Oregon Health Resources Commission

Thiazolidinediones

Subcommittee Report
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Overview

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

In the summer of 2006 the Oregon Health Resources Commission (HRC) appointed a subcommittee to perform an evidence-based review of the use of Thiazolidinediones (TZD). Members of the subcommittee consisted of four doctors, one physician assistant, one pharmacist and one nurse. The subcommittee had four meetings. All meetings were held in public with appropriate notice provided.

Subcommittee members worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities.

Using standardized methods, the Oregon Evidence-based Practice Center (EPC) reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The Oregon EPC's report, "Drug Class Review on Thiazolidinediones" was completed in May 2006, circulated to subcommittee members and posted on the web. The subcommittee met on June 1, 2006 to review the document and by consensus agreed to adopt the EPC report. Time was allotted for public comment, questions and testimony at each meeting

This report does not recite or characterize all the evidence that was discussed by the Oregon EPC or the Health Resources Commission. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the Health Resources Commission in providing recommendations to the Department of Human Services.

The Standing Update Committee of the Health Resources Commission, working together with the EPCs, Center, OMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. At least once per year new pharmaceuticals in this class will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration (FDA) changes in indications and safety recommendations will be evaluated. The

Thiazolidinediones report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene the Thiazolidinediones Subcommittee.

The full OHSU Evidence-based Practice Center's draft report, *Drug Class Review on Thiazolidinediones*" is available on the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website: http://egov.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website:

http://www.oregon.gov/DAS/OHPPR/HRC/PMPDP.shtml

You may request more information including copies of the draft report, minutes and tapes of subcommittee meetings, from:

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

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

Critical Policy

- *Senate Bill 819*
  - "The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price."

- *Health Resources Commission*
  - "Clinical outcomes are the most important indicators of comparative effectiveness"
  - "If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

Quality of the Evidence

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

Internal validity of each trial was based on:

1. Methods used for randomization
2. Allocation concealment and blinding
3. Similarity of compared groups at baseline and maintenance of comparable groups.
4. Adequate reporting of dropouts, attrition, and crossover
5. Loss to follow-up
6. Use of intention-to-treat analysis

External validity of trials was assessed based on:

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

Weighing the Evidence

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

Clinical Overview

Diabetes

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

The prevalence and incidence of diabetes are increasing both in the U.S. and world-wide. The total prevalence of diabetes in the U.S. for all ages is estimated at 7.0%, or 20.8 million people; approximately one-third of those cases are undiagnosed. The prevalence of type 2 diabetes varies among racial and ethnic groups: non-Hispanic blacks 20 year or older 13.3%, Hispanic/Latino Americans 9.5%, American Indians and Alaska natives 12.8%, and 8.7% among non-Hispanic whites. The prevalence of type 2 diabetes is increasing among children and adolescents. True prevalence data are not available as yet, however, the percentage of children with newly diagnosed diabetes who are classified as having type 2 diabetes has risen from <5% before 1994 to 30-50% subsequent to that year.

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

Heart disease is the leading cause of diabetes-related deaths and adults with diabetes have a death rate from heart disease that is 2 to 4 times higher than adults without diabetes. The risk for stroke is 2 to 4 times higher among people with diabetes and two-thirds of people with diabetes

die of heart disease or stroke. Diabetes is associated with other diseases and cardiovascular risk factors including hypertension.

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

Diabetes treatment

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

Pre-diabetes

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

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

with IGT when compared to placebo, after approximately 30 months of treatment and 8 months of post-treatment follow-up.

Metabolic Syndrome

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

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

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

[1] National Institutes of Health. Third Report of the National Cholestrol Education Program. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Daults (Adult Treatment Panel III) Bethesda, MD: National Institutes of Health, 2001.

Definition of Thiazolidinediones

There are two thiazolidinediones approved for prescription use in the United States, rosiglitazone maleate (Avandia™) and pioglitazone hydrochloride (Actos™) (Table 2). A third TZD (Troglitazone™) was removed from the market in 1999 due to adverse hepatic effects. Both rosiglitazone and pioglitazone are approved by the U.S. Food and Drug Administration (FDA) for use in adults for the treatment of type 2 diabetes, either as monotherapy, or in combination with insulin, metformin, or sulfonylurea when diet, exercise and a single agent does not results in adequate glycemic control. *Neither drug is currently approved for use in pre-diabetes or the metabolic syndrome.*

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

Other uses of thiazolidinediones

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

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

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

Scope and Key Questions

Key Questions

1a. For patients with type 2 diabetes, do thiazolidinediones differ in the ability to reduce A1C levels when used as monotherapy?

There is good quality evidence from three head-to-head trials that both pioglitazone and rosiglitazone appear to have similar efficacy in reducing A1C by 1%.[2,3,4] This evidence is

[2] Derosa G, Cicero AF, Gaddi A, et al. Metabolic effects of pioglitazone and rosiglitazone in patients with diabetes and metabolic syndrome treated with glimepiride:a twelve-month, multicenter, double-blind, randomized, controlled, parallel-group trial. *Clin Ther* 2004;26(5):744-54.

[3] Derosa G, Cicerao AFG, Gaddi A, et al. A comparison of the effects of pioglitazone and rosiglitazone combined with glimpiride on prothrombotic state in type 2 diabetic patients with the metabolic syndrome. *Diabetes Res Clin Pract* 2005;69(1):5-13.

further supported by indirect comparison of pioglitazone and rosiglitazone from 9 fair/good quality placebo-controlled trials that demonstrated no significant difference between these drugs.

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

There is only one head-to-head trial where pioglitazone and rosiglitazone are used in combination therapy with glimepiride and substituted for troglitazone (removed from the market for liver toxicity.)[5] This trial revealed no significant difference between the newer TZDs.

There were no acceptable trials that compared TZDs to other oral hypoglycemic agents.

Key Question 1

The TZD Subcommittee agrees by consensus that:

1a. There is good evidence that thiazolidinediones do not significantly differ in their ability to reduce A1C levels when used as monotherapy for patients with type 2 diabetes.

1b. There is one fair quality study demonstrating that thiazolidinediones do not significantly differ in their ability to reduce A1C levels when substituted for troglitazone in patients with type 2 diabetes already on glimeperide.

2a. For patients with type 2 diabetes, do thiazolidinediones differ in the ability to prevent the macrovascular and microvascular complications of diabetes when used as monotherapy?

The body of evidence was insufficient to answer these questions. No studies were reported for microvascular complications. For macrovascular complications there were two placebo-controlled studies, but the study designs were so heterogeneous that no valid comparisons could be made. Both studies provide some evidence of positive effects of these drugs on macrovascular outcomes among patients with preexisting coronary artery disease.

One short (6 month), small (N=70) trial[6] with diabetics who had rosiglitazone added to their regimen (41% already had taken other oral hypoglycemic agents) and who already had a

[4] Goldberg RB, Kendall DM, Deeg MA, et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 2005;28(7):1547-54.
[5] Khan MA, St Peter JV, Xue JL. A prospective, randomized comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. *Diabetes Care* 2002;25(4):708-11.

percutaneous transthoracic coronary artery (PTCA) intervention showed a statistically significant diminution in further coronary events, increase in HDL, and decrease in C Reactive Protein (CRP). However, the subcommittee felt that this solitary study lacked the power and length to be clinically credible.

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

A large (N=5238) good quality European multicenter randomized, placebo-controlled trial[7] with type 2 diabetics and evidence of macrovascular disease received the addition of pioglitazone or placebo. Nearly all (96%) were already taking other oral hypo-glycemic medications. The primary end-point was a composite of all-cause mortality, non-fatal MI, stroke, acute coronary syndrome, surgical intervention in the coronary or leg arteries, or leg amputation. Although the primary individual endpoints were not statistically significant, a main secondary endpoint that was a composite of all-cause mortality, MI, or stroke did reach statistical significance. (HR=0.84 [0.72-0.98])

The available data provide little information on the question of comparative effectiveness of Pioglitazone or Rosiglitazone when used as monotherapy, or when added to, or substituted for other oral hypoglycemic agents.

Key Question 2

The TZD Subcommittee agrees by consensus that:

2a. The body of evidence is insufficient to compare the effectiveness of pioglitazone vs. rosiglitazone as monotherapy to prevent macrovascular complications for patients with type 2 diabetes. There is no fair or better quality data on microvascular complications.

2b. The body of evidence is insufficient to compare the effectiveness of pioglitazone vs. rosiglitazone when added to other agents to prevent macrovascular complications for patients with type 2 diabetes. There is no fair or better quality data on microvascular complications.

[6] Wang G, Wei J, Guan Y, et al. Perosixome proliferator-activated receptor-gamma agonist rosiglitazone reduces clinical inflammatory responses in type 2 diabetes with coronary artery disease after copronary angioplasty. *Metabolism* 2005;54(5):590-7.

[7] Dormandy JA, Charbonnel B, Ecklund DJA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (Prospective Pioglitazone Clinical Trial in Marcrovascular Events): a randomized controlled trial. *Lancet* 2005;366(9343):1279-89.

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?

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

b. when added to metformin?

Pioglitazone, either alone or in combination with metformin was associated with an increase in weight compared to metformin as monotherapy.[11]

Key Question 3

The TZD Subcommittee agrees by consensus that:

3a. The body of evidence is insufficient to compare the effectiveness of pioglitazone vs. rosiglitazone as monotherapy to improve weight control.

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

[8] Derosa G, Cicerao AFG, Gaddi A, et al. A comparison of the effects of pioglitazone and rosiglitazone combined with glimpiride on prothrombotic state in type 2 diabetic patients with the metabolic syndrome. *Diabetes Res Clin Pract* 2005;69(1):5-13.

[9] Hung YJ, Hsieh CH, Pei D, et al. Rosiglitazone imporves insulin sensitivity and glucose tolerance in subjects with impaired glucose tolerantce. *Clin Endorcinol* 2005;62(1):85-91.

[10] Wang TD, Chen WJ, Lin JW, et al. Effects of rosiglitazone on endotherlial function, C-reactive protein, and components of the metabolic syndrome in nondiabetic patients with the metabolic syndrome. *A J Cardiology* 2004;93(3):362-5.

[11] Lester JW, Fernandes AW. Pioglitazone in a subgroup of patients with type 2 diabetes meeting the criteria for metabolic syndrome. *Int J Clin Pract* 2005;59(2):134-42.

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?

Only two relevant studies were identified which examined the occurrence of clinical diabetes with pioglitazone or rosiglitazone,[12] but neither of the studies were designed to investigate the comparative effectiveness of these two drugs or to allow a comparison with a comparable placebo group for the outcome of diabetes incidence.

Key Question 4

The TZD Subcommittee agrees by consensus that:

4. The body of evidence is insufficient to compare the effectiveness of pioglitazone vs. rosiglitazone in delaying the occurrence of 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?

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

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

Key Question 5

The TZD Subcommittee agrees by consensus that:

5. The body of evidence is insufficient to compare the effectiveness of pioglitazone vs. rosiglitazone on cardiovascular risk factors .

[12] Durbing RJ Thiazolidinedione therapy in the prevention/delay of type 2 diabetes in patients with impaired glucose tolerance and insulin resistance. *Diabetes Obes Metab* 2004;6(4):280-5.
[13] Durbing
[14] Derosa

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?

Two head-to-head efficacy trials in patients with type 2 diabetes for pioglitazone and rosiglitazone showed no differences between the drugs in withdrawals due to adverse events including weight changes, liver function tests, creatine phosphokinase, blood pressure, heart rate, hemoglobin and hematocrit, hypoglycemic episodes, edema, or congestive heart failure. Total withdrawals and withdrawals due to adverse events were similar.

In a head-to-head trial in patients with type 2 diabetes or metabolic syndrome[15] there was no significant difference in the increase in BMI after 12 months of treatment with rosiglitazone or pioglitazone.

Indirect evidence from pooling of eight placebo-controlled trials of pioglitazone and 11 trials of rosiglitazone was similar for withdrawals for pioglitazone (-1.0 [95% CI-3.0%, 1.0%] and rosiglitazone trials (-3.0% [95%CI-9.0%, 2.0%]). For withdrawals due to adverse events, 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.

For specific adverse events: edema was reported in 14 placebo-controlled trials rates from 9-27% greater than control. The pooled risk difference in five rosiglitazone trials was 8%. The pooled risk difference compared to placebo was 4% (95% CI 2% to 5%).

For hypoglycemia, the pooled risk difference compared to placebo for either drug was not significantly different.

In December 2005 the manufacturer of rosiglitazone issued a warning letter regarding post-marketing reports of new onset and worsening macular edema for patients receiving rosiglitazone or another TZD. In the majority of cases, the patients also reported concurrent peripheral edema.[16] Recently reported was increased intraocular pressure in a patient taking rosiglitazone. Of interest is an observational 4 year study that reported decreased bone mineral density thought to be due to the similarity of osteocyte and adiposite progenitor cells.[17]

[15] Derosa
[16] Ryan EH Jr., Han DP, Ramsay RC, et al. Diabetic macular edema associated with glitazone use. *Retina.* 2006 May-Jun 26:562-70
[17] Swartz

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

A head-to-head study of patients who were switched to pioglitazone or rosiglitazone from troglitazone reported a similar weight gain in both groups. Other adverse events were not reported.

Key Question 6

6a. The TZD Subcommittee agrees by consensus that:

- **There is good evidence that the TZDs are similar in overall withdrawals and in withdrawals due to adverse events.**
- **Pioglitazone and rosiglitazone are both associated with weight gain, but there is no significant difference between drugs.**
- **The Key Questions for the next update should be modified by adding macular edema, increased intra-ocular pressure, and decreased bone density to the list of potential adverse events.**

6b. The TZD Subcommittee agrees by consensus that:

- **There is good evidence that pioglitazone and rosiglitazone had similar effects on weight gain following substitution for troglitazone.**

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

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

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

[18] Rosenstock J. Effect of early addition of rosiglitazone to sulphonylurea therapy in older type 2 diabetes patients (>60 years): the Rosiglitazone Early vs. Sulphonylurea Titration (RESULT) study. *Diabetes Obes Metab* 2006;8(1):49-57.

monotherapy with the sulfonylurea. In all 3 studies the rates for hypoglycemic events were higher with the combined therapy.

Key Question 7

The TZD Subcommittee agrees by consensus that:

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

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?

Two publications examined subgroups defined by age.[19, 20] The first review found no difference between patients <70 and >70 for A1c, and found both groups tolerated rosiglitazone well. The second review compared the pooled data of the effect of pioglitazone on glucose control and lipid levels in patients <65 and >65. Both age groups demonstrated comparable improvements in both A1c and lipid levels with pioglitazone monotherapy or combined therapy. Adverse cardiovascular events and hypoglycemia were similar in the younger and older age groups treated with pioglitazone monotherapy and with pioglitazone combined with metformin.

Key Question 8

The TZD Subcommittee agrees by consensus that:

- **There are very limited data on the comparative effectiveness of pioglitazone and rosiglitazone among persons with various demographic characteristics.**
- **No conclusion can be drawn as to which drug is more effective or associated with fewer side effects in population subgroups.**

[19] Kreider M, Heise M. Rosiglitazone in the management of older patients with type 2 diabetes mellitus. *Int J Clin Pract* 2002;56(7):538-41.
[20] Rajagopalan R, Perez A, Ye A, et al. Pioglitazone is effective therapy for elderly patients with type 2 diabetes mellitus. *Drug Aging* 2004;21(4):259-71.

Conclusion

It is the decision of the TZD Subcommittee that:

1. ***Good quality evidence shows no difference between pioglitazone and rosiglitazone in:***
   - ***Reducing A1C levels when used as monotherapy***
   - ***Total withdrawals and withdrawals due to adverse events***
   - ***Effects on weight gain.***

2. ***The body of evidence was insufficient to draw conclusions for the other Key Questions.***

3. ***The subcommittee is aware of pertinent studies after the cut-off date that may answer some of these Key Questions in the next update.***

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Health Resources Commission

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

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