

Drug Class Review on Thiazolidinediones

Update #2: Preliminary Scan Report #1

September 2009

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Report

August 2008 (searches through November 2007).

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. For persons with type 2 diabetes, do pioglitazone and rosiglitazone differ from each other, from placebo, and from other oral hypoglycemic agents in the ability to reduce and maintain A1C levels?
2. For persons with type 2 diabetes, do pioglitazone and rosiglitazone differ from each other, from placebo, and from other oral hypoglycemic agents in their effects on macrovascular and microvascular complications, and mortality from diabetes?
3. For persons with pre-diabetes or the metabolic syndrome, do pioglitazone and rosiglitazone differ from one another or from placebo in delaying or preventing the occurrence of type 2 diabetes?
4. For persons with type 2 diabetes what are the adverse events related to pioglitazone and rosiglitazone, and how do these differ from each other, from placebo, and from other oral hypoglycemic agents?
5. Are there subgroups of persons with type 2 diabetes based on demographic characteristics or co-morbidities for which the benefits and adverse effects of pioglitazone or rosiglitazone differ from those in general populations, compared to each other and to other hypoglycemic agents?

Inclusion Criteria

Populations

1. Adults (≥ 18 years) and children (< 18 years) with type 2 diabetes
2. Adults (≥ 18 years) and children (< 18 years) with prediabetes defined as impaired fasting glucose and/or impaired glucose tolerance
3. Adults (≥ 18 years) and children (< 18 years) with metabolic syndrome defined as central obesity plus any two of the following four factors:
 - raised triglyceride level
 - low HDL-cholesterol
 - raised blood pressure
 - raised fasting plasma glucose

Interventions

Thiazolidinediones (TZDs) available on the U.S. market:

- Pioglitazone hydrochloride (Actos®)
- Rosiglitazone maleate (Avandia®)

Pioglitazone and rosiglitazone will be considered when used as:

- monotherapy
- when added to other oral diabetes agents
- when substituted for other oral hypoglycemic agents

Minimum duration of the use of pioglitazone and rosiglitazone use in the study for assessing both benefits and harms: 12 weeks

Comparators

1. Within-class review: pioglitazone vs. rosiglitazone
2. Between-class review, pioglitazone or rosiglitazone vs:
 - placebo
 - no treatment
 - other oral hypoglycemic agents: 2nd generation sulphonylureas, alpha-glucosidase inhibitors, metformin, metglitnides, fixed-dose combination products

Inclusion criteria for comparative studies: One or more intervention groups receiving a TZD and one or more comparison groups not receiving a TZD

Exclusion: insulin as a comparator or as add-on therapy to a TZD

Effectiveness outcomes

1. For prediabetes (Key Question 3):
 - incidence of type 2 diabetes, both clinically diagnosed and diagnosed by screening
2. For type 2 diabetes (Key Question 2):
 - Durability of control, including time to requiring insulin, time to monotherapy failure
 - Progression or occurrence of long-term microvascular disease (nephropathy as evidenced by proteinuria/dialysis/transplant/end-stage renal disease, retinopathy including proliferative retinopathy and blindness, and neuropathy)
 - Progression or occurrence of macrovascular disease (cardiovascular disease and mortality, myocardial infarction, stroke, coronary disease, angioplasty, coronary artery bypass grafting, amputation)
 - All-cause mortality
 - Quality of life

Safety outcomes

1. Total adverse events
2. Withdrawals due to adverse events
3. Specific adverse events, including but not limited to:
 - Hypoglycemic episodes
 - Cardiovascular events
 - Mortality: cardiovascular-specific and total
 - Heart failure
 - Pulmonary edema
 - Weight change
 - Liver toxicity
 - Peripheral edema
 - Fractures
 - Macular edema
 - Other serious adverse events (requiring assistance of a third person; leading to hospital admission; leading to significant morbidity, mortality, or significant functional limitation)

Study designs

1. Key Question 1 (effect on A1c): RCTs; good quality systematic reviews
2. Key Question 2,3 (effectiveness outcomes): RCTs; controlled clinical trials; retrospective or prospective cohort studies with a comparison group; good-quality systematic reviews
3. Key Question 4 (for adverse events): RCTs; controlled clinical trials; retrospective or prospective cohort studies with or without a comparison group; case-control studies; good quality systematic reviews
4. For subgroup examination (Key Question 5):

1. Designs as noted above for effectiveness and adverse events studies

For trials used in all key questions:

1. Both crossover trials and parallel group trials
2. Placebo-controlled, head-to-head, and active-controlled trials (with comparators noted above)

For all study designs and all key questions (both efficacy/effectiveness and adverse effects):
duration of study \geq 12 weeks

Exclude for all key questions: case reports, case series

Subgroups

Subpopulations based on the following characteristics will be examined using studies fulfilling inclusion criteria noted above:

Demographic characteristics

- age
- race/ethnicity

Co-morbidities

- Cardiovascular disease
- Heart failure
- Osteoporosis
- Renal insufficiency
- Obesity

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE, Ovid MEDLINE Daily Update, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from November 2007 through August Week 4 2009, using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (<http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php>) web sites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X1) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

Searches resulted in 243 citations. Of those, there are 22 new potentially relevant new trials (see Appendix A, attached). Fifteen of these (9 pioglitazone, 6 rosiglitazone) are placebo or active control efficacy trials reporting changes in A1c.

Two head-to-head efficacy trials reporting changes in A1c were also identified: One compared pioglitazone to rosiglitazone in combination with glimepiride (Chogtu 2009), and one compared pioglitazone monotherapy to rosiglitazone monotherapy (Miyazaki 2008).

Three studies reported post hoc analyses from effectiveness trials already included in the TZDs report (Dormandy 2009, Schneider 2008, Kahn 2008). These included analyses of the PROactive Trial (pioglitazone vs placebo) examining cardiovascular outcomes in subgroups of patients with peripheral artery disease and chronic kidney disease, and an analysis of fracture rates in ADOPT (rosiglitazone vs metformin or glyburide).

We identified 2 new effectiveness trials (Giles 2008, Home 2009). One is the RECORD trial (rosiglitazone + metformin or a sulfonyleurea vs metformin + a sulfonyleurea). Previously, an interim analysis of the RECORD was published and is included in the TZDs report. The other new effectiveness trial assessed cardiovascular mortality and hospitalization or emergency department visits for heart failure in patients with type 2 diabetes, heart failure and systolic dysfunction who were randomized to pioglitazone or glyburide.

New Drugs/Indications

No new drugs or indications were identified.

New Safety Alerts

No new safety alerts were identified.

APPENDIX A. Potentially Relevant New Trials (n=22)

Abe, M., K. Okada, et al. (2008). "Clinical investigation of the effects of pioglitazone on the improvement of insulin resistance and blood pressure in type 2-diabetic patients undergoing hemodialysis." Clinical Nephrology **70**(3): 220-8.

AIMS: Type 2 diabetes is characterized by a combination of insulin resistance, dyslipidemia, and increased blood pressure. In this study, we evaluated the clinical efficacy of pioglitazone in the treatment of diabetic patients with hypertension undergoing hemodialysis (HD). **METHODS:** An open-label, randomized study was performed using 40 subjects assigned to two groups: one group (pioglitazone group) was administered an add-on pioglitazone therapy (fixed dose, 30 mg) plus conventional oral antidiabetic agents, and the other group (control group) was administered conventional oral agents alone. The treatment efficacy was determined by monitoring the glycemic control and insulin resistance, which were assessed based on the homeostasis model assessment for insulin resistance (HOMA-IR). The safety of and tolerance to the drug were determined by monitoring clinical and laboratory parameters. **RESULTS:** Pioglitazone was effective in reducing the plasma glucose and hemoglobin A1c levels from the baseline values, beginning at 4 weeks of treatment. It was also effective in reducing the triglyceride levels. The HOMA-IR decreased significantly in the pioglitazone group, and this decrease was maintained until the last measurement, which was at 24 weeks. The systolic and diastolic blood pressure values were statistically lower in the pioglitazone group than in the control group. No serious adverse effects were observed in any of the patients. **CONCLUSIONS:** Pioglitazone is safe and effective for the treatment of Type 2-diabetic patients undergoing HD therapy. A daily dose of 30 mg pioglitazone is sufficient for treating HD patients, regardless of whether or not they are obese. Furthermore, pioglitazone reduced the systolic and diastolic blood pressure in our patients, and this effect requires further investigation.

Chogtu, B., N. P. Singh, et al. (2009). "Impact of glitazones on metabolic and haemodynamic parameters in patients with type 2 diabetes mellitus." Singapore Medical Journal **50**(4): 395-9.

INTRODUCTION: Diabetes mellitus is a common disorder associated with a number of metabolic abnormalities such as insulin resistance, dyslipidaemia and high blood pressure. These abnormalities are recognised risk factors for cardiovascular diseases. Insulin-sensitising drugs exert an effect on these cardiovascular risk factors. The present study was done with the objective of elucidating the differences in glycaemic control, plasma lipid levels and blood pressure in diabetic patients who were prescribed glitazones in combination with sulphonylureas. **METHODS:** Patients were randomly assigned to receive either pioglitazone or rosiglitazone in addition to glimepiride in an open-labelled study. Fasting and postprandial blood glucose levels, glycosylated haemoglobin, fasting lipid profile and blood pressure were recorded at baseline and at various intervals until the end of the study period at 12 weeks. **RESULTS:** A total of 56 patients (28 in the pioglitazone group and 28 in the rosiglitazone group) completed the study. There was no significant difference in the baseline values of various parameters

between the two treatment groups. The efficacy of the two treatment groups was similar in terms of the maintenance of blood glucose levels (fasting blood glucose, p-value is 0.10; postprandial blood glucose, p-value is 0.95; glycosylated haemoglobin, p-value is 0.30) and the effect on blood pressure (systolic blood pressure, p-value is 0.45; diastolic blood pressure, p-value is 0.95), while the pioglitazone group showed significantly better efficacy in improving the lipid profile compared to the rosiglitazone group (total cholesterol, p-value is 0.002; triglycerides, p-value is 0.002; low density lipoprotein, p-value is 0.005; and high density lipoprotein, p-value is 0.43). **CONCLUSION:** The two drugs showed a similar effect on blood glucose levels and blood pressure. However, the pioglitazone group was superior to the rosiglitazone group in improving the lipid profile.

Comaschi, M., A. Corsi, et al. (2008). "The effect of pioglitazone as add-on therapy to metformin or sulphonylurea compared to a fixed-dose combination of metformin and glibenclamide on diabetic dyslipidaemia." *Nutrition Metabolism & Cardiovascular Diseases* **18**(5): 373-9.

BACKGROUND AND AIMS: Diabetic dyslipidaemia contributes to the increased risk of cardiovascular disease in patients with Type 2 diabetes. This paper examines the effectiveness of adding pioglitazone to metformin or a sulphonylurea (SU) compared with a fixed-dose combination of metformin and glibenclamide on diabetic dyslipidaemia in patients with Type 2 diabetes. **METHODS AND RESULTS:** Patients (n=250) treated with metformin (< or =3g/day) or an SU as monotherapy at a stable dose for > or =3 months were randomised to receive either pioglitazone (15-30 mg/day) in addition to their metformin or SU, or a fixed-dose combination tablet containing metformin (400mg) and glibenclamide (2.5 mg) [up to 3 tablets daily] for 6 months. Addition of pioglitazone tended to increase plasma high-density lipoprotein-cholesterol (HDL-C) [0.04 mmol/L; P=0.051] at 6 months and significantly reduced plasma triglycerides (-0.25 mmol/L; P=0.013) compared with baseline. Patients treated with metformin/glibenclamide for 6 months had reduced HDL-C (-0.09 mmol/L; P<0.01) and no change in plasma triglyceride levels (0.03 mmol/L; P=0.733). Both treatment regimes resulted in a similar level of glycaemic control. **CONCLUSION:** The beneficial effects of pioglitazone on diabetic dyslipidaemia may help combat the increased cardiovascular morbidity and mortality observed in patients with Type 2 diabetes while providing stable glycaemic control.

Comaschi, M., A. Demicheli, et al. (2007). "Effects of pioglitazone in combination with metformin or a sulphonylurea compared to a fixed-dose combination of metformin and glibenclamide in patients with type 2 diabetes." *Diabetes Technology & Therapeutics* **9**(4): 387-98.

BACKGROUND: This study was designed to compare the effectiveness of co-administration of pioglitazone with metformin or a sulphonylurea (SU), with a fixed-dose combination of metformin and glibenclamide on glycaemic control and beta-cell function in patients with type 2 diabetes. **METHODS:** Patients (n = 250) treated with metformin (<or=3 g/day) or an SU as monotherapy for >3 months and with

glycosylated hemoglobin (HbA(1c)) between 7.5% and 11% inclusive were randomized to receive either pioglitazone (15-30 mg/day) as add-on therapy to metformin or an SU or a fixed-dose combination of metformin (400 mg) and glibenclamide (2.5 mg) (up to three tablets per day) for 6 months. HbA(1c) and fasting plasma glucose (FPG) were measured at baseline and 2, 4, and 6 months. C-peptide levels were measured at baseline and 6 months, and post-challenge glucose and insulin responses were measured. **RESULTS:** After 6 months, pioglitazone-based and fixed-dose metformin + glibenclamide resulted in similar reductions in HbA(1c) (-1.11% vs. -1.29%, respectively; $P = 0.192$) and FPG (-2.13 vs. -1.81 mmol/L, respectively; $P = 0.370$). Patients treated with pioglitazone for 6 months had significantly reduced C-peptide levels compared with baseline (-0.09 nmol/L, $P = 0.001$), while patients receiving fixed-dose metformin + glibenclamide combination had slightly increased C-peptide levels (+0.04 nmol/L, $P = 0.08$). Pioglitazone treatment also improved post-challenge insulin responses. **CONCLUSIONS:** Co-administration of pioglitazone with metformin or an SU is an effective alternative to fixed-dose metformin + glibenclamide combination for patients with type 2 diabetes. The complementary effects of pioglitazone with either metformin or an SU may also have the potential to preserve beta-cell function and delay the progression of type 2 diabetes.

Davidson, J. A., S. O. McMorn, et al. (2007). "A 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and tolerability of combination therapy with rosiglitazone and sulfonylurea in African American and Hispanic American patients with type 2 diabetes inadequately controlled with sulfonylurea monotherapy." Clinical Therapeutics **29**(9): 1900-14.

BACKGROUND: Type 2 diabetes mellitus is twice as prevalent in African Americans and Hispanic Americans as in non-Hispanic whites. However, the effectiveness and safety profile of rosiglitazone maleate used as combination therapy with sulfonylureas in the management of diabetes and its effect on cardiovascular disease (CVD) biomarkers/parameters have not been studied in these populations. **OBJECTIVE:** The purpose of this study was to determine the efficacy and tolerability of the addition of rosiglitazone to a regimen of glyburide once daily in African American and Hispanic American patients with type 2 diabetes previously inadequately controlled with sulfonylurea monotherapy. **METHODS:** This randomized, double-blind, placebo-controlled, parallel-group study was conducted at 38 centers in the United States. Eligible patients were aged ≤ 21 years, had type 2 diabetes, a fasting plasma glucose (FPG) level ≥ 140 mg/dL, and a glycosylated hemoglobin (HbA(1c)) value $\geq 7.5\%$, and had been treated with sulfonylurea monotherapy for at least 2 months before screening. Patients were assigned to receive treatment with glyburide 10 or 20 mg/d plus rosiglitazone 8 mg (GLY+RSG) or placebo (GLY+PBO) PO (tablets) QD for 24 weeks. The primary efficacy end point was the change from baseline in HbA(1c) after 24 weeks of treatment. Secondary end points included change in FPG; proportion of patients achieving HbA(1c) targets ($<7.0\%$ and $<6.5\%$); and changes in biomarkers for CVD risk, including C-reactive protein (CRP), plasminogen activator inhibitor (PAI)-I activity, fibrinogen, tissue plasminogen activator (tPA) antigen, von Willebrand

factor (vWF), soluble vascular cell adhesion molecule (sVCAM), lipoprotein-associated phospholipase A 2 activity, and urinary albumin/creatinine ratio (UACR). Tolerability was assessed using physical examination, including vital-sign measurement, clinical laboratory tests, and adverse event (AE) reports collected at each study visit. **RESULTS:** A total of 245 patients (101 African American and 144 Hispanic American) were enrolled. Demographic characteristics were comparable between the GLY+RSG and GLY+PBO groups: mean (SD) age (52 [11.9] vs 53 [10.4] years), HbA(1c) (9.2% [1.3%] vs 9.4% [1.4%]), sex (men/women, 45.3%/54.7% vs 48.3%/51.7%), race (African American/Hispanic American, 43.6%/56.4% vs 37.9%/62.1%), and mean (SD) weight (86.3 [18.8] vs 88.3 [19.4] kg). In the overall study population, treatment with GLY+RSG was associated with a significantly greater mean (95% CI) reduction from baseline in HbA(1c) compared with GLY+PBO (between-group Delta, -1.4% [-1.7% to -1.1%]; $P < 0.001$). When assessed by ethnicity, HbA(1c) values were significantly reduced with GLY+RSG compared with GLY+PBO in African American patients (between-group Delta, -1.4%) and in Hispanic American patients (between-group Delta, -1.5%) (both, $P < 0.001$), as were FPG levels (between-group Deltas, -3.1 mmol/L [57 mg/dL] and -3.8 mmol/L [-69 mg/dL], respectively; both, $P < 0.001$). With GLY+RSG, 9151 (17.6%) African American patients and 17/66 (25.8%) Hispanic American patients achieved HbA(1c) $< 7\%$, compared with 2/44 (4.5%) and 1/72 (1.4%) patients, respectively, who achieved this goal with GLY+PBO. Homeostasis model assessment estimates of insulin sensitivity and beta-cell function were significantly improved with GLY+RSG compared with GIX+PBO (between-group Deltas, 29.3% and 78.4%, respectively; both, $P < 0.001$). With regard to CVD biomarkers, there were potentially deleterious changes compared with baseline in the GLY+PBO group for CRP (+29.4%; $P = 0.042$), PAI-1 activity (+27.0%; $P = 0.006$), fibrinogen (+15.7%; $P = 0.007$), and sVCAM (+7.0%; $P = 0.035$), whereas there were no significant increases in these factors in the GLY+RSG group. In the GLY+RSG group, there were significant improvements in tPA (-17.8%; $P < 0.001$), vWF (-11.3%; $P = 0.019$), and UACR (-17.2%; $P = 0.028$) over 24 weeks' treatment, whereas there were no significant changes in any of these factors in the GLY+PBO group. As a result, significant treatment effects w

Derosa, G., P. Maffioli, et al. (2009). "Direct comparison among oral hypoglycemic agents and their association with insulin resistance evaluated by euglycemic hyperinsulinemic clamp: the 60's study." *Metabolism: Clinical & Experimental* **58**(8): 1059-66.

The aim of the study was to compare the long-term effect of 4 antidiabetic treatment protocols on insulin resistance evaluated by euglycemic hyperinsulinemic clamp in type 2 diabetes mellitus patients. Two hundred seventy-one type 2 diabetes mellitus patients with poor glycemic control and who were overweight were enrolled in this study. Patients were randomized and titrated to take pioglitazone, metformin, pioglitazone + metformin, or glimepiride + metformin for 15 months. They underwent a euglycemic hyperinsulinemic clamp at baseline, after 3 months, and after 15 months. Anthropometric and metabolic measurements were assessed at baseline, after 3 months, and after 15 months. There was a decrease in glycated hemoglobin in all groups, but glycated hemoglobin value was lower in the group

treated with pioglitazone + metformin compared with the groups treated with metformin alone and with pioglitazone alone. There was a decrease in fasting plasma glucose and postprandial plasma glucose values in all groups, but values obtained with pioglitazone + metformin were lower compared with values in the groups treated with metformin alone and with pioglitazone alone. Fasting plasma insulin and postprandial plasma insulin values were higher in the group treated with glimepiride + metformin compared with the other groups. After 15 months, glucose infusion rate and total glucose requirement values observed in the groups treated with pioglitazone alone and with pioglitazone + metformin were higher compared with the values in the group treated with metformin alone and with glimepiride + metformin; furthermore, values obtained in the group treated with pioglitazone + metformin were higher than the value obtained with pioglitazone alone. Pioglitazone-metformin-based therapeutic control is associated with the most quantitatively relevant improvement in insulin resistance-related parameters, whereas the sulfonylurea-metformin-including protocol has less relevant effects.

Derosa, G., R. Mereu, et al. (2009). "Pioglitazone metabolic effect in metformin-intolerant obese patients treated with sibutramine." *Internal Medicine* **48**(5): 265-71.

OBJECTIVE: Metformin is the drug of choice to treat obese type 2 diabetes patients because it reduces either insulin-resistance and body weight. We aimed to comparatively test the efficacy and tolerability of pioglitazone and sibutramine in metformin-intolerant obese type 2 diabetic patients treated with sibutramine.

MATERIALS AND METHODS: Five hundred and seventy-six consecutive Caucasian obese type 2 diabetic patients were evaluated during a 12-months period and fifty-two patients were resulted intolerant to metformin at maximum dosage (3,000 mg/day). All intolerant patients to metformin received a treatment with pioglitazone (45 mg/day) and sibutramine (10 mg/day) and they were compared with fifty-three patients treated with metformin (3,000 mg/day) and sibutramine (10 mg/day) for 6 months in a single-blind controlled trial. We assessed body mass index, waist circumference, glycated hemoglobin, Fasting Plasma glucose, postprandial plasma glucose, fasting plasma insulin, postprandial plasma insulin, lipid profile, systolic blood pressure, diastolic blood pressure and heart rate at baseline and after 3, and 6 months.

RESULTS: No body mass index change was observed at 3, and 6 months in pioglitazone + sibutramine group, while a significant reduction of body mass index and waist circumference was observed after 6 months in metformin + sibutramine group ($p < 0.05$). A significant decrease of glycated hemoglobin, Fasting Plasma glucose, postprandial plasma glucose, fasting plasma insulin, postprandial plasma insulin and HOMA index was observed after 3, and 6 months in both groups ($p < 0.05$, and $p < 0.01$, respectively). A significant Tg reduction was present after 6 months ($p < 0.05$) in both groups respect to the baseline values. No systolic blood pressure, diastolic blood pressure and heart rate change was obtained after 3, and 6 months in both groups.

CONCLUSION: Pioglitazone and sibutramine combination appears to be a short-term equally efficacious and well-tolerated therapeutic alternative respect to metformin-intolerant obese type 2 diabetic patients treated with sibutramine.

Derosa, G., S. A. T. Salvadeo, et al. (2008). "Rosiglitazone therapy improves insulin resistance parameters in overweight and obese diabetic patients intolerant to metformin." Archives of Medical Research **39**(4): 412-9.

BACKGROUND: Few studies have directly compared rosiglitazone and metformin effects on adipocytokines. The aim was to observe the possible effects of rosiglitazone and metformin on glycemic control, insulin sensitivity, plasma leptin (pL), adiponectin (ADN), tumor necrosis factor-alpha (TNF-alpha), and resistin (R) in overweight and obese diabetic patients intolerant to metformin. **METHODS:** Six hundred and ninety-four consecutive overweight and obese type 2 diabetic patients were evaluated and 56 patients were intolerant to metformin at maximum dosage. We added rosiglitazone to metformin in these intolerant patients (RM) and we compared them with 61 patients treated with metformin (M) in a single-blind placebo-controlled trial. We evaluated body mass index (BMI), glycated hemoglobin (HbA(1c)), fasting plasma glucose (FPG), fasting plasma insulin (FPI), pL, ADN, TNF-alpha, and R at baseline and after 3 and 6 months. Furthermore, we calculated insulin resistance index (HOMA-index) using FPG and FPI. **RESULTS:** Glycated hemoglobin, FPG, FPI, and HOMA-index results were lower than baseline values in RM and M groups. Glycated hemoglobin and HOMA-index values were significantly lower in RM group compared to M group at 6 months. Plasma leptin, ADN, TNF-alpha, and R were significantly improved in RM group compared to M group at 6 months. **CONCLUSIONS:** No BMI change was observed, probably because rosiglitazone was added to metformin, that could mitigate the body increase of rosiglitazone. Rosiglitazone improved glycemic control and insulin resistance-correlated parameters when added to intolerant metformin patients. These data suggest that rosiglitazone may be the drug of choice for the treatment of overweight and obese type 2 diabetic patients.

Dormandy, J. A., D. J. Betteridge, et al. (2009). "Impact of peripheral arterial disease in patients with diabetes--results from PROactive (PROactive 11)." Atherosclerosis **202**(1): 272-81.

We compared cardiovascular disease outcomes according to the presence of peripheral arterial disease (PAD) at baseline in a post hoc analysis from the PROactive study. Of the 5238 patients in PROactive (a study of pioglitazone versus placebo in patients with type 2 diabetes and macrovascular disease; mean follow-up=34.5 months), 1274 had PAD at baseline (619=pioglitazone; 655=placebo). Patients with PAD at baseline showed significantly higher rates of the primary endpoint, main secondary endpoint, all-cause mortality (all $P < 0.0001$), and stroke ($P = 0.0175$) than those with no PAD at baseline. The risk of PAD alone was similar to that of myocardial infarction alone. In patients with no PAD at baseline, the event rates of the primary endpoint ($P = 0.0160$), main secondary endpoint ($P = 0.0453$), and acute coronary syndrome ($P = 0.0287$) were significantly lower with pioglitazone than with placebo. This beneficial effect of pioglitazone was not seen in patients with PAD at baseline. In the total population, there was a higher frequency of leg revascularizations with pioglitazone than placebo--this was wholly due to first events that occurred within the initial 12 months of treatment. The presence of PAD increased the risk of all major cardiovascular events. Those without PAD at baseline

seemed to benefit more from pioglitazone treatment than the overall PROactive population.

Erdem, G., T. Dogru, et al. (2008). "The effects of pioglitazone and metformin on plasma visfatin levels in patients with treatment naive type 2 diabetes mellitus." Diabetes Research & Clinical Practice **82**(2): 214-8.

AIMS: Circulating visfatin levels are altered in insulin resistant states. We evaluated the effects of two insulin-sensitizing hypoglycemic agents on plasma visfatin and adiponectin levels in patients with newly diagnosed and untreated type 2 diabetes mellitus (T2DM). **METHODS:** Forty-four patients with T2DM were randomized to treatment either with pioglitazone (15-45mg/day) or metformin (1000-2000mg/day). Plasma visfatin and adiponectin levels and homeostasis model assessment of insulin resistance (HOMA-IR) scores were determined at baseline and at 12th week of treatment. **RESULTS:** By the end of the 12th week, fasting plasma glucose, HbA1c, HOMA-IR scores and waist circumferences improved equally in both treatment arms. HDL cholesterol and adiponectin levels increased only in the pioglitazone group (p=0.01 and p=0.003, respectively). On the other hand, metformin treatment had additional regulatory effects on BMI, blood pressure and total and LDL-cholesterol levels (p=0.002, p=0.01, p=0.004, p=0.001 and p<0.001, respectively). Neither pioglitazone nor metformin displayed a significant effect on circulating visfatin concentration. **CONCLUSIONS:** Despite improvements in insulin sensitivity and glycemic regulation, either pioglitazone or metformin treatment did not result in any effect on blood visfatin levels in patients with treatment naive T2DM.

Giles, T. D., A. B. Miller, et al. (2008). "Pioglitazone and heart failure: results from a controlled study in patients with type 2 diabetes mellitus and systolic dysfunction.[see comment]." Journal of Cardiac Failure **14**(6): 445-52.

BACKGROUND: Thiazolidinediones are associated with fluid retention, often interpreted as worsening cardiac function, limiting their use in patients with heart failure (HF). We compared the effects of pioglitazone and glyburide on cardiac function in patients with type 2 diabetes, systolic dysfunction, and New York Heart Association (NYHA) functional Class II/III HF. **METHODS AND RESULTS:** Participants received pioglitazone or glyburide (+/-insulin) for 6 months in this double-blind, randomized, multicenter study. The primary end point was time to HF, a composite of cardiovascular mortality and hospitalization or emergency room (ER) visit for HF. Secondary endpoints included echocardiographic and functional classification assessments. An earlier time to onset and higher incidence of the primary endpoint was noted with pioglitazone (13%) versus glyburide (8%) (P = .024). Hospitalization or ER visit occurred in 30 pioglitazone and 15 glyburide participants, 19 and 12 of whom, respectively, continued treatment. Cardiac mortality (5 versus 6 participants, respectively) and cardiac function, as measured by change in ventricular mass index (P = .959), ejection fraction (P = .413), or fractional shortening (P = .280), were similar between treatments. **CONCLUSIONS:** Pioglitazone was associated with a higher incidence of hospitalization for HF

without an increase in cardiovascular mortality or worsening cardiac function (by echocardiography).

Hamann, A., J. Garcia-Puig, et al. (2008). "Comparison of fixed-dose rosiglitazone/metformin combination therapy with sulphonylurea plus metformin in overweight individuals with Type 2 diabetes inadequately controlled on metformin alone." Experimental & Clinical Endocrinology & Diabetes **116**(1): 6-13.

AIM: This 52-week, randomized, double-blind, parallel-group study was designed to compare rosiglitazone/metformin fixed-dose combination therapy with combination sulphonylurea plus metformin therapy in overweight individuals with inadequately controlled type 2 diabetes mellitus. METHOD: Individuals with inadequate glycaemic control (HbA (1c) > or =7%) while on metformin monotherapy (> or =0.85 g/day) entered a 4-week run-in period during which they received metformin 2 g/day. At the end of the run-in, individuals with fasting plasma glucose > or =7.0 mmol/l were randomized to treatment with metformin (2 g/day) and either rosiglitazone (4 mg/day; RSG+MET [N=294]) or a sulphonylurea (glibenclamide 5 mg/day or gliclazide 80 mg/day; SU+MET [N=302]). Medications were up-titrated to maximum tolerated doses (rosiglitazone 8 mg, glibenclamide 15 mg or gliclazide 320 mg plus metformin 2 g/day) during the first 12 weeks of double-blind treatment. The primary efficacy end point was the change in HbA (1c) from baseline after 52 weeks of treatment. RESULTS: RSG+MET was non-inferior to SU+MET with respect to changes in HbA (1c) after one year of treatment (DeltaHbA (1c)= -0.78% and -0.86%, respectively; treatment difference =0.09%, 95% CI=-0.08, 0.25). The HbA (1c) reductions with RSG+MET, but not SU+MET, were accompanied by significant improvements in measures of beta-cell function including proinsulin:insulin ratio. The degree of beta-cell failure was significantly greater with SU+MET compared to RSG+MET as measured by the coefficient of failure (0.543 vs. 0.055 HbA (1c)%/year, respectively, p=0.0002). The proportion of individuals who experienced hypoglycaemic events was significantly (p<0.0001) lower with RSG+MET (6%) than with SU+MET (30%). Diastolic ambulatory blood pressure and cardiovascular biomarkers (high-sensitivity C-reactive protein and plasminogen activator inhibitor-1) were also reduced following one year of treatment with RSG+MET but not SU+MET. Both treatments were generally well tolerated. CONCLUSION: Fixed-dose combination therapy with rosiglitazone/metformin is non-inferior to sulphonylurea plus metformin combination therapy in reducing HbA (1c) over one year of treatment. Improvements in measures of beta-cell function suggest that the improvements in glycaemic control may be better maintained in long-term therapy with the rosiglitazone/metformin combination.

Home, P. D., S. J. Pocock, et al. (2009). "Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial.[see comment]." Lancet **373**(9681): 2125-35.

BACKGROUND: Rosiglitazone is an insulin sensitiser used in combination with metformin, a sulphonylurea, or both, for lowering blood glucose in people with type 2 diabetes. We assessed cardiovascular outcomes after addition of rosiglitazone to

either metformin or sulfonylurea compared with the combination of the two over 5-7 years of follow-up. We also assessed comparative safety. **METHODS:** In a multicentre, open-label trial, 4447 patients with type 2 diabetes on metformin or sulfonylurea monotherapy with mean haemoglobin A(1c) (HbA(1c)) of 7.9% were randomly assigned to addition of rosiglitazone (n=2220) or to a combination of metformin and sulfonylurea (active control group, n=2227). The primary endpoint was cardiovascular hospitalisation or cardiovascular death, with a hazard ratio (HR) non-inferiority margin of 1.20. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00379769. **FINDINGS:** 321 people in the rosiglitazone group and 323 in the active control group experienced the primary outcome during a mean 5.5-year follow-up, meeting the criterion of non-inferiority (HR 0.99, 95% CI 0.85-1.16). HR was 0.84 (0.59-1.18) for cardiovascular death, 1.14 (0.80-1.63) for myocardial infarction, and 0.72 (0.49-1.06) for stroke. Heart failure causing admission to hospital or death occurred in 61 people in the rosiglitazone group and 29 in the active control group (HR 2.10, 1.35-3.27, risk difference per 1000 person-years 2.6, 1.1-4.1). Upper and distal lower limb fracture rates were increased mainly in women randomly assigned to rosiglitazone. Mean HbA(1c) was lower in the rosiglitazone group than in the control group at 5 years. **INTERPRETATION:** Addition of rosiglitazone to glucose-lowering therapy in people with type 2 diabetes 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, rosiglitazone does not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs. **FUNDING:** GlaxoSmithKline plc, UK.

Iliadis, F., N. P. Kadoglou, et al. (2007). "Metabolic effects of rosiglitazone and metformin in Greek patients with recently diagnosed type 2 diabetes." *In Vivo* **21**(6): 1107-14.

The aim of this study was to evaluate the comparative effects of rosiglitazone and metformin on metabolic parameters in recently diagnosed type 2 Greek diabetic patients. A total of 41 drug-naive individuals, with recently diagnosed type 2 diabetes, were randomized in 3 groups: DIET, diet alone; ROSI, diet plus rosiglitazone; and MET, diet plus metformin. Anthropometric indexes, blood pressure, hematological and biochemical parameters were estimated at baseline and after 18 weeks of treatment. We observed a significant decrease of fasting glucose (FBG) ($p < 0.001$), glycated haemoglobin (HbA1c) (ROSI: $p = 0.001$, MET: $p < 0.001$), homeostasis model assessment for insulin resistance (HOMA-IR) (ROSI: $p = 0.006$, MET: $p = 0.009$) and glutamic pyruvic transaminase (SGPT) (ROSI: $p = 0.004$, MET: $p = 0.003$) in both ROSI and MET groups. Metformin significantly reduced fasting insulin ($p = 0.04$), body weight ($p = 0.026$), body mass index (BMI) ($p = 0.022$), waist circumference ($p = 0.022$) and gamma glutamyl transpeptidase (gamma-GT) ($p = 0.039$), while rosiglitazone decreased blood pressure (systolic: $p = 0.05$, mean: $p = 0.03$) and alkaline phosphatase (ALP) ($p = 0.001$) compared to baseline values. Combined intervention with rosiglitazone and diet led to a slight, not significant, weight loss. Rosiglitazone and metformin are equally effective in controlling diabetes, decreasing insulin resistance and improving liver function. However, considering the more favorable effects of metformin on body composition and its

documented cost-effectiveness, it seems to be preferable in newly diagnosed Greek diabetic patients.

Kahn, S. E., B. Zinman, et al. (2008). "Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT)." Diabetes Care **31**(5): 845-51.

OBJECTIVE: The purpose of this study was to examine possible factors associated with the increased risk of fractures observed with rosiglitazone in A Diabetes Outcome Progression Trial (ADOPT). **RESEARCH DESIGN AND METHODS:** Data from the 1,840 women and 2,511 men randomly assigned in ADOPT to rosiglitazone, metformin, or glyburide for a median of 4.0 years were examined with respect to time to first fracture, rates of occurrence, and sites of fractures. **RESULTS:** In men, fracture rates did not differ between treatment groups. In women, at least one fracture was reported with rosiglitazone in 60 patients (9.3% of patients, 2.74 per 100 patient-years), metformin in 30 patients (5.1%, 1.54 per 100 patient-years), and glyburide in 21 patients (3.5%, 1.29 per 100 patient-years). The cumulative incidence (95% CI) of fractures in women at 5 years was 15.1% (11.2-19.1) with rosiglitazone, 7.3% (4.4-10.1) with metformin, and 7.7% (3.7-11.7) with glyburide, representing hazard ratios (95% CI) of 1.81 (1.17-2.80) and 2.13 (1.30-3.51) for rosiglitazone compared with metformin and glyburide, respectively. The increase in fractures with rosiglitazone occurred in pre- and postmenopausal women, and fractures were seen predominantly in the lower and upper limbs. No particular risk factor underlying the increased fractures in female patients who received rosiglitazone therapy was identified. **CONCLUSIONS:** Further investigation into the risk factors and underlying pathophysiology for the increased fracture rate in women taking rosiglitazone is required to relate them to preclinical data and better understand the clinical implications of and possible interventions for these findings.

Kaku, K. (2009). "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." Current Medical Research & Opinion **25**(5): 1111-9.

OBJECTIVE: To assess the efficacy and safety of combination therapy with pioglitazone and metformin in Japanese patients with type 2 diabetes. **RESEARCH DESIGN AND METHODS:** During a 12-week observation period 236 patients were treated with metformin 500 or 750 mg/day. 169 patients with a confirmed HbA(1c) level $\geq 6.5\%$ were randomized (stratified according to metformin dosage) to receive pioglitazone 15 mg/day for 12 weeks then increased to 30 mg/day for a further 16 weeks (n = 83), or placebo (n = 86). Outcome measures included HbA(1c), fasting blood glucose (FBG), percentage of patients achieving HbA(1c) $< 6.5\%$, lipid profile, and other metabolic parameters. **RESULTS:** Mean HbA(1c) was reduced by 0.67% in patients receiving pioglitazone plus metformin versus an increase of 0.25% in those receiving metformin alone (p < 0.0001). After 8 weeks' treatment and until the end of the study, HbA(1c) was significantly lower with pioglitazone plus metformin and more patients in this group achieved an HbA(1c) $< 6.5\%$ (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-cholesterol, total cholesterol, and adiponectin, and significantly decreased levels of fasting insulin, free fatty acids, and homeostasis model assessment insulin resistance (HOMA-R) compared with metformin monotherapy. Overall, 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%).

CONCLUSION: Pioglitazone plus metformin significantly improved glycemic control (HbA(1c) and FBG), and markers associated with increased insulin resistance and cardiovascular risk compared with metformin monotherapy.

CLINICAL TRIAL REGISTRATION NUMBER: UMIN 000001110.

Kawai, T., O. Funae, et al. (2008). "Effects of pretreatment with low-dose metformin on metabolic parameters and weight gain by pioglitazone in Japanese patients with type 2 diabetes." *Internal Medicine* **47**(13): 1181-8.

OBJECTIVE: We investigated whether or not "low dose" metformin could prevent weight gain induced by pioglitazone. RESEARCH DESIGN AND METHODS: Sixty-nine patients with type 2 diabetes received 500-750 mg metformin a day for 12 weeks as an observation period before the start of the intervention. After an observation period, inadequately controlled patients (hemoglobin A1c $\geq 7.5\%$, $n=34$) received additional treatment with 15 mg pioglitazone (+P, M+P group). The other patients ($n= 35$) continued metformin monotherapy (Met group). In addition, another group consisting of 28 patients treated with 15 mg pioglitazone alone (Pio group) was observed. Body mass index (BMI), as well as several clinical parameters of glycemic control and lipid metabolism, was compared before and after 24 weeks of intervention. RESULTS: BMI increased significantly in the Pio group [24.0+/-3.8 vs. 24.8+/-4.3 kg/m(2), (mean +/- SD), $p<0.001$], but not in the M+P group (25.1+/-3.5 vs. 25.3+/-3.4 kg/m(2), NS) and Met group (24.0+/-3.3 vs. 24.0+/-3.5 kg/m(2), NS). In addition to improvement in glycemic control, a significant reduction in the atherogenic index of plasma (AIP), defined as $\log [TG \times 0.0112/HDL-C \times 0.02586]$, was observed in the Pio group (0.06+/-0.23 vs. -0.04+/-0.27, $p<0.05$) and M+P group (0.08+/-0.24 vs. -0.001+/-0.252, $p<0.01$), but not in the Met group. CONCLUSION: This study indicates potential benefits of the addition of pioglitazone to "low dose" metformin in terms of improvement of glucose and lipid metabolism without weight gain.

Khanolkar, M. P., R. H. K. Morris, et al. (2008). "Rosiglitazone produces a greater reduction in circulating platelet activity compared with gliclazide in patients with type 2 diabetes mellitus--an effect probably mediated by direct platelet PPARgamma activation." *Atherosclerosis* **197**(2): 718-24.

AIMS: Type 2 diabetes mellitus (T2DM) is associated with enhanced platelet activation. We conducted a randomised double-blind study to compare the effects of combination metformin and rosiglitazone or metformin and gliclazide therapy on platelet function in persons with T2DM. METHODS: Fifty subjects on metformin

monotherapy received either rosiglitazone 4 mg or gliclazide 80 mg. HbA1c, HOMA-R, markers of platelet activation, inflammation, endothelial activation and oxidative stress were measured at baseline and after 24 weeks of treatment. Separate in vitro platelet function studies were conducted on platelets pre-incubated with rosiglitazone and gliclazide. **RESULTS:** A significantly greater reduction in platelet aggregation was observed in the rosiglitazone treated group compared to gliclazide. HbA1c and markers of endothelial activation were reduced to a similar extent in both groups. A significant reduction in HOMA-R, markers of inflammation and oxidative stress was only observed with rosiglitazone. Reduction in platelet aggregation with rosiglitazone correlated with reduction in oxidative stress. In the in vitro study, rosiglitazone produced significantly greater reduction in platelet aggregation compared with gliclazide. **CONCLUSION:** Greater reduction in platelet activity observed with rosiglitazone may be related to reduced oxidative stress and a possible direct PPARgamma mediated effect on platelet function.

Miyazaki, Y. and R. A. DeFronzo (2008). "Rosiglitazone and pioglitazone similarly improve insulin sensitivity and secretion, glucose tolerance and adipocytokines in type 2 diabetic patients." *Diabetes, Obesity & Metabolism* **10**(12): 1204-11.

OBJECTIVE: We examined the effects of rosiglitazone treatment on profiles of adipocytokines levels, postprandial insulin and glucose excursion, lipids levels, comparing with those of pioglitazone treatment in patients with type 2 diabetes mellitus (T2DM). **METHODS:** Changes in body weight, haemoglobin A(1c) (HbA(1c)), glucose/insulin/C-peptide/free fatty acid (FFA) during 75 g oral glucose tolerance test (OGTT), HDL-/LDL-cholesterol, triglyceride (TG) and adipocytokines [tumour necrosis factor (TNF)-alpha, leptin and adiponectin] were measured in T2DM patients treated with rosiglitazone, 8 mg/day (n = 35), or pioglitazone, 45 mg/day (n = 21), for 3 months. **RESULTS:** After rosiglitazone or pioglitazone treatment, HbA(1c) (8.6-7.2 vs. 8.3-6.9%, rosiglitazone vs. pioglitazone), fasting plasma glucose (190-144 vs. 178-140 mg/dl), fasting FFA (729-595 vs. 641-526 microEq/l), mean plasma glucose-OGTT (292-229 vs. 285-233 mg/dl) and mean FFA-OGTT (580-430 vs. 488-377 microEq/l) decreased similarly and all were statistically significant (p < 0.01). The insulinogenic index (DeltaI(0-120)/DeltaG(0-120)) (0.19-0.30 vs. 0.17-0.26) and Matsuda index of insulin sensitivity (2.0-3.1 and 2.7-4.3) increased (p < 0.01) similarly, despite increase in body weight (85-88 vs. 81-84 kg). 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 microg/ml) increased (p < 0.01), while leptin did not change following either treatment. After rosiglitazone treatment, plasma HDL-cholesterol (34-38 mg/dl) and LDL-cholesterol (103-120 mg/dl) increased (p < 0.01), while TGs (177-167 mg/dl) did not change significantly. After pioglitazone treatment, plasma HDL-cholesterol (34-37 mg/dl) increased (p < 0.05), while LDL-cholesterol (104-105 mg/dl) did not change and TGs (153-106 mg/dl) decreased (p < 0.01). **CONCLUSIONS:** Rosiglitazone and pioglitazone have similar beneficial effects on glycaemic control insulin sensitivity, insulin secretion and plasma adipocytokine levels. However, pioglitazone has a more beneficial effect on the plasma lipid profile than rosiglitazone.

Rosenstock, J., H. S. Chou, et al. (2008). "Potential benefits of early addition of rosiglitazone in combination with glimepiride in the treatment of type 2 diabetes." Diabetes, Obesity & Metabolism **10**(10): 862-73.

AIM: To assess the efficacy and tolerability of early combination therapy with rosiglitazone (RSG) and glimepiride (GLIM) vs. GLIM monotherapy in patients with type 2 diabetes mellitus (T2DM). METHODS: Strategies for the addition of RSG in combination with GLIM were evaluated with data from two randomized, double-blind, placebo (PBO)-controlled studies. Study A - addition of RSG (4 or 8 mg) or PBO to continued GLIM 3 mg once daily; study B - addition of low-dose RSG (4 mg) prior to uptitration of GLIM (from 2 to 4 mg) vs. continued uptitration of GLIM (from 2 to 8 mg). RESULTS: Study A reported significant reductions in fasting plasma glucose (FPG) from baseline to week 26 with the addition of both 4 and 8 mg RSG to GLIM 3 mg [-21 mg/dl (-1.2 mmol/l), $p = 0.0019$ and -43 mg/dl (-2.4 mmol/l), $p < 0.0001$, respectively] and in haemoglobin A(1c) (HbA(1c)) (-0.63%, $p = 0.00015$ and -1.17%, $p < 0.0001$, respectively) from a baseline of 8.2 and 8.1%, respectively. At the end of the study, target HbA(1c) $< 7.0\%$ was achieved in 43 and 68% of patients in the RSG 4 mg + GLIM and RSG 8 mg + GLIM groups, respectively, compared with 32% in the PBO + GLIM (GLIM alone) group. In study B, addition of RSG to GLIM reduced mean FPG and HbA(1c) levels at week 24 from baseline [-28 mg/dl (-1.5 mmol/l), $p < 0.0001$, and -0.68%, $p < 0.0001$, respectively]. There were no significant changes with GLIM monotherapy in either study. Favourable effects of RSG + GLIM on insulin sensitivity, beta-cell function and cardiovascular disease biomarkers were also observed. All treatments were similarly well tolerated. CONCLUSIONS: Early addition of RSG to GLIM is an effective and well-tolerated treatment option to improve glycaemic control in sulphonylurea-treated patients with T2DM.

Schneider, C. A., E. Ferrannini, et al. (2008). "Effect of pioglitazone on cardiovascular outcome in diabetes and chronic kidney disease.[see comment]." Journal of the American Society of Nephrology **19**(1): 182-7.

Patients with diabetes and chronic kidney disease (CKD) are at particularly high risk for cardiovascular disease (CVD). This post hoc analysis from the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) investigated the relationship between CKD and incident CVD in a population of patients with diabetes and documented macrovascular disease, as well as the effects of pioglitazone treatment on recurrent CVD. CKD, defined as an estimated GFR < 60 ml/min per 1.73m², was present in 597 (11.6%) of 5154 patients. More patients with CKD reached the primary composite end point (all-cause mortality, myocardial infarction (MI), stroke, acute coronary syndrome, coronary/carotid arterial intervention, leg revascularization, or amputation above the ankle) than patients without CKD (27.5 versus 19.6%; $P < 0.0001$). Patients with CKD were also more likely to reach a secondary composite end point (all-cause mortality, MI, and stroke). Patients who had CKD and were treated with pioglitazone were less likely to reach the secondary end point (hazard ratio 0.66; 95% confidence interval 0.45 to 0.98), but this association was not observed among those with better renal function. In addition, there was a greater decline in estimated GFR with pioglitazone

(between-group difference 0.8 ml/min per 1.73 m²/yr) than with placebo. In conclusion, CKD is an independent risk factor for cardiovascular events and death among patients with diabetes and preexisting macrovascular disease. Patients who had CKD and were treated with pioglitazone were less likely to reach a composite end point of all-cause death, MI, and stroke, independent of the severity of renal impairment.

Seufert, J. and R. Urquhart (2008). "2-year effects of pioglitazone add-on to sulfonylurea or metformin on oral glucose tolerance in patients with type 2 diabetes." Diabetes Research & Clinical Practice **79**(3): 453-60.

AIM: We report the effectiveness of the thiazolidinedione, pioglitazone, as add-on medication to metformin or sulfonylurea in reducing post-load serum glucose levels, as assessed by 3-h oral glucose tolerance testing (OGTT). **METHODS:** Adult patients with Type 2 diabetes took part in one of two large-scale, 2-year clinical trials. One study compared pioglitazone treatment as add-on to failing metformin therapy (N=317) with add-on gliclazide treatment to metformin (N=313). The other study compared combination therapy with pioglitazone added to existing failing sulfonylurea therapy (N=319) with metformin treatment in addition to sulfonylurea (N=320). HbA(1c) and fasting plasma glucose concentrations were measured at baseline and throughout the study and at the final visit at week 104. At selected centers (N=299 patients), a 3-h OGTT was performed at baseline and at week 104. **RESULTS:** At week 104, mean HbA(1c) reduction from baseline was 0.89% for pioglitazone and 0.77% for gliclazide addition to metformin (p=0.200) and 1.03% with pioglitazone and 1.16% with metformin addition to sulfonylurea (p=0.173) in the total patient cohort. In the 299 patients who underwent OGTT, 2 years of treatment with pioglitazone, whether added to existing metformin or sulfonylurea medication, resulted in decreases in glucose excursions after an oral glucose load without increasing post-load serum insulin concentrations. In contrast, gliclazide in combination with metformin therapy caused increases in both post-load serum glucose and insulin excursions after 2 years, whereas metformin add-on to sulfonylurea did not have a significant effect on post-load serum glucose concentrations and resulted in an increase in insulin levels. **CONCLUSIONS:** There were no significant differences in HbA(1c) levels between groups. However, 2-year treatment with pioglitazone as an add-on to either failing metformin or sulfonylurea therapy improved post-load glucose excursions without affecting insulin secretion. In contrast, glucose excursions were not improved by gliclazide or metformin add-on therapy, despite increases in post-load insulin levels. These data suggest that pioglitazone reduces peripheral insulin resistance via mechanisms different from those of metformin.

van der Meer, R. W., L. J. Rijzewijk, et al. (2009). "Pioglitazone improves cardiac function and alters myocardial substrate metabolism without affecting cardiac triglyceride accumulation and high-energy phosphate metabolism in patients with well-controlled type 2 diabetes mellitus.[see comment]." Circulation **119**(15): 2069-77.

BACKGROUND: Cardiac disease is the leading cause of mortality in type 2 diabetes mellitus (T2DM). Pioglitazone has been associated with improved cardiac

outcome but also with an elevated risk of heart failure. We determined the effects of pioglitazone on myocardial function in relation to cardiac high-energy phosphate, glucose, and fatty acid metabolism and triglyceride content in T2DM patients.

METHODS AND RESULTS: Seventy-eight T2DM men without structural heart disease or inducible ischemia as assessed by dobutamine stress echocardiography were assigned to pioglitazone (30 mg/d) or metformin (2000 mg/d) and matching placebo for 24 weeks. The primary end point was change in cardiac diastolic function from baseline relative to myocardial metabolic changes, measured by magnetic resonance imaging, proton and phosphorus magnetic resonance spectroscopy, and [(18)F]-2-fluoro-2-deoxy-D-glucose and [(11)C]palmitate positron emission tomography. No patient developed heart failure. Both therapies similarly improved glycemic control, whole-body insulin sensitivity, and blood pressure. Pioglitazone versus metformin improved the early peak flow rate ($P=0.047$) and left ventricular compliance. Pioglitazone versus metformin increased myocardial glucose uptake ($P<0.001$), but pioglitazone-related diastolic improvement was not associated with changes in myocardial substrate metabolism. Metformin did not affect myocardial function but decreased cardiac work relative to pioglitazone ($P=0.006$), a change that was paralleled by a reduced myocardial glucose uptake and fatty acid oxidation. Neither treatment affected cardiac high-energy phosphate metabolism or triglyceride content. Only pioglitazone reduced hepatic triglyceride content ($P<0.001$).

CONCLUSIONS: In T2DM patients, pioglitazone was associated with improvement in some measures of left ventricular diastolic function, myocardial glucose uptake, and whole-body insulin sensitivity. The functional changes, however, were not associated with myocardial substrate and high-energy phosphate metabolism.