The COMPACT-Study: Pioglitazone vs. standard oral antidiabetic agents for treatment of patients with type-2-diabetes mellitus - focus on metabolic effectiveness

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INTRODUCTION

Pioglitazone (PIO), a peroxisome proliferator-activated receptor (PPAR)-γ agonist, is a member of a class of oral antidiabetic agents targeted to treat insulin resistance, the major underlying cause of type-2-diabetes mellitus. Metformin and Sulfonylurea represent both the established classes of most commonly used oral antidiabetic drugs (OAD). Combination therapy of Metformin and Sulfonylurea is the most frequently used approach in patients insufficiently controlled under monotherapy with a single agent.

Several large randomized long-term studies revealed a more sustained and durable HbA_{1C} reduction with PIO compared to Gliclazide and Metformin, respectively [2, 4, 6, 7, 8]. In addition by improving insulin resistance PIO significantly lowers elevated fasting and post-challenge insulin levels [9]. Compared to Metformin as well as Gliclazide PIO leads to an improved glucose profile during a standard OGTT [1] which is sustained for up to 104 weeks. Diabetic dyslipidaemia is increasingly recognised as an important risk factor contributing to the massively excess cardiovascular risk in patients with type-2-diabetes mellitus (T2DM). PIO has consistently shown to offer unique benefits in improving dyslipidaemia - such as decrease of fasting and postprandial triglycerides, small-dense-LDL-particle and free fatty acids combined with a marked increase of HDL-cholesterol [3, 10, 11]. This study is aimed to compare both treatment options in dual combination therapy under the conditions of daily practice with regard to metabolic control.

DESIGN AND METHODS

- Prospective, controlled, nonrandomised, nonintervention comparison of treatment cohorts in a primary care setting
- Study centers: 51 diabetes specialist practices
- Patient selection, allocation to treatment, and dose left to physician discretion
- Study participants assigned to one of the following treatment groups: PIO (oral combination on top of Metformin monotherapy, 209 patients) or OAD (130 patients: 118 Sulfonylurea introduced on top of Metformin monotherapy; 3 Metformin without Sulfonylurea; 9 Sulfonylurea without Metformin)
- Study duration/Observation period (April 2001 to October 2002): 24 weeks
- Primary target parameter: change in HbA_{1C} compared with that at baseline, as measured in a central laboratory by cation exchange high-performance liquid chromatography (coefficient of variance: <2%; reference range: 3.4%-6%). All other laboratory values were measured also centrally with commercially available assays.
- The Metabolic Syndrome was defined according to the ATP III criteria issued by the NCEP.

ENTRY CRITERIA

Inclusion

- Patients with T2DM
- HbA_{1C} between 6.5% and 10.0%, with diabetes treatment considered unsatisfactory

Exclusion

- Serum alanine aminotransferase or aspartate aminotransferase greater than 2.5 times the upper limit of normal
- Congestive heart failure

Contraindications of medication were taken into account.

STATISTICAL METHODS AND DATA HANDLING

All data were entered into a relational database and analysed with SPSS version 10.0. A 1-sided test after an analysis of variance-covariance with baseline values as covariate was performed (ie, testing was conducted on adjusted mean HbA_{1C} values). The noninferiority bound for HbA_{1C} changes was defined as 0.5% point.

The analysis was based on the data set of patients with complete observations. Data are presented as means and their standard deviation and 95% confidence intervals, respectively.

Vascular risk was assessed according to the IDF-categories.

Quality standards included:

- External monitoring and on-site audits to ensure quality of data
- Plausibility and completeness check of obligatory parameters

SUMMARY OF RESULTS

Parameter	PIO	OAD
Total number of patients	209	130
Male (%)	56%	48%
Age at beginning (yrs), mean ± SD	59.58 ± 11.57	64.64 ± 11.43
Known diabetes duration (yrs), mean ± SD	8.69 ± 6.89	8.99 ± 7.86
Family history of diabetes (%)	49.76%	46.15%
Hypertension * (%)	62.2%	74.2%
Dyslipidaemia (%)	55.5%	53.8%

** Hypertension defined according to German guidelines as blood pressure higher than 140/90 mmHG*

Table 1: Demographic Data at Baseline

Parameter [mean ± SD]	PIO	OAD
HbA_{1C} (%)	7.91 ± 0.89	7.81 ± 0.89
Fasting glucose (mg/dl)	160.0 ± 43.16 (n=185)	162.1 ± 42.5 (n = 110)
Postprandial glucose (mg/dl)	195.95 ± 54.5 (n=143)	197.1 ± 59.7 (n= 81)
Triglycerides (mg/dl)	263.1 ± 194.5	234.6 ± 150.6
HDL-cholesterol (mg/dl)	40.1 ± 12.8	40.3 ± 12.1

Table 2: Baseline Data of Metabolic Control

Also for concomitant medication and diseases as well as complications both groups revealed no significant differences (data not shown).

Parameter (Mean ± SD), [95%CI]	PIO	OAD
Δ HbA_{1C} (%)	-0.70 (+/- 0.998) [-0,839; -0,566]	-0.53 (+/- 1.003) [-0.702; -0,356]
Δ Fasting Glucose (mg/dl)	-24.5 (+/- 48.48) [-30.20; -18.81]	-19.6 (+/- 50.76) [-26.96; -12.21]
Δ postprandial Glucose (mg/dl)	-40,9** (+/- 51.01) [-47.88; -33.93]	-21.7** (+/- 70.12) [-31.26; -12.09]
Δ Fasting Triglycerides (mg/dl)	-57.1** (+/- 136.07) [-72.95; -41.29]	-20.9* (+/- 146.92) [-40.95; -0.88]
Δ HDL-Cholesterol (mg/dl)	+4.6* (+/- 11.18) [+3.36; +5.76]	+2.2* (+/- 8.82) [+0.68; +3.72]
Δ HbA_{1C} (%) Metabolic Syndrome. (ATP III, NCEP)		
■ yes	- 0.74 (+/- 1.004) [-0.90; -0.58]	- 0.58 (+/- 1.209) [-0.78; -0.38]
■ no	- 0.46 (+/- 1.015) [-0.81; -0.12]	- 0.30 (+/- 1.120) [-0.69; -0.09]

** p < .05 (Δ values PIO vs. OAD)* *** p < .01 (Δ values PIO vs. OAD)*

Glucose Control

- PIO was noninferior to OAD with regard to lowering HbA_{1C} and fasting glucose
- PIO effectively reduced postprandial glucose excursions
- There was a trend (p = 0.06) for a better HbA_{1C} response in patients having the Metabolic Syndrome compared to those not fulfilling the ATP III criteria

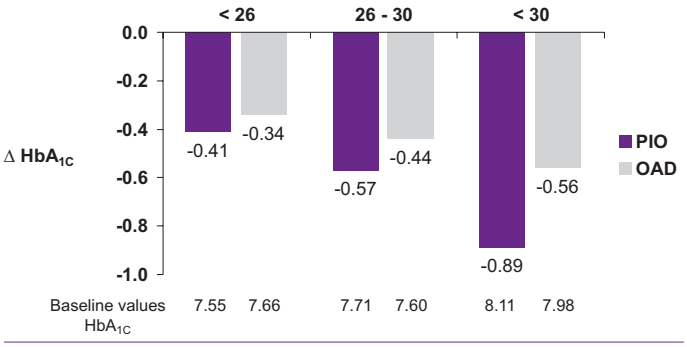

Figure 1: HbA_{1C} Reduction According to BMI Clusters

Lipid Control

- PIO significantly reduced fasting triglyceride levels and increased levels of HDL-cholesterol compared to OAD treatment
- The effect on both parameters was nearly twice as strong in the PIO group. It was also much more robust reflected by the range of the confidence interval.

Risk for Vascular Complications

The impact of the beneficial changes in triglycerides and HDL-cholesterol according to IDF-categories for vascular risk is illustrated in figures 2 and 3.

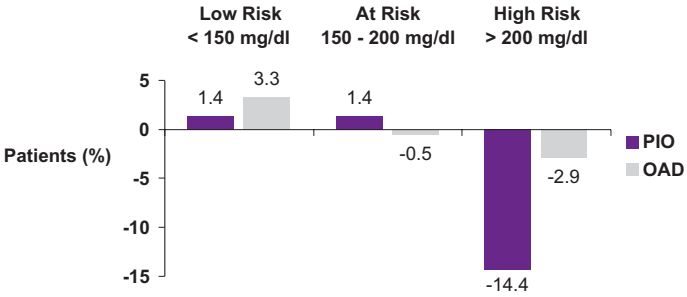

Figure 2: Triglycerides - Changes in IDF-Risk Categories

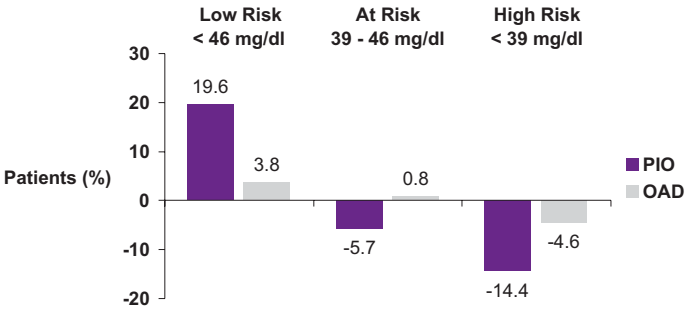

Figure 3: HDL-Cholesterol - Changes in IDF-Risk Categories

CONCLUSIONS

PIO proved to be noninferior to OAD treatment with regard to HbA_{1C} reduction but reveals additional benefits in terms of extended metabolic control over a treatment period of 24 weeks. Although the present study is observational and cannot control for confounders relevant baseline data showed a similar data revealing any significant result between both treatment groups. Therefore a clinical relevant bias towards the PIO group seems unlikely. The study results confirm the results of large randomized clinical trials demonstrating advantages for PIO compared to Sulfonylurea and Metformin in terms of improving diabetic dyslipidaemia and postprandial hyperglycaemia. The latter may be the result of markedly improved hepatic insulin sensitivity reported with PIO [5]. PIO offers benefits for a broader metabolic control. This holds true especially in more obese patients or with a diagnosis of the Metabolic Syndrome suggesting a higher degree of insulin resistance compared to those not fulfilling the criteria. Improvements in dyslipidaemia may be relevant for amelioration of cardiovascular prognosis by PIO highlighted by impressive shifting of patients from high to low risk categories.

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