Drug Class Review
on
Thiazolidinediones

Final Report Update 1

September 2008

The Agency for Healthcare Research and Quality has not yet seen or approved this report

Original Report Date: May 2006
A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). Prior version of this report can be accessed at the DERP website.

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More information on the Drug Effectiveness Review Project is available at http://www.ohsu.edu/drugeffectiveness/
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INTRODUCTION

Diabetes

Diabetes mellitus (diabetes) is a group of diseases characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both.[1] There are 4 main categories for the etiology of diabetes. 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 often in childhood or in young adulthood, but can occur in adults as well. Insulin treatment is required to supplement the body's abnormally low or nonexistent 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 has an increased risk of having or developing type 2 diabetes) and of the fetus and newborn. The third category consists of other specific types of diabetes caused by genetic defects in insulin action or beta cell function, diseases of the exocrine pancreas, endocrinopathies, and various other causes of impaired insulin secretion or action.[2]

The fourth category, type 2 diabetes, accounts for 90% to 95% 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 obesity, family history of diabetes, history of gestational diabetes, impaired glucose tolerance or impaired fasting glucose, physical inactivity, and race or ethnicity.[1]

The prevalence and incidence of diabetes is increasing both in the United States and worldwide. The prevalence of diabetes in the United States for all ages is estimated at 7.8%, or 23.6 million people. Approximately 5.7 million of those cases are undiagnosed.[1]

The prevalence of type 2 diabetes varies among racial and ethnic groups: In non-Hispanic blacks 20 year or older the prevalence is 14.7%; Hispanic/Latino Americans, 9.5%; American Indians and Alaska natives, 14.2%; and non-Hispanic whites, 9.8%.[1] 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% to 50% subsequent to that year.[3]

Diabetes has a major impact on the health and welfare of affected individuals. Diabetes was the seventh leading cause of death listed on United States death certificates in 2006. This statistic likely underestimates the mortality rates from diabetes, which is often not listed on the death certificate of an affected person.[1] Individuals with diabetes have an overall risk of death about twice that of individuals without diabetes.[1] Heart disease is the leading cause of diabetes-related deaths. Adults with diabetes have a death rate from heart disease that is 2 to 4 times higher than adults without diabetes.[1] 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.[1]

In addition to macrovascular sequelae, diabetes leads to numerous microvascular 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 nontraumatic lower limb amputations occur among persons with diabetes; periodontal disease is more common; and pregnancy is complicated.[1]

The cost of diabetes in America is enormous. It is estimated that the total costs (2007) are $174 billion, with direct medical costs accounting for $116 billion. The remainder of costs are indirect, including those attributed to disability, work loss, and premature mortality.[1]

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 1 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 as follows: 12% use both insulin and oral drugs, 16% use insulin only, 57% use oral agents only, and 15% do not use pharmacotherapy.[1]

Prediabetes

Prediabetes refers to the condition of having impaired fasting glucose, impaired glucose tolerance, or both. The term prediabetes was coined as it was recognized that both impaired fasting glucose and impaired glucose tolerance are associated with a significant risk of developing diabetes.[4] Impaired fasting glucose 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 (≥126 mg/dL). Impaired glucose tolerance is defined as blood glucose level of 140-199 mg/dL after a 2-hour oral glucose tolerance test (diabetes is diagnosed if the blood glucose level is ≥200 mb/dL).[2]

Prediabetes has a high prevalence: In 1988-1994, 33.8% of US adults aged 40 to 74 years had impaired fasting glucose, 15.4% had impaired glucose tolerance, and 40.1% had prediabetes (impaired fastng glucose, impaired glucose tolerance, or both).[1] The risk increases with age and reaches a peak in people aged 60 to74 years. The risk also increases with increased body mass index.[4]

Prediabetes may be the most important risk factor for progression to type 2 diabetes. The cumulative 5- to 6-year incidence of developing type 2 diabetes in persons with either impaired glucose tolerance or impaired fasting glucose is 20% to 34%.[5] The risk of diabetes is even higher among persons with both impaired glucose tolerance and impaired fasting glucose. Impaired glucose tolerance is associated with an increased risk for cardiovascular and all-cause mortality; the association with impaired fasting glucose is not as strong.[5]

Lifestyle changes can prevent or delay the onset of type 2 diabetes among high-risk persons. In the Diabetes Prevention Project (DPP),[6] a lifestyle intervention decreased by 58% the development of diabetes at follow-up of over 3 years. Similar results were noted in the Diabetes Prevention Study.[7]

Pharmacotherapy, such as metformin, acarbose, and thiazolidinediones, has also been shown to delay the progression of prediabetes to diabetes. In the Diabetes Prevention Project[6] metformin was particularly effective in persons 25 to 40 years of age and 50 to 80 pounds overweight. In the STOP-NIDDM trial[8] 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 impaired glucose tolerance when compared with placebo after approximately 30 months of treatment and 8 months of post-treatment follow-up.[9]

Metabolic syndrome

The metabolic syndrome has been proposed as a compilation of metabolic disturbances that are risk factors for cardiovascular disease. The concept of the metabolic syndrome has existed for at least 80 years and terminology and definitions have evolved.[10] In 1988 Reaven[11] noted that several risk factors for cardiovascular disease commonly cluster together. He called this cluster syndrome X; its components are dyslipidemia, hypertension, and hyperglycemia.

Today the term "metabolic syndrome" is most frequently used for the cluster of cardiovascular risk factors that co-occur in individuals more often than might be expected by chance. The abnormalities involved in the metabolic syndrome include glucose intolerance (type 2 diabetes, impared fasting glucose, or impaired glucose tolerance), insulin resistance, central obesity, dyslipidemia, and hypertension. A variety of definitions have been put forward[10] that vary with respect to specific components as well as criteria.

The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III)[12] identified 5 components of the metabolic syndrome (Table 1). The World Health Organization proposed a working definition of the metabolic syndrome in 1999, which differed somewhat from ATP III in that insulin resistance was a required component for diagnosis and a higher blood pressure was required.[13] The American Association of Clinical Endocrinologists proposed a third set of clinical criteria, which appears to be a hybrid of the APTP III and the World Health Organization criteria.[14] Efforts are underway to achieve a universal definition.[10]

The prevalence of the metabolic syndrome varies widely, in part due to differing definitions. Prevalence also varies between sexes and across ethnicities, geographic settings, and age. The prevalence in the United States was reported as 7% among persons 20 to 29 years, 44% among persons 60 to 69 years (data collected 1988-1994),[15] and 4.2% among adolescents.[16]

The metabolic syndrome is associated with an increased risk of diabetes and cardiovascular disease.[10] 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.[17]

The pathogenesis of the metabolic syndrome has not been defined. It appears to be associated with obesity, insulin resistance, deregulation of adipocyte-derived hormones, a proinflammatory state, and other endocrine factors.[18]

Management of the metabolic syndrome involves careful appraisal of cardiovascular risk and appropriate management of the underlying risk factors.[10]

Table 1. National Cholesterol Education Program's Adult Treatment Panel III definition of the metabolic syndrome[19]

Persons having three or more of the following criteria are defined as having the metabolic syndrome:
- Central obesity: waist circumference >102 cm (male), >88 cm (female)
- Hypertriglyceridemia: triglycerides ≥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 ≥135/85 mm Hg or taking medications
- Fasting plasma glucose ≥6.1 mmol/L (110 mg/dL)

Thiazolidinediones

There are 2 thiazolidinediones approved for prescription use in the United States, rosiglitazone maleate (Avandia™) and pioglitazone hydrochloride (Actos®) (Table 2). A third thiazolidinedione (Troglitazone™) was removed from the market in 1999 due to adverse hepatic effects.

Both rosiglitazone and pioglitazone are approved by the United States Food and Drug Administration 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 result in adequate glycemic control. Neither drug is currently approved for use in prediabetes or the metabolic syndrome.

The mechanisms of action of thiazolidinediones in lowering plasma glucose among persons with type 2 diabetes are thought to include the following: increase in insulin sensitivity, decrease endogenous glucose production and postprandial gluconeogenesis, increase fasting and postprandial glucose clearance, and have beneficial effects on beta-cell function.[20] 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.[21] Much of the data for these mechanisms are based on animal models.

The glycemic effects of thiazolidinediones are thought to be mediated by binding to the peroxisome proliferators-activated receptor (PPAR) gamma receptors. These receptors are expressed in the liver, heart, adipose tissue, skeletal muscle, and smooth muscle, and endothelial cells of the vasculature of the kidneys and the gut.[22]

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[23]	Actos®	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	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. Not recommended in patients with symptomatic heart failure. Initiation in patients with established NYHA Class III or IV heart failure is contraindicated. May be used In combination with insulin in patients with insufficient glycaemic control on insulin for whom metformin is not tolerated or contraindicated.

Drug	Trade name	Labeled indications	Dosage, how supplied	Boxed warnings
Rosiglitazone[24]	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	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. Not recommended in patients with symptomatic heart failure. Initiation of Avandia™ in patients with established NYHA Class III or IV heart failure is contraindicated. 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. Coadministration of Avandia™ and insulin is not recommended.

Abbreviations: NYHA, New York Heart Association

Other uses of thiazolidinediones

Thiazolidinediones have been studied in several other clinical conditions where insulin resistance is a central part of the pathophysiology. These conditions are not included in this review, although studies show that thiazolidinediones may be useful in these conditions:[25] polycystic ovary syndrome,[26] nonalcoholic steatohepatitis,[27] and HIV-infected patients using antiretroviral therapy. Persons with these conditions are only included in this review if they have been diagnosied with one or more of prediabetes, type 2 diabetes, or the metabolic syndrome.

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*.[28] 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.

The participating organizations of the Drug Effectiveness Review Project approved the following key questions for this update:

1. 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?

2. 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?

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?

4. For persons with pre-diabetes or the metabolic syndrome, do pioglitazone and rosiglitazone differ from one another or from placebo in delaying or preventing the occurrence of type 2 diabetes?

5. **(NOT UPDATED)** 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?

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?

7. **(NOT UPDATED)** How do thiazolidinediones compare to sulfonylureas in serious hypoglycemic events, functional status, and quality of life?

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?

METHODS

Literature Search

To identify relevant citations for the original report, 2 independent reviewers identified potentially relevant titles and abstracts from the Cochrane Central Register of Controlled Trials (3rd quarter 2005), Cochrane Database of Systematic Reviews, DARE, MEDLINE (1966 to July, week 4, 2005), and EMBASE (3rd quarter 2005). Search terms included drug names and indications. (See Appendix A for complete search strategies.) To identify additional studies, we also searched reference lists of included studies and reviews and we reviewed dossiers submitted by pharmaceutical companies. All citations were imported into an electronic database (EndNote 9.0.0, Thomson Reuters).

For the update the original search terms were used, but titles and abstracts and then full-text articles were screened to include additional active-control studies that address the updated key questions and new head-to-head and placebo-controlled studies. Updated searches were conducted in November 2007 (Appendix A). Electronic searches were supplemented by hand searches of dossiers received from the makers of pioglitazone and rosiglitazone, and medical and statistical reviews available on the Food and Drug Administration website.

Articles deemed potentially relevant after review of titles and abstracts were retrieved in full-text form. Two independent reviewers achieved consensus on all included and excluded articles. Excluded articles were coded in the EndNote database with the reason for exclusion.

Study Selection

The pharmacotherapeutic agents reviewed were the 2 thiazolidinediones currently available in the United States: pioglitazone hydrochloride (Actos®) and rosiglitazone maleate (Avandia™). Muraglitazar (Pargluva™) was not reviewed as it was not available in the United States as of January 1, 2008.

Participants in included studies were adults with type 2 diabetes, prediabetes, or the metabolic syndrome. As noted above, various definitions exist for the metabolic syndrome. Any study examining persons with the metabolic syndrome was included if the authors used 1 of the widely accepted definitions mentioned above (see Table 1).

Included studies examining type 2 diabetes had to present 1 or more of the primary outcomes of interest to this review: glycemic control (A1c), time to initiation of insulin for glycemic control, progression or occurrence of microvascular disease (nephropathy, retinopathy, and neuropathy), progression or occurrence of macrovascular disease (cardiovascular disease, cerebral vascular disease, amputation), other complications of diabetes, mortality, and quality of life.

Included studies examined either effectiveness or efficacy of the 2 included drugs. The purpose of this report was primarily to examine effectiveness; however, since there were very few data available on effectiveness, efficacy studies were included and reviewed in detail.

For efficacy, effectiveness, and safety, published and unpublished English-language reports in any geographic setting were included if they had a total sample size of ten or more participants. We included letters if primary data were presented and there was sufficient detail to evaluate quality. We excluded abstracts and conference proceedings, as these publications

generally do not have sufficient detail to assess internal or external validity. Theses were not included as the full text is frequently difficult to retrieve.

Selection criteria for the original report

For the assessment of efficacy and effectiveness in the original report, we included reports of randomized controlled trials and controlled clinical trials. We included trials comparing rosiglitazone and pioglitazone (head-to-head trials), as well as trials comparing either one of these drugs to placebo. We also included trials comparing these drugs to another pharmacotherapeutic agent (active-control trials) only if they examined effectiveness outcomes or population subgroups.

For examination of efficacy and effectiveness among subgroups, we expanded our inclusion criteria to encompass all study designs (that is, observational, before-after, case-control studies, and time series) where data were available. We used this approach because few controlled trials were available that examined subgroups; therefore, we expanded our inclusion criteria in order to examine the best available evidence, recognizing that study designs that do not involve randomization are weaker designs and are more likely to be biased or confounded by known or unknown factors affecting the outcomes of interest.

For the assessment of tolerability and adverse effects, we included observational studies, including case series with a sample size greater than ten, before-after studies, randomized controlled trials, and controlled clinical trials. Clinical trials are often not designed to assess adverse events, may select low-risk patients (in order to minimize drop-out rates), or may have too short a follow-up period in which to adequately assess safety. Observational studies designed to assess adverse event rates may include broader populations, carry out observations over a longer time period, use higher quality methodological techniques for assessing adverse events, or examine larger sample sizes.

Safety and tolerability were examined using data provided on overall and serious adverse events, withdrawals due to adverse effects, and other relevant specific adverse events including hypoglycemia, liver toxicity, heart failure, pulmonary edema, weight gain, and edema.

Selection criteria for the updated report

For the updated report we expanded our inclusion criteria with respect to study designs for effectiveness outcomes in order to be consistent with criteria used in the Agency for Healthcare Research and Quality report. Most notably, we expanded our examination of active-control comparisons, which was previously restricted by sample size, follow-up interval, or outcomes. These criteria are listed in Table 3, where they are contrasted with those of the prior report and of the Agency for Healthcare Research and Quality report.

Table 3. Inclusion criteria for the original and updated reports

Criteria domain and key question	Original DERP report	Updated DERP report	AHRQ report
Population	Type 2 diabetes: adults ≥ 18 years	Type 2 diabetes: adults ≥ 18 years	Type 2 diabetes: adults ≥ 18 years
	Prediabetes: adults ≥ 18 years	Prediabetes: adults ≥ 18 years	
	Metabolic syndrome as defined by ATPIII criteria: adults ≥ 18 years	Metabolic syndrome as defined by ATPIII criteria: adults ≥ 18 years	
Interventions			
	Rosiglitazone, pioglitazone	Rosiglitazone, pioglitazone	Oral hypoglycemic drugs
			Drugs not on US market if members of their class were in use (voglibose, gliclazide, glibenclamide)
			Combination of 2 included oral agents
			Excluded: 1st-generation SU, insulin, troglitazone
Comparisons			
Within class	Rosiglitazone compared with pioglitazone	Rosiglitazone compared with pioglitazone	Rosiglitazone compared with pioglitazone
	Rosiglitazone or pioglitazone compared with placebo	Rosiglitazone or pioglitazone compared with placebo	Rosiglitazone or pioglitazone compared with placebo
Between classes	Rosiglitazone or pioglitazone compared with other active hypoglycemic drug when study examined effectiveness outcomes or or population subgroups	Rosiglitazone or pioglitazone compared with other oral hypoglycemic agents Excluded: insulin and 1st-generation SU	Rosiglitazone or pioglitazone compared with other oral hypoglycemic agents Exclude: insulin and 1st-generation SU
Study designs			
General features	Excluded: non-English studies, letters, editorials, abstracts, and theses	Excluded: non-English studies, letters, editorials, abstracts, and theses	Study duration and size: ≥3 months, ≥ 40 subjects Excluded: non-English studies, letters, editorials, abstracts, and theses
Efficacy	RCTs or CCTs	RCTs or SRs	RCTs
Effectiveness	RCTs or CCTs	RCTs, CCTs, cohort with comparison group or SRs	RCTs, CCTs or cohort studies with or without a comparison group Excluded: case reports or case series
Adverse events	RCTs, CCTs, cohort studies with or without a comparison group, case-control studies, case series (N>10), or SRs	RCTs, CCTs, cohort studies with or without a comparison group, case-control studies, and SRs Excluded: case reports	RCTs, CCTs, cohort studies with or without a comparison group, or case-control studies Excluded: case reports and

Criteria domain and key question	Original DERP report	Updated DERP report	AHRQ report
	Excluded: case reports		case series
Population subgroups	As above for efficacy, effectiveness, or adverse events	As above for efficacy, effectiveness, or adverse events	As above for efficacy, effectiveness, or adverse events
Outcomes			
Efficacy	A1c	A1c	A1c, postprandial glucose, blood pressure, and lipids
Effectiveness	For prediabetes: incidence of type 2 diabetes For type 2 diabetes: durability of control, progression or occurrence of micro- or macrovascular disease, mortality, and QoL	For prediabetes: Incidence of type 2 diabetes For type 2 diabetes: durability of control, progression or occurrence of micro- or macrovascular disease, mortality, and QoL	CVD events, death, stroke, nephropathy, neuropathy, PVD, amputations, QoL, and functional status
Adverse events	Hypoglycemia, liver failure, heart failure, lactic acidosis, anemia, liver function, edema, gastrointestinal effects, weight, macular edema, fractures, and others	Hypoglycemia, liver failure, heart failure, lactic acidosis, anemia, liver function, edema, gastrointestinal effects, weight, macular edema, fractures, and others	Hypoglycemia, liver failure, heart failure, lactic acidosis, anemia, liver function, edema, gastrointestinal effects, and others

Abbreviations: A1c, hemoglobin A1c; AHRQ, Agency for Healthcare Research and Quality; ATP III, Adult Treatment Panel III of the National Cholesterol Education Program; CCTs, controlled clinical trials; CVD, cardiovascular disease; DERP, Drug Effectiveness Review Project; N, sample size; PVD, peripheral vascular disease; QoL, quality of life; RCTs, randomized controlled trials; SRs, good-quality systematic reviews; SU, sulfonylureas.

Data Abstraction

The following data were abstracted from included trials into a relational database developed for this review: study design; setting; population characteristics (including sex, age, race/ethnicity, diagnosis, duration of type 2 diabetes, A1c, weight, and body mass index); eligibility and exclusion criteria; drug dosage and frequency; treatment duration; comparison group care; numbers screened, eligible, enrolled, and lost to follow-up; and results for each prespecified outcome. Similar data were abstracted for studies that were not controlled trials and which examined adverse events.

We recorded results achieved with an intention-to-treat analytic approach, when reported. If only per protocol results were reported, we specified the nature of these results and reported them. In trials with crossover, outcomes for the first intervention were recorded if available. This was because of the potential for bias due to differential withdrawal prior to crossover, the possibility of a "carryover effect" (from the first treatment) in studies without a washout period, and a "rebound" effect from withdrawal of the first intervention.

Quality Assessment

We assessed the internal validity (quality) of controlled clinical trials using the predefined criteria listed in the quality assessment tool found in Appendix C. These criteria are based on those used by the US Preventive Services Task Force[29] and the National Health Service Centre for Reviews and Dissemination.[30] For each included trial we assessed methods for the following charateristics: randomization; allocation concealment; blinding of participants, investigators, and assessors of outcomes; the similarity of comparison groups at baseline; adequate reporting of attrition, crossover, adherence, and contamination; post-allocation exclusions; and use of intention-to-treat analysis.

We based assessment of observational and other study designs with adverse event data on unbiased selection of patients, loss to follow-up, unbiased and accurate ascertainment of events, and control for potential confounders (Appendix C).

These criteria were then used to categorize studies as good-, fair-, and poor-quality studies. Studies that had a significant flaw in design or implementation such that the results were potentially not valid were categorized as "poor". Studies that met all quality criteria were rated good quality. The remainder were rated fair. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses.

Studies were not excluded on the basis of poor quality as there is a lack of empirical evidence for a relationship between criteria thought to measure validity and actual study outcomes.[31] Studies rated as poor-quality were carefully examined and the potential sources of bias and its potential impact are presented in the evidence tables. If data were sufficient, a sensitivity analysis was performed to compare results between studies with high and low risk of bias.

External validity of studies was assessed by examining the following: adequacy of population description; inclusion and exclusion criteria; and whether the treatment received by the comparison group was reasonably representative of standard practice.

Systematic reviews that fulfilled inclusion criteria were rated for quality using pre-defined criteria (see Appendix C) to ensure the following: clear statement of the questions and inclusion criteria; adequate search strategy; adequate assessment of individual trials; adequate provision of information; and appropriate methods of synthesis.

Data Analysis and Synthesis

Important descriptive information about the population, setting, intervention, and quality assessment of studies are presented in tables, and synthesis is presented in narrative. When there were sufficient data on the primary outcome of A1c and studies were considered to be homogeneous with respect to important variables (population characteristics, drug dosage, follow-up interval, and the application of any co-intervention), we performed a meta-analysis. We also performed a meta-analysis of two key outcomes related to adverse events: the total number of withdrawals and the withdrawals related to adverse events.

We recorded the mean difference between baseline and follow-up measures for control and intervention groups and the standard error of each difference. If the standard error of the difference for each group was not given, it was estimated from the standard error of the groups at baseline, assuming a correlation between baseline and follow-up of 0.75. If data were presented only in graphs, point estimates were determined from published graphs. Pooled effects of the

randomized controlled trials were determined with each study weighted by the inverse of the study variance, using a random effects model with the DerSimonian and Laird formula for calculating between-study variance.[32] The R statistical environment and Review Manager (RevMan) was used for the meta-analysis.

An adjusted indirect comparison was performed for the outcome of A1c by combining the results of the meta-analysis comparing pioglitazone to placebo with the results of the meta-analysis comparing rosiglitazone with placebo. The variance of the estimate of effect was estimated as the sum of the variances of the 2 meta-analyses being pooled.[33]

Heterogeneity between trial results was tested for using a standard chi-squared test using a significance level of alpha=0.1, in view of the low power of such tests.[31] We also examined inconsistency among studies with I^2, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (that is, chance).[34] A value >50% may be considered substantial heterogeneity. If heterogeneity was found, we attempted to determine potential sources by examining individual study characteristics. If heterogeneity was too great to meaningfully pool the results in a quantitative manner, the results are presented in narrative.

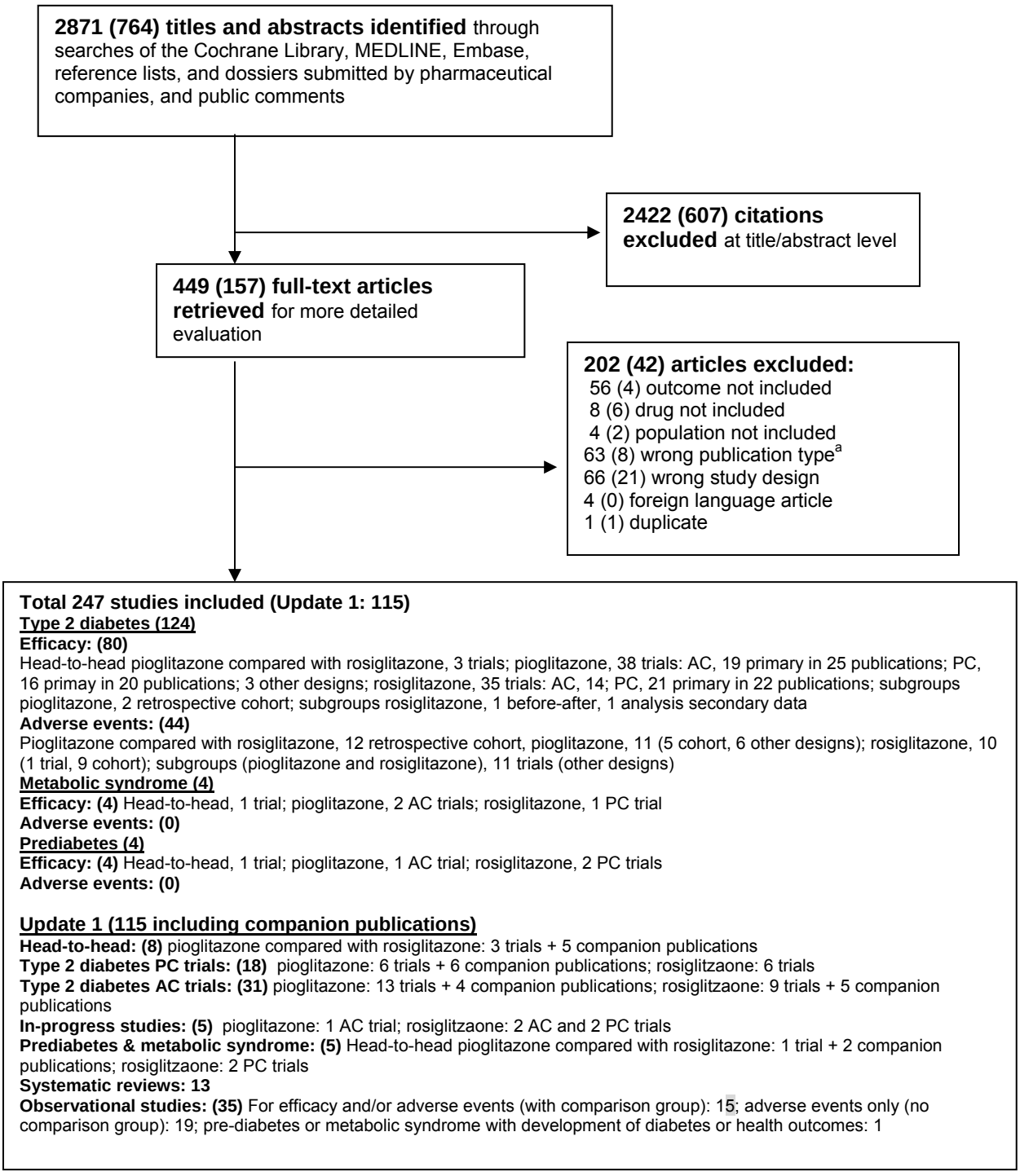
In the original report (and not in the update), meta-regression was performed to determine whether the study-level characteristics duration of intervention and study sponsorship (industry or private) affected between-group change in A1c in placebo-controlled trials. For studies using a combination of a thiazolidinedione and another hypoglycemic agent, we examined the effects of insulin, metformin, and sulfonylurea on A1c. For the meta-regression we used STATA (version 9, StataCorp LP, College Station, Texas).

RESULTS

In the original report our searches identified 87 randomized controlled trials examining the efficacy or effectiveness of pioglitazone or rosiglitazone and 42 studies examining the safety and tolerability of these drugs.

For the updated report we added 3 head-to-head trials of pioglitazone compared with rosiglitazone in patients with type 2 diabetes, 12 placebo-controlled trials in type 2 diabetes, 22 active-control trials in type 2 diabetes, and 2 placebo-controlled trials in patients with prediabetes or the metabolic syndrome. We also identified 11 new systematic reviews, 14 comparative observational studies, and 20 non-comparative observational studies with information about adverse events. The study flow diagram is provided in Figure 1 and studies excluded after review of the full text are listed in Appendix D.

Figure 1. Literature search results



Abbreviations: AC, active-control; PC, placebo-controlled.
Numbers in parentheses ( ) represent number of publications.
Shaded numbers in parenthesis ( ) represent studies pertaining to update 1.
[a] Wrong publication type (letter, editorial, non-systematic review, case report, case series <10 patients).

Findings of Prior Systematic Reviews

Efficacy and effectiveness

Original report

Ten reviews reporting comprehensive searches were identified (Evidence Tables 1 and 2). Six of the reviews were rated poor quality, as they lacked 1 or more of the following: explicit inclusion criteria, specification of the search strategy, quality assessment of individual studies, or sufficient detail on the individual studies.[35, 36 37-40] Details of the 4 fair- to good-quality systematic reviews are provided in Evidence Table 1.

In a 2001 publication, Chilcott and colleagues[41] examined pioglitazone exclusively and noted that there were no studies at that time directly comparing pioglitazone to other antidiabetic drugs. Compared to placebo, pioglitazone decreased triglyceride concentrations (30-70 mg/dL), increased HDL (4-5 mg/dL), produced no significant differences in LDL and total cholesterol (with a paucity of data), and was associated with a dose-related increase in weight (up to 4 kg over 16 weeks). These reviewers also noted mild edema (incidence up to 11.7%) and a clinically nonsignificant decrease in hemoglobin concentration.

Three systematic reviews examined both pioglitazone and rosiglitazone.[42-44] Boucher and colleagues[42] compared the 2 thiazolidinediones to other antidiabetic drugs; they did not directly compare pioglitazone and rosiglitazone. They concluded that as monotherapy these 2 drugs have effects on A1c similar to the other antidiabetic drugs, and when added to one of those drugs significantly improved A1c compared withthe original treatment regimen. Both drugs were well tolerated, with a few cases of heart failure and severe hypoglycemia noted with combined therapies. No liver toxicity was observed.

Chiquette and coauthors[43] reviewed placebo-controlled trials of pioglitazone and rosiglitazone and noted the need for head-to-head studies. They concluded that both drugs decreased A1c and increased weight to a similar degree. Pioglitazone lowered triglyceride levels ($P<0.05$), increased HDL concentrations ($P<0.05$), and had no significant effect on LDL or total cholesterol levels. Rosiglitazone increased HDL, LDL, and total cholesterol (all $P<0.05$) and had no significant effect on triglycerides. Baseline lipid levels were not adjusted for in these analyses, making it difficult to draw conclusions about the comparative effect of pioglitazone and rosiglitazone on lipid concentrations.

In a systematic review for the Health Technology Assessment Programme of the National Health Service,[44] Czoski-Murray and colleagues also noted that both pioglitazone and rosiglitazone produced similar improvements in A1c (approximately 1.0%). They did not identify any randomized controlled trials comparing the 2 drugs and noted that there were no peer-reviewed data on long-term effects.

Updated report

For the updated report we identified 11 recent systematic reviews (Appendix E).[28, 45-54]
In these reviews both pioglitazone and rosiglitazone reduced A1c by approximately 1.0 absolute percentage point, similar to the change produced with other oral agents, including metformin, glibenclamide, and glimepiride.[28, 45, 48, 50, 55] This reduction was also similar to the changes noted in placebo-controlled trials in this report.

These recent reviews did not provide additional direct head-to-head data for A1c change for pioglitazone and rosiglitazone. In placebo-controlled trials, Phatak and Yin[48] noted a

weighted mean change in A1c from baseline of -1.03% (standard deviation 0.19) for pioglitazone and -0.98% (standard deviation 0.18) for rosiglitazone. Head-to-head studies were not examined and indirect comparisons were not performed. In the Agency for Healthcare Research and Quality report,[28] Bolen and colleagues examined 4 head-to-head studies comparing pioglitazone with rosiglitazone and did not find a significant difference for A1c between these 2 drugs.

Adverse events

A number of systematic reviews examined adverse effects in both the original[36, 39, 42-44] and updated reports (See Appendix F). Four of the reviews in this update focused exclusively on adverse effects;[45, 47, 53, 54] 5 other systematic reviews examined data on adverse effects as well as on efficacy and effectiveness outcomes.[28, 46, 50-52]

Mortality

Few reviews examined mortality (total or cardiovascular).[28, 46, 52, 53] Eurich and colleagues[46] examined the use of various antidiabetic agents in patients with heart failure and diabetes and identified 3409 thiazolidinedione-treated subjects. Pooled odds ratios for thiazolidinediones compared with other hypoglycemic agents for all-cause mortality was 0.83 (95% CI 0.71 to 0.97, *P*=0.02) when 4 studies of varying designs (three were observational studies) were pooled (I^2 = 52%, *P*=0.10). Pioglitazone and rosiglitazone were combined in the studies contributing to these pooled effects. These authors note that the finding of lower all-cause mortality with thiazolidinediones should be interpreted with caution, as 3 of the 4 studies contributing to this estimate were observational in design, and subjects receiving these drugs may have been at lower risk for heart failure due to the commonly perceived risk of using them among persons with higher risk of cardiovascular events and congestive heart failure.

In contrast to Eurich and colleagues,[46] Singh, Loke, and Furberg[53] found no difference in all-cause mortality when they examined only rosiglitazone. In 4 trials, the relative risk for all-cause mortality was 0.99 (95%, 0.80 to 1.23; *P*=0.92). Cardiovascular mortality rates were similar to all-cause rates (RR 0.90 [95% CI 0.63 to 1.26], *P*=0.53).

The Singh, Loke, and Furberg[53] review differed from that of Eurich and colleagues[46] as the former review included subjects with either type 2 diabetes or prediabetes, included randomized controlled trials only, and was not restricted to subjects with heart failure. Both of the reviews included active drug and placebo comparisons, and only the randomized controlled trial by Dargie[56] was included in both the reviews.

In a systematic review of thiazolidinedione use in subjects who underwent coronary stent implantation, at 6-month follow-up mortality rate was 2/259, a death in each the control and rosiglitazone arms.[52] Bolen and colleagues[28] did not identify sufficient studies examining mortality to permit calculation of a pooled estimate.

Cardiovascular morbidity

Only 3 reviews examined the effects of thiazolidinediones on cardiovascular events; 2 focused on rosiglitazone[50, 53] and the third on both thiazolidinediones.[28] Richter and colleagues only identified data from ADOPT[57] (discussed below). Singh, Loke, and Furburg[53] identified 3 randomized controlled trials in type 2 diabetes,[56-58] all of which were included in this update. Pooled estimates were obtained for these 3 randomized controlled trials and the DREAM trial of persons with prediabetes.[59] These studies compared various drugs at a variety of follow-up intervals, although statistical tests for heterogeneity were not significant by usual criteria. The

relative risk for myocardial infarction of rosiglitazone compared with other drugs was 1.42 (95% CI 1.06 to 1.91); as noted above, the relative risk for cardiovascular mortality was not increased.

Bolen[28] stratified studies by the drug used for comparison and did not obtain pooled estimates because of clinical and methodological diversity. Three randomized controlled trials comparing thiazolidinediones and metformin and 2 randomized controlled trials comparing thiazolidinediones and sulfonylureas reported similar rates of nonfatal myocardial infarction or coronary heart disease between the thiazolidinedione and the comparison drug. Five short-duration, placebo-controlled studies also found similar rates of cardiovascular disease events and the PROACTIVE placebo-controlled trial also demonstrated no significant difference.[60] Three randomized controlled trials examining restenosis rates noted fewer cardiovascular disease events with thiazolidinediones than with placebo in patients at high risk.

Congestive heart failure

In a review of persons with diabetes or prediabetes using rosiglitazone,[53] the relative risk of heart failure for rosiglitazone compared with various other antidiabetic drugs was 2.09 (1.52 - 2.88), corresponding to a number needed to harm of 383 per year if baseline risk was 0.24% per year (low risk, from the ADOPT trial).[57]

Singh and colleagues[54] also examined onset of congestive heart failure in both pioglitazone and rosiglitazone compared with placebo in 3 randomized controlled trials with subjects with either type 2 diabetes or prediabetes. The odds ratio for all heart failure adverse events was 2.10 (95% CI 1.08 to 4.08). Four observational studies produced an odds ratio1.55 (95% CI 1.33 to 1.80). These authors also examined case reports, including 162 case subjects with 99 analyzable cases. Among these cases, the median time to onset of congestive heart failure was 24 weeks, although failure could occur early and did not appear to relate to dosage. Heart failure was not limited to the elderly; 26% of cases were in subjects less than 60 years of age.

Hospital admission for heart failure was elevated with thiazolidinediones compared with other treatments (pooled odds ratio 1.13 [95% CI 1.04 to 1.22], P=0.004; 4 studies, including 3 of observational design).[46]

In a Cochrane review of placebo-controlled trials of rosiglitazone,[50] the authors identified data only from the ADOPT trial.[57]

In a review of oral hypoglycemic agents, Bolen and colleagues[28] noted that the risk for congestive heart failure was higher with thiazolidinediones as either monotherapy or combination therapy than with metformin or sulfonylureas, with a range of 0.8% to 3.6% for thiazolidinediones and 0 to 2.6% for nonthiazolidinediones.

In a systematic review of thiazolidinediones use in diabetes and prediabetes,[47] Lago, Singh, and Nesto noted an increased risk of congestive heart failure compared with controls (placebo-controlled and active-control trials): relative risk 1.72 (95% CI 1.21 to 2.42). For placebo-controlled trials only, the relative risk was 1.97 (95% CI 0.94 - 4.13). When examined separately, the relative risk for pioglitazone was 1.32 (95% CI 1.04 to 1.68); for rosiglitazone the relative risk was 2.18 (95% CI 1.44 to 3.32). The overall event rate for congestive heart failure with thiazolidinediones was 2.3% and with the comparison drugs 1.4%. The number needed to harm for congestive heart failure was 107 over the 29.7-month follow-up (Number needed to harm ranged across studies from 35 to 491). Although the risk of heart failure was increased, the risk of cardiovascular death was not significant: relative risk 0.93 (95% CI 0.67 to 1.29); placebo-controlled trials only: relative risk 1.08 (95% CI 0.66 to 1.76); pioglitazone only:

relative risk 1.01 (95% CI 0.51 to 2.09); rosiglitazone only: relative risk 0.91 (95% CI 0.63 to 1.3).

Edema

Bolen and colleagues[28] noted that the risk for edema was higher with thiazolidinediones than metformin or second generation sulfonylureas. Although few cases were considered serious, withdrawals secondary to edema were common. Both pioglitazone and rosiglitazone were associated with higher rates of edema than placebo; the between-group difference (in favor of placebo) was 0% to 3.4% for pioglitazone and 2.5% to 17% for rosiglitazone.

In a Cochrane review of pioglitazone,[51] the authors pooled data on all available randomized controlled trials regardless of comparisons and noted a relative risk of edema of 2.86 (95% CI 1.14 to 3.18). Richter and colleagues did a similar review of rosiglitazone[50] and noted an odds ration for edema of 4.62 (95% CI 2.28 - 9.38).

Berlie and colleagues[45] examined the risk of edema in a systematic review and the odds ratio for pioglitazone and rosiglitazone combined (from comparisons with various drugs) was 2.26 (95% CI 2.02 to 2.53, $P<0.00001$). These authors attempted to compare the rates with rosiglitazone and pioglitazone and found the rates higher with rosiglitazone (odds ratio 3.75 [95% CI 2.70 to 5.20]) compared with pioglitazone (odds ratio 2.42 [95% CI 1.90 to 3.08]).

Hypoglycemia

Hypoglycemia was fairly uncommon with both thiazolidinediones. The combination of insulin and a thiazolidinedione increased rates of hypoglycemia.[28, 51, 61] Hypoglycemia rates with thiazolidinediones were lower than rates with sulfonylureas.[28, 50, 51] Thiazolidinediones cause less hypoglycemia than second generation sulfonylureas, with risk differences ranging between 0.3 and 0.25 (overall risk difference 0.09, 95% CI 0.03 to 0.25). Rates with metformin were similar to those with thiazolidinediones (obtained from indirect comparisons).[28]

Elevated serum aminotransferase levels

Bolen and colleagues[28] found that rates of significant increases in serum aminotransferase levels (> 1.5 to 2 times normal) were low (<1%) and were similar to rates with metformin and second generation sulfonylureas. Other systematic reviews reached similar conclusions.[36, 41, 42]

Weight change

Thiazolidinediones caused similar weight gain compared with sulfonylureas either as mono- or combined therapy. Metformin consistently caused weight loss compared with thiazolidinediones and other oral agents.[28] These authors identified 2 head-to-head randomized controlled trials and noted similar increases in weight with pioglitazone and rosiglitazone.

Other reviews

In addition to the systematic reviews identified for the updated report, we identified 2 reviews (Appendix G) that were not systematic and therefore did not fulfil our inclusion criteria.[62, 63]

Nissen and Wolski[63] examined the cardiovascular morbidity and mortality associated with rosiglitazone in a meta-analysis of 42 trials which included data from the Food and Drug Administration Web site, a clinical trials registry maintained by GlaxoSmithKline, and a search of the published literature. This paper was not a systematic review and therefore did not fulfil inclusion criteria for this report. Evidence of a comprehensive literature search and data synthesis

was not provided in the publication. Two large trials (DREAM and ADOPT) were the only included trials from the published literature. These authors noted an odds ratio for myocardial infarction of 1.43 (95% CI 1.03 to 1.98) and for death from cardiovascular causes of 1.64 (95% CI 0.98 to 2.74).

Lincoff and colleagues[62] examined the effect of pioglitazone on ischemic cardiovascular disease complications in diabetes using a database of individual patient data from Takeda Pharmaceuticals, the manufacturers of pioglitazone. The primary composite endpoint (death, nonfatal myocardial infarction, and nonfatal stroke) was decreased with pioglitazone as mono- or combination therapy with a variety of antidiabetic drugs (hazard ratio 0.82 [95% CI 0.72 to 0.94; *P*=0.005]). For placebo-controlled trials the hazard ratio was 0.09 (95% CI 0.01 to 0.84). The risk of serious heart failure was increased with pioglitazone (hazard ratio 1.41 [95% CI 1.14 to 1.76; *P*=0.002]).

One additional review by Padwal and colleagues[64] examined various drugs in the prevention of diabetes and included several studies on troglitazone, but none on pioglitazone or rosiglitazone.

Key Question 1. 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?

Summary of the Evidence

Pioglitazone compared to rosiglitazone:

- Prior systematic reviews found both drugs appear to have similar effects on A1c, producing a decrease of approximately 1%, similar to the change produced with other oral agents (including metformin, glibenclamide, or glimepiride).
- 5 head-to-head studies demonstrated no significant difference between pioglitazone and rosiglitazone on A1c.
- Indirect comparison demonstrated no difference between pioglitazone and rosiglitazone (difference: -0.13% (95% CI -0.41, 0.33)].
- Effect of both pioglitazone and rosiglitazone appears to be similar when used in either monotherapy or combination therapy.

Thiazolidinediones compared to other oral hypoglycemic agents:

- In a prior systematic review, 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 with repaglinide.
- One trial comparing pioglitazone to acarbose favored pioglitazone for A1c reduction.

Detailed Assessment

Head-to-head trials

Three fair-quality, head-to-head, randomized controlled trials (in 4 publications) were identified examining persons with type 2 diabetes (Table 4 and Evidence Table 3).[65-68] Quality assessment of all trials is shown in Evidence Table 4. Two randomized, controlled, double-blind trials demonstrated significant improvements in A1c at follow-up[65 67] with no significant differences between groups. In an open-label trial, Kahn and colleagues[68] noted no significant change in A1c in either group when the study drugs were used after troglitazone was discontinued with a 2-week wash-out period.

In the updated search, we identified 2 additional head-to-head trials.[69, 70] We also identified a new companion paper[71] to a trial included in the original report.[65, 66] The companion paper did not provide any additional relevant information or outcomes; rather it focused on lipoprotein (a) and homocysteine concentrations.

Derosa and colleagues published a new study comparing pioglitazone and rosiglitazone, both combined with metformin 1500-3000 mg daily.[70, 72-74] 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.

The second head-to-head study identified for the updated report was a small, poor-quality, cross-over study (N=17) comparing rosiglitazone and pioglitazone among persons with type 2 diabetes, and no significant difference between groups was noted for A1c ($P=0.43$) at 12-week follow-up.[69]

Table 4. Head-to-head trials comparing pioglitazone with rosiglitazone in persons with type 2 diabetes

Study Sample size	Dosages	Combination therapy	Follow-up; Other characteristics	A1c (%) baseline; Change from baseline (mean, SD)	Quality; Funder
Chappuis[71] 2007 N=17	Pio 30-45 mg daily Rosi 4-8 mg daily	Monotherapy	12 wk for each cross-over period, 8-wk wash-out period	Pio: 7.6 (0.6); -0.3 (0.6) Rosi: 7.6 (0.6); -0.5 (0.6); *P*=0.43	Poor; Swiss Diabetes Foundation
Derosa 2004[65], 2005[66] Derosa 2006[71] [75] N=87	Pio 15 mg daily Rosi 4 mg daily	Both groups glimepiride 4 mg daily	12 mo follow-up; participants had metabolic syndrome	Pio: 8.2 (0.7); -1.4 (NR) Rosi: 8.0 (0.8); -1.3 (NR) Within groups *P*<0.01; NSD between groups	Fair; NR
Derosa 2006[70] Derosa 2006[72] Derosa 2007[73] Derosa 2007[74] N=103	Pio 15 mg daily Rosi 4 mg daily	Both groups metformin 1500- 3000 mg daily	12 mo follow-up; participants had metabolic syndrome	Pio: 8.2 (0.8); - 1.4 (NR) Rosi: 8.1 (0.9); - 1.3 (NR) Within-group *P*<0.01 both groups Between-group *P* value NR	Fair; NR
Goldberg 2005[67] N=735	Pio 30-45 mg daily Rosi 4mg daily or twice a day	Monotherapy	24 wk Participants had untreated dyslipidemia	Pio: 7.6 (1.2); -0.7 (1.9) Rosi: 7.5 (1.2); -0.6 (1.9) Between-group *P*=0.129	Fair; Eli Lilly and Takeda Pharmaceuticals, North America
Kahn 2002[68] N=127	Pio 15-45mg daily Rosi 2 mg daily to 4 mg twice a day	Monotherapy; troglitazone withdrawn	16 wk Open-label	Pio: 8.0 (1.7); NR Rosi: 7.9 (1.9); NR NSD at follow-up in either group	Fair; NR

Abbreviations: wk, weeks; mo, months; NR, not reported; NSD, no significant difference; pio, pioglitazone; rosi, rosiglitazone.

In view of the paucity of data allowing direct comparisons between pioglitazone and rosiglitazone for the outcome of A1c, we proceeded with an examination of placebo-controlled trials allowing indirect comparisons.

Placebo-controlled trials of pioglitazone

In the original report, we identified 16 trials comparing pioglitazone to placebo in at least 1 study arm (Table 5 and Evidence table 5). All but 1 of these trials had sufficient data to permit a meta-analysis (Figure 2); a study by Saad and colleagues[76] did not provide a measure of dispersion.

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 weighted mean difference was -1.06% (95% CI -1.27% to -0.84%) (Table 6). In other words, overall, pioglitazone improved A1c about 1.0% compared with placebo. Heterogeneity among these studies was

significant ($P<0.00001$). Poor-quality studies produced a similar improvement in A1c compared with placebo (Table 6).

Results were somewhat more pronounced when pioglitazone monotherapy was compared with placebo than when combined therapy (the addition of pioglitazone to another hypoglycemic drug) was compared with placebo added to the other hypoglycemic drug, although the differences between monotherapy and combined therapy were not significant (Table 6).

The study with the most pronounced net decrease in A1c[77] was a small study (N=58) where the change in the 45 mg daily group was -1.8% and the placebo group 1.2% (although the table and narrative present inconsistent data). In other words, the placebo group had a large increase in A1c, contributing to the large between-group difference. No co-interventions were reported that might have contributed to the marked effect noted in the treatment group.

Two studies did not find a significant change in A1c compared with placebo.[60, 78] Dormandy and colleagues,[60] 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[78] was small and the control group also improved.

Since the time of the original publication of PROACTIVE[60] additional subgroup analyses have been published, including for subjects with prior myocardial infarction[79] or stroke[80] (see subgroup section on comorbidities, below).

In the updated review we identified 4 new placebo-controlled trials, two of combination therapy[83, 84] and 2 of monotherapy,[85, 86] along with a no-treatment comparison[87] 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.[85] In the pioglitazone plus sulfonylurea arm of a study by Gastaldelli and colleagues,[83] 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.[84, 86, 87]

Table 5. Pioglitazone placebo-controlled trials: Study and population characteristics

Study	Pioglitazone dosage Combination therapy	Sample size intervention group	Sample size placebo group	Follow-up	[a]Mean age (SD) Gender Other population characteristics	[a]Baseline mean Weight (SD) BMI (SD) A1c (SD)	Quality Funder
Aronoff 2000[81]	7.5, 15, 30, 45 mg daily Monotherapy	320	79	26 wk	53.7 (NR) yr 42% female (data for all groups combined)	90.4 (13.1) kg NR 10.4% (2.0%)	Poor Takeda
Belfort 2006[82]	45 mg daily Both groups: 500 kcal/d deficit diet	26	21	26 wk	51 (10) yr 55% female Participants had IGT or DM2 and NASH	90.2 (15.4) kg 32.9 (4.4) kg/m^2 6.2% (1.1%)	Fair National Center for Research Resources, Takeda, VA Medical Research Fund
Dormandy 2005[60], Charbonnel 2005[83] PROActive Study	Titrated up to 45 mg daily Combined with various hypoglycemic agents	2605	2633	156 wk (mean 34.5 mo)	61.6 (7.8) yr 34% female All subject had evidence of macrovascular disease	NR 31.0 (4.8) kg/m^2 7.9% (NR)	Good Takeda and Eli Lilly and Company
Gastadelli 2007[84]	45 mg daily Combined with various SU Study had another arm with randomization to rosiglitazone or placebo	10	10	16 wk	55 (13) yr 30% female	NR 29.9 (4.4) kg/m^2 8.3% (1.3%)	Poor Takeda, GlaxoSmithKline, NIH, Veterans Administration Merit Award
Herz 2003[85]	30, 45 mg daily Monotherapy	99	99	16 wk	58.0 (10.7) yr 51% female All subjects had controlled DM2 on diet only	86.3 (17.4) kg 31.7 (4.5) kg/m^2 7.5% (NR)	Fair Eli Lilly
Kipnes 2001[86]	15, 30 mg daily Added to SU	184+189	187	16 wk	56.8 (8.9) yr 42% female	NR 32.0 (4.9) kg/m^2 9.9% (1.4%)	Fair Takeda

Study	Pioglitazone dosage Combination therapy	Sample size intervention group	Sample size placebo group	Follow-up	[a]Mean age (SD) Gender Other population characteristics	[a]Baseline mean Weight (SD) BMI (SD) A1c (SD)	Quality Funder
Mattoo 2005[87]	30 mg daily Combined with insulin	142	147	26 wk	58.8 (7.4) yr 57% female All subjects were using insulin for ≥3m	NR 32.5 (4.8) kg/m^2 8.9% (1.3%)	Fair Eli Lilly and Takeda
McMahon 2005[88]	45 mg daily Combined with insulin	8	8	12 wk	52.5 (NR) yr 11% female Using insulin	NR 32.3 (4.1) kg/m^2 7.7% (0.6%)	Poor Takeda, American Heart Association, NHLBI
Miyazaki 2002[77]	7.5, 15 mg daily Monotherapy	47	11	26 wk	58.0 (9.9) yr 73% female	90 (13.3) kg 32.8 (5.3) kg/m^2 8.6% (1.7%)	Fair Takeda
Miyazaki 2001[89] 2004[90] Gastaldelli 2006[91]	45 mg daily Added to SU	12	11	16 wk	55 (13.3) yr 45% female Generally healthy	82 (16.6) kg 30 (3.3) kg/m^2 8.2% (1.0%) Data from 2004 (2001 baseline data slightly different)	Poor Takeda (in part) Gastaldelli 2006 funded by and NIH grant and a Veterans Administration Merit Award
Negro 2004[92]	45 mg daily Added to metformin	20	20	8 wk	61.9 (6.0) yr NR	NR 26.7 (2.4) kg/m^2 7.7% (0.6%)	Poor NR
NIshio 2006[93]	30 mg daily starting 2w after stent placement Monotherapy Control group no treatment	26	28	26 wk	67.5 (10.3) yr 28% female All subjets had acute coronary syndrome and received coronary stenting	NR 24.6 (3.5) kg/m^2 6.9% (1.6%)	Poor NR
Rosenblatt 2001[94]	30 mg daily Monotherapy	101	96	16 wk	55.2 (10.0) yr 44% female	87.2 kg (18.4) 30.7 (5.0) kg/m^2 10.4% (1.7%)	Fair Takeda
Rosenstock 2002[95]	15, 30 mg daily Monotherapy	379	187	16 wk	56.7 (9.4) yr 55% female All subjects were using insulin	95.4 (17) kg 33.2 (5.2) kg/m^2 9.8% (0.1%)	Fair Takeda

Study	Pioglitazone dosage Combination therapy	Sample size intervention group	Sample size placebo group	Follow-up	[a]Mean age (SD) Gender Other population characteristics	[a]Baseline mean Weight (SD) BMI (SD) A1c (SD)	Quality Funder
Saad 2004[76]	45 mg daily Monotherapy	147	30	12 wk	54 (NR) yr 40% female	NR 31 (NR) kg/m^2 8.1% (NR)	Fair Funding NR; 1 author affiliation Novo-Nordisk Pharmaceuticals, Princeton, NJ
Scherbaum 2002[96]	15, 30 mg daily Monotherapy	76+83	76	26 wk	59.1 (NR) yr 44% female	84.8 (NR) kg 29.2 (NR) kg/m^2 8.8% (1.1%)	Poor Takeda, Europe
Smith 2004[97] Bogacka 2004[98]	45 mg daily Monotherapy	21	21	24 wk	53.1 (9.3) yr 53% female	91.5 (14.9) kg 31.9 (5.0) kg/m^2 6.5% (0.7%)	Poor Takeda USA
Sourij 2006	30 mg daily Monotherapy	21	21	12 wk	60.3 (7.5) yr 7.1% female All subjects had newly-detected DM2 with CAD	NR 28.2 (4.1) kg/m^2 6.1% (0.5%)	Poor Takeda Austria
Takagi T 2003[78]	30 mg daily Combined with various treatments	23	21	26 wk	65 (9) yr 50% female Known CAD	NR 24.5 (NR) kg (2.9) (NR) kg/m^2 6.7% (1.2%)	Poor NR
Tseng C-H 2005[99]	30 mg daily Combined with SU	23	25	12 wk	54.1 (14.9) yr 65% female All subjects were using SU	62.6 (13.3) kg NR NR	Fair-poor NR
Wallace 2004[100]	45 mg daily Monotherapy	19	11	12 wk	62.6 (10) yr 27% female All subject were diet-controlled DM2	85.2 (4.3) kg 28.9 (2.8) kg/m^2 6.7% (0.9%)	Fair Takeda UK
Summary	**7.5 to 45 mg daily**	**10 to 2605**	**10 to 2633**	**8 to 156 wk**	**51.0-67.5 yr 7.1-73% female**	**62.6 to 90.4 kg 24.5 to 33.2 kg/m^2**	**Good: 1 Fair: 10 Poor: 10**

Abbreviations: BMI, body mass index; CAD, coronary artery disease; DM2, type 2 diabetes mellitus; IGT, impaired glucose tolerance; mo, month; NASH, nonalcoholic steatohepatitis; NR, not reported; SD, standard deviation; SU, sulfonylurea; wk, week(s); yr, year(s).
[a] Baseline mean values are given for the control group. Standard deviation is given in parentheses ( ). If standard error was provided in the original study, we converted standard error to standard deviation.

Table 6. Meta-analysis results for A1c

	Number of studies	Total N 11,148	Weighted mean difference in A1c (95% CI)[a]	Test for heterogeneity (*P* value)
Pioglitazone				
Good/fair-quality studies	9	6787	-0.95 (-1.24 to -0.67)	<0.0001
All studies	19	7324	-0.90 (-1.16 to -0.65)	<0.0001
Monotherapy	10	929	-0.92 (-1.33 to -0.51)	<0.0001
Combined therapy	9	6395	-0.90 (-1.26 to -0.55)	<0.0001
Rosiglitazone				
Good/fair-quality studies	23	3417	-0.92 (-1.15 to -0.68)	<0.0001
All studies	27	3824	-0.95 (-1.17 to -0.73)	<0.0001
Monotherapy	11	1196	-0.82 (-1.30 to -0.34)	<0.0001
Combined therapy	16	2628	-1.02 (-1.20 to -0.85)	<0.0028

Abbreviations: CI, confidence interval; N, sample size.
[a] A1c given as %. Net change is the difference in A1c between the end of the study period and baseline.

Placebo-controlled trials of rosiglitazone

In the original report, twenty-five trials compared the efficacy or effectiveness of rosiglitazone to placebo (Table 7 and Evidence Table 6). Four rosiglitazone studies did not provide adequate information for inclusion in the meta-analysis: Honisett et al.[101] did not provide a measure of dispersion; the units for A1c in a paper by Raskin and colleagues[102] were difficult to interpret; Wang et al.[103] provided graphical data only; and Nolan and colleagues[104] provided a measure of fasting glucose but not A1c.

Mean differences are presented in Table 6. 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 (Table 8).

Using meta-regression, we examined placebo-controlled trials of either pioglitazone or rosiglitazone and found no significant relationships between change in A1c and follow-up interval or funder (industry or other). When studies using combination therapy (either thiazolidinedione combined with insulin, sulfonylurea, or metformin) were examined, there were no significant differences among the various treatment combinations for change in A1c.

In the updated review of placebo-controlled trials of rosiglitazone, we identified 8 new studies,[56, 84, 105-110] including 3 poor-quality studies.[84, 107, 108] All but 1 study[84] were combination therapy studies.

Dargie and colleagues[56] 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) ≤ 45%. Subjects took various other oral hypologycemic 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[106] 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[110] 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). Attrition rates were high in both groups (35% overall), primarily due to lack of efficacy in the placebo group and to adverse events in the rosiglitazone group. However, intention-to-treat analyses were performed with 99% of the study population included. Deterioration in glycemic control, defined as the time at which the fasting plasma glucose rose to ≥ 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[111] noted a decrease in A1c with the addition of glimiperide 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 rosiglitzone 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%).[105]

In addition, 3 poor-quality studies were identified.[84, 107, 108] A small (N=16) trial demonstrated a decrease in A1c compared with placebo (P=0.024).[108] In the rosiglitazone monotherapy arm of the study[84] A1c increased 0.6% compared with a decrease of 1.4% (between-group P<0.001). In the third trial, A1c decreased 1.1% with rosiglitazone and increased 0.2% with placebo, both groups receiving metformin.[107]

Figure 2. Pioglitazone compared with placebo for A1c (%)

Review: TZD
Comparison: 01 Pioglitazone versus placebo
Outcome: 01 HbA1c, change from baseline

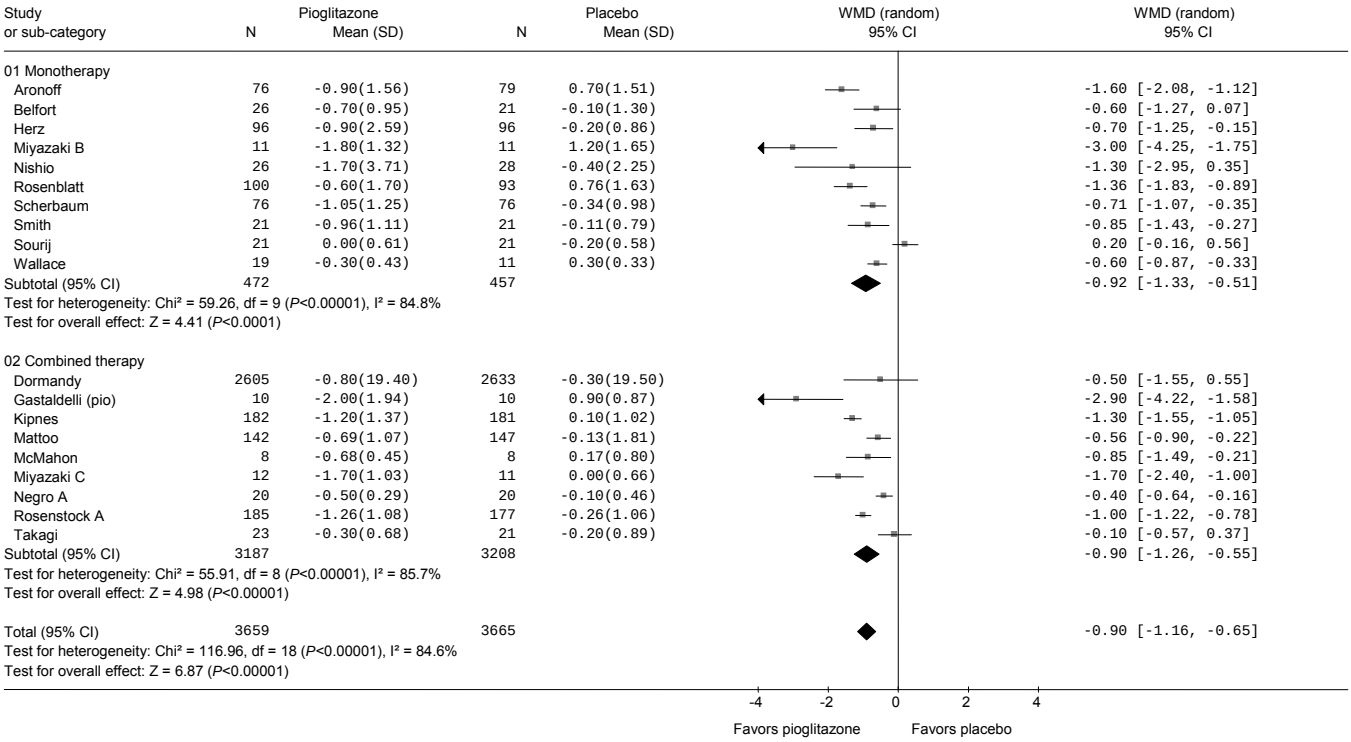
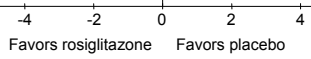


Figure 3. Rosiglitazone compared with placebo for A1c (%)

Review: TZD
Comparison: 02 Rosiglitazone versus placebo
Outcome: 01 HbA1c, change from baseline

Study or sub-category	Rosiglitazone N	Rosiglitazone Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (random) 95% CI
01 Monotherapy					
Hallisten	14	-0.30(0.52)	14	-0.20(0.35)	-0.10 [-0.43, 0.23]
Iozzo	9	-0.36(0.47)	10	0.01(0.01)	-0.37 [-0.68, -0.06]
Kim	60	-1.20(2.68)	60	-0.10(0.39)	-1.10 [-1.79, -0.41]
Leibovitz	169	-0.60(1.96)	158	0.90(2.83)	-1.50 [-2.03, -0.97]
Miyazaki A	15	-1.30(1.16)	14	0.50(1.12)	-1.80 [-2.63, -0.97]
Natali	24	0.09(0.21)	22	1.30(1.27)	-1.21 [-1.75, -0.67]
Patel	79	-0.10(1.16)	74	0.30(1.12)	-0.40 [-0.76, -0.04]
Phillips	187	-0.70(0.97)	173	1.20(1.32)	-1.90 [-2.14, -1.66]
Tan	24	-0.50(0.69)	24	-0.10(0.69)	-0.40 [-0.79, -0.01]
van Wijk	19	0.00(2.04)	19	0.10(2.47)	-0.10 [-1.54, 1.34]
Virtanen	14	-0.30(0.52)	14	-0.20(0.35)	-0.10 [-0.43, 0.23]
Subtotal (95% CI)	614		582		-0.82 [-1.30, -0.34]
Test for heterogeneity: Chi² = 147.34, df = 10 (*P*<0.00001), I² = 93.2%					
Test for overall effect: Z = 3.34 (*P*=0.0008)					
02 Combined therapy					
Agarawal	255	-0.60(1.60)	259	0.50(1.61)	-1.10 [-1.38, -0.82]
Barnett	84	-1.16(3.12)	87	0.26(0.71)	-1.42 [-2.10, -0.74]
Dargie	108	-0.50(0.74)	110	0.20(0.77)	-0.70 [-0.90, -0.50]
Fonseca	110	-0.78(2.42)	113	0.45(1.42)	-1.23 [-1.75, -0.71]
Gastaldelli (rosi)	12	-1.40(1.56)	12	0.60(0.94)	-2.00 [-3.03, -0.97]
Gomez-Perez	36	-1.20(1.96)	34	0.30(1.54)	-1.50 [-2.32, -0.68]
Jones	21	-0.30(1.30)	21	0.30(1.30)	-0.60 [-1.39, 0.19]
Lautamaki	27	-0.40(0.56)	27	0.20(0.51)	-0.60 [-0.89, -0.31]
Negro B	19	-1.10(2.28)	19	0.20(0.41)	-1.30 [-2.34, -0.26]
Pfutzner	41	-1.30(2.34)	30	0.00(0.78)	-1.30 [-2.07, -0.53]
Raskin	103	-1.20(1.10)	103	0.10(1.00)	-1.30 [-1.59, -1.01]
Reynolds	8	-1.10(1.13)	10	-1.30(1.58)	0.20 [-1.05, 1.45]
Rosenstock B	115	-0.65(1.73)	110	0.13(1.03)	-0.78 [-1.15, -0.41]
Wolffenbuttel	183	-0.90(3.06)	192	0.20(1.50)	-1.10 [-1.59, -0.61]
Yang	30	-0.70(1.00)	34	0.40(1.30)	-1.10 [-1.66, -0.54]
Zhu	210	-1.49(1.48)	105	-0.40(1.31)	-1.09 [-1.41, -0.77]
Subtotal (95% CI)	1362		1266		-1.02 [-1.20, -0.85]
Test for heterogeneity: Chi² = 34.58, df = 15 (*P*=0.003), I² = 56.6%					
Test for overall effect: Z = 11.43 (*P*< 0.00001)					
Total (95% CI)	1976		1848		-0.95 [-1.17, -0.73]
Test for heterogeneity: Chi² = 184.80, df = 26 (*P*< 0.00001), I² = 85.9%					
Test for overall effect: Z = 8.43 (*P*<0.00001)					



WMD (random) 95% CI

Table 7. Rosiglitazone placebo-controlled trials: Study and population characteristics

Study	Rosiglitazone dosage Combination therapy	Sample size intervention group(s)	Sample size placebo group	Follow-up	[a]Mean age (SD) Gender Other population characteristics	[a]Baseline mean weight (SD) BMI (SD) A1c (SD)	Quality Funder
Agrawal 2003[112]	4 mg daily, 2 mg twice daily Combined with Various SU	260	263	26 wk	61.6 (NR) yr 38% female Normal renal function (see subgroups for renal-impaired)	NR 30.7 (NR) kg/m^2 9.2% (NR)	Fair (based on secondary data) Funder NR
Barnett 2003[113]	4 mg twice daily combined with various SU	84	87	26 wk	54.2 (NR) yr 22% female Participants Indian 60% Pakistani 27%	NR 26.4 (NR) kg/m^2 9.1% (NR)	Fair SmithKline Beecham Pharmaceuticals
Dailey 2004[105]	4-8 mg daily Both groups: glyburide/metformin 1.5/500 to 10/2000 mg daily	181	184	24 wk	57 (10) yr 39% female Inadequately controlled on an oral agent	93 (18) kg 32 (5) kg/m^2 8.1% (0.8%)	Fair Bristol-Myers Squibb Research Institute, Princeton New Jersey
Dargie 2007[56]	4-8 mg daily Combined with various other hypoglycemic agents (not insulin or metformin)	110	114	52 wk	63.9 (8.6) yr 20.9 % female NYHA functional class I to II CHF with LVEF ≤ 45%	84.3 (14.3) kg 28.6 (3.5) kg/m^2 7.8% (1.3%)	Fair GlaxoSmithKline
Fonseca 2000[114]	4,8 mg daily Combined with metformin	226	113	26 wk	58 (NR) yr 32 % female	NR 30.3 (4.4) kg/m^2 8.6% (1.3%)	Fair SmithKline Beecham Pharmaceuticals
Gastaldelli 2007[84]	8 mg daily Monotherapy (SU withdrawn) Study has another arm with randomization to pioglitazone or placebo	12	12	16 wk	55(10) yr 50 % female	NR 29.8 (4.2) kg/m^2 8.1% (1.9%)	Poor Takeda Pharmaceuticals, GlaxoSmithKline, NIH, Veterans Administration Merit Award
Gomez-Perez 2002[115]	2 mg twice daily, 4 mg twice daily Combined with metformin	71	34	26 wk	53.1 (NR) yr 74 % female	NR 28.5 (3.9) kg/m^2 9.8% (NR)	Fair Funder NR; 3 authors (including corresponding author) from GlaxoSmithKline

Study	Rosiglitazone dosage Combination therapy	Sample size intervention group(s)	Sample size placebo group	Follow-up	[a]Mean age (SD) Gender Other population characteristics	[a]Baseline mean weight (SD) BMI (SD) A1c (SD)	Quality Funder
Hallsten 2002[116]	4 mg twice daily Monotherapy	14	14	26 wk	58.0 (NR) yr 32 % female Without complications	88.3 (9.4) kg NR 6.3% (0.4%)	Fair Academy of Finland, Novo Nordisk Foundation, Finnish Diabetes Research Society, and GlaxoSmithKline
Honisett 2003[101]	4 mg daily Monotherapy	21	10	12 wk	NR 100 % female Postmenopausal women	NR NR 7.6% (3.2%) (Rosi group)	Poor Funder NR
Iozzo 2003[117]	8 mg daily Monotherapy	9	10	26 wk	58 (NR) yr 33 % female No prior pharmacotherapy for DM2	NR 31.5 (4.7) kg/m^2 6.1% (0.7%)	Fair GlaxoSmithKline
Jones 2003[118]	4,8 mg daily Combined with metformin	80+44	93	26 wk	59.9 (NR) yr 32 % female BMI 25-30 (obese presented in subgroups)	NR 27.7 (1.4) kg/m^2 8.8% (1.4%)	Fair Funder NR; 3 of 4 authors from GlaxoSmithKline
Kim 2005[119]	4 mg daily Monotherapy	60	60	12 wk	58.4 (9.1) yr 65% female Taking metformin or SU	62.3 (11.0) kg 24.5 (3.0) kg/m^2 9.3% (1.3%)	Fair National R&D program, Ministry of Science Technology, Republic of Korea
Lautamaki 2005[106]	4,8 mg daily Combined with metformin or SU	27	27	16 wk	63.2 (7.4) yr 30 % female Known coronary artery disease	89.1 (14.3) kg 26.9 (3.4) kg/m^2 7.1% (0.9%)	Fair Academy of Finland, Turku University Hospital, GlaxoSmithKline
Lebovitz HE 2001[120]	4,8 mg daily Monotherapy	169+166	158	26 wk	60 (NR) yr 34% female	NR 29.9 (4.1) kg/m^2 9.0% (1.7%)	Poor Funder NR; 5 of 6 authors from SmithKline Beecham Pharmaceuticals
Miyazaki 2001[121]	8 mg daily Monotherapy	15	14	12 wk	56 (2) yr 36 % female	87.0 (18.7) kg 30.1 (3.7) kg/m^2 8.3% (1.5%)	Fair SmithKline Beecham

Study	Rosiglitazone dosage Combination therapy	Sample size intervention group(s)	Sample size placebo group	Follow-up	[a]Mean age (SD) Gender Other population characteristics	[a]Baseline mean weight (SD) BMI (SD) A1c (SD)	Quality Funder
Natali 2004[122]	8 mg daily Monotherapy	22	24	8 wk	58 (9) yr 18% female	NR 30.2 (3.1) kg/m^2 7.6% (0.8%)	Fair GlaxoSmithKline
Negro 2005[107]	4 mg twice daily Metformin up to 2550 mg daily	19	19	52 wk	59 (8) yr 37% female Blood pressure non dippers	83.6 (4.4) kg 28.7 (1.9) kg/m^2 8.1% (0.5%)	Poor GlaxoSmithKline
Osman 2004[108]	4-8 mg daily Combined with other oral agents or insulin continued	8	8	26 wk	57.3 (NR) yr 38% female Referred for coronary stenting	NR NR 8.7% (1.9%)	Poor Funded in part by NIH
Nolan 2000[104]	4,8,12, mg daily Monotherapy	276	93	8 wk	62.8 (9.5) yr 39% female	81.3 (14.5) kg 29.6 (4.4) kg/m^2 NR	Fair Funder NR; 3 of 4 authors from SmithKline Beecham Pharmaceuticals
Patel 1999[123]	0.05, 0.25, 1.0, 2.0 mg twice daily Monotherapy	74+72+79 +90	74	12 wk	56.8 (11.5) yr 31% female	NR 29.1 (4.2) kg/m^2 8.9% (1.5%)	Fair Funder NR; authors from SmithKline Beecham and VA
Phillips 2001[124]	2 mg twice daily, 4 mg daily, 4 mg twice daily, 8 mg daily Monotherapy	735	173	26 wk	56.8 (9.2) yr 31% female	NR 29.1 (4.2) kg/m^2 8.9% (1.5%)	Fair Funder NR, author affiliations include SmithKline Beecham Pharmaceuticals, USA
Pfutzner 2006[111] Hammann 2003	4, 8 mg daily Combined with glimepiride 3 mg daily	31+41	31	16 wk	63.7 (9.0) yr 50% female	NR 30.0 (3.4) kg/m^2 7.7% (1.4%)	Fair GlaxoSmithKline, Munich, Germany

Study	Rosiglitazone dosage Combination therapy	Sample size intervention group(s)	Sample size placebo group	Follow-up	[a]Mean age (SD) Gender Other population characteristics	[a]Baseline mean weight (SD) BMI (SD) A1c (SD)	Quality Funder
Raskin 2000[102]	2,3,6 mg, twice daily	215	69	8 wk	60.1 (9.4) yr 40.6 % female	NR 30.4 (4.2) kg/m^2 0.087% (0.0163%) (reference range <0.065)	Fair Funder NR; 5 of 6 authors from SmithKline Beecham Pharmaceuticals
Raskin 200[125]	2, 4 mg twice daily Combined with insulin	103+106	104	26 wk	55.6 (10.3) yr 44 % female	NR 32.7 (4.5) kg/m^2 8.9% (1.1%)	Good Funder NR Individual authors have received support from SmithKline Beecham
Reynolds 2002[126]	4 mg daily Combined with insulin	11	10	24 wk	NR NR BMI>27	108.0 (29) kg 36.3 (2.5) kg/m^2 9.8% (1.6%)	Poor Health management Resources and GlaxoSmithKline
Rosenstock 2006[110] RESULT Study	4 mg daily Combined with glipizide 10 mg twice daily	116	111	104 wk	68.2 (6.3) yr 28.2% female	NR 30.5 (4.9) kg/m^2 7.7% (1.0%)	Fair-poor NR; data analysis and some coauthors from GlaxoSmithKline
Tan 2005(a)[127]	4 mg twice daily Monotherapy	12	12	12 wk	52.3 (10.1) yr 46% female No prior pharmacotherapy for DM2	NR 32.8 (4.9) kg/m^2 7.5% (1.0%)	Fair GlaxoSmithKline
Van Wijk 2005[128]	4 mg twice daily Monotherapy	19 (cross-over)	19 (cross-over)	8 wk	60 (NR) yr 26% female	NR 29.2 (4.8) kg/m^2 6.2% (0.9%)	Fair GlaxoSmithKline
Virtanen 2003[129]	4 mg twice daily Monotherapy	14	14	26 wk	58 (7.5) yr 40 % female	88.3 (9.7) kg 30.7 (4.9) kg/m^2 6.3% (0.4%)	Fair Academy of Finland, Novo Nordisk Foundation, Finnish Diabetes Research Society, GlaxoSmithKline
Wang 2005[103]	4 mg daily Monotherapy	35	35	26 wk	62.2 (8.6) yr 20% female Coronary artery disease; recent	NR 25.6 (2.7) kg/m^2 7.33%	Fair Major National Basic Research

Study	Rosiglitazone dosage Combination therapy	Sample size intervention group(s)	Sample size placebo group	Follow-up	[a]Mean age (SD) Gender Other population characteristics	[a]Baseline mean weight (SD) BMI (SD) A1c (SD)	Quality Funder
					percutaneous coronary intervention	(0.17%)	Program of PR China and Chinese National Natural Science Foundation
Wolffenbuttel 2000[130]	1,2 mg twice daily Combined with various SU	183+199	192	26 wk	61.9 (9.1) yr 43% female Using SU for >6m	NR 28.1 (4.1) kg/m^2 9.2% (1.3%)	Fair Funder NR 1 of 5 authors from SmithKline Beecham
Yang 2002[131]	4 mg daily Combined with various SU	30	34	26 wk	57.8 (8.9) yr 61.8% female	65.3 (11.2) kg 25.8 (3.5) kg/m^2 9.7% (1.4%)	Fair Smith-Kline Beecham Pharmaceuticals and a grant from the Department of Education of the Republic of China
Zhu 2003[132]	2,4 mg twice daily Combined with various SU	425	105	24 wk	58.9 (7.7) yr 54% female Chinese, no hepatic impairment	NR 25.1(2.8) kg/m^2 9.8% (1.3%)	Fair SmithKlineBeecham Research and Development
Range	**1 to 12 mg daily**	**8 to 735**	**10 to 263**	**8 to 104 wk**	**52.3 to 63.9 yr 18% to 100% female**	**62.3 to 93.0 kg 24.5 to 36.3 kg/m^2**	**Good: 1 Fair: 25 Poor: 6**

Abbreviations: BMI, body mass index, kg/m^2; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NR, not reported; SU, sulfonylurea; m, months; DM2, type 2 diabetes mellitus; wk, week(s); yr, year(s).

[a] Baseline values are given for the control group.

If standard error was provided in the original study, we have converted standard error to standard deviation.

Table 8. Indirect comparison of pioglitazone and rosiglitazone for A1c (%)

	Difference in A1c (%) (pioglitazone-rosiglitazone)	95% CI
Good/fair studies	-0.04	-0.41 to 0.33
All studies	-0.13	-0.46 to 0.19
Monotherapy	-0.30	-0.82 to 0.22
Combined therapy	-0.08	-0.49 to 0.33

Active-control trials

For the original report, we did not include active-controlled studies for the outcome of A1c. We did, however, include these studies for examination of effectiveness outcomes anad for examination of patient subgroups (See Key Questions 2 and 3).

For the updated report, we were asked to include active-control studies for both pioglitazone and rosiglitazone for the outcome of A1c in order to update the Agency for Healthcare Research and Quality report on oral hypoglycemic agents whose search ended January 2006.[28] Bolen and colleagues 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 compared with an active control

We identified 11 active-controlled trials involving pioglitazone for the updated report (Tables 9 and 10),[111, 133-142] including 2 poor-quality studies.[135, 136] Six monotherapy trials compared pioglitazone to a sulfonylurea[134-136, 138, 140, 142] or to metformin.[142] Trials examining combination therapy compared pioglitazone to a sulfonylurea with both groups receiving various oral hypoglycemic agents or insulin[111, 133, 137] or metformin.[141] Pioglitazone was compared to metformin with both groups receiving gliclazide in 1 trial.[139] 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.[137, 138, 142]

Effects on A1c were similar between treatment groups, with no significant difference noted between groups in 9 of the eleven trials. In a small (N=92), monotherapy study in Japan,[140] A1c decreased more with glibenclamide (change in A1c -1.43%) than with pioglitazone (change in A1c -0.80%, between-group $P<0.05$) at 24 weeks follow-up. In an 18-month trial of glibenclamide compared with pioglitazone in newly-diagnosed diabetic subjects taking a variety of concurrent hypoglycemic agents including insulin,[137] A1c improved in both groups to a similar degree to week 32, then the improvement was maintained with pioglitazone but not with glimepiride. At the final follow-up (week 72), the between-group difference (in favor of pioglitazone) was 0.32% (95% CI -0.52 to -0.12).

Rosiglitazone compared with an active control

We identified 10 active-control trials involving rosiglitazone for the updated report (Tables 11 and 12),[57, 143-151] including 1 poor-quality study.[149] There were 3 monotherapy trials comparing rosiglitazone to metformin[57] or rosiglitazone to a sulfonylurea.[57, 147, 149] The combined therapy trials compared rosiglitazone to a sulfonylurea with both groups receiving metformin[143-145] or compared rosiglitazone to metformin with both groups receiving sulfonylureas[151] or various hypoglycemic agents.[148] Raskin and colleagues[150] compared rosiglitazone to repaglinide and to the combination of the 2 drugs. Goldstein and colleagues[146] 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[149] to 4 years,[57] with 4 trials having follow-up of 1 year or more.[57, 144, 147, 148] Mean age of study subjects was mid 50s, with 2 studies enrolling older subjects, with mean ages 60[143] and 65 years.[151]

Among the monotherapy trials, the Diabetes Outcomes Progression Trial (ADOPT) was recently published.[57] ADOPT was a large (N=4360), 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, with the greatest effect with glyburide and A1c curves were similar between metformin and rosiglitzone for the first 1 year. 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).

ADOPT was rated fair quality. 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.

The results of 2 smaller rosiglitazone monotherapy trials with active controls were similar to the results from ADOPT when appropriate follow-up intervals are compared. Hanefeld and coauthors found no significant difference between glibenclamide and rosiglitazone at 52-week follow-up.[147] A poor-quality study demonstrated no significant difference between rosiglitazone and glibenclamide at 12 weeks.[149] This follow-up interval is too short to be meaningful when examining thiazolidinediones.

Among the combination therapy trials of rosiglitazone and metformin, 2 trials did not show significant differences between rosiglitazone and metformin.[143, 144] On the other hand, Garber and colleagues[145] 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.[148, 151] A combination of rosiglitazone and repeglanide[150] demonstrated superiority for the combination product over rosiglitazone monotherapy. Rosiglitazone was superior to repeglanide (each as monotherapy; no statistics provided).

In a substudy of the EMPIRE study examining cardiovascular biomarkers,[146] 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[58] (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[151] in all 4 treatment groups, with no statistically significant difference between rosiglitazone and other drugs in the background metformin and background sulfonylurea groups.

Table 9. Pioglitazone active-control trials: Study and population characteristics

Study	Dosage Combination therapy	Sample size intervention group	Sample size placebo group	Follow-up	[a]Mean age (SD) Gender Other population characteristics	[a]Baseline mean Weight (SD) BMI (SD) A1c (SD)	Quality Funder
Agarwal 2005[133]	Glipizide: start 5 mg daily; mean maximal dosage 41 mg daily Pio: start 15 mg daily, mean maximal dosage 19 mg daily Combined with various oral hypoglycemic agents or insulin	22	22	16 wk	67 (8.5) yr 0% female % on insulin at baseline: 68 (59% in glipizide group) 100% with overt diabetic nephropathy	97.5 (6.0) kg 32.2 (6.0) kg/m^2 7.7% (2.2%)	Fair (open label) Takeda Pharmaceuticals North America, Inc.
Basu 2006[134]	Glipizide: 10 mg daily (median dose) Pio: 45 mg daily Monotherapy	8	11	12 wk	56 (2) yr 33% female	92 (SE 7) kg 32 (SE 2) kg/m^2 6.9% (SE 3)	Fair Takeda Pharmaceuticals
Heliovaara 2007[135]	Pio 30-45 mg daily Glibenclamide 1.75-10.5 mg daily Monotherapy	29	30	52 wk	57.2 (SE 1.8) yr 30% female Failed diet or monotherapy	NR 30.5 (SE 0.9) kg/m^2 8.35% (SE 0.12)	Poor Funder NR Several authors from Eli Lilly and Co.
Jain 2006[136]	Pioglitazone 15-45 mg daily Glyburide 5-15 mg daily Monotherapy	251	251	56 wk	52.1 (12.4) yr 44% female Newly-diagnosed type 2 diabetes; failed diet and exercise therapy	94.3 (20.0) kg 32.8 (5.7) kg/m^2 9.2% (1.3%)	Poor Takeda Pharmaceuticals North America, Inc.
Mazzone 2006[137]	Pio 15-45 mg daily Glimepiride 1-4 mg daily Add-on metformin or insulin as needed (12%-13% took insulin during study)	230	228	72 wk	59.9 (8.2) yr 37% female Newly diagnosed on any therapy	NR 31.9 (5.0) kg/m^2 7.4% (1.0%)	Fair Takeda Pharmaceuticals, North America Inc.
Perriello 2006[138]	Pio 30-45 mg daily Gliclazide 80-320 mg daily	146	137	52 wk	59 (assume SD 7) yr 36% female A1c>7.5%	78.8 (assume SD 10.7) kg 28.8 (assume SD 2.8) kg/m^2 8.7% (assume SD 0.9%)	Fair Funder NR Oone author was Medical Director

Study	Dosage Combination therapy	Sample size intervention group	Sample size placebo group	Follow-up	[a]Mean age (SD) Gender Other population characteristics	[a]Baseline mean Weight (SD) BMI (SD) A1c (SD)	Quality Funder
	Appears to be monotherapy (some patients on 1 oral agent prior to study)						Takeda, Italy
Pfutzner 2005[111]	Pio 24 mg daily Glimepiride 1-6 mg daily Other oral agents permitted in both groups, except metformin with pio and TZDs with glimepiride	92	87	26 wk	63.0 (7.4) yr 38% female Failed various oral agents; no prior TZD use	NR 31.8 (4.3) kg/m^2 7.44% (0.89%)	Fair Takeda Pharma GmbH, Aachen, Germany
Sharma 2006[139]	Pio 15-30 mg daily Metformin 1000-2000 mg daily Gliclazide 30-60 mg daily added to both arms if needed	17	18	12 wk	47.7 (9.5) yr 33% female Newly diagnosed type 2 diabetes	70.7 (9.9) kg 28.6 (3.9) kg/m^2 8.03% (0.9%)	Fair Funder NR
Teramoto 2007[140]	Pio 15-30 mg daily Glibenclamide 1.25-2.5 mg daily Monotherapy	46	46	24 wk	56.4 (10.5) yr 24% female Triglycerides 150-500 mg/dl	67.7 (14.5) kg 25.2 (4.8) kg/m^2 8.36% (1.29%)	Fair Japan Pioglitazone Study Group
Umpierrez 2006[141]	Pio 30-45 mg daily Glimepiride 2-8 mg daily Add-on to metformin therapy	109	101	26 wk	51.6 (11.8) yr 45% female Inadequately controlled on metformin monotherapy	NR 34.5 (6.7) kg/m^2 8.4% (0.7)%	Fair Sanofi-Aventis, Bridgewater, New Jersey
Yamanouchi 2005[142]	Pioglitazone 30-45 mg daily Metformin 750 mg daily Glimepiride 1.0-2.0 mg daily Monotherapy	38	Metformin: 39 Glimepiride: 37	52 wk	Metformin group: 54.7 (9.8) yr 49% female Japanese subjects Not on oral agents previously	Metformin group: NR 26.2 (3.8) kg/m^2 9.9% (0.7)%	Fair Funder NR

Study	Dosage Combination therapy	Sample size intervention group	Sample size placebo group	Follow-up	[a]Mean age (SD) Gender Other population characteristics	[a]Baseline mean Weight (SD) BMI (SD) A1c (SD)	Quality Funder
Range	**15-45 mg daily**	**8-251**	**11-251**	**12-72 wk**	**47.7-67.0 yr 0-49% female**	**67.7-97.5 kg 25.2-34.5 kg/m^2 7.4%-9.9%**	**9 Fair 2 Poor**

Abbreviations: BMI, body mass index.; NR, not reported; pio, pioglitazone; SD, standard deviation; SE, standard error; TZD, thiazolidinedione.
[a] Baseline data are from the comparison group. Data shown are mean (SD) unless otherwise indicated.

Table 10. Pioglitazone active-control studies: Change in A1c

Study	Follow-up (weeks)	Treatments	A1c baseline pioglitazone group (SD)	A1c at follow-up pioglitazone group (SD)	A1c baseline comparison group (SD)	A1c at follow-up, comparison group (SD)	A1c between-group difference (pioglitazone – compared drug (95% CI)	Between-group *P* value
Agarwal 2005	16	Glipizide start 5 mg daily, mean maximal dosage 41 mg daily. Pioglitazone start 15 mg daily, mean maximal dosage 19 mg daily.	7.2% (1.4)	7.1% (1.3%) Change: -0.1% (1.2%)	7.7% (2.5%)	7.3% (1.8%) Change -0.4% (1.8%)	0.3% (-0.76 to 1.3)	0.52
Basu 2006	12	Glipizide 10 mg daily (median dose) Pioglitazone 45 mg daily Monotherapy	6.9% (SE 0.3)	7.5% (SE 0.8) Change: 0.6%	6.5% (SE 0.3)	6.9% (SE 0.8) Change 0.4%	0.2% (NR)	*P*>0.05
Heliovaara 2007	52	Pioglitazone 30-45 mg daily Glibenclamide 1.75-10.5 mg daily Monotherapy	8.2% (SE 0.1)	7.6% (SE 0.2) *P*<0.05	8.4% (SE 0.1)	7.8% (SE 0.2) *P*<0.001	0 (NR)	NR
Jain 2006	56	Pioglitazone 15-45 mg daily Glyburide 5-15 mg daily	9.2% (1.2%)	Change: -2.07%	9.2% (1.3%)	Change: -2.02%	-0.05%	0.669

Study	Follow-up (weeks)	Treatments	A1c baseline pioglitazone group (SD)	A1c at follow-up pioglitazone group (SD)	A1c baseline comparison group (SD)	A1c at follow-up, comparison group (SD)	A1c between-group difference (pioglitazone – compared drug (95% CI)	Between-group *P* value
		Monotherapy						
Mazzone 2006	18 months	Pioglitazone 15-45 mg daily Glimepiride 1-4 mg daily Add-on metformin or insulin as needed (12-13% took insulin during study)	7.43% (0.99%)	Change at week 72 (from graph): -0.35%	7.40% (0.97%)	Change week 72 (from graph): 0	Week 72: -0.32% (95% CI -0.52 to -0.12)	Week 72: 0.002
Perriello 2006	52	Pioglitazone 30-45 mg daily Gliclazide 80-320 mg daily Appears to be monotherapy (some patients on 1 oral agent prior to study)	8.77% (0.81%) (unclear if SD or SE)	7.98% (1.4%)	8.67% (0.9%)	7.88% (1.2%)	0 (NR)	*P*>0.05
Pfutzner 2005	26	Pioglitazone 24 mg daily Glimepiride 1-6 mg daily Other oral agents permitted in both groups except metformin in the pioglitazone group and thiazolidinediones in the glimepiride group	7.52% (0.85%) (assumed SD)	6.71% (0.89%) Change: -0.8% (0.9%) *P*<0.001	7.44% (0.89) *P*<0.001	6.83% (0.85) Change: -0.6% (0.8%) *P*<0.001	0.2% (NR)	*P*>0.05
Sharma 2006	12	Pioglitazone 15-30 mg daily Metformin 1000-2000 mg	7.72% (1.1%)	7.3% (0.8%) *P*=0.34	8.03% (0.9%)	7.56% (0.8%) *P*=0.14	-0.05% (NR)	0.43

Study	Follow-up (weeks)	Treatments	A1c baseline pioglitazone group (SD)	A1c at follow-up pioglitazone group (SD)	A1c baseline comparison group (SD)	A1c at follow-up, comparison group (SD)	A1c between-group difference (pioglitazone – compared drug (95% CI)	Between-group *P* value
		daily Gliclazide 30-60 mg daily added to both arms if needed						
Teramoto 2007	24	Pioglitazone 15-30 mg daily Glibenclamide 1.25-2.5 mg daily	8.01% (1.29%)	7.21% (1.35%) *P*<0.05	8.21% (1.29%)	6.93% (0.74%) *P*<0.05	0.63% (NR)	<0.05
Umpierrez 2006	26	Pioglitazone 30-45 mg daily Glimepiride 2-8 mg daily Add-on to metformin therapy	8.31% (0.77%)	Change: -1.23% (SE 0.073) A1c ≤ 7.0% in 55% of group	8.4% (0.72%)	Change: -1.30% (SE 0.077) A1c ≤ 7.0% in 56% of group	0.07% (NR)	0.4825
Yamanouchi 2005	52	Pioglitazone 30-45 mg daily Metformin 750 mg daily Glimepiride 1.0-2.0 mg daily Monotherapy	10.2% (0.8%)	7.9% (1.0%) *P*<0.005	Metformin: 9.9% (0.7%) Glimepiride: 9.8% (0.7%)	Metformin: 7.8% (1.0%) *P*<0.005 Glimepiride 7.7% (0.9%) *P*<0.005	Metformin: -0.2% (NR) Glimepiride: -0.2% (NR)	NSD among the 3 groups

Abbreviations: CI, confidence interval; NR, not recorded; NSD, no significant difference; SE, standard error.

Table 11. Rosiglitazone active-controll trials: Study and population characteristics

Study	Dosage Combination therapy	Sample size intervention group	Sample size placebo group	Follow-up	[a]Mean age (SD) Gender Other population characteristics	[a]Baseline mean Weight (SD) BMI (SD) A1c (SD)	Quality Funder
Bakris 2006[143]	Rosi: start 4 mg daily Glyburide: start 5 mg daily Both groups received metformin ≥ 1000 mg daily	194	180	32 wk	ITT population: 58.8 (SE 9.8) yr 31% female	90.3 (SE 19.0) kg 31.8 (SE 6.0) kg/m^2 8.3% (SE 1.6)	Fair GlaxoSmithKline Pharmaceuticals
Derosa 2006[144]	Rosi 4 mg daily Glimiperide 2 mg daily Both groups received metformin 1500 mg daily	48	47	52 wk	52 (5) yr 48% female All subjects had the metabolic syndrome (ATPIII definition) in addition to type 2 diabetes	NR 26.8 (1.5) kg/m^2 7.9% (0.6%)	Good Funder NR
Garber 2006[145]	Rosi 4-8 mg daily and metformin 1500-2000 mg daily Glibenclamide-metformin 5/1000 mg to 10/2000 mg daily (combination product) Combination therapy	158	160	24 wk	ITT population 56 (NR) yr 44% female 80% White Inadequately controlled on metformin at baseline	ITT population 93 (17) kg 32 (5) kg/m^2 8.5% (1.2%)	Fair Funder NR Corresponding author is an employee of Briston-Meyers Squibb Pharmaceutical Research Institute
Goldstein 2006[146]	Rosi 4-8 mg daily plus metformin 1000 mg/d Metformin up to 1500-2000 mg/d Monotherapy	71	51	24 wk	Substudy population 56.0 (NR) yr 35.3% female	NR 32.1 (NR) kg/m^2 8.26% (95% CI +/-1.4%)	Fair GlaxoSmithKline Pharmaceuticals
Hanefeld 2007[147]	Rosi 4 mg daily Rosi 8 mg daily Glibenclamide 2.5-15 mg daily Monotherapy	Rosi 4 mg 195 Rosi 8 mg 189	Glibenclamide 203	52 wk	Glibenclamide group: 60.1 (8.3) yr 32% female Oral agents stopped prior to study	NR 28.7 (3.9) kg/m^2 8.2% (1.3%)	Fair SmithKline Beecham
Home 2007[148] RECORD Study	Add-on rosi 4-8 mg daily Add-on metformin (up to 2550 mg daily) or SU	2220	2227	3.75 yr (mean, for interim analysis)	58.5 (8.3) yr 48% female Inadequate control on SU or metformin	NR 31.5 (4.9) kg/m^2 7.9% (0.7%)	Fair GlaxoSmithKline Pharmaceuticals

Study	Dosage Combination therapy	Sample size interventi on group	Sample size placebo group	Follow-up	[a]Mean age (SD) Gender Other population characteristics	[a]Baseline mean Weight (SD) BMI (SD) A1c (SD)	Quality Funder
	Preexisting SU or metformin continued; SU or metformin or insulin added as needed				monotherapy		
Kahn 2006,[57] Viberti 2006, 2002 ADOPT	Rosi 4-8 mg daily Glyburide: 2.5-7.5 mg daily Metformin: 500-2000 mg daily Monotherapy	1456	Glyburide: 1441 Metformin: 1454	Median 4.0 yr	Glyburide group: 56.4 (10.2) yr 58% female Failed lifestyle therapy, recently diagnosed, not on oral agents previously	92.0 (20.0) kg 32.2 (6.3) kg/m^2 7.35% (0.92%)	Fair GlaxoSmithKline
Kulenovic 2006[149]	Rosi 4-8 mg daily Glibenclamide 3.5-10.5 mg daily Monotherapy	10	10	12 wk	53.7 (11.2) yr % female NR Failed to achieve metabolic control with diet	NR 25.9 (1.3) kg/m^2 7.8% (1.1)%	Poor Funder NR
Raskin 2004[150]	Rosi: 2-4 mg twice daily Repaglinide: 0.5-4 mg per meal Rosi + repaglinide Monotherapy and combination	63	Repaglinide: 62 Rosi+repaglanide: 127	24 wk	Rosi+repaglinide group: 57.5 (10.8) yr 49% female Failed monotherapy (withdrawn for study)	Rosi+repaglanide group: NR 32.3 (5.2) kg/m^2 9.1% (NR)	Fair-poor Funder NR Two authors from Novo Nordisk
Stocker 2007[151]	Rosi 4 mg daily Metformin 850 mg twice daily Monotherapy or combined therapy: could continue SU taken prior to study (unknown %)	45	47	24 wk	65 (10) yr 47% female Failed diet and/or sulfonylurea therapy	84.9 (2.1) kg 29.7 (0.7) kg/m^2 8.5% (0.3%)	Fair GlaxoSmithKline
Range	**4 mg-8 mg daily**	**10-2220**	**10-2227**	**12-52 wk**	**52-65 yr** **32%-58% female**	**84.9-93 kg** **25.9-32.3 kg/m^2** **7.35%-9.1%**	**1 Good** **7 Fair** **1 Fair-Poor** **1 Poor**

Abbreviations: CI, confidence interval; NR, not reported; SU, sulfonylurea; BMI, body mass index; rosi, rosiglitazone; wk, week(s); yr, year(s).
[a] Baseline data are from the comparison group. Data shown are mean (SD) unless otherwise indicated.

Table 12. Rosiglitazone active-control studies: Change in A1c

Study	Follow-up interval (weeks)	Treatments	A1c baseline rosiglitazone group (SD)	A1c at follow-up rosiglitazone group (SD)	A1c baseline comparison group (SD)	A1c at follow-up, comparison group (SD)	A1c between-group difference (rosiglitazone – comparator) (95% CI)	Between-group *P* value
Bakris 2006[143]	32	Rosi: start 4 mg daily Glyburide: start 5 mg daily Both groups received metformin ≥ 1000 mg daily	8.5% (SE 1.7)	Change -0.72% (SE 0.10)	8.3% (SE 1.6)	Change -0.92% (SE 0.08)	0.2% (NR)	NR
Derosa 2005[144]	52	Rosi 4 mg daily Glimiperide 2 mg daily Both groups received metformin 1500 mg daily	8.0% (0.7%)	6.8% (0.6)%	7.9% (0.6%)	7.0% (0.7%)	-0.3% (NR)	>0.05
Garber 2006[145]	24	Rosi 4-8 mg daily and metformin 1500-2000 mg daily Glibenclamide/metformin 5/1000 to 10/2000 mg daily	8.4% (1.1%)	Change: -1.1%	8.5% (1.2%)	Change: -1.5%	0.4% (NR)	<0.001
Goldstein 2006[146]	24	Rosiglitazone 4-8 mg daily plus metformin 1000 mg daily	8.18% (95% CI +/-1.23)	Change: -0.61% (95% CI +/- 1.16)	8.26% (95% CI +/- 1.40)	Change: -0.65% (95% CI 1.18)	0.04% (NR)	>0.05

Study	Follow-up interval (weeks)	Treatments	A1c baseline rosiglitazone group (SD)	A1c at follow-up rosiglitazone group (SD)	A1c baseline comparison group (SD)	A1c at follow-up, comparison group (SD)	A1c between-group difference (rosiglitazone – comparator) (95% CI)	Between-group *P* value
		Metformin up to 1500-2000 daily						
Hanefeld 2007[147]	52	Rosiglitazone 4 mg daily Rosiglitazone 8 mg daily Glibenclamide 2.5-15 mg daily	Rosi 4 mg: 8.1% (1.3%) Rosi 8 mg: 8.2% (1.4%)	Change Rosi 4mg: -0.3% (*P*=0.0003) Rosi 8 mg: -0.5% (*P*<0.0001) % achieving <7.0%: Rosi 4: 39.5% Rosi 8: 43.9%	8.2% (1.3%)	Change: -0.7% (*P*<0.0001) % achieving <7.0%: 46.5%	Rosi 8 mg compared with glibenclamide: 0.2% (NR)	Rosi 8 mg compared with glibenclamide: *P*>0.05
Home 2007[148] RECORD Study	18m (for A1c outcomes)	Rosiglitazone 4-8 mg daily Metformin various to 2550 mg daily Preexisting sulfonylurea or metformin continued; sulfonylurea or metformin or insulin added as needed	Rosiglitazone (background metformin): 7.9% (0.7%) Rosiglitazone (background SU): 8.0% (0.69%)	Change -0.48 % (95% CI -0.59 to -0.36) -0.55% (-0.67 to -0.44)	SU (background metformin): 7.8% (0.66%) Metformin (background SU): 8.0% (0.77%)	Change -0.55% (CI -0.66 to -0.44%) -0.61% (-0.70 to -0.51%)	Background metformin: 0.07% (-0.09 to 0.23) Background SU: 0.06% (-0.09 to 0.20)	Background metformin: *P*>0.05 Background SU: *P*>0.05
Kahn 2006,[57] Viberti 2006, 2002 ADOPT	Median 4.0 years	Rosiglitazone: 4-8 mg daily Glyburide: 2.5-7.5 mg daily Metformin: 500-2000 mg daily	7.36% (0.93%)	A1c<7.0% at 4 y: 40% Monotherapy failure at 5 y (FPG>180 mg/dl): 15%	Glyburide: 7.35% (0.92%) Metformin: 7.36% (0.935%)	A1c<7.0% at 4y: Glyburide: 26% Metformin: 36% Monotherapy failure at 5y	Treatment difference at 4y: Rosi compared with metformin: -0.13% (-0.22 to -0.05) Rosi compared	Monotherapy failure at 5y: Rosi compared with metformin *P*<0.001 Rosi

Study	Follow-up interval (weeks)	Treatments	A1c baseline rosiglitazone group (SD)	A1c at follow-up rosiglitazone group (SD)	A1c baseline comparison group (SD)	A1c at follow-up, comparison group (SD)	A1c between-group difference (rosiglitazone – comparator) (95% CI)	Between-group *P* value
		Monotherapy				(FPG>180 mg/dl): glyburide: 34%, metformin 21%	with glyburide: -0.42% (-0.50 to -0.33)	compared with glyburide: *P*<0.02
Kulenovic 2006[149]	12	Rosiglitazone 4-8 mg daily Glibenclamide 3.5-10.5 mg daily Monotherapy	7.7% (1.0%)	6.6% (0.8%) *P*=0.010	7.8% (1.1%)	6.5% (1.0%) *P*<0.01	0.2% (NR)	NR
Raskin 2004[150]	24	Rosiglitazone: 2-4 mg twice daily Repaglinide: 0.5-4 mg per meal Rosi + repaglinide	9.0% (NR)	8.5% (NR) Change (SE): -0.56 (0.14)	Repaglinide: 9.3% (NR) Repaglinide+rosi: 9.1%	Change (SE): Repeglanide: -0.17% (SE 0.14) Repeglanide+rosi: -1.43% (SE 0.10) % ≤ 7.0%: Rosi: 16% Repaglinide: 5% Repaglinide+rosi: 39%	Rosi compared with repeglanide: -0.39% Rosi compared with repeglanide/rosi: 0.87% (*P*<0.001)	Rosi compared with repeglanide/rosi *P*<0.001
Stocker 2007[151]	24	Rosiglitazone 4 mg daily Metformin 850 mg twice daily	8.5% (0.3%)	Change: -1.08% (0.14%)	8.5% (0.2%)	Change: -1.19% (0.13%)	0.11%	*P*>0.05

Abbreviations: CI, confidence interval; NR, not reported; SU, sulfonylurea; BMI, body mass index; rosi, rosiglitazone.

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?

Summary of the Evidence

- Data were not sufficient to determine the comparative effectiveness of pioglitazone and rosiglitazone on microvascular or macrovascular complications of diabetes.
- There were no head-to-head data
- Two trials of pioglitazone compared to glimepiride that were designed to measure progression of atherosclerosis found a low incidence of cardiovascular events and no difference between groups on clinical endpoints.

Detailed Assessment

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,[60, 103, 152] including the PROACTIVE trial.[60] 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.

In the PROACTIVE trial[60], a good-quality, European, multicenter, randomized, placebo-controlled trial of 5238 patients with type 2 diabetes and evidence of macrovascular disease, treatment patients received pioglitazone titrated from 15 mg up to 45 mg daily. Ninety-six percent of patients were taking other glucose-lowering agents, including insulin. The average follow-up period was 34.5 months. The primary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. The hazard ratio for this endpoint was 0.90 (95% CI 0.80 to 1.02). Congestive heart failure was not included in this composite endpoint, although congestive heart failure was examined as an adverse event. When examined individually (as secondary endpoints), none of the components of the primary endpoint changed significantly ($P>0.05$). The hazard ratio of the main secondary endpoint (a composite of all-cause mortality, myocardial infarction [excluding silent myocardial infarction], and stroke) was 0.84 (95% CI 0.72 to 0.98).

Wang and colleagues[103] performed a randomized controlled trial comparing rosiglitazone 4 mg daily to no treatment (N=70) over 6 months. Included patients were aged 50 to 73 years, had a diagnosis of coronary artery disease (>50% stenosis as proven on angiography), had established type 2 diabetes, and had undergone a percutaneous coronary intervention (Evidence Table 9). Forty-one percent took other anti-diabetic medications. At 6-month follow-up the incidence of coronary events was decreased in the rosiglitazone group (between-group $P<0.05$ for the composite endpoint), with 4 events in the rosiglitazone group (recurrent angina[153] and coronary artery bypass grafting [1]) and 12 in the control group (recurrent angina [5], repeated angioplasty,[153] and coronary artery bypass grafting[153]).

A single-center poor-quality study examined the preventive effects of rosiglitazone on restenosis after coronary stent implantation among 95 persons with type 2 diabetes.[152] In this

open-label, randomized controlled trial, the treatment group was placed on rosiglitazone 8 mg before undergoing catheterization and 4 mg daily thereafter, combined with conventional antidiabetic therapy using a variety of agents (details of concurrent therapy were not provided). The comparison group received conventional therapy only. The rate of restenosis was 18% in the rosiglitazone group and 38% in the control group (between-group *P*=0.03). There was also a significant difference in stenosis diameter between groups at 6 months (*P*=0.004) in favor of the rosiglitazone group.

The available data provided no information on the comparative effectiveness of pioglitazone and rosiglitazone on macro- and microvascular outcomes when used as monotherapy or when added to or substituted for other oral hypoglycemic agents. Dormandy and colleagues[60] addressed the question of combined therapy as pioglitazone was added to other anti-diabetic therapy in 96% of patients. In the study by Wang and coauthors[103] monotherapy and combined therapy patients were aggregated, so conclusions cannot be drawn about each of these 2 approaches.

In the updated review 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.[137, 154]

The CHICAGO trial[137] 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 ofwhich 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.[154] 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.[82] 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,[93] patients 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.[78] 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 updated search identified several important recent trials of rosiglitazone reporting vascular or mortality outcomes: the RECORD trial[148] and ADOPT.[57] An interim analysis of the RECORD trial was published by Home and colleagues in 2007.[148] 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 ≤ 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 sulfonylurea) compared with metformin plus a sulfonylurea 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.[63] 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[57], 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.[155] 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 (further details are presented in Key Question 8). 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.

Several additional, smaller rosiglitazone trials were also identified in the updated search.[108, 110] In a very small (N=16), poor-quality, randomized controlled trial, subjects with coronary stent implantation were randomized to rosiglitazone 4-8 mg daily or placebo for 6 months. Rosiglitazone did not reduce in-stent restenosis and there were no differences in cardiac events between the groups.[108]

In a study of older adults with type 2 diabetes, Rosenstock and colleagues[110] noted no significant difference between rosiglitazone and placebo (both groups received glipizide) in SF-36 component scores, although the rosiglitazone group had more markedly improved scores on the Diabetes Treatment Satisfaction Questionnaire (DTSQ) than the glipizide only group ($P<0.001$).

Key Question 3 (NOT UPDATED).
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?**

Summary of the Evidence

- It is not possible to conclude whether there is a difference in weight change between pioglitazone and rosiglitazone.

Detailed Assessment

Updated report: This question was not included for the updated report. The effects of pioglitazone and rosiglitazone on weight are reviewed in the section addressing adverse events.

There is a paucity of data on the comparative effect of pioglitazone and rosiglitazone and the effect of these drugs compared with placebo on weight or abdominal obesity. It is not possible to conclude whether there is a difference in weight change with 1 of the thiazolidinediones.

Weight or body mass index was measured in 6 studies of prediabetes or the metabolic syndrome (Table 13), including 2 head-to-head studies. One head-to-head study[66] reported increased weight with both pioglitazone and rosiglitazone with no significant difference between groups; the other study[156] reported weight gain with pioglitazone (2.5 kg, standard deviation 6.3), rosiglitazone (0.3 kg, standard deviation 5.5), and the control group (2.0 kg, standard deviation 1.6; statistics were not reported).

Pioglitazone, either alone or in combination with metformin or a sulfonylurea was associated with an increase in weight compared with metformin or a sulfonylurea as monotherapy.[157] Rosiglitazone did not produce a significant change in weight compared with

placebo in 1 small study[158] and in an additional poor-quality study.[159] Waist-to-hip ratio[159] and waist circumference[158] also did not change with rosiglitazone compared to placebo.

Key Question 4. For patients with prediabetes or the metabolic syndrome, do thiazolidinediones differ from one another or from placebo in delaying the occurrence of clinical diabetes?

Updated 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?

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 (Evidence Tables 3 and 10, Table 13).[158, 161] Neither of these studies was designed to investigate the comparative effectiveness of these 2 drugs or to allow a comparison with a placebo group for the outcome of diabetes incidence.

A fair-quality, controlled trial compared a no-treatment group with pioglitazone and rosiglitazone groups (both as monotherapy) in 172 persons with impaired glucose tolerance.[158] At 3-year follow-up the incidence rate of diabetes was 3.0% among participants taking either rosiglitazone or pioglitazone and 26.7% among the placebo group. The study was not powered to compare the 2 thiazolidinediones for this outcome.

In a small, poor-quality trial, Hung and colleagues[159] compared rosiglitazone as monotherapy with placebo among persons with impaired glucose tolerance at 12 weeks follow-up. They noted a reversal to a normal oral glucose tolerance test in 33% of participants taking rosiglitazone (compared with a placebo rate of 13%). One participant in the placebo group developed type 2 diabetes over the course of the study. This small, short-term study was not designed to demonstrate differences between rosiglitazone and placebo for the outcome of new cases of type 2 diabetes.

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[59] the metabolic syndrome.[160] In the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial,[161] 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 ($P< 0.0001$).[59] 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.[160] 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 (NOT UPDATED).
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?

Summary of the Evidence

- Data are insufficient to determine the comparative effectiveness of Pio and Rosi on cardiovascular risk factors among persons with prediabetes or the metabolic syndrome.
- There were no data to address comparative effect on blood pressure.
- One fair-quality head-to-head study demonstrated improved lipid levels with pioglitazone compared to rosiglitazone.
- Data on both drugs from placebo-controlled trials showed mixed effects on lipid levels.
- Data on the effect of Pio and Rosi on weight and abdominal obesity are few and, as noted above in Key Question 3, it is not possible to conclude if there is a difference between the two drugs for these two outcomes.

Detailed Assessment

This question was not included in the updated report.

Data are insufficient to determine the comparative effectiveness of pioglitazone and rosiglitazone on cardiovascular risk factors among persons with prediabetes or the metabolic syndrome. There were no data to address comparative effects on blood pressure. One fair-quality head-to-head study demonstrated improved lipid levels with pioglitazone compared to rosiglitazone. Data on both drugs from placebo-controlled trials showed mixed effects on lipid levels. Data on the effect of pioglitazone and rosiglitazone on weight and abdominal obesity are few and, as noted above in Key Question 3, it is not possible to conclude if there is a difference between the 2 drugs for these 2 outcomes.

More detailed information on the 6 studies which examined cardiovascular risk factors among persons with prediabetes or the metabolic syndrome are presented in Table 13 and Evidence Tables 2, 9, and 10. Pioglitazone produced a significant ($P<0.05$) decrease in LDL, total cholesterol, and triglycerides compared to rosiglitazone in a head-to-head study.[65, 66] Lester and colleagues[157] noted a significant increase in total cholesterol (5.8%), LDL (8.9%), and HDL (20.1%) with pioglitazone monotherapy compared to metformin or sulfonylurea monotherapy, as well as a decrease in triglycerides (12.8%). Combined therapy of pioglitazone and either sulfonylurea or metformin produced similar lipid changes to pioglitazone monotherapy.

In a small study,[158] rosiglitazone increased HDL (P=0.032) and LDL (P=0.025) compared to placebo. Rosiglitazone increased total cholesterol (P<0.001), HDL (P<0.05), and LDL (P<0.05) compared to baseline values in a poor-quality study.[159]

Table 13. Use of thiazolidinediones in prediabetes and the metabolic syndrome

Study Quality	Study design Total sample size Follow-up	Drug, dosage Combination therapy	Population Mean age (years) Comorbidities	Change in A1c (%)[a]	Change in blood pressure[a] (mm Hg)	Change in lipid levels[a] (mg/dl)	Change in weight[a], BMI (kg/m^2)[a], or central obesity[a]	Occurrence of clinical diabetes
Head-to-head trials								
Derosa G 2004[65], 2005[66] Fair	RCT 91	Pio 15 mg daily or Rosi 4 mg daily Added to glimepiride	Metabolic syndrome 54 DM2	Pio: -1.4 Rosi -1.3 *P*>0.05	NR	Total cholesterol: Pio -11; Rosi 29 (*P*<0.05) LDL: Pio -15; Rosi 20 (*P*<0.05) HDL: Pio 6; Rosi 1 (*P*>0.05) TG: Pio -26; Rosi 31 (*P*<0.05)	BMI: Pio: 1.2 Rosi: 1.5 *P*>0.05	NA
Durbin R 2004[156] Fair	Controlled trial 172 3 years	Pio 30 mg or Rosi 4 mg daily Monotherapy (treatment groups were on troglitazone previously)	Prediabetes (IGT) 56.4 Insulin resistance	Pio: -0.12 Rosi: -0.14 Control: 0.43 TZD compared with control *P*<0.001; no comparison Pio and Rosi	NR	NR	Weight (kg): Pio 2.5(6.3); Rosi 0.3(5.5); control 2.0(1.6) No *P* values reported	Progression to DM2 at 3 years: number of cases Pio: 3%; Rosi: 3% Control 19/71=26.7% Crude incidence (case per 100 person-years): TZD 1.4; control 9.4 (*P*<0.001) Number needed to treat with TZD to prevent 1 case of DM2 in 3 years: 4.2
Pioglitazone								
Lester JW 2005[157] Based on 4 fair-quality studies	4 RCTs (subset analysis) 3186 16-40 weeks	Pio 15-45 mg daily Monotherapy and combined	Metabolic syndrome NR DM2 inadequately managed with metformin	Pio: -1.6 Pio+SU -1.3 Pio+metformin -1.1 Pio compared with SU: *P*<0.05	NR	% change: Total cholesterol Pio: 5.8; Pio+SU 3.2; Pio+metformin 5.9 HDL: Pio 20.1; Pio+SU 17.4; Pio+metformin 19.8	Weight (kg) Pio 2.5; Pio+SU 3.0; Pio+metformin NR Increased weight in Pio compared with	NR

Study Quality	Study design Total sample size Follow-up	Drug, dosage Combination therapy	Population Mean age (years) Comorbidities	Change in A1c (%)[a]	Change in blood pressure[a] (mm Hg)	Change in lipid levels[a] (mg/dl)	Change in weight[a], BMI (kg/m^2)[a], or central obesity[a]	Occurrence of clinical diabetes
						LDL: Pio 8.9; Pio+SU 5.1; Pio+metformin 9.7 TG: Pio -12.8; Pio+SU -12.2; Pio+metformin -12.8	metformin or SU alone (*P*<0.05)	
Rasouli N 2005[162] Poor	RCT 23 12 weeks	Pio 45 mg daily With metformin	Prediabetes (IGT) 56.4 healthy; no coronary heart disease	Pio 0.1; metformin -0.1 No between-group *P* values given	NR	Total cholesterol (mmol/L): Pio -0.4; metformin 0 HDL: Pio 0.1; metformin 0 LDL: Pio -0.3; metformin 0.1 TG: Pio -0.2; metformin 0.3 No between-group *P* values given	BMI: Pio 0.9 Metformin -0.3 No between-group *P* values given	NR
Rosiglitazone								
Bennett S 2004[163] Fair	RCT 18 12 weeks	Rosi 4 mg twice daily Monotherapy	Prediabetes (IGT) 59.7	Between-group difference 0.04% (*P*=0.76) FPG (mmol/l) Rosi -0.28 Placebo -0.50 *P*=0.18	SBP: Rosi -7.0; Placebo 2.6 (*P*=0.007) DBP: Rosi -6.4; placebo 2.5 (*P*=0.013)	NR	NR	NR
Hung Y 2005[159] Poor	RCT 30 12 weeks	Rosi 4 mg daily Monotherapy	IGT 54.8	NR	NR	Total cholesterol: Rosi 21.3; placebo -7.0 HDL: Rosi 7.0; Placebo 0 LDL: Rosi 25.9; Placebo -2.7	BMI: Rosi: 0; placebo -0.3 Waist-hip ratio: Rosi -0.01; placebo -0.014 Between-	Reversal to normal oral glucose tolerance test: Rosi 33%, placebo 13% Progression to DM2: Rosi: 0

Study Quality	Study design Total sample size Follow-up	Drug, dosage Combination therapy	Population Mean age (years) Comorbidities	Change in A1c (%)[a]	Change in blood pressure[a] (mm Hg)	Change in lipid levels[a] (mg/dl)	Change in weight[a], BMI (kg/m^2)[a], or central obesity[a]	Occurrence of clinical diabetes
						Between-group *P* values NR	group *P* values NR	cases; placebo 1 case
Wang T 2004[158] Fair	RCT 50 8 weeks	Rosi 4 mg daily Monotherapy	Metabolic syndrome 59.5	NR FPG: Rosi -2.0; Placebo -1.0 mmol/l *P*=0.37	SBP: Rosi -10; Placebo 1 (*P*=0.002) DBP: Rosi -7; placebo 1 (*P*=0.080)	Total cholesterol: Rosi: 22; placebo -5 (*P*=0.0.014) HDL: Rosi 2.0; placebo 0 (*P*=0.032) LDL: Rosi 20; placebo -5 (*P*=0.025) TG: Rosi -22.0; placebo -11.0 (*P*=0.717)	BMI: Rosi: 0.1; placebo 0 (*P*=0.957) Waist circumference (cm): Rosi: 1; placebo 0 (*P*=0.894)	NR

Abbreviations: IGT, impared glucose tolerance; DM2, type 2 diabetes mellitus; BMI, body mass index; RCT, randomized controlled trial; NR, not reported; SU, sulfonylurea; BMI, body mass index; rosi, rosiglitazone; pio, pioglitazone.
[a] Absolute changes unless otherwise noted.
P values given are between-group values.

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?

Summary of the Evidence

- Adverse events occurring with pioglitazone and rosiglitazone were similar in 3 head-to-head trials.
- Withdrawals due to adverse events did not differ from placebo in trials of pioglitazone (difference from placebo 0%, 95% CI –2% to 2%) or rosiglitazone (–1%, 95% CI –3% to 0%).
- The incidence of edema was greater for pioglitazaone and rosiglitazone than for placebo, with pooled risk differences from placebo of 4% for pioglitazone (95% CI 2% to 7%) and 8% for rosiglitazone (95% CI 3% to 13%).
- Rosiglitazone use was associated with an increase in fractures in women in the ADOPT trial. 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). Preliminary analysis of a second, ongoing trial is consistent with this finding.

Detailed Assessment

Direct evidence comparing pioglitazone to rosiglitazone

Three head-to-head efficacy trials with adverse event data were identified.[67, 68 65] In 1,[67] 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±0.2 kg for pioglitazone compared with 1.6±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.[68] 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,[65] 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^2) or rosiglitazone 4 mg (1.5 kg/m^2), with both groups receiving glimepiride. Of the 87 patients (96%) who completed the study, 6.7% of subjects in the pioglitazone group and 11.9% in the rosiglitazone group had mild to moderate adverse events (transient headache and flatulence), with none resulting in withdrawal. 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[70-72, 144] 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. These adverse events were transient headache and flatulence (metformin was new to some of the study subjects).[74] 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 umol/L and with rosiglitazone was -2.4umol/L.

The second new head-to-head trial did not report adverse event data.[69]

Indirect Evidence

Overall withdrawals

Nine placebo-controlled trials of pioglitazone[60, 76, 82, 85-88, 96, 97] and 16 of rosiglitazone[56, 101, 102, 104-106, 110, 115, 116, 120-122, 124, 128, 129, 131, 132, 158, 159] 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

Figures 4 and 5 show withdrawals due to adverse events reported in placebo-controlled trials of pioglitazone and of rosiglitazone. 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.

Figure 4. Withdrawals due to adverse events in placebo-controlled trials of pioglitazone

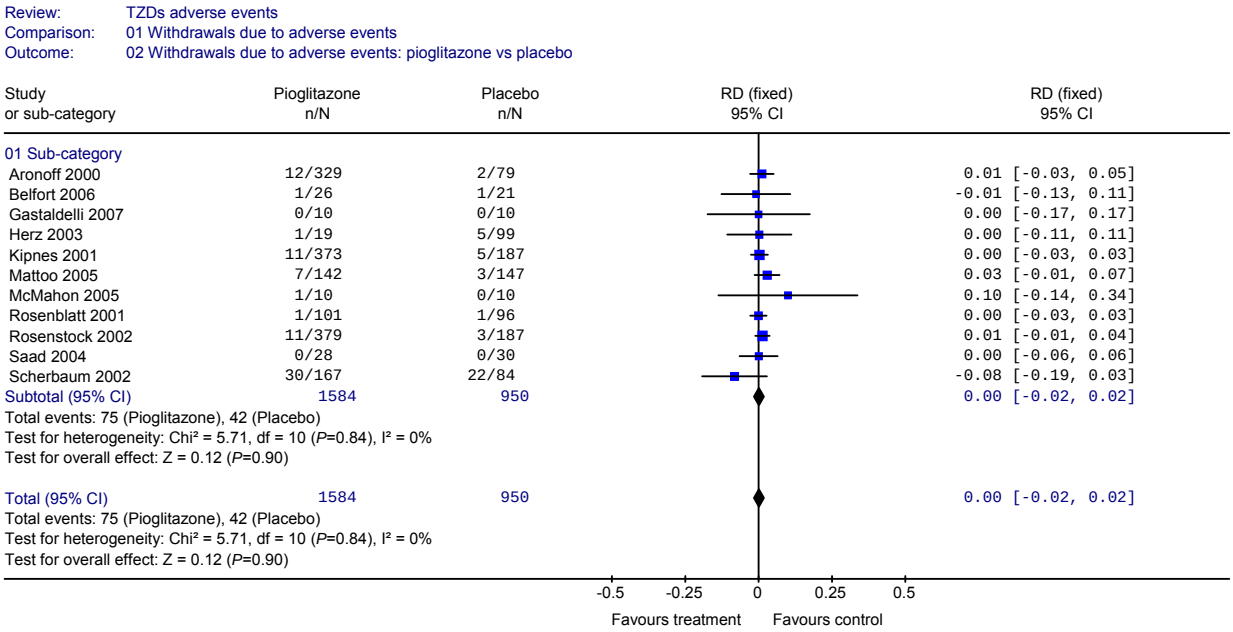
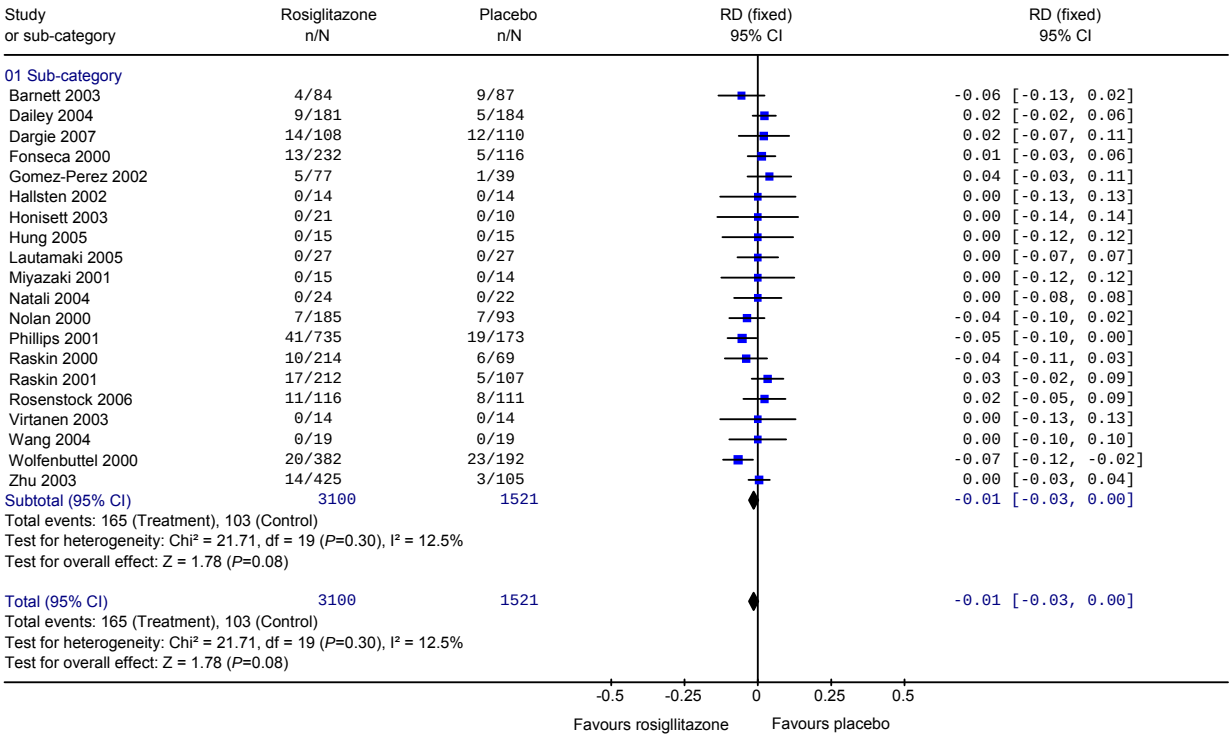


Figure 5. Withdrawals due to adverse events in placebo-controlled trials of rosiglitazone



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 (Evidence Table 11). Most studies did not prespecify which events were evaluated and did not report details about ascertainment methods.

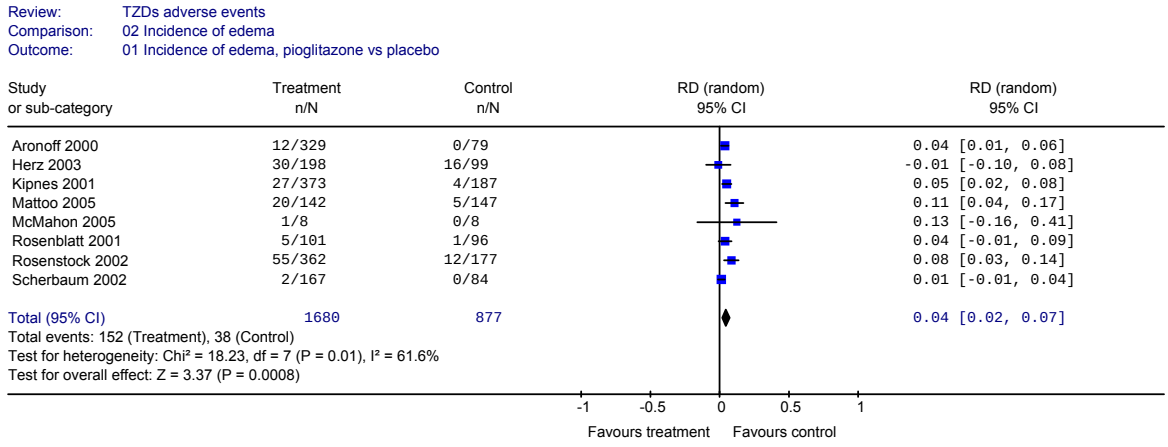
Appendix H summarizes the specific adverse events reported in placebo-controlled efficacy trials. Details are provided in Evidence Table 12 (pioglitazone) and Evidence Table 13 (rosiglitazone). In most cases, there was no difference from placebo in the number of patients reporting an adverse event. The most frequently reported adverse events were edema, hypoglycemia, and weight gain.

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.

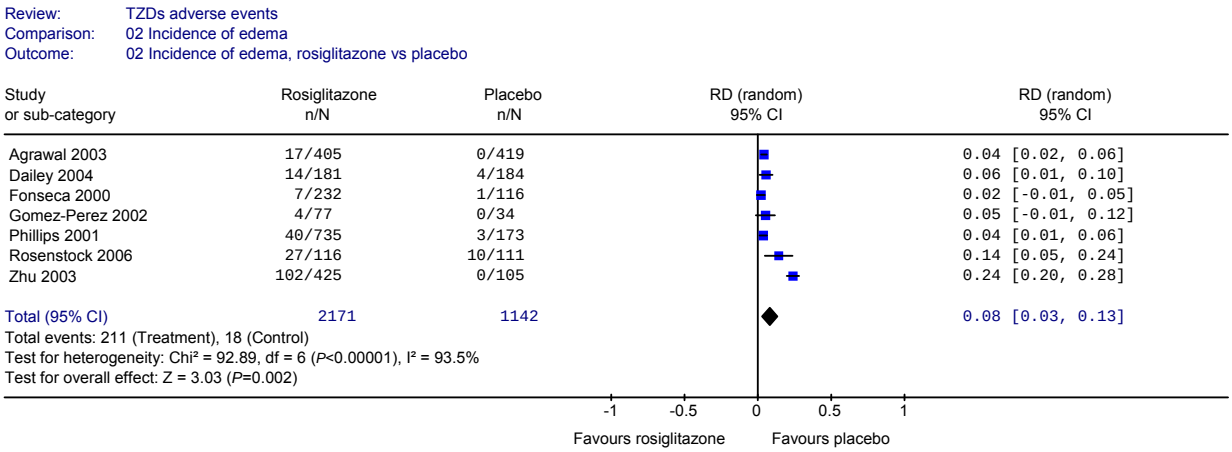
The pooled risk difference was significantly greater than placebo in pioglitazone trials (4%, 95% CI 2% to 7%) (Figure 6).

Figure 6. Incidence of edema in placebo-controlled trials of pioglitazone



Rosiglitazone was also associated with an increased risk of edema (Figure 7). The pooled risk difference in 7 placebo-controlled trials[105, 110, 112, 114, 115, 124, 132] 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%).[110, 132] The incidence in the other 5 trials ranged from 3% to 8%, with differences from placebo ranging from 2% to 6%.

Figure 7. Incidence of edema in placebo-controlled trials of rosiglitazone



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, however (see Figures 8 and 9).

The trials of rosiglitazone examined combination therapy with sulfonylureas[110, 112, 113] or triple therapy with sulfonylurea and metformin[105]. In pioglitazone trials, 3 used monotherapy,[81, 85, 94] 1 used combination therapy with sulfonylureas,[86] and 3 used combination therapy with insulin.[87, 88, 95] Pooled risk differences were not significantly different from placebo in pioglitazone trials using monotherapy (1%, 95% CI -1% to 2%), combination therapy with sulfonylureas (1%, 95% CI -1% to 2%), or insulin (7%, 95% CI -4% to 19%). The highest rates of hypoglycemic events in pioglitazone studies were noted where pioglitazone was combined with insulin.[87, 88]

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.

Figure 8. Incidence of hypoglycemic episodes in placebo-controlled trials of pioglitazone

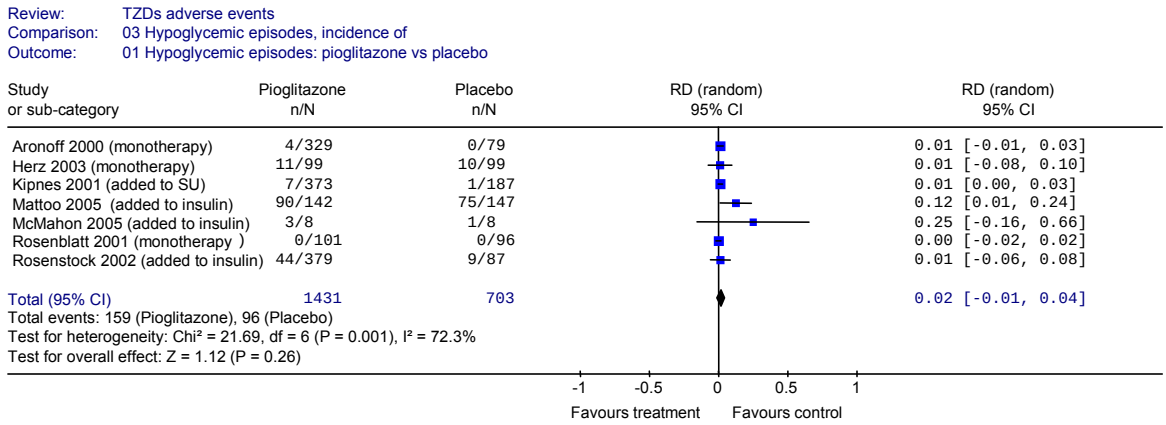
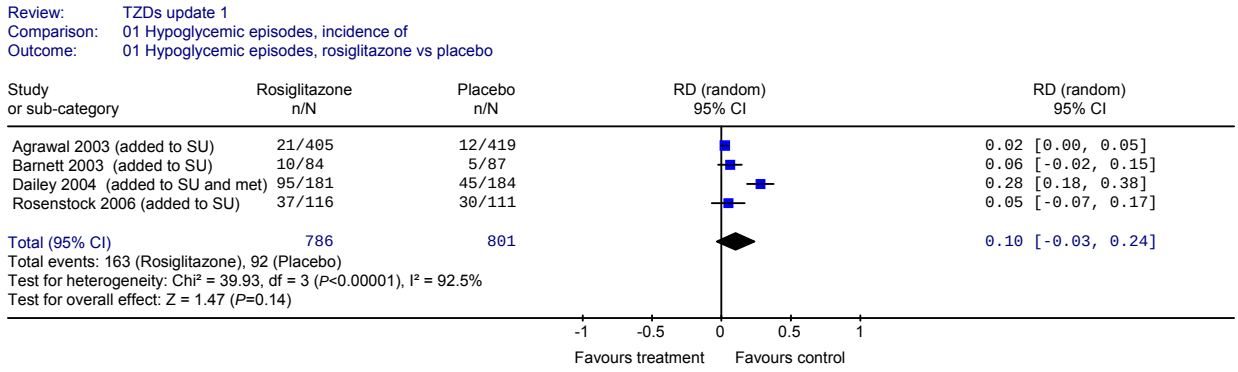


Figure 9. Incidence of hypoglycemic episodes in placebo-controlled trials of rosiglitazone



Weight gain

Twenty-six placebo-controlled trials provided information about weight gain in patients taking pioglitazone or rosiglitazone. It was not possible to calculate a pooled estimate for all of these studies to make indirect comparisons, because of differences in the methods of measuring the outcome (for example, body mass index, change in weight, or patients gaining >5% of body weight) and limited reporting of results (for example, means were reported without a measure of dispersion). Table 14 shows the range of weight gain reported in placebo-controlled trials. Trials with several doses found increased weight gain associated with higher doses.

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)[120, 131] and rosiglitazone (3.50 kg, 95% CI 2.25 to 4.75),[89, 97] 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.[65, 67, 68]

Table 14. Weight gain reported in placebo-controlled trials

Outcome	Weight gain with pioglitazone	Weight gain with rosiglitazone
Weighted mean difference compared with placebo (kg)	3.69 kg (95% CI 2.48 to 4.89)[120, 131]	3.50 kg (95% CI 2.25 to 4.75)[89, 97]
Monotherapy trials	0.3 to 0.8 kg [96](*P* NR) 0.35 to 0.82 kg [85a] 0.74 kg [100] 1.35 kg [94a] 1.3 to 2.8 kg [81] 2.0 kg, 3.0 kg [a] 4.5 kg [77a] 2.5 kg [82] 3.6 kg [60a] 4.0 kg [84]	0[129] 0.5 kg [122] (*P* NR) 0.6 kg [116] (*P* NR) 1.2 to 3.3 kg [124](*P* NR) 1.3 kg [56] 1.6 to 3.5 kg [120] (*P* NR) 1.9 kg [106] 3.7 kg [121a] 4.3 kg [110]
Combination therapy trials	1.2 kg [99] 1.9 to 2.9 kg [86a] 2.3 to 3.7 kg [95](*P* NR) 3.6 kg [89] 3.88 kg [97] (*P* NR)	0.26 to 2.42 kg [115](*P* NR) 3.0 kg [131](*P* NR) 3.0[105]

Abbreviations: CI, confidence interval; NR, not recorded
[a] Significantly greater than placebo (*P*<0.05).

A 2004 meta-analysis[43] 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).

The range of weight gain reported in active control trials is shown in Appendix I. 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% (See Appendixes H and I).

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.[164] 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[24] 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.

Two placebo-controlled trials of pioglitazone added to insulin reported incidences of congestive heart failure of 12.5%[88] and 1%.[95]

The pioglitazone product label[23] 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.

In the PROACTIVE trial,[60] 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 ($P=0.634$)

Adverse events reported in active-control trials

Overall withdrawals, withdrawals due to adverse events, and specific adverse events reported in active-control trials are shown in Appendix I.

Observational studies of adverse events

Direct evidence comparing pioglitazone compared with rosiglitazone

Overview

We identified 12 observational studies that compared adverse events in patients taking pioglitazone with those in patients taking rosiglitazone (Evidence Table 14). Five of these were designed to assess specific adverse events; in the others, adverse events were reported but were not the primary outcome. No new observational studies that directly compared pioglitazone and rosiglitazone were identified for the update.

Observational studies can provide evidence about safety when long-term trials are not available. Few observational studies followed patients for longer than 12 months, however. Quality assessment of these studies is shown in Evidence Table 15.

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.[165] 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,[166] 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[167] 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 post-marketing reports of new onset and worsening diabetic macular edema for patients receiving rosiglitazone.[168] 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. Abnormal vision was reported in 2.3% of patients in 1 trial of rosiglitazone in combination with sulfonylureas,[132] but this was lower than the rate in the placebo group (5.4%).

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.[169] 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).

A retrospective database study designed to assess the prevalence of edema found no documentation of new-onset heart failure or exacerbations of existing heart failure in patients initiating thiazolidinediones therapy plus insulin.[165] The study authors caution, however, that documentation of heart failure was poor and that the data may be unreliable.

Weight gain

Seven comparative observational studies reported weight gain in follow-up periods ranging from 8 weeks to 1 year (Table 15).[166, 170-175] There was no difference in the amount of weight gain in patients taking pioglitazone compared with rosiglitazone in any study.

Table 15. Range of weight gain reported in comparative observational studies

Study[a]	Duration	Weight gain with pioglitazone (kg)	Weight gain with rosiglitazone (kg)
King 2000[175]	16 weeks	0.5	2.6
LaCivita 2002[171]	6 months (range 3-11 months)	1.6	1.5
Boyle 2002[170]	18 weeks	2.0	1.6
Olansky 2003[172]	12 weeks or longer	2.0	1.6
Harmel 2002[174]	25-27 weeks	2.2	1.6
Hussein 2004[166]	8 weeks or longer	2.3	2.9
Gegick 2004[173]	1 year	4.1	3.0

[a] There was no significant difference between drugs 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 (Table 16, Evidence Tables 16 and 17).[176-182] The adverse events they examined included mortality, coronary heart disease events, heart failure, cancer incidence, and progression to insulin use. 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.[178, 181] 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.[181]

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.[177] The other found similar risks with rosiglitazone compared with sulfonylureas, metformin, or insulin, either alone or in combination.[182] Both studies also found no increased risk in the individual components of the composite outcome with thiazolidinedione use.

Table 16. Observational studies comparing adverse events associated with thiazolidinediones to adverse events associated with active controls

Author, Year (Quality)	Comparison	Sample size	Data source, Population description	Main outcomes	Main results
Kahler 2007[178] (Fair)	TZD vs. SU monotherapy vs. metformin monotherapy vs. metformin + SU vs. no drugs	39721	Veterans Health Administration data	All-cause mortality (15 months)	Adjusted odds ratio (95% CI) SU (reference): 1.00 TZDs: 1.04 (0.75 to 1.46) Metformin: 0.87 (0.68 to 1.10) Metformin + SU: 0.92 (0.82 to 1.05) No drugs: 0.90 (0.74 to 1.09)
Masoudi 2005[181] (Good)	TZDs vs. metformin vs. no insulin sensitizer	16417	Medicare Older patients with heart failure	All-cause mortality (1 year)	Adjusted hazard ratio (95% CI) TZDs: 0.87 (0.80 to 0.94) Metformin: 0.86 (0.78 to 0.97) SU: 0.99 (0.91 to 1.08) Insulin: 0.96 (0.88 to 1.05) TZD+metformin: 0.76 (0.58 to 0.99)
Johannes 2007	TZDs vs. metformin + SU	25140	US health insurance	Coronary heart disease events	Adjusted hazard ratio (95% CI)

Author, Year (Quality)	Comparison	Sample size	Data source, Population description	Main outcomes	Main results
(Good)[177]			claims data	(myocardial infarction or coronary revascularization)	TZDs: 1.02 (0.87 to 1.20) Metformin+SU (reference): 1.00
McAfee 2007 (Good)[182]	Rosiglitazone vs. metformin vs. sulfonylurea	26 931	US health insurance claims data Patients with type 2 diabetes	Coronary heart disease events (myocardial infarction or coronary revascularization)	Adjusted hazard ratio (95% CI) Rosiglitazone vs. metformin: 1.07 (0.85 to 1.34) Rosiglitazone vs. SU: 0.82 (0.67 to 1.02) Rosiglitazone combined with insulin vs. other oral antidiabetics combined with insulin: 0.88 (0.59 to 1.32) Rosiglitazone therapy vs. all other non-rosiglitazone therapies: 0.93 (0.80 to 1.10)
Karter 2005 (Fair)[179]	Pioglitazone vs. SU vs. metformin vs. insulin	23 440	Kaiser Permanente Northern California Diabetes Registry	Hospital admission for heart failure (mean 10.2 months)	Adjusted hazard ratio (95% CI) Pioglitazone: 1.28 (0.85 to 1.92) Insulin: 1.56 (1.00 to 2.45) Metformin: 0.70 (0.49 to 0.99) SU (reference): 1.00
Hartung 2005 (Fair)[183]	TZDs vs. SU vs. metformin vs. metformin + SU vs. insulin vs. insulin + TZD vs. alpha-glucosidase inhibitor	1940	Oregon Medicaid Claims data	Hospital admission for heart failure (within 60 days)	Adjusted odds ratio (95% CI) TZDs: 1.37 (0.98 to 1.92 SU: 0.95 (0.73 to 1.24) Metformin: 0.97 (0.72 to 1.30) Metformin+SU: 0.90 (0.60 to 1.34) Insulin: 1.25 (0.92 to 1.69) Insulin+TZDs: 1.35 (0.84 to 2.18) Alpha-glucosidase inhibitor: 0.82 (0.28 to 2.18)
Koro 2007 (Fair)[180]	TZDs vs. other antidiabetic agents	126 971	US Integrated Healthcare Information Services database	Cancer incidence	Adjusted odds ratio (95% CI) TZDs (mono- or combination therapy) compared with other anti-diabetic agents Breast cancer: 0.89 (0.68 to 1.15) Colon cancer:

Author, Year (Quality)	Comparison	Sample size	Data source, Population description	Main outcomes	Main results
					1.03 (0.84 to 1.32) Prostate cancer: 1.04 (0.83 to 1.31)
Hanefeld 2006 (Poor)[176]	Pioglitazone vs. glibenclamide	500	Primary care sites, Germany Patients with type 2 diabetes insufficiently controlled on metformin alone	Progression to insulin	Pioglitazone: 55/250 (22%) Glibenclamide: 138/250 (55%) *P*<0.001

Abbreviations: CI, confidence interval; SU, sulfonylurea; TZD, thiazolidinedione.

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.[179] Relative to patients initiating therapy with sulfonylrueas, 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.[183] 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.[180]

A study conducted in 500 primary care patients in Germany found fewer patients progressed to insulin therapy when taking pioglitazone than when taking a sulfonylurea.[176] However, because this study did not control for confounders and did not clearly report its recruitment strategy and other methods, these results may be biased.

We identified 43 additional uncontrolled studies of adverse events associated with individual thiazolidinediones.[184-221] These studies are summarized in Evidence Tables 18 (pioglitazone), 19 (rosiglitazone), and 20 (new studies added for the updated report). Their results were consistent with evidence from randomized controlled trials and comparative observational studies. Conclusions that can be drawn from this body of evidence are limited because the studies do not provide information about comparative safety of the drugs.

Key Question 7 (NOT UPDATED).
How do thiazolidinediones compare to sulfonylureas in serious hypoglycemic events, functional status, and quality of life?

Summary of the Evidence

Hypoglycemia

Pioglitazone
- 1 fair-quality study reported significantly fewer hypoglycemic events with pioglitazone than with a sulfonylurea ($P<0.05$).
- Severe hypoglycemic episodes were not reported in any patient taking pioglitazone.

Rosiglitazone
- The incidence of hypoglycemia was variable compared to a sulfonylurea (4 studies).
- Combination therapy (rosiglitazone + various sulfonylureas or rosiglitazone + glibenclamide) increased rates of hypoglycemia over sulfonylurea monotherapy (2 studies).

Functional status and quality of life
- No evidence upon which to draw conclusions

Detailed Assessment

Update report: This question was not included in the updated report. The effects of pioglitazone and rosiglitazone on hypoglycemic events are reviewed in the section addressing adverse events.

Trials comparing pioglitazone or rosiglitazone to a sulfonylurea are presented in Tables 17 and 18. There were no comparative data on functional status or quality of life from any efficacy or effectiveness trial that compared thiazolidinediones and sulfonylureas for the time period for study inclusion. We did, however, identify a study after our cut-off point for our search, and we discuss this study separately below.[110] There were no direct comparisons of the incidence of hypoglycemic events with pioglitazone and rosiglitazone compared with a sulfonylurea. Comparisons of pioglitazone and a sulfonylurea revealed fewer events with pioglitazone. Comparisons of rosiglitazone to sulfonylurea had variable effects on hypoglycemic episodes.

Six trials examined the incidence of hypoglycemic events among pioglitazone and sulfonylurea treatment groups and the incidence was less with pioglitazone in all 6 studies, 2 of which were of poor quality (Table 17). Statistical comparisons were presented in only 3 of these studies, however, and 2 demonstrated significantly lower rates of hypoglycemia with pioglitazone (fair quality, $P=0.024$[222] and poor quality, $P<0.001$[223]). Severe hypoglycemic episodes (variably defined among studies) were not reported in any patient taking pioglitazone.

The incidence of hypoglycemic events among persons taking rosiglitazone monotherapy compared to sulfonylurea monotherapy was only examined in 1 study (Table 18). The incidence was lower with rosiglitazone compared to glyburide.[224] Three additional studies examined combined therapy with rosiglitazone and a sulfonylurea compared with monotherapy with the sulfonylurea. In all 3 studies the rates for hypoglycemic events were higher with the combined therapy.[225-227]

Rosenstock and colleagues[110] published a study after our cut-off for inclusion, as mentioned above. This randomized controlled trial compared rosiglitazone 4 mg daily to placebo, with both treatment groups receiving glipizide 10 mg twice daily. At 2-year follow-up, the incidence of symptomatic hypoglycemia was similar in the 2 treatment groups (32% with rosiglitazone plus glipizide compared with 27% with glipizide alone). The rosiglitazone group had high scores on the Diabetes Treatment Satisfaction Questionnaire than the control group ($P<0.001$). Health-related quality of life as measured by the SF-36 deteriorated in the comparison group (suggesting deterioration in health) while there were no significant changes in the rosiglitazone group (no data values or statistics were presented, however).

Table 17. Comparisons of pioglitazone to sulfonylureas for the outcomes of serious hypoglycemic events, functional status, and quality of life

Study	Dosage	Comparison sulfonylurea	Hypoglycemic events (% of patients with an event)	Functional status HRQL	Study quality
Charbonnel BH 2004[228]	45 mg daily	Gliclazide up to 160 mg twice daily	Pio: 3.5% Gliclazide: 10.1%, 1/63 required hospitalization No statistics	NR NR	Poor
Langenfeld MR 2005[229] Pfutzer A 2005[230]	45 mg daily	Glimepiride 1-6 mg daily; Average 2.7 mg daily	Pio: 21 episodes in 17/89 patients (19%) Glimepiride: 26 episodes in 17/84 patients (20%) *P*=0.86 No episodes of severe hypoglycemia (need for external aid)	NR NR	Fair
Matthews 2005[231]	15-45 mg daily 70% on 45 mg daily All received metformin	Gliclazide 80-320 mg daily 33% on 320 mg daily All received metformin	Pio: 1.3% Gliclazide: 11.2%; 2/35 withdrew None reported as severe	NR NR	Fair
Tan 2004 (a[223])	30-45 mg daily 75% on 45 mg daily	Glibenclamide: 1.75-10.5 mg daily 62% on 10.5 mg daily	Incidence of any hypoglycemia greater in glibenclamide group (*P*<0.0001) Number of events NR	NR NR	Poor
Tan 2004[222]	15-45 mg daily Mean dosage 37 mg daily	Glimepiride 2-8 mg daily Mean dosage 6 mg daily	Pio: 15.7% Glimepiride: 30.9% *P*=0.024 No data on severity	NR NR	Fair
Watanabe 2004[232]	15 mg or more daily (range NR) Mean 17.3 mg daily	Glibenclamide: 1.25-2.5 mg daily Mean dosage 1.56 mg daily	Pio: no events Glibenclamide: 1 episode in 14 patients (7.1%); led to withdrawal from study; no other details	NR NR	Fair

Abbreviations: NR, not recorded; pio, pioglitazone.

Table 18. Comparisons of rosiglitazone to sulfonylureas for the outcomes of hypoglycemic events, functional status, and quality of life

Study	Dosage	Comparison sulfonylurea	Incidence of hypoglycemic events (% of patients with an event)	Functional status HRQL	Study quality
Baski A 2004[225]	4 mg twice daily + gliclazide 160 mg daily	Gliclazide 160 mg daily	Rosi: 6% total; 1% severe Gliclazide: 2% total; 0.4% severe Definition: Inability to perform normal daily activities	NR NR	Fair
Kerenyi A 2004[227]	8 mg daily + glibenclamide 7.5 mg daily	Glibenclamide 7.5 - 15 mg daily	Rosi + glibenclamide: 18.5% total; 0.6%; 6/165 withdrawals for hypoglycemia Glibenclamide: 4.1% total; 0% severe; no withdrawals for hypoglycemia	NR NR	Fair
St John Sutton M 2002[224]	4 mg twice daily	Glyburide mean 10.5 mg daily	Rosi: 1.9% had signs or symptoms; none required treatment Glyburide: 7.1% (3/7 required treatment); no withdrawals	NR NR	Fair
Vongthavaravat V 2002[226]	2 mg twice daily + various SU	Various SU	Rosi: 11.6% total; severe in 1/19 episodes SU: 1.2% total; 0% severe Between-group *P*<0.001	NR NR	Fair

Abbreviations: NR, not reported; SU, sulfonylurea; rosi, rosiglitazone.

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 form those in general populations, compared to each other and to other hypoglycemic agents?

Studies examining subgroups based on demographic characteristics or comorbidities are summarized in Table 19. Most studies were conducted in the United States or in Western Europe and examined white populations. Some studies included minority populations but did not present subgroup analyses on these populations.[156] Thus there are very limited data on the comparative effectiveness of pioglitazone and rosiglitazone among persons with various demographic characteristics and no conclusions can be drawn as to which drug is more efficacious or effective, or associated with fewer side effects in population subgroups.

Most of the studies identified in this review examined persons with type 2 diabetes without significant comorbidities such as coronary heart disease, heart failure, or renal insufficiency. Thus there is a paucity of data on the interaction of thiazolidinediones and micro- and macrovascular diseases that are highly prevalent among persons with diabetes, and no conclusions can be drawn on the comparative effectiveness of the 2 drugs under review among populations with significant comorbidities.

Subgroups based on demographic characteristics

In the original report, only 2 publications examined subgroups defined by age. Kreider and colleagues[233] pooled the results of 8 randomized controlled trials examining monotherapy with rosiglitazone and examined subgroups of age less than and greater than 70 years. They found no differences between the 2 age groups for A1c and found rosiglitazone well tolerated in both age groups. The percentage of persons with at least 1 adverse event was comparable between the rosiglitazone and placebo groups, and between persons older and younger than 70 years. The incidence of anemia was higher in older patients taking rosiglitazone than in younger patients taking the drug and treatment patients had higher rates of anemia than patients in the placebo group. Weight gain was higher in the under-seventy group (2.14 kg) than the over-seventy group (1.66 kg) and the placebo groups (<70 years, -0.41 kg; >70 years, -1.34 kg).

Rajagopalan and colleagues[202] examined the effect of pioglitazone on glucose control and lipid levels in patients <65 and ≥65 years using data from 5 separate trials (4 trials were unpublished data from Takeda Pharmaceuticals and the fifth study was by Rosenblatt et al.,[94] a placebo-controlled trial found in Evidence Table 5). The study by Rosenblatt and colleagues[94] was of fair quality; we were unable to assess the quality of the unpublished trials. 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. Hypoglycemia was 2-fold higher in the older-aged group using pioglitazone combined with a sulfonylurea or insulin.

Several studies examined racial or ethnic minorities. King compared Mexican Americans with non-Hispanic persons in a retrospective cohort study and found that A1c and weight changed to a similar degree in both populations. Jun and colleagues[234] examined 100% Hispanics, and pioglitazone produced a decrease in A1c of 2.0% at 6 months. Twelve Chinese persons with nephropathy and type 2 diabetes were exposed to rosiglitazone over 15.5 months with improved A1c, a nonsignificant increase in weight, and no adverse events.[235] Pioglitazone was as effective as glimepiride among 244 Mexican patients.[222]

Barnett and colleages[113] examined the use of rosiglitazone in an Indian and Pakistani population in the United Kingdom and noted results and adverse events comparable to other placebo-controlled trials discussed above. Vongthavaravat et al.[226] examined a mixed Asian and white population and their results were also consistent with findings in largely white populations in other studies of rosiglitazone.

In the updated report, several additional studies of rosiglitazone provided data on subgroups based on demographic data.[57, 105, 110, 145] In a combination therapy, double-blind study (N=365) 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.[105]

In a study of older adults with type 2 diabetes,[110] 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%, $P<0.0001$).

In a double-blind study (N=318) in subjects who had failed to achieve adequate control on metformin,[145] 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,[57] rosiglitazone was more effective than glyburide in all subgroups for the primary outcome of monotherapy failure: age ≤ 50 years, between 50 and 59 years, and ≥ 60 years; males and females; body mass index ≤ 30 kg/m^2, between 30 and 35 kg/m^2, and ≥ 35 kg/m^2; baseline fasting plasma glucose ≤ 140 mg/dL and > 140 mg/dL; and waist circumference ≤ 99 cm, >99 – 110 cm, and > 110 cm.

Comorbidities and other population characteristics

Patients with impaired renal function were examined in several studies. Agrawal and colleagues[112] 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 retrospective chart review[236] of patients on dialysis with end stage renal disease, rosiglitazone was associated with weight gain and a decrease in hematocrit at 3-month follow-up compared with pioglitazone. Data for pioglitazone, however, were not presented, limiting conclusions that can be drawn.

In a fair-quality study pooling 2 randomized controlled trials that compared rosiglitazone plus metformin combined therapy with metformin monotherapy, Jones and colleagues[118] examined subgroups with body mass index < 25 kg/m^2, 25-30 kg/m^2, and >30 kg/m^2. 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^2) 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.

Patients with diagnosed coronary artery disease were examined in 3 studies which were described above in Key Question 2, as these were the only studies that reported cardiovascular outcomes. Wang and colleagues[103] 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). Wang and colleagues[158] also examined Chinese persons with metabolic syndrome and found that fasting plasma glucose did not improve significantly in either the rosiglitazone or the placebo group (A1c was not presented).

In a poor-quality study, Choi and colleagues[152] compared treatment with rosiglitazone plus conventional antidiabetic therapy among patients undergoing coronary catheterization to conventional treatment. At 6-month follow-up there were no significant differences in glycemic control or lipid concentrations between the 2 groups. The rate of restenosis and the stenosis diameter were less in the rosiglitazone group (between-group P=0.03).

Thirty-one postmenopausal women were examined in a poor-quality, placebo-controlled trial of rosiglitazone 4 mg daily.[101] Results were similar to other placebo-controlled trials and no adverse events were reported.

No studies explicitly examined populations with a history of hypoglycemic episodes. Nor were studies identified that examined the effect of concomitant medications on the comparative effectiveness of pioglitazone and rosiglitazone. Most studies permitted the use of a variety of antihypertensive, cardiac, and cholesterol-lowering medications among participants. Subgroup or

other stratified analyses were not performed to allow examination of drug-drug interactions with the thiazolidinediones.

In the updated report, we identified new data on the use of thiazolidinediones in persons with comorbidities, particularly with cardiovascular disease. Since the publication of the large PROACTIVE study[60] (discussed above) which compared pioglitazone with placebo, several additional subgroup analyses have been published, including of subjects with prior myocardial infarction[79] or stroke.[80] In the subgroup of patients with a previous myocardial infarction at baseline[79] (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.[80] 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.

Several other smaller recent trials also examined comorbidity subgroups with pioglitazone. In a small, open-label study in subjects with overt diabetic nephropathy (mean creatinine 2.6 mg/dL and 2.4 mg/dL in the pioglitazone and glipizide groups, respectively), A1c decreased more with pioglitazone (change -0.1 [standard deviation 1.2]) than with glipizide (change -0.4 [standard deviation 1.8]) (between-group *P* value 0.52).[133] A small, placebo-controlled pioglitazone monotherapy study in persons newly diagnosed with type 2 diabetes and coronary heart disease found was no significant difference between groups in change in A1c.[237]

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.[82] 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.

In another small study, patients with acute coronary syndrome received pioglitazone or no additional treatment starting 2 weeks after percutaneous, bare metal stent placement.[93] 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.

Several studies in the updated report examined rosiglitazone with comorbidities. In a very small (N=16), poor-quality randomized controlled trial, subjects with coronary stent implantation were randomized to rosiglitazone 4-8 mg daily or placebo for 6 months. Rosiglitazone did not reduce in-stent restenosis. There were no differences in cardiac events between the groups.[108] Lautamaki and colleagues noted a decrease in A1c compared with placebo in a study of combination therapy in patients with coronary artery disease (*P*<0.0001 compared with placebo).[106]

Table 19. Studies examining subgroups based on demographic characteristics or comorbidities

Author, Year Quality	Country Setting	Study design	Race/ ethnicity	Concurrent hypoglycemic treatment	Inclusion criteria Exclusion criteria	Mean age (SD) Gender	Baseline A1c (SD) Weight (SD) or BMI (SD)	A1c outcomes	Adverse events and tolerability
Pioglitazone									
Jun JK 2003 Fair, for case series	USA Single center	Time series retrospective chart review	Hispanic 100%	SU 50% Insulin 52% Metformin 70%	Hispanic, >18 y, DM2, uncontrolled hyperglycemia with A1c≥8.0%; have taken Pio for at least 6m; A1c within 1m before start of Pio; have at least 2 A1c measures at 3-m intervals during the 6-m period; lipid panel within 1m before start Exclusion criteria: noncompliant with Pio as noted in chart	54.6 (8.5) yr 83% female	10.4% (1.7%) 78.9 (21.4) kg 32.0 (8.1) kg/m^2	6-month follow-up A1c: -2.0% (P<0.0001)	8 patients (5.6%) withdrew secondary to significant peripheral edema; 1 patient had exacerbation of congestive heart failure, 1 reported myalgias.
King AB 2003 Fair (for cohort study)	USA Single center	Cohort with comparison group Retrospective chart review	98 non-Hispanic Caucasians and 81 Mexican-Americans	SU 55% Insulin 0% Metformin 21%	Clinic patients with DM2, treated with Pio 45 mg/d for 6m or more without interruption; A1c and lipids available on the chart within 4w of starting treatment and approximately 4m into treatment Exclusion criteria: patients whose lipid-lowering medication was changed during study period	Hispanics: 52.7 (15.2) yr Non-Hispanics: 61.2 (12.8) yr % female NR	Hispanics: 8.2% (1.9%) non-Hispanics: 8.0% (1.9%) Hispanics: 89.2 (NR) kg Non-Hispanics: 99.6 (NR) kg	A1c at 3-m follow-up Hispanic: -1.2(1.8) Non-Hispanic: 1.1(1.4)	No AEs presented Weight gain: Hispanics 1.41 kg, Caucasians 1.64 kg (P=0.54)
Rajagopalan R., 2004 NA (based on 5 other studies, 1 of fair quality; data not available in 4)	Countries NR Multicenter trials	5 RCTs, 1 published (Rosenblatt 2001), others unpublished by Takeda Pharmaceuticals	NR	2 placebo-controlled Pio monotherapy trials; 1trial each of Pio combined with metformin, sulfonylurea, or insulin	Inclusion: Patients 30-75 years, BMI 25-40 mg/m^2, fasting c-peptide >0.331 nmol/L, normal thyroid function Exclusion: NYHA class III or IV status , significant renal or hepatic disease, uncontrolled hypertension, coronary artery disease or stroke in last 6m	Two subgroups examined: <65 and ≥65 years; mean age and % female NR	< and >65 years reported as ranges for the 5 studies combined A1c: 9.8% to 10.9%; 8.9% to 10.3% BMI, weight NR	Mean decrease from baseline in A1c 0.53 to 1.94%; older group had similar response to younger group; both groups also benefits to a comparable degree for lipid levels	Adverse cardiovascular events and hypoglycemia were similar in the younger and older age groups treated with Pioglitazone monotherapy and with Pioglitazone combined with metformin. Hypoglycemia was 2-fold higher in the

Author, Year Quality	Country Setting	Study design	Race/ ethnicity	Concurrent hypoglycemic treatment	Inclusion criteria Exclusion criteria	Mean age (SD) Gender	Baseline A1c (SD) Weight (SD) or BMI (SD)	A1c outcomes	Adverse events and tolerability
									older-aged group using Pioglitazone combined with a sulfonylurea or insulin.
Tan M 2004 (glimepiride study) Fair	Mexico Multicenter	RCT, AC, DB	Hispanic 99%, white 1%	None	Patients with DM2 and A1c >7.5% and ≤11.0%in patients who were not receiving oral hypoglycemic agents, and >7.5% and ≤9.5% in patients who were receiving oral agents. Patients must have had a trial of diet and lifestyle interventions before study enrollment Exclusion criteria: significant functional limitation (NYHA class III or IV; triglycerides >400 mg/dl; serum creatinine >2.0 mg/dl; renal transplantation or current renal dialysis; ALT or AST > 2.5 times upper limit of normal; clinical signs or symptoms of liver disease; Hg<115 g/l for women and <115g/l for men; BMI <25 or >35 kg/m^2; signs or symptoms of substance abuse	55.3 (NR) yr 51% female	NR 74.4 (NR) kg	A1c at 1-year follow-up Pio: -0.8% Glimepiride: -0.7% Between-group *P*value = 0.64	Incidence of treatment-emergent and severe AEs was similar in the 2 groups
Rosiglitazone									
Agrawal, A 2003 Fair, based on secondary data	UK Multicenter	RCT, PC, DB, secondary data from 3 RCTs examined subgroup with decreased renal function	NR	Added to various SU	Patients currently treated with SU Exclusion criteria: patients of child-bearing potential, serum creatinine level >1.8 mg/dl	61.6 (NR) yr 38% female	9.15% (NR) 28.8 (NR) kg/m^2	A1c at 6m: Between-group change -1.1% for both renal impaired and nonimpaired patients	% AEs was similar for patients in both treatment groups when comparing those with renal impairment and those without, including incidence

Author, Year Quality	Country Setting	Study design	Race/ ethnicity	Concurrent hypoglycemic treatment	Inclusion criteria Exclusion criteria	Mean age (SD) Gender	Baseline A1c (SD) Weight (SD) or BMI (SD)	A1c outcomes	Adverse events and tolerability
		(creatinine clearance 30-80 ml/min)							of hypoglycemia; edema more common in patients with normal renal function in both treatment groups (no statistics)
Barnett, A 2003 Fair	UK Multicenter	RCT, PC, DB	Indian: 60%; Pakistani: 27%; Bangladeshi: 9.5%; Sri Lankan: 3%; Mauritian: less than 1%	Added to SU	Patients with DM2 taking SU for at least 4 months with dose unchanged within 2 months before start of study, those taking medications that affect glucose or lipids were eligible if doses remained constant at screening and during study period Exclusion criteria: patients of child-bearing potential, severe hypertension, anemia or blood disorders, congestive heart failure, significant liver disease, a weight variance of >5% between screening baseline	54.2 (NR) yr 22% female	9.13% (NR) 26.6 (NR) kg/m^2	A1c at 26 weeks Rosi: -1.16, Placebo 0.26 (*P*<0.001)	Treatment-emergent AEs in 70% Rosi and 75% with placebo; withdrawals for AEs: Rosi 5%, placebo 10% Weight (kg): Rosi 3.9, placebo -0.1 (*P*<0.001)
Chan NN 2004 (Observational study)	USA Single center	Cohort, single group	Chinese	Monotherapy	Twelve insulin-treated DM2 patients with nephropathy who were started on ROSI due to suboptimal glycemic control and progressive weight gain All patients had diabetic nephropathy, with urinary albumin-creatinine ratio >25 mg/mmol; mean serum creatinine 223.1 (68.1) Exclusion criteria: none reported	65 (8.3) yr 58% female	8.6% (NR) 71.7 (NR) kg	A1c at 15.5m: -1.1 (*P*=0.01)	LFT: no significant increase in ALT Hematocrit: NSD weight gain 2.2 kg (*P*=0.08)

Author, Year Quality	Country Setting	Study design	Race/ ethnicity	Concurrent hypoglycemic treatment	Inclusion criteria Exclusion criteria	Mean age (SD) Gender	Baseline A1c (SD) Weight (SD) or BMI (SD)	A1c outcomes	Adverse events and tolerability
Choi D 2004 (Observational study)	Korea Single center	RCT	Korean	Combined therapy with a variety of hypoglycemic agents used by both groups (SU, metformin, α-glucosidase inhibitor, or insulin); % son each drug not specified	95 previously-treated diabetics who had recent acute MI or stable or unstable angina and underwent coronary stent implantation at a Korean university hospital Exclusion criteria: prior treatment with TZDs, ejection fraction <35%, liver or renal disease, pregnancy, reference vessel diameter <2.75mm	59.9 (9.3) yr 30%	7.72% (1.13%) 68.1 (11.0) kg 24.8 (3.35) kg/m^2	6 months: Intervention change: -0.61 (1.15) Control change: -0.75 (1.07)	"No patient had significant side effects, such as an elevation in the liver enzyme levels."
Honisett, S 2003 Poor	Australia NR	RCT, PC, DB	NR	80% continued their use of metformin, SU, or both	Women, diagnosed with DM2 1-12 years prior to study; all postmenopausal Exclusion criteria: none reported	NR 100% female	NR NR	A1c change at 12 weeks: -1.2%, *P*=0.001	No AEs were reported to the investigators
Jones, T 2003 Fair	USA NR	RCT, PC, open-label	NR	Added to metformin	Patients of non-child-bearing potential, aged 40-80 years, diagnosed with DM2, fasting C-peptide >0.8 ng/ml at screening, maintaining a FPG level (between >140 mg/dL- <300 mg/dL) prior to randomization Exclusion criteria: patients with clinically significant renal or hepatic disease, angina, cardiac insufficiency, symptomatic diabetic neuropathy, significant clinical abnormality on ECG, history of chronic insulin therapy, participation in any previous rosi-related study	59.9 (NR) yr 32% female	8.83% (NR) 28.2 kg/m2	BMI<25: Rosi 8 mg+metformin -0.3; metformin alone 0.3 BMI 25-30: Rosi 8 mg+ metformin: -0.7; metformin alone 0.1 BMI >30: Rosi: 8 mg+ metformin -1.0; metformin alone 0.2 Data from graphs, exact values NR rosi vs. metformin *P*<0.025 for all 3 groups	AE profile not different between normal weight, overweight, and obese

Author, Year Quality	Country Setting	Study design	Race/ ethnicity	Concurrent hypoglycemic treatment	Inclusion criteria Exclusion criteria	Mean age (SD) Gender	Baseline A1c (SD) Weight (SD) or BMI (SD)	A1c outcomes	Adverse events and tolerability
Kreider M 2002 NA (based on 8 other studies, primary data not available)	USA Multicenter	Secondary data: 8 studies, either PC or AC, DB	% White: <70years: 79% >70years: 91%	Monotherapy, elderly	DM2, FPG varied among studies, range 7.8-16.9 mmol/l; age varied, range 30-80y; BMI 22-38 kg/m2 Patients stratified by < or >=70y Efficacy data pooled from 3 monotherapy studies of 26w duration Significant renal disease; angina or cardiac insufficiency, symptomatic diabetic neuropathy, hepatic disease, history of diabetic ketoacidosis, history of chronic insulin use, other serious major illness	<70 years: 56 >70 years: 73 37% female	<70 years: Rosi: 8.8% (1.5%); placebo 9.0% (1.7%) >70 years: rosi: 8.6% (1.4%); placebo 8.9% (1.5%) BMI: <70 years: Rosi: 29.8 (4.1) kg/m^2; placebo 29.8 (4.2) kg/m^2 >70 years: Rosi: 28.3 (3.9) kg/m^2; placebo 28.4 (4.1) kg/m^2	A1c at 26 weeks <70 years: Rosi 4 mg daily: -0.2; 8 mg daily -0.5; placebo 0.8 >70 years: Rosi 4 mg daily: -0.1; 8 mg daily: -0.4; placebo 1.0 NSD between the 2 age groups	Hypoglycemic episodes occurred in <1% on ROSI in either age group; 2 patients <70y in Rosi group discontinued treatment because of hypoglycemia
Vongthavaravat V., 2002 Fair	Various Asia and South AmericaMulticenter	RCT, no-treatment control, open-label	White (38.3%); Black (3.0%); Asian (57.5%); Other (1.2%)	Added to SU	Patients with DM2 (as defined by the National Diabetes Data group criteria) who had been receiving SU therapy (glibenclamide, glipizide, gliclazide, chlorpropamide, tolbutamide, or glimepiride) for at least 6 months and if SU dose had been constant for at least 2 months before the screening visit; between 40 and 80 years of age and FPG 126 to 270 mg/dl at screening.Exclusion criteria: Significant renal or hepatic impairment, hypertension, anemia, abnormal blood cell counts or hypertension;	56.0 (NR) yr 56% female	NR 68.9 kg 27.1 kg/m^2	A1c change at 26 weeks:Rosi+SU: -1.1(95% CI -1.37, -0.89); SU control: 0.1(-0.1-0.2)	Hypoglycemia (%)Rosi+SU: 11.6; SU control: 1.2 (*P*<0.001) Serious AE (%): Rosi+SU: 2.4; SU control: 5.3

Author, Year Quality	Country Setting	Study design	Race/ ethnicity	Concurrent hypoglycemic treatment	Inclusion criteria Exclusion criteria	Mean age (SD) Gender	Baseline A1c (SD) Weight (SD) or BMI (SD)	A1c outcomes	Adverse events and tolerability
					severe angina, coronary insufficiency, heart failure, EKG evidence of left ventricular hypertrophy; patients requiring insulin or who had taken investigational drugs within 30 days of screening.				
Wang G., 2005 Fair	China Single center	RCT, no-treatment control, open-label	Chinese (assumed)	Monotherapy	Aged 50 to 73, with a diagnosis of coronary artery disease (>50% stenosis as proven on angiography) and established DM2 Exclusion criteria: Acute MI during the preceding 12 weeks, cardiac insufficiency, renal function impairment, liver function impairment, systemic inflammatory disease, infectious disease, cancer, or a serious illness that would affect participation; insulin treatment.	61.2 (8.6) yr 18% female	7.33% (0.17%) 25.6 (2.7) kg/m^2	Change in A1c reported graphically only (difficult to interpret) Rosi: decreased at 6m compared to control group (P<0.05)	Weight gain: NSD from baseline level and from control group (data not provided)

Author, Year Quality	Country Setting	Study design	Race/ ethnicity	Concurrent hypoglycemic treatment	Inclusion criteria Exclusion criteria	Mean age (SD) Gender	Baseline A1c (SD) Weight (SD) or BMI (SD)	A1c outcomes	Adverse events and tolerability
Wang, T 2004 (Metabolic syndrome only) Fair	Taiwan Multicenter	RCT, PC, open-label	Chinese (assumed)	Monotherapy	Presence of metabolic syndrome and meet at least of the following 3 criteria: waist circumference of >90 cm in men and >80 cm in women, serum TG > 150 mg/dl, HDL <40 mg/dl in men and <50 mg/dl in women, IFG 110-125 mg/dl, BP >130/85 mm Hg or treated hypertension. Exclusion criteria: Patients with acute coronary events, stroke or coronary revascularization within the preceding 3 months; diabetes mellitus according to the criteria of the American Diabetes Association, overt liver disease, chronic renal failure, hypothyroidism, myopathy alcohol/drug abuse, several other significant diseases, use of other lipid-lowering therapy, immunosuppressants, erythromycin, hormone replacement therapy.	59.5 (NR) y 42% female	NR 25.4 (NR) kg/m^2	A1c NR FPG: NSD within or between groups (*P*>0.05)	AEs reported as none

Author, Year Quality	Country Setting	Study design	Race/ ethnicity	Concurrent hypoglycemic treatment	Inclusion criteria Exclusion criteria	Mean age (SD) Gender	Baseline A1c (SD) Weight (SD) or BMI (SD)	A1c outcomes	Adverse events and tolerability
Pioglitazone and rosiglitazone									
Manley HJ 2003 Fair (Cohort study)	USA Single Center	Retrospective cohort	NR	Combined therapy, various	Chart review of patients receiving hemodialysis at a US clinic who were prescribed either rosi or pio from 4/2001 to 5/2002 Diabetes was the cause of ESRD in 92.5% Exclusion criteria: none reported	64.8 (11.5) yr Range: 46-85 yr 35% female	8.6% (2.2%) NR	Comparison of rosi to pio: interdialytic weight change Rosi: 3.6 kg at baseline and 3.97 at 3m follow-up (*P*= 0.0032); hematocrit: Rosi 34.89 at baseline and 34.0 at follow-up; data not provided for pio, but difference between pio and rosi for these 2 variables was reported as significant, but NR direction of pio effects compared to rosi	No data provided on AEs.

Abbreviations: AE, adverse event; DB, double blind; MI, myocardial infarction; NR, not recorded; NSD, no significant difference; NYHA, New York Heart Association; PC, placebo-controlled; pio, pioglitazone; RCT, randomized controlled trial; rosi, rosiglitazone; SU, sulfonylurea.

CONCLUSIONS

Table 20 summarizes results of this review.

Table 20. Summary of the evidence by Key Question

Key question	Quality of evidence	Conclusion
Key Question 1: 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?	Good	**Pioglitazone compared to rosiglitazone:** Prior systematic reviews: - Both drugs appear to have similar effects on A1c, producing a decrease of approximately 1%, similar to the change produced with other oral agents (including metformin, glibenclamide, or glimepiride). 5 head-to-head studies demonstrated no significant difference between pioglitazone and rosiglitazone on A1c. - Indirect comparison demonstrated no difference between pioglitazone and rosiglitazone (difference: -0.13% (95% CI -0.41, 0.33)]. - In the longest duration pioglitazone trial (PROACTIVE, mean follow-up 34.5 months), both treatment groups optimized glycemic control with multiple oral agents. A1c change was -0.8% compared with baseline in the pioglitazone group; change ws -0.3% in the placebo groups. - In the RESULT study, A1c change was maintained at 2 years with rosiglitazone compared to placebo with both groups receiving glipizide Effect of both pioglitazone and rosiglitazone appears to be similar when used in either monotherapy or combination therapy. **TZDs compared to other oral hypoglycemic agents:** In a prior systematic review, 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 with repaglinide. One trial comparing pioglitazone to acarbose favored pioglitazone for A1c reduction.
Key Question 2: For persons with type 2 diabetes, do pioglitazone and rosiglitazone differ from	Insufficient	Data are not sufficient to determine the comparative effectiveness of pioglitazone and rosiglitazone on microvascular or macrovascular complications of diabetes as there are no head-

Key question	Quality of evidence	Conclusion
each other, from placebo, and from other oral hypoglycemic agents in their effects on macrovascular and microvascular complications, and mortality from diabetes?		to-head data and indirect data are sparse. There are also insufficient data to show that either pio or rosi improves macrovascular complications relative to other oral diabetes agents or to placebo treatment. There are no data on microvascular outcomes.
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 when used as monotherapy? b. when added to metformin?	Body of evidence is insufficient: - There are few studies examining the effect of Pio and Rosi in these populations on the outcomes of weight or abdominal obesity.	- It is not possible to conclude whether there is a difference in weight change between Pio and Rosi.
Key Question 4: For persons with pre-diabetes or the metabolic syndrome, do pioglitazone and rosiglitazone differ from one another or from placebo in delaying or preventing the occurrence of type 2 diabetes?	Insufficient for the comparison of pio to rosi Insufficient for comparisons of thiazolidinediones to other oral hypoglycemic agents Fair for rosiglitazone vs. Placebo	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. In a large, placebo-controlled trial (DREAM), the hazard ratio for risk of incident diabetes or death was 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 for new onset type 2 diabetes 0.38 (95% CI 0.33 to 0.44; *P*<0.0001). A smaller trial found a nonsignificant reduction in cases of new onset diabetes with rosiglitazone compared to placebo. (0% compared with 3.3%, *P*=0.08).
Key Question 5: **(NOT UPDATED)** 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?	Body of evidence is insufficient - Four fair-quality studies provided data relevant to this question.	- Data are insufficient to determine the comparative effectiveness of Pio and Rosi on cardiovascular risk factors among persons with prediabetes or the metabolic syndrome. - There were no data to address comparative effect on blood pressure. - One fair-quality head-to-head study demonstrated improved lipid levels with pioglitazone compared to rosiglitazone. - Data on both drugs from placebo-controlled trials showed mixed effects on lipid levels. - Data on the effect of Pio and Rosi on weight and abdominal obesity are few and, as noted above in Key Question 3, it is not possible to conclude if there is a difference between the two drugs for these two outcomes.
Key Question 6: For persons with type 2 diabetes what are the adverse events related to	Good to fair	Adverse events occurring with pioglitazone and rosiglitazone were similar in 3 head-to-head trials. Withdrawals due to adverse events did not differ

Key question	Quality of evidence	Conclusion
pioglitazone and rosiglitazone, and how do these differ from each other, from placebo, and from other oral hypoglycemic agents?		from placebo in trials of pioglitazone (difference from placebo 0%, 95% CI –2% to 2%) or rosiglitazone (–1%, 95% CI –3% to 0%). The incidence of edema was greater for pioglitazaone and rosiglitazone than for placebo, with pooled risk differences from placebo of 4% for pioglitazone (95% CI 2% to 7%) and 8% for rosiglitazone (95% CI 3% to 13%).
Key Question 7 (NOT UPDATED): How do thiazolidinediones compare to sulfonylureas in serious hypoglycemic events, functional status, and quality of life?	Body of evidence is insufficient - Four fair-quality studies were identified relevant to hypoglycemia and sulfonylureas - There were no comparative data on functional status or quality of life from any efficacy or effectiveness trial which compared thiazolidinediones and sulfonylureas.	Hypoglycemia: Pioglitazone - 1 fair-quality study reported significantly fewer hypoglycemic events with Pio than with a sulfonylurea ($P<0.05$). - Severe hypoglycemic episodes were not reported in any patient taking pioglitazone. Rosiglitazone - The incidence of hypoglycemia was variable compared to a sulfonylurea (4 studies). - Combination therapy (Rosi + various sulfonylureas or Rosi + glibenclamide) increased rates of hypoglycemia over sulfonylurea monotherapy (2 studies). Functional status and quality of life - No evidence upon which to draw conclusions
Key Question 8: Are there subgroups of persons with type 2 diabetes based on demographic characteristics or comorbidities for which the benefits and adverse effects of pioglitazone or rosiglitazone differ from those in general populations, compared to each other an to other hypoglycemic agents?	Fair for demographic characteristics Poor for comorbidities and other characteristics	Demographic characteristics - The vast majority of studies were conducted in the United States or in Western Europe and examined Caucasian populations. - Indirect evidence suggests that Pio and Rosi are equally effective among minority populations. - No conclusions can be drawn as to which drug is more efficacious or effective, or associated with fewer side effects in population subgroups including olderaged persons. - Analysis of secondary data suggest that both Pio and Rosi monotherapy are well-tolerated in older adults. Comorbidities and other characteristics - No conclusions can be drawn on the comparative effectiveness of the 2 drugs under review among populations with significant comorbidities.

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234. Jun JK, Gong WC, Mathur R. Effects of pioglitazone on diabetes-related outcomes in Hispanic patients. *Am J Health Syst Pharm.* 2003;60(5):469-473.
235. Chan NN, Tong PC, So WY, Leung WY, Chiu CK, Chan JC. The metabolic effects of insulin and rosiglitazone combination therapy in Chinese type 2 diabetic patients with nephropathy. *Med Sci Mon.* 2004;10(3):PI44-48.
236. Manley HJ, Allcock NM. Thiazolidinedione safety and efficacy in ambulatory patients receiving hemodialysis. *Pharmacotherapy.* 2003;23(7):861-865.
237. Sourij H, Zweiker R, Wascher TC. Effects of pioglitazone on endothelial function, insulin sensitivity, and glucose control in subjects with coronary artery disease and new-onset type 2 diabetes. *Diabetes Care.* 2006;29(5):1039-1045.

Appendix A. Search strategies for update 1

Database: Ovid MEDLINE(R) <1996 to October Week 5 2007>

Search Strategy: (duplicate)

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1 exp THIAZOLIDINEDIONES/ (4461)

2 Pioglitazone.mp. (1409)

3 Rosiglitazone.mp. (1989)

4 THIAZOLIDINEDIONE$.mp. (5176)

5 1 or 2 or 3 or 4 (5482)

6 exp Diabetes Mellitus/dt [Drug Therapy] (17188)

7 5 and 6 (1694)

8 limit 7 to english language (1468)

9 limit 8 to (clinical trial or evaluation studies or guideline or meta analysis) (287)

10 exp Epidemiologic Studies/ (634578)

11 Comparative Study/ (0)

12 exp Evaluation Studies/ (326058)

13 10 or 11 or 12 (923686)

14 7 and 13 (382)

15 9 or 14 (609)

16 ((2006$ not (200601$ or 200602$)) or 2007$).ed. (1107381)

17 15 and 16 (165)

18 from 17 keep 1-165 (165)

Database: Ovid MEDLINE(R) <1996 to October Week 5 2007>

Search Strategy:

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1 exp THIAZOLIDINEDIONES/ (4461)

2 (Pioglitazone or Rosiglitazone or THIAZOLIDINEDIONE$).mp. (5482)

3 1 or 2 (5482)

4 exp Prediabetic State/ (513)

5 exp Metabolic Syndrome X/ (5599)

6 (pre-diabet$ or prediabet$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1271)

7 (metabolic adj syndrome$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (8462)

8 4 or 5 or 6 or 7 (9591)

9 3 and 8 (333)

10 limit 9 to english language (289)

11 ((2006$ not (200601$ or 200602$)) or 2007$).ed. (1107381)

12 10 and 11 (116)

13 from 12 keep 1-116 (116)

Database: Ovid MEDLINE(R) <1996 to October Week 5 2007>

Search Strategy:

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1 exp THIAZOLIDINEDIONES/ (4461)

2 (Pioglitazone or Rosiglitazone or THIAZOLIDINEDIONE$).mp. (5482)

3 1 or 2 (5482)

4 exp Hemoglobin A, Glycosylated/ or HbA1C.mp. or (hba adj 1c).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (10623)

5 3 and 4 (475)

6 ((2006$ not (200601$ or 200602$)) or 2007$).ed. (1107381)

7 5 and 6 (135)

8 from 7 keep 1-135 (135)

Database: Ovid MEDLINE(R) <1996 to October Week 5 2007>

Search Strategy:

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1 exp THIAZOLIDINEDIONES/ (4461)

2 (Rosiglitazone or Pioglitazone or THIAZOLIDINEDIONE$).mp. (5482)

3 exp Diabetic Angiopathies/ (13326)

4 1 and 3 (117)

5 (((vascula$ or macrovascula$ or microvascula$) adj3 (complicat$ or disease$ or damag$ or disorder$)) or angiopath$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (36059)

6 1 and 5 (228)

7 4 or 6 (235)
8 limit 7 to english language (196)
9 ((2006$ not (200601$ or 200602$)) or 2007$).ed. (1107381)
10 8 and 9 (56)
11 from 10 keep 1-56 (56)

Database: Ovid MEDLINE(R) <1996 to October Week 5 2007>
Search Strategy:

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1 (Pioglitazone or Rosiglitazone or THIAZOLIDINEDIONE$).mp. (5482)
2 (ae or po or to or ct).fs. (552630)
3 1 and 2 (920)
4 limit 3 to (humans and english language) (719)
5 ((2006$ not (200601$ or 200602$)) or 2007$).ed. (1107381)
6 4 and 5 (234)
7 from 6 keep 1-234 (234)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2007>
Search Strategy:

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1 Pioglitazone.mp. (220)
2 Rosiglitazone.mp. (284)
3 THIAZOLIDINEDIONE$.mp. (549)
4 1 or 2 or 3 (622)
5 from 4 keep 1-622 (622)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <4th Quarter 2007>
Search Strategy:

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1 Pioglitazone.mp. (15)
2 Rosiglitazone.mp. (15)
3 THIAZOLIDINEDIONE$.mp. (17)

4 1 or 2 or 3 (22)
5 from 4 keep 1-22 (22)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2007>
Search Strategy:

1 Pioglitazone.mp. (6)
2 Rosiglitazone.mp. (6)
3 THIAZOLIDINEDIONE$.mp. (10)
4 1 or 2 or 3 (10)
5 from 4 keep 1-10 (10)

Appendix B. Excluded active-control trials

1. Aljabri, K., Kozak, S. E., Thompson, D. M. Addition of pioglitazone or bedtime insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: a prospective, randomized trial. Am. J. Med. 2004; 116 (4):230-5. Excluded due to wrong outcome.

2. Bakris G, Viberti G, Weston WM, Heise M, Porter LE, Freed MI. Rosiglitazone reduces urinary albumin excretion in type II diabetes. J Hum Hypertens 2003; 17 (1):7-12.

3. Ceriello, A., Johns, D., Widel, M., Eckland, D. J., Gilmore, K. J., Tan, M. H. Comparison of effect of pioglitazone with metformin or sulfonylurea (monotherapy and combination therapy) on postload glycemia and composite insulin sensitivity index during an oral glucose tolerance test in patients with type 2 diabetes. Diabetes Care 2005; 28 (2):266-72. Excluded due to wrong outcome.

4. Einhorn, D., Rendell, M., Rosenzweig, J., Egan, J. W., Mathisen, A. L., Schneider, R. L. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: A randomized, placebo-controlled study. Clin. Ther. 2000; 22 (12):1395-409. Excluded due to wrong outcome.

5. Goke, B., German Pioglitazone Study, G. Improved glycemic control and lipid profile in a randomized study of pioglitazone compared with acarbose in patients with type 2 diabetes mellitus. Treatments in Endocrinology 2002; 1 (5):329-36. Excluded due to wrong outcome.

6. Jovanovic, L., Hassman, D. R., Gooch, B., Jain, R., Greco, S., Khutoryansky, N., Hale, P. M. Treatment of type 2 diabetes with a combination regimen of repaglinide plus pioglitazone. Diabetes Res Clin Pract 2004; 63 (2):127-34. Excluded due to wrong publication type.

7. Lawrence, J. M., Reid, J., Taylor, G. J., Stirling, C., Reckless, J. P. Favorable effects of pioglitazone and metformin compared with gliclazide on lipoprotein subfractions in overweight patients with early type 2 diabetes. Diabetes Care 2004; 27 (1):41-6. Excluded due to wrong outcome.

8. McCluskey, D., Touger, M. S., Melis, R., Schleusener, D. S., McCluskey, D. Results of a randomized, double-blind, placebo-controlled study administering glimepiride to patients with type 2 diabetes mellitus inadequately controlled with rosiglitazone monotherapy. Clin. Ther. 2004; 26 (11):1783-90. Excluded due to wrong outcome.

9. Nagasaka, S., Abe, T., Kawakami, A., Kusaka, I., Nakamura, T., Ishikawa, S., Saito, T., Ishibashi, S. Pioglitazone-induced hepatic injury in a patient previously receiving troglitazone with success. Diabet Med 2002; 19 (4):347-8. Excluded due to wrong study design.

10. Nakamura, T., Ushiyama, C., Osada, S., Shimada, N., Ebihara, I., Koide, H. Effect of pioglitazone on dyslipidemia in hemodialysis patients with type 2 diabetes. Ren. Fail. 2001; 23 (6):863-4. Excluded due to wrong outcome.

11. Pavo, I., Jermendy, G., Varkonyi, T. T., Kerenyi, Z., Gyimesi, A., Shoustov, S., Shestakova, M., Herz, M., Johns, D., Schluchter, B. J., Festa, A., Tan, M. H. Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes. J Clin Endocrinol Metab 2003; 88 (4):1637-45. Excluded due to wrong outcome.

12. Poulsen, M. K., Henriksen, J. E., Hother-Nielsen, O., Beck-Nielsen, H. The combined effect of triple therapy with rosiglitazone, metformin, and insulin aspart in type 2 diabetic patients. Diabetes Care 2003; 26 (12):3273-9. Excluded due to wrong outcome.

13. Ramachandran, A., Snehalatha, C., Salini, J., Vijay, V. Use of glimepiride and insulin sensitizers in the treatment of type 2 diabetes--a study in Indians. J. Assoc. Physicians India 2004; 52:459-63. Excluded due to wrong outcome.

14. Tan, M. H., Johns, D., Glazer, N. B. Pioglitazone reduces atherogenic index of plasma in patients with type 2 diabetes. Clin.Chem. 2004; 50 (7):1184-8. Excluded due to wrong outcome.

15. Tan MH, Baksi A, Krahulec B, et al. Comparison of pioglitazone and gliclazide in sustaining glycemic control over 2 years in patients with type 2 diabetes. *Diabetes Care.* Mar 2005;28(3):544-550.

16. Tiikkainen, M., Hakkinen, A. M., Korsheninnikova, E., Nyman, T., Makimattila, S., Yki-Jarvinen, H. Effects of rosiglitazone and metformin on liver fat content, hepatic insulin resistance, insulin clearance, and gene expression in adipose tissue in patients with type 2 diabetes. Diabetes 2004; 53 (8):2169-76. Excluded due to wrong outcome.

17. Viberti, G., Kahn, S. E., Greene, D. A., Herman, W. H., Zinman, B., Holman, R. R., Haffner, S. M., Levy, D., Lachin, J. M., Berry, R. A., Heise, M. A., Jones, N. P., Freed, M. I. A diabetes outcome progression trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. Diabetes Care 2002; 25 (10):1737-43. Excluded due to wrong outcome.

18. Watanabe, I., Tani, S., Anazawa, T., Kushiro, T., Kanmatsuse, K. Effect of pioglitazone on arteriosclerosis in comparison with that of glibenclamide. Diabetes Res Clin Pract 2005; 68 (2):104-10. Excluded due to wrong outcome.

19. Yang, J., Di, F., He, R., Zhu, X., Wang, D., Yang, M., Wang, Y., Yuan, S., Chen, J. Effect of addition of low-dose rosiglitazone to sulphonylurea therapy on glycemic control in type 2 diabetic patients. Chin.Med. J. 2003; 116 (5):785-7. Excluded due to

wrong publication type.

20. Yosefy, C., Magen, E., Kiselevich, A., Priluk, R., London, D., Volchek, L., Viskoper, R. J., Jr. Rosiglitazone improves, while Glibenclamide worsens blood pressure control in treated hypertensive diabetic and dyslipidemic subjects via modulation of insulin resistance and sympathetic activity. J. Cardiovasc. Pharmacol. 2004; 44 (2):215-22. Excluded due to wrong outcome.

Appendix C. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

Study quality is objectively assessed using predetermined criteria for internal validity, based on the combination of the US Preventive Services Task Force and the NNS Center for Reviews and Dissemination criteria.

Regardless of design, all studies that are included are assessed for quality and assigned a rating of "good," "fair," or "poor," Studies with fatal flaws are rated poor quality. A fatal flaw is failure to meet combinations of criteria which may be related in indicating the presence of bias. An example would be inadequate procedure for randomization or allocation concealment combined with important differences in prognostic factors at baseline. Studies that meet all criteria are rated good quality, and the remainder is rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are likely to be valid, while others are only probably valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs.

Systematic Reviews

1. Does the review report a clear review question and inclusion/exclusion criteria that relate to the primary studies? A good-quality review should focus on a well-defined question or set of questions, which ideally are reflected in the inclusion/exclusion criteria, which guide the decision of whether to include or exclude specific primary studies. The criteria should relate to the 4 components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, such as how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

If details of electronic database searches and other identification strategies are given, the answer to this question usually is yes. Ideally, details of the search terms, date, and language restrictions should be presented. In addition, descriptions of hand searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only MEDLINE was searched for a review looking at health education, then it is unlikely that all relevant studies were located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (for example, how randomization was done, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use a published checklist or scale or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (how many reviewers were

involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgment on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results, and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (for example, according to sample size or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Controlled Trials

Assessment of Internal Validity

1. Was assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, dates of birth, or days of week
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially numbered identical containers
        - On-site computer-based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:
        - Use of alternation, case record numbers, dates of birth, or days of week
        - Open random numbers lists

Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of follow-up? (Give numbers at each stage of attrition.)

Non-randomized studies

Assessment of Internal Validity

1. Was the selection of patients for inclusion unbiased; that is, was any group of patients systematically excluded?

2. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)

3. Were the investigated events specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there unbiased and accurate ascertainment of events (independent ascertainers, validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of follow-up correlate with reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

5. What was the funding source and role of funder(s) in the study?

References:

Anonymous (2001). Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews CRD Report Number 4 (2nd edition). York, UK, NHS Centre for Reviews and Dissemination.

Harris, R. P., M. Helfand, et al. (2001). "Current methods of the third U.S. Preventive Services Task Force." American Journal of Preventive Medicine **20**(3S): 21-35.

Appendix D. Excluded papers

160 papers were excluded after reviewing the full-text of the paper. Exclusion codes are shown below:

Codes:
1 = Foreign language
2 = Other outcome
3 = Wrong drug (including combination therapy)
4 = Wrong population
5 = Wrong publication type (letter, editorial, non-systematic review, case report, case series <10 patients)
6 = Wrong design (including placebo trials ≤ 3 months' duration, dose-ranging study, pharmacokinetics, single-dose study, drug interaction)
7 = cannot find the study
8 = duplicated study
AO = abstract only

Studies	Code
Aljabri, K., Kozak, S.E., Thompson, D.M. Addition of pioglitazone or bedtime insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: a prospective, randomized trial. Am. J. Med. 2004; 116 (4):230-5.	2
Al-Salman, J., Arjomand, H., Kemp, D. G., Mittal, M. Hepatocellular injury in a patient receiving rosiglitazone. A case report. Ann. Intern. Med. 2000; 132 (2):121-4.	5
Alsheikh-Ali, A. A., Abourjaily, H. M., Karas, R. H. Risk of adverse events with concomitant use of atorvastatin or simvastatin and glucose-lowering drugs (thiazolidinediones, metformin, sulfonylurea, insulin, and acarbose). Am J Cardiol 2002; 89 (11):1308-10.	6
Alsheikh-Ali, A. A., Karas, R. H. Adverse events with concomitant use of simvastatin or atorvastatin and thiazolidinediones. Am J Cardiol 2004; 93 (11):1417-8.	6
Anderson Jr, D. C. Pharmacologic prevention or delay of type 2 diabetes mellitus. Ann. Pharmacother. 2005; 39 (1):102-9.	5
Angelo, J. B., Huang, J., Carden, D. Diabetes prevention: A review of current literature. Advanced Studies in Medicine 2005; 5 (5):250-9.	5
Anonymous. Improved risk profile with pioglitazone. Br J Diabetes Vasc Dis 2003; 3:446.	5
Anonymous. Inhaled insulin superior to rosiglitazone in patients with uncontrolled type 2 diabetes. Formulary 2003; 38:408.	5
Anonymous. Insulin sensitizer has favorable effects on blood pressure, lipids. Formulary 2004; 39:346.	5
Anonymous. Lipid effects of pioglitazone studied. Br J Diabetes Vasc Dis 2004; 4:209.	5
Asnani, S., Richard, B. C., Desouza, C., Fonseca, V. Is weight loss possible in patients treated with thiazolidinediones? Experience with a low-calorie diet. Curr Med Res Opin 2003; 19 (7):609-13.	6
Baba, S. Pioglitazone: a review of Japanese clinical studies. Curr Med Res Opin. 17 (3):166-89.	2

Baba, T., Shimada, K., Neugebauer, S., Yamada, D., Hashimoto, S., Watanabe, T. The oral insulin sensitizer, thiazolidinedione, increases plasma vascular endothelial growth factor in type 2 diabetic patients. Diabetes Care 2001; 24 (5):953-4.	5
Bailey, C. J., Day, C. Antidiabetic drugs. Br J Cardiol 2003; 10 (2):128-36.	5
Bajaj, M., Suraamornkul, S., Piper, P., Hardies, L. J., Glass, L., Cersosimo, E., Pratipanawatr, T., Miyazaki, Y., DeFronzo, R. A. Decreased plasma adiponectin concentrations are closely related to hepatic fat content and hepatic insulin resistance in pioglitazone-treated type 2 diabetic patients. J Clin Endocrinol Metab 2004; 89 (1):200-6.	6
Bajaj, M., Suraamornkul, S., Pratipanawatr, T., Hardies, L. J., Pratipanawatr, W., Glass, L., Cersosimo, E., Miyazaki, Y., DeFronzo, R. A. Pioglitazone reduces hepatic fat content and augments splanchnic glucose uptake in patients with type 2 diabetes. Diabetes 2003; 52 (6):1364-70.	5
Bakris, G., Viberti, G., Weston, W. M., Heise, M., Porter, L. E., Freed, M. I. Rosiglitazone reduces urinary albumin excretion in type II diabetes. J Hum Hypertens 2003; 17 (1):7-12.	2
Baksi, A., James, R. E., Zhou, B., Nolan, J. J. Comparison of uptitration of gliclazide with the addition of rosiglitazone to gliclazide in patients with type 2 diabetes inadequately controlled on half-maximal doses of a sulphonylurea. Acta Diabetol. 2004; 41 (2):63-9.	2
Balkrishnan, R., Rajagopalan, R., Shenolikar, R. A., Camacho, F. T., Whitmire, J. T., Anderson, R. T. Healthcare costs and prescription adherence with introduction of thiazolidinedione therapy in Medicaid type 2 diabetic patients: a retrospective data analysis. Curr Med Res Opin. 20 (10):1633-40.	2
Belcher, G., Matthews, D. R. Safety and tolerability of pioglitazone. Exp Clin Endocrinol Diabetes 2000; 108 (Suppliment 2):S267-S73.	2
Bell, D. S., Ovalle, F. How long can insulin therapy be avoided in the patient with type 2 diabetes mellitus by use of a combination of metformin and a sulfonylurea? Endocrine Practice 2000; 6 (4):293-5.	3
Bell, D. S., Ovalle, F. Outcomes of initiation of therapy with once-daily combination of a thiazolidinedione and a biguanide at an early stage of type 2 diabetes. Diabetes Obes Metab 2004; 6 (5):363-6.	6
Bell, D. S. H. Management of type 2 diabetes with thiazolidinediones: Link between (beta)-cell preservation and durability of response. Endocrinologist 2004; 14 (5):293-9.	5
Bell, D. S. H., Ovalle, F. Long-term efficacy of triple oral therapy for type 2 diabetes mellitus. Endocr Pract 2002; 8 (4):271-5.	2
Bell, D. S. H., Ovalle, F. Tissue triglyceride levels in type 2 diabetes and the role of thiazolidinediones in reversing the effects of tissue hypertriglyceridemia: Review of the evidence in animals and humans. Endocr Pract 2001; 7 (2):135-8.	6
Berry, P. Severe congestive cardiac failure and ischaemic hepatitis associated with rosiglitazone. Practical Diabetes International 2004; 21 (5):199-200.	6
Bertoni, A. G. Achieving control of diabetic risk factors in primary care settings. Am J Manag Care 2001; 7 (4):411-21.	5
Bloomgarden, Z. T. Definitions of the Insulin Resistance Syndrome: The 1st World Congress on the Insulin Resistance Syndrome. Diabetes Care 2004; 27 (3):824-30.	5
Bloomgarden, Z. T. Dyslipidemia and the metabolic syndrome. Diabetes Care 2004; 27 (12):3009-16.	5
Bluher, M., Lubben, G., Paschke, R. Analysis of the relationship between the Pro12Ala variant in the PPAR-gamma2 gene and the response rate to therapy with pioglitazone in patients with type 2 diabetes. Diabetes Care	5

2003; 26 (3):825-31.	
Bonkovsky, H. L., Azar, R., Bird, S., Szabo, G., Banner, B. Severe cholestatic hepatitis caused by thiazolidinediones: risks associated with substituting rosiglitazone for troglitazone. Dig Dis Sci 2002; 47 (7):1632-7.	6
Bragg, T. Rosiglitazone and type 2 diabetes mellitus Lancet 2001; 357:1451.	5
Bruun, J. M., Pedersen, S. B., Richelsen, B. Interleukin-8 production in human adipose tissue. Inhibitory effects of anti-diabetic compounds, the thiazolidinedione Ciglitazone and the biguanide Metformin. Horm Metab Res 2000; 32 (11-12):537-41.	3
Buchanan, T. A. Pancreatic beta-cell loss and preservation in type 2 diabetes. Clin.Ther. 2003; 25 (Suppl. B):B32-B46.	2
Burk, M., Morreale, A. P., Cunningham, F. Conversion from troglitazone to rosiglitazone or pioglitazone in the VA: A multicenter DUE. Formulary 2004; 39 (6):310-7.	6
Ceriello, A., Johns, D., Widel, M., Eckland, D. J., Gilmore, K. J., Tan, M. H. Comparison of effect of pioglitazone with metformin or sulfonylurea (monotherapy and combination therapy) on postload glycemia and composite insulin sensitivity index during an oral glucose tolerance test in patients with type 2 diabetes. Diabetes Care 2005; 28 (2):266-72.	2
Chan, K. A., Truman, A., Gurwitz, J. H., Hurley, J. S., Martinson, B., Platt, R., Everhart, J. E., Moseley, R. H., Terrault, N., Ackerson, L., Selby, J. V. A cohort study of the incidence of serious acute liver injury in diabetic patients treated with hypoglycemic agents. Arch. Intern. Med. 2003; 163 (6):728-34.	6
Chase, M. P., Yarze, J. C. Pioglitazone-associated fulminant hepatic failure. Am. J. Gastroenterol. 2002; 97 (2):502-3.	6
Cheng, A. Y., Fantus, I. G. Thiazolidinedione-induced congestive heart failure. Ann. Pharmacother. 2004; 38 (5):817-20.	6
Chitturi, S., George, J. Hepatotoxicity of commonly used drugs: nonsteroidal anti-inflammatory drugs, antihypertensives, antidiabetic agents, anticonvulsants, lipid-lowering agents, psychotropic drugs. Semin. Liver Dis. 2002; 22 (2):169-83.	5
Cluxton, R. J., Jr., Li, Z., Heaton, P. C., Weiss, S. R., Zuckerman, I. H., Moomaw, C. J., Hsu, V. D., Rodriguez, E. M. Impact of regulatory labeling for troglitazone and rosiglitazone on hepatic enzyme monitoring compliance: findings from the state of Ohio Medicaid program. Pharmacoepidemiology & Drug Safety 2005; 14 (1):1-9.	5
Dandona, P., Aljada, A., Chaudhuri, A. Vascular reactivity and thiazolidinediones. Am. J. Med. 2003; 115 Suppl 8A:81S-6S.	2
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Excluded papers Update 1

41 papers were excluded after reviewing full text of the paper.

Excluded Studies	Code
Bailey CJ, Bagdonas A, Rubes J, et al. Rosiglitazone/metformin fixed-dose combination compared with uptitrated metformin alone in type 2 diabetes mellitus: a 24-week, multicenter, randomized, double-blind, parallel-group study. Clin Ther. Oct 2005;27(10):1548-1561.	3
Berhanu P, Kipnes MS, Khan MA, et al. Effects of pioglitazone on lipid and lipoprotein profiles in patients with type 2 diabetes and dyslipidaemia after treatment conversion from rosiglitazone while continuing stable statin therapy.[erratum appears in Diab Vasc Dis Res. 2006 Sep;3(2):71]. Diabetes & Vascular Disease Research. May 2006;3(1):39-44.	6
Cao Z, Zhou YJ, Zhao YX, Liu YY, Guo YH, Cheng WJ. Rosiglitazone could improve clinical outcomes after coronary stent implantation in nondiabetic patients with metabolic syndrome. Chin Med J. 2006;119(14):1171-1175.	2
Cobitz A, Zambanini A, Sowell M, al. e. A retrospective evaluation of congestive heart failure and myocardial ischemia events in 14 237 patients with type 2 diabetes mellitus enrolled in 42 short-term, double-blind, randomized clinical studies with rosiglitazone. . Pharmacoepidemiology & Drug Safety. 2008;17:769-781.	6
Colucciello M. Vision loss due to macular edema induced by rosiglitazone treatment of diabetes mellitus. Arch Ophthalmol. Sep 2005;123(9):1273-1275.	5
Dagdelen S, Gedik O. Rosiglitazone-associated pseudotumour cerebri. Diabetologia. Jan 2006;49(1):207-208.	5
Davidson JA, Perez A, Zhang J, The Pioglitazone 343 Study G. Addition of	6

Excluded Studies	Code
pioglitazone to stable insulin therapy in patients with poorly controlled type 2 diabetes: results of a double-blind, multicentre, randomized study. Diabetes Obes Metab. 2006;8(2):164-174.	
Esposito K, Ciotola M, Carleo D, et al. Effect of rosiglitazone on endothelial function and inflammatory markers in patients with the metabolic syndrome. Diabetes Care. 2006;29(5):1071-1076.	2
Feig DS, Briggs GG, Koren G. Oral antidiabetic agents in pregnancy and lactation: a paradigm shift? The Annals of pharmacotherapy. 2007;41(7):1174-1180.	5
Garg R, Gopal J, Jones GR. Rosiglitazone: safety and efficacy in combination with insulin in poorly controlled type 2 diabetes mellitus patients treated with insulin alone. Journal of diabetes and its complications. 2007;21(1):1-6.	6
Goldstein BJ, Weissman PN, Wooddell MJ, Waterhouse BR, Cobitz AR. Reductions in biomarkers of cardiovascular risk in type 2 diabetes with rosiglitazone added to metformin compared with dose escalation of metformin: an EMPIRE trial sub-study. Curr Med Res Opin. 2006;22(9):1715-1723.	3
Govindarajan R, Ratnasinghe L, Simmons DL, et al. Thiazolidinediones and the risk of lung, prostate, and colon cancer in patients with diabetes. J Clin Oncol. Apr 20 2007;25(12):1476-1481.	2
Hollander P, Yu D, Chou HS. Low-dose rosiglitazone in patients with insulin-requiring type 2 diabetes. Arch Intern Med. 2007;167(12):1284-1290.	6
Home PD, Bailey CJ, Donaldson J, Chen H, Stewart MW. A double-blind randomized study comparing the effects of continuing or not continuing rosiglitazone + metformin therapy when starting insulin therapy in people with Type 2 diabetes. Diabet Med. Jun 2007;24(6):618-625.	6
Investigators DT, Bosch J, Yusuf S, et al. Effect of ramipril on the incidence of diabetes. The New England journal of medicine. 2006;355(15):1551-1562.	3
Jacob AN, Salinas K, Adams-Huet B, Raskin P. Weight gain in type 2 diabetes mellitus. Diabetes Obes Metab. 2007;9(3):386-393.	3
Kendall C, Wooltorton E. Rosiglitazone (Avandia) and macular edema. CMAJ Canadian Medical Association Journal. Feb 28 2006;174(5):623.	5
Khan M, Murray FT, Karunaratne M, Perez A. Pioglitazone and reductions in post-challenge glucose levels in patients with type 2 diabetes. Diabetes Obes Metab. 2006;8(1):31-38.	2
Ko GT, Tsang PC, Wai HP, Kan EC, Chan HC. Rosiglitazone versus bedtime insulin in the treatment of patients with conventional oral antidiabetic drug failure: a 1-year randomized clinical trial. Advances in therapy. 2006;23(5):799-808.	6
Meymeh RH, Wooltorton E. Diabetes drug pioglitazone (Actos): risk of fracture. CMAJ Canadian Medical Association Journal. Sep 25 2007;177(7):723-724.	5
Nichols GA, Gomez-Caminero A. Weight changes following the initiation of new anti-hyperglycaemic therapies. Diabetes Obes Metab. Jan 2007;9(1):96-102.	6
Osei K, Gaillard T, Cook C, Kaplow J, Bullock M, Schuster D. Discrepancies in the regulation of plasma adiponectin and TNF-alpha levels and adipose tissue gene expression in obese African Americans with glucose intolerance: a pilot study using rosiglitazone. Ethnicity & Disease. 2005;15(4):641-648.	6
Raz I, Stranks S, Filipczak R, et al. Efficacy and safety of biphasic insulin aspart 30 combined with pioglitazone in type 2 diabetes poorly controlled on glibenclamide (glyburide) monotherapy or combination therapy: an 18-week, randomized, open-label study. Clin Ther. 2005;27(9):1432-1443.	6
Reynolds LR, Kingsley FJ, Karounos DG, Tannock LR. Differential effects of rosiglitazone and insulin glargine on inflammatory markers, glycemic control, and lipids in type 2 diabetes. Diabetes Res Clin Pract. 2007;77(2):180-187.	6
Riedel AA, Heien H, Wogen J, Plauschinat CA. Secondary failure of glycemic control for patients adding thiazolidinedione or sulfonylurea therapy to a	6

Excluded Studies	Code
metformin regimen. Am J Manag Care. Aug 2007;13(8):457-463.	
Riedel AA, Heien H, Wogen J, Plauschinat CA. Loss of glycemic control in patients with type 2 diabetes mellitus who were receiving initial metformin, sulfonylurea, or thiazolidinedione monotherapy. Pharmacotherapy. Aug 2007;27(8):1102-1110.	6
Roden M, Laakso M, Johns D, et al. Long-term effects of pioglitazone and metformin on insulin sensitivity in patients with Type 2 diabetes mellitus. Diabetic medicine : a journal of the British Diabetic Association. 2005;22(8):1101-1106.	8
Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. Diabetes Care. 2006;29(3):554-559.	6
Seber S, Ucak S, Basat O, Altuntas Y. The effect of dual PPAR alpha/gamma stimulation with combination of rosiglitazone and fenofibrate on metabolic parameters in type 2 diabetic patients. Diabetes Res Clin Pract. Jan 2006;71(1):52-58.	6
Sivagnanam G. Rosiglitazone and macular edema. CMAJ Canadian Medical Association Journal. Aug 1 2006;175(3):276.	5
Stewart MW, Cirkel DT, Furuseth K, et al. Effect of metformin plus roziglitazone compared with metformin alone on glycaemic control in well-controlled Type 2 diabetes. Diabetic medicine : a journal of the British Diabetic Association. 2006;23(10):1069-1078.	3
Strowig SM, Raskin P. The effect of rosiglitazone on overweight subjects with type 1 diabetes. Diabetes Care. 2005;28(7):1562-1567.	4
Tang WHW. Do thiazolidinediones cause heart failure? A critical review.[erratum appears in Cleve Clin J Med. 2006 Jun;73(6):588]. Cleveland Clinic Journal of Medicine. Apr 2006;73(4):390-397.	5
Tran MT, Navar MD, Davidson MB. Comparison of the glycemic effects of rosiglitazone and pioglitazone in triple oral therapy in type 2 diabetes. Diabetes Care. Jun 2006;29(6):1395-1396.	6
Triplitt C, Glass L, Miyazaki Y, et al. Comparison of glargine insulin versus rosiglitazone addition in poorly controlled type 2 diabetic patients on metformin plus sulfonylurea. Diabetes Care. Nov 2006;29(11):2371-2377.	6
Turk T, Pietruck F, Dolff S, et al. Repaglinide in the management of new-onset diabetes mellitus after renal transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2006;6(4):842-846.	3
Villanueva G, Baldwin D. Rosiglitazone therapy of posttransplant diabetes mellitus. Transplantation. Nov 27 2005;80(10):1402-1405.	6
Vinik AI, Zhang Q. Adding insulin glargine versus rosiglitazone: health-related quality-of-life impact in type 2 diabetes. Diabetes Care. 2007;30(4):795-800.	6
Weissman PN, Goldstein BJ, Rosenstock J, et al. Effects of rosiglitazone added to submaximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE Study. Curr Med Res Opin. 2005;21(12):2029-2035.	6
Xiang AH, Peters RK, Kjos SL, et al. Effect of pioglitazone on pancreatic beta-cell function and diabetes risk in Hispanic women with prior gestational diabetes. Diabetes. Feb 2006;55(2):517-522.	4
Yokoyama J, Sutoh N, Higuma T, et al. Efficacy and safety of low-dose pioglitazone after primary coronary angioplasty with the use of bare metal stent in patients with acute myocardial infarction and with type 2 diabetes mellitus or impaired glucose tolerance. Heart & Vessels. May 2007;22(3):146-151.	6

Appendix E. Systematic reviews identified for the update review

Author Year Quality	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients	Characteristics of identified articles: Study designs	Characteristics of identified articles: populations
Berlie 2007	To obtain a precise estimate of the odds for developing TZD-induced edema and to compare rates between pio and rosi and with various combinations of oral agents	Medline (1966-5/2006), CINHAL (1982-5/2006), Cochrane Control Trials Register (to 1st quarter 2006), EMBASE (1996-2005) "manual search for review articles and original manuscript" (no details) Abstracts; ADA, AHA, ACC (2003-present) Takeda and GlaxoSmithKline were contacted for studies in their new Drug Applications	Prospective, RCTS, active- or placebo-controlled; monotherapy or combined therapy; data on edema	26 RCTs 15,332 subjects with DM2	7/26 were open label trials	All subjects with DM2 Average age range across studies: 53.7 to 61.9y Average duration diabetes across studies: 5.6m to 13.6y Mean baseline A1c across studies 7.5 to 10.2% with pio and 7.9 to 9.1% with rosi

Appendix E. Systematic reviews identified for the update review

Author Year	Quality	Characteristics of identified articles: Interventions	Efficacy and effectiveness results	Subgroups	Adverse events	Comments
Berlie 2007		Total daily dosage (mg) Monotherapy-placebo trials: pio 7.5-45, rosi 4-8 Combination trials: pio 15-30; rosi 4-8	A1c mean reduction; 0.56 - 2.3%	None	Weight gain (kg): pio -0.59 3.86; rosi 1.2 to 5.0 Pooled OR: All included studies (pio and rosi, all comparators): 2.26(95% CI, 2.02 - 2.53), *P* <0.000001 Placebo-controlled pio compared with rosi, indirect comparisons: 3.03(95% CI, 2.15 - 3.91) TZD monotherapy placebo-controlled studies: 2.35 (95% CI, 1.40 - 3.91) TZD combination therapy placebo- or no-treatment control: 2.14 (95% CI, 1.88 - 2.43)	

Appendix E. Systematic reviews identified for the update review

Author Year Quality	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients	Characteristics of identified articles: Study designs	Characteristics of identified articles: populations
Bolen 2007 (and AHRQ 2007 Review)	To summarize the literature on the benefits and harms of oral agents in the treatment of adults with type 2 diabetes	Medline, EMBASE, Cochrane Central Register of Controlled Trials (inception to 1/2006); industry data and FDA web-site; hand search 15 journals, reviewed reference lists	English-language, assessed benefits and/or harms of oral diabetes drugs (excluding 1st generation SU) compared to other oral agents (not insulin)	RCTs: 216 Systematic reviews: 2	Intermediate outcomes: 135 RCTs and 1 systematic review Final health outcomes: Adverse events: 167 studies, 1/3 of which were RCTs; 2 systematic reviews	Adults with type 2 diabetes
Eurich 2007	To review literature on the association between antidiabetic agents and morbidity and mortality in people with heart failure and diabetes	Medline, Health-STAR, EMBASE, CINAHL, international Pharmaceutical Abstracts, Allied and Complementary Medicine, cochran Controlled Trials Register date of inception to 7/07 Manual search reference lists; contacted experts	Contemporaneous comparison group; examined association between antidiabetic agents and hospital admission or mortality	4 TZD trials 22,476 patients	Unclear from review; reviewing primary studies, 1 RCT and 3 cohort with comparison	Patients with diabetes and heart failure

Appendix E. Systematic reviews identified for the update review

Author Year Quality	Characteristics of identified articles: Interventions	Efficacy and effectiveness results	Subgroups	Adverse events	Comments
Bolen 2007 (and AHRQ 2007 Review)	Various dosages and combinations	A1c: decreased 1% which was similar to SU and metformin HDL: pio increased more than rosi (1-2 mg/dL); pio increased compared with metformin or SU (3-5 mg/dL) LDL: rosi increased LDL more than pio (10-15 mg/dL) Triglycerides: pio decreased (15-52 mg/dL) compared with rosi (increase 6-13 mg/dL); pio decreased more than metformin	Age, sex, comorbidities	Mortality: insufficient data CV D mortality: insufficient data CHF: risk is increased with TZDs compared with other oral agents Microvascular outcomes: insufficient data Weight: TZDs increased weight similar to SU (3kg) as monotherapy or in combination with other oral agents; TZDs increased weight compared with metformin, acarbose, and repaglinide Hypoglycemia: less frequent with TZDs than SU (risk difference 4-9%) Edema: TZDs higher risk than SU (absolute risk difference 2 to 21%) CHF: TZDs higher risk than with metformin or SU, absolute risks 0.8 to 3.6%; absolute risk difference 0.7 to 2.2%) Mild anemia: TZDs higher risk than other drugs (absolute risk difference 1 to 5%) Elevated ALT: low rates (<1%) with TZDs Hospitalizations for acute cholecystitis: pio 12 patients compared with placebo 1 patient (pooled, unpublished analysis of 1526 patients)	
Eurich 2007	TZD compared with a variety of comparators and placebo	NR	NR	Pooled OR for TZDs compared with other treatments for all cause mortality: 0.83 (95% CI, 0.71 - 0.97) Pooled OR for TZDs compared with other treatments on hospital admissions for heart failure 1.13 (95% CI, 0.1.04 - 1.22)	Pooled estimates included observational studies and RCTs AEs

Appendix E. Systematic reviews identified for the update review

Author Year Quality	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients	Characteristics of identified articles: Study designs	Characteristics of identified articles: populations
Lagu 2007	To examine the risk of heart failure and of cardiac death in patients given TZDs	Medline, Database of Abstracts of Reviews of Effects, Cochrane Library; up to 3/2007; start date NR; databases of European Society of Cardiology, AHA, ACC, ADA by hand; reference lists	RCTs, double-blind studies with risk estimates or frequency data for congestive heart failure and cardiovascular death	7 trials 20191 patients	RCTs only	Diabetes and prediabetes
Phatak, 2006	To examine factors affecting the size of A1c response to TZDs	PubMed, EBSCO, Sci-lit; dates NR GlaxoSmithKline public web-site	RCTs, English-language, placebo- and active-controlled	42 8322 subjects	RCTs only	Diabetes; mean age 57.5y; 42.3% female subjects; baseline A1c 8.9% (SD 0.8)

Appendix E. Systematic reviews identified for the update review

Author Year Quality	Characteristics of identified articles: Interventions	Efficacy and effectiveness results	Subgroups	Adverse events	Comments
Lagu 2007	TZD compared with a variety of comparators and placebo	NR	NR	Risk of CHF compared to controls (placebo- and active-controlled trials): RR 1.72 (95% CI, 1.21 - 2.42), *P* =0.002; placebo-controlled trials only: RR 1.97 (95% CI, 0.94 - 4.13); pio only: RR 1.32 (95% CI, 1.04 - 1.68); rosi only: RR 2.18 (95% CI, 1.44 - 3.32), *P* =0.0003 Risk of cardiovascular death compared to controls: RR 0.93 (95% CI, 0.67 - 1.29), *P* =0.68; placebo-controlled trials only: RR 1.08 (95% CI, 0.66 - 1.76): pio only: RR 1.01 (95% CI, 0.51 - 2.09); rosi only: RR 0.91 (95% CI, 0.63 - 1.3) Pio: Overall event rate for CHF: TZD 2.3%; comparator group 1.4% NNH for CHF 107 over 29.7m F/U; range 35 to 491	
Phatak, 2006	TZDs compared with a variety of comparators and placebo; 50% of studies were monotherapy; mean baseline A1c 9.1%(SD 1.0)	Weighted between-group change in A1c (all comparators) TZDs: -0.82% (SD 0.13) Pio: -1.04% (SD 0.07) Rosi: -0.67% (SD 0.10) Weighted between-group change in A1c for placebo-controlled trials: Pio: -1.03 (SD 0.19) Rosi: -0.98 (SD 0.18) Change in A1c greater with higher baseline A1c (>9.0%) (no statistics) Duration of study treatment correlated with decrease in A1c (*P* =0.003)	Study duration, age, sex duration therapy examined with meta-regression	NR	

Appendix E. Systematic reviews identified for the update review

Author Year Quality	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients	Characteristics of identified articles: Study designs	Characteristics of identified articles: populations
Riche, 2007	To evaluate the impact of TZDs on repeat TVR after PCI	Medline, EMBASE, CINAHL, Cochrane database; through 7/2006 (start date NR); English only; abstracts from AHA, ACC, ADA searched 2001 - 2006	RCTS evaluating TZDs compared with standards of care; ≥ 6m follow-up; data provided on repeat TVR with number of patients receiving repeat TVR reported	7 608 subjects	RCTs only; all placebo-controlled with comparator standard drug therapy	1/7 studies non-diabetic; 1/7 metabolic syndrome; 5/7 type 2 diabetes
Richter, 2007 (Rosi cochran)	To assess the effects of rosi in the treatment of type 2 diabetes	Medline, EMBASE, Cochrane database; last search 8/2006; reference lists searched	RCTs in adults with type 2 diabetes; study duration ≥ 24w	18 3888	RCTs only; various comparators	Type 2 diabetes, largely Caucasian populations; mostly persons on other oral hypoglycemic agents; mean age patients 47 - 61y; diabetes duration 4 - 9y; baseline A1c 6.8 - 9.5%, mean 8.8%

Appendix E. Systematic reviews identified for the update review

Author Year Quality	Characteristics of identified articles: Interventions	Efficacy and effectiveness results	Subgroups	Adverse events	Comments
Riche, 2007	Pio or rosi given at various dosages either 1-day pre-operatively or 1-2 weeks post-operatively	Repeat TVR RR Overall: range 0.13 to 0.67; pooled estimate 0.35 (95% CI, 0.22 - 0.57) Pio: 0.24 (95% CI, 0.11 - 0.51) Rosi: 0.45 (95% CI, 0.25 - 0.83) Diabetes: 0.34 (95% CI, 0.19 - 0.63) No diabetes: 0.37 (95% CI, 0.18 - 0.77)	Pio, rosi, diabetes, no diabetes	NR	
Richter, 2007 (Rosi cochran)	Rosi mono- or combined therapy at various dosages	Mortality: only reported by 1 study (ADOPT): 2.3% with rosi, 2.1% metformin, 2.2% glyburide A1c: similar reductions with rosi as metformin, glibenclamide, or glimepiride	NR	Edema: OR rosi compared with comparators, random effects model: 4.62 (95% CI, 2.28 - 9.38) Severe hypoglycemic episodes: somewhat lower with rosi than active monotherapy, particularly SU; no pooled data and no statistics From ADOPT trial only: CVD events: % serious/% total events: rosi 3.4/4.3; metformin 3.2/4.0; glyburide 1.8/ 2.8 CHF, total events (%): rosi 1.5, metformin 1.3, glyburide 0.6 Fracture rates: higher with rosi than; no statistics reported	

Appendix E. Systematic reviews identified for the update review

Author Year Quality	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients	Characteristics of identified articles: Study designs	Characteristics of identified articles: populations
Richter, 2006 (Pio cochran)	To assess the effects of pio in the treatment of type 2 diabetes	Medline, EMBASE, Cochrane database; last search 8/2006; reference lists searched	RCTs in adults with type 2 diabetes; study duration ≥ 24w	22 6200	RCTs only; various comparators	Type 2 diabetes, largely Caucasian populations; mostly persons on other oral hypoglycemic agents; mean age patients 53 - 63y; diabetes duration 3 - 14y; baseline A1c 7.4 - 10.3%
Rosmarakis, 2007	To review RCT evidence on the effect of TZDs on in-stent restenosis after PCI	PubMed, last search 6/2006; reference lists reviewed	RCTs examining TZDs compared with various comparators and effect on in-stent restenosis after coronary stent implantation; in English	5 235 (text states 259)	RCTs only; various comparators	4/5 studies diabetes; 1/5 non diabetes
Singh 2007 (Diabetes Care)	To evaluate the risk of CHF with TZDs in type 2 diabetes and to classify this AE under the dose-time-susceptibility system	RCTS: existing reviews; PubMed (1/2003 to 9/2006); manufacturer's web-site Controlled observational studies and case reports: PubMed (to 9/2006, start date NR); Web of Knowledge Cited References and PubMed related articles Case reports also: EMBASE, Google Scholar (to 9/2006, start date NR)	Controlled observational studies with data to calculate OR of new onset CHF in patients receiving TZDs compared with other oral agents Case reports with CHF and TZD	RCTs: 3 10,731 Observational studies: 4 67,382 Case reports: 162 case subjects	RCTs, observational studies, case reports	Prediabetes or diabetes

Appendix E. Systematic reviews identified for the update review

Author Year Quality	Characteristics of identified articles: Interventions	Efficacy and effectiveness results	Subgroups	Adverse events	Comments
Richter, 2006 (Pio cochran)	Pio mono- or combined therapy at various dosages	Mortality: only reported by 1 study (Proactive) as part of a composite endpoint (mortality, stroke, nonfatal MI, surgical vascular intervention: placebo-controlled, HR 0.90 (95% CI, 0.80 - 1.02) A1c: reductions similar to other oral agents	NR	7/22 trials reported AEs Overall and serious AEs comparable between intervention groups Hb: decrease noted in 6 studies examining this outcome: range 0.5 - 0.75 g/dL Weight: increased in 15 studies examining this outcome: up to 3.9kg Edema: RR 2.86 (95% CI, 1.14 - 3.18) Hypoglycemia episodes: Pio rates < SU rates; pio + insulin increased rates No pooled data and no statistics	
Rosmarakis, 2007	Pio or rosi; dosages and use of other oral agents NR; first dose of TZD given between 1d prior to procedure up to 2w after; 3/5 studies compared pio to standard treatment; 2/5 studies compared pio to rosi; all studies 6 month duration	Restenosis rate measured with quantitative coronary angiography at 6m: pio or rosi compared with standard therapy: OR 0.29 (95% CI, 0.15 - 0.56)	NR	Mortality: 2/259: 1 in control arm; 1 with TZD "No drug-related side effects"	
Singh 2007 (Diabetes Care)	TZD compared with placebo at various dosages	NR	NR	New onset CHF: RCTs: (3): OR 2.1 (95% CI, 1.08 - 4.08) Observational studies: (4): OR 1.55 (95% CI, 1.33 - 1.80) Case reports: 162 case subjects with 99 analyzable cases; median duration of onset of CHF 24w; CHF occurred in subjects <60y (26% of cases) and with low and high dosage	

Appendix E. Systematic reviews identified for the update review

Author Year Quality	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients	Characteristics of identified articles: Study designs	Characteristics of identified articles: populations
Singh 2007 (JAMA)	To review the long-term cardiovascular risks of rosi	Medline, GlaxoSmithKline clinical trials register, FDA web-site; product information sheets; last search 5/2007	RCTs in DM2 or IGT and trial duration ≥ 12m; provided numerical data on all AEs and monitored CVD AEs	4 14,291 Also 3 systematic reviews	RCTs, systematic reviews, meta-analyses; rosi compared with placebo or active oral agent	Prediabetes or type 2 diabetes

Appendix E. Systematic reviews identified for the update review

Author Year Quality	Characteristics of identified articles: Interventions	Efficacy and effectiveness results	Subgroups	Adverse events	Comments
Singh 2007 (JAMA)	Rosi compared with active drug or placebo	NR	NR	Relative risk (95% CI) rosi compared with comparator: MI: 1.42 (1.06 - 1.91) Heart failure: 2.09 (1.52 - 2.88) CV mortality: 0.90 (0.63 - 1.26) Number needed to harm: MI: 822 per year with rosi if baseline risk 0.29% (low risk, ADOPT) CHF; 383 per year with rosi if baseline risk 0.24 (low risk, ADOPT)	

Abbreviations: ACC, American College of Cardiology; AEs, adverse events; ADA, American Diabetes Association; AHA, American Heart Association; CHF, congestive heart failure; CVD, cardiovascular disease; DM2, type 2 diabetes mellitus; m, month(s); MI, myocardial infarction; NR, not reported; NSD, no significant difference; OR, odds ratio; PCI, percutaneous coronary intervention; pio, pioglitazone; RCTs, randomized controlled trials; rosi, rosiglitazone; RR, relative risk; SU, sulfonylurea; TVR, target vessel revascularization; TZD, thiazolidinedione; w, week(s); y, year(s).

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Objective	Databases and search dates	Study designs	Number studies Number patients
Berlie 2007	To obtain a precise estimate of the odds for developing TZD-induced edema and to compare rates between pio and rosi and with various combinations of oral agents	Medline (1966-5/2006), CINHAL (1982-5/2006), Cochrane Control Trials Register (to 1st quarter 2006), EMBASE (1996-2005) "manual search for review articles and original manuscript" (no details) Abstracts; ADA, AHA, ACC (2003-present) Takeda and GlaxoSmithKline were contacted for studies in their new Drug Applications	RCTs, mono- and combined therapy Type 2 diabetes	RCTs: 26 15,332

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Weight change	Edema	Congestive heart failure
Berlie 2007	Weight gain (kg): Pio -0.59 3.86; rosi 1.2 to 5.0 Pooled OR: All included studies (pio and rosi, all comparators): 2.26(95% CI, 2.02 - 2.53), *P* <0.000001 Placebo-controlled pio compared with rosi, indirect comparisons: 3.03 (95% CI, 2.15 - 3.91) TZD monotherapy placebo-controlled studies: 2.35 (95% CI, 1.40 - 3.91) TZD combination therapy placebo- or no-treatment control: 2.14 (95% CI, 1.88 - 2.43)		

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Myocardial infarction	Anemia	Elevated liver function tests	Cardiovascular mortality
Berlie 2007				

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Total mortality	Hypoglycemia	Other
Berlie 2007			

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Objective	Databases and search dates	Study designs	Number studies Number patients
Bolen 2007 (and AHRQ 2007 Review)	To summarize the literature on the benefits and harms of oral agents in the treatment of adults with type 2 diabetes	Medline, EMBASE, Cochrane Central Register of Controlled Trials (inception to 1/2006); industry data and FDA web-site; hand search 15 journals, reviewed reference lists	RCTs and observational studies, mono- and combined therapy Type 2 diabetes	RCTs, all included drugs: 216 Systematic reviews, all included drugs: 28
Boucher M 2002, 2003 COHTA Report	To evaluate the evidence that compares rosiglitazone or pioglitazone with other oral antidiabetic agents, either when used alone or when added to non-thiazolidinedione agent in the treatment of type 2 diabetes	1999-2001	RCTs, mono- and combined therapy Type 2 diabetes	Rosi: 11 studies (3 full-text, 8 abstracts) Pio: 8 studies

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Weight change	Edema	Congestive heart failure
Bolen 2007 (and AHRQ 2007 Review)	Weight: TZDs increased weight similar to SU (3kg) as monotherapy or in combination with other oral agents; TZDs increased weight compared with metformin, acarbose, and repaglinide	Edema: TZDs higher risk than SU (absolute risk difference 2 to 21%)	CHF: risk is increased with TZDs compared with other oral agents CHF: TZDs higher risk than with metformin or SU, absolute risks 0.8 to 3.6%; absolute risk difference 0.7 to 2.2%)
Boucher M 2002, 2003 COHTA Report	Rosi: Increased up to 5.3 kg; higher increases with insulin Pio: Gained 0.95 to 3.6 kg; highest occurrence of edema when used with insulin	Rosi: 2.5 to 3.5% on monotherapy; 10.8% when combined with gliclazide, 13.1 to 16.2% when combined with insulin Pio: Most marked with insulin	

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Myocardial infarction	Anemia	Elevated liver function tests	Cardiovascular mortality
Bolen 2007 (and AHRQ 2007 Review)		Mild anemia: TZDs higher risk than other drugs (absolute risk difference 1 to 5%)	Elevated ALT: low rates (<1%) with TZDs	CV D mortality: Insufficient data
Boucher M 2002, 2003 COHTA Report		Rosi: Hb change -3.9 to 12 g/l; rarely led to clinical anemia; 2 withdrawals due to anemia Pio: small decrease in Hb (-0.48 g/dL compared to SU, *P* <0.05) and hematocrit; stabilized within 12 weeks; no patient withdrew due to anemia	Rosi: Vast majority of subjects in trials maintained normal liver enzyme levels; no serious liver AEs noted Pio: Vast majority of subjects in trials maintained normal liver enzyme levels; no serious liver AEs noted	

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Total mortality	Hypoglycemia	Other
Bolen 2007 (and AHRQ 2007 Review)	Mortality: insufficient data to assess	Hypoglycemia: less frequent with TZDs than SU (risk difference 4-9%)	Microvascular outcomes: Insufficient data Hospitalizations for acute cholecystitis: Pio 12 patients compared with placebo 1 patient (pooled, unpublished analysis of 1526 patients)
Boucher M 2002, 2003 COHTA Report		Rosi monotherapy; 0.5 to 1.0%; when used as add-on therapy: 2.6 to 6.1%; particularly common when combined with insulin; 4 withdrawals due to hypoglycemia Pio: uncommon; increased occurrence when used as add-on, especially with insulin; no withdrawals for hypoglycemia	

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Objective	Databases and search dates	Study designs	Number studies Number patients
Chiquette E 2004	To review RCTs of pio and rosi in patients with type 2 diabetes to evaluate their effect on glycemic control, lipids, blood pressure, and weight	1966 (or start of database) - 1/2004	RCTs, mono- and combined therapy Type 2 diabetes	23 studies
Czoski-Murray 2004 HTA report	To evaluate the use of pioglitazone and rosiglitazone, in terms of both clinical and cost-effectiveness in the treatment of type 2 diabetes	1966 (or start of database) - 6/2002	RCTs, mono- and combined therapy Type 2 diabetes	Rosi: 8 studies, data NR for 7/8 as proprietary (Table 6) Pio: 3 studies of combination therapy
Eurich 2007	To review literature on the association between antidiabetic agents and morbidity and mortality in people with heart failure and diabetes	Medline, Health-STAR, EMBASE, CINAHL, international Pharmaceutical Abstracts, Allied and Complementary Medicine, cochran Controlled Trials Register date of inception to 7/07 Manual search reference lists; contacted experts	Contemporaneous comparison group	4 TZD trials 22,476 patients

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Weight change	Edema	Congestive heart failure
Chiquette E 2004	Weight change within 6 months of starting treatment: 2.7 kg (95% CI 1.8 to 3.7 kg)		
Czoski-Murray 2004 HTA report		Rosi: Edema higher with rosi combination therapies than for controls Pioglitazone See Chilcott 2001 review	
Eurich 2007			

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Myocardial infarction	Anemia	Elevated liver function tests	Cardiovascular mortality
Chiquette E 2004				
Czoski-Murray 2004 HTA report		Rosi: anemia higher with rosi combination therapies than for controls Pioglitazone See Chilcott 2001 review		
Eurich 2007				

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Total mortality	Hypoglycemia	Other
Chiquette E 2004			
Czoski-Murray 2004 HTA report		Rosi: Addition to metformin associated with significant reduction in risk of hyperglycemia in 1 study; no significant effect when added to SU Pioglitazone See Chilcott 2001 review	
Eurich 2007	Pooled OR for TZDs compared with other treatments for all cause mortality: 0.83 (95% CI, 0.71 - 0.97)		Pooled OR for TZDs compared with other treatments on hospital admissions for heart failure 1.13 (95% CI, 0.1.04 - 1.22)

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Objective	Databases and search dates	Study designs	Number studies Number patients
Inzucchi SE 2002	To review the literature regarding the efficacy of oral antidiabetic agents, both as monotherapy and in combination	Medline; dates NR	RCTs of oral agents Type 2 diabetes	3 studies identified: Rosi compared with placebo: 493+959 Pio compared with placebo: 408 (3 trials of troglitazone also reported)
Lago 2007	To examine the risk of heart failure and of cardiac death in patients given TZDs	Medline, Database of Abstracts of Reviews of Effects, Cochrane Library; up to 3/2007; start date NR; databases of European Society of Cardiology, AHA, ACC, ADA by hand; reference lists	RCTs, mono- and combined therapy Type 2 diabetes and prediabetes	7 20191 patients
Rosmarakis, 2007	To review RCT evidence on the effect of TZDs on in-stent restenosis after PCI	PubMed, last search 6/2006; reference lists reviewed	RCTs, mono- and combined therapy Type 2 diabetes	5 235 (text states 259)

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Weight change	Edema	Congestive heart failure
Inzucchi SE 2002	Weight gain, which can be as great or greater than with SU		
Lago 2007			Risk of CHF compared to controls (placebo- and active-controlled trials): RR 1.72 (95% CI, 1.21 - 2.42), *P* =0.002; placebo-controlled trials only: RR 1.97 (95% CI, 0.94 - 4.13); pio only: RR 1.32 (95% CI, 1.04 - 1.68); rosi only: RR 2.18 (95% CI, 1.44 - 3.32), *P* =0.0003 Risk of cardiovascular death compared to controls: RR 0.93 (95% CI, 0.67 - 1.29), *P* =0.68; placebo-controlled trials only: RR 1.08 (95% CI, 0.66 - 1.76): pio only: RR 1.01 (95% CI, 0.51 - 2.09); rosi only: RR 0.91 (95% CI, 0.63 - 1.3)
Rosmarakis, 2007			

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Myocardial infarction	Anemia	Elevated liver function tests	Cardiovascular mortality
Inzucchi SE 2002			Pio and rosi not coincidentally associated with liver injury	
Lago 2007				
Rosmarakis, 2007				

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Total mortality	Hypoglycemia	Other
Inzucchi SE 2002			
Lago 2007			
Rosmarakis, 2007	Mortality: 2/259: 1 in control arm; 1 with TZD		No drug-related side effects

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Objective	Databases and search dates	Study designs	Number studies Number patients
Singh 2007 (Diabetes Care)	To evaluate the risk of CHF with TZDs in type 2 diabetes and to classify this AE under the dose-time-susceptibility system	RCTS: existing reviews; PubMed (1/2003 to 9/2006); manufacturer's web-site Controlled observational studies and case reports: PubMed (to 9/2006, start date NR); Web of Knowledge Cited References and PubMed related articles Case reports also: EMBASE, Google Scholar (to 9/2006, start date NR)	Controlled observational studies, case reports New onset CHF in patients receiving TZDs compared with other oral agents	RCTs: 3 10,731 Observational studies: 4 67,382 Case reports: 162 case subjects
Stolar 2003 Review of AEs only	To provide an overview of the cardiovascular risk profile of patients with type 2 diabetes and discusses the cardiovascular consequences of use of the [TZDs] in the treatment of type 2 diabetes	Medline: 1966-4/2003	NR	NR; total number of studies NR

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Weight change	Edema	Congestive heart failure
Singh 2007 (Diabetes Care)			New onset CHF: RCTs: (3): OR 2.1 (95% CI, 1.08 - 4.08) Observational studies: (4): OR 1.55 (95% CI, 1.33 - 1.80) Case reports: 162 case subjects with 99 analyzable cases; median duration of onset of CHF 24w; CHF occurred in subjects <60y (26% of cases) and with low and high dosage
Stolar 2003 Review of AEs only		Peripheral edema occurs in approximately 2 to 5% of patients receiving rosi or pio	

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Myocardial infarction	Anemia	Elevated liver function tests	Cardiovascular mortality
Singh 2007 (Diabetes Care)				
Stolar 2003 Review of AEs only				

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Total mortality	Hypoglycemia	Other
Singh 2007 (Diabetes Care)			
Stolar 2003 Review of AEs only			

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Objective	Databases and search dates	Study designs	Number studies Number patients
Adverse effects of rosiglitazone in systematic reviews				
Richter, 2007 (Rosi cochrane)	To assess the effects of rosi in the treatment of type 2 diabetes	Medline, EMBASE, Cochrane database; last search 8/2006; reference lists searched	RCTs, mono- and combined therapy Type 2 diabetes	18 3888
Singh 2007 (JAMA)	To review the long-term cardiovascular risks of rosi	Medline, GlaxoSmithKline clinical trials register, FDA web-site; product information sheets; last search 5/2007	RCTs Type 2 diabetes or IGT	4 14,291 Also 3 systematic reviews

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Weight change	Edema	Congestive heart failure
Adverse effects of rosiglitazone in systematic reviews			
Richter, 2007 (Rosi cochrane)		Edema: OR rosi compared with comparators, random effects model: 4.62 (95% CI, 2.28 - 9.38)	CHF, total events (%): rosi 1.5, metformin 1.3, glyburide 0.6 (from ADOPT trial only)
Singh 2007 (JAMA)			Relative risk (95% CI) rosi compared with comparator: Heart failure: 2.09 (1.52 - 2.88) Number needed to harm: CHF; 383 per year with rosi if baseline risk 0.24 (low risk, ADOPT)

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Myocardial infarction	Anemia	Elevated liver function tests	Cardiovascular mortality
Adverse effects of rosiglitazone in systematic reviews				
Richter, 2007 (Rosi cochrane)	CVD events: % serious/% total events: rosi 3.4/4.3; metformin 3.2/4.0; glyburide 1.8/ 2.8 (from ADOPT trial only)			
Singh 2007 (JAMA)	Relative risk (95% CI) rosi compared with comparator: MI: 1.42 (1.06 - 1.91) Number needed to harm: MI: 822 per year with rosi if baseline risk 0.29% (low risk, ADOPT)			Relative risk (95% CI) rosi compared with comparator: CV mortality: 0.90 (0.63 - 1.26)

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Total mortality	Hypoglycemia	Other
Adverse effects of rosiglitazone in systematic reviews			
Richter, 2007 (Rosi cochrane)		Severe hypoglycemic episodes: somewhat lower with rosi than active monotherapy, particularly SU; no pooled data and no statistics	Fracture rates: higher with rosi than; no statistics reported (from ADOPT trial only)
Singh 2007 (JAMA)			

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Objective	Databases and search dates	Study designs	Number studies Number patients
Adverse effects of pioglitazone in systematic reviews				
Chilcott J 2001 overlaps with HTA report; examines Pio only	"presents a systematic review of the published literature on the effectiveness of pioglitazone in the treatment of type 2 diabetes…"	1966 (or start of database) - 3/2001	RCTs, mono- and combined therapy Type 2 diabetes	11 studies ; total 2669 patients
Richter, 2006 (Pio cochrane)	To assess the effects of pio in the treatment of type 2 diabetes	Medline, EMBASE, Cochrane database; last search 8/2006; reference lists searched	RCTs, mono- and combined therapy Type 2 diabetes	22 6200

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Weight change	Edema	Congestive heart failure
Adverse effects of pioglitazone in systematic reviews			
Chilcott J 2001 overlaps with HTA report; examines Pio only		Edema: more frequent in pio than placebo; overall 'figures' 6.6% Pio, 2.3% placebo (FDA 2000); Japanese studies 1.55 to 11.7%, more common treatment than placebo groups	
Richter, 2006 (Pio cochrane)	Weight: increased in 15 studies examining this outcome: up to 3.9kg	Edema: RR 2.86 (95% CI, 1.14 - 3.18)	

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Myocardial infarction	Anemia	Elevated liver function tests	Cardiovascular mortality
Adverse effects of pioglitazone in systematic reviews				
Chilcott J 2001 overlaps with HTA report; examines Pio only		Reduction in Hb: small decrease noted with pio monotherapy; thought to be due to hemodilution; clinical anemia not a concern	Hepatotoxicity: FDA 2000: incidence of alanine aminotransferase levels >3 times upper limit normal: NSD pio and placebo; pio 0.26%; NSD in 3 Japanese studies	
Richter, 2006 (Pio cochrane)		Hb: decrease noted in 6 studies examining this outcome: range 0.5 - 0.75 g/dL		

Appendix F. Systematic reviews reporting adverse events with thiazolidinediones

Review	Total mortality	Hypoglycemia	Other
Adverse effects of pioglitazone in systematic reviews			
Chilcott J 2001 overlaps with HTA report; examines Pio only			Cardiac effects: (FDA 2000): 1 report LVH and LBBB; new ECG finds NSD placebo or pio groups; in Japanese studies NS cardiac abnormalities with pio Elevation creatine phosphokinase: FDA 2000: 7/1510 patients in treatment arms had increased CPK >10 times normal; placebo data NR; other studies reported 9.6% compared with 2.8% placebo and 6.0% compared with 1.5% placebo; no information about skeletal muscle symptoms
Richter, 2006 (Pio cochrane)		Hypoglycemia episodes: Pio rates < SU rates; pio + insulin increased rates No pooled data or statistics	Overall and serious AEs comparable between intervention groups 7/22 trials reported AEs

Abbreviations: ACC, American College of Cardiology; AEs, adverse events; ADA, American Diabetes Association; AHA, American Heart Association; CHF, congestive heart failure; CVD, cardiovascular disease; DM2, type 2 diabetes mellitus; m, month(s); MI, myocardial infarction; NR, not reported; NSD, no significant difference; OR, odds ratio; PCI, percutaneous coronary intervention; pio, pioglitazone; RCTs, randomized controlled trials; rosi, rosiglitazone; RR, relative risk; SU, sulfonylurea; TVR, target vessel revascularization; TZD, thiazolidinedione; w, week(s); y, year(s).

Appendix G. Other (nonsystematic) reviews of thiazolidinediones

Author Year Quality	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Lincoff, 2007	To evaluate the effect of pio on ischemic CVD complications in diabetes	Database of individual patient data from Takeda (manufacturers of pio)	RCTs, double-blind, active- or placebo-controlled	19 16,390 patients	RCTs only	Diabetes
Nissen, 2007	To assess the effect of rosiglitazone on cardiovascular outcomes	FDA web-site, a clinical trials registry maintained by GlaxoSmithKline, search of the published literature; 2 large trials included from the published literature; no information provided on additional searching of bibliographic databases	RCTs, similar duration of treatment in all groups, >24 weeks duration, outcome data on MI and death from CVD causes	42 27,847	RCTs only	Largely type 2 diabetes; also prediabetes, psoriasis, Alzheimer's disease

Appendix G. Other (nonsystematic) reviews of thiazolidinediones

Author Year Quality	Characteristics of identified articles: interventions	Efficacy and effectiveness results	Subgroups	Adverse events	Comments
Lincoff, 2007	TZD compared with a variety of comparators and placebo	NR	Age, sex, BMI, study duration, control therapy	Primary composite endpoint (death, nonfatal MI, nonfatal stroke): HR 0.82 (95% CI, 0.72 - 0.94), *P* =0.005; for placebo only trials HR 0.09 (95% CI, 0.01 - 0.84) MI: HR 0.81 (95% CI, 0.64 - 1.02) Stroke: HR 0.80 (95% CI, 0.62 - 1.04) Serious heart failure: HR 1.41 (95% CI, 1.14 - 1.76) Subgroups NSD between sexes, age > or < 65y, or BMI < or > 30 mg/m^2	Not a systematic review
Nissen, 2007	Rosi compared with a variety of comparators and placebo	NR	NR	MI, OR: 1.43 (95% CI, 1.03 – 1.98) Death from cardiovascular causes, OR: 1.64 (95% CI, 0.98 – 2.74).	Not a systematic review

Appendix G. Other (nonsystematic) reviews of thiazolidinediones

Author Year Quality	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Paudwal, 2005	To review the evidence for the prevention of type 2 diabetes by pharmacological therapies	Medline, EMBASE, Cochrane controlled Trials Register (inception date to 6/2004)	RCTS and cohort studies with relevant data and an intention-to-treat analysis	2 (for TZDs) 438	RCTs and cohort studies with TZD compared to placebo or control group	Both studies examined troglitazone

Appendix G. Other (nonsystematic) reviews of thiazolidinediones

Author Year Quality	Characteristics of identified articles: interventions	Efficacy and effectiveness results	Subgroups	Adverse events	Comments
Paudwal, 2005	Both studies examined troglitazone	Not relevant (troglitazone)	NR	Not relevant (troglitazone)	Not relevant (troglitazone)

Abbreviations: ACC, American College of Cardiology; AEs, adverse events; ADA, American Diabetes Association; AHA, American Heart Association; CHF, congestive heart failure; CVD, cardiovascular disease; DM2, type 2 diabetes mellitus; m, month(s); MI, myocardial infarction; NR, not reported; NSD, no significant difference; OR, odds ratio; PCI, percutaneous coronary intervention; pio, pioglitazone; RCTs, randomized controlled trials; rosi, rosiglitazone; RR, relative risk; SU, sulfonylurea; TVR, target vessel revascularization; TZD, thiazolidinedione; w, week(s); y, year(s).

Appendix H. Adverse events reported in placebo-controlled trials (% of patients)

Adverse event	Pioglitazone compared with placebo	Rosiglitazone compared with placebo
Anemia		
Monotherapy		Change in Hb: rosi 4-8 mg daily -1.19 g/dL compared with placebo 0.13 g/dL[1]
Combination therapy	Decreased Hb: 1.1% compared with 0 % (glyburide/metformin)[2]	1.9% compared with 0.7%[3], (SU) 7.1% compared with 2.2%[4] (MET)[a] Incidence "low" rosi 4 mg daily (with SU)[5]
Arthralgia, myalgia, back pain, leg pain	3% (30 mg), 10%[a] (45 mg) compared with 2%[6]	
Monotherapy	0% (15 mg), 4% (30 mg) compared with 5%[7]	
Combination therapy	Muscular pain: 6 compared with 12% (glyburide/metformin)[2]	2% compared with 7%[8] (SU)
Cardiac-related events	3.6% compared with 6.3%[9]	
Monotherapy	Major adverse cardiac events: 7.7% pio 30 mg daily, placebo 60.7%, *P*<0.0001)[10]	MI: Rosi 4-8 mg daily 4.5% compared with placebo 0%[1]
Combination therapy	5.9% compared with 5%[11] (SU) 7.9% compared with 7.0%[12] (insulin)	0.2% compared with 0%[13] (SU) 3.9% compared with 2.9%[14] (MET)
Congestive heart failure	11% compared with 8%[a15]	
Monotherapy	Severe CHF: 0% pio 30 mg daily, placebo 0% [10]	Worsening CHF: 4-8 mg daily 4.5% compared with placebo 3.5% (*P*=0.858)[1] Worsening of NYHA functional class: Rosi 4-8 mg daily 16.8% compared with placebo 17.5%[1]
Combination therapy	1% compared with 0%[12] (insulin) 12.5% compared with 0%[16] (insulin)	3.4% (4 mg daily) compared with 2.7% placebo (with SU) [5]
Cough		
Monotherapy		
Combination therapy	11.5% pio 30 mg, placebo 8% (with SU)[17] 8 compared with 6% (glyburide/metformin)[2]	7% compared with 5%[8] (SU)
Diarrhea, flatulence		
Monotherapy		
Combination therapy	6 compared with 7 % (glyburide/metformin)[2]	12.7% compared with 15.6%[4] (MET) 7% compared with 2%[8] (SU)
Dizziness		
Monotherapy		
Combination therapy		5% compared with 8%[8] (SU)
Edema, peripheral	0% (15 mg), 3% (30 mg) compared with 0%[7]	5.2% (4 mg), 6.4% (8 mg), 4.1% (2 mg twice daily), 6.6% (4 mg twice daily)[a] compared with 1.6%[a20]
Monotherapy	3.6% compared with 0%[9] 5% compared with 1%[18]	

Adverse event	Pioglitazone compared with placebo	Rosiglitazone compared with placebo
	14% (30 mg), 16% (45 mg) compared with 16%[6] 15.3% compared with 7%[a12] 22% compared with 13%[a15] 45 mg daily 4.5% (1 case), placebo 0%[19] 0% pio 30 mg daily, placebo 0%[10]	Edema: Rosi 4-8 mg daily 25% compared with placebo 8% (*P*=0.005)[1]
Combination therapy	7%[11] compared with 2% (SU)[a] 12.5% compared with 0%[16](insulin) 14.1% compared with 3.4%[21](insulin)[a] 8% compared with 2% (glyburide/metformin)[2]	2.5% (4 mg), 3.5% (8 mg) compared with 1.6%[22] (MET) 4.1% compared with <1%[3](SU)[a] 5.2% compared with 0%[14] (MET) Legs: 9.5% (4 mg)[a], 12.2% (8 mg)[a] compared with 0% Face: 4.1% (4 mg)[a], 5.0% (8 mg)[a] compared with 0%(SU)[13] 23%(4 mg daily) compared with 9% placebo (with SU)[5]
Fatigue		
Monotherapy		
Combination therapy	6% compared with 5% (glyburide/metformin)[2]	5.9% compared with 4.0%[4] (MET)
Headache	5.3% compared with 0%[23]	
Monotherapy	12.4% compared with 10.1%[9]	
Combination therapy		4.9% compared with 7.9%[3] (SU) 6% compared with 9%[8] (SU) 6.5% compared with 8.9%[4] (MET)
Hyperglycemia		
Monotherapy		
Combination therapy		1% compared with 9%[8] (SU) 5.3% (4 mg), 9.3% (2 mg), compared with 17.2%[24] (SU)
Hypoglycemia	0% compared with 0%[18]	
Monotherapy	1.2% compared with 0%[9] 10% (30 mg), 11% (45 mg), compared with 11%[6] 28% compared with 20%[a15]	
Combination therapy	0% (15 mg), 3.8% (30 mg) compared with <1%[11] (SU) 8% (15 mg), 15% (30 mg)[a] compared with 5% (insulin)[12] 37.5% compared with 12.5%[16] (insulin) 63.4% compared with 51.0%[a] (insulin)[21] 53% compared with 25% (glyburide/metformin)[2]	3.4% (2 mg), 5.3% (4 mg) compared with 2.0%[24] (SU) 5.1% compared with 2.9%[3] (SU) 12% compared with 6%[8] (SU) 2.6% (4 mg), 4.5% (8 mg) compared with 1.8%[22] Symptomatic: 32% (4 mg daily) compared with 27% placebo (with SU)[5]
Influenza-like symptoms	2% (15 mg), 9% (30 mg) compared with 8%[7]	
Monotherapy		
Combination therapy		10% compared with 14%[8] (SU)
Injury/accident	2% compared with 2%[15]	

Adverse event	Pioglitazone compared with placebo	Rosiglitazone compared with placebo
Monotherapy		
Combination therapy		0.9% (4 mg), 1.4% (8 mg) compared with 5.4%[13] (SU) 6.6% compared with 5.7%[3] (SU) 8% compared with 7.6%[4] (Metformin)
Liver function test abnormal (ALT>3 times ULN) Monotherapy	0.77% compared with 1.3%[15] 1.3% (7.5 mg, 2.4% (30 mg) compared with 1.3%[9]	0.44% compared with 0%[25] 0% (2 mg), 0.6% (4 mg) compared with 0%[26] 0% compared with 0%[27] 0.14% compared with 0%[20]
Combination therapy	0% compared with 0%[11] (SU) 0% (15 mg), 0.5% (30 mg) compared with 0%[12] (insulin) 0% pio 30 mg, 0% placebo[17] 1.7% compared with 0.5% % (glyburide/metformin)[2]	0% compared with 0%[14] (Metformin)) 0% compared with 0.5%[3] (SU) 0% rosi (4 mg daily) and 0% placebo (with SU)[5]
Nausea Monotherapy		
Combination therapy	6 compared with 7% (glyburide/metformin)[2]	
Paresthesia Monotherapy		
Combination therapy		6% compared with 3%[8] (SU)
Thrombocytopenia Monotherapy		
Combination therapy		4.1% (4 mg), 7.7[a] (8 mg) compared with 3.6%[13] (SU)
URTI, rhinitis, sinusitis, bronchitis Monotherapy	3% (15 mg), 4% (30 mg) compared with 6%[7] 15.2% compared with 11.4%[9] URTI: 24 compared with 20% % (glyburide/metformin)[2] Sinus abnormality: 11% compared with 9% (glyburide/metformin)[2]	
Combination therapy		8% compared with 2%[8](SU) 8.6% compared with 7.9%[3] (SU) 15.9% compared with 8.9%[a4] 16.7% (4 mg), 10.0% (8 mg)[a] compared with 5.4%[13] (SU)
Urinary tract infection, cystitis Monotherapy	6.7% (15 mg), 3.8% (30 mg) compared with 7%[7]	
Combination therapy		9.0% (4 mg),[a] 10.9% (8 mg)[a] compared with 7.1% (SU)[13]
Vision abnormal Monotherapy		
Combination therapy		2.3% compared with 0% (SU)[13]

Abbreviations: MI, myocardial infarction; pio, pioglitazone; rosi, rosiglitazone; SU, sulfonylurea
[a] Significantly greater than placebo ($P<0.05$)

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Appendix I. Adverse events reported in active-control trials

Monotherapy	Pioglitazone	Rosiglitazone
Total withdrawals	Pio: 1/22(4.5%); glipizide: 3/22 (13.6%) Agarwal 2005[1]	Rosi 4 mg: 47/207 (22.7%); rosi 8 mg: 33/191 (17.3%); glibenclamide: 34/207 (16.4%) (Hanefeld 2007)[2]
	Pio: NR; Glibenclamide: NR Heliovaara, 2007[3]	Rosi: 539/1456 (37%); metformin 551/1454 (37.9%); glyburide 634/1441 (44%) (Kahn 2006)[4]
	Pio: 2/8 (25%); glipizide 0/11(0%) Basu, 2006[5]	
	Pio: 123/251 (49.0%); glyguride: 117/251(46.6%) Jain, 2006[6]	
	Pio: NR, gliclazide: NR Parriello, 2006[7]	
	Pio: 3/38 (7.9%); metformin: 2/39 (5.1%); glimepiride 3/37(8.1%) Yamanouchi, 2005[8]	
Withdrawals due to adverse events	Pio: 0/22 (0%); glipizide: 0/22 (0%) Agarwal 2005[1]	Rosi 4 mg: 12/200 (6%); rosi 8 mg: 9/191 (4.7%); glibenclamide: 13/207 (6.3%) (Hanefeld 2007)[2]
	Pio: 0/8 (0%); glipizide 0/11(0%) Basu, 2006[5]	Rosi: 169/1456 (11.6%); metformin 178/1454 (12.2%); glyburide 215/1441 (14.9%) (Kahn 2006)[4]
	Pio: NR; Glibenclamide: NR Heliovaara, 2007 [3]	
	Pio: 14/251(5.57%); glyguride: 25/251(10%) Jain, 2006[6]	
	Pio: 7/140(5%); gliclazide: 11/135(8.1%) Parriello, 2006 [7]	
	Pio: 1/46 (2.17%); glibenclamide 3/46 (6.5%) Teramoto, 2007[9]	
	Pio: 2/38 (5.3%); metformin: 0/39 (0%); glimepiride 0/37 (0%)Yamanouchi, 2005[8]	
Subjects with severe AEs	Pio: 7/22 (31.8%); glipizide: 7/22 (31.8%) Agarwal 2005[1]	Rosi: 346/1456 (23.8%); metformin 331/1454 (22.8%); glyburide 308/1441 (21.4%) (Kahn 2006)[4]
	Pio: 23/251 (9.1%); glyguride: 22/251 (8.8%) Jain,2006[6]	
	Pio: NR gliclazide: NR Parriello,2006[7]	
Subjects with mild AEs	Agarwal 2005: NR	
	Pio: 40/140 (28.6%); gliclazide: 31/135 (23%) (Parriello, 2006)[7]	
Subjects with any AEs	Pio: NR; Glibenclamide: NR (Heliovaara 2007)[3]	Rosi 4 mg: 150/200 (75%); rosi 8 mg: 144/191 (75.4%); glibenclamide: 144/207 (69.6%) (Hanefeld 2007)[2]

	Pio: 205/251 (81.7%); glyguride: 209/251 (83.3%) (Jain 2006)[6]	Rosi: 1338/1456 (91.9%); metformin 1341/1454 (92.2%); glyburide 1321/1441 (91.7%) (Kahn 2006)[4]
	Pio: 30/46 (65.2%); glibenclamide 32/46 (69.6%) (Teramoto 2007)[9]	
	Pio: 4/38 (10.5%); metformin: 0/39; glimepiride: 1/37 (2.7%) (Yamanouchi 2005)[8]	
Death	Pio: 0/22 (0%); glipizide: 1/22 (4.5%)(Agarwal 2005)[1]	Rosi 4 mg: 0/200; rosi 8 mg: 0/191 (0%); glibenclamide: 0/207 (0%) (Hanefeld 2007)
	Pio: 0/8 (0%); glipizide 0/11 (0%) (Basu 2006)[5]	Rosi: 34/1456 (2.3%); metformin 31/1454 (2.1%); glyburide 31/1441 (2.2%) (Kahn 2006)[4]
	Pio: 0/251 (0%); glyguride: 2/251 (0.8%) (coronary heart disease and respiratory failure) (Jain 2006)[6]	
	Pio: 0/140 (0%); gliclazide: 0/135 (0%) (Perriello 2006)[7]	
	Pio: 0/38 (0%); metformin: 0/39; glimepiride: 0/37 (0%) (Yamanouchi 2005)[8]	
Combination therapy	**Pioglitazone**	**Rosiglitazone**
Total withdrawals	Pio: 2/17 (11.8%); metformin 3/18 (16.7%) (unknown % on gliclazide) (Sharma 2006)[10]	Rosi: 1/47 (2.1%); glimepiride: 2/48 (4.2%) (metformin) (Derosa 2006, pg 197)
	Pio: 9/92 (9.8%); glimepiride: 6/87 (6.9%) (unknown % on other oral agents) (Pfutzner 2005)[11]	Rosi: 40/204 (19.6%); glyburide: 31/185 (16.8%) (metformin) (Bakris 2006)[12]
	Pio: 15/109 (13.8%); glimepiride: 11/101(10.9%) (metformin) (Umpierrez 2006)[13]	Rosi: 25/158 (15.8%); glibenclamide: 29/160 (18.1%)(metformin) (Garber 2006)[14]
	Pio: 72/232 (31.0%); glimepiride 63/230 (27.4%) (Mazzone 2006)[15]	Rosi: NR, no treatment: NR (for CV biomarkers study) (metformin) (Goldstein 2006)[16]
		Rosi: 8/45 (17.8%); metformin 9/47 (19.1%) (unknown % on sulfonylurea) (Stocker 2007)[17]
		Rosi: 292/2220 (13.2%); control: 313/2227(14.1%) (Home 2007 NEJM)[18]
		Rosi: 25/62 (40.3%); repeglanide: 25/63 (39.7%); rosi+repeglanide: 21/127 (77.8%) (Raskin 2004)[19]
Withdrawals due to adverse events	Pio: 0/17 (0%); metformin 0/18 (0%) (unknown % on gliclazide) (Sharma 2006)[10]	Rosi: 0/47 (0%); glimepiride: 0/48 (0%) (metformin) (Derosa 2006(pg 197)[20]

	Pio: 1/92 (1.1%); glimepiride: 0/87 (0%) (unknown % on other oral agents) (Pfutzner 2005)[11]	Rosi: 13/204 (6.4%); glyburide: 15/185 (8.1%) (metformin) (Bakris 2006)[12]
	Pio: 4/109 (3.7%); glimepiride: 1/101(10%) (metformin) (Umpierrez 2006)[13]	Rosi: 2/158 (1.3%); glibenclamide: 9/160 (5.6%) (metformin) (Garber 2006)[14]
	Pio: 26/230 (11.3%); glimepiride 19/228 (8.3%) (Mazzone 2006)[15]	Rosi: NR, no treatment: NR (for CV biomarkers study) (metformin) (Goldstein 2006)[16]
		Rosi: 4/45 (8.9%); metformin 7/47 (14.9%) (unknown % on sulfonylureas) (Stocker 2007)[17]
		Rosi: 6/62 (9.7%); repeglanide: 4/63 (6.3%); rosi+repeglanide: 4/127 (3.1%) (Raskin 2004)[19]
Any AEs	Pio: NR; metformin NR (unknown % on gliclazide) (Sharma 2006)[10]	Rosi: 13/133 (9.8%); glyburide: 17/124(13.7%) (metformin) (Bakris 2006)[12]
	Pio: NR; glimepiride: NR (unknown % on other oral agents) (Pfutzner 2005)[11]	Rosi: 98/158 (62.0%); glibenclamide: 108/160 (67.5%) (metformin) (Garber 2006)[14]
	Pio: 206/230 (89.6%); glimepiride 203/228 (89.0%) (Mazzone 2006)[15]	Rosi: 36/75 (48%); no treatment: 23/60 (38.3%) (for CV biomarkers study) (metformin) (Goldstein 2006)[16]
		Rosi: NR; metformin NR (unknown % on sulfonylureas) (Stocker 2007)[17]
		Rosi: NR; repeglanide: NR; rosi+repeglanide: NR (Raskin 2004)[19]
Subjects with severe AEs	Pio: 7/109 (6.4%); glimepiride: 7/101(6.9%) (metformin) (Umpierrez 2006)[13]	Rosi: 0/47 (0%); glimepiride: 0/48 (0%) (metformin) (Derosa 2006, pg 197)[20]
	Pio: 25/230 (10.9%); glimepiride 30/228(13.2%) (Mazzone 2006)[15]	Rosi: 0/158 (0%); glibenclamide: 1/160 (0.6%) (overdose) (metformin) (Garber 2006)[14]
		Rosi: 0/75 (0%); no treatment: 0/60 (0%) (for CV biomarkers study) (metformin) (Goldstein 2006)[16]
Subjects with mild AEs		Rosi: 4/47 (8.5%); glimepiride: 6/48 (metformin) (Derosa 2006, pg 197)[20]
		Rosi: 36/75 (3648%); no treatment: 23/60 (38.3%) (for CV biomarkers study) (metformin) (Goldstein 2006)[16]
Death	Pio: 0/17 (0%); metformin 0/18 (0%)(unknown % on gliclazide) (Sharma 2006)[10]	Rosi: 0/47 (0%); glimepiride: 0/48 (0%) (metformin) (Derosa 2006, pg 197)[20]

	Pio: 09/92 (9.8%); glimepiride: 0/87 (0%) (unknown % on other oral agents) (Pfutzner 2005)[11]	Rosi: 1/204 (0.5%); glyburide: 0/185 (0%) (metformin) (Bakris 2006)[12]
	Pio: 0/109 (0%); glimepiride: 0/101(0%) (metformin) (Umpierrez 2006)[13]	Rosi: 0/158 (0%); glibenclamide: 0/160 (0%) (metformin) (Garber 2006)[14]
	Pio: 1/230 (0.4%)(pancreatic cancer); glimepiride 0/228 (0%) (Mazzone 2006)[15]	Rosi: 0/75 (0%); no treatment: 0/60 (0%) (for CV biomarkers study) (metformin) (Goldstein 2006)[16]
		Rosi: 0; metformin 0 (unknown % on sulfonylureas) (Stocker 2007)[17]
		Rosi: 74/2220 (3.3%); control: 80/2227 (3.6%) (Home 2007 NEJM)[18]

Adverse event	Pioglitazone	Rosiglitazone
Anemia Monotherapy		Change hematocrit: Rosi 4 mg: -1.92%; rosi 8 mg: -3.33%; glibenclamide: NR (Hanefeld 2007)[2]
		Hematocrit ≥ 5 percentage points below reference rage (% of patients): Rosi: 2.8; metformin 1.5; glyburide: 1.0; rosi compared with metformin or glyburide *P*<0.001 (Kahn 2006)[4]
Combination therapy	Pio: 0/17(0%); metformin 0/18 (0%)(unknown % on gliclazide) (Sharma 2006)[10]	Rosi: 9/133 (6.8%); glyburide: 12/124(9.7%) (metformin) (Bakris 2006)[12]
Arthralgia, myalgia, back pain, leg pain Monotherapy	Arthrlagia: Pio: 13/251(5.2%); glyguride: 19/251(7.6%)(Jain 2006)[6] Back pain: Pio: 12/251(4.8%); glyguride: 18/251(7.2%) (Jain 2006)[6] Pain in limb: Pio: 10/251(4%); glyguride: 14/251 (5.6%) (Jain 2006)[6]	Back pain: Rosi 4 mg: 14/200 (7%); rosi 8 mg: 13/191(6.8%); glibenclamide: 13/207 (6.3%) (Hanefeld 2007)[2]
Combination therapy	Arthralgia, extremity or back pain combined; Pio: 53/230 (23%); glimepiride: 53/228 (23.2%) (Mazzone 2006)[15]	Rosi: 14/155 (9.0%); glibenclamide: 14/159 (8.8%) URTI (metformin) (Garber 2006)[14]
		Backpain: Rosi: 2/62 (3.2%); repeglanide: 5/63 (7.9%); rosi+repeglanide: 10/127 (37.0%)
Cancer Monotherapy	Colon: Pio: 0/251(0%); glyguride: 2/251(0.8%) (Jain 2006)[6]	
Combination therapy		

Adverse event	Pioglitazone	Rosiglitazone
Cardiac-related events Monotherapy	Arrhythmia: Pio: 0/22 (0%); glipizide: 1/22 (4.5%) (Agarwal 2005)[1]	Fatal MI: Rosi: 2/1456 (0.1%); metformin 2/1454 (0.1%); glyburide 3/1441(0.2%) (Kahn 2006)[4] Nonfatal MI: Rosi: 25/1456 (1.7%); metformin 21/1454 (1.4%); glyburide 15/1441(1.040) (Kahn 2006)[4]
	Any CV event: Pio: 22/251(8.8%); glyguride: 11/251(4.4%) (*P*=0.0478) (Jain 2006)[6] Myocardial infarct: Pio: 2/251(0.8%); glyguride: 2/251 (0.8%) (Jain 2006)[6]	
	Pio: 6/140 (4.3%); gliclazide: 3/135 (2.2%) (Perriello 2006)[7]	
	Pio: 0/38 (0%); metformin: 0/39 (0%); glimepiride: 0/37 (0%) (Yamanouchi 2005)[8]	
Combination therapy	Cardiac disorders not specified: Pio: 2/109 (1.8%); glimepiride: 3/101(3%)(metformin) (Umpierrez 2006)[13]	
	Nonfatal MI: Pio: 0/230 (0%); glimepiride 1/228 (0.4%) Coronary revascularization Pio: 3/230 (1.3%); glimepiride 8/228 (3.5%) PCI: Pio: 2/230 (0.9%); glimepiride 6/228 (2.6%) CABG: Pio: 1/230 (0.4%); glimepiride 2/228 (0.9%) (Mazzone 2006)[15] CEA or stenting; hospitalization for unstable angina: none in either group	
Congestive heart failure Monotherapy	Pio: 2/22 (9.1%); glipizide: 2/22 (9.1%) (Agarwal 2005)[1]	Rosi: 22/1456 (1.5%); metformin 19/1454 (1.3%); glyburide 9/1441(0.6%); for adjudicated CHF (total 21 cases, rosi compared with glybiride *P*=0.26 HR rosi compared with glyburide: 2.23 (1.01 to 4.79) HR rosi compared with metformin: 1.22 (0.66 to 2.26) (Kahn 2006)[4]
	Pio: 1/251 (0.4%); glyguride: 1/251 (0.4%)(Jain 2006)[6]	

Adverse event	Pioglitazone	Rosiglitazone
Combination therapy	Pio: 2/92 (2.2%) (requiring hospitalization); glimepiride: 0/87 (unknown % on other oral agents) (Pfutzner 2005)[11]	Rosi: 0/45 (0%); metformin 0/47 (0%)(unknown % on sulfonylureas) (Stocker 2007)[17]
	Pio: NR; glimepiride: NR (metformin) (Umpierrez 2006)[13]	
	New CHF: Pio: 1/230 (0.4%); glimepiride 0/228 (0%) (no exacerbated CHF ineither group) (Mazzone 2006)[15]	
Constipation Monotherapy		
Combination therapy		Rosi: 4/75 (5.3%); no treatment: 0/60 (0%) (for CV biomarkers study) (metformin) (Goldstein 2006)[16]
Cough Monotherapy		
Combination therapy	Pio: 16/230 (7%); glimepiride 15/228 (6.6%) (Mazzone 2006)[15]	
Diarrhea, flatulence Monotherapy	Pio: 15/251(5.8%); glyguride: 16/251(6.4%) (Jain 2006)[6]	Rosi 4 mg: 11/200 (5.5%); rosi 8 mg: 5/191 (2.6%); glibenclamide: 7/207 (3.4%) (Hanefeld 2007)[2]
		Rosi: 129/1456 (8.9%); metformin 345/1454 (23.7%); glyburide 142/1441(9.9%) (Kahn 2006)[4]
Combination therapy	Pio: 5/109 (4.6%); glimepiride: 6/101(5.9%) (metformin) (Umpierrez 2006)[13]	Rosi: 5/155 (3.2%); glibenclamide: 10/159 (6.3%)(metformin) (Garber 2006)[14]
	Pio: 16/230 (7%); glimepiride 17/228 (7.5%)(Mazzone 2006)[15]	Diarrhea: Rosi: 4/75 (5.3%); no treatment: 6/60 (10%); flatulence rosi 6/75 (8%); no treatment 1/60 (1.7%) (for CV biomarkers study) (metformin) (Goldstein 2006)[16]
Dizziness Monotherapy		
Combination therapy	Pio: 15/230 (6.5%); glimepiride 22/228(9.6%) (Mazzone 2006)[15]	
Dyspnea Monotherapy		
Combination therapy	Pio: 3/92 (3.3%); glimepiride: 0/87(0%) (unknown % on other oral agents) (Pfutzner 2005, Forst 2005 Microcirculation)[11, 21]	
Edema Monotherapy	Pio: 2/8 (25%); glipizide 0/11(0%) (Basu 2006)[5]	Rosi 4 mg: 7/200 (3.5%); rosi 8 mg: 17/191 (3.7%); glibenclamide: 4/207(1.9%) (Hanefeld 2007)[2]

Adverse event	Pioglitazone	Rosiglitazone
	Pio: 20/251(8%); glyguride: 12/251(4.8%); 1 Pio subject discontinued because of edema (Jain 2006)[6]	Rosi: 205/1456 (14.1%); metformin 104/1454 (7.2%); glyburide 123/1441 (8.5%); rosi compared with metformin or glyburide *P*<0.001 (Kahn 2006)[4]
	Pio: 3/140 (2.1%); gliclazide: 1/135 (0.7%)(Perriello 2006)[7]	
	Pio: 4/38 (10.5%) (2 discontinued study); metformin: 0/39 (0%); glimepiride: 0/37(0%) (Yamanouchi 2005)[8]	
Combination therapy	Pio: 3/17 (17.6%); metformin 0/18 (0%) (unknown % on gliclazide) (Sharma 2006)[10]	Rosi: 11/133 (8.3%); glyburide: 4/124 (3.2%)(metformin) (Bakris 2006)[12]
	Pio: 21/92 (22.8%); glimepiride: 2/87 (2.3%) (unknown % on other oral agents) (Pfutzner 2005)[11]	Rosi: 8/45 (17.8%) (3 withdrew); metformin 0/47 (0%) (unknown % on sulfonylureas) (Stocker 2007)[17]
	Pio: 4/109 (3.7%); glimepiride: 1/101(1%) (metformin) (Umpierrez 2006)[13]	Rosi: 2/62 (3.2%); repeglanide: 0/63 (0%); rosi+repeglanide: 5/127 (4%) (Raskin 2004)[19]
	Pio: 30/230 (13.0%); glimepiride 16/228 (7.0%)(Mazzone 2006)[15]	
Eye disorders Monotherapy		
Combination therapy	Unspecified: Pio: 3/109 (2.8%); glimepiride: 4/101(4%) (metformin) (Umpierrez 2006)[13]	
Fatigue Monotherapy		
Combination therapy	Pio: 16/230 (7%); glimepiride 18/228 (7.9%) (Mazzone 2006)[15]	Rosi: 1/62 (1.6%); repeglanide: 1/63 (1.6%); rosi+repeglanide: 7/127 (5.5%) (Raskin 2004)[19]
Gastrointestinal, not otherwise specified Montherapy		Nausea + vomiting (combined): Rosi: 170/1456 (11.7%); metformin 254/1454 (17.5%); glyburide 144/1441 (10%) (Kahn 2006)[4]
Combination therapy	Rosi: 0/45 (0%); metformin 15/47(31.9%) (6 withdrew) (unknown % on sulfonylureas) (Stocker 2007)[17]	Rosi: 16/155 (10.3%); glibenclamide: 18/159 (11.3%) (overdose) (metformin) (Garber 2006)[14]
		Rosi: 6/75 (8%); no treatment: 3/60 (5%) (for CV biomarkers study) (metformin) (Goldstein 2006)[16]
Headache Monotherapy	Pio: 19/251(7.6%); glyguride: 22/251(8.8%) (Jain 2006)[6]	Rosi: 2/47 (4.3%); glimepiride: 2/48 (4.2%)(metformin) (Derosa 2006, pg 197)[20]

Adverse event	Pioglitazone	Rosiglitazone
		Rosi 4 mg: 17/200 (8.5%); rosi 8 mg: 16/191 (7.9%); glibenclamide: 14/207 (6.8%) (Hanefeld 2007)[2]
Combination therapy	Pio: 20/230 (8.7%); glimepiride 23/228 (10.1%) (Mazzone 2006)[15]	Rosi: 12/155 (7.7%); glibenclamide: 9/159 (5.7%) URTI (metformin) (Garber 2006)[14]
Hematology Monotherapy	Decreased hematocrit in Pio at 12m (*P*=0.005), NSD with gliclazide (Perriello 2006)[7]	
Combined therapy		
Hyperglycemia Monotherapy		Rosi 4 mg: 11/200 (5.5%); rosi 8 mg: 3/191 (1.6%); glibenclamide: 3/207 (Hanefeld 2007)[2]
Combination therapy		
Hypertension Monotherapy		
Combination therapy	Pio: 12/230 (5.2%); glimepiride 14/228 (6.1%) (Mazzone 2006)[15]	
Hypoglycemia Monotherapy	Pio: 2/22 (9.0%); glipizide: 1/22 (4.5%) (Agarwal 2005)[1]	Rosi 4 mg: 1/200 (0.5%); rosi 8 mg: 3/191 (1.6%); glibenclamide: 25/207 (12.1%) (Hanefeld 2007)[2]
	Pio: 11/251 (4.4%); glyguride: 61/251(24.3%) (*P*<0.001) (Jain 2006)	Rosi: 142/1456 (9.8%); metformin 168/1454 (11.6%); glyburide 557/1441 (38.7%); rosi compared with glyburide *P*<0.001 (Kahn 2006)[4]
	Pio: 1/140 (0.7%); gliclazide: 2/135 (1.5%) (Perriello 2006)[7]	
Combination therapy	Pio: 3/17 (17.6%) (undocumented); metformin 0/18(0%) (unknown % on gliclazide) (Sharma 2006)[10]	Rosi: 2/133 (1.5%); glyburide: 23/124 (18.5%) (severity NR) (metformin) (Bakris 2006)[12]
	Severe: Pio: 0/92 (0%); glimepiride: 0/87 (0%) (unknown % on other oral agents) (Pfutzner 2005)[11] Hypoglycemia episodes: 21/92 (22.8%); glimepiride: 26/87 (29.9%)	Rosi: 41/155 (26.5%); glibenclamide: 116/159 (73%; all mild-moderate (metformin) (Garber 2006)[14]
	Pio: 1/109 (0.9%); glimepiride: 33/101 (32.7%), *P*=0.0001; no severe hypoglycemia in either group (metformin) (Umpierrez 2006)[13]	Minor: Rosi: 1/62 (1.6%); repeglanide: 4/63 (6.3%); rosi+repeglanide: 11/127 (8.7%); RR rosi compared with combination therapy 0.17(0.02 to 1.3) Major: Rosi: 0/62 (0%); repeglanide: 0/63 (0%); rosi+repeglanide: 1/127 (0.8%) (Raskin 2004)[19]

Adverse event	Pioglitazone	Rosiglitazone
	Pio: 0/38 (0%); metformin: 0/39; glimepiride: 1/37 (2.7%) (Yamanouchi 2005)[8]	
	Pio: 45/230 (19.6%); glimepiride 53/228 (23.2%) (Mazzone 2006)[15]	
Infection		
Monotherapy		
Combination therapy		Rosi: 5/75 (6.7%); no treatment: 1/60 (1.7%) (for CV biomarkers study) (metformin) (Goldstein 2006)[16]
Influenza		
Monotherapy		
Combination therapy	Pio: 20/230 (8.8%); glimepiride 21/228 (9.2%) (Mazzone 2006)[15]	
Injury/accident		Rosi 4 mg: 17/200 (8.5%); rosi 8 mg: 16/191 (8.4%); glibenclamide: 14/207 (6.8%) (Hanefeld 2007)[2]
Monotherapy		
Combination therapy		Rosi: 2/75 (2.7%); no treatment: 4/60 (for CV biomarkers study) (metformin) (Goldstein 2006)[16]
Liver function test abnormal (ALT>3 times ULN)	Pio: 1/251(0.4%) (discontinued drug); glyburide: 0/251 (0%) (Jain 2006)[6]	No significant increases in any group: rosi 4 mg; rosi 8 mg; glibenclamide (Hanefeld 2007)[2]
Monotherapy		
	Pio: 5/140 (3.8%); gliclazide: 5/135 (3.7%) (degree NR) (Perriello 2006)[7]	(%) Rosi: 1.0; metformin 1.1; glyburide 0.8 (Kahn 2006)[4]
	Pio: 0/38 (0%); metformin: 0/39 (0%); glimepiride: 0/37 (0%) (Yamanouchi 2005)[8]	
Combination therapy	Pio: 1/17 (5.9%); metformin 0/18 (0%) (<3 times ULN) (unknown % on gliclazide) (Sharma 2006)[10]	Rosi: 0/47 (0%); glimepiride: 0/48 (0%) (metformin); transient elevation 1.5 times normal in 3/47 rosi (6.4%) (Derosa 2006, pg 197)[20]
		Rosi: 2/155 (1.3%); glibenclamide: 3/159 (1.9%), drug not discontinued (metformin) (Garber 2006)[14]
		Rosi: 0/62 (0%); repeglanide: 1/63 (1.6%); rosi+repeglanide: 0/127 (0%) (Raskin 2004)[19]
Nausea		
Monotherapy		
Combined therapy	Pio: 14/230 (6.1%); glimepiride: 9/228 (3.9%) (Mazzone 2006)[15]	Rosi: 1 0/62 (16.1%); repeglanide: 0/63 (0%); rosi+repeglanide: 6/127 (4.7%) (Raskin 2004)[19]
Paresthesia		
Monotherapy		

Adverse event	Pioglitazone	Rosiglitazone
Combination therapy		
Stroke Monotherapy		Rosi: 205/1456 (14.1%); metformin 104/1454 (7.2%); glyburide 123/1441(8.5%) (Kahn 2006)[4]
Combination therapy	Nonfatal: Pio: 0/230 (0%); glimepiride 1/228 (0.4%) (Mazzone 2006)[15]	
Thrombocytopenia Monotherapy		
Combination therapy		
URTI, rhinitis, sinusitis, bronchitis Monotherapy	URTI: Pio: 32/251(12.7%); glyguride: 31/251 (12.4%) (Jain 2006)[6] Sinusitis: Pio: 15/251 (6%); glyguride: 24/251(9.6%) (Jain 2006)[6] Bronchitis: Pio: 19/251 (7.6%); glyguride: 8/251 (3.2%) (Jain 2006)[6]	URTI: Rosi 4 mg: 6/200 (3%); rosi 8 mg: 12/191 (6.3%); glibenclamide: 13/207 (6.3%) (Hanefeld 2007) Various URT infections/symptoms (combined); Rosi 4 mg: 62/200 (31%); rosi 8 mg: 44/191 (23.0%); glibenclamide: 58/207 (28.0%) (Hanefeld 2007)[2]
Combination therapy	URTI: Pio: 26/230 (11.3%); glimepiride; 20/228 (8.8%) Nasopharyngitis: Pio: 30/230 (13.0%); glimepiride 33/228 (14.5%)(Mazzone 2006)[15]	Rosi: 22/155 (14.2%); glibenclamide: 21/159 (13.2%)URTI (metformin) (Garber 2006)[14]
		Rosi: 10/75 (13.3%); no treatment: 6/60 (10%) (for CV biomarkers study) (metformin) (Goldstein 2006)[16]
		URTI: Rosi: 3/62 (4.8%); repeglanide: 6/63 (9.5%); rosi+repeglanide: 16/127 (12.6%) Sinusitis, bronchitis combined: Rosi: 0/62 (0%); repeglanide: 3/63 (4.8%); rosi+repeglanide: 14/127 (11.0%) (Raskin 2004)[19]
Urinary tract infection, cystitis Monotherapy		Rosi 4 mg: 18/200 (9%); rosi 8 mg: 6/191 (3.1%); glibenclamide: 10/207 (4.8%) (Hanefeld 2007)[2]
Combination therapy		
Vision abnormal Monotherapy		
Combination therapy		
Weight gain (kg) Monotherapy	BMI: Pio: 0.5 (NR); Glibenclamide: 0.2 (NR) (Heliovaara 2007)[3]	BMI: Rosi: -0.4(NR); glibenclamide: 1.2(NR) (Kulanovic 2006)[22]
	Pio: 3.66 (SD 6.138); glyguride: 1.95 (SE 5.354; *P*<0.001); 1 subject in each group discnotinued for weight gain (Jain 2006)[6]	Rosi 4 mg: 1.75; rosi 8 mg: 2.95; glibenclamide: 1.90; rosi 8 compared with glibemclamide: *P*=0.01 (Hanefeld 2007)[2]

Adverse event	Pioglitazone	Rosiglitazone
	Pio: 2; gliclazide: 2; *P*=0.005 both groups (Perriello 2006)[7]	Difference at 4y: Rosi compared with metformin: 6.9 (6.3 to 7.4), *P*<0.001 Rosi compared with glyburide; 2.5 (2.0 to 3.1), *P*<0.001 (Kahn 2006)[4]
	Pio: 0.9; metformin: 0.7; glimepiride: -0.2 (Yamanouchi 2005)[8]	
Combination therapy	Pio: 4.35; metformin 1.5 (unknown % on gliclazide) (Sharma 2006)[10]	Rosi: 1.94 (SE 4.63); glyburide: 1.50 (SE 3.53) (metformin) (Bakris 2006)[12]
	BMI: Pio: 0.1(NR); glimepiride: -1.3(NR), between-group *P*<0.001 (unknown % on other oral agents) (Pfutzner 2005)[11]	Rosi: 1.4; glibenclamide: 3.0; between-group *P*<0.001 (metformin) (Garber 2006)[14]
	Rosi: 1.6(1.5); metformin -2.0(1.4); between-group *P*=0.001 (unknown % on sulfonylureas) (Stocker 2007)[17]	Rosiglitazone (background metformin): 2.3 (95% CI, 1.7 to 2.9) Rosiglitazone (background SU): 3.4 (3.9 to 4.0) SU (background metformin): 1.1 (0.6 to 1.6) Metformin (background SU): -0.9 (-1.4 to -0.4) (mean follow-up 3.75y) Home 2007 NEJM)[18]
	Pio: 1.85(SE 0.38); glimepiride: 1.74(SE 0.41) (between-group *P*=0.84) (metformin) (Umpierrez 2006)[13]	Rosi: 2.3; repeglanide: 1.6; rosi+repeglanide: 4.4 (Raskin 2004)[19]

Abbreviations: ACC, American College of Cardiology; AEs, adverse events; ADA, American Diabetes Association; AHA, American Heart Association; BMI, body mass index; CHF, congestive heart failure; CVD, cardiovascular disease; DM2, type 2 diabetes mellitus; m, month(s); MI, myocardial infarction; NR, not reported; NSD, no significant difference; OR, odds ratio; PCI, percutaneous coronary intervention; pio, pioglitazone; RCTs, randomized controlled trials; rosi, rosiglitazone; RR, relative risk; SU, sulfonylurea; TVR, target vessel revascularization; TZD, thiazolidinedione; w, week(s); y, year(s).

References for Appendix I

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