

**The Insulin Resistance Intervention after Stroke (IRIS)
trial: a perspective on future practice and research**

Journal:	<i>International Journal of Stroke</i>
Manuscript ID	IJS-03-16-4899
Manuscript Type:	Leading Opinion (invited)
Date Submitted by the Author:	29-Mar-2016
Complete List of Authors:	Bath, Philip; University of Nottingham, Stroke, Division of Clinical Neuroscience Appleton, Jason; University of Nottingham, Stroke, Division of Clinical Neuroscience Sprigg, Nikola; University of Nottingham, Division of Stroke Medicine;
Keywords:	Prevention, Ischaemic stroke, Clinical trial, Stroke, Treatment, Vascular events

INVITED COMMENTARY**The Insulin Resistance Intervention after Stroke (IRIS) trial: a perspective on future practice and research**

Philip M Bath, FRCP DSc; Jason P Appleton, MRCP(UK); Nikola Sprigg, MRCP(UK)

Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham,
Nottingham NG5 1PB UK

Correspondence: Prof Philip Bath

Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham,
Nottingham NG5 1PB UK

Tel: 0115 823 1765

Fax: 0115 823 1767

Email: Philip.bath@nottingham.ac.uk

Words 1035

Abstract

The prevention of recurrent events after ischaemic stroke and transient ischaemic attack (TIA) is well established and based on life style changes, antithrombotics, statins, antihypertensives and carotid surgery. The international IRIS trial assessed whether pioglitazone, a glucose-lowering insulin-sensitising drug, would reduce recurrent vascular events in patients with ischaemic stroke or TIA. After 4.8 years, pioglitazone therapy was associated with reduced vascular events and new diabetes, and an increase in weight, oedema and bone fractures. Pioglitazone may add to the strategies for preventing further events in patients with stroke or TIA.

Commentary

The prevention of recurrent events after ischaemic stroke and transient ischaemic attack (TIA) is well established and based on life style changes (exercise, diet, weight reduction, alcohol moderation, smoking cessation), antithrombotics, statins, antihypertensives and carotid surgery. These interventions, when prescribed and delivered, can together reduce recurrence by up to 80%. Hence, finding an additional intervention that would further reduce recurrent events in a reasonable proportion of patients has been considered challenging for many years. Thus, the positive findings of the IRIS secondary prevention trial,⁽¹⁾ which aimed to moderate insulin resistance in non-diabetic patients, adds hope that we can further reduce recurrent events on top of established interventions. IRIS studied pioglitazone, a member of the thiazolidinedione class of peroxisome proliferator-activated receptor gamma (PPAR- γ , or glitazone receptor) agonists that has an insulin sensitising role. Although licensed for lowering glucose in diabetic patients, pioglitazone has not previously been tested in non-diabetic stroke patients in a large trial.

IRIS was an international double-blind trial in patients with recent ischaemic stroke or TIA.⁽¹⁾ Patients did not have diabetes but had insulin resistance determined as an elevated 'homeostasis model assessment of insulin resistance' index (HOMA-IR >3 (2)). Key exclusion criteria included a history of heart failure or bladder cancer, and severely disabling stroke. Almost two-thirds of patients screened for the trial were deemed to be resistant to insulin.⁽¹⁾ The majority of patients were taking

conventional secondary prophylaxis at baseline. 3876 patients were randomised to pioglitazone (target dose 45 mg daily) or placebo for an average of 4.8 years (15,903 person years). At final follow-up, fatal or nonfatal stroke or myocardial infarction (primary outcome) was 9.0% in the pioglitazone group and 11.8% in the placebo group, amounting to a hazard ratio of 0.76 (95% confidence intervals 0.62-0.93, $p=0.007$), absolute risk reduction 2.8%, and relative risk reduction 23.7%.⁽¹⁾ None of the pre-specified subgroups showed an interaction between treatment and primary outcome. The development of diabetes was less in the pioglitazone group (3.8% vs 7.7% participants, $p<0.001$). The rate of death from any cause did not differ between the treatment groups. However, pioglitazone was associated with weight gain (mean gain at 4 years: 2.6 kg vs. -0.5 kg, $p<0.001$) and oedema (35.6% vs 24.9% participants, $p<0.001$) and, importantly, more bone fractures needing surgery or hospitalisation (5.1% vs 3.2% participants, $P=0.003$).⁽¹⁾ Earlier concerns that pioglitazone might increase bladder cancer (3) and heart failure (4) were not seen in IRIS. Overall, treatment with pioglitazone in 100 patients with insulin resistance and recent ischaemic stroke/TIA for about 5 years might prevent three patients from having a stroke or MI, but contribute to the development of serious bone fractures in two patients.⁽¹⁾ The results are compatible with a published systematic review of earlier and smaller trials of PPAR- γ drugs (pioglitazone, rosiglitazone),⁽⁵⁾ a trial of pioglitazone in patients with diabetes,⁽⁶⁾ and a systematic review of the relationship between glitazones and fractures,⁽⁷⁾ i.e. glitazones reduce vascular events but increase oedema, weight gain and fractures.

The IRIS results are important generically in two ways: IRIS is the first demonstration that a glucose-lowering drug with insulin-sensitising properties reduces stroke and myocardial infarction in patients with recent ischaemic stroke or TIA; and assessment of insulin resistance may need to become a routine part of the investigational work-up of patients with a recent stroke or TIA.

So do these results suggest we should start using pioglitazone in insulin resistant patients? First, if a manufacturer had sponsored and funded IRIS, a second randomised controlled trial might be required to confirm the results before a marketing authorisation was issued. IRIS was funded by the US government and pioglitazone is already licensed (and available in generic formulations) although its use in non-diabetic patients would be off-label. Although it is unlikely that the results of IRIS reflect chance (since they are comparable with the results of earlier trials and

systematic reviews) the need for a second trial has to be considered. Second, trials of other insulin-sensitising drugs such as metformin may be warranted in patients with ischaemic stroke or TIA, not least because this 'old' antidiabetic drug may have life-extending properties. Third, patients prescribed pioglitazone would need to fulfil the specific and somewhat stringent IRIS inclusion and exclusion criteria, as listed above.(8) Fourth, the HOMA-IR test is not used frequently in clinical practice; in IRIS, HOMA was assayed centrally in core laboratories. HOMA can be calculated from local assays of fasting glucose and insulin although laboratories will need to standardise the latter. Alternatively, other surrogate markers of insulin resistance, such as the individual components of HOMA, waist circumference, or HbA1c, could be used although these would require validation in stroke patients. And last, the types and sites of fractures occurring in IRIS need to be identified so that patients at particular risk can be recognised in advance. For example, would DEXA scan measurement of bone mineral density identify patients at risk, or concurrent administration of calcium and vitamin D reduce fracture risk? In a meta-analysis of previous trials of glitazones, increased fracture risk was associated with female sex but not age or duration of exposure.(7) No doubt future IRIS publications will examine this issue in more detail.

In summary, whilst the positive results from IRIS are very welcome, two uncertainties need further consideration and research prior to routine use, in particular relating to the need for widespread and standardised measurement of insulin resistance, and better understanding of the cause and risk factors for the development of fractures. In the meantime, patients who are likely to have insulin resistance can have the results of IRIS and potential benefits and risks of pioglitazone discussed with them, and they should be reminded that life-style changes also have insulin-sensitising effects.

Declarations

PB is Stroke Association Professor of Stroke Medicine; he was Principal Investigator for the recruiting IRIS trial site in Nottingham.

Contributions

PB wrote the first manuscript draft. JA and NS contributed to the manuscript and checked contents.

For Review Only

References

1. Kernan W, Viscoli C, Furie K, et al. Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. *The New England Journal of Medicine* 2016.
2. Matthews D, Hosker J, Rudenski A, Naylor B, Treacher D, Turner R. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28(7):412-9.
3. Colmers I, Bowker S, Majumdar S, Johnson J. Use of thiazolidinediones and the risk of bladder cancer among people with type 2 diabetes: a meta-analysis. *Canadian Medical Association Journal* 2012;184(12):E675-83.
4. Lago R, Singh P, Nesto R. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. *Lancet* 2007;370(9593):1129-36.
5. Liu J, Wang L. Peroxisome proliferator-activated receptor gamma agonists for preventing recurrent stroke and other vascular events in patients with stroke or transient ischaemic attack. *The Cochrane database of systematic reviews* 2015(10).
6. Dormandy J, Charbonnel B, Eckland D, 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(9493):1279-89.
7. Zhu Z, Jiang Y, Ding T. Risk of fracture with thiazolidinediones: an updated meta-analysis of randomized clinical trials. *Bone* 2014;68:115-23.
8. Semenkovich C. Insulin Resistance and a Long, Strange Trip. *The New England Journal of Medicine* 2016.