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Pioglitazone versus sulfonylureas: cardiovascular outcomes with older diabetes drugs

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With a plethora of new drugs for diabetes, and distinct differences in their mechanisms of action and non-glycaemic effects, the selection of a second-line medication to add to metformin is now a complex decision. Guidelines^{1,2} offer some suggestions for individualisation of treatment, based on efficacy, side-effects, and cost. But the appropriate choice might be challenging for clinicians, patients, and payers, and older (and cheaper) drugs such as sulfonylureas and thiazolidinediones remain in use despite concerns about side-effects. The scarcity of data on the long-term comparative effectiveness of these drugs is a limitation, although some ongoing trials such as CAROLINA³ and GRADE⁴ might offer some insight in the future. However, the GRADE study will provide limited information on complications because it focuses on glycaemic control, and pioglitazone, sodium-glucose co-transporter-2 inhibitors, and some others are not among the comparator arms, while CAROLINA is comparing the dipeptidyl peptidase-4 inhibitor linagliptin with the sulfonylurea glimepiride. The results of the TOSCA.IT trial,⁵ which investigated the cardiovascular effects, safety, and glycaemic efficacy of pioglitazone versus sulfonylureas as add-ons to metformin, reported in *The Lancet Diabetes & Endocrinology*, might help to fill some of this void and provide useful insight into these drugs.

The trial was done at 57 sites in Italy and included 3028 randomly assigned patients aged 50–75 years with type 2 diabetes inadequately controlled with metformin alone. It had a pragmatic design, with the choice of pioglitazone or sulfonylurea (mostly glimepiride or gliclazide) used as determined by local practice. The trial was stopped early, after a median follow-up of 57.3 months, on the basis of a futility analysis, with no between-group difference identified in the primary cardiovascular outcome (a composite of first occurrence of all-cause death, non-fatal myocardial infarction, non-fatal stroke, or urgent coronary revascularisation; hazard ratio [HR] 0.96, 95% CI 0.74–1.26, $p=0.79$). The study futility highlights the changing nature of the clinical expression of type 2 diabetes, with the low cardiovascular event rate attributable to effective preventive measures, such as use of statins, antihypertensive agents, and antiplatelet agents. The event rate was less than half of that estimated, based on what was seen in PROACTIVE trial just a decade earlier.⁶ Diabetes is no longer universally a cardiovascular risk equivalent, and an appropriate risk evaluation is needed for every patient, although improved methods of risk stratification are needed. One conclusion that could be drawn from TOSCA.IT is that for patients with early diabetes

(baseline HbA_{1c} in the TOSCA.IT trial was 7.7%) the choice of a second-line drug might not matter as compared with patients who are poorly controlled (HbA_{1c} of 9% or 10%).

A design issue that affects interpretation of TOSCA.IT is the choice of primary composite outcome, which was broader than the primary major adverse cardiac events composite used in other recent cardiovascular outcome trials.^{7,8} The choice of primary outcome could lead to misinterpretation of results, as was the case for PROACTIVE,⁶ and makes it difficult to compare results of TOSCA.IT with those from other trials.

Perhaps clinicians should move away from giving a particular drug to everyone with diabetes just because it lowers glucose, and move towards a more personalised approach. In the IRIS trial of pioglitazone,⁹ participants without diabetes (though many had prediabetes) were only included if they had insulin resistance and had previously had a stroke, and the drug significantly reduced cardiovascular events compared with placebo. In TOSCA.IT, however, pioglitazone did not reduce cardiovascular events (compared with sulfonylureas) when given for primary prevention to patients who were in need of improved glycaemic control, but who mostly did not have pre-existing cardiovascular disease (only 335 [11%] participants had a previous cardiovascular event at baseline). Indeed, the population in TOSCA.IT did not seem to have classic features of insulin resistance, with only moderate obesity and absence of classic diabetic dyslipidaemia, which possibly contributed to the low event rate.

The apparent absence of benefit in primary prevention of cardiovascular events of a drug (pioglitazone) that has been shown to be beneficial for secondary prevention in other trials⁹ raises questions about the universal applicability of other positive results in cardiovascular outcome trials done in the context of secondary prevention, such as trials of empagliflozin (EMPA-REG OUTCOME⁷) and liraglutide (LEADER⁸). With a reduction in the need for primary cardiovascular prevention, perhaps clinicians should refocus attention away from cardiovascular outcome trials back to long-term glycaemic control to prevent microvascular complications; end-stage renal disease, for example, remains a major serious complication. In this regard, durability of glycaemic control is important, as it would lead to a reduced need for therapeutic management over time. The thiazolidinediones have produced the best durability of glycaemic control to date, as compared with metformin or glibenclamide.¹⁰ This finding was confirmed in TOSCA.IT, with fewer patients having treatment failure with pioglitazone than with sulfonylureas (193 patients [13%] vs 295 [20%]; HR 0.63, 95% CI 0.52–0.75, $p<0.0001$) and fewer patients in the pioglitazone group needing rescue insulin therapy (164 [11%] vs 233 [16%], $p<0.0001$). However, treatment failure would ideally have been defined at a lower HbA_{1c} than was used in TOSCA.IT, because 8% (64 mmol/mol) is quite high for patients with short diabetes duration who are free of comorbidities. The difference in durability might have been greater if the cutoff for treatment failure had been 7.0% or 7.5%. Hypoglycaemia rates with sulfonylureas might also have been higher had the participants had better glycaemic control or been closer to goal (lower HbA_{1c}).

The low rates of side-effects reported in TOSCA.IT are remarkable. Weight gain was mild in both groups (<2 kg on average), hypoglycaemia was less frequent than might be expected in patients given sulfonylureas, and the known side-effects of pioglitazone were infrequent.

These low rates might be related to the doses of drugs used in both groups of the trial, which were not maximal (another important lesson for clinical practice), but might also be due to clinicians being more attuned to the side-effect profile of pioglitazone and stopping treatment well before serious problems arose, as has been described in clinical practice.¹¹ Discontinuation of study drug occurred more frequently in the pioglitazone group than in the sulfonylureas group, but this might have been clinically appropriate as noted by Olga Vaccaro and colleagues (eg, when patients had significant weight gain or oedema, or due to safety concerns raised in 2012). The safety and relative durability of pioglitazone in such a population is worth highlighting,¹² because the drug has been unfairly side-lined in practice and no substitute insulin sensitiser is available. If used appropriately, neither congestive heart failure nor fractures are a major problem. The study was not adequately powered to detect a difference in cancer occurrence, but pioglitazone use was not associated with a significant increased risk of bladder cancer in another, larger study.¹³

In summary, TOSCA.IT is an important pragmatic trial, despite some limitations. The results provide 5-year comparative safety data for two widely used drug classes, with few side-effects for both sulfonylureas and pioglitazone when given at the right doses to the right patients. These findings also remind us that pioglitazone lowers glucose effectively and durably, and that it is essentially the only available insulin sensitiser that still has a place in clinical practice. The confirmed safety profile, in combination with affordability of pioglitazone and sulfonylureas, might result in continued use of these drugs and stimulate the design of clinical trials to generate more comparative outcome data with newer (more expensive) antihyperglycaemic drugs.

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