

PROactive study shows reduced heart attacks and strokes in type 2 diabetics on pioglitazone HCl (Actos®) therapy

The ambitious PROactive study, initiated in 2001, is the first prospective, randomised, double-blind, placebo-controlled trial of an oral glucose-lowering medication's ability to significantly improve cardiovascular outcomes over 2.5 years of therapy in type 2 diabetics. The study added pioglitazone to the treatment of type 2 diabetics who were already receiving standard-care therapy including dietary modification, glucose lowering (using metformin, sulphonylureas and insulin), blood pressure regulation, lipid lowering and anti-thrombotic agents, according to the 1999 IDF (European) guidelines.

Results from the PROactive study (Prospective pioglitazone control trial in macrovascular events), announced last week at the European Association for the Study of Diabetes (EASD) meeting in Athens, showed that the addition of pioglitazone resulted in a 10%

relative-risk reduction in the primary end-point (all cause mortality, non-fatal MI, stroke, leg amputation, acute coronary syndrome, CABG or PCI and leg vascularisation procedures), which was not significant. The composite of the three principal secondary end-points, representing life-threatening events, all-cause mortality, non-fatal myocardial infarction (MI) and stroke, did show a significant 16% relative risk reduction for pioglitazone ($p = 0.027$).

In addition, pioglitazone on top of 'optimised' standard therapy with antiplatelet, antihypertensive and lipid-lowering agents halved the requirement for progression to permanent insulin therapy (Fig. 3), reduced HbA_{1c} by 0.5%, improved lipid profiles mainly by raising HDL cholesterol and lowering triglycerides, and reduced systolic blood pressure by 3 mmHg. Study chairman, Prof. John Dormandy of St George's Hospital, London, said pioglitazone reduced the risk of all prespecified end-points except leg revascularisation. Curves showing time to events

started to diverge before 18 months, whereas curves showing progression to permanent insulin therapy diverged widely within a few months.

This study was undertaken in Europe and evaluated 5 238 patients with type 2 diabetes at high risk of cardiovascular events. Patients with evidence of type 1 diabetes and patients requiring insulin as sole therapy for glycaemic control and heart failure (NYHA class II–IV) were excluded from this study. The Nottingham Clinical Research Centre acted as study co-ordinating centre and ICON Clinical Research managed and monitored sites throughout Europe.

Pioglitazone therapy was initiated at 15–30 mg in the first month and up-titrated to a maximum dose of 45 mg after the second month. The dose could be modified during the study and 90% of patients achieved the target dose. A summary of other glucose-lowering medication at baseline appears in Table 1 and concomitant cardiovascular medication in Table 2. Median HbA_{1c} level was 7.8% at entry to the study.

Figure 1

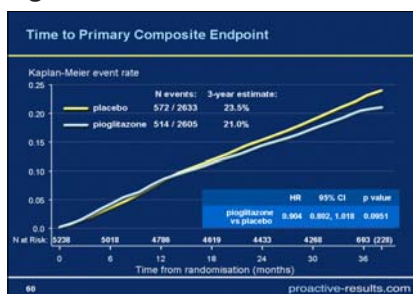


Figure 2

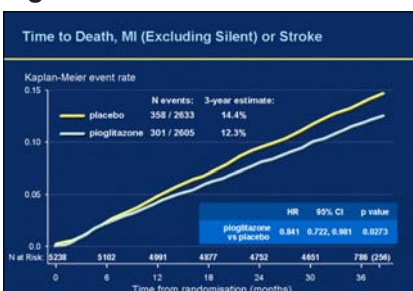


Figure 3

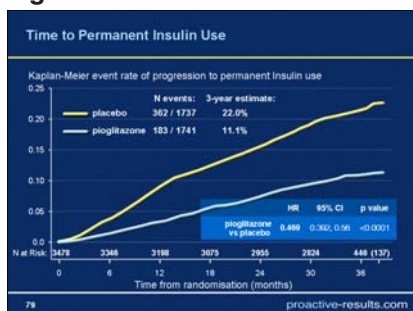


Table 1. Glucose-lowering medication at baseline

	Pioglitazone (%)	Placebo (%)
Metformin only	9.7	9.9
Sulphonylureas only	19.5	18.7
Metformin and sulphonylureas	25.1	25.1
Insulin and metformin	17.5	18.0
Insulin and sulphonylureas	8.0	8.3
Insulin, metformin and sulphonylureas	4.0	4.1
Other combinations (including diet alone)	16.1	15.9
Patients taking each of the following alone or in combination		
Metformin	61.2	61.8
Sulphonylurea	62.3	61.8
Insulin	33.2	34.0
Statins	42.5	43.2
Fibrates	10.1	11.2

Table 2. Cardiovascular medication at baseline

	Pioglitazone (%)	Placebo (%)
Any cardiovascular medication	95.1	94.8
ACE inhibitors	62.6	63.0
Beta-blockers	54.6	54.5
Angiotensin II antagonists	6.5	7.0
Calcium channel blockers	34.2	36.6
Nitrates	39.1	39.7
Thiazide diuretics	15.4	16.3
Loop diuretics	14.3	14.4
Cardiac glycosides	5.0	4.8

The PROactive study was also designed to further examine the safety of Actos in this high-risk patient group. The results demonstrated that adverse events reported in this study were consistent with the known safety profile. Known side-effects of Actos[®], including weight gain, oedema, non-serious hypoglycaemia and heart failure were observed more frequently, compared to placebo. However, the benefits of Actos[®] in the study outweighed the risks. In addition, there were no reports of acute liver toxicity.

Actos[®] has demonstrated a unique profile in earlier, comparative clinical studies, by providing benefits beyond glycaemic control on markers of cardiovascular risk', commented Dr Kitazawa, a member of the board of Takeda Pharmaceutical Company, Osaka, Japan. 'However, the clinical significance of these effects of pioglitazone was unknown until we heard the exciting news from the PROactive study. Additional clinical studies are being funded by Takeda to further improve our understanding of how Actos achieves the results we have seen in the PROactive study, specifically the reduction in risk of heart attack, stroke and death.'

Prof. Dormandy added, 'Until we know how pioglitazone works to provide these life-saving benefits, the beneficial results of PROactive should not be generalised to any other glucose-lowering medication.'

In the critique of the study at EASD, Prof. Hennele Jki-Jarvinen of the University of Finland, pointed out that before adjudication, heart failure was reported in 281 patients receiving pioglitazone and 198 receiving placebo. Although investigators said around half were misdiagnosed due to oedema, there was a 1.6% net increase in heart failure (non-significant) and an 8.6% increase in peripheral oedema for patients receiving pioglitazone, contributing to an average weight gain of 3.6 kg per patient. Patients in the

placebo arm showed similar weight gain.

Comments from South African specialists

Dr Steve Komati, physician in private practice, Louis Pasteur Hospital, Pretoria

Q: What is your comment on the increased numbers of new-onset heart failure in the pioglitazone compared to the placebo group?

A more detailed cardiovascular evaluation at entry to the study, measuring ejection fraction, for example, would have been valuable. Therefore, an important opportunity was missed in the study. We do not now know which type 2 diabetic patients with CAD have the greatest risk of developing chronic heart failure following introduction of pioglitazone.

Q: Where do you believe pioglitazone should be placed in the therapy regimens of type 2 diabetic patients?

I believe that it should be used early on – particularly in type 2 diabetic patients with the metabolic syndrome. We need to exercise caution in its use in patients with established cardiovascular disease who are at risk of developing heart failure.

Q: Should medical aids start paying for more type 2 diabetes patients to get access to Actos[®] based on the results of PROactive?

A selling point for the medical aids should be the impact of pioglitazone on the need for insulin therapy. The delay in the progression to the introduction of insulin in type 2 diabetic patients is important, particularly as in our black community there is not a tradition of

insulin use, and perhaps even a resistance to its use.

Dr Maligay Naiker, private practice, diabetologist, St Augustines Hospital, Durban

Q: What is your comment on the increased numbers of new-onset heart failure in the pioglitazone compared to the placebo group?

This aspect is worrying and limits the usefulness of the drug in the setting of type 2 diabetics with high risk of CV events. We will have to take this seriously and need the investigators to clarify, if they can, which particular subgroup of patients is at greater risk.

Q: Where do you believe pioglitazone should be placed in the therapy regimens of type 2 diabetic patients?

Pioglitazone is very valuable firstly, in the patient with insulin resistance and type 2 diabetes who cannot tolerate metformin, and secondly, in the patient who is receiving metformin therapy, yet has severe insulin resistance. A third group of patients are newly diagnosed type 2 diabetics who are conscious of the need to preserve β -cell function as long as possible. Younger patients are likely to fall into this category.

Q: Should medical aids start paying for more type 2 patients to get access to Actos[®] based on the results of PROactive?

Clearly, pioglitazone should be funded by medical aids in the first two categories I mentioned. In the third category, the patient should be encouraged to either pay for the medication himself or pay from his medical savings account.