Thiazolidinediones: rosiglitazone and pioglitazone
VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The 2 currently available thiazolidinediones (TZDs), rosiglitazone (Glaxo SmithKline) and pioglitazone (Takeda), will be reviewed. Published clinical trials and transcripts from the FDA Center for Drug Evaluation and were used for this review. Abstracts will be presented in cases where there are no published data. Much work is ongoing looking at the nonglycemic effects of the TZDs, such as their effect on proteinuria, PAI-1, effects on vascular wall and atherosclerotic plaque, vascular reactivity and endothelial function, and pancreatic β-cell function.[1] Although these data hold promise, they are preliminary at best and will therefore be excluded for the purpose of this review.

TABLE 1.   FDA-APPROVED INDICATIONS

	Monotherapy	Combination with sulfonylureas	Combination with metformin	Combination with insulin	Combination with repaglinide
Rosiglitazone	Yes	Yes	Yes	Yes	Yes
Pioglitazone	Yes	Yes	Yes	Yes	Yes

TABLE 2.   PHARMACOKINETICS

	Rosiglitazone	Pioglitazone
Bioavailability	99%	83%
Tmax	1 hour	2 hours
Vd/protein binding	0.1-0.2 L/kg; > 99% protein bound primarily to albumin	0.6L/kg; > 99% protein bound primarily to albumin
Metabolism	Metabolized by CYP 2C8 with CYP 2C9 contributing as a minor pathway	Metabolized by CYP 2C8 and CYP 3A4 resulting in 6 metabolites, 3 which are active

GLUCOSE LOWERING EFFECTS
Please refer to Appendix 1 located at the end of this review for detailed descriptions of the clinical trials.

Monotherapy trials
There are 3 short-term (8-12 week) trials,[2, 3, 52] two 26-week trials[4, 5], and one 52-week trial with rosiglitazone monotherapy.[6] There is one 16-week[7] and two 26-week monotherapy trials with pioglitazone.[8, 9] The populations studied included both patients who were drug therapy naïve having failed diet and exercise and those who were withdrawn from active therapy.

In an 8-week dose ranging study, rosiglitazone 2mg BID, 4mg BID, and 6mg BID reduced fasting plasma glucose (FPG) by 36, 43.2, and 45mg/dL respectively from a mean baseline of approximately 228mg/dL. The difference between the 4mg and 6mg BID dose was not significant suggesting that the top of the dosage range was reached.[2]

In another 8-week trial, rosiglitazone was taken once daily as 4mg, 8mg, and 12mg. Fasting plasma glucose decreased by 16.2, 36, and 30.6mg/dl with each dose respectively compared to an increase of 7.2mg/dl with placebo. This trial also demonstrated that no further benefit was obtained with the 12mg dose.[52]

A 12-week dose ranging study found that FPG was decreased by 25.2mg/dL with rosiglitazone 1mg BID and by 36mg/dL with 2mg BID from a baseline of 218mg/dL. The 0.05mg BID and 0.25mg BID doses did not differ from that of placebo.[3]

In the two 26 week placebo controlled rosiglitazone trials, approximately 25% of the patients were drug therapy naïve.[4, 5] When looking at the 4mg daily dose, the mean decrease in HbA1c ranged from as low as

0.3% in the Lebovitz study to as high as 0.9% in the Phillips study. A similar trend was observed for the 8mg daily dose, where the mean decrease in HbA1c ranged from 0.6% to 1.5%. The Phillips study also stratified the results for the drug therapy naïve group and the prior therapy group. The drug therapy naïve group had much greater improvements in HbA1c compared to those whose prior therapy was withdrawn. In this later group, HbA1c actually increased by a small amount with the 4mg daily dose.

Rosiglitazone was compared to glyburide in a 52-week study. Patients were randomized to receive rosiglitazone 2mg BID, 4mg BID or glyburide, Glyburide was titrated over a 12 week period then held constant for the remainder of the study. The median dose was 7.5mg daily. Other oral hypoglycemic agents were discontinued. The mean HbA1c was around 8.1% at baseline, which decreased by a mean of 0.27%, 0.53%, and 0.72% respectively for the 3 groups. Patients receiving glyburide had a greater decrease in HbA1c; however, after week 26, the HbA1c in the glyburide group began to slightly rise such that the mean value at the end of the study was similar among the 3 groups. From week 26, the HbA1c for the rosiglitazone groups remained steady.[6]

In the 16-week placebo controlled trial, pioglitazone 30mg once daily lowered HbA1c by 0.6% in all patients compared to an increase of 0.76% in the placebo group. When analyzed according to prior therapy, HbA1c decreased by 0.89% in patients who were drug therapy naïve and by 0.35% in the group whose prior diabetes medication was discontinued.[7]

Study 012 was a 26-week forced titration trial. Patients were randomized to one of 3 arms. In one arm, pioglitazone was given as 7.5mg x 4 weeks, followed by 15mg x 4 weeks then 30mg for the remainder of the study (low pioglitazone group). The second arm began with pioglitazone 15mg x 4 weeks, followed by 30mg x 4weeks then 45mg for the remainder of the study (high pioglitazone group). The third arm received placebo. In the treatment naïve group, the decrease in HbA1c, presented as placebo-subtracted values, was 2.28% for the low pioglitazone group and 2.59%. For those whose prior therapy was discontinued, HbA1c decreased by 1.31% and 1.42% for the low and high group respectively.[8]

Aronoff, et al. compared pioglitazone 7.5, 15, 30, and 45mg with placebo. As seen in the other studies, patients whose prior therapy was discontinued had a lesser response than those who were treatment naïve. Decrease in HbA1c for those who were treatment naïve was 0.3%, 0.3%, and 0.9% for the 15mg, 30mg and 45mg groups respectively compared to decreases of 0.1, 0, and 0.6% for those on prior therapy.[9]

Combination with sulfonylureas
There are three 26-week combination trials with rosiglitazone and sulfonylureas [10-12] and one 16-week trial combining pioglitazone and a sulfonylurea.[13]

Patients who were inadequately controlled on glyburide 10mg BID or micronized 12mg for at least 30 days were randomized to receive rosiglitazone 2mg BID monotherapy, glyburide 10mg BID monotherapy, or combination of both agents at the above mentioned doses. Prior to study entry, 60% of patients were receiving glyburide monotherapy and 40% were on combination therapy with another agent, the majority being metformin. During the run-in, concomitant antidiabetic drugs were discontinued. Mean baseline HbA1c was 9.2%, which increased by 1.9% in the rosiglitazone monotherapy arm and by 0.9% in the glyburide monotherapy arm. In the group receiving both agents, HbA1c decreased by 0.5%.[10]

Patients inadequately controlled on at least the half maximal dose of glyburide (mean dose 15mg) were eligible. Patients continued their usual dose of glyburide and were randomized to receive either rosiglitazone 2mg QD, 4mg QD, or placebo. Thirty percent were on prior combination therapy, which was discontinued during the run-in period. Mean baseline HbA1c was 9.1%. HbA1c increased by 0.55% for those receiving glyburide monotherapy compared to a decrease of 0.3% in the group receiving rosiglitazone 4mg plus glyburide. No significant change was seen in the rosiglitazone 2mg plus glyburide group.[11]

Patients who had a HbA1c >7.5% and FPG <170mg/dl while on a sulfonylurea were eligible (mean doses glyburide 12.6mg, gliclazide 185mg, glipizide 17mg). In addition to their stable dose of sulfonylurea, patients were randomized to receive rosiglitazone 1mg BID, rosiglitazone 2mg BID, or placebo. Baseline HbA1c was approximately 9.2%. HbA1c decreased by 0.52% and 0.875% respectively for the 1mg BID

and 2mg BID groups and increased by 0.5% in the group who continued to receive sulfonylurea monotherapy.[12]

Patients with HbA1c >8% on sulfonylurea monotherapy or combination therapy with metformin or acarbose (13% of patients) were eligible. Patients continued their usual SU dose. Other diabetes medications were discontinued during the run-in for those on combination therapy. Approximately 70% of the patients were on at least half the maximal SU dose. Patients were randomized to receive 15mg or 30mg of pioglitazone or placebo. Mean baseline HbA1c was approximately 10% in all 3 groups. The mean decrease in HbA1c was 0.8% and 1.2% for the 15mg and 30mg groups respectively, compared to an increase of 0.1% in the monotherapy arm.[13]

Some studies stratified the results for patients on monotherapy versus combination therapy prior to study entry. Adding a TZD to a sulfonylurea was not effective in decreasing HbA1c in patients who previously receiving combination therapy.

Combination with metformin
There are two 26-week trials that combine rosiglitazone and metformin[14, 15] and one 16-week trial with pioglitazone and metformin.[16]

In the study by Fonesca et al, patients whose FPG remained between 140-300mg/dl for at least 3 weeks while on metformin 2500mg were randomized to receive rosiglitazone 4mg or 8mg QD or placebo. At study entry, approximately 44% of the patients were receiving monotherapy with a sulfonylurea or acarbose and the remainder receiving combination sulfonylurea and metformin. Sulfonylureas and acarbose was discontinued before the study. HbA1c at baseline ranged from 8.6 –8.9%. The mean decrease in HbA1c was 0.56% with rosiglitazone 4mg, 0.78% with 8mg, and an increase of 0.45% in those receiving metformin and placebo. At least a 1% decrease in HbA1c value was seen with 33 and 37% of the patients taking 4mg and 8mg respectively.[14]

Study 093 was similar to the study described above, except patients were randomized to metformin + placebo, rosiglitazone 4mg BID + placebo, or a combination of both drugs. The combination resulted in a 0.6% reduction in HbA1c. HbA1c increased in both monotherapy arms, by 1.2% with rosiglitazone and 0.12% with metformin.[15]

Patients with HbA1c $\geq$ 8% while on a stable dose of metformin were randomized to receive 30mg of pioglitazone or placebo. Patients continued their usual dose of metformin (mean 1555 mg/d). Those on combination therapy at study entry (~30%) had their other diabetes medications discontinued. HbA1c decreased by a mean of 0.64% in the combination group and increased by 0.19% in the metformin group from a baseline of 9.86% and 9.75% respectively.[16]

Combination with insulin
There are two 26-week trials combining rosiglitazone and insulin[17, 18] and one 16-week trial combining pioglitazone and insulin.[19] In all 3 studies, no attempt was made to adjust the insulin dose unless the patient was hypoglycemic.

In the 2 rosiglitazone studies, mean baseline HbA1c ranged from 8.8 - 9.1% and the mean baseline insulin dose ranged from 65 – 77 units per day. Treatment with insulin and rosiglitazone 2mg BID and 4mg BID resulted in a mean decrease in HbA1c of 0.6% and 1.2% respectively. In the second trial where insulin was combined with rosiglitazone 4mg QD and 8mg QD, the decrease was 0.4% and 0.7% respectively. In both trials, when insulin was administered alone, HbA1c increased by a mean of 0.1%.[17, 18]

In the pioglitazone and insulin study, baseline HbA1c was 9.8% and the mean insulin dose was 71 units/day. Concomitant oral diabetes medications were discontinued (12% of patients). When insulin was combined with pioglitazone 15mg, HbA1c decreased by 0.99% versus by 1.26% with the 30mg dose. A decrease of 0.26% was seen in the arm receiving insulin alone.[19]

Combination with repaglinide
Combination of a TZD with repaglinide was approved in October 2002. The following data were obtained from the product package insert for repaglinide.[53] Patients previously treated with sulfonylurea or metformin monotherapy were randomized to receive monotherapy with pioglitazone 30mg or repaglinide (median dose 10mg/day), or a combination of pioglitazone + repaglinide (median dose 6mg/day) for 24 weeks. Baseline HbA1c was not provided. Only data from the group completing the study (66%) were presented. HbA1c decreased by 0.1%, 0.1%, and 1.9% for each of the monotherapy groups and the combination group respectively.

In a second study, patients previously treated with a sulfonylurea or metformin monotherapy were randomized to receive monotherapy with rosiglitazone (median dose 8mg/day) or repaglinide (median dose 12mg/day), or a combination of rosiglitazone (median dose 4mg/day) + repaglinide (median dose 6mg/day) for 24 weeks. Mean baseline HbA1c was 9.1%. In an intent-to-treat analysis, HbA1c decreased by 0.56, 0.17, and 1.43 in the rosiglitazone, repaglinide, and combination groups respectively.

Extension trials
Extension trials for both agents demonstrate sustained improvement on glycemic parameters. Compared to a mean baseline HbA1c of 8.5% (n=217), monotherapy with rosiglitazone 8mg resulted in a decrease in HbA1c to 7.5% after 15 months, the effect, which was maintained after 30 months. (Data on file GSK)

Patients from study 079, who were receiving rosiglitazone 2mg BID and glyburide 10mg BID were able to enter the open label extension study. Seventy-six patients completed at least 24 months of combination therapy. Mean baseline HbA1c at the start of the double blind phase was 9.4%. After 12 months, HbA1c decreased to 8.3% and was maintained after 24 months of therapy. (Data on file GSK)

Patients from studies 093 and 094 who were receiving rosiglitazone 8mg daily in combination with metformin 2500mg daily were able to enter the open label trial. 186 patients completed at least 24 months of combination therapy. Mean baseline HbA1c for the double blind phase was 8.8%. After 12 months, HbA1c was decreased to 7.5%. This response was maintained after 24 months of treatment. (Data on file GSK)

In study 031, patients from the pioglitazone combination studies could continue their same treatment or could discontinue or decrease the dose of the concomitant drug at the discretion of the investigator. Glycemic parameters were assessed at 24 and 72 weeks after the end of the double-blind study. At the end of the double-blind studies, mean HbA1c was 9.1%. At 24 weeks, HbA1c decreased to 8.53% (n=641) and at 72 weeks, decreased to a mean of 8.23% (n=398). [20]

In study 011, 569 patients from the monotherapy trials or who were newly enrolled were evaluated. Approximately half the patients had no prior exposure to pioglitazone. The baseline HbA1c for those newly enrolled, those rolled over from placebo, and rollover pioglitazone were 9.71%, 9.86%, and 9.59% respectively. After 48 weeks (n=274), the HbA1c decreased by a mean of 1.57%, 0.99%, and 1.03% for each group as mentioned above. [21] At 108 weeks (n=198), improvement in HbA1c was maintained. (Data on file Takeda)

Head-to head studies
One randomized, open-label [22] and 2 uncontrolled studies, [23, 24] found both TZDs to be equal in their glucose lowering effects. In another small study (n=39), presented as an abstract, patients given pioglitazone had lowered their HbA1c from 7.5% to 7.1% versus no change in the rosiglitazone group. [25] In 2 retrospective chart reviews, both agents resulted in a similar decrease in HbA1c.[49, 50]

EFFECTS ON LIPIDS
Please refer to appendix 2 for tables comparing lipid effects.

Increases in low-density lipoprotein-cholesterol (LDL-C), with means ranging from 3% to 19% have been observed with rosiglitazone and from 4.8% to 9.8% with pioglitazone. Mean increases in high-density lipoprotein-cholesterol (HDL-C), ranged from 8.4% to 15% with rosiglitazone and 5% to 19% with pioglitazone. Total cholesterol increased from means ranging from 8.5% to 22% and 3.2 to 6.4% for rosiglitazone and pioglitazone respectively. The LDL/HDL ratio is preserved, although with rosiglitazone, there is a lag time of several months before HDL-C rises relative to LDL-C. When looking at the 3 longer rosiglitazone monotherapy trials, 25% of patients had no change or a decrease in LDL and 25% of the patients had greater than a 30% increase compared to baseline. The percentage of patients having 0-10%, 10-20%, and 20-30% increase in LDL from baseline was somewhat similar to placebo. When looking at LDL: HDL, 50% of patients had no change and 22% had a greater than 30% increase in the ratio. The groups having 0-10%, 10-20%, and 20-30% changes were similar to the placebo group.[48]

Triglycerides decrease with pioglitazone, whereas the effect with rosiglitazone is variable. The mean values from clinical trials range from decreases of 6.4% to 16% with pioglitazone. The mean values for rosiglitazone ranged from changes that were insignificant to increases of 19%.

In the double-blind clinical trials with rosiglitazone, 17-28% of patients were taking concomitant lipid lowering medications.[43] In the double-blind clinical trials with pioglitazone, 11-15% of patients in the monotherapy trials and 20%, 28%, and 22% in the combination sulfonlyurea, insulin, and metformin studies respectively were taking concomitant lipid lowering agents. (Data on file, Takeda)

In a study designed specifically to assess lipid changes, Freed et al administered rosiglitazone 4mg BID for 8 weeks in an unblinded fashion. LDL and HDL increased by 9% and 5.8% respectively and triglycerides and free fatty acids decreased by 2% and 21.6% respectively. After the 8-week open label period, patients were randomized to atorvastatin 10mg, 20mg, or placebo in addition to rosiglitazone for an additional 16 weeks. There was a further 0.5% increase in LDL in the placebo + rosiglitazone arm versus a decrease of 31.5% and 38.8% in the 10 and 20mg atorvastatin + rosiglitazone groups. HDL decreased by 4.4% in the placebo arm whereas the atorvastatin 10 and 20mg groups had a further increase of 2.9 and 4.8% respectively. Triglycerides were essentially unchanged in the placebo group and decreased by 18.5% and 27.2% in the atorvastatin groups.[27]

Head-to-head studies
After a 2-week washout from troglitazone, 127 patients were randomized to pioglitazone or rosiglitazone. Dosing was based on the prior troglitazone dose. For example, patients who were on 200mg would receive 15mg of pioglitazone or 2mg of rosiglitazone; 400mg of troglitazone would receive 30mg of pioglitazone or 4mg of rosiglitazone and so on. An equal proportion of patients in both groups were receiving statins, with the dose remaining fixed during the study period. All blood samples were obtained under fasting conditions. After 4 months of treatment with pioglitazone, the total cholesterol, LDL, and triglycerides decreased by 20, 17, and 15mg/dl and the HDL increased by 2mg/dl. In the group receiving rosiglitazone, the total cholesterol increased by 4mg/dl, the LDL decreased by 2mg/dl, triglycerides increased by 6mg/dl and HDL increased by 1mg/dl. The change in cholesterol and LDL with pioglitazone was considered significant compared to rosiglitazone.[22]

In an observational study, 101 patients who were on the maximal recommended dose of troglitazone, rosiglitazone, or pioglitazone and had a stable weight and were on stable lipid lowering drugs were compared. There was no mention if blood samples were obtained fasting or randomly. Values obtained while on 2-4 months of TZD treatment were compared to baseline values. HDL-C increased by 0.5mg/dL and 6.5mg/dL in patients receiving rosiglitazone and pioglitazone respectively. LDL-C increased by 11.5mg/dL with rosiglitazone and decreased by 1.1mg/dL with pioglitazone. Triglycerides increased by 47mg/dl and decreased by 21mg/dl for the groups as mentioned above.[23]

In a non-randomized study, patients previously receiving troglitazone were switched to rosiglitazone or pioglitazone. Patients underwent a 1-week washout period before starting the new agent. Prior to

conversion, 66% of the pioglitazone and 48% of the rosiglitazone patients were receiving a statin. No changes to lipid-lowering medications were allowed. The mean observation period post-switch was 3.2 months. Approximately 80% were receiving maximal doses of rosiglitazone or pioglitazone. The majority of blood samples were obtained in the fasting state. The change in total cholesterol, triglycerides, HDL, and LDL were –4.7%, -11.3%, +2.6%, and –7.3% respectively for pioglitazone and +8.5%, +38.4%, –6.3%, and +8.1% for rosiglitazone. [24]

The medical records of 1115 randomly selected patients receiving uninterrupted pioglitazone or rosiglitazone were retrospectively reviewed. Patients had to have received either pioglitazone or rosiglitazone for > 12 weeks and have had no change in lipid lowering medications. Approximately 60% of patients were receiving an anti hyperlipemic agent with the majority using a statin. It was assumed that biochemical results were based on appropriately collected and analyzed samples. Triglycerides decreased by 22.5% with pioglitazone and 5.57% with rosiglitazone from a baseline value of 245 and 239mg/dL respectively. LDL decreased by 4.31% and increased by 3.12% for pioglitazone and rosiglitazone respectively from a mean baseline value of approximately 115mg/dL. HDL increased by 6.14% from a baseline of 43.18mg/dL with pioglitazone and decreased by 0.26% from a baseline of 46.11mg/dL with rosiglitazone.[49]

In a retrospective chart review, 20 patients who were consecutively treated with rosiglitazone 4mg BID for a minimum of 3 months, followed by pioglitazone 45mg for at least 3 months were evaluated. Dosages of concomitant medications could not be changed during the study period. After rosiglitazone, the percent increase from baseline for triglycerides, total cholesterol, HDL, and LDL were 13%, 22%, 8%, and 35% respectively. After treatment with pioglitazone triglycerides and total cholesterol decreased by 14% and 1% and HDL and LDL increased by 8% and 1% respectively when compared to baseline.[50]

Presented as an abstract, 39 patients who were previously maintained on troglitazone were randomly switched to pioglitazone 45mg or rosiglitazone 8mg daily and followed for a 6-month period. Patients with LDL > 100mg/dL were also being treated with lipid lowering agents. Though not clear, it is implied that the dose of the lipid-lowering agents could be titrated during the study. Maximal mean changes in the 6 months following the switch are presented. LDL decreased from 91 to 84mg/dl with pioglitazone and increased from 105 to 115 with rosiglitazone. Triglycerides decreased from 183 to 156mg/dl with pioglitazone and increased from 178 to 188 with rosiglitazone. The HDL increased by 7mg/dl with both drugs and was considered to be significant compared to baseline. [25]

Long-term follow-up
The open label extension from the 52-week glyburide controlled study indicates that the LDL decreases and approaches baseline values, while HDL continues to rise in patients receiving rosiglitazone monotherapy for up to 18 months. Between weeks 52 and 78, patients receiving RSG 8mg had a reduction in mean LDL from 156mg/dL (n=123) to 148mg/dL (n=95). During this same time frame, mean HDL increased from 49mg/dL to 57mg/dL. LDL: HDL and TC: HDL remains unchanged or begins to decrease toward baseline values. At month 18, LDL: HDL decreased from a mean of 3.1 to 2.78. Thirty-month data was provided for TC: HDL whereby the ratio went from a baseline of 5.0 to 4.0. (Data on file GSK).

In another open-label trial comparing rosiglitazone 4mg BID to glyburide (mean dose 10.5mg/day), lipids were assessed as secondary endpoints (Data on file GSK). This is a 3-year study that is still ongoing; therefore interim results at 52 and 100 weeks are presented. At 52 weeks, there was a 4mg/dL difference in HDL between rosiglitazone and glyburide, favoring rosiglitazone. Mean LDL increased by 6.4 ± 32.72mg/dL with rosiglitazone and decreased by 8.9± 21.06mg/dL with glyburide. There were no statistically significant changes in triglycerides with either group.

After 100 weeks, HDL increased by approximately 20% from a mean baseline of 46.6mg/dL to 55.7mg/dL. LDL peaked between weeks 12-28 and remained elevated through week 52, after which it began to decline. The mean LDL was 132.4mg/dL at week 100 compared to a baseline of 134.1mg/dL.

In a study designed primarily to look at change in left ventricular mass index, lipids were evaluated as secondary endpoints. This 52-week open label trial compared rosiglitazone 4mg BID to glyburide (mean dose 10.5mg). The changes in LDL, HDL, and TG for rosiglitazone were +6.3mg/dl, +7.7mg/dl, and –2.8mg/dl respectively. For glyburide, the changes were –8.9mg/dl, and –13.8mg/dl for LDL and triglycerides respectively. Value for HDL was not provided. The percentage of patients who had an LDL > 100mg/dl were 89% with rosiglitazone and 77% with glyburide.[33]

Results from open label extension trials with pioglitazone at 48 weeks and 108 weeks show decreased triglycerides and increased HDL levels. Total cholesterol and LDL were not adversely affected. At the end of 108 weeks, HDL increased by a mean of 4.1mg/dL from a mean baseline of 40.1mg/dL (n=194) and triglycerides decreased by a mean of 80mg/dL from a baseline of 280mg/dL (n=197). Values for LDL were not provided. (Data on file Takeda)

LDL size and atherogenicity
Although still considered to be controversial, there are data suggesting that larger buoyant particles of LDL may be less atherogenic than the smaller, dense LDL. There are a few studies evaluating LDL subfractions during TZD therapy. Eighteen patients on stable anti-lipid therapy having lipid values pre-TZD, while on troglitazone, and on rosiglitazone after being switched from troglitazone were studied. The measured LDL for the 3 periods was 79.5 ± 3.2, 83.4 ± 3.6, and 79.5 ± 5.3mg/dL respectively. The particle sizes for LDL range are designated as 1-4 with 1 being largest and least dense. The average LDL particle size for each period was 2.58 ± 0.12, 2.48 ± 0.14 and 2.12 ± 0.15. Those having a predominance of LDL peak size larger than 25.5nm are classified as Pattern A and less than or equal to 25.5nm are classified as Pattern B. In the pre-TZD phase, 61% were classified as pattern B. During the troglitazone phase, this percentage was unchanged. After treatment with rosiglitazone, 11% of patients were considered as pattern B. No information on duration of treatment with troglitazone and rosiglitazone was provided. [26]

In another study, patients with type 2 diabetes who were treated with diet/exercise alone or sulfonylurea monotherapy and had a LDL-C $\geq 100 \leq 160$mg/dl were eligible. Those who were on lipid-lowering agents underwent a 4-week washout. Rosiglitazone 4mg BID was then added to their usual diabetes treatment for 8 weeks. There was a 9% increase in LDL-C and an increase in the relative flotation (Rf) at the end of 8 weeks. An increase in relative flotation indicates a change from small dense LDL particles to the larger buoyant type. Of the 243 patients enrolled in this study, 128 had a predominance of small dense LDL (Rf < 0.2632). After 8 weeks of treatment, over half of the 128 patients shifted to a predominance of large buoyant LDL (Rf $\geq$ 0.2632). [27]

LDL particle size can also be estimated by using the LDL to Apo B ratio. In study 020, LDL size increased by 0.012 and 0.037 in the group receiving rosiglitazone 2mg BID and 4mg BID respectively after 52-weeks of therapy. (Data on file GSK)

The effect of monotherapy with pioglitazone 45mg on LDL subfractions was evaluated in 30 patients. Total LDL was not significantly changed; however, the average calculated diameter of the LDL particles increased from 19.5 to 19.8nm (p=0.007). [28]

HDL can be subclassified into 2 types. HDL_2 is the larger and less dense particle and HDL_3 is the smaller and denser particle. Like LDL, the larger and less dense HDL particle may be less atherogenic. In the 2 studies described above the HDL subclass was also assessed. In the study by Ovalle, HDL_2 increased to 6.9ng/dL during the troglitazone phase, from a pre-TZD value of 6.6ng/dL. After switching to rosiglitazone, the HDL_2 increased to 8.2ng/dL. HDL_3 also increased from a pre-TZD value of 25.8ng/dL to 29.4ng/dL on troglitazone. After the switch to rosiglitazone the value decreased to 28.6ng/dL.[26] Freed et al found that after 8 weeks of rosiglitazone, HDL increased by 5.8% from a baseline of 39.1mg/dL. The increase in the HDL_2 subclass was 12.6% and 4.6% with HDL_3 subclass. [27]

SAFETY

Edema

Edema is a class effect of the thiazolodinediones and appears to be dose-related. The highest incidence is seen when combining a TZD with insulin. The table below shows the frequency of edema seen during the clinical trials. Subjects with NYHA Class III and IV cardiac status were excluded. The duration of these trials ranged from 16-26 weeks. These values do not distinguish between new onset edema and worsening edema (those with baseline edema).

In the open-label monotherapy extension trial, edema was reported in 9.1% of patients receiving pioglitazone (mean dose 36.8mg). (Data on file Takeda) According to GSK, The rate of edema has not increased with continued treatment with rosiglitazone in the open label trials during monotherapy or combination therapy with sulfonylureas, metformin, or insulin. In the 52-week cardiovascular trial comparing rosiglitazone 8mg to glyburide, the incidence of edema was 6.7% with rosiglitazone and 1% with glyburide.[33]

TABLE 3.   FREQUENCY OF EDEMA

	Rosiglitazone	Pioglitazone
Monotherapy	4.8% (placebo 1.3%)	4.8% (placebo 1.2%)
Combination with sulfonylureas	3% (SU alone 1%)	7.5% (SU alone 2.1%)
Combination with metformin	4.4% (metformin alone 2.2%)	6% (metformin alone 2.5%)
Combination with insulin	14.7% (insulin alone 5.4%)	15.3% (insulin alone 7%)

Heart failure

Both rosiglitazone and pioglitazone have been associated with the development of heart failure. In the two 26-week insulin trials, CHF was reported in 1% of patients on insulin alone, 1.9% receiving insulin + rosiglitazone 4mg, and 3.0% receiving insulin + rosiglitazone 8mg. During the open-label extension study, patients all received rosiglitazone 8mg + insulin. CHF was reported in 3.6% of these patients. When expressed as 100 patient years, there were 7.4 cases and 2.2 cases/100 patient years for the combination and insulin alone respectively. [29]

Heart failure was reported in 0.3% on the rosiglitazone and metformin combination with a rate of 0.7 cases/100 patient years versus 0 for metformin alone. Combination with a sulfonylurea resulted in a 0.7% incidence and a rate of 0.6 cases/100 patient years versus 0.4% and 0.6 cases/100 patient years with sulfonylurea monotherapy. Monotherapy with rosiglitazone resulted in heart failure in 0.4% of patients with a rate of 0.6 cases/100 patient years. Patients receiving only placebo in these studies had heart failure reported in 0.2% with a rate of 0.6 cases/100 patient years. [29]

In the 16-week trial of insulin + pioglitazone, 4 patients (1.05%) developed CHF versus none in the group receiving insulin alone. One patient in the metformin + pioglitazone trial developed CHF. All of these patients had previous histories of cardiovascular problems, such as CAD, MI, and prior CABG procedures.[19]

In the pioglitazone open-label monotherapy extension trial, 4 cases of CHF were reported, of which 3 had a history of cardiovascular disease. In the open label combination trials, 13 cases were reported, 12 who had a history of cardiovascular disease. Seven of the 13 cases during combination with sulfonylureas (4 with rosiglitazone combination and 3 with placebo) and 6 cases were during combination with insulin (4 with rosiglitazone and 2 with placebo). These open label trials evaluated over 1300 patients; therefore, an approximate incidence of heart failure would be 17/1300 or 1.3% (Data on file Takeda).

Based on echocardiographic evaluations, it appears that the TZDs do not have a direct effect on cardiac structure or function. In pioglitazone monotherapy study 001, patients who had echocardiographs at baseline and endpoint were assessed. Mean changes from baseline in left ventricular mass index, cardiac index, and fractional shortening were negligible.[31] These cardiac variables were also evaluated in the pioglitazone long-term extension trial 011. Echocardiographic changes were negligible in patients receiving pioglitazone for up to 48 weeks.[32] There is no evidence of echocardiographic changes in patients receiving pioglitazone for up to 2 years (Data on file Takeda)

Rosiglitazone 4mg BID for 52 weeks resulted in a small, but clinically insignificant increase in left ventricular mass index and left ventricular end diastolic volume. Ejection fraction was unchanged. [33]

Hematologic effects
Hemoglobin and hematocrit decrease in a dose-dependent manner with the majority of change occurring during the first 12 weeks. It appears to be dilutional due to the increase in intravascular volume rather than a decrease in red cell mass.

Based on the results from the randomized controlled trials, the mean drop in hemoglobin with rosiglitazone 4mg is around 0.5-0.6g/dl and 0.8-1.0g/dl with the 8mg dose. The average drop with pioglitazone was around 0.4 g/dl with the 15mg dose and between 0.5-0.7g/dl with the 30mg dose. Both monotherapy and combination therapy resulted in similar changes in Hgb.

In the 52-week trial comparing rosiglitazone and glyburide, anemia (not defined) was reported in 6.7% of the rosiglitazone and 1% of the glyburide patients.[33]

In the combination studies with pioglitazone (+ sulfonylurea, metformin, and insulin), anemia was reported in 0.3%, 1.2%, and 1.6% of patients. When sulfonylurea, metformin, and insulin were administered as monotherapy, the incidence was 1.6%, 0, and 1.6% respectively. [48]

Hepatic effects
Phase II and III trials have shown that rosiglitazone and pioglitazone do not cause hepatotoxicity any more than placebo. With rosiglitazone, ALT $\geq$ 3 times the upper limit of normal was seen in 0.2%, 0.2%, and 0.5% of patients receiving rosiglitazone, placebo, and comparator drug respectively. One patient receiving rosiglitazone had an ALT > 10 x ULN. As of November 1999, an analysis of over 5000 patients from all rosiglitazone clinical trials, revealed that 0.32% of rosiglitazone treated, 0.17% of placebo treated and 0.4% of combination (sulfonylurea, metformin, insulin) treated patients developed an ALT > 3 x ULN while on therapy. When converted to 100 person-years of exposure, the rates were 0.29, 0.59, and 0.64 respectively.[51]

In the U.S. clinical placebo-controlled trials, values of 0.26% and 0.25% were seen with pioglitazone and placebo respectively. During all U.S. clinical trials, ALT levels > 3x ULN were seen in 0.43% receiving pioglitazone. No patient had a value > 10 x ULN. All patients with follow-up values had reversible elevations in ALT.

In post-marketing experience with these agents, hepatitis and elevation of liver enzymes $\geq$ 3 times the upper limit of normal has been reported; however, causality has not been established. In the literature, 5 case reports of hepatotoxicity have been reported with rosiglitazone[36-40] and 5 with pioglitazone[41-45]. Two of the rosiglitazone cases were attributed to other causes. [36, 37]

Weight gain
In the 16-week and 26-week trials, both rosiglitazone and pioglitazone cause a comparable dose-dependent increase in weight. When combined with a sulfonylurea, insulin, or repaglinide, the increase in weight is greater than that seen with monotherapy. When combined with metformin, the increase in weight is generally less than that seen with monotherapy. (Table 4)

In the two 52-week rosiglitazone trials, the mean weight gain with 4mg BID was 2.95[6] and 5kg.[33] Waist-to-hip ratios were unchanged. Interestingly, greater weight gain was associated with greater decreases in HbA1c.

The increase in weight in the head-to-head studies was 2 kg with either agent in the Khan study[22], 0.5kg and 2.6kg with rosiglitazone and pioglitazone respectively in the King study[23], 1kg and 1.2kg respectively in the Gegick study[24], 0.74 and 0.89kg in the Boyle study, [44] and 1.5kg and 1.6kg in the LaCivita study.[50]

TABLE 4.   WEIGHT GAIN DURING 26 AND 52 WEEK TRIALS

Rosiglitazone			Pioglitazone		
Monotherapy					
Phillips[4] 26 weeks	4mg QD 2mg BID 8mg QD 4mg BID Placebo	+1.2kg +1.5kg +2.6kg +3.3kg -0.9kg	Aronoff[9] 26 weeks	15mg 30mg 45mg Placebo	+1.3kg +1.3kg +2.8kg -1.3kg
Lebovitz[5] 26 weeks	2mg BID 4mg BID	+1.6kg +3.5kg	Rosenblatt[7] 16 weeks	30mg Placebo	+1.35kg -1.87kg
Freed[27] 26 weeks	4mg BID	+2.0-2.5kg	Study 012[8] 26 weeks	7.5/15/30 15/30/45 Placebo	+0.49kg +1.82kg -1.81kg
Study 020[6] 52 weeks	2mg BID 4mg BID Glyburide	+1.7kg +2.95kg +1.9kg			
Sutton[33] 52 weeks	4mg BID Glyburide	+5kg +3.4kg			
Combination with sulfonylurea					
Wolffenbuttel[12] 26 weeks	RSG 1mg BID + SU RSG 2mg BID + SU	+0.8kg +1.8kg	Kilpnes[13] 16 weeks	PIO 15mg + SU PIO 30mg + SU SU alone	+1.9kg +2.9kg -0.8kg
Study 079[10] 26 weeks	RSG 2mg BID alone Glyburide alone RSG 2mg BID + glyburide	+1.53kg No change +3.8kg			
Study 096[11] 26 weeks	RSG 2mg QD + glyburide RSG 4mg QD + glyburide Glyburide alone	+1.88kg +2.64kg +0.22kg			
Combination with metformin					
Fonesca[14] 26 weeks	RSG 4mg QD + metformin RSG 8mg QD + metformin Metformin alone	+0.7kg +1.9kg -1.2kg	Einhorn[16] 16 weeks	PIO 30mg + metformin Metformin alone	+0.95kg -1.36kg
Combination with insulin					
Raskin[17] 26 weeks	RSG 2mg BID + insulin RSG 4mg BID + insulin Insulin alone	+4.0kg +5.3kg +0.9kg	*Rosenstock[19] 16 weeks	PIO 15mg + insulin PIO 30mg + insulin Insulin alone	+2.3kg +3.7kg -0.04kg
Combination with repaglinide					
Package insert[53] 24 weeks	Repaglinide RSG RSG + repaglinide	+1.3kg +3.3kg +4.5kg	*Package insert[53] 24 weeks	Repaglinide PIO 30mg alone PIO 30mg + repaglinide	+0.3kg +2kg +5.5kg

*Data only from those completing the study

Hypoglycemia
Since hypoglycemia was not defined in the studies, comparisons between agents cannot be made. Overall, the incidence is low when used as monotherapy and increases when used in combination with sulfonylureas and insulin.

In a 52-week trial, hypoglycemia occurred in 1.9% of patients receiving rosiglitazone and in 7.1% of those receiving glyburide.[33]

TABLE 5.   INCIDENCE OF HYPOGLYCEMIA

Monotherapy		Combination with sulfonylureas		Combination with metformin		Combination with insulin		Combination with repaglinide	
RSG	< 1.0%	RSG 2mg BID + GLY 10mg BID	8.1%	RSG 4mg QD + metformin 2.5g QD	2.5%	RSG 2mg BID + insulin	53%	TZD + repaglinide	7%
PIO	1.2%	RSG 2mg QD + GLY	4.3%	RSG 8mg QD + metformin 2.5g QD	4.5%	RSG 4mg BID + insulin	67%		
		RSG 4mg QD + GLY	2.6%	PIO 30mg QD + metformin	0.6%	PIO 15mg + insulin	8%		
		RSG 1mg BID + SU	3.4%			PIO 39MG + insulin	15%		

		RSG 2mg BID + SU	5.3%				
		PIO 15mg QD + SU	0				
		PIO 30mg QD + SU	3.8%				

DRUG INTERACTIONS

Rosiglitazone and pioglitazone do not appear to inhibit any of the major P450 enzymes. Rosiglitazone does not appear to induce CYP3A4 metabolism when coadministered with CYP3A4 substrates, ethinylestradiol norethindrone, and nifedipine. One study (abstract) found that administration of pioglitazone 45mg did not induce or inhibit the metabolism of ethinylestradiol/norethindrone or ethinylestradiol/estrone. [46] However, the manufacturers' package insert recommends additional caution be used with contraception when pioglitazone and oral contraceptives are concomitantly taken. The coadministration of rosiglitazone or pioglitazone did not alter the pharmacokinetics of metformin, digoxin, ranitidine, or warfarin.

Acarbose when administered for 7 days had a small, but clinically insignificant decrease in the area under the curve of rosiglitazone when given as a single 8mg dose. [47]

Ketoconazole, a potent CYP3A4 inhibitor, significantly inhibited the metabolism of pioglitazone. It is unknown at this time if other CYP3A4 inhibitors or inducers affect the metabolism of pioglitazone. For a list of cytochrome P450 drug interactions, refer to http://medicine.iupui.edu/flockhart/.

DOSAGE AND ADMINISTRATION

- May be given without regard to meals
- No dosage adjustment required for renal insufficiency
- The current sulfonylurea, metformin, or insulin dose should be continued when adding rosiglitazone or pioglitazone. When using with insulin, if plasma glucose levels decrease to less than 100-120 mg/dL, the dose of insulin should be decreased by 10-25%. Continue to monitor the patient for further adjustments.

	Rosiglitazone	Pioglitazone
Monotherapy	4-8mg/day given once daily or divided into 2 doses	15-45mg once daily
Combination with SU	4mg given once daily or divided into 2 doses	15-30mg once daily
Combination with metformin	4-8mg/day given once daily or divided into 2 doses	15-30mg once daily
Combination with insulin	4mg given once daily or divided into 2 doses	15-30mg once daily

AVAILABILITY

Rosiglitazone is available as 2, 4, and 8mg pentagonal-shaped film-coated tablets in bottles of 30, 60 (2mg and 4mg only), 100, and 500 tablets and in unit dose packs of 100.

Pioglitazone is available as 15, 30, and 45 mg round, non-scored tablets in bottles of 30, 90, and 500 tablets.

SUMMARY

The glucose lowering effect of rosiglitazone and pioglitazone are probably comparable. There were some baseline differences among the study populations, which should be kept in mind when comparing results. For example, patients with higher baseline HbA1c may have a greater decrease in HbA1c. Also, patients who are drug therapy naïve have a greater response than those who had been on prior therapy. Similarly for the combination studies, patients who were receiving monotherapy at study entry had a better response than those who previously were taking combination therapy. The head-to-head trials, suggest that glycemic control is similar with the 2 agents.

TABLE 6.   SUMMARY TABLE

	Rosiglitazone monotherapy	Pioglitazone monotherapy
Baseline HbA1c	8.9% (2 placebo controlled trials) 8.1% (SU controlled)	10.2%
% drug therapy naïve	22-29%	24-40%
↓ in HbA1c	-0.3-0.9% (RSG 4mg) -0.5-1.5% (RSG 8mg)	-0.3% (PIO 15mg) -0.3 – 0.6% (PIO 30mg)
	Rosiglitazone + sulfonylurea	**Pioglitazone + sulfonylurea**
Baseline HbA1c	9.2%	10%
% taking combo tx prior to study entry	30-40%	14-16%
↓ in HbA1c	-0.3-0.87% (RSG 4mg)	-0.8% (PIO 30mg) -1.2% (PIO 30mg)
	Rosiglitazone + metformin	**Pioglitazone + metformin**
Baseline HbA1c	8.9%	9.86%
% taking combo tx prior to study entry	50%	30%
↓ in HbA1c	-0.56% (RSG 4mg) -0.6-0.78 (RSG 8mg)	-0.64% (PIO30mg)
	Rosiglitazone + insulin	**Pioglitazone + insulin**
Baseline HbA1c	9%	9.85%
Mean insulin dose	74 units	71 units
↓ in HbA1c	-0.4-0.6% (RSG 4mg) -0.7-1.2% (RSG 8mg)	-0.99% (PIO 15mg) -1.26% (PIO 30mg)

Both agents increase LDL; however, pioglitazone increases LDL to a lesser extent than rosiglitazone. Based on non head-to-head trials, the difference in change in LDL between rosiglitazone and pioglitazone is approximately 10mg/dl. Based on 52-week data, the extent to which LDL increases with rosiglitazone appears to diminish over time. There are no long-term trials that evaluate whether the differences in LDL between pioglitazone and rosiglitazone are of clinical significance. Both agents have studies showing that there is an increase in LDL particle size, which may be associated with less atherogenicity than smaller and denser LDL particles.   HDL increases to a similar extent with both drugs. Triglycerides decrease with pioglitazone, whereas the effect with rosiglitazone is variable.

Both drugs can cause edema, with the risk being the greatest when used in combination with insulin. Both drugs have been associated with patients developing heart failure.

One of the pathways of metabolism for pioglitazone is via the CYP3A4 isoenzyme. Metabolism of pioglitazone has been significantly inhibited by ketoconazole; therefore, the potential for drug interactions with other CYP3A4 inhibitors or inducers exists. The major metabolic pathway for rosiglitazone is CYP2C8. At present, CYP2C8 does not appear to be involved in the metabolism of many drugs; therefore the potential for drug interactions is low.

REFERENCES

1. Parulkar AA, Pendergrass ML, Granda-Ayala R, et al. Nonhypoglycemic effects of thiazolidinediones. Ann Intern Med 2001; 134:61-71.

2. Raskin P, Rappaport EB, Cole ST, et al. Rosiglitazone short-term monotherapy lowers fasting and post-prandial glucose in patients with type 2 diabetes. Diabetologia 2000; 43:278-284.

3. Patel J, Anderson RJ, Rappaport EB, et al. Rosiglitazone monotherapy improves glycaemic control in patients with type 2 diabetes: a twelve-week, randomized, placebo-controlled study, Diabet Obes Metab 1999; 1:165-172.

4. Phillips LS, Grunberger G, Miller E, Patwardhan R, et al. Once- and twice-daily dosing with rosiglitazone improves glycemic control in patients with type 2 diabetes. Diabetes Care 2001; 24:308-315.

5. Lebovitz HE, Dole JF, Patwardhan R, et al. Rosiglitazone monotherapy is effective in patients with type 2 diabetes. J Clin Endocrinol Metab 2001; 86:280-288.

6. Study 020. Food and Drug Administration Center for Drug Evaluation and Research: Seventy-third Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee.

7. Rosenblatt S, Miskin B, Glazer NB, et al. The impact of pioglitazone on glycemic control and atherogenic dyslipidemia in patients with type 2 diabetes mellitus. Coron Artery Dis 2001; 12:413-423.

8. Study 012. Piogltiazone monotherapy. Center for Drug Evaluation and Research. Application number: 021073. http://www.fda.gov/cder/foi/nda/99/021073A_Actos.htm

9. Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, et al. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes. Diabetes Care 2000; 23:1605-1611.

10. Study 079. Avandia in combination with sulfonylureas. Center for Drug Evaluation and Research. Application number: 21-071/001. http://www.fda.gov/cder/foi/nda/2000/21-071S001_Avandia.htm

11. Study 096. Avandia in combination with sulfonylureas. Center for Drug Evaluation and Research. Application number: 21-071/001. http://www.fda.gov/cder/foi/nda/2000/21-071S001_Avandia.htm

12. Wolffenbuttel BHR, Gomis R, Squatrito S, Jones NP, et al. Addition of low-dose rosiglitazone to sulfonylurea therapy improves glycaemic control in type 2 diabetic patients. Diabet Med 2000; 17:40-47.

13. Kipnes MS, Krosnick A, Rendell MS, Egan JW, et al. Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. Am J Med 2001; 111:10-17.

14. Fonesca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus. JAMA 2000; 283:1691702.

15. Study 093. Rosiglitazone and metformin. Food and Drug Administration Center for Drug Evaluation and Research: Seventy-third Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee.

16. Einhorn D, Rendell M, Rosenzweig J, et al. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. The pioglitazone 027 study group. Clin Ther 2000; 22:1385-1409.

17. Raskin P, Rendell M, Riddle MC, Dole JF, et al. A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes. Diabetes Care 2001; 24:1226-1232.

18. Study 095. Rosiglitazone and insulin. Data on file A, GlaxoSmithKline.

19. Rosenstock J, Einhorn D, Hershon K, et al. Efficacy and safety of pioglitazone in type 2 diabetes: a randomized, placebo-controlled study in patients receiving stable insulin therapy. Int J Clin Pract 2002; 56:251-257.

20. Einhorn D, Kipnes M, Glazer NB, Pioglitazone 031 Study Group. Durability of glycemic control with pioglitazone in long-term combination and monotherapy. Diabetes 2001; 50 (suppl 2):A111.

21. Mathisen A, Rubin C, Study Group Pioglitazone 011. The long-term effect of pioglitazone on glucose control and lipid profile in patients with type 2 diabetes. [abstract 1518-PO]. Diabetes 2000; 49 (suppl 1): A361-362.

22. Khan MA, Peter JV, Xue JL.   A prospective randomized comparison of the metabolic effects of pioglitazone vs. rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. Diabetes Care 2002; 25:708-711.

23. King AB. A comparison in a clinical setting of the efficacy and side effects of three thiazolodinediones. Diabetes Care 2000; 23:557.

24. Gegick CG, Altheimer MD. Comparison of effects of thiazolodinediones on cardiovascular risk factors: observations from a clinical practice. Endocrin Pract 2001; 7: 162-169.

25. Davidson PC, Sabbah HT, Steed RD, et al. Pioglitazone versus rosiglitazone therapy in randomized follow-up in patients previously treated with troglitazone. [Abstract 437-P]. Diabetes 2001; 50 (suppl 1): A109.

26. Ovalle F and Bell DS. Differing effects of thiazolidinediones on LDL subfractions. [Abstract 1896-PO]. Diabetes 2001; 50 (suppl 2).

27. Freed MI, Ratner R, Marcovina SM, et al. Effects of rosiglitazone alone and in combination with atorvastatin on the metabolic abnormalities in type 2 diabetes mellitus. Am J Cardiol 2002; 90: 947-952

28. Winkler K, Friedrich I, Nauck M, et al. Pioglitazone reduces dense LDL-particles in patients with type 2 diabetes. [Abstract 592-P]. Diabetes 2001; 50 (suppl 2).

29. Avandia in combination with sulfonylureas. Center for Drug Evaluation and Research. Application number: 21-071/001. http://www.fda.gov/cder/foi/nda/2000/21-071S001_Avandia.htm

30. Actos product package insert. July 2002.

31. Rubin CJ, Shaffer S, et al. Echocardiographic assessment in patients with type 2 diabetes mellitus treated with pioglitazone. (Abstract) 60th American Diabetes Association Scientific Sessions. San Antonio, Texas 2000.

32. Schneider RL, Shaffer SJ, et al. Long-term echocardiographic assessment in patients with type 2 diabetes mellitus treated with pioglitazone. (Abstract) 60th American Diabetes Association Scientific Sessions. San Antonio, Texas 2000.

33. St. John Sutton MS, Rendell M, Dandona P, et al. A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycemic control in patients with type 2 diabetes. Diabetes Care 2002; 25: 2058-2064.

34. Scheen AJ. Thiazolidinediones and liver toxicity. Diabetes Metab 2001; 27:305-313.

35. Avandia product package insert. March 2003.

36. Al-Salman J, Arjomand H, Kemp DG, et al. Hepatocellular injury in a patient receiving rosiglitazone. Ann Intern Med 2000; 132:121-124.

37. Forman LM, Simmons DA, Diamond RH. Hepatic failure in a patient taking rosiglitazone. Ann Intern Med 2000; 132:118-121.

38. Gouda HE, Khan A, Schwartz J, et al. Liver failure in a patient treated with long-term rosiglitazone therapy. Am J Med 2001; 111:584-585.

39. Ravinuthala RS, Nori U. Rosiglitazone toxicity. Ann Intern Med 2000; 133:658.

40. Bonkovsky HL, Bird AR, Szabo G, et al. Severe cholestatic hepatitis caused by thiazolidinediones: risks associated with substituting rosiglitazone for troglitazone. Dig Dis Sci 2002; 47: 1632-1637.

41. Maeda K. Hepatocellular injury in a patient receiving pioglitazone. Ann Intern Med; 2001:306.

42. May LD, Lefkowitch JH, Kram MT, et al. Mixed hepatocellurlar-cholestatic liver injury after pioglitazone therapy. Ann Intern Med 2002; 136: 449-483.

43. Nagasaka S, Abe T, Kawakami A, et al. Pioglitazone-induced hepatic injury in a patient previously receiving troglitazone with success. Diabetic Med 2002; 19: 344-348.

44. Pinto A, Cummings OW, Chalasani N. Severe but reversible cholestatic liver injury after pioglitazone therapy. Ann Intern Med 2002; 137: 857.

45. Chase MP, Yarze JP. Pioglitazone-associated fulminant hepatic failure. Am J Gastroenterol 2002; 97: 502-503.

46. Carey RA, Liu Y. Pioglitazone does not markedly alter oral contraceptive or hormone replacement theray pharmacokinetics. [Abstract 405-P]. Diabetes 2000; 49 (Suppl. 1): A100.

47. Miller AK, Inglis A, Culkin KT, et al. The effect of acarbose on the pharmacokinetics of rosiglitazone. Eur J Clin Pharmacol 2001; 57:105-109.

48. Food and Drug Administration Center for Drug Evaluation and Research: Seventy-third Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. NDA 21-071 Avandia.

49. Boyle PJ, King AB, Olansky L, et al. Effects of pioglitazone and rosiglitazone on blood lipid levels and glycemic control in patients with type 2 diabetes mellitus: a retrospective review of randomly selected medical records. Clin Ther 2002; 24:378-396.

50. LaCivita KA, Villarreal G. Differences in lipid profiles of patients given rosiglitazone followed by pioglitazone. Curr Med Res Opin 2002; 18:363-370.

51. Lebovitz HE, Kreider M, Freed MI. Evaluation of liver function in type 2 diabetic patients during clinical trials. Evidence that rosiglitazone does not cause hepatic dysfunction. Diabetes Care 2002; 25: 815-821.

52. Nolan JJ, Jones NP, Patwardhan R, et al. Rosiglitazone taken once daily provides effective glycemic control in patients with type 2 diabetes. Diabetic Med 2000; 17: 287-294.

53. Prandin product package insert. October 2002.

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APPENDIX 1. CLINICAL TRIALS

Monotherapy studies

Phillips 2001[4] (study 024)
R, DB, PC U.S. multicenter **Rosiglitazone vs. placebo** N=959 26 weeks ITT for primary analysis

Inclusion: 40-80 y/o BMI 22-38 Type 2 DM FPG 140-300 Fasting C-peptide $\geq$ 0.8ng/ml at the time of screening

Dosing: OHA d/c'd 14 days prior to 4-week placebo run-in. RSG 4mg QD vs. 2mg BID vs. 8mg QD vs. 4mg BID. Baseline = values after 4wk placebo run-in

Demographics

	4mg qd 2mg bid	8mg qd 4mg bid	Placebo
HbA1c	8.9 (1.6) 8.9 (1.5)	8.9 (1.5) 9 (1.5)	8.9 (1.5)
FPG	228.6 (61.2) 225 (55.8)	228.6 (57.6) 228.6 (57.6)	225 (57.6)
Yrs. of DM	5.4 (6.1) 5.5 (6.1)	6.1 (6.7) 5.9 (6.1)	6.6 (6.9)
BMI	29.9 (4.1) 30 (4.2)	30 (4.3) 29.9 (4.3)	29.1 (4.2)
Diet only	22.1% 24.7%	29.3% 25.1%	22.5%
Oral monotx	61.3% 55.9%	54.7% 64.7%	61.8%
Oral combotx	16.6% 19.4%	16% 10.2%	15.6%

Mean (SD)

Results

HbA1c	4mg qd	2mg bid	8mg qd	4mg bid	Placebo
All pts^	-0.8*	-0.9*	-1.1*	-1.5*	
Tx naïve	-0.85	-0.89	-0.8	-1.11	+0.35
HbA1c $\leq$ 7%	38%	25%	31%	40%	17%
Mono tx	+0.14	+0.02	-0.26	-0.54	+0.98
HbA1c $\leq$ 7%	21%	21%	13%	25%	6%
Combo Tx	+0.8	+0.43	+0.4	-0.43	+0.70
HbA1c $\leq$ 7%				33%	0%

Mean values presented
^Results presented as placebo-subtracted
*Significant vs. placebo

Adverse events

	4mg qd 2mg bid	8mg qd 4mg bid	Placebo
Dropouts/due to AE/due to LOE	20.7%/5.6%/6.6%		38.4%/ 10.8%/ 16.8%
Edema	5.2% 4.1%	6.4% 6.6%	1.6%
Weight (kg)	1.2*^ 1.5*^	2.6*^ 3.3*^	-0.9
Hb	-0.5 to –0.9 g/dl *^ (dose dependent)		
HCT	-1.6 to 2.5 % *^ (dose dependent)		
↑ ALT	N=1		N=1

*Significant vs. placebo
^Significant vs. baseline

Lebovitz 2001[5] (Study 011)
R, DB, PC U.S. multicenter **Rosiglitazone vs. placebo** N=493 26 weeks ITT

Inclusion: 36-81y/o type 2 DM FPG 140-300 Fasting C-peptide > 0.26nmol/L BMI 22-38kg/m2

Dosing: OHA d/c'd during 2 week screen 4-week placebo run-in. RSG 2mg BID vs. RSG 4mg BID vs. placebo

Demographics

	2mg bid	4mg bid	Placebo
% white/ % male	75.3/ 64.4	73.4/ 66.8	74/65.8
HbA1c	9 (1.5)	8.8 (1.6)	9 (1.7)
FPG	226.8 (62)	219.8 (64)	228.8 (59)
Yrs. of DM	4.8(5.8)	5.4 (6)	4.6 (4.8)
Diet only (%)	26.5	26.6	28.5
Monotx (%)	68.7	65.7	63.9
Combo tx (%)	4.8	7.7	7.6
BMI	30.2 (4.1)	29.1 (3.9)	29.9 (4.1)

Mean (SD)

Results

	2mg bid	4mg bid	Placebo
Δ HbA1c	-0.3%*^	-0.6%*^	+0.9%
% pts w/ HbA1c ↓ $\geq$ 1%	29.5	36.1	3.8
HbA1c $\leq$ 7%	20.5%	29.6%	5.1%
FPG mg/dl	-38 (52)*^	-54 (51)*^	+20 (64)

*Significant vs. baseline
^Significant vs. placebo

Adverse events

	2mg bid	4mg bid	Placebo
Dropouts/due to LOE	26%/ 5.1%	25%/ 8.2%	44%/ 20.5%
Hgb (g/dl)	-0.6	-1.0	
HCT (%)	-0.8	-2.1	
Edema (n)	10	18	3
↑ ALT	0	1	0
Weight (kg)	+1.6	+3.5	-1.0

Mean values

Study 020[6]
R, DB, DD Multicenter **Rosiglitazone vs. glyburide** N=587 52 weeks

Inclusion/Dosing: OHA d/c'd 4-week placebo run-in. RSG 2mg BID vs. R SG 4mg BID vs. GLY (12 week titration then held constant for rest of study)

Demographics

	RSG 2mg BID	RSG 4mg BID	GLY
FPG	190	196	190
HbA1c	8.07%	8.21%	8.15%

Mean

Results

	RSG 2mg BID	RSG 4mg BID	GLY
HbA1c	-0.27 (1.04)	-0.53 (1.31)	-0.72 (1.0)
FPG mg/dl	-25 (42)	-41 (46)	-30 (45)
% with FPG < 140	36%	51%	37%

Mean dose of glyburide 7.5mg Mean (SD)

Adverse events

	2mg BID	4mg BID	GLY
Weight		+2.9kg	+1.9kg
Hypogly	0.5%	1.6%	12.1%
d/c 2° hypogly	0	0.5%	2.9%
HCT	-2%	-3.5%	

Rosenblatt 2001[7] R, DB, PC Multicenter **Pioglitazone vs. placebo** N=194 16 weeks ITT	Type 2 DM HbA1c ≥ 8% after washout c-peptide > 0.33nmol/l BMI 25-40	5-week placebo washout PIO 30mg vs. placebo	60% received prior tx; 40% treatment naïve					

60% received prior tx; 40% treatment naïve

	PIO	PL
Age (yrs)	53.8 (10)	55.2 (10)
Weight (kg)	89.9 (18)	87.2 (18.4)
BMI (kg/m2)	31.5 (4.7)	30.7 (5)
HbA1c (%)	10.65 (1.77)	10.42 (1.7)
FPG (mg/dl)	276.1 (70.88)	272.3 (72.74)

Mean (SD)

	Pioglitazone	Placebo
HbA1c (all pts)	-0.60% (0.17)*	+0.76% (0.17)*
HbA1c (tx. naïve/prior tx)	-0.89%/-0.35%	+0.09%/+0.97%
FPG (all pts)	-49.8 (6.8)*^	+0.43 (0.39)

*Significant vs. baseline
^Significant vs. placebo
Mean (SD)
HbA1c results for tx naïve and prior tx groups from FDA transcripts

	PIO	PL
Completed study	73%	
Dropout due to LOE	7.9%	15%
Mean weight Δ	+1.35kg* ^	-1.87kg*
Mild peripheral edema	N=5	N=1
Mean HgbΔ	-0.5gm/dl	+0.03gm/dl

*Significant vs. baseline
^Significant vs. placebo
Data on Hgb from FDA transcripts

Study 012[8] R, DB, PC Multicenter **Pioglitazone vs. placebo** N=260 26 weeks	HbA1c > 8% at baseline	6-week washout Forced titration from PIO 7.5 to 15 to 30mg vs. 15 to 30 to 45 mg vs. placebo (titrated over 8 wks)	24% drug therapy naïve HbA1c ≈ 10.3% FBG ≈ 245mg/dl Prior therapy – 76% HbA1c ≈ 10.6% FBG ≈ 285mg/dl

	Low PIO	High PIO
HbA1c (tx. naïve/prior tx)	-2.28/-1.31	-2.59/-1.42
FPG (tx. naïve/prior tx)	-63/-55	-95/-60

**Values are placebo subtracted

	Low PIO	High PIO	Placebo
Weight (kg)	+0.49	+1.82	-1.81
Weight (completers)	+1.27	+2.58	-1.7
Hgb (g/dl)	-0.45	-0.7	-0.08
HCT (%)	-1.1	-2.2	-1.2

Aronoff 2000[9] (Study 001) R, DB, PC U.S. multicenter **Pioglitazone vs. placebo** N=408 26 weeks ITT for primary analysis	HbA1c ≥ 7.0% at end of washout FPG ≥ 140 Fasting C-peptide ≥ 1ng/ml	OHA d/c'd 6-8 week placebo washout PIO 7.5mg vs. PIO 15mg vs. PIO 30mg vs. PIO 45mg vs. placebo

	15mg	30mg	45mg	PL
White/male	78%/58%			
HbA1c	10.2 (0.22)	10.2 (0.21)	10.3 (0.22)	10.4 (0.22)
HbA1c tx naïve	9.9 (0.37)	9.3 (0.38)	10 (0.43)	9.0 (0.38)
HbA1c Prior tx	10.4 (0.26)	10.4 (0.25)	10.6 (0.26)	10.9 (0.26)
FPG	267 (7.94)	269.4 (7.72)	275.5 (8.05)	268.1 (7.93)
Wt. (kg)	91.2 (1.8)	90.3 (1.58)	90.8 (1.56)	90.4 (1.47)
% tx naïve	33	30.5	27.6	31.6

Mean (SEM)

	15mg	30mg	45mg	PL
HbA1c Δ from baseline	-0.3 (0.17)*^	-0.3 (0.17)*^	-0.9 (0.18)*^	+0.7 (0.17)*
HbA1c tx naïve	-0.8 (0.28)*^	-0.6 (0.29)*^	-1.9 (0.33)*^	+0.6 (0.29)*
HbA1c Prior tx	-0.1 (0.2)^	0 (0.19)^	-0.6 (0.2)*^	+0.8 (0.2)*
FPG	-29.6 (31.8)*^	-31.8 (6.66)*^	-55.9 (6.9)*^	+9.4 (6.72)

*Significant vs. baseline
^Significant vs. placebo
Mean (SEM)

	15mg	30mg	45mg	PL
Wt.	+1.3 (0.33)	+1.3 (0.38)	+2.8 (0.39)	-1.3 (0.36)
Edema	3.6%			0
Hypogly	N=4 (one in 7.5mg arm)			0
ALT ≥ 3xULN	N=3 (one in 7.5mg arm)			N=1 (1.3%)
ALT ≥ 1.5xULN	N=2 2.5%	N=4 4.7%	0	N=2 2.6%
Hgb g/dl HCT%	Dose related decrease; greatest with 45mg (-0.74/-1.3%)			

Combination with sulfonylureas

Study	Inclusion	Dosing	Demographics	Results	Adverse events
Study 079[10] R, DB, DD Multicenter **Rosiglitazone vs. glyburide vs glyburide + rosiglitazone** N=309 26 weeks ITT	Inadequate control on GLY 20mg/d FPG 140-300	4-week run-in on GLY 10mg BID; **other antidiabetic meds d/c'd** GLY 10mg BID vs. RSG 2mg BID vs. GLY 10mg BID + RSG 2mg BID	72% with BMI ≥ 27 70% white 60% prior GLY monotherapy, 40% on combination (31-37% metformin) mean duration of DM- 7yrs. HbA1c – GLY 9.3 (1.43); RSG 9.1 (1.14); GLY +RSG 9.2 (1.34) LDL- 125mg/dl	(see results table below)	(see adverse events table below)

Study 079 Results:

	GLY	RSG	GLY +RSG
ΔHbA1c	+0.9 (1.17)*^ [0.6, 1.1]	+1.9 (1.17)*^ [1.5, 2.2]	-0.5 (1.14)* [-0.7, -0.3]
Prior monotx			-0.7%
Prior combo			-0.1%

*Significant vs. baseline
^Significant vs. GLY+RSG
Mean (SD) [95% CI]

Study 079 Adverse events:

	GLY	RSG	GLY +RSG
Withdrew	55.7%	42.4%	21.2%
d/c 2° LOE	9%	20%	7%
Weight	No Δ	+1.53kg*	+3.8kg*
Edema		1.9%	7.1%
Cardiac death	N=1	N=1	
Hypogly	5.7%	0	8.1%

*Significant vs. baseline

Study	Inclusion	Dosing	Demographics
Study 096[11] R, DB, PC Multicenter **Rosiglitazone + glyburide vs. glyburide** 26 weeks ITT	Inadequate control on at least GLY 10mg/d 40-80y/o C-pep >0.8ng/ml FPG 140-300	4 week placebo run-in Cont. prior GLY (mean dose 15mg/d); **other antidiabetic meds d/c'd** RSG 2mg QD + GLY vs. RSG 4mg QD + GLY vs. GLY	88% with BMI ≥ 27 90% white 30% on prior combination therapy HbA1c – 9.1% FPG- 215mg/dl LDL- 122mg/dl

Study 096 Results:

	RSG 2 + GLY	RSG 4 + GLY	GLY
Δ HbA1c	No Δ	-0.3%	+0.55%
FPG mg/dl	-11	-25	+23

Mean

Adding RSG to GLY was not effective in patients who had been on combination therapy prior to study entry.

Study 096 Adverse events:

	RSG 2 + GLY	RSG 4 + GLY	GLY
d/c 2° LOE	4.3%	2.6%	7.8%
Weight	+1.88kg*	+2.64kg*	+0.22kg
Hypogly	6%	2.6%	1.7%

Study	Inclusion	Dosing
Wolffenbuttel 2000 (study 015)[12] R, DB, PC, Pr European multicenter **Rosiglitazone + SU vs. placebo + SU** N=574 26 weeks ITT	30-80 y/o BMI 22-38 Type 2 DM FPG ≤ 270 HBA1c ≥ 7.5% C-peptide ≥ 0.27nmol/l SU ≥ 6 mos **Mean SU doses** Glic 185mg Glyb 12.6mg Glip 17mg	2-4 week run-in with SU + PL RSG 1mg BID vs. RSG 2mg BID vs placebo added to SU Pts. withdrawn if: •FPG ≥ 270 on 2 consecutive occas during 1st 12-wks •FPG ≥ 216 " " after 1st 12 wks •>1 ↓ in SU dose or > 50% dose ↓ after hypoglycemia

Study 015 Demographics:

	1mg bid + SU	2mg bid + SU	SU
Yrs. DM (range)	7 (0-34)	7 (0-33)	8 (0-30)
BMI	28 (3.9)	28.3 (3.9)	28.1 (4.1)
HbA1c	9.2 (1.19)	9.23 (1.18)	9.21 (1.3)
FPG	203.8 (45.2)	205.4 (49.1)	207.4 (43.4)
White/ male	95.5%/ 63%	98%/ 55.2%	97%/ 57.3%

Mean (SD)

Study 015 Results:

	1mg bid + SU	2mg bid + SU	SU
HbA1c	-0.52*^	-0.875*^	+0.5
% pts. w/ ↓ ≥ 0.7%	39^	60^	19
FPG	-17*^	-37.6*^	-5.76

*Significant vs. baseline
^Significant vs. placebo

Study 015 Adverse events:

	1mg bid + SU	2mg bid + SU	SU
Wt.	+0.8*	+1.8*	
Hb g/dl HCT %	-0.39 -1.52	-0.66 -2.34%	
LFT ≥ 3x ULN	0	0	0
Hypogly	3.4%	5.3%	2%
Dropouts	28%	24%	36%
d/c 2° AE/LOE	4.9%/ 11.7%	5.3%/ 8.4%	11.6%/ 15.7%

*Significant vs. baseline

Kipnes 2001[13] (study 010) R, DB, PC U.S. multicenter **Pioglitazone + SU vs. placebo + SU** N=560 16 weeks ITT	30-75 y/o SU stable dose ≥30 days BMI 25-45 HbA1c ≥ 8% at end of run-in C-peptide ≥ 1ng/ml 70% of pts. on ≥ 50% of max. dose	2 week screen 1-4 week run-in with SU + PL other antidiabetic meds d/c'd PIO 15mg +SU vs. PIO 30mg + SU vs. Placebo + SU SU doses **not** to be ↑

	15mg + SU	**30mg + SU**	**SU**
HbA1c	10 (9.8, 10.2)	9.9 (9.7, 10.1)	9.9 (9.7, 10.1)
FPG	247 (238, 256)	239 (230, 248)	236 (227, 245)
Monotx	84%	86%	90%
White/ male	79%/ 59%	83%/ 60%	75%/ 58%
BMI	31.4	32.4	32

Mean (95% CI)

	15mg + SU	**30mg + SU**	**SU**
HbA1c	-0.8 (-1.0, -0.6)*^	-1.2 (-1.4, -1.0)*^	+0.1 (-0.1, 0.2)
FPG	-33.8 *^ (-41.4, -26.3)	-52.3 *^ (-59.7, -44.8)	5.6 (-1.9, 13.1)

Least square mean (95% CI)
*Significant vs. baseline
^Significant vs. placebo

	15mg + SU	**30mg + SU**	**SU**
d/c 2° LOE	10%	4.2%	10%
d/c 2° AE	3%		3%
Edema	1.1%	6.3%	2.1%
hypogly	0	N=7	N=1
Weight	1.9^	2.9^	-0.8
Hgb	-0.4 (0.7)	-0.5 (0.9)	-0.02 (0.8)

^Significant vs. placebo

Combination with metformin

Study	Inclusion	Dosing	Demographics	Results	Adverse events
Fonesca 2000 (study 094) [14] R, DB, PC U.S. multicenter **Rosiglitazone + metformin vs. placebo + metformin** N=348 26 weeks ITT	40-80 y/o FPG 140-300 at screening and while taking 2.5g/d of metformin c-peptide $\geq$ 0.8ng/ml BMI 22-38	3-wk metformin titrated to 2.5gm 4-wk metformin + PL run-in RSG 4mg/d + met 2.5g vs. RSG 8mg/d + met 2.5g vs. placebo + met 2.5g *All OHAs were d/c'd except metformin*	<table><tr><td></td><td>R4 + M</td><td>R8 + M</td><td>Met</td></tr><tr><td>Yrs. DM</td><td>7.5 (6.3)</td><td>8.3 (6.3)</td><td>7.3 (5.7)</td></tr><tr><td>monotx</td><td>39.7</td><td>43.6</td><td>48.7</td></tr><tr><td>comb tx</td><td>54.3%</td><td>51.8%</td><td>46.9%</td></tr><tr><td>HbA1c</td><td>8.9 (1.3)</td><td>8.9 (1.5)</td><td>8.6 (1.3)</td></tr><tr><td>BMI</td><td>30.2 (4.2)</td><td>29.8 (3.9)</td><td>30.3 (4.4)</td></tr><tr><td>FPG</td><td>214.2 (56.9)</td><td>219.4 (54.72)</td><td>213.6 (54)</td></tr></table> Mean (SD)	<table><tr><td></td><td>R4 + M</td><td>R8+M</td><td>Met</td></tr><tr><td>HbA1c</td><td>-0.56*^</td><td>-0.78*^</td><td>+0.45</td></tr><tr><td>% pts. w/ 1.0% ↓ HbA1c</td><td>32.8^</td><td>37.2^</td><td>7</td></tr><tr><td>% w/ HbA1c 7.0%</td><td>Not given</td><td>28.1</td><td>7.6</td></tr><tr><td>FPG</td><td>-33*^</td><td>-48.4*^</td><td>+5.9</td></tr></table> *Significant vs. baseline ^Significant vs. placebo	<table><tr><td></td><td>R4+M</td><td>R8+M</td><td>Met</td></tr><tr><td>Dropouts</td><td>15%</td><td>16%</td><td>19%</td></tr><tr><td>Mild-mod Hypogly (n)</td><td>3</td><td>5</td><td>2</td></tr><tr><td>Hgb g/dL</td><td>-0.5*</td><td>-0.8*</td><td></td></tr><tr><td>HCT%</td><td>-1.8*</td><td>-2.5*</td><td></td></tr><tr><td>Edema</td><td>2.5%*</td><td>3.5%*</td><td>0.9%</td></tr><tr><td>Weight (kg)</td><td>0.7*</td><td>1.9*</td><td>-1.2</td></tr><tr><td>ALT $\geq$ 3xULN</td><td>0</td><td>0</td><td>0</td></tr></table> *Significant
Einhorn 2000 [16] (Study 027) R, DB, PC Multicenter **Pioglitazone + metformin vs. placebo + metformin** N=328 16 weeks ITT	HbA1c $\geq$ 8 Fasting c-pep > 1.0ng/ml Stable dose metformin $\geq$ 30 days BMI 25-45	1-4 week run-in PIO 30mg + metformin vs. placebo + metformin *Dosage of metformin not adjusted unless pt. hypoglycemic.* *60% of pts. on <2000mg/d of metformin (mean dose 1555mg/d)* *Other antidiabetic meds were d/c'd*	<table><tr><td></td><td>PIO + met</td><td>Met</td></tr><tr><td>% white/ male</td><td>81/ 54.8</td><td>86.9/60</td></tr><tr><td>% on OHA other than metformin</td><td>28.6</td><td>30.6</td></tr><tr><td>BMI*</td><td>32.11 (5.3)</td><td>32.12 (5.5)</td></tr><tr><td>FPG**</td><td>252.3 (69.7)</td><td>258.6 (68.6)</td></tr><tr><td>HbA1c**</td><td>9.86 (1.4)</td><td>9.75 (1.3)</td></tr></table> *Mean (SD) **Mean (SE)	<table><tr><td></td><td>PIO + met</td><td>Met</td></tr><tr><td>HbA1c</td><td>-0.64%*</td><td>+0.19%</td></tr><tr><td>FPG</td><td>-43mg/dl*</td><td>-5 mg/dl</td></tr><tr><td>C-pep</td><td>-0.1ng/ml*</td><td>+0.1ng/ml</td></tr><tr><td>Fasting insulin</td><td>-2.1 ng/ml*</td><td>-0.4ng/ml</td></tr><tr><td>Insulin resist (HOMA-IR)</td><td>-16.2%*^</td><td>+17.6%^</td></tr><tr><td>β cell fx (HOMA-BCF)</td><td>+45%^</td><td>+39.3%^</td></tr></table> *Significant vs. met ^Significant vs. baseline	<table><tr><td></td><td>PIO + met</td><td>Met</td></tr><tr><td>Dropouts (LOE)</td><td>13%</td><td>23%</td></tr><tr><td>Dropouts (AE)</td><td>3%</td><td>2%</td></tr><tr><td>ALT $\geq$ 3x ULN</td><td>0</td><td>0</td></tr><tr><td>Edema</td><td>5.9%</td><td>2.5%</td></tr><tr><td>Hypogly (n)</td><td>1</td><td>1</td></tr><tr><td>Weight</td><td>+0.95kg</td><td>-1.36kg</td></tr><tr><td>Hgb/HCT</td><td colspan="2">-0.46g/dl / -1.4%*</td></tr></table> *Placebo subtracted values
Study 093 [15] **Rosiglitazone + metformin vs. metformin+ PL vs. rosiglitazone + PL** 26 week N=105		RSG 4mg BID + metformin 2.5gm vs. metformin 2.5gm + PL vs. RSG 4mg BID + PL		<table><tr><td></td><td>R + M</td><td>RSG</td><td>Met</td></tr><tr><td>FPG</td><td>-50</td><td>+30</td><td>+7</td></tr><tr><td>% w/ ↓ FPG $\geq$ 30</td><td>67</td><td>15</td><td>22</td></tr><tr><td>HbA1c</td><td>-0.6</td><td>+1.2</td><td>+0.12</td></tr></table>	

Combination with insulin

Study	Inclusion	Dosing	Demographics	Results	Adverse events

Raskin 2001[17] (Study 082) R, DB, PC U.S. multicenter **Rosiglitazone + insulin vs. insulin** N=319 26 weeks ITT, LOCF

Inclusion: 18-80y/o ≥ insulin 30u/d C-peptide ≥ 0.4ng/ml HbA1c > 7.5% FBG 140-300 on insulin

Dosing: 4-week insulin standization period to twice daily injections

4-week SB, placebo-insulin run-in

RSG 2mg BID + insulin vs. RSG 4mg BID + insulin vs. insulin +PL

No attempt made to change insulin dose unless patient hypoglycemic

Demographics:

	R4+I	R8+I	I
%White/black	76/20	73/16	71/19
BMI	32.1 (4.8)	32.3 (4.9)	32.7 (4.5)
Duration of DM (yrs)	12.7 (7.3)	12.5 (8.0)	11.7 (6.2)
HbA1c	9.1 (1.3)	9.0 (1.3)	8.9 (1.1)
FPG	212.4 (57.6)	208.8 (57.6)	194.4 (52.2)
Insulin dose Units/d	71.3 (43.8)	77.7 (36.4)	70.1 (30.3)

Mean (SD)

Results:

	R4+I	R8+I	I
HbA1c	-0.6 (1.1)*^	-1.2 (1.1)*^	0.1 (1.0)
FPG	-41.4 (70.2)*^	-45 (59.4)*^	10.8 (68.4)
Insulin dose %Δ	-5.6 (15.9)	-12 (20.2)	-0.6 (8.2)
TC	19.72 * (44.47)	29* (52.59)	7.35 * (32.87)

Mean (SD) unless otherwise indicated
*significant vs. baseline
^Significant vs. PL+I

Adverse events:

	R4+I	R8+I	I
Hypogly*	53%	67%	38%
Edema*	13.1%	16.2%	4.7%
Hgb.(g/dl)/ Hct %	-0.5/ -1.9	-1.0/ -3.0	0/-0.3
Wt.(kg)	4.0	5.3	0.9
LFT >2.5x ULN	0	0	0
Bili >1.5X ULN	0	0	0
Heart failure (n)	1	1	1

*Events classified as mild-moderate

Study 095[18] R, DB, PC Multicenter **Rosiglitazone + insulin vs. insulin** N=287 26 weeks

Inclusion: Insulin ≥30u/d C-peptide ≥ 0.4ng/ml HbA1c > 7.5% FBG 140-300 on insulin

Dosing: 4-week insulin std period 4-week SB, placebo-insulin run-in

RSG 4mg QD + insulin vs. RSG 8mg QD + insulin vs. insulin + PL

No attempt made to change insulin dose unless patient hypoglycemic

Demographics:

	R4+I	R8+I	I
HbA1c	8.8 (1.1)	9.1 (1.0)	9.1 (1.2)
FPG	199 (66.3)	199 (61.3)	203 (57.3)
Insulin dose u/day	76 (44.8)	74 (29.4)	65 (29.3)

Mean (SD)

Results:

	R4+I	R8+I	I
HbA1c	-0.4 (1.0)*^	-0.7 (1.0)*^	0.1 (1.0)
FPG	-25 (66)*^	-34 (65.3)*^	6 (64.6)
Insulin dose %Δ	-9.1 (16.2)^	-14.5 (23.2)^	0.2 (14)

Mean (SD)
*Significant vs. baseline
^Significant vs. PL+I

Rosenstock 2002[19] (Study 014) R, DB, PC U.S. multicenter **Pioglitazone + insulin vs. insulin** 16 weeks N=566

Inclusion: HbA1c > 8% On insulin ≥ 4 mos Stable dose ≥ 30u ≥ 30days Fasting C-peptide ≥ 0.7ng/ml

Dosing: 2-week insulin run-in 1-4 week SB PL + insulin.

PIO 15mg + insulin vs. PIO 30mg + insulin vs. insulin + PL

Other OHAs were d/c'd (12% of patients)

No attempt made to change insulin dose unless patient hypoglycemic

Demographics:

	P15+I	P30+I	I
HbA1c	9.84 (1.45)	9.86 (1.29)	9.83 (1.36)
FBG	223.7 (71.89)	227.5 (68.36)	220.6 (72.48)
C-pep	1.61 (0.8)	1.57 (0.8)	1.54 (0.71)
Insulin dose	Median dose 61u/d Mean dose 71 u/d		
% white	73.1%		
BMI	33.6		

Mean (SD)

Results:

	P15+I	P30+I	I
HbA1c	-0.99*^	-1.26*^	-0.26*
HbA1c diff from PL (95% CI)	-0.73 (-1.00, -0.47)		-1.00 (-1.27, -0.74)
FBG	-35	-48	-0.57
HDL	2.8 ^ (0.66)	3.4 ^ (0.66)	-0.7 (0.67)
Δinsulin dose	-3 units	-8 units	-0.6 units

LSM change from baseline (SE)
*Significant vs. baseline
^Significant vs. PL+I

Adverse events:

	P15 + I	P30 + I	I
CPK > 3x ULN	1	7	1
d/c (n/%)	30/15.7%	16/8.5%	23/12.3%
LOE/AE	3/5	5/6	3/3
Wt. (kg)	2.3	3.7	-0.04
Hypogly	8%	15%	4.8%
Edema	12.6%	17.6%	7.0%
Hgb (g/dl)	-0.35	-0.67	-0.1
HCT	-0.6%	-1.5%	0
Anemia	1.6%		1.6%

Combination with meglitinides

Study	Inclusion	Dosing	Demographics	Results					Adverse events				
Product package insert **Repaglinide vs. rosiglitazone vs. repaglinide + rosiglitazone** 24 weeks N=246	HbA1c > 7% Monotherapy with SU or metformin	Repaglinide titrated (median dose 12mg/d) vs. RSG (median dose 8mg/d) vs. RSG (median dose 4mg/d) + repaglinide (median dose 6mg/d)	HbA1c (%)- repaglinide 9.3; RSG 9.0; repaglinide + RSG 9.1 FPG (mg/dL)- repaglinide 269; RSG 252; repaglinide + RSG 257		**Repag**	**RSG**	**Repag + RSG**				**Repag**	**RSG**	**Repag + RSG**
				HbA1c (%)	-0.17	-0.52	-1.43*		Weight (kg)		+1.3	+3.3	+4.5*
				FPG (mg/dL)	-54	-67	-94*		*Significant vs. repaglinide				
				*Significant vs. either monotherapy									
Product package insert **Repaglinide vs. pioglitazone vs. repaglinide + pioglitazone** 24 weeks N=252 ITT	HbA1c > 7% Monotherapy with SU or metformin												

Head-to-head trials

Study	Inclusion	Dosing	Demographics	Results
Khan 2002[22] R, open label Single-center **Pioglitazone vs. rosiglitazone** 4 months N=186 (127 patients had usable data)	Taking troglitazone	2-week washout from TROG If on TROG 600mg/d: Switch to PIO 45mg QD, RSG 4mg BID On TROG 400mg/d: Switch to PIO 30mg or RSG 4mg QD On TROG 200mg/d: Switch to PIO 15mg or RSG 2mg QD *Concomitant lipid lowering agents held constant*	<table><tr><td></td><td>PIO</td><td>RSG</td></tr><tr><td>HbA1c %</td><td>8.0 ± 1.7</td><td>7.9 ± 1.9</td></tr><tr><td>Weight (kg)/ BMI</td><td>101.4 ± 24.2 35.2 ± 7.4</td><td>103.2 ± 24.8 35.6 ± 7.4</td></tr><tr><td>%Concurrent metformin/ insulin/SU</td><td>33/58/61</td><td>27/42/67</td></tr><tr><td>% put on max PIO or RSG dose</td><td>76.1</td><td>76.7</td></tr><tr><td>% put on PIO 30 or RSG 4mg</td><td>22.4</td><td>16.7</td></tr><tr><td>% using HMG-CoA</td><td>60</td><td>58</td></tr><tr><td>Cholesterol/LDL/ Triglycerides/HDL</td><td>196.9 ± 44.5 116.2 ± 38 181 ± 110.1 44.7 ± 15.6</td><td>190.7 ± 44.1 105.9± 29.7 236 ± 222 45.3 ± 15.2</td></tr></table>Mean ± SD	<table><tr><td></td><td>PIO</td><td>RSG</td></tr><tr><td>HbA1c</td><td colspan=2>No apparent Δ in either group</td></tr><tr><td>Weight</td><td>+2kg*</td><td>+2kg*</td></tr><tr><td>Cholesterol</td><td>-20mg/dl*^</td><td>+4mg/dl</td></tr><tr><td>LDL</td><td>-17mg/dl*^</td><td>-2mg/dl</td></tr><tr><td>Triglycerides</td><td>-15mg/dl</td><td>+6mg/dl</td></tr><tr><td>HDL</td><td>+2mg/dl</td><td>+1mg/dl</td></tr></table>*Significant vs. baseline ^Significant vs. RSG
King 2000[23] Observational, nonrandomized **Troglitazone vs. rosiglitazone vs. pioglitazone** 2-4 month period N=101	TZD clinically indicated On maximal TZD dose	TROG 600mg RSG 8mg PIO 45mg *Pts. could not start on a medication that could influence weight or lipids during observation period*	<table><tr><td></td><td>RSG</td><td>PIO</td></tr><tr><td>HbA1c</td><td>8.73%</td><td>8.72%</td></tr><tr><td>Weight</td><td>92.1kg</td><td>87.2kg</td></tr><tr><td>Taking concomitant hyperglycemia medications</td><td>76%</td><td>81%</td></tr></table>Data for RSG and PIO	<table><tr><td></td><td>RSG</td><td>PIO</td></tr><tr><td>HbA1c</td><td>-1.89</td><td>-1.93</td></tr><tr><td>Initial HbA1c >7.9%</td><td>-2.66</td><td>-2.54</td></tr><tr><td>Weight</td><td>+0.5kg</td><td>+2.6kg</td></tr><tr><td>Triglycerides Mg/dl</td><td>+47</td><td>-21</td></tr><tr><td>LDL mg/dl</td><td>+11.5</td><td>-1.1</td></tr><tr><td>HDL mg/dl</td><td>+0.5</td><td>+6.5</td></tr></table>Data for RSG and PIO
Gegick 2001[24] Observational, non randomized **Rosiglitazone vs. pioglitazone** 1-5 month observation period N=144	Reached or near target glycemic goal with troglitazone On maint dose of TROG ≥ 4 months Had at least 2 HbA1c values on TROG	1 week troglitazone washout If on TROG 600mg/d: Switch to PIO 45mg or RSG 8mg If on TROG 200-400mg, dose selected based on clinical judgement: PIO 15-45mg or RSG 4-8mg *No changes made with other glycemic meds or lipid lowering agents* *Mean observation period 3.2 months*	<table><tr><td></td><td>PIO</td><td>RSG</td></tr><tr><td>HbA1c%</td><td>7.1 ± 0.9</td><td>6.97 ± 0.8</td></tr><tr><td>Weight (kg)</td><td>98.3 ± 19.1</td><td>103 ± 24.5</td></tr><tr><td>On TZD monotx</td><td>10%</td><td>9%</td></tr><tr><td>On SU/meglitinide</td><td>67%</td><td>66%</td></tr><tr><td>On metformin</td><td>30%</td><td>35%</td></tr><tr><td>On insulin</td><td>45%</td><td>40%</td></tr><tr><td>On lipid lowering agent</td><td>67%</td><td>50.6%</td></tr><tr><td>Cholesterol/ TG/ HDL/LDL</td><td>190.6/ 208.5/ 46.7/104.6</td><td>180/178.7/ 44.1/100</td></tr></table>Mean ± SD	<table><tr><td></td><td>PIO</td><td>RSG</td></tr><tr><td>HbA1c</td><td>7.02 ± 1.0</td><td>6.89 ± 0.8</td></tr><tr><td>Weight</td><td>99.5 ± 19.1</td><td>104 ± 25.2</td></tr><tr><td>Cholesterol</td><td>-4.7%^</td><td>+8.4%*</td></tr><tr><td>Triglycerides</td><td>-11.3%^</td><td>+38.4%*</td></tr><tr><td>HDL</td><td>+2.6%^</td><td>-6.3%</td></tr><tr><td>LDL</td><td>-7.3%^</td><td>+8.1%*</td></tr></table>^Significant vs. RSG *Significant vs. baseline N=125 for the lipid evaluation

Study	Methods	Population / Baseline	Results

LaCivita 2002[50]
Retrospective chart review
Rosiglitazone vs. pioglitazone
N=20

Consecutive treatment with RSG 4mg BID ≥ 3 months followed by PIO 45mg for ≥ 3 months

Dosages of concomitant meds could not be changed

All Hispanic adults
Maen age 66 (range 37-80)
16 females/4 males
Mean duration of DM 24 months (1-8 yrs.)
Receiving anti-lipid meds n=12
On combination DM tx n=7
HbA1c – 7.6 ± 2.1%
TG – 180 ± 95mg/dl
TC- 176 ± 43.4mg/dl
HDL- 44 ± 13.8mg/dl
LDL- 95 ± 37.4mg/dl
Duration of RSG- 6 mos. (3-11 mos.)
Duration of PIO – 6 mos. (3-12 mos.)

Mean ± SD

	After RSG	After PIO
TG (mg/dl) % change from baseline	203 ± 122 13%	154 ± 69.8^ -14%^
TC (mg/dl) % change from baseline	214 ± 37.5* 22%*	174 ± 24.9^ -1%^
HDL (mg/dl) % change from baseline	48.5 ± 11.9 8%	47.9 ± 13.5 7%
LDL (mg/dl) % change from baseline	128 ± 26* 35%*	96 ± 20.5^ 1%^
HbA1c (%)	6.6 ± 0.92*	6.3 ± 1.06*
Ankle edema (n)	1	1
Weight (kg)	1.5 ± 2.4*	1.6 ± 2.4*

*Significant vs. baseline
^Significant between treatments
Mean ± SD

Davidson [25]
(abstract)
R, PR
Rosiglitazone vs. pioglitazone
N=39
6 months

Beneficial effect on troglitazone
Switched to RSG 8mg or PIO 45mg

HbA1c prior to troglitazone 8.1%

	RSG	PIO
HbA1c	7.9%	7.5%
TC (mg/dl)	177	183
HDL (mg/dl)	40	47
TG (mg/dl)	178	183
LDL (mg/dl)	105	91
Weight (lb)	214	198

Mean values

	Rosiglitazone	Pioglitazone
HbA1c	7.9	7.1
TC (mg/dl)	193*	171
HDL (mg/dl)	47*	54*
TG (mg/dl)	188	156
LDL (mg/dl)	115	84
Weight (lb)	213	203

*Significant vs. baseline
Values represent maximal mean changes

Boyle 2002[49]
Retrospective chart review
Multicenter
Pioglitazone vs. rosiglitazone
N=1115

Type 2 DM
≥ 18 y/o
Began a TZD between 8/1/99 – 8/31/00
RSG dose 4-8mg and PIO dose 30-45mg
Uninterrupted tx for ≥ 12 weeks
Pt had ≥ office visits separated by 12 – 26 weeks
No change in lipid meds between baseline and followup visits
Had ≥ 2 sets of lab tests coinciding approximately with baseline and followup visits
Patient could not have started or have a change in dose (if on stable regimen) of concomitant drugs known to influence lipid or glucose profiles during the study period

Age (yrs)- PIO 60 ± 11.28; RSG 60.59 ± 11.25
% male – PIO 57.66; RSG 52.73
% white – PIO 71.79; RSG 72.79
Weight (lb)- PIO 209.25 ± 48.34; RSG 209.6 ± 48.05
BMI- PIO 33.05 ± 7.35; RSG 33.12 ± 7.7
Duration of TZD tx (weeks) – PIO 17.73 ± 3.83; RSG 17.41 ± 3.91

Mean ± SD

	Pioglitazone	Rosiglitazone
HbA1c (%)	-1.04*	-1.18*
Weight (lbs)	+1.97*	+1.64*
TG (mg/dl)	-55.17 ± 8.5*^ (22.5%)	-13.34 ± 6.5* (5.57%)
LDL (mg/dl)	-5.05 ± 1.6 *^ (4.31%)	+3.56 ± 1.63* (3.12%)
TC (mg/dl)	-8.45 ± 1.75*^ (4.17%)	+4.81± 1.9 (2.39%)
HDL (mg/dl)	+2.65 ± 0.62* (6.14%)	-0.12 ± 1.31 (0.26%)
% using any statin	53.33	53.73
Mean daily dose of atorva/ prava/ simva	22 / 34 / 29	19 / 33 / 30

*Significant vs. baseline
^Significant vs. rosiglitazone
Mean ± SE

APPENDIX 2: LIPID CHANGES

Pivotal clinical trials

Phillips[4]
Rosiglitazone monotherapy
26 weeks

	4mg QD	2mg BID	8mg QD	4mg BID	Placebo
TG	+26.57mg/dl 19.6%[12.5, 27.3]*	+20.37mg/dl 10.9%[4.2, 18.1]*	+25.68mg/dl 17.6%[8.4, 28]*	0 5.2%[-2.1, 13.2]	-3.54mg/dl 7.2%[0.3, 14.6%]
LDL	+14.3mg/dl 10.6%[7.1, 14.4] *^	+13.9mg/dl 9.5%[12.6, 24.2] *^	+20.9mg/dl 18.3%[12.6, 24,2] *^	+15.1mg/dl 14.3%[10.3, 18.6] *^	-2.7mg/dl 1.7%[-1.6, 4.9]*
HDL	+3.86mg/dl 10.7%[7.8, 13.7]*	+3.86mg/dl 10.2%[7.7, 12.7]*	+4.25mg/dl 11.8%[8.9, 14.9]*	+5.8mg/dl 13.9%[10.9, 17.1*	+5mg/dl 8.1%[5.3, 10.9]*
TC	+23.97mg/dl 12.4%[9.8, 15.1] *^	+23.58mg/dl 9.6%[7.2, 12.1] *^	+32.9mg/dl 17.5%[13.9, 21] *^	+29mg/dl 13.5%[10.6, 16.5] *^	-0.77mg/dl 3%[0.8, 4.9]
LDL:HDL	-0.25	-0.05	+0.13	-0.02	-0.3

Median change from baseline (calculated by subtracting median endpoint value from median baseline value)
Median % difference from baseline [95%CI]
*Significant versus baseline
^Significant versus placebo

Aronoff[9]
Pioglitazone monotherapy
26 weeks

	15mg	30mg	45mg	Placebo
TG	-57.8mg/dl 9%± 4.74*	-35.9mg/dl 9.6%± 4.65*	-40.8mg/dl 9.3%± 4.81*	-10.1mg/dl 4.8% ± 4.7
LDL	+6.3mg/dl 7.2%± 2.67*	+3.8mg/dl 5.2%±2.47	+8.7mg/dl 6%±2.69*	+3.1mg/dl 4.8%± 2.62
HDL	+5mg/dl 14.1%± 2*	+4.2mg/dl 12.2%± 2.04*	+7.1mg/dl 19.1%±2.07*^	+2.6mg/dl 8.1% ± 2*
TC	+6.3mg/dl 4.6%± 1.56*	+4.8mg/dl 3.3%± 1.54	+12.5mg/dl 6.4%±1.59*	+6.8mg/dl 4.4% ± 1.55*

LS mean change from baseline calculated by subtracting mean endpoint value from mean baseline value
LS mean % change from baseline ± SEM
*Significant versus baseline
^Significant versus placebo

Lebovitz[5]
(Study 011)
Rosiglitazone Monotherapy
26 weeks

	2mg	4mg	Placebo
TG	Δ not significant (data not shown)		
LDL	+15.46± 27mg/dl* 13.7%	+23.59 ± 31.3mg/dl* 19%	+5.8 ±25.1mg/dl* 4.7%
HDL	+4.25± 7mg/dl* 10%	+4.25± 8.9mg/dl* 10%	+2.3 ± 7.3mg/dl* 5.4%
TC	+25.52 ±45.2mg/dl* 7%	+28.2± 43.7mg/dl* 12.9%	+5.8 ± 27.8 mg/dl* 2.7%
TC:HDL	+0.21 ± 1.5	+0.37 ± 2.1^	-0.12 ± 1.1

Mean change from baseline ± SD
% change from baseline (calculated by mean change from baseline ÷ mean baseline value)
*Significant versus baseline

Study 012[8]
Pioglitazone monotherapy
24 weeks

	15/30/45	Placebo
TG	-40.5mg/dl (12.4%)	+3.83mg/dl (1.26%)
LDL	+12.23mg/dl (9.86%)	+8.52mg/dl (6.2%)
HDL	+5.2mg/dl (13.1%)^	+1.88mg/dl (4.29%)
TC	+7.45mg/dl (3.4%)	+8.16mg/dl (3.6%)

Mean change from baseline value was calculated by multiplying the mean baseline value by the mean % change from baseline
(Mean % change from baseline)
^Significant versus placebo

Study 020[6]
Rosiglitazone monotherapy
52 weeks

Rosiglitazone 4mg BID
TG variable and not significantly different from placebo or glyburide controls
FFAs –22%
LDL +6.4± 32.72mg/dl (12%)
HDL +19%
TC:HDL- unchanged from baseline
LDL: HDL –0.1% (absolute value) versus –0.3% with glyburide

Rosenblatt[7]
Pioglitazone monotherapy
16 weeks

	Pioglitazone 30mg	Placebo
TG	-59.3mg/dl (14.81%)^	+6mg/dl (1.79%)
LDL	+6.2mg/dl (4.81%)	+6.67mg/dl (5.08%)
HDL	+6.26mg/dl (15.8%)^	+1.24mg/dl (3.16%)
TC	+7.16mg/dl (3.19%)	0

Mean change from baseline value was calculated by multiplying the mean baseline value by the mean % change from baseline
(Mean % change from baseline)
^Significant vs. placebo

Freed
Rosiglitazone monotherapy ± atorvastatin
26 weeks

	RSG+PL	RSG+ATV10	RSG+ATV20
LDL (8-week open label)	+ 9 ± 1.4%		
LDL (Weeks 8-24)	+0.5%	-31.5%	-38.5%
HDL (8-week open label)	+5.8 ± 1.1%		
HDL (Weeks 8-24)	-4.4%	+2.9%	+4.8%
TG (8-week open label)	-2.0 ± 2.9%		
TG at 24 weeks	+2.2%	-18.5%	-27.2%
FFA at 24 weeks	-10.2%	-2.6%	-0.5%

Fonesca[14]
Rosiglitazone + metformin
26 weeks

	4mg + metformin	8mg + metformin	Metformin
TG	+7.1 ± 119mg/dl 3.1%	0	0
LDL	+17.8 ±22.4mg/dl*^ 15.38%	+20.5 ± 29.4mg/dl*^ 18.2%	+3.9 ± 17mg/dl* 3.3%
HDL	+5 ± 5.4mg/dl*^ 11%	+6.2 ± 7.3mg/dl*^ 13.3%	+1.93 ± 9.3mg/dl* 4.38%
TC	+27.8 ± 28.6mg/dl*^ 13.7%	+31.7 ± 41mg/dl*^ 15.8%	+6.9 ± 23.6mg/dl* 3.38%
TC:HDL	0	0	-0.38

Mean change from baseline ± SD
% change from baseline (calculated by mean change from baseline ÷ mean baseline value)
*Significant versus baseline
^Significant versus metformin alone

Einhorn[16]
Pioglitazone + Metformin
16 weeks

	30mg + metformin	Metformin
TG	-29mg/dl 9.7% ± 3.58*^	+25.5mg/dl 8.5%± 3.72
LDL	+9.18mg/dl 7.7% ± 6.65*	+14mg/dl 11.9% ± 6.9
HDL	+4.3mg/dl 10.2% ±1.82	+0.63mg/dl 1.5% ± 1.92
TC	+8.72mg/dl 4.1% ± 1.2*	+2.3mg/dl 1.1% ± 1.25
TC:HDL	-0.4 ± 1.85	0.3 ± 1.95
LDL:HDL	-0.02 ± 0.06	0.01 ± 0.06
% using statins	22%	

Mean change from baseline (calculated by multiplying the LS mean % change from baseline with the LS mean baseline value)
LS %change from baseline± SE
*Significant versus baseline
^Significant versus metformin alone

Wolffenbuttel[12]
Rosiglitazone +SU
26 weeks

	1mg BID + SU	2mg BID + SU	SU
TG	+35.4mg/dl*^ 21%	+17.7mg/dl* 10%	+8.8 mg/dl 5.5%
LDL	+3.86mg/dl 2.9%	+7.7mg/dl*^ 5.5%	0
HDL	+3.86mg/dl* 9%	+3.86mg/dl*^ 9%	0
TC	+11.6mg/dl*^ 5.2%	+15.5mg/dl*^ 7.1%	+3.86mg/dl 1.8%
TC:HDL	-0.1	-0.3	+0.1
LDL:HDL	-0.2	-0.1	0

Mean change from baseline (calculated by mean baseline – mean endpoint value)
% change from baseline (calculated by mean change from baseline ÷ mean baseline value)
*Significant versus baseline
^Significant versus SU alone

Kipnes[13]
Pioglitazone +SU
16 weeks

	15mg	30mg	SU
TG	-42mg/dl -6.4% [-12.9, 0.1]*	-62mg/dl -15.9% [-22.4, -9.4] *^	+8mg/dl 10.2%[3.7, 16.6]*
LDL	+4mg/dl +4.8%[1.5, 8.1]*	+3mg/dl +6.6% [3.2, 9.9]*	+7mg/dl 7.0%[3.7, 10.4]*
HDL	+3mg/dl +5% [2.1, 7.8] *^	+4mg/dl +12%[9.2, 14.8] *^	-2mg/dl 1% [-3.8, 1.9]
TC	+2mg/dl 1.4% [-1.0, 3.9]	+2mg/dl 2.3% [-0.1, 4.7]	+9mg/dl 4.1 [1.7, 6.5]
TC:HDL	-0.1	-0.5	+0.3
LDL:HDL	-0.1	-0.1	+0.4
% using statins	20%		

LS mean change from baseline calculated by subtracting mean endpoint value from mean baseline value)
LS mean % change from baseline [95% CI]
*Significant versus baseline
^Significant versus SU alone

Study 096[11]
Rosiglitazone +
glyburide
26 weeks

	R2 + GLY	R4 + GLY	GLY
TG	+48mg/dl*	Variable, NS from baseline	Variable, NS from baseline
LDL	+12mg/dl*^	+18mg/dl*^	+3mg/dl
TC	+15mg/dl (GLY subtracted)^	+22mg/dl (GLY subtracted)^	Data not shown
LDL/HDL	Data not shown	+0.324*	+0.029

Mean change from baseline
*Significant versus baseline ^significant versus glyburide

Study 079[10]
Glyburide +
rosiglitazone
26 weeks

	GLY	RSG	GLY +RSG
TG	Rose in all groups, but greatest with RSG monotx		
LDL	+0.3mg/dl	+22mg/dl*	+13mg/dl*
TC/HDL	Rose significantly in both RSG groups		
LDL/HDL	Rose significantly in both RSG groups		

*Significant vs. baseline

Raskin[17]
Rosiglitazone +
insulin
26 weeks

	4mg + insulin	8mg + insulin	Insulin
TG	+22 ± 287mg/dl 9.4%	+4.4 ± 152mg/dl 2%	+47 ± 20mg/dl4* 20.6%
LDL (median)	+10.8mg/dl* 8.8%	+14.69mg/dl* 11.7%	0.38mg/dl 0.32%
HDL	+2.7 ± 14mg/dl 14%	+6.2 ± 18mg/dl* 13.5%	+2.32 ± 7.7mg/dl* 5%
TC	+20 ± 44mg/dl* 9.3%	+29 ± 53mg/dl* 13.8%	+7.35 ± 33mg/dl* 3.5%
TC:HDL	+0.11	+0.06	-0.13
LDL:HDL	+0.05	+0.07	-0.13*

Mean change from baseline ± SD unless otherwise indicated
%change from baseline (calculated by change from baseline ÷ mean baseline value)
*Significant versus baseline

Study 014[19]
Pioglitazone
+ insulin
16 weeks

	P15 +I	P30 +I	I alone
TG		-27.28mg/dl (10.4%)^	+32.25mg/dl (13.3%)
LDL		+3.4mg/dl (2.8%)	-1.83mg/dl (1.4%)
HDL	+2.8	+3.88mg/dl (9.1%)^	-0.8mg/dl (0.2%)
TC		+0.83mg/dl (0.4%)	-1.5mg/dl (0.7%)
% using statins	28%		

Mean change from baseline value was calculated by multiplying the mean baseline value by the mean % change from baseline
(Mean % change from baseline)
^Significant versus insulin alone

Head to head trials

Khan[22] PIO vs. RSG 4 months n=97		Pioglitazone	Rosiglitazone
	TG	-15mg/dl (8.3%)	+6mg/dl (2.5%)
	LDL	-17mg/dl (14.6%)*^	-2mg (1.9%)
	TC	-20mg/dl (10.1%)*^	+4mg/dl (2.1%)
	HDL	+2mg/dl (4.4%)	+1mg/dl (2.2%)
	% using statins	60%	58%

Change from baseline estimated from graph
Mean % change calculated by mean change from baseline ÷ mean baseline value
*Significant versus baseline
^Significant vs. RSG

Gegick[24] PIO vs. RSG Mean 3.2 months N=144		Pioglitazone	Rosiglitazone
	TG	-23.6mg/d (11.3%)^	+68.7mg/dl (38%)*
	LDL	-7.6mg/dl (7.3%)^	+8.1mg/dl (8.1%)*
	TC	-9mg/dl (4.7%)*^	+15.2mg/dl (8.5%)*
	HDL	+1.2mg/dl (2.6%)^	-2.8mg/dl (6.3%)
	% using statins	66%	48%

Mean change from baseline calculated by subtracting mean endpoint value from the mean baseline value
Mean % change from baseline
*Significant versus baseline
^Significant versus rosiglitazone

King[23] PIO vs. RSG 2-4 months n=66		Pioglitazone	Rosiglitazone
	TG	-21 mg/dl (10.1%)	+47 mg/dl (27.3%)
	LDL	-1.1 mg/dl (1.1%)	+11.5 mg/dl (11.2%)
	HDL	+6.5 mg/dl (12.8%)	+0.5 mg/dl (1.1%)

Mean change from baseline
% change from baseline calculated by mean change from baseline ÷ mean baseline value
No statistical analysis provided

Boyle[49] Retrospective chart review N=1115 Duration of tx 17.5 ± 3.85 weeks		Pioglitazone	Rosiglitazone
	TG	-55.17 ± 8.5mg/dl*^ (22.5%)	-13.34 ± 6.5mg/dl* (5.57%)
	LDL	-5.05 ± 1.6mg/dl*^ (4.31%)	+3.56 ± 1.63mg/dl* (3.12%)
	TC	-8.45 ± 1.75mg/dl*^ (4.17%)	+4.81 ± 1.9mg/dl (2.39%)
	HDL	+2.65 ± 0.62mg/dl* (6.14%)	-0.12 ± 1.31mg/dl (0.26%)
	% using statins	58.7%	60.2%

Mean change from baseline ± SE
Mean % change from baseline
*Significant versus baseline
^Significant versus rosiglitazone

Davidson[25] PIO vs. RSG 6 months n=39		Pioglitazone	Rosiglitazone
	TG	-27mg/dl (14.7%)	+10mg/dl (5.6%)
	LDL	-7mg/dl (7.7%)	+10mg/dl (9.5%)
	TC	-12mg/dl (6.5%)	+16mg/dl (9%)*
	HDL	+7mg/dl (14.9%)*	+7mg/dl (17.5%)*

Mean change from baseline calculated by subtracting mean endpoint value from the mean baseline value
%change from baseline calculated by mean change from baseline ÷ mean baseline value
*Significant versus baseline

LaCivita[50] 2002 Retrospective chart review N=20		After RSG	After PIO
	TG (mg/dl)	203 ± 122 (13%)	154 ± 69.8^ (-14%^)
	TC (mg/dl)	214 ± 37.5* (22%*)	174 ± 24.9^ (-1%^)
	HDL (mg/dl)	48.5 ± 11.9 (8%)	47.9 ± 13.5 (7%)
	LDL (mg/dl)	128 ± 26* (35%*)	96 ± 20.5^ (1%^)

*Significant vs. baseline
^Significant between treatments
Mean ± SD