United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

February 18, 2010

Via Electronic Transmission

The Honorable Margaret A. Hamburg, MD
Commissioner
U.S. Food and Drug Administration
White Oak Building 1
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Hamburg:

As senior members of the United States Senate and Chairman and Ranking Member of the Committee on Finance (Committee), we have a duty under the Constitution to conduct oversight into the actions of executive branch agencies, including the Food and Drug Administration (FDA). In this capacity, we must ensure that FDA properly fulfill their mission to advance the public's welfare, safeguard the nation's drug supply, and protect patients participating in clinical trials.

We recently released a report raising concerns about Avandia, a diabetes drug made by GlaxoSmithKline (GSK). We began this inquiry after the *New England Journal of Medicine* published a study in May 2007 warning of the possible cardiovascular risk of Avandia.

Our report was based on a review of hundreds of thousands of pages of internal GSK documents and concluded:

> The totality of evidence suggests that GSK was aware of the possible cardiac risks associated with Avandia years before such evidence became public…. Based on this knowledge, GSK had a duty to sufficiently warn patients and the FDA of its concerns in a timely manner. Instead, GSK executives intimidated independent physicians, focused on strategies to minimize findings that Avandia may increase cardiovascular risk, and sought ways to downplay findings that the rival drug ACTOS (pioglitazone) might reduce cardiovascular risk.

In 2007, the FDA asked GSK to perform a cardiovascular safety trial, called TIDE (Thiazolidinedione Intervention With Vitamin D Evaluation), to compare Avandia to other diabetes treatments such as ACTOS (piolglitazone). According to clinicaltrials.gov, the TIDE trial is currently recruiting patients. [ATTACHMENT A]

In response to several document requests made to the FDA, we received and reviewed an analysis conducted by two FDA safety officials. It is our understanding that this analysis, conducted in October 2008, reviewed all available studies comparing rosiglitazone (Avandia) to pioglitazone (ACTOS). The analysis by these FDA officials raise some alarms. For instance, they wrote:

> [T]here is no evidence that rosiglitazone confers any unique health benefits over pioglitazone while there is strong evidence that rosiglitazone confers an increased risk of [heart attacks] and heart failure compared to pioglitazone. [ATTACHMENT B]

Even more alarming, they concluded that "any proposed head-to-head trial of rosiglitazone vs. pioglitazone would be unethical and exploitative."

Two days after releasing this analysis, one of these same safety officers reviewed the protocol for the TIDE trial. This safety officer wrote that because of cardiovascular concerns with Avandia "the safety of the study itself cannot be assured, and is not acceptable." [Attachment C]

After reading these documents, we would like to know what steps the FDA has taken to protect patients in the TIDE trial, and why this trial is allowed to continue. We would also like to know if the Office for Human Research Protection (OHRP) was notified about the safety concerns of the TIDE trial identified by the FDA. Further, we were alarmed to learn that the warnings from these safety officers do not appear to be addressed in the consent form that was handed out to patients that were enrolled in the study. [Attachment D]

We look forward to hearing from you by no later than March 4, 2010. All documents responsive to this request should be sent electronically in PDF format to Brian_Downey@finance-rep.senate.gov. If you have any questions, please do not hesitate to contact Chris Law (Senator Baucus) or Paul Thacker (Senator Grassley) at (202) 224-4515.

Sincerely,

Max Baucus
Chairman

Charles E. Grassley
Ranking Member

Attachments

ATTACHMENT A

Thiazolidinedione Intervention With Vitamin D Evaluation (TIDE)

This study is currently recruiting participants.
Verified by GlaxoSmithKline, June 2009

First Received: April 2, 2009 Last Updated: June 18, 2009 History of Changes

Sponsored by:	**GlaxoSmithKline**
Information provided by:	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT00879970

Purpose

This study will answer two separate questions.

The first question is to test the cardiovascular effects of long-term treatment with **rosiglitazone** or **pioglitazone** when used as part of standard of care compared to similar standard of care without **rosiglitazone** or **pioglitazone** in patients with type 2 diabetes who have a history of or are at risk for cardiovascular disease.

The second question will compare the effects of long-term supplementation of vitamin D on death and cancer

Condition	Intervention	Phase
Cardiovascular Disease Type 2 Diabetes Mellitus	Drug: **pioglitazone** Drug: placebo Dietary Supplement: vitamin D Dietary Supplement: placebo Drug: **rosiglitazone**	Phase IV

Study Type: Interventional
Study Design: Treatment, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Factorial Assignment, Safety/Efficacy Study

Official Title: Thiazolidinedione Intervention With Vitamin D Evaluation (TIDE) A Multicenter Randomized Double-Blind Placebo Controlled Trial of a Thiazolidinedione or Placebo and of Vitamin D or Placebo In People With Type 2 Diabetes at Risk For Cardiovascular Disease

Resource links provided by NLM:

MedlinePlus related topics: Cancer Diabetes Dietary Supplements Diets

Drug Information available for: Pioglitazone Pioglitazone hydrochloride Rosiglitazone Rosiglitazone Maleate Vitamin D

U.S. FDA Resources

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measures:

- The composite primary outcome for the vitamin D research question is death or serious cancer requiring hospitalization, chemotherapy or surgery. [Time Frame: up to 10 years] [Designated as safety issue: Yes]
- The composite cardiovascular primary outcome for the TZD research questions is the first occurrence of either: a) cardiovascular death; b) nonfatal myocardial infarction (MI); or c) nonfatal stroke. [Time Frame: Approximately 5.5 years] [Designated as safety issue: Yes]

Secondary Outcome Measures:

- All-cause mortality, a composite microvascular outcome, hospitalization for heart failure, revascularization, angina, cancer and fracture [Time Frame: Approximately 5.5 years] [Designated as safety issue: Yes]

Estimated Enrollment:	16000
Study Start Date:	May 2009
Estimated Study Completion Date:	October 2015
Estimated Primary Completion Date:	October 2015 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
TZD placebo: Placebo Comparator	Drug: placebo thiazolidinedione factor intervention
vitamin D placebo: Placebo Comparator	Dietary Supplement: placebo Vitamin D factor intervention
pioglitazone: Active Comparator	Drug: **pioglitazone** thiazolidinedione factor intervention
rosiglitazone: Active Comparator	Drug: **rosiglitazone** thiazolidinedione factor intervention
vitamin D: Active Comparator	Dietary Supplement: vitamin D vitamin D factor intervention

Eligibility

Ages Eligible for Study:	50 Years and older
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Men or women with: a) newly detected type 2 diabetes based on a fasting plasma glucose greater than or equal to 7.0 mmol/l (126 mg/dL) or a 2 hour plasma glucose (FPG) greater than or equal to 11.1 mmol/l (200 mg/dL) on an oral glucose tolerance test, or b) a history of type 2 diabetes
- Hemoglobin A1c (A1C) 6.5-9.5% inclusive (for assays with upper limit of normal of 6%) within one month of screening
- Age ≥ 50 years and evidence of vascular disease defined as ≥1of:
    - prior myocardial infarction
    - prior stroke
    - coronary, carotid or peripheral artery revascularization ≥ 4 years earlier
    - previous documented myocardial ischemia on either an exercise stress test or on any cardiac imaging, or previous unstable angina with ECG changes or cardiac enzyme elevation OR
- Age ≥ 55 years and evidence of subclinical vascular disease defined as ≥1 of:
    - microalbuminuria or proteinuria
    - history of treated or untreated hypertension with left ventricular hypertrophy by electrocardiogram (ECG) or echocardiogram
        - 50% stenosis on any imaging of coronary, carotid or lower extremity arteries
    - ankle/brachial index <0.9 OR
- Age ≥ 60 years and at least 2 of the following cardiovascular disease risk factors:
    - current tobacco use
    - LDL-c ≥3.4 mmol/L (130 mg/dL) or on a lipid lowering medication
    - HDL-c < 1.0 mmol/L (40 mg/dL) for men and < 1.3 mmol/L (50 mg/dL) for women or triglycerides
        - 2.3 mmol/L (200 mg/dL)
    - BP lowering medication use or untreated SBP ≥ 140 mmHg or DBP ≥ 95 mmHg
    - Waist to hip ratio > 1.0 for men and > 0.8 for women
- On no insulin and on less than or equal to 2 anti-diabetes drugs where at least one drug is at or below the half-maximal dose (as indicated in the MOP) with stable dosing for 10 weeks prior to screening

Exclusion Criteria:

- Type 1 diabetes
- Current need for insulin treatment
- Symptomatic hyperglycemia requiring immediate therapy in the judgment of the physician
- An acute cardiovascular event within 30 days prior to randomization
- Symptomatic heart failure (i.e. New York Heart Association class II or higher) or any episode of previous pulmonary edema or known ejection fraction < 0.4 or current use of loop diuretics
- Any fracture within the past 1 year
- Currently planned coronary, carotid or peripheral artery revascularization or cardiac valve surgery
- Coronary, carotid or peripheral artery revascularization within the 4 years prior to screening in the absence of angina, MI, or stroke in the intervening period
- End stage renal disease requiring renal replacement therapy
- Receiving drug therapy to treat liver disease
- A diagnosis of cancer (other than superficial squamous, basal cell skin cancer, or adequately

treated cervical carcinoma in situ) in the past 3 years or current treatment for the active cancer (other than prophylactic)

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level > 2.5 times the upper limit of normal
- A prior heart transplant or awaiting a heart transplant
- Previous or current hypercalcemia, hyperparathyroidism, osteomalacia or other contraindication for vitamin D therapy
- Regular use of or indication for greater than 400IU of vitamin D daily
- Clinically or medically unstable with expected survival < 1 year
- Unwillingness to permit sites to contact their primary physicians to communicate information about the study and the participant's data
- Any other factor likely to limit protocol compliance or reporting of adverse events
- Inability to discontinue a TZD (if taking one) in the judgement of the physician/investigator
- Contraindications to or history of hypersensitivity to the investigational products
- History of renal stones within the past 2 years
- Participation in another clinical trial of an investigational agent

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT00879970

Contacts

Contact: US GSK Clinical Trials Call Center 877-379-3718

Locations

United States, New York

GSK Investigational Site **Recruiting**
Westfield, New York, United States, 14787
Principal Investigator: Donald Brautigam

Canada, Manitoba

GSK Investigational Site **Recruiting**
Winnipeg, Manitoba, Canada, R2H 0R8
Principal Investigator: Pravinsagar G Mehta

Canada, Ontario

GSK Investigational Site **Recruiting**
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Principal Investigator: James Cha

GSK Investigational Site **Recruiting**
Oakville, Ontario, Canada, L6H 3P1
Principal Investigator: Yaw D Twum-Barima

GSK Investigational Site **Recruiting**
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Principal Investigator: Kim Tan

GSK Investigational Site **Recruiting**
Toronto, Ontario, Canada, M4R 2G4
Principal Investigator: Ronnie Aronson

GSK Investigational Site **Recruiting**

Barrie, Ontario, Canada, L4M 7G1
Principal Investigator: Suzan Abdel-Salam

GSK Investigational Site **Recruiting**
Thornhill, Ontario, Canada, L4J 8L7
Principal Investigator: Ronald M Goldenberg

Sponsors and Collaborators

GlaxoSmithKline

Investigators

Study Director: GSK Clinical Trials GlaxoSmithKline

More Information

No publications provided

Responsible Party:	GSK (Study Director)
Study ID Numbers:	111960
Study First Received:	April 2, 2009
Last Updated:	June 18, 2009
ClinicalTrials.gov Identifier:	NCT00879970 History of Changes
Health Authority:	United States: Food and Drug Administration

Keywords provided by GlaxoSmithKline:
Cardiovascular Outcomes
Academic Research Collaborator: Population Health Research Institute / Hamilton Health Sciences / McMaster University / Ontario Canada

Additional relevant MeSH terms:

Pioglitazone
Rosiglitazone
Metabolic Diseases
Growth Substances
Physiological Effects of Drugs
Diabetes Mellitus
Ergocalciferols
Endocrine System Diseases
2,4-thiazolidinedione
Bone Density Conservation Agents
Pharmacologic Actions
Hypoglycemic Agents
Vitamin D
Vitamins
Diabetes Mellitus, Type 2
Cardiovascular Diseases
Micronutrients
Glucose Metabolism Disorders

ClinicalTrials.gov processed this record on September 30, 2009

ATTACHMENT B

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	October 7, 2008
To:	Mary Parks, MD, Director Division of Metabolism and Endocrinology Products (DMEP)
Thru:	Gerald Dal Pan, MD, MHS, Director Office of Surveillance and Epidemiology (OSE)
From:	David J. Graham, MD, MPH Associate Director for Science and Medicine Office of Surveillance and Epidemiology (OSE) Kate Gelperin, MD, MPH Division of Epidemiology (DEpi)
Subject:	Benefit-risk assessment of rosiglitazone vs. pioglitazone
Drug Name(s):	Rosiglitazone (AVANDIA®, GlaxoSmithKline, IND 43,468, NDA 21-071) Pioglitazone (ACTOS®, Takeda, NDA 21-073)
Submission Number:	
Application Type/Number:	
Applicant/sponsor:	GlaxoSmithKline (GSK)
OSE RCM #:	2007-1945, 2008-278

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

CONTENTS

EXECUTIVE SUMMARY 2
1 BACKGROUND 5
1.1 Introduction 5
1.2 Thiazolidinedione History 5
1.3 New Developments since FDA Advisory Committee Meeting 6
2 METHODS and MATERIALS 6
2.1 Randomized Controlled Clinical Trials 6
2.2 Observational Studies 6
2.3 Summary and Meta-analysis 6
2.4 Drug Utilization 7
2.5 Expert Opinion: Published Literature Review 7
3 RESULTS 7
3.1 Randomized Controlled Clinical Trials 7
3.2 Observational Studies 15
3.3 Meta-Analyses of Acute Myocardial Infarction and Heart Failure Risk 24
3.4 Drug Utilization 38
4 BENEFITS and RISKS of THIAZOLIDINEDIONES 39
4.1 Glycemic Control 39
4.2 Lipid Effects 39
4.3 Body Composition and Blood Pressure Effects 39
4.4 Kidney Effects 39
4.5 Bone Fractures 40
4.6 Malignancy Risk 41
4.7 Surrogate Measures of Cardiovascular Risk or Disease 41
4.8 Heart Failure 42
4.9 Microvascular Disease Prevention 42
4.10 Macrovascular Disease Prevention 42
4.11 Mortality 44
5 DISCUSSION 45
5.1 Main Findings 45
5.2 Drug Usage and Expert Opinion 50
5.3 Ethical Considerations 51
6 CONCLUSIONS 54
7 RECOMMENDATIONS 54
8 REFERENCES 55
9 APPENDIX 62

EXECUTIVE SUMMARY

In early 2007, a study-level meta-analysis of clinical trials of rosiglitazone found a 43% increase in risk of acute myocardial infarction (AMI) and a 64% increase in risk of cardiovascular death with rosiglitazone vs. comparator therapy. The FDA performed a patient-level meta-analysis of rosiglitazone clinical trials and found that rosiglitazone was associated with a 40% increase in ischemic myocardial events. In July 2007, a FDA advisory committee voted to keep rosiglitazone on the market, and subsequently, myocardial ischemia was added as a boxed warning to the rosiglitazone label. The manufacturer, GlaxoSmithKline, was also asked to perform a cardiovascular outcomes trial of rosiglitazone vs. other oral therapies, with a secondary analysis of rosiglitazone vs. pioglitazone.

During the past year, several new meta-analyses of randomized controlled trials addressing the issues of AMI and heart failure risk with rosiglitazone and pioglitazone have been published. In addition, a number of observational studies with direct comparison of rosiglitazone vs. pioglitazone for the occurrence of AMI have become available. The purpose of this review is to assess new information that has become available since the July 2007 advisory committee meeting, place it in the context of information discussed at that advisory meeting, and formulate a conclusion about the relative benefits and risks of rosiglitazone compared to pioglitazone.

Seven observational epidemiologic studies were identified in which rosiglitazone was compared to pioglitazone for the occurrence of AMI. In all seven, the relative risk for AMI was increased with rosiglitazone compared to pioglitazone. A meta-analysis of these observational studies showed an increased risk of AMI with rosiglitazone, with a summary relative risk of 1.19 (95% CI 1.11-1.28). There was virtually no heterogeneity among the studies ($I^2 = 0\%$).

There are no large randomized head-to-head cardiovascular outcomes trials comparing rosiglitazone and pioglitazone. Only one randomized controlled trial has been performed directly comparing rosiglitazone vs. pioglitazone, but this trial was of small size, short duration (24 weeks), and was designed to study changes in lipid profiles with each TZD. Cardiovascular events were collected but not adjudicated. Risk of an ischemic cardiac event was increased with rosiglitazone compared to pioglitazone in this study.

Published randomized controlled trials of rosiglitazone generally have reported increased point estimates for the risk of AMI. Three separate meta-analyses of randomized trials including published and unpublished trials uniformly reported statistically significant increased risks of AMI or myocardial ischemia with rosiglitazone. In contrast, a large cardiovascular outcomes trial for pioglitazone reported a non-statistically significant reduction in risk of a composite outcome that included all-cause mortality, nonfatal AMI, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, or amputation above the ankle (HR=0.90, 95% CI 0.80-1.02, p=0.095). In a composite secondary outcome of all-cause mortality, nonfatal AMI, or stroke, a statistically significant reduction in risk favoring pioglitazone was observed (HR=0.84, 95% CI 0.72-0.98, p=0.027).

Several meta-analyses have been published to address the question of AMI risk with rosiglitazone and pioglitazone. The meta-analysis by Nissen et al. was based on 42 controlled trials (40 shorter-term, DREAM, ADOPT). This analysis included 26,005 enrolled patients and found an increased relative risk for AMI with rosiglitazone of 1.43 (95% CI 1.03-1.98). The rosiglitazone meta-analysis by Singh et al. included four published randomized controlled trials that were at least 12 months in duration involving 14,291 patients (DREAM, ADOPT, RECORD + one smaller study). They found a relative risk for AMI with rosiglitazone of 1.42 (95% CI 1.06-1.91). The pioglitazone meta-analysis by Linkoff et al included 19 randomized trials (two published, 17 unpublished) that had

enrolled 16,390 patients. They found a relative risk of AMI with pioglitazone of 0.81 (95% CI 0.64-1.02).

In this review, each of the two rosiglitazone meta-analyses was compared to the one pioglitazone meta-analysis in an effort to determine whether the risk of AMI with each of the currently available TZDs was the same or different. For both comparisons, the difference in relative risk of AMI between the two TZDs was statistically significant, favoring pioglitazone. Based on the findings from these meta-analyses, the relative risk of AMI for rosiglitazone vs. pioglitazone is estimated to be approximately 1.75. Using this estimate of relative risk, the net absolute increase in AMI risk associated with rosiglitazone use compared to pioglitazone was 1.58 per 100 person-years, translating to a number needed to harm (NNH) of 63 person-years (1 additional excess AMI for every 63 patients treated for a year). In a sensitivity analysis, we utilized data from an unpublished meta-analysis of rosiglitazone trials that included studies with no outcome events in either treatment group, and to which the interim results from RECORD were added, and obtained a relative risk estimate of AMI for rosiglitazone vs. pioglitazone of 1.56, yielding a NNH of 100 person-years.

We also evaluated the literature from published and unpublished randomized controlled trials for the occurrence of heart failure in patients with T2DM treated with rosiglitazone or pioglitazone. Four separate meta-analyses of heart failure with rosiglitazone or pioglitazone have been published. These meta-analyses differed somewhat in their inclusion and exclusion criteria. The meta-analysis by Lago et al. examined studies of both rosiglitazone and pioglitazone while the meta-analysis by Singh et al. focused on rosiglitazone and that by Linkoff et al. and Mannucci et al. focused on pioglitazone. The summary relative risk for heart failure with rosiglitazone ranged between 2.09 and 2.14, while for pioglitazone, the summary relative risk ranged from 1.32 to 1.41, suggesting a difference in risk between the two TZDs, with a relative risk of about 1.5 favoring pioglitazone.

Based on mortality data from the FDA meta-analysis of rosiglitazone clinical trials, as well as data from ADOPT, DREAM and RECORD, the relative risk of all-cause mortality with rosiglitazone was 1.00 (95% CI 0.80-1.24) and for cardiovascular mortality, 1.00 (95% CI 0.69-1.43). It should be noted that ascertainment of deaths over time and duration of follow-up in these studies was probably inadequate since only one of these rosiglitazone trials was prospectively designed to capture cardiovascular outcomes. For pioglitazone, a meta-analysis of all randomized clinical trials of pioglitazone vs. comparator that included shorter-term studies in addition to data from the PROactive trial reported a hazard ratio for all-cause mortality of 0.92 (95% CI 0.76-1.11). From the data presented in that meta-analysis, it was not possible to estimate the hazard ratio for cardiovascular mortality with pioglitazone.

Rosiglitazone and pioglitazone have similar effects with regard to glycemic control. Both are associated with a comparable increase in body weight and body fat, a slight decrease in blood pressure, and an increased risk of bone fractures. There are clear differences in lipid effects produced by these agents. Rosiglitazone increases HDL-C levels by a small amount while increasing LDL-C and triglyceride levels by a sizable amount. Pioglitazone increases HDL-C levels more than twice as much as rosiglitazone, and increases LDL-C levels by about one-half as much. Pioglitazone, but not rosiglitazone, reduces triglyceride levels. Several animal studies suggest that both TZDs may prevent renovascular disease and proteinuria, and several studies in humans have reported a reduction in proteinuria. Concerns about bladder cancer with pioglitazone based on animal data and an imbalance of cases in PROactive have not been confirmed in observational studies or in ongoing clinical trials with pioglitazone. Both TZDs reduce the level of inflammatory biomarkers in the blood, and decrease in-stent restenosis after percutaneous coronary revascularization. Pioglitazone has been shown to reduce progression of carotid artery and coronary artery atherosclerosis.

In summary, there was no evidence that rosiglitazone confers any unique health benefit over pioglitazone while there was strong evidence that rosiglitazone confers an increased risk of AMI and

heart failure compared to pioglitazone. These increased risks have caused a substantial excess number of cases of AMI and heart failure that would not have occurred had pioglitazone been used instead. We conclude that the cardiovascular risks associated with rosiglitazone are excessive given the availability of a safer alternative and the absence of a compelling and unique health benefit that might justify its use.

From the prescription drug use data, it appears that a substantial majority of the medical community have reached a similar conclusion. Prior to May 2007, utilization patterns for rosiglitazone and pioglitazone were virtually identical. Today, rosiglitazone use accounts for about 25% of the TZD market. While some may argue that this fall-off in rosiglitazone use has resolved the public health problem, we disagree. At current levels of use, rosiglitazone continues to generate an excess of about 500 AMI cases and 300 heart failure cases per month, compared to what would occur if pioglitazone were used exclusively.

It should also be noted that in the year since the advisory committee meeting, several professional organizations have issued clinical management recommendations for diabetes. In late 2007, The Medical Letter® recommended that "as monotherapy for diabetes and as a second drug, a sulfonylurea or metformin is preferred. If a thiazolidinedione is chosen as a third drug, pioglitazone is preferred over rosiglitazone." A clinical practice review in Journal Watch®, a publication of the Massachusetts Medical Society, concluded that "current evidence suggests potential cardiotoxicity with rosiglitazone and potential cardioprotection with pioglitazone," and went on to recommend that "treatment with rosiglitazone should not be initiated in rosiglitazone-naïve patients." In 2008, the Drug and Therapeutics Bulletin concluded that "if a thiazolidinedione is thought to be necessary, pioglitazone is probably safer [than rosiglitazone]." To our knowledge, no professional organization has recommended that rosiglitazone be used in preference to pioglitazone.

In light of the findings of this review, we have serious reservations regarding a planned head-to-head cardiovascular outcomes trial of rosiglitazone vs. pioglitazone as we believe equipoise does not exist with regard to cardiovascular risks. There are a number of different working definitions of "equipoise" but in general, they all require that there be equal evidence favoring both therapies. But that is not the case here because a credible case cannot be made that rosiglitazone is safer than or preferable to pioglitazone. The Belmont Report concluded that for clinical research to be ethical, the risks to subjects must be outweighed by the sum of the anticipated benefits to the subject. The proposed clinical trial of rosiglitazone vs. pioglitazone fails this standard of "positive expected value" because the two drugs are equivalent with respect to glycemic control but are likely very different with respect to risks and harms. Trials in which study subjects have a very low probability of experiencing a meaningful health benefit, but would be subjected to "non-negligible risk of serious harm" have been labeled "bad deal" trials in the literature. Such trials are unethical and are always exploitative. Based on these concerns, the proposed head-to-head trial of rosiglitazone vs. pioglitazone would be unethical and exploitative.

The cardiovascular risks of rosiglitazone use are serious and exceed those for pioglitazone based on the best available evidence. The documented "benefits" of these drugs are comparable. Rosiglitazone confers no unique and medically important benefit that distinguishes it from pioglitazone. The risks of rosiglitazone use exceed its benefits compared to pioglitazone. Rosiglitazone should be removed from the market.

1 BACKGROUND

1.1 INTRODUCTION

Type 2 diabetes mellitus (T2DM) affects over 20 million Americans, representing 7% of the US population.[1] It is a an important risk factor for cardiovascular disease, particularly acute myocardial infarction (AMI).[1-3] The risk of cardiovascular disease is increased 2-4-fold in patients with T2DM, and accounts for 65% of deaths in this group.[1-3]

While a primary goal of therapy for T2DM is the prevention of vascular complications,[4] careful control of blood glucose levels has not been shown to reduce the occurrence of cardiovascular disease or mortality. The UK Prospective Diabetes Study (UKPDS) randomized 3,867 patients with newly diagnosed T2DM to intensive therapy with sulfonylureas or insulin, or conventional therapy (diet + oral therapy as needed to maintain fasting plasma glucose below 15 mmol/L), and followed them for up to 10 years for the occurrence of a variety of macro- and microvascular outcomes.[5] The relative risk (RR) of AMI in the intensively-treated group was 0.84 (95% CI 0.71-1.00, p=0.052); for stroke 1.11 (95% CI 0.81-1.51); for diabetes-related death 0.90 (95% CI 0.73-1.11); and for all-cause mortality 0.94 (95% CI 0.80-1.10).[5] For microvascular complications (retinopathy requiring photocoagulation, vitreous hemorrhage, and fatal or nonfatal kidney failure), the relative risk was 0.75 (95% CI 0.60-0.93, p=0.01). Within a subgroup of 753 overweight patients enrolled in the UKPDS, intensive therapy with metformin (n=342) vs. conventional therapy (n=411) was evaluated.[6] In this patient population, metformin reduced the risk of AMI (RR=0.61; 95% CI 0.41-0.89), diabetes-related death (RR=0.58; 95% CI 0.37-0.91), and all-cause mortality (RR=0.64; 95% CI 0.45-0.91).[6] However, in overweight patients treated with metformin + sulfonylurea, the risk of diabetes-related death was increased (RR=1.96; 95% CI 1.02-3.75) compared with sulfonylurea alone. No subsequent clinical trials have been performed that demonstrate a protective effect of oral therapy, particularly metformin, on the risk of major cardiovascular events or cardiovascular or all-cause mortality. Recently, the intensive treatment arm (HbA1c < 6.0%) of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was prematurely terminated due to an increase in all-cause and cardiovascular mortality compared to patients treated less intensively.[7]

1.2 THIAZOLIDINEDIONE HISTORY

The first thiazolidinedione (TZD) to be marketed in the US, troglitazone, was withdrawn from the market as an "outmoded" drug in 2000, after two newer TZDs, rosiglitazone and pioglitazone, were found to not increase the risk of acute liver failure, based on analysis of spontaneously reported cases to FDA.[8,9] Since then, both TZDs have been shown to increase the risk of new-onset heart failure and to worsen pre-existing heart failure.[10-14] A meta-analysis of randomized clinical trials found that while both TZDs increased the risk of heart failure, rosiglitazone (RR= 2.18; 95% CI 1.44-3.32) was significantly worse than pioglitazone (RR=1.32; 95% CI 1.04-1.68; p-value for heterogeneity = 0.01).[15]

In early 2007, a study-level meta-analysis of clinical trials of rosiglitazone found a 43% increase in risk of AMI and a 64% increase in risk of cardiovascular death with rosiglitazone compared to comparator therapy.[16] The FDA performed a patient-level meta-analysis of rosiglitazone clinical trials and found that rosiglitazone was associated with a 40% increase in ischemic myocardial events.[17]

1.3 New Developments since FDA Advisory Committee Meeting

In July 2007, an FDA advisory committee voted to keep rosiglitazone on the market,[18] and subsequently, myocardial ischemia was added as a boxed warning to the rosiglitazone label.[19] The manufacturer, GlaxoSmithKline, was also asked to perform a cardiovascular outcomes trial of rosiglitazone vs. other oral therapies, with a secondary analysis of rosiglitazone vs. pioglitazone.

During the past year, several new meta-analyses of randomized controlled trials addressing the issues of AMI and heart failure risk with rosiglitazone and pioglitazone have been published. In addition, a number of observational studies with direct comparison of rosiglitazone vs. pioglitazone for the occurrence of AMI have become available.

The purpose of this review is to assess new information that has become available since the July 2007 advisory committee meeting, place it in the context of information discussed at that advisory meeting, and formulate a conclusion about the relative benefits and risks of rosiglitazone compared to pioglitazone.

2 METHODS AND MATERIALS

2.1 Randomized Controlled Clinical Trials

A literature review was performed using PubMed to identify published clinical trials or meta-analyses of clinical trials addressing cardiovascular risk with rosiglitazone, pioglitazone, or both if individually described. Details of trial design and results were abstracted and summarized. Studies grouping both TZDs together and not reporting findings for rosiglitazone and pioglitazone separately were excluded. The reference lists of these publications were also reviewed for publications that may not have been identified through PubMed.

2.2 Observational Studies

A literature review was performed using PubMed to identify published observational studies addressing cardiovascular risk with rosiglitazone, pioglitazone, or both if individually described. Details of study design and results were abstracted and summarized. Studies grouping both TZDs together and not reporting findings for rosiglitazone and pioglitazone separately were excluded. The reference lists of these publications were also reviewed for publications that may have not been identified through PubMed. In addition, two unpublished observational studies with partial results available to us were included in this analysis.

2.3 Summary and Meta-analysis

The main findings from randomized controlled trials, meta-analyses of controlled trials, and observational studies were reviewed and summarized. Using a fixed-effects model, a meta-analysis was performed using results from published meta-analyses or randomized controlled trials and separately for published observational studies, published abstracts of observational studies, and unpublished observational studies of which FDA had knowledge and access to study results.[20] A cumulative meta-analysis was also performed in which studies were entered into the analysis in order of publication date.[21] Studies were assessed for heterogeneity using the Q and I^2 statistics.[22,23] While the Q statistic yields a p-value for heterogeneity, the I^2 statistic describes the degree of variability between contributing studies that are not explained by chance. Values $\leq 25\%$ suggest that only a small degree of inconsistency is not explained by chance, while values $\geq 75\%$ suggest a very high degree of inconsistency between studies. Funnel plots and Egger's test for publication bias were also performed.[24] Stata version 7 (Stata Corporation, College Station, TX) was used for all analyses.

2.4 DRUG UTILIZATION

Prescription data from Verispan were obtained for rosiglitazone and pioglitazone for the period from marketing to the present.[25] For the years 1999-2006, annual prescription counts were collected, and for 2007-present, monthly prescription counts were collected to track the effect of scientific publications, publicity, and regulatory actions on product use.[25]

2.5 EXPERT OPINION: PUBLISHED LITERATURE REVIEW

A literature review was performed using PubMed to identify recent editorials or expert reviews assessing relative benefits versus risks of rosiglitazone and pioglitazone, to facilitate comparison of the two agents. An annotated bibliography is presented in the Appendix (section 9.1).

3 RESULTS

3.1 RANDOMIZED CONTROLLED CLINICAL TRIALS

3.1.1 Summary of published randomized clinical trials of rosiglitazone

The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006; 368(9541):1096-105. Erratum in: Lancet. 2006 Nov 18; 368(9549):1770[11]

The DREAM trial was an international, randomized, double-blind, 2x2 factorial design trial involving 5,269 participants with impaired glucose tolerance and/or impaired fasting glucose (pre-diabetes). Patients were randomized to rosiglitazone or placebo and independently randomized to ramipril or placebo. Results showed a statistically significant increased risk of confirmed heart failure in subjects randomized to rosiglitazone compared to placebo (0.5% vs. 0.1%, HR=7.03 (95% CI 1.60-30.9), p=0.01). Although not statistically significant, a consistent trend toward increased cardiovascular adverse events was noted in the rosiglitazone-treated group, including AMI (0.6% vs. 0.3%, HR=1.66, 95% CI 0.73-3.80), cardiovascular death (0.5% vs. 0.4%, HR=1.20, 95% CI 0.52-2.77), new angina (0.9% vs. 0.8%, HR=1.20, 95% CI 0.66-2.17), and revascularization (1.3% vs. 1.0%, HR=1.29, 95% CI 0.78-2.14). A between group comparison for the composite outcome of cardiovascular death, nonfatal AMI, or nonfatal stroke showed a non-statistically significant hazard ratio of 1.39 (95% CI 0.81-2.37) and a comparison for the composite of all cardiovascular events showed a hazard ratio of 1.37 (95% CI 0.97-1.94, p=0.08) which approached statistical significance. Ramipril did not show an effect on the occurrence of AMI, stroke, or cardiovascular death. A concern was raised about the possibility of an interaction between rosiglitazone and ramipril on the occurrence of cardiovascular outcomes, but the authors reported that an interaction was not present (p=0.07). The data for various cardiovascular outcomes from DREAM are shown in table 1 below, stratified by factorial arm.[26]

Table 1. Distribution of cardiovascular outcomes from the DREAM trial, stratified by factorial arm of treatment assignment.

	Ramipril + Rosiglitazone N=1310		Ramipril Only N=1313		Rosiglitazone Only N=1325		Placebo N=1321	
	N	%	N	%	N	%	N	%
CV Composite	45	3.4	24	1.8	32	2.4	32	2.4
MI	11	0.8	3	0.2	5	0.4	6	0.5
Stroke	2	0.2	2	0.2	5	0.4	3	0.2
All Death	15	1.1	16	1.2	15	1.1	17	1.3
CV Death	7	0.5	5	0.4	5	0.4	5	0.4
Revasc	18	1.4	10	0.8	19	1.4	19	1.4
New Angina	15	1.1	9	0.7	9	0.7	11	0.8
CHF	11	0.8	1	0.1	3	0.2	1	0.1

There were several limitations to this study. Patients with a history of cardiovascular disease or heart failure were excluded from the trial. Also, the number of cardiovascular events was low as would be expected in a population of pre-diabetic patients. There were only 23 AMI events and only 55 events for the composite outcome of cardiovascular death, nonfatal AMI, or nonfatal stroke.

Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone,metformin, or glyburide monotherapy. N Engl J Med 2006; 355(23):2427-43[27]

and

Food and Drug Administration. FDA Briefing Document. Division of Metabolism and Endocrine Products and Office of Surveillance and Epidemiology. Joint meeting of the EMDAC and DSaRM held on July 30, 2007. Available at: http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-02-fda-backgrounder.pdf[28]

ADOPT was a multi-center, randomized, double-blind, controlled clinical trial to evaluate the effect of monotherapy with rosiglitazone, metformin, or glyburide on duration of glycemic control. Patients were recently diagnosed with T2DM (duration < 2 years in 96%). This study was not designed as a cardiovascular outcomes trial and cardiovascular events other than heart failure were not pre-specified or centrally adjudicated. Although this study followed patients for 5 years, there were only 161 cardiovascular events of which 68 were AMI. There were 96 deaths from any cause, with 17 due to cardiovascular causes.

While relative risks for particular cardiovascular events were not presented in the published manuscript,[27] some were presented in FDA's analysis[28,29] and published meta-analyses.[30] Total person-years of exposure follow-up were 4,954 for rosiglitazone, 4,906 for metformin, and 4,244 for glyburide. The risk of AMI was non-statistically significantly increased for rosiglitazone vs. metformin (RR=1.3; (95% CI 0.7-2.3)[28,29] and for rosiglitazone vs. glyburide (RR=1.6; (95% CI 0.8-3.1).[28,29] For rosiglitazone vs. metformin or glyburide, the relative risk of AMI was 1.4 (95% CI 1.1-1.9).[30] For all-cause mortality, the relative risk for rosiglitazone vs. metformin or glyburide was 1.00 (95% CI 0.63-1.54).

Of note, the risk of congestive heart failure was equal for patients treated with rosiglitazone and metformin (RR=0.99, 95% CI 0.51-1.94) but was substantially greater compared with glyburide (RR=2.42, 95% CI 1.07-5.97, p=0.02).

The most important limitations of this trial were that it was conducted in T2DM patients at relatively low risk of cardiovascular disease, there was not a systematic adjudication process for cardiovascular events, and there was an overall drop-out rate of 40%, with no follow-up for outcomes after drop-out.. Event rates were very low, compromising statistical power. Also, ascertainment of cardiovascular events was probably incomplete.

Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones JP, et al. Rosiglitazone evaluated for cardiovascular outcomes - an interim analysis. N Engl J Med 2007; 357(1):28-38[12]

RECORD is a randomized, open-label cardiovascular outcomes trial comparing T2DM patients treated with metformin *or* sulfonylurea + rosiglitazone vs. patients treated with metformin + sulfonylurea without rosiglitazone. An unplanned interim analysis of this trial was conducted and published in 2007 due to concerns about myocardial ischemia risk with rosiglitazone. The analysis included 2,220 patients randomized to add-on rosiglitazone, and 2,227 randomized to the combination of metformin + sulfonylurea (control group). The primary endpoint was hospitalization or death from cardiovascular causes (AMI, congestive heart failure, stroke, unstable angina, unplanned cardiovascular revascularization, amputation of extremities, or any other definite cardiovascular reason). Interim results showed 217 patients in the rosiglitazone group and 202 patients in the control group with the primary endpoint (HR 1.08, 95% CI 0.89 – 1.31). The risk of AMI was non-statistically significantly increased with rosiglitazone (HR=1.16, 95% CI 0.75-1.81) while there was no increase in the composite outcome of cardiovascular death, all-cause mortality , nonfatal AMI, or nonfatal stroke (HR=0.97, 95% CI 0.73-1.29), or in the individual outcomes of cardiovascular death (HR=0.83, 95% CI 0.51-1.36) or all-cause mortality (HR=0.93, 95%CI 0.67-1.27). Rosiglitazone was associated with an excess risk of heart failure (HR 2.15, 95% CI 1.30 – 3.57).

There are a number of limitations to this trial. It is open-label, the primary outcome is extremely broad and non-specific, and the study population was relatively healthy with respect to the expectation of future cardiovascular events (only 17% of enrolled subjects had a history of ischemic heart disease, most of which was stable angina, and less than 1% had a past history of congestive heart failure). As a consequence, the number of AMI events was low (n=80), emphasizing the low statistical power of this study.

Gerstein HC, Miller ME, Byington RP, Goff DC, Bigger T, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358(24):2545-59[7]

ACCORD trial was a randomized controlled trial to evaluate the effect of intensive glycemic control on the occurrence of cardiovascular events and mortality. The mean age of patients enrolled in the trial was 62 years and 35% had a history of a prior cardiovascular event. Using a double 2x2 factorial design (intensive blood pressure control and lipid control were also studied), 5,128 patients were randomized to intensive glycemic control (HbA1c < 6%) and 5,123 to standard control (HbA1c 7%-7.9%). For the primary outcome of nonfatal AMI, nonfatal stroke, and cardiovascular death, the hazard ratio with intensive therapy was 0.90 (95% CI 0.78-1.04, p=0.16). All-cause mortality and cardiovascular mortality were both statistically significantly increased in the intensive therapy group (all-cause: HR=1.22, 95% CI 1.10-1.46, p=0.04; cardiovascular mortality: HR=1.35, 95% CI 1.04-1.76, p=0.02).

This trial was not designed to assess the effect of TZDs. However, a series of post hoc exploratory analyses were reportedly conducted to examine the effect of individual medications and combinations of medications. Rosiglitazone was used by 91% of patients in the intensive therapy group and by 58% in the standard therapy group. A brief comment in the published paper stated, "Preliminary nonprespecified exploratory analyses of…differences in the use of drugs

(including rosiglitazone) did not identify an explanation for the mortality finding." Pioglitazone was used by only a handful of patients.

One of the major limitations of this study is that it was not designed to assess the effect of rosiglitazone or pioglitazone on the occurrence of cardiovascular events, particularly AMI. The observed event rate in this trial was substantially lower than expected, reducing study power. More importantly, the use of rosiglitazone was non-random, and the statistical power to draw reliable conclusions about cardiovascular risk with this specific agent was low.

Duckworth WC, McCarren M, Abraira C. Glucose control and cardiovascular complications: the VA Diabetes Trial. Diabetes Care 2001; 24(5):942-45[31]

and

Duckworth WC, Moritz TE. Press conference. 68th Scientific Meeting of the American Diabetes Association, San Francisco, CA, June 8, 2008. Available at: http://www.medpagetoday.com/MeetingCoverage/ADA/tb/9749. Accessed June 23, 2008[32]

The Veterans Affairs Diabetes Trial (VADT) was a randomized controlled trial examining the effect of intensive glycemic control (mean HbA1c = 6.9%) vs. standard therapy (mean HbA1c = 8.4%) on the occurrence of cardiovascular events or death. A total of 1,791 patients were enrolled, with a mean age of 60 years and mean duration of diabetes of 10 years. Forty percent of patients had a history of a prior cardiovascular event. Rosiglitazone was used by 85% of patients in the intensive group and 78% in the standard therapy group. There was no significant reduction in the hazard ratio for a cardiovascular event in the intensive therapy group (HR=0,87, p=0.12).

An unplanned, post hoc case-control analysis was performed to evaluate the effect of rosiglitazone on the occurrence of cardiovascular events. Specific results were not presented but during a press conference, two co-authors stated that cardiovascular risk was not increased with rosiglitzone.

There are many limitations to this study. First, the results could not be closely examined. The study was underpowered for its primary comparison (intensive vs. standard therapy) because there were from 150-200 fewer outcome events than originally planned. Given the high level of use of rosiglitazone in both the intensive and standard therapy groups, the statistical power to show an increased risk with rosiglitazone would be extremely low. Further, the post hoc nature of the analysis and the methods related to the analysis were problematic. Pioglitazone was apparently used rarely or not at all.

Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007; 356(24):2457-71[16]

The authors conducted a meta-analysis of publicly available data from clinical trials involving rosiglitazone with data relevant to cardiovascular morbidity and mortality. The authors identified 42 trials (inlcuding DREAM[11] and ADOPT[27]) that met their inclusion criteria: study duration > 24 weeks, a randomized control group not receiving rosiglitazone, and the availability of outcome data for AMI and cardiovascular death. A fixed-effects model was used for the analysis. The odds ratio for myocardial infarction was 1.43 (95% CI 1.03–1.98, p=0.03) in subjects randomized to rosiglitazone compared to the control therapy. The odds ratio for death from cardiovascular causes was 1.64 (95% CI 0.98-2.74, p=0.06). In a non-pre-specified analysis, the odds ratio for all-cause mortality was 1.18 (95% CI 0.89-1.55).

There were several limitations to this study. The authors did not have patient-level data and had to rely on summarized trial-level data for their analysis. Most of the trials did not centrally adjudicate cardiovascular events, and many of the trials were small and of relatively short duration.

Mele J. Statistical review and evaluation of rosiglitazone clinical trials (meta-analysis). US Food and Drug Administration, June 4, 2007. Available at: http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-02-fda-backgrounder.pdf, pp 13-105. Accessed May 30, 2008[17]

A separate meta-analysis of patient level clinical trial data submitted by GSK was conducted by FDA of shorter-term randomized controlled trials that excluded the long-term trials, DREAM[11] and ADOPT.[27] Studies (n=42) were combined into meta-groups based on similarity of design (table 2).

Table 2. Meta-groups of rosiglitazone use as reported in the FDA review document, page 12.

Meta-group	Control	Number of studies	Number of Patients
Monotherapy RSG	PLA or MET or SU	15	4,236
RSG+Background Medications	PLA	3	479
RSG+Sulfonylurea	PLA+SU	14	4,245
RSG+Metformin	PLA+MET or SU+MET	10	3,469
RSG+Insulin	PLA+INS	5	1,530
RSG+Metformin+Sulfonylurea	PLA+MET+SU	1	837

Odds ratios and risk differences for total ischemic events by meta-group are summarized in table 3 and figure 1 below (reproduced from pages 26 and 27 of the review document). For cardiac ischemic events, the odds ratio was increased for rosiglitazone across all meta-groups combined (OR=1.4, 95% CI 1.1-1.8) and was particularly increased in combination with insulin (OR=2.1, 95% CI 0.9-5.1, p=0.07) and in combination with metformin (OR=3.2, 95% CI 1.2-9.8, p=0.01).

The odds ratio for all-cause mortality was increased in rosiglitazone-treated patients (OR=1.7, 95% CI 0.8-3.4, p=0.15), ischemic heart disease without heart failure (OR=1.3, 95% CI 0.5-3.5, p=0.60), and ischemic heart disease plus heart failure (OR=1.6, 95% CI 0.7-3.8, p=0.40). None of these reached traditional levels of statistical significance.

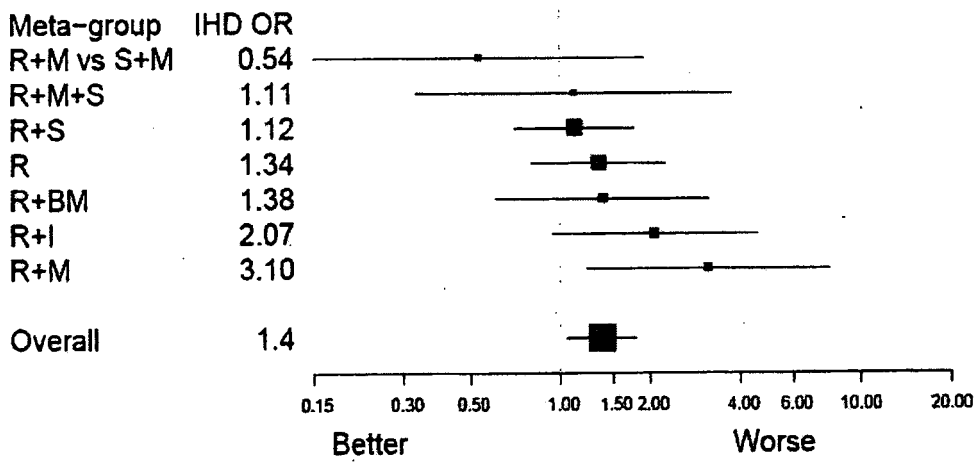
Table 3. Summary of myocardial ischemic events in 7 meta-groups corresponding to rosiglitazone use in different therapeutic combinations.

Table 3.3.8 Summary of the ischemic events results in 7 meta-groups

RSG GROUP	RSG events/N	CONTROL events/N	RD (95% CI)	OR (95% CI)
R+M vs S+M	4/274 (1.5%)	7/260 (2.7%)	**-1.3% (-3.8%, +1.2%)**	**0.5 (0.1, 2.1) [p=0.37]**
R+M+S	9/561 (1.6%)	4/276 (1.4%)	**+0.2% (-1.6%, +1.9%)**	**1.1 (0.3, 5) [p>0.99]**
R+S	47/2413 (1.9%)	32/1832 (1.7%)	**+0.6% (-0.3%, +1.5%)**	**1.4 (0.8, 2.3) [p=0.20]**
R	51/2687 (1.9%)	22/1549 (1.4%)	**+0.4% (-0.5%, +1.2%)**	**1.3 (0.7, 2.1) [p=0.28]**
R+BM	15/240 (6.2%)	11/239 (4.6%)	**+1.7% (-2.3%, +5.7%)**	**1.4 (0.6, 3.5) [p=0.42]**
R+I	24/867 (2.8%)	9/663 (1.4%)	**+1.4% (-0.1%, +2.9%)**	**2.1 (0.91, 5.1) [p=0.07]**
R+M	21/1562 (1.3%)	6/1373 (0.4%)	**+0.9% (+0.2%, +1.7%)**	**3.2 (1.2, 9.8) [p=0.01]**
Overall Weighted by meta-groups	171/8604 (2.0%)	85/5633 (1.5%)	**+0.5% (+0.1%, +1%)**	**1.4 (1.1, 1.8) [p=0.02]**

Figure 1. Summary of odds ratios of myocardial ischemia in association with rosiglitazone use by meta-group and overall.

Figure 3.3.12 Forest plot of odds ratios (±95% CI) for IHD by meta-group ordered by OR



Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA 2007; 298(10):1189-95[30]

This was a meta-analysis of randomized controlled trials of at least 12 months duration comparing treatment with rosiglitazone vs. comparator therapies. Four studies met the inclusion criteria for this analysis, including DREAM,[11] ADOPT,[27] and RECORD.[12] The analysis was based on 6,421 patients treated with rosiglitazone and 7,870 controls. There were a total of 94 AMI events with rosiglitazone and 83 among the controls (RR=1.42, 95% CI 1.06-1.91). For cardiovascular death, there were 59 with rosiglitazone and 72 among controls (RR=0.90, 95% CI 0.63-1.26). For congestive heart failure, there were 102 events with rosiglitazone and 62 among controls (RR=2.09, 95% CI 1.52-2.88). There was minimal heterogeneity among the four contributing studies.

The most important limitation of this study was that patient-level data were not available, precluding an analysis of time-to-event.

3.1.2 Summary of published randomized clinical trials of pioglitazone

Dormandy JA, Charbonnel B, Eckland DJA, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005; 366(9493):1279-89[10]

A total of 5,238 patients 35 to 79 years of age with HbA1c levels greater than 6.5% despite treatment with diet alone or with oral glucose-lowering agents with or without insulin were randomized to treatment with pioglitazone (n = 2,605) or placebo (n = 2,633), in addition to baseline treatment. Enrollment criteria included a history of "extensive macrovascular disease" although patients with NYHA class II heart failure or worse were excluded from study participation. Mean observation time was 34.5 months. The primary endpoint was the time from randomization to the first occurrence of any of the following: all-cause mortality, nonfatal MI (including silent infarction), stroke, acute coronary syndrome (ACS), cardiac intervention (including coronary artery bypass graft (CABG) or percutaneous coronary intervention(PCI)), leg revascularization, or amputation above the ankle. At least one event in the primary composite endpoint was observed in 514 patients in the pioglitazone group and 572 patients in the placebo group (HR 0.90, 95% CI 0.80 – 1.02, p=0.095). The main secondary endpoint (composite of all cause mortality, nonfatal MI, and nonfatal stroke) was reached in 301 pioglitazone-treated patients, and 358 patients receiving placebo (HR 0.84, 95% CI 0.72 – 0.98, p=0.027). The hazard ratio for nonfatal AMI was also reduced but not significantly so (HR=0.83, 95% CI 0.65-1.06). There was no effect on all-cause mortality (HR=0.96, 95% CI 0.78-1.18). A statistically significant excess risk of heart failure was observed in subjects randomized to pioglitazone, with 11% of subjects in the pioglitazone group experiencing heart failure, compared to 8% of subjects in the placebo group (HR=1.42, 95% CI 1.19-1.70, p<0.0001). There was no between-group difference in mortality rates from heart failure.

There were several limitations. The secondary outcome, while specified prior to data analysis, was not specified at the time the original protocol was written or prior to initiation of patient recruitment. The choice of a primary outcome involving 3 separate vascular beds and including an overly broad array of conditions was problematic. While the patient population studied represented the most severe end of the spectrum in terms of underlying vascular disease, and hence may not be representative of patients with less severe or mild underlying cardiovascular disease, one would expect this population to be a sensitive indicator of drug-related cardiovascular toxicity.

Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus. A meta-analysis of randomized trials. JAMA 2007; 298(10):1180-88[33]

This was a patient-level meta-analysis of 19 randomized controlled trials of pioglitazone (n=8,554) vs. comparator (n=7,836), including PROactive.[10] The primary outcome was all-cause mortality, nonfatal AMI, or nonfatal stroke, but results for individual components were also presented. There were 825 primary outcome events (pioglitazone: 375, control: 450), of which 290 were AMIs. The hazard ratio of AMI for pioglitazone vs. control was 0.81 (95% CI 0.64-1.02), for stroke, 0.80 (95% CI 0.62-1.04), and for all-cause mortality, 0.92 (95% CI 0.76-1.11). For the composite outcome of all-cause mortality, nonfatal AMI, or nonfatal stroke, the hazard ratio was statistically significantly reduced (HR=0.82, 95% CI 0.72-0.94). Similar results were obtained when stratified by PROactive (HR=0.84, 95% CI 0.72-0.98) and all other trials (HR=0.75, 95% CI 0.56-1.02). The hazard ratio for serious heart failure with pioglitazone was increased (HR=1.41, 95% CI 1.14-1.76). The heart failure finding was virtually identical in PROactive and all other trials.

The most important limitation of this study was that for most of the contributing trials, cardiovascular outcomes were not uniformly adjudicated or assessed using standardized definitions, and baseline predictors of cardiovascular events were not uniformly collected across all trials, precluding the ability to perform multivariate adjustment. Nonetheless, because these were randomized trials, the effect of these limitations on the overall findings should be minimal.

3.1.3 Summary of published randomized clinical trials of rosiglitazone compared to pioglitazone

Goldberg RB, Kendall DM, Deeg MA. Comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care 2005; 28(7):1547-54[34]

and

Misbin R. Medical officer review of GLAI study, NDA 210783. US Food and Drug Administration, April 23, 2007[35]

This was a 24 week randomized, controlled, double-blind study comparing rosiglitazone (n=402) to pioglitazone (n=400) for changes in lipid profile. Cardiovascular events were collected but not adjudicated. Case-report summaries were available for review in FDA documents. The treatment groups were well-balanced and equivalent at baseline. Similar levels of glycemic control were achieved. A number of differences in lipid profile changes were noted. Rosiglitazone use led to increased triglyceride levels as well as LDL-C particle concentration compared with decreases for pioglitazone (table 4, below). Additionally, rosiglitazone induced a larger increase in LDL-C levels and a smaller increase in HDL-C levels than pioglitazone. In the rosiglitazone cohort, there were 7 reported cardiovascular events (1 sudden death; 1 AMI; 4 emergency CABG; 1 unstable angina) for an incidence rate of 4.1 per 100 person-years. In the pioglitazone cohort, there were 2 reported cardiovascular events (1 AMI; 1 emergency CABG) for an incidence rate of 1.2 per 100 person-years. The relative risk of a reported cardiovascular event for rosiglitazone vs. pioglitazone was 3.52 (95% CI 0.67-34.7, p=0.11).

The most important limitation of this study is that it was designed to assess changes in lipid profile, not cardiovascular outcomes. The study was markedly underpowered to evaluate such outcomes and cardiac events were not adjudicated.

Table 4. Changes in glycated hemoglobin and lipid levels in patients treated with rosiglitazone (RSG) or pioglitazone (PIO). Source: GLAI.[32]

	RSG	PIO	p-value
HbA1c			
Baseline	7.5	7.6	
Change	-0.6	-0.7	0.13
Triglycerides, mg/dl			
Baseline	235	258	
Change	+13	-52	<0.001
HDL-C, mg/dl			
Baseline	40	39	
Change	+2.4	+5.2	<0.001
LDL-C, mg/dl			
Baseline	109	107	
Change	+21	+12	<0.001

3.2 OBSERVATIONAL STUDIES

3.2.1 Summary of published observational studies of rosiglitazone

McAfee AT, Koro C, Landon J, Ziyadeh N, Walker AM. Coronary heart disease outcome in patients receiving antidiabetic agents. Pharmacoepidemiol Drug Saf 2007; 16(7):711-25[36]

An observational study was conducted in the Ingenix Research Database, which covers ~23 million insured individuals across the US. Propensity-score matched cohorts of type 2 diabetic patients who were new users of monotherapy with rosiglitazone (RSG), metformin (M), or sulfonylurea (S); or dual oral therapy (RSG+M, RSG+S, M+S); or of oral therapy plus insulin (I) (RSG+I, other+I) were generated and analyzed using Cox proportional hazards modeling. There were 26,931 monotherapy-treated patients (8,977 per exposure cohort) followed for an average of 1.1 years; 4,086 dual therapy-treated patients (1,392 per exposure cohort) followed for an average of 1.2 years; and 2,346 oral plus insulin-treated patients (1,173 per exposure cohort) followed for an average of 1.7 years. The primary outcome was hospitalized AMI + coronary revascularization (CR), but separate analyses for AMI alone were presented. The study was funded by GSK, the manufacturer of rosiglitazone.

Among the comparisons for the composite outcome of AMI+CR, none were statistically significant except for the comparison of M vs. S (HR=0.77, 95% CI 0.62-0.97). For the outcome of AMI alone, the risk of AMI was increased in patients treated with RSG compared to M and reduced in patients treated with RSG compared to S, as monotherapy (table 5), but neither reached statistical significance. The risk of AMI with monotherapy M compared to S was significantly reduced. For dual therapy, the risk of AMI with RSG+S was increased compared to M+S, but did not reach statistical significance.

Table 5. Hazard ratios and 95% confidence intervals for hospitalized acute myocardial infarction in patients treated with rosiglitazone (RSG), metformin (M) or sulfonylureas (S) as mono- or dual-therapy.

	Hazard ratio	95% CI
Monotherapy		
RSG vs. M	1.19	0.84-1.68
RSG vs. S	0.79	0.58-1.07
M vs. S	0.60	0.43-0.84
Dual therapy		
RSG+S vs. M+S	1.45	0.76-2.75

There were several limitations to this study. Pioglitazone was not included. Also, there were relatively few patients over the age of 64 and follow-up time was limited. The analysis counted outcome events during time not on therapy, which amounts to misclassification of exposure time, which will reduce the hazard ratios (bias towards the null).[37,38] Importantly, because propensity score matching was used, calculation of hazard ratios required a separate Cox regression model for each comparison, making cross-comparisons inappropriate because different data were used in each regression. As a result, the hazard ratio estimates could be inaccurate.

Wang CP, Haffner S, DeFronzo R, Pugh J. Differential rosiglitazone effects on cardiovascular disease in VA type 2 diabetes patients (abstract). Presented at the American Diabetes Association meeting, San Francisco, June 2008. Available at: http://scientificsessions.diabetes.org/index.cfm?fuseaction=Locator.SearchAbstracts&CalledByID=1052. Accessed July 23, 2008.[39]

This observational cohort study has been published only in abstract form and hence, a detailed description is not available. This study followed an observational cohort of 11,283 patients with T2DM within the VA health care system. They evaluated patients on various antidiabetic treatment regimens for the occurrence of ischemic heart disease (UKPDS definition) or stroke. For patients without cardiovascular disease at baseline, rosiglitazone increased the risk of an outcome by 28% (95% CI 6%-54%) compared to treatment with the combination of sulfonylurea + metformin. For patients with established cardiovascular disease at baseline, rosiglitazone use increased the risk of an outcome by 27% (95% CI 0.01% - 64%). The analysis was adjusted for age, race, diabetes duration, body weight, HbA1c, blood pressure, cholesterol level, and use of ACE inhibitors or statins.

3.2.2 Summary of published observational studies of pioglitazone

Xu Y, Vallarino R, Baran W, Spanheimer R. Risk of stroke and myocardial infarction is reduced in patients with type 2 diabetes treated with pioglitazone: results of a retrospective, claims-based study (abstract). Diabetologia 2007; 50(Suppl 1):S513-14[40]

This observational cohort study has been published only in abstract form and hence, a detailed description is not available. The study was performed by Takeda, the manufacturer of pioglitazone, using the i3 Innovus database (Ingenix) covering ~24 million lives during the study period, 2003-2006. This study compared T2DM patients age 45 and older treated with pioglitazone against those treated with non-TZD agents, for occurrence of AMI or stroke. Events during the first month of therapy were excluded from analysis. For AMI, the hazard ratio for pioglitazone vs. non-TZD agents was 0.62 (95% CI 0.50-0.77). For stroke, the hazard ratio was 0.80 (95% CI 0.72-0.89).

Because of the abstract format, a detailed description of study methods was not available. The reason for excluding outcome events during the first month of therapy was not given and it would be preferable to analyze all events. Similarly, details about cohort characteristics, variables used for adjustment, and analysis methods were not provided. The outcomes were not validated, although AMI has been well-validated in the Ingenix database in the past.

3.2.3 Summary of published or fully reported observational studies of rosiglitazone compared to pioglitazone

Lipscombe LL, Gomes T, Lévesque LE, Hux JE, Juurlink DN, Alter DA. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. JAMA 2007; 298(22):2634-43[41]

This was an observational study using healthcare databases for the province of Ontario, Canada, covering patients with type 2 diabetes mellitus over the age of 65 years. Patients with TZD use were compared together, and separately for rosiglitazone (RSG) and pioglitazone (PIO), against patients treated with combination oral therapy (mostly metformin+sulfonylurea) using a nested case-control approach, with 5 controls per case matched on age, gender, duration of diabetes, history of heart failure (HF) or AMI, and other prior cardiovascular disease. Outcomes of interest included HF, AMI, and all-cause mortality. From a base cohort of 159,026 elderly patients with T2DM, 12,491 cases of HF, 12,578 cases of AMI, and 30,265 deaths from any cause were observed during a median follow-up of 3.8 years.

Use of TZDs as mono- or combination-therapy increased the risk of HF. This increase in risk was limited to rosiglitazone use and was not observed with pioglitazone (RSG mono: OR=1.98, 95% CI 1.44-2.72; RSG+other: OR=1.43, 95% CI 1.25-1.63; PIO mono: OR=0.91, 95% CI 0.52-1.59; PIO+other: OR=1.09, 95% CI 0.90-1.32). TZD use increased AMI risk as monotherapy but not in combination with other medications including insulin. This increase in AMI risk was due to rosiglitazone (RSG: OR=1.76, 95% CI 1.27-2.44; PIO: OR=0.73, 95% CI 0.40-1.36). Use of TZDs was also associated with an increased risk of all-cause mortality with both mono- and combination-therapy. For monotherapy, the increased risk was due to rosiglitazone use (RSG: OR=1.47, 95% CI 1.12-1.93; PIO: OR=0.94, 95% CI 0.61-1.45). For combination therapy, risk was increased with both TZDs, though the association reached statistical significance only with rosiglitazone (RSG: OR=1.26, 95% CI 1.10-1.44; PIO: OR=1.20, 95% CI 0.98-1.47). Of note, monotherapy with metformin or sulfonylurea was not associated with any increase in risk of HF or AMI, but was associated with a reduction in all-cause mortality.

Using data presented in the published manuscript, it was possible to estimate the crude, unadjusted odds ratio and 95% confidence intervals for the comparison of monotherapy with rosiglitazone vs. pioglitazone (table 6). To perform this analysis, we took the numbers of cases and controls exposed to either rosiglitazone or pioglitazone from Tables 3-5 in the Lipscombe et al. paper, and calculated the odds ratio for exposure to rosiglitazone vs. pioglitazone among these cases and controls. As would be expected, the odds ratio for rosiglitazone vs. pioglitazone was increased for HF, AMI, and all-cause mortality. Although these are unadjusted odds ratios, the likely similarity between patients treated with rosiglitazone and pioglitazone would mean that multivariable adjustment probably would not meaningfully alter the crude estimate. Also, as can be seen in Table 6, the lower bound of the 95% confidence interval for rosiglitazone excluded the point estimate for pioglitazone and the upper bound for pioglitazone excluded the point estimate for rosiglitazone. This is usually an indicator of a statistically significant difference.

Table 6. Comparison of odds ratios for heart failure, acute myocardial infarction, and all-cause mortality, with rosiglitazone, pioglitazone, and rosiglitazone (RSG) compared to pioglitazone (PIO), as monotherapy.

	Heart failure	AMI	All-cause mortality
Rosiglitazone[1]	1.98 (1.44-2.72)	1.76 (1.27-2.44)	1.47 (1.12-1.93)
Pioglitazone[1]	0.91 (0.52-1.59)	0.73 (0.40-1.36)	0.94 (0.61-1.45)
RSG vs. PIO[2]	2.21 (1.17-4.35)	2.43 (1.19-5.29)	1.57 (0.94-2.68)

[1] Fully adjusted estimates

[2] Crude, unadjusted estimates derived from data presented in the published manuscript.

The most serious limitation of this study was the relatively low number of pioglitazone-exposed cases and controls for each of the above outcomes, due to greater use of rosiglitazone than pioglitazone in Ontario during the period covered by this study. These relatively low numbers are reflected in the somewhat wide confidence intervals for the comparisons involving rosiglitazone and pioglitazone. Nonetheless, clear differences in risk associated with rosiglitazone compared to pioglitazone were demonstrated by the authors. Based on examination of confidence interval overlap and the 95% confidence intervals for the unadjusted comparisons, these differences are probably statistically significant. While residual confounding due to selection (channeling) bias may account for some of the differences observed when comparing all TZD use vs. other therapy, this bias does not account for the comparisons of rosiglitazone vs. pioglitazone. In this study, patients treated with rosiglitazone and pioglitazone were similar with respect to cardiovascular risk factors, making channeling bias unlikely to account for the differences seen. Another unresolved issue relates to the fact that an AMI effect for TZDs was observed with TZD monotherapy, but not combination therapy in this study. It should be noted that in the category of combination therapy, the risk of AMI was increased with rosiglitazone compared to pioglitazone, but the difference was not statistically significant (OR=1.16, 95% CI 0.92-1.47).

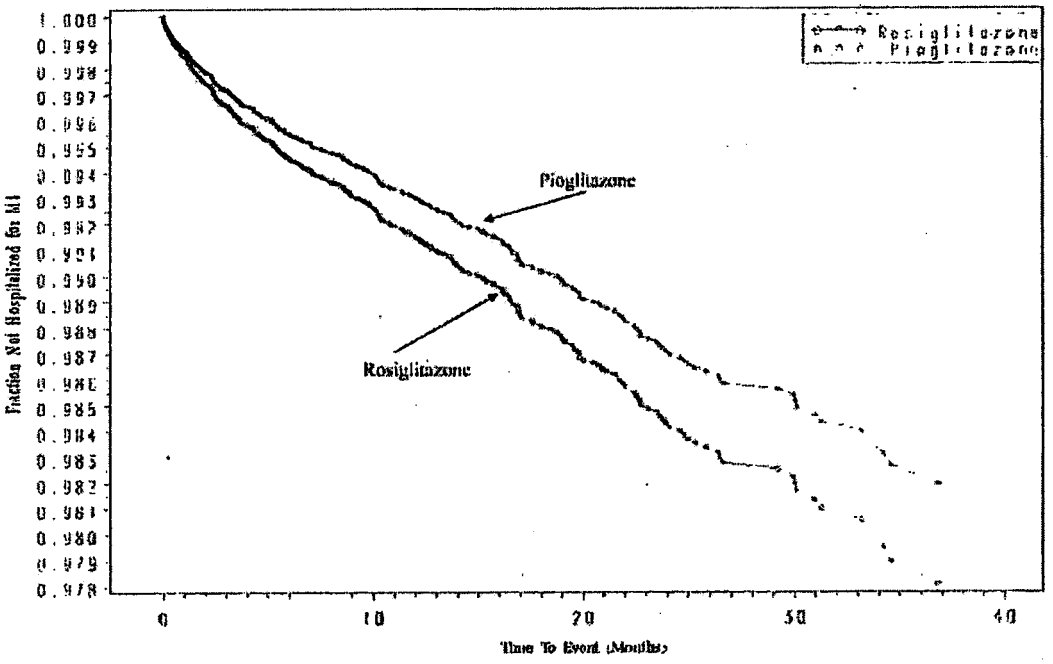
Finally, pioglitazone was not associated with HF in this study although randomized controlled trials suggest an increased risk of 30%-40%.[15,33] The relatively lower level of pioglitazone use in this database may have reduced the statistical power to identify the risk. Also, it is possible that the outcome definition, which included emergency department visits, may have been too broad, resulting in misclassification that masked an association. Such misclassification would also have affected rosiglitazone meaning that its risk for HF would be higher than found here. The comparison of rosiglitazone vs. pioglitazone should not be affected by such misclassification except to reduce the magnitude of the odds ratio for HF.[37]

Gerrits CM, Bhattacharya M, Manthena S, Baran R, Perez A, Kupfer S. A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes. Pharmacoepidemiol Drug Saf 2007; 16(12):1314-16[42]

This was a retrospective cohort study of T2DM patients, comparing incident (new) users of rosiglitazone vs. pioglitazone within the Ingenix Research Database for the years 2003-2006. Among 1.24 million patients with T2DM in the database, patients were excluded if age was below 45 years, if they had less than 6 months of enrollment in the insurance database prior to their first diagnosis of diabetes, or if they received no additional TZD prescriptions during the 6-months following their first TZD prescription (this will essentially exclude cases occurring during the first month of use). The primary outcome was hospitalized AMI.

There were 15,104 patients in the rosiglitazone cohort and 14,807 in the pioglitazone cohort, followed for an average of 1.3 years and 1.2 years respectively. The cohorts were well-balanced with respect to demographics, cardiovascular risk factors, and medical utilization. There was more concomitant use of metformin in the rosiglitazone cohort (55%) compared to the pioglitazone cohort (42%). There were 214 (1.4%) AMI events in the rosiglitazone cohort and 161 (1.1%) in the pioglitazone cohort. The hazard ratio, calculated as pioglitazone vs. rosiglitazone by the investigators, was 0.78 (95% CI 0.63-0.96). Rearranged to show rosiglitazone vs. pioglitazone, the hazard ratio was 1.28 (95% CI 1.04-1.59). Of note, a separation in survival curves was apparent by the second month (recall that events during the first month were excluded).

Figure 2. Adjusted survival analysis for hospitalized acute myocardial infarction with rosiglitazone and pioglitazone. Source: Gerrits et al. Pharmacoepidemiol Drug Saf 2007; 16(12):1314-16.[42]



The most important limitation of this study was that it excluded patients who received only one prescription for rosiglitazone or pioglitazone. However, this exclusion was applied to both cohorts.

Walker AM, Koro CE, Landon J. Coronary heart disease outcomes in patients receiving antidiabetic agents in the PharMetrics database, 2000-2007. Pharmacoepidemiol Drug Saf 2008; published online February 2008, DOI: 10.1002pds.1598[43]

A cohort study comparing rosiglitazone vs. pioglitazone was performed using the PharMetrics database, which includes data from over 80 health plans. Propensity score-matched cohorts of patients aged 18 or older with T2DM and treated with rosiglitazone, pioglitazone, metformin or sulfonylurea were created. The rosiglitazone and pioglitazone cohorts were similar

with respect to demographics and cardiovascular risk factors except that the pioglitazone cohort had more baseline dyslipidemia.

Two types of analyses were performed. The first involved analysis over the entire period of observation within the database, regardless of whether the patients continued to take a particular antidiabetic medication, thereby introducing substantial misclassification of exposure time.[37] The second analysis was confined to time while on therapy. For AMI, the hazard ratio for rosiglitazone vs. pioglitazone using all observation time within the database was 1.07 (95% CI 0.89-1.27). The hazard ratio for AMI using on-treatment time was 1.21 (95% CI 0.95-1.54).

There were a number of limitations to this study. Outcomes within the PharMetrics database have never been validated to our knowledge. The study population within this database had only a small number of patients over 64 years of age and a study based primarily on younger patients with lower expected AMI rates would reduce study power. Finally, the epidemiologically appropriate analysis was the on-treatment approach, as it appropriately accounts for exposure time and minimizes misclassification bias towards the null.[38,39]

Casscells SW, Granger E, Swedorske J, Goldhammer R, Shaheen M, Dorris J, et al. A comparison of select cardiovascular outcomes by antidiabetic prescription drug classes used to treat type 2 diabeted among military health system beneficiaries, fiscal year 2003-2006. Am J Ther 2008; 15(3):198-205[44]

This was a cross-sectional prevalence analysis of data from the US military health system beneficiaries TRICARE database for the years 2003-2006. The study team identified all patients dispensed a prescription for rosiglitazone, pioglitazone, or other antidiabetic agents (metformin, sulfonylurea, insulin, other) and within each group, identified all diagnoses of AMI (outpatient and inpatient) without regard for whether the patient was using the drug when the AMI diagnosis was made. Prior medical history was not collected; prior medication use was not ascertained; new users were not distinguished from prevalent users; current users were not distinguished from former users; person-time of exposure was not calculated; actual cohorts were not formed; and no adjustment was performed for imbalances in cardiovascular risk factors. Because of the study design, patients were frequently in multiple "exposure" groups at the same time regardless of whether they were still exposed to any of the medications to which groups they had been assigned. As a result, between-group comparisons are not valid.

Margolis DJ, Hoffstad O, Strom BL. Association between serious ischemic cardiac outcomes and medications used to treat diabetes. Pharmacoepidemiol Drug Saf 2008; published online: Jul 9 2008 DOI: 10.1002/pds.1630[45]

This was a retrospective cohort study of patients with diagnosed diabetes using The Health Information Network (THIN), an electronic medical record database from the UK that includes data from approximately 300 general practices. The study period was 2002-2006 and the primary outcome was a composite of AMI, cardiovascular death, unstable angina, and coronary revascularization or reperfusion. The antidiabetic medications studied included insulin, sulfonylureas, biguanides, meglitinides, and TZDs. The criteria for defining drug exposure were not described, but from other descriptions in the paper, it appears that follow-up began with a first prescription and may have continued until the end of 2006, regardless of whether the patient stopped the drug in the meantime. Two analyses were performed. The first was based on prevalent and incident treatment of diabetes, so that patients on particular agents at the time the study began were included regardless of duration of prior use. Patients who experienced outcome events and stopped their medications or died before the study began were not included. The second analysis was based only on incident users of the various antidiabetic agents, thereby reducing survival bias.

For the comparison of rosiglitazone vs. pioglitazone, the hazard ratio for the composite outcome was 1.0 (95% CI 0.8-1.3) in the prevalence cohort analysis and 1.1 (95% CI 0.7-1.7) for the inception (new user) cohort analysis.

There were many limitations to this study. First, no data relating to number of cases or amount of person-time of exposure for each diabetes drug were presented so it was not possible to replicate or assess the reported findings. While the diagnosis of AMI has been validated in THIN, the other components of the composite outcome used here have not been validated. The authors did not present the actual number of the component events comprising the composite outcome so it was not possible to assess whether there were sufficient AMI cases with the TZDs to provide stable estimates of risk. This study did not adjust for many important potential confounding factors such as cardiovascular or lipid-lowering medications and presented no data on cardiovascular risk factors. Most importantly, the definition of exposed time was not clearly defined. From the description given, it seems likely that unexposed time was added to exposed time, which would introduce misclassification bias that would tend to reduce or mask differences between TZDs.[38,39]

GSK study WE145available at: http://ctr.gsk.co.uk/Summary/rosiglitazone/studylist.asp[46]

This observational study was posted on the GSK clinical trials website and has been submitted for consideration of publication in a peer-reviewed journal. This study compared patients treated with rosiglitazone, pioglitazone, switchers from one to the other TZD, and other antidiabetic therapies (oral ± insulin) in the Integrated Healthcare Information System claims database of 41 million patients followed in managed care, with an average duration of follow-up of 22 months from 1999-2006. Our office is not familiar with this data resource, although a Google search revealed that this company is now a subsidiary of Ingenix, a company that our office is familiar with. It is not clear whether the database used for this study is completely different from the Ingenix Research Database, or also includes data from Ingenix.

Within a cohort of 891,901 patients with T2DM and no history of AMI in the year prior to cohort entry, a nested case-control study was performed. A total of 9,870 patients with hospital diagnosis of AMI were matched to 29,610 controls on age, gender, and duration of diabetes (how this was determined was not described). Current exposure was defined as any drug use within the 3 months preceding the date of AMI in cases, or the corresponding index date in controls. Analyses were adjusted for age, hypertension, hypercholesterolemia, and use of ACE inhibitors, β-blockers, diuretics, and nitrates. In a single regression model that adjusted for a variety of potential confounders and that used non-TZD antidiabetic therapy as the reference, the odds ratio for AMI with rosiglitazone was 1.02 (95% CI 0.94-1.11) and for pioglitazone was 0.90 (95% CI 0.80-0.98). Of note, the lower bound of the 95% confidence interval for rosiglitazone excluded the point estimate for pioglitazone and the upper bound for pioglitazone excluded the point estimate for rosiglitazone. This is usually an indicator of a statistically significant difference. Finally, using the numbers of cases and controls exposed to rosiglitazone or pioglitazone, the crude, unadjusted odds ratio for the comparison of rosiglitazone vs. pioglitazone was estimated, yielding an OR=1.14 (95% CI 1.03-1.27, p=0.01). It was not possible to derive an adjusted estimate of the odds ratio from the data presented.

There are several limitations to this study. The summary available to us is abbreviated and many details related to methods are not described. More importantly, the definition of current exposure has undoubtedly resulted in exposure misclassification because patients who stopped using a TZD up to 90 days before the AMI/index date were considered exposed when they were no longer using these medications. This created a particular type of exposure misclassification referred to as "immortal time bias" because the unexposed time between the end of exposure and the event, is by design, free from the possibility of the event (i.e., immortal).[47] Such

misclassification would mask an increased risk due to rosiglitazone and underestimate the "protective effect" of pioglitazone observed here. For the comparison of rosiglitazone vs. pioglitazone, this misclassification of exposure would cause underestimation of the excess risk of AMI with rosiglitazone.[37,47]

3.2.4 Summary of unpublished observational studies of rosiglitazone compared to pioglitazone

Miller DR, Christiansen C, Palnatti M, Lafrance JP, Pogach L, Cunningham FE. VA study of cardiovascular disease risks with use of rosiglitazone or pioglitazone. Manuscript in preparation[48]

Investigators within the Veterans' Health Administration conducted an observational study comparing rosiglitazone to pioglitazone for the occurrence of AMI. Between October 1999 and September 2004, 73,760 new TZD users and 543,026 new users of other antidiabetic medications were identified. Patients were excluded from the study if they had less than 6 months contact with the VA prior to initiating therapy for T2DM, or had prior heart failure, AMI, cardiac surgery, or kidney failure. Within the VA system, TZDs were recommended as 3rd-line therapy for diabetes, that is, for use by patients who had failed on monotherapy (1st-line) or dual oral therapy involving non-TZD medications (2nd-line). As 3rd-line therapy, add-on rosiglitazone or add-on pioglitazone were compared to non-TZD oral therapy plus add-on insulin.

Two analyses were performed. The first used standard Cox proportional hazards modeling with adjustment for HbA1c, renal function, and comorbidity index based on a composite of healthcare utilization, numerous diagnoses, and medication use. For AMI, the hazard ratio for add-on rosiglitazone vs. non-TZD + insulin was 0.98 (95% CI 0.88-1.09) and for add-on pioglitazone vs. non-TZD + insulin, the hazard ratio was 0.80 (95% CI 0.67-0.96). The hazard ratio for rosiglitazone + other oral vs. pioglitazone + other oral was 1.18 (95% CI 1.00-1.39). For the comparison of rosiglitazone + insulin vs. pioglitazone + insulin, the hazard ratio was 1.42 (95% CI 1.02-1.98). In the second analysis, propensity score matching was performed instead of conventional adjustment for covariates. For AMI, the hazard ratio for rosiglitazone + other oral vs. pioglitazone + other oral was 1.10 (95% CI 0.86-1.40), and for the comparison of rosiglitazone + insulin vs. pioglitazone + insulin, the hazard ratio was 1.53 (95% CI 1.08-2.16).

The most important limitation of this study is that we were unable to fully evaluate its design, methods, or analyses because a full write-up was not available for review. Details surrounding the propensity score approach are needed to assess whether it was performed properly.

Singh G, Graham DJ, Triadilopoulos G. Acute myocardial infarction risk in patients treated for type 2 diabetes within California Medicaid. Manuscript in preparation[49]

A nested case-control study was performed using the California Medicaid database. The base population cohort was defined as all patients age 40 years or older initiating oral antidiabetic therapy between 1997 and 2005. All cases of hospitalized AMI were identified and matched to 4 controls (non-cases) on age, gender, and time. Current exposure to rosiglitazone, pioglitazone, metformin, sulfonylurea, and various combinations of these drugs was compared to remote exposure to any diabetes therapy. Conditional logistic regression was performed with adjustment for over 30 potential confounding factors including aspirin use. Insulin was treated as a covariate.

From a cohort of 165,740 T2DM patients followed for 660,000 person-years, 6,643 AMI cases were identified and matched to 26,561 controls. For monotherapy, the odds ratios of AMI were: rosiglitazone: 1.32 (95% CI 1.12-1.54); pioglitazone: 1.03 (95% CI 0.87-1.21); metformin: 0.85 (95% CI 0.75-0.95); and sulfonylurea: 1.11 (95% CI 1.01-1.23). For the comparison of

rosiglitazone vs. pioglitazone, the odds ratio was 1.28 (95% CI 1.05-1.56). When combined with metformin, risk was not increased for rosiglitazone, pioglitazone, or sulfonylurea.

The most important limitation of this study was that AMI diagnoses were not validated. However, the algorithm used to identify cases (primary discharge diagnosis of AMI, hospitalization ≥ 3 days unless fatal) has been shown to have a positive predictive value of about 95%. Because of the case-control approach, incidence rates and time-to-event could not be determined. Also, out-of-hospital sudden death was not captured.

3.2.5 Summary of unpublished observational studies of rosiglitazone and pioglitazone not permitting direct comparison of the two drugs

Nussbaum SR. Risk for myocardial infarction in patients treated with thiazolidinediones. Presented at the joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, Gaithersburg, MD, July 30, 2007. Transcript and slides available at: http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4308s1-00-index.htm. Accessed June 5, 2008[50]

This observational study was presented using PowerPoint slides during the open public session of the July 30, 2007 advisory committee meeting to discuss cardiovascular risk with rosiglitazone. A retrospective cohort study was performed using data from 5 health plans within the WellPoint network of 14 plans. For the years 2001-2006, patients initiating rosiglitazone or pioglitazone were compared to patients treated with non-TZD antidiabetic medications. The primary outcome was a hospital or emergency department diagnosis of AMI. The secondary outcome was a hospital or emergency department diagnosis of AMI or ACS. Adjustment was made for several cardiovascular risk factors. The methods were not clearly described, but it appears that separate regression models were run for each comparison (rosiglitazone vs. other non-TZD; and pioglitazone vs. other non-TZD), rather than including both rosiglitazone and pioglitazone in a single regression model, which is the correct way to analyze these data.[36,51] No direct comparisons were made of rosiglitazone vs. pioglitazone.

There were 22,050 patients in the rosiglitazone cohort, 23,768 in the pioglitazone cohort, and 120,771 in the non-TZD cohort. The relative risk of a hospital or emergency department diagnosis of AMI for rosiglitazone vs. other non-TZDs was 0.95 (95% CI 0.66-1.36); and for pioglitazone vs. other non-TZDs 0.90 (95% CI 0.63-1.28). For the outcome of AMI + ACS, the relative risk for rosiglitazone was 1.16 (95% CI 0.96-1.40) and for pioglitazone was 0.91 (95% CI 0.72-1.16). Because a single regression was not performed and the data needed to make a direct comparison of the two TZDs were not provided, it was not possible to estimate the 95% confidence intervals for the relative risk of rosiglitazone vs. pioglitazone. Crude, unadjusted point estimates of the relative risk of AMI and AMI + ACS for rosiglitazone vs. pioglitazone for all use (mono- or combined-therapy) and as monotherapy are shown below (table 7). They were obtained by dividing the relative risk for rosiglitazone by that for pioglitazone for both outcomes.

Table 7. Point estimates of the relative risk of acute myocardial infarction (AMI) with and without acute coronary syndrome (ACS) for rosiglitazone (RSG) compared to pioglitazone (PIO).

	AMI	AMI + ACS
RSG vs. PIO (all use)	1.06	1.19
RSG vs. PIO (monotherapy)	1.14	1.27

Limitations of this study relate to performing multiple regressions rather than a single regression that included both rosiglitazone and pioglitazone, and the failure to directly compare these TZDs. As a result, the point estimates in table 7 may be inaccurate. Also, the methods suggest that unexposed time may have been included as exposed time, representing misclassification of exposure. This would bias the relative risk estimates shown in table 7 towards the null, thereby understating the degree of difference between rosiglitazone and pioglitazone.

3.3 META-ANALYSES OF ACUTE MYOCARDIAL INFARCTION AND HEART FAILURE RISK

3.3.1 Summary of results pertaining to AMI risk with rosiglitazone, pioglitazone, and rosiglitazone vs. pioglitazone from randomized controlled trials and observational studies

Rosiglitazone studies. Published randomized controlled trials of rosiglitazone generally reported increased point estimates for the risk of AMI (table 8) and three separate meta-analyses of randomized trials including published and unpublished trials, uniformly reported statistically significant increased risks of AMI or myocardial ischemia.[16,17,30] One observational study reported that rosiglitazone neither increased nor decreased AMI risk compared to other antidiabetic drugs not including pioglitazone,[36] while another reported an increased risk of ischemic cardiac events and stroke with rosiglitazone compared to metformin + sulfonylurea.[39]

Pioglitazone studies. One large cardiovascular outcomes trial for pioglitazone reported a non-statistically significant reduction in risk of a composite outcome that included all-cause mortality, nonfatal AMI, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, or amputation above the ankle (HR=0.90, 95% CI 0.80-1.02, p=0.095).[11] In a composite secondary outcome of all-cause mortality, nonfatal AMI, or stroke, a statistically significant reduction in risk favoring pioglitazone was observed (HR=0.84, 95% CI 0.72-0.98, p=0.027).[11] A meta-analysis of randomized trials including published and unpublished trials, found an overall reduction in risk of AMI for pioglitazone of borderline statistical significance and a statistically significant reduction in risk of the composite outcome of all-cause mortality, nonfatal AMI, or stroke (table 8).[33] One observational study comparing pioglitazone vs. other non-TZD medications reported a protective effect against AMI for pioglitazone.[40]

Studies comparing rosiglitazone to pioglitazone. Only one randomized controlled trial has been performed directly comparing rosiglitazone vs. pioglitazone, but this trial was of small size, short duration (24 weeks), and was designed to study changes in lipid profiles with each TZD (table 3, above).[34,35] Cardiovascular events were collected but not adjudicated. Risk of an ischemic cardiac event was increased with rosiglitazone compared to pioglitazone in this study.

All seven of the observational studies (5 published, 2 unpublished) that permitted a direct or indirect comparison of rosiglitazone vs. pioglitazone found an increased risk of AMI with rosiglitazone compared to pioglitazone, with definite statistical significance in three and probable statistical significance in two (table 8).[41-43,45,46,48,49] One other study did not calculate the relative risk and 95% confidence intervals for AMI with rosiglitazone vs. pioglitazone, but crude point estimates of the relative risk were derived (see table 7).[50] These probably underestimated the actual relative risk because of exposure misclassification in the analysis, described previously. In general terms, these estimates were consistent with those from the other seven observational studies.

Table 8. Summary of randomized controlled trials and observational studies of acute cardiovascular risk with rosiglitazone (RSG), pioglitazone (PIO), and rosiglitazone vs. pioglitazone.

Study	Outcome	Design†	Exposed cases (n) RSG	PIO	RR (95% CI)
RSG controlled trials					
DREAM[11]	AMI	RCT	15	-	1.66 (0.63-3.80)
	AMI+stroke+CV death		32	-	1.39 (0.81-2.37)
ADOPT[27] RSG vs. All	AMI	RCT	27	-	1.4 (1.1-1.9)[30]
RSG vs. Glyburide					1.6 (0.8-3.1)[29]
RSG vs. Metfoemin					1.3 (0.7-2.3)[29]
RECORD[12]	AMI	RCT	43	-	1.16 (0.75-1.81)
	CV hosp/death		217	-	1.08 (0.89-1.31)
Nissen et al. meta-analysis[16]	AMI	Meta	86	-	1.43 (1.03-1.98)
	CV death		39	-	1.64 (0.98-2.74)
FDA meta-analysis[17]	Myocardial ischemia	Meta	171	-	1.4 (1.1-1.8)
Singh et al. meta-analysis[30]	AMI	Meta	94	-	1.42 (1.06-1.91)
RSG observational studies					
McAfee et al.[36]	Hospitalized AMI	Cohort	120	-	0.92 (0.73-1.16)
Wang et al.[39]	Ischemic cardiac events	Cohort	?	?	1.28 (1.06-1.54)
PIO controlled trials					
PROactive[10]	AMI	RCT	-	119	0.83 (0.65-1.06)
	AMI+stroke+death		-	301	0.84 (0.72-0.98)
Lincoff et al. meta-analysis[33]	AMI	Meta	-	131	0.81 (0.64-1.02)
	AMI+stroke+death		-	375	0.82 (0.72-0.94)
PIO observational studies					
Xu et al.[40]	Hospitalized AMI	Cohort	?	?	0.62 (0.50-0.77)
RSG vs. PIO controlled trials					
GLAI[34,35]	Cardiac events	RCT	7‡	2‡	3.52 (0.67-34.7)
RSG vs. PIO observational studies*					
Lipscombe et al.[41]	Hospitalized AMI	NCC	62	16	2.43 (1.19-5.29)+
Gerritts et al.[42]	Hospitalized AMI	Cohort	214	161	1.28 (1.04-1.59)
Walker et al.[43]	Hospitalized AMI	Cohort	44	66	1.21 (0.95-1.54)
Margolis et al.[45]	AMI, ACS, revasc	Cohort	?	?	1.1 (0.7-1.7)
WE145[46]	Hospitalized AMI	NCC	1149	910	1.14 (1.03-1.27)+
Miller et al.[48] (TZD+other oral)	Hospitalized AMI	Cohort			1.18 (1.00-1.39) or 1.10 (0.86-1.40)#
(TZD+insulin)					1.42 (1.02-1.98) or 1.53 (1.08-2.16)#
Singh et al.[49]	Hospitalized AMI	NCC	298	277	1.28 (1.05-1.56)

† RCT = randomized controlled trial; Meta = meta-analysis; NCC = nested case-control

‡ For RSG: 1 sudden death, 1 AMI, 4 emergency coronary bypass surgeries, 1 unstable angina;
For PIO: 1 AMI, 1 emergency coronary bypass surgery

+ Unadjusted estimate calculated from data presented in the study

Relative risk was estimated by two methods: Cox regression and propensity score matching

* Note: when more than one comparison of rosiglitazone vs. pioglitazone was presented in an individual study, we included results based on the following hierarchy: 1) on-therapy analyses were selected in preference to analyses based on total time on- and off-therapy; 2) analyses based on inception (new user) cohorts were selected in preference to those based on prevalence cohorts.

3.3.2 Meta-analysis of AMI risk from randomized controlled trials and observational studies of rosiglitazone and pioglitazone

3.3.2.1 Meta-analysis of randomized controlled trials

There are no large randomized head-to-head cardiovascular outcomes trials comparing rosiglitazone and pioglitazone. However, several meta-analyses have been published to address the question of AMI risk with each of the two TZDs (figures 3a and 3b). The meta-analysis by Nissen et al. was based on 42 controlled trials (40 shorter-term, DREAM,[11] ADOPT[27]).[16] This analysis included 26,005 enrolled patients and found an increased relative risk for AMI with rosiglitazone of 1.43 (95% CI 1.03-1.98). The rosiglitazone meta-analysis by Singh et al.[30] included 4 published randomized controlled trials that were at least 12 months in duration involving 14,291 patients (DREAM,[11] ADOPT,[27] RECORD,[12] and one smaller study[51]). They found a relative risk for AMI with rosiglitazone of 1.42 (95% CI 1.06-1.91). The pioglitazone meta-analysis by Linkoff et al.[33] included 19 randomized trials (2 published, 17 unpublished) that had enrolled 16,390 patients. They found a relative risk of AMI with pioglitazone of 0.81 (95% CI 0.64-1.02).

By visual inspection, there is a clear qualitative difference in AMI risk between the results from meta-analyses of rosiglitazone and pioglitazone (figures 3a and 3b). In addition, the lower bound of the 95% confidence interval for rosiglitazone meta-analyses excluded the point estimate for pioglitazone meta-analyses and the upper bound of the 95% confidence interval for pioglitazone meta-analyses excluded the point estimate for rosiglitazone meta-analyses. Indeed, there was complete absence of confidence interval overlap between the risk estimates of the two drugs, indicating a highly statistically significant difference in AMI risk, favoring pioglitazone. In one other comparison, we compared the two rosiglitazone meta-analyses to the one pioglitazone meta-analysis in an effort to determine whether the risk of AMI with each of the TZDs was the same or different (figures 3a, 3b). We performed a meta-analysis of these meta-analyses to permit statistical testing for heterogeneity. If marked heterogeneity was present, this would suggest that the meta-analyses for rosiglitazone and pioglitazone described statistically significantly different risks rather than a single shared risk. For both comparisons, the test for heterogeneity suggested that the difference in relative risk of AMI between the two TZDs was statistically significant, with pioglitazone having substantially lower risk. Based on the findings from these meta-analyses, the relative risk of AMI for rosiglitazone vs. pioglitazone was estimated to be approximately 1.75 (RR_{PIO}/RR_{RSG}).

Figure 3a. Comparison of results for acute myocardial infarction risk from meta-analyses of randomized controlled trials of rosiglitazone and pioglitazone.

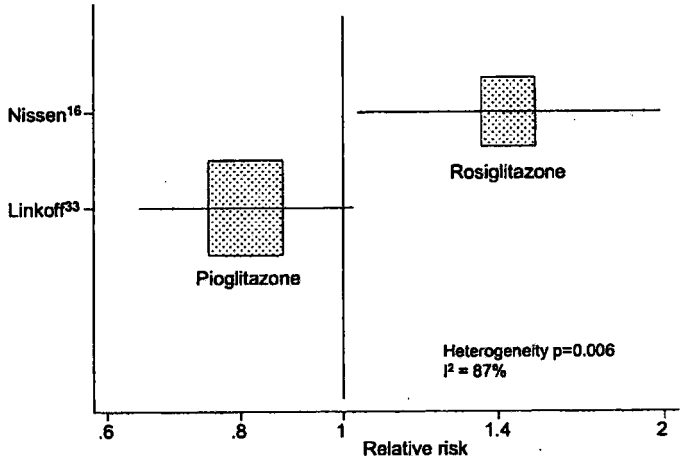
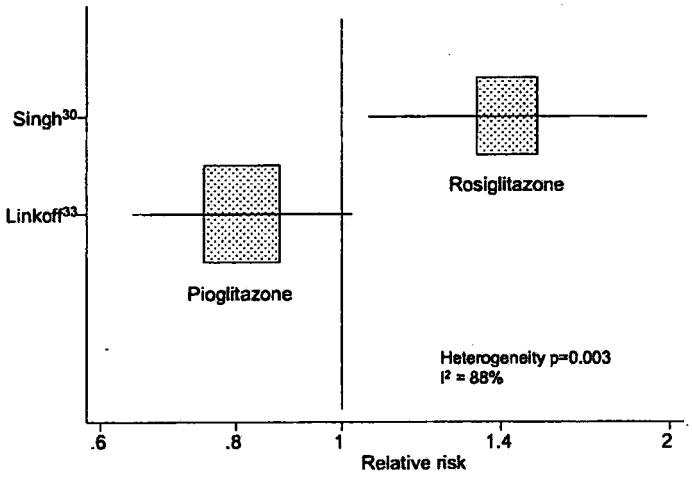


Figure 3b. Comparison of results for acute myocardial infarction risk from meta-analyses of randomized controlled trials of rosiglitazone and pioglitazone.



Subsequent to our search of the medical literature for articles related to cardiovascular risks with TZDs, an article posted on a university biostatistics department website as a "working paper" was brought to our attention.[52] In this paper, Tian et al. presented a newly developed method for calculating 95% confidence intervals around the risk difference (RD) from a meta-analysis of studies with an experimental and control group, in which some of the studies contributing to the meta-analysis had no events in either group.[52] The authors illustrated their method using the Nissen et al. meta-analysis[16] of cardiovascular risk with rosiglitazone.

The authors noted that Nissen et al. had excluded 6 studies from their meta-analysis because they had no AMI events in either the rosiglitazone or control groups and as the authors explained, it is not possible to directly calculate an odds ratio (OR) for studies in which there are no events. However, the authors stated that it is possible to estimate the RD between exposure groups within a study, even if neither the experimental or control group have any outcome events, and a meta-analysis can be performed that includes all studies, if based on the RD rather than the odds ratio. Using their new method, the authors performed a meta-analysis of all 48 potential rosiglitazone studies (including the 6 with no AMI events) and estimated that the 95% confidence interval around the RD between rosiglitazone and control therapy was -0.0008 to 0.0038, with p-value=0.27. They concluded that while the AMI risk with rosiglitazone was increased, this increase over control was not statistically significant. In their paper, Tian et al.[52] also presented 95% confidence intervals for the RD based on the 42 studies included in the meta-analysis by Nissen et al.,[16] reporting a 95% confidence interval of 0.0002 to 0.0042.

Using the data presented by Tian et al.,[52] we were able to estimate the OR and 95% confidence intervals corresponding to the confidence intervals based on RDs. Odds ratios are not linear in form. On the OR scale, the distance from 1 to 0.5 is not the same as the distance from 1 to 1.5. Rather, the distance from 1 to 0.5 is equivalent to the distance of 1 to 2. On the natural log (ln) scale, ORs are linear.[53] For example, ln(1)=0; ln(0.5)= -0.693; ln(2)= 0.693. We transformed the OR and 95% confidence interval for AMI from Nissen et al.[16] to the log linear scale, and compared this to the 95% confidence interval for the RD of the same 42 trials included by Nissen et al., reported by Tian et al.[52] Risk differences are already on a linear scale. By calculating the ratio between ln(OR) and RD, we were able to transform the RDs presented by Tian et al.[52] into their corresponding values in terms of the ln(OR). We exponentiated the resulting values to obtain the OR and 95% confidence intervals for AMI, based on all 48 trials shown in Tian et al.[52] This process is illustrated in the Table 9.

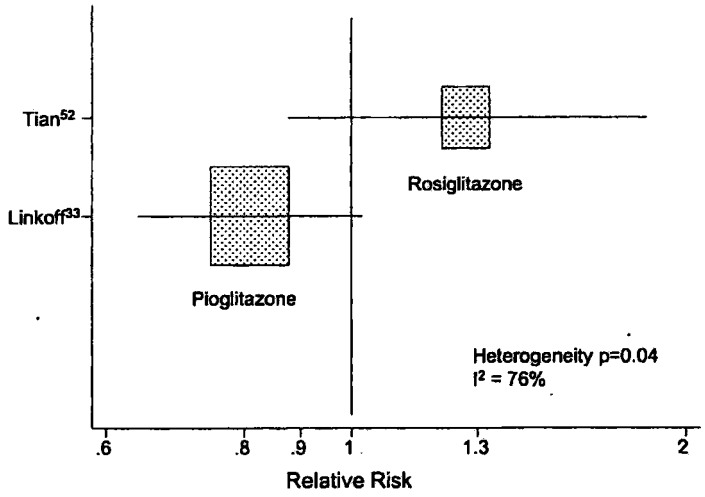
By calculating ln(1.43), we obtained the value 0.3577, which represents the OR from the Nissen et al.[16] meta-analysis on a log linear scale. The RDs for the same 42 trials included by Nissen et al.[16] in their meta-analysis are shown in the row below as reported by Tian et al.[52] The ratio to convert units of RD into units on the natural log scale was calculated. By multiplying this conversion factor by the 95% confidence interval for the risk difference based on all 48 clinical trials (-0.0008, 0.0038), we obtained the value of these confidence intervals in natural log units. The point estimate of the odds ratio is the midpoint between the lower and upper bounds of the 95% confidence interval,[37] when measured on the natural log scale. By exponentiating the natural log estimates of the point estimate and its 95% confidence interval, we obtained the odds ratio and 95% confidence interval for all 48 trials, corresponding to the risk differences reported by Tian et al.[52] The risk difference of -0.0008 to 0.0038 corresponds to an odds ratio of 1.28 (95% CI 0.89-1.85).

Table 9. Estimation of the odds ratio and 95% confidence intervals for acute myocardial infarction for a meta-analysis of 48 clinical trials comparing rosiglitazoneto control therapy

	Point estimate	Lower bound (95% CI)	Upper bound (95% CI)
Odds ratio for AMI, Nissen et al.[16]	1.43	1.03	1.98
ln(OR), Nissen et al.[16]	0.3577	0.0296	0.6831
Risk difference for AMI based on 42 studies from Nissen et al,[16] presented in Tian et al.[52]		0.0002	0.0042
Ratio ln(OR)/RD		148	162
Risk difference for AMI based on 48 studies, Tian et al.[52]		-0.0008	0.0038
ln(OR) for AMI based on 48 studies from Tian et al.[52]		-0.1184	0.6156
ln (OR) for point estimate based on 48 studies from Tian et al.[52]	0.2486		
Point estimate and 95% CI of the odds ratio, based on 48 studies from Tian et al.[52]	1.28	0.89	1.85

We compared this OR (95% CI) from the meta-analysis of all 48 rosiglitazone studies to the meta-analysis of pioglitazone studies by Linkoff et al.[33] (Figure 4). As was seen with the comparison of the meta-analyses of Nissen et al.[16] and Linkoff et al.[33] and that of Singh et al.[30] and Linkoff et al.,[33] there was a qualitatively visible difference between rosiglitazone and pioglitazone. Additionally, the lower bound of the 95% confidence interval from the Tian et al.[52] meta-analysis did not include the point estimate of the pioglitazone meta-analysis, and the upper bound of the 95% confidence interval from the Linkoff et al.[33] study did not include the point estimate for Tian et al.,[52] suggesting a statistically significant difference between the AMI risk with these two drugs. A formal test for heterogeneity yielded a p-value of 0.04 and the I^2 statistic was 76%, suggesting extreme inconsistency between the two drugs. Importantly, the paper by Tian et al.[52] has not been published in a peer-reviewed journal to our knowledge, but was posted as a "working paper" on the website of a university biostatistics department.

Figure 4. Comparison of results for acute myocardial infarction risk from meta-analyses of randomized controlled trials of rosiglitazone and pioglitazone.

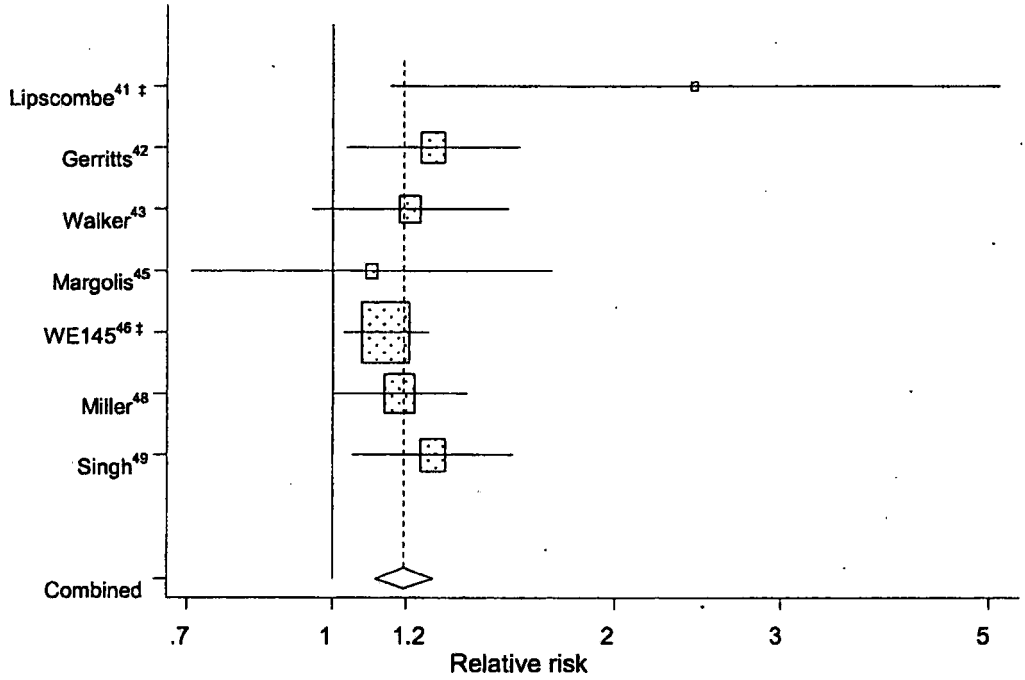


The meta-analysis by Tian et al.[52] did not include results from RECORD.[12] We combined the results from Tian et al.[52] with those from RECORD[12] for the outcome of AMI, and compared the resulting relative risk with that from Linkoff et al.[33] When only adjudicated AMI cases from RECORD were used, the summary relative risk for AMI with rosiglitazone was 1.23 (95% CI 0.93-1.63). When both adjudicated and unadjudicated AMI cases from RECORD were included, the relative risk was 1.26 (95% CI 0.96-1.65). Comparison of the pioglitazone relative risk for AMI with that for rosiglitazone yielded a heterogeneity p-value of 0.025 with I^2=80% (Tian et al. + RECORD adjudicated only) and a heterogeneity p-value of 0.015 with I^2=83% (Tian et al. + RECORD adjudicated and unadjudicated). Even when the results from RECORD are included, there remains a substantial difference in AMI risk (RR_{RSG}/RR_{PIO}=1.56).

3.3.2.2 Meta-analysis of observational studies

Seven observational epidemiologic studies were identified in which rosiglitazone was compared to pioglitazone for the occurrence of AMI.[41-43, 45,46,48,49] In all seven, the relative risk for AMI was increased with rosiglitazone compared to pioglitazone. A meta-analysis of these observational studies showed an increased risk of AMI with rosiglitazone, with a summary relative risk of 1.19 (95% CI 1.11-1.28) (figure 5). Statistical heterogeneity among the studies was insignificant and inconsistency was very low ($I^2 = 0\%$). There was some clinical heterogeneity in that the studied populations could differ with respect to age or geographic location. Of note, because each study's comparison of rosiglitazone vs. pioglitazone was based on the same population, the potential for confounding, particularly by channeling bias, or spurious associations was reduced.

Figure 5. Meta-analysis of 7 observational studies comparing rosiglitazone vs. pioglitazone for occurrence of acute myocardial infarction.†



† Note: when more than one comparison of rosiglitazone vs. pioglitazone was presented in an individual study, we included results based on the following hierarchy: 1) on-therapy analyses were selected in preference to analyses based on total time on- and off-therapy; 2) analyses based on inception (new user) cohorts were selected in preference to those based on prevalence cohorts.

‡ Unadjusted odds ratios were used because adjusted values were not provided and could not be derived.

Several sensitivity analyses were performed. In one, a meta-analysis was performed multiple times, with each study excluded in succession (table 10). Results were insensitive to study removal.

Table 10. Sensitivity analysis involving repeated iterations of the meta-analysis in which each contributing study is sequentially removed, under a fixed-effect assumption. P-values for heterogeneity are based on Cochran's Q statistic.

Scenario	Relative risk	95% CI	Heterogeneity p-value
All studies	1.19	1.11-1.28	0.51
Without Lipscombe et al.[41†]	1.19	1.10-1.27	0.88
Without Gerritts et al.[42]	1.18	1.10-1.27	0.44
Without Walker et al.[43]	1.19	1.11-1.28	0.38
Without Margolis et al.[44]	1.20	1.11-1.28	0.40
Without WE145[46†]	1.24	1.13-1.36	0.55
Without Miller et al.[48]	1.20	1.11-1.29	0.38
Without Singh et al.[49]	1.18	1.09-1.27	0.45

† Unadjusted odds ratios were used because adjusted values were not provided and could not be derived.

In another sensitivity analysis, the relative risk of AMI was increased for rosiglitazone vs. pioglitazone in a meta-analysis limited to published studies only (RR=1.18, 95% CI 1.08-1.29) and limited to unpublished studies only (RR=1.22, 95% CI 1.08-1.39). There was no statistical difference between these estimates. The relative risk for studies using a cohort approach showed an increased AMI risk for rosiglitazone (RR=1.21, 95% CI 1.08-1.35) and a similar result obtained using a nested case-control approach (RR=1.18, 95% CI 1.08-1.30). There was no statistical difference between these estimates. Relative risk estimates were also similar when stratified by funding source (industry: RR=1.17, 95% CI 1.07-1.28; public: RR=1.23. 95% CI 1.09-1.39). A cumulative meta-analysis was performed in which the cumulative relative risk of AMI for rosiglitazone vs. pioglitazone was estimated following the addition of each observational study as it became available (table 11) and suggested a statistically significant and relatively stable excess risk for rosiglitazone.

Table 11. Cumulative meta-analysis (relative risk [RR]) of observational studies comparing rosiglitazone vs. pioglitazone for occurrence of acute myocardial infarction

	Cumulative RR	Cumulative 95% confidence interval	Cumulative p-value
Lipscombe et al.[41 †]	2.43	1.15-5.12	0.02
Gerritts et al.[42]	1.34	1.10-1.65	0.005
Walker et al.[43]	1.29	1.10-1.50	0.002
Margolis et al.[45]	1.26	1.09-1.46	0.002
WE145[46 †]	1.18	1.08-1.29	<0.001
Miller et al.[48]	1.18	1.09-1.27	<0.001
Singh et al.[49]	1.19	1.11-1.28	<0.001

† Unadjusted odds ratios were used because adjusted values were not provided and could not be derived.

3.3.3 Summary and meta-analysis of heart failure risk with rosiglitazone and pioglitazone

We also evaluated the literature from published and unpublished randomized controlled trials for the occurrence of heart failure in patients with T2DM treated with rosiglitazone or pioglitazone. Four separate meta-analyses of heart failure with rosiglitazone or pioglitazone have been published.[15,30,33,53] These meta-analyses differed somewhat in their inclusion and exclusion criteria as shown in table 12.

Table 12. Comparison of study criteria for published meta-analyses of heart failure with rosiglitazone (RSG) and pioglitazone (PIO).

Study	RSG	PIO	Published only	Published + unpublished	Adjudicated cases only	"Serious" cases	Hospitalized cases	All cases
Lago[15]	X	X	X		X		X	
Singh[30]	X		X					X
Linkoff[33]		X		X		X		
Mannucci[53]		X		X			X	

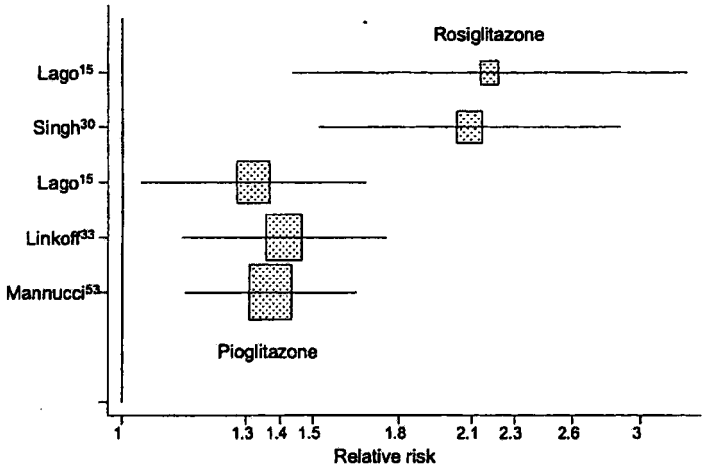
The meta-analysis by Lago et al.[15] examined studies of both rosiglitazone and pioglitazone while the meta-anlaysis by Singh et al.[30] focused on rosiglitazone and that by Linkoff et al.[33] and Mannucci et al.[53] focused on pioglitazone. The analyses by Lago et al.[15] and Singh et al.[30] were limited to published studies only, and for rosiglitazone, only studies with more than 12 months of follow-up. The meta-analysis by Linkoff et al.[33] included shorter-term and unpublished studies but was restricted to "serious" cases of heart failure only, without defining "serious". Mannucci et al. included all hospitalized cases regardless of adjudication or publication status.[53]

The relative risks of heart failure from the major large randomized trials for rosiglitazone and pioglitazone are shown, along with results from the 4 published meta-analyses (table 13). The summary relative risk for heart failure from published meta-analyses with rosiglitazone ranged between 2.09 and 2.14, while for pioglitazone, the summary relative risk for heart failure from published meta-analyses ranged from 1.32 to 1.41, suggesting a difference in risk between the two TZDs, with a relative risk of about 1.5 favoring pioglitazone. This difference is visibly present when the data are presented on a log scale, where it can be seen that the lower bound of the 95% confidence intervals for the rosiglitazone studies excluded the point estimates for pioglitazone and the upper bound of the 95% confidence interval for the pioglitazone studies excluded the point estimates for rosiglitazone (figure 6).

Table 13. Relative risk estimates and 95% confidence intervals for the occurrence of heart failure with rosiglitazone and pioglitazone.

TZD	Study	Population	Comparator	TZD-exposed cases (n)	RR (95% CI)
Rosiglitazone					
	DREAM[11]	Pre-diabetes	Placebo	16	7.03 (1.60-30.9)
	ADOPT[27]	Recently diagnosed	Metformin or Glyburide	50	1.56 (0.90-2.72)
	RECORD[12]	Failed monotherapy	Metformin + Sulfonyurea	69	2.15 (1.30-3.57)
	Lago et al.[15]	Meta-analysis	Various	104	2.14 (1.44-3.32)
	Singh et al.[30]	Meta-analysis	Various	164	2.09 (1.52-2.88)
Pioglitazone					
	PROactive[10]	Established macrovascular disease	Placebo	257	1.42 (1.19-1.70)
	Lago et al.[15]	Meta-analysis	Various	356	1.32 (1.04-1.68)
	Linkoff et al.[33]	Meta-analysis	Various	339	1.41 (1.14-1.76)
	Mannucci et al.[53]	Meta-analysis	Various	455	1.37 (1.14-1.64)

Figure 6. Relative risk and 95% confidence intervals of heart failure from published meta-analyses for rosiglitazone and pioglitazone.



We compared the summary relative risk estimates for each TZD from the published meta-analyses using the test for heterogeneity as an indicator of whether these relative risks described a common risk or two different risks (table 14). If the p-value was ≤ 0.05, that would indicate that the two relative risks were different, and not from a common, shared relative risk. The analysis published by Mannucci et al.[53] excluded trials in which no heart failure events were recorded, resulting in a loss of useful information. If these other trials were included, a more accurate and precise estimate of the relative risk was obtained. Both are shown in table 14. In 5 of the comparisons, the p-value was below 0.05, and in one other, the p-value was close to 0.05, suggesting that the relative risk of HF was greater for rosiglitazone than pioglitazone. The only comparison where a clear difference between pioglitazone and rosiglitazone was not shown involved the analysis by Mannucci et al.,[53] which excluded clinical trials with no heart failure events. With inclusion of these trials, a clear difference between the TZDs was seen. Of note, the p-values below underestimated the true difference between TZDs because our comparisons relied on weighted estimates from separate completed meta-analyses and were not performed at the level of the individual studies contributing to those meta-analyses. As an illustration, our comparison of rosiglitazone vs. pioglitazone using data from Lago et al.[15] (highlighted cell in table 13), yielded a p-value for a difference of 0.041, while Lago et al. reported a p-value of 0.01 for this same comparison, based on individual study-level data.[15] Another measure of heterogeneity is the I^2 statistic, which is a measure of inconsistency between the relative risks under comparison. Its values range from 0% to 100%), with values $\leq 25\%$ representing high consistency (minimal or no heterogeneity) and values $\geq 75\%$ indicating extreme inconsistency (extreme heterogeneity). For all comparisons except those based on the analysis by Mannucci et al.[53] that excluded 0-event trials, the I^2 statistic suggested extreme inconsistency between the two TZDs.

Table 13. Heterogeneity (p-values and I^2 statistics) for differences in the relative risk of heart failure between rosiglitazone and pioglitazone, as reported in published meta-analyses.

			Rosiglitazone	
			Lago[15]	Singh[31]
		Relative risk (95% CI)	2.18 (1.44-3.32)	2.09 (1.52-2.88)
Pioglitazone	Lago[15]	1.32 (1.04-1.68)	p=0.041 I^2=76%	p=0.024 I^2=80%
	Linkoff[33]	1.41 (1.14-1.76)	p=0.07 I^2= 70%	p=0.046 I^2=75%
	Mannucci[53] (excludes 0-event trials)	1.38 (0.90-2.12)	p=0.13 I^2=55%	p=0.11 I^2=61%
	Mannucci[53] (all trials)	1.37 (1.14-1.64)	p=0.046 I^2=75%	p=0.024 I^2=80%

3.3.4 Estimated population impact of excess risk of acute myocardial infarction and heart failure with rosiglitazone

3.3.4.1 Estimation of excess cases of acute myocardial infarction with rosiglitazone

Two separate meta-analyses of randomized controlled trials with rosiglitazone[15,30] were compared to the only published meta-analysis of controlled trials with pioglitazone.[33] We found a statistically significant difference in AMI risk between the two TZDs, favoring pioglitazone. Based on these comparisons, rosiglitazone was estimated to confer a 56% to 75% increase in AMI risk compared to pioglitazone. We also examined the results from 7 observational studies where an estimate of AMI risk for rosiglitazone vs. pioglitazone was available.[41-42,45,46,48,49] All 7 reported an increased risk of AMI for rosiglitazone. A meta-analysis of these studies yielded a summary relative risk estimate of 1.19 (95% CI 1.11-1.28).

We used these estimates of excess AMI risk with rosiglitazone compared to pioglitazone to estimate the population impact of this excess risk on US patients. Based on a review of AMI risks in patients with T2DM from published clinical trials of antihypertensive drugs, cholesterol lowering drugs, and anti-diabetic drugs, we previously estimated that the average annual rate of AMI was about 2.1 per 100 person-years in this population.[18] Using the estimated relative risk of AMI with rosiglitazone compared to pioglitazone obtained from meta-analyses based on randomized controlled trials (RR=1.75), the net absolute increase in AMI risk due to use of rosiglitazone rather than pioglitazone was 1.58 per 100 person-years, translating to a number needed to harm (NNH) of 63 person-years. Using the meta-analysis results from the observational studies (RR=1.19), the net absolute increase in AMI risk resulting from the use of rosiglitazone rather than pioglitazone was 0.4 per 100 person-years, translating to a number needed to harm of 251 person-years.

Prescription data for rosiglitazone (see section 3.4 below) was used to estimate the person-years of population exposure to the drug for the time period from start of marketing in 1999 through April 2007, preceding concerns about an increased AMI risk. Person-years of exposure were also estimated for three different intervals after April 2007, corresponding to different milestones in FDA's handling of this safety issue. The period from May 2007 to June 2008 corresponded to the time since publication of the meta-analysis by Nisssen et al.[16] and general awareness of a possible concern about increased AMI risk with rosiglitazone. The period from August 2007 to June 2008 corresponded to time since FDA convened an advisory committee meeting to discuss cardiovascular risks with rosiglitazone.[18] The period from November 2007 to June 2008 corresponded to the time since concern about a potential increase in myocardial ischemia risk was added to rosiglitazone's label. The population impact of rosiglitazone's increased AMI risk for these various time periods is shown in table 14.

Table 14. Excess cases of acute myocardial infarction attributable to use of rosiglitazone rather than pioglitazone for various time periods since the start of marketing in 1999.

	NNH	1999-Apr 2007	May 2007-June 2008	August 2007-June 2008	November 2007-June 2008
Based on RCT meta-analyses	63	79,159	9,290	6,192	4,141
Based on meta-analysis of observational studies	251	19,869	2,332	1,554	1,039

For the period from the start of marketing through April 2007, just prior to publication of the meta-analysis by Nissen et al.,[16] the excess number of AMI cases due to rosiglitazone use was between 20,000 and 79,000. From the time of first publication of increased rosiglitazone risk through June 2008, the number of excess cases was between 2,300 and 9,300. For the period following FDA's July 2007 advisory committee meeting on rosiglitzone risk through June 2008, the number of excess cases was between 1,500 and 6,200, and for the period since FDA's addition of myocardial ischemia risk to rosiglitazone's label, the number of excess cases was between 1,000 and 4,100. Of note, the estimates based on randomized controlled trials are probably closer to reality. Observational studies tend to underestimate risk because of methodologic issues related to misclassification and incomplete case ascertainment. For example, with rofecoxib, the relative risk of AMI was 2 in a randomized trial of the 25 mg/d dose, and 5 in a randomized trial of the 50 mg dose. Observational studies that included both dose levels tended to obtain relative risk estimates below 1.5.

3.3.4.2 Estimation of excess cases of heart failure with rosiglitazone

As described above, we found that rosiglitazone increases the risk of heart failure by about 50% compared to pioglitazone. In order to use this information to estimate the number of excess cases of heart failure in US patients, we had to obtain an estimate of the background rate for heart failure in patients with T2DM. We used the reported occurrence of heart failure in the control groups from ADOPT,[27] PROactive,[11] and RECORD[12] to provide a range of background rates from which to estimate the number of excess cases. The patients included in ADOPT[27] were recently diagnosed type 2 diabetics and the rate of heart failure in the control group was 0.3 per 100 person-years. The patients included in PROactive had established macrovascular disease with an average time since diagnosis of T2DM of 8 years.[11] The rate of hospitalized heart failure in the control group was 1.4 per 100 person-years and for any heart failure, 2.6 per 100 person-years. RECORD included patients with an average time since diagnosis of T2DM of 7 years, and 25% had a history of macrovascular disease.[12] The rate of heart failure in the control group was 0.26 per 100 person-years, nearly identical with that from ADOPT, suggesting that many cases were not ascertained in this open-label trial.

The range of excess cases of hospitalized heart failure attributable to the use of rosiglitazone rather than pioglitazone for different time intervals was estimated (table 15). Because of the probable marked undercounting of heart failure cases in RECORD,[12] we calculated an "average" heart failure rate based on ADOPT[27] and PROactive[11] (hospitalized heart failure 0.9 per 100 person-years). Since the July 2007 FDA advisory committee meeting, there were an estimated 3,600 excess cases of hospitalized heart failure attributable to the use of rosiglitazone rather than pioglitazone. Over the marketing history of the drug, this number was about 52,000 (46,629 + 5,472).

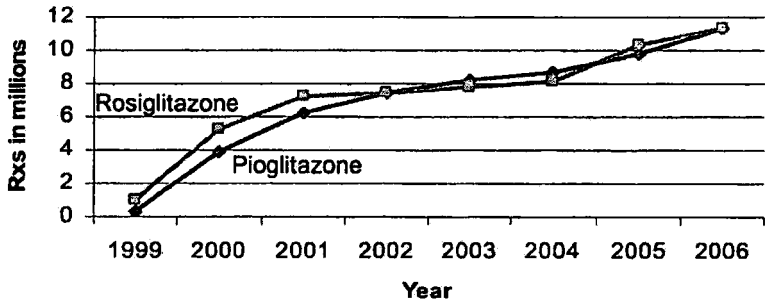
Table 15. Excess cases of hospitalized heart failure attributable to use of rosiglitazone rather than pioglitazone for various time periods since the start of marketing in 1999.

	NNH	1999-Apr 2007	May 2007-June 2008	August 2007-June 2008	November 2007-June 2008
ADOPT[27]	291	17,141	2,012	1,341	897
RECORD[12]	350	14,263	1,674	1,116	746
PROactive[10]	65	76,801	9,013	6,007	4,018
"Average"	107	46,629	5,472	3,647	2,439

3.4 DRUG UTILIZATION

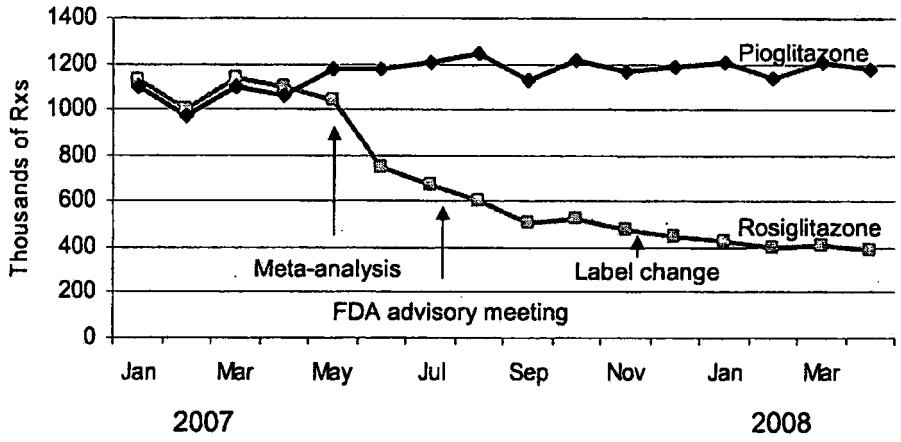
Both rosiglitazone and pioglitazone were marketed in the US beginning in 1999. Between the start of marketing and 2006, annual prescription use of each TZD was very similar (figure 7).

Figure 7. Annual prescription use of rosiglitazone and pioglitazone, 1999-2006. Source: Verispan Vector One®[24]



In 2007, prescriptions for rosiglitazone began to fall (figure 8) following publication of the meta-analysis of rosiglitazone clinical trials by Nissen et al. in May 2007.[16] Use did not decline much following the addition of myocardial ischemia to the rosiglitazone label, and has leveled off at ~400,000 prescriptions per month. Overall, rosiglitazone use declined about 65% between May 2007 and April 2008, and now accounts for about 25% of the TZD market.

Figure 8. Monthly number of prescriptions for rosiglitazone and pioglitazone, 2007-April 2008. Source: Verispan Vector One®[25]



4 BENEFITS AND RISKS OF THIAZOLIDINEDIONES

4.1 GLYCEMIC CONTROL

Thiazolidinediones bind to the nuclear transcription factor peroxisome-proliferator-activated-receptor γ (PPARγ), which regulates the transcription of a variety of different genes.[54] The TZDs increase insulin sensitivity of adipose and muscle tissue and inhibit gluconeogenesis, and reduce fasting and postprandial blood glucose levels.[54] The two marketed TZDs are comparable in the degree of glycemic control achieved, generally amounting to a reduction of HbA1c ranging from 0.5% to 1.5% depending on dose,[19,54-58] a somewhat lower effect than seen with recommended doses of sulfonyureas or metformin.[54,58] There is no evidence to suggest a difference in degree of glycemic control with either rosiglitazone or pioglitazone,[58] and in one randomized trial comparing the two drugs, the level of glycemic control was identical.[34] There are no data to suggest that either rosiglitazone or pioglitazone would achieve glycemic control in the setting where control had not been achieved with use of the other TZD.[56-58]

4.2 LIPID EFFECTS

One head-to-head randomized trial has been performed comparing lipid effect in patients treated with rosiglitazone vs. pioglitazone.[34] Rosiglitazone increased triglyceride levels and resulted in greater increases in LDL cholesterol and smaller increases in HDL cholesterol than pioglitazone. LDL particle concentration and LDL particle size also changed more favorably with pioglitazone than rosiglitazone.[34,35] Overall, compared to rosiglitazone, pioglitazone was associated with significantly greater improvement in a variety of lipid indices. These differences in lipid effects may relate to differential agonist effects of the two TZDs, with pioglitazone being a partial PPARα agonist in addition to being a PPARγ agonist while rosiglitazone is a pure PPARγ agonist.[54] A meta-analysis of 23 TZD clinical trials also concluded that pioglitazone produced a more favorable lipid profile than rosiglitazone, from a cardiovascular perspective.[59]

4.3 BODY COMPOSITION AND BLOOD PRESSURE EFFECTS

Both rosiglitazone and pioglitazone cause similar increases in body weight (primarily fluid retention and subcutaneous fat) for comparable levels of HbA1c reduction (2-3 kg increase per 1% reduction in HbA1c).[54] Fluid retention and edema also are associated with both TZDs.[54,56-58] A systematic review of the literature from 2004 concluded that neither TZD exerted an effect on blood pressure,[60] although since then, several large trials have reported modest reductions in blood pressure with both TZDs.[10,11,61,62]

4.4 KIDNEY EFFECTS

The first study suggesting a renoprotective effect of TZD was published nearly 15 years ago, when troglitazone was show to reduce urine protein excretion and blood pressure in obese Zucker rats.[63,64] Since then, other animal studies of TZDs have shown anti-inflammatory, anti-proliferative, and anti-fibrotic effects in glomeruli and proximal tubule cells, as well as prevention of proteinurea or delay in progression to nephropathy.[65-68] Rosiglitazone prevented glomerular injury in diabetic rats by reducing reactive oxygen species (a mediator of vascular complications in diabetes) and by reducing activation of nuclear factor-κβ and the expression of MCP-1, both involved in the pathogenesis of diabetic nephropathy.[67] Pioglitazone was shown to limit cyclosporine nephrotoxicity in adult male Wistar rats through down regulation of pro-fibrotic cytokine PAI-1 and overexpression of an intermediate protein that modulates the transcription of specific genes involved in cyclosporine nephrotoxicity.[68] Pioglitazone also reduced renovascular injury in obese Zucker rats with nephropathy, presumably by reducing nitrative stress.[69]

Several studies in humans have shown significant reductions in urine albumin-to-creatinine ratio (ACR), considered to be an intermediate marker of diabetic nephropathy. Of note, decreases in ACR were independent of glycemic control in these studies, but were confounded by blood pressure reductions.[62] Human studies reporting decreased urine albumin excretion have been published for troglitazone, pioglitazone, and rosiglitazone.[64]

The DREAM trial assessed pre-specified renal composite and individual component outcomes in 5,269 people with impaired glucose tolerance and/or impaired fasting glucose during a 3-year observation period. Patients were randomized to ramipril vs. placebo and rosiglitazone vs. placebo according to a 2 x 2 factorial design.[70]

The pre-specified composite cardiorenal outcome in DREAM included either: 1) a composite cardiovascular outcome defined as the first occurrence of any cardiovascular death, successful cardiac resuscitation, nonfatal MI, stroke, revascularization, new stable or unstable angina with documented ischemia, or heart failure; or 2) a composite renal outcome defined as any of the following: progression from normoalbuminuria to either microalbuminuria or proteinuria; progression from microalbuminuria to proteinuria; a decrease in estimated glomerular filtration rate (eGFR) of ≥30%; or renal insufficiency requiring dialysis or transplantation.[70]

Compared to placebo, neither ramipril nor rosiglitazone reduced the risk of the cardiorenal composite outcome. However, rosiglitazone reduced the risk of the renal component (HR 0.80, 95% CI 0.68 – 0.93, p=0.005). This was due to a reduction in progression of albuminuria (HR 0.82, 95% CI 0.69 – 0.98, p=0.031). Although reduction of cardiovascular outcomes and progression of albuminuria in patients at high risk of cardiovascular disease was shown for ramipril in the HOPE study,[71] no such benefit was seen for ramipril in DREAM, possibly due to low activation of the renin-angiotensin system in the lower risk DREAM participants. A potential limitation of DREAM was that renal outcomes were only available for 78% of participants at study end.[70]

In an open-label randomized cross-over study of 40 adults with chronic non-diabetic kidney disease, rosiglitazone reduced proteinuria. This finding was confounded by an associated 7.8 mmHg (95% CI 2.6 – 13.1, p=0.006) reduction in systolic blood pressure in the rosiglitazone group.[72] In a *post hoc* analysis of the PROactive trial, the relationship between chronic kidney disease (CKD) and incident cardiovascular disease was evaluated.[73] Patients with baseline CKD (defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min per 1.73 m^2) who were treated with pioglitazone had a greater decline in eGFR than those treated with placebo (between-group difference 0.8 ml/min per 1.73 m^2/yr). Results of urinary albumin measurements were not reported.[73]

4.5 Bone Fractures

An increased risk of fractures was observed with rosiglitazone in ADOPT.[27] The increased fracture risk was observed in women only (RR=2.17, 95% CI 1.52-3.13, p<0.001) and primarily involved the upper and lower limbs. No specific risk factors were identified. Increased risk of fractures was also seen with pioglitazone. Takeda conducted an analysis of clinical trials with pioglitazone and found more reports of fractures in women taking pioglitazone than those taking a comparator drug.[74] The majority of fractures were in the distal upper forearm or distal lower limb. The fracture incidence calculated was 1.9 fractures per 100 patient-years in the pioglitazone group and 1.1 fractures per 100 patient-years in the comparator group, yielding a point estimate for the relative risk of 1.7 (estimated 95% CI 1.2-2.5).[74] An observational study using the UK General Practice Research Database showed an association between longer-term (12 to 18 months) therapy and bone fractures with both rosiglitazone and pioglitazone.[75] This effect was independent of patient age and gender and tended to increase with dose. Fractures were primarily localized to the hip or wrist.

Preclinical data provide insight into TZD effects on bone. Rosiglitazone was found to counteract osteoblastogenesis and induce a preferential differentiation into adipocytes in human mesenchymal stem cells.[76] In a mouse model, Wan et al. showed that PPAR-γ and its ligands have a previously unrecognized role in promoting osteoclast differentiation and bone resorption.[77] The likely mechanism of TZD-induced skeletal fragility is inhibition of bone formation by PPAR-γ mediated diversion of mesenchymal progenitor cells into the adipocyte lineage at the expense of osteoblastogenesis.[78,79]

Potential mechanisms underlying this risk were studied in 50 postmenopausal women randomized to rosiglitazone or placebo for 14 weeks.[80] The primary endpoint was biochemical markers of bone formation. Secondary outcomes were biochemical markers of bone resorption and bone mineral density measured at the spine and hip. In patients randomized to rosiglitazone, two specific markers of bone formation declined by 10%-12% compared with placebo. There was no change in a biochemical marker of bone resorption. Changes in bone turnover were accompanied by a significant 2% decline in total hip bone mineral density in the rosiglitazone group, even within the short time frame of the study. In another study of rosiglitazone using a retrospective case-control design, increased bone loss at total hip and femoral neck areas in diabetic men was observed.[81]

4.6 Malignancy Risk

In pre-approval animal studies, pioglitazone was found to increase the occurrence of urinary bladder cancer in male rats.[82] The formation of urinary calculi was raised as a potential explanation for the findings in male rats.[82] No tumors were noted in similar studies performed in mice.[82] In over 1,800 patients from clinical trials treated with pioglitazone for up to one year, no new bladder tumors were noted.[82] Abnormal cytology results were noted in 0.72% of pioglitazone-treated patients and in 0.88% of placebo-treated patients.[79] In the PROactive study, a marginally significant increase in bladder cancer and a statistically significant decrease in breast cancer were observed in pioglitazone-treated patients.[10] Cancer incidence with antidiabetic drugs including TZDs has been evaluated using observational study designs in US population-based databases. Results were inconsistent, and in some studies, suggested a protective effect.[84-86] No published literature was identified that provides a meaningful basis for differentiation of cancer risk with rosiglitazone or pioglitazone.

4.7 Surrogate Measures of Cardiovascular Risk or Disease

Several studies have been performed to assess the effect of TZDs on potential cardiovascular risk factors related to inflammation. Both rosiglitazone[87] and pioglitazone[88] reduce blood levels of C-reactive protein, a non-specific marker of inflammation that may important to cardiovascular risk.[89,90] Both TZDs also reduce circulating levels of adipocytokines, also theorized by some to be a cardiovascular risk factor.[91]

Several studies have also been performed to examine the effect of TZD use on progression of documented vascular disease. In a 72-week randomized controlled trial of pioglitazone vs. glimepiride, pioglitazone was shown to statistically significantly reduce progression of carotid artery intima-media thickness (atherosclerotic plaque), a marker of coronary atherosclerosis.[92] In an 18-month randomized controlled trial of pioglitazone vs. glimepiride, pioglitazone was found to statistically significantly reduce progression of coronary atherosclerosis, using coronary intravascular ultrasonogragraphy.[93] Similar studies with rosiglitazone have not been published.

A meta-analysis of published randomized trials concluded that both rosiglitazone and pioglitazone reduced the rate of in-stent restenosis and the need for target-vessel revascularization among patients who had undergone percutaneous coronary intervention.[94]

4.8 HEART FAILURE

While both TZDs have been reported to cause heart failure, and product labeling for both includes a boxed warning for heart failure,[95,96] our review of the literature, including 4 published meta-analyses,[15,30,33,53] suggests that there is a medically important and statistically significant difference in heart failure risk between rosiglitazone and pioglitazone. Although pioglitazone does increase heart failure risk (RR=1.4), the risk with rosiglitazone (RR=2.1) is about 50% greater than the risk conferred by pioglitazone. The meta-analysis by Lago et al.[15] suggested that this increase in heart failure risk is not associated with an increase in mortality.

4.9 MICROVASCULAR DISEASE PREVENTION

Through 2007, there were no published randomized controlled trials showing a protective effect of either TZD against microvascular complications of T2DM such as retinopathy, peripheral neuropathy, or nephropathy.[56-58]

In June 2008, a small observational study was published that reported a borderline statistically significant reduction in progression from severe non-proliferative to proliferative diabetic retinopathy in a subset of 7 patients treated with rosiglitazone vs. 12 patients treated with other therapies (including diet).[97] This study was poorly described and designed, was not embedded within a definable base population, involved multiple subgroup analyses, and did not adjust for the effect of lower HbA1c in the rosiglitazone group or for duration of treatment with rosiglitazone, so that it was not possible to distinguish an effect due to rosiglitazone from an effect due to improved glycemic control. Also, at baseline, patients in the control group were 2.8-times (95% CI 1.3-6.0) more likely to have established proliferative diabetic retinopathy than patients in the rosiglitazone group (p=0.008) and were 1.6-times (95% CI 1.1-2.2) more likely to have moderate-to-severe non-proliferative diabetic retinopathy (p=0.006). These differences cast doubt on the study findings.

Also in 2008, additional analyses from the DREAM trial reported that rosiglitazone reduced the occurrence of the renal component of a composite cardiorenal outcome (HR=0.80, 95% CI 0.68-0.93).[70] A small (n=60) randomized clinical trial in diabetic patients with stage 3 or 4 chronic kidney disease reported that pioglitazone added to losartan significantly slowed the progression of proteinuria and decline in glomerular filtration rate compared to treatment with losartan alone.[98]

4.10 MACROVASCULAR DISEASE PREVENTION

Rosiglitazone. There are no published randomized controlled trials that demonstrate a reduction in cardiovascular death, AMI, stroke, or peripheral vascular disease risk with rosiglitazone. As described in Section 3, above, the risk of AMI in patients with impaired fasting glucose treated with rosiglitazone was greater than that of patients treated with placebo in the DREAM trial (RR=1.66, 95% CI 0.73-3.80), and so was the risk of the composite outcome of cardiovascular death, AMI, or stroke (RR=1.39, 95% CI 0.81-2.37), although neither reached statistical significance.[11] In the ADOPT trial of patients recently diagnosed with T2DM, the risk of AMI was higher in patients treated with rosiglitazone than in patients treated with either metformin or glyburide.[29] Pooling both comparator groups from this trial, the risk of AMI was greater in patients treated with rosiglitazone (RR=1.4; 95% CI 1.1-1.9).[30] In a third large, longer-term trial (RECORD),[12] interim results showed an increased risk of AMI (RR=1.16, 95% CI 0.75-1.81) and a smaller increase in the primary composite outcome of cardiovascular hospitalization (for AMI, stroke, transient ischemic attack, unstable angina, congestive heart failure, extremity amputation, unplanned revascularization procedure) or cardiovascular death (RR=1.08, 95% CI 0.89-1.31). A meta-analysis of published and unpublished randomized controlled trials involving rosiglitazone found an increased risk of AMI (RR=1.43, 95% CI 1.03-1.98) and cardiovascular death (RR=1.64, 95% CI 0.98-2.74).[16] Most of the studies included in this meta-analysis were of short duration (24-26 weeks). A patient-level meta-

analysis of short-term trials involving rosiglitazone by FDA found an increased risk of cardiac ischemic events (RR=1.4, 95% CI 1.1-1.8).[17] A meta-analysis of longer-term trials (≥ 12 months duration) involving rosiglitazone found an increased risk of AMI (RR=1.42, 95% CI 1.06-1.91).[30] This analysis included findings from DREAM,[11] ADOPT,[27] and RECORD.[12]

Pioglitazone. One large randomized controlled trial in patients with established macrovascular disease (PROactive) found a non-statistically significant decrease in risk for the composite outcome of all-cause mortality, nonfatal AMI, nonfatal stroke, ACS, revascularization of coronary or leg arteries, or amputation of the lower extremity (RR=0.90; 95% CI 0.80-1.02).[10] A secondary analysis for the outcome of all-cause mortality, nonfatal AMI, or nonfatal stroke found a statistically significant reduction in risk with pioglitazone (RR=0.84, 95% CI 0.72-0.98). A meta-analysis of 19 clinical trials with pioglitazone reported a borderline statistically significant reduction in AMI (RR= 0.81, 95% CI 0.64-1.02, p=0.08) and a statistically significant reduction in the composite outcome of all-cause mortality, nonfatal AMI, and nonfatal stroke (RR=0.82, 95% CI 0.72-0.94, p=0.005).[33]

Rosiglitazone vs. pioglitazone. A comparison of rosiglitazone vs. pioglitazone, based on available meta-analyses[16,30,33] strongly suggested an estimated 75% increase in AMI risk with rosiglitazone. An analysis of 7 observational studies (5 published, 2 unpublished) permitting comparison of rosiglitazone vs. pioglitazone found an increased risk of AMI with rosiglitazone in all 7. The summary estimate of the relative risk of AMI with rosiglitazone compared to pioglitazone was 1.19 (95% CI 1.11-1.28). These elevated relative risks translate to an estimated 20,000 to 79,000 excess cases of AMI due to use of rosiglitazone rather than pioglitazone since 1999, when both TZDs came to market.

4.11 MORTALITY

Rosiglitazone. The majority of clinical trials with rosiglitazone are unpublished and mortality data from these trials are not described in any single publication. Data from these studies were captured in the FDA meta-analysis of rosiglitazone clinical trials.[17] The FDA analysis did not include findings from ADOPT,[27] DREAM,[11] or RECORD,[12] but these have been published so mortality data from them are available for evaluation. The results of meta-analyses for all-cause and cardiovascular mortality for rosiglitazone from these shorter- and longer-term studies are shown in figures 9 and 10. The relative risk of all-cause mortality was 1.00 (95% CI 0.80-1.24) and for cardiovascular mortality, 1.00 (95% CI 0.69-1.43).

Figure 9. Meta-analysis of shorter- and longer-term randomized clinical trials of rosiglitazone vs. comparator for occurrence of death from all causes.

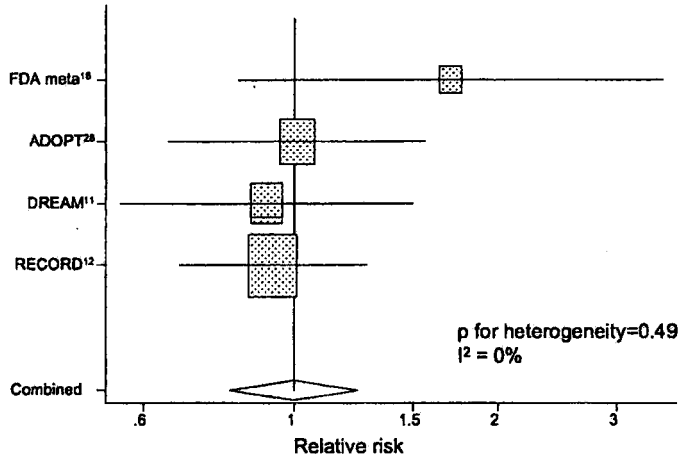
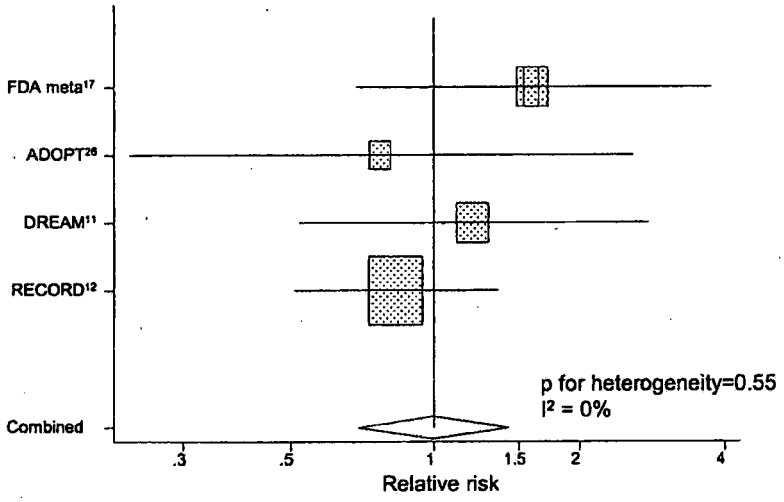


Figure 10. Meta-analysis of shorter- and longer-term randomized clinical trials of rosiglitazone vs. comparator for occurrence of cardiovascular death.



Pioglitazone. A meta-analysis of all randomized clinical trials of pioglitazone vs. comparator that included shorter-term studies in addition to PROactive reported a hazard ratio for all-cause mortality with pioglitazone of 0.92 (95% CI 0.76-1.11).[31] From the data presented in that meta-analysis, it was not possible to estimate the hazard ratio for cardiovascular mortality with pioglitazone.

5 DISCUSSION

5.1 MAIN FINDINGS

Type 2 diabetes is a chronic metabolic disorder affecting over 20 million Americans.[1] Cardiovascular disease, primarily AMI, is increased 2-4-fold over background in patients with T2DM, and is responsible for 65% of deaths in this patient population.[1-3] Microvascular complications of T2DM include retinopathy, nephropathy, and peripheral neuropathy, potentially culminating in blindness and end-stage kidney disease.[1]

The primary goal of therapy for T2DM has focused on achieving and maintaining glycemic control in the face of diabetes progression. More recently, intensive treatment of comorbid conditions such as hypertension and dyslipidemia has also become a therapeutic focus.[99-102] Tight glycemic control has been shown to delay the onset and reduce the risk of diabetic retinopathy and nephropathy,[5,103] but has not been shown to reduce the occurrence of cardiovascular disease in general, or AMI and cardiovascular death in particular.[5] The prevention of microvascular complications was related to the degree of glycemic control and was not dependent on use of a particular antidiabetic agent to achieve that control.[5,103]

Following publication of a meta-analysis of randomized controlled trials that found a 43% increase in AMI risk and a 64% increase in cardiovascular death with rosiglitazone compared to other therapies,[16] FDA conducted its own meta-analysis, which found a 40% increase in risk of myocardial ischemic events.[17] Risk was particularly increased when rosiglitazone was used in combination with metformin (RR=3.2, 95% CI 1.2-9.8) or insulin (RR=2.1, 95% CI 0.9-5.1). A FDA advisory committee concluded that rosiglitazone probably increased cardiovascular risk but recommended that it remain on the market.[18] *Of note, the committee did not discuss or consider the comparative risks and benefits of rosiglitazone vs. pioglitazone, the other marketed TZD.*

Since then, a number of meta-analyses of AMI risk with rosiglitazone or pioglitazone have been published, as have analyses of heart failure risk with these agents. In addition, a number of observational studies directly comparing rosiglitazone to pioglitazone have been published. This new information permitted a more robust analysis of cardiovascular risks with TZDs, particularly an informed comparison of rosiglitazone vs. pioglitazone.

We conducted a benefit risk assessment of rosiglitazone and pioglitazone, the results of which are summarized in table 16. The two TZDs were indistinguishable with respect to degree of glycemic control,[19,54-58] and both were associated with a comparable increase in body weight and body fat,[54,56-58] and increased risk of bone fractures in women by about 2-fold.[27,74,75] There was no clear difference in risk of malignancy between the two agents.[10,82,84-87] Both drugs also appeared to reduce blood pressure slightly.[10,11,61,62] There were clear differences in lipid effects produced by these agents. Rosiglitazone increased HDL-C levels by a small amount while increasing LDL-C and triglyceride levels by a sizable amount.[34,35] Pioglitazone increased HDL-C levels more than 2-times as much as and increased LDL-C levels by about one-half that of rosiglitazone, and substantially reduced triglyceride levels.[34,35] A meta-analysis concluded that the lipid profile produced by pioglitazone was more favorable than that of rosiglitazone from a cardiovascular perspective.[59]

There have been no long-term randomized controlled trials showing a protective effect of either TZD against the development of microvascular complications such as kidney failure, retinopathy, or blindness.[56-58] Several animal studies suggest that both TZDs might prevent renovascular disease and proteinuria.[63,64] Several studies in humans reported a reduction in proteinuria with either TZD, but these were small in size and short in duration.[65] The DREAM trial examined the effect of rosiglitazone and ramipril on a composite cardiorenal outcome in pre-diabetic patients.[72] In a secondary analysis, the effect on kidney function was examined. This analysis found that rosiglitazone reduced progression of albuminuria by 17%, while ramipril had no effect.[72] This latter finding was at odds with the HOPE trial, which found that ramipril reduced the development of overt nephropathy by 24%.[71] Of note, rosiglitazone had no effect on the estimated glomerular filtration rate. The authors suggested that the delay in progression to frank diabetes in the rosiglitazone-treated group may have been responsible for the reduction in progression of albuminuria.[72] An important limitation of this study was that only 78% of subjects had an end-of-study measure of urinary protein excretion. Excluded patients were younger, had lower serum creatinine levels, and lower fasting blood glucose levels than those included in the analysis.

Both TZDs reduced the level of inflammatory biomarkers in the blood,[87,88,90] and in-stent restenosis in patients who had undergone percutaneous coronary revascularization.[91] Pioglitazone reduced progression of carotid artery and coronary artery atherosclerosis.[92,93]

Although no head-to-head randomized controlled trials of rosiglitazone vs. pioglitazone for the occurrence of heart failure or AMI have been performed, a large number of individual studies and meta-analyses have been performed that permit a comparison to be made. Based on meta-analyses of randomized controlled trials, rosiglitazone appears to confer a 55%-75% increase in AMI risk compared with pioglitazone.[16,30,33] While both TZDs cause heart failure,[95,96] our analysis of published

meta-analyses[15,30,33,53] found that rosiglitazone increased heart failure risk by 50% compared with pioglitazone. These differences were statistically significant.

Table 16. Comparison of rosiglitazone and pioglitazone for benefits and risks

	Rosiglitazone (RSG)	Pioglitazone (PIO)
Glycemic control	Lowers HbA1c	Lowers HbA1c
Lipid effects	Unfavorable vs. PIO	Favorable vs. RSG
Body mass	Increases weight and body fat	Increases weight and body fat
Blood pressure	Small reduction	Small reduction
Kidney effects	Possible reduction in proteinuria	Possible reduction in proteinuria
Bone Fractures	Increases risk ~2-fold in women	Increases risk ~2-fold in women
Malignancy risk	No convincing evidence	No convincing evidence
Cardiovascular surrogates	Reduces inflammatory markers Reduces in-stent restenosis	Reduces inflammatory markers Reduces in-stent restenosis Reduces progression of coronary atherosclerosis
Heart failure	Increases risk 2.1-fold vs. other (50% higher risk vs. PIO)	Increases risk 1.4-fold vs. other
Microvascular disease	Minimal evidence for prevention	Minimal evidence for prevention
Cardiovascular disease	Increased risk vs. PIO	Reduced risk vs. RSG
Mortality	Neutral	Neutral

Although we found strong and consistent evidence that the risk of AMI and heart failure is substantially increased by rosiglitazone compared to pioglitazone, we did not find a difference in overall mortality. Possible explanations for this discordance between increased risk of AMI and heart failure without an accompanying increase in mortality include incomplete ascertainment of deaths in some clinical trials, high loss to follow-up in some studies, and relatively short duration of follow-up to determine the long-term effect of these events on mortality. Nonetheless, even in the absence of an increase in mortality, an increased risk of AMI and hospitalized heart failure with rosiglitazone represents a substantial additional morbidity burden that patients treated with pioglitazone do not face.

In an effort to determine whether the differences in AMI and heart failure risks between rosiglitazone and pioglitazone could be due to the types of patients enrolled in their respective clinical trials, we examined the demographic and treatment information presented in the rosiglitazone meta-analysis by Nissen et al.[16] and the pioglitazone meta-analysis by Linkoff et al.[33] (table 17). For the rosiglitazone trials, there were 14,371 patients randomized to rosiglitazone and 11, 634 patients enrolled to comparator therapy. For the pioglitazone trials, the corresponding numbers were 8,554 and 7,836.

Patients included in the pioglitazone trials were slightly older and more often male than patients included in rosiglitazone trials. The mean baseline HbA1c level appeared to be slightly greater among rosiglitazone patients, although this information was lacking for over 50% of pioglitazone patients, and the 7.9% HbA1c level shown for pioglitazone in table 17 was obtained from the PROactive trial.

Pioglitazone controlled trials had a greater proportion of patients treated for longer periods of time than rosiglitazone trials. Sixty-three percent of pioglitazone-treated patients in these trials were followed for more than 52 weeks compared to only 29% of patients for rosiglitazone. There were also differences in the distribution of concomitant diabetes therapy in the TZD arms of rosiglitazone and pioglitazone trials. The rosiglitazone arm of trials more often involved monotherapy, and were much less likely to consist of combination therapy with insulin or with metformin + sulfonylurea. Only 7% of patients included in the rosiglitazone arm of these trials were treated with in combination with insulin or in combination with both metformin and sulfonylurea, compared with 28% of patients in the pioglitazone arm of pioglitazone trials.

Review of the pattern of comparator therapies in rosiglitazone and pioglitazone trials also demonstrated major differences between the two TZDs. Placebo was the comparator therapy for 39% of rosiglitazone control patients compared with only 6% of pioglitazone controls. At the other end of therapeutic complexity, rosiglitazone controls were treated with insulin or with metformin + sulfonylurea in only 10% compared with 44% among pioglitazone controls. Among the subset of trials involving TZD monotherapy, only 40% of rosiglitazone controls received active therapy compared with 89% for pioglitazone.

From this analysis, it is clear that patients randomized into pioglitazone controlled trials required more complex diabetes therapy and had more advanced T2DM than those randomized into rosiglitazone trials. This is indicated by the much higher proportion of patients in the rosiglitazone and control arms of rosiglitazone trials who were treated with TZD monotherapy or placebo compared with pioglitazone trials. The much higher proportion of pioglitazone and control patients in the pioglitazone trials who were treated with the combination of metformin + sulfonylurea or with insulin in any combination also indicates that patients in the pioglitazone trials had more advanced T2DM than patients in rosiglitazone trials. Coupled with the older age and higher proportion of men in the pioglitazone trials, it is very likely that patients in the pioglitazone trials had a substantially greater burden of underlying cardiovascular disease than those in rosiglitazone trials. In support of this, we know that all patients enrolled in PROactive had established macrovascular disease[10] and this trial was the single largest contributor to the pioglitazone meta-analysis. In marked contrast, two of the largest rosiglitazone trials, DREAM[11] and ADOPT,[7] included only patients with pre-diabetes or newly diagnosed diabetes. The lower degree of underlying cardiovascular risk among rosiglitazone patients would be expected to have resulted in substantially lower risks of AMI and heart failure compared with pioglitazone. Despite the intrinsic bias against showing an excess risk with rosiglitazone introduced by the lower risk patients enrolled in rosiglitazone trials, our analysis has revealed a marked difference in risk between the two drugs, but in the direction opposite what *a priori* expectations might have suggested.

Table 17. Comparison of patient and treatment characteristics from randomized controlled trials contributing to the rosiglitazone meta-analysis by Nissen et al.[16] and the pioglitazone meta-analysis by Linkoff et al.[33]

		Rosiglitazone	Pioglitazone
Demographics (mean)	Age	56.1	58.1
	% Men	53.3	59.3
	% Caucasian	77.5	84
	% HbA1c	8.2	7.9†
Trial duration (weeks)	16-24	2956 (19%)	1938 (23%)
	25-52	8173 (52%)	1246 (15%)
	53-104	116 (1%)	1714 (20%)
	>104	4369 (28%)	3656 (43%)
TZD treatment combinations	Monotherapy	9282 (61%)	3199 (43%)
	+SU	2054 (13%)	1200 (16%)
	+Met	2482 (16%)	738 (10%)
	+Met/SU	0 (0%)	654 (9%)
	+Insulin	1127 (7%)	1406 (19%)
	+Other	110 (1%)	305 (4%)

		vs. any RSG		vs. any PIO	
		comb	vs. RSG mono	comb	vs. PIO mono
Comparator combinations	PBO	4562 (39%)	4562 (60%)	364 (6%)	259 (11%)
	SU	3021 (26%)	1635 (21%)	1697 (28%)	1510 (64%)
	Met	2638 (23%)	1451 (19%)	1018 (27%)	597 (25%)
	Met/SU	487 (4%)	0 (0%)	1293 (22%)	0 (0%)
	Insulin	714 (6%)	0 (0%)	1327 (22%)	0 (0%)
	Other	185 (2%)	0 (0%)	305 (5%)	0 (0%)

† From PROactive only because summary statistics for other studies not readily available.

PBO=placebo, SU=sulfonylurea, Met=metformin

Pioglitazone study OPI-506 was not included because study report submitted to FDA could not be located. This study population was listed as having "inadequately controlled DM-2" (as was the population enrolled in PROactive), making it highly unlikely that half of enrolled patients were treated with placebo and the other half with pioglitazone monotherapy.

This review provides a basis for concluding that despite similar effects on glycemic control, not all TZDs are the same with respect to off-target effects. Troglitazone, the first marketed TZD was shown to be a potent hepatotoxin. In 1999, at the time of approval of rosiglitazone and pioglitazone, the FDA's major safety concern was whether these TZDs would also prove to be hepatotoxic.

Rosiglitazone and pioglitazone are not particularly hepatotoxic, but our review demonstrates that there are important and serious differences between these two drugs with respect to AMI and heart failure risk. Of note, muraglitazar, a dual-PPAR agonist (α and γ) was shown to significantly increase cardiovascular risk, providing clear evidence that these agents can produce a wide variety of unexpected and differential off-target effects.[104] Peroxisome proliferator-activated receptors are nuclear transcription factors that affect the expression of multiple different genes.[54,105] Microarray analyses of troglitazone, rosiglitazone, and pioglitazone have demonstrated that while there are some genes for which transcription is increased by all three drugs, each also has unique gene transcription targets, which probably accounts for pleiotropic and differential off-target effects of these agents.[54,105-107] Recently experimental studies examining gene transcription in heart tissue from animals treated with rosiglitazone found that this TZD substantially increased the expression of metalloproteinase-3 (MMP-3), the gene that encodes for the matrix metalloprotein, stromelysin, which has been shown to promote atherosclerotic plaque rupture and AMI.[107] Perhaps also of importance, PPAR-γ agonist potency may correlate with atherosclerotic risk.[106] In this regard, muraglitazar had higher PPAR-γ potency than rosiglitazone, and rosiglitazone higher potency than pioglitazone.[106]

In summary, there was no evidence that rosiglitazone confers any unique health benefit over pioglitazone while there was strong evidence that rosiglitazone confers an increased risk of AMI and heart failure compared to pioglitazone. This increased risk has caused a substantial excess number of cases of AMI and heart failure that would not have occurred had pioglitazone been used instead. We conclude that the risks associated with rosiglitazone use are excessive given the availability of a safer alternative and the absence of a compelling and unique health benefit that might justify its use.

5.2 Drug Usage and Expert Opinion

From the prescription drug use data, it appears that a substantial majority of the medical community has reached a similar conclusion. Prior to May 2007, utilization patterns for rosiglitazone and pioglitazone were virtually identical. Today, rosiglitazone use accounts for about 25% of the TZD market. While some may argue that this fall-off in rosiglitazone use has resolved the public health problem, we disagree. At current levels of use, rosiglitazone continues to generate an excess of about 500 AMI cases and 300 heart failure cases per month, compared to what would occur if pioglitazone were used exclusively.

It should also be noted that in the year since the rosiglitazone advisory committee meeting, several professional organizations have issued clinical management recommendations for diabetes. In late 2007, the Medical Letter recommended that "as monotherapy for diabetes and as a second drug, a sulfonylurea or metformin is preferred. If a thiazolidinedione is chosen as a third drug, pioglitazone is preferred over rosiglitazone."[108] The publication, Journal Watch, concluded that, although study results "cannot be considered conclusive, current evidence suggests a potential cardiotoxicity with rosiglitazone and potential cardioprotection with pioglitazone."[109] One of the clinical recommendations was that "treatment with rosiglitazone should not be initiated in rosiglitazone-naïve patients."[109] In 2008, the Drug and Therapeutics Bulletin concluded that "if a thiazolidinedione is thought to be necessary, pioglitazone is probably safer [than rosiglitazone]."[110]

In September of last year, an editorial in JAMA accompanying publication of two new (post-AC) meta-analyses cautioned that rosiglitazone and pioglitazone have "strikingly different profiles in their effects on ischemic cardiovascular outcomes."[111] This editorial also stated that "decisions for

initial approval of a drug and subsequent continued marketing should be symmetric," and asserted that "the public expects that FDA approval is a seal of safety."[111] An editorial in the New England Journal of Medicine sounded a similar theme, and pointed out that "the level of risk with rosiglitazone is substantial and approximately equivalent in magnitude, but in the opposite direction, to the health benefits of lipid lowering statin drugs."[112] Finally, it also should be noted that we were unable to identify a single publication where rosiglitazone was recommended in preference to pioglitazone. A synopsis of editorials and commentaries from the literature published since 2007 is included in the Appendix.

5.3 Ethical Considerations

In light of our review, we have serious reservations regarding a planned head-to-head cardiovascular outcomes trial of rosiglitazone vs. pioglitazone, announced in a FDA press release in November 2007.[113] First, equipoise does not exist. There are a number of different working definitions of "equipoise." Freedman described equipoise as a condition reflected by "*equivalent evidence*" (emphasis added) for alternative hypotheses.[114] That is, there must be equal evidence favoring both therapies. But that is not the case here because no one has argued that rosiglitazone is safer than or preferable to pioglitazone. It is also difficult to argue that there is "imminent conflict in the clinical community over what treatment is preferred,"[114] given that the ratio of pioglitazone to rosiglitazone use in the US stands at 3:1, suggesting a clear preference in favor of pioglitazone.

In another formulation, Djulbegovic described equipoise as a condition of "maximum uncertainty" regarding the choice of one therapy over another.[115] He proposed that for equipoise to exist, there must be "equally distributed uncertainty" about the relative effects of competing therapies.[115] With the TZDs, there appears to be no meaningful difference regarding glycemic control and the evidence for cardiovascular harm is decidedly one-sided, implicating rosiglitazone but not pioglitazone.

The Belmont Report concluded that for clinical research to be ethical, the risks to subjects must be outweighed by the sum of the anticipated benefits to the subject.[116] The proposed clinical trial of rosiglitazone vs. pioglitazone[113] fails this standard of "positive expected value" because the two drugs are equivalent with respect to glycemic control but are likely very different with respect to risks and harms.

The question reduces to whether it is ethical to conduct a clinical trial when there is no unique health benefit to be gained from trial participation, but there are substantial likely risks if subjects are treated with the drug associated with a greater risk of serious injury or harm (in this case, rosiglitazone). The ethical argument against such a study is increased when the true purpose of the study is to establish whether one drug is more harmful than another, rather than one drug being more beneficial or efficacious than another. No one would argue about the ethical permissibility of a trial that offered subjects a treatment that is better than any alternative they could receive outside the trial, or that if it didn't offer such benefits, imposed insignificant or no risks of harm. However, when there is no prospect of a clinically meaningful added benefit, but one of the options offered poses a "non-negligible risk of significant harm," you have what has been described as a "bad deal" trial.[117] Participation in such a trial is not in the best interests of at least some of the subjects who will be enrolled. The performance of such a trial ultimately relies on exploitation of study participants for its completion.[117] This exploitation is not mitigated by "informed consent" because the distribution of "benefits" arising from the study are too one-sided.[117] As noted by Nycum and Reid, most "bad deal" trials are likely to occur during Phase 1, where small numbers of usually healthy subjects are exposed to an experimental agent and where the "benefits," if any, are minimal, while the potential for harm is relatively greater.[118] Applying their reasoning to the currently proposed head-to-head trial, there is at best only a remote to non-existent possibility that individual study participants randomized to

rosiglitazone will experience a clinically meaningful health benefit above that of pioglitazone, while the *a priori* likelihood of clinically meaningful excess harm from rosiglitazone is much very high.[118]

Two "tests" have been offered to help establish if exploitation is present within a "bad deal" trial. The first test requires that all participants be "completely altruistic" and that there be an important net societal benefit to knowing the results of such a trial.[117] It is virtually impossible to be certain that "complete altruism" is present in a given potential study subject, let alone the many thousands that would be needed for the proposed TZD trial. It also is difficult to argue that there is a substantial societal benefit to knowing with definitive certainty that rosiglitazone increases AMI or heart failure risk when the concern relates to safety and harms rather than efficacy and health benefits. The medical community and patients would be no worse off were rosiglitazone no longer marketed. The second "test" requires that we examine the distribution of benefits and costs (including harms) associated with the trial. If the benefits and harms are not equally distributed among study participants, the trial is exploitative.[117] In the TZD setting, none of the participants will derive any additional meaningful health benefit from rosiglitazone, but among the 50% of subjects who receive rosiglitazone, they will be subjected to a treatment that poses a "non-negligible risk of significant harm." The requirement for balanced distribution of benefits and harms is especially important when dealing with a severe harm (e.g., AMI, heart failure), where the tolerance for an imbalance in risk between treatments must be very low.[117]

The proposed head-to-head trial of rosiglitazone vs. pioglitazone is a "bad deal" trial, and by its nature, exploitative. While a utilitarian argument holds that the social value of certain research may be sufficient to override the welfare of individual study participants, investigators and regulators have a "duty of non-exploitation," whereby utilitarian considerations are constrained and limited, and individual subjects are protected.[119] Of note, informed consent does not render an exploitative study non-exploitative because it does not alter the underlying dynamic whereby some study participants are placed at increased risk of severe harm without expectation of added or enhanced health benefits.[120]

Djulbegovic examined clinical trial participation and ethics from the perspective of game theory, where one seeks to optimize the Nash equilibrium, which he conceptualized as "the probability of random allocation at which both researcher and patient are most likely to achieve their strategic goals."[121] Under this analysis, randomization is only rational if the distribution of success with one of the therapies is about equal to that of the comparator.[121] Deviation from the optimal solution of Nash equilibrium suggests that a trial is unethical.[121] On the basis of rationality, patients would be expected to select the therapeutic "option with the highest expected utility,"[121] which based on the available evidence, would be pioglitazone.

As discussed, the patients participating in a head-to-head trial of rosiglitazone vs. pioglitazone would not benefit from the trial, but the organization sponsoring the trial (e.g., the drug manufacturer) could very well benefit. This is an exploitative distribution of trial benefits because study participants do not benefit from participation, but the company potentially does.[115,117,118,121] The ethics literature states that risks within a trial that are not offset by benefits to individuals could still be ethical if they are sufficiently offset by gains in knowledge that the research is designed to generate. In a "bad deal" trial, there is only a remote possibility of individual benefit and relatively low possibility of social benefit.[118]

Emmanuel et al. have explored why informed consent, by itself, does not make clinical research ethical.[120] To be ethical, clinical research must improve patient health or develop knowledge that improves patient health. In the latter context, the potential for exploitation exists because the risk of harm would be experienced by study participants while the benefit, if any, would accrue to others not in the study.[120] The proposed TZD study fails to meet this first requirement because the two drugs in question are comparable with respect to glycemic control and any other putative health benefit, but

differ with respect to risk of serious harms. As a result, this research will not improve the health of participants. Since there is no expectation that rosiglitazone provides better treatment of type 2 diabetes or is meaningfully safer than pioglitazone, it's also difficult to maintain that this trial would improve the health of other patients.

The methodology employed in the study must be rigorous and valid. Unsound research is unethical.[120] If the proposed study asks the wrong question, or is underpowered, or can't enroll sufficient numbers of subjects, it would be unethical. In this regard, what level of excess cardiovascular risk with rosiglitazone can be justified, given that it confers no additional or unique health benefits compared to pioglitazone? Even a 5% increase in AMI or heart failure risk with rosiglitazone would translate into hundreds of excess cases per year in exchange for no material benefit.

To be ethical, a study must also adhere to "fair subject selection."[120] There are two components to this requirement. Those who bear the risks and burdens of the research should be in a position to enjoy its benefits.[116] This presumes that the study under consideration is focused on establishing superior benefits. However, the proposed TZD study is about harms. There are no "net benefits" to be shared or enjoyed by the study participants. This asymmetry of benefits (none) and harms (potentially severe and relatively frequent) violate the principle of fair subject selection.[120] The second component of this requirement is that eligible patients at substantially higher risk of experiencing harm should be excluded from the study.[120] The proposed TZD study may also violate this component because the harms under study (AMI, heart failure) are known to be increased in patients with T2DM, and diabetic patients with underlying macrovascular disease would be expected to be at even greater risk.

A fourth requirement of an ethical study is that there is a favorable benefit-risk balance within the study.[120] For this to be so, potential risks to subjects must be minimized, potential benefits to individual subjects must be maximized, and the potential benefits to individuals and society must be proportionate to or outweigh the risks.[120] The proposed TZD study appears to fail this requirement. Risks can not be minimized because the risks in question are intrinsic properties of one of the study drugs. There are no health benefits to be maximized because both rosiglitazone and pioglitazone are comparable with respect to glycemic control. Finally, given there is no unique and substantial health benefit associated with rosiglitazone compared to pioglitazone, there are no net benefits for study subjects or society that will exceed the risks experienced by subjects randomized to rosiglitazone.

A fifth requirement for an ethical study is that there be independent review.[120] This poses a problem because most of those involved in the design or review of a proposed TZD study will have received compensation from the sponsoring company. More importantly, it is well-established that industry funded studies are much more likely to obtain results favorable to the sponsoring company's drug than similar studies funded by public entities.[122-128]

An ethical study also requires informed consent.[116,120] What would informed consent for a proposed TZD study look like? Would patients be told that there are no unique health advantages for rosiglitazone over pioglitazone and that there is nothing beneficial to be gained by participating in the study? Would patients be told that there is no net societal benefit to this study because pioglitazone treats T2DM just as well as rosiglitazone, but rosiglitazone probably increases the risk of AMI and heart failure? In this context, FDA's labeling of rosiglitazone cardiovascular risks while semantically correct, is very misleading.[19] To say that the results of various studies are "inconclusive" ignores the fact that multiple meta-analyses convincingly show that there is, in all likelihood, a meaningful excess risk associated with rosiglitazone compared to pioglitazone. The Agency's standard of "definitive proof" (generally defined as a p-value < 0.05 for some effect) may be appropriate for the evaluation of drug efficacy, but it is not an appropriate standard of evidence for harm, especially when the harm is serious and there is no unique and off-setting health benefit for the drug in question.

Finally, would patients be fully informed about what is known about the comparative risks of rosiglitazone and pioglitazone? Even if all these concerns were fully addressed, there would still remain the problem that informed consent can not render a "bad deal" trial ethical.[117,118]

The final requirement of an ethical study is that there be respect for study subjects.[117] The proposed TZD study may not be able to meet this requirement because it probably would be exploitative, a direct violation of respect for subjects.[115,116-118] In addition, it is difficult to convincingly claim that the welfare of study subjects (a component of "respect") is a primary value of investigators who are conducting a study, the purpose of which is to establish if one of the study drugs (rosiglitazone) is more harmful than an equally effective alternative (pioglitazone). Now it is possible that sponsors of this study might try to portray this proposed study of rosiglitazone and pioglitazone as a study to establish health benefits, but based on the 2007 advisory committee meeting,[18] internal discussions, and this review, the study we are talking about specifically relates to harms, with the concern that rosiglitazone is more harmful than pioglitazone.

6 CONCLUSIONS

Rosiglitazone and pioglitazone have comparable efficacy with respect to glycemic control in patients with T2DM. Rosiglitazone confers no unique health benefits beyond those conferred by pioglitazone. Based on the most recent and best available evidence, rosiglitazone increases AMI risk compared to pioglitazone and this increase is clinically important in this population. While both rosiglitazone and pioglitazone increase the risk of heart failure, the increase caused by rosiglitazone is substantially greater than that caused by pioglitazone. Based on these findings, any proposed head-to-head trial of rosiglitazone vs. pioglitazone would be unethical and exploitative.

7 RECOMMENDATIONS

The risks of rosiglitazone use are serious and exceed those for pioglitazone. Rosiglitazone confers no unique and medically important benefit that distinguishes it from pioglitazone. The risks of rosiglitazone use exceed its benefits compared to pioglitazone. Rosiglitazone should be removed from the market.

8 REFERENCES

1. National Institute of Diabetes and Digestive Diseases. National Institutes of Health. Available at: http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm. Accessed June 3, 2008.
2. Haffner SM, Lehto S, Ronnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998; 339(4):229-34.
3. Gu K, Cowie CC, Harris MI. Diabetes and decline in heart disease mortality in US adults. JAMA 1999; 281(14):1291-97.
4. Riddle MC, Genuth S. Type 2 diabetes mellitus. In: ACP Medicine (2007), Federman DD, Dale DC, eds. WebMD Corporation, New York, 2007. Available at: http://online.statref.com/TOC/TOC.aspx?SessionId=C84998TQXPUPIXVU. Accessed June 3, 2008.
5. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352(9131):837-53.
6. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352(9131):854-65.
7. Gerstein HC, Miller ME, Byington RP, Goff DC, Bigger T, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358(24):2545-59.
8. HHS press release. Rezulin to be withdrawn from the market. March 21, 2000. Available at: http://www.fda.gov/bbs/topics/NEWS/NEW00721.html. Accessed June 3, 2008.
9. Lumpkin MM. Troglitazone: presentation to the advisory committee. Meeting of the FDA's Endocrine and Metabolic Drugs Advisory Committee. Rockville, MD, May 21, 2000. Available at: http://www.fda.gov/ohrms/dockets/ac/00/slides/3615s1.htm. Accessed June 3, 2008.
10. Dormandy JA, Charbonnel B, Eckland DJA, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005; 366(9493):1279-89.
11. The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006; 368(9541):1096-105.
12. Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones JP, etal. Rosiglitazone evaluated for cardiovascular outcomes - an interim analysis. N Engl J Med 2007; 357(1):28-38.
13. Singh S, Loke YK, Furberg CD. Thiazolidinediones and heart failure: a teleo-analysis. Diabetes Care 2007; 30(8):2148-53.
14. Eurich DT, McAlister FA, Blackburn DF, Majumdar SR, Tsuyuki RT, Vamey J, et al. Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. BMJ 2007; 335(7618):497.
15. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis. Lancet 2007; 370(9593):1129-36.
16. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007; 356(24):2457-71.

17. Mele J. Statistical review and evaluation of rosiglitazone clinical trials (meta-analysis). US Food and Drug Administration, June 4, 2007. Available at: http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-02-fda-backgrounder.pdf, pp 13-105. Accessed May 30, 2008.
18. Joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. Gaithersburg, MD, July 30, 2007. Transcript available at: http://www.fda.gov/ohrms/dockets/ac/cder07.htm#EndocrinologicMetabolic. Accessed June 3, 2008.
19. Avandia® (rosiglitazone maleate) Tablets label. November 14, 2007. Available at: http://www.fda.gov/cder/foi/label/2007/021071s031lbl.pdf. Accessed June 3, 2008.
20. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and practice. BMJ 1997; 315(7121):1533-37.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clin Trials 1986; 7:177-88. .
22. Petitti DB. Meta-analysis, decision analysis and cost-effectiveness analysis, 2nd ed. Oxford University Press, New York, 2000:213-43.
23. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327(7414):557-60.
24. Egger M, Davey-Smith G, Schneider M... Bias in meta-analysis detected by a simple graphical test. BMJ 1997; 315(7109):629-34.
25. Verispan Vector One® : national, years 1999-2006 and months January 2007 through May 2008, data extracted 3/27/07 and 6/10/08.
26. Mahoney KM. Avandia NDA 21071 Supplement 22 Complete Response. Clinical Review. Food and Drug Administration. August 12, 2008.
27. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, etal. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006; 355(23):2427-43.
28. Food and Drug Administration. FDA Briefing Document. Division of Metabolism and Endocrine Products and Office of Surveillance and Epidemiology. Joint meeting of the EMDAC and DSaRM held on July 30, 2007. Available at: http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-02-fda-backgrounder.pdf. Accessed June 19, 2008.
29. Mele J. Statistical review and evaluation. Addendum to review completed 6/4/07. US Food and Drug Administration, July 3, 2007.
30. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA 2007; 298(10):1189-95.
31. Duckworth WC, McCarren M, Abraira C. Glucose control and cardiovascular complications: the VA Diabetes Trial. Diabetes Care 2001; 24(5):942-45.
32. Duckworth WC, Moritz TE. Press conference. 68th Scientific Meeting of the American Diabetes Association, San Francisco, CA, June 8, 2008. Available at: http://www.medpagetoday.com/MeetingCoverage/ADA/tb/9749. Accessed June 23, 2008.
33. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus. A meta-analysis of randomized trials. JAMA 2007; 298(10):1180-88.
34. Goldberg RB, Kendall DM, Deeg MA. Comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care 2005; 28(7):1547-54.
35. Misbin R. Medical officer review of GLAI study, NDA 210783. US Food and Drug Administration, April 23, 2007.

36. McAfee AT, Koro C, Landon J, Ziyadeh N, Walker AM. Coronary heart disease outcome in patients receiving antidiabetic agents. Pharmacoepidemiol Drug Saf 2007; 16(7):711-25.
37. Rothman KJ, Greenland S. Modern epidemiology, 2nd edition. Lippincott-Raven Publishers, Philadelphia, 1998.
38. Clayton D, Hills M. Statistical models in epidemiology. Oxford University Press, New York, 1994.
39. Wang CP, Haffner S, DeFronzo R, Pugh J. Differential rosiglitazone effects on cardiovascular disease in VA type 2 diabetes patients (abstract). Presented at the American Diabetes Association meeting, San Francisco, June 2008. Available at: http://scientificsessions.diabetes.org/index.cfm?fuseaction=Locator.SearchAbstracts&CalledByID=1052. Accessed July 23, 2008.
40. Xu Y, Vallarino R, Baran W, Spanheimer R. Risk of stroke and myocardial infarction is reduced in patients with type 2 diabetes treated with pioglitazone: results of a retrospective, claims-based study (abstract). Diabetologia 2007; 50(Suppl 1):S513-14.
41. Lipscombe LL, Gomes T, Lévesque LE, Hux JE, Juurlink DN, Alter DA. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. JAMA 2007; 298(22):2634-43.
42. Gerrits CM, Bhattacharya M, Manthena S, Baran R, Perez A, Kupfer S. A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes. Pharmacoepidemiol Drug Saf. 2007; 16(12):1314-6.
43. Walker AM, Koro CE, Landon J. Coronary heart disease outcomes in patients receiving antidiabetic agents in the PharMetrics database, 2000-2007. Pharmacoepidemiol Drug Saf 2008; published online February 2008, DOI: 10.1002pds.1598.
44. Casscells SW, Granger E, Swedorske J, Goldhammer R, Shaheen M, Dorris J, et al. A comparison of select cardiovascular outcomes by antidiabetic prescription drug classes used to treat type 2 diabeted among military health system beneficiaries, fiscal year 2003-2006. Am J Ther 2008; 15(3):198-205.
45. Margolis DJ, Hoffstad O, Strom BL. Association between serious ischemic cardiac outcomes and medications used to treat diabetes. Pharmacoepidemiol Drug Saf 2008; published online: Jul 9 2008 DOI: 10.1002/pds.1630.
46. GlaxoSmithKline. Study WE145. Available at: http://ctr.gsk.co.uk/Summary/rosiglitazone/studylist.asp. Accessed May 30, 2007.
47. Suissa S. Immortal time bias in pharmacoepidemiology. Am J Epidemiol 2007; 167(4):492-99.
48. Miller DR, Christiansen C, Palnatti M, Lafrance JP, Pogach L, Cunningham FE. VA study of cardiovascular disease risks with use of rosiglitazone or pioglitazone. Manuscript in preparation.
49. Singh G, Graham DJ, Triadilopoulos G. Acute myocardial infarction risk in patients treated for type 2 diabetes within California Medicaid (unpublished, manuscript in preparation)
50. Nussbaum SR. Risk for myocardial infarction in patients treated with thiazolidinediones. Presented at the joint meeting of Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee, Gaithersburg, MD, July 30, 2007. Transcript and slides available at: http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4308s1-00-index.htm. Accessed June 5, 2008.
51. Dargie H, Hildebrandt PR, Riegger GAJ, McMurray JJ, McMorn SO, Roberts JN, et al. A randomized, placebo-controlled trial assessing the effects of rosiglitazone on echocardiographic function and cardiac status in type 2 diabetic patients with New York Heart Association functional class I or II heart failure. J Am Coll Cardiol 2007; 49(16):1696-704.
52. Mannucci E, Monami M, Lamanna C, Gensini GF, Marchionni N. Pioglitazone and cardiovascular risk. A comprehensive meta-analysis of randomized clinical trials. Diabetes Obes Metab 2008; published online May 26. DOI: 10.1111/j.1463-1326.2008.00892.x.

53. Hosmer DW, Lemeshow S. Applied logistic regression, 2nd edition. John Wiley and Sons, Inc., New York, 2000.
54. Yki-Järvinen H. Thiazolidinediones. N Engl J Med 2004; 351(11):1106-18.
55. Actos® (pioglitazone hydrochloride) Tablets label. September 6, 2007. Available at: http://www.fda.gov/cder/foi/label/2007/021073s030lbl.pdf. Accessed June 6, 2008.
56. Richter B, Bandiera-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Rosiglitazone for type 2 diabetes. Cochrane Database System Rev 2007 Jul 18; (3):CD006063.
57. Richter B, Bandiera-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Pioglitazone for type 2 diabetes. Cochrane Database Syst Rev 2007 Oct 18; (4):CD006060
58. Bolen S, Felman L, Vassy J. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med 2007; 147(6):386-99.
59. Chiquette E, Ramirez G, DeFronzo R. A meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors. Arch Intern Med 2004; 164(19):2097-104.
60. Czosky-Murray C, Warren E, Chilcott J, Beverley C, Psyllaki MA, Cowan J. Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation. Health Technol Assess 2004; 8(13):1-91.
61. de Rivas B, Luque M, Maartell N, Fernández C, Fernández-Cruz A. Pioglitazone decreases ambulatory blood pressure in type 2 diabetics with difficult-to-treat hypertension. J Clin Hypertens 2007; 9(7):530-37.
62. Komajda M, Curtis P, Hanefeld M, Beck-Nielsen H, Pocock SJ, Zambanini A, et al. Effect of the addition of rosiglitazone to metformin or sulfonylureas versus metformin / sulfonylurea combination therapy on ambulatory blood pressure in people with type 2 diabetes: a randomized controlled trial (the RECORD study). Cardiovasc Diabetol 2008; 7:10.
63. Yoshioka S, Nishino H, Shiraki T et al. Antihypertensive effects of CS-045 treatment in obese Zucker rates. Metabolism 1993; 42: 75-80.
64. Sarafidis PA, Bakris GL. Protection of the kidney by thiazolidinediones: an assessment from bench to bedside. Kidney Int. 2006; 70(7):1223-33.
65. Rohatgi A, McGuire DK. Effects of the thiazolidinedione medications on micro- and macrovascular complications in patients with diabetes-Update 2008. Cardiovasc Drugs Ther 2008; Mar 29.
66. Zheng F, Guan Y. Thiazolidinediones: a novel class of drugs for the prevention of diabetic nephropathy? Kidney Int. 2007; 72(11):1301-03.
67. Bao Y, Jia RH, Yuan J, Li J. Rosiglitazone ameliorates diabetic nephropathy by inhibiting reactive oxygen species and its downstream-signaling pathways. Pharmacology 2007; 80(1):57-64.
68. Pereira MG, Câmara NO, Campaholle G, Cenedeze MA, de Paula Antunes Teixeira V, dos Reis MA, et al. Pioglitazone limits cyclosporine nephrotoxicity in rats. Int Immunopharmacol 2006; 6(13-14):1943-51.
69. Namikoshi T, Satoh M, Tomita N, Haruna Y, Kobayashi S, Komai N, Sasaki T, Kashihara N. Pioglitazone ameliorates endothelial dysfunction in obese rats with nephropathy. Biochem Biophys Res Commun 2007; 361(4):835-40.
70. Dagenais GR, Gerstein HC, Holman R, Budaj A, Escalante A, Hedner T, et al. Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. Diabetes Care 2008; 31(5):1007-14.
71. The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators: effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and Micro-HOPE substudy. Lancet 2000; 355(): 253-59.

72. Kincaid-Smith P, Fairley KF, Farish S, Best JD, Proietto J. Reduction of proteinuria by rosiglitazone in non-diabetic renal disease. Nephrology 2008; 13(1):58-62.
73. Schneider CA, Ferrannini E, Defronzo R, Schernthaner G, Yates J, Erdmann E. Effect of pioglitazone on cardiovascular outcome in diabetes and chronic kidneydisease. J Am Soc Nephrol 2008; 19: 182-87.
74. Takeda. Observation of an increased incidence of fractures in female patients who received long-term treatment with Actos® (pioglitazone HCl) tablets for type 2 diabetes mellitus. March 2007. Available at: http://www.fda.gov/medwatch/safety/2007/Actosmar0807.pdf. Accessed July 11, 2008.
75. Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, Meier CR. Use of thiazolidinediones and fracture risk. Arch Intern Med 2008; 168(8):820-25.
76. Benvenuti S, Cellai I, Luciani P, Deledda C, Baglioni S, Giuliani C, Saccardi R, Mazzanti B, Dal Pozzo S, Mannucci E, Peri A, Serio M. Rosiglitazone stimulates adipogenesis and decreases osteoblastogenesis in human mesenchymal stem cells. J Endocrinol Invest 2007; 30(9):RC26-30.
77. Wan Y, Chong LW, Evans RM. PPAR-gamma regulates osteoclastogenesis in mice. Nat Med. 2007; 13(12):1496-503.
78. Grey AB. Skeletal toxicity of thiazolidinediones. Ann Intern Med 2008; 148(7):563.
79. Grey A. Skeletal consequences of thiazolidinedione therapy. Osteoporos Int 2008; 19(2):129-37.
80. Grey A, Bolland M, Gamble G, et al. The peroxisome proliferator-activated receptor-gamma agonist rosiglitazone decreases bone formation and bone mineral density in healthy postmenopausal women: a randomized, controlled trial. J Clin Endocrinol Metab 2007; 92:1305-1310.
81. Yaturu S, Bryant B, Jain SK. Thiazolidinedione treatment decreases bone mineral density in type 2 diabetic men. Diabetes Care 2007; 30(6):1574-76.
82. Final printed labeling. Actos (pioglitazone), NDA 21-073, July 1999. Available at: http://www.fda.gov/cder/foi/nda/99/021073A_Actos.htm. Accessed August 1, 2008.
83. Cohen S. Effects of PPAR-γ and combined agonists on the urinary tract of rats and other species. Toxicol Sci 2005; 87: 322-327.
84. Oliveria SA, Koro CE, Ulcickas-Yood M, Sowell M. Cancer incidence among patients treated with antidiabetic pharmacotherapy. Diabetes and Metabolic Syndrome: Clinical Research and Reviews 2008; 2(1): 47-57.
85. Ramos-Nino ME, MacLean CD, Littenberg B. Association between cancer prevalence and use of thiazolidinediones: results from the Vermont Diabetes Information System. BMC Med. 2007; 5:17
86. Govindarajan R, Ratnasinghe L, Simmons DL, Siegel ER, Midathada MV, Kim L, Kim PJ, Owens RJ, Lang NP. Thiazolidinediones and the risk of lung, prostate, and colon cancer in patients with diabetes. J Clin Oncol 2007; 25(12):1476-81.
87. Haffner SM, Greenberg AS, Weston WM, Chen H, Williams K, Freed MI. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. Circulation 2002; 106(6):679-84.
88. Szapary PO, Bloedon LT, Samaha FF, Duffy D, Wolfe ML, Soffer D, et al. Effects of pioglitazone on lipoproteins, inflammatory markers, and adipokines in nondiabetic patients with metabolic syndrome. Atheroscler Thromb Vasc Biol 2006; 26(1):182-88.
89. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002; 347(20):1557-65.
90. Schulze MB Rimm EB, Li T, Rifai N, Stampfer MJ, Hu FB. C-reactive protein and incident cardiovascular events among men with diabetes. Diabetes Care 2004; 27(4):889-94.

91. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006; 6(10):772-83.
92. Mazzone T, Meyer PM, Feinstein MB, Davidson MH, Kondos GT, D'Agostino RB Sr, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. JAMA 2006; 296(21):2572-81.
93. Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, et al. Comparison of pioglitazone vs glimepiride on progressive coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA 2008; 299(13):1561-73.
94. Rosmarakis ES, Falagas ME. Effect of thiazolidinedione therapy on restenosis after coronary stent implantation: a meta-analysis of randomized controlled trials. Am Heart J 2007; 154(1):144-50.
95. Labeling for Avandia® (rosiglitazone maleate) tablets. Available at: http://www.fda.gov/cder/foi/label/2008/021071s026lbl.pdf. Accessed July 16, 2008.
96. Labeling for Actos® (pioglitazone hydrochloride) tablets. Available at: http://www.fda.gov/cder/foi/label/2007/021073s030lbl.pdf. Accessed July 16, 2008.
97. Shen LQ, Child A, Weber GM, Folkman J, Aiello LP. Rosiglitazone and delayed onset of proliferative diabetic retinopathy. Arch Ophthalmol 2008; 126(6):793-99.
98. Jin HM, Pan Y. Renoprotection provided by losartan in combination with pioglitazone is superior to renoprotection provided by losartan in patients with type 2 diabetic nephropathy. Kidney Blood Press Res 2007; 30(4):203-11.
99. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998; 317(7160):703-13.
100. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ 1998; 317(7160):713-20.
101. Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G, et al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). Diabetes Care 1997; 20(4):614-20.
102. Sever PS, Poulter NR, Dahlöf B, Wedel H, Collins R, Beevers G, et al. Reduction of cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes. Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA). Diabetes Care 2005; 28(5):1151-57.
103. Stratton IM, Adler AI, Neil AW, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321(7258):405-12.
104. Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major cardiovascular events in patients with type 2 diabetes mellitus. JAMA 2005; 294(20):2581-86.
105. Hsiao A, Worrall DS, Olefsky JM, Subramanium S. Variance-modelled posterior inference of microarray data: detecting gene expression changes in 3T3-L1 adipocytes. Bioinformatics 2004; 20(17):3108-27.
106. Lehmann DF, Lohray BB. A lesson in moderation: applying pharmacodynamics to clarify the relationship between thiazolidinediones and adverse vascular outcomes in type 2 diabetes (letter). J Clin Pharmacol 2008; 98:999-1002.
107. Wilson KD, Li Z, Wagner R, Yue P, Tsao P, Nestorova G, et al. Transcription alteration in the diabetic heart by rosiglitazone: implications for cardiovascular mortality. PLoS ONE 2008; 3(7):e2609.
108. Thiazolidinediones and cardiovascular disease. Med Lett 2007; 49(1267):57-58.
109. Pendergrass M. Clinical decision making regarding the use of glitazones: making practice out of incomplete information. In: Physician's First Watch, Fairchild D (Ed.). Available at:

http://www.jwatch.org/misc/fdpprems/PFW_Rosiglitazone_Report.pdf. Accessed June 3, 2008.
110. Glitazones in type 2 diabetes: an update. Drug Ther Bull 2008; 46(4):25-29.
111. Solomon DH, Winkelmayer WC. Cardiovascular risk and the thiazolidinediones: déjà vu all over again? JAMA 2007; 298(10):1216-18.
112. Psaty BM, Furberg CD. The record on rosiglitazone and the risk of myocardial infarction. N Engl J Med 2007; 357: 67-69.
113. FDA press release. FDA adds boxed warning for heart-related risks to anti-diabetes drug Avandia. November 14, 2007. Available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01743.html. Accessed August 4, 2008.
114. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987; 317(3):141-45.
115. Djulbegovic B. Articulating and responding to uncertainties in clinical research. J Med Phil 2007; 32:79-88.
116. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: ethical principles and guidelines for the protection of human subjects of research. US Department of Health, Education and Welfare, publication no. 78-0012. Washington, DC: Government Printing Office; 1978. Available at: http://ohsr.od.nih.gov/guidelines/belmont.html. Accessed May 15, 2008.
117. Jansen LA. A closer look at the bad deal trial. Beyond clinical equipoise. Hastings Center Report 2005; 35(5):29-36.
118. Nycum G, Reid L. The harm-benefit tradeoff in "bad deal" trials. Kennedy Inst Ethics J 2008; 17(4):1321-50.
119. London AJ. Two dogmas of research ethics and the integrative approach to human-subjects research. J Med Phil 2007; 32:99-116.
120. Emmanuel E, Wendler D, Grady C. What makes clinical research ethical? JAMA 2000; 283(20):2701-11.
121. Djulbegovic B, Lacevic M. Cantor A, Fields KK, Bennett CL, Adams JR, et al. The uncertainty principle and industry-sponsored research. Lancet 2000; 356:635-38.
122. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ 2003; 326:1167-70.
123. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. JAMA 2003; 289:454-65.
124. Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse effects? JAMA 2003; 290:921-28.
125. Bhandari M, Busse JW, Jackowski D, Montori VM, Schuneman H, et al. Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. CMAJ 2004; 170:477-80.
126. Fries JF, Krishnan E. Equipoise, design bias, and randomized controlled trials: the elusive ethics of new drug development. Arthritis Res Ther 2004; 6(3):R250-R255.
127. Jørgensen A, Jørgen H, Gøtzsche PC. Cochrane reviews compared with industry-supported meta-analyses and other meta-analyses of the same drugs: a systematic review. BMJ 2006; 332(7572):782-85.
128. Bero L, Oostvogel F, Bacchetti P, Lee K. Factors associated with findings of published trials of drug-drug comparisons: why some statins appear more efficacious than others. PLoS Med 2007; 4(6):e184.

9 APPENDIX

Betteridge DJ, DeFronzo RA, Chilton RJ. PROactive: time for a critical appraisal. Eur Heart J 2008; 29(8):969-83

Author's affiliation(s): Department of Medicine, Royal Free and University College Medical School, London, and Division of Diabetes, University of Texas Health Science Center, San Antonio, TX. *(Note: the author (DJB) has served as a consultant to Takeda and is a Principal Investigator for PROactive; RAD has received grants from BMS, Amylin, Eli Lilly, Novartis, Pfizer, Takeda, and Roche, and is on the Speakers' Bureau for Amylin and Takeda; RLC has received honoraria from Pfizer, MSD, GSK, Takeda, Medtronics, and Boston Scientific for lectures.)*

Main argument(s): There has been much debate on the relative merits of the statistically non-significant 10% decrease in the primary endpoint vs. the statistically significant 16% decrease in the main secondary endpoint seen with pioglitazone. Although the definition of the main secondary endpoint (i.e. time to the first event of death, MI [excluding silent MI], or stroke), was not stated in the baseline characteristics paper, a working party recognized the importance of this composite endpoint and added it to the formal statistical analysis plan for the study in March 2005, sending it to FDA on May 17 2005, with formal database lock on May 25, 2005. The statistical analysis of unblinded data commenced following that date.

Conclusion(s): PROactive provides good evidence of a macrovascular benefit with pioglitazone, particularly in terms of major adverse CV events (all cause mortality, MI and stroke), despite only showing a statistical trend towards benefit for the primary composite outcome. Most importantly, it is notable that the impact of pioglitazone on macrovascular outcomes was evident despite contemporary guideline driven attention to classical risk factors, although it should be noted that treatment of these risk factors remained sub-optimal. The driver of the favorable effects of pioglitazone is unknown, but favorable lipid, glucose, and/or blood pressure changes may have contributed to the outcome.

Devchand PR. Glitazones and the cardiovascular system. Curr Opin Endocrinol Diabetes Obes 2008; 15(2):188-92

Author's affiliation(s): Center for Excellence in Vascular Biology, Division of Cardiovascular Medicine, Brigham & Women's Hospital, Harvard University, Boston, MA.

Main argument(s): Pioglitazone and rosiglitazone are classified as thiazolidinediones based on the signature pentane ring components and defined as functional activators and ligands of peroxisome proliferator-activated receptors (PPARs). Recent studies show that pharmacological ligands may have 'off-target' effects on other nuclear receptors – a concept of relevance to understanding mechanisms of action of pioglitazone and rosiglitazone and evaluation of whether adverse or beneficial effects are due to the drug.

Conclusion(s): There is an urgency to explore alternative targets of TZDs, and to define molecular mechanisms of rosiglitazone and pioglitazone to understand how the drugs affect patients.

Doggrell SA. Clinical trials with thiazolidinediones in subjects with Type 2 diabetes--is pioglitazone any different from rosiglitazone? Expert Opin Pharmacother 2008; 9(3):405-20

Author's affiliation(s): RMIT University, School of Medical Sciences, Victoria, Australia.

Main argument(s): A comprehensive review of available clinical data on TZD surrogate endpoints, as well as cardiovascular outcomes is described. Beneficial effects, such as decrease in inflammatory markers, small decrease in blood pressure, improved endothelial function, and reduction in restenosis have been shown with both rosiglitazone and pioglitazone. However, rosiglitazone and pioglitazone have markedly different effects on lipids. rosiglitazone increases total, low- and high-density lipoprotein (LDL and HDL) cholesterol and triglycerides, whereas pioglitazone has no effect on total or LDL cholesterol, increases HDL cholesterol and decreases triglycerides.

Conclusion(s): rosiglitazone has no effect or may even increase cardiovascular outcomes, whereas in high risk subjects, pioglitazone has a marginal ability to decrease cardiovascular outcomes. Unless the TZDs are shown to improve cardiovascular or other outcomes (e.g., renal) in the next few years, their continued use in T2DM should be questioned.

Drazen JM, Morrissey S, Curfman GD. Rosiglitazone – continued uncertainty about safety (editorial). N Engl J Med 2007; 357(1): 63-64

Author's affiliation(s): Editors, New England Journal of Medicine

Main argument(s): The upper bound of 1.81 for the myocardial infarction endpoint in the RECORD trial is not discordant with the results of the analysis by Nissen and Wolski, given that the 95% confidence intervals in the two studies overlap extensively.

Conclusion: Although there may be uncertainty about a drug's safety, all available data should be reported.

Gerstein HC, Yusuf S. Does treatment with rosiglitazone increase cardiovascular risk of patients with type 2 diabetes mellitus? Nat Clin Pract Endocrinol Metab 2007; 3(12):798-9

Author's affiliation(s): Division of Endocrinology and Metabolism and Population Research Institute, McMaster University, Hamilton, ON, Canada.

Main argument(s): Some generally accepted statistical criteria were not met in the meta-analysis of Nissen and Wolski. As only one or two events were identified in most of the trials, the consequences of even minor outcome misclassification are large. The RECORD study suggested a non-significant 17% reduction in cardiovascular death (HR 0.83; 95% CI 0.51 – 1.36) – an evaluation that excluded the estimate of 1.64 (95% CI 0.98 – 2.74) reported in the meta-analysis. The interim analysis of RECORD had insufficient power to prove an effect of rosiglitazone with respect to cardiovascular death or myocardial infarction.

Conclusion(s): Interpreting the interim results of RECORD as either supporting or refuting a cardiovascular effect of rosiglitazone is untenable.

Goldfine AB. The rough road for rosiglitazone (editorial review). Curr Opin Endocrinol Diabetes Obes 2008; 15(2): 113-17

Author's affiliation(s): Harvard Medical School and Joslin Diabetes Center, Boston, MA. (*note: author participated in the Joint Meeting of the Endocrine and Metabolic Drugs Advisory Committee on July 30, 2007; he states that he may receive funds from GSK or other pharmaceutical companies in mutual and managed fund accounts)*

Main argument(s): Meta-analysis of controlled clinical trials suggests increased risk of cardiovascular events for patients using rosiglitazone. Increased ischemic cardiovascular risk may be particularly manifest in patients taking nitrates or insulin.

Conclusion(s): There continues to be uncertainty regarding risk of ischemic heart disease associated with rosiglitazone. Caution should be used in patients with underlying heart disease using nitrates, or when added to insulin therapy.

Joffe HV, Parks MH, Meyer RJ, Jenkins JK, Temple R. Rosiglitazone and the FDA. N Engl J Med. 2007; 357(17):1775-6; author reply 1777

Author's affiliation(s): FDA, Silver Spring, MD.

Main argument(s): All drugs currently approved for the treatment of diabetes are indicated to improve glycemic control. Reductions in glycated hemoglobin levels directly reflect improved glycemic control, leading to a lessening of hyperglycemic symptoms, including polydipsia, polyuria, and blurred vision. A proposal to base future approvals on evidence of long-term cardiovascular benefit would significantly delay the availability of new drugs for diabetes, and might make development of new drugs impossible.

Conclusion(s): A reasonable approach might be to approve new entities on the basis of improved glycemic control and to ensure that well-designed, long-term studies comparing the new treatment with established therapy, with cardiovascular outcomes as end points of interest, are conducted in a timely manner after approval.

Kapoor JR. Controversy over the cardiovascular effects of thiazolidinediones (letter). Am J Med 2008; 121(4): e9

Author's affiliation(s): Division of Cardiology, Stanford University, Stanford, CA.

Main argument(s): Although a recent review (Fonseca 2007) claims that insulin sensitizing therapy translates into clinical benefit in patients with diabetes, several observational and randomized controlled studies have shown increased heart failure with TZDs, and increased risk of myocardial infarction with rosiglitazone.

Conclusion(s): The purported beneficial effects of TZDs on cardiovascular outcomes should be tempered by increasing adverse outcomes shown in several studies.

Krall RL. Rosiglitazone and the FDA. N Engl J Med. 2007; 357(17):1776-7; author reply 1777

Author's affiliation(s): GlaxoSmithKline, King of Prussia, PA.

Main argument(s): Although the Advisory Committee voted 20 to 3 that rosiglitazone increases cardiac risk in patients with type 2 diabetes, many members of the committee made statements accompanying their votes that drew a distinction between the risk as compared with placebo and the risk as compared with other antidiabetic drugs. The committee recommended by a vote of 22 to 1 that rosiglitazone should remain available to physicians and patients.

Conclusion(s): GSK is actively discussing with the FDA additional language for the label along with educational efforts to clarify the potential for myocardial ischemic events.

Thiazolidinediones and Cardiovascular Disease. Med Lett 2007; 49(1267): 57-58

Author's affiliation(s): Medical Letter consultants.

Main argument(s): Pioglitazone has a more favorable lipid profile than rosiglitazone. Available clinical studies offer no convincing evidence that rosiglitazone increases or decreases the risk of ischemic cardiovascular disease. Both rosiglitazone and pioglitazone increase the risk of congestive heart failure.

Conclusion(s): As monotherapy for diabetes and as a second drug, a sulfonylurea or metformin is preferred. If a thiazolidinedione is chosen as a third drug, pioglitazone is preferred over rosiglitazone.

Nathan DM. Rosiglitazone and cardiotoxicity – weighing the evidence. N Engl J Med 2007; 357(1): 64-66

Author's affiliation(s): Diabetes Center at Massachusetts General Hospital, Harvard Medical School, Boston, MA.

Main argument(s): The primary endpoint of the RECORD trial consists of an aggregate of time to first hospitalization for a cardiovascular event or death from cardiovascular causes. Unfortunately, the unexpectedly low rate of events and a higher than expected rate of loss to follow up have left RECORD extremely underpowered for the primary outcome. In addition, the choice of active comparator is problematic. Nonetheless, the results of the interim analysis suggest a possible adverse effect of treatment with rosiglitazone on the primary outcome. Considering the low power of the study and the trend for more cardiovascular outcomes in the rosiglitazone group, it is highly unlikely that the study will ever show a cardiovascular benefit for rosiglitazone.

Conclusion(s): The interim results of the RECORD trial do not provide any assurance of the safety of rosiglitazone. The jury may still be out with regard to the cardiotoxicity of rosiglitazone, but "first, do no harm" should outweigh any presumption of innocence.

Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: update regarding the thiazolidinediones. Diabetologia. 2008; 51(1):8-11

Author's affiliation(s): Diabetes Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA; University of North Carolina School of Medicine, Chapel Hill, NC; Diabetes Trials Unit, Oxford Centre for Diabetes, Oxford, UK; Yale University School of Medicine, New Haven, CT; Samuel Lunenfeld Research institute, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada.

Main argument(s): The consensus algorithm for the management of type 2 diabetes was developed on behalf of the American Diabetes Association and the European Association for the Study of Diabetes by the authors in 2006. This update addresses new data regarding the advantages and disadvantages of the TZDs, and also includes sitagliptin. The original consensus algorithm included the TZDs as one of three possible choices (insulin and sulfonylurea were the other two) that should be added to metformin and lifestyle intervention if target HbA1c levels (<7%) were not achieved. Recent meta-analyses have suggested a 30-40% relative increase in risk of myocardial infarction with R, although the data are less than definitive.

Conclusion(s): The clinical trial data regarding the increased or decreased risk of myocardial infarctions with rosiglitazone or pioglitazone, respectively, are not definitive. The increased risk of CHF or fractures with the TZDs is not of a magnitude to warrant their removal as one of the possible

second step medications, given that they cause hypoglycemia less frequently than the other second step drugs in the algorithm. Clinicians should consider more carefully whether to use a TZD vs. insulin or sulfonylureas as the second step in the algorithm. There may well be clinically important differences between rosiglitazone and P. Greater caution is recommended in using TZDs, especially in patients at risk of, or with, CHF.

Pendergrass M. Clinical decision making regarding the use of glitazones: making practice out of incomplete information. In, Physician's First Watch, Fairchild D (Ed.). Available at http://www.jwatch.org/misc/fdpprems/PFW_Rosiglitazone_Report.pdf. *Accessed June 3, 2008*

Author's affiliation(s): Consultant for Journal Watch; Associate Professor of Medicine at Harvard Medical School and Clinical Director of Diabetes at Brigham and Women's Hospital, Boston, MA.
Main argument(s): There are numerous problems with the available data on cardiovascular risks with R. The evidence cannot be considered conclusive; however, in aggregate, all analyses support the concern that rosiglitazone is cardiotoxic. This is somewhat surprising since TZDs, including R, had previously been shown to improve a number of cardiovascular risk factors and surrogate cardiovascular endpoints such as dyslipidemia, markers of inflammation, vascular smooth muscle proliferation, vascular reactivity, endothelial function, and carotid intima media thickness.
Conclusion(s): Although the results of the studies described above cannot be considered conclusive, current evidence suggests potential cardiotoxicity with rosiglitazone and potential cardioprotection with pioglitazone. Treatment with rosiglitazone should not be initiated in rosiglitazone-naïve patients.

Psaty BM, Furberg CD. The record on rosiglitazone and the risk of myocardial infarction. N Engl J Med 2007; 357(1): 67-69

Author's affiliation(s): Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology and Health Sciences, University of Washington, and the Center for Health Studies, Group Health, Seattle; and the Division of Public Health Sciences, Wake Forest University, Winston-Salem, NC.

Main argument(s): The RECORD trial has several weaknesses in design and conduct, including the primary outcome, a composite of all hospitalizations and deaths from cardiovascular causes, which was a weak choice for a non-inferiority design. In addition, although outcomes were reviewed in a blinded fashion, the randomization was not concealed. A variance weighted fixed effects meta-analysis that includes the RECORD trial, ADOPT, DREAM, and the stratum of small trials in the meta-analysis by Nissen and Wolski suggests an increased risk of myocardial infarction with rosiglitazone (OR 1.33; 95% CI, 1.02 – 1.72).

Conclusion(s): The level of risk with rosiglitazone is substantial and approximately equivalent in magnitude, but in the opposite direction, to the health benefits of lipid lowering statin drugs. The major benefits of rosiglitazone appear to be glycemic control and durability. Adverse effects of rosiglitazone include weight gain, LDL cholesterol levels, increased risk of heart failure, increased fractures in women, and an apparent increase in the risk of myocardial infarction.

Psaty BM, Lumley T. Surrogate End Points and FDA Approval: A Tale of 2 Lipid-Altering Drugs. JAMA 2008; 299(12):1474-1476

Author's affiliation(s): Cardiovascular Health Research Unit, Dept of Medicine, Epidemiology, Health Services and Dept of Biostatics, University of Washington; and Center for Health Studies, Group Health, Seattle, WA.

Main argument(s): Over the last several decades, the development and widespread use of drugs to reduce the levels of risk factors such as high blood pressure, elevated LDL cholesterol levels, and

high blood glucose levels, has been a mainstay of cardiovascular disease prevention efforts. Risk factor levels serve as surrogate end points for the outcomes of primary interest – the incidence of cardiovascular disease.

Conclusion(s): The public health advantages of rapid approval for drugs that turn out to be safe and effective need to be balanced against harms that might occur when drugs approved on the basis of surrogate endpoints turn out later either to have significant safety problems or to lack efficacy.

Rohatgi A, McGuire DK. Effects of the Thiazolidinedione Medications on Micro- and Macrovascular Complications in Patients with Diabetes-Update 2008. Cardiovasc Drugs Ther 2008; Mar 29 [epub ahead of print]

Author's affiliation(s): Cardiovascular Division, University of Texas Southwestern Medical Center, Dallas, TX.

Main argument(s): This review includes a summary of available studies of microvascular and macrovascular outcomes with TZDs. There is an inconsistency of cardiovascular effects within the TZD class despite the fact that both rosiglitazone and pioglitazone exert similar favorable effects on metabolic parameters and CVD risk intermediates, including glucose control via insulin sensitization, adipocyte metabolism, reduction in inflammatory markers, improvement in peripheral and coronary endothelial function, reduction in blood pressure, and reduced progression of CIMT [carotid intima media thickness]. Although rosiglitazone and pioglitazone affect lipid metabolism differently (pioglitazone decreases while rosiglitazone increases triglycerides and LDL), the signal for increased CVD risk with rosiglitazone emerged as early as six months in one meta-analysis, probably too early to have been caused solely by unfavorable lipid alterations. In microarray analyses of RNA expression from adipocytes, there was only 40% concordance between pioglitazone and rosiglitazone in gene expression, suggesting that these drugs do indeed behave differently.

Conclusion(s): The observed differences in cardiovascular risk between rosiglitazone and pioglitazone are likely due to undiscovered explanations, and the varying lipid effects are markers of underlying fundamental differences in the pharmacologic and biologic effects of the two drugs.

Rosen CJ. The rosiglitazone story -- lessons from an FDA advisory committee meeting. N Engl J Med 2007; 357(9):844-846

Author's affiliation(s): Maine Center for Osteoporosis, St. Joseph Hospital, Bangor, and the Jackson Laboratory, Bar Harbor, Maine. *(Note: the author reports receiving a lecture fee from GSK and grant support from Eli Lilly, Merck, and Novartis.)*

Main argument(s): The author chaired the joint meeting of the FDA's Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on July 30, 2007. The committee concluded that rosiglitazone was associated with a greater risk of myocardial ischemic events than placebo, metformin, or sulfonylureas based on three independently conducted meta-analyses. Two observational studies presented at the meeting had indeterminate results.

Conclusion(s): It will be costly to undertake true safety and efficacy studies of drugs using clinical outcomes as primary measures, but in the long run, these efforts will save time, energy, and money.

Solomon DH, Winkelmayer WC. Cardiovascular risk and the thiazolidinediones: déjà vu all over again? JAMA 2007; 298(10):1216-18

Author's affiliation(s): Division of Pharmacoepidemiology and Rheumatology, Immunology, and Allergy, and Renal Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA. (Financial Disclosures: Dr Solomon reports that he has received salary

support from research grants from Pfizer, Merck, Savient, Procter & Gamble, and GlaxoSmithKline in the last 3 years. He reports having served as an invited guest without honorarium to an advisory panel for Abbott. He also reports having received consulting fees from D2 Hawkeye, a health information technology company. Dr Winkelmayer reports that he has received salary support from research grants from Amgen, GlaxoSmithKline, and Astellas in the last 3 years. He reports having served as an invited guest without honorarium to advisory boards for Genzyme and Roche. He also reports having received consulting fees from ZDAssociates and RTI(hc), 2 contract research companies, for work on projects authorized by Nitromed and Amgen, respectively.)

Main argument(s): Two meta-analyses of the cardiovascular effects of rosiglitazone and pioglitazone were published in the same issue of JAMA as this editorial: Singh et al performed a meta-analysis of rosiglitazone trials and included only studies of at least 12 months' duration that prospectively collected information on cardiovascular events. Singh found a 42% increase in risk of myocardial infarction ($p = .02$), but no significant increase in the risk of cardiovascular mortality was detected. Lincoff et al performed a pooled analysis of cardiovascular events using patient-level data from trials comparing pioglitazone with a range of alternative regimens. Among patients randomized to receive pioglitazone, the rate of death, myocardial infarction, or stroke was reduced by 18% compared with controls ($p = .005$).

Conclusion(s): The two TZDs currently marketed, although both representing the same class of drugs, have strikingly different profiles in their effects on ischemic cardiovascular outcomes. Both agents reduce blood glucose levels and glycated hemoglobin levels to a similar degree and both appear to cause excess heart failure risk; however, their effects on cardiovascular ischemic events differ based on the currently available data. Since much of the morbidity and mortality associated with diabetes is due to macrovascular ischemic complications, even small increases in relative risks translate into major decrements in public health. Moreover, with many other available oral agents for diabetes, the potential benefit of TZDs requires reevaluation. Decisions for initial approval of a drug and subsequent continued marketing should be symmetric. When considered for initial approval, a drug must be shown to be efficacious and safe. The recent deliberations over rosiglitazone, in which there was almost unanimous agreement that the drug was associated with cardiovascular risk, resulted in a vote to allow for its continued marketing. It would be unlikely for the drug to be initially approved for marketing with such agreement about its cardiovascular risk. However, the recent FDA committee did not believe that this risk warranted removal of rosiglitazone. Although removal of a medication creates tremendous patient inconvenience, the public expects that FDA approval is a seal of safety.

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

/s/

David Graham
10/7/2008 04:34:05 PM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
10/14/2008 01:16:45 PM
DRUG SAFETY OFFICE REVIEWER
I will provide my views on this subject in a separate memorandum.

ATTACHMENT C

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	October 9, 2008
To:	Mary Parks, MD, Director Division of Metabolism and Endocrinology Products (DMEP)
Through:	Solomon Iyasu, MD, MPH, Director Division of Epidemiology Office of Surveillance and Epidemiology (OSE)
From:	Kate Gelperin, MD, MPH Division of Epidemiology, OSE
Subject:	Safety review: Proposed required postmarketing protocol entitled "Thiazolidinedione Intervention with vitamin D Evaluation (TIDE)"
Drug Name(s):	AVANDIA (rosiglitazone maleate)
Application Type/Number:	IND 43,468; NDA 21-071
Submission Number:	
Applicant/sponsor:	GlaxoSmithKline (GSK)
OSE RCM #:	2008-1147

1 INTRODUCTION

DMEP has requested assistance from OSE Division of Epidemiology for a safety review of a draft protocol (TIDE) which is a required postmarketing protocol per 505(o)(3) of FDCA. The proposed clinical protocol is intended to assess the effect of Avandia (rosiglitazone) on macrovascular events in patients with T2DM, and required to include at least three treatment groups: rosiglitazone, pioglitazone, and placebo.

In response to FDA's request, GSK has submitted a draft protocol for a multicenter, international, randomized double-blind placebo-controlled trial entitled "Thiazolidinedione Intervention with vitamin D Evaluation (TIDE)". The stated study objectives are to "evaluate the effects of the addition of once daily rosiglitazone or pioglitazone or placebo, over a mean duration of five years, to the care of approximately 15,560 participants with T2DM and other cardiovascular risk factors on a composite outcome (CV death, non-fatal myocardial infarction and non-fatal stroke)."

According to the authors of the TIDE study protocol, sample size assumptions are based on adherence to proposed inclusion criteria which "predict that up to 3.5% of participants in the placebo group will sustain one of the components" of the primary outcome during the course of the study.

DMEP provided initial comments to GSK on July 31, 2008, which outlined 14 additional recommendations including 1) that the study should not include vitamin D as a design factor; 2) a request to include additional secondary endpoints such as angina and revascularization procedures; and, 3) a request for clarification of exclusion criteria regarding which patients with heart failure should be excluded from study participation based on the NYHA classification scheme. DMEP also informed GSK at that time that additional comments will be provided to them from OSE after the protocol has been further developed.

2 MATERIAL REVIEWED

- IND 43,468, AVANDIA® (rosiglitazone maleate) Tablets; REQUIRED POSTMARKETING PROTOCOL UNDER 505(o); Serial No.650 submitted by GSK on July 30, 2008.
- IND 43,468, AVANDIA® (rosiglitazone maleate) Tablets; Communication: IND Advice/Information Request (COR-INDAD-02) to GSK from Dr Mary Parks, FDA/CDER/DMEP on July 31, 2008.
- DRAFT FDA/CDER/OSE Review: Graham DJ, Gelperin K. Benefit-risk assessment of rosiglitazone vs pioglitazone. RCM #2007-1945, and #2008-278.
- Current approved labeling for AVANDIA (rosiglitazone) and ACTOS (pioglitazone) in US, EU, Canada, and Australia.

3 DISCUSSION

A signal for increased risk of myocardial ischemia has been identified with rosiglitazone, but not for pioglitazone. An OSE draft review comparing the overall benefits and risks of these two drugs has been completed in a separate document.[1] The review found that rosiglitazone is associated

[1] Graham DJ, Gelperin K. Benefit-risk assessment of rosiglitazone vs pioglitazone (draft). RCM #2007-1945, and #2008-278.

with an increased risk of cardiovascular adverse events compared to pioglitazone, with no offsetting benefit that might counterbalance the cardiovascular risks.

Clinical Equipoise

Clinical equipoise, as an ethical basis for entering patients into this proposed large international trial, is lacking here in the sense that a convincing case cannot be made that "some physicians prefer one treatment and other physicians prefer the other." The clinical judgment of the international medical community has been reflected over the past year in the addition of new Warnings and Contraindications to approved labeling for rosiglitazone in the US, EU, Australia, and Canada.

Myocardial Ischemia

In current approved labeling in EU, use of rosiglitazone is "contraindicated in patients with an Acute Coronary Syndrome (unstable angina, NSTEMI and STEMI)." Additional clarification of this Contraindication is provided in section 4.4 of the SPC "Special warnings and precautions for use", as follows (in part):

> Myocardial Ischaemia
>
> There are limited clinical trial data in patients with ischaemic heart disease and/or peripheral arterial disease. Therefore, as a precaution, the use of rosiglitazone is not recommended in these patients, particularly those with myocardial ischaemic symptoms. [2]

Similarly, a new Boxed Warning has been added to approved labeling for Avandia in Australia:

> The use of AVANDIA is not recommended in patients with known ischaemic heart disease, particularly in those taking nitrates. AVANDIA has been shown to be associated with an increased risk of myocardial ischaemia (angina, infarction) in pooled short-term clinical studies, particularly in those who needed several antidiabetic drugs or nitrates. [3]

Reflecting similar concerns about high risk patients, the current approved USPI for rosiglitazone states in the Warnings and Precautions section that "Use of AVANDIA with nitrates is not recommended."

The proposed TIDE Inclusion criteria (see Appendix) would permit enrollment of patients age ≥50 yrs with "unstable angina with ECG changes or cardiac enzyme elevation" or "prior myocardial infarction" unless they have a planned or recent (<4 yrs) revascularization or "acute coronary event within 7 days prior to screening."

Clearly, these criteria would allow enrollment of very high risk patients with ischemic heart disease, and for whom rosiglitazone use is contraindicated in several countries.

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[2] EMEA Summary of Product Characteristics (SPC) for AVANDIA (rosiglitazone). Available at http://www.emea.europa.eu/humandocs/Humans/EPAR/avandia/avandia.htm.

[3] Australia Product Monograph for AVANDIA (rosiglitazone). Available at http://www.gsk.com.au/resources.ashx/prescriptionmedicinesproductschilddataproinfo/501/FileName/6DDF19D75EBCDC90DE87A24CA6B2F32D/Avandia_PI.pdf.

In addition, patients taking nitrates would not be excluded from the proposed trial, despite the fact that treatment with Avandia is specifically not recommended for patients requiring nitrate therapy in the current approved product labeling for Avandia in US, EU, and Australia.

Inclusion of patients for whom treatment with rosiglitazone is "Contraindicated" or "not recommended" is inappropriate for a Phase 4 postmarketing trial expected to be conducted within the requirements of approved product labeling.

Asymptomatic Heart Failure

In current approved labeling for EU, both rosiglitazone and pioglitazone use is contraindicated "in patients with cardiac failure or history of cardiac failure (NYHA class I to IV)." This implies that the benefits of these drugs do not exceed their risks in patients with heart failure, even in asymptomatic patients (as outlined below in a definition of the NYHA classification):

New York Heart Association classification of functional capacity in heart failure:

- NYHA class I: asymptomatic left ventricular dysfunction
- NYHA class II: dyspnea with significant exertion
- NYHA class III: dyspnea with minimal activity including usual activities of daily living
- NYHA class IV: dyspnea at rest

According to Harrison's textbook, "the most useful index of left ventricular (LV) function is the ejection fraction (EF = stroke volume divided by end-diastolic volume)." In general, "when the EF is normal (≥50%), systolic function is usually adequate, and when the EF is significantly depressed (<30-40%), contractility is usually also depressed." [4]

The proposed exclusion from TIDE of patients with "symptomatic heart failure or any episode of previous pulmonary edema or known ejection fraction <30% or current use of loop diuretics" would fail to exclude potential study subjects with class I or II heart failure for whom both rosiglitazone and pioglitazone therapies are contraindicated in EU, and for whom rosiglitazone (but not pioglitazone) therapy is contraindicated in Canada and Australia. [5]

4 CONCLUSIONS AND RECOMMENDATIONS

Although the proposed TIDE trial is motivated by a desire for definitive answers regarding the cardiovascular safety of the drug rosiglitazone, the safety of the study itself cannot be assured, and is not acceptable.

The addition over the past year of Contraindications and Warnings regarding myocardial ischemia with rosiglitazone but not pioglitazone demonstrates a growing consensus of concern in the international medical community. This judgment, reflected in approved product labeling worldwide, precludes a condition of clinical equipoise for the proposed comparison of rosiglitazone and pioglitazone.

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[4] Harrison's Principles of Internal Medicine - 17th Ed. (2008); accessed September 12, 2008 via FDA Biosciences Library online resources (Stat!Ref).

[5] *Note: In current approved labeling in Canada and Australia, rosiglitazone use is Contraindicated in NYHA Class I to IV heart failure patients, whereas for pioglitazone there is a Contraindication only for NYHA Class III and IV patients. In the current USPI, both drugs are Contraindicated in NYHA Class III and IV heart failure, and use is" not recommended" in "patients with symptomatic heart failure."*

APPENDIX

TIDE PROTOCOL INCLUSION AND EXCLUSION CRITERIA RELEVANT TO CARDIOVASCULAR RISK FACTORS:[6]

INCLUSION CRITERIA (only those relevant to pre-existing heart disease or heart failure):

Criterion #3:

A) Age ≥ 50 years and evidence of vascular disease:
   a) prior myocardial infarction
   b) prior stroke
   c) coronary, carotid or peripheral artery revascularization ≥ 4 years earlier
   d) documented myocardial ischemia on either an exercise stress test or on any cardiac imaging, or unstable angina with ECG changes or cardiac enzyme elevation

OR

B) Age ≥ 55 years and evidence of subclinical vascular disease:
   a) microalbuminuria or proteinuria
   b) history of treated or untreated hypertension with left ventricular hypertrophy by ECG or echocardiogram
   c) >50% stenosis on any imaging of coronary, carotid or lower extremity arteries
   d) ankle/brachial index <0.9

OR

C) Age ≥ 60 years and at least 2 of the following CVD risk factors:
   a) current tobacco use
   b) LDL-C ≥3.4 mmol/L (130 mg/dl)
   c) HDL-C < 1.0 mmol/L (40 mg/dl) for men and < 1.3 mmol/L (50 mg/dl) for women or triglycerides ≥ 2.3 mmol/L (200 mg/dl)
   d) BP lowering medication use or untreated SBP ≥140 mmHg or DBP ≥95 mmHg
   e) Waist to hip ratio > 1.0 for men and > 0.8 for women

EXCLUSION CRITERIA (only those relevant to pre-existing heart disease or heart failure):

#4: An acute coronary event within 7 days prior to screening

#5: Symptomatic heart failure or any episode of previous pulmonary edema or known ejection fraction < 0.3 or current use of loop diuretics

#7: Currently planned coronary, carotid or peripheral artery revascularization

#8: Coronary, carotid or peripheral artery revascularization within the 4 years prior to screening in the absence of angina, MI, or stroke in the intervening period

#12: A prior heart transplant or awaiting a heart transplant

[6] Excerpted from sections 4.2 and 4.3 of the proposed TIDE clinical protocol.

ATTACHMENT D

CONSENT FORM: TIDE TRIAL

Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE)
Sponsor: GlaxoSmithKline Inc

Study Title

Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE). A Multicenter Randomized Double-Blind Placebo-Controlled Trial of a Thiazolidinedione (TZD) or Placebo and of Vitamin D or Placebo In People With Type 2 Diabetes at Risk For Cardiovascular Disease (AVD 111960)

Principal Investigator

(Insert local principal investigator info here)

Introduction

You are invited to take part in a research project. You have been considered because you have type 2 diabetes and other characteristics that increase your future chance of having a heart attack or stroke. It is important that you read the information about the study. You need to understand what you will be asked to do if you decide to be in the study. You also need to understand the possible risks of participation. If you do decide to participate, you will need to sign this form, which states that you have given your consent to participate. Feel free to discuss this with your family, friends, and your doctor before you make your decision. You can take as much time as you like.

Purpose

People with type 2 diabetes are at risk of having a heart attack, stroke and even death. They are also at risk for broken bones and some cancers. Some studies suggest that a class of diabetes drugs called thiazolidinediones (TZDs) and/or vitamin D may lower the chance of some or all of these diseases occurring. Other studies have suggested that the TZDs rosiglitazone or pioglitazone may increase the risk of some or all of these outcomes. This study will compare adding a TZD (either rosiglitazone or pioglitazone) to adding a placebo (a pill with no active ingredients). The effects of these study drugs, both good and bad, on the chance of heart attacks, stroke and death will be studied. It will also compare adding vitamin D to adding a vitamin D placebo to see if vitamin D can reduce the number of deaths or cancers requiring hospitalization, chemotherapy or surgery.

The study will be done in about 30 countries around the world and will include about 16,000 women and men. The study protocol and this consent form have been carefully reviewed and approved by an independent review board or ethics committee at every site in the world that is now actively recruiting participants. These committees are set up to protect the rights and well being of people participating in research projects like this one.

Study Procedures to be Followed

If you agree to be considered for this study, you will be asked questions about your health history and medication use. Your weight, height, body fat, blood pressure, heart rate, and waist and hip circumference will be measured. Blood and urine will be collected. You will have up to 30-45 cc (1-1.5 oz, or 2-3 tablespoons) of blood drawn at the first visit (screening) after fasting 8 hours. Fasting is when you don't have anything to eat or drink except water. If you do not fast before your scheduled visits, you will have to return at another time when you have fasted. The blood samples that are drawn will be used to check your blood sugar levels, kidney and liver function, and dietary fat levels in your blood. A pregnancy test (if needed) will also be done if you are a woman who is capable of conceiving. In addition, blood and urine samples will be stored and may be used to

measure various risk factors or risk markers for obesity, heart disease, disease of the blood vessels, cancers and other chronic diseases.

If you are eligible to participate, you will be scheduled for the run-in visit or the investigator may decide to combine this with your first visit. If you are currently taking either pioglitazone or rosiglitazone you will be asked to stop taking the medication while you are taking the TZD study drug. During the 3-week run-in period you will take 1 tablet of TZD study drug by mouth which could be either rosiglitazone or placebo and 1 tablet of vitamin D study drug by mouth, which could be vitamin D or placebo. If vitamin D study drug is not available when you enter the run-in, you will only take the TZD study drug. If after 3 weeks, either you or the study staff thinks that you are unable to tolerate the pills or participate in the rest of the study, you will be excluded. You will be asked to return all unused drug.

If you successfully complete the run-in period and agree to participate you will be scheduled for a randomization visit. At this visit you will be provided with either rosiglitazone (4 mg daily), pioglitazone (30 mg daily) or a placebo. At the same time or when available you will also be provided with either vitamin D (1000 IU daily) or placebo. Which study drugs you are provided with will be decided by chance using a computer. You have a slightly higher chance of taking placebo compared to rosiglitazone or pioglitazone. For example, in 100 patients participating in this study, 30 will receive rosiglitazone, 30 will receive pioglitazone and 40 will receive placebo. You will have the same chance of taking vitamin D or placebo (like the flip of a coin). Neither you, the research coordinator nor your doctor will know if you are taking active drugs or placebo(s). If there is an emergency, your physician can find out what treatment you are taking. At the randomization visit we will perform a simple test that measures the electrical activity of the heart called an electrocardiogram or ECG, and ask you to do a simple visual test. At this visit and at every future visit we will discuss ways to improve your health with lifestyle changes. At the randomization, 2-year and final visits you may also be asked to complete questionnaires that measure your quality of life, your thinking processes and your erectile function if you are male.

After the randomization visit, you will return to the study center after 1 month, 2 months, 6 months and then every 6 months. Participants will be asked to take the TZD study drug for up to approximately 5 years and the vitamin D study drug for up to approximately 5 years and potentially up to 10 years. We may also call you between visits to remind you to take your medications, answer any questions you may have, review your study medications and check on any side effects. It is important that you bring all of your study medications to each visit. At each visit you: a) will be asked about your health, your medications and any side effects; b) may have your blood pressure, heart rate, weight, height, and waist and hip measurement recorded and c) may be given a new supply of study drugs. You will have approximately 5-15 cc (1-3 teaspoons) of blood drawn at the 2-month visit. The same amount of blood will be drawn at the yearly visits to check your glucose, A1C and calcium levels after 8 hours of fasting.

At the 6 month or 1-year visit, the dose of your TZD drug will be increased (to 8 mg for rosiglitazone, or 45 mg for pioglitazone) if your study doctor thinks it is appropriate.

At the 2-year and final visits, you will also a) have an ECG; b) a simple visual test c) supply a first morning urine sample; and d) have up to 30-45 cc (1-1.5 oz, or 2-3 tablespoons) of blood drawn after 8 hours of fasting. Some of the blood and urine samples will be stored and may be used to measure various risk factors or risk markers for obesity, heart disease, disease of the blood vessels, cancers and other chronic diseases. Your blood sugar levels, kidney and liver function will also be checked.

Breast feeding and pregnant women are not allowed to take part in the study. If you are a woman who is able to have children, you need to use a reliable form of birth control (either the birth control pill, hormonal injections or implants, an intrauterine device, or a combination of spermicide and

condoms) to prevent any pregnancy during the study. If you become pregnant despite these precautions you will immediately notify the study team.

Long-Term Follow-Up

After the trial is complete and you have finished taking all the study medication, you may be contacted either by mail or telephone and asked to participate in a longer-term follow-up study.

To make it easier to contact you during the long-term follow-up, we will give your contact information to the Population Health Research Institute (PHRI) at Hamilton Health Sciences, McMaster University. The PHRI will only use this information for the purposes of contacting you regarding this follow-up. All your personal information will be kept in confidence and will not be given to anyone within the provisions of the law. If you do not agree to participate in the long-term follow-up, you can still participate in the trial. If you agree, we will also ask you to give us information that will allow us to use hospital and government databases to track whether you have been in hospital and why and the health care services you have used for up to 5 years after the completion of the trial, without having to contact you directly. In order to use this information, we would require your health card number or social insurance number. It is your choice to provide us with this information, but it helps us to know about your health status.

Possible Side Effects, Risks, and Discomforts

The study medications may cause some known side effects. In addition, there may be some side effects that have not been identified so far. Every measure will be taken to identify possible side effects as well as any benefits of the study pills. You must therefore notify the study staff of any changes in your health, newly started pills from the pharmacist and over-the-counter drugs, and symptoms you may notice (even if you think these changes or symptoms are not related to the study medication).

Side Effects Reported with Thiazolidinediones (Rosiglitazone and/or Pioglitazone)

Rosiglitazone is the active ingredient in Avandia and pioglitazone is the active ingredient of Actos. Some people who have taken rosiglitazone or pioglitazone had the following side effects:

- Fluid retention which may lead to swelling (for example ankle swelling), weight gain and rarely heart failure and difficulty breathing
- Swelling of the face, lips, mouth, tongue, or throat, which may cause difficulty in swallowing or breathing (angioedema)
- Decreased or blurred vision due to swelling (or fluid) in the back of the eye (macular edema)
- Anemia (low red blood cell count, which can cause fatigue)
- Increases in liver enzymes (which may indicate liver abnormalities)
- Modest increases in cholesterol
- Weight gain
- Low blood sugar (hypoglycemia) which may occur if a thiazolidinedione is taken with other diabetes medications
- Hives or rash (which may be itchy)
- Bone fractures especially in women and in the hand, upper arm, or foot.

Some people who have taken pioglitazone also had the following side effects:

- Erectile dysfunction
- Joint pain
- Flatulence (passing gas)

Some people who have taken rosiglitazone also had the following side effects:

- Constipation
- Increased appetite

GlaxoSmithKline (GSK) has analyzed heart safety data from their studies previously conducted in patients with diabetes. The results suggested that rosiglitazone might increase the chance of a heart attack especially in the presence of insulin or nitrate medication. However, other studies have not confirmed this observation.

During the study, if you get chest pain or chest tightness, or you feel chest pain more often or chest tightness, please get urgent medical attention and tell your study doctor at your next visit. You should also do this if you become short of breath or have trouble breathing (especially when you lie down), or if you gain weight quickly or notice swelling of your limbs.

One of the inactive ingredients in rosiglitazone and pioglitazone is lactose. You should tell the study doctor if you have severe lactose intolerance.

If important new information develops during the study, which may relate to your willingness to continue participation it will be provided to you in a timely manner.

Side effects reported with vitamin D

Some people who have taken vitamin D can have the following side effects:

- An allergic reaction (swelling of tongue, lips or throat, hives or itchy rash)
- Constipation
- Nausea, vomiting or decreased appetite
- Increased thirst and/or urination
- Muscle weakness
- Confusion
- Kidney stones

Use of Other Medicines and Possible Drug Interaction

It is important to tell the study staff about all other drugs you are taking, including those obtained without a prescription.

Monitoring of Safety During the Study

An independent group of people who are not otherwise involved in this study will regularly review the safety of people participating in this study as well as information regarding the safety of rosiglitazone, pioglitazone, vitamin D from other sources. This group may recommend changes to the study (or even early stopping of all or part of the study) based on their review of this information.

Other Potential Risks

When blood samples are taken, you may have some discomfort (brief pain) or develop some bruising or very rarely, a minor infection where the needle went in. Every precaution will be taken to prevent infection. Some people feel dizzy when they have blood drawn, but this goes away when the person lies down.

An ECG is painless. When first applied, the disks may be cold and in rare circumstances, you may develop a localized rash or irritation where the patches are placed.

Possible Benefits of Participation

Taking part in this study may or may not make your health/condition better.

The information obtained from your participation in this study may help us understand more about whether the drugs being studied can increase or reduce the risk of cardiovascular and chronic diseases.

You will receive some counselling regarding a healthy lifestyle, and will receive all of your study medications free of charge.

Proven Ways to Prevent Cardiovascular Disease and Lower Glucose

Several studies have now shown that you may lower your risk of heart attacks, strokes or cardiovascular death by several approaches. These include: a) drugs that lower blood pressure; b) statin drugs that lower cholesterol; c) ACE inhibitor drugs; d) aspirin and e) beta blocker drugs. You will be permitted to take any of these drugs during the study and, depending on your medical condition, one or more of these drugs may be prescribed by your usual physician. Studies have also shown that there are many alternative ways of lowering blood sugar levels in people with diabetes and you will be able to take any of these drugs (except for a TZD) during the study, depending on the judgment of your physician.

Compensation

The study medication and clinic visits will be provided free of charge. No compensation will be provided for your participation. You and your health insurance company / the National Health Services will continue to pay for your regular health care.

Study Sponsor:

GlaxoSmithKline is a company that creates and makes medicines and other health products. It is also called "GSK".

GSK pays the study doctor and ***<institution>*** to run this study.

Information about this study is confidential. We ask that you keep it private. You can discuss this information in private with your doctor or family to talk about your healthcare or to decide about taking part in this study.

As the sponsor, GSK will be the owner of the study results. GSK plans to use the results and may get patents or make profits other ways. You will not be paid any part of this.

Liability

GSK will pay your out-of-pocket costs (not covered by insurance) for reasonable and necessary care if you are hurt by the study drug or a procedure that is done to you only because you are part of this study.

Signing this consent form does not change any legal rights you may have.

Right to Withdraw or Stop Study Medication

Participation in this study is voluntary. Should you decide not to take part in this study your health care treatment will not be affected by this decision. Refusal to participate will not affect any benefits you are entitled. If you decide to take part in the study, you will need to sign this form, which says

that you have consented to participate. If you agree to participate, you may withdraw from the study at any time without affecting any benefits to which you are entitled, although it is advisable to tell the investigator if you intend to do this. You have the right to withdraw from the study completely (this means you do not wish to be contacted by any study staff after you withdraw) or you may just wish to stop one or both of your study medications, but will allow study staff to contact you to see how you are doing. If you stop taking any of the study medications for any reason during the study, we will ask you to return any leftover drug. However, even if you are no longer taking the study medications, the information you are providing is still very important for the study and you will be asked to continue attending regular study visits or allow the staff to contact you or a family member by phone.

It is very important for the success of the study that we are able to collect information on you throughout the duration of the study. If you agree to participate, you are giving permission for your doctors to provide information about your health, in confidence, even if you do not wish to be contacted again by any study staff. If you agree, we will also ask you to give us information that will allow us to use hospital and government databases to track whether you have been in the hospital and why and the health care services you have used for up to 10 years. This information will be collected even if you decide to withdraw from the study and do not wish to be contacted again by any study staff after you withdraw.

Any important new information that develops during the course of the study, which may relate to your willingness to continue participation, will be given to you or your legally acceptable representative in a timely manner.

GSK (the study sponsor), the steering committee, the regulatory authority, or the study doctor may choose to stop the study drugs or your participation in the study if:

- The results of certain tests show that you are not right for this study or for the study drug.
- You get any new health problems during the study
- You get pregnant or decide that you want to become pregnant
- The study doctor thinks it is in your best interest to stop.

There may be other unexpected reasons your participation in the study is stopped. If this should happen, you will be made aware of the reason at that time. However, even if one or both of the study drugs are stopped you will still be followed in the study.

Confidentiality

During your participation in this clinical study the research staff will collect personal information (such as name and address) and information related to your health. Your collected data will be reported to the Population Health Research Institute at Hamilton Health Sciences, McMaster University who are performing this study. The Project Office at Hamilton Health Sciences will process your data with electronic data processing systems. In the electronic database, your data will be identified with a code number and your initials. If you decide to take part in the study, your information will be stored in this way until the study is over, including the length of time that we must keep records about the study.

The data will be analyzed in order to determine the effectiveness and safety of rosiglitazone or pioglitazone or vitamin D, as well as for general health research. Your data may be shared with GSK and others including local and foreign drug regulatory agencies who oversee drugs like rosiglitazone or pioglitazone or vitamin D and may be used in scientific publications. Your data may also be forwarded immediately to local and foreign drug regulatory agencies in case you suffer an adverse reaction to any of the study drug.

The data may be shared with other companies or universities to better understand diabetes or to further develop the study drugs or other drugs. The data may be used to help plan new studies. Your name will not appear in any of these reports.

Representatives of the Project Office at Hamilton Health Sciences, GSK, the independent ethics committee/institutional review board, or local or foreign regulatory authorities, and others working with GSK or Hamilton Health Sciences, may directly access your medical records at your doctor's site in order to determine the accuracy of the reported data. These representatives will observe professional secrecy and keep your identity confidential to the extent permitted by law. You have the right to see your study data at your doctor's office, and to request corrections of any data that are wrong.

You will be given a copy of this informed consent document and may ask for additional information, at any time during the study, from †‡ **(insert name and telephone number of investigator)**. You may also contact †‡ **(insert name and telephone number)** if you have questions about your rights as a research subject. Contact **(insert name and telephone number of investigator)** if you think you have been hurt from taking part in this study, or have any questions about side effects.

Personal and medical information about you will be kept confidential. It will be kept in a secured file.

Study information about you that is not helpful to your health care will not be given to you or others. This means that no one (not you, your family, your doctor, your insurance company, or your employer) will have access to this information during or after the study.

If you have a serious event that it not expected and is related to the study drug, regulatory agencies and other clinical investigators may be informed about the event and which treatment you are on. Your name and contact information will not be disclosed and you will only be referred to by a code number.

When you sign this consent form, you agree to have your personal and medical information used as described here.

I have read, or had read to me, the informed consent document for this trial. By signing below I show that:

- I have read this form, and the study has been explained to me
- I have discussed the study and asked questions. I am satisfied with the answers
- I have had time to make my decision
- I freely agree to take part in the study described in this form
- I have been given names of study staff whom I can call
- I agree that GSK, study staff, and others may have access to my medical and personal information as described in this form
- I agree that my information may be shared with people who are not healthcare providers and that the information would no longer be protected by Health Insurance Portability and Accountability Act HIPAA.
- I agree that the study doctor may tell my doctor that I am taking part in this study.
- I agree to take part in this trial and to follow all study procedures as detailed above.

1. I agree to provide my health card number or social security number for linkage and tracking purposes

   ☐ **YES** Please provide your health card or social security number here: _____ ☐ **NO**

2. I agree to have my contact information sent to Hamilton Health Sciences to be used and stored in a confidential manner

   ☐ **YES** ☐ **NO**

3. I agree to continued participation in the long term follow-up study (for up to 10 years)

   ☐ **YES** ☐ **NO**

If you mark "no" to questions 1, 2, or 3you may still participate in the trial.

Last name: _____ **First name:** _____
(block letters) **(block letters)**

Signature: _____ **Date:** _____
(to be completed by participant at time of consent)

(Where required) [In Countries that do not require a witness the following lines for witness should be deleted before submitting the consent to the ethics committee; note the signature of the investigator]

Witness
Last name: _____ **First name:** _____
(block letters) (block letters)

Signature: _____ **Date:** _____

Investigator/Sub-investigator or person who conducted the Informed Consent discussion

I confirm that I have personally explained the nature, purpose, duration, and foreseeable effects and risks of the trial to the subject named above.

I have carefully explained the nature of the above research study to the participant. I hereby certify that to the best of my knowledge, the person signing this consent form understands the nature, demands, benefits, and risks of participating and that his/her signature is valid. A medical problem or language or educational barrier has not precluded this understanding.

Last name: _____ **First name:** _____
(block letters) (block letters)

Signature: _____ **Date:** _____

A signed and dated copy of this document shall be given to the person signing this form.