



Hypoglycemics, Thiazolidinediones (TZDs) Therapeutic Class Review (TCR)

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
TZDs		
pioglitazone (Actos®) ¹	generic; Takeda	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)
rosiglitazone (Avandia®) ²	GlaxoSmithKline	Adjunct to diet and exercise to improve glycemic control in adults with T2DM
TZDs and glimepiride		
pioglitazone/ glimepiride (Duetact®) ³	generic; Takeda	Adjunct to diet and exercise to improve glycemic control in adults with T2DM who are already treated with a thiazolidinedione and sulfonylurea combination or who are not adequately controlled on either agent alone
TZDs and metformin		
pioglitazone/ metformin (Actoplus Met®) ⁴	generic; Takeda	Adjunct to diet and exercise to improve glycemic control in adults with T2DM who are already treated with a thiazolidinedione and metformin combination or who are not adequately controlled on either agent alone
pioglitazone/ metformin extended-release (Actoplus Met XR®) ⁵	Takeda	Adjunct to diet and exercise to improve glycemic control in adults with T2DM who are already treated with a thiazolidinedione and metformin combination or who are not adequately controlled on either agent alone

A fixed-combination of pioglitazone and DPP-4 inhibitor, pioglitazone/alogliptin (Oseni®), is approved as adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both pioglitazone and alogliptin is appropriate. Oseni will not be reviewed here.

OVERVIEW

It is estimated that 30.3 million Americans have diabetes.⁶ Increasing rates of obesity support the projection that cases of diabetes will continue to grow. Diabetes causes a significant economic burden, both in terms of direct and indirect costs, to society. It is also responsible for increased morbidity and mortality. Adequate glycemic control is crucial to minimize chronic complications, including blindness and renal dysfunction.⁷

Three metabolic defects are responsible for the progression to T2DM: peripheral insulin resistance, impaired β -cell function, and increased hepatic glucose production.⁸ The thiazolidinediones (TZDs) work by decreasing insulin resistance. Combination products of TZDs with metformin, alogliptin, and glimepiride are available and may improve adherence for those patients requiring combination therapy.

The American Diabetes Association (ADA) Standards of Medical Care in Diabetes position statement, updated in 2019, recommends HbA1c < 7%, as a reasonable target for most nonpregnant patients.⁹ However, more stringent HbA1c goals of < 6.5% for select patients (e.g., those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease [CVD]) may be considered if this can be achieved without significant hypoglycemia. Likewise, less-stringent HbA1c goals (< 8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain. Metformin is recommended for the treatment of T2DM, along with lifestyle interventions at the time of diagnosis, unless metformin is

contraindicated. If metformin cannot be used, another initial agent could be chosen from the following classes based on patient factors: sulfonylurea (SU), thiazolidinedione (TZD), DPP-4 inhibitor, sodium-glucose cotransporter-2 (SGLT2) inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist, or basal insulin. In patients *without* atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD), if initial therapy at maximal tolerated doses does not achieve or maintain the hemoglobin A1c (HbA1c) target after 3 months, an agent from a different class (listed above) should be added. In patients *with* ASCVD or CKD, the addition of an agent with known cardiovascular (CV) or renal benefit (select GLP-1 agonist or select SGLT2 inhibitor) is preferred. TZDs should be avoided in patients with heart failure. In patients newly diagnosed with T2DM who are markedly symptomatic and/or have elevated blood glucose or HbA1c levels, insulin therapy should be considered, with or without additional agents. Therapy should be individualized based on the needs, preferences, and tolerances of each patient.

The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) 2019 diabetes management algorithm for T2DM and the 2015 guidelines for developing a diabetes care plan also provide guidance on treatment.^{10,11} In order to minimize the risk of diabetes related complications, the algorithm specifies a target HbA1c of $\leq 6.5\%$ if it can be reached without substantial hypoglycemia or other adverse effect. A target HbA1c above 6.5% may be individualized for patients with concurrent serious illness and a high risk of hypoglycemia. Patients are stratified based on their current HbA1c levels to monotherapy, dual therapy, or triple therapy. The choices of medications are prioritized according to safety, risk of hypoglycemia, efficacy, simplicity, anticipated degree of patient adherence, and cost. These guidelines state HbA1c targets should be individualized and take into account residual life expectancy, duration of disease, cardiovascular disease risk factors, and comorbid conditions. The patient's psychological, social, and economic status should also be considered. For the patient with an HbA1c $< 7.5\%$, it is possible that a single agent might achieve the HbA1c goal of 6.5%. Metformin is the cornerstone of therapy and is usually the most appropriate initial choice for monotherapy, unless contraindicated. Agents for use as alternative monotherapy or as add-on therapy, listed in order of strength of recommendation, include GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors, and then TZDs. Although, alpha-glucosidase inhibitors (AGI) and sulfonylureas/glinides now fall below TZDs in strength of recommendation according to the algorithm, TZDs should still be used with caution due to adverse effects. TZD use is limited by associated weight gain, increased bone fracture risk in postmenopausal females and elderly males, and elevated risk for chronic edema or heart failure. These adverse effects may be diminished by using a moderate dose (e.g., ≤ 30 mg) of pioglitazone, or in the case of fluid retention, by combining the TZD with an SGLT2 inhibitor. Of note, pioglitazone may confer ASCVD benefits, while rosiglitazone has a neutral effect on ASCVD risk.

In 2017, the American College of Physicians (ACP) updated their recommendations for oral pharmacologic therapy for T2DM.¹² They recommend metformin as first-line therapy and advise that it can be safely used in patients with mild renal impairment and in select patients with moderate impairment. They recommend to add a SU, TZD, SGLT-2 inhibitor, or DPP-4 inhibitor as second-line therapy. In 2018, the ACP developed a statement to guide clinicians in selecting targets for pharmacologic treatment of T2DM, including recommending a goal HbA1c level between 7% and 8% in most patients.¹³ In addition, they state that clinicians should consider deintensifying pharmacologic therapy in patients who achieve HbA1c $< 6.5\%$, treat patients to minimize symptoms related to

hyperglycemia, and avoid targeting an HbA1c level in patients with a life expectancy < 10 years due to advanced age because the harms outweigh the benefits in this population.

In 2018, the World Health Organization (WHO) released guidelines for treatment intensification in patients with T2DM.¹⁴ They recommend addition of a DPP-4 inhibitor, a SGLT2 inhibitor, or a TZD if insulin is unsuitable in patients with T2DM who do not achieve glycemic control with metformin and/or a sulfonylurea.

TZDs have been reported to increase high-density lipoprotein cholesterol (HDL-C), and reduce triglyceride levels (pioglitazone only), blood pressure, inflammatory markers, hepatic steatosis, and carotid and coronary artery thickening. TZDs may also help prevent central nervous system insulin resistance-related cognitive dysfunction.^{15,16}

PHARMACOLOGY^{17,18,19,20,21}

TZDs bind and activate peroxisome proliferator-activated receptor gamma (PPAR- γ) in skeletal muscle, adipose tissue, and the liver, resulting in improved insulin action by enhancing the sensitivity of peripheral muscle glucose uptake and possibly reducing hepatic glucose production. The TZDs require the presence of insulin to exert their antihyperglycemic effect.

The biguanide metformin (Glucophage[®]) is a component of pioglitazone/metformin (Actoplus Met) and pioglitazone/metformin extended-release (Actoplus Met XR). Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Glimepiride (Amaryl[®]), a component of pioglitazone/glimepiride (Duetact), is a member of the sulfonylureas, which enhance response of pancreatic beta cells to glucose, in turn stimulating the release of insulin.

TZDs and sulfonylureas primarily affect fasting blood glucose. Metformin affects both fasting and postprandial blood glucose levels. The reduction of HbA1c due to any of these agents is expected to be approximately 1% to 1.5%. The duration of glycemic control with TZDs appears to be maintained over periods up to 5 to 6 years. Glucose lowering is maximal at 6 months with sulfonylureas, and glucose levels return towards baseline at about 3 years. Metformin appears intermediate in duration in its glucose lowering effects.^{22,23}

PHARMACOKINETICS^{24,25,26,27,28,29,30,31}

Drug	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion (%)
glimepiride (Amaryl)	100	5–9.2	Two inactive metabolites	renal: 60 feces: 40
metformin (Glucophage)	50–60	6.2	None	renal: >90
pioglitazone (Actos)	--	3–7 (parent); 16–24 (parent plus metabolites)	M-II, M-III, M-IV (active in animal models)	renal: 15–30 (as metabolites) feces: majority of dose
rosiglitazone (Avandia)	99	3–4	Yes, inactive	renal: 64 feces: 23

In bioequivalence studies of all combination products, both the TZD and the metformin or glimepiride component were bioequivalent to the single agents administered together.

CONTRAINDICATIONS/WARNINGS^{32,33,34,35,36}

TZD-containing products carry boxed warnings regarding the development or exacerbation of congestive heart failure in some patients. After initiation of TZD therapy, and after dose increases, patients should be observed carefully for signs and symptoms of heart failure, including excessive, rapid weight gain, dyspnea, and/or edema. If these signs and symptoms develop, heart failure should be managed according to the current standards of care. Discontinuation or dose reduction of TZD must be considered as well. The initiation of TZD therapy in patients with NYHA Class III or IV heart failure is contraindicated.

Use of pioglitazone, rosiglitazone, metformin, or glimepiride is contraindicated in patients with known hypersensitivity to these products or any of their components.

Due to some data suggesting elevated risk of cardiovascular events with rosiglitazone, use of rosiglitazone and rosiglitazone-containing medicines was significantly restricted in 2011.³⁷ However, in 2013, the FDA found that evidence of increased risk of heart attack or death in patients treated with rosiglitazone was lacking and removed restrictions.^{38,39}

Labeling for pioglitazone/glimepiride (Duetact) contains a warning for increased risk of cardiovascular mortality due to the sulfonylurea component. In addition, the glimepiride component may cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. A non-sulfonylurea should be considered as an alternative in these patients.

In 2016, the FDA issued an updated safety communication concluding that all pioglitazone-containing products may be linked to an increase risk of bladder cancer. This is a follow-up to the initial FDA safety announcement in 2010 that reported a possible increased risk of bladder cancer with pioglitazone when used for over 1 year.⁴⁰ The FDA urged patients taking pioglitazone to contact a medical professional if they experience signs or symptoms associated with bladder cancer such as blood in urine or pain while urinating. Also, in 2016 the results from an observational cohort study of over 145,000 patients initiated on antidiabetic medications over a 13 year period suggest that the risk of bladder cancer increases with duration of time and the amount or dose of pioglitazone used. However, an increased risk of bladder cancer was not associated with rosiglitazone use.⁴¹ Consequently, use of pioglitazone is not recommended in patients with active bladder cancer and should be used with caution in those with a prior history of bladder cancer, considering the benefits of glycemic control versus unknown risks for cancer recurrence.

Use of metformin-containing products is contraindicated in patients with an eGFR < 30 mL/min/1.73 m², and starting a metformin-containing product in patients with an eGFR of 30 to 45 mL/min/1.73 m² is not recommended. Patients whose eGFR falls below 30 mL/min/1.73m² should discontinue metformin; a risk assessment should occur in those with an eGFR that falls to 30 to 45 mL/min/1.73m² while on metformin. Finally, the metformin component should be temporarily discontinued at the time of or before a procedure requiring iodinated contrast imaging in those with an eGFR of 30 to 60 mL/min/1.73m²; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be receiving intra-arterial iodinated contrast.

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age \geq 65 years, radiological contrast study, surgical procedures, acute congestive heart failure, excessive alcohol intake, and hepatic impairment. If metformin-associated lactic acidosis is suspected, immediately discontinue rosiglitazone/metformin or pioglitazone/metformin combination products and seek emergency medical attention.

For all products containing pioglitazone or rosiglitazone, liver function tests are recommended at the start of therapy, then periodically thereafter at the discretion of the physician. Increased in alanine aminotransferase (ALT) levels should be monitored closely; and if ALT exceeds 2.5 to 3 times the upper limit of normal (ULN), the drug should be discontinued.

Dose-related weight gain has been observed in patients taking pioglitazone and rosiglitazone either alone or in combination with other hypoglycemic agents.

TZDs should be used with caution in patients with edema. Edema was reported more frequently in patients treated with pioglitazone or rosiglitazone than placebo; effects appear to be dose related.

Dose-related fluid retention may occur particularly when TZDs are used in combination with insulin, and may lead to or exacerbate heart failure. Patients treated with insulin and a PPAR- γ agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be treated appropriately, and dose reduction or discontinuation of the PPAR- γ agonist must be considered.

Dose-related decreases in mean hemoglobin and hematocrit may occur in adults taking pioglitazone or rosiglitazone, either alone or in combination with other hypoglycemic agents.

In premenopausal anovulatory women, the initiation of therapy with pioglitazone or rosiglitazone may cause ovulation; therefore, patients may be at an increased risk for pregnancy. Adequate contraception is recommended.

Do not use pioglitazone or rosiglitazone to treat type 1 diabetes (T1DM) or diabetic ketoacidosis.

In PROactive, a randomized trial included patients with T2DM, an increased incidence of bone fractures was noted in pioglitazone use (5.1% versus 2.5% for placebo). This difference was noted after the first year of treatment and remained during the course of the study. The majority of fractures were nonvertebral (lower and upper limb), and no increase was seen in men taking pioglitazone.

Based on a review of the safety data from the ADOPT study, rosiglitazone labeling indicates an increased number of arm, hand, and foot fractures among women taking rosiglitazone for newly diagnosed T2DM.⁴² The fracture rate was 2.74 per 100 patient-years for the 645 women treated with rosiglitazone versus 1.54 per 100 patient-years for the 590 women in the metformin arm and 1.29 per 100 patient-years for 605 women treated with glyburide. The increase in fractures was in the humerus, hand, and foot for women taking rosiglitazone; there was no increase in hip or spine fractures, usually associated with postmenopausal osteoporosis.

Macular edema has been reported in post-marketing experience in diabetic patients on TZD therapy. Some patients had improvement in their macular edema after discontinuation of TZD therapy. It is not known if not there is a causal relationship between TZDs and macular edema. Patients with diabetes should have regular eye examinations by an ophthalmologist and should be promptly referred to an ophthalmologist if any type of visual symptom is reported.

Risk Evaluation and Mitigation Strategy (REMS)^{43,44,45}

REMs from pioglitazone- and rosiglitazone-containing products have been eliminated; however, the Medication Guides are still maintained as part of the approved labeling.

DRUG INTERACTIONS^{46,47,48,49,50}

Pioglitazone and rosiglitazone are predominantly metabolized by CYP2C8. If an inhibitor or inducer of CYP2C8 is initiated or discontinued during treatment with pioglitazone or rosiglitazone, changes in treatment may be needed based on clinical response. Additionally, to a much lesser extent, rosiglitazone is also metabolized by CYP2C9, and pioglitazone is metabolized by CYP3A4.

Exercise caution when using TZDs with drugs that are known to exacerbate hyperglycemia.

Although, no dosing changes are recommended, there is a potential for drug interactions with TZDs and cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, vancomycin) that are eliminated by renal tubular secretion. Increased metformin plasma concentrations can occur during concurrent administration with cimetidine, furosemide, and nifedipine; as well as renal tubular transport inhibitors such as ranolazine, vandetanib, dolutegravir. No specific dosing changes for metformin are recommended in presence of these potential drug interactions, yet they may increase risk of lactic acidosis.

Concurrent use of topiramate with a pioglitazone-containing product may reduce the exposure of pioglitazone; clinical relevance is unknown.

ADVERSE EFFECTS^{51,52,53,54,55,56}

Drug	Headache	Edema	Myalgia/ Fatigue	Anemia	Hyperglycemia	Diarrhea	Hypoglycemia
glimepiride (Amaryl) n=746	1.5	nr	nr	nr	nr	<1	0.9–1.7
metformin (Glucophage) n=141	5.7 (4.8)	nr	1–5	nr	nr	53.2 (11.7)	1–5
pioglitazone (Actos)	9.1 (6.9)	4.8 (1.2)	5.4 (2.7)	≤2	5.1 (8.1)	nr	reported
rosiglitazone (Avandia) n=2,526	5.9 (5)	4.8 (1.3)	3.6 (5)	1.9 (0.7)	3.9 (5.7)	2.3 (3.3)	0.6 (0.2)

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and therefore, should not be considered comparative or all-inclusive. Incidences in parentheses are placebo. nr = not reported.

Adverse effects reported in the labeling for Actoplus Met, Actoplus Met XR, and Duetact do not reflect the specific combination product.

Edema and CHF

In clinical studies, the incidence of edema with the combination of pioglitazone and insulin was 15.3% and with insulin and placebo was 7%. In a 16-week study, 1.1% of patients receiving insulin and pioglitazone developed heart failure, compared to no patients on insulin therapy alone.

In a 26-week study, the incidence of edema with rosiglitazone in combination with insulin was 14.7%, whereas insulin alone was 5.4%. New onset of heart failure was 1% with insulin, 2% with rosiglitazone 4 mg in combination with insulin, and 3% with rosiglitazone 8 mg in combination with insulin.

Combined and peripheral edema was reported more frequently in patients taking combination pioglitazone/metformin therapy (6%) than metformin/placebo (2.5%). Edema was also higher in patients receiving rosiglitazone/metformin therapy (4.4%) than metformin/placebo (2.2%).

Hypoglycemia

Hypoglycemia was reported more frequently in patients taking combination rosiglitazone/metformin therapy (3%) than rosiglitazone (0.6%) or metformin (1.3%) monotherapy.

Anemia

Anemia was also reported in a greater number of patients taking combination rosiglitazone/metformin therapy (7.1%) compared to rosiglitazone (1.9%) or metformin (2.2%) monotherapy. Anemia was reported in < 2% of patients taking pioglitazone/metformin therapy.

Effect on Cholesterol/Triglycerides

Drug	Total-Cholesterol	HDL Cholesterol	LDL Cholesterol	Triglycerides
pioglitazone (Actos) versus placebo	↑ 3.3–6.4%*	↑ 12.2–19.1%	↑ 5.2–7.2%*	↓ 9–9.6%
	↑ 4.4%	↑ 8.1%	↑ 4.8%	↑ 4.8%
rosiglitazone (Avandia) versus placebo	↑ (percent increase not reported)	↑ 11.4–14.2% ↑ 8%	↑ 14.1–18.6% ↑ 4.8%	variable

*not significantly different from placebo

SPECIAL POPULATIONS^{57,58,59,60,61}

Pediatrics

The safety and effectiveness have not been established for pioglitazone (Actos) or rosiglitazone (Avandia) or their combination products in pediatric patients.

Pregnancy

All rosiglitazone-containing products are Pregnancy Category C. While labeling for all pioglitazone-containing products previously indicated the products were Pregnancy Category C, labels have been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and now state that there are limited data in pregnant women to determine drug associated risk in pregnant women for products containing pioglitazone.

Abnormal blood glucose levels during pregnancy are associated with increased neonatal morbidity and mortality, and a higher incidence of congenital anomalies. The use of insulin during pregnancy is most often recommended to manage blood glucose levels in pregnant patients with diabetes.

DOSAGES^{62,63,64,65,66,67,68}

Drug	Initial dose	Maintenance dose	Availability
TZDs			
pioglitazone (Actos)	15 mg to 30 mg daily	15 mg to 45 mg daily	15 mg, 30 mg, 45 mg tablets
rosiglitazone (Avandia)	4 mg daily OR 2 mg twice daily	2 mg to 4 mg twice daily OR 8 mg daily	2 mg, 4 mg tablets*
TZDs and glimepiride			
pioglitazone/glimepiride (Duetact)	Prior therapy with glimepiride or pioglitazone: 30/2 mg or 30/4 mg once daily with the first meal of the day Maximum daily dose: 45/8 mg		30/2 mg, 30/4 mg tablets
TZDs and metformin			
pioglitazone/metformin (Actoplus Met)	15/500 mg or 15/850 mg tablets once or twice daily with food Max daily dose: 45 mg/2,550 mg administered in divided doses with food		15/500 mg, 15/850 mg tablets
pioglitazone/metformin extended-release (Actoplus Met XR)	15/1,000 mg or 30/1,000 mg tablets once daily with evening meal Max daily dose: 45/2,000 mg administered once daily with evening meal		15/1,000 mg, 30/1,000 mg tablets

Pioglitazone and rosiglitazone may be taken without regard to meals. No dosage adjustment is required in patients with renal impairment.

CLINICAL TRIALS

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all brand names in this class. Randomized, comparative, controlled trials performed in the United States comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance. In countries outside of the U.S., blood glucose values are typically reported in mmol/L. For those studies reporting blood glucose values in mmol/L, the value in mg/dL can be estimated by multiplying the mmol/L value by 18.

Very few comparative clinical trials of the combination products are available at this time. There is 1 trial comparing a fixed-dose combination product to its component ingredients.

The literature review of significant trials comparing agents within this therapeutic class is complete as of March 10, 2019.

pioglitazone (Actos) versus placebo

A total of 408 patients with T2DM were randomized in a multicenter, double-blind, placebo-controlled trial.⁶⁹ Patients had HbA1c > 7% and fasting plasma glucose (FPG) > 140 mg/dL, and were randomized to receive placebo or pioglitazone 7.5, 15, 30, or 45 mg daily for 26 weeks. Patients treated with 15, 30, or 45 mg pioglitazone had significant mean decreases in HbA1c (-1% to -1.6% difference from placebo) and FPG (-39.1 to -65.3 mg/dL difference from placebo). The decreases in FPG were observed as early as the second week of therapy; maximal decreases occurred after 10 to 14 weeks and were maintained until the end of therapy. The subset of patients naïve to therapy had greater improvements in HbA1c and FPG (difference from placebo of -2.55% and -79.9 mg/dL for the 45 mg group, respectively) compared with previously treated patients. The overall adverse event profile of pioglitazone was similar to that of placebo; there was no evidence of hepatotoxicity or ALT elevations.

Patients (n=197) with T2DM, HbA1c > 8%, and FPG > 7.7 mmol/L were enrolled in a 23-week, double-blind trial and randomized to receive either placebo or pioglitazone 30 mg daily.⁷⁰ Efficacy parameters included HbA1c and FPG. Compared with placebo, pioglitazone significantly (p=0.0001) reduced HbA1c (-1.37%) and FPG (-3.19 mmol/L). The overall adverse event profile of pioglitazone was similar to that of placebo, with no evidence of drug-induced elevations of ALT concentrations or hepatotoxicity.

A double-blind, randomized, placebo-controlled study involved daily administration of pioglitazone 15 or 30 mg or placebo daily in patients with T2DM (n=251) for 26 weeks.⁷¹ HbA1c was reduced by -0.92% and -1.05% in the pioglitazone groups, respectively, and fasting blood glucose (FBG) was reduced by -34.3 and -36 mg/dL, respectively, compared with placebo. Both doses of pioglitazone significantly reduced postprandial blood glucose levels at all visits (-163 and -165 mg/dL/hour, respectively) compared with an increase of 47.7 mg/dL/hour on placebo. The type and frequency of adverse events were similar in all treatment groups.

pioglitazone (Actos) plus insulin

In a 16-week, double-blind, multicenter study, 566 patients currently on a stable insulin regimen for at least 30 days who continued to have an HbA1c > 8% were randomized to receive daily placebo or pioglitazone 15 or 30 mg.⁷² At the end of treatment, patients receiving pioglitazone 15 or 30 mg had mean decreases in HbA1c (-1% and -1.3%, respectively; p<0.0001) and FPG (-34.5 and -48 mg/dL, respectively; p<0.0001) that were significantly lower than baseline and the placebo group. The 15 and 30 mg pioglitazone groups had significant increases in HDL-C, while the 30 mg group showed significant mean reductions in triglyceride levels compared to placebo. The incidences of weight increase, hypoglycemia, and edema were higher among patients receiving insulin plus pioglitazone.

pioglitazone (Actos) plus insulin, with or without metformin (Glucophage)

In a multicenter, double-blind study, 222 patients with HbA1c > 8% at screening were given titrated insulin therapy and then were randomly assigned to 20-week treatment with pioglitazone or placebo in combination with insulin, with or without concurrent metformin therapy.⁷³ More than 98% of patients were taking metformin prior to and during the study. Pioglitazone significantly reduced insulin dose requirements 2 weeks after treatment initiation (p<0.05). At the end of the study, pioglitazone reduced

daily insulin dosages by 12 units ($p < 0.001$). Relative to placebo, pioglitazone reduced daily insulin dosages by 12.7 units, while improving mean HbA1c levels (pioglitazone -1.6% versus placebo -1.4%; $p = \text{NS}$). More pioglitazone-treated patients experienced edema and weight gain than placebo-treated patients.

pioglitazone/metformin (Actoplus Met) versus pioglitazone (Actos) versus metformin (Glucophage)

In a double-blind, randomized, parallel-group, controlled, 24-week study, 600 patients with T2DM were randomized to receive pioglitazone 15 mg/metformin 850 mg twice daily, pioglitazone 15 mg twice daily, or metformin 850 mg twice daily.⁷⁴ The primary endpoint was change from baseline in HbA1c of pioglitazone/metformin combination therapy compared with pioglitazone and metformin monotherapy. Secondary endpoints included change from baseline in FPG, fasting insulin, and homeostasis model assessment of insulin resistance (HOMA-IR). Safety and tolerability of pioglitazone/metformin combination therapy and its individual components were also evaluated. Patients with HbA1c $> 8.6\%$ at baseline showed the greatest decrease in HbA1c with the fixed-dose combination product (-1.83%; $p < 0.0001$) versus with monotherapy pioglitazone (-0.96%) and with monotherapy metformin (-0.99%). In addition, 63.8% of patients using the fixed-dose combination achieved HbA1c of 7% or less versus 46.9% and 38.9% of patients receiving pioglitazone and metformin monotherapy, respectively. The decrease from baseline FPG was significantly larger in the pioglitazone/metformin fixed-dose combination group (-39.9 mg/dL; $p < 0.01$) compared with either monotherapy. Also, the decrease in mean HOMA-IR was greatest with the combination therapy group. Overall, treatment with combination therapy demonstrated greater efficacy than its individual components. The fixed-dose combination was well tolerated, with reduced or similar adverse event rates compared with each individual monotherapy. This study was funded by the manufacturer of the fixed dose combination product.

pioglitazone (Actos), rosiglitazone (Avandia), and glimepiride (Amaryl)

A 12-month, multicenter, double-blind, randomized, controlled, parallel-group trial assessed 91 patients with T2DM and metabolic syndrome.⁷⁵ All patients had poor glycemic control or experienced 1 or more adverse effects with diet and oral hypoglycemic agents, such as sulfonylureas or metformin. All patients received a fixed oral dose of glimepiride 4 mg/day for 12 months. Patients also were randomized to receive pioglitazone 15 mg once daily or rosiglitazone 4 mg once daily for 12 months. Patients in both groups experienced significant increases in mean body mass index (BMI) at 12 months compared with baseline (4.92% and 6.17%, respectively; $p < 0.05$). At 12 months, a 1.3% reduction in mean values for HbA1c ($p < 0.01$), 19.3% in FPG ($p < 0.01$), and 16.3% in postprandial plasma glucose ($p < 0.01$) were observed; no significant differences were found between treatment groups. Although the glimepiride/pioglitazone group experienced a significant improvement at 12 months in almost all variables of lipid metabolism from baseline, the glimepiride/rosiglitazone group experienced a significant increase in most lipid-related risk factors for cardiovascular disease. Of the 87 patients who completed the study, 6.7% of patients in the glimepiride/pioglitazone group and 11.9% of patients in the glimepiride/rosiglitazone group had transient, mild to moderate adverse events that did not cause withdrawal from the trial.

pioglitazone (Actos), rosiglitazone (Avandia), glimepiride (Amaryl), and metformin (Glucophage)

A randomized, double-blind, placebo-controlled, parallel-group, 2-arm study enrolled 170 patients with T2DM.⁷⁶ Patients received glimepiride 2 mg (titrated to effect) or placebo in combination with an established regimen of immediate- or extended-release metformin and rosiglitazone or pioglitazone for 26 weeks. The primary efficacy outcome was the change in HbA1c from baseline. HbA1c was significantly improved at endpoint with glimepiride combination therapy compared with placebo (-1.31% versus -0.33%, respectively; $p < 0.001$). Of the patients who received glimepiride, 62.2% achieved an HbA1c $< 7\%$, compared with 26% of patients receiving placebo ($p < 0.001$). At endpoint, the glimepiride combination significantly lowered FPG (-37.4 mg/dL; $p < 0.001$), as well. Clinically significant adverse events, laboratory abnormalities, and rates of severe hypoglycemia were similar between treatment groups. The overall incidence of hypoglycemia, however, was 51.2% in the glimepiride group and 8.3% in the placebo group ($p < 0.001$).

rosiglitazone (Avandia) versus placebo

Three hundred and sixty-nine patients with T2DM were enrolled in a double-blind, parallel-group, placebo-controlled study.⁷⁷ Patients were randomly assigned to receive placebo or rosiglitazone at doses of 4, 8, or 12 mg daily. At 8 weeks, FPG decreased significantly in the rosiglitazone 4 mg, 8 mg, and 12 mg groups (-0.9, -2, and -1.7 mmol/L; $p = 0.0003$, $p < 0.0001$, and $p < 0.0001$, respectively) compared with placebo (+0.4 mmol/L). Improvements in FPG were seen for rosiglitazone 4 and 8 mg groups, but the 12 mg/day dose produced no additional improvement. The overall incidence of adverse events was similar in all treatment groups.

In a double-blind study, 959 patients were randomized to placebo or rosiglitazone 4 mg or 8 mg for 26 weeks. The primary measure of efficacy was change in the HbA1c concentration.⁷⁸ Rosiglitazone produced reductions in HbA1c of -0.8% to -1.5% compared with placebo. Approximately 33% of drug-naïve patients treated with rosiglitazone achieved HbA1c $< 7\%$ at study end. The proportions of patients with at least 1 adverse event were comparable among the rosiglitazone and placebo groups, with no evidence of hepatotoxicity in any treatment group.

After a 4-week placebo run-in period, 493 patients with T2DM were randomized in a double-blind manner to receive rosiglitazone 2 or 4 mg or placebo twice daily for 26 weeks.⁷⁹ The primary endpoint was change in HbA1c. Rosiglitazone 2 and 4 mg twice daily decreased mean HbA1c relative to placebo by -1.2% and -1.5%, respectively, and reduced FPG concentrations relative to placebo by -3.22 and -4.22 mmol/L, respectively. There was no increase in adverse events with rosiglitazone.

After a 2-week placebo run-in phase, 303 patients with T2DM were randomly assigned in double-blind fashion to 8 weeks of treatment with placebo or 2, 4, or 6 mg of rosiglitazone twice daily (FDA-approved maximum dose is 8 mg daily).⁸⁰ All rosiglitazone doses significantly reduced FPG compared with baseline and showed significantly reduced peak postprandial glucose concentrations compared with baseline ($p < 0.001$) and with placebo ($p < 0.0001$). Rosiglitazone 4 and 6 mg twice daily regimens prevented increases in HbA1c that were observed in the placebo group. The proportion of patients with 1 or more adverse event was similar in all 4 treatment groups with no evidence of hepatotoxicity.

A randomized, double-blind, placebo-controlled, parallel-group study was performed to determine the efficacy and tolerability of the addition of rosiglitazone to a regimen of glyburide once daily in African

American and Hispanic American patients with T2DM inadequately controlled with sulfonylurea monotherapy.⁸¹ Patients were assigned to receive treatment with glyburide 10 or 20 mg daily plus rosiglitazone 8 mg or placebo daily for 24 weeks. The primary efficacy endpoint was the change from baseline in HbA1c after 24 weeks of treatment. A total of 245 patients (101 African Americans, 144 Hispanic Americans) were enrolled. In the overall study population, a significantly greater mean reduction from baseline in HbA1c was seen with glyburide/rosiglitazone compared with glyburide/placebo (between-group difference: -1.4%; $p < 0.001$). When assessed by ethnicity, HbA1c values were significantly reduced with glyburide/rosiglitazone compared with glyburide/placebo in African American patients and in Hispanic American patients (both $p < 0.001$). With glyburide/rosiglitazone, 17.6% of African American patients and 25.8% of Hispanic American patients achieved HbA1c $< 7\%$, compared with 4.5% and 1.4% of glyburide/placebo patients, respectively. The most frequently reported adverse events with glyburide/rosiglitazone were edema and weight increase.

rosiglitazone (Avandia) plus glyburide (Micronase[®], Diabeta[®]) and metformin (Glucophage)

The efficacy and safety of adding rosiglitazone to an established regimen of glyburide/metformin in patients with T2DM who had not achieved adequate glycemic control (HbA1c between 7% and 10%) were evaluated.⁸² Following an open-label, lead-in phase, 365 patients randomly received rosiglitazone 4 mg once daily or placebo in a double-blind manner. Based on glycemic response, rosiglitazone dose was maintained or increased to 4 mg twice daily. After 24 weeks, therapy with glyburide/metformin plus rosiglitazone resulted in a greater reduction (-1%, $p < 0.001$) in HbA1c levels compared with combination therapy that included placebo (+0.1%). A larger proportion of patients (42% versus 14%) in the triple combination group attained HbA1c $< 7\%$. The difference in FBG levels between groups was -48 mg/dL ($p < 0.001$), favoring glyburide/metformin plus rosiglitazone. Adverse events of rosiglitazone reflected those reported in similar studies.

rosiglitazone (Avandia) plus glipizide (Glucotrol)

A total of 227 patients with T2DM who were being treated with submaximal doses of sulfonylureas were randomized to receive rosiglitazone 4 mg or placebo daily in combination with glipizide 10 mg twice daily for 2 years in a double-blind, parallel-group study.⁸³ Rosiglitazone/glipizide significantly decreased HbA1c, FPG, insulin resistance, plasma free fatty acids, and medical care utilization and improved treatment satisfaction compared with glipizide alone.

rosiglitazone (Avandia) plus insulin

Three hundred nineteen patients with T2DM with mean baseline HbA1c $> 7.5\%$ and taking insulin twice daily were randomized in a double-blind manner to 26 weeks of additional treatment with rosiglitazone 4 or 8 mg daily or placebo.⁸⁴ Insulin dose could be decreased for safety reasons. The primary endpoint was reduction of HbA1c from baseline. By intent-to-treat analysis, treatment with rosiglitazone plus insulin resulted in a mean reduction from baseline in HbA1c of -1.2% ($p < 0.0001$), with a 12% mean reduction of insulin dosage. Serious adverse events did not differ among groups.

rosiglitazone (Avandia) plus metformin (Glucophage) versus metformin (Glucophage)

The efficacy of the combination of metformin and rosiglitazone compared to metformin alone was evaluated in 348 patients with T2DM who were inadequately controlled on metformin alone.⁸⁵ Patients were randomized in a double-blind fashion to metformin 2,500 mg daily plus placebo, metformin 2,500 mg plus rosiglitazone 4 mg daily, or metformin 2,500 mg daily plus rosiglitazone 8 mg daily for 26 weeks. HbA1c, FPG, insulin sensitivity, and β -cell function improved significantly with the combination therapy in a dose-dependent manner. The mean HbA1c decrease was 1% in the rosiglitazone 4 mg group and 1.2% in the rosiglitazone 8 mg group. Twenty-eight percent of patients in the rosiglitazone 8 mg group achieved HbA1c < 7%. Dose-dependent increases in body weight and lipid profiles were observed. Adverse effects were similar in all groups.

The efficacy and safety of rosiglitazone 2 mg or 4 mg twice daily, in combination with metformin 2,500 mg daily, were evaluated in 116 patients whose T2DM was inadequately controlled with metformin alone.⁸⁶ The randomized, double-blind, placebo-controlled study was conducted for 26 weeks. Mean HbA1c levels decreased significantly from baseline to week 26 in the rosiglitazone 2 mg (-0.7%; $p=0.0052$) and 4 mg (-1.2%; $p=0.0008$) groups, but increased in the placebo group (+0.3%; $p=0.2651$). Mean FBG levels also improved significantly with metformin plus rosiglitazone therapy in a dose-dependent manner compared with placebo ($p<0.0019$). The proportion of patients with 1 or more adverse events was similar across all three groups, with no cases of hepatotoxicity.

In a double-blind, randomized, parallel-group study, 766 subjects with a baseline metformin dose of 1,000 mg/day were randomized to receive either rosiglitazone 4 mg daily (4 mg/1,000 mg) or an additional 500 mg/day of metformin.⁸⁷ Increases in the study medications to maximum doses were performed after 8 weeks. After 24 weeks, rosiglitazone 8 mg/metformin 1,000 mg was at least as effective as 2,000 mg/day of metformin in improving HbA1c with mean reductions of -0.93% and -0.71%, respectively, from baseline in subjects that completed the study. In addition, a higher percentage of subjects in the rosiglitazone/metformin group achieved HbA1c < 7% (58.1% versus 48.4%). The percentage of subjects experiencing a gastrointestinal side effect was 27.9% and 38.7% for the rosiglitazone/metformin and metformin groups, respectively.

META-ANALYSES

pioglitazone (Actos)

To systematically evaluate the effect of pioglitazone on ischemic cardiovascular events, a database containing individual patient-level, time-to-event data collected during pioglitazone clinical trials was transferred from the drug's manufacturer for independent analysis. Trials were included if they were randomized, double-blinded, and controlled with placebo or active comparator.⁸⁸ The primary outcome was a composite of death, myocardial infarction, or stroke. Secondary outcome measures included the incidence of serious heart failure. Data from a total of 19 trials, enrolling 16,390 patients, were combined by means of a fixed-effects model. Study drug treatment duration ranged from 4 months to 3.5 years. The primary outcome occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,836 patients (5.7%) receiving control therapy (hazard ratio [HR], 0.82; 95% CI, 0.72 to 0.94; $p=0.005$). Individual components of the primary endpoint were all reduced by a similar magnitude with pioglitazone treatment, with HRs ranging from 0.8 to 0.92. Serious heart failure was reported in 200 (2.3%) of the pioglitazone (Actos)-treated patients and 139 (1.8%) of the control patients (HR, 1.41; 95% CI, 1.14 to 1.76; $p=0.002$). Serious heart failure is increased by pioglitazone,

although without an associated increase in mortality. Similar findings were reported in patients with T2DM in a systematic review and meta-analysis that included controlled trials from 1966 to May 2016 with follow-up of at least 1 year.⁸⁹

pioglitazone (Actos) versus rosiglitazone (Avandia)

A systematic review and meta-analysis of 7 randomized, double-blind clinical trials of drug-related congestive heart failure in patients given TZDs (either rosiglitazone or pioglitazone) was performed.⁹⁰ The main outcome measures were development of congestive heart failure and the risk of cardiovascular death. Of the 20,191 patients, 360 who had either prediabetes or T2DM had congestive heart failure events (214 with TZDs and 146 with comparators). Results showed no heterogeneity of effects across studies, which indicated a class effect for TZDs. Compared with controls, patients given TZDs had increased risk for development of congestive heart failure across a wide background of cardiac risk (relative risk [RR], 1.72; $p=0.002$). By contrast, the risk of cardiovascular death was not increased with either of the 2 TZDs (RR, 0.93; $p=0.68$).

rosiglitazone (Avandia)

Published literature, the FDA website, and a clinical trials registry maintained by the drug manufacturer were searched for studies with the following criteria: study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes.⁹¹ The inclusion criteria were met by 42 studies. All occurrences of myocardial infarction and death from cardiovascular causes were tabulated. Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline HbA1c was approximately 8.2%. Compared to the control group, the odds ratio for the rosiglitazone group for myocardial infarction was 1.43 (95% CI, 1.03 to 1.98; $p=0.03$), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; $p=0.06$).

TZDs and bone loss

A meta-analysis was conducted in patients with T2DM to confirm the effects of TZDs on bone are a drug class effect.⁹² PPAR- γ activation with TZDs leads to unbalanced bone remodeling: bone resorption increases and bone formation decreases. Risk factors for development of TZD-induced secondary osteoporosis are gender (women), age (elderly), and duration of treatment.

SUMMARY

As seen in the clinical trials, pioglitazone (Actos) and rosiglitazone (Avandia) are capable of lowering HbA1c by approximately 1% to 1.5% when used as monotherapy in the treatment of type 2 diabetes mellitus (T2DM). In combination with other agents used to lower blood glucose levels, including metformin and glimepiride, the level of HbA1c lowering is approximately an additional 0.5% to 1%.

In measuring the ability of pioglitazone and rosiglitazone to reduce other markers, such as fasting plasma glucose, reductions of 40 to 60 mg/dL are possible with monotherapy, according to clinical trials. In combination with other antidiabetic agents, additional decreases of 25 to 50 mg/dL are seen.

Safety concerns with both agents are similar; however, the use of pioglitazone for more than 1 year may be associated with an increased risk of bladder cancer.

The addition of metformin or glimepiride to a thiazolidinedione (TZD) as a combination product allows for more convenient administration for patients who require multiple drugs, but with added precautions for their use. Comparative data with these agents are limited and only include ingredient comparisons to the fixed-dose combination products or their components.

Both the American Association of Clinical Endocrinologists/American College of Endocrinology (AAACE/ACE) 2019 treatment algorithm and the American Diabetes Association (ADA) 2019 treatment guidelines recommend metformin as the first-line oral agent for the treatment of T2DM, unless contraindicated. TZDs, as well as other hypoglycemic classes, may be considered as add-on therapy in patients unable to achieve treatment goals or as an alternative oral treatment in those unable to use metformin. Choice of medication should be based on patient-specific considerations, such as comorbid conditions (e.g., atherosclerotic cardiovascular disease, chronic kidney disease), safety, adherence, and cost.

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