



# **Thiazolidinediones**

**May 2009**  
Final Draft

**Produced by:**  
The Health Resources Commission  
Office for Oregon Health Policy & Research  
1225 Ferry Street SE Salem, OR 97301 Phone: 503.373.1629

## **Health Resources Commission**

Chair: James MacKay, MD  
Vice Chair: Dan Kennedy, RPh  
Manny Berman  
Dean Haxby, PharmD  
Justin Leonard, JD.  
Diane Lovell  
John Muench, MD  
Katherine Merrill, MD  
William Origer, MD  
George Waldman M.D.

## **Subcommittee Members**

Bill Origer, MD  
Ruth Medak, MD  
Tracy Klein, FNP  
Nicole O’Kane, PharmD  
Rich Clark, MD  
Kathy Ketchum, MPA, HA

## **Health Resources Commission Staff**

Director: David Pass M.D.  
Assistant: Tina Huntley

## **Health Resources Commission**

The State of Oregon’s Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

## ***Overview***

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

In 2007 the Oregon Health Resources Commission (HRC) appointed a pharmaceutical subcommittee to perform evidence-based reviews of pharmaceutical agents. Members of the subcommittee consist of three Physicians, a Nurse Practitioner, a PhD, MPA and a PharmD. All meetings were held in public with appropriate notice provided. The HRC

director worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The EPC's report, *Drug Class Review: Thiazolidinediones update 1*, September 2008, was circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately once per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. This report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a subcommittee.

The full OHSU Evidence-based Practice Center's draft report, "*Drug Class Review: Thiazolidinediones update 1*" is available via the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website:

[www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence\\_based\\_reports.shtml](http://www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml)

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: <http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml>

You may request more information including copies of the draft report from:

David Pass, MD

Director, Health Resources Commission

Office for Oregon Health Policy & Research

1225 Ferry St. SE

Salem, Oregon 97301

Phone: 503-373-1629 (HRC Assistant)

Fax: 503-378-5511

Email: [HRC.info@state.or.us](mailto:HRC.info@state.or.us)

Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

Alison Little, MD

Assistant Director for Health Projects

Oregon Health & Science University

Center for Evidence-based Policy

2611 SW Third Avenue, MQ280

Portland, OR 97201-4950

Phone: 503-494-2691

E-mail: [littlea@ohsu.edu](mailto:littlea@ohsu.edu)

There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

### ***Critical Policy***

#### *Senate Bill 819*

– “The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”

#### *Health Resources Commission*

– “Clinical outcomes are the most important indicators of comparative effectiveness”

– “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

### ***Clinical Overview***

#### **Diabetes**

Diabetes mellitus is a group of diseases characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both. Type 1 diabetes accounts for 5 to 10% of all diagnosed cases of diabetes and is the result of a failure of the pancreatic beta cells to produce insulin. The onset of type 1 diabetes is usually in childhood or in young adults and insulin treatment is required to replace the body’s endogenous insulin. Gestational diabetes is a form of glucose intolerance that is diagnosed during pregnancy and has important implications for the health of the mother (who is an increased risk of having or developing type 2 diabetes) as well as the health of the fetus and newborn. Type 2 diabetes accounts for about 90% of all diagnosed cases of diabetes. It is characterized by insulin resistance initially, but over time, inadequate pancreatic production of insulin occurs. Type 2 disease is associated with age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose tolerance or impaired fasting glucose, physical inactivity, and race/ethnicity.

The prevalence and incidence of diabetes are increasing both in the U.S. and world-wide. The total prevalence of diabetes in the U.S. for all ages is estimated at 7.0%, or 20.8 million people; approximately one-third of those cases are undiagnosed. The prevalence of type 2 diabetes varies among racial and ethnic groups: non-Hispanic blacks 20 year or older 13.3%, Hispanic/Latino Americans 9.5%, American Indians and Alaska natives 12.8%, and 8.7% among non-Hispanic whites. The prevalence of type 2 diabetes is increasing among children and adolescents. True prevalence data are not available as yet,

however, the percentage of children with newly diagnosed diabetes who are classified as having type 2 diabetes has risen from <5% before 1994 to 30-50% subsequent to that year.

Diabetes has a major impact on the health and welfare of affected individuals. Diabetes was the sixth leading cause of death listed on U.S. death certificates in 2000, and this statistic likely underestimates the mortality rates from diabetes, which is often not listed on the death certificate of affected persons. Individuals with diabetes have an overall risk of death about twice that of unaffected persons.

Heart disease is the leading cause of diabetes-related deaths and adults with diabetes have a death rate from heart disease that is 2 to 4 times higher than adults without diabetes. The risk for stroke is 2 to 4 times higher among people with diabetes and two-thirds of people with diabetes die of heart disease or stroke. Diabetes is associated with other diseases and cardiovascular risk factors including hypertension.

In addition to macro-vascular sequelae, diabetes leads to numerous micro-vascular complications. Diabetes is the leading cause of end-stage renal disease and new cases of blindness among adults age 20-74 years; 60% to 70% of people with diabetes have peripheral neuropathy; more than 60% of non-traumatic lower limb amputations occur among persons with diabetes; periodontal disease is more common; and pregnancy is complicated.

### **Diabetes treatment**

Diabetes is a chronic condition that requires continuing medical care and self-management in order to minimize the risk of complications and mortality. The goals of treatment are to: 1) achieve optimal glycemic control; 2) reduce other cardiovascular risk factors, including hypertension, hyperlipidemia, and overweight and obesity; and 3) diminish complications such as heart disease, peripheral vascular disease, renal disease, and neuropathy. Type 2 diabetes may be treated by diet and exercise, often combined with one or more oral hypoglycemic agents. Optimal treatment, however, may require the use of insulin with or without oral agents. Among adults with diagnosed diabetes, the current distribution of types of treatment is: 57% use oral agents only, 12% use both insulin and oral drugs, 16% use insulin only, and 15% do not use pharmacotherapy.

### **Pre-diabetes**

Pre-diabetes refers to the condition of having one or the other, or both, of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). The term pre-diabetes was coined as it was recognized that both IFG and IGT were associated with a significant risk of developing diabetes. IFG is diagnosed when the fasting blood glucose level is elevated (100 to 125 mg/dl) after an overnight fast, but the glucose level does not fit criteria for diabetes ( $\geq 126$  mg/dl). IGT is defined a blood glucose of 140-199 mg/dl after a 2-hour oral glucose tolerance test (diabetes is diagnosed if the blood glucose level is  $\geq 200$ ). Pre-diabetes has a high prevalence; in a cross-section of U.S. adults aged 40-74 years, 40% had pre-diabetes. The risk increases with age and reaches a peak in people aged 60-74 years. The risk also increases with increased body mass (BMI) index. Pre-diabetes may be the most important risk factor for progression to type 2 diabetes. The cumulative 5-6 year incidence of developing type 2 diabetes in persons with either IGT or IFG is 20-34%. The risk of diabetes is even higher among persons with both IGT and IFG. IGT is associated with an increased risk for cardiovascular and all-case mortality; the link between for IFG is not as strong.

Pharmacotherapy has been shown to delay the progression of pre-diabetes to diabetes, including metformin, acarbose, as well as thiazolidinediones. In the Diabetes Prevention Project (DPP), metformin was particularly effective in persons 25 to 40 years of age and 50-80 pounds overweight. In the STOP-NIDDM trials acarbose decreased the risk of developing diabetes by 25% over 3 years. In the Troglitazone in Prevention of Diabetes (TRIPOD) study, troglitazone was associated with a decrease in the progression to type 2 diabetes among Hispanic women with IGT when compared to placebo, after approximately 30 months of treatment and 8 months of post-treatment follow-up.

### **Metabolic Syndrome**

The metabolic syndrome has been proposed as a compilation of metabolic disturbances which are risk factors for cardiovascular disease. The abnormalities involved in the metabolic syndrome include glucose intolerance (type 2 diabetes, IFT, or IGT), insulin resistance, central obesity, dyslipidemia, and hypertension. The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) identified five components of the metabolic syndrome (Table 1).

The metabolic syndrome is associated with an increased risk of both diabetes and cardiovascular disease. The risk of cardiovascular disease mortality in persons with the metabolic syndrome compared to those without is 2.26 in men and 2.78 in women. The pathogenesis of the metabolic syndrome has not been defined. It appears, however, to be associated with obesity, insulin resistance, and deregulation of adipocyte-derived hormones, a proinflammatory state, and other endocrine factors. Management of the metabolic syndrome involves careful appraisal of cardiovascular risk and appropriate management of the underlying risk factors.

**Table 1. National Cholesterol Education Program's Adult Treatment Panel III definition of the metabolic syndrome: Persons having three or more of the following criteria were defined as having the metabolic syndrome:**

Central obesity: waist circumference >102 cm (male), >88 cm (female)
Hypertriglyceridemia: triglycerides $\geq$ 1.7 mmol/L (150 mg/dL)
Low HDL cholesterol: <1.04 mmol/L (40 mg/dL) (male), <1.29 mmol/L (50 mg/dL) (female)
Hypertension: blood pressure $\geq$ 135/85 mm Hg or taking medications
Fasting plasma glucose $\geq$ 6.1 mmol/L (110 mg/dL)

### ***Definition of Thiazolidinediones***

There are two thiazolidinediones approved for prescription use in the United States, rosiglitazone maleate (Avandia™) and pioglitazone hydrochloride (Actos™) (Table 2). A third TZD (Troglitazone™) was removed from the market in 1999 due to adverse hepatic effects. Both rosiglitazone and pioglitazone are approved by the U.S. Food and Drug Administration (FDA)

for use in adults for the treatment of type 2 diabetes, either as monotherapy, or in combination with insulin, metformin, or sulfonylurea when diet, exercise and a single

agent does not results in adequate glycemic control. *Neither drug is currently approved for use in pre-diabetes or the metabolic syndrome.*

The mechanisms of action of TZDs in lowering plasma glucose among persons with type 2 diabetes are thought to include the following: increase in insulin sensitivity, decrease in endogenous glucose production and postprandial gluconeogenesis, suppression of free fatty acid release from the liver, increase in fasting and postprandial glucose clearance, and beneficial effects on beta-cell function. In addition to hypoglycemic effects, thiazolidinediones may have cardioprotective effects that are independent of glucose lowering and may be due to anti-oxidant, anti-inflammatory, or calcium channel-blocking properties. The glycemic effects of TZDs are thought to be mediated by binding to the peroxisome proliferators-activated receptor (PPAR) gamma receptors. These receptors are expressed in the liver, adipose tissue, skeletal muscle, the heart, smooth muscle cells and endothelial cells of the vasculature, the kidneys, and the gut. This nuclear receptor is a transcription factor that regulates the transcription of genes whose proteins are involved in glucose and lipid metabolism as well as inflammation and endothelial function.

**Other uses of thiazolidinediones**

Thiazolidinediones have been studied in several other clinical conditions where insulin resistance is a central part of the pathophysiology. Persons with these conditions may or may not have pre-diabetes, type 2 diabetes, or the metabolic syndrome. These conditions are, therefore, not included in this review. Such conditions include polycystic ovary syndrome and nonalcoholic steatohepatitis (NASH). HIV-infected patients using anti-retroviral therapy often have metabolic abnormalities, including loss of subcutaneous fat, insulin resistance, and hypertriglyceridemia. Early studies show that thiazolidinediones may be useful in this population.

**Table 2. Characteristics of thiazolidinediones approved for use in the United States and Canada**

Drug	Trade name	Labeled indications	Dosage, how supplied	Boxed warnings
Pioglitazone <sup>23</sup>	Actos <sup>®</sup>	Type 2 diabetes monotherapy or in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent do not result in adequate glycemic control.	15-30 mg every day, maximum 45 mg every day; supplied as 15,30,45 mg tablets	<p>Thiazolidinediones cause or exacerbate congestive heart failure in some patients. Observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation or dose reduction must be considered.</p> <p>Not recommended in patients with symptomatic heart failure. Initiation in patients with established NYHA Class III or IV heart failure is contraindicated.</p> <p>May be used In combination with insulin in patients with insufficient glycaemic control on insulin for whom metformin is not tolerated or contraindicated.</p>

Drug	Trade name	Labeled indications	Dosage, how supplied	Boxed warnings
Rosiglitazone <sup>24</sup>	Avandia	Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.	4 mg every day or divided into twice a day, maximum 8 mg once a day; supplied as 2,4,8, mg tablets	<p>Thiazolidinediones cause or exacerbate congestive heart failure in some patients. Observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation or dose reduction must be considered.</p> <p>Not recommended in patients with symptomatic heart failure. Initiation of Avandia™ in patients with established NYHA Class III or IV heart failure is contraindicated.</p> <p>A meta-analysis of 42 clinical studies (mean duration 6 months: 14,237 total patients), most of which compared Avandia™ to placebo, showed Avandia™ to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing Avandia™ to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.</p> <p>Coadministration of Avandia™ and insulin is not recommended.</p>

---

Abbreviations: NYHA, New York Heart Association

Muraglitazar (Pargluva®) was not reviewed as it was not available in the United States as of January 1<sup>st</sup> 2008.

### ***Quality of the Evidence***

For quality of evidence the EPC and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

- 1) Methods used for randomization
- 2) Allocation concealment and blinding
- 3) Similarity of compared groups at baseline and maintenance of comparable groups

- 4) Adequate reporting of dropouts, attrition, and crossover
- 5) Loss to follow-up
- 6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

- 1) Adequate description of the study population
- 2) Similarity of patients to other populations to whom the intervention would be applied
- 3) Control group receiving comparable treatment
- 4) Funding source that might affect publication bias.

### ***Weighing the Evidence***

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the body of evidence relevant to that question.

### ***Scope and Key Questions***

The objectives and scope of the updated report were modified from those of the original report. For this update, our objective was to update the recent Comparative Effectiveness Review produced by the Agency for Healthcare Research and Quality, Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults with Type 2 Diabetes.<sup>28</sup> The Agency for Healthcare Research and Quality report compared available oral medications for the treatment of adults with type 2 diabetes for efficacy, effectiveness, and adverse events. Studies that included comparison with insulin were excluded. The key questions for this Drug Effectiveness Review Project updated report were thus modified from the prior Drug Effectiveness Review Project report in order to address both within- and between-class comparisons encompassing rosiglitazone and pioglitazone.

Our search covered the Cochrane databases through the 4<sup>th</sup> quarter 2007 and other sources through October week 5 2007. See appendix A of the DERP report for a detailed summary of the search methods utilized.

#### **Key Questions:**

KQ1. For persons with type 2 diabetes, do pioglitazone and rosiglitazone differ from each other, from placebo, and from other oral hypoglycemic agents in the ability to reduce and maintain A1c levels?

KQ2. For persons with type 2 diabetes, do pioglitazone and rosiglitazone differ from each other, from placebo, and from other oral hypoglycemic agents in their effects on macrovascular and microvascular complications and mortality from diabetes?

KQ3. For patients with prediabetes or metabolic syndrome, do thiazolidinediones differ from one another or from placebo in improving weight control

- a. When used as monotherapy?
- b. When added to metformin?

KQ4. For persons with prediabetes or the metabolic syndrome, do thiazolidinediones differ from one another or from placebo in delaying or preventing the occurrence of type 2 diabetes?

KQ5. For patients with prediabetes or metabolic syndrome, is the use of different thiazolidinediones associated with reversal or slower progression of cardiac risk factors, including lipid levels, central obesity, or elevated blood pressure?

KQ6. For persons with type 2 diabetes what are the adverse events related to pioglitazone and rosiglitazone, and how do these differ from each other, from placebo, and from other oral hypoglycemic agents?

KQ7. How do thiazolidinediones compare to sulfonylureas in serious hypoglycemic events, functional status, and quality of life?

KQ8. Are there subgroups of persons with type 2 diabetes based on demographic characteristics or co-morbidities for which the benefits and adverse effects of pioglitazone or rosiglitazone differ from those in general populations, compared to each other and to other hypoglycemic agents?

## **Conclusions:**

### KQ1

Good quality evidence shows that:

1. Pioglitazone and rosiglitazone have similar effects on A1c, yielding a decrease of approximately 1%. There are no significant differences between these two drugs for effect on A1c
2. TZDs have a similar effect on A1C as metformin, glibenclamide, or glimepiride.
3. There is no difference between TZDs and metformin or sulfonylureas in their ability to lower A1c.

### KQ2.

There is insufficient data to determine the effectiveness of pioglitazone and rosiglitazone on microvascular or macrovascular complications of DM.

### KQ3.

For patients with prediabetes or metabolic syndrome evidence shows that both rosiglitazone and pioglitazone produce a similar small weight gain when used as monotherapy or added to metformin.

### KQ4.

1. TZDs delayed the onset of diabetes compared to placebo but in a three year study there was no difference in mortality. Long term clinical significance is unknown.

*Conclusions continued next page*

## Conclusions – continued

### KQ5.

There is insufficient evidence to determine the effectiveness of pioglitazone vs. rosiglitazone on cardiovascular risk factors (lipid levels, central obesity, or elevated blood pressure).

### KQ6.

1. There is insufficient evidence to determine a difference between rosiglitazone and pioglitazone for adverse events, or withdrawals due to adverse events.
2. Good to fair evidence shows that the TZD's are associated with an increased incidence of edema compared to placebo.

### KQ7.

1. There are no quality studies on functional status or quality of life comparing TZDs versus sulfonylureas.
2. There is fair evidence that pioglitazone, and minimal evidence that rosiglitazone, is associated with less hypoglycemia than sulfonylureas

### KQ8.

1. Fair quality indirect evidence suggests that pioglitazone and rosiglitazone are equally effective among minority populations.
2. Evidence is insufficient to determine a comparative difference in effectiveness or adverse effects for rosiglitazone or pioglitazone for older populations.
3. Evidence is insufficient to determine comparative effectiveness of these drugs in populations with significant comorbidities (coronary heart disease, congestive heart failure, or renal insufficiency).

## Supporting Evidence:

KQ1. For persons with type 2 diabetes, do pioglitazone and rosiglitazone differ from each other, from placebo, and from other oral hypoglycemic agents in the ability to reduce and maintain A1c levels?

### Direct Evidence

Four fair-quality, head-to-head, randomized controlled trials were identified examining persons with type 2 diabetes.<sup>65-68, 70</sup> Two randomized, controlled, double-blind trials demonstrated significant improvements in A1c at follow-up<sup>65 67</sup> with no significant differences between groups. Derosa and colleagues published a new study comparing pioglitazone and rosiglitazone, both combined with metformin 1500-3000 mg daily.<sup>70</sup> A1c decreased in both groups (pioglitazone -1.4%, rosiglitazone -1.3%; within-group  $P < 0.01$  for both treatment groups), with no significant difference between groups.

### Indirect Evidence

Placebo controlled trials

### *Pioglitazone*

In the original review sixteen trials were identified that compared pioglitazone to placebo in at least on study arm and fifteen .of these were usable in a meta-analysis. The mean difference between groups for all good and fair-quality studies comparing pioglitazone with placebo ranged from -3.0% to -0.5% and the pooled weight mean difference was -1.06% (95% CI:-1.27% -0.84%). Heterogeneity among these studies was significant ( $P<0.00001$ ).

Two studies did not find a significant change in A1c compared with placebo.<sup>60, 78</sup> Dormandy and colleagues,<sup>60</sup> in PROspective PioglitAzone Clinical Trial in macroVascular

Events (PROACTIVE), examined 5238 patients with a mean follow-up of 34.5 months, the largest sample size and the longest follow-up of any study examined. At baseline subjects were taking multiple hypoglycemic medications (including more than 30% taking insulin) which were continued during the study. Throughout the trial, investigators were required to increase all therapy to an optimum, with particular attention to reaching an A1c level below 6.5% in both groups. These researchers noted a decrease in A1c of 0.8% and 0.3% in the intervention and placebo groups, respectively; thus the between-group change was modest. In addition, despite the large sample size, confidence intervals were wide for within-group changes. These factors, in addition to the focus on optimal glycemic control in both groups, contributed to a nonsignificant ( $P>0.05$ ) between-group difference in change in A1c. The participants in this study were fairly well controlled at baseline (mean A1c 7.8% in the pioglitazone group and 7.9% in the placebo group) on multiple medications (only 4% of both study groups were on diet-only therapy); baseline A1c was 7.8 % and 7.9% in the pioglitazone and placebo groups, respectively. These factors likely also contributed to the relatively small between-group change. The study by Takagi<sup>78</sup> was small and the control group also improved.

Since the time of the original publication of PROACTIVE<sup>60</sup> additional subgroup analyses have been published. we identified 4 new placebo-controlled trials, two of combination therapy<sup>83, 84</sup> and 2 of monotherapy,<sup>85, 86</sup> along with a no-treatment comparison<sup>87</sup> study. A1c

improved more than in the control group in 1 small, monotherapy study of nonalcoholic steatohepatitis in persons with either type 2 diabetes or impaired glucose tolerance.<sup>85</sup> In the pioglitazone plus sulfonylurea arm of a study by Gastaldelli and colleagues,<sup>83</sup> A1c improved more in the treatment arm (change -2.0%) than in the placebo arm (change +0.9%; between group  $P<0.001$ ). A1c did not decrease significantly compared with control in 3 small studies.<sup>84, 86, 87</sup>

### *Rosiglitazone*

In the original review twenty-five trials compared the efficacy or effectiveness of rosiglitazone to placebo. Four rosiglitazone studies did not provide adequate information for inclusion in the meta-analysis. Results are similar to those noted for pioglitazone, with a mean change in A1c for all fair-quality studies of -0.94 (95% CI -1.26 to -0.63). Again, heterogeneity was significant among studies and there were no significant differences between monotherapy and combined therapy. Adjusted indirect comparisons of pioglitazone and rosiglitazone revealed no significant differences between the 2 drugs for A1c.

Five new fair quality or better studies were identified for this review. All but 1 study<sup>84</sup> were combination therapy studies.

Dargie and colleagues<sup>56</sup> examined 224 persons with type 2 diabetes and with New York Heart Association congestive heart failure class I and II and with left ventricular ejection fraction (LVEF)  $\leq 45\%$ . Subjects took various other oral hypoglycemic agents (excluding metformin). After 1-year follow-up, A1c was significantly lower in the rosiglitazone group (adjusted mean difference  $-0.65\%$  (95% CI  $-0.94$  to  $-0.37$ )).

Lautamaki and colleagues<sup>106</sup> noted a decrease in A1c compared to placebo in a study of combination therapy in patients with coronary artery disease ( $P < 0.0001$  compared with placebo).

In a study of older adults with type 2 diabetes, Rosenstock and colleagues<sup>110</sup> noted significant improvement in A1c with rosiglitazone plus glipizide 10 mg twice daily compared with glipizide alone titrated to maximal dosage; at 2-year follow-up between-group change in A1c was  $-0.79\%$  ( $P < 0.0001$ ). Deterioration in glycemic control, defined as the time at which the fasting plasma glucose rose to  $\geq 10$  mmol/L, occurred in 28.7% of the titrated sulfonylurea group and 2.0% of the rosiglitazone group ( $P < 0.0001$ ).

Pfutzner and colleagues<sup>111</sup> noted a decrease in A1c with the addition of glimepiride 4 mg daily (1.2%) or 8 mg daily (1.3%) to rosiglitazone over 4 months, compared with glimepiride plus placebo (0%) (within-group comparisons for both rosiglitazone groups  $P < 0.005$ ). In a combination therapy, double-blind trial (N=365), both groups received combination tablets of glyburide/metformin. Addition of rosiglitazone achieved greater reduction in A1c than addition of placebo (between-group difference  $-1.0\%$ ,  $P < 0.001$ ). The percentage of subjects with A1c  $< 7.0\%$  at study end was greater in the rosiglitazone group than with placebo (42% compared with 14%).<sup>105</sup>

#### Active control trials

Bolen and colleagues<sup>28</sup> concluded that there were no between-group differences between thiazolidinediones and metformin (7 randomized controlled trials) or second generation sulfonylureas (13 randomized controlled trials). Thiazolidinedione plus metformin compared with a second-generation sulfonylurea plus metformin (2 randomized controlled trials) did not show a consistent effect favoring 1 of the combinations, nor did 2 randomized controlled trials comparing thiazolidinediones compared with repaglinide. One trial comparing pioglitazone to acarbose favored pioglitazone for A1c reduction.

#### *Pioglitazone*

Nine new studies were identified including 2 that were rated better than poor quality. Four monotherapy trials compared pioglitazone to a sulfonylurea<sup>134, 138, 140, 142</sup> or to metformin.<sup>142</sup> Trials examining combination therapy compared pioglitazone to a sulfonylurea with both groups receiving various oral hypoglycemic agents or insulin<sup>111, 133, 137</sup> or metformin.<sup>141</sup> Pioglitazone was compared to metformin with both groups receiving gliclazide in 1 trial.<sup>139</sup> Drug dosing across studies was fairly consistent, with most study populations 50-60 years of age. Studies ranged between 3 and 18 months, with only 3 fair-to-good quality trials with follow-up greater than 6 months.<sup>137, 138, 142</sup> Effects on A1c were similar between treatment groups, with no significant difference noted between groups in 7 of the 9 trials

### *Rosiglitazone*

We identified 9 fair or better quality active-control trials involving rosiglitazone for the updated report. There were 2 monotherapy trials comparing rosiglitazone to metformin<sup>57</sup> or rosiglitazone to a sulfonylurea.<sup>57, 147</sup> The combined therapy trials compared rosiglitazone to a sulfonylurea with both groups receiving metformin<sup>143-145</sup> or compared rosiglitazone to metformin with both groups receiving sulfonylureas<sup>151</sup> or various hypoglycemic agents.<sup>148</sup> Raskin and colleagues<sup>150</sup> compared rosiglitazone to repaglinide and to the combination of the 2 drugs. Goldstein and colleagues<sup>146</sup> compared rosiglitazone plus metformin to metformin alone. Across active-control studies, rosiglitazone dosing was either 4 or 8 mg daily. Follow-up intervals ranged from 12 weeks<sup>149</sup> to 4 years,<sup>57</sup> with 4 trials having follow-up of 1 year or more.<sup>57, 144, 147, 148</sup> Mean age of study subjects was mid 50s, with 2 studies enrolling older subjects, with mean ages 60<sup>143</sup> and 65 years.<sup>151</sup>

ADOPT<sup>57</sup> was a large (N=4360), fair quality multicenter, double-blind, randomized controlled trial designed to evaluate monotherapy with rosiglitazone, metformin, or glyburide among subjects recently diagnosed (within 3 years) with type 2 diabetes and who had failed lifestyle therapy but had not started on oral hypoglycemic agents. The primary outcome was monotherapy failure defined as fasting plasma glucose level of >180 mg/dl. Subjects with significant comorbidities were excluded, including congestive heart failure of any New York Heart Association class. Maximal drug dosages were rosiglitazone 4 mg twice a day, metformin 1000 mg twice a day, and glyburide 7.5 mg twice a day. Randomized subjects numbered 4360, of which 95% were included in the intention-to-treat analysis. Median duration of treatment with rosiglitazone was 4 years. Mean age was 57 years (standard deviation 10) and 57.5% were men. The cumulative incidence of monotherapy failure at 5 years was 15% with rosiglitazone, 21% with metformin, and 34% with glyburide ( $P<0.001$  for both rosiglitazone comparisons). A1c decreased in all treatment groups in the first 6 months of treatment, then A1c rose steadily in all treatment groups, with the rate of increase lowest with rosiglitazone ( $P<0.001$ ). At 4-year follow-up, the percentage of subjects with A1c <7.0% was 40% for rosiglitazone, 36% for metformin ( $P=0.03$  compared with rosiglitazone), and 26% for glyburide ( $P<0.001$  compared with rosiglitazone). The proportion of subjects who either reached the primary outcome or completed the study was 63% for rosiglitazone, 62% for metformin, and 56% for glyburide. Subjects who withdrew had similar baseline characteristics to completers. The choice of primary outcome of FPG greater than 180 mg/dl was unusual, as current recommendations are to achieve far lower FPG levels.

Among the combination therapy trials of rosiglitazone and metformin, 2 trials did not show significant differences between rosiglitazone and metformin.<sup>143, 144</sup> On the other hand, Garber and colleagues<sup>145</sup> did demonstrate more benefit for the fixed combination of glibenclamide 5 mg/metformin 1000 mg (once or twice daily) than for rosiglitazone 4-8 mg daily combined with metformin 1500-2000 mg daily (between-group difference in A1c 0.4%,  $P<0.001$ ).

Combination therapy studies comparing rosiglitazone to metformin with both groups receiving other oral agents did not show significant differences between treatment groups.<sup>148, 151</sup> A combination of rosiglitazone and repaglanide<sup>150</sup> demonstrated

superiority for the combination product over rosiglitazone monotherapy. Rosiglitazone was superior to repeganide (each as monotherapy; no statistics provided).

In a substudy of the EMPIRE study examining cardiovascular biomarkers,<sup>146</sup> no significant difference was noted on A1c at 24 weeks between rosiglitazone 4-8 mg daily combined with metformin 1000 mg daily, and metformin titrated up to 2000 mg daily. In the large trial RECORD<sup>58</sup> (discussed further in Key Question 2), subjects who were already taking a sulfonylurea were randomized to add-on rosiglitazone 4 mg daily (titrated up to 8 mg daily) or metformin (titrated up to 2550 mg daily). Subjects taking metformin at study entry were randomized to add-on sulfonylurea. If adequate glycemic control ( $A1c \leq 8.5\%$ ) was not obtained on maximal dosage dual therapy, a third drug was added (either a sulfonylurea or metformin to rosiglitazone subjects and insulin in the control group). A1c decreased by approximately 0.5% at 18 months follow-up<sup>151</sup> in all 4 treatment groups, with no statistically significant difference between rosiglitazone and other drugs in the background metformin and background sulfonylurea groups.

**Key Question 2:** For patients with type 2 diabetes do thiazolidinediones differ from each other, from placebo, and from other oral hypoglycemic agents in their effects on macrovascular and microvascular complications, and mortality from diabetes?

None of the head-to-head studies identified in the original or updated review examined macro- or microvascular outcomes. Three placebo-controlled or no-treatment comparison studies identified in the original review examined cardiovascular outcomes; all examined patients with known macrovascular disease and type 2 diabetes, <sup>60, 103, 152</sup> including the PROACTIVE trial.<sup>60</sup> Studies examined microvascular outcomes. These 3 trials did not provide sufficient data to determine comparative effectiveness of pioglitazone and rosiglitazone on microvascular or macrovascular complications of diabetes. Both studies provided some evidence of positive effects of these drugs on macrovascular outcomes among patients with preexisting coronary artery disease.

For this update several additional trials provided evidence on macrovascular outcomes and on mortality, with 5 trials providing additional evidence on pioglitazone. Two of these studies were published after the end-date for our searches.<sup>137, 154</sup>

The CHICAGO trial<sup>137</sup> was a multicenter study of pioglitazone 15 to 45 mg per day compared with glimepiride 1 to 4 mg per day in 462 adults who were newly diagnosed with type 2 diabetes. The primary endpoint was the change in carotid artery intima-media thickness after 72 weeks. Secondary endpoints included the composite of cardiovascular mortality, non-fatal MI, or nonfatal stroke, and the composite of these outcomes plus coronary revascularization, carotid endarterectomy/carotid stenting, hospitalization for unstable angina, or hospitalization for heart failure. There were few events reported, and no cardiovascular deaths. There were 2 instances of the first composite endpoint in the glimepiride group and none in the pioglitazone group. On the second composite endpoint, there were 10 events in the glimepiride group (8 of which were coronary revascularization) and 4 in the pioglitazone group (3 coronary revascularization).

PERISCOPE was another trial of pioglitazone compared to glimepiride designed to measure progression of atherosclerosis in patients with type 2 diabetes.<sup>154</sup> After 18 months of follow-up, there was no difference between groups in the occurrence of

clinical endpoints, including the composite of cardiovascular death, nonfatal MI, or nonfatal stroke (2.2% for glimepiride compared with 1.9% for pioglitazone;  $P=0.78$ ), the composite of cardiovascular death, onfatal MI, nonfatal stroke, hospitalization for unstable angina, or congestive heart failure 4.8% for glimepiride compared with 4.1% for pioglitazone;  $P=0.70$ ) or any components of the composite outcomes. There were 3 cardiovascular deaths in the pioglitazone group and 1 in the glimepiride group ( $P=0.37$ ).

In a small, fair-quality, randomized controlled trial ( $N=47$ ), patients with impaired glucose tolerance or type 2 diabetes (combined in the analysis) in addition to nonalcoholic steatohepatitis, received either pioglitazone 45 mg daily or placebo, in addition to a weight loss intervention.<sup>82</sup> Glycemic control improved with pioglitazone compared with placebo ( $P<0.001$ ), with a decrease in weight and body mass index with treatment compared with placebo ( $P=0.003$  and  $0.005$ , respectively). Plasma aspartate and alanine aminotransferase levels and hepatic fat content all decreased with treatment compared with placebo ( $P<0.05$ ) and liver aminotransferase levels normalized with pioglitazone. Histologic changes in the liver also improved significantly with pioglitazone.

In another small trial,<sup>93</sup> patients ( $n=108$ ) with acute coronary syndrome received pioglitazone or no additional treatment starting 2 weeks after percutaneous, bare metal stent placement. At 6 months follow-up these researchers demonstrated that late luminal loss was less in the pioglitazone group than in the control group ( $P=0.0008$ ); the same was found for restenosis rate (between-group  $P=0.0052$ ; both assessed with quantitative angiography). Major cardiac events (myocardial infarction or revascularization of the target lesion) were significantly decreased in the pioglitazone group at 6 months compared with the control group (7.7% compared with 60.7%,  $P<0.0001$ ). There were no deaths in either group.

Takagi and colleagues compared pioglitazone with placebo in 44 patients with type 2 diabetes who had undergone coronary stent implantation.<sup>78</sup> After 6 months of follow-up, angiographic in-stent restenosis (19% compared with 46%;  $P=0.0994$ ) and target lesion revascularization (12% compared with 38%;  $P=0.0835$ ) were less frequent in the pioglitazone group, but the differences were not statistically significant. There was no difference in A1c levels at follow-up in this study (See Key Question 1).

The RECORD trial<sup>148</sup> and ADOPT<sup>57</sup> reported on vascular or mortality outcomes. An interim analysis of the RECORD trial was published by Home and colleagues in 2007.<sup>148</sup> In this open-label, multicenter, noninferiority, randomized controlled trial ( $N=4458$ ), subjects who were already taking a sulfonylurea were randomized to add-on rosiglitazone 4 mg daily (titrated up to 8 mg daily) or metformin (titrated up to 2550 mg daily). Subjects taking metformin at study entry were randomized to add-on sulfonylurea (glyburide, gliclazide or glimepiride, depending on physician preference). If adequate glycemic control ( $A1c \leq 8.5\%$ ) was not obtained on maximal dosage dual therapy, a third drug was added (either a sulfonylurea or metformin for rosiglitazone subjects and insulin in the control group).

The primary outcome for the RECORD study was hospitalization for any of the following: acute myocardial infarction, congestive heart failure, stroke, unstable angina pectoris, transient ischemic attack, unplanned cardiovascular revascularization, amputation of an extremity for any other definite cardiovascular reason, or death from cardiovascular causes. For the adjudicated primary endpoint of hospitalization or death

from cardiovascular disease, the hazard ratio for rosiglitazone (plus metformin or a sulfonyleurea) compared with metformin plus a sulfonyleurea was 1.08 (95% CI 0.89 to 1.31). The time-to-event curves suggested divergence of treatment effects after 2.5 years of follow-up, but a small number of subjects contributed to that analysis. There were no significant differences between rosiglitazone and the control groups for secondary endpoints of acute myocardial infarction, death, or a composite of cardiovascular death, myocardial infarction, and stroke. The elevated hazard ratio for the primary endpoint was mainly driven by the increase in congestive heart failure in the rosiglitazone group compared with the control group (hazard ratio for adjudicated events 2.24, 95% CI 1.27 to 3.97). The RECORD study underwent the interim analysis discussed herein due to concerns raised about the safety of rosiglitazone and its potential for causing congestive heart failure and cardiac events.<sup>63</sup> Because this was an interim analysis, the study was not powered to detect differences in cardiovascular end points in this follow-up period. Thus interpretation of this interim analysis must be done with great caution.

The large ADOPT<sup>57</sup>, discussed above for the outcome of monotherapy failure, compared rosiglitazone, glyburide, and metformin in subjects newly diagnosed with type 2 diabetes. Subjects with significant renal or hepatic disease, unstable or severe angina, or congestive heart failure of any New York Heart Association class were excluded. Approximately half of subjects had hypertension, 81% had metabolic syndrome, and 45% were smokers.<sup>155</sup> The number of deaths from all causes was similar across the 3 groups, but more cardiovascular events were reported in the rosiglitazone group (4.3%) than in the metformin (4.0%) or glyburide groups (2.8%; no significant differences among groups). Congestive heart failure events were higher with rosiglitazone than with glyburide. The lower rates of cardiovascular events in the glyburide group were primarily due to lower rates of nonfatal myocardial infarction and congestive heart failure in this group.

**Key Question 3: [Not Updated].** For patients with prediabetes or the metabolic syndrome, do thiazolidinediones differ from one another or from placebo in improving weight control?

- a. when used as monotherapy?
- b. when added to metformin?

There is a paucity of data on the comparative effect of pioglitazone and rosiglitazone compared to placebo on weight or abdominal obesity. Weight was measured in six studies of prediabetes or the metabolic syndrome, including two head-to-head studies. One head-to-head study reported increased weight with both pioglitazone and rosiglitazone with no significant difference between the groups.<sup>8</sup> Rosiglitazone did not produce a significant change in weight compared to placebo in two small studies.<sup>9,10</sup>

Pioglitazone, either alone or in combination with metformin was associated with an increase in weight compared to metformin as monotherapy.<sup>11</sup>

**Key Question 3 The TZD Subcommittee agrees by consensus that:  
3a. The body of evidence is insufficient to compare the effectiveness of pioglitazone vs. rosiglitazone as monotherapy to improve weight control.**

**3b. The body of evidence is insufficient to compare the effectiveness of pioglitazone vs. rosiglitazone when added to metformin to improve weight control.**

**Key Question 4:** For persons with prediabetes or the metabolic syndrome, do thiazolidinediones differ from one another or from placebo in delaying or preventing the occurrence of type 2 diabetes?

In the original review there were insufficient data to determine whether pioglitazone and rosiglitazone have different effects on the incidence of diabetes among persons with either prediabetes or the metabolic syndrome. Only 2 relevant studies were identified, both involving monotherapy. [158](#), [161](#)

For the updated report we identified 1 new large clinical trial and 1 smaller randomized controlled trial comparing rosiglitazone with placebo in persons with prediabetes<sup>59</sup> or the metabolic syndrome.<sup>160</sup>

In the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial,<sup>161</sup> a large (N=5269), multicenter, international, randomized controlled trial of adults with prediabetes (impaired fasting glucose and/or impaired glucose tolerance) and no preexisting cardiovascular disease, subjects were randomized to rosiglitazone 4 mg daily for 2 months, then 8 mg daily or to placebo. In addition, subjects were also randomized to ramipril 15 mg daily or placebo in a 2x2 factorial design. Subjects were followed for a median of 3 years.

The primary outcome was a composite of incident diabetes or death: hazard ratio 0.40 (95% CI 0.35 to 0.46,  $P<0.0001$ ). The hazard ratio for death alone was 0.91 (95% CI 0.55 to 1.49,  $P=0.7$ ) and the hazard ratio for new onset type 2 diabetes 0.38 (95% CI 0.33 to 0.44,  $P<0.0001$ ). The rates of progression to diabetes over 3 years were 10.6% with rosiglitazone and 25% with placebo ( $P<0.0001$ ).<sup>59</sup> The groups had similar frequency of the composite cardiovascular outcome (myocardial infarction, stroke, cardiovascular death, new angina, revascularization procedure, heart failure) and all but 1 of the components of the composite: heart failure (hazard ratio 7.03, 95% CI 1.60 to 30.9,  $P=0.01$ ). The effects of rosiglitazone were the same in all regions of the world, with different ethnic groups, in both sexes, and across all ages. For every 1000 people treated with rosiglitazone for 3 years, 144 cases of diabetes would be prevented, with an excess of 4 to 5 cases of congestive heart failure.

In a pilot randomized controlled trial (N=200), rosiglitazone was compared with placebo in persons with the metabolic syndrome undergoing percutaneous coronary interventions.<sup>160</sup> Rosiglitazone 4 mg twice daily was given immediately before the intervention and then for 1 year of follow-up. There was no significant difference in rates of death, myocardial infarction, or stroke at 12 months. There were fewer cases of new-onset diabetes in the rosiglitazone group than with placebo, but this did not reach statistical significance (0% compared with 3.3%,  $P=0.08$ ).

**Key Question 5:** For patients with prediabetes or metabolic syndrome, is the use of different thiazolidinediones associated with reversal or slower progression of cardiac risk factors, including lipid levels, central obesity, or elevated blood pressure?

Six studies provided data relevant to this question. Rosiglitazone produced a decrease in both systolic and diastolic pressure compared to placebo in two small studies.<sup>13</sup> There were no data to address comparative effects of blood pressure.

One fair-quality head-to-head study demonstrated improved lipid levels with pioglitazone compared to rosiglitazone. However data on both drugs from placebo-controlled trials showed mixed effects on lipid levels. Pioglitazone produced a significant ( $P < 0.05$ ) decrease in LDL, total cholesterol, and triglycerides compared to rosiglitazone in a head-to-head study.<sup>14</sup> Rosiglitazone increased HDL ( $p=0.032$ ) and LDL ( $p=0.025$ ) compared to placebo.

**The TZD Subcommittee agrees by consensus that:  
The body of evidence is insufficient to compare the effectiveness of pioglitazone vs. rosiglitazone on cardiovascular risk factors .**

**Key Question 6.** For persons with type 2 diabetes what are the adverse events related to pioglitazone and rosiglitazone, and how do these differ from each other, from placebo, and from other oral hypoglycemic agents?

#### Direct Evidence

Three head-to-head efficacy trials with adverse event data were identified.<sup>67, 68 65</sup> In the first study <sup>67</sup> (n=719) patients with both type 2 diabetes and dyslipidemia were randomized to treatment with pioglitazone 30 mg daily for 12 weeks followed by 45 mg for an additional 12 weeks, or rosiglitazone 4 mg daily followed by 8 mg for the same intervals. There were no differences between the drugs in adverse events including weight change ( $2.0 \pm 0.2$  kg for pioglitazone compared with  $1.6 \pm 0.2$  kg for rosiglitazone,  $P=0.164$ ), liver function tests, creatine phosphokinase level, blood pressure and heart rate, hemoglobin and hematocrit, hypoglycemic episodes, edema, or congestive heart failure. Data on the incidence of specific adverse events were not reported. Total withdrawals (19.0% for pioglitazone compared with 21.9% for rosiglitazone) and withdrawals due to adverse events (2.7% for both drugs) were similar.

A second study included patients who were switched to pioglitazone or rosiglitazone from troglitazone.<sup>68</sup> There was no information reported about adverse events in this study, with the exception of a similar weight gain in both groups (data not reported).

In a head-to-head trial in patients with type 2 diabetes and metabolic syndrome,<sup>65</sup> there was no significant difference in the increase in body mass index after 12 months of treatment with pioglitazone 15 mg ( $1.2$  kg/m<sup>2</sup>) or rosiglitazone 4 mg ( $1.5$  kg/m<sup>2</sup>), with both groups receiving glimepiride. There were no significant differences between treatment groups in serum alanine (ALT) or aspartate (AST) aminotransferase at 12-month follow-up. In 1 subject in the pioglitazone group (N=45) ALT and AST increased to 1.5 times the upper limit of normal but returned to normal range after 15 days. With rosiglitazone (N=42) 2 subjects increased AST.

One of the head-to-head studies identified for the updated report presented both tolerability and adverse events data. Derosa and colleagues<sup>70-72, 144</sup> noted among study completers (93% completion rate) that the rate of any side effect was 8.3% in the

pioglitazone group and 10.4% in the rosiglitazone group (between-group  $P$  value  $>0.05$ ), with both groups also taking metformin. In this trial, there were no significant differences between treatment groups in ALT or AST at 12-month follow-up. In 2 subjects in the pioglitazone group (N=48) ALT and AST increased to 1.5 times the upper limit of normal, but regressed to normal range after 15 days. With rosiglitazone (N=48) in 3 subjects AST and ALT increased to 2.0 times the upper limit of normal and also regressed. No other adverse events were reported in this study. Hematocrit decreased significantly in both treatment groups ( $P<0.05$ ): Change with pioglitazone was -2.3  $\mu\text{mol/L}$  and with rosiglitazone was -2.4  $\mu\text{mol/L}$ .

### Indirect Evidence

#### *Overall withdrawals*

Nine placebo-controlled trials of pioglitazone and 16 of rosiglitazone reported overall withdrawal rates. Treatment group withdrawal rates ranged from 7% to 33% in pioglitazone trials and 0 to 28% in rosiglitazone trials. Pooled risk differences showed trends for lower overall withdrawals in treatment groups than placebo groups for both pioglitazone (-1.0%; 95% CI -3.0% to 1.0%) and rosiglitazone (-5.0%; 95% CI -10.0% to 0.0%). There was significant heterogeneity among rosiglitazone trials.

#### *Withdrawals due to adverse events*

Overall, the proportion of patients who withdrew due to adverse events was similar for the 2 drugs: 4.7% in pioglitazone trials and 5.3% in rosiglitazone trials. Pooled risk differences showed no differences from placebo in either pioglitazone (0%; 95% CI -2% to 2%) or rosiglitazone (-1%; 95% CI -3% to 0%) trials. The proportion of withdrawals due to adverse events in the placebo groups differed between these groups of studies (4.4% in pioglitazone studies compared with 6.8% in rosiglitazone studies), so the pooled risk differences were not directly comparable.

#### *Specific adverse events reported in placebo-controlled trials*

The quality of reporting of adverse events in randomized controlled trials designed to measure efficacy was fair to poor. Most studies did not pre-specify which events were evaluated and did not report details about ascertainment methods.

### Edema

The incidence of edema reported in 16 placebo-controlled trials ranged from 0% to 27%. The incidence of edema was significantly greater with both pioglitazone and rosiglitazone than placebo.

The pooled risk difference was significantly greater than placebo in pioglitazone trials (4%, 95% CI 2% to 7%)

The pooled risk difference for rosiglitazone in 7 placebo-controlled trials was 8% (95% CI 3% to 13%). There was significant heterogeneity among the rosiglitazone trials, due to a higher incidence of edema in 2 of the trials (23% and 24%).<sup>110, 132</sup> The incidence in the other 5 trials ranged from 3% to 8%, with differences from placebo ranging from 2% to 6%.

### Hypoglycemia

The incidence of hypoglycemic episodes was reported in 11 placebo-controlled efficacy trials. The incidence ranged from 0 to 37.5% in 7 studies of pioglitazone and from 5.2% to 52.5% in 4 studies of rosiglitazone. The pooled risk difference between treatment and placebo was not significantly different for either drug. The highest rates of hypoglycemic events in pioglitazone studies were noted where pioglitazone was combined with insulin.<sup>87, 88</sup> Hypoglycemia is more likely to occur with lower baseline A1c levels, however, we only had access to study-level data, and could therefore not examine the relationship between baseline A1c and rates of hypoglycemia at the individual subject level.

### Weight Gain

Only 4 trials provided sufficient information to calculate a weighted mean difference. The pooled estimates for these trials were very similar for pioglitazone (3.69 kg, 95% CI 2.48, to 4.89)<sup>120, 131</sup> and rosiglitazone (3.50 kg, 95% CI 2.25 to 4.75),<sup>89, 97</sup> indicating that the drugs cause a similar amount of weight gain. This evidence is consistent with the findings of no difference between the drugs in weight gain reported in head-to-head trials.<sup>65, 67, 68</sup>

A 2004 meta-analysis<sup>43</sup> found similar results in an analysis of 11 trials. Within 6 months of initiating therapy, the average weight gain was 2.7 kg (95% CI 1.8 to 3.7 kg), and drug grouping was not a predictor of heterogeneity ( $P>0.10$ ). In most trials reporting weight gain, patients taking pioglitazone or rosiglitazone gained more weight than those taking a sulfonylurea or metformin.

### Liver function abnormalities

The first thiazolidinedione approved for use in the United States, troglitazone, was withdrawn from the United States market in 2000 due to concerns about liver damage. Elevations in ALT (>3 times the upper limit of normal) were rare in efficacy trials of pioglitazone and rosiglitazone, with either no cases or reported incidences of less than 1%

### Risk of fracture

Based on data from ADOPT, in February 2007 GlaxoSmithKline issued a safety warning regarding increased risk of fractures associated with use of rosiglitazone. An analysis of these data was recently published.<sup>164</sup> Significantly more female patients who received rosiglitazone experienced fractures than did female patients who received either metformin or glyburide (9.3% compared with 5.1% and 3.5% respectively). The incidence in women was 2.74 per 100 patient years with rosiglitazone, 1.54 per 100 patient-years with metformin, and 1.29 per 100 patient- years with glyburide. The majority of these fractures were in the upper arm (humerus), hand, or foot. The observed incidence of fractures for male patients in ADOPT was similar among the three treatment groups.

At GlaxoSmithKline's request, an independent safety committee reviewed an interim analysis of fractures in another large ongoing, long-term, controlled rosiglitazone clinical trial, which compared rosiglitazone in combination with either metformin or sulfonylurea to combination therapy with metformin and sulfonylurea. The results of the preliminary analysis were reported to GSK as being consistent with the observations from ADOPT. Final results of this study are anticipated to be available in 2009.

### Heart failure and other cardiac adverse events

The product label states that rosiglitazone is not indicated in combination with insulin based on an increased incidence of cardiac failure and other cardiovascular adverse events observed in patients on insulin plus rosiglitazone compared with patients using insulin plus placebo<sup>24</sup> Patients who experienced heart failure were on average older, had a longer duration of diabetes, and were for the most part taking rosiglitazone 8 mg daily.

The pioglitazone product label <sup>23</sup> cites a 24-week postmarketing study comparing pioglitazone with glyburide in patients with New York Heart Association class II and III heart failure. Over the course of the study, overnight hospitalization for congestive heart failure was reported in 9.9% of patients on pioglitazone compared with 4.7% of patients on glyburide. This adverse event associated with pioglitazone was more marked in patients using insulin at baseline and in patients over 64 years of age. No difference in cardiovascular mortality between the treatment groups was observed.

Two placebo-controlled trials of pioglitazone added to insulin reported incidences of congestive heart failure of 12.5%<sup>88</sup> and 1%.<sup>95</sup>

In the PROACTIVE trial,<sup>60</sup> rates of any report of congestive heart failure were increased with pioglitazone compared with placebo ( $P<0.0001$ ), but rates of fatal heart failure were not different between groups ( $P=0.634$ )

### **Observational studies of adverse events**

#### Direct evidence comparing pioglitazone compared with rosiglitazone

#### Lower extremity and pulmonary edema

The prevalence of edema was the primary outcome in a retrospective chart review of 99 patients receiving thiazolidinediones in combination with insulin.<sup>165</sup> The prevalence of edema was 12.7% for patients taking rosiglitazone 4 mg and 5.1% in those taking rosiglitazone 8 mg. Among patients taking pioglitazone, there was an increase in edema with increasing dose (1.3% with 15 mg and 6.3% with 30 mg). There was 1 case of pulmonary edema in a patient taking rosiglitazone.

In a retrospective chart review,<sup>166</sup> pulmonary edema was noted in 2 patients (1.9%) taking pioglitazone and 3 taking rosiglitazone (3.1%). Four of these had existing congestive heart failure treated with diuretics. Another study<sup>167</sup> reported edema in patients with documented heart failure. Fluid retention was seen with the use of both pioglitazone (15.6%) and rosiglitazone (14.3%) across all dosages. Two patients (11%) had physical signs of pulmonary edema, but the study does not report which drug the patients were taking.

#### Macular edema

The manufacturer of rosiglitazone issued a warning letter in December 2005 regarding postmarketing reports of new onset and worsening diabetic macular edema for patients receiving rosiglitazone.<sup>168</sup> The incidence is not reported, but the warning letter states that reports were very rare. In the majority of these cases, the patients also reported concurrent peripheral edema. We identified no reports of macular edema in placebo-controlled trials or observational studies.

#### Heart failure

A retrospective cohort study used claims data to assess the risk of developing heart failure in patients taking pioglitazone (N=1347) or rosiglitazone (1882) for up to 40 months.<sup>169</sup> Compared with a control group of patients who did not take thiazolidinediones, the hazard ratio for pioglitazone was 1.92 (95% CI 1.24 to 2.97), and for rosiglitazone 2.27 (95% CI 1.65 to 3.13). There was no significant difference in the risk of developing heart failure between these 2 drugs ( $P=0.091$ ).

### Weight gain

Seven comparative observational studies reported weight gain in follow-up periods ranging from 8 weeks to 1 year. There was no difference in the amount of weight gain in patients taking pioglitazone compared with rosiglitazone in any study.

### **Evidence comparing pioglitazone or rosiglitazone to active controls**

Seven observational studies reported adverse events associated with thiazolidinediones compared with other active drugs.<sup>176-182</sup> Because these studies did not report results separately for pioglitazone and rosiglitazone or they included only 1 of the thiazolidinediones, they do not provide information about the comparative safety of the thiazolidinediones. They do provide information about thiazolidinediones as a class compared with other antidiabetic agents.

In 2 studies, thiazolidinediones were not associated with increased mortality compared with other oral hypoglycemic agents.<sup>178, 181</sup> In older patients with heart failure thiazolidinediones, either alone or combined with metformin, were associated with a lower risk of death over a 15-month period compared with patients not treated with an insulin sensitizer.<sup>181</sup>

Two studies reported the incidence of coronary heart disease events (myocardial infarction or revascularization) with thiazolidinediones compared with metformin or sulfonylureas. A good-quality study using United States health insurance data found no increased risk of coronary heart disease events in patients initiating thiazolidinedione monotherapy compared with those initiating metformin plus sulfonylurea combination therapy.<sup>177</sup> The other found similar risks with rosiglitazone compared with sulfonylureas, metformin, or insulin, either alone or in combination.<sup>182</sup> Both studies also found no increased risk in the individual components of the composite outcome with thiazolidinedione use.

Hospital admission for congestive heart failure was the main outcome in a fair-quality cohort study that used data from a Kaiser Permanente diabetes registry.<sup>179</sup> Relative to patients initiating therapy with sulfonylureas, patients initiating therapy with thiazolidinediones were no more likely to experience a hospitalization for heart failure after an average of 10.2 months of follow-up. A case-control study based on Oregon Medicaid claims data, in contrast, found a trend suggesting increased risk of hospitalization for heart failure associated with exposure to thiazolidinediones within the previous 60 days.<sup>183</sup> Increased risk was also found with exposure to insulin and to the combination of insulin plus thiazolidinediones, but not for other oral antidiabetic agents.

A series of nested case-control studies found no difference in the incidence of breast, colon, or prostate cancer associated with exposure to thiazolidinediones compared with other oral diabetic medications or insulin.<sup>180</sup>

**Key Question 7:[Not Updated]** How do thiazolidinediones compare to sulfonylureas in serious hypoglycemic events, functional status, and quality of life?

There was one trial by Rosenstock<sup>18</sup> that the EPC added to their review because it was the only study looking at quality of life. This RCT compared rosiglitazone 4 mg vs. placebo with both groups receiving glipizide 10 mg BID. At 2 year follow-up the rosiglitazone had significantly higher scores on the Diabetes Treatment Satisfaction Questionnaire than the control group. However there were no comparative studies of pioglitazone and rosiglitazone.

Six trials examined pioglitazone and sulfonylurea and the incidence of hypoglycemia was less in the pioglitazone group in all six studies. There was only one study of the incidence of hypoglycemic events in persons taking rosiglitazone monotherapy compared to sulfonylurea monotherapy and reported the incidence of hypoglycemia was lower with rosiglitazone. Three additional studies examined combined therapy with rosiglitazone and a sulfonylurea versus monotherapy with the sulfonylurea. In all 3 studies the rates for hypoglycemic events were higher with the combined therapy.

**Key Question 7 The TZD Subcommittee agrees by consensus that:**

- **There are no quality studies on functional status or quality of life comparing TZDs versus sulfonylureas.**
- **There is fair evidence that pioglitazone, and minimal evidence that rosiglitazone, is associated with less hypoglycemia than sulfonylureas**
- **There is fair evidence for rosiglitazone compared to sulfonylureas that the combination produces more hypoglycemia than either monotherapy. There were no quality studies of the combination of pioglitazone and sulfonylureas on this issue.**

**Key Question 8.** Are there subgroups of persons with type 2 diabetes based on demographic characteristics or co-morbidities for which the benefits and adverse effects of pioglitazone or rosiglitazone differ from those in general populations, compared to each other and to other hypoglycemic agents?

In the first review two publications examined subgroups defined by age and several by race.

*Multiple demographic differences*

For this review we identified a combination therapy, double-blind study (N=365) <sup>105</sup> in which both groups received combination tablets of glyburide/metformin. The addition of rosiglitazone achieved greater reduction in A1c than the addition of placebo (between-group difference -1.0%,  $P<0.001$ ). An improvement in A1c was demonstrated across age, sex, and racial subgroups.

In a double-blind study (N=318) in subjects who had failed to achieve adequate control on metformin, <sup>145</sup> metformin 1000 mg/glibenclamide 5 mg was compared with metformin 1500- 2000 mg plus rosiglitazone 4 mg daily. Reduction in A1c was greater in the glibenclamide group at 24 weeks follow-up as noted above. This larger decrease in

A1c occurred in the glibenclamide group across strata defined by sex, race, age, baseline A1c, or entry metformin dose

In ADOPT,<sup>57</sup> rosiglitazone was more effective than glyburide in all subgroups for the primary outcome of monotherapy failure: age  $\leq 50$  years, between 50 and 59 years, and  $\geq 60$  years; males and females; body mass index  $\leq 30$  kg/m<sup>2</sup>, between 30 and 35 kg/m<sup>2</sup>, and  $\geq 35$  kg/m<sup>2</sup>; baseline fasting plasma glucose  $\leq 140$  mg/dL and  $> 140$  mg/dL; and waist circumference  $\leq 99$  cm,  $>99 - 110$  cm, and  $> 110$  cm.

### *Age*

The first review<sup>233</sup> found no difference between patients  $<70$  and  $>70$  for A1c, and found both groups tolerated rosiglitazone well. The second review<sup>202</sup> compared the pooled data of the effect of pioglitazone on glucose control and lipid levels in patients  $<65$  and  $>65$ . Both age groups demonstrated comparable improvements in both A1c and lipid levels with pioglitazone monotherapy or combined therapy. Adverse cardiovascular events and hypoglycemia were similar in the younger and older age groups treated with pioglitazone monotherapy and with pioglitazone combined with metformin.

For the update we identified a study of older adults with type 2 diabetes,<sup>110</sup> A1c improved with rosiglitazone plus glipizide 10 mg twice a day compared with glipizide alone at 2-year follow-up (between-group change in A1c  $-0.79\%$ ,  $P<0.0001$ ).

### *Comorbidities*

Agrawal and colleagues<sup>112</sup> examined patients with renal impairment (creatinine clearance 30-80 mL/min) and found that rosiglitazone had similar effects on A1c in patients with and without renal impairment.

In a fair-quality study pooling 2 randomized controlled trials that compared rosiglitazone plus metformin combined therapy with metformin monotherapy, Jones and colleagues<sup>118</sup> examined subgroups with body mass index  $< 25$  kg/m<sup>2</sup>, 25-30 kg/m<sup>2</sup>, and  $>30$  kg/m<sup>2</sup>. They noted greater improvement in A1c with rosiglitazone 4 or 8 mg daily plus metformin than with metformin monotherapy ( $P=0.025$ ). Safety profiles were similar in all 3 subgroups. Weight gain was noted in the obese group (body mass index  $> 30$  kg/m<sup>2</sup>) receiving metformin plus rosiglitazone (2.5 kg), while weight loss of 0.9 kg was found in obese patients on metformin alone. Weight change was not reported for the other body mass index subgroups.

Wang and colleagues<sup>103</sup> examined 70 Chinese with coronary artery disease and type 2 diabetes and noted significant improvement in A1c with rosiglitazone with change in weight similar to the to no-treatment control group. The primary and composite endpoint of coronary events (including death) was significantly decreased in the rosiglitazone group ( $P$  value reported as both  $<0.05$  and  $<0.01$ ).

From the PROACTIVE<sup>60</sup> study several subgroup analyses have been published. In the subgroup of patients with a previous myocardial infarction at baseline<sup>79</sup> (N=2445) pioglitazone had a significant beneficial effect on fatal and nonfatal myocardial infarction (28% risk reduction,  $P=0.045$ ) and acute coronary syndrome (37% risk reduction,  $P=0.035$ ). There were no significant differences between groups for cardiovascular death or nonfatal myocardial infarction, or stroke, although event rates in the pioglitazone group were consistently lower than with placebo. Rates of heart failure requiring hospitalization or fatal heart failure were not significantly different between the

pioglitazone and placebo groups, but heart failure occurred in a greater proportion of patients in the myocardial infarction subgroup (11.6%) than in subjects without prior myocardial infarction (7.0%,  $P < 0.0001$ ). The change in A1c was -0.8% (interquartile range -1.6% to -0.1%) in the pioglitazone group and -0.4% (interquartile range -1.1% to 0.3%) in the placebo group (between-group  $P < 0.0001$ ).

In another prespecified subgroup analysis of the PROACTIVE trial, pioglitazone was examined in subjects with ( $N=984$ ) and without ( $N=4254$ ) a prior stroke.<sup>80</sup> In subjects with prior stroke, there was a trend towards benefit with pioglitazone for the primary composite endpoint (all-cause death, nonfatal myocardial infarction, acute coronary syndrome, and cardiac interventions, stroke, amputation above the ankle, or revascularization) (hazard ratio 0.78, 95% CI 0.60 to 1.02). Also in the group with prior stroke, pioglitazone reduced fatal or nonfatal stroke (hazard ratio 0.53, 95% CI 0.34 to 0.85). In the subgroup without prior stroke, pioglitazone did not reduce the risk of first stroke.

In another small study, patients with acute coronary syndrome received pioglitazone or no additional treatment starting 2 weeks after percutaneous, bare metal stent placement.<sup>93</sup> Determined from quantitative angiography at 6 months, the late luminal loss was less in the pioglitazone group than in the control group ( $P=0.0008$ ) and the restenosis rate was decreased (between-group  $P=0.0052$ ). Major cardiac events (myocardial infarction or revascularization of the target lesion) were significantly decreased in the pioglitazone group at 6 months compared with the control group (7.7% compared with 60.7%,  $P < 0.0001$ ). No deaths occurred in either group.

In a small randomized controlled trial ( $N=47$ ) patients with impaired glucose tolerance or type 2 diabetes in addition to nonalcoholic steatohepatitis received either pioglitazone 45 mg daily or placebo, in addition to a weight loss intervention.<sup>82</sup> Glycemic control improved with pioglitazone compared with placebo ( $P < 0.001$ ), with a decrease in weight and body mass index with pioglitazone compared with placebo ( $P=0.003$  and  $0.005$ , respectively). Liver aminotransferase levels normalized with pioglitazone, and plasma aspartate and alanine aminotransferase levels, along with hepatic fat content, all decreased with pioglitazone compared with placebo ( $P < 0.05$ ). Histologic changes in the liver also improved significantly with pioglitazone. In this fair-quality trial, patients were not stratified with respect to type 2 diabetes or impaired glucose tolerance status.