IOWA MEDICAID P&T COMMITTEE

THERAPEUTIC CLASS REVIEW

NOVEMBER 12, 2009

HYPOGLYCEMICS, TZD AGENTS

SYNOPSIS

Diabetes mellitus (DM) continues to be a growing problem worldwide and in the United States. The American Diabetes Association (ADA) reports 23.6 million children and adults (7.8% of the population) have diabetes, with 17.9 million being diagnosed and 5.7 million unaware that they have the disease. It has been further estimated that 90% of all new diagnoses are for Type 2 DM.[9] This has created a strain on the healthcare system, as diabetic patients are more likely to die prematurely of heart related incidents, have a higher risk for stroke, and have a higher risk for developing macrovascular complications.

Diabetes mellitus is a disease where the body is unable to either produce or appropriately utilize insulin. Insulin is a hormone that signals the conversion of sugar and starches into needed energy.[9] When glucose is ingested in a subject with normal glucose tolerance, there is a resultant increase in the release of insulin. This combination of increased insulin and increased glucose causes a chain reaction to stimulate uptake of glucose by the liver and peripheral muscle tissues, as well as to curb the production of hepatic glucose. However, in a subject with diabetes, there is either a lack of insulin synthesis (type 1 DM) or there could be an occurrence of several abnormalities (type 2 DM), including impaired insulin secretion, insulin resistance in the muscle, liver, and adipocytes, and abnormalities in the liver/gut glucose uptake.[8]

Per the ADA, a DM diagnosis is founded on having a plasma glucose taken anytime throughout the day without regard to meal time (nonfasting plasma glucose) of ≥200mg/dL, a fasting plasma glucose of ≥126mg/dL on two different occasions, or an oral glucose tolerance test that demonstrates a two-hour plasma glucose of 200mg/dL on two different occasions. Furthermore, the ADA classifies a fasting blood sugar of ≥100mg/dL as abnormal. A fasting blood sugar between 100 and 126mg/dL is classified as impaired fasting glucose, or prediabetes. In the Unites States, there are currently 57 million people with pre-diabetes.[9]

It is currently estimated that those with pre-diabetes have a 1.5 fold increased risk of developing cardiovascular disease versus those with normal blood glucose, and those with diabetes have a 2- to 4-fold increased risk of cardiovascular disease developing. [9] Cardiovascular disease complications that may occur due to DM include coronary artery disease, peripheral vascular disease, stroke, hypertension, and dyslipidemia. In addition, other complications of diabetes include retinopathy, neuropathy, and nephropathy. All complications of DM put a subject at risk of increased morbidity and mortality. [11]

Several non-pharmacologic therapies should be implemented that can help prevent DM in those diagnosed with pre-diabetes or that can help prevent further complications in those already diagnosed with DM. Lifestyle modifications, including establishing a better diet and exercising daily, are important strategies to help eliminate complications.[11] Furthermore, being educated about the disease and the potential complications is important as well.

As the number of diabetic patients has increased, so have the number of pharmacologic treatment options that have become available. In particular, the thiazolidinedione class was first introduced to the healthcare community in 1997. Thiazolidinediones (TZD) are thought to help in the treatment of type 2 diabetes by increasing insulin sensitivity, decreasing endogenous glucose production and postprandial gluconeogenesis, suppression of free fatty acid release from the liver, and by increasing fasting and postprandial glucose clearance.[4] Troglitazone was the first TZD approved by the FDA; however, this drug was removed from the market in 1999 due to adverse hepatic side effects. Other drugs in the class, pioglitazone (Actos®) and rosiglitazone (Avandia®) were subsequently approved by the FDA. Most recently, a number of combination products with the thiazolidinediones combined with either metformin or glimepiride have been approved.

The drugs included in this therapeutic class review include: pioglitazone (Actos®) and rosiglitazone (Avandia®). These agents are also available as combination forms that include: pioglitazone/glimepiride (Duetact®), pioglitazone/metformin (Actoplus® Met), rosiglitazone/glimepiride (Avandaryl®), and rosiglitazone/metformin (Avandamet®).

FDA APPROVED INDICATIONS[1-2, 13-16, 34]

Both pioglitazone (Actos®) and rosiglitazone (Avandia®) are indicated to be used as treatment of type 2 diabetes mellitus. They are indicated as adjunct treatment to both diet and exercise. Both can be used as either monotherapy or as combination therapy with other diabetic medications to aid in enhancing glycemic control; however, only pioglitazone (Actos®) can be used in combination with metformin, a sulfonylurea, or insulin while rosiglitazone (Avandia®) is only indicated to be used in combination with metformin or a sulfonylurea. Furthermore, since both pioglitazone (Actos®) and rosiglitazone (Avandia®)

are only active with endogenous insulin, they should be avoided in those with type 1 DM or for treatment of diabetic ketoacidosis.

All combination products are also indicated to be used as adjunct treatment to diet and exercise to increase glycemic control in those with type 2 DM. Combination products should not be used in those with type 1 DM.

DOSAGE FORMS, DOSE, AND MANUFACTURER[1-2, 13-16]

Dosage for the combination products should be individualized based on clinical effectiveness as well as tolerability, but not to exceed the maximum recommended dose.

Drug	Dosage Forms	Dose	Manufacturer
pioglitazone (Actos®)	Tablets: 15mg, 30mg, 45mg	15-30mg QD; max 45mg	Takeda
pioglitazone/glimepiride (Duetact®)	Tablets: 30/2mg, 30/4mg	30/2 or 30/4 QD	Takeda
pioglitazone/metformin (Actoplus® Met)	Tablets: 15/500mg, 15/850mg	15/500 or 15/850mg QD-BID	Takeda
rosiglitazone (Avandia®)	Tablets: 2mg, 4mg, 8mg	4-8mg QD-BID, starting at 4mg QD or 2mg BID	GlaxoSmithKline
rosiglitazone/glimepiride (Avandaryl®)	Tablets: 4/1mg, 4/2mg, 4/4mg, 8/2mg, 8/4mg	QD to a max of 8/4mg QD	GlaxoSmithKline
rosiglitazone/metformin (Avandamet®)	Tablets: 2/500mg, 4/500mg, 2/1000mg, 4/1000mg,	1 tablet BID, to a max of 8/1000mg daily	GlaxoSmithKline

PHARMACOLOLOGY[1-2, 13-16]

Both pioglitazone (Actos®) and rosiglitazone (Avandia®) are selective peroxisome proliferator-activated receptor-gamma (PPARγ) agonists. PPARγ receptors are found in the skeletal muscles, liver tissue, and

adipose tissue, all major tissues that are important for insulin action. Both agents increase insulin-dependent glucose disposal, as well as decrease hepatic glucose output by decreasing insulin resistance in the periphery and liver.

Combination products with pioglitazone (Actos®) or rosiglitazone (Avandia®) contain either metformin (Glucophage®) or the sulfonylurea glimepiride (Amaryl®). Pioglitazone (Actos®) and rosiglitazone (Avandia®) have a further effect on lowering blood glucose when glimepiride is added to either active ingredient (Duetact® and Avandaryl® respectively). Glimepiride acts to lower blood glucose by way of increasing insulin release from the pancreatic beta-cells. Additionally, pioglitazone (Actos®) and rosiglitazone (Avandia®) have a further effect on lowering blood glucose when metformin is added to either ingredient (Avandamet® and Actoplus® Met respectively) due to metformin's ability to decrease both hepatic glucose production and intestinal absorption of glucose while increasing peripheral glucose uptake and utilization.

Drug	Mechanism of Action
pioglitazone (Actos®)	↑ insulin-dependent glucose disposal and ↓ hepatic glucose output by ↓ insulin resistance in the periphery and in the liver (↑ insulin sensitivity)
rosiglitazone (Avandia®)	enhancement of peripheral glucose utilization with improved glycemic control (↑ insulin sensitivity); involvement in regulation of fatty acid metabolism

PHARMACOKINETICS[1-2, 13-16, 33, 34]

These two drugs have half lives that allow for once-a-day dosing with pioglitazone (Actos®) and once-to-twice daily dosing with rosiglitazone (Avandia®). Both drugs undergo extensive hepatic metabolism and require dosing adjustments when used in patients with hepatic insufficiency.

Drug	Time to Peak Plasma Concentration	Half Life	Elimination
pioglitazone (Actos®)	2-4 hrs	3-7 hrs	renal: 15-30% /fecal: majority, as metabolite or unchanged
pioglitazone/glimepiride (Duetact®)	2-3.5 hrs[a]	8-11 hrs[a,c]	renal: 15-30% /fecal: majority, as metabolite or unchanged[b]
		5-15 hrs[a,b]	renal: 60% /fecal: 40%[c]

pioglitazone/metformin (Actoplus® Met)	1-2 hrs[b]	3-7 hrs[b]	renal: 15-30% /fecal: majority, as metabolite or unchanged[b]
	2-3 hrs[d]	6.2 hrs[d]	renal: 90% /fecal: negligible[d]
rosiglitazone (Avandia®)	1 hr	3-4 hrs	renal: 64%/fecal: 23%
rosiglitazone/glimepiride (Avandaryl®)	1 hr[e]	3.53 hrs[e]	renal: unspecified/fecal: 23%[e]
	3.02 hr[c]	7.63 hrs[c]	renal: 60% (metabolite) /fecal: 40%[c]
rosiglitazone/metformin (Avandamet®)	1 hr[e]	3-4 hrs[e]	renal: unspecified/fecal: 23%[e]
	3 hrs[d]	1-5-6.2 hrs[d]	renal: 90% /fecal: negligible[d]

[a] dose-related [b] pioglitazone in combination [c] glimepiride in combination
[d] metformin in combination [e] rosiglitazone in combination

CLINICAL TRIALS

Efficacy Trials:

pioglitazone (Actos®)

The safety and efficacy of pioglitazone was demonstrated in 3 randomized, double-blind, placebo-controlled trials with durations ranging from 16 to 26 weeks, in a total of 865 patients with Type 2 DM.

In a 26-week dose-ranging study, 408 patients were randomized to receive either pioglitazone 7.5, 15, 30, or 45 mg or placebo once daily. Therapy with any previous antidiabetic agent was discontinued 8 weeks prior to the double-blind period. Treatment with pioglitazone 15, 30, and 45 mg produced statistically significant improvements in HbA_{1c} and fasting plasma glucose (FPG) compared with placebo.[1]

Assessed outcome	placebo	pioglitazone 15 mg	pioglitazone 30 mg	pioglitazone 45 mg
Number of patients	N= 79	N= 79	N=85	N= 76
HbA1c (%) baseline	10.4	10.2	10.2	10.3
HbA1c change from baseline	+0.7	-0.3	-0.3	-0.9
HbA1c difference from placebo	-	-1	-1	-1.6
Number of patients	79	79	84	77

FPG (mg/dL) baseline	268	267	269	276
FPG change from baseline	+9	-30	-32	-56
FPG difference from placebo	-	-39	-41	-65

In a 24-week, placebo-controlled study, 260 patients with type 2 diabetes were randomized to 1 of 2 forced-titration pioglitazone treatment groups or a mock titration placebo group. Therapy with any previous antidiabetic agent was discontinued 6 weeks prior to the double-blind period. In one pioglitazone treatment group, patients received an initial dosage of 7.5 mg once daily. After 4 weeks, the dosage was increased to 15 mg once daily and after another 4 weeks, the dosage was increased to 30 mg once daily for the remainder of the study (16 weeks). In the second pioglitazone treatment group, patients received an initial dosage of 15 mg once daily and were titrated to 30 mg once daily and 45 mg once daily in a similar manner. Treatment with pioglitazone, as described, produced statistically significant improvements in HbA_{1c} and FPG compared with placebo.[1]

Assessed outcome	**placebo**	**pioglitazone 30 mg**	**pioglitazone 45 mg**
Number of patients	N= 83	N=85	N= 85
HbA1c baseline	10.8	10.3	10.8
HbA1c change from baseline	+0.9	-0.6	-0.6
HbA1c difference from placebo	-	-1.5	-1.5
Number of patients	N=78	N=82	N=85
FPG baseline	279	268	281
FPG change from baseline	+18	-44	-50
FPG difference from placebo	-	-62	-68

In a 16-week study, 197 patients with type 2 diabetes mellitus were randomized to treatment with pioglitazone 30 mg or placebo once daily. Therapy with any previous antidiabetic agent was discontinued 6 weeks prior to the double-blind period. Treatment with pioglitazone 30 mg produced statistically significant improvements in HbA_{1c} and FPG at end point compared with placebo. [1]

Assessed outcome	**Placebo**	**pioglitazone 30 mg**
Number of patients	N= 93	N=100
HbA1c baseline	10.3	10.5
HbA1c change from baseline	+0.8	-0.6

HbA1c difference from placebo	-	-1.4
Number of patients	N=91	N=99
FPG baseline	270	273
FPG change from baseline	+8	-50
FPG difference from placebo		-58

rosiglitazone (Avandia®)

In clinical studies, treatment with rosiglitazone resulted in an improvement in glycemic control, as measured by fasting plasma glucose (FPG) and HbA_{1c}, with a concurrent reduction in insulin and C-peptide levels. Postprandial glucose and insulin also were reduced. The improvement in glycemic control was maintained for up to 52 weeks.

A total of 2,315 patients with type 2 diabetes previously treated with diet alone or antidiabetic medications were treated with rosiglitazone as monotherapy in 6 double-blind studies, which included two 26-week, placebo-controlled studies; one 52-week, glyburide-controlled study; and 3 placebo-controlled, dose-ranging studies of 8 to 12 weeks' duration. Previous antidiabetic medications were withdrawn and patients entered a 2- to 4-week placebo run-in period prior to randomization.

Two 26-week, double-blind, placebo-controlled trials in patients with type 2 diabetes (N = 1,401) with inadequate glycemic control (mean baseline fasting plasma glucose (FPG) approximately 228 mg/dL; mean baseline HbA_{1c} 8.9%), were conducted. Treatment with rosiglitazone produced statistically significant improvements in FPG and HbA_{1c} compared with placebo. Data from 1 of these studies are summarized in the table below.[2]

Assessed outcome	placebo	rosiglitazone 4 mg daily	rosiglitazone 2 mg BID	rosiglitazone 8 mg daily	rosiglitazone 4 mg BID
Number of Patients	173	180	186	181	187
HbA1c baseline	8.9	8.9	8.9	8.9	9.0
HbA1c change from baseline	+0.8	0	-0.1	-0.3	-0.7
HbA1c difference from placebo	-	-0.8	-0.9	-1.1	-1.5
FPG baseline	225	229	225	228	228
FPG change from baseline	+8	-25	-35	-42	-55

FPG difference from placebo	-	-31	-43	-49	-62

Comparative trials/Safety issues:

Two head-to-head randomized, controlled, double blind studies have been published that compared pioglitazone (Actos®) and rosiglitazone (Avandia®). The first, conducted by Derosa et al,[5] compared pioglitazone (Actos®) 15mg QD to rosiglitazone (Avandia®) 4mg QD in 87 patients over a 12 month time period. The baseline A1C was 8.2% for the pioglitazone (Actos®) group and 8.0% for the rosiglitazone (Avandia®) group. Following twelve months of therapy, the pioglitazone (Actos®) group reported a -1.4% decrease in A1C from baseline compared to -1.3% decreases in A1C from baseline with the rosiglitazone (Avandia®) group.

A second head-to-head trial was published in 2005 comparing the two thiazolidinediones. In this study, 735 patients received 30 – 45mg of pioglitazone (Actos®) QD or 4mg of rosiglitazone (Avandia®) QD or BID over 24 weeks. The baseline A1C for the two groups was 7.6% for the patients receiving pioglitazone (Actos®) and 7.5% for the patients receiving rosiglitazone (Avandia®). The final reported A1C taken for the two groups showed a -0.7% decrease in A1C in the patients receiving pioglitazone (Actos®) and -0.6% decrease in A1C in patients receiving rosiglitazone (Avandia®). This study also confirmed that pioglitazone (Actos®) and rosiglitazone (Avandia®) have differing effects on lipid parameters. Triglyceride levels were significantly reduced with pioglitazone (Actos®) compared to rosiglitazone ((Avandia®); -51.9 mg/dl vs +13.1 mg/dl; $p<0.001$, respectively). Treatment with pioglitazone (Actos®) was also associated with a statistically significant increase in HDL (5.2 vs 2.4) and a lesser effect on LDL compared to rosiglitazone ((Avandia®); 12.3 vs 21.3; $p<0.001$ for both outcomes).[6]

A published study which received much attention was an article published in *New England Journal of Medicine* in May, 2007.[7] This article was a retrospective meta-analysis of summary information from 42 clinical studies conducted at several different sites involving 14,237 patients that analyzed the potential for increased risk of myocardial infarction (MI) and death from cardiovascular causes in those patients who took rosiglitazone (Avandia®). Results of this meta-analysis suggest that, when compared with placebo, "rosiglitazone was associated with a significant increase in the risk of MI and with an increase in the risk of death from cardiovascular causes that was of borderline significance".[7] The odds ratio for MI was 1.43 ($p=0.03$) and the odds ratio for death from cardiovascular causes was 1.64 ($p=0.06$). The authors did indicate that these results were based on a small number of events. The authors concluded that risks associated with rosiglitazone use in Type 2 DM should be carefully reviewed by providers and patients until exact measures of cardiovascular risks can be defined.

GlaxoSmithKline, the manufacturer of rosiglitazone (Avandia®), and the study's author were quick to point out the limitations of the published study. GlaxoSmithKline has countered this assertion with their own data from three studies comparing rosiglitazone (Avandia®) to other approved oral antidiabetic regimens

or placebo. In these data, confirmation or exclusion of this increased risk of myocardial ischemic events has been inconclusive. Regardless, additional warnings have been added to the black box warning for rosiglitazone (Avandia®) against a possible increased risk of myocardial ischemia.

A second 2007 meta-analysis by Singh et al of trials involving over 14,000 patients found a significantly increased risk of myocardial infarction and heart failure associated with rosiglitazone (Avandia®) use, without a significantly increased risk of cardiovascular mortality.[24]

In 2008, ACCORD (Action to Control Cardiovascular Risk in Diabetes) was a major multi-arm randomized study funded under the auspices of the National Institute of Diabetes and Digestive and Kidney Diseases, the National Eye Institute, and Centers for Disease Control and Prevention. The study involved over 10,000 patients. The trial assigned patients to intensive therapy (target Hb1Ac < 6.0%) or standard therapy (HbA1c 7.0-7.9%) groups and studied various modes of antidiabetic drug therapy, including monotherapies and combinations with metformin, glimepiride, repaglinide, both thiazolidinediones, incretin, exenatide and insulins. Compared to standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. After reviewing mortality trends for several months, on January 8, 2008, the ACCORD subgroup committee concluded that the harm associated with the increased rate of death from any cause in the intensive-therapy group, as compared with that in the standard-therapy group, outweighed any potential benefits and recommended that the intensive regimen be discontinued for safety reasons. No specific breakdown of deaths associated with specific therapies was noted. [22, 23]

Current clinical literature has also noted an increased incidence of limb fractures, notably in women, among thiazolidinedione users (see Adverse Drug Reactions section). A 2009 meta-analysis by Loke et al, examining 10 randomized controlled trials and 2 observational trials covering in excess of 45,000 patients, observed a doubled risk of fractures among women with Type 2 DM who used thiazolidinediones, without a significant increase in the risk of fractures among men. [21]

The following table includes current clinical trials reinforcing thiazolidinedione effects on reducing glycemic and lipid values, as well as trials examining cardiovascular safety issues.

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
Habib et al[28] 2009	Retrospective cohort study thiazolidinediones (TZDs) as a class, and pioglitazone and rosiglitazone individually	N=19171 1/1/2000-12/1/2006	- Adult type 2 diabetics treated with oral medications between 1/1/2000-12/1/2006	- Fatal and non-fatal acute myocardial infarction (AMI). - Hospitalizations for congestive heart failure (CHF) - Fatal/non-fatal cerebro vascular accidents (CVA) and transient ischemic attacks (TIA) - Combined coronary heart disease (CHD) events, and all-cause mortality.	- Use of TZDs overall, rosiglitazone individually, and pioglitazone individually were not associated with a higher risk of AMI. - Pioglitazone use was associated with a reduction in all-cause mortality. - Compared with rosiglitazone, pioglitazone use was associated with a lower risk of all outcomes assessed, particularly CHF ($p = 0.013$) and combined CHD events ($p = 0.048$).	- Pioglitazone may have a more favorable risk profile when compared to rosiglitazone, arguing against a singular effect for TZDs on cardiovascular outcomes.
Home et al[30] 2009	Multicenter, open-label trial rosiglitazone PLUS metformin or sulfonylurea Vs.	N=4447 5-7 years	- Patients with type 2 DM on metformin or sulfonylurea monotherapy with mean HbA1c of 7.9%	- Incidence of cardiovascular hospitalization or cardiovascular death - Incidence of limb fracture	- Heart failure causing admission to hospital or death occurred in 61 people in the rosiglitazone group and 29 in the active control group. - Upper and distal lower limb fracture rates were increased mainly in women randomly assigned to rosiglitazone.	Addition of rosiglitazone to glucose-lowering therapy in type 2 diabetics is confirmed to increase the risk of heart failure and of some fractures, mainly in women. Although the data are inconclusive about any possible effect on myocardial infarction,

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
	metformin or sulfonylurea as monotherapy			- Change in mean HbA1c	- Mean HbA1c was lower in the rosiglitazone group than in the control group at 5 years.	rosiglitazone does not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs.
Kaku et al[27] 2009	Double-blind, placebo-controlled, randomized trial metformin PO 500-750mg QD PLUS pioglitazone PO 15-30mgQD Vs. metformin PO 500-750mg QD plus placebo	N=236 16 weeks	- Adult patients with type 2 DM	- HbA1c and fasting blood glucose (FBG) - Percentage of patients achieving HbA1c < 6.5% - Lipid profile and other metabolic parameters - Incidence of adverse events	- Mean HbA1c was reduced by 0.67% in patients receiving pioglitazone plus metformin vs. an increase of 0.25% in those receiving metformin alone ($p < 0.0001$). - After 8 weeks' treatment and until the end of the study, HbA1c was significantly lower with pioglitazone plus metformin and more patients in this group achieved an HbA1c < 6.5% (38.6% vs. 8.1%; $p < 0.0001$). FBG was also reduced by a significantly greater amount in patients receiving pioglitazone plus metformin compared with metformin monotherapy (-20.5 vs. 1.9 mg/dl; $p < 0.0001$). - Combination therapy was associated with significantly increased HDL, total cholesterol and adiponectin, and significantly decreased levels of fasting insulin, free fatty acids, and homeostasis model assessment of insulin resistance	- Pioglitazone plus metformin significantly improved glycemic control and markers associated with increased insulin resistance, and cardiovascular risk compared with metformin monotherapy.

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
					(HOMA) compared with metformin monotherapy. - Combination therapy and monotherapy were equally well tolerated and the incidence of adverse effects 'possibly' related to therapy was 15.7% and 11.6% (p = 0.505), respectively. Edema occurred slightly more often in the combination group (6.0 vs. 1.2%).	
Miyazaki et al[19] 2008	Randomized study rosiglitazone 8mg QD Vs. pioglitazone 45mg QD	N=56 months	- Adult patients with type 2 DM	- Changes in glycemic values: HbA1c, FPG, glucose/insulin/ C-peptide/FFA during oral glucose tolerance test (OGTT) - Changes in body weight and measures of insulin resistance - Changes in lipid values: HDL, LDL, TG and adipocytokines	- After treatment: HbA1c (8.6-7.2 vs. 8.3-6.9%, rosiglitazone vs. pioglitazone), FPG 190-144 vs. 178-140 mg/dl, fasting FFA (729-595 vs. 641-526 µEq/l), mean plasma glucose-OGTT (292-229 vs. 285-233 mg/dl) and mean FFA-OGTT (580-430 vs. 488-377 µEq/l) decreased similarly and all were statistically significant ($p < 0.01$). - Insulinogenic index and Matsuda index of insulin sensitivity increased similarly, despite increase in body weight. - After rosiglitazone treatment, HDL (34-38 mg/dl) and LDL (103-120 mg/dl) increased ($p < 0.01$), while TGs (177-167 mg/dl) did not change significantly. After pioglitazone treatment, HDL (34-37 mg/dl) increased (p	- Rosiglitazone and pioglitazone have similar beneficial effects on glycemic control, insulin sensitivity, insulin secretion, and plasma adipocytokine levels. However, pioglitazone has a more beneficial effect on the plasma lipid profile than rosiglitazone.

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
				(TNF-alpha, leptin , adiponectin)	< 0.05), while LDL (104-105 mg/dl) did not change and TGs (153-106 mg/dl) decreased (p < 0.01). - TNF-alpha (3.8-3.4 vs. 5.2-4.5 pg/ml) decreased (p < 0.05) and adiponectin (6.3-17.8 vs. 7.1-16.4 mcg/ml) increased (p < 0.01), while leptin did not change following either treatment.	
Nissen et al[29] 2008	Double-blind, multicenter, randomized trial pioglitazone PO 15-45mg QD Vs. glimepiride PO 1-4mg QD	N=543 18 months	- Patients with type 2 DM and pre-existing coronary artery disease	- Change in percent atheroma volume (PAV) from baseline to study completion - Change in mean HbA1c and fasting insulin levels - Change in mean lipid values - Incidence of adverse events	- Mean PAV increased 0.73% (95% CI, 0.33% to 1.12%) with glimepiride and decreased 0.16% (95% CI, -0.57% to 0.25%) with pioglitazone (p = .002). - Mean baseline HbA1c levels were 7.4% in both groups and declined during treatment an average 0.55% with pioglitazone and 0.36% with glimepiride (p =0 .03). - Median fasting insulin levels decreased with pioglitazone and increased with glimepiride (p <0 .001). - In the pioglitazone group, vs. glimepiride, HDL increased 5.7 mg/dL vs. 0.9 mg/dL), and median TG decreased 16.3 mg/dL vs. an increase of 3.3 mg/dL (p < .001 for both comparisons).	-In patients with type 2 DM and coronary artery disease, treatment with pioglitazone resulted in a significantly lower rate of progression of coronary atherosclerosis compared with glimepiride.

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
					- Hypoglycemia was more common in the glimepiride group and edema, fractures and decreased hemoglobin levels occurred more frequently in the pioglitazone group.	
Home et al[32] 2007	Double-blind randomized study premixed insulin SC, sliding-scale dose BID , PLUS rosiglitazone + metformin PO 8/2000mg per day (dose division not specified) Vs. Premixed insulin SC, sliding-scale dose BID, PLUS placebo	N=324 24 weeks	- Patients with type 2 DM inadequately controlled on maximum dose rosiglitazone + metformin therapy	- Improvement in glycemic control at 24 weeks - Adverse events/weight gain	- Insulin dose at week 24 was significantly lower with rosiglitazone + metformin (33.5 +/- 1.5 U/day, vs. placebo (59.0 +/- 3.0 U/day). - There was greater improvement in HbA1c rosiglitazone + metformin vs. placebo [6.8 +/- 0.1 vs. 7.5 +/- 0.1%, $p < 0.001$] and more individuals achieved HbA1c < 7.0%, 70 vs. 34% ($p < 0.001$). - The proportion of individuals reporting ≥ 1 hypoglycemic event during the last 12 weeks of treatment was similar in the two groups. - Both treatment regimens were well tolerated but more participants had edema and there was more weight with rosiglitazone + metformin vs. placebo.	- Addition of insulin to rosiglitazone + metformin enabled more people to reach glycemic targets with less insulin, and was generally well tolerated.

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
Rosen-stock et al[25] 2006	Double-blind, multicenter, randomized trial rosiglitazone/ metformin PO 2mg/500mg QD, titrated up to 8mg/2000mg QD (RSG/MET) Vs. metformin PO 500-2000mg QD (MET) Vs. rosiglitazone PO 4-8mg QD (RSG)	N=468 32 weeks	-Adult, drug-naïve patients with type 2 DM	- Change in A1c from baseline to week 32. - Proportion of patients achieving recommended HbA1c and FPG targets for glycemic control - Incidence of adverse events	- At week 32, RSG/MET showed significant improvements in A1c from a baseline of 8.9 ± 1.1% to 6.6 ± 1.0% at study end, and this 2.3% reduction was significantly greater than the reductions achieved individually with MET (-1.8%; p = 0.0008) and RSG (-1.6%; p < 0.0001). - Greatest mean decrease in FPG was seen with RSG/MET (-4.1 mmol/l) and was significant compared with MET (-2.8 mmol/l; p < 0.0001) and RSG (-2.6 mmol/l; p < 0.0001). - Target HbA1c of ≤ 6.5% and < 7% were achieved in more patients in RSG/MET group (60% , 77%) than with MET (39%, 57%) or RSG (35%, 58%) respectively. - Treatment was well tolerated, with nausea, vomiting and diarrhea as the most commonly reported AEs. Edema was comparable between RSG/MET (6%) and RSG (7%) and lower in the MET group (3%). No new safety and tolerability issues were observed in the RSG/MET group.	- As first-line therapy in patients with uncontrolled type 2 DM, rosiglitazone/ metformin combination therapy achieved significant reductions in HbA1c and FPG compared with either rosiglitazone or metformin monotherapy. Rosiglitazone/ metformin were generally well tolerated as initial therapy, with no new tolerability issues identified with the fixed-dose combination.
Bailey et al[18]	Double-blind, multicenter,	N=568	- Patients with type 2 DM	- Mean changes in (HbA1c), FPG	- RSG/MET reduced HbA1c from 7.4% to 7.1% at week 24, compared to 7.5% to	- Rosiglitazone/ metformin were an effective and well-

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
2005	parallel-group, randomized trial -First 4 weeks: rosiglitazone/ metformin PO 4mg/2 g per day (RSG/MET) Vs. metformin PO 2.5g per day (MET) - Remainder of trial: rosiglitazone/ metformin PO 8mg/2 g per day Vs. metformin PO 3g per day	24 weeks		and C-reactive protein at week 24 - Change in HOMA of insulin sensitivity at week 24 - Incidence of adverse events	7.4% with MET (p= 0.001). In addition, 54% of patients treated with RSG/MET achieved HbA1c levels <7.0%, compared with 36% with MET (p < 0.001). - FPG decreased from 166.2 to 144.1 mg/dL with RSG/MET and from 169.3 to 164.0 mg/dL with MET (p < 0.001); RSG/MET decreased C-reactive protein by a mean of 39.4% vs. 16.0% with MET (p < 0.001). - RSG/MET increased HOMA by 34.4% vs. 6.5% with MET (p < 0.001). HOMA beta-cell function increased by 15.9% with RSG/MET vs. 2.5% with MET (p < 0.001). - RSG/MET was generally well tolerated, with the majority of adverse events mild to moderate in nature. -Overall rates of GI adverse events were 23% with RSG/MET and 26% with MET; there was an increased incidence of diarrhea (14% vs. 6%) and abdominal pain (9% vs. 6%) with MET.	tolerated treatment for type 2 DM and enabled more patients to reach glycemic targets than high-dose metformin.

CONTRAINDICATIONS[1-2, 13-16]

Both thiazolidinediones are contraindicated in patients with heart failure, New York Heart Association Class III or IV, or who have a history of hypersensitivity to pioglitazone or rosiglitazone. Black Box Warnings appear on both drugs warning of the potential to develop or exacerbate congestive heart failure. Rosiglitazone (Avandia®) carries a Black Box Warning about the possible increased risk of myocardial ischemia.

SPECIAL POPULATIONS[1-2, 13-16, 33, 34]

There are currently not any medications in this therapeutic class that have established safety and efficacy in children under the age of 18. Periodic liver function testing should be performed during use with pioglitazone (Actos®) or rosiglitazone (Avandia®) containing products. Use of metformin is contraindicated in renal impairment, thus any combination product containing metformin is also contraindicated in renal impairment.

Drug	Pediatrics	Pregnancy Category	Dosage change with Renal Insufficiency	Dosage change with Hepatic Insufficiency
pioglitazone (Actos®)	No	C	Not required	ALT < 2.5 X UNL: Use with caution. ALD and/or ALT > 2.5 X UNL: Avoid use
pioglitazone/glimepiride (Duetact®)	No	C	Initiate: 1mg of glimepiride, then titrate.	
pioglitazone/metformin (Actoplus® Met)	No	C	Use contraindicated	
rosiglitazone (Avandia®)	No	C	Not required	
rosiglitazone/glimepiride (Avandaryl®)	No	C	Initiate: 4mg rosiglitazone and 1mg of glimepiride then titrate.	
rosiglitazone/metformin (Avandamet®)	No	C	Use contraindicated	

ALD- Active Liver Disease. UNL- Upper Normal Limit

ADVERSE DRUG REACTIONS[1-2, 13-16, 17, 33, 34]

Both pioglitazone (Actos®) and rosiglitazone (Avandia®) have black box warnings about the potential increased risk of exacerbation of congestive heart failure with use. Signs and symptoms of heart failure,

such as excessive and rapid weight gain, dyspnea, and/or edema should be monitored. If signs/symptoms occur, either discontinuation or dose reduction of the thiazolidinediones (TZD) should be considered.

An additional black box warning indicates that neither pioglitazone (Actos®) nor rosiglitazone (Avandia®) is to be used in patients with symptomatic heart failure. Furthermore, both TZDs are contraindicated for use in patients with NYHA Class III or IV heart failure.

A potential for increased risk of bone fractures reported has been noted in female patients with type 2 diabetes taking pioglitazone-containing products. The FDA submitted results of an investigation of clinical trials and reported an increase in fractures in women taking pioglitazone (Actos®) vs. either placebo or other active comparator. It was noted that the fractures seen were most notably nonvertebral fractures and were in the distal upper limb, including the forearm, hand, and wrist, or the lower distal limb, including the foot, ankle, fibula and tibia. This reported increase in fractures was not found in men taking pioglitazone (Actos®).[17]

Likewise, the ADOPT study included 4,360 female patients taking either rosiglitazone (Avandia®) or metformin or glyburide to also determine potential for increased risk of bone fractures. Results indicated that more female patients in the rosiglitazone (Avandia®) group experienced fractures of the upper arm, hand, or foot than the comparators. The FDA, therefore, has recommended that healthcare professionals take into consideration the potential for increased risk of fracture in women with type 2 DM taking pioglitazone-containing or rosiglitazone-containing products.[35, 17]

Black box warnings associated with TZD/metformin combinations (Actoplus® MET, Avandamet®) warn of the possible occurrence of lactic acidosis, with increased risk in the presence of sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. In cases of suspected acidosis, the medication should be discontinued and the patient hospitalized immediately.[1]

***The occurrence of side effects for the drugs listed in the tables below have been adjusted so that they reflect only the extent that they exceed placebo for pioglitazone only. Prescribing information for the other class agents did not report the extent to which adverse events exceed placebo; table entries reflect major adverse events noted. Pioglitazone/glimepiride results represent adverse events reported in a 24 week clinical trial of subjects taking pioglitazone 30mg. ***

CNS Adverse Reaction	PIO	PIO/GLI	PIO/MET	ROS	ROS/GLI	ROS/MET
Dizziness	-	-	4.8-5.4%	-	-	8%
Headache	2.2%	7%	4.6-5.3%	<1%	-	11%

- Event not reported.
PIO-pioglitazone (Actos®): PIO/GLI-pioglitazone/glimepiride (Duetact®): PIO/MET-pioglitazone/metformin (Actoplus® MET); rosiglitazone (Avandia®); ROS/GLI- rosiglitazone/glimepiride (Avandaryl®); ROS/MET- rosiglitazone/metformin (Avandamet®).

Musculoskeletal Adverse Reaction	PIO	PIO/GLI	PIO/MET	ROS	ROS/GLI	ROS/MET
Arthralgia	-	-	-	-	-	5%
Back Pain	-	-	-	-	<1%	-
Bone fractures	2.6%	2.6%	-	-	-	-
Myalgia	2.7%	-	-	-	-	-

- Event not reported.
PIO-pioglitazone (Actos®): PIO/GLI-pioglitazone/glimepiride (Duetact®): PIO/MET-pioglitazone/metformin (Actoplus® MET); rosiglitazone (Avandia®); ROS/GLI- rosiglitazone/glimepiride (Avandaryl®); ROS/MET- rosiglitazone/metformin (Avandamet®).

Respiratory Adverse Reaction	PIO	PIO/GLI	PIO/MET	ROS	ROS/GLI	ROS/MET
Pharyngitis	4.3%	-	-	-	-	6%
Sinusitis	1.7%	-	4.4-5%	-	-	-
Upper respiratory infection	-	-	5.3-5.8%	-	-	-

- - Event not reported.
PIO-pioglitazone (Actos®): PIO/GLI-pioglitazone/glimepiride (Duetact®): PIO/MET-pioglitazone/metformin (Actoplus® MET); rosiglitazone (Avandia®); ROS/GLI- rosiglitazone/glimepiride (Avandaryl®); ROS/MET- rosiglitazone/metformin (Avandamet®).

Miscellaneous Adverse Reaction	PIO	PIO/GLI	PIO/MET	ROS	ROS/GLI	ROS/MET
Accident/accidental injury	-	-	-	3.3%	-	-
Hypoglycemia	-	13.4%	-	<1%	-	-
Urinary tract infection	-	-	5.3-5.8	-	-	-
Weight increased	4%	9.1%	2.9-6.7%	-	-	-

- Event not reported.
PIO-pioglitazone (Actos®): PIO/GLI-pioglitazone/glimepiride (Duetact®): PIO/MET-pioglitazone/metformin (Actoplus® MET); rosiglitazone (Avandia®); ROS/GLI- rosiglitazone/glimepiride (Avandaryl®); ROS/MET- rosiglitazone/metformin (Avandamet®).

DRUG-DRUG INTERACTIONS[1-2, 13-16, 33, 34]

Interactions in common:

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Corticosteroids	Inhibition of peripheral glucose utilization/ enhanced hepatic gluconeogenesis	↓ Hypoglycemic effect of TZDs/TZD combos; Monitor combination.
CYP2C8 Inducers	CYP2C8 induction	↑ Metabolism of TZDs; Monitor combination.
CYP2C8 Inhibitors	CYP2C8 inhibition	↓ Metabolism of TZDs; Consider therapy modification.
CYP2C8 substrates[a] [High risk]	CYP2C8 inhibition [a]	↓ Metabolism of CYP2C8 substrate; Monitor combination. [a]
CYP2D6 substrates	CYP2D6 inhibition by TZD	↓ Metabolism of CYP2D6 substrate; Monitor combination.
Insulin	Unclear	↑ fluid-retaining effect of TZDs; Monitor combination.
Pregabalin	Additive fluid-retaining effects	↑ fluid-retaining effect of TZDs; Monitor combination.
Thiazide diuretics	Impairment of insulin sensitivity/ ↑ insulin resistance, basal insulin concentrations or plasma glucose concentrations	↓ Therapeutic effect of TZDs; Monitor combination.
Trimethoprim	Inhibition of TZD metabolism	↓ Metabolism of TZDs; Monitor combination.

[a] pioglitazone and rosiglitazone are both CYP2C8 substrates and CYP2C8 inhibitors

pioglitazone/pioglitazone combinations (Actos®, Duetact®, Actoplus® Met):

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Codeine	CYP2D6 inhibition by pioglitazone	↓ Therapeutic effect of codeine; Monitor combination.
Tamoxifen		↓ Metabolism of tamoxifen; Consider therapy modification.
Thioridazine		↓ metabolism of thioridazine; Avoid concomitant use.

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Tramadol		↓ Therapeutic effect of tramadol; Monitor combination.

rosiglitazone/rosiglitazone combinations (Avandia®, Avandaryl®, Avandamet®):

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Vasodilators (organic nitrates)	Not reported	↑ adverse/toxic effect of rosiglitazone; Consider therapy modification.

TZD/glimepiride combinations (Duetact®, Avandaryl®):

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Beta-blockers	Inhibition of insulin release/inhibition of gluconeogenesis	↑ Hypoglycemic effect of glimepiride; Monitor combination.
Cimetidine/ranitidine	↓ hepatic metabolism/renal transport of glimepiride mediated by cimetidine	↑ Serum concentration of glimepiride; Monitor combination.
Cyclosporine	Unknown	↑ Serum concentration of cyclosporine; Monitor combination.
CYP2C9 inducers	CYP2C9 induction	↑ Metabolism of glimepiride; Monitor combination.
CYP2C9 Inhibitors	CYP2C9 inhibition	↓ Metabolism of glimepiride; monitor combination.
Quinolones	Unclear	↑ OR ↓ hypoglycemic effect of glimepiride; Monitor combination.
Salicylates	Additive hypoglycemic effects of agents	↑ Hypoglycemic effect of glimepiride; Monitor combination.
Sulfonamides	Inhibition of metabolism /displacement from protein binding site of glimepiride	↑ Hypoglycemic effect of glimepiride; Monitor combination.

TZD/metformin combinations (Actoplus® Met, Avandamet®):

Drug/Class	Mechanism of Drug Interaction	Clinical Recommendation
Cephalexin	Impaired renal clearance of metformin	↑ Serum concentration of metformin; Monitor combination.
Cimetidine	Impaired renal clearance of metformin	↓ Excretion of metformin; Monitor combination.

SUMMARY

Since first being introduced to the US market in 1997, thiazolidinediones have offered physicians an additional oral agent for the treatment of type 2 diabetes mellitus. Thiazolidinediones are used as monotherapy or in combination with other oral antidiabetic agents in the maintenance of type 2 diabetes mellitus.

In 2007, the ADA and the European Association for the Study of Diabetes developed and published an evidence-based algorithm to aid health care providers in selecting the most appropriate diabetic therapy. The algorithm commenced with lifestyle modification along with metformin therapy; however, if the subject's hemoglobin levels did not decrease to below 7%, it was recommended that either one of three therapies be added: (1) basal insulin, (2) a sulfonylurea, or (3) a TZD. However, since the date of this published algorithm, many studies have been published regarding the potential for increased risk of cardiovascular mortality with use of either pioglitazone (Actos®) or rosiglitazone (Avandia®). Therefore, the ADA and European Association for the Study of Diabetes issued an update to the algorithm in regards to the thiazolidinediones studies. The update concluded that the information available in the studies was not enough to warrant removal of TZD therapy from the algorithm and that it would be up to the prescriber to use TZD therapy with discretion in those subjects that were at higher risk for incurring additional risks with TZD use.

The two single agents on the market, pioglitazone (Actos®) and (Avandia®) are comparable to each other for decreasing HbA1c levels when compared in head-to-head trials; however, they offer different kinetic profiles. Pioglitazone (Actos®) is dosed once-a-day, whereas rosiglitazone (Avandia®) can be dosed either once or twice daily. The contraindications and side effect profile between the two products is also comparable. While recent data published suggests a higher risk of myocardial ischemia with use of rosiglitazone (Avandia®), final judgment on the overall safety of this class of drugs has not been made.

Type 2 diabetes has long been associated with substantially increased cardiovascular mortality. The need to reduce the progression of atherosclerosis alongside lowering blood glucose levels is now well established. Of the newer antidiabetic agents, the thiazolidinediones have been the most widely studied. While they improve glycemic index, have a favorable effect on fat distribution and may improve lipid

profiles, safety issues surrounding use of these agents, concerning increased cardiovascular mortality as well as increased incidence of limb fractures, still remain unresolved.

Other than the caveats listed above, there is no evidence that supports that one single agent product is more effective than another.

REFERENCES

[1] Actos® [Package Insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc; September 2009.

[2] Avandia® [Package Insert]. Research Triangle Park, NC: GlaxoSmithKline; October 2008.

[3] Centers for Disease Control and Prevention. National Diabetes fact sheet: general information and national estimates on diabetes in the United States, 2005. Atlanta, GA: Department of Health and Human Services. Centers for Disease Control and Prevention 2005.

[4] Wagstaff, A. J., Goa, K. L. Rosiglitazone: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 2002; 62 (12):1805-37.

[5] Derosa, G., Cicero, A. F., Gaddi, A., Ragonesi, P. D., Fogari, E., Bertone, G., Ciccarelli, L., Piccinni, M. N. 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.

[6] Goldberg, R. B., Kendall, D. M., Deeg, M. A., Buse, J. B., Zagar, A. J., Pinaire, J. A., Tan, M. H., Khan, M. A., Perez, A. T., Jacober, S. J. 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.

[7] Nissen, Steven E., Wolski, K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes *N Engl J Med* 2007 356: 2457-2471

[8] DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. *Med Clin North Am.* 2004; 88;787-835.

[9] American Diabetes Association. All About Diabetes. Website: http://www.diabetes.org/about-diabetes.jsp. Accessed February 25, 2009.

[10] Institute of Clinical Systems Improvement. Health Care Guideline: Diagnosis and Management of Type 2 Diabetes Mellitus in Adults. Twelfth Edition. March 2008. Website:

http://www.icsi.org/diabetes_mellitus_type_2/management_of_type_2_diabetes_mellitus_9.html. Accessed February 25, 2009.

[11] Sherwin RS, Anderson RM, Buse JB, et al. Prevention or Delay of Type 2 Diabetes. *Diabetes Care*. 2004. 27(1); 47-54.

[12] Nathan DM, Buse JB, Davidson MB et al. Management of Hyperglycemia in Type 2 Diabetes: A Concensus Algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008. 31(1); 173-175.

[13] Actoplus® Met [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc; December 2008.

[14] Duetact ® [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc; September 2009.

[15] Avandaryl® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; December 2008.

[16] Avandamet ® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; December 2008.

[17] FDA Medwatch. Actos (pioglitazone) tablets- Evaluation of safety data showed increased incidence of fractures in femal patients. Website: http://www.fda.gov/medwatch/safety/2007/safety07.htm#Actos. Accessed February 26, 2009.

[18] Bailey CJ, Bagdonas A, Rubes J, et al. Rosiglitazone/metformin fixed-dose combination compared with uptitrated metformin alone in type 2 diabetes mellitus: a 24-week, multicenter, randomized, double-blind, parallel-group study. *Clin Ther*. 2005; 27(10): 1548-61.

[19] Miyazaki Y, DeFronzo RA. Rosiglitazone and pioglitazone similarly improve insulin sensitivity and secretion, glucose tolerance and adipocytokinies in type 2 diabetic patients. *Diabetes Obes Metab*. 2008; 10(12):1204-11.

[20] Winkelmayer WC, Setoguchi S, Levin R, et al. Comparison of cardiovascular outcomes in elderly patients with diabetes who initiated rosiglitazone vs pioglitazone therapy. *Arch Intern Med*. 2008; 168(21): 2368-5.

[21] Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ* 2009 Jan 6; 180 (1):32-39. *(*Epub *2008 Dec 10)*

[22] ACCORD trial Web site. http://www.accordtrial.org/web/public/index.cfm. Accessed September 21, 2009.

[23] Gerstein HC, Miller ME, Byington RP et al (Action to Control Cardiovascular Risk in Diabetes Study Group). Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008 Jun 12; 358(24):2545-59. *(Epub 2008 Jun 6)*

[24] Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA*. 2007 Sep 12;298(10):1189-95.

[25] Rosenstock J, Rood J, Cobitz A, Biswas N, Chou H, Garber A. Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. *Diabetes Obes Metab*. 2006 Nov;8(6):650-60.

[26] Papanas N, Maltezos E. Oral antidiabetic agents: anti-atherosclerotic properties beyond glucose lowering? *Curr Pharm Des.* 2009; 15(27):3179-92.

[27] Kaku K. Efficacy and safety of therapy with metformin plus pioglitazone in the treatment of patients with type 2 diabetes: a double-blind, placebo-controlled, clinical trial. *Curr Med Res Opin*. 2009 May;25(5):1111-9.

[28] Habib ZA, Tzogias L, Havstad SL, Wells K, Divine G, Lanfear DE, Tang J, Krajenta R, Pladevall M, Williams LK. Relationship between thiazolidinedione use and cardiovascular outcomes and all-cause mortality among patients with diabetes: a time-updated propensity analysis. *Pharmacoepidemiol Drug Saf*. 2009 Jun;18(6):437-47.

[29] Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, Jure H, De Larochellière R, Staniloae CS, Mavromatis K, Saw J, Hu B, Lincoff AM, Tuzcu EM; PERISCOPE Investigators. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. *JAMA*. 2008 Apr 2;299(13):1561-73.

[30] Home PD, Pocock SJ, Beck-Nielsen H et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet*. 2009 Jun 20;373(9681):2125-35.

[31] Ratner RE, Cannon CP, Gerstein HC, Nesto RW, Serruys PW, Van Es GA, Kolatkar NS, Kravitz BG, Zalewski A, Fitzgerald PJ; APPROACH Study Group. Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in diabetes patients with Cardiovascular History (APPROACH): study design and baseline characteristics. *Am Heart J*. 2008 Dec; 156(6):1074-9.

[32] Home PD, Bailey CJ, Donaldson J, Chen H, Stewart MW. A double-blind randomized study comparing the effects of continuing or not continuing rosiglitazone + metformin therapy when starting insulin therapy in people with Type 2 diabetes. *Diabet Med*. 2007 Jun;24(6):618-25. Epub 2007 Apr 2.

[33] Lexi-Comp® Online Web site. http://online.lexi.com/crlsql/servlet/crlonline . Accessed September 16, 2009.

[34] Micromedex® Healthcare Series, (electronic version). Thomson Micromedex, Greenwood Village, CO, USA. Available at: http://www.thomsonhc.com. Accessed September 16, 2009.

[35] FDA Medwatch. Avanida (rosiglitazone maleate)- Increased incidence of fractures in females noted in clinical trial. Website: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm150833.htm. Accessed September 2009.