



## Important New Evidence Service In Partnership with The Centre for Medicines Optimisation at Keele University

ScriptSwitch<sup>™</sup> Rapid Update 3 – October 2017

### Type 2 Diabetes: Cardiovascular outcomes with pioglitazone versus sulfonylureas

A recently published multicentre randomised controlled trial ([TOSCA.IT](#)) of more than 3,000 people with type 2 diabetes who were inadequately controlled with metformin has found no significant difference in the incidence of cardiovascular events between treatment with a sulfonylurea and pioglitazone. Importantly, people with heart failure were excluded from the study, as glitazones are known to increase the risk of heart failure. The early discontinuation of this study after a median duration of nearly five years may have limited the long-term outcomes data associated with either treatment option.

**Reference:** Vaccaro O, Masulli M, Nicolucci A *et al.* [Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin \(TOSCA.IT\): a randomised, multicentre trial.](#) *Lancet Diabetes Endocrinology.* 2017. doi.org/10.1016/S2213-8587(17)30317-0

#### What do we know already?

- The NICE clinical guideline for the management of type 2 diabetes in adults ([NG28](#)) recommends that metformin should be offered as first-line treatment. Other blood glucose-lowering drugs (e.g. DPP-4 inhibitors, sulfonylureas, pioglitazone or SGLT-2 inhibitors) may be considered if initial drug treatment with metformin does not adequately control HbA<sub>1c</sub>, or if metformin is contraindicated or not tolerated. Recommendations on blood glucose lowering therapy are summarised in a treatment [algorithm](#).
- A [systematic review and meta-analysis](#) found that metformin is an appropriate first-line therapy for type 2 diabetes, given its relative safety and beneficial effects on HbA<sub>1c</sub> and cardiovascular mortality.
- Currently, there is some uncertainty about the best add-on treatment for patients whose glycaemia is inadequately controlled with metformin alone. NICE recommend an individualised approach to care, with drug choice based on effectiveness, safety, tolerability, the person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost.
- Although pioglitazone and sulfonylureas are commonly used when intensification of drug treatment is required, both are associated with notable [adverse effects](#) and data on cardiovascular outcomes are limited. The efficacy and safety of these drugs have not previously been compared in a long-term head- to-head RCT.

#### What does this evidence add?

- This multicentre, open-label, blinded endpoint RCT found that in people with type 2 diabetes, pioglitazone and sulfonylureas (mostly glimepiride or gliclazide) as add-on treatments to metformin were associated with similar rates of cardiovascular events and clinically relevant side effects when used appropriately in terms of patient selection and dose.
- However, this study excluded patients with heart failure i.e. New York Heart Association (NYHA) class 1 or higher. In addition, the dose of pioglitazone was on average around half of the maximum recommended dose, and the rate of discontinuation of the study medications was significantly higher in those patients treated with pioglitazone.
- An acknowledged limitation within this study was that the incidence of the primary endpoint was lower than anticipated, giving a lower statistical power than planned.
- This study supports NICE recommendations for the management of blood glucose in those with type 2 diabetes. A person-centred approach to reduce CV risk and agreement on a manageable HbA<sub>1c</sub> target is central to this guidance.

## Study details

### Participants:

- Eligible participants were men and women aged 50 to 75 years, who had type 2 diabetes of at least two years duration and were on stable treatment with full dose metformin (2 to 3 g per day), had a HbA<sub>1c</sub> of 7 to 9% (53 to 75 mmol/mol), and a BMI of 20 to 45 kg/m<sup>2</sup>.
- Mean age of participants overall, and in both the treatment groups, was 62 years. At baseline, more participants in the pioglitazone group than the sulfonylurea group had a history of cardiovascular disease (12% vs. 10%), and were taking antiplatelet medicines (42% vs. 38%).
- Key exclusion criteria were acute cardiovascular events in previous six months, chronic heart failure (NYHA class 1 or higher) and a serum creatinine concentration greater than 132 µmol/L.

### Intervention and comparison:

- A multicentre, prospective, randomised, open label, blinded endpoint study conducted across 57 diabetes clinics in Italy.
- Metformin dose remained unchanged throughout the study. Add on medications could be titrated at the investigators' discretion as: pioglitazone 15 to 45 mg; glibenclamide 5 to 15 mg; gliclazide 30 to 120 mg; glimepiride 2 to 6 mg.
- Due to the observed event rate during follow-up being lower than expected, a futility analysis was conducted. On the basis of this, the study was discontinued in May 2017. This gave a median observation period of almost five years (57.3 months).
- The primary outcome was a composite of first occurrence of all-cause death, non-fatal myocardial infarction, non-fatal stroke or urgent coronary revascularisation, assessed in the modified intention-to-treat population (all randomly assigned participants with baseline data available and without any protocol violations in relation to inclusion or exclusion criteria)
- The key secondary outcome was a composite of ischaemic cardiovascular disease, which included first occurrence of sudden death, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, leg amputation above the ankle, and any revascularisation of the coronary, leg or carotid arteries.
- Incidence rates using cumulative incidence curves were compared using log-rank analysis. Primary and secondary endpoints were based on a two-sided Cox proportional-hazards model. Incidence and severity of hypoglycaemia events between groups used a Poisson regression model with correction for over dispersion.

### Outcomes and results:

- Study groups were well balanced with respect to baseline demographic characteristics, including major cardiovascular risk factors. Patients were started on the lowest recommended dose of study drugs. Mean doses were: pioglitazone 23.0 mg; glibenclamide 7.6 mg; gliclazide 42.0 mg; glimepiride 2.5 mg. Only 2% of patients received glibenclamide.
- There was no significant difference between the groups in the primary outcome, which occurred in 105 patients in pioglitazone group and 108 patients in the sulfonylurea group ([hazard ratio \[HR\]](#) 0.96, 95% [confidence interval \[CI\]](#) 0.74–1.26, [p](#) = 0.79).
- The key secondary outcome occurred in 74 patients in the pioglitazone group and in 83 patients in the sulfonylureas group (HR 0.88, 95% CI: 0.65–1.21, [p](#) = 0.44).
- Post-hoc on treatment analysis of the components of the primary outcome found none to be significantly different between the two groups. However similar analysis of the key secondary outcome found a significant reduction in the pioglitazone group compared to the sulfonylurea group (HR 0.67, 95% CI: 0.47-0.96, [p](#) = 0.03).
- Fewer patients experienced hypoglycaemia in the pioglitazone group compared with the sulfonylureas group (10% vs. 34%, [p](#) < 0.0001).
- Rates of heart failure, bladder cancer and fractures were not significantly different between treatment groups.
- Premature permanent discontinuation of study medications was significantly more frequent in the metformin plus pioglitazone group than the metformin plus sulfonylurea group (28% vs. 16%, [p](#)<0.0001).

### Level of evidence:

Level 2 (limited quality patient-oriented evidence) according to the [SORT criteria](#).

### Study funding:

Italian Medicines Agency, Diabete Ricerca, and Italian Diabetes Society.