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Pioglitazone for Secondary Prevention after Ischemic Stroke and Transient Ischemic Attack: Rationale and Design of the Insulin Resistance Intervention after Stroke (IRIS) Trial

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Abstract

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Trial Registration: NCT00091949

Background: Recurrent vascular events remain a major source of morbidity and mortality after stroke or transient ischemic attack (TIA). The Insulin Resistance Intervention after Stroke (IRIS) trial is evaluating an approach to secondary prevention based on the established association between insulin resistance and increased risk for ischemic vascular events. Specifically, IRIS will test the effectiveness of pioglitazone, an insulin-sensitizing drug of the thiazolidinedione class, for reducing the risk for stroke and myocardial infarction (MI) among insulin resistant, non-diabetic patients with a recent ischemic stroke or TIA.

Design: Eligible patients for IRIS must have had insulin resistance defined by a Homeostasis Model Assessment-Insulin Resistance greater than 3.0 without meeting criteria for diabetes. Within 6 months of the index stroke or TIA, patients were randomly assigned to pioglitazone (titrated from 15mg to 45mg/day) or matching placebo and followed for up to 5 years. The primary outcome is time to stroke or MI. Secondary outcomes include time to stroke alone, acute coronary syndrome, diabetes, cognitive decline and all-cause mortality. Enrollment of 3876 participants from 179 sites in seven countries was completed in January, 2013. Participant follow-up will continue until July, 2015.

Summary: The IRIS Trial will determine whether treatment with pioglitazone improves cardiovascular outcomes of non-diabetic, insulin-resistant patients with stroke or TIA. Results are expected in early 2016.

BACKGROUND

Stroke is the second leading cause of death and the third leading cause of disability worldwide[1-3]. Despite effective strategies, including antithrombotic therapy, statins, blood pressure reduction and carotid revascularization, survivors of ischemic stroke face a high risk for myocardial infarction (MI) and recurrent stroke[4,5]. Transient ischemic attacks (TIAs) produce less immediate disability than stroke but have a similar risk of subsequent cardiovascular events[6].

Insulin resistance affects almost all patients with type 2 diabetes mellitus (DM2) and a majority of non-diabetic patients with ischemic stroke or TIA[7,8]. In epidemiologic research, insulin resistance has been associated with increased risk for coronary heart disease, stroke, and several vascular risk factors including hypertension, dyslipidemia, dysglycemia, vascular inflammation, endothelial dysfunction, hypercoagulability, and abnormal adipose tissue distribution and biology.[9-12] Based on these associations and data from preliminary therapeutic studies, investigators have hypothesized that modification of insulin resistance may reduce the incidence of stroke and MI.

Strategies to improve insulin resistance include nutritional changes, exercise, weight reduction and medications such as metformin or thiazolidinediones (TZD). The therapeutic potential of pioglitazone, a TZD used in the treatment of DM2, has been demonstrated in research showing that this agent has profound effects on numerous biological events related to the insulin resistant state, including inflammation, vascular cell proliferation, dyslipidemia, vascular lesion formation, and thrombosis. In diabetic patients, pioglitazone reduces insulin resistance and improves glycemic control, favorably modifies plasma lipid concentrations, reduces the progression of atherosclerosis in the carotid arteries[13] and may

improve cardiovascular outcomes[14,15]. In the PROactive trial, among a sub-group of diabetic patients with a history of prior stroke, pioglitazone was associated with a significant reduction in the risk for recurrent stroke[16]. In non-diabetic patients, pioglitazone has been shown to increase insulin sensitivity[17] and reduce the rate of progression to DM2[18].

The IRIS trial is testing the hypothesis that treatment with pioglitazone will reduce risk for stroke and MI in non-diabetic, insulin-resistant patients. The selection of a non-diabetic study population is a novel and important aspect of the trial design, which addresses the risk of metabolic disturbances in patients with vascular disease prior to the onset of overt hyperglycemia. Because pioglitazone reduces both insulin resistance and circulating glucose, the exclusion of patients with established DM2 also results in a more specific test of the effect of lowering insulin resistance apart from the treatment of hyperglycemia. This exclusion also reduces the potential for TZD use in the control arm and for differential use of other diabetic treatments in the compared groups that could confound assessment of the study treatment.

DESIGN

Study Objective

IRIS (www.clinicaltrials.gov NCT00091949) is an investigator-initiated, international, multicenter, randomized, double-blind, placebo-controlled study in 3876 insulin-resistant, non-diabetic patients with a recent stroke or TIA. The primary objective is to evaluate whether pioglitazone, initiated within 6 months of a stroke or TIA, reduces the incidence of subsequent stroke and MI. The study is approved in each participating center by the responsible ethics committee. The IRIS trial is funded by the US NINDS, award number U01 NS 44876. Takeda Pharmaceuticals USA provides study medication and funds the storage of blood from a subgroup of IRIS participants. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Study population

Inclusion and exclusion criteria are shown in Table 1. Eligible men and women were at least 40 years of age and had a recent ischemic stroke or TIA, without a prior or current diagnosis of diabetes. A qualifying ischemic stroke was defined by focal neurologic symptoms or signs persisting for at least 24 hours and/or associated with a new area of infarction on brain imaging in an appropriate location. Patients with isolated monocular symptoms were required to have acute parenchymal ischemic abnormalities on brain imaging. After initiation of recruitment in January 2005, the protocol was amended in November 2005 to allow enrollment of patients with non-valvular atrial fibrillation. In 2006, eligibility was further broadened to include selected TIA syndromes. A qualifying TIA was defined as an acute neurological deficit attributable to brain ischemia that lasted at least 10 minutes, but less than 24 hours, without imaging evidence of acute cerebral infarction. To enroll patients with a high likelihood of a vascular etiology for their symptoms, eligible TIA deficits were restricted to hemiplegia or hemiparesis, monoplegia or monoparesis, and a language disturbance other than isolated dysarthria[19]. In 2007, eligibility was extended to patients

with stroke manifest by non-focal neurological symptoms (e.g. dizziness, confusion, headache) if the symptoms lasted at least 24 hours and were associated with a focal abnormality on diffusion weighted MRI. (See Table 2 for full timeline and rationale for protocol modifications.)

The Homeostatis Model Assessment-Insulin Resistance (HOMA-IR) (calculated as [fasting insulin,μU/ml X fasting glucose, mmol/L]/22.5[20]) was used to identify patients with insulin resistance. HOMA-IR correlates with physiological tests of insulin resistance, such as the hyperinsulinemic euglycemic clamp and intravenous glucose tolerance tests, but is based on a simple blood sample and is practical for use in a large, multicenter trial. It has shown significant associations with glucose intolerance[21], progression to DM2[22,23], metabolic syndrome[24], and cardiovascular disease[25,26]. A HOMA-IR threshold of > 3.0 was chosen to define insulin resistance because this value represented the highest quartile of values among non-diabetic populations in research available at the initiation of IRIS.[27]

Due to the known potential for TZD drugs to precipitate or worsen CHF, patients with New York Heart Association class 3 or 4 heart failure were excluded, although those with class 2 CHF (symptomatic with moderate activity) were initially eligible at US sites if their ejection fraction was at least 40%. In 2007, based on updated prescribing guidelines for pioglitazone, patients with symptomatic CHF were no longer permitted to enroll and, in 2008, patients with any history of CHF were excluded from participation. Patients with moderate or severe lower extremity edema were also excluded because pioglitazone can also cause edema.

Additional external developments during the trial led to several protocol modifications to ensure the safety of participants and conformity with evolving regulations. When IRIS began in 2005, there was no evidence to suggest an association between pioglitazone treatment and bladder cancer in humans. With the emergence of data from other trials suggesting a possible imbalance of bladder cancer in pioglitazone treated diabetic patients, the IRIS protocol was revised in 2007 to minimize potential risk by excluding enrollment of patients with a history of bladder cancer and, in 2011, those with specific risk factors for bladder cancer, such as prior pelvic radiation or cytoxan exposure or uninvestigated macroscopic hematuria.

Study procedures

Patients providing informed consent underwent a screening interview, physical examination and fasting blood test (Table 3). Because insulin resistance may be impaired transiently after a cerebrovascular event[28], the screening blood test to measure HOMA-IR was conducted a minimum 14 days after the index stroke or TIA. Blood samples were processed centrally by Esoterix Inc. or an affiliate laboratory. The Linco Human Insulin Specific radio immuno-assay (RIA) was used at the laboratories in North America and Australia to measure circulating insulin concentrations. Because this assay was not available at the laboratories in Europe and Israel, the Linco Animal Serum Free ELISA assay was used and results converted to RIA values by means of an internal LINCO correlation equation (Insulin RIA [ulU/mL] = 1.1056 × (Insulin ELISA [ulU/mL]) + 2.1494).

Patients with HOMA-IR > 3.0 and no excluded conditions were randomly assigned in a 1:1 ratio to initial treatment with one 15 mg pioglitazone or placebo tablet daily by mouth. Placebo and active tablets were identical in appearance and texture. Randomization was performed using a random permuted block design with variable block sizes stratified by site. To conceal the allocation sequence, randomization lists were kept only at the central pharmacy and the statistical center. The Investigational Drug Service at Yale-New Haven Hospital prepared all medication bottles, including starter supplies that were stored at the research sites. At the baseline visit, a structured interview was administered and the starter bottle with the participant's assigned randomization number was dispensed.

Follow-up interviews were scheduled every two weeks during the first three months. Study medication dose was increased at 4 weeks to two tablets daily (pioglitazone 30 mg or matching placebo) and at 8 weeks to three tablets daily (pioglitazone 45 mg or matching placebo). Participants at full protocol dose were supplied with pioglitazone 45mg or matching placebo tablets at 12 weeks.

Study medication is permanently discontinued if a participant develops CHF, non-traumatic fractures on two occasions involving bones other than the fingers and toes, bladder cancer, or macular edema. Dose can be reduced to manage side effects that are possibly drug-related (e.g., weight gain, edema). Adherence is calculated from pill counts of returned bottles as mgs taken compared to mgs prescribed per protocol, with zero adherence imputed for any periods off drug.

After month 4, participants are contacted every 4 months. Annual in-person assessments include a physical examination, Modified Mini-Mental State (3MS) test[29] and fasting blood test. Participants who experience a stroke or MI are maintained on study medication. IRIS investigators monitor vascular risk factors, report them to participants and physicians annually and encourage participants to achieve their treatment goals but the provision of standard secondary preventive care is the responsibility of personal physicians. Participants are followed for up to 5 years or until the last scheduled contact falling before the common trial end date (July 1, 2015), whichever comes first.

Trial Outcomes

The primary outcome is time to first occurrence of stroke or MI. Secondary outcomes are shown in Table 4. Clinical Event Committees for adjudicating neurology, cardiology and endocrinology events are comprised of a chairperson and three or more specialists. Two reviewers adjudicate each potential outcome, with a third reviewer added if needed to reach a majority decision. Reviewers are blinded to treatment allocation and receive training in IRIS outcome criteria (Appendix A). To provide comparability to other research, sensitivity analyses will be conducted using published revised definitions for stroke[30], MI[31] and diabetes[32].

Safety outcomes of special interest include heart failure, bone fracture and bladder cancer. During the course of the trial, several developments led to protocol and informed consent modifications (Table 2). In 2006, a randomized trial reported a higher rate of fractures in women receiving rosiglitazone, another drug in the TZD class[33]. In March 2007, the

manufacturer of pioglitazone alerted health care providers to a similar finding based on analysis of its clinical trial database. In response, in April 2007, the IRIS informed consent was revised to describe this potential new risk and a query for fractures was added to interviews; enrolled participants were asked to complete a retrospective survey for fractures and all participants are advised to follow standard recommendations to preserve bone health. The 2007 informed consent revision also described new information from clinical trials in humans that suggested an association between pioglitazone use and increased risk for bladder cancer. In 2011, after several observational studies reported higher rates of bladder cancer in diabetic patients treated with pioglitazone[34,35], the informed consent was again revised and the protocol modified to exclude participants who may be at higher risk for bladder cancer. Enrolled participants who met criteria for higher bladder cancer risk were removed from study medication.

Statistical considerations

When the study was planned, a sample size of 3136 was calculated to provide 90% power to detect a 20% relative reduction in the 4-year cumulative rate of the stroke and MI using a log-rank test, with a type I error of 5% (2-sided), and the following assumptions: linear recruitment over 36 months, 4-year primary outcome rate of 27% in placebo group, 1% losses to follow-up for the primary outcome per year, 5% change to off-drug from active arm per year, 1% cross-overs to active from placebo arm per year and a minimum of three interim analyses using O'Brien-Fleming stopping boundaries for efficacy and futility.[36] Sample size calculation used the method of Lakatos[37,38] and stopping boundaries were determined using EaSt 2000 software (Cytel Corporation, Cambridge, MA)[39-41]. The stopping boundaries were designed to be flexible and the actual timing of the interim analyses is based on DSMB requests.

Because enrollment fell below planning estimates, in July 2007 enrollment was extended to achieve the original sample size. In February 2011, based on the results of the first blinded interim analysis, the DSMB recommended increasing person-years in the trial by further extension of recruitment through June 2012 and follow-up through June 2015. In mid-2012, the DSMB allowed recruitment to continue at selected high-recruiting sites through the end of 2012. Recruitment ended on January 15, 2013 with a cohort of 3876 participants. Baseline characteristics of the enrolled cohort are shown in Appendix.

All analyses will be conducted using the intention-to-treat principle (i.e., according to participants' original treatment assignment). The analysis of the primary outcome will be tested by the stratified log rank statistic[42], with a type I error of 0.05 (2-sided) experiment-wide level of significance. Cumulative event rates will be calculated using the method of Kaplan-Meier. The treatment effect will be summarized as a hazard ratio from a Cox proportional-hazards model with 95% confidence interval adjusted for interim looks[43]. In a pre-specified sensitivity analysis, a Cox model will be used to assess the effect of treatment adjusted for pre-specified baseline features that may affect prognosis or treatment effect. The effect of treatment will also be examined in subgroups defined by age, sex, race, Hispanic ethnicity, history of hypertension, history of coronary heart disease, BMI, fasting

plasma glucose, HDL cholesterol, triglyceride, HOMA-IR, HbA1c, and medication adherence via treatment by covariate interactions.

Except for cognitive decline, secondary outcomes will be analyzed as time to first event in the same manner as the primary outcome. For cognitive decline, repeated measures of the 3MS will be analyzed by longitudinal mixed model methods[44]. For participants with a normal 3MS score (>90) at entry, a logistic model will be used to evaluate the effect of treatment on risk for cognitive decline (exit score < 78). To provide control for multiplicity, the Hochberg procedure will be used to determine significance for secondary outcomes using an overall type I error of 0.05 (two-sided) [45].

Discussion

IRIS is the only trial to date to test the effect of an insulin-sensitizing intervention on cardiovascular outcomes in non-diabetic patients or in patients with cerebrovascular disease. An earlier trial of pioglitazone for prevention of cardiovascular outcomes in DM2 patients found a non-significant reduction in the primary endpoint (all-cause mortality, non-fatal MI and stroke, acute coronary syndrome, CABG, percutaneous coronary intervention, major leg amputation or revascularization). However, there was a reduced risk for the more restricted and usual outcome of non-fatal MI and stroke and all-cause mortality (12.3% vs 14.4% in placebo; p=0.03). Furthermore, among patients with a history of prior stroke, there was a reduced risk for recurrent stroke (5.6% vs 10.2% in placebo, P=0.0085)[14,16]. In contrast, trials of another insulin-sensitizing drug, rosiglitazone, have failed to demonstrate significant reductions in cardiovascular risk in DM2 patients[45,46]. Pioglitazone differs from rosiglitazone in that it has mild PPAR-α effects, as wells as PPAR-γ actions, which lead to a more favorable effect on plasma lipid levels.

By testing pioglitazone in a non-diabetic population, IRIS differs in significant ways from these earlier trials. First, IRIS recognizes the prevalence of metabolic abnormalities in vascular disease patients prior to the onset of diabetes and postulates that modification of insulin resistance at an earlier stage might have greater consequent cardiovascular benefit than treating hyperglycemia *per se*. Second, IRIS avoids the confounding effects of diabetes studies in which comparator groups either are assigned to other anti-diabetic drugs or are subject to different levels of hyperglycemia, allowing a clearer evaluation of the effects of pioglitazone. Third, IRIS is the first stroke study to specifically test the effects of metabolic intervention. Because cardiovascular risk after stroke is related to insulin resistance, our study population with cerebrovascular disease may derive particular benefit from treatment with pioglitazone. Study results, expected in 2016, are likely to contribute significantly to our understanding of the complex interaction between vascular disease and metabolism.

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Table 1

Final Inclusion and Exclusion Criteria

Inclusion Criteria
Ischemic stroke or TIA within 6 months of randomization
Insulin resistance as defined by HOMA-IR >3.0
Age ≥ 40 years at randomization [1]
Ability and willingness to provide informed consent
Exclusion Criteria
Stroke or TIA related to structural cardiac lesion[2]
Stroke related to head trauma, proximal arterial dissection or medical procedures[3]
Diabetes mellitus[4]
Congestive heart failure (NYHA class 1-4) or history of CHF
History of bladder cancer or high risk for bladder cancer[5]
Active liver disease[6]
Inability to participate in follow-up activities
Irreversible medical conditions with predicted survival <4 years
Oral or patch estrogen contraceptive use
Ongoing use of oral corticosteroids
History of intolerance to a TZD
Pregnancy, desire to become pregnant, or currently breastfeeding
Current participation in conflicting clinical trial[7]
ALT>2.5 upper limit of normal
Hemoglobin<8.5 gm/dL
Moderate to severe pitting edema of feet or legs
Carotid surgery or carotid stenting procedure within 14 days of randomization

[1] Changed from 45 years in October 2007.

[2] Mechanical aortic or mitral valves, left atrial thrombus or ventricular mural thrombus, atrial myxoma or other left-sided cardiac tumors, infective endocarditis, mitral stenosis associated with enlarged left atrium (>5.5 cm), spontaneous echo contrast, or valvular atrial fibrillation.

[3] Stroke within 24 hours of carotid endarterectomy, percutaneous coronary interventional procedure, CABG, intra-aortic balloon pump, valvuloplasty, left-sided electrophysiologic procedures, or cardioversion.

[4] Outpatient use of diabetes medication for diagnosis of diabetes in 90 days preceding screening test or fasting plasma glucose > 125 mg/dL (confirmed on repeat testing) or HgbA1c >=7.0% on screening test.

[5] Current uninvestigated macroscopic hematuria, prior cyclophosphamide exposure, or irradiation to pelvic region.

[6] Known liver disease with cirrhosis, significant cholestasis, portal hypertension, hepatic encephalopathy, hepatic synthetic dysfunction, or expected significant loss of liver function during study. Patients with active hepatitis B were ineligible based on an empiric recommendation from the manufacturer of pioglitazone.

[7] Trial with any of following: Intervention known to affect the incidence of stroke or MI or that is an experimental drug, outcome that includes stroke or MI, exclusion for participation in another trial.

Table 2

Protocol Adaptations

Issue	Change	Rationale
Index Neurological Event	November 2005 Removal of requirement that patients with atrial fibrillation have lacunar syndrome or ipsilateral carotid stenosis; patients with atrial fibrillation eligible if no mitral stenosis.	Substantial proportion of recurrent strokes in patients with atrial fibrillation attributable to non-cardioembolic etiologies.
	April 2006 Inclusion of selected TIA syndromes.	Expand applicability of results and pool of potential participants.
	December 2007 Inclusion of non-focal strokes.	Bring stroke definition into harmony with newer international criteria.
	December 2008 Inclusion of non-ambulatory patients if baseline wheelchair/bed weight obtained and re-weighing possible.	Expand range of stroke severity and generalizability of trial results.
Congestive Heart Failure	December 2007 Exclusion of patients with NYHA class 2 CHF symptoms at all sites.	Revision of pioglitazone US package insert In September 2007 to include 'black box' warning based on post-marketing adverse event reports that drug may cause or exacerbate CHF in some patients and recommendation against use in patients with symptomatic CHF.
	December 2008 Exclusion of patients with history of CHF (NYHA class 1-4).	Pragmatic consideration that these patients are at increased risk for heart failure recurrence, which would lead to study medication discontinuation, and planned expansion of recruitment network to Europe, where pioglitazone not used in patients with history of CHF.
Bladder Cancer	January 2007 Exclusion of patients with history of bladder cancer.	Revision of pioglitazone US package insert In November 2006 to include data from two 3-year clinical trials that showed a disparity in incidence of bladder cancers in diabetic patients assigned to pioglitazone versus comparator drugs.
	August 2011 Exclusion of patients with cyclophosphamide or pelvic radiation exposure, or uninvestigated macroscopic hematuria.	Revision of pioglitazone US package insert in July 2011 to include description of two observational studies that reported an association between long-term use of pioglitazone for diabetes and increased risk for bladder cancer and recommendation against use in persons with bladder cancer. European Medicine Agency recommended similar changes and included unexplained macroscopic hematuria as contraindication for pioglitazone.
Diabetes Outcome Event	January 2007 Permit deviations from ADA criteria.	Evolving practice patterns whereby diabetes may be diagnosed and medications prescribed after single fasting test or in hospitalized patients.
	December 2008 Permit glucose measures obtained by glucometer in healthcare setting.	Current medical practice patterns in community and need to preserve face value of outcome results.
Sample Size	February 2011 Increase in sample size and extension of follow-up.	DSMB instructions following first interim analysis.
Drug Dosing	August 2011 Restriction of study medication dose to 15 mg for participants also taking gemfibrozil.	Newly recognized interaction that co-administration may increase serum concentration of pioglitazone.

Table 3

Timetable of Assessments

	Screen-ing	Base-line	Week 2,4,6, 8,10,12	Month			Q 4M	Q 12M	EXIT
				4	8	12			
Physical examination[1]	X					X		X	X
Medical history	X	X							
Blood test									
Hemoglobin	X								
HbA1c	X								
Alanine transaminase	X					X		X	X
Fasting glucose	X					X		X	X
Fasting lipid profile	X					X		X	
Fasting insulin	X					X			
HS C-reactive protein	X					X			
NIH Stroke Scale		X							
Medication inventory		X				X		X	X
Modified Mini-mental Exam		X				X		X	X
Lifestyle survey[3]		X				X		X	X
Safety and outcome screening [4]			X	X	X	X	X	X	X
Study medication dose changes			4 and 8 weeks						
Study medication resupply			12 weeks		X	X	X	X	X

[1] Blood pressure, weight, height, edema grade, waist and hip measurements.

[3] Tobacco use, alcohol use, exercise habits.

[4] Self-reported weight, edema symptoms, shortness of breath, muscle aches, macroscopic hematuria; new diagnoses of stroke, MI, diabetes, CHF, cancer, fracture, macular edema; all hospitalizations.

Table 4

Trial Outcomes[1]

Primary Outcome
Fatal or non-fatal stroke or MI
Secondary Outcomes
Stroke (fatal and non-fatal) alone
Acute coronary syndrome (MI or unstable angina)
Diabetes onset
Cognitive decline
Stroke, MI or severe CHF
All-cause mortality

[1] Outcome criteria are shown in Appendix A.