

RAPID APPRAISAL

Name of Trial: Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: The PERISCOPE randomised controlled trial.

Reference: Nissen SE, Nicholls, SJ, Wolski K et al. JAMA 2008;299:1561-73

Question: Does treatment with pioglitazone result in a lower rate of coronary atherosclerosis progression in patients with type 2 diabetes and coronary artery disease compared with glimepiride?

Summary: The results of this study indicate that, after treatment for 18 months, the rate of coronary atherosclerosis progression in patients with type 2 diabetes and mild coronary atherosclerotic disease was slower in pioglitazone- than glimepiride-treated patients. The primary end point was the change from baseline to study completion in percent atheroma volume (PAV - a surrogate marker for atherosclerosis progression) which increased in the glimepiride group by 0.73% (95% CI 0.33% to 1.12%, $p < 0.001$) compared with a non-significant reduction of 0.16% in the pioglitazone group (95% CI -0.57% to 0.25%, $p = 0.44$). Although the difference between the two groups was significant, it was small (0.89%, $p = 0.002$) and its clinical significance is unclear. There is no evidence that it correlates to a difference in cardiovascular outcomes in this patient group.

Based on the results of this study, until further evidence of the effects of pioglitazone on cardiovascular mortality and morbidity is available, a change in prescribing practice is not recommended.

Did the study ask a clearly focussed question?

Yes – The study was designed to compare the progression of coronary atherosclerosis in patients with type 2 diabetes and coronary artery disease who were treated with pioglitazone (15 - 45 mg daily) or glimepiride (1 - 4 mg daily).

The primary end point was the change from baseline in percent atheroma volume (PAV) measured using intravascular ultrasound (IVUS) examination after 18 months of treatment.

Was the study design appropriate?

Yes – The study was a double-blind, multi-centre, randomised controlled trial ($n = 543$). Patients aged 35 to 85 years were eligible if they had a baseline glycosylated haemoglobin (HbA_{1c}) level of 6.0% to 9.0% if taking hypoglycaemic agents, or 6.5% to 10% if not receiving drug therapy. They were required to have coronary angiography performed for clinical indications that demonstrated ≥ 1 angiographic stenosis with $\geq 20\%$ but $< 50\%$ narrowing (i.e. relatively mild atherosclerosis).^{1, 2} Concurrent treatment with antidiabetic drugs other than glitazones, sulphonylureas or other insulin secretagogues was allowed.

Patients were excluded for the following reasons: type 1 diabetes, taking ≥ 3 antidiabetic drugs, use of a glitazone within the past 12 weeks, serum creatinine level > 2.0 mg/dL, triglycerides > 500 mg/dL, uncontrolled hypertension, or liver disease.

This study was sponsored by Takeda Pharmaceuticals, manufacturers of pioglitazone (Actos®).

Were participants appropriately allocated to intervention and control groups?

Yes – Patients were randomly allocated to pioglitazone ($n = 270$) or glimepiride ($n = 273$) treatment, stratified according to diabetes treatment at the time of randomisation.

Titration to the maximum dose (pioglitazone 45 mg or glimepiride 4 mg daily) was performed over the first 16 weeks, where tolerated. The mean titrated daily doses were 37.4 mg and 2.9 mg, respectively. Metformin and/or insulin could be added or their doses could be increased to achieve the target HbA_{1c} level of $< 7.0\%$. If a patient experienced hypoglycaemic symptoms, other glucose-lowering therapies were reduced to maintain maximal study medication doses.

The baseline characteristics of both groups were similar. However, patients in the glimepiride group were more likely to have a history of hypertension than those in the pioglitazone group (92% vs 83%, $p=0.002$), although the baseline blood pressures were similar, and patients in the glimepiride group were more likely to be current smokers ($p = 0.01$). A high proportion of the study population was using concurrent medication for the prevention or treatment of coronary heart disease: aspirin (91%), beta-blockers (77%), ACE inhibitors or angiotensin-2 receptor blockers (ARBs; 82%), statins (82%). The percentages of patients on insulin and metformin at baseline in the two groups

did not differ significantly; no other details of antidiabetic drug use are given.

Were participants, staff and study personnel 'blind' to participants study group?

Yes – All staff and patients were unaware of treatment allocation. An independent committee adjudicated on adverse cardiovascular events.

Were all participants who entered into the trial accounted for at its conclusion?

Yes – All patients randomised to treatment were accounted for. Thirty-four percent of patients were not included in the efficacy analysis due to absent or unanalysable IVUS examinations. This resulted in a high drop-out rate of 34% that was similar across the two treatment groups. The demographic and laboratory characteristics of those completing and not completing the study were reported to be similar (data not provided)¹

Were participants in all groups followed up and data collected in the same way?

Yes – All consenting patients, regardless of whether they continued to take study treatment, underwent a follow-up IVUS examination after 18 months of treatment, except those requiring cardiac catheterisation for a clinical indication between 12 and 18 months who had PAV measurements conducted at this point, and were not reassessed.

Was the study large enough?

Yes - A sample size of 440 patients, resulting in 330 evaluable patients, allowing for drop-outs, was estimated to provide 90% power at a two-sided α of 0.05 to detect a difference of 1.8%. During the study a higher than expected drop-out rate was observed (35% compared with the expected 25%) and therefore the sample size was increased to 540 patients.

How are the results presented and what is the main result?

The primary end point was the change in PAV from baseline, which increased in the glimepiride group by 0.73% (95% confidence interval [CI] 0.33% to 1.12%, $p < 0.001$). The pioglitazone group demonstrated a non-significant reduction of 0.16% (95% CI -0.57% to 0.25%, $p = 0.44$). The between-group difference was statistically significant, $p = 0.002$.

Prespecified secondary end points included the change in maximal atheroma thickness, which increased in the glimepiride group (+0.011 mm) and decreased in the pioglitazone group (-0.011 mm; between-group difference $p = 0.006$). Other secondary end points that did not differ significantly between the groups were: normalised

total atheroma volume and change in the most diseased 10-mm segment.

How safe were the regimens?

Overall, the incidences of serious adverse events in the two treatment groups were similar with only a few differing significantly (summarised in the table below).

Adverse effects differing significantly between the groups

Adverse event	Glimepiride (n = 273)	Pioglitazone (n = 270)	p
Hypoglycaemia	37.0%	15.2%	<0.001
Angina	12.1%	7.0%	0.05
Peripheral oedema	11.0%	17.8%	0.02
Bone fracture	0%	3.0%	0.004
Weight gain	1.6 kg	3.6 kg	<0.001
Haemoglobin decrease > 3g/dL	0.7%	4.1%	0.01
Serum urea nitrogen > 30 mg/dL	4.8%	10.7%	0.009

How precise are the results?

The results are confounded by the 34% drop-out rate, despite increased patient recruitment. To investigate this effect, a sensitivity analysis, in which values were imputed for each randomised patient not completing the study, was performed. The mean PAV changes in the glimepiride and pioglitazone groups were 0.64% (95% CI 0.23% to 1.05%) and -0.062% (95% CI -0.47% to 0.35%), respectively. The between-group difference for the primary end point was still significant, but the significance level was reduced ($p = 0.02$) compared with the results for the completers. No details are given, but the authors state that analysis of the primary end point adjusting for baseline differences in smoking did not significantly alter the results.

Can the results be applied to the local population?

Yes - This study was conducted in North and South American populations that were predominantly white (81%), male (67%), elderly (mean age 60 years) and obese (body mass index > 30).¹ However, the study results might not be applicable to other groups of patients that do not match these characteristics, e.g. patients of Asian origin. Patients in this study had mild coronary stenosis (20% to 50% narrowing), so the results cannot be extrapolated to patients with more severe coronary atherosclerotic disease, or to those without pre-existing coronary artery disease. In line with UK practice, the study patients were treated with standard medications for the prevention and treatment of coronary heart disease associated with type 2 diabetes (statins, aspirin, ACE inhibitors or ARBs, and beta-blockers).

Does treatment with pioglitazone result in a lower rate of progression of coronary atherosclerosis compared with glimepiride?

The results of this study indicate that, after treatment for 18 months, the rate of coronary atherosclerosis progression in patients with type 2 diabetes and mild coronary atherosclerotic disease was slower in pioglitazone- than glimepiride-treated patients. However, the difference between the changes in PAV (which is a surrogate marker for the progression of coronary artery disease) for the two groups was small (0.89%), and its clinical significance is unclear. This study has provided no evidence that it correlates to a difference in cardiovascular outcomes in this patient group. No significant differences between the two groups with respect to the frequencies of various individual and composite cardiovascular events (including cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, coronary or carotid revascularisation, hospitalisation for unstable angina or congestive heart failure) were reported, although the study was not powered to determine differences in clinical outcomes. However, these findings are in agreement with those of the PROactive trial, in which patients who had type 2

diabetes with evidence of macrovascular disease were treated with pioglitazone for nearly three years, which did not result in a significant reduction in the primary composite end point of death, MI, stroke revascularisation and amputation.³ As metformin has been shown to reduce the risk of diabetes-related death and prevent cardiovascular events in patients with type 2 diabetes,⁴ determining the effect of metformin, rather than glimepiride, on the PAV would have been of relevance.

There are issues concerning around the cardiovascular safety of glitazones. A meta-analysis demonstrated that rosiglitazone is associated with an increased risk of MI,⁵ whereas a meta-analysis of pioglitazone trials did not demonstrate an increased risk of cardiac ischaemia.⁶ Heart failure is a recognised risk with glitazones, and the MHRA has issued advice on the use of rosiglitazone and pioglitazone in patients with heart failure, and rosiglitazone in patients with ischaemic heart disease.⁷

Based on the results of the PERISCOPE study, until further evidence of effects of pioglitazone on cardiovascular mortality and morbidity is available, a change in prescribing practice is not recommended.

REFERENCES

1. Nissen S et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes. JAMA 2008;299:1561-73 (RCT)
2. Steg PG, Marre M. Does PERISCOPE provide a new perspective on diabetic treatment? JAMA 2008;299:1603-4 (E)
3. Dormandy JA et al. 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;366:1270-89 (RCT)
4. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854-65 (RCT)
5. Nissen SE and Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457-71 (MA)
6. Lincoff AM et al. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus. A meta-analysis of randomised trials. JAMA 2007;298:1180-88 (MA)
7. Medicines and Healthcare products Regulatory Agency. Rosiglitazone and pioglitazone: cardiovascular safety. Drug Safety Update December 2007; 1:5-6. <http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON2033216>

KEY: RCT - randomised controlled trial, E - editorial, MA - meta-analysis

Regional Drug and Therapeutics Centre (Newcastle)
Wolfson Unit, Claremont Place, Newcastle upon Tyne NE2 4HH
Tel: 0191 232 1525 Fax 0191 260 6192 E-mail: nyrdtc.di@ncl.ac.uk
www.nyrdtc.nhs.uk

NOT FOR COMMERCIAL USE