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Evaluation of the Impact of Cardiovascular Safety Concerns of Thiazolidinediones on the Utilization of Oral Antidiabetic Drugs

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Evaluation of the Impact of Cardiovascular Safety Concerns of Thiazolidinediones on the Utilization of Oral Antidiabetic Drugs

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Dedication

This thesis is dedicated to Mom and Dad, who always make sacrifices for, encourage, and support me to follow my dreams.

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Abstract

Evaluation of the Impact of Cardiovascular Safety Concerns of Thiazolidinediones on the Utilization of Oral Antidiabetic Drugs

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The overall objective of this study was to evaluate the impact of cardiovascular safety concerns on the utilization of the thiazolidinediones (TZDs), pioglitazone and rosiglitazone, and other oral antidiabetic drugs. In May 2007, a meta-analysis was published that found a potential increased risk of myocardial infarction (MI) associated with TZDs, particularly with rosiglitazone.

A two-year retrospective study of patients diagnosed with type 2 diabetes (ICD9 250.xx) using prescription and medical databases from the Scott & White Health System (SWHS) was conducted. Patients aged 18 or older who were continuously enrolled with SWHS from 2006 to 2008 and had high adherence (Medication Adherence Ratio ≥80%) for either pioglitazone or rosiglitazone during the pre-safety warning period (May 2006-

April 2007) were included. Patients were followed through the post-safety warning period (May 2007 - October 2008) or occurrence of event (discontinuation of index TZD drug). Patients who discontinued their index TZD drug by April 2008 were identified if they had a prescription filled for a new oral antidiabetic drugs (OADs), and followed until October 2008 or occurrence of event (discontinuation of new OAD). Cox proportional hazards models were used to assess the rate of and time to discontinuation of index TZD and new OAD with adjustment of age, gender and Charlson Comorbidity Index (CCI).

A total of 531 patients (58 percent male; mean age [SD] = 61 [9.1] years) were included in the final analysis, 255 and 276 patients in the rosiglitazone and pioglitazone groups, respectively. The rate of discontinuation for the pioglitazone and rosiglitazone groups began to separate within 90 days of the index event (meta-analysis published in May 2007). In the pioglitazone group, the rate of discontinuation was significantly lower than in the rosiglitazone group (HR = 0.56; 95% CI = 0.47, 0.67). A total of 21 patients did not experience discontinuation of their index medication. Among patients receiving a new OAD after discontinuing their index TZD (N = 95 rosiglitazone and N = 33 pioglitazone patients), there was no statistical significant in the rate of discontinuing their new OAD between the rosiglitazone and pioglitazone groups (HR = 0.98; 95% CI = 0.61, 1.59). However, patients who received metformin/sulfonylurea combinations had a lower rate of discontinuation compared to patients who received sulfonylureas (HR = 0.38; 94% CI = 0.21, 0.66).

The analysis showed the cardiovascular safety concern of TZDs had a significant impact on the utilization of oral antidiabetic drug utilization.

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Chapter One: Introduction and Literature Review

INTRODUCTION

This chapter provides a general background on type 2 diabetes, and reviews the literature on the cardiovascular (CV) safety of thiazolidinediones (TZDs) and the Food and Drug Administration (FDA) regulatory interventions and impact on clinical practice.

OVERVIEW OF TYPE 2 DIABETES

Pathophysiology of Type 2 Diabetes

Type 2 diabetes is a chronic, progressive condition. The pathophysiology is multifactorial, often characterized by the imbalance of glucose and insulin regulation.[1, 2] This imbalance is due to a cyclic, deteriorating process of insufficient insulin production by the pancreatic beta-cell, increased tissue resistance to insulin, and inappropriate increased glucose production by the liver.[2-5] The body's ability to maintain normal blood glucose level deteriorates with uncontrolled and longer duration of type 2 diabetes.[6, 7]

Several risk factors predispose an individual to develop type 2 diabetes.[1, 8] These risk factors include: age, overweight, metabolic syndrome, limited physical activity, high blood pressure, high cholesterol level, and family history or history of cardiovascular disease (CVD).[1] For example, individuals aged 65 years or older have higher percentage of diabetes (26.9 percent) compared to those aged 20 to 64 years (11.3 percent).[9] Another risk factor is pre-diabetes, defined by the presence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or glycosylated hemoglobin A_{1c} (HbA_{1c}) level ranging from 5.7 to 6.4 percent.[1] Approximately 60 percent of pre-diabetic individuals progress to type 2 diabetes at least five years later. [8]

Diagnosis of type 2 diabetes is both subjective and objective. Symptoms of type 2 diabetes include frequent urination, thirst, and hunger. In addition, repeated levels of blood glucose are greater than 200 mg/dL two hours after meals.[1]

Prevalence and Costs of Type 2 Diabetes

Type 2 diabetes is the seventh leading cause of death in the United States (U.S.).[9] In 2010, approximately 25.8 million (8.3 percent) American adults have type 2 diabetes including 18.8 million diagnosed and 7.0 million undiagnosed.[1] In 2007, the U.S. spent an estimated $174 billion on type 2 diabetes treatment, which included $116 billion in direct, $58 billion in indirect medical costs.[9, 10] In 2007, an estimated 12.5 million type 2 diabetic patients were taking an oral antidiabetic drug or insulin.[11] Furthermore, type 2 diabetes has become a global concern affecting approximately 285 million people worldwide.[12]

Type 2 Diabetes-related Complications

Type 2 diabetic individuals are at risk for many diabetes-related complications. These individuals often have comorbid conditions, such as high blood pressure, CVD, and high cholesterol levels, which are risk factors for CV complications.[1] Those who have prolonged, uncontrolled type 2 diabetes have an increased risk of (1) kidney failure requiring renal dialysis or transplant, (2) neuropathy leading to blindness and limp amputations, (3) CV events including myocardial infarction (MI), heart failure (HF) and stroke, and (4) death.[1, 13] Furthermore, type 2 diabetes is considered a risk factor for heart diseases including HF and stroke.[1, 14] Studies show that compared to individuals without type 2 diabetes, those with type 2 diabetes have two- to four-fold increased risk of experiencing fatal and non-fatal CV events including fatal MI and stroke.[9] The

prevalence of ischemic heart disease (IHD) is also higher among individuals with diabetes compared to those without diabetes with similar age.[9] Particularly, individuals with type 2 diabetes are twice as likely to die compared to those in the same age group without diabetes.[9]

Treatment of Type 2 Diabetes

The treatment goals are to prevent the progression type 2 diabetes, achieve glycemic control and prevent diabetes-related complications.[1]

Prevention of Type 2 Diabetes

Among pre-diabetic individuals, studies show lifestyle modification and drug therapy slow down the progression of type 2 diabetes.[15, 16] In two prospective, randomized controlled studies, lifestyle management—consisting of dietary changes, weight loss and increased physical activity—reduced the incidence of diabetes by 58 percent compared to general advice.[15, 16] Importantly, for pre-diabetic individuals, weight loss is key to prevent the onset of type 2 diabetes.[15] However, intensive lifestyle management is difficult to maintain long-term; half of patients failed to achieve the weight loss goal within six months.[15]

Drug therapy has been shown to reduce the incidence of type 2 diabetes from 14 percent to 38 percent.[17-21] Among overweight, pre-diabetic individuals, metformin prevented the incidence of diabetes by 31 percent [16] and acarbose, by 25 percent.[17] For pre-diabetic individuals without known CVD or renal disease, rosiglitazone significantly reduced the incidence of diabetes by 38 percent for up to three years compared to placebo (95% CI = 0.33, 0.44).[18-21] However, among pre-diabetic individuals with a high risk of CVD, [22, 23] nateglinide did not significantly reduce the incidence of type 2 diabetes compared to placebo (HR = 1.07; 95% CI = 1.00, 1.15), while valsartan plus lifestyle

modification significantly reduced the incidence by 14 percent (95% CI = 0.80, 0.92). Drugs which act on the renin-angiotensin system, such as valsartan, are suggested to prevent diabetes in people with CVD or high blood pressure.[22, 23] However, individuals who receive valsartan also receive lifestyle management, making it difficult to determine whether lifestyle management or valsartan contributed to the reduction of the incidence of type 2 diabetes.

While it is important to prevent the onset of diabetes among pre-diabetic individuals, it is difficult to achieve. The majority of pre-diabetic patients progress to type 2 diabetes and require treatment.[8]

Glycemic Control

Slowing down or preventing the progression of diabetes-related complications and death is a key treatment goal. These diabetes-related outcomes are measured by a surrogate marker, glycosylated HbA_{1c}. Glycosylated HbA_{1c} level is important to control because it increases with duration of type 2 diabetes[6] and has been associated with diabetes-related complications, including CV events and death.[8] It is documented that a one percent reduction in glycosylated HbA_{1c} decreases the risk of CV events by 18 percent.[1]

The American Diabetes Association (ADA) recommends treatment to target reduction of glycosylated HbA_{1c} level to at least less than 7.0 percent.[1] The benefit of aggressive treatment targeting glycosylated HbA_{1c} level below 6.5 percent is uncertain. Results from recent studies have failed to demonstrate the CV and mortality benefits with glycosylated HbA_{1c} level of at least less than 6.5 percent[24] or normal glycosylated HbA_{1c} level of 6.0 percent or less.[25-27]

The treatment of type 2 diabetes is complex. It is an individualized process consisting of a combination of a healthy lifestyle, drug therapy and multidisciplinary disease management programs for high blood pressure, high cholesterol level and diabetes.[6, 28-30] A healthy lifestyle which includes a balanced diet and exercise provides an effective option to reduce glycosylated HbA_{1c} level.[15, 16] However, lifestyle changes are difficult for patients to sustain, and thus it is difficult for the patient to reach and or maintain glycemic control. Studies show approximately 80 percent of type 2 diabetic patients eventually require drug therapy.[6, 29] For these patients, there are currently seven classes of antidiabetic drugs available which reduce glycosylated HbA_{1c} levels from 0.5 percent to 1.5 percent for oral drugs and up to 2.5 percent for insulin.[1] Studies have shown that most patients achieve glycemic control with one antidiabetic drug and approximately 15 percent to 34 percent of patients will require combination antidiabetic drugs after five years.[1, 31, 32] These antidiabetic drug combinations may include either TZD (pioglitazone or rosiglitazone), sulfonylurea, metformin, or insulin in reducing HbA_{1c}, as appropriate.[30, 33, 34] However, specific combinations have not been recommended over others.[35]

Medication adherence is a challenge among patients with type 2 diabetes. Medication non-adherent rates for antidiabetic drugs range from 65 percent to 85 percent.[36] Poor medication adherence reduces the chance of glycemic control[36] and has been associated with increased hospitalization.[37] Reasons for medication non-adherence has been attributed to side effects,[36] pill burden,[38] cost-sharing,[39-41] and patients' perceptions of drug benefits.[36, 42] Different interventions have been used in an attempt to improve medication adherence and persistence, including diabetes management[43] and co-pay waiver programs.[28, 44, 45]

Furthermore, individuals who have type 2 diabetes often have high blood pressure and high cholesterol level. These comorbid conditions are important to treat because they are risk factors for CV complications. Continuous monitoring is required to establish individualized regimens consisting of a combination of lifestyle management and drug therapy as appropriate. Thus, treatment of type 2 diabetes requires a multidisciplinary strategy.

Prevention of Diabetes-Related Complications and Death

Slowing down and preventing the onset of type 2 diabetes-related complications including MI, angina, HF, stroke, renal failure, and death are important treatment goals.[1] Diabetes-related complications are associated with increased levels of glycosylated HbA_{1c}.[1] Although antidiabetic drugs reduce glycosylated HbA_{1c} level, there is limited evidence that these drugs reduce diabetes-related complications. Of the seven classes of antidiabetic drugs available, metformin and sulfonylureas have demonstrated reduced CV risks. In a prospective, randomized controlled United Kingdom Prospective Diabetes (UKPD) study of newly diagnosed type 2 diabetic patients, sulfonylureas significantly reduced diabetes-related events including MI, angina, HF, stroke, renal failure, or death by 12 percent (95% CI = 0.79, 0.99) and microvascular events by 25 percent (95% CI = 0.60, 0.93) compared to diet alone.[6] However, sulfonylurea did not significantly reduce diabetes-related death (RR = 0.90; 95% CI = 0.73, 1.11) or death from any cause (RR = 0.94; 95% CI = 0.80, 1.10) compared to diet alone. The UKPD Study[29] showed that among a subset of overweight, type 2 diabetic patient, metformin significantly reduced the risk of diabetes-related events by 32 percent (95% CI = 0.53, 0.87), diabetes-related death by 42 percent (95% CI = 0.37, 0.91), and death from any cause by 36 percent (95% CI = 0.45, 0.91) compared with diet alone. Furthermore, a ten-year post-UKPD study

follow-up without additional intervention showed that metformin persisted in significantly reducing any diabetes-related events by 21 percent (95% CI = 0.66, 0.95), MI by 33 percent (95% CI = 0.51, 0.89), and death from any cause by 27 percent (95% CI = 0.59, 0.89).[30]

Evidence of long-term outcomes associated with newer oral antidiabetic drugs is limited and uncertain. Oral antidiabetic drug classes such as alpha-glucosidase inhibitors, glinides, and dipeptidyl peptidase-4 inhibitors are recently available and have not reported long-term outcomes. Furthermore, current literature has raised concerns whether the two TZDs (pioglitazone and rosiglitazone) have long-term CV risks.[46-49] The following section will further discuss this.

BACKGROUND ON THE SAFETY OF THIAZOLIDINEDIONES

Thiazolidinediones

TZDs are a newer class of oral antidiabetic drugs and considered insulin-sensitizing agents. TZDs are selective ligands of the nuclear transcription factor peroxisome-proliferator-activated receptor γ (PPAR γ) agonists.[50] PPAR γ are mainly expressed in the adipose tissue and involved in fatty acid uptake and storage, glucose uptake and metabolism, and lipolysis. Particularly, TZDs increase insulin sensitivity and effectively reduce glycosylated HbA_{1c} in type 2 diabetic patients. This led the FDA to approve of three TZDs, troglitazone in 1997 and rosiglitazone and pioglitazone in 1999, for the treatment of type 2 diabetes.

Commonly reported adverse drug reactions with TZDs (rosiglitazone and pioglitazone) include weight gain, swelling (or edema) and the risk of HF.[50] Particularly, rosiglitazone is significantly associated with more weight gain than other antidiabetic drugs (6.9 percent versus 1.2 percent versus 3.3 percent; $P < 0.001$, rosiglitazone,

metformin, and glyburide, respectively) and edema (14.1 percent versus 7.2 percent versus 8.5 percent; $P < 0.001$, rosiglitazone, metformin, and glyburide, respectively).[31] Furthermore, rosiglitazone has been reported to increase mean low-density lipoprotein cholesterol (LDL-C) levels by 18.6 percent at the highest approved dose (8mg)[51] and pioglitazone, by 6 percent at highest approved dose (45 mg).[52]

The clinical effects of this new mechanism are not fully understood. PPAR γ agonists are thought to provide a unique opportunity to reverse insulin resistance and thus potentially have positive CV effects.[50] First, Chiquette *et al.*[53] evaluated the effect of TZDs on CV risk factors such as glycemic control, lipid profile, and weight in a meta-analysis study. Results showed that rosiglitazone and pioglitazone had similar effects on glycemic control and the increase in body weight but had some differences in lipid profile. Pioglitazone reduced triglyceride levels and increased high-density lipoprotein cholesterol (HDL-C), but had no effect on LDL-C and total cholesterol levels. Rosiglitazone had no effect on triglyceride, and increased HDL-C, but also increased LDL-C and total cholesterol levels. [53] It is important to note that studies have shown that elevated LDL-C levels are associated with an increased risk of CV events[1] and drugs such as statins have demonstrated that improved lipid profiles lead to reduced mortality. However, the impact of lipid profiles of TZD treatment on CV events is not well understood.

Second, a review by Zinn *et al.*[54] reported studies which explored the potential protective effect of TZDs on CV surrogate markers, such as restenosis postcoronary stenting and atherosclerosis, as measured by the progression of carotid intima-medial thickness (CIMT). A double-blind randomized controlled CHICAGO (Carotid Intimal-medial Thickness in Atherosclerosis using Pioglitazone) study shows that pioglitazone reduced the progression of CIMT more than glimepiride.[55] However, in the STARR

(Study of Atherosclerosis with Ramipril and Rosiglitazone) study, rosiglitazone did not significantly reduce the progression of CIMT more than placebo.[56] Results of these studies were exploratory and require further research to confirm the benefits of TZDs on CV events.

However, edema, one of the adverse drug reactions seen with the use of TZDs, is a concern because it precipitates and worsens HF, a risk factor for MI events. Particularly, reports show rosiglitazone precipitates congested heart failure (CHF).[14] In 2003, the World Health Organization (WHO) drug safety surveillance worldwide reported signals of cardiac events including HF and ischemic events among individuals who received rosiglitazone.[57] Furthermore, two retrospective studies showed that patients discharged with TZDs had an increased risk of readmission for HF compared to patients discharged with non-insulin-sensitizing antidiabetic drugs among patients hospitalized for acute myocardial infarction (AMI) or HF (HR = 1.17; 95% CI = 1.05,1.30)[58] and for CHF (HR = 1.06; 95% CI = 1.00, 1.12).[59] Thus, reviews of the effects of rosiglitazone use led the American Heart Association (AHA) and the ADA to caution against rosiglitazone use among patients who may be at risk for HF.[14]

Early Signals of Cardiovascular Events with Rosiglitazone

Early studies by both the manufacturer of rosiglitazone, GlaxoSmithKline (GSK), and the FDA indicated CV safety concerns, particularly the risk of myocardial ischemic events.[60-62] In 2005, using the GSK Integrated Clinical Trial (ICT) database of rosiglitazone phase 2 and 3 clinical trials, GSK reported to the FDA results of the first internal meta-analysis showing a non-significant 29 percent increased risk of myocardial ischemic events including angina and MI compared to placebo.[61] However in the following year, an updated meta-analysis of the ICT data which included more clinical

trials showed rosiglitazone was significantly associated with a 31 percent (95% CI = 1.01, 1.7) increased risk of myocardial ischemic events compared to placebo.[60] Furthermore, an observational study by McAfee *et al.*, which used a large national health plan database, United Health Care, showed rosiglitazone was not significantly associated with increased risk of myocardial ischemic events compared to metformin (HR = 1.19; 95% CI = 0.84, 1.68) and sulfonylurea (HR = 0.79; 95% CI = 0.58, 1.07).[62] Results also showed rosiglitazone had similar risks of cardiac events (myocardial ischemic events or coronary revascularization) compared to metformin (HR = 1.07; 95% CI = 0.85, 1.34) and sulfonylureas (HR = 0.82; 95% CI = 0.67, 1.02).[62] GSK concluded that these studies indicate rosiglitazone potentially increased the risk of myocardial ischemic events compared to placebo, but not to other antidiabetic drugs.[63]

Furthermore, the FDA simultaneously conducted a separate internal analysis of the ICT database.[57] Results showed rosiglitazone had a 'numerical disadvantage' in CV events including CHF and myocardial ischemic events including angina and MI. In 2006, the FDA concluded that the 'numerical disadvantage' was sufficiently important and required a labeling change to include study results and cardiac adverse effects in the warning section.[57]

THIAZOLIDINEDIONES AND THE RISK OF CARDIOVASCULAR EVENTS

Myocardial Infarction and Rosiglitazone

In May of 2007, a meta-analysis by Nissen and Wolski[47] initiated a public discourse on the potential risk of MI associated with TZDs, particularly with rosiglitazone.

Nissen and Wolski, evaluated rosiglitazone and the risk of MI.[47] Published and unpublished studies were collected from the published literature, the Web site of the

FDA, and a clinical-trials registry maintained by GSK. Included studies were randomized controlled trials which had control groups not receiving rosiglitazone, had follow-up duration of more than 24 weeks and reported outcomes data for MI and death from CV causes. Forty-two phase 2, 3, and 4 clinical trials provided 27,847 patients, with a large number of patients (n = 9,260) from the DREAM[a] and ADOPT[b] studies. Although the DREAM[19] and ADOPT[31] studies did not evaluate the effect of rosiglitazone on CV outcomes, they were included because a large number of patients received rosiglitazone. The authors excluded six trials that did not report any MI or CV death. Of the 42 trials included, 38 trials reported at least one MI and 23 trials reported at least one death from CV causes. Nissen and Wolski used the Peto fixed-effects model to pool data comparing rosiglitazone to other oral antidiabetic drugs.

At baseline, patients had a mean age of 65 years and mean glycosylated HbA_{1c} level of 8.2 percent. Results[47] showed patients who received rosiglitazone experienced more MI (86 of 15,556) than patients who received placebo or with oral antidiabetic drugs (metformin and sulfonylureas) (72 of 12,277). Compared with placebo or with oral antidiabetic drugs, rosiglitazone was significantly associated with a 43 percent increased risk of MI (OR = 1.43; 95% CI = 1.03, 1.98; P = 0.03). When results of the interim-analysis of the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) study[48] was included in a reanalysis of this meta-analysis, rosiglitazone was significantly associated with a 33 percent increased risk of MI (95% CI

Note:

[a] The DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) study, a randomized controlled trial in IGT / IFT patients without known CVD or renal disease, evaluated a composite of incident diabetes or death with placebo, ramipril monotherapy, rosiglitazone monotherapy, or ramipril and rosiglitazone combination during a 3-year follow-up.

[b] ADOPT (A Diabetes Outcomes Progression Trial) study, a randomized, double-blind, parallel group study of newly diagnosed with type 2 diabetes and drug treatment naïve, evaluated time to monotherapy failure with rosiglitazone, metformin, and sulfonylurea.

= 1.02, 1.72) compared with placebo or with oral antidiabetic drugs,[64] similar to findings observed by Nissen and Wolski.[47]

There were limited results from randomized controlled trials to confirm the potential increased risk of MI associated with rosiglitazone. At the time, only an opened-label, non-inferiority RECORD study was in progress, but not completed.[48] The RECORD study evaluated whether the CV effect of rosiglitazone was non-inferior to comparators (metformin and sulfonylurea) as an add-on therapy among 4,447 patients who failed to reach glycemic control with background drugs (sulfonylurea or metformin). The study specified the margin of non-inferiority at 1.2 for the time to reach first composite endpoint of CV death or CV hospitalizations.[48] This margin required the upper bound of a two-sided 95 percent confidence interval for the hazards ratio to be below 1.2 in order to demonstrate non-inferiority—that rosiglitazone would not be worse than comparators on CV effects.

In response to results by Nissen and Wolski,[47] the RECORD authors reported results of an unplanned interim analysis.[48] Among 419 patients (N = 217 rosiglitazone and N = 202 comparator) evaluated, results showed increased risk of MI or death from CV causes or any cause with rosiglitazone versus comparator (HR = 1.08; 95% CI = 0.93, 1.32).[48] However, the findings were inconclusive because the reported upper bound of the 95 percent confidence interval (1.32) failed to exclude the pre-specified non-inferiority margin of 1.2. The study had a short mean (3.45 years) follow-up time, insufficient sample size, and thus insufficient power to detect treatment difference. The RECORD authors concluded that the risk of MI events associated with rosiglitazone was inconclusive.[48]

The RECORD[48] study has several limitations. In addition to insufficient follow-up period, low sample size and low power of the RECORD study, there were concerns

whether CV events including MI were appropriately ascertained.[57] While clinical trials could confirm the effect of rosiglitazone on MI events, the open-label and non-inferiority design of the RECORD made the interpretation of the results difficult to either demonstrate the benefit or confirm the increased risk of CV events, particularly with the underpowered interim analysis.[57]

The discordant findings lead to additional observational studies evaluating the risk of MI with rosiglitaozne. Reviewers[65, 66] cited that the risk of MI was uncertain because there were limitations in the study by Nissen and Wolski.[47] These included the methodology,[65, 67] the exclusion of studies which reported zero CV event,[66] the inclusion of a heterogeneous patient population (type 2 diabetic patients, pre-diabetic patients, and non-diabetics patients who had Alzheimer's or psoriasis), [68] and the lack of access to the original data sources with patient-level information. Nissen and Wolski[47] attempted but were unable to obtain patient level data from the manufacturer of rosiglitazone[69] and acknowledged that this limited the ability to estimate time-to-event, a precursor step to estimate risk ratio. Furthermore, Nissen and Wolski[47] included trials which did not clearly specify CV events or MI. For example, one of the studies included was the DREAM study[19] which reported CV composite events including MI, stroke, CV death, HF, new angina, and revascularization, Thus, it was possible that pooled data from the DREAM study could include patients who were counted for more than one of the components of the CV composite events.

Studies raised concerns regarding the appropriateness of using the Peto fixed-effect methodology when the data pooled were heterogeneous.[65, 67] Heterogeneity assessments test the null hypothesis that pooled studies share a common effect size, an important criterion for meta-analysis in making selection between fixed and random effects model. Fixed effects model is used when pooled studies are homogeneous and

provides an estimate of a common treatment effect.[67, 70] Fixed effects mode is used when pooled studies are heterogeneous and provide estimates of the average treatment effect with wider confidence interval, and with less precision.[67, 70] Subsequently, Shuster et al.[67] reported the relative risk (RR) with discordant *p*-values between fixed and random effects model for rosiglitazone and the risk of MI (RR = 1.43; 95% CI = 1.03, 1.98; *P* = 0.03 versus RR = 1.51; 95% CI = 0.91, 2.48; *P* = 0.11, respectively), and p-values for cardiac death (RR = 1.64; 95% CI = 0.98, 2.74; *P* = 0.06 versus RR = 2.37; 95% CI = 1.38, 4.07; *P* = 0.0017, respectively). The authors concluded that there was a potential variance among effect size suggesting a fixed-effect model would not fit the data when fixed and random effect models showed different results.[67] Although there are limitations with the Peto method, Nissen and Wolski acknowledged that it is considered the best method with the least bias when event rates are less than one percent.[66, 71]

Other studies used different methodologies and reported inconsistent findings. Results either showed that the risk of MI significantly increased by 33 percent to 42 percent[60, 64, 72] or that the risk was not significantly increased.[65, 67, 73] For example, Diamond *et al.*[65] reanalyzed the data from by Nissen with the inclusion of zero event studies. Diamond *et al.* used the Mantel-Haenszel fixed effects model with continuity correction to estimate the odd ratios of CV death and MI. Results showed rosiglitazone was not significantly associated with increased risk for MI (OR = 1.26; 95% CI = 0.93, 1.69) or CV death (OR = 1.17; 95% CI = 0.77, 1.77). Although Kaul and Diamond[65, 74] critiqued that the results by Nissen and Wolski may have been exaggerated and received unnecessary public attention, the authors acknowledged that the possibility of risk may exist.[65]

Findings from a meta-analysis study by Singh *et al*. showed rosiglitazone was associated with increased risk of MI.[72] Singh *et al*. set tighter criteria which included

randomized controlled studies of rosiglitazone to have either pre-diabetic or type 2 diabetes followed for at least 12 months, specify CV adverse events, and provide numerical data on all adverse events. Four of the 140 trials included in the analysis provided 14,291 patients from the DREAM study,[19] the ADOPT study,[31] the interim-analysis of RECORD study,[48] and a randomized controlled trial in patients who had New York Heart Association (NYHA) functional class I or II heart failure status.[75] Tests for heterogeneity showed homogeneity among trials for MI ($I^2 = 0\%$). Thus, the authors used a fixed-effects method to estimate the relative risks of MI. Results showed patients who received rosiglitazone experienced more MI events (94 of 6421 patients) compared with placebo or active control (83 of 7870 patients). This difference showed rosiglitazone was significantly associated with an increased risk of MI (RR = 1.42; 95% CI = 1.06, 1.91; P = 0.02). Singh *et al*.[72] concluded rosiglitazone was significantly associated with an increased risk of MI.

Using the ICT database, the FDA and GSK conducted separate meta-analysis studies to evaluate rosiglitazone and the risk of myocardial ischemic events. Results from the meta-analyses by the FDA[57, 60] and GSK[63] showed similar risks of MI associated with rosiglitazone to those reported by Nissen and Wolski.[47] Unlike Nissen and Wolski,[47] the FDA and GSK used the GSK's ICT database which contained patient-level data of 42 phase 2 and phase 3 double-blind, randomized controlled trials of type 2 diabetic patients who received rosiglitazone (N = 8,604) or non-rosiglitazone therapy (N = 5,633).[57, 60, 63] Pooled data from ICT included a heterogeneous population consisting of newly diagnosed patients who were treatment-naïve, long-standing patients who had multiple-drug regimens including insulin, and patients who had established heart disease or HF (NYHA functional class I or II). Study durations ranged from less than six months (N = 8 studies), six months (N = 30 studies) and up to more than a year (N = 4 studies).

Since included trials were not designed to evaluate CV endpoints, these endpoints were retrospectively adjudicated for most trials with the exception of one study which had a pre-planned blinded adjudication committee for CV endpoints. The ICT originally defined a broad criteria related to myocardial ischemia events (fatal and nonfatal IHD and serious IHD only) and CHF (fatal and nonfatal CHF and serious CHF only). Specific CV endpoints were added to include any major adverse cardiac event (MACE) and its individual components which included CV death, nonfatal MI or nonfatal stroke.

Demographic characteristics of patients in the ICT are as follows. Most patients were between 50 and 66 years old, and 29 percent were 65 years or older. The median duration of diabetes from diagnosis ranged from five to seven years, except for patients in the insulin trials who had a median duration of twelve to thirteen years. The median baseline glycosylated HbA_{1c} level ranged from 6.5 percent to 10.9 percent.

From the pooled analysis of the ICT database, the incidence of fatal and nonfatal myocardial ischemic events occurred in 171 of 8,604 (2 percent) patients taking rosiglitazone containing regimens and 85 of 5,633 (1.5 percent) patients in the comparator regimens.

Using the ICT database described above, the GSK authors[63] estimated the risk of rosiglitazone and the overall risk of myocardial ischemic events including HF. Using Cox proportional hazards regression, results showed rosiglitazone use was significantly associated with an increased risk of myocardial ischemic events (OR = 1.31; 95% CI = 1.01, 1.70; $P = 0.04$) and remained significant after adjusting for major risk factors (OR = 1.4; 95% CI = 1.1, 1.8; $P = 0.01$). The GSK authors concluded that the incidence of myocardial ischemic events (171 events in rosiglitazone versus 85 events in comparator regiments) was low.

The FDA [57, 60] estimated odds ratios for the risk of myocardial ischemic events using the exact test and Mantel-Haenszel fixed-effects model with continuity correction. Results from the Mantel-Haenszel fixed-effects model showed rosiglitazone was significantly associated with an increased risk of fatal or nonfatal myocardial ischemic events compared with placebo or active controls (OR = 1.4; 95% CI = 1.1, 1.8; $P = 0.02$). The overall risk of myocardial ischemic events using the exact test showed a significant increased risk associated with rosiglitazone (OR = 1.32; 95% CI = 1.02, 1.72; $P = 0.04$). However, evaluation of fatal myocardial ischemic events alone showed rosiglitazone had an increased risk compared with placebo or active controls (OR = 1.44; 95% CI = 0.98, 2.1; $P = 0.06$), but the risk were not significant.

In summary, the RECORD study[48] showed uncertain risk of MI associated with rosiglitazone, but results from meta-analyses by Nissen and Wolski,[47] GSK[63] and the FDA[57, 60] consistently showed a significant 31 percent to 43 percent increased risk of MI.

Myocardial Infarction and Pioglitazone

These findings regarding rosiglitazone raised concerns about whether or not there is a risk of MI associated with another TZD, pioglitazone. Lincoff and Wolski[46] conducted a meta-analysis evaluating pioglitazone and the risk of composite events including death, MI, or stroke. Patient-level, time-to-event data were provided by the drug manufacture, Takeda. The authors included 19 randomized, double-blinded, control trials which consisted of pioglitazone (N = 8,554) and control (placebo or active comparator) (N = 7,836) groups. Study follow-up durations ranged from 4 months to 3.5 years. Tests for evidence of heterogeneity showed similarity across trials for composite endpoint ($I^2 = 0\%$; $P = 0.87$). Using a fixed-effects model, results showed patients who received pioglitazone experienced less composite events including death, MI, or stroke

compared to control (375 [4.4%] versus 450 [5.7%], respectively) and a significant decreased risk of composite events by 18 percent (HR = 0.82; 95% CI = 0.72, 0.94; *P* = 0.005). Furthermore, pioglitazone reduced the composite risk approximately after one year of therapy. When the individual components of the primary composite events were considered, pioglitazone did not significantly reduce the risk of death (HR = 0.92; 95% CI = 0.76, 1.11), MI (HR = 0.81; 95% CI = 0.64, 1.02), or stroke (HR = 0.80; 95% CI = 0.62, 1.04) compared to placebo. The authors concluded that pioglitazone was associated with a significantly lower risk of composite events including death, MI, or stroke among a diverse population of patients with diabetes.

Similar findings were seen in the randomized controlled PROACTIVE (Prospective pioglitazone clinical trial in macrovascular events) study.[76] The PROACTIVE study evaluated CV events with pioglitazone as an add-on therapy. Among the 5,238 patients (N = 2,605 pioglitazone and N = 2,633 control) randomized into the study, results showed pioglitazone as an add-on therapy significantly reduced the risk of the secondary composite endpoint including death from any cause, non-fatal MI (excluding silent MI), and stroke by 16 percent (95% CI = 0.72, 0.98).[76] However, pioglitazone did not significantly reduce the risk of events in the primary composite endpoint (all-cause mortality, non-fatal MI [including silent MI], stroke, acute coronary syndrome (ACS), coronary or leg revascularisation, or major leg amputation) compared to placebo (HR = 0.90, 95% CI = 0·80, 1·02; *P* = 0.095).[76] Furthermore, a subgroup analysis[49] of patients who previously had a MI showed similar results to the primary study. Pioglitazone did not significantly reduce the risk of the main study primary endpoint (HR = 0.88; 95% CI = 0.75, 1.04) and secondary endpoint (HR = 0.81; 95% CI = 0.65, 1.01). However, among this subgroup of patients who previously had a MI, pioglitazone significantly reduced the risk of fatal and nonfatal MIs (excluding silent

MIs) by 28 percent (95% CI = 0.52, 0.99) and ACS by 37 percent (95% CI = 0.41, 0.97) compared with placebo.[49] The PROACTIVE study authors concluded pioglitazone reduced the risk of death from any cause, non-fatal MI, and stroke[76] as well as fatal and nonfatal MI and ACS among those with previous MI.[49]

Myocardial Infarction with Rosiglitazone versus Pioglitazone

A retrospective observation study [77] evaluated the risk of hospitalization for AMI with rosiglitazone versus pioglitazone. The study evaluated 29,911 patients aged 45 years or older who were newly initiated on either rosiglitazone or pioglitazone monotherapy using the United Health Care database from 2003 through 2006. The study excluded patients who received both pioglitazone and rosiglitazone during the follow-up period. At follow-up (mean 1.2 years for pioglitazone and 1.3 years for rosiglitazone), patients who received pioglitazone experienced less hospitalization for AMI compared to rosiglitazone (161 of 14 807 [1.1 percent] versus 214 of 15 104 [1.42 percent]) and were significantly associated with a 22 percent relative risk reduction (adjusted HR = 0.78; 95% CI = 0.63, 0.96). [77] Furthermore, results showed pioglitazone was significantly associated with reduced risk of composite of AMI or coronary revascularization compared to rosiglitazone (adjusted HR = 0.85; 95% CI = 0.75, 0.98). The authors concluded pioglitazone was associated with a 22 percent relative risk reduction of hospitalization for AMI compared to rosiglitazone.

Myocardial Infarction with Thiazolidinediones and Other Antidiabetic Drugs

McAfee *et al.*[62] evaluated rosiglitazone and the composite risk of hospitalizations for MI or coronary revascularization using the United Health Care database. The study identified 33,363 patients who initiated rosiglitazone, metformin, or sulfonylurea from

2000 through 2004. Results showed rosiglitazone monotherapy was not associated with an increased risk of composite risk of hospitalization for MI or coronary revascularization compared to metformin monotherapy (HR = 1.07, 95% CI = 0.85, 1.34) and sulfonylurea monotherapy (HR = 0.82, 95% CI = 0.67, 1.02). In addition, insulin in combination with rosiglitazone was not associated with an increased composite risk of hospitalization for MI or coronary revascularization (HR = 0.88, 95% CI = 0.59, 1.32) compared with insulin in combination with other oral antidiabetic drugs. Results showed rosiglitazone was not associated with MI compared to metformin monotherapy (HR = 1.19; 95% CI = 0.84, 1.68), or sulfonylurea monotherapy (HR = 0.79; 95% CI = 0.58, 1.07). Compared with non-rosiglitazone therapy, rosiglitazone therapy was not associated with an increased risk for composite outcomes including MI and coronary revascularization events (HR = 0.93; 95% CI = 0.80, 1.10) or individual event of the composite outcomes. The authors concluded that there is little difference in risk associated with the use of rosiglitazone compared to other non-rosiglitazone therapy.

Rosen[78] evaluated the risk of MI between TZDs (rosiglitazone and pioglitazone) and other oral antidiabetic drugs using data from WellPoint submitted to the FDA advisory committee in 2007. The analysis of 142,821 diabetics showed rosiglitazone (HR = 1.03; 95% CI = 0.89, 1.19) and pioglitazone (HR = 1.04; 95% CI = 0.91, 1.2) were not associated with an increased risk of MI when compared to other oral antidiabetic drugs.[78] The author concluded that rosiglitazone was not associated with increased risk of MI.

Potential Sub-groups at Risk for Myocardial Infarction

The FDA and GSK conducted subgroup analyses which compared six meta-groups of rosiglitazone (monotherapy, combination, or add-on with metformin, sulfonylureas, or insulin) versus control groups (placebo or different active control

combinations with sulfonylurea, metformin, or insulin). Of the six meta-groups, results from the FDA study (OR = 3.2; 95% CI = 1.2, 9.8) and GSK study (OR = 2.7, 95% CI = 1.2, 7) showed patients who received rosiglitazone in combination with metformin had a significant increased risk of myocardial ischemic events compared to patients who receive metformin alone. Moreover, the FDA (OR = 2.1; 95% CI = 0.91, 5.1) and GSK (OR = 2.1; 95% CI = 0.91, 5.1) reported patients who received rosiglitazone in combination with insulin had increased risks of myocardial ischemic events compared to patients who received insulin alone, although the risks were not significant. Additional post-hoc analyses excluded studies showing greatest risk such as those with rosiglitazone as an add-on to insulin and metformin, either together or alone. Results showed rosiglitazone was not significantly associated with increased risk of MI after excluding studies which included rosiglitazone in combination with metformin (OR = 1.27; P = 0.09), insulin (OR = 1.31; P = 0.06) and both insulin and metformin (OR = 1.17; P = 0.32). The FDA concluded that the observed risk of myocardial ischemic events with rosiglitazone was similar compared to placebo or other oral antidiabetic drugs (metformin and sulfonylureas), but the risk was greater when rosiglitazone was combined with metformin or insulin compared to other non-rosiglitazone therapy combinations.

To further consider the characteristics which may predispose patients to the risk of myocardial ischemic events associated with rosiglitazone, the FDA conducted *post hoc* sub-analyses of all patients and patients without insulin use.[60] Among all studied patients, results showed rosiglitazone was associated with an increased risk of myocardial ischemic events versus comparators among patients who at baseline were 65 years or older (OR = 2.0, 95% CI = 1.3, 3.2), were overweight with a body mass index (BMI) greater than 30 (OR = 1.8; 95% CI = 1.2, 2.6), and had previously been treated with an antidiabetic drug (OR = 1.6, 95% CI = 1.2, 2.1), ACEI (OR = 1.8; 95% CI = 1.1, 2.8) or

nitrate (OR = 2.9, 95% CI = 1.4, 5.9). Additionally, there was a significant increased risk for myocardial ischemic events among patients who had a history of CHD (OR = 1.5; 95% CI = 1.0, 2.2) or history of CHD with nitrate use (OR = 3.0, 95% CI = 1.5, 6.2) as well as a history of CHF (OR = 3.2, 95% CI = 1.1, 10).

Similar findings were shown after removing patients who received insulin at baseline.[60] There was a significant increased risk of myocardial ischemic events among patients who at baseline were 65 years or older (OR = 1.9; 95% CI = 1.1, 3.1), were overweight with a BMI greater than 30 (OR = 1.8, 95% CI = 1.1, 2.7), and had previously been treated with antidiabetic drugs (OR = 1.5, 95% CI = 1.1, 2.1), ACEI (OR = 1.6; 95% CI = 1.0, 2.6) or nitrate (OR = 3.1; HR = 1.5, 6.8). Additionally, there was a significant increased risk of myocardial ischemic events among patients who had a history of CHD (OR = 1.5; 95% CI = 1.0, 2.3) and history of CHD plus nitrate use (OR = 3.3; 95% CI = 1.6, 7.3). However, patients who had a history of CHF showed a non-significant increased risk of myocardial ischemic events after removing insulin use at baseline (OR = 2.8; 95% CI = 0.98, 9.2). The FDA concluded there may be potential differential treatment effects across several sub-groups of patients such as those who were previously treated compared to naïve patients.

Myocardial Infarction Events with Thiazolidinediones in the Elderly

Lipscombe *et al.* conducted a retrospective nested case-control study using a health care database in Ontario, Canada[79] to evaluate the risk of AMI among elderly patients taking TZDs (rosiglitazone and pioglitazone) compared to other oral antidiabetic drug combinations. The study identified a total of 159,026 type 2 diabetic patients aged 66 years or older treated with at least one oral antidiabetic drug from 2002 through 2005. Cases were identified as patients who experienced an event and controls were assigned a

study index date of their respective cases. Cases and controls were 1:5 matched based on age, gender, duration of diabetes, and history of CVD. The rate ratio was estimated and adjusted for demographics and clinical characteristics, antidiabetic and concomitant CV drug use and comorbidities. Patients were followed until the occurrence of an AMI or March 31st, 2006. Any emergency department visit or hospitalization for AMI was measured as a secondary outcome.

During a median follow-up of 3.8 years, 12,578 (7.9%) patients were hospitalized or had an emergency visit for AMI.[79] There was an increased risk of AMI associated with TZDs compared to other antidiabetic drugs (65 cases; adjusted rate ratio [RR] = 1.40; 95% CI = 1.05, 1.86; *P* = 0.02). Rosiglitazone monotherapy was associated with increased risk of AMI compared to other antidiabetic drugs (53 cases; RR = 1.76; 95% CI = 1.27, 2.44; *P* <0.001), but pioglitazone was not significantly associated with increased risk of AMI compared to other oral antidiabetic drugs (12 cases; RR = 0.73; 95% CI =0.40, 1.36; *P* = 0.33). The authors concluded that TZD treatment, primarily with rosiglitazone, was associated with an increased risk of AMI.[79]

Cardiovascular Death and Death From Any Cause

While the risk of MI remains uncertain, studies consistently reported that TZDs were not associated with an increased risk of CV death and death from any cause, except for an observational study among the elderly population.[79] The meta-analysis by Nissen and Wolski[47] reported death from CV cause occurred in 39 patients taking rosiglitazone compared to 22 patients in the control group (placebo or antidiabetic drugs), but the increased risk was not significant (OR = 1.64; 95% CI = 0.98, 2.74). In addition, a meta-analysis study by Singh *et al*.[72] showed rosiglitazone was not significantly associated with risk CV death (RR = 0.90; 95% CI = 0.63, 1.26) compared with control. A meta-

analysis by Lincoff and Wolski[46] showed pioglitazone was not significantly associated with increased risk of death (HR = 0.92; 95% CI = 0.76, 1.11). Moreover, among pre-diabetic and diabetic patients, Lago *et al.*[80] showed that either rosiglitazone or pioglitazone was associated with increased risk of CV death compared to controls (RR = 0.93; 95% CI = 0.67, 1.29).

However, in a retrospective nested case-control study by Lipscombe *et al.*[79] previously described, results showed a potential risk of all-cause mortality with TZDs among the elderly population (N = 159,026) compared to other oral antidiabetic drug combinations. During a median follow-up of 3.8 years, 30 265 (19%) patients died.[79] TZD was associated with increased risk of death compared to other oral antidiabetic drugs (102 cases; RR = 1.29; 95% CI = 1.02, 1.62). Rosiglitazone was associated with increased risk of death compared to other oral antidiabetic drugs (76 cases; RR = 1.47; 95% CI = 1.12, 1.93), but pioglitazone was not (26 cases, respectively; RR = 0.94; 95% CI = 0.61, 1.45). The authors concluded that TZD treatment, primarily with rosiglitazone, was associated with an increased risk of all-cause mortality.[79]

Heart Failure

Studies confirmed the risk of HF with TZDs. The RECORD study noted a significant increased risk of HF among patients who received rosiglitazone versus active comparator (HR = 2.15; 95% CI = 1.30, 3.57) with both the lower and upper bound of the 95 percent confidence interval above the pre-specified non-inferiority margin of 1.2.[48] Results from the PROACTIVE study showed patients who received pioglitazone had more HF events (417 events, 281 (11 percent) patients) compared with patients who received placebo (302 events, 198 (8 percent) patients) ($P < 0.0001$). Furthermore, meta-analysis studies showed patients who received rosiglitazone (RR = 2.09; 95% CI = 1.52,

2.88; $P < 0.001$) [72] and pioglitazone (HR = 1.41; 95% CI = 1.14, 1.76) [46] were associated with a significant increased risk of HF.

Similar findings were observed in additional observational studies. A meta-analysis by Lago *et al.*[80] evaluated the risk of CHF in pre-diabetic and diabetic patients. Included studies were required to report drug-related CHF in patients receiving TZDs (either rosiglitazone or pioglitazone) compared to controls. Seven randomized double-blind controlled trials (N = 20,191patients) were included. Lago *et al.* used a random-effects model to estimate the risk ratios for development of CHF in the TZD group versus control group. The test of heterogeneity among the trials was not significant (I^2 = 22.8 percent; P = 0.26). Results showed patients who received TZDs experienced more CHF compared to those who did not receive TZDs (214 versus 146 patients, respectively) and were significantly associated with an increased risk of CHF compared to control (RR = 1.72, 95% CI = 1.21, 2.42). The authors concluded that the risk of CHF in patients taking TZDs might not be similar to the risk associated with CHF caused by progressive decline in systolic or diastolic function of the left ventricle.[80]

Among the elderly population, results showed TZDs were significantly associated with HF. In a retrospective nested case-control study using a health care database in Ontario, Canada, Lipscombe *et al.*,[79] evaluated the risk of CHF among patients taking TZDs (rosiglitazone and pioglitazone) compared to other oral antidiabetic drug combinations. The primary outcomes were an emergency department visit or hospitalization for congestive HF. During a median follow-up of 3.8 years, 12,491 (7.9%) patients had an emergency department visit or hospitalization for CHF.[79] Current treatment with TZD monotherapy was associated with a significantly increased risk of CHF (78 cases versus 273 control cases; adjusted RR = 1.60; 95% CI = 1.21, 2.10). Rosiglitazone was associated with an increased risk of CHF compared to other

antidiabetic drugs (62 versus 151 cases, respectively; adjusted RR = 1.98; 95% CI = 1.44, 2.72) but pioglitazone was not (16 cases versus 86 control; adjusted RR = 0.91; 95% CI = 0.52, 1.59). The authors concluded TZDs were significantly associated with increased risk of MI among elderly population, particularly with rosiglitazone.

Summary

In conclusion, current studies show inconclusive risks of MI associated with rosiglitazone [47, 48, 65, 67, 73]and potential positive CV effects of pioglitazone.[46, 49, 76] While the risk of MI remains uncertain, studies consistently reported that TZDs are not associated with increased risk of CV death and death from any cause, except an observational study among the elderly population.[79] Furthermore, consistent with the TZD effect profiles, particularly the edema adverse events, studies confirmed the increased risk of HF with TZDs.

It is important to note that different findings from meta-analysis and retrospective database studies may be due to the varied study designs, the duration of diabetes and study observation period, the study outcomes (MI, HF, and CV events), and the drug comparisons. Furthermore, retrospective observational studies may be affected by confounding factors or bias.[81] Randomized controlled studies are considered the standard approach to confirm long-term effects of drugs. However, current randomized controlled studies have not confirmed the risk of MI associated with rosiglitazone.[48]

It has been reported that an estimated 83,000 MI events had been reported among those who received rosiglitazone from when rosiglitazone entered the market in 1999 through 2007.[69]

THE FOOD AND DRUG ADMINISTRATION REGULATORY ACTION

The FDA responded by convening the FDA Advisory Committee meeting to evaluate the benefits and risks of rosiglitazone. The FDA committee members agreed in a 20 to 3 vote that available studies supported a signal of harm with rosiglitazone. However, the FDA committee members voted 22 to 1 to keep rosiglitazone on the market.[82] To express the concern of drug safety, the FDA required that black-boxed warnings about the potential increased risks of CHF be placed on both rosiglitazone and pioglitazone labels[83] and the potential risk of MI on rosiglitazone label.[84] Black-boxed warning is considered the strongest warning and communication of risks that may lead to death or serious injury to clinicians.[85]

IMPACT OF SAFETY WARNINGS ON CLINICAL PRACTICE

Black-boxed Warnings and Letters to Clinicians

Drugs approved by the FDA are required to show safety and efficacy based on findings from phase 2- and phase 3-clinical trials. Phase-3 clinical trials are large-scale human studies in several thousands of patients and have duration ranging from eight to 52 weeks. Although these trials are large-scale, they are short-term and have limited numbers of patients to detect adverse events.[86] Furthermore, these studies are conducted under very controlled environment which include specific clinical population, drug usage (dose and concomitant medication) and careful, routine monitoring of patients condition. For example, considering the edema drug reaction and potential HF exacerbation, the TZD safety and efficacy trials excluded high risk patients who had NYHA functional class III (moderate) or IV (severe) heart failure status.[14] Thus, the exclusion of high risk patients, the limited numbers of patients and the controlled settings of these clinical trials limit the ability to observe drug reactions, which may be rare, delayed due to interaction

with concomitant medicine excluded from trials, or due to drug reactions that are specific to certain patients, realized in a real world setting.[86] To ensure the safety of patients, the FDA requires that the drug manufacturer conduct continuous safety monitoring and reporting as part of the safety surveillance of marketed products.[87]

The FDA may take several actions when a marketed drug poses a risk to patients. Findings from postmarketing experiences are updated in the drug information labels which include a comprehensive presentation of the risks and benefits of drug products. Furthermore, drugs with serious risks that may lead to death or serious injury require black-boxed warnings. Black-boxed warnings are considered the strongest FDA warning and are prominently presented on the drug label to provide detailed information of the risks and recommendation to monitor patients.

However, studies showed that FDA warnings, including professional label changes such as black-boxed warnings, often have limited impact in clinical practice.[85, 88-93] A review of 96 types of medications that had black- boxed warnings showed that over 40 percent of patients inappropriately received medication or were not monitored appropriately.[85]Although guidelines provide clinical guidance for best practices, they are often not followed, even among high risk patients who recently had an MI.[94] Furthermore, it is suggested that unclear outcomes or unclear risks of a drug may play a role in physicians' practice.[85]

For example, observational studies[90, 92, 93] evaluated the impact of three labeling changes including the first black-boxed warning in 1995 and letters to providers about cisapride, an oral prokinetic drug approved in July of 1993 for the treatment of nocturnal heart burn due to gastroesophageal reflux. From February 1995 to June 1998, these actions warned providers about the risk of serious and fatal cardiac arrhythmia when cisapride were concomitantly used with drugs (such as antifungal, antibacterial,

antidepressant and protease inhibitors) that inhibit the cytochrome P450 isoform 3A4 liver enzyme from metabolizing cisapride and drugs (such as antiarrhythmics, cyclic antidepressants and antipsychotics) that prolong the QT interval. However, serious cardiac arrhythmia persisted from July 1993 through May 1999, resulting in more than 270 cases including 70 deaths. Subsequently, cisapride was withdrawn from the market.

Smalley *et al.*[92] evaluated the impact of codispensing cisapride with contraindicated drugs and heart conditions (HF and other IHD) before and after the regulatory interventions (FDA black-boxed warnings and accompanying publicity including letters to physicians). Using three large national insurance databases including Medicare and the United Health Group, 24,840 patients were identified to have one codispensing of cisapride with a contraindicated drug or heart condition before the regulatory intervention, and 22,459 patients after. The proportion of patients who received codispensing of cisapride with either contraindicated drugs or heart conditions ranged from 26 percent to 60 percent before and ranged from 24 percent to 56 percent after regulatory intervention among three different insurance databases. The authors concluded regulatory interventions did not impact clinical practice, despite repeated and prominent publications and notifications.

In a time-series analysis of 38,757 patients from July 1993 to December 1998, Guo *et al*.[90] showed an overall decreasing trend in the proportion of any contraindicated drugs dispensed concomitantly with cisapride. Particularly, the proportion of concomitant dispensing decreases after each label change and letter to physicians, but the proportion peaked during the winter period. The authors concluded there was a decrease in codispensing cisapride with contraindicated drugs, but there remained a 3.1 percent of codispensing after the fourth letter to physicians.[90] Furthermore, the same group of

authors, Jones *et al.*, noticed that the majority of codispensing and coprescribing of cisapride were from the same pharmacies and physicians.[93]

There was limited impact on clinical practice with the FDA warnings of liver failure with troglitazone, the first approved TZD in 1997. Cluxton *et al.*[88] and Graham *et al.*[91] evaluated the impact of liver failure black-boxed warnings on clinical practice with troglitazone. Shortly after approval, there were several case reports of liver failures leading to black-boxed warnings and four separate letters sent to physicians with recommendations to monitor liver enzyme before (baseline) and after (monthly) starting a patient on troglitazone. Using a large national insurance database, United Health Group, a total of 7603 patients who received their first troglitazone were identified.[91] Compared to the first and the fourth warning, Graham *et al.*[91] found an overall increase in the proportion of patients who received either baseline (15 percent versus 45 percent) or at least one monthly follow-up (4 percent versus 33 percent) liver enzyme testing. However, among patients who received their first troglitazone prescription during the fourth warning, only 18 percent received both baseline and month one follow-up liver enzyme. Graham *et al.*[91] concluded that the extensive methods to communicate risk, including black-boxed warnings and informational letters with monitoring recommendations to providers, have had limited influences.

Similar findings were seen in a study using an Ohio Medicaid database.[88] Cluxton *et al.*[88] compared baseline and follow-up liver enzyme testing between patients who received troglitazone prescription before the regulatory interventions (N = 3,019) and patients who received troglitazone after the intervention (N = 4,207). Results showed patients who received troglitazone (19 percent) after regulatory interventions were more than twice as likely (HR = 2.5; 95% CI = 2.16, 2.93) to receive baseline liver enzyme testing compared to patients who received troglitazone (8 percent) before regulatory

actions. Similarly, patients who received troglitazone after regulatory interventions were more than twice as likely (HR = 2.77; 95% CI = 2.47, 3.12) to receive follow-up liver enzyme than patients who received troglitazone before regulatory interventions. However, the time for half of the patients (50 percent) to receive their first follow-up liver enzyme test was six months. The authors concluded regulatory intervention had modest effects on liver enzyme testing. The FDA subsequently removed troglitazone from the market.

In summary, while black-boxed warnings and direct communications are provided to clinicians regarding the safety of a drug, clinical practice with considerations for these safety concerns are limited.

After Nissen and Wolski reported the potential risk of MI in May of 2007, studies have shown that physicians have reduced their numbers of rosiglitazone prescriptions[95] and the utilization of rosiglitazone declined. Rosiglitazone was one of the most widely used drugs, claiming 37 percent of the market share of the oral antidiabetic drugs in the United States in 2006.[96] However, sales of rosiglitazone declined 29 percent by the fourth quarter of 2007.[97] Furthermore, results from a prescription claim analysis showed prescription for rosiglitazone decreased by 70 percent, while pioglitazone increased by 8 percent one year after the regulatory warning.[98]

Past studies have shown that safety concerns[99] for or the removal of one type of medication from the market[100] may lead to increased prescribing of alternative agents. The impact of safety concerns and discordant literature surrounding TZDs would likely influence the utilization of both TZDs and other oral antidiabetic drugs, but the affects have not been thoroughly assessed. The aim of this study is to evaluate the impact of safety concerns on the utilization of TZDs and other oral antidiabetic drugs. The impact of safety concerns will be measured using the time to discontinuation of a prescribed

TZD among patients with high medication adherence, defined as 80 percent or greater.[37, 39]

OBJECTIVES

The overall objective of this study is to evaluate the impact of safety concerns on the utilization of TZDs and oral antidiabetic drugs. Using the Scott & White Health Plan database from May 2006 through October 2008, the specific objectives are as follows.

Objective I: Among patients who had one year high adherence to an index TZD drug pre-safety warning period, compare the discontinuation of rosiglitazone versus pioglitazone post-safety warning period

Objective II: Among patients who were prescribed with new oral antidiabetic drugs after discontinuing index TZD during the post-safety period, compare the discontinuation of new antidiabetic drugs between rosiglitazone versus pioglitazone groups

HYPOTHESES

The specific hypotheses for are listed below.

Objective I: Among patients who had one year high adherence to an index TZD drug pre-safety warning period,

H_{01}: There is no difference in the discontinuation curve (days) of rosiglitazone group versus pioglitazone group post-safety warning period

H_{02}: There is no difference in the discontinuation rate (percent of patient) of index TZD between rosiglitazone group and pioglitazone group post-safety warning period

Objective II: Among patients prescribed with new oral antidiabetic drugs after discontinuing index TZD during the post-safety period,

H_{03}: There is no difference in the discontinuation curve (days) of new oral antidiabetic drugs between rosiglitazone group versus pioglitazone group

H_{04}: There is no difference in the discontinuation rate (percent of patients) of new oral antidiabetic drugs between rosiglitazone group and pioglitazone group

H_{05}: There is no difference in the discontinuation curve (days) of new oral antidiabetic drugs between sulfonylureas, metformin and metformin/sulfonylurea combination groups

H_{06}: There is no difference in the discontinuation rate (percent of patients) of new oral antidiabetic drugs between sulfonylureas, metformin and metformin/sulfonylurea combination groups

Chapter Two: Methods

INTRODUCTION

The overall objective of this study was to evaluate the impact of safety concerns of TZDs on oral antidiabetic drugs utilization. The findings provide further understanding of the impact of discordant literature and safety concern on clinical practice and medication utilization.

This chapter describes the data source, study design, study population, and statistical analyses that were used in this study.

STUDY DATA SOURCE

This study used data from the Scott & White Health System (SWHS) from May 2006 through October 2008. The SWHS is a 550-bed acute care hospital, a 600-physician clinic organization, and a staff-model health maintenance organization with over 220,000 covered lives in Central Texas. The SWHS databases are electronically maintained and consist of (1) electronic medical records (EMR) which contained details of clinical encounters [i.e., date of service and glycosylated hemoglobin $A1_c$ ($HbA1_c$) level], (2) health plan enrollment benefit information, (3) medical diagnoses (*The International Classification of Diseases* [ICD]-9 codes), (4) and pharmacy claims. The pharmacy claim database includes patients' unique identification numbers, age, gender, adjudicated drug name, date filled, and quantity of drug supplied. This information was not captured in the pharmacy claims data if patients paid out-of-pocket for their prescriptions. The pharmacy benefit coverage was based on a three-tier system in which the co-payment varied. Study was approved by the Scott & White Institutional Review Board and The University of Texas at Austin Institutional Review Board.

Data Selection

We selected antidiabetic drugs based on drug coverage at Scott & White to ensure similar access. Metformin, sulfonylureas, and TZDs were covered and considered maintenance drugs. Maintenance drugs were qualified to be dispensed for 90 days of therapy per persciption. Insulin was not included in the analysis because of variability in dosing that is often not accurately captured in claims databases.[101] Prescription claims for alpha-glucosidase, meglitinides and gliptin were extracted but not included in the study because of their limited use.

National Drug Codes (NDCs), 10-digit codes assigned by the FDA to each drug to identify the drug, dosage and package size, were available. However, selection of drug from prescription claims using NDC may be challenging because an extensive list of NDC would be required to capture all drugs of interest. Alternatively, the American Hospital Formulary Services (AHFS) codes allow searches for drug by therapeutic class.[101] Adjudicated prescription claims for oral antidiabetic drugs were identified based on the AHFS as follows.

682028: Thiazolidinediones (rosiglitazone and pioglitazone)

682020: Sulfonylureas (glipizide, glimepiride and glyburide)

682004: Biguanides (metformin)

682002: Alpha-glucosidase

682016: Meglitinides

682005: Gliptin

ICD-9 diagnosis codes were used to identify patients with diagnosis for type 2 diabetes, to capture cardiovascular comorbidities, and to calculate an adaptation of the Charlson Comorbidity Index (CCI).[102, 103]

Glycosylated HbA_{1c} levels were collected for patients who had any measurements during the study period. For patients who had multiple glycosylated HbA_{1c} measurements, an average value was calculated for pre-index and post-index periods.

STUDY DESIGN

This study used a pre-post retrospective observational design to determine and compare the rate of and time to discontinuation of an index TZD and new oral antidiabetic drugs between rosiglitazone versus pioglitazone. The pre-post design allowed observation of drug utilization before and after the safety warnings. Further, patients who received pioglitazone served as the comparator group because pioglitazone did not receive a FDA black-boxed warning for MI. A comparison group strengthens internal validity of the pre-post study design by limiting history (the possibility of other events) and maturation (the progression of patients' characteristics and conditions) which may have impacted the discontinuation of antidiabetic drugs.[104]

Study Time Period

The events in the study were determined based on the following dates with respect to the meta-analysis by Nissen *et al.*,[47] which raised concerns of TZD safety in May of 2007.

Safety warning date (index):	May 2007 was used as the first event date because of high publicity and immediate response from the FDA to review the risks and benefits of rosiglitazone.
Pre-safety warning period:	May 2006 through April 2007
Post- safety warning period:	May 2007 through October 2008
Index TZD:	A prescribed TZD (rosiglitazone or pioglitazone) during the pre-safety warning period
New oral antidiabetic drug:	A prescribed metformin or sulfonylureas (glipizide, glimepiride and glyburide) filled on new index date.
New index date:	Date of the first prescription claim for oral antidiabetic drugs within 90 days before or after the last index TZD prescription claim date during the post-safety warning period. The first prescription claim for an oral antidiabetic drug must have occurred by April 30th, 2008 and was not filled six months prior to safety warning date.
Discontinuation date:	Last prescription filled date plus days' supply.
End date (censored):	October 31st, 2008

The study end date was selected based on changes in the American Diabetes Association (ADA) treatment guideline for type 2 diabetes and the Scott & White formulary coverage. Before the safety warning, both rosiglitazone and pioglitazone had the same pharmacy preferred coverage status. Shortly after the safety warning and the FDA decision to require labeling changes to include warnings of potential myocardial infarction, the ADA recommended reserving rosiglitazone for patients whose benefit out-weighted the risk. Subsequently, the pharmacy and therapeutic (P&T) committee at Scott & White decided to keep pioglitazone at current preferred coverage status and change rosiglitazone to a non-preferred coverage status. The changes in guidelines by the ADA and formulary coverage for thiazolidinediones may impact physician practice and prescription utilization. Thus selecting an end date which corresponded to these changes would ensure all eligible patients had similar access to TZDs after the safety warning event.[105]

STUDY DEFINITIONS

Medication Adherence

Medication adherence to a prescribed index TZD (rosiglitazone or pioglitazone) for each patient was determined using medication possession ratio (MPR). Medication adherence was defined as total days' supply divided by the total days from the first and last prescription filled plus days' supplied from the last prescription filled during the pre-safety warning period.[106, 107] High adherence to a prescribed drug was defined as 80 percent of MPR or greater.[37, 39]

Initiation of a New Antidiabetic Drug

Patients who had high adherence to their prescribed index TZD drug during the pre-safety warning period, but discontinued during the post-safety period were identified

for use of a new antidiabetic drug. The following criteria were used to identify a new antidiabetic drug. An antidiabetic drug was considered new if it was not filled six months[108] prior to safety warning date (May 1, 2007) and filled within 90 days before or after the date of the last index TZD prescription claim. The 90-day time period reflects the 90 days of supply for maintenance drugs such as antidiabetic drugs. The date of the first new oral antidiabetic drugs must be on or before April 30, 2008. This allowed at least six months of follow-up.

STUDY POPULATION

We identified all patients aged 18 years or older that had continuous enrollment eligibility with coverage for both pharmacy and medical services throughout the study period from May 2006 through October 2008. Continuous eligibility ensures studied patients had access to prescription coverage and limits the bias of misclassifying discontinuation of drug therapy.[101]

We then identified type 2 diabetic patients by requiring a presence of at least one clinical encounter with a coded diagnosis of type 2 diabetes, ICD-9 code 250.xx and prescription claims for a prescribed TZD. This requirement ensures the internal and construct validity that studied individuals were type 2 diabetic patients.[109]

For objective I, to minimize bias and alternative reasons to discontinue drug treatment such as cost or side effects, we identified patients who were established, stable users of a prescribed TZD. We required patients to have at least 80 percent adherence, considered high adherent, to a prescribed TZD during the pre-safety period.

Further, considering medication adherence rate is based on the average days patients received medication, it is possible that patients may have had most of their TZD filled earlier and discontinued before the safety warning date. To limit immortal time

bias,[110] we also required patients to have at least one day of supply for the prescribed TZD anytime during the post-safety warning period.

For objective II, patients were identified as follows. Among patients who had discontinued a prescribed index TZD (from objective I), patients were identified for a new oral antidiabetic drug, as described previously.

Study Groups for Objective I

Rosiglitazone group: Patients who had high adherence to a prescribed rosiglitazone during one year pre-safety warning period

Pioglitazone group: Patients who had high adherence to a prescribed pioglitazone during one year pre-safety warning period

Study Groups for Objective II

Rosiglitazone group: Patients who discontinued rosiglitazone and were prescribed a new oral antidiabetic drug during the one-year post-safety warning period

Pioglitazone group: Patients who discontinued pioglitazone and were prescribed a new oral antidiabetic drug during the one-year post-safety warning period

Outcome Measures

The impact of safety concerns were measured as the time to discontinuation of prescribed and dispensed oral antidiabetic medication as follows.

Among patients who had high adherence for an index TZDs during the pre-safety period, patients were observed until the date of first discontinuation of an index TZD or end of study (October 2008), whichever came first.

Among patients who received a new oral diabetic drug after discontinuing their index TZDs, patients were observed until the date of the first discontinuation of a newly prescribed oral antidiabetic drug or end of study (October 2008), whichever came first.

Comorbidities were calculated using the Charlson Comorbidity Index (CCI).[102] The CCI identifies 16 conditions and weights the severity of each condition to predict patients' risk of death. These conditions include the following: with a weight of 1 - MI, CHF, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, and diabetes without complications; with a weight of 2 - diabetes with chronic complications, hemiplegia or paraplegia, renal disease, and any malignancy, including leukemia and lymphoma; with a weight of 3 - moderate or severe liver disease and metastatic solid tumors,; and with a weight of 6 – AIDS. Each patient CCI was calculated based on the total weighted score of each condition that a patient had. ICD-9-CM codes categorized by Deyo[103] were used to identify these 16 conditions and are listed in Appendix A. Furthermore, the presence of CV comorbidities was identified, including CHF, ischemic heart disease, dyslipidemia, obesity, and renal disease. The ICD-9-CM codes used to identify these CV conditions are presented in Appendix B.

STATISTICAL ANALYSES OF DATA

The following variables were considered: dependent variable (DV), independent variable (IV) and a priori covariate variables (CV). A priori covariates were determined to control for potential confounders.[105]

DV: Discontinuation of a drug

IV: Time measured in days, drug

CV: Gender, age, CCI, mean glycosylated HbA_{1c}

Statistical Approaches

Descriptive analyses of continuous variables such as age and glycosylated HbA_{1c} were calculated using mean, Student's t-tests and ANOVAs. Descriptive analyses of categorical and ordinal variables such as gender, cardiovascular comorbidity, CCI were calculated using frequency, X^2 statistics, and nonparametric Wilcoxon tests.

Descriptive Analyses for Objective I are as follows.

H_0: There is no difference in gender between rosiglitazone and pioglitazone groups during the pre-safety warning period

H_0: There is no difference in mean age between rosiglitazone and pioglitazone groups during the pre-safety warning period

H_0: There is no difference in cardiovascular comorbidity between rosiglitazone and pioglitazone groups during the pre-safety warning period

H_0: There is no difference in CCI between rosiglitazone and pioglitazone groups during the pre-safety warning period

H_0: There is no difference in mean glycosylated HbA_{1c} between rosiglitazone and pioglitazone groups during the pre-safety warning period

H_0: There is no difference in mean glycosylated HbA_{1c} between rosiglitazone and pioglitazone groups during the post-safety warning period

Descriptive Analyses for Objective II are as follows.

H_0: Among patients who discontinued index TZDs, there is no difference in gender between the types of new oral antidiabetic drugs prescribed during the post-safety warning period

H_0: Among patients who discontinued index TZDs, there is no difference in the mean age between the types of new oral antidiabetic drugs prescribed during the post-safety warning period

H_0: Among patients who discontinued index TZDs, there is no difference in the cardiovascular comorbidity between the types of new oral antidiabetic drugs prescribed during the post-safety warning period

H_0: Among patients who discontinued index TZDs, there is no difference in the CCI between the types of new oral antidiabetic drugs prescribed during the post-safety warning period

H_0: Among patients who received a new oral antidiabetic, there is no difference in the age between rosiglitazone and pioglitazone groups after safety warnings during the post-safety warning period

H_0: Among patients who received a new oral antidiabetic, there is no difference in cardiovascular comorbidity between rosiglitazone and pioglitazone groups during the post-safety warning period

H_0: Among patients who received a new oral antidiabetic, there is no difference in CCI between rosiglitazone and pioglitazone groups during the post-safety warning period

Comparisons of the proportion and rate of patients who discontinued a prescribed index TZD and antidiabetic drug between the rosiglitazone and pioglitazone groups were estimated using Cox proportional hazards model. The model description is as follows.

Unit of Analyses

The unit of analyses for objective I and II was time measured in days for time to discontinuation of a drug and person for proportion of patients who discontinued a drug.

Time to Discontinuation of a Drug

The time to discontinuation of a drug was measured in days. Specifically, time was calculated based on the total of days patients had an index TZD or new oral antidiabetic drug. Total of days on a TZD was the days of supply from the first and last TZD prescription claim for each patient during the post-safety warning period. For patients who had both metformin and sulfonylurea claims (filled separately), their time was the maximum total of days' supplied for either metformin or sulfonylurea.

Proportion of Patients who Discontinued a Drug

The proportion of patients who discontinued a drug was measured in person units. Patients who discontinued a drug were divided by the total patients identified from objective I and objective II.

Cox Proportional Hazards Model

Objective I

Objective I: Among patients who had one year high adherence to an index TZD drug pre-safety warning period,

H_{01}: There is no difference in the discontinuation curve (days) of rosiglitazone versus pioglitazone groups post-safety warning period

H_{02}: There is no difference in the discontinuation rate (percent patients) of index TZD between rosiglitazone and pioglitazone groups post-safety warning period

The Cox proportional regression equation used to estimate the hazard ratio of discontinuation was as follows.[111, 112]

$\text{Log}\,[h\,(t \mid X) / h_0\,(t)] = \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_4X_4 + \beta_5X_5$, where

$h\,(t \mid X)$ = resultant hazard function for discontinuation of index TZD at time t given the predictors X

$h_0\,(t)$ = baseline hazard

t = time, which was censored on October 31st, 2008

β_1X_1 = estimated coefficient for a TZD (study groups)

β_2X_2 = estimated coefficient for age

β_3X_3 = estimated coefficient for gender

β_4X_4 = estimated coefficient for comorbidity index

β_5X_5 = estimated coefficient for mean glycosylated HbA_{1c} pre-safety period

The reference TZD was rosiglitazone and coded as '0' and pioglitazone coded as '1.'

The discontinuation of index TZD was coded as '1' and continuation as '0.'

For gender, female was coded as '1' and male as '0.'

CCI had severity score from 0 (least) to 8 (more severe).

Assumptions of Cox Proportional Hazards Model[111]

Cox proportional hazards model is a semiparametric model. It makes no assumptions about the underlying hazard function, h(t), but assumes parametric form for the model parameters, as follows.

Linearity and additivity of the predictor variables

Proportionality: The predictor variables have constant effect on the hazard function

Independence of observations: Chances of entry into the current state do not depend on the chance of entry into the previous state

Fixed: Model parameters and hazard function are constant overtime

Test of Proportionality Assumption

Univariate Analyses and Kaplan-Meier Curves [113]

1. Log-rank test of equality across strata (a non-parametric test) was used to test categorical variables such as gender and CCI

   H_0: There is no difference in the time to discontinuation curve (days) for index TZD by gender

   H_0: There is no difference in the time to discontinuation curve (days) for TZD by CCI

2. Univariate Cox proportional hazards regression (semi-parametric model) was used to test continuous variables age and mean glycosylated $HbA1_c$

   H_0: There is no difference in the time to discontinuation curve (days) for TZD by age

   H_0: There is no difference in the time to discontinuation curve (days) for TZD by mean glycosylated $HbA1_c$ pre-safety warning period

Objective II

Objective II: Among patients who were prescribed with new oral antidiabetic drugs after discontinuing index TZD during the post-safety warning period,

H_{03}: There is no difference in the discontinuation curve (days) of new oral antidiabetic drugs between rosiglitazone versus pioglitazone groups

H_{04}: There is no difference in the discontinuation rate (percent patients) of new oral antidiabetic drugs between rosiglitazone and pioglitazone groups

H_{06}: There is no difference in the discontinuation curve (days) of new oral antidiabetic drugs between sulfonylureas, metformin and metformin/sulfonylurea combination groups

H_{07}: There is no difference in the discontinuation rate (percent of patients) of new oral antidiabetic drugs between sulfonylureas, metformin and metformin/sulfonylurea combination groups

The Cox proportional regression equation used to estimate the hazard ratio of discontinuation was as follows.[111, 112]

$\text{Log}\,[h(t \mid X) / h_0(t)] = \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_4X_4 + \beta_5X_5$, where

$h(t \mid X)$ = resultant hazard function for discontinuation of a new oral antidiabetic drug at time t given the predictors X

$h_0(t)$ = baseline hazard

t = time, which was censored on October 31st, 2008

β_1X_1 = estimated coefficient for a TZD (study groups)

β_2X_2 = estimated coefficient for age

β_3X_3 = estimated coefficient for gender

β_4X_4 = estimated coefficient for comorbidity index

β_5X_5 = estimated coefficient for new oral antidiabetic drugs

The reference TZD was rosiglitazone and coded as '0' and pioglitazone coded as '1.'

The discontinuation of new oral antidiabetic drugs coded as '1' and continuation as '0.'

For new oral antidiabetic drugs, sulfonylureas was coded as '0,' metformin '1'and metformin/sulfonylurea as 2

For gender, female was coded as '1' and male as '0.'

CCI had severity score from 0 (least) to 8 (more severe).

Assumptions of Cox Proportional Hazards Model[111]

Cox proportional hazards model is a semiparametric model. It makes no assumptions about the underlying hazard function, h(t), but assumes parametric form for model parameters, as follows.

Linearity and additivity of the predictor variables

Proportionality: The predictor variables have constant effect on the hazard function

Independence of observations: Chances of entry into the current state do not depend on the chance of entry into the previous state

Fixed: Model parameters and hazard function are constant overtime

Test of Proportionality Assumption

Univariate Analyses and Kaplan-Meier Curves [113]

1. Log-rank test of equality across strata (a non-parametric test) was used to test categorical variables such as gender and CCI
   - Ho: There is no difference in the time to discontinuation curve (days) for new oral antidiabetic drugs by gender
   - Ho: There is no difference in the time to discontinuation curve (days) for new oral antidiabetic drugs by CCI
2. Univariate Cox proportional hazards regression (semi-parametric model) was used to test continuous variable age
   - Ho: There is no difference in the time to discontinuation curve (days) for new oral antidiabetic drugs by age

Chapter Three: Results

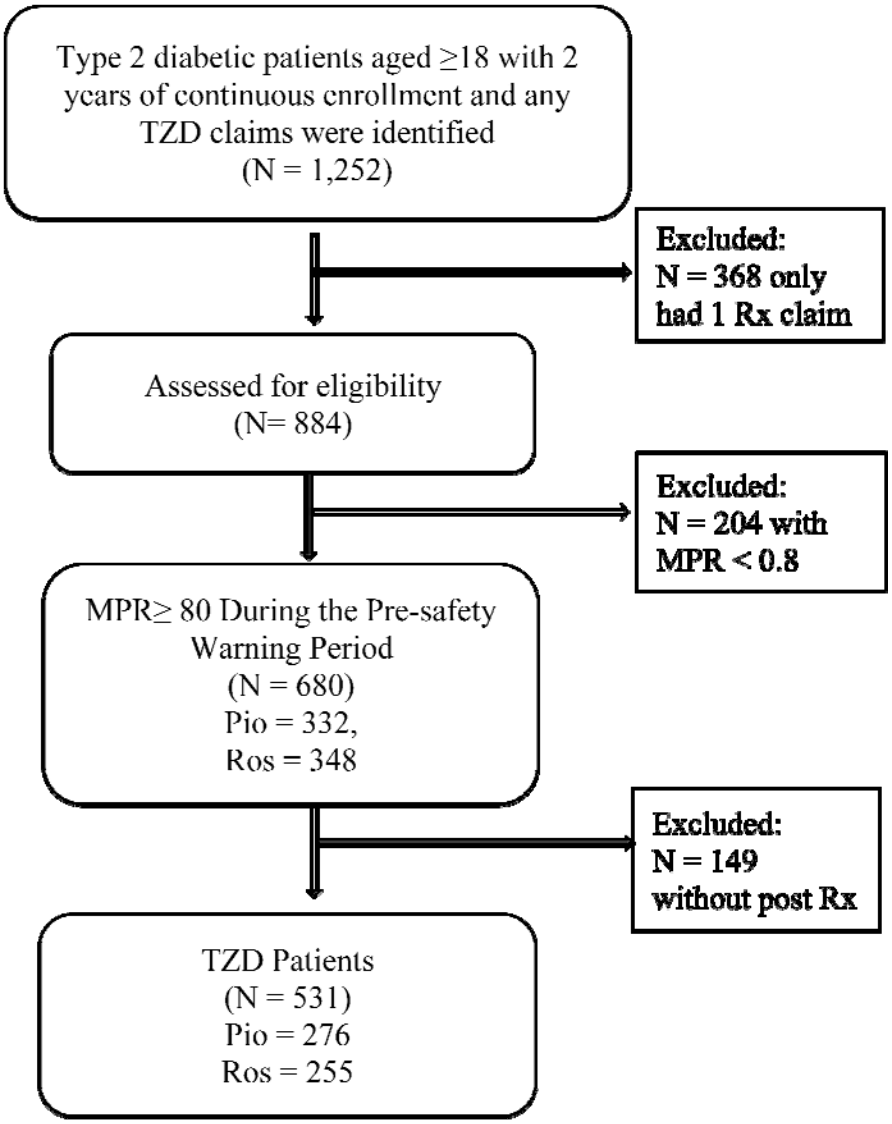
INTRODUCTION

This chapter presents results of objectives I and II. Results for each objective are categorized as follows: descriptive statistics of studied groups, tests for proportionality assumptions and Cox proportional hazards function.

PATIENT SELECTION

Figure 3.1 illustrates the patient selection process. The study identified 1,252 type 2 diabetic patients who were 18 years and older, had two years of continuous enrollment at the Scott & White Health Plan from May 2006 through October 2008, and had at least one prescription for an index TZD, rosiglitazone or pioglitazone. Fifty-four percent (N = 680) of these patients had medication adherence of at least 80 percent or greater as measured by MPR. Of these, a total of 149 (22 percent) patients did not have a prescription for an index TZD during the post-safety period and were excluded. These patients may have discontinued before the safety event date. A total of 531 patients (276 and 255 pioglitazone and rosiglitazone, respectively) were included in the analysis. Selected patients were mostly male (58 percent), and had a mean age of 61 (SD = 9.1) years. The most common CV comorbidities were dyslipidemia (41 percent) and IHD (21 percent). During the pre-safety warning period, the mean glycosylated HbA_{1c} level was 7.7 (SD = 1.2).

Figure 3. 1: Patient Selection Flow Chart



Notes: CE = continuous enrollment, TZD = thiazolidinedione, Rx = drug prescription, MPR = medication possession ratio

OBJECTIVE I

Demographic Characteristics

Baseline demographic characteristics were similar between the rosiglitazone and pioglitazone groups. There was a similar proportion of female (41 percent versus 44 percent, respectively) and male (59 percent versus 56 percent, respectively) between the rosiglitazone and pioglitazone groups ($X^2 = 0.51$; d.f. = 1; $P = 0.5$), as presented in Table 3.1. The mean (SD) age was similar between rosiglitazone (61[8.9]) and pioglitazone (62[9.2]) (Student's t-test = 0.04; d.f. = 529; $P = 1.0$), as seen in Table 3.2. Rates of CV comorbidities were similar between the rosiglitazone and pioglitazone including dyslipidemia ($X^2 = 0.10$; d.f. = 1; $P = 0.8$), HF ($X^2 = 0.00$; d.f. = 1; $P = 1.0$), ischemic heart disease (IHD) ($X^2 = 0.81$; d.f. = 1; $P = 0.4$), obesity ($X^2 = 2.56$; d.f. = 1; $P = 0.1$) and renal diseases ($X^2 = 0.35$; d.f. = 1; $P = 0.6$), as presented in Table 3.3. The most common CV comorbidities among the rosiglitazone and pioglitazone groups were dyslipidemia (42 percent and 40 percent, respectively) and IHD (23 percent and 20 percent, respectively). Furthermore, the proportion of patients with different CCI scores between those who received rosiglitazone and pioglitazone was similar ($Z = -0.52$; $P = 0.6$), with most patients having CCI of four or less (Table 3.4).

During the pre-safety warning period, the rosiglitazone and pioglitazone groups had similar mean (SD) glycosylated HbA_{1c} level (7.8 [1.3] versus 7.6 [1.1], respectively; Student's t-test = 1.78; d.f. = 389 $P = 0.08$), as presented in Table 3.5. During the post-safety warning period, the rosiglitazone and pioglitazone groups had similar mean (SD) glycosylated HbA_{1c} level (7.6 [1.4] versus 7.7 [1.4], respectively; Student's t-test = -0.56; d.f. = 385; $P = 0.6$), as presented in Table 3.6.

Table 3. 1: Distribution of Gender Between Rosiglitazone and Pioglitazone Groups During the Pre-safety Warning Period

Gender	TZD					
	Rosiglitazone		Pioglitazone		Total	
	N (Column %)		N (Column %)		N (Column %)	
Female	104	(41)	121	(44)	225	(42)
Male	151	(59)	155	(56)	306	(58)
Total N (Row %)	255	(48)	276	(52)	531	(100)

$X^2 = 0.51$; d.f. = 1; $P = 0.5$

Table 3. 2: Mean Age Between Rosiglitazone and Pioglitazone Groups During the Pre-safety Warning Period

Variable	TZD					
	Rosiglitazone (N = 255)		Pioglitazone (N = 276)		Total (N = 531)	
	Mean Age (S.D.)		Mean Age (S.D.)		Mean Age (S.D.)	
Age	61	(8.9)	62	(9.2)	61	(9.1)

Student's t-test = 0.04; d.f. = 529; $P = 1.0$

Table 3. 3: Distribution of Cardiovascular Comorbidity Between Rosiglitazone and Pioglitazone Groups During the Pre-safety Warning Period

CV Comorbidities†	TZD						Descriptive Statistics		
	Rosiglitazone (N = 255)		Pioglitazone (N = 276)		Total (N = 531)				
	N (Column %)		N (Column %)		N (Column %)		X^2	D.F.	P Value
Dyslipidemia	106	(42)	111	(40)	217	(41)	0.10	1	0.8
Heart Failure	10	(4)	11	(4)	21	(4)	0.00	1	1.0
Ischemic Heart Disease	58	(23)	54	(20)	112	(21)	0.81	1	0.4
Obesity	23	(9)	15	(5)	38	(7)	2.56	1	0.1
Renal Disease	20	(8)	18	(7)	38	(7)	0.35	1	0.6

† CV comorbidities were not mutually exclusive.

Table 3. 4: Distribution of CCI Scores Between Rosiglitazone and Pioglitazone Groups During the Pre-safety Warning Period

CCI	TZD					
	Rosiglitazone (N = 255)		Pioglitazone (N = 276)		Total (N = 531)	
	N (Column %)		N (Column %)		N (Column %)	
0	26	(10)	23	(8)	49	(9)
1	56	(22)	55	(20)	111	(21)
2	50	(20)	54	(20)	54	(20)
3	44	(17)	59	(21)	103	(19)
4	45	(18)	54	(20)	99	(19)
5	15	(6)	22	(8)	37	(7)
6	12	(5)	4	(1)	16	(3)
7	6	(2)	5	(2)	11	(2)
8	1	(0)	0	(0)	1	(0)

$Z = -0.52$; $P = 0.6$

Table 3. 5: Mean Glycosylated HbA1c Level Between Rosiglitazone and Pioglitazone Groups During the Pre-safety Warning Period

Variable	TZD					
	Rosiglitazone (N = 190)		Pioglitazone (N = 201)		Total (N = 391)	
	Mean HbA_{1c} (S.D.)		Mean HbA_{1c} (S.D.)		Mean HbA_{1c} (S.D.)	
HbA_{1c}	7.8	(1.3)	7.6	(1.1)	7.7	(1.2)

Student's t-test = 178; d.f. = 389; $P = 0.08$

Table 3. 6: Mean Glycosylated HbA1c Between Rosiglitazone and Pioglitazone Groups During the Post-safety Warning Period

Variable	TZD					
	Rosiglitazone (N = 189)		Pioglitazone (N = 198)		Total (N = 387)	
	Mean HbA_{1c} (S.D.)		Mean HbA_{1c} (S.D.)		Mean HbA_{1c} (S.D.)	
HbA1c	7.6	(1.4)	7.7	(1.4)	7.6	(1.4)

Student's t-test = -0.56; d.f. = 385; $P = 0.6$

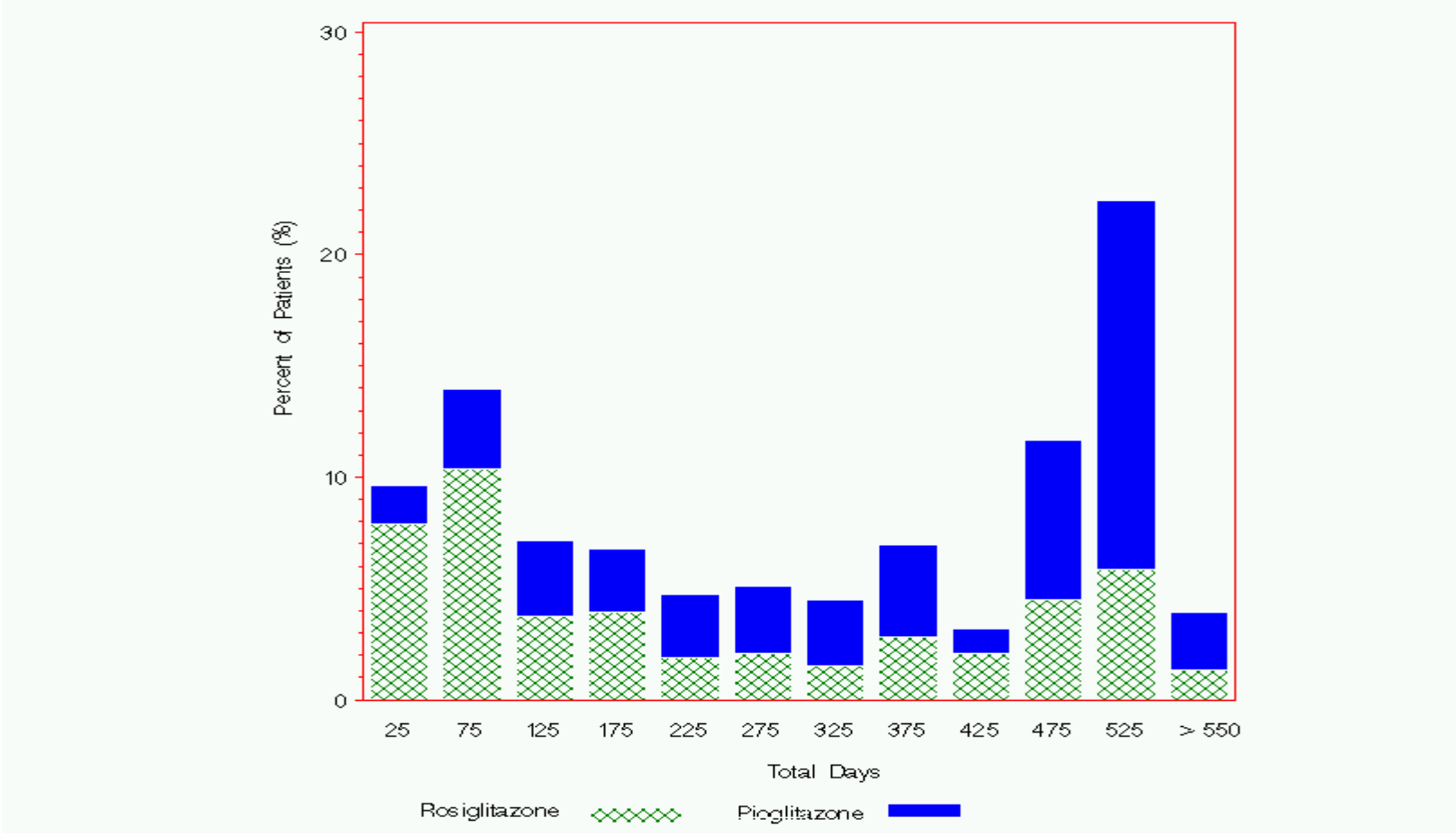
Concomitant oral antidiabetic drug use six month pre-safety warning period was identified from November 1, 2006 to April 30, 2007, as presented in Table 3.7. During this time period, a total of 171 had monotherapy with an index TZD while 360 patients had an index TZD combined with sulfonylureas and or metformin.

Table 3. 7: Distribution of Types of Oral Antidiabetic Drug Use Six Months Pre-safety Warning Period

Oral Antidiabetic Drug	TZD					
	Rosiglitazone (N = 255)		Pioglitazone (N = 276)		Total (N = 531)	
	N (Column %)		N (Column %)		N (Column %)	
Monotherapy	72	(28)	99	(36)	171	(32)
Free-dose Combination						
Metformin	46	(18)	56	(20)	102	(19)
Sulfonylureas	28	(11)	41	(15)	69	(13)
Met-Sul Combo	72	(28)	77	(28)	149	(28)
Fixed-dose Combination						
Metformin	18	(7)	3	(1)	21	(4)
Sulfonylureas	4	(2)	0	(0)	4	(1)
Met-Sul Combo	15	(6)	0	(0)	15	(3)
All N (Row %)	255	(48)	276	(52)	531	(100)

Figure 3.2 presents the distribution of days of supply that patients received rosiglitazone and pioglitazone during the post-safety warning period. The distribution of days of supply for index TZDs is not normally distributed, but skewed to the left with two peaks. The first peak occurred in the ranges from 20 days to 98 days. The second peak occurred around 544 days.

Figure 3. 2: Distribution of Total Days for Index TZD Between Rosiglitazone and Pioglitazone Groups During the Post-safety Warning Period



Test of Proportionality

Among 531 patients, 510 patients discontinued an index TZD and 21 patients continued an index TZD by the end of the observation period, October 31, 2008. Figure 3.3 shows the Kaplan-Meier curve of patients discontinuing an index TZD over time. Approximately 23 percent of patients started to discontinue an index TZD in 90 days and 96 percent of patients had discontinued by the end of the study period (Table 3.8). The median continuation time was 330 days (95% CI = 270, 360), as presented in Table 3.9.

Table 3. 8: Survival Estimate of Index TZD

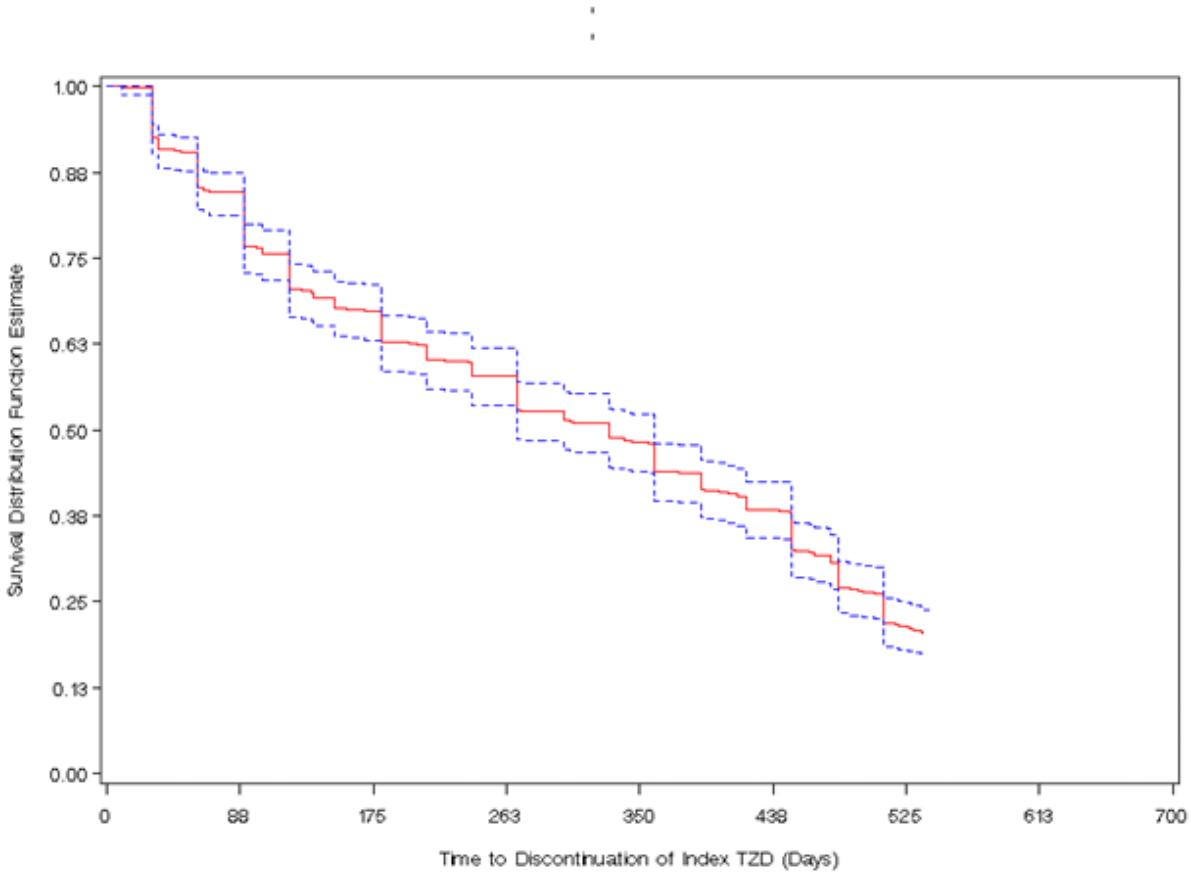
Days	Continued TZD	Discontinued TZD	Continued Standard	Discontinued	Remained
	Percent	Percent	Error	Number	Number
0	1	0	0.000	0	531
90	0.77	0.23	0.018	124	407
180	0.63	0.37	0.021	198	333
270	0.53	0.47	0.022	250	281
360	0.44	0.56	0.022	298	233
450	0.33	0.67	0.020	358	173
540	0.05	0.95	0.010	504	27
545	0.04	0.96	0.008	510	21

Table 3. 9: Quartile Estimate of Index TZD

Quartile Estimates

Percent	Continuation Time	95% Confidence Interval	
	Median	Lower	Upper
75	510	480	520
50	330	270	360
25	120	90	120

Figure 3. 3: Kaplan-Meier Curve with 95 % Confidence Interval of Time to Discontinuation of Index TZD



Kaplan-Meier curve showed the time to discontinuation of rosiglitazone and pioglitazone separated approximately 90 days after the safety warning event (Figure 3.4). Approximately 38 percent of patients discontinued rosiglitazone in 90 days while only ten percent of patients discontinued pioglitazone (Table 3.10). By the end of the study period, 97 percent (N = 248) of rosiglitazone and 95 percent (N = 262) pioglitazone patients had discontinued their index TZD. The log-rank test showed a statistically significant difference between the survival rates over time (X^2 = 51.9; d.f. = 1; P < 0.0001) (Table 3.15). Median continuation time was 180 days for rosiglitazone (95% CI = 120, 240) and 450 days for pioglitazone (95% CI = 390, 465) (Table 3.11).

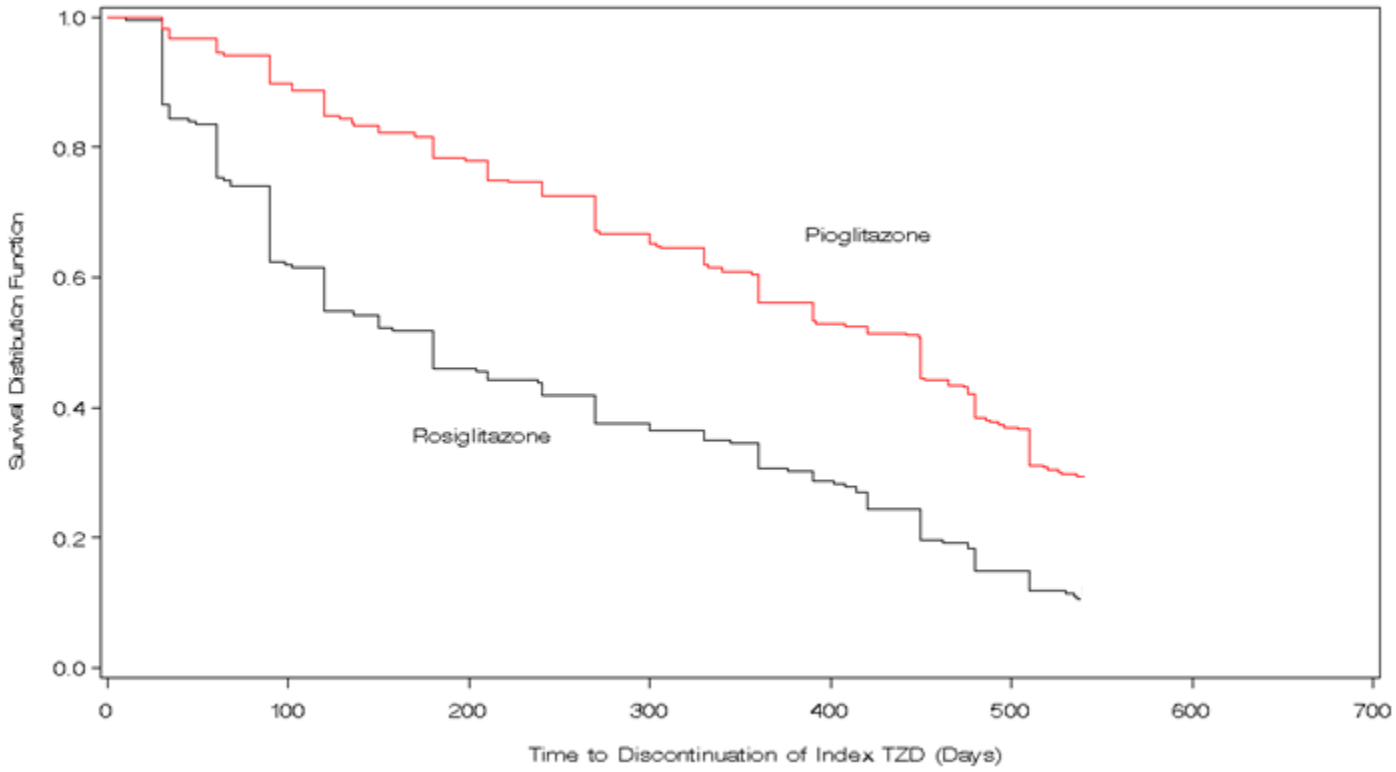
Table 3. 10: Survival Estimate of Index TZD by Rosiglitazone and Pioglitazone Groups

Index TZD	Days	Continued TZD Percent	Discontinued TZD Percent	Continued Standard Error	Discontinued Number	Remained Number
Rosiglitazone						
	0	1.00	0.00	0.000	0	255
	90	0.62	0.38	0.030	96	159
	180	0.46	0.54	0.031	138	117
	270	0.38	0.62	0.030	159	96
	360	0.31	0.69	0.029	177	78
	450	0.20	0.80	0.025	205	50
	540	0.04	0.96	0.012	246	9
	544	0.03	0.97	0.010	248	7
Pioglitazone						
	0	1.00	0.00	0.000	0	276
	90	0.90	0.10	0.018	28	248
	180	0.78	0.22	0.025	60	216
	270	0.67	0.33	0.028	91	185
	360	0.56	0.44	0.030	121	155
	450	0.45	0.55	0.030	153	123
	540	0.07	0.93	0.015	258	18
	545	0.05	0.95	0.013	262	14

Table 3. 11: Quartile Estimate of Index TZD by Rosiglitazone and Pioglitazone Groups

Quartile Estimates				
Index TZD	Percent	Continuation Time	95% Confidence Interval	
		Median	Lower	Upper
Rosiglitazone				
	75	420	360	450
	50	180	120	240
	25	64	60	90
Pioglitazone				
	75	540	526	540
	50	450	390	465
	25	216	180	270

Figure 3. 4: Kaplan-Meier Curve of Time to the Discontinuation of Pioglitazone versus Rosiglitazone Groups



Among female and male patients, Kaplan-Meier curve showed similar time to discontinuation of an index TZD (Figure 3.5). Similar proportion of female (23 percent) and male patients (23 percent) started to discontinue an index TZD in 90 days (Table 3.12). The log-rank test showed the difference between the continuation rates over time was not statistically significant for male versus female ($X^2 = 2.7$; d.f. = 1; $P = 0.1$) (Table 3.15). The median continuation time was 270 days (95% CI = 210, 330) for female and 360 days (95% CI = 300, 420) for male (Table 3.13).

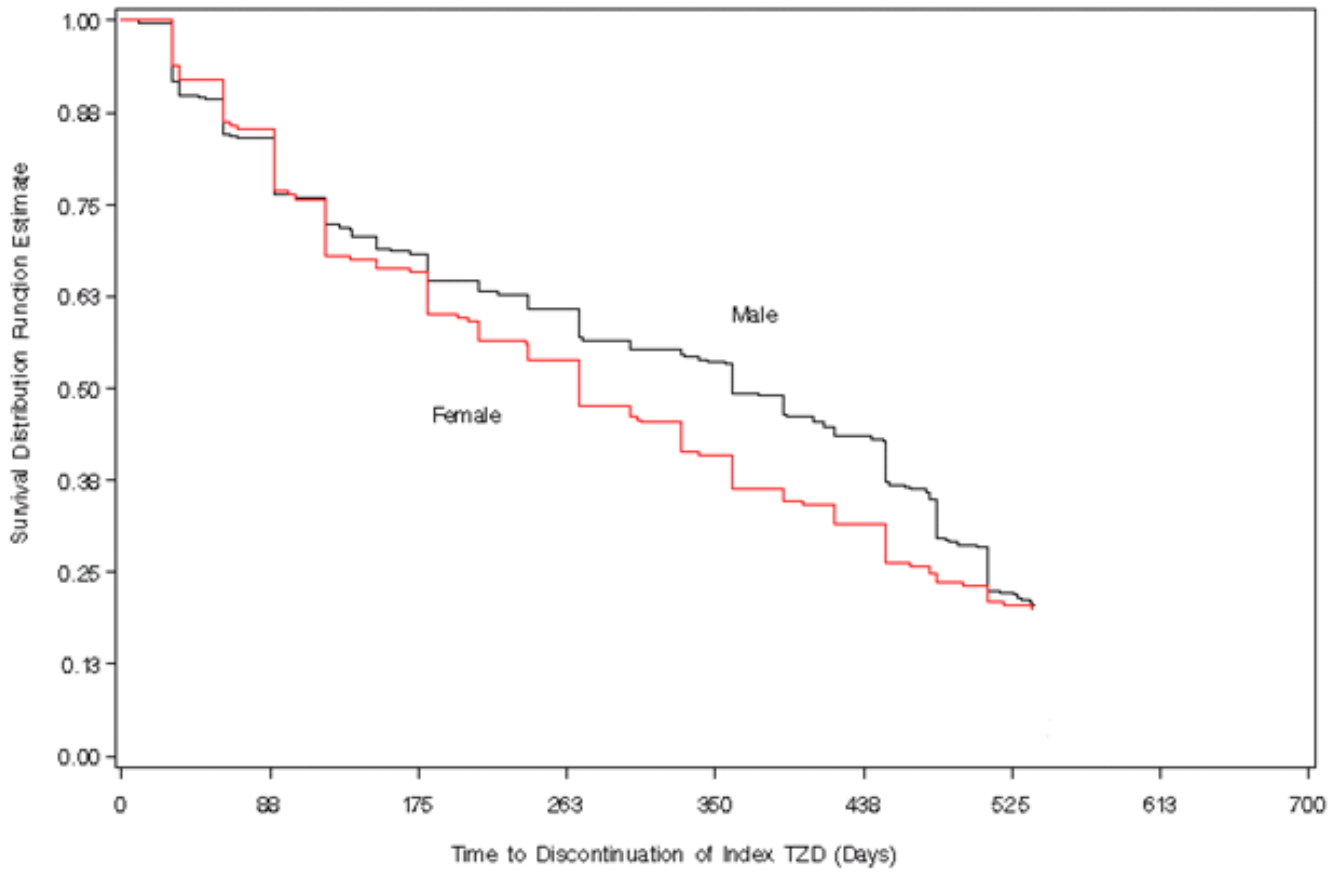
Table 3. 12: Survival Estimate of Index TZD by Gender

Gender	Days	Continued TZD Percent	Discontinued TZD Percent	Continued Standard Error	Discontinued Number	Remained Number
Male						
	0	1	0	0	0	306
	90	0.7647	0.2353	0.0242	72	234
	180	0.6471	0.3529	0.0273	108	198
	270	0.5686	0.4314	0.0283	132	174
	360	0.4935	0.5065	0.0286	155	151
	450	0.3725	0.6275	0.0276	192	114
	540	0.0654	0.9346	0.0141	286	20
	545	0.049	0.951	0.0123	291	15
Female						
	0	1	0	0	0	225
	90	0.7689	0.2311	0.0281	52	173
	180	0.6	0.4	0.0327	90	135
	270	0.4756	0.5244	0.0333	118	107
	360	0.3644	0.6356	0.0321	143	82
	450	0.2622	0.7378	0.0293	166	59
	540	0.0311	0.9689	0.0116	218	7
	544	0.0267	0.9733	0.0107	219	6

Table 3. 13: Quartile Estimate of Index TZD by Gender

Index TZD	Percent	Quartile Estimates: Continuation Time	95% Confidence Interval	
		Median	Lower	Upper
Rosiglitazone				
	75	510	480	540
	50	360	300	420
	25	120	90	150
Pioglitazone				
	75	476	450	540
	50	270	210	330
	25	120	90	120

Figure 3. 5: Kaplan-Meier Curve of Time to Discontinuation of Index TZD by Gender



Comorbidities as measured by CCI were considered as a potential covariate for the discontinuation of an index TZD. The log-rank test showed the difference between the continuation rates over time was not statistically significant for CCI scores (X^2 = 11.8; d.f. = 8; P = 0.16) (Table 3.15). The median continuation time for an index TZD was 240 days (95% CI = 120, 480) for CCI of 0, 304 days (95% CI = 270, 390) for CCI of 1, 286 days (210, 420) for CCI of 2, 408 days (95 % CI = 330, 450) for CCI of 3, 270 days (95% CI = 180, 420) for CCI of 4, 360 days (95% CI = 180, 450) for CCI of 5, 180 days (95% CI = 90, 360) for CCI of 6, and 390 (95% CI = 120, 540) for CCI of 7. One patient had CCI of 8 and had a survival time of 68 days (Table 3.14)

Table 3. 14: Survival Estimate of Index TZD by CCI

		Quartile Estimates		
CCI	Percent	Continuation Time	95% Confidence Interval	
		Median	Lower	Upper
0				
	75	480	390	480
	50	240	120	408
	25	90	60	120
1				
	75	488	450	536
	50	304	270	390
	25	120	90	180
2				
	75	510	450	540
	50	286	210	420
	25	120	90	180
3				
	75	510	480	540
	50	408	330	450
	25	180	120	270
4				
	75	528	450	540
	50	270	180	420
	25	90	90	120
5				
	75	510	360	540
	50	360	180	450
	25	68	45	240
6				
	75	405	180	540
	50	180	90	360
	25	62	30	180
7				
	75	540	390	544
	50	390	120	540
	25	120	30	390

Table 3.15 presents variables which were tested for inclusion into the model Variables were considered a significant predictor and included in the final model if the *P* value was 0.25 or less. The log-rank test of equality across strata showed gender (log-rank Chi square = 2.7; *P* = 0.10), index TZD (log-rank Chi square = 51.9; *P* <0.0001), CCI (log-rank Chi-square = 11.8; d.f. = 8; *P* = 0.16) as potential predictors for time to discontinuation of an index TZD. While univariate Chi-square showed age was not a significant predictor (univariate Chi-square = 1.1; *P* = 0.3), age was included in the model because it was an important factor. Univariate Chi-square showed pre-index glycosylated HbA_{1c} was not a significant predictor for discontinuation of index TZD (univariate Chi-square = 3.2; *P* = 0.7). Among the 531 patients, 391 patients (190 rosiglitazone and 201 pioglitazone) had pre-index glycosylated HbA_{1c} and were analyzed in an alternative Cox proportional hazards model for objective I.

A test of time-dependent variables were conducted to determine proportionality in addition to the visual evidence from the Kaplan-Meier curves showing that the curves separated and were approximately parallel (Table 3.16). Tests of time-dependent variables were not significant for the individual variables, the interaction terms or the overall model (Table 3.16). A test of proportionality did not provide enough evidence to reject proportionality and thus, it was assumed that proportionality was met.

Table 3. 15: Variables Tested for Inclusion into Model

Model Variables	Univariate Chi-square	Log-rank Chi-square	D.F.	*P* Value
Index TZD		51.9	1	<.0001
Gender		2.7	1	0.10
CCI		11.8	8	0.16
Age	0.82			0.99
Pre-index HbA_{1c}	0.62			0.43

Table 3. 16: Test of Proportionality of Model Variables

Analysis of Maximum Likelihood Estimates

Variable	D.F.	Parameter Estimate	Standard Error	Chi-square	*P* Value	Hazard Ratio
Age	1	0.02	0.034	0.20	0.65	1.02
Gender	1	0.09	0.106	0.72	0.40	1.09
Pre-index HbA1c	1	0.29	0.225	1.62	0.20	1.33
CCI	1	0.01	0.042	0.03	0.86	1.01
Index TZD * CCI	1	-0.08	0.065	1.67	0.20	0.92
Index TZD *Pre-index HbA1c	1	0.01	0.084	0.02	0.88	1.01
Index TZD	1	-0.40	0.686	0.33	0.56	0.67
Age * Log Time	1	0.00	0.006	0.28	0.60	1.00
Pre-index HbA1c * Log Time	1	-0.04	0.043	1.07	0.30	0.96

Overall model: Wald Chi-square = 1.1; d.f. = 2; *P* = 0.56

Cox Proportional Hazards Model

A Cox proportional hazards model was conducted to assess the time to discontinuation of index TZDs. Results from Cox proportional hazards model of 531 patients (501 patients discontinued and 21 patients were censored) are presented in Table 3.17. The model showed there was no statistical difference in the time to discontinuation of an index TZD for age (HR = 1.00; 95 % CI = 0.99, 1.01; $P = 0.43$), for male versus female (HR = 1.17; 95 % CI = 0.98, 1.39; $P = 0.09$) and for CCI scores (HR = 0.98; 95 % CI = 0.93, 1.04; $P = 0.49$). There was a lower probability of discontinuation of an index TZD for patients who received pioglitazone compared to rosiglitazone (HR = 0.56; 95 % CI = 0.47, 0.67; $P < 0.0001$).

When pre-index glycosylated HbA_{1c} was considered in the model, similar results were observed among 391 patients (376 patients discontinued and 15 patients were censored). Table 3.18 presents the results. There was no statistical difference in the time to discontinuation of an index TZD for age (HR = 1.00; 95 % CI = 0.99, 1.01; $P = 0.67$), for male versus female (HR = 1.09; 95 % CI = 0.89, 1.34; $P = 0.43$), for pre-index glycosylated HbA_{1c} (HR = 1.06; 95 % CI = 0.97, 1.15; $P = 0.19$), and for CCI scores (HR = 0.97; 95 % CI = 0.91, 1.04; $P = 0.38$). Similarly, there was a lower probability of discontinuing pioglitazone than rosiglitazone (HR = 0.58; 95 % CI = 0.47, 0.71; $P < 0.0001$).

Table 3. 17: Cox Proportional Hazards Model Without HbA1c Variable on Discontinuation for Index TZD During the Post-safety Warning Period

Cox Proportional Hazards Model for Time to Discontinuation of Index TZD

Variable	D.F.	Parameter Estimate	Standard Error	Hazard Ratio	95% Hazard Ratio Confidence Interval		Chi-square	*P* Value
Age	1	-0.004	0.005	1.00	0.99	1.01	0.61	0.43
Gender	1	0.153	0.090	1.17	0.98	1.39	2.87	0.09
CCI	1	-0.019	0.027	0.98	0.93	1.04	0.47	0.49
Index TZD	1	-0.582	0.090	0.56	0.47	0.67	41.94	<0.0001

Table 3. 18: Cox Proportional Hazards Model With HbA1c Variable on Discontinuation for Index TZD During the Post-safety Warning Period

Cox Proportional Hazards Model for Time to Discontinuation of Index TZD

Variable	D.F.	Parameter Estimate	Standard Error	Hazard Ratio	95% Hazard Ratio Confidence Interval		Chi-square	*P* Value
Age	1	-0.003	0.006	1.00	0.99	1.01	0.18	0.67
Gender	1	0.084	0.105	1.09	0.89	1.34	0.64	0.43
Pre-index HbA1c	1	0.055	0.042	1.06	0.97	1.15	1.73	0.19
CCI	1	-0.029	0.033	0.97	0.91	1.04	0.76	0.38
Index TZD	1	-0.549	0.105	0.58	0.47	0.71	27.29	<0.0001

OBJECTIVE II

Patient Selection

A total of 128 patients (N = 95 rosiglitazone and N = 33 pioglitazone groups) were identified with new oral antidiabetic drugs for sulfonylureas (N = 46), metformin (N = 48) or a combination of metformin and sulfonylureas (N = 34). These patients had a median continuation days for index TZD of 90 days (95% CI = 60, 90) (Table 3.19).

A total of 403 (N = 21 censored, N = 382 discontinued) patients did not have new oral antidiabetic drugs during the screening period. These patients had a median continuation days of 420 days (95% CI = 390, 450) (Table 3.20). Most of these patients discontinued after the screening date (April 30th, 2008) and might have had a new oral antidiabetic drug later which would not be captured in the analysis.

Table 3. 19: Quartile Estimate of Index TZD for Patients Received New OAD

Quartile Estimates			
Percent	Continuation Time	95% Confidence Interval	
	Median	Lower	Upper
75	120	90	136
50	90	60	90
25	34	30	60

Table 3. 20: Quartile Estimate of Index TZD for Patients Who Did not Receive New OAD by April 30th, 2008

Quartile Estimates			
Percent	Continuation Time	95% Confidence Interval	
	Median	Lower	Upper
75	540	510	540
50	420	390	450
25	240	204	270

Demographic Characteristics of Patients with New Oral Antidiabetic Drugs

Demographic characteristics of patients (N = 128) identified with new oral antidiabetic drugs are as follows. There was a similar proportion of female between patients who received sulfonylureas (40 percent), metformin (44 percent) and metformin/sulfonylurea combination (49 percent) (X^2 = 0.64; d.f. = 2; *P* = 0.7), as presented in Table 3.21

Patients who received metformin/sulfonylurea combination were older (mean [SD] = 63.9 [7.5] years) than those who received sulfonylureas (mean [SD] = 59.4 [10.47] years) or metformin (mean [SD] = 58.8 [8.61] years), as presented in Table 3.22. There was statistical significant difference in the mean age between patients who received sulfonylureas, metformin, and metformin/sulfonylurea combination (F = 4.6; d.f. = 2; *P* = 0.01). Post-hoc Tukey's comparison showed patients who received metformin/sulfonylurea combination was significantly older than patients who received metformin ($P < 0.05$). Patients who received sulfonylureas had similar age as those who received metformin or metformin/sulfonylurea combination.

Most CV comorbidities, with the exception of obesity, were similar among patients who received new sulfonylureas, metformin, and metformin/sulfonylurea combination, as presented in Table 3.230. There was a higher proportion of patients with obesity among those who receive a new metformin prescription (13 percent) than new sulfonylureas (nine percent) and new metformin/sulfonylurea combinations (zero percent) ($P = 0.04$). Dyslipidemia and ischemic heart disease were the most common CV comorbidities for patients who received sulfonylurea (46 percent and 29 percent, respectively), metformin (40 percent and 27 percent, respectively) and metformin/sulfonylurea combination (33 percent and 31 percent, respectively).

There was no statistical difference in the CCI score among patients who received sulfonylureas, metformin or metformin/sulfonylurea combination (Kruskal-Wallis Chi-square = 1.98; d.f. = 2; $P = 0.37$). Most patients had a CCI score of six or less, as presented in Table 3.24.

Table 3. 21: Distribution of Gender Among Patients Receiving New Oral Antidiabetic Drugs Prescribed During the Post-safety Warning Period

Gender	New Oral Antidiabetic Drugs							
	Sulfonylureas		Metformin		Met-Sul Combo		Total	
	N (Column %)		N (Column %)		N (Column %)		N (Column %)	
Female	14	(40)	21	(44)	22	(49)	57	(45)
Male	21	(60)	27	(56)	23	(51)	71	(55)
Total N (Row %)	35	(27)	48	(38)	45	(35)	128	(100)

$X^2 = 0.64$; d.f. = 2; $P = 0.7$

Table 3. 22: Mean Age Among Patients Receiving New Oral Antidiabetic Drugs Prescribed During the Post-Safety Warning Period

Variable	New Oral Antidiabetic Drug		
	Sulfonylureas (N = 35)	Metformin* (N = 48)	Met-Sul Combo* (N = 45)
	Mean Age (S.D.)	Mean Age (S.D.)	Mean Age (S.D.)
Age	59.4 (10.5)	58.8 (8.6)	63.9 (7.5)

ANOVA test for new oral antidiabetic drug groups: F = 4.6; d.f. = 2; $P = 0.01$

*Post-hoc Tukey's comparisons: Met-Sul Combo versus Metformin, $P < 0.05$

Table 3. 23: Distribution of Cardiovascular Comorbidity Among Patients Receiving New Oral Antidiabetic Drugs Prescribed During the Post-safety Warning Period

CV Comorbidities†	New Oral Antidiabetic Drugs								Descriptive Statistics		
	Sulfonylureas (N = 35)		Metformin (N = 48)		Met -Sul Combo (N = 45		Total (N = 128)				
	N (Column %)		N (Column %)		N (Column %)		N (Column %)		Chi-square	D.F.	*P* Value
Dyslipidemia	16	(46)	19	(40)	15	(33)	50	(39)	1.28	2	0.53
Heart Failure ‡	1	(3)	1	(2)	1	(2)	3	(2)	0.22		1.00
Ischemic Heart Disease	10	(29)	13	(27)	14	(31)	37	(29)	0.19	2	0.91
Obesity ‡	3	(9)	6	(13)	0	(0)	9	(7)	0.00		0.04
Renal Disease ‡	6	(17)	3	(6)	1	(2)	10	(8)	0.01		0.05

† CV comorbidities were not mutually exclusive.

‡ Fisher Chi-square was calculated.

Table 3. 24: Distribution of CCI Among Patients Receiving New Oral Antidiabetic Drugs Prescribed During the Post-safety Warning Period

CCI	New Oral Antidiabetic Drugs							
	Sulfonylureas (N = 35)		Metformin (N = 48)		Met-Sul Combo (N = 45)		Total (N = 128)	
	N (Column %)		N (Column %)		N (Column %)		N (Column %)	
0	3	(9)	7	(15)	7	(16)	17	(13)
1	7	(20)	7	(15)	9	(20)	23	(18)
2	3	(9)	9	(19)	10	(22)	22	(17)
3	8	(23)	6	(13)	3	(7)	17	(13)
4	7	(20)	12	(25)	13	(29)	32	(25)
5	2	(6)	2	(4)	2	(4)	6	(5)
6	5	(14)	4	(8)	0	(0)	9	(7)
7	0	(0)	1	(2)	1	(2)	2	(2)
8	0	(0)	0	(0)	0	(0)	0	(0)

Kruskal-Wallis Chi-square = 1.98; d.f. = 2; $P = 0.37$

Demographic Characteristics of Rosiglitazone and Pioglitazone Groups

The proportion of females was similar between rosiglitazone and pioglitazone groups among patients who received new sulfonylureas ($X^2 = 0.29$; d.f. = 1; $P = 1.00$), metformin ($X^2 = 0.04$; d.f. = 1; $P = 0.84$) and metformin/sulfonylurea combination ($X^2 = 3.31$; d.f. = 1; $P = 0.07$) (Table 3.25).

Table 3.26 present the descriptive statistics for age. Factorial ANOVA of index TZD and new oral antidiabetic drugs showed the overall model was not significant (F = 1.4; d.f. = 5; $P = 0.23$) for age. There was no significant difference in the mean age between rosiglitazone and pioglitazone among patients who received sulfonylureas, metformin or metformin/sulfonylurea combination (F = 0.64; d.f. = 1; $P = 0.43$). However, there was statistical significant difference in the mean age between new oral antidiabetic drugs (F = 3.94; d.f. = 2; $P = 0.02$). Post-hoc Tukey's comparison showed patients who received metformin/sulfonylurea combination were significantly older than patients who received metformin ($P < 0.05$). Patients who received sulfonylureas had similar age as those who received metformin or metformin/sulfonylurea combination.

There was no difference between the rosiglitazone and pioglitazone groups for CV comorbidities among patients who received new oral antidiabetic drugs including metformin, sulfonylureas or metformin and sulfonylureas combination, as presented in Table 3.27. Among patients who received sulfonylureas, dyslipidemia and ischemic heart disease were the two most common CV comorbidities for the rosiglitazone (46 percent and 27 percent, respectively) and pioglitazone (44 percent and 33 percent) groups. Among patients who received metformin, dyslipidemia and ischemic heart disease were the two most common CV comorbidities for the rosiglitazone (49 percent and 31 percent, respectively) and pioglitazone (15 percent and 15 percent) groups. Among patients who

received metformin/sulfonylureas combination, dyslipidemia and ischemic heart disease were the two most common CV comorbidities for the rosiglitazone (32 percent and 35 percent, respectively) and pioglitazone (36 percent and 18 percent).

There was no difference in CCI score between rosiglitazone and pioglitazone groups among patients who received sulfonylureas (Z = -0.90; P = 0.37), metformin (Z = -1.46, *P* = 0.14), or metformin/sulfonylurea combination (Z = -0.27; P = 0.79). Most patients had a CCI score of six or less, as presented in Table 3.28.

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Table 3. 25: Distribution of Gender Among Patients Receiving New Oral Antidiabetic Drugs Between Rosiglitazone and Pioglitazone Groups

New Oral Antidiabetic Drug	Gender	TZD						Descriptive Statistics	
		Rosiglitazone		Pioglitazone		Total			
		N (Column %)		N (Column %)		N (Column %)		X^2	*P* Value
Sulfonylureas								0.29	1.00
	Female	10	(38)	4	(44)	14	(40)		
	Male	16	(62)	5	(56)	21	(60)		
	Total N (Row %)	26	(74)	9	(26)	35	(100)		
Metformin								0.04	0.84
	Female	15	(43)	6	(46)	21	(44)		
	Male	20	(57)	7	(54)	27	(56)		
	Total N (Row %)	35	(73)	13	(27)	48	(100)		
Met-Sul Combo								3.31	0.07
	Female	14	(41)	8	(73)	22	(49)		
	Male	20	(59)	3	(27)	23	(51)		
	Total N (Row %)	34	(76)	11	(24)	45	(100)		
All N (Row %)		95	(74)	33	(26)	128	(100)		

Table 3. 26: Mean Age Between Rosiglitazone and Pioglitazone Groups Among Patients Receiving New Oral Antidiabetic Drugs

New Oral Antidiabetic Drug Group	TZD								
	Rosiglitazone (N = 95)			Pioglitazone (N = 33)			Total (N = 128)		
	N	(Mean Age)	[S.D.]	N	(Mean Age)	[S.D.]	N	(Mean Age)	[S.D.]
Sulfonylureas	26	(59.9)	[11.32]	9	(58.0)	[7.89]	35	(59.4)	[10.47]
Metformin	35	(59.3)	[8.18]	13	(57.2)	[9.88]	48	(58.8)	[8.61]
Met-Sul Combo	34	(64.0)	[6.95]	11	(63.6)	[9.26]	45	(63.9)	[7.45]
All	95	(61.2)	[8.94]	33	(59.6)	[9.36]	128	(60.8)	[9.04]

ANOVA test for rosiglitazone versus pioglitazone groups: F = 0.64; d.f. = 1; $P = 0.43$

ANOVA test for new oral antidiabetic groups: F = 3.94; d.f. = 2; $P = 0.02$

Post-hoc Tukey's comparisons: Met-Sul combo versus metformin, $P < 0.05$

Table 3. 27: Distribution of Cardiovascular Comorbidity Between Rosiglitazone and Pioglitazone Groups Among Patients Receiving New Oral Antidiabetic Drugs

New Oral Antidiabetic Drug Group	CV Comorbidities†	TZD						Fisher's Exact Test
		Rosiglitazone		Pioglitazone		Total		
		N = 95		N = 33		N = 128		
		N	(Column %)	N	(Column %)	N	(Column %)	*P* Value
Sulfonylureas	N	26		9		35		
	Dyslipidemia	12	(46)	4	(44)	16	(46)	1.00
	Heart Failure	0	(0)	1	(11)	1	(3)	0.26
	Ischemic Heart Disease	7	(27)	3	(33)	10	(29)	0.69
	Obesity	2	(8)	1	(11)	3	(9)	1.00
	Renal Disease	5	(19)	1	(11)	6	(17)	1.00
Metformin	N	35		13		48		
	Dyslipidemia	17	(49)	2	(15)	19	(40)	0.05
	Heart Failure	1	(3)	0	(0)	1	(2)	1.00
	Ischemic Heart Disease	11	(31)	2	(15)	13	(27)	0.47
	Obesity	6	(17)	0	(0)	6	(13)	0.17
	Renal Disease	2	(6)	1	(8)	3	(6)	1.00
Met-Sul Combo	N	34		11		45		
	Dyslipidemia	11	(32)	4	(36)	15	(33)	1.00
	Heart Failure	0	(0)	1	(9)	1	(2)	0.24
	Ischemic Heart Disease	12	(35)	2	(18)	14	(31)	0.46
	Obesity	0	(0)	0	(0)	0	(0)	N/A
	Renal Disease	1	(3)	0	(0)	1	(2)	1.00

† CV comorbidities were not mutually exclusive.

Table 3. 28: Distribution of CCI Between Rosiglitazone and Pioglitazone Groups Among Patients Receiving New Oral Antidiabetic Drugs

New Oral Antidiabetic Drug Group	CCI	TZD						Descriptive Statistics	
		Rosiglitazone		Pioglitazone		Total			
		N (Column %)		N (Column %)		N (Column %)		*Z*	*P* Value
Sulfonylureas	N	26		9		35		-0.90	0.37
	0	1	(4)	2	(22)	3	(9)		
	1	5	(19)	2	(22)	7	(20)		
	2	2	(8)	1	(11)	3	(9)		
	3	7	(27)	1	(11)	8	(23)		
	4	6	(23)	1	(11)	7	(20)		
	5	2	(8)	0	(0)	2	(6)		
	6	3	(12)	2	(22)	5	(14)		
	7	0	(0)	0	(0)	0	(0)		
	8	0	(0)	0	(0)	0	(0)		
Metformin	N	35		13		48		-1.46	0.14
	0	5	(14)	2	(15)	7	(15)		
	1	3	(9)	4	(31)	7	(15)		
	2	7	(20)	2	(15)	9	(19)		
	3	4	(11)	2	(15)	6	(13)		
	4	10	(29)	2	(15)	12	(25)		
	5	1	(3)	1	(8)	2	(4)		
	6	4	(11)	0	(0)	4	(8)		
	7	0	(0)	0	(0)	0	(0)		
	8	0	(0)	0	(0)	0	(0)		
Met-Sul Combo	N	34		11		45		0.27	0.79
	0	6	(18)	1	(9)	7	(16)		
	1	6	(18)	3	(27)	9	(20)		
	2	8	(24)	2	(18)	10	(22)		
	3	3	(9)	0	(0)	3	(7)		
	4	8	(24)	5	(45)	13	(29)		
	5	2	(6)	0	(0)	2	(4)		
	6	0	(0)	0	(0)	0	(0)		
	7	1	(3)	0	(0)	1	(2)		
	8	0	(0)	0	(0)	0	(0)		

Test of Proportionality

Among 128 patients who received new oral antidiabetic drugs, a total of 93 patients discontinued and 35 patients continued a prescribed new OAD by the end of the observation period, October 31, 2008. Figure 3.7 shows the Kaplan-Meier curve of patients discontinuing a new oral antidiabetic drug over time. Approximately 20 percent of patients started to discontinue a new oral antidiabetic drug after one year and 73 percent of patients had discontinued by the end of the study period (Table 3.29). The median continuation time was 528 days (95% CI = 510, 538), as presented in Table 3.20.

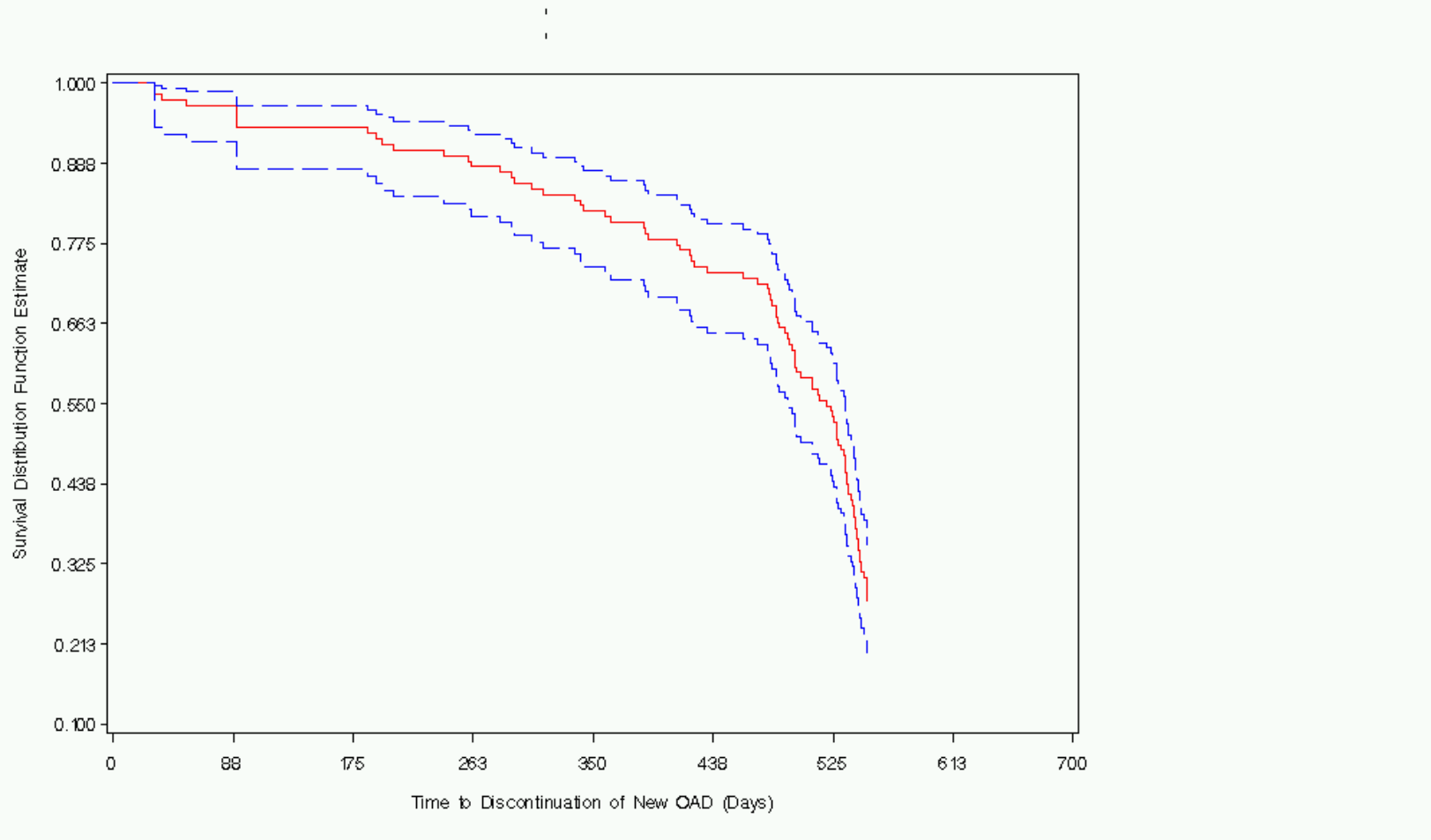
Table 3. 29: Survival Estimate of New OAD

Days	Continued TZD	Discontinued TZD	Continued Standard	Discontinued	Remained
	Percent	Percent	Error	Number	Number
0	1.00	0.00	0.000	0	128
90	0.94	0.06	0.021	8	120
185	0.93	0.07	0.023	9	119
282	0.88	0.13	0.029	16	112
363	0.80	0.20	0.035	25	103
459	0.73	0.27	0.039	35	93
540	0.39	0.61	0.043	78	50
549	0.27	0.73	0.039	93	35

Table 3. 30: Quartile Estimate of New OAD

Quartile Estimates			
Percent	Continuation Time	95% Confidence Interval	
	Median	Lower	Upper
75	-	-	-
50	528	510	538
25	423	359	484

Figure 3. 6: Kaplan-Meier Curve with 95 % Confidence Interval of Time to Discontinuation of New OAD



Kaplan-Meier curve showed the time to discontinuation of sulfonylureas, metformin and metformin/sulfonylurea combination separated approximately 350 days of new oral antidiabetic medication use (Figure 3.8). By the end of the study period, 86 percent (N = 30) of sulfonylureas, 79 percent (N = 38) of metformin and 56 percent (N = 25) of metformin and sulfonylurea patients discontinued their new antidiabetic drug (Table 3.31). The log-rank test showed a statistically significant difference between the survival rates over time (X^2 = 14.51; d.f. = 2; P = 0.0007) (Table 3.38). Median continuation time was 497 days (95% CI = 477, 534) for sulfonylureas (95% CI = 477, 534), 499 days (95% CI = 413, 534) for metformin and 545 days for metformin and sulfonylurea combination (Table 3.32).

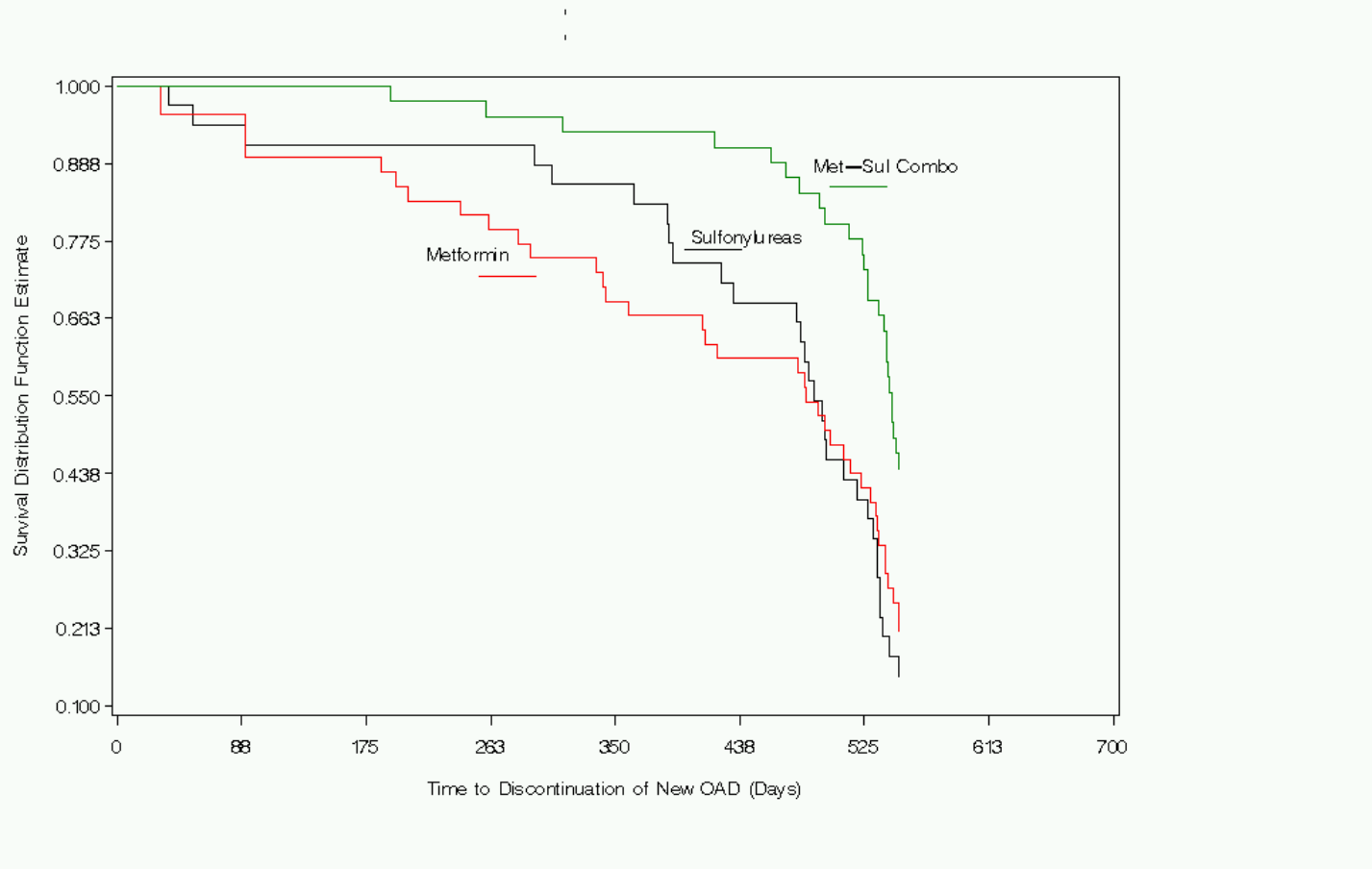
Table 3. 31: Survival Estimate of New OAD by Sulfonylureas, Metformin and Metformin/ Sulfonylurea Combination Groups

New OAD	Days	Continued OAD Percent	Discontinued OAD Percent	Continued Standard Error	Discontinued Number	Remained Number
Sulfonylureas						
	0	1.00	0.00	0.000	0	35
	90	0.91	0.09	0.047	3	32
	293	0.89	0.11	0.054	4	31
	363	0.83	0.17	0.064	6	29
	477	0.66	0.34	0.080	12	23
	543	0.17	0.83	0.064	29	6
	549	0.14	0.86	0.059	30	5
Metformin						
	0	1.00	0.00	0.000	0	48
	90	0.90	0.10	0.044	5	43
	185	0.88	0.13	0.048	6	42
	282	0.77	0.23	0.061	11	37
	359	0.67	0.33	0.068	16	32
	478	0.58	0.42	0.071	20	28
	540	-	-	-	33	15
	549	0.21	0.79	0.059	38	10
Met-Sul Combo						
	0	1.00	0.00	0.000	0	45
	192	0.98	0.02	0.022	1	44
	259	0.96	0.04	0.031	2	43
	313	0.93	0.07	0.037	3	42
	459	0.89	0.11	0.047	5	40
	541	0.60	0.40	0.073	18	27
	549	0.44	0.56	0.074	25	20

Table 3. 32: Quartile Estimate of New OAD by Sulfonylureas, Metformin and Metformin/ Sulfonylurea Combination Groups

		Quartile Estimates		
New OAD	Percent	Continuation Time	95% Confidence Interval	
		Median	Lower	Upper
Sulfonylureas	75	536	520	-
	50	497	477	534
	25	390	305	486
Metformin				
	75	547	533	-
	50	499	413	534
	25	313.5	204	422
Met-Sul Combo				
	75	-	-	-
	50	545	541	-
	25	525	479	541

Figure 3. 7: Kaplan-Meier Curve of Time to Discontinuation of New OAD Between Sulfonylureas, Metformin and Metformin/ Sulfonylurea Combination Groups



Kaplan-Meier curve showed similar time to discontinuation of new oral antidiabetic drugs between rosiglitazone and pioglitazone with some separation approximately 260 after receiving a new oral antidiabetic drug (Figure 3.9) Among patients who received new oral antidiabetic drugs, 73 percent (N = 69) of rosiglitazone and 73 percent (N = 24) of pioglitazone patients had discontinued their new oral antidiabetic drugs by the end of the study period (Table 3.33). The log-rank test showed no statistical difference between the survival rates over time (X^2 = 0.03; d.f. = 1; *P* = 0.86) (Table 3.38). The median continuation time was 527 days (95% CI = 510, 538) for rosiglitazone and 534 days (95% CI = 477,544) for pioglitazone group (Table 3.34).

Table 3. 33: Survival Estimate of New OAD by Rosiglitazone and Pioglitazone Groups

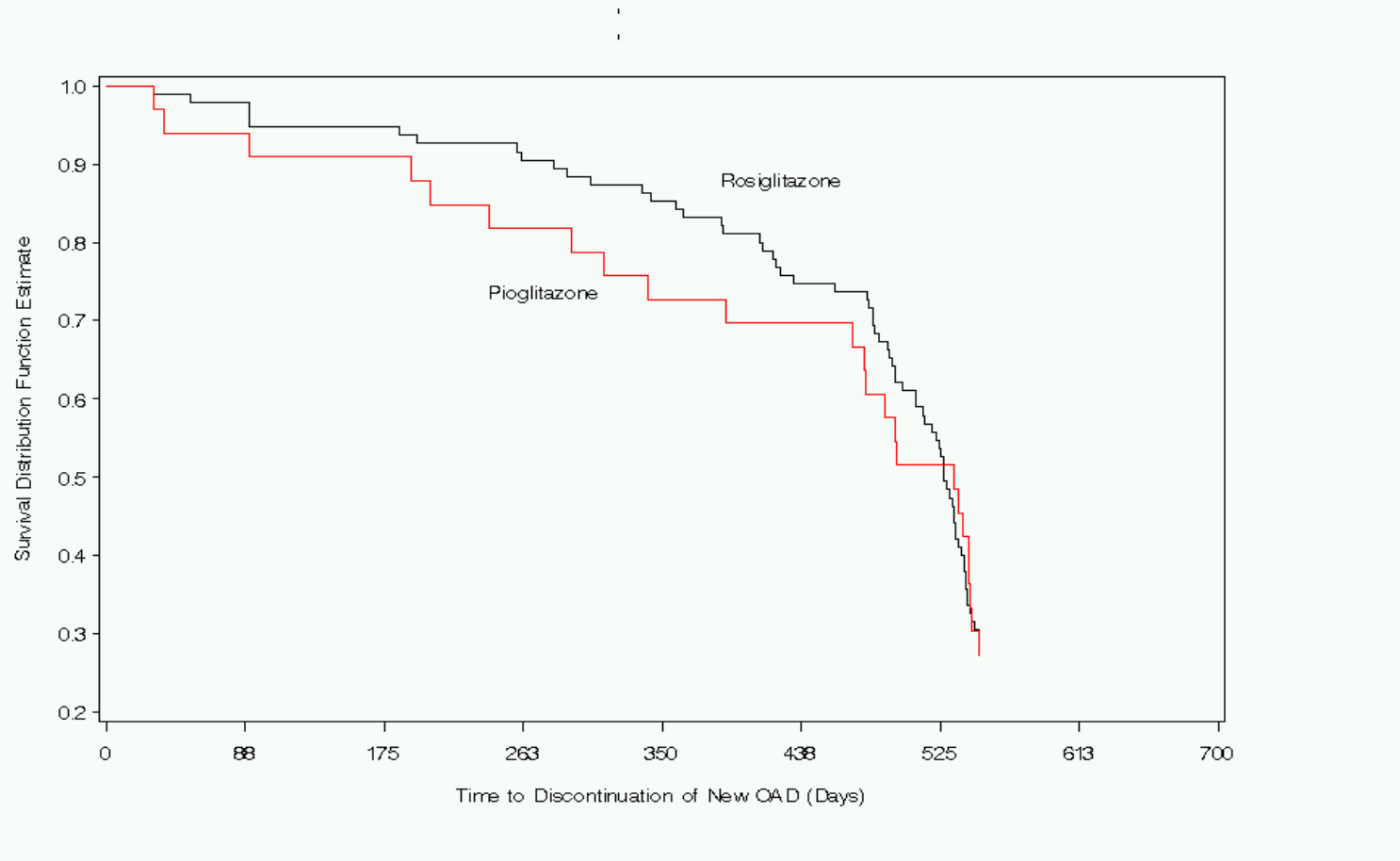
Index TZD	Days	Continued New OAD Percent	Discontinued New OAD Percent	Continued Standard Error	Discontinued Number	Remained Number
Rosiglitazone						
	0	1.00	0.00	0.000	0	95
	90	0.95	0.05	0.023	5	90
	185	0.94	0.06	0.025	6	89
	282	0.89	0.11	0.032	10	85
	363	0.83	0.17	0.038	16	79
	459	0.74	0.26	0.045	25	70
	540	0.38	0.62	0.050	59	36
	549	0.27	0.73	0.046	69	26
Pioglitazone						
	0	1.00	0.00	0.000	0	33
	90	0.91	0.09	0.050	3	30
	293	0.79	0.21	0.071	7	26
	390	0.70	0.30	0.080	10	23
	470	0.67	0.33	0.082	11	22
	543	0.36	0.64	0.084	21	12
	549	0.27	0.73	0.078	24	9

Table 3. 34: Quartile Estimate of New OAD by Rosiglitazone and Pioglitazone Groups

Quartile Estimates

New OAD	Percent	Continuation Time	95% Confidence Interval	
		Median	Lower	Upper
Rosiglitazone				
	75	-	-	-
	50	527	510	538
	25	433	387	493
Pioglitazone				
	75	-	-	-
	50	534	477	544
	25	341	204	490

Figure 3. 8: Kaplan-Meier Curve of Time to Discontinuation of New OAD Between Pioglitazone Versus Rosiglitazone



Among female and male patients, Kaplan-Meier curve showed similar time to discontinuation of new OAD (Figure 3.10 Table 3.35). The log-rank test showed the difference between the continuation rates over time was not statistically significant for male versus female ($X^2 = 0.97$; d.f. = 1; $P = 0.32$) (Table 3.38). The median continuation time was 497 days (95% CI = 478, 540) for female and 534 days (95% CI = 515, 541) for male (Table 3.36).

The median continuation time for new OAD by CCI score is presented in Table 3.37. The log-rank test showed the difference between the discontinuation rate over time was not statistically significant for CCI ($X^2 = 5.55$; d.f. = 7; $P = 0.59$) (Table 3.38).

Table 3. 35: Survival Estimate of New OAD by Gender

Gender	Days	Continued New OAD Percent	Discontinued New OAD Percent	Continued Standard Error	Discontinued Number	Remained Number
Female						
	0	1.00	0.00	0.000	0	57
	90	0.98	0.02	0.017	1	56
	185	0.96	0.04	0.024	2	55
	282	0.89	0.11	0.041	6	51
	363	0.77	0.23	0.056	13	44
	459	0.65	0.35	0.063	20	37
	540	0.37	0.63	0.064	36	21
	549	0.25	0.75	0.057	43	14
Male						
	0	1.00	0.00	0.000	0	71
	90	0.90	0.10	0.035	7	64
	261	0.86	0.14	0.041	10	61
	359	0.83	0.17	0.045	12	59
	470	0.77	0.23	0.050	16	55
	540	0.41	0.59	0.058	42	29
	549	0.30	0.70	0.054	50	21

Table 3. 36: Quartile Estimate of New OAD by Gender

Quartile Estimates

Gender	Percent	Continuation Time	95% Confidence Interval	
		Median	Lower	Upper
Female				
	75	549	540	-
	50	497	478	540
	25	411	305	478
Male				
	75	-	-	-
	50	534	515	541
	25	483	359	510

Figure 3. 9: Kaplan-Meier Curve of Time to Discontinuation of New OAD by Gender

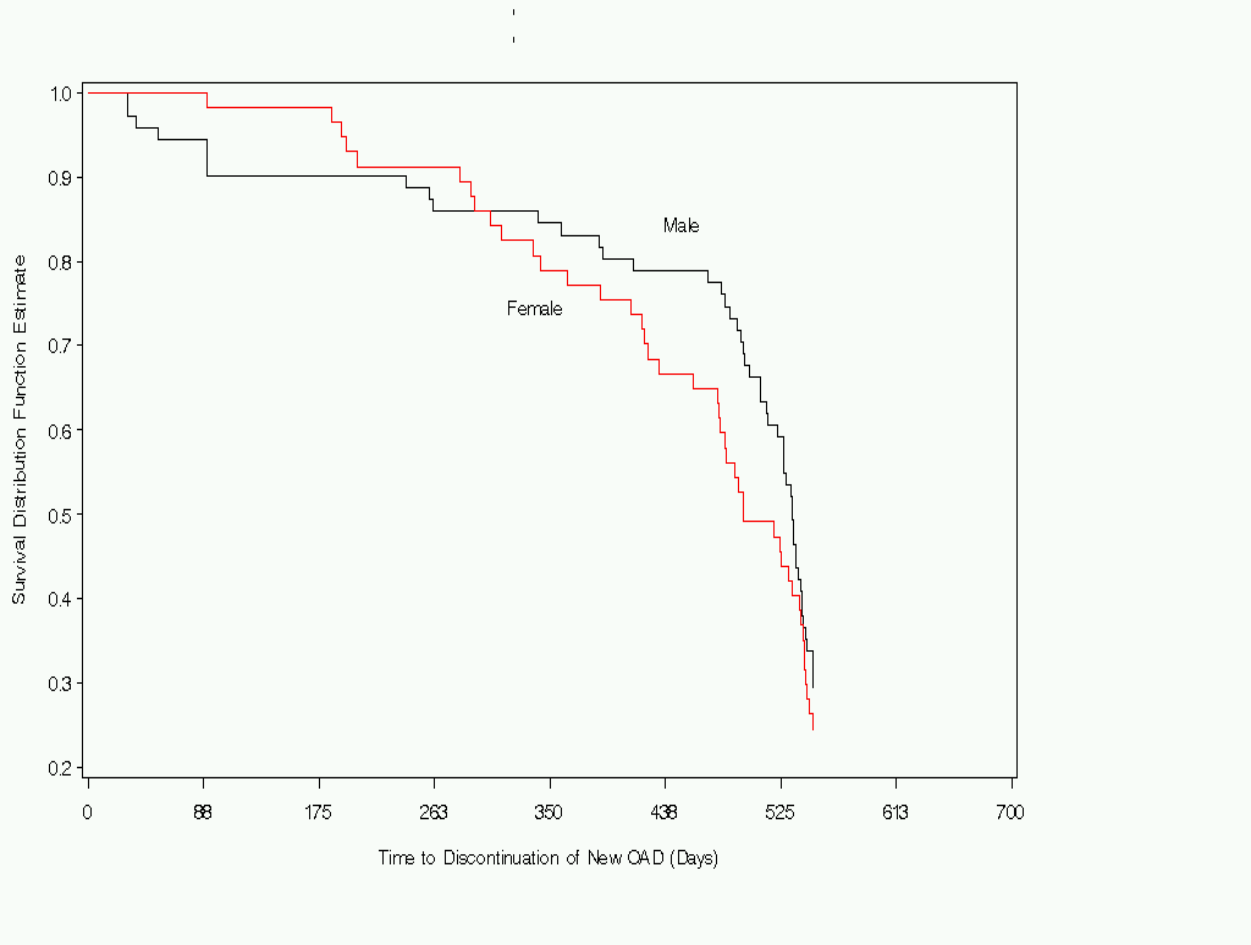


Table 3. 37: Survival Estimate of New OAD by CCI

CCI	Percent	Quartile Estimates: Continuation Time Median	95% Confidence Interval Lower	95% Confidence Interval Upper
0				
	75	-	-	-
	50	540	477	-
	25	477	290	540
1				
	75	-	-	-
	50	536	492	-
	25	433	282	534
2				
	75	-	-	-
	50	521	483	-
	25	343	90	515
3				
	75	538	483	.
	50	483	413	538
	25	413	204	483
4				
	75	-	-	-
	50	534	510	547
	25	477	313	523
5				
	75	541	305	-
	50	416	185	541
	25	185	90	527
6				
	75	540	510	549
	50	531	411	540
	25	411	293	536
7				
	75	527	501	527
	50	514	501	527
	25	501	501	527

Table 3.35 presents variables tested inclusion into the model. Variables were considered a significant predictor and included in the final model if the *P* value was 0.25 or less. The log-rank test of equality across strata showed gender (log-rank Chi-square = 0.97; *P* = 0.32), index TZD (log-rank Chi- square = 0.03; *P* 0.86), CCI (log-rank Chi-square = 5.55; df = 7; *P* = 0.59) were not significant predictor for time to discontinuation of an index TZD. However, these variables were included in the model because they were important. Although univariate Chi-square showed age was not a significant predictor (univariate Chi-square = 0.10; *P* = 0.76), age was included in the model because it was an important factor.

Furthermore, test of time-dependent variables were conducted to check for proportionality in addition to the visual evidence from the Kaplan-Meier curves showing that the curves separated and were approximately parallel (Table 3.39). Tests of time-dependent variables were not significant for the individual variable age log time (Chi-square = 3.95; *P* = 0.05). Test of proportionality did not provide enough evidence to reject proportionality and thus, the model assumed proportionality was met.

Table 3. 38: Variables Tested for Inclusion into Model

Model Variables	Univariate Chi-square	Log-rank Chi-square	D.F.	*P* Value
Index TZD		0.03	1	0.86
New OAD		14.51	2	0.0007
Gender		0.97	1	0.32
CCI		5.55	7	0.59
Age	0.10			0.76

Table 3. 39: Test of Proportionality of Model Variables

Analysis of Maximum Likelihood Estimates

Variable	D.F.	Parameter Estimate	Standard Error	Chi-square	*P* Value	Hazard Ratio
Age	1	0.26	0.125	4.17	0.04	1.29
Gender	1	0.35	0.217	2.57	0.11	1.42
CCI	1	0.04	0.061	0.48	0.49	1.04
New OAD	1	-0.48	0.133	12.71	0.00	0.62
Index TZD	1	-0.03	0.246	0.02	0.90	0.97
Age* Log Time	1	-0.04	0.021	3.95	0.05	0.96

Overall model: Wald Chi-square = 3.95; d.f. = 1; *P* = 0.05

Cox Proportional Hazards Model

A Cox proportional hazards model was conducted to control for the time to discontinuation of new oral antidiabetic drugs. Results from Cox proportional hazards model of 128 patients (93 patients discontinued and 35 patients were censored) are presented in Table 3.30. The model showed there was no statistical difference in the time to discontinuation of new oral antidiabetic drug for age (HR = 1.00; 95 % CI = 0.99, 1.04; *P* = 0.45), for male and female (HR = 1.40; 95 % CI = 0.91, 2.14; *P* = 0.12) and for CCI score (HR = 1.04; 95 % CI = 0.92, 1.17; *P* = 0.54). There was no statistical significant difference in the probability of discontinuation of new oral antidiabetic for patients who had pioglitazone as their first (index) medication compared to rosiglitazone as first medication (HR = 0.98; 95 % CI = 0.61, 1.59; *P* = 0.95). Compared to sulfonylureas, patients who received metformin or metformin/sulfonylurea combinations had a lower probability of discontinuing their new oral antidiabetic drug (HR = 0.62; 95% CI = 0.48, 0.81; *P* = 0.0004. When each group was evaluated, patients receiving sulfonylureas were significantly more likely to discontinue their medication compared to patients receiving metformin/sulfonylurea combination (HR = 0.38; 94% CI = 0.21, 0.66), but not compared to patients receiving metformin (HR = 0.91; 95% CI = 0.56-1.50) (Table 3.42).

Table 3. 40: Cox Proportional Hazards Model on Discontinuation for New OAD During the Post-safety Warning Period

Cox Proportional Hazards Model for Time to Discontinuation of New OAD

Variable	D.F.	Parameter Estimate	Standard Error	Hazard Ratio	95% Hazard Ratio Confidence Interval		Chi-square	*P* Value
Age	1	0.01	0.013	1.01	0.99	1.04	0.58	0.45
Gender	1	0.33	0.217	1.40	0.91	2.14	2.38	0.12
CCI	1	0.04	0.061	1.04	0.92	1.17	0.38	0.54
Index TZD	1	-0.02	0.246	0.98	0.61	1.59	0.00	0.95
New OAD	1	-0.47	0.134	0.62	0.48	0.81	12.43	0.0004

Table 3. 41: Summary of Objectives

Outcome Measure	N (Column %)				Hazard Ratio (95% Hazard Ratio Confidence Interval)			
	Rosiglitazone (N = 255)		Pioglitazone (N = 276)		Unadjusted		Adjusted*	
Objective I								
Discontinuation of Index TZD†	248	(97)	262	(95)	0.55	(0.47-0.66)	0.56	(0.47-0.67)
Objective II								
Discontinuation of New OAD	69	(73)	24	(73)	1.04	(0.65-1.66)	0.98	(0.61-1.59)

*Cox proportional hazards model adjusted for age, gender and CCI

† Sub-group of patients with HbA_{1c}, HR adjusted for age, gender, CCI and HbA_{1c} = 0.58; 95% CI = 0.47, 0.71

Table 3. 42: Summary of Objective II Sub-analysis

Outcome Measure	No. Event N (Column %) Sulfonylureas (N = 35)		Metformin (N = 48)		Met-Sul Combo (N = 45)		Hazard Ratio (95% Hazard Ratio Confidence Interval) Unadjusted		Adjusted*	
Discontinuation of New OAD†	30	(86)	38	(79)	25	(56)	0.64	(0.5-0.82)	0.62	(0.48-0.81)
Discontinuation of New Metformin††	-	-	-	-	-	-	0.89	(0.55-1.44)	0.91	(0.56-1.50)
Discontinuation of New Met-Sul Combo††	-	-	-	-	-	-	0.40	(0.23-0.68)	0.38	(0.22-0.66)

*Cox proportional hazards model adjusted for age, gender, CCI, and index TZD

† Reference group = sulfonylurea; comparison groups: sulfonylurea versus metformin and metformin/sulfonylurea combination

†† Reference group = sulfonylurea

Chapter Four: Discussion and Conclusion

INTRODUCTION

This chapter summarizes the study findings, and discusses the limitations of the study and implications of the findings.

DISCUSSION

A total of 531 patients were included in the analyses (276 for pioglitazone and 255 for rosiglitazone) Among patients who had a high adherence (MPR > 80%) to an index TZD drug during the pre-safety warning period (May 2006 - May 2007), we compared the discontinuation curve (days) and discontinuation rate (percent of patients) of index TZD between rosiglitazone and pioglitazone groups post-safety warning period. Results from the Kaplan-Meier curve showed more discontinuation of rosiglitazone than the discontinuation of pioglitazone over time after the safety warning event (May 2007). The discontinuation of rosiglitazone (38 percent) and pioglitazone (10 percent) separated approximately 90 days after the safety warning event. During this time, the FDA had issued letters to clinicians regarding the results by Nissen and Wolski.[47] Furthermore, after 180 days, by the time the FDA had issued black-boxed warning in November of 2007, over half (54 percent) of patients receiving rosiglitazone had discontinued their medication compared to 22 percent of patients receiving pioglitazone. By the one-year mark (May 2008) about two-thirds (69 %) of rosiglitazone patients and about half (55 percent) of the patients who received pioglitazone discontinued their medication.. By the end of the study period (October 2008), 97 percent (N = 248) of rosiglitazone and 95 percent (N = 262) pioglitazone patients had discontinued their index TZD. Thus, while the risk of myocardial infarction remained uncertain, results showed an immediate decrease in the utilization of rosiglitazone. Interestingly, although the safety warning and

media coverage focused on rosiglitazone, there was also an impact on the utilization of pioglitazone.

An unadjusted hazard ratio showed patients who received pioglitazone were less likely to discontinue their medication compared to patients who received rosiglitazone. (HR = 0.56; 95% CI = 0.47, 0.66) (Table 3.41). After adjusting for age, gender, and CCI, patients who received pioglitazone were less likely to discontinue their medication than patients who received rosiglitazone (HR = 0.56; 95% CI = 0.47, 0.67). Furthermore, for the subset of patients who had a glycosylated HbA1c value recorded (N = 391), after adjusting for age, gender, CCI and glycosylated HbA1c for), a similar likelihood of discontinuation was observed (HR = 0.58; 95% CI = 0.47; 0.71).

Our findings are consistent with previously reported TZD prescription trends after the safety warning. Cohen *et al.*[95] conducted a time-series regression to examine the prescription use of TZD from January 2003 through May 2008 using data from the Institute of Medicine National Disease and Therapeutic Index (IMS NDTI). Results showed rosiglitazone and pioglitazone had similar annual growth rates from 2003 through January 2007. However, the utilization trend for rosiglitazone decreased (60 percent; 95% CI = -64 percent, -56 percent) more than pioglitazone (9 percent; 95% CI = -17 percent, -0.3 percent) during the FDA advisory period (February 2007 through May 2008). Furthermore, Starner *et al.*[98] observed similar decrease in rosiglitazone prescription (33 percent) after the release of the meta-analysis by Nissen and Wolski[47] (from May 2007 through July 2007) and an additional 31.1 percent decrease by the end of December 2007, after the FDA had issued black-boxed warning. However, the utilization of pioglitazone was steady, with a small increase (two percent) in use after the safety warning.

In our second objective, we identified patients who were prescribed a new oral antidiabetic drug after discontinuing their index TZD during the post-safety period. The purpose was to compare the discontinuation curve and discontinuation rate of the new OADs between rosiglitazone and pioglitazone groups post-safety warning period. Results from the Kaplan-Meier curve showed similar discontinuation of new OAD among patients who had rosiglitazone or pioglitazone as their first prescription. An unadjusted hazard ratio showed no statistical difference in the likelihood that patients in the pioglitazone group would discontinue their new OAD compared to patients in the rosiglitazone group (HR = 1.044; 95% CI = 0.66, 1.66). After adjusting for age, gender, and CCI, patients in the pioglitazone and rosiglitazone groups again had a similar likelihood of discontinuing their new OAD (HR = 0.98; 95% CI = 0.61, 1.59).

We also compared the discontinuation curve and discontinuation rate of the new OAD between the new OAD groups (sulfonylureas, metformin, or metformin/sulfonylurea combination) post-safety warning period. The Kaplan-Meier curve showed patients who received a metformin/sulfonylurea combination had a lower likelihood of discontinuing their medication over time. An unadjusted hazard ratio showed patients receiving sulfonylureas were more likely to discontinue their medication compared to patients who received metformin or metformin/sulfonylureas combination (HR = 0.64; 95% CI = 0.5, 0.82) (Table 3.42). Patients receiving sulfonylureas were more likely to discontinue their medication compared to patients receiving metformin/sulfonylurea combination (HR = 0.40; 94% CI = 0.23, 0.68), but not compared to patients receiving metformin (HR = 0.89; 95% CI = 0.55-1.44) (Table 3.42).

Furthermore, after adjusting for age, gender, CCI and TZD groups, patients who received sulfonylureas were more likely to discontinue their medication than patients who received new metformin or metformin/sulfonylureas combination (HR = 0.62; 95%

CI = 0.48, 0.81). Particularly, compared to patients receiving sulfonylurea, patients receiving metformin/sulfonylurea combination had a lower likelihood of discontinuing their medication (HR = 0.38; 95% CI = 0.22, 0.66) (Table 3.42). This may be due to the adverse drug reaction such as hypoglycemia associated with sulfonylureas. Also, patients who received metformin/sulfonylurea combination may have received more monitoring and medication adjustments. This may be due to their older age compared to than patients receiving sulfonylurea ($P > 0.5$) and metformin ($P < 0.05$). Furthermore, the last prescription for metformin or sulfonylurea prescription was considered for the metformin/sulfonylurea combination. Thus, one of the drugs in the combination could have been discontinued earlier, but not captured.

Seventy-five percent (N = 328) of patients who discontinued were not captured in our second analysis. These patients had a median continuation days of 420 days (95% CI = 390, 450). Thus, they had discontinued after the screening date (April 30, 2008) and might have had a new oral antidiabetic drug later, which would not have been captured in the analysis. These patients warrant monitoring for diabetic control.

Unlike previous studies reporting the delay in clinical responses to safety warnings,[88, 90, 91] our study showed immediate response to the safety warning for TZD. This may be due to the wide media coverage of rosiglitazone adverse events and more active participation from patients in their health care services. Previous methods to communicate safety warnings mainly used labeling changes,[90] including warnings to monitor liver function with trosligitazone.[88, 91] Label-based warnings have had a low impact on clinical practice and were often ignored.[114] Furthermore, the safety concerns of rosiglitazone occurred after the removal of the painkiller rofecoxib, which was still available on the market after evidence of a high risk of cardiovascular (CV) deaths.. Although the magnitude of the impact of the rofecoxib case on the public perception of

the benefits of pharmaceutical products is unclear, the high discontinuation of TZD may indicate the public's cautionary perception of the benefits of medication.

Importantly, our patient population had risk factors which may predispose them to the potential risk of myocardial infarction (MI) associated with rosiglitazone. These risk factors were identified in the sub-analysis studies by the FDA and the manufacture of rosiglitazone, GlaxoSmithKline (GSK) including patients who had ischemic heart disease (IDH) and were elderly.[57, 60] The mean age of our patient population was 61 (SD = 8.9) years for rosiglitazone and 62 (SD = 9.2) years for pioglitazone. Furthermore, IHD and dyslipidemia, which are risk factors for myocardial infarctions, were common in our study. These patients may have received more frequent healthcare services and careful monitoring for comorbid conditions and diabetes.

After the FDA regulatory action in 2007, additional studies evaluated the risk of CV associated with TZD. A recent retrospective study by Graham *et al.*[115] showed elderly patients receiving rosiglitazone may be at risk for CV events. Graham *et al.*[115] compared the risk of CV events between rosiglitazone and pioglitazone using Medicare Part D prescription drug plan data from July 2006-June 2009 among the 227,571 Medicare beneficiaries aged 65 years or older. Compared to patients receiving pioglitazone after three years, patients receiving rosiglitazone had an increased risk of acute myocardial infarction (AMI) (HR =1.06; 95% CI = 0.96, 1.18), stroke (HR = 1.27; 95% CI = 1.12,1.45), heart failure (HF) (HR =1.25; 95% CI = 1.16, 1.34) death (HR = 1.14; 95% CI = 1.05, 1.24), and composite endpoint of AMI, stroke, heart failure or death (HR = 1.18; 95% CI = 1.12, 1.23).[115]

The final results of the RECORD study showed uncertain risk of MI associated with rosiglitazone, similar to the interim analysis.[116] After a mean 5.5 years of follow-up, patients receiving rosiglitazone showed an increased risk of MI (fatal and nonfatal)

compared to those who did not receive rosiglitazone. However, the upper bound of the 95 percent confidence interval failed to exclude the pre-specified non-inferiority margin of 1.2 (HR=1.14; 95% CI=0.80,1.63).[116]

The RECORD confirmed the increased risk of HF with rosiglitazone. The risk of HF was twice as likely to occur in patients who receive rosiglitazone (N = 61 events) versus comparators (metformin and sulfonylurea) (N = 29 events) (HR=2.10; 95% CI= 1.35, 3.27) with both the with the lower and upper bound of the 95 percent confidence interval above the pre-specified non-inferiority margin of 1.2.[116] Results showed rosiglitazone was not inferior to comparators on the risk of CV death or CV hospitalization (HR=0.99; 95% CI=0.85, 1.16) with the upper bound of this margin below the pre-specified non-inferiority margin of 1.2.[116]

In July of 2010, the FDA Advisory Committee convened to consider the risks and benefits of rosiglitazone.[114] An updated meta-analysis by GSK of 52 trials[63] showed rosiglitazone was significantly associated with increased risk, especially among patients receiving rosiglitazone in combination with metformin (OR=2.7, 95%CI = 1.2, 7) and insulin (OR = 2.1; 95% CI = 0.91, 5.1). With the new information, the FDA voted differently than in 2007 when the FDA committee members decided 22 to 1 to keep rosiglitazone on the market.[82] Twelve of the 33 members voted to remove rosiglitazone from the market. Ten members voted to increase label warning and restrict usage, but seven members voted to only increase label warning. Three members voted to continue to market rosiglitazone without changes and one member abstained. The FDA decided to increase safety warnings and limit access to rosiglitazone for patients who have failed other treatments.[114] Importantly, these patients must understand and acknowledge the risks and benefits of rosiglitazone before receiving treatment.[114] Furthermore, the FDA reviewed the results of RECORD and removed the risk warning for MI from black-boxed

warning section. The remaining language in the black-boxed warning is for heart failure, which is a class effect for both rosiglitazone and pioglitazone.[57, 63]

Following the decision in July 2010 to keep rosiglitazone on the market with limited use, the FDA placed the Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE) trial on partial clinical hold which no new patients may be enrolled until further notice.[117] The TIDE trial was a non-inferiority trial intended to evaluate the CV safety of rosiglitazone compared with other antidiabetic drugs among 16,000 anticipated patients, initiated in May of 2009. However, the FDA raised the ethical question regarding the methodology to determine the risk associated with a drug post marketed, including the use of clinical trials. The Institute of Medicine recommended that the safety trial of approved drugs is "critical from an ethics standpoint that existing evidence be insufficient to make an appropriate policy determination…It is never ethical to involve research participants in an inappropriate designed or inappropriately conducted study or any study that does not have a reasonable prospect of answering the research question under study."[118] Furthermore, Drs. Graham and Gelperin in their presentation at the FDA Advisory Meeting raised concern about whether the TIDE study addresses the safety of rosiglitazone versus pioglitazone when the primary endpoint compares rosiglitazone with other antidiabetic drugs and the selected 30 percent non-inferiority margin is not justified.[119]

LIMITATIONS

This was a retrospective study which had several limitations. The CV risk of rosiglitazone remained uncertain and controversial. Multiple studies attempted to evaluate the risk associated with rosiglitazone. Thus, we focused on the impact of discordant medical literature on the utilization of TZDs and other oral antidiabetic drugs

There were potentially incomplete medical and pharmacy claims. While the Scott & White Health Plan maintained integrated medical and pharmacy information, glycolysated HbA_{1c} levels were not captured for many patients. Our study identified patients based on the availability of pharmacy prescription claims. Patients who received their prescriptions away from the Scott & White Pharmacy or paid cash were not included. Furthermore, the recent four dollar for a month of supply for a generic drug allowed patients to pay cash without adjudicating a prescription claim to the insurance.[120] Our retrospective database study would not capture these patients' drug utilization, which may lead to selection bias.

Furthermore, we only studied patients who were established users of TZDs with at least 80% adherence. These patients may be more knowledgeable and active about their conditions to maintain high adherence to their index TZD. To evaluate the impact of safety warnings on medication utilization, these patients provided an established baseline. However, it was possible that these patients might be more active to make medication changes in response to the media coverage of the safety of rosiglitazone.

We did not follow patients after October 31, 2008 and thus were not able to observe adherence rates for patients who discontinued their index TZD after April 1, 2008. Our study focused on TZD patients who received a new OAD but did not evaluate patients who had TZD in combination with an oral OAD during the pre-safety period. These patients may have a more severe condition and require multiple drug therapy. The discontinuation of TZDs among these patients may warrant additional drug use such as insulin. However, we excluded the use of insulin, as it was not reliably captured in claims databases.

These findings may be limited to settings similar to an integrated health care system such as the Scott & White Health Plan. The Scott & White Health Plan has a

diabetes management program which provides integrated services, including prescription management, to patients with diabetes monthly. Patients identified in our study may have received care from the diabetes management program and thus, may have received recommendations to carefully monitor and/or change their medication.

CONCLUSION

In conclusion, our findings showed that most patients discontinued their TZD within 1.5 years after the first safety warning event date. Particularly, patients who received rosiglitazone were more likely to discontinue their medication than patients who received pioglitazone. Among patients who received a new OAD after discontinuing their TZD, there was no difference in the discontinuation of new OAD between patients who had high adherence for rosiglitazone or pioglitazone during the pre-safety warning period. However, patients who received sulfonylureas were more likely to discontinue their medication than patients who received metformin or a metformin/sulfonylureas combination. The discordant medical literature warrants changes in medication use and clinical monitoring. Further research on the impact of discontinuing oral OADs on insulin use and glycemic control is warranted.

Appendices

APPENDIX A ICD-9 CODES FOR CHARLSON COMORBIDITY INDEX

Diagnostic category	ICD-9-CM codes	Description
Myocardial infarction	410–410.9	Acute myocardial infarction
	412*	Old myocardial infarction
Congestive heart failure	428–428.9	Heart failure
Peripheral vascular disease	443.9*	Peripheral vascular disease, incl. intermittent claudication
	441.441.9*	Aortic aneurysm
	785.4*	Gangrene
	V43.4*	Blood vessel replaced by prosthesis
	procedure 38.48	Resection and replacement of lower limb arteries
Cerebrovascular disease	430–438†	Cerebrovascular disease
Dementia	290–290.9*	Senile and presenile dementias
Chronic pulmonary disease	490–496*	Chronic obstructive pulmonary disease
	500–505*	Pneumoconioses
	506.4*	Chronic respiratory conditions due to fumes and vapors
Rheumatologic disease	710.0*	Systemic lupus erythematosus
	710.1*	Systemic sclerosis
	710.4*	Polymyositis
	714.0–714.2*	Adult rheumatoid arthritis
	714.81*	Rheumatoid lung
	725*	Polymyalgia rheumatica
Peptic ulcer disease	531–534.9	Gastric, duodenal and gastrojejunal ulcers
	531.4–531.7	Chronic forms of peptic ulcer disease* (subset of above lis
	532.4–532.7	
	533.4–533.7	
	534.4–534.7	
Mild liver disease	571.2*	Alcoholic cirrhosis
	571.5*	Cirrhosis without mention of alcohol
	571.6*	Biliary cirrhosis
	571.4–571.49*	Chronic hepatitis
Diabetes	250–250.3*	Diabetes with or without acute metabolic disturbances
	250.7*	Diabetes with peripheral circulatory disorders
Diabetes with chronic complications	250.4–250.6*	Diabetes with renal, ophthalmic, or neurological manifestations
Hemiplegia or paraplegia	344.1*	Paraplegia
	342–342.9*	Hemiplegia
Renal disease	582–582.9*	Chronic glomerulonephritis
	583–583.7*	Nephritis and nephropathy
	585*	Chronic renal failure
	586*	Renal failure, unspecified
	588–588.9*	Disorders resulting from impaired renal function
Any malignancy, including leukemia and lymphoma	140–172.9	Malignant neoplasms‡
	174–195.8	Malignant neoplasms‡
	200–208.9	Leukemia and lymphoma
Moderate or severe liver disease	572.2–572.8*	Hepatic coma, portal hypertension, other sequelae of chronic liver disease
	456.0–456.21*	Esophageal varices
Metastatic solid tumor	196–199.1	Secondary malignant neoplasm of lymph nodes and other organs
AIDS	042–044.9§	HIV infection with related specified conditions

APPENDIX B ICD-9 CODES CV COMORBIDITY

CV Comorbidities	ICD-9 Codes
Dyslipidemia	272.00-270.4
Heart Failure	428.00-428.99, 429.3, 401.01, 401.11, 402.91, 425.00-425.9
Ischemic Heart Disease	410.00-414.00
Obesity	278-279.99
Renal Disease	585-586.99

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