Clinical Medicine Reviews in Vascular Health

Libertas Academica
FREEDOM TO RESEARCH

CMR
Clinical Medicine Reviews

REVIEW

Rosiglitazone Maleate and Glimepiride in Fixed Combination for the Metabolic Control of Type 2 Diabetes

Giuseppe Derosa and Pamela Maffioli

Department of Internal Medicine and Therapeutics, University of Pavia, Fondazione IRCCS Policlinico S. Matteo, PAVIA, Italy. Corresponding author email: giuseppe.derosa@unipv.it

Abstract: Type 2 diabetes mellitus (T2DM) is a constantly progressing disease and monotherapy may last for approximately 5–10 years before a further increase in glycated hemoglobin (HbA_{1c}) indicates the requirement of a combination therapy. We conducted a review focusing our attention on the effects of a combination of rosiglitazone plus glimepiride on metabolic control. We performed a defined search string in PubMed and Embase for relevant clinical trials, literature reviews and selected clinical trials about the use of rosiglitazone and glimepiride published in the last ten years. We observed that the combination of rosiglitazone plus glimepiride gives an improvement of glycemic control, even if a little weight is gained. Furthermore the association of rosiglitazone and glimepiride gives also an improvement of fasting plasma insulin. However, even if this combination proved to be effective, it is not an option available anymore, due to the recent withdrawn of rosiglitazone. Other possibilities should be considered, for example, substitute rosiglitazone with pioglitazone that proved to be safe on cardiovascular risk.

Keywords: rosiglitazone glimepiride, combination, metabolic control, adverse effects

Clinical Medicine Reviews in Vascular Health 2011:3 31–38

doi: 10.4137/CMRVH.S1627

This article is available from http://www.la-press.com.

Introduction

The importance of an early, intensified approach to metabolic control has been clearly demonstrated by the long-term results of the United Kingdom Prospective Diabetes Study (UKPDS), showing that the benefits of tight blood glucose control extended well beyond the end of the study and persisted after over 10 years.[1] Type 2 diabetes mellitus (T2DM) is a constantly progressing disease and monotherapy may last for approximately 5–10 years before a further increase in glycated hemoglobin (HbA_{1c}) indicates the requirement of more intensive treatment regimens.[2,3] For these reasons the combination therapy has emerged as an alternative approach, getting more patients to the goal initially and avoiding or delaying the need for subsequent treatment regimen changes to maintain glycemic targets.[4] One approach may be the combination of sulphonylureas and thiazolidinediones in order to benefit from the synergistic therapeutic actions of both classes of drugs.[5]

Glimepiride acts stimulating β-cell secretion by binding to a 65 kDa β-cell receptor leading to a decrease in gluco/hexokinase and to an increase in the expression of glucokinase mRNA. By increasing β-cell output, glimepiride lowers blood glucose levels and HbA_{1c}, the major treatment targets in the management of T2DM.[6]

On the other side rosiglitazone belongs, together with pioglitazone, to a class of anti-diabetic drugs, thiazolidinediones, that targets insulin resistance by binding to the transcription factor peroxisome proliferator-activated receptor-γ (PPAR-γ) that is involved in the regulation of carbohydrate and lipid metabolism,[7,8] promoting synthesis of glucose transporters and activating adipocyte differentiation.[9–12]

The metabolic effects of PPAR-γ activation by rosiglitazone comprise an increase in peripheral insulin sensitivity in muscle, liver, and adipose tissue, improvement of post-prandial and fasting glucose concentrations as well as long-term glycemic control.[13,14]

In the past years our group conducted several studies about rosiglitazone, both in addition to metformin,[15,16] or glimepiride.[17,18] We have also conducted a review about the effects of pioglitazone and rosiglitazone combined with metformin on body weight and metabolic control,[19] showing that, even if a small increase in mean body weight is observed in patients treated with thiazolidinediones plus metformin therapy, the weight gain is less than previously reported and it is also considerably less than what might have been expected given the large improvement in glycemic control. We have also conducted a review comparing the effect of thiazolidinediones and sulphonylureas,[20] concluding that both give a similar improvement of glycemic control: sulphonylureas have an immediate action on HbA_{1c}, whereas thiazolidinediones need some weeks to express their action. Thiazolidinediones give also an improvement of insulin resistance and insulin sensitivity parameters not reported with sulphonylureas. We have already conducted a review about the possible combination of pioglitazone and glimepiride;[21] this time we decided to conduct a review focusing our attention on the effects of a combination of rosiglitazone plus glimepiride on metabolic control.

Patients and Methods

We performed a defined search string in PubMed and Embase for relevant clinical trials, literature reviews and selected clinical trials about the use of rosiglitazone and glimepiride published in the last ten years. Several searches of databases and the Internet were also carried out, providing an overview of the subject. It was also discovered that some reports have only been published in Japanese or Hungarian; to avoid problems and limitations with the translation of these reports, we decided to perform this review by including only studies published in English. The strategy was to develop a defined search string that would find all relevant clinical trials registered in PubMed. The reference list of the selected trials has been carefully examined to identify any additional study not registered in the PubMed database. We used as keywords "rosiglitazone" "glimepiride", "combination of rosiglitazone and glimepiride", "rosiglitazone and glimepiride" as key words. We considered as primary end points HbA_{1c}, fasting plasma glucose (FPG), fasting plasma insulin (FPI), body weight, body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP, respectively), and, when available, data on lipid profile. We also recorded the frequency of adverse events such edema and heart failure.

Rosiglitazone and Glimepiride

The combination of a sulphonylurea with metformin is commonly used in clinical practice. But when

this potent combination is no longer able to provide acceptable glycemic control, the addition of a thiazolidinedione may lead to improved metabolic control. This was showed by Kiayias et al[22] they evaluated the effects of twenty weeks of therapy with 4 or 8 mg of rosiglitazone added to a regimen of glimepiride (6 mg/day) and metformin (2,550 mg/day) in type 2 diabetic patients inadequately controlled by the current therapy. After the addition of rosiglitazone there was a statistically significant decrease in HbA_{1c} both with 4 and 8 mg of rosiglitazone: in the group treated with 4 mg the average HbA_{1c} went from 8.9% ± 1.1 to 7.8% ± 0.9% ($P < 0.001$), and FPG went from 10.7 ± 2.2 mmol/l to 8.9 ± 1.2 mmol/l ($P < 0.0001$). In the group treated with 8 mg of rosiglitazone, the average HbA_{1c} went from 9.0 ± 1.1% to 7.6 ± 0.8 and FPG went from 10.8 ± 2.3 mmol/l to 7.9 ± 1 mmol/l ($P < 0.0001$ for both).

The treatment with rosiglitazone was well tolerated. Hypoglycemia was the most frequent side effect in both patient groups (18.6% at 4 mg/day and 28% at 8 mg/day). The dose of glimepiride and/or metformin was reduced in patients with hypoglycemic episodes, and the reduction proved to be effective in avoiding hypoglycemic reactions. Mean body weight increased in both rosiglitazone groups (4.2 kg at 4 mg/day and 4.6 kg at 8 mg/day). No mention of cardiovascular events was done.

Chogtu et al[23] instead, compared pioglitazone 30 mg or rosiglitazone 4 mg in addition to glimepiride 2 mg. Compared to the baseline values, the mean fall in the FPG and PPG levels was significant at week 12 in both groups ($P < 0.05$), without significant differences between the two groups. HbA_{1c} levels also decreased significantly in the two groups of patients ($P < 0.05$), with no significant inter-group difference. However, 37.9% of patients in the pioglitazone group and 17.8% in the rosiglitazone group had $HbA_{1c} < 7.0\%$ at the end of the study.

Lipid profile parameters showed significant differences between the two groups. Pioglitazone gave a better decrease of total cholesterol (TC) compared to rosiglitazone and the difference between the two groups was significant ($P = 0.004$). Triglycerides (Tg) decreased significantly ($P = 0.0006$) in the pioglitazone group in comparison to the rosiglitazone group ($P = 0.255$) at 12 weeks with a P value of 0.002. LDL-cholesterol (LDL-C) also showed a significant decrease ($P = 0.005$) at the end of the study in the pioglitazone group, compared to the rosiglitazone group. HDL-cholesterol (HDL-C) increased non-significantly ($P = 0.83$) in the pioglitazone group as compared to the rosiglitazone group, in which there was a decrease in the HDL-C levels ($P = 0.03$). However, the inter-group change in the HDL-C levels was not statistically significant ($P > 0.05$).

Systolic, and diastolic blood pressure in patients in the pioglitazone group and the rosiglitazone group showed a non-significant decrease ($P = 0.079$ and $P = 0.32$, respectively), without significant differences between the two groups, probably because the patients in the present study were not hypertensive, and that could be the reason for a non-significant fall in their blood pressure. There was a body weight increase in the two groups, but the difference between the two groups was not significant ($P = 0.10$).

Derosa et al[17] evaluated the effects of a fixed dose of 4 mg/day glimepiride plus 15 mg/day of pioglitazone or 4 mg/day of rosiglitazone for 12 months. After 9 and 12 months, there were significant decreases of HbA_{1c}, mean FPG, PPG, FPI, and PPI in both treatment groups ($P < 0.05$ at 9 months and $P < 0.01$ at 12 months for all parameters). Furthermore, homeostasis model assessment index (HOMA index) improvement was obtained at 9 and 12 months ($P < 0.05$ and $P < 0.01$, respectively) in both groups. Significant SBP and DBP improvements ($P < 0.05$, respectively) were observed in both groups after 12 months, even if the antihypertensive effect of thiazolidinediones appears to be mainly related to the decrease in insulin-resistance and the consequent improvement of endothelial function. A significant BMI increase was present after 12 months compared to the baseline ($P < 0.05$) in both groups, without any differences between the two groups. No cardiovascular events were reported.

Roberts et al[24] evaluated the addition of glimepiride titrated sequentially from 2 to 4 to 8 mg/day over 6 weeks, followed by 20 weeks of maintenance therapy or placebo in combination with an established regimen of metformin and rosiglitazone 8 mg or pioglitazone 45 mg. The majority of patients (62.2%) who received glimepiride achieved a HbA_{1c} value of ~7%, compared with 26.0% of patients receiving placebo ($P < 0.001$ between groups). At the end, the adjusted mean differences between treatments

significantly favoured the glimepiride combination in terms of FPG (–37.4 ± 4.0 mg/dL, $P < 0.001$), FPI (4.06 ± 1.69 pIU/mL, $P < 0.03$), and C-peptide (124.5 ± 35.9 pmol/L, $P < 0.001$). The adjusted mean changes in body mass index from baseline to the end were 1.26 ± 0.16 kg/m^2 with glimepiride and 0.17 ± 0.16 kg/m^2 with placebo ($P < 0.001$). Similarly, the mean change in weight was greater with glimepiride than with placebo (3.76 ± 0.54 vs. 0.45 ± 0.52 kg, $P < 0.001$). There were no significant differences in lipid levels between groups. Notwithstanding the study limitations such as the relatively small patient population and short duration of treatment, the findings of this study suggest that the addition of a drug having a different mechanism of action may improve glycemic control in patients with T2DM.

Pfutzner et al[25] compared the effects of 3 mg/day of glimepiride + placebo (group 0), 3 mg/day of glimepiride + 4 mg rosiglitazone (group 4), 3 mg/day of glimepiride + 8 mg rosiglitazone (group 8) after 0 and 16 weeks of treatment. Substantial and significant dose-dependent improvements were observed after the addition of rosiglitazone for FPG (group 0: –9 ± 48 mg/dL; group 4: –38 ± 47 mg/dL; group 8: –46 ± 53 mg/dL), HbA_{1c} (–0.1% ± 0.7%, –1.1% ± 1.2%, –1.3% ± 1.2%), FPI (+1.4 ± 6.2, –1.2 ± 5.3, –3.7 ± 9.9 μU/mL), intact proinsulin (+1.6 ± 7.1, –2.0 ± 4.6, –3.1 ± 6.1 pmol/L), and high-sensitivity C-reactive protein (+0.2 ± 2.6, –1.7 ± 3.5, –2.1 ± 3.5 mg/L). After adjustment for changes in body weight, significant increases in adiponectin were detected with rosiglitazone, whereas glimepiride alone did not induce a comparable effect (–0.5 ± 5.8, +8.8 ± 22.9, +14.3 ± 19.9 mg/L). The number of insulin-resistant patients decreased in both rosiglitazone treatment groups, whereas no change was seen with glimepiride alone. Next to the reported effects on glucose control, rosiglitazone provided an additional beneficial effect on insulin resistance, β-cell function, and cardiovascular risk markers. In this study, addition of rosiglitazone to an underlying sulphonylurea treatment resulted in additional β-cell protective and anti-inflammatory therapeutic effects and an overall improvement of long-term glycemic control. These results are in line with the current knowledge on thiazolidinedione effects in vitro and in animal experiments. However, this study also shows that rosiglitazone is able to completely prevent the negative effects of sulphonylurea drugs on β-cell dysfunction, insulin resistance, and cardiovascular risk markers in a dose-dependent fashion.

Orbay et al[26] conducted a study to determine the efficacy and safety of adding rosiglitazone 4 mg to a combination of glimepiride 6 mg and metformin 1700 mg therapy with insufficiently controlled T2DM for 26 weeks. Mean HbA_{1c} levels decreased significantly from 7.54 ± 0.9% to 6.57 ± 0.7% ($P < 0.001$) at the 26th week. FPG levels fell from 169.39 ± 37.8 mg/dl to 135.69 ± 28.0 mg/dl ($P < 0.001$), respectively. Insulin levels decreased from 19.60 ± 9.8 U/L to 14.66 ± 11.6 U/L ($P = 0.026$) at the 26th week. Regarding adverse events, oedema was detected in 3% of patients, and there was a statistically significant increase of BMI from baseline to the end of the study.

Chou et al[27] assessed the efficacy and safety of two different dosing regimens of fixed-dose combination rosiglitazone 4 plus glimepiride 4/4 mg/day or 8/4 mg/day compared with 8 mg of rosiglitazone or 4 mg of glimepiride monotherapy in drug-naive subjects with T2DM. Both rosiglitazone plus glimepiride regimens improved HbA_{1c} (–2.4 ± 1.4% with rosiglitazone 4 mg plus glimepiride 4 mg and –2.5 ± 1.4% with rosiglitazone 8 mg plus glimepiride 4 mg) to a greater extent than rosiglitazone (–1.8 ± 1.5%) or glimepiride (–1.7 ± 1.4%) monotherapy ($P < 0.0001$ vs. both rosiglitazone and glimepiride). Significantly more subjects achieved HbA_{1c} target levels of ≤6.5 and <7% with either rosiglitazone plus glimepiride regimen compared with rosiglitazone or glimepiride alone ($P < 0.0001$ for both comparisons). Similarly, a significantly greater reduction in FPG levels was observed in subjects treated with rosiglitazone plus glimepiride (–69.5 ± 57.5 mg/dl with rosiglitazone 4 mg plus glimepiride 4 mg; –79.9 ± 56.8 with rosiglitazone 8 mg plus glimepiride 4 mg) compared with rosiglitazone (–56.6 ± 58.1) or glimepiride (–42.2 ± 66.1) monotherapy ($P < 0.0001$ for both comparisons). Improvement in C-reactive protein was also observed in subjects who were treated with rosiglitazone plus glimepiride or rosiglitazone monotherapy compared to glimepiride monotherapy. Rosiglitazone plus glimepiride was generally well tolerated, with no new safety or tolerability issues identified from its monotherapy components, and a similar adverse events profile was observed across regimens. The most commonly reported adverse event was hypoglycemia, and the incidence of confirmed

symptomatic hypoglycemia (3.6%–5.5%) was comparable among subjects treated with rosiglitazone plus glimepiride and glimepiride monotherapy. A possible limitation of this study is the relatively short duration of 28 weeks. Long-term safety and efficacy for T2DM patients must therefore be inferred from longer term combination studies. In addition, the high baseline HbA_{1c} values seen in this study population favours a significant treatment difference with combination therapy over monotherapy and may also make differentiation of combination therapy and glimepiride monotherapy difficult when looking at hypoglycemia.

McCluskey et al[28] enrolled 40 patients who failed on rosiglitazone monotherapy and treated them with additional glimepiride vs. placebo for 26 weeks. The outcomes were greater reductions for the glimepiride vs. the placebo combination in HbA_{1c} ($-1.2\% \pm 0.1\%$ vs. $-0.3\% \pm 2\%$, $P < 0.001$) and FPG (-24.4 ± 6.0 mg/dL vs. 5.9 ± 8.0 mg/dL, $P < 0.01$). More patients in the glimepiride group achieved the HbA_{1c} target of $\leq 7\%$ (60% vs. 14%, $P < 0.01$). Regarding lipid profile, no significant differences were observed compared to baseline, or in group to group comparison. There were no significant differences in the rate or type of adverse events between groups, and no episodes of severe hypoglycemia occurred with either treatments.

Discussion

All the studies reported above (Table 1) showed that the combination of rosiglitazone plus glimepiride gives an improvement of glycemic control, even if a little weight is gained. However we have already reported that the weight increase obtained with thiazolidinediones may be partly due to fluid retention,[19] but mainly because of the deposition of subcutaneous adipose tissue, consistent with the mode of action of thiazolidinediones.[29] Although visceral adipose tissue also expresses PPAR-γ, this depot appears little affected by thiazolidinediones therapy; whether the continuously high turnover of this depot reduces the influence of a thiazolidinedione is not clear.[29] Because visceral adipose tissue is cited as a source of greater vascular risk than subcutaneous adipose tissue, the increase in the latter (but not the former) is believed to minimize any specific threat to cardiovascular disease.[30] Furthermore the association of rosiglitazone and glimepiride give also an improvement of FPI: we already showed that thiazolidinediones gave an improvement of insulin resistance and insulin sensitivity parameters not reported with sulphonylureas.[20] It is conceivable that the reduction in demand for insulin secretion due to chronic insulin resistance by thiazolidinediones greatly decreased the excess stimulation of β-cells to release insulin.

Despite its proven effectiveness, however, since 2005 an increasing worrying regarding the possible differences between rosiglitazone and pioglitazone in terms of cardiovascular risk started rising.[31,32] In that period, in fact the data from the DREAM study (Diabetes REduction Assessment with Ramipril and Rosiglitazone Medication) showed that patients who

Table 1. Effects of rosiglitazone plus glimepiride on body weight and glycemic profile.

Author last name	Duration months	Weight (Kg)	FPG Mg/dl	FPI µU/ml	HbA_{1c} %	ROSI (mg)	GLIM (mg)
Kiayias (2002)	5	+4.2	–32.4°	/	–1.1***	4	6
Kiayias (2002)	5	+4.6	–52.2°	/	–1.4°	8	6
Chogtu (2009)	3	/	–32 mg/dL*	/	–0.4*	4	2
Derosa (2005)	12	+4.1*	–31**	–10.8**	–1.3**	4	4
Roberts (2005)	6.5	/	–37.4***	+4.06	–1.31***	8	8
Pfutzner (2006)	4	/	–39.6***	–1.2	–1.2***	4	3
Pfutzner (2006)	4	/	–46.8***	–3.7*	–1.3***	8	3
Chou (2008)	7	/	–69.5+	/	–2.4+	4	4
Chou (2008)	7	/	–79.9+	/	–2.5+	8	4
Orbay (2004)	6.5	+1.21 (BMI)***	–33.7***	–4.94**	–0.97***	4	6
McCluskey (2004)	7.5	+5.1+	–24.4*		–1.2*	4/8	4/8

Notes: *$P < 0.05$ vs. baseline; **$P < 0.01$ vs. baseline; ***$P < 0.001$ vs. baseline; °$P < 0.0001$ vs. baseline; +P vs. baseline not given; ROSI plus GLIM data are reported as Δ compared to baseline values.
Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HbA_{1c}, glycated hemoglobin; ROSI, rosiglitazone; GLIM, glimepiride.

received rosiglitazone were numerically more likely to have cardiovascular events, including heart failure, myocardial infarction, stroke, angina, receipt of revascularization, or cardiac death, than those who received placebo, even if the differences in rates did not reach statistical significance.[33]

This was confirmed by the study ADOPT (A Diabetes Outcome and Progression Trial): patients who received rosiglitazone were numerically more likely to have cardiovascular adverse events, including myocardial infarction, congestive heart failure, and stroke.[34] The RECORD study (Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes), instead, showed no increase in overall cardiovascular morbidity or mortality associated with the use of rosiglitazone.[35] Moreover Nissen's meta-analysis confirmed an increased risk for myocardial infarction,[36] although not for cardiovascular disease or all-cause mortality with rosiglitazone suggesting an unfavourable benefit to risk ratio for rosiglitazone. On the basis of these data, on 23rd September 2010, during the annual EASD (European Association of the Study of Diabetes) congress in Stockholm, the EMA has recommended the suspension of diabetes drug rosiglitazone from the market in Europe. The statement by the EMA says that they now believe the "benefits of rosiglitazone no longer outweigh its risks", pointing to new studies that support an increased cardiovascular risk.

In the United States, on the other side, the US Food and Drug Administration (FDA) has recommended a package of measures to try to determine the safety of the drug and further restrict its use.

So, what to do now? Given the good results obtained by a combination of glimepiride and rosiglitazone, the most obvious choice should be substitute rosiglitazone with pioglitazone.[37] We have already conducted several studies about the combination of pioglitazone and glimepiride, in particular we evaluated the effects of glimepiride 4 mg/die combined with pioglitazone 15 mg or rosiglitazone 4 mg for 1 year. At the end of the year, both treatment groups had significant increases from baseline in BMI (4.9% glimepiride plus pioglitazone, 6.2% glimepiride plus rosiglitazone; $P < 0.05$). Both treatments gave an improvement of glycemic control, but pioglitazone group had also significant improvements from baseline in TC (–11.1%), LDL-C (–12.0%), HDL-C (15.0%), and Tg (22.4%) ($P < 0.05$ for all). The change from baseline in Lp(a) was significant in the pioglitazone group, both relative to baseline and compared with the rosiglitazone group (–19.7% vs. 0.5%, respectively; $P < 0.05$ vs. baseline and vs. rosiglitazone). Changes from baseline in homocysteine were significant in both the pioglitazone and rosiglitazone group (–20.2% and –25.0%, respectively; $P < 0.05$).[38]

We have also conducted a review[21] about the potential benefits of combining pioglitazone plus glimepiride on patient compliance, targeting the dual effects of insulin resistance and β-cell dysfunction and affecting a number of metabolic and cardiovascular parameters. These two therapies act synergistically to treat T2DM: glimepiride therapy achieves rapid reductions in HbA_{1c}, whereas pioglitazone sustains glycemic control in the longer term. In addition to glucose-lowering efficacy and a favourable efficacy/safety profile, the combination of pioglitazone and glimepiride provides a host of pleiotropic effects with potentially beneficial metabolic consequences. Pioglitazone, in particular, has beneficial effects on the atherogenic lipid profile that is often seen in diabetes, an effect that is significantly greater than that seen with rosiglitazone[39,40] or other oral agents.[41–43] In addition, pioglitazone also improves a number of atherosclerotic risk markers that appear to translate into clinical benefits on macrovascular outcomes. Glimepiride may also improve several atherosclerotic risk markers and lipoproteins.

The cardiovascular safety profile of pioglitazone, has also been investigated with the PROactive study, the only large treatment trial specifically designed a priori to examine the cardiovascular endpoints in diabetic patients treated with pioglitazone.[44] A total of 5238 patients with T2DM and macrovascular disease were enrolled and randomized to receive either pioglitazone (15 to 45 mg daily) or placebo, while continuing existing therapies with glucose-lowering agents, lipid-lowering medications, and antihypertensives. The primary endpoint was the composite of all-cause mortality, nonfatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. The Authors concluded that pioglitazone reduces the composite of all-cause

mortality, non fatal myocardial infarction, and stroke, in patients with T2DM who have a high risk of macrovascular events.

Conclusion

Even if a combination of rosiglitazone and glimepiride proved to be effective on glycemic control, and in improving fasting plasma insulin, it is not an option available anymore, due to the recent withdrawn of rosiglitazone. Other possibilities should be considered, for example, substitute rosiglitazone with pioglitazone. In this way we can maintain all the positive effects of thiazolidinediones without the additive risk of cardiovascular events linked to rosiglitazone.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors certify that they have no affiliation with, or financial involvement in, any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript.

The peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

References

1. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. *N Engl J Med*. 2008;359(15):1577–89.
2. Liebl A, Mata M, Eschwege E. Evaluation of Risk Factors for Development of Complications in Type II Diabetes in Europe. *Diabetologia*. 2002; 45:S23–8.
3. Saydah SH, Fradkin J, Cowie CC. Poor Control of Risk Factors for Vascular Disease among Adults with Previously Diagnosed Diabetes. *JAMA*. 2004;291:335–42.
4. Canadian Diabetes Association, Clinical Practice Guidelines Expert Committee: Canadian Diabetes Association. Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes*. 2003;27(Suppl 2):S1–152.
5. Pfützner A, Wilhelm B, Forst T. Rosiglitazone and Glimepiride: Review of Clinical Results Supporting a Fixed Dose Combination. *Vasc Health Risk Manag*. 2007;3(2):211–20.
6. McCall AL. Clinical Review of Glimepiride. *Expert Opin Pharmacother*. 2001;2:699–713.
7. Kersten S, Desvergne B, Wahli W. Roles of PPARs in Health and Disease. *Nature*. 2000;405:421–4.
8. Schoonjans K, Auwerx J. Thiazolidinediones: an Update. *Lancet*. 2000; 355:1008–10.
9. Wagstaff AJ, Goa KL. Rosiglitazone: a Review of its Use in the Management of Type 2 Diabetes Mellitus. *Drugs*. 2002;62:1805–37.
10. Elbrecht A, Chen Y, Cullinan CA, et al. Molecular Cloning, Expression and Characterization of Human Peroxisome Proliferator Activated Receptors Gamma 1 and Gamma 2. *Biochem Biophys Res Commun*. 1996;224: 431–7.
11. Spiegelman BM. PPAR-gamma: Adipogenic Regulator and Thiazolidinedione Receptor. *Diabetes*. 1998;47:507–14.
12. Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA. An Antidiabetic Thiazolidinedione is a High Affinity Ligand for Peroxisome Proliferator-Activated Receptor Gamma. *J Biol Chem*. 1995;270:12953–6.
13. Saltiel AR, Olefsky JM. Thiazolidinediones in the Treatment of Insulin Resistance and Type 2 Diabetes. *Diabetes*. 1996;45:1661–9.
14. Young PW, Cawthorne MA, Coyle PJ. BRL 49653C Normalizes Glycemic Control in Zucker Fatty fa/fa Rats by Improving Hepatic and Peripheral Tissue Sensitivity to Insulin. *Diabetologia*. 1993;36:A184.
15. Derosa G, Salvadeo SAT, D'Angelo A, et al. Rosiglitazone Therapy Improves Insulin Resistance Parameters in Overweight and Obese Diabetic Patients Intolerant to Metformin. *Arch Med Res*. 2008;39:412–9.
16. Derosa G, Fogari E, Cicero AF, et al. Blood Pressure Control and Inflammatory Markers in Type 2 Diabetic Patients Treated with Pioglitazone or Rosiglitazone and Metformin. *Hypertens Res*. 2007;30(5):387–94.
17. Derosa G, Cicero AFG, D'Angelo A, et al. Thiazolidinedione Effects on Blood Pressure in Diabetic Patients with Metabolic Syndrome Treated with Glimepiride. *Hypertens Res*. 2005;28:917–24.
18. Derosa G, Cicero AF, Gaddi A, et al. Metabolic Effects of Pioglitazone and Rosiglitazone in Patients with Diabetes and Metabolic Syndrome Treated with Glimepiride: a Twelve-Month, Multicenter, Double-Blind, Randomized, Controlled, Parallel-Group Trial. *Clin Ther*. 2004;26(5):744–54.
19. Derosa G, Tinelli C, Maffioli P. Effects of Pioglitazone and Rosiglitazone Combined with Metformin on Body Weight in People with Diabetes. *Diabetes Obes Metab*. 2009;11:1091–9.
20. Derosa G, Maffioli P. Effects of Thiazolidinediones and Sulfonylureas in Patients with Diabetes. *Diabetes Technol Ther*. 2010;12(6):491–501.
21. Derosa G. Pioglitazone plus Glimepiride: a Promising Alternative in Metabolic Control. *Int J Clin Pract Suppl*. 2007;153:28–36.
22. Kiayias JA, Vlachou ED, Theodosopoulou E, Lakka-Papadodima E. Rosiglitazone in Combination with Glimepiride plus Metformin in Type 2 Diabetic Patients. *Diabetes Care*. 2002;25(7):1251–2.
23. Chogtu B, Singh NP, Chawla S, Gupta U. Impact of Glitazones on Metabolic and Haemodynamic Parameters in Patients with Type 2 Diabetes Mellitus. *Singapore Med J*. 2009;50(4):395–9.
24. Roberts VL, Stewart J, Issa M, Lake B, Melis R. Triple Therapy with Glimepiride in Patients with Type 2 Diabetes Mellitus Inadequately Controlled by Metformin and a Thiazolidinedione: Results of a 30-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study. *Clinical Therapeutics*. 2005;27(10):1535–47.
25. Pfutzner A, Schfndorf T, Seidel D, et al. Impact of Rosiglitazone on Beta-Cell Function, Insulin Resistance, and Adiponectin Concentrations: Results from a Double-Blind Oral Combination Study with Glimepiride. *Metabolism Clin Exper*. 2006;55:20–5.
26. Orbay E, Sargin M, Sargin H, Gözü H, Bayramiçli OU, Yayla A. Addition of Rosiglitazone to Glimepiride and Metformin Combination Therapy in Type 2 Diabetes. *Endocr J*. 2004;51:521–7.
27. Chou HS, Palmer JP, Jones AR, et al. Initial Treatment with Fixed-Dose Combination Rosiglitazone/Glimepiride in Patients with Previously Untreated Type 2 Diabetes. *Diabetes Obes Metab*. 2008;10(8):626–37.
28. McCluskey D, Touger MS, Melis R, Schleusener DS, McCluskey D. Results of a Randomized, Double-Blind, Placebo-Controlled Study Administering Glimepiride to Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Rosiglitazone Monotherapy. *Clin Ther*. 2004;26: 1783–90.
29. Katoh S, Mori Y, Yokoyama J. Effect of Oral Hypoglycaemic Agents on Fat Distribution and Glucose Tolerance in Non-Insulin-Dependent Diabetes Mellitus Patients. *J Jpn Diabetes Soc*. 1998;41:289–93.
30. Diamant M, Heine R. Thiazolidinediones in Type 2 Diabetes Mellitus: Current Clinical Evidence. *Drugs*. 2003;63:1373–405.

31. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of Rosiglitazone on the Frequency of Diabetes in Patients with Impaired Glucose Tolerance or Impaired Fasting Glucose: a Randomised Controlled Trial. *Lancet*. 2006;368:1096–105.
32. Kahn SE, Haffner SM, Heiase MA; ADOPT Study Group. Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. *N Engl J Med*. 2006;355:2427–43.
33. Barnett AH. Redefining the Role of Thiazolidinediones in the Management of Type 2 Diabetes. *Vasc Health Risk Manag*. 2009;5:141–51.
34. Bloomgarden ZT. The Avandia Debate. *Diabetes Care*. 2007;30:2401–8.
35. Home PD, Pocock SJ, Beck-Nielsen H; RECORD Study Team. Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD): a Multicentre, Randomised, Open-Label Trial. *Lancet*. 2009;373:2125–35.
36. Nissen SE, Wolski K. An Updated Meta-Analysis of Risk for Myocardial Infarction and Cardiovascular Mortality. *N Arch Intern Med*. 2010;10.1001/archinternmed.2010.207.
37. Derosa G. Efficacy and Tolerability of Pioglitazone in Patients with Type 2 Diabetes Mellitus: Comparison with Other Oral Antihyperglycaemic Agents. *Drugs*. 2010;70(15):1945–61.
38. Derosa G, Cicero AFG, D'Angelo, et al. Effects of 1 year of treatment with pioglitazone or rosiglitazone added to glimepiride on lipoprotein (a) and homocysteine concentrations in patients with type 2 diabetes mellitus and metabolic syndrome: a multicenter, randomized, double-blind, controlled clinical trial. *Clin Ther*. 2006;28(5):679–88.
39. Shinall S, Buse J, Tan M, et al. Glycemic and lipid effects of pioglitazone and rosiglitazone in patients naıve to oral antidiabetic medications. *Diabetologia*. 2006;49:703–4.
40. Goldberg RB, Kendall DM, Deeg MA, et al. GLAI Study Investigators. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care*. 2005;28:1547–54.
41. Pavo I, Jermendy G, Varkonyi TT, et al. Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2003;88:1637–45.
42. Schernthaner G, Matthews D, Charbonnel B, et al. Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial. *J Clin Endocrinol Metab*. 2004;89:6068–76.
43. Korytkowski M. Sulfonylurea treatment of type 2 diabetes mellitus: focus on glimepiride. *Pharmacotherapy*. 2004;24:606–20.
44. Dormandy JA, Charbonnel B, Eckland DJ; PROactive investigators. Secondary Prevention of Macrovascular Events in Patients with Type 2 Diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a Randomised Controlled Trial. *Lancet*. 2005;366(9493):1279–89.