Drug Class Review on Thiazolidinediones

Final Report

May 2006

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

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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 four 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 usually in childhood or in young adults and insulin treatment is required to replace the body's endogenous insulin. Gestational diabetes is a form of glucose intolerance that is diagnosed during pregnancy and has important implications for the health of the mother (who is an increased risk of having or developing type 2 diabetes) as well as the health of the fetus and newborn. The third category consists of other specific types of diabetes caused by genetic defects in insulin action or β-cell function, diseases of the exocrine pancreas, endocrinopathies, and various other causes of impaired insulin secretion or action.[2]

Type 2 diabetes accounts for about 90% of all diagnosed cases of diabetes. It is characterized by insulin resistance initially, but over time, inadequate pancreatic production of insulin occurs. Type 2 disease is associated with age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose tolerance or impaired fasting glucose, physical inactivity, and race/ethnicity.[1]

The prevalence and incidence of diabetes are increasing both in the U.S. and world-wide. The total prevalence of diabetes in the U.S. for all ages is estimated at 7.0%, or 20.8 million people; approximately one-third of those cases are undiagnosed.[1]

The prevalence of type 2 diabetes varies among racial and ethnic groups: non-Hispanic blacks 20 year or older 13.3%, Hispanic/Latino Americans 9.5%, American Indians and Alaska natives 12.8%, and 8.7% among non-Hispanic whites.[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 30-50% subsequent to that year.[3]

Diabetes has a major impact on the health and welfare of affected individuals. Diabetes was the sixth leading cause of death listed on U.S. death certificates in 2000, and this statistic likely underestimates the mortality rates from diabetes, which is often not listed on the death certificate of affected person.[1] Individuals with diabetes has an overall risk of death about twice that of unaffected persons.[1]

Heart disease is the leading cause of diabetes-related deaths and adults with diabetes have a death rate from heart disease that is 2 to 4 times higher than adults without diabetes. The risk for stroke is 2 to 4 times higher among people with diabetes and two-thirds of people with diabetes die of heart disease or stroke. Diabetes is associated with other diseases and cardiovascular risk factors including hypertension.[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 (2002) are $132 billion, with direct medical costs accounting for $92 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 one or more oral hypoglycemic agents. Optimal treatment, however, may require the use of insulin with or without oral agents. Among adults with diagnosed diabetes, the current distribution of types of treatment is: 12% use both insulin and oral drugs, 16% use insulin only, and 57% use oral agents only, and 15% do not use pharmacotherapy.[1]

Prediabetes

Prediabetes refers to the condition of having one or the other, or both, of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). The term prediabetes was coined as it was recognized that both IFG and IGT were associated with a significant risk of developing diabetes.[4] IFG is diagnosed when the fasting blood glucose level is elevated (100 to 125 mg/dl) after an overnight fast, but the glucose level does not fit criteria for diabetes (≥126 mg/dl). IGT is defined a blood glucose of 140-199 mg/dl after a 2-hour oral glucose tolerance test (diabetes is diagnosed if the blood glucose level is ≥200).[2]

Prediabetes has a high prevalence; in a cross-section of U.S. adults aged 40-74 years, 40% had prediabetes.[1] The risk increases with age and reaches a peak in people aged 60-74 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 5-6 year incidence of developing type 2 diabetes in persons with either IGT or IFG is 20-34%.[5] The risk of diabetes is even higher among persons with both IGT and IFG. IGT is associated with an increased risk for cardiovascular and all-case mortality; the link between for IFG is not as strong.[5]

Lifestyle changes can prevent or delay the onset of type 2 diabetes among high risk persons. In the Diabetes Prevention Project[6] (DPP), 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 has also been shown to delay the progression of prediabetes to diabetes, including metformin, acarbose, as well as thiazolidinediones. In the DPP[6], metformin was

particularly effective in persons 25 to 40 years of age and 50-80 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 IGT when compared to 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 which 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 and he called this clustering syndrome X: dyslipidemia, hypertension, and hyperglycemia.

Today the term "metabolic syndrome" is most frequently used for the clustering of cardiovascular risk factors which 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, IFT, or IGT), insulin resistance, central obesity, dyslipidemia, and hypertension. A variety of definitions have been put forward,[10] which 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 six 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 WHO 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 U.S. was reported as 7% among persons 20-29 years, 44% among persons 60-69 years (data collected from 1988-1994),[15] and 4.2% among adolescents.[16]

The metabolic syndrome is associated with an increased risk of both 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, however, to be associated with obesity, insulin resistance, and 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 were 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 two thiazolidinediones approved for prescription use in the United States, rosiglitazone maleate (Avandia™) and pioglitazone hydrochloride (Actos™) (Table 2). A third TZD (Troglitazone™) was removed from the market in 1999 due to adverse hepatic effects.

Both rosiglitazone and pioglitazone are approved by the U.S. Food and Drug Administration (FDA) for use in adults for the treatment of type 2 diabetes, either as monotherapy, or in combination with insulin, metformin, or sulfonylurea when diet, exercise and a single agent does not results in adequate glycemic control. Neither drug is currently approved for use in prediabetes or the metabolic syndrome.

The mechanisms of action of TZDs in lowering plasma glucose among persons with type 2 diabetes are thought to include the following: increase in insulin sensitivity, decrease in endogenous glucose production and postprandial gluconeogenesis, suppression of free fatty acid release from the liver, increase in fasting and postprandial glucose clearance, and beneficial effects on beta-cell function.[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 TZDs are thought to be mediated by binding to the peroxisome proliferators-activated receptor (PPAR) gamma receptors. These receptors are expressed in the liver, adipose tissue, skeletal muscle, the heart, smooth muscle cells and endothelial cells of the vasculature, the kidneys, and the gut. This nuclear receptor is a transcription factor that regulates the transcription of genes whose proteins are involved in glucose and lipid metabolism as well as inflammation and endothelial function.[22]

Table 2. Characteristics of thiazolidinediones approved for use in the U.S.

Drug	Trade name	Dosage, How supplied	Precautions Contraindications	Pregnancy category	Dose adjustments, Monitoring
Pioglitazone[23]	Actos	15-30 mg qd, maximum 45 mg qd; supplied as 15,30,45 mg tablets	Contraindications: hypersensitivity to pioglitazone or any of its components Precautions: CHF, active liver disease, aminotransferase levels >2.5 times the upper limit of normal, edema, lack of adequate contraception in premenopausal woman, NYHA class III or IV CHF[23]	C	Decrease and careful titration with congestive heart failure; monitor liver function at baseline and periodically thereafter
Rosiglitazone[24]	Avandia	4 mg qd or divided bid, maximum 8 mg qd. Supplied: 2,4,8, mg tablets	Contraindications: type 1 diabetes; hypersensitivity to rosiglitazone or any of its components Precautions: edema, increased cardiovascular risk factors, concurrent use of insulin or oral hypoglycemic agents, lack of adequate contraception in premenopausal woman, hepatic dysfunction, NYHA class III or IV CHF[24]	C	Monitor liver function at baseline and periodically thereafter

Other uses of thiazolidinediones

Thiazolidinediones have been studies in several other clinical conditions where insulin resistance is a central part of the pathophysiology. Persons with these conditions may or may not have prediabetes, type 2 diabetes, or the metabolic syndrome. These conditions are, therefore, not included in this review. Such conditions include polycystic ovary syndrome[25] and nonalcoholic steatohepatitis (NASH).[26] HIV-infected patients using anti-retroviral therapy often have metabolic abnormalities, including loss of subcutaneous fat, insulin resistance, and hypertriglyceridemia. Early studies show that thiazolidinediones may be useful in this population.[27]

Scope and Key Questions

Key Questions

1. For patients with type 2 diabetes, do thiazolidinediones differ in the ability to reduce A1C levels
   a. when used as monotherapy?
   b. when added to or substituted for other oral hypoglycemic agents?

2. For patients with type 2 diabetes, do thiazolidinediones differ in the ability to prevent the macrovascular and microvascular complications of diabetes
   a. when used as monotherapy?
   b. when added to or substituted for other oral hypoglycemic agents?

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

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

6. For patients with type 2 diabetes, prediabetes, or the metabolic syndrome, do thiazolidinediones differ in safety or adverse effects (e.g., congestive heart failure, pulmonary edema, weight gain, liver toxicity, hypoglycemia)?
   a. when used as monotherapy?
   b. when added to or substituted for other oral hypoglycemic agents?

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

8. Are there subgroups of patients based on demographics (age, racial groups, gender), concomitant medications (drug-drug interactions), co-morbidities (i.e. obesity), or history of hypoglycemic episodes for which one thiazolidinediones is more effective or associated with fewer adverse effects?
   a. when used as monotherapy?
   b. when added to or substituted for other oral hypoglycemic agents?

METHODS

Literature Search

To identify relevant citations, two 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, Thompson Scientific).

Articles deemed potentially relevant after review of titles and abstracts were then 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 two drugs 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, 2006.

Participants in included studies were adults with type 2 diabetes, pre-diabetes, 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 one of the widely accepted definitions mentioned above.

Included studies examining type 2 diabetes had to present one or more of the primary outcomes of interest to this review: glycemic control (either A1c or fasting blood sugar); 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 efficacy or effectiveness of the two included drugs. The purpose of this report was primarily to examine the latter, however, since there were very little data available on effectiveness, efficacy studies were included and reviewed in detail.

For both efficacy/effectiveness as well as safety, published and as well as 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.

For the assessment of efficacy and effectiveness, we included reports of randomized controlled trials (RCTs) and controlled clinical trials. We included trials comparing rosiglitazone and pioglitazone (head-to-head trials), as well as trials comparing either of these drugs to placebo. We searched for, and identified trials where the comparator was another pharmacotherapeutic agent (active-control trials), but only included these in the primary results if they provided data population subgroups, if they had a follow-up period greater than 12 months, if they had a very large sample size (>500 persons), or examined health or quality-of-life outcomes. Active-controlled trials which were not included in the primary synthesis are listed in Appendix C.

For examination of efficacy and effectiveness among subgroups, we expanded our inclusion criteria to encompass all study designs where data were available (i.e., observational, before-after, and case-control studies, as well as time series). We took this approach because few controlled trials were available which examined subgroups and we therefore 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 assessment of tolerability and adverse effects, we included observational studies, before-after studies, and case series with a sample size greater than ten, in addition to RCTs 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, utilize 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 adverse events (including, hypoglycemia, liver toxicity, heart failure, pulmonary edema, weight, and edema).

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 or 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 pre-specified 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 B. These criteria are based on those used by the U.S. Preventive Services Task Force[28] and the National Health Service Centre for Reviews and Dissemination.[29] For each included trial, we assessed the following criteria: methods used for 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 the use of intention-to-treat analysis.

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

These criteria were then used to categorize studies into good, fair, and poor quality studies. Studies that had a significant flaw in design or implementation such that the results were potentially not valid (i.e. the results were at least as likely due to other factors as the

intervention), were categorized as "poor". Studies which 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.[30] 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 versus low risk of bias.

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

Systematic reviews which fulfilled inclusion criteria were rated for quality using pre-defined criteria (see Appendix B): a clear statement of the questions and inclusion criteria; adequacy of the search strategy; quality assessment of individual trials; the adequacy of information provided; and appropriateness of the methods of synthesis.

Data Analysis and Synthesis

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

We recorded the mean difference between baseline and follow-up measures for the 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 or the groups at baseline, assuming a correlation between baseline and follow-up of 0.75. If data were only presented in graphical form, point estimates were determined from published graphs. Pooled effects of the RCTs 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.[31] Review Manager (RevMan) was used for the meta-analysis (version 4.2 for Windows; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003).

An adjusted indirect comparison was performed for the outcome of A1c by combining the results of the meta-analysis comparing pioglitazone and placebo, with the meta-analysis comparing rosiglitazone with placebo. The variance of the estimate of effect was estimated as the sum of the variances of the two meta-analyses being pooled.[32]

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.[33] We also examined

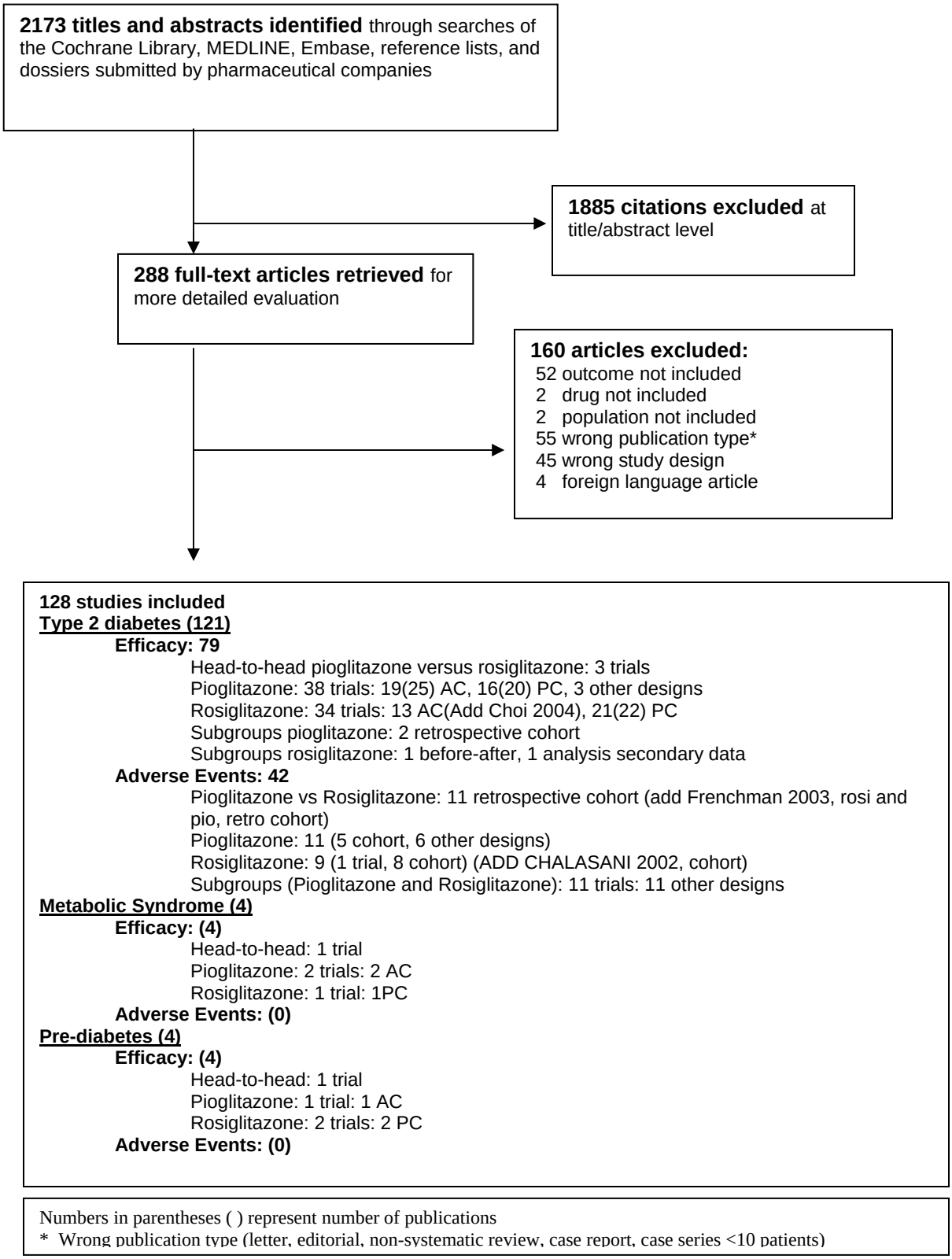
inconsistency among studies with I^2, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (i.e. chance).[30] A value >50% may be considered substantial heterogeneity. If heterogeneity was found, we attempted to determine potential reasons for this by examining individual study characteristics and those of subgroups of the main body of evidence. If heterogeneity was too great to meaningfully pool the results in a quantitative manner, the results are presented in a narrative fashion.

Meta-regression was performed to determine whether the study-level characteristics of duration of the intervention and study sponsorship (industry or private) affected the between-group change in A1c for placebo-controlled trials. For studies using a combination of a thiazolidinedione and another hypoglycemic agent, we examined the effects of insulin, metformin or sulfonylurea on A1c. For the meta-regression we used STATA (version 9, StataCorp LP, College Station, Texas, USA).

RESULTS

Our searches identified 87 RCTs examining the efficacy or effectiveness of pioglitazone or rosiglitazone and 42 studies examining the safety and tolerability of these drugs. 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



Findings of prior systematic reviews

Ten reviews reporting comprehensive searches were identified (Evidence Tables 1 and 2). Six of the reviews were rated of poor quality, as they lacked one 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.[34; 35 36-39] Details of the four fair- to good-quality systematic reviews are provided in Evidence Table 1.

Chilcott and colleagues[40] examined pioglitazone exclusively and noted that there were no studies at that time (publication year 2001) directly comparing pioglitazone to other antidiabetic drugs. They noted a decrease in triglyceride concentrations (30-70 mg/dl), an increase in HDL (4-5 mg/dl), no significant differences in LDL and total cholesterol (with a paucity of data), and 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 concentrations.

Three systematic reviews examined both pioglitazone and rosiglitazone.[41-43] Boucher and colleagues[41] compared the two thiazolidinediones to other antidiabetic drugs; their stated objective was not to compare the effectiveness of pioglitazone and rosiglitazone. They concluded that as monotherapy these two drugs have effects similar to comparator drugs on A1c, and when added to another antidiabetic agent the A1c is significantly improved compared to the original treatment regime. Both drugs were well tolerated, with a few cases of heart failure and severe hypoglycemia noted with combined therapies, and no liver toxicity was observed.

Chiquette et al.[42] reviewed pioglitazone and rosiglitazone placebo-controlled trials 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,[43] Czoski-Murray and colleagues also noted that both pioglitazone and rosiglitazone produced similar improvements in A1c (approximately 1.0%). They did not identify any RCTs comparing the two drugs, and noted that there were no peer-reviewed data on long-term effects.

Key Question 1. For patients with type 2 diabetes, do thiazolidinediones differ in the ability to reduce A1C levels

a. when used as monotherapy?
b. when added to or substituted for other oral hypoglycemic agents?

Head-to-head trials

Three fair-quality, head-to-head RCTs (in four publications) were identified examining persons with type 2 diabetes (Table 3 and Evidence Table 3).[44-47] Two randomized, controlled, double-blind trials demonstrated significant improvements in A1c at follow-up[44 46] with no significant differences between groups. In an open-label trial, Kahn and colleagues[47] 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.

Table 3. Head-to-head trials comparing pioglitazone to rosiglitazone in persons with type 2 diabetes

Study	Dosages	Combination therapy	Total sample size; Follow-up; Other characteristics	A1c (%) baseline; Change from baseline (mean, SD)	Quality; Funder
Derosa 2004[44], 2005[45]	PIO: 15mg qd ROSI: 4 mg qd	Both groups received glimepiride 4mg qd	87 12m Participants also 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
Goldberg 2005[46]	PIO: 30-45 mg qd ROSI: 4mg qd-bid	Monotherapy	735 24w 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 Study jointly funded by Eli Lilly and Takeda Pharmaceuticals, North America
Kahn 2002[47]	PIO: 15-45mg qd ROSI: 2 mg qd to 4 mg bid	Monotherapy; Troglitazone withdrawn	127 16w Open-label	Pio: 8.0(1.7); NR Rosi: 7.9(1.9); NR NSD at follow-up in either group	Fair NR

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

We identified 16 trials comparing pioglitazone to placebo in at least one study arm (Table 4 and Evidence table 4). All but one of these trials had sufficient data to permit a meta-analysis; a study by Saad and colleagues[48] did not provide a measure of dispersion. The weighted mean difference between groups for all studies comparing pioglitazone to placebo ranged from -3.0% to -0.1%; the pooled weighted mean difference was -0.99 (95% CI, -1.18 to -0.81) (Table 4). In other words, overall, pioglitazone improved A1c about 1.0% compared to placebo. Heterogeneity among these studies was significant ($p<0.00001$).

Results were somewhat more pronounced when monotherapy with pioglitazone was compared to placebo, than when combined therapy (the addition of pioglitazone to another hypoglycemic drug) was compared to placebo added to the other drug, although the differences among these groups were not significant (Table 4).

The study with the most pronounced net decrease in A1c was by Miyazaki and colleagues 2002.[49] This small study (total sample size 58) produced a change in the 45-mg-daily group and the placebo group of -1.8% and 1.2%, respectively (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 cointerventions 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 to placebo.[50; 51] Dormandy and colleagues[50] 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. These researchers noted a decrease in A1c of 0.8% and 0.3% in the intervention and control 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 contributed to a non-significant ($p>0.05$) effect on A1c, as well as the down-weighting of the study in our pooled estimate of A1c. The participants in this study were relatively well controlled at baseline 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. This factors likely also contributed to the relatively small between-group change. The study by Tagagi[51] was small and the control group also improved.

Placebo-controlled trials of rosiglitazone

Twenty-two trials compared the efficacy or effectiveness of rosiglitazone to placebo (Table 4 and Evidence Table 5). Three rosiglitazone studies did not provide adequate information for inclusion in the meta-analysis: Honisett et al.[52] did not provide a measure of dispersion; the units for A1c in a paper by Raskin and colleagues[53] were difficult to interpret; and Nolan and colleagues[54] provided a measure of fasting glucose but not A1c.

Mean weighted differences are presented in Table 4. Results are similar to those noted for pioglitazone, with a mean change in A1c for all studies of approximately -1.0`%. Again, heterogeneity is 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 two drugs for the outcome of A1c (Table 5).

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 on the outcome of change in A1c.

Table 4. Pioglitazone placebo-controlled trials: study and population characteristics

Study	Dosage Combination therapy	Sample size intervention group	Sample size placebo group	Follow-up (weeks)	Age (years); % Female; Other population characteristics	Baseline Weight (kg) BMI (kg/m^2) A1c (%)	Quality Funder
Aronoff 2000[55]	7.5, 15, 30, 45 mg qd Monotherapy	320	79	26	53.79NR0 42% For all groups combined	90.4(13.1) NR 10.4(2.0)	Poor Takeda America
Dormandy 2005[50], Charbonnel 2005[56]	Titrated up to 45 mg qd Combined with various hypoglycemic agents	2605	2633	156 (mean 34.5m)	61.6(7.8) 34% Evidence of macrovascular disease	NR 31.0(4.8) 7.9(NR)	Good Takeda Pharmaceutical company and Eli Lilly and Company
Herz 2003[57]	30, 45 mg qd Monotherapy	99	99	16	58.0(10.7) 50.5 Poorly controlled DM2 on diet only	86.3(17.4) 31.7(4.5) 7.5(NR)	Fair Eli Lilly
Kipnes 2001[58]	15, 30 mg qd Added to SU	184+189	187	16	56.8(8.9) 42%	NR 32.0(4.9) 9.9(1.4)	Fair Takeda Pharmaceuticals
Mattoo 2005[59]	30 mg qd Combined with insulin	142	147	26	58.8(7.4) 57% Using insulin for ≥3m	NR 32.5(4.8) 8.9(1.3)	Fair Eli Lilly and Takeda
McMahon 2005[60]	45 mg qd used with insulin	8	8	12	52.5(NR) 11% Using insulin	NR 32.3(4.1) 7.7(0.6)	Poor Takeda, American Heart Association, NHLBI
Miyazaki 2002[49]	7.5, 15 mg qd Monotherapy	47	11	26	58.0(9.9) 73%	90(13.3) 32.8(5.3) 8.6(1.7)	Fair Takeda
Miyazaki 2001[61] 2004[62]	45 mg qd Added to SU	12	11	16	55(13.3) 45% Generally healthy	82(16.6) 30(3.3) 8.2(1.0) Data from 2004 (2001 baseline	Poor Takeda America (in part)

Table 4. Pioglitazone placebo-controlled trials: study and population characteristics

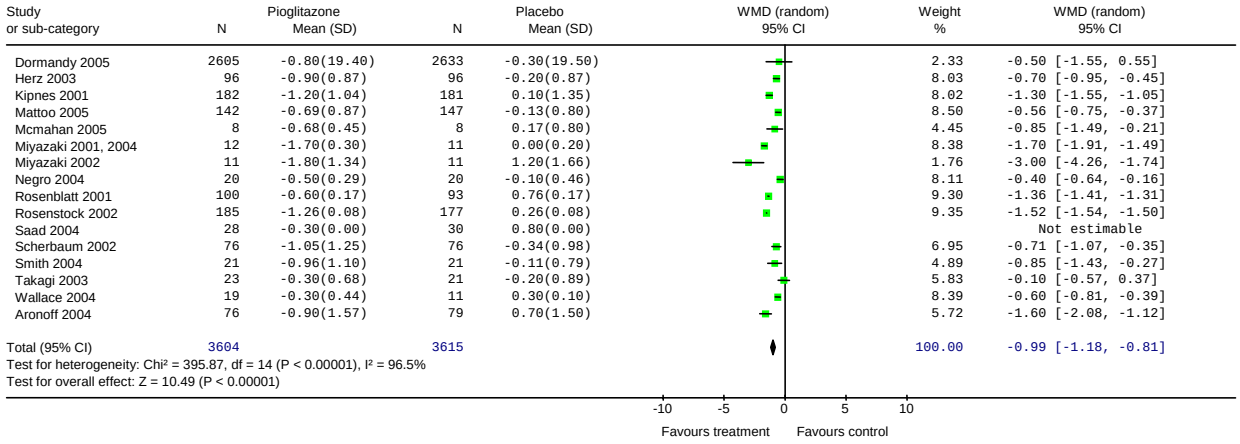
Study	Dosage Combination therapy	Sample size intervention group	Sample size placebo group	Follow-up (weeks)	Age (years); % Female; Other population characteristics	Baseline Weight (kg) BMI (kg/m^2) A1c (%)	Quality Funder
						data slightly different)	
Negro 2004[63]	45 mg qd Added to metformin	20	20	8	61.9(6.0) NR On metformin	NR 26.7(2.4) 7.7(0.6)	Poor NR
Rosenblatt 2001[64]	30 mg qd Monotherapy	101	96	16	55.2(10.01) 43.8%	87.2(18.4) 30.7(5.0) 10.4(1.7)	Fair Takeda Pharmaceuticals
Rosenstock 2002[65]	15, 30 mg qd Monotherapy	379	187	16	56.7(9.4) 55 Using insulin	95.4(17) 33.2(5.2) 9.8(0.1)	Fair Takeda Pharmaceuticals
Saad 2004[48]	45 mg qd Monotherapy	147	30	12	54 40%	NR 31(NR) 8.1(NR)	Fair Funding NR; one author affiliation Novo-Nordisk Pharmaceuticals, Princeton, NJ
Scherbaum 2002[66]	15, 30 mg qd Monotherapy	76+83	76	26	59.1(NR) 44	84.8(NR) 29.2(NR) 8.8(1.1)	Poor Takeda Pharmaceuticals, Europe
Smith 2004[67] Bogacka 2004[68]	45 mg qd Monotherapy	21	21	24	53.1(9.3) 53%	91.5(14.9) 31.9(5.0) 6.5(0.7)	Poor Takeda Pharmaceuticals, Inc, USA
Takagi T 2003[51]	Combined with various treatments	23	21	26	65(9) 50% Known coronary heart disease	NR 24.5(2.9) 6.7(1.2)	Poor NR
Wallace 2004[69]	45 mg qd Monotherapy	19	11	12	62.6(10) 27% Diet-controlled	85.2(4.3) 28.9(2.8) 6.7(0.9)	Fair Takeda UK
Range	7.5 to 45 mg qd	11 to 2605	11 to 2633	8 to 156w	54 to 64 0 to 57%	81.4 to 90.4 kg 23 to 32 kg/m^2	Good: 1 Fair: 8 Poor: 8

Table 5. Meta-analysis results for A1c

Drug	Number of studies	Total N	Weighted mean difference (95% CI)	Test for heterogeneity (p-value)
Pioglitazone				
All studies	16	7219	-0.99(-1.18, -0.81)	<0.00001
Monotherapy	9	1206	-1.10(-1.31, -0.92)	<0.00001
Combined therapy	7	6013	-0.80(-1.28, -0.32)	<0.00001
Rosiglitazone				
All studies	21	3204	-0.92(-1.2, -0.64)	<0.00001
Monotherapy	11	1196	-0.86(-1.42, -0.31)	0.002
Combined therapy	10	2008	-1.01 (-1.2, -0.81)	<0.00001

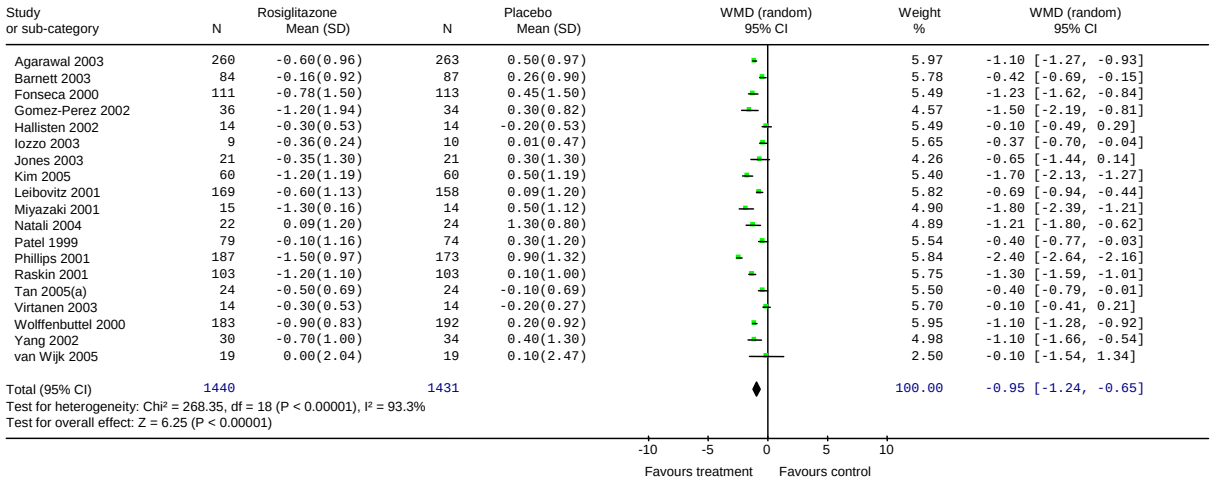
A1c values given as (%). Net change is the difference in A1c between the end of the study period and baseline. CI, confidence interval; N, sample size

Figure 2. Pioglitazone versus placebo for A1c (%)



Both monotherapy and combined therapy are presented.

Figure 3. Rosiglitazone versus placebo for A1c (%)



Both monotherapy and combined therapy are presented.

Table 6. Rosiglitazone placebo-controlled trials: study and population characteristics

Study	Dosage Combination therapy	Sample size intervention group(s)	Sample size placebo group	Follow-up (weeks)	Age (years); % Female; Other population characteristics	Baseline Weight (kg) BMI (kg/m^2) A1c (%)	Quality Funder
Agrawal A 2003[70]	4 mg qd, 2 mg bid Various SU	260	263	26	61.6 38% Normal renal function (see subgroups for renal-impaired)	NR 30.7 9.2	Fair (based on secondary data) NR
Barnett A 2003[71]	4 mg bid Various SU	84	87	26	54.2 22% Participants Indian 60%) Pakistani (27%)	NR 26.4 9.1	Fair SmithKlineBeecham Pharmaceuticals
Fonseca V 2000[72]	4,8 mg qd With metformin	226	113	26	58 32%	NR 30.3(4.4) 8.6(1.3)	Fair SmithKline Beecham Pharmaceuticals
Gomez-Perez FJ 2002[73]	2 mg bid, 4 mg bid With metformin	71	34	26	53.1 74%	NR 28.5(3.9) 9.8(NR)	Fair Not reported; 3 authors (including corresponding author) from GlaxoSmithKline
Hallsten K 2002[74]	4 mg bid Monotherapy	14	14	26	58.0 32% Without complications	88.3(9.4) NR 6.3(0.4)	Fair Academy of Finland, Novo Nordisk Foundation, Finnish Diabetes Research Society, and GlaxoSmithKline

Table 6. Rosiglitazone placebo-controlled trials: study and population characteristics

Study	Dosage Combination therapy	Sample size intervention group(s)	Sample size placebo group	Follow-up (weeks)	Age (years); % Female; Other population characteristics	Baseline Weight (kg) BMI (kg/m^2) A1c (%)	Quality Funder
Honisett SY 2003[52]	4 mg qd Monotherapy	21	10	12	NR 100% Postmenopausal women	NR NR 7.6(3.2) (Rosi group)	Poor NR
Iozzo 2003[75]	8 mg qd Monotherapy	9	10	26	58 33% No prior pharmacotherapy for DM2	NR 31.5(4.7) 6.1(0.7)	Fair GlaxoSmithKline
Jones 2003[76]	4,8 mg qd With metformin	80+44	93	26	59.9 32% BMI 25-30 (obese presented in subgroups)	NR 27.7(1.4) 8.8(1.4)	Fair Funder NR; 3 of 4 authors from GlaxoSmithKline
Kim 2005[77]	4 mg qd Monotherapy	60	60	12	58.4(9.1) 65% Taking metformin or SU	62.3(11.0) 24.5(3.0) 9.3(1.3)	Fair National R&D program, Ministry of Science Technology, Republic of Korea
Lebovitz HE 2001[78]	4,8 mg qd Monotherapy	169+166	158	26	60 34%	NR 29.9(4.,1) 9.0(1.7)	Poor Not reported. 5 of 6 authors from SmithKline Beecham Pharmaceuticals

Table 6. Rosiglitazone placebo-controlled trials: study and population characteristics

Study	Dosage Combination therapy	Sample size intervention group(s)	Sample size placebo group	Follow-up (weeks)	Age (years); % Female; Other population characteristics	Baseline Weight (kg) BMI (kg/m^2) A1c (%)	Quality Funder
Miyazaki 2001[79]	8 mg qd Monotherapy	15	14	12	56(2) 36%	87.0(18.7) 30.1(3.7) 8.3(1.5)	Fair SmithKline Beecham
Natali 2004[80]	8 mg qd Monotherapy	22	24	8	58(9) 18%	NR 30.2(3.1) 7.6(0.8)	Fair GlaxoSmithKline
Nolan 2000[54]	4,8,12, mg qd Monotherapy	276	93	8	62.8(9.5) 39%	81.3(14.5) 29.6(4.4) NR	Fair Funder NR; 3 of 4 authors from SmithKline Beecham Pharmaceuticals
Patel 1999[81]	0.05, 0.25, 1.0, 2.0 mg bid Monotherapy	74+72+79+90	74	12	56.8(11.5) 31%	NR 29.1(4.2) 8.9(1.5)	Fair Authors from SmithKline Beecham and VA funding NR
Phillips 2001[82]	2 bid, 4 qd, 4 bid, 8 qd Monotherapy	735	173	26	56.8(9.2) 31%	NR 29.1(4.2) 8.9(1.5)	Fair Funder NR, author affiliations include SmithKline Beecham Pharmaceuticals, USA

Table 6. Rosiglitazone placebo-controlled trials: study and population characteristics

Study	Dosage Combination therapy	Sample size intervention group(s)	Sample size placebo group	Follow-up (weeks)	Age (years); % Female; Other population characteristics	Baseline Weight (kg) BMI (kg/m^2) A1c (%)	Quality Funder
Raskin 2001[83]	2, 4 mg bid With insulin	103+106	104	26	55.6(10.3) 44%	NR 32.7(4.5) 8.9(1.1)	Good Not reported; individual authors have received support from SmithKline Beecham
Reynolds LR 2002	4 mg qd With insulin	11	10	24	NR NR BMI>27	108.0(29) 36.3(2,5) 9.8(1.6)	Poor Health management Resources and GlaxosmithKline
Raskin 2000[53]	2,3,6, bid	215	69	8	60.1(9.4) 40.6%	NR 30.4(4.2) 0.087(0.0163) (reference range <0.065)	Fair Funder NR; 5 of 6 authors from SmithKline Beecham Pharmaceuticals
Tan GD 2005(a)[84]	4 mg bid Monotherapy	12	12	12	52.3(10.1) 46% No prior pharmacotherapy for DM2	NR 32.8(4.9) 7.5(1.0)	Fair GlaxoSmithKline
van Wijk JPH 2005[85]	4 mg bid Monotherapy	19 (cross-over)	19 (cross-over)	8	60 26%	NR 29.2(4.8) 6.2(0.9)	Fair GlaxoSmithKline

Table 6. Rosiglitazone placebo-controlled trials: study and population characteristics

Study	Dosage Combination therapy	Sample size intervention group(s)	Sample size placebo group	Follow-up (weeks)	Age (years); % Female; Other population characteristics	Baseline Weight (kg) BMI (kg/m^2) A1c (%)	Quality Funder
Wang G 2005	4 mg qd Monotherapy	35	35	26	62.2(8.6) 20% Coronary artery disease after percutaneous coronary intervention	NR 25.6(2.7) 7.33(0.17)	Fair Major National Basic Research Program of PR China and Chinese National Natural Science Foundation
Virtanen KA 2003[86]	4 mg bid Monotherapy	14	14	26	58(7.5) 40%	88.3(9.7) 30.7(4.9) 6.3(0.4)	Fair Academy of Finland, Novo Nordisk Foundation, Finnish Diabetes Research Society, and GlaxoSmithKline
Wolffenbuttel 2000[87]	1,2 mg bid With various SU	183+199	192	26	61.9(9.1) 43% Using SU for >6m	NR 28.1(4.1) 9.2(1.3)	Fair Not reported. One of 5 authors from SmithKlineBeecham
Yang 2002[88]	4 mg qd With various SU	30	34	26	57.8(8.9) 61.8%	65.3(11.2) 25.8(3.5) 9.7(1.4)	Fair Smith-Kline Beecham Pharmaceuticals and a grant from the Department of Education of the Republic of China

Table 6. Rosiglitazone placebo-controlled trials: study and population characteristics

Study	Dosage Combination therapy	Sample size intervention group(s)	Sample size placebo group	Follow-up (weeks)	Age (years); % Female; Other population characteristics	Baseline Weight (kg) BMI (kg/m^2) A1c (%)	Quality Funder
Zhu XX 2003	2,4 mg bid With various SU	425	105	24	58.9(7.7) 54% Chinese, no hepatic impairment	NR 25.1(2.8) 9.8(1.3)	Fair SmithKlineBeecham Research and Development
Range	4 to 12 mg qd	9 to 276	10 to 263	8 to 26w	55 to 61.6y 16 to 100%	88.3 to 62 24.5 to 32.8 kg/m^2	Good: 1 Fair: 19 Poor: 1

Baseline values are given for the control group.
Standard deviation is given in brackets ( ).
If standard error was provided in the original study, we have converted that to standard deviation.

Table 7. Indirect comparison of pioglitazone and rosiglitazone for A1c (%)

`	Difference in A1c (%) (pioglitazone-rosiglitazone)	95% CI
All studies	0.07	-0.41, 0.27
Monotherapy	-0.24	-0.83, 0.35
Combined therapy	0.21	-0.31, 0.73

Active-controlled trials

Selected active-controlled trials were identified based on our *a priori* inclusion criteria of follow-up period >12 months, sample size >500, health or quality-of life outcomes, or examination of population subgroups. These studies are presented in Evidence Tables 6 and 7. Since these studies did not provide data on comparative efficacy or effectiveness, we do not disucss them further. Active-controlled trials not reviewed herein are listed in Appendix B. In Key Question 8, several active-controlled trials are presented as they provided data on demographic and comorbidity subgroups.

Key Question 2. For patients with type 2 diabetes do thiazolidinediones differ in the ability to prevent the macrovascular and microvascular complications of diabetes

a. **when used as monotherapy?**
b. **when added to or substituted for other oral hypoglycemic agents?**

Three studies identified in this review examined cardiovascular outcomes; all examined patients with known macrovascular disease and type 2 diabetes[50; 89; 90] No studies examined microvascular outcomes. These two studies do not provide sufficient data to determine comparative effectiveness of pioglitazone and rosiglitazone on microvascular or macrovascular complications of diabetes. Both studies provide some evidence of positive effects of these drugs on macrovascular outcomes among patients with preexisting coronary artery disease.

Wang and colleagues[89] performed an RCT of rosiglitazone 4 mg daily for 6 months compared to no treatment (total sample size 70). 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 5). 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 four events in the rosiglitazone group (recurrent angina [3] and coronary artery bypass grafting [1]) and 12 in the control group (recurrent angina [5], repeated angioplasty [3], and coronary artery bypass grafting [4]) and 12 events in the control group not receiving rosiglitazone. An increase in HDL (between-group $p>0.05$ at 6 months) and a decrease

C-reactive protein (between-group p-value <0.05 at 6 months) and other inflammatory markers led the authors to suggest that rosiglitazone may protect the vascular wall through both improved metabolic parameters as well as by a reduction in proinflammatory responses.

In a good-quality, European multicenter, randomized, placebo-controlled, trial of 5238 patients with type 2 diabetes and evidence of macrovascular disease,[50] 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 of this endpoint was 0.90 (95% CI, 0.80 – 1.02). When examined individually, 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 (0.72 – 0.98).

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.[90] In this open-label, RCT, the treatment group was placed on 8 mg of rosiglitazone before undergoing catheterization and 4 mg daily thereafter, combined with conventional antidiabetic therapy using a variety of agents (details of concurrent therapy are not provided). The comparison group received conventional therapy only. The rate of restenosis was 17.6% in the rosiglitazone group and 38.2% 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 provide little information on the question of comparative effectiveness of pioglitazone and rosiglitazone when used as monotherapy, or when added to, or substituted for, other oral hypoglycemic agents. Dormandy and colleagues[50] addressed the question of combined therapy (pioglitazone was added to other anti-diabetic therapy in 96% of patients). In the study by Wang et al.[89]monotherapy and combined therapy patients were aggregated, so conclusions can not be drawn about each of these two approaches.

Key Question 3. 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?**

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

Weight or BMI were measured in six studies of prediabetes or the metabolic syndrome (Table 8), including two head-to-head studies. One head-to-head study[45] reported increased weight with both pioglitazone and rosiglitazone with no significant difference between groups;

the other study[91] reported weight gain with pioglitazone (2.5 kg, SD 6.3), rosiglitazone (0.3 kg, SD 5.5), and the control group (2.0 kg, SD 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 to metformin or a sulfonylureas as monotherapy.[92] Rosiglitazone did not produce a significant change in weight compared to placebo in two small studies.[93; 94] Waist-to-hip ratio[93] and waist circumference[94] 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?

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 two relevant studies were identified, both involving monotherapy (Evidence Table 3 and 9; Table 8).[91; 93] Neither of these studies was designed to investigate the comparative effectiveness of these two drugs or to allow a comparison with a placebo group for the outcome of diabetes incidence.

A controlled trial compared a no-treatment group, pioglitazone, and rosiglitazone (both as monotherapy) in 172 persons with IGT.[91] At three-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 two thiazolidinediones for this outcome.

In a small, poor quality trial, Hung and colleagues[93] compared rosiglitazone as monotherapy to placebo among persons with IGT at 12 weeks follow-up. They noted a reversal to a normal oral glucose tolerance test in 33% of participants taking rosiglitazone (versus 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.

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

Data are insufficient to determine the comparative effectiveness of pioglitazone and rosiglitazone on cardiovascular risk factors among persons with prediabetes or the metabolic syndrome. Six studies provided data relevant to this question. 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 two drugs for these two outcomes.

More detailed information on the studies which examined cardiovascular risk factors among persons with prediabetes or the metabolic syndrome are presented in Table 8 and Evidence Tables 2, 8, and 9. Pioglitazone produced a significant ($p<0.05$) decrease in LDL, total cholesterol, and triglycerides compared to rosiglitazone in a head-to-head study.[44; 45] Pioglitazone produced small improvements in lipids compared to metformin in a poor-quality study, but between-group p-values were not presented.[92; 95] Lester and colleagues[92] 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.

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.[93] In another small study,[94] rosiglitazone increased HDL ($p=0.032$) and LDL ($p=0.025$) compared to placebo.

Rosiglitazone produced a decrease in both systolic and diastolic pressure compared to placebo in two small studies.[93; 94]

Table 8. 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 (%)*	Change in blood pressure* (mm Hg)	Change in lipid levels* (mg/dl)	Change in weight*, BMI*, or central obesity*	Occurrence of clinical diabetes
Head-to-head trials								
Derosa G 2004[44], 2005[45] Fair	RCT 91	Pio 15 mg qd or Rosi 4 mg qd 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 (kg/m^2) Pio: 1.2 Rosi: 1.5 p>0.05	NA
Durbin R 2004[91] Fair	Controlled trial 172 3 years	Pio 30 mg or Rosi 4 mg qd Monotherapy (treatment groups were on troglitazone previously)	Prediabetes (IGT) 56.4 Insulin resistance	Pio: -0.12 Rosi: -0.14 Control: 0.43 TZD vs 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[92] Based on 4 fair-quality studies	4 RCTs (subset analysis) 3186 16-40 weeks	Pio 15-45 mg qd Monotherapy and combined	Metabolic syndrome NR DM2 inadequately managed with metformin	Pio: -1.6 Pio+SU -1.3 Pio+metformin -1.1 Pio vs 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 LDL: Pio 8.9; Pio+SU 5.1;	Weight (kg) Pio 2.5; Pio+SU 3.0; Pio+metformin NR Increased weight in Pio vs metformin or SU alone (p<0.05)	NR

Table 8. 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 (%)*	Change in blood pressure* (mm Hg)	Change in lipid levels* (mg/dl)	Change in weight*, BMI*, or central obesity*	Occurrence of clinical diabetes
						Pio+metformin 9.7 TG: Pio -12.8; Pio+SU -12.2; Pio+metformin -12.8		
Rasouli N 2005[95] Poor	RCT 23 12 weeks	Pio 45 mg qd 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 (kg/m^2) Pio 0.9 Metformin -0.3 No between-group p-values given	NR
Rosiglitazone								
Bennett S 2004[96] Fair	RCT 18 12 weeks	Rosi 4 mg bid 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[93] Poor	RCT 30 12 weeks	Rosi 4 mg qd 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 Between-group p-values NR	BMI: Rosi: 0; placebo -0.3 Waist-hip ratio: Rosi -0.01; placebo -0.014 Between-group p-values NR	Reversal to normal oral glucose tolerance test: Rosi 33%, placebo 13% Progression to DM2: Rosi: 0 cases; placebo 1

Table 8. 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 (%)*	Change in blood pressure* (mm Hg)	Change in lipid levels* (mg/dl)	Change in weight*, BMI*, or central obesity*	Occurrence of clinical diabetes
Wang T 2004[94] Fair	RCT 50 8 weeks	Rosi 4 mg qd 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)	case NR

P-values given are between-group values.
* Absolute changes unless otherwise noted

Key Question 6. For patients with type 2 diabetes, prediabetes, or the metabolic syndrome, do thiazolidinediones differ in safety or adverse effects (e.g., congestive heart failure, pulmonary edema, weight gain, liver toxicity, hypoglycemia)?

a. when used as monotherapy?
b. when added to or substituted for other oral hypoglycemic agents?

Direct Evidence

Two head-to-head efficacy trials were conducted in patients with type 2 diabetes.[46; 47] In one,[46] 719 patients with both type 2 diabetes and dyslipidemia were randomized to treatment with pioglitazone 30 mg for 12 weeks followed by 45 mg for an additional 12 weeks, or rosiglitazone 4 mg followed by 8 mg for the same intervals. There were no differences between the drugs in adverse events including weight changes (2.0±0.2 kg for pioglitazone vs 1.6±0.2 kg for rosiglitazone; p=0.164), liver function tests, creatine phosphokinase, 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 vs 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.[47] 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 or metabolic syndrome,[44] there was no significant difference in the increase in BMI after 12 months of treatment with pioglitazone 15 mg (1.2 kg/m^2) or rosiglitazone 4 mg (1.5 kg/m^2). Other adverse events were not reported.

Indirect Evidence

Overall withdrawals

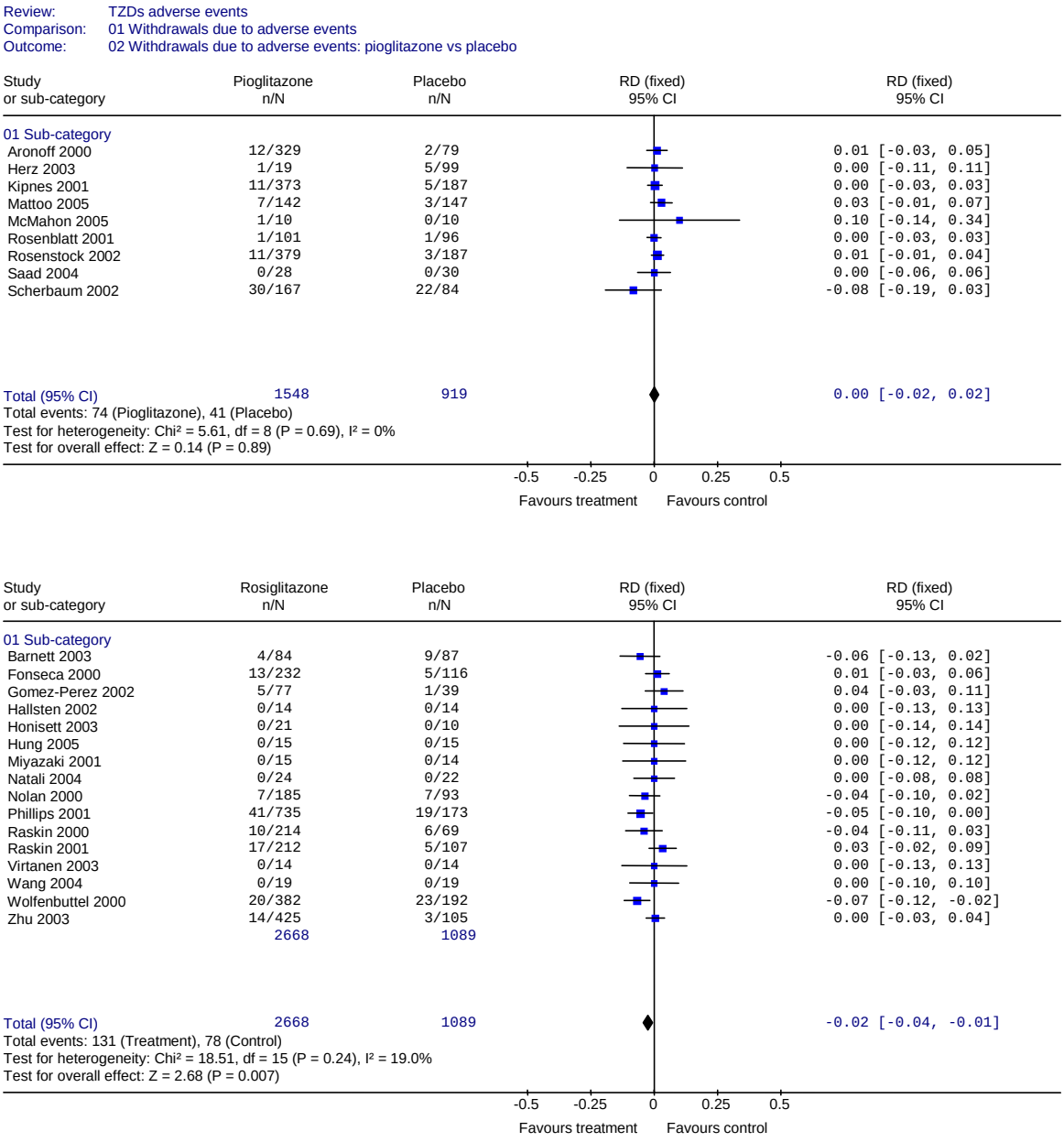
Eight placebo-controlled trials of pioglitazone[48; 50; 57-60; 66; 67] and 11 of rosiglitazone[52-54; 73; 74; 78-80; 82; 85; 86; 88; 93; 94; 97] reported overall withdrawal rates. Treatment group withdrawal rates ranged from 7% to 33% in pioglitazone trials and 0 to 27% in rosiglitazone trials. Withdrawals were not significantly higher than placebo in any study, and the pooled risk difference versus placebo was similar for pioglitazone trials (–1.0%[95% CI –3.0%, 1.0%]) and rosiglitazone trials (–3.0% [95% CI –9.0%, 2.0%]).

Withdrawals due to adverse events

Figure 4 shows withdrawals due to adverse events reported in placebo-controlled trials of rosiglitazone and of pioglitazone. The overall rates were similar: 4.8% in pioglitazone trials and 4.9% in rosiglitazone trials, and were not significantly different from placebo in most trials. The pooled risk difference was significantly lower than placebo in rosiglitazone trials (–2% [95% CI –4% to –1%]) and not significantly different from placebo in pioglitazone trials (0% [95% CI –

2% to 2%]). However, the rate of withdrawals due to adverse events in the placebo groups differed between these groups of studies (4.5% in pioglitazone studies vs 7.2% in rosiglitazone studies), so the pooled risk differences were not directly comparable.

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



Specific adverse events

The quality of reporting of adverse events in RCTs designed to measure efficacy was fair to poor (Evidence Table 15). Most studies did not pre-specify which events were evaluated and did not report details about ascertainment methods.

Table 9 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.

Table 9. Adverse events reported in placebo-controlled trials (% of patients)

Adverse event	Pioglitazone	Rosiglitazone
Anemia		
Monotherapy		
Combination therapy		1.9%[70], (SU) 7.1%[76] (MET)*
Arthralgia, myalgia, back pain, leg pain		
Monotherapy	3% (15mg) to 10%* (30mg)[57] 3%[66] 10%* (30 mg)[57]	
Combination therapy		6%[71] (SU)
Cardiac-related events		
Monotherapy	3.6%[55]	
Combination therapy	5.9%[58] (SU)	0.2%[97] (SU) 3.9%[73] (MET)
Congestive heart failure		
Monotherapy	11%*[50]	
Combination therapy	1%[65] (INSULIN) 12.5%[60] (INSULIN)	
Cough		
Monotherapy		
Combination therapy		7%[71]
Diarrhea, flatulence		
Monotherapy		
Combination therapy		12.7%[76] (MET) 7%[71]
Dizziness		
Monotherapy		5%[71]
Combination therapy		5%[71]
Edema		
Monotherapy	0% (15 mg) to 3% (30 mg) [66] 3.6%[55] 5%[64] 14%-16%[57] 15.3%*[65] 22%*[50]	6.6% (4 mg bid)*[82]
Combination therapy	7%[58] (SU)*	2.5%(4 mg)-3.5%(8 mg)[72] (MET)

Table 9. Adverse events reported in placebo-controlled trials (% of patients)		
Adverse event	**Pioglitazone**	**Rosiglitazone**
	12.5%[60](INSULIN) 14.1%[59](INSULIN)*	4.1%[70](SU)* 5.2%[73] (MET) Legs: 9.5%(4mg)* to 12.2%(8mg)* Face: 4.1% (4 mg)* to 5.0%(8 mg)* (SU)[97]
Fatigue Monotherapy		
Combination therapy		5.9%[76] (MET)
Headache Monotherapy	5.3%[69] 12.4%[55]	
Combination therapy		4.9%[70] (SU) 6%[71] (SU) 6.5%[76] (MET)
Hyperglycemia Monotherapy		
Combination therapy		1%[71] (SU) 5.3% (4 mg) to 9.3% (2 mg)[87] (SU)
Hypoglycemia Monotherapy	0%[64] 1.2% [55] 10%(30mg) to 11%(45mg)[57] 28%*[50]	
Combination therapy	1.9%[58] (SU) 8% (15mg) to 15% (30mg)* (INSULIN) [65] 37.5%[60] (INSULIN) 63.4%* (INSULIN)[59]	3.4% (2 mg) to 5.3% (4 mg) [87] (SU) 5.1%[70] (SU) 12%[71] (SU)
Influenza-like symptoms Monotherapy	2% to 9% [66]	
Combination therapy		10%[71] (SU)
Injury/accident Monotherapy	2%[50]	
Combination therapy		0.9% (4. mg), 1.4% (8 mg)[97] (SU) 6.6%[70] (SU) 8%[76] (Metformin)
Liver function test abnormal (ALT>3 times ULN) Monotherapy	0.77%[50] 0.94%[55]	0.44%[81] 0.30%[78] 0%[54] 0.14%[82]
Combination therapy	0%[58] (SU) 0.26%[65] (insulin)	0%[73] (Metformin)) 0%[70] (SU)
Paresthesia Monotherapy		
Combination therapy		6%[71] (SU)
Thrombocytopenia Monotherapy		
Combination therapy		4.1% (4 mg), 7.7* (8 mg)[97] (SU)
URTI, rhinitis, sinusitis, bronchitis Monotherapy	3% to 4%[66] 15.2%[55]	
Combination therapy		8% (NS)[71](SU) 8.6%[70] (SU) 15.9%*[76] 16.7% (4 mg), 10.0% (8 mg)*[97] (SU)

Table 9. Adverse events reported in placebo-controlled trials (% of patients)		
Adverse event	**Pioglitazone**	**Rosiglitazone**
Urinary tract infection, cystitis Monotherapy	1% to 5%[66]	
Combination therapy		9.0%(4mg)* to 10.9% (8 mg)* (SU)[97]
Vision abnormal Monotherapy		
Combination therapy		2.3% (4 mg), 2.3% (8 mg) (SU)[97]
Weight gain	See Table 10	See Table 10

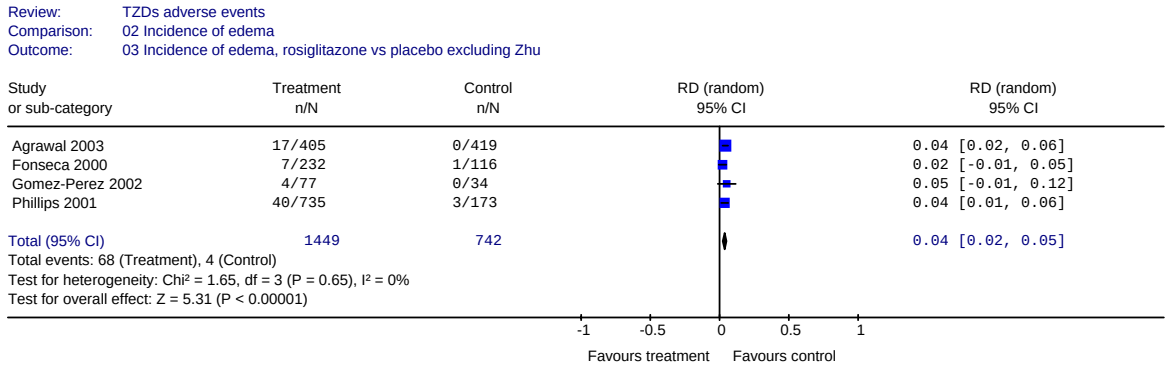
*significantly greater than placebo ($p<0.05$)

Edema

The incidence of edema reported in 14 placebo-controlled trials ranged from 0% to 27%. The incidence of edema was significantly greater with both pioglitazone and rosiglitazone than placebo.

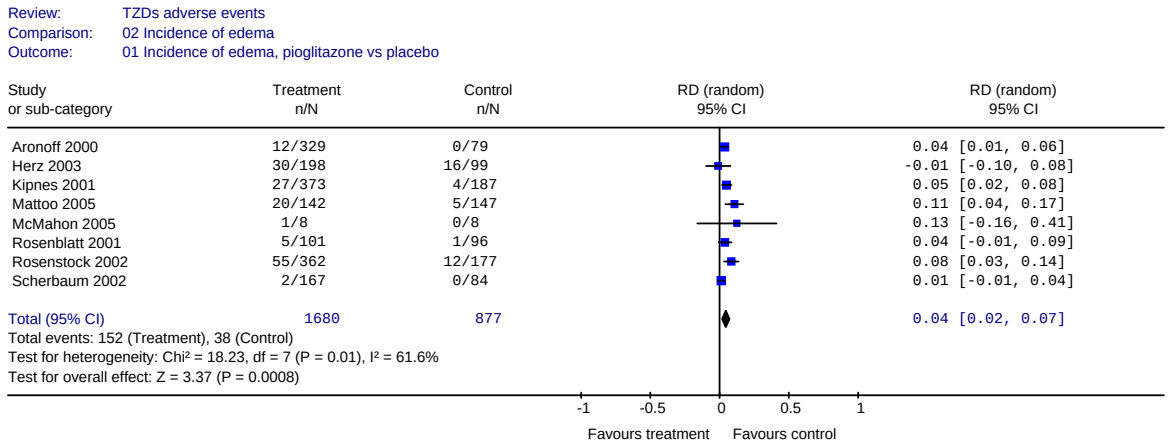
The pooled risk difference in five rosiglitazone trials[70; 72; 73; 82; 97] was 8% (95% CI 1% to 14%). One trial of rosiglitazone 4 mg or 8 mg added to patients taking sulfonylureas had a much higher incidence of edema than the other four trials (24%).[97] Excluding this trial (Figure 5), the pooled risk difference compared to placebo was 4% (95% CI 2% to 5%).

Figure 5. Incidence of edema in placebo-controlled trials of rosiglitazone



The pooled risk difference was also greater than placebo in pioglitazone trials and was similar to rosiglitazone (risk difference 4%; 95% CI 2% to 7%) (Figure 6).

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

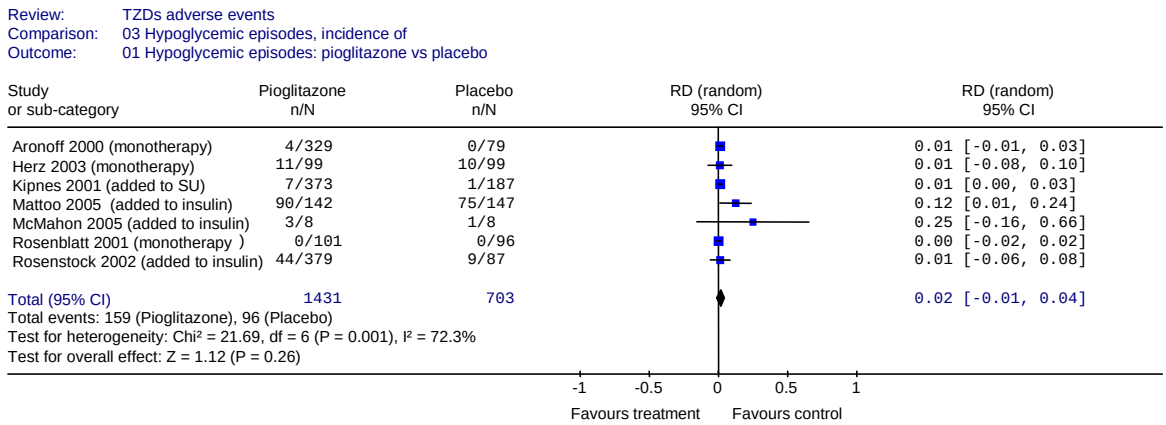


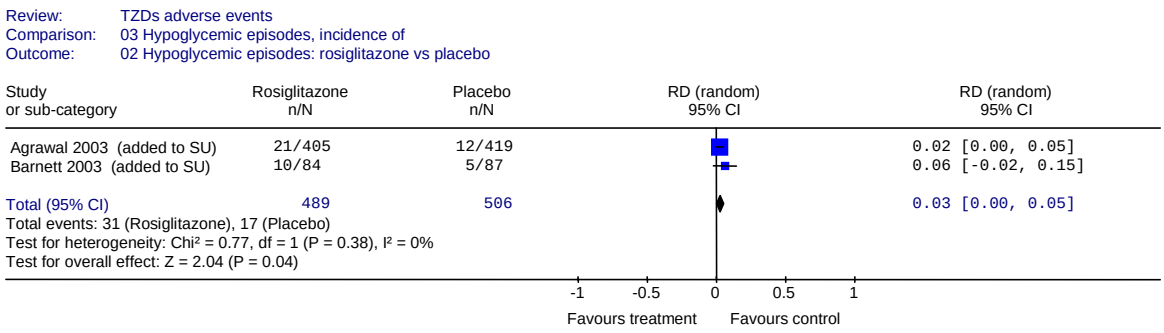
Hypoglycemia

The incidence of hypoglycemic episodes was reported in nine placebo-controlled efficacy trials. The incidence was 5.2% and 11.9% in two studies of rosiglitazone, and ranged from 0 to 37.5% in seven studies of pioglitazone. The pooled risk difference compared with placebo was not significantly different for either drug, however (see Figure 7).

In both trials of rosiglitazone, combination therapy with sulfonylureas was used.[70; 71] In pioglitazone trials, three used monotherapy,[55; 57; 64] one used combination therapy with sulfonylureas,[58] and three used combination therapy with insulin.[59; 60; 65] Pooled risk differences were not significantly different from placebo in pioglitazone trials using monotherapy (1%; 95% CI –1% to 2%), or combination therapy with sulfonylureas (1%; 95% CI –1%, 2%), or insulin (7%; 95% CI –4%, 19%). The highest rates of hypoglycemic events were noted in two studies where pioglitazone was combined with insulin.[59; 60]

Figure 7. Incidence of hypoglycemic episodes in placebo-controlled trials





Weight gain

Nineteen 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 (e.g., BMI, change in weight, or patients gaining >5% of body weight) and limited reporting of results (e.g., means were reported without a measure of dispersion). Table 10 shows the range of weight gain reported in placebo-controlled trials. Trials with several doses found increased weight gain associated with higher doses.

Only four 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, 4.89)[78; 88] and rosiglitazone (3.50 kg; 95% CI 2.25, 4.75), [61; 67] 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 in three head-to-head trials.[44; 46; 47]

Table 10. Weight gain reported in placebo-controlled trials

Outcome	Pioglitazone	Rosiglitazone
Weighted mean difference vs placebo (kg)	3.69 (95% CI 2.48, 4.89) [78; 88]	3.50 (95% CI 2.25, 4.75) [61; 67]
Range of weight gain (kg)	0.3 to 0.8[66](p NR)	0[86]
Monotherapy	0.35 to 0.82[57]*	0.5[80] (p NR)
	0.74[69]	0.6[74] (p NR)
	1.35[64]*	1.2 to 3.3[82](p NR)
	1.3 to 2.8[55]	1.6 to 3.5[78] (p NR)
	2.0, 3.0*, 4.5*[49]	3.7[79]*
	3.6[50]*	
Range of weight gain (kg)	1.9 to 2.9[58]*	0.26 to 2.42[73](p NR)
Combination therapy	2.3 to 3.7[65](p NR)	3.0[88](p NR)
	3.6[61]	
	3.88[67] (p NR)	

*significantly greater than placebo ($p<0.05$)

A 2004 meta-analysis[42] 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 ($p>0.10$).

Liver function abnormalities

The first TZD approved for use in the U.S., troglitazone, was withdrawn from the US 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 incidences of less than 1% reported (See Table 9).

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 and rosiglitazone compared with patients using insulin and 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%[60] and 1%.[65]

The pioglitazone product label[23] cites a 24-week postmarketing study comparing pioglitazone to 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 to 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.

Observational studies comparing adverse events in pioglitazone and rosiglitazone

Overview

We identified 12 observational studies that compared adverse events in patients taking pioglitazone versus patients taking rosiglitazone (Evidence Table 16). Five of these were designed to assess specific adverse events; in the others, adverse events were reported but were not the primary outcome.

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 17.

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.[98] 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 one case of pulmonary edema in a patient taking rosiglitazone.

In a retrospective chart review,[99] pulmonary edema was noted in two patients (1.9%) taking pioglitazone and three taking rosiglitazone (3.1%). Four of these had existing congestive heart failure treated with diuretics. Another study[100] 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.[101] 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 one trial of rosiglitazone in combination with sulfonylureas,[97] 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=1,347) or rosiglitazone (1,882) for up to 40 months.[102] Compared to 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 two 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.[98] 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 11).[99; 103-108] There was no difference in the amount of weight gain in patients taking pioglitazone versus rosiglitazone in any study.

Table 11. Range of weight gain (kg) reported in comparative observational studies

Study*	Duration of use	Pioglitazone	Rosiglitazone
King 2000[108]	16 weeks	0.5	2.6
LaCivita 2002[104]	6 months (range 3-11 months)	1.6	1.5
Boyle 2002[103]	18 weeks	2.0	1.6
Olansky 2003[105]	12 weeks or longer	2.0	1.6
Harmel 2002[107]	25-27 weeks	2.2	1.6
Hussein 2004[99]	8 weeks or longer	2.3	2.9
Gegick 2004[106]	1 year	4.1	3.0

*There was no significant difference between drugs in any study

Other Observational Studies of Adverse Events

We identified 20 additional observational studies of adverse events associated with individual thiazolidinediones; they are detailed in Evidence Tables 17 (pioglitazone), 18 (rosiglitazone), and 19 (quality assessment).[109-128] Their results were consistent with evidence from RCTs 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. How do thiazolidinediones compare to sulfonylureas in serious hypoglycemic events, functional status, and quality of life?

Trials comparing pioglitazone or rosiglitazone to a sulfonylurea are presented in Tables 12 and 13). 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.[129] There were no direct comparisons of the incidence of hypoglycemic events with pioglitazone and rosiglitazone versus 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 six studies (Table 12). Statistical comparisons were presented in only three of these studies, however, and two demonstrated significantly lower rates of hypoglycemia with pioglitazone ($p=0.024$)[130]and $p<0.001$[131]). 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 one study (Table 13). The incidence was lower with rosiglitazone compared to glyburide.[132] Three additional studies examined combined therapy with rosiglitazone and a sulfonylurea versus monotherapy with the sulfonylurea. In all three studies the rates for hypoglycemic events were higher with the combined therapy.[133-135]

Rosenstock and colleagues[129] published a study after our cut-off for inclusion, as mentioned above. This RCT 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 two treatment groups (32% with rosiglitazone plus glipizide versus 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 12. Comparisons of pioglitazone to sulphonylureas for the outcomes of serious hypoglycemic events, functional status, and quality of life

Study	Dosage	Comparison sulphonylurea	Hypoglycemic events (% of patients with an event)	Functional status HRQL	Study quality
Charbonnel BH 2004[136]	45 mg qd	Gliclazide up to 160 mg bid	Pio: 3.5% Gliclazide: 10.1%, 1/63 required hospitalization No statistics	NR NR	Poor
Langenfeld MR 2005[137] Pfutzer A 2005[138]	45 mg qd	Glimepiride 1-6 mg qd; Average 2.7 mg qd	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[139]	15-45 mg qd 70% on 45 mg qd All received metformin	Gliclazide 80-320 mg qd 33% on 320 mg qd All received metformin	Pio: 1.3% Gliclazide: 11.2%; 2/35 withdrew None reported as severe	NR NR	Fair
Tan 2004 (a[131])	30-45 mg qd 75% on 45 mg qd	Glibenclamide: 1.75-10.5 mg qd 62% on 10.5 mg qd	Incidence of any hypoglycemia greater in glibenclamide group (p<0.0001) Number of events NR	NR NR	Poor
Tan 2004[130]	15-45 mg qd Mean dosage 37 mg qd	Glimepiride 2-8 mg qd Mean dosage 6 mg qd	Pio: 15.7% Glimepiride: 30.9% P=0.024 No data on severity	NR NR	Fair
Watanabe 2004[140]	15 mg or more qd (range NR) Mean 17.3 mg qd	Glibenclamide: 1.25-2.5 mg qd Mean dosage 1.56 mg qd	Pio: no events Glibenclamide: 1 episode in 14 patients (7.1%); led to withdrawal from study; no other details	NR NR	Fair

Table 13. Comparisons of rosiglitazone to sulphonylureas for the outcomes of hypoglycemic events, functional status, and quality of life

Study	Dosage	Comparison sulphonylurea	Incidence of hypoglycemic events (% of patients with an event)	Functional status HRQL	Study quality
Baski A 2004[133]	4 mg bid + gliclazide 160 mg qd	Gliclazide 160 mg qd	Rosi: 6% total; 1% severe Gliclazide: 2% total; 0.4% severe Definition: Inability to perform normal daily activities	NR NR	Fair
Kerenyi A 2004[135]	8 mg qd + glibenclamide 7.5 mg qd	Glibenclamide 7.5 - 15 mg qd	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[132]	4 mg bid	Glyburide mean 10.5 mg qd	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[134]	2 mg bid + 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

Key Question 8. Are there subgroups of patients based on demographics (age, racial groups, gender), concomitant medications (drug-drug interactions), co-morbidities (i.e. obesity), or history of hypoglycemic episodes for which one thiazolidinedione is more effective or associated with fewer adverse effects?

a. when used as monotherapy?

b. when added to or substituted for other oral hypoglycemic agents?

The majority of studies were conducted in the United States or in Western Europe, and examined Caucasian populations. Some studies included minority populations but did not present subgroup analyses on these populations.[91] 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 two drugs under review among populations with significant comorbidities.

Subgroups based on demographic characteristics

Only two publications examined subgroups defined by age. Kreider and colleagues[141] pooled the results of eight RCTs examining monotherapy with rosiglitazone, and examined subgroups of age less than and greater than 70 years. They found no differences between the two age groups for A1c and found rosiglitazone well-tolerated in both age groups. The percentage of persons with at least one adverse 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 either younger patients taking the drug or the placebo group. Weight gain was higher in the under-seventy group (2.14 kg) than the over-seventy group (1.66 kg) or the placebo groups (<70 years -0.41 kg; >70 years -1.34 kg).

Rajagopalan and colleagues[127] examined the effect of pioglitazone on glucose control and lipid levels in patients <65 and ≥65 years, using data from five separate trials (four trials were unpublished data from Takeda Pharmaceuticals and the fifth study was by Rosenblatt et al.,[64] a placebo-controlled trial found in Evidence Table 4). The study by Rosenblatt and colleagues[64] 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 and 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[142] 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.[143] Pioglitazone was equally as effective as glimepiride among 244 Mexican patients.[130]

Barnett and colleages[71] 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.[134] examined a mixed Asian and Caucasian population and their results were also consistent with findings in largely Caucasian populations in other studies of rosiglitazone.

Comorbidities and other population characteristics

Patients with impaired renal function were examined in several studies. Agrawal and colleagues[70] examined patients with renal impairment (creatinine clearance 30-80 ml/min) and

found that rosiglitazone had similar effects on A1c compared to patients without renal impairment. In a retrospective chart review[144] 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 to pioglitazone. Data for pioglitazone, however, were not presented, limiting conclusions that can be drawn.

In a fair-quality study which pooled two RCTs comparing rosiglitazone and metformin combined therapy to metformin monotherapy, Jones and colleagues,[76] examined subgroups with BMI < 25 kg/m^2, 25-30 kg/m^2, and >30 kg/m^2. They noted greater improvement in A1c with both rosiglitazone 4 and 8 mg daily, compared to metformin monotherapy (p=0.025). Safety profiles were similar in all three subgroups. Weight gain was noted in the obese group (BMI > 30 kg/m^2) receiving metformin and rosiglitazone (2.5 kg) compared with a loss of 0.9 kg in obese patients on metformin alone. Weight change was not reported for the other BMI subgroups.

Patients with diagnosed coronary artery disease were examined in three studies which were described above in Key Question 2, as these were the only studies which reported cardiovascular outcomes. Wang and colleagues[89] 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[94] also examined Chinese persons with the metabolic syndrome and found that fasting plasma glucose did not improve significantly in either the rosiglitazone or the placebo group (A1c was not presented).

Choi and colleagues[90] 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 two 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 placebo-controlled trial of rosiglitazone 4 mg daily.[52] 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 which 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.

Table 14. Studies examining subgroups based on demographic characteristics or comorbidities

Author, year Quality rating	Country Setting	Study design	Race/ ethnicity	Concurrent hypoglycemic treatment	Inclusion criteria Exclusion criteria	Age (years) (SD) Female (%)	Baseline A1c (%) (SD) Weight (kg) or BMI (kg/m^2)	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, >18y, 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) 83%	10.4(1.7) 78.9 (21.4) 32.0(8.1)	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 45mg/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) Non-Hispanics: 61.2(12.8) NR	Hispanics: 8.2 (1.9) non-Hispanics: 8.0(1.9) Hispanics: 89.2 kg Non-Hispanics: 99.6 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	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: NY Heart Association 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 older-aged group

									using pioglitazone combined with a sulfonylurea or insulin.
Tan M (glimepiride) 2004 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 (NY Heart Association 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) 51%	NR 74.4kg	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 2' data	UK Multicenter	RCT, PC, DB, secondary data from 3 RCTs examined subgroup with decreased renal function (creatinine clearance 30-80 ml/min)	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) 38%	9.15(NR) 28.8 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 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) 22%	9.13(NR) 26.6mg/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	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) 58%	8.6 71.7kg	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)

Choi D 2004	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) 30%	7.72 (1.13) 68.1 (11.0) 24.8 (3.35)	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%	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) 32%	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

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%	<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); placebo 29.8(4.2) >70 years: Rosi: 28.3(3.9); placebo 28.4(4.1)	A1c at 26 weeks <70 years: Rosi 4 mg qd: -0.2; 8 mg qd -0.5; placebo 0.8 >70 years: Rosi 4 mg qd: -0.1; 8 mg qd: -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; 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.	56.0(NR)56%	NR68.9 kg27.1 kg/m2	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

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) 18%	7.33(0.17) 25.6(2.7) mg/m2	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)
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) 42%	NR 25.4(NR) mg/m2	A1c NR FPG: NSD within or between groups (p>0.05)	AEs reported as none

Pioglitazone and rosiglitazone									
Manley HJ 2003 Fair, for 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) Range: 46-85 35%	8.6(2.2) NR	Comparison of Rosi to Pio: interdialytic weight change ROSI: 3.6kg 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.

CONCLUSIONS

Table 15. Summary of the evidence by Key Question

Key Question	Quality of Evidence	Conclusion:
Key Question 1: For patients with type 2 diabetes, do TZDs differ in the ability to reduce A1c levels when used as a) monotherapy? b) when added to or substituted for other oral hypoglycemic agents?	Good	Prior systematic reviews: - These did not identify head-to-head data comparing Pio and Rosi. - Both drugs appear to have similar effects on A1c, producing a decrease of approximately 1%. - Side effect profiles appear to be similar. Outcomes of this review: - 3 head-to-head studies demonstrated NSD between Pio and Rosi on A1c. - Indirect comparison of Pio and Rosi demonstrated no difference between Pio and Rosi [(Pio- Rosi): -0.04% (95% CI, -0.39, 0.31)]. Effect of both Pio and Rosi appears to be similar when used in either monotherapy or combination therapy.
Key Question 2: For patients with type 2 diabetes, do TZDs differ in the ability to prevent the macrovascular and microvascular complications of diabetes a) when used as monotherapy? b) when added to or substituted for other oral hypoglycemic agents?	Body of evidence is insufficient	- Two studies examined cardiovascular outcomes in patients with known macrovascular disease. - No studies examined microvascular outcomes. - Data are not sufficient to determine the comparative effectiveness of Pio and Rosi on microvascular or macrovascular complications of diabetes. - Both studies provide evidence of positive effects of these drugs on macrovascular outcomes among patients with preexisting coronary artery disease.
Key Question 3: For patients with prediabetes or metabolic syndrome, do TZDs differ from one another or from placebo in improving weight control a) when used as monotherapy? b) when added to metformin?	Body of evidence is insufficient	- There are very 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 patients with prediabetes or metabolic syndrome, do TZDs differ from one another or from placebo in delaying the occurrence of clinical diabetes?	Body of evidence is insufficient	- Two studies were identified which examined the occurrence of clinical diabetes in these populations; both involved monotherapy. - There are insufficient data to determine whether Pio and Rosi have different effects on the incidence of diabetes among persons with either prediabetes or the metabolic syndrome.
Key Question 5: For patients with prediabetes or metabolic syndrome, is the use of different TZDs associated with reversal or slower progression of cardiac risk factors, including lipid levels, central obesity, or elevated blood pressure?	Body of evidence is insufficient	- Data are insufficient to determine the comparative effectiveness of Pio and Rosi on cardiovascular risk factors among persons with prediabetes or the metabolic syndrome. - Six studies provided data relevant to this question. - 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

Table 15. Summary of the evidence by Key Question

Key Question	Quality of Evidence	Conclusion:
		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 patients with type 2 diabetes, prediabetes, or metabolic syndrome, do TZDs differ in safety or adverse effects (e.g., congestive heart failure, pulmonary edema, weight gain, liver toxicity, hypoglycemia)? a) when used as monotherapy? b) when added to or substituted for other oral hypoglycemic agents?	Good to fair	- Head-to-head and placebo-controlled trials provide good evidence that the TZDs are similar on withdrawals and withdrawals due to adverse events. - Head-to-head trials, placebo-controlled trials, and observational studies found weight gain associated with both TZDs, but no difference between the drugs in the amount of weight gained. - The incidence of other specific adverse events, including edema and hypoglycemic episodes, was similar for the TZDs in placebo-controlled trials. The incidence of edema was greater than placebo for both TZDs. - The quality of reporting of adverse events in trials was fair to poor.
Key Question 7: How do TZDs compare to sulfonylureas in serious hypoglycemic events, functional status, and quality of life?	Body of evidence is insufficient	Hypoglycemia: - Few studies compared TZDs and sulfonylureas for hypoglycemia Pioglitazone - Two of six studies which examined hypoglycemia reported significantly fewer events with Pio than 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 - There were no comparative data on functional status or quality of life from any efficacy or effectiveness trial which compared TZDs and sulfonylureas.
Key Question 8: Are there subgroups of patients based on demographics (age, racial groups, gender), concomitant medications (drug-drug interactions), co-morbidities (i.e. obesity), or history of hypoglycemic episodes for which one TZD is more effective or associated with fewer adverse effects? a) when used as monotherapy? b) when added to or substituted for other oral hypoglycemic agents	Demographic characteristics: Fair quality evidence Comorbidities and other characteristics: Poor quality evidence	Demographic characteristics - The vast majority of studies were conducted in the United States or in Western Europe and examined Caucasian populations. - There are limited data, derived from indirect comparisons (placebo-controlled studies), on the comparative effectiveness of Pio and Rosi among persons with various demographic characteristics. - This 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 older-aged persons. Analysis of secondary data suggest that both Pio and Rosi monotherapy are well-tolerated in older adults. Comorbidities and other characteristics

Table 15. Summary of the evidence by Key Question

Key Question	Quality of Evidence	Conclusion:
		- Most of the studies identified in this review examined persons with type 2 diabetes without significant comorbidities. - There is a paucity of data on the interaction of TZDs and micro- and macrovascular diseases and no conclusions can be drawn on the comparative effectiveness of the two drugs under review among populations with significant comorbidities.

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Appendix A. Search Strategies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2005>
Search Strategy:
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1 Pioglitazone.mp. (79)
2 Rosiglitazone.mp. (101)
3 THIAZOLIDINEDIONE$.mp. (261)
4 1 or 2 or 3 (287)
5 from 4 keep 1-287 (287)

Database: Ovid MEDLINE(R) <1966 to July Week 4 2005>
Search Strategy:
---
1 (Pioglitazone or Rosiglitazone or THIAZOLIDINEDIONE$).mp. (3741)
2 (ae or po or to or ct).fs. (1086710)
3 1 and 2 (559)
4 limit 3 to (humans and english language) (436)
5 from 4 keep 1-436 (436)Database: Ovid MEDLINE(R) <1966 to June Week 2 2004>
Search Strategy:

Database: Ovid MEDLINE(R) <1966 to July Week 4 2005>
Search Strategy:
---
1 exp THIAZOLIDINEDIONES/ (3020)
2 (Pioglitazone or Rosiglitazone or THIAZOLIDINEDIONE$).mp. (3741)
3 1 or 2 (3741)
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] (12960)
5 3 and 4 (292)
6 from 5 keep 1-292 (292)

Database: Ovid MEDLINE(R) <1966 to July Week 4 2005>
Search Strategy:
---
1 exp THIAZOLIDINEDIONES/ (3020)
2 Pioglitazone.mp. (859)
3 Rosiglitazone.mp. (1142)

4 THIAZOLIDINEDIONE$.mp. (3580)
5 1 or 2 or 3 or 4 (3741)
6 exp Diabetes Mellitus/dt [Drug Therapy] (27833)
7 5 and 6 (1081)
8 limit 7 to english language (922)
9 limit 8 to (clinical trial or evaluation studies or guideline or meta analysis) (222)
10 exp Epidemiologic Studies/ (818610)
11 Comparative Study/ (1203918)
12 exp Evaluation Studies/ (526275)
13 10 or 11 or 12 (2240935)
14 7 and 13 (308)
15 9 or 14 (447)
16 from 15 keep 1-447 (447)

Database: Ovid MEDLINE(R) <1966 to July Week 4 2005>
Search Strategy:
---
1 exp THIAZOLIDINEDIONES/ (3020)
2 (Rosiglitazone or Pioglitazone or THIAZOLIDINEDIONE$).mp. (3741)
3 exp Diabetic Angiopathies/ (23486)
4 1 and 3 (70)
5 (((vascula$ 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] (64492)
6 1 and 5 (145)
7 4 or 6 (149)
8 limit 7 to english language (125)
9 from 8 keep 1-125 (125)

Database: Ovid MEDLINE(R) <1966 to July Week 4 2005>
Search Strategy:
---
1 exp THIAZOLIDINEDIONES/ (3020)
2 (Pioglitazone or Rosiglitazone or THIAZOLIDINEDIONE$).mp. (3741)
3 1 or 2 (3741)
4 exp Prediabetic State/ (2038)
5 exp Metabolic Syndrome X/ (1858)
6 (pre-diabet$ or prediabet$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2882)
7 (metabolic adj syndrome$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3580)
8 4 or 5 or 6 or 7 (6407)
9 3 and 8 (160)
10 limit 9 to english language (135)

11 from 10 keep 1-135 (135)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2005>
Search Strategy:
---
1 Pioglitazone.mp. (7)
2 Rosiglitazone.mp. (9)
3 THIAZOLIDINEDIONE$.mp. (12)
4 1 or 2 or 3 (13)
5 from 4 keep 1-13 (13)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2005>
Search Strategy:
---
1 Pioglitazone.mp. (4)
2 Rosiglitazone.mp. (4)
3 THIAZOLIDINEDIONE$.mp. (6)
4 1 or 2 or 3 (6)
5 from 4 keep 1-6 (6)

Appendix B. Excluded Active-Controlled 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. 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.

16. 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.

17. 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.

18. 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.

19. 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 individual studies for the Drug Effectiveness Review Project

This document outlines the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, to produce drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the conclusions from this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the National Health Service Centre for Reviews and Dissemination(CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and The Database of Abstracts of Reviews of Effects (DARE) in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are 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 the true difference between the compared drugs.

Controlled trials

Assessment of Internal Validity

1. Was the 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, birth dates or week days
    - 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, birth dates or week days

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 (i.e., 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 followup or overall high loss to followup? (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 followup? (Give numbers at each stage of attrition.)

Studies using designs other than controlled clinical trials

(Studies used for the examination of safety, tolerability, and adverse events, as well as the efficacy or effectiveness among subpopulations)

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

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

3. Were the events investigated specified and defined?

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

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

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

7. Did the duration of followup correlate to 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 in the study?

Systematic reviews

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

   A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four 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, i.e., 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?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, 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, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been 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 (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either 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 (i.e. how many reviewers 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 judgement 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 (e.g., 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.

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	Codes
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	5

Dis 2004; 4:209.	
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	2

type 2 diabetes mellitus. Endocr Pract 2002; 8 (4):271-5.	
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 2003; 26 (3):825-31.	5
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	6

failure. Am. J. Gastroenterol. 2002; 97 (2):502-3.	
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
Decsi, T., Molnar, D. Insulin resistance syndrome in children : pathophysiology and potential management strategies. Paediatr Drugs 2003; 5 (5):291-9.	2
Derosa, G., Cicero, A. F. G., Murdolo, G., Ciccarelli, L., Fogari, R. Comparison of metabolic effects of orlistat and sibutramine treatment in Type 2 diabetic obese patients. Diabetes, Nutri Metab Clin 2004; 17 (4):222-9.	5
Desmet, C., Warzee, B., Gosset, P., Melotte, D., Rongvaux, A., Gillet, L., Fievez, L., Seumois, G., Vanderplasschen, A., Staels, B., Lekeux, P., Bureau, F. Pro-inflammatory properties for thiazolidinediones. Biochem. Pharmacol. 2005; 69 (2):255-65.	2
Dhawan, M., Agrawal, R., Ravi, J., Gulati, S., Silverman, J., Nathan, G., Raab, S., Brodmerkel, G., Jr. Rosiglitazone-induced granulomatous hepatitis. J. Clin. Gastroenterol. 2002; 34 (5):582-4.	6
Diamant, M., Heine, R. J. Thiazolidinediones in type 2 diabetes mellitus: current clinical evidence. Drugs 2003; 63 (13):1373-405.	5
Ebcioglu, Z., Morgan, J., Carey, C., Capuzzi, D. Paradoxical lowering of high-density lipoprotein cholesterol level in 2 patients receiving fenofibrate and a thiazolidinedione. Ann. Intern. Med. 2003; 139 (9):W80.	5
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.	2
Farley-Hills, E., Sivasankar, R., Martin, M. Fatal liver failure associated with pioglitazone. Br. Med. J. 2004; 329 (7463):429.	6
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Appendix E. Abbreviations used in the TZD report

A1c: Hemoglobin A1c, HbA1c
ADA: American Diabetes Association
AEs: adverse events
ALT: alanine aminotransferase
AST: aspartate aminitransferase
bid: twice daily
BMI: body mass index
BP: blood pressure
CI: confidence interval
CRP: C-reactive protein
CVA: cerebrovascular attack
d: day(d)
DBP: diastolic blood pressure
FPG: fasting plasma glucose
HDL: high density lipoprotein, HDL-C
HR: hazards ratio
HRQL: health-related quality of life
kg: kilogram(s)
LDL: low density lipoprotein, LDL, C
LFT: liver function tests
LOCF: last outcome carried forward
m: month(s)
MI: myocardial infarction
NA: not applicable
NR: not reported
NSD: no significant difference
PIO: pioglitazone
PPG: post-prandial glucose
qd: daily
ROSI: rosiglitazone
SBP: systolic blood pressure
SD: standard deviation
SE: standard error of the mean
SU: sulfonylurea
TC: total cholesterol
TG: triglycerides
tid: three times daily
URTI: upper respiratory tract infection
y: year(s)