)	-0.0007 (-0.0010, -0.0004)	-2.97% (-3.63%, -2.30%)	-31.17% (-36.13%, -26.21%)	-0.0222 (-0.0281, -0.0163)	0.0008 (0.0002, 0.0014)	-1.22% (-1.81%, -0.62%)	-86.80% (-112.64%, -60.97%)
2. Use of rosiglitazone among prevalent diabetes patients with treated diabetes (number of prescription / number of DM patient visit per month) – with/without cardiovascular disease history										
with history	0.1233	-0.0005 (-0.0008, -0.0003)	-0.0289 (-0.0349, -0.0229)	-0.0006 (-0.0009, -0.0003)	-3.66% (-4.45%, -2.87%)	-36.88% (-42.17%, -31.58%)	-0.0178 (-0.0234, -0.0122)	NS	-1.78% (-2.34%, -1.22%)	-101.67% (-118.69%, -84.66%)
without history	0.1264	-0.0007 (-0.0009, -0.0005)	-0.0189 (-0.0243, -0.0135)	-0.0007 (-0.0010, -0.0005)	-2.76% (-3.46%, -2.05%)	-28.92% (-34.36%, -23.48%)	-0.0226 (-0.0289, -0.0163)	0.0009 (0.0003, 0.0016)	-1.17% (-1.80%, -0.54%)	-88.04% (-117.03%, -59.05%)
B. Pioglitazone										
Effects of bladder cancer risk warning for pioglitazone (2010)										
Effects of pioglitazone among all patients (including prevalent and new patients) with treated diabetes (number of prescription / number of DM patient visit per month)										
all	0.0315	0.0018 (0.0016, 0.0021)	NS	NS	0.00%	0.00%	NS (-0.0064, -0.0037)	-0.0050	-6.03% (-7.62%, -4.43%)	-33.22% (-40.78%, -25.67%)
2. Use of pioglitazone among prevalent diabetes patients with treated diabetes (number of prescription / number of DM patient visit per month) – with/without cardiovascular disease history										
with history	0.0337	0.0014 (0.0012, 0.0017)	0.0125 (0.0008, 0.0242)	NS	1.25% (0.09%, 2.42%)	13.00% (-0.25%, 26.26%)	NS (-0.0051, -0.0034)	-0.0043	-3.86% (-5.93%, -1.79%)	-25.63% (-36.55%, -14.70%)
without history	0.0315	0.0019 (0.0017, 0.0021)	NS	NS	0.00%	0.00%	NS (-0.0064, -0.0036)	-0.0050	-6.01% (-7.67%, -4.36%)	-31.86% (-39.47%, -24.25%)

* Absolute and relative changes were estimated at 12 months post-regulatory actions, compared to projected rates based on pre-existing level and trend.

* We used backward elimination and excluded non-significant terms (P>0.05). All terms with p-value 0.05 were retained in final models. For example, the final model for use of rosiglitazone among all patients with treated diabetes (in Table 2A) is: “Y = 0.1239 + (-0.0007 × time) + (-0.0213 × intervention1) + (-0.0007 × time_after_intervention1) + (-0.0222 × intervention2) + (0.0008 × time_after_intervention2)” ; The final model for use of pioglitazone among all patients with treated diabetes (in Table 2B) is: “Y = 0.0315 + (0.0018×time) + (-0.0005×time_after_intervention2)”.

* NS = non-significant.