IRIS: Trial Summary

Pioglitazone ACTOS after Ischemic Stroke or Transient Ischemic Attack in Patients with Insulin Resistance

BOTTOM LINE [1]

- **For every 100 patients with recent history of stroke, transient ischemic attack (TIA) and insulin resistance, but NOT diabetes, giving pioglitazone 45mg daily for ~5 years will result in approximately 3 less cases of stroke or MI, 4 less cases of diabetes, 2 extra cases of serious bone fracture, 7 extra cases of weight gain > 13.6kg, and 11 extra cases of edema.** (Note – those with various degrees of heart failure, pitting edema, etc. were excluded.)
- **Given the significant impact of both benefits and harms on patient quality of life, secondary prevention with pioglitazone should be carefully discussed relative to individual patient values and other alternatives.**
- **The trial should not eclipse the primary role of LIFESTYLE for addressing insulin resistance and improving health!**

BACKGROUND [1]

- Insulin resistance is very common (>50%) in patients without diabetes who have had an ischemic stroke or TIA.
- Presence of insulin resistance increases the risk of vascular disease. Pioglitazone is an insulin-sensitizing drug.

TRIAL BACKGROUND

DESIGN: Randomized, double-blind, placebo-controlled multi-centre trial (followed between 2005-2013)

PATIENT GROUP: Patients at least 40 years of age with a recent history (<6 months) of **ischemic stroke or TIA**, with **insulin resistance** (based on HOMA-IR index ≥ 14 days after index event) but **WITHOUT diabetes.**

EXCLUSION: Presence of diabetes; A1C ≥ 7%; Class 3-4 HF, or Class 2 HF with reduced ejection fraction; liver disease or elevated LFT; Hb <8.5; mod-severe pitting edema; carotid revascularization in past 14 days; use of estrogen contraceptive or oral glucocorticoid.

POPULATION at baseline: **n=3876** (1939 + 1937): Age ~63.5 ± 10.6yrs; ~65% male; ~85% Caucasian; BMI~30; A1C=5.8%; Hypertensive ~71% (BP ave 133/79 mm Hg); LDL ~2.3 mmol/L; HOMA-IR Index ~4.7; Modified MMSE ~96 (out of 100); Meds: statin ~82.5%, antiplatelet ~92%; relatively low rate of ACEI or ARB use (~55%); oral anticoagulant ~11-12%.

INTERVENTION/CONTROL: Pioglitazone (titrated from 15mg/daily to target dose of **45mg once daily** over 12 weeks) vs. **placebo**

Median daily dose ranged from **29-40mg/day**. Pioglitazone dosing titration was adjusted if any symptoms of worsening edema, shortness of breath, myalgia or excessive weight gain. Pioglitazone was stopped if: a) HF, b) bladder ca, c) ≥2 low energy fractures. Patients were contacted every 4 months for up to 5 years.

RESULTS

Follow-up: 4.8yrs (median)

TABLE 1: EFFICACY & SAFETY - PRIMARY & SECONDARY ENDPOINTS

CLINICAL ENDPOINTS ITT ANALYSIS	PIOGLITAZONE TARGET 45MG/DAY n=1939	PLACEBO n=1937	HR 95% CI	P VALUE	ARR/ARI	NNT/NNH /4.8YRS	COMMENTS
PRIMARY ENDPOINT							
Stroke or MI*	9.0% (n=175)	11.8% (n=228)	0.76 (0.62-0.93)	=0.007	2.8%	36	Mostly driven by non-fatal stroke (5.9% vs 7.1%) & non-fatal MI (2.3% vs 3.3%)
SECONARY ENDPOINTS							
Stroke	6.5% (n=127)	8.0% (n=154)	0.82 (0.61-1.10)	=0.19	-	-	Pioglitazone had no significant effect on cognitive decline vs. placebo (P=0.88).
ACS, MI, or unstable angina	5.0% (n=96)	6.6% (n=128)	0.75 (0.52-1.07)	=0.11	-	-	
Stroke, MI or serious HF	10.6% (n=206)	12.9% (n=249)	0.82 (0.65-1.05)	=0.11	-	-	
Diabetes	3.8% (n=73)	7.7% (n=149)	0.48 (0.33-0.69)	<0.001	3.9	26	
All-cause death	7.0% (n=136)	7.5% (n=146)	0.93 (0.73-1.17)	=0.52	-	-	

* For patients who had both a stroke and an MI after the trial began, only the first of these events was counted.

TABLE 2 – ADVERSE EVENTS

CLINICAL ENDPOINTS		PIOGLITAZONE TARGET 45MG/DAY n=1939	PLACEBO n=1937	P VALUE	ARR/ARI	NNT/NNH /4.8YRS	COMMENTS
SAE	HOSPITALIZATION	46.8% (n=908)	48.8% (n=946)	0.21	-	-	Population exclusions were fairly broad to accommodate known pioglitzone AEs, and still significant AEs occurred. {Fairly consistent with previous data that has found edema, weight gain, heart failure, bladder cancer and fractures to be of concern.}
	CANCER - ANY	6.9% (n=133)	7.7% (n=150)	0.29	-	-	
	CANCER - BLADDER	0.6% (n=12)	0.4% (n=8)	0.37	-	-	
	BONE FRACTURE	5.1% (n=99)	3.2% (n=62)	0.003	1.9%	53	
	HEART FAILURE	2.6% (n=51)	2.2% (n=42)	0.35	-	-	
OTHER AE	WEIGHT GAIN						
	>4.5 kg	52.2% (n=1013)	33.7% (n=653)	<0.001	18.5%	6	
	>13.6 kg	11.4% (n=221)	4.5% (n=88)	<0.001	6.9%	14	
	EDEMA	35.6% (n=691)	24.9% (n=483)	<0.001	10.7%	9	
	SHORTNESS OF BREATH	17.6% (n=342)	15.1% (n=292)	0.03	2.5%	40	
	ALT > ULN	1.3% (n=26)	3.0% (n =59)	<0.001	1.7%	59	
	MACULAR EDEMA	0.2% (n=3)	0.1% (n=2)	0.66	-	-	

SAE=serious adverse events

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Independently funded by the National Institute of Neurological Disorders and Stroke. Takeda, the manufacturer of pioglitazone, donated the pioglitazone and placebo tablets but had no role in development of the protocol or conduct of the trial.

LIMITATIONS:

- 5.9% withdrew consent; 2.6% lost to follow=up
- Pioglitazone group had less adherence (60% vs 67%) – especially due to edema or weight gain
- Potential for un-blinding over time with the effect on weight gain in pioglitazone group
- HOMA-IR index lacks standardization

UNCERTAINITIES:

- Unknown potential presence of atrial fibrillation (not looking for on ECG); only ~12% on oral anticoagulant.
- While enhancement of insulin sensitivity may have an important role in the benefit of pioglitazone on the primary outcome (stroke or MI), other measured and unmeasured factors may also play a part. The mechanism by which pioglitazone increases the risk of bone fractures is also unknown. While the study did not find a significant impact of pioglitazone on cancer rates, it was not powered to detect this.

HOW DOES THIS TRIAL COMPARE TO PREVIOUS OUTCOME TRIAL(S) WITH PIOGLITAZONE?

The only outcome trial that has looked at pioglitazone previously has been PROACTIVE (n=5238 patients **with diabetes** [type 2] and a history of macrovascular complications: MI 46.7%, coronary artery revascularization 30.8%, ACS >3 months 13.7%, stroke > 6 months 18.8%, symptomatic PAD 19.9%, other 48.1%*; 66% male, mean age 61.8 years; follow-up 34.5 months).

Consistencies

- CV composite endpoints show some benefit
- Weight gain, edema always worse with pioglitazone vs. placebo

Inconsistencies

- Heart failure only trended towards increase in IRIS, but could relate to exclusion criteria

*Numbers do not add to 100% since some patients had more than one item.

RxFILES RELATED LINKS

- **RxFiles Diabetes Agents Outcomes Table:** http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Agents-Outcomes-Comparison-Summary-Table.pdf
- **RxFiles Diabetes – Landmark Trials and Links**: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf

X =non-formulary in SK ⊗=not covered by NIHB ☎=Exceptional Drug Status in SK ♂=male **AE**=adverse event **ACS**=acute coronary syndrome **CAD**=coronary artery disease **CVD**=cardiovascular disease **DPP4-I**=dipeptidyl peptidase-4 inhibitor **dx**=disease **GI**=gastrointestinal **GLP1-A**=glucagon-like peptide-1 agonist **HF**=heart failure **MI**=myocardial infarction **PAD**=peripheral artery disease **SU**=sulfonylurea **T2DM**=type 2 diabetes mellitus **TIA**=transient ischemic attack **tx**=treatment **UTI**=urinary tract infection

Reference

Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, et al; **IRIS** Trial Investigators. Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. N Engl J Med. 2016 Feb 17.

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 RCT. Lancet. 2005; 366: 1279-1289

ACKNOWLEDGEMENTS: Contributors & Reviews: Thanks to those who provided review including Trish Rawn (Pharmacist). **Prepared By**: Loren Regier BSP, BA