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Pioglitazone Prevents Stroke in Patients with a Recent TIA or Ischemic Stroke: A Planned Secondary Analysis of the IRIS Trial

Running Title: *Yaghi et al.; Pioglitazone Prevents Stroke After Stroke or TIA*

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Abstract

***Background*—**The Insulin Resistance Intervention after Stroke (IRIS) trial demonstrated that pioglitazone reduced the risk for a composite outcome of stroke or myocardial infarction among non-diabetic patients with insulin resistance and a recent stroke or TIA. The current planned secondary analysis uses updated 2013 consensus criteria for ischemic stroke to examine the effect of pioglitazone on stroke outcomes.

Methods—Participants were randomized to receive pioglitazone (45 mg per day target dose) or placebo within 180 days of a qualifying ischemic stroke or transient ischemic attack and were followed for a maximum of 5-years. An independent committee, blinded to treatment assignments, adjudicated all potential stroke outcomes. Time to first stroke event was compared by treatment group, overall and by type of event (ischemic or hemorrhagic), using survival analyses and Cox proportional hazards models.

Results—Among 3876 IRIS participants (mean age 63 years, 65% male), 377 stroke events were observed in 319 participants over a median follow-up of 4.8 years. Pioglitazone was associated with a reduced risk for any stroke at 5-years (8.0% compared to 10.7 for placebo group; hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.60 to 0.94; log-rank p=0.01). Pioglitazone reduced risk for ischemic strokes (HR, 0.72; 95% CI, 0.57 to 0.91; p=0.005) but had no effect on risk for hemorrhagic events (HR, 1.00; 95% CI, 0.50-2.00; p=1.00).

***Conclusions*—**Pioglitazone was effective for secondary prevention of ischemic stroke in non-diabetic patients with insulin resistance.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT00091949.

Key Words: insulin resistance; stroke, ischemic; stroke, hemorrhagic; cerebrovascular disease/stroke; clinical trial; pioglitazone

Clinical Perspective

What is new?

- Pioglitazone has been shown to reduce by 24% the composite outcome of stroke or MI among non-diabetic patients with a recent ischemic stroke or TIA and insulin resistance.
- This study shows for the first time that pioglitazone also prevents stroke as a single, stand-alone outcome.
- Using the American Heart Association 2013 updated definition for stroke, pioglitazone reduced the risk by 25% (5-year risk, 8.0% vs 10.7%; hazard ratio, 0.75; 95% confidence interval, 0.60-0.94; p=0.01).
- The findings are from a planned, secondary analysis of data from the Insulin Resistance Intervention after Stroke (IRIS) trial.

What are the clinical implications?

- In non-diabetic patients with insulin resistance and a recent ischemic stroke or TIA, pioglitazone prevents stroke during five years of therapy.
- This finding adds to the evidence that pioglitazone is a potent therapy for vascular disease risk reduction.
- The new finding may help inform shared decision making by providers and patients for use of pioglitazone after ischemic stroke or TIA.

The Insulin Resistance Intervention after Stroke (IRIS) Trial recently reported that pioglitazone reduced risk for stroke or myocardial infarction among non-diabetic patients with a recent ischemic stroke or transient ischemic attack (TIA) and insulin resistance.[1] The observed absolute risk reduction for the primary outcome (2.8% over five years) and relative risk reduction (24%) were comparable to treatment effects observed for established therapies, including aspirin and statins.[2] Stroke alone, which was a secondary outcome, occurred in 6.5% of 1939 patients assigned to pioglitazone and in 8.0% of 1937 in the placebo group (HR, 0.82; 95% CI, 0.61-1.10; p, 0.19). The findings for stroke alone (for which IRIS was not powered) suggested a treatment benefit, but did not reach statistical significance.

While the trial was on-going, an international consensus panel proposed an updated definition for ischemic stroke[3] and the IRIS Data and Safety Monitoring Committee approved a planned secondary analysis of the IRIS trial using the updated definition. In this paper, we report the effect of pioglitazone when stroke outcomes are examined according to the most current 2013 stroke definition. This updated definition was less restrictive and included ischemic stroke events with confirmatory brain imaging findings but clinical syndromes lasting less than 24 hours. This was a planned analysis before data lock, with cases adjudicated by the independent, blinded Neurology Review Committee during conduct of the trial.

Methods

The data and study materials used in the current study are available to other researchers through the NIH/NINDS data archive.[4]

Patient Population

Participants were enrolled in the IRIS trial, a randomized, double-blinded clinical trial conducted during 2005-2015. The IRIS trial was approved by local institutional review boards and informed consent was obtained from all study participants. Patients were eligible for randomization if they were at least 40 years of age, had a qualifying ischemic stroke or TIA within 180 days, and insulin resistance as determined by the Homeostasis Model Assessment (HOMA-IR). Patients were excluded for diabetes, according to the definitions recommended by the American Diabetes Association at that time.[5] Participants were randomly assigned in a 1:1 ratio to placebo or pioglitazone (titrated to 45 mg daily) and followed for up to five years.

At initiation of the IRIS trial, a qualifying ischemic stroke required focal neurologic symptoms or signs lasting at least 24 hours or, for syndromes lasting less than 24 hours, a new area of infarction on brain imaging in an appropriate location. In 2006, eligibility was broadened to include selected TIA syndromes (acute neurological deficits of hemiplegia, hemiparesis, monoplegia, monoparesis, or aphasia, lasting at least 10 minutes, but less than 24 hours, without imaging evidence of acute cerebral infarction). In 2007, eligibility was further extended to patients who had non-focal stroke syndromes (e.g., dizziness, confusion, headache) lasting at least 24 hours with a focal abnormality on diffusion weighted MRI. Patients whose ischemic stroke or TIA was related to a structural cardiac lesion, significant head trauma, proximal arterial dissection or medical instrumentation were excluded. Subtypes for the index neurologic events were determined by the local site investigator based upon the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[6]

Outcomes

When the IRIS protocol was established in 2004, a stroke outcome was defined as an acute neurological event with focal signs or symptoms lasting at least 24 hours, with an appropriate new or extended abnormality on brain imaging or a one-point or greater increase from baseline on the NIH stroke scale in a previously normal section. Non-traumatic intracerebral and subarachnoid hemorrhages, but not subdural and epidural hematomas, were counted as outcomes. An external review committee of neurologists, blinded to treatment assignment, adjudicated all suspected stroke events and a consensus opinion of two reviewers was required to confirm a stroke outcome, the type (hemorrhagic or ischemic), and the subtype for ischemic events. Reviewers based subtype on TOAST criteria and the diagnostic evaluation performed at the local site.[6] A stroke was classified as fatal if death occurred within 30 days or if, in the opinion of the review committee, it was a direct result of the stroke event.

In 2014, a secondary analysis of stroke events using the AHA/ASA updated definition for stroke was added to the IRIS statistical plan.[3, 5] All stroke events meeting the original IRIS outcome criteria by definition also met the updated criteria. In addition, events were classified as stroke by the updated criteria if either signs or symptoms of an acute neurological event lasted at least 24 hours or brain imaging confirmed a new infarction consistent with the clinical syndrome. If there was no consensus on these criteria using the original reviewer assessments, the event was reviewed by a third member of the review committee before the trial was unblinded and the majority opinion was counted. Committee assessments for events captured by the updated criteria, however, did not include classification of event type or subtype. Thus, after the trial was completed, these events were reviewed by two neurologists (SY, HK), blinded to treatment assignment, who independently extracted this information using the protocol criteria for type and

subtype classification. Any differences were reconciled by consensus with a third neurologist (KF).

Because IRIS participants were not required to have MR brain imaging at trial entry, at exit, and during workup for all suspected outcome events, covert (or silent) ischemic and hemorrhagic events were not identified and counted as outcomes in the current analysis although they are considered strokes by the 2013 definition. For the same reason, some events that we counted as TIAs would have been counted as ischemic stroke by the revised criteria.

Statistical Analyses

For the present study, we examined the effect of pioglitazone on risk for any stroke, type of stroke (i.e., hemorrhagic vs. ischemic) and subtype defined by the TOAST criteria. In addition, we examined risk for stroke according to characteristics of the index neurological event and other baseline patient features. The principal analyses were conducted using the 2013 criteria for stroke outcomes, although results using the original 2004 criteria are also reported. Outcomes were analyzed as time-to-first-event and the effect of pioglitazone compared with placebo was estimated as a hazard ratio from a Cox model with 95% confidence intervals.[7] All analyses were performed with treatment as-randomized (i.e., by intention-to-treat). Cumulative event-free probabilities were calculated by the method of Kaplan-Meier and tested by the log-rank statistic using a type I error of 0.05 (2-sided).[8] As specified in the IRIS Statistical Analysis Plan, an adjusted analysis was conducted in which the hazard ratio for the primary outcome was calculated after inclusion of nine baseline covariates (age, sex, prior history of stroke, stroke [vs. TIA] as index event, history of hypertension, history of coronary artery disease, current smoker, and systolic and diastolic blood pressure). Results of statistical testing have not been adjusted for multiple comparisons.

Results

Baseline Characteristics

A total of 3876 patients were enrolled in IRIS and are included in the analysis. The mean age of participants was 63 years and 65% were male. Eighteen patients (11 in pioglitazone group and 7 in placebo group) did not have a qualifying index ischemic stroke or TIA and were randomized in error. Median time from entry neurologic event to randomization was 80 days (interquartile range, 51-121 days). Most patients entered with an ischemic stroke, with minor residual impairment as measured by the NIH Stroke Scale at randomization. Subtypes for the majority of index events were lacunar (30%) or large vessel atherosclerotic (26%). However, a third of entry events were classified as uncertain subtype by the site investigator, including a majority of the index TIAs (52%). Patient characteristics were similar at baseline by treatment group (Table 1).

Effect of Pioglitazone on Risk of Stroke

Over a median follow-up of 4.8 years, there were a total of 155 strokes in 138 participants in the pioglitazone group compared to 222 strokes in 181 participants in the placebo group (5-year risk, 8.0% compared with 10.7%; hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.60-0.94; p=0.01) (Table 2). Use of the 2013 criteria increased the number of adjudicated strokes compared to the original 2004 criteria, with 14 additional ischemic strokes in the pioglitazone group (in 11 additional patients) and 33 additional ischemic strokes and 1 additional undetermined type stroke (in 27 additional patients) in the placebo group (Supplemental Table 1). The majority of added strokes in both treatment groups had clinical syndromes lasting less than 24 hours with imaging evidence for infarction. None of the added outcomes were fatal. Overall, the mean NIHSS stroke scale score for all outcome stroke events was 3 (interquartile range 1 to 7) and 9% were fatal. Results after adjustment for baseline covariates were essentially

unchanged (HR, 0.74; 95% CI, 0.59-0.92; p=.007). Event-free survival curves for stroke began to diverge in the first year of follow-up (Figure 1). Lower risk in the pioglitazone group compared with the placebo group was observed for ischemic stroke outcomes (7.1% versus 9.9%; HR, 0.72; 95% CI, 0.57-0.91; p=0.005), but not for hemorrhagic strokes (1.0% versus 1.0%; HR, 1.00; 95% CI, 0.50-2.00; p=1.00) (Table 2).

In both treatment groups, most ischemic strokes outcomes were classified as uncertain subtype (61% and 56% for the pioglitazone and placebo groups, respectively). Pioglitazone was associated with a significant reduction in risk for lacunar strokes (HR, 0.46; 95% CI, 0.22-0.93; p=0.03), and a trend towards reduced risk for large vessel disease (HR, 0.59; 95% CI, 0.33-1.04; p=0.07). Stroke severity, as measured by NIH stroke scale scores, was nearly identical (data not shown).

Risk of Stroke According to Baseline Characteristics

At study entry, 3375 (87%) participants presented with ischemic stroke (versus TIA) as their qualifying index event and the vast majority of index event strokes were associated with focal symptoms. A reduction in risk for stroke during follow-up in the pioglitazone group compared with placebo group was observed in patients who entered the trial with an ischemic stroke (7.8% versus 11.3%; HR, 0.70; 95% CI, 0.55-0.88; p=0.003). For the 483 patients who entered the trial with a TIA, pioglitazone was not associated with risk for stroke (9.9% versus 6.8%; HR, 1.40; 95% CI, 0.71-2.73; p=0.33) (Table 3). (Test for interaction of hazard ratio and type of index event, p=0.05.)

Pioglitazone was associated with a hazard ratio less than 1.0 for all entry stroke subtypes except for stroke of uncertain cause (Table 3). For two of the subtypes, stroke related to large

vessel atherosclerosis and cardioembolism, the hazard ratios were statistically significant in directions that suggested strong protective effects.

Analyses of subgroups defined by other baseline patient features did not reveal significant modifications of the treatment effect, except for a potential interaction between pioglitazone and history of stroke before the index event. Pioglitazone was associated with reduced risk for stroke in patients who reported no history of stroke (HR, 0.65; 95% CI, 0.50-0.84), but no effect was observed in 488 patients who did report a prior stroke (HR, 1.23; 95% CI, 0.77-1.95; p-value for interaction, 0.02) (Figure 2).

Comparison with Results using 2004 Definition

The inclusion of the 48 additional ischemic stroke outcomes captured by the 2013 criteria resulted in more pronounced estimates of benefit for pioglitazone compared to results using the original stroke criteria (Supplemental Tables 2 and 3; Supplemental Figures 1 and 2). Compared with the hazard ratio of 0.75 using the 2013 criteria, the risk for any stroke using the 2004 definition was 7.4% in pioglitazone group compared with 9.1% in placebo group (HR, 0.82; 95% CI, 0.65-1.03; p=0.09 [results not adjusted for multiple secondary outcomes]). Point estimates for hazard ratios by the 2013 criteria were also lower for total ischemic stroke and all subtypes of ischemic stroke except for the uncertain and other subtypes which were unchanged (Supplemental Table 2).

Effect of 2013 Stroke Definition on other IRIS Outcomes

The protective effect of pioglitazone, compared with placebo, on the IRIS primary composite outcome of stroke or MI was strengthened using the updated stroke criteria (original criteria: HR, 0.76; 95% CI, 0.62-0.93; p=0.007; 2013 criteria: HR, 0.72; 95% CI, 0.59-0.87; p=0.0006). Similarly, results for the IRIS composite outcome of stroke, MI or serious heart failure were

more pronounced (original criteria: HR, 0.82; 95% CI, 0.65-1.05; p=0.11; 2013 criteria: HR, 0.78; 95% CI, 0.68-0.93; p=0.007) (Supplemental Table 4).

Discussion

In this planned secondary analysis of the IRIS trial, pioglitazone was associated with a reduced risk of any stroke (HR, 0.75; 95% CI 0.60-0.94; p=0.01) and ischemic stroke (HR 0.72; 95% CI 0.57-0.91; p=0.005). It had no effect on risk for hemorrhagic stroke. The number needed to treat (NNT) is 36 to prevent one patient from having an ischemic stroke during 5 years of therapy, which compares favorably to other primary and secondary stroke prevention strategies.[9, 10] This secondary analysis was based on an updated definition for ischemic stroke which was published in 2013, eight years after the trial began.[3] The updated definition captured 48 additional stroke outcomes in 38 patients compared with the definition in the original 2004 version of the IRIS protocol. All newly captured events were adjudicated and classified before the trial was unblinded. Compared with the primary IRIS analysis published in 2016, this planned secondary analysis found that pioglitazone had a larger effect on stroke prevention.

IRIS participants assigned to pioglitazone had lower rates of every subtype of ischemic stroke compared with participants assigned to placebo, but our findings only reached or approached statistical significance for lacunar infarction (HR, 0.46; 95% CI, 0.22-0.93; p=0.03) and infarction due to large vessel atherosclerosis (HR, 0.59; 95% CI 0.33-1.04; p=0.07). These findings suggest that pioglitazone has favorable effects on diverse vascular mechanisms of stroke, but they must be regarded as only suggestive. This secondary analysis did not include enough outcome events in each subtype to provide adequate a-priori statistical power to detect effects on each subtype and we did not adjust the statistical testing for multiple comparisons to

safeguard against type 1 error. Despite these statistical limitations, our findings are consistent with the known diverse biological effects of the drug.

Pioglitazone improves insulin sensitivity, reduces plasma glucose, reduces biomarkers of systemic inflammation, and improves vasomotor reactivity.[11] It has favorable effects on lipid metabolism,[12] blood pressure,[13] and thrombosis.[14] Not surprisingly given these biological effects, in clinical trials, pioglitazone reduced the progression of atherosclerosis in carotid[15-17] and cardiac[18-20] arteries and prevented progression from pre-diabetes to diabetes.[21, 22] Ours is the first study to report the effects of pioglitazone on specific stroke subtypes and gives preliminary support to the idea that it works through a myriad of pathways that are important to cerebral vascular biology and function.

The effect of pioglitazone on risk for stroke has been examined as part of a composite outcome in one other randomized clinical trial, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE).[23] PROACTIVE tested the effect of pioglitazone, compared with placebo, for preventing the composite of all-cause mortality, non-fatal MI, stroke, acute coronary syndrome, vascular surgery, or amputation above the ankle among patients with diabetes and macrovascular disease. During an average of 34.5 months of follow-up, stroke was observed in 86 of 2605 (3.3%) of patients assigned to pioglitazone and 107 of 2633 (4.1%) of patients assigned to placebo (HR, 0.81; 95% CI, 0.61-1.07). In an unplanned secondary analysis among patients who entered PROACTIVE with an ischemic stroke, pioglitazone was associated with reduced risk for fatal or non-fatal stroke (HR, 0.53; 95% CI, 0.34-0.85) and the composite of stroke, MI, or cardiovascular death (HR, 0.72; 95% CI, 0.52-1.00)[24]. Thus, our findings are consistent with the PROACTIVE trial results.

In our examination of treatment effect according to pre-treatment patient features, we found evidence for possible effect modification by history of stroke and type of entry event. IRIS participants with no history of stroke had a greater benefit from pioglitazone compared with participants with prior stroke. The p-value for a test of interaction (unadjusted for multiple comparisons) was significant. The biological rationale for this interaction is not apparent. Because of lack of biological plausibility, this finding needs to be confirmed.

Similarly, our findings for effect modification by type of entry event are suggestive, but not proven. Based on the hazard ratios, we observed a treatment benefit for IRIS participant who entered because of a recent ischemic stroke but not for TIA. The hazard ratio was less than 1.0 for all entry stroke subtypes except for stroke of uncertain cause. For stroke related to large vessel atherosclerosis and cardioembolism, the hazard ratios reached statistical significance, supporting again the idea that pioglitazone seems to ameliorate disparate biological pathologies.

Our analysis has some limitations. First, we did not systematically survey for covert (i.e., silent) ischemic stroke and, therefore, could not fully apply the revised 2013 diagnostic criteria for ischemic stroke. Second, site investigators were not required to submit for adjudication neurological events with symptoms that lasted less than 24 hours (even with positive imaging). It is possible, therefore, that events meeting the 2013 stroke definition were missed among our trial participants. Third, MR brain imaging was not required for suspected outcome events and this may have resulted in fewer events meeting the 2013 stroke criteria. Despite these three limitations, we have no reason to believe that there was differential surveillance, imaging, or reporting of neurological events between treatment groups. To check for the possibility of underreporting, we examined hospitalizations among participants, as all hospitalizations had to be reported according to the IRIS protocol. We identified no stroke hospitalizations that were

not submitted for adjudication, suggesting that underreporting was not a significant problem. The net effect of missing covert ischemic strokes and imaging positive TIAs would be to undercount ischemic stroke in our study. Had counting been more complete, our effect estimate probably would not have changed significantly, but our statistical power would likely have been greater and the findings of our study might have been strengthened.

Second, our ability to analyze treatment effects by ischemic stroke subtypes was limited by a protocol which did not require investigators to routinely perform intracranial vascular imaging or prolonged cardiac rhythm monitoring. This is one reason that many baseline stroke events were classified as being of uncertain subtype. Third, due to the small rate of recurrent stroke among certain subtypes, the analysis was underpowered to detect an association between pioglitazone and stroke risk for these subtypes. Fourth, the IRIS trial enrolled patients up to 6 months after a qualifying ischemic stroke or TIA. Because the risk of recurrence is highest soon after a stroke or TIA, the IRIS trial could not test the effect of pioglitazone on very early recurrent events.[25-27] Finally, the insulin resistant patients enrolled in the IRIS trial may not be representative of all patients with stroke, and the generalizability of our findings to patients with comorbid conditions such as diabetes and heart failure, or more severe deficits is uncertain.

In conclusion, in patients with insulin resistance and a recent stroke or TIA, pioglitazone reduced the risk of ischemic stroke using prevailing and now widely accepted clinical criteria. The effect was quantitatively substantial (2.8% absolute risk difference over 5 years) and statistically significant. More research is needed to study the effects of pioglitazone and other interventions that improve insulin resistance for preventing recurrent vascular events, including very early events, and improving function in patients with established cerebrovascular disease.

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Disclosures

CMV received a consulting fee (modest) from Takeda Pharmaceuticals International for analyzing prostate cancer data in the IRIS trial. SEI is a consultant to or has served on research steering committees for AstraZeneca (modest), Boehringer Ingelheim (significant), Daichii Sankyo (modest), Lexicon (modest) Janssen (modest), Merck (significant), Poxel (modest), Sanofi (modest), and vTv Pharmaceuticals (modest.) He has also served on data monitoring committees for Novo Nordisk (modest) and Intarcia (significant). No other potential conflicts of interest relevant to this article were reported.

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Table 1. Baseline Features of IRIS Participants

Feature	Pioglitazone (n=1939)	Placebo (n=1937)
Demographic features		
Age, years	63 ±11	63 ±11
Male sex	1293 (67)	1245 (64)
Black race	218 (11)	225 (12)
Hispanic ethnicity	75 (4)	72 (4)
Index event		
Ischemic stroke (vs. TIA)	1690 (87)	1682 (87)
Index event subtype		
Lacunar	587 (30)	560 (29)
Large vessel	502 (26)	505 (26)
Cardioembolic	147 (8)	137 (7)
Other defined	38 (2)	61 (3)
Uncertain	629 (32)	643 (33)
Unknown	36 (2)	31 (2)
Modified Rankin scale at screening, 0-2	1770 (91)	1782 (92)
NIH stroke scale at randomization, 0-4	1846 (95)	1850 (96)
Clinical History		
Prior stroke (before index event)	246 (13)	242 (13)
Hypertension	1380 (71)	1390 (72)
Coronary artery disease	241 (12)	221 (11)
Carotid artery intervention*	132 (7)	155 (8)
Atrial fibrillation	134 (7)	130 (7)
Current cigarette smoking	323 (17)	299 (15)
Physical examination		
Body mass index, kg/m^2	29.9 ±5.6	30.0 ±5.3
Systolic blood pressure, mmHg	133 ±18	133 ±17
Diastolic blood pressure, mmHg	79 ±11	79 ±11
Laboratory data		
HOMA-IR	4.7 (3.8, 6.2)	4.6 (3.7, 6.2)
HbA1c, %	5.8 ±0.4	5.8 ±0.4
LDL cholesterol, mmol/L	2.28 ±0.80	2.28 ±0.80
Triglycerides, mmol/L	1.62 ±0.84	1.57 ±0.81
C-reactive protein	2.2 (1.0, 4.9)	2.3 (1.1, 5.0)
Concomitant medications		
Statin	1594 (83)	1592 (82)
Antiplatelet	1781 (92)	1786 (92)
Anticoagulant	232 (12)	209 (11)

Continuous variables are shown as mean (standard deviation(SD)), or median (1st quartile, 3rd quartile), if distribution is skewed. Categorical variables are shown as counts (%).

*Carotid endarterectomy, angioplasty or stenting before or after index event.

Number of participants with missing data (pioglitazone, placebo): Race(33, 33); Hispanic ethnicity(12, 8); prior stroke (1, 2); Rankin (0, 1); NIHSS (1, 1);hypertension history(1, 1); atrial fibrillation(2, 0); BMI (6, 6); blood pressure (6, 6); LDL (21, 17); triglycerides (4, 3); C-rp(17, 12); medications (7, 5).

Table 2. Risk of Stroke Outcomes, Overall and by Stroke Type and Subtype*, by Treatment Group

Stroke Outcome	Pioglitazone (n=1939)			Placebo (n=1937)			Hazard Ratio (95% CI)§	P‖
	Events	Pts†	Risk‡	Events	Pts†	Risk‡		
Any Stroke	155	138	8.0%	222	181	10.7%	0.75 (0.60, 0.94)	0.01
Hemorrhagic Stroke	17	16	1.0%	19	16	1.0%	1.00 (0.50, 2.00)	1.00
Non-fatal	11	10	0.6%	12	9	0.6%	1.11 (0.45, 2.73)	0.82
Fatal	6	6	0.4%	7	7	0.4%	0.86 (0.29, 2.55)	0.78
Ischemic Stroke	137	123	7.1%	202	169	9.9%	0.72 (0.57, 0.91)	.005
Non-fatal	131	118	6.9%	191	161	9.3%	0.72 (0.57, 0.92)	.008
Fatal	6	6	0.3%	11	11	0.8%	0.55 (0.20, 1.47)	0.23
Ischemic Stroke Subtype								
Uncertain	83	79	4.7%	113	96	5.7%	0.82 (0.61, 1.10)	0.19
Large vessel	23	19	1.0%	34	32	1.9%	0.59 (0.33, 1.04)	0.07
Cardioembolic	17	17	1.0%	26	24	1.5%	0.71 (0.38, 1.32)	0.27
Lacunar	12	11	0.7%	24	24	1.3%	0.46 (0.22, 0.93)	0.03
Other defined	2	2	0.1%	5	5	0.3%	0.40 (0.08, 2.07)	0.27

*1 fatal event in pioglitazone group and 1 non-fatal event in placebo group was uncertain type and are excluded from analysis by type and subtype.
†Number of participants with outcome.
‡5-year risk from life-table.
§Unadjusted hazard ratios calculated by Cox regression model with corresponding 95% confidence intervals (CI).
‖Unadjusted P-value from log-rank test.

Table 3. Risk of Stroke within Subgroups defined by Index Event Type and Subtype*, by Treatment Group

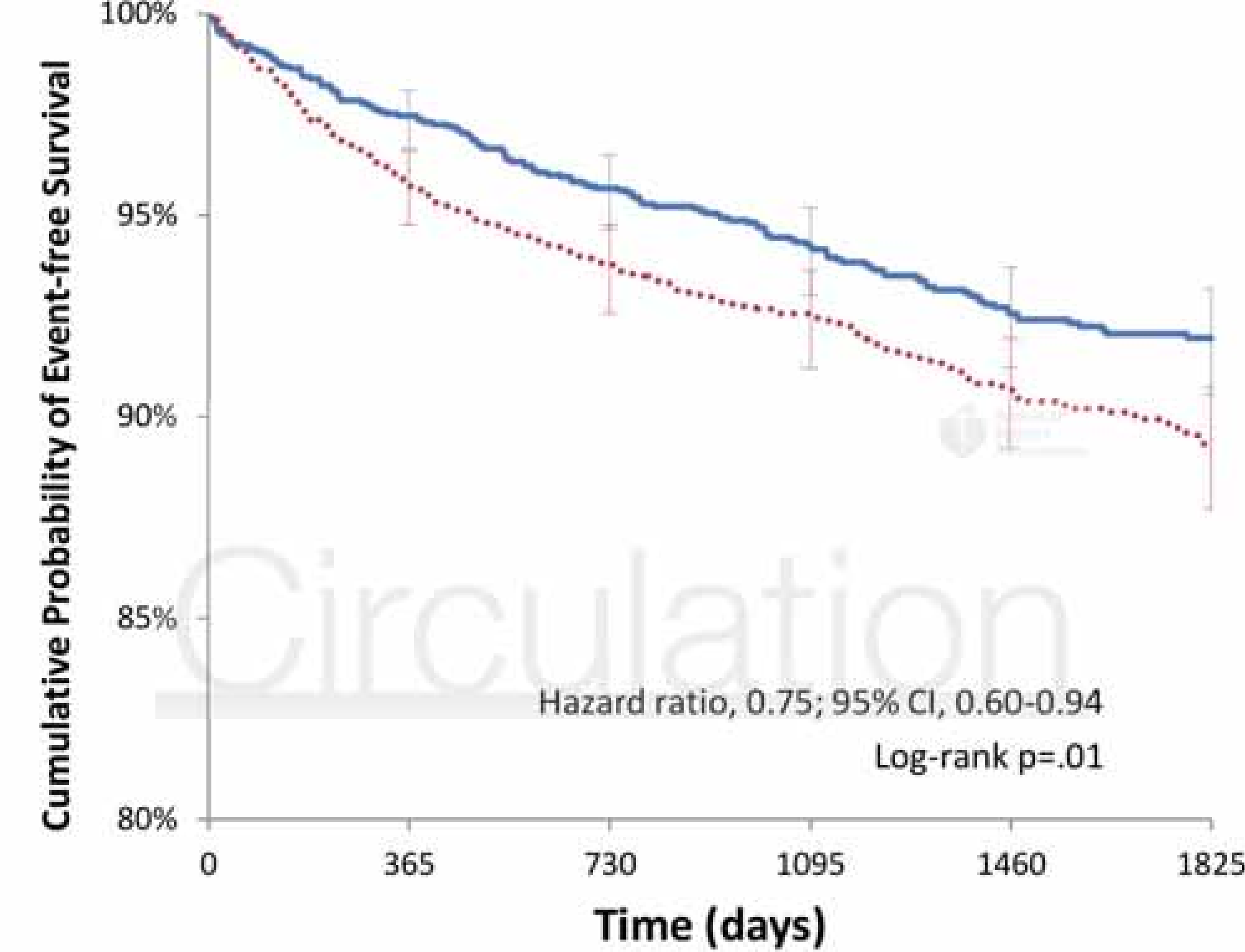
Group	Pioglitazone Event† / N			Risk‡	Placebo Event†/N			Risk‡	Hazard Ratio (95% CI)§	P‖
Index Event Type**										
Ischemic stroke	118	/	1693	7.8%	166	/	1682	11.3%	0.70 (0.55, 0.88)	0.003
Focal stroke	118	/	1670	7.9%	164	/	1660	11.3%	0.71 (0.56, 0.90)	0.004
Non-focal stroke	0	/	23	0.0%	2	/	22	9.5%	--	--
TIA	20	/	235	9.9%	15	/	248	6.8%	1.40 (0.71, 2.73)	0.33
Index Event Subtype										
Lacunar	41	/	587	8.0%	47	/	560	9.5%	0.85 (0.56, 1.29)	0.44
Large vessel	30	/	502	6.4%	54	/	505	12.2%	0.54 (0.35, 0.84)	0.007
Cardioembolic	10	/	147	7.9%	20	/	137	16.3%	0.43 (0.20, 0.93)	0.03
Other defined	1	/	38	2.6%	8	/	61	16.8%	0.19 (0.02, 1.49)	0.11
Uncertain	53	/	629	9.6%	48	/	643	8.5%	1.13 (0.77, 1.67)	0.54
Unknown	3	/	36	9.2%	4	/	31	14.5%	0.61 (0.14, 2.71)	0.51

*11 participants in pioglitazone group and 7 participants in placebo group had ineligible index events and are excluded from analyses by index event type and subtype; no stroke outcomes occurred in these patients.
†Number of participants with stroke outcome.
‡5-year risk from life-table.
§Unadjusted hazard ratios calculated by Cox regression model with corresponding 95% confidence intervals (CI).
‖Unadjusted P-value from log-rank test.
**P-value for test of interaction between index event type and hazard ratio: 0.05.

Figure Legends

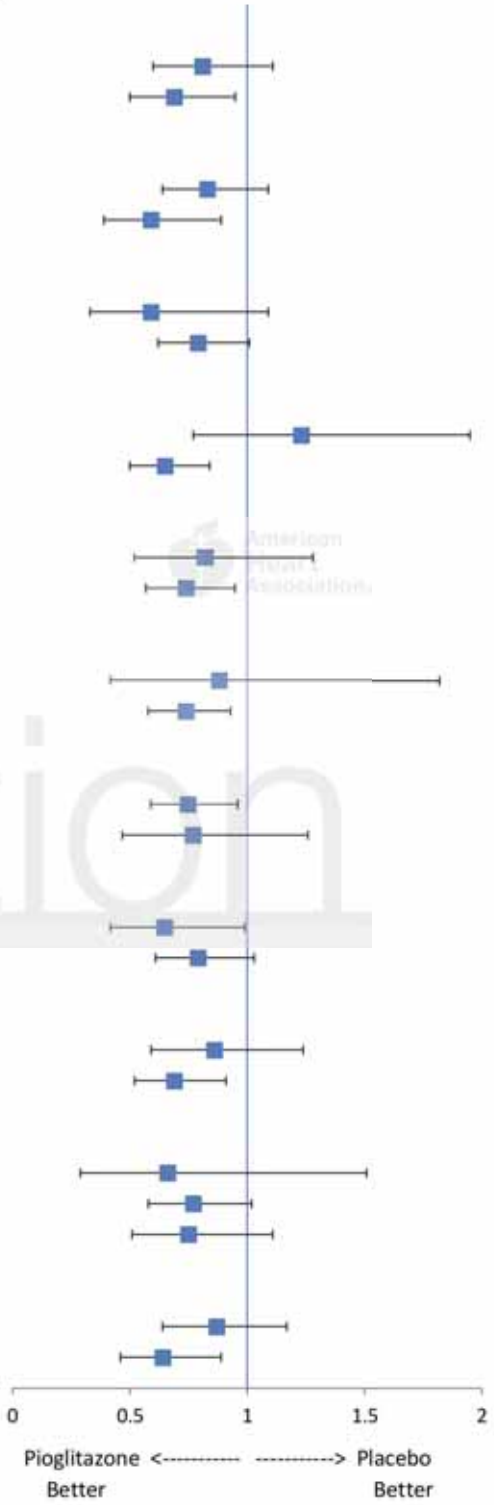
Figure 1. Time to First Stroke by Treatment Group (pioglitazone=solid line, placebo=dashed line).

Figure 2. Risk of Stroke by Treatment Group within Patient Subgroups. *P-value is the test for interaction between treatment and each subgroup unadjusted for multiplicity. †Participants with HbA1c below the usual target for treatment of 7.0% were permitted to enroll.

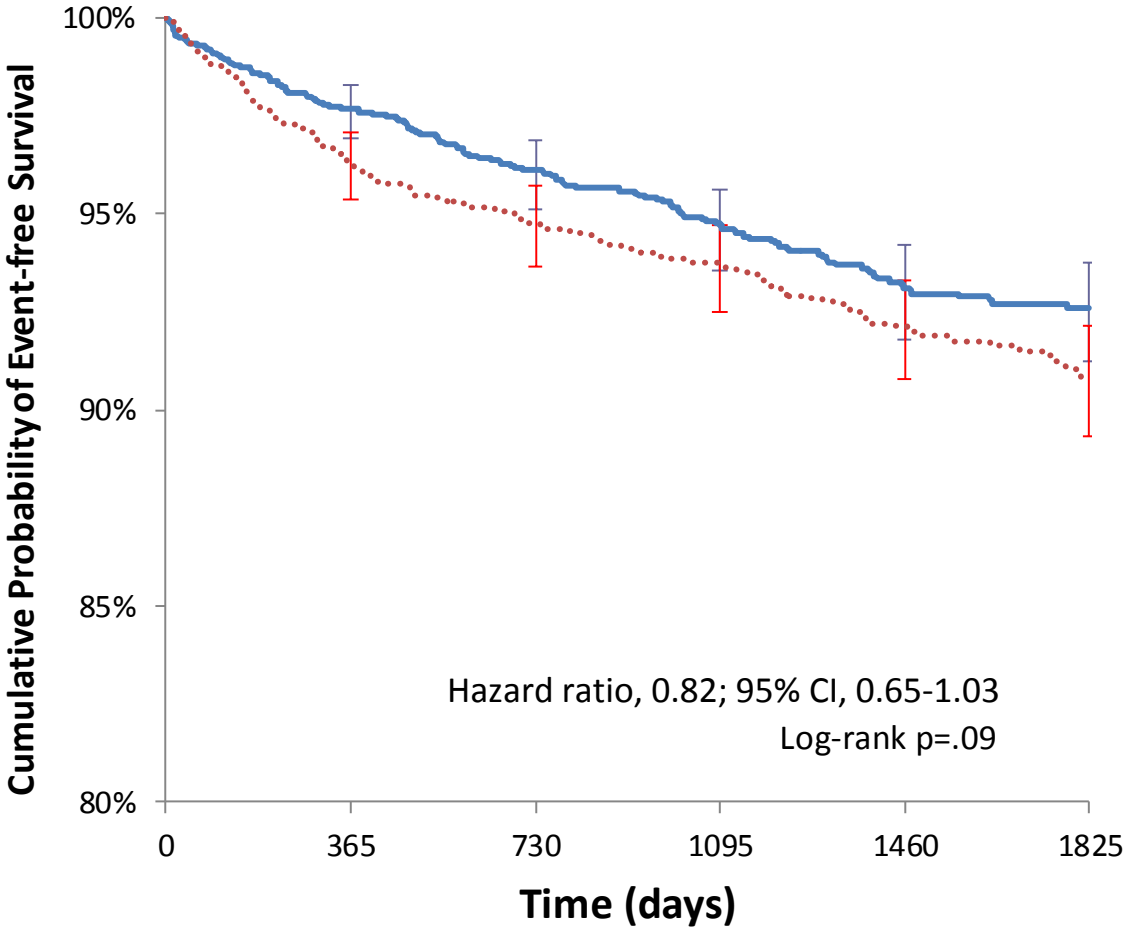


No. at Risk:						
Pioglitazone	1939	1804	1712	1509	1214	536
Placebo	1937	1780	1698	1495	1199	505

Group	Pioglitazone Events / N	Risk	Placebo Events / N	Risk	Hazard Ratio (95% CI)	Int. P*
Age						
≥65 years	75 / 826	(10.6)	91 / 822	(12.6)	0.81 (0.60, 1.11)	0.47
<65 years	63 / 1113	(6.1)	90 / 1115	(9.2)	0.69 (0.50, 0.95)	
Gender						
Male	102 / 1293	(8.7)	116 / 1245	(10.7)	0.83 (0.64, 1.09)	0.17
Female	36 / 646	(6.6)	65 / 692	(10.6)	0.59 (0.39, 0.89)	
Race						
Black or African American	17 / 218	(8.8)	28 / 225	(13.9)	0.59 (0.33, 1.09)	0.38
White/other	121 / 1688	(8.1)	151 / 1679	(10.3)	0.79 (0.62, 1.01)	
Prior Stroke						
Yes	40 / 246	(18.3)	32 / 242	(14.9)	1.23 (0.77, 1.95)	0.02
No	98 / 1692	(6.6)	149 / 1693	(10.1)	0.65 (0.50, 0.84)	
Carotid Stenosis						
Yes	34 / 349	(10.3)	43 / 371	(13.4)	0.82 (0.52, 1.28)	0.69
No	104 / 1588	(7.5)	138 / 1564	(10.0)	0.74 (0.57, 0.95)	
Atrial Fibrillation						
Yes	14 / 134	(11.5)	15 / 130	(12.8)	0.88 (0.42, 1.82)	0.67
No	123 / 1803	(7.7)	166 / 1807	(10.5)	0.74 (0.58, 0.93)	
Hypertension History						
Yes	109 / 1380	(8.9)	145 / 1390	(11.9)	0.75 (0.59, 0.96)	0.92
No	29 / 558	(5.8)	36 / 546	(7.4)	0.77 (0.47, 1.26)	
LDL-cholesterol						
≥2.59 mmol/L	35 / 584	(6.7)	51 / 560	(10.2)	0.65 (0.42, 0.99)	0.43
<2.59 mmol/L	101 / 1334	(8.5)	129 / 1360	(10.9)	0.79 (0.61, 1.03)	
Body Mass Index						
≥30 kg/m²	52 / 825	(7.1)	63 / 858	(8.8)	0.86 (0.59, 1.24)	0.36
<30 kg/m²	85 / 1108	(8.7)	117 / 1073	(12.2)	0.69 (0.52, 0.91)	
Glycated Hemoglobin						
6.5-6.9%†	9 / 116	(9.3)	15 / 129	(12.3)	0.66 (0.29, 1.51)	0.96
5.7%-6.4%	84 / 1150	(8.2)	106 / 1118	(11.1)	0.77 (0.58, 1.02)	
<5.7%	45 / 672	(7.6)	60 / 690	(9.6)	0.75 (0.51, 1.11)	
HOMA >median						
Yes	79 / 976	(9.1)	89 / 957	(10.6)	0.87 (0.64, 1.17)	0.19
No	59 / 963	(7.1)	92 / 980	(10.7)	0.64 (0.46, 0.89)	



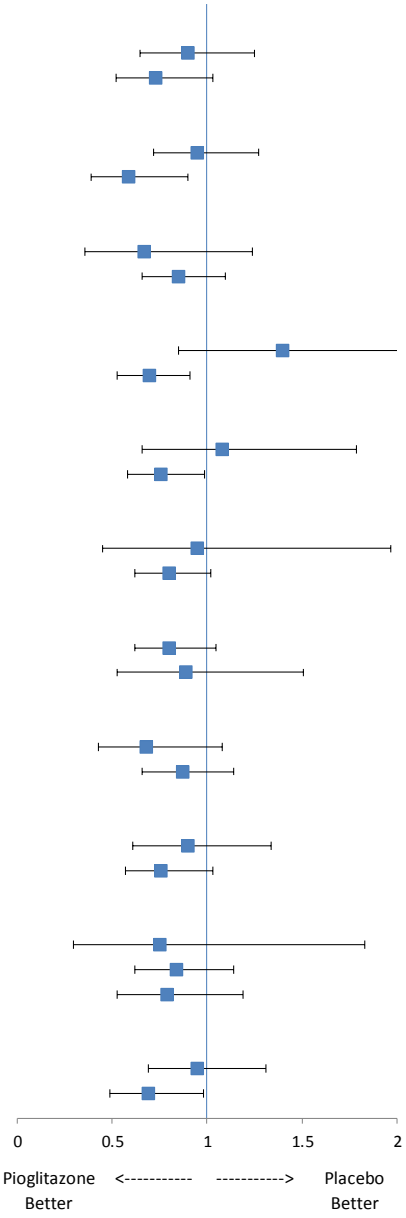
*P-value is the test for interaction between treatment and each subgroup unadjusted for multiplicity.
†Participants with HbA1c below the usual target for treatment of 7.0% were permitted to enroll.



No. at Risk:						
Pioglitazone	1939	1808	1720	1517	1221	538
Placebo	1937	1789	1716	1511	1217	516

Supplemental Figure 1. Time to first stroke (2004 criteria) in the pioglitazone arm (solid line) and placebo (dotted line)

Group	Pioglitazone Events / N (%)	Placebo Events / N (%)	Hazard Ratio (95% CI)	Int. P.*
Age				
≥65 years	70 / 826 (9.8)	77 / 822 (10.8)	0.90 (0.65, 1.25)	0.38
<65 years	57 / 1113 (5.6)	77 / 1115 (7.9)	0.73 (0.52, 1.03)	
Gender				
Male	94 / 1293 (8.0)	94 / 1245 (8.7)	0.95 (0.72, 1.27)	0.07
Female	33 / 646 (6.1)	60 / 692 (9.9)	0.59 (0.39, 0.90)	
Race				
Black or African American	17 / 218 (8.8)	25 / 225 (12.5)	0.67 (0.36, 1.24)	
White/other	110 / 1688 (7.4)	128 / 1679 (8.8)	0.85 (0.66, 1.10)	0.48
Prior Stroke				
Yes	37 / 246 (17.1)	26 / 242 (12.3)	1.40 (0.85, 2.31)	
No	90 / 1692 (6.0)	128 / 1693 (8.7)	0.70 (0.53, 0.91)	0.02
Carotid Stenosis				
Yes	31 / 349 (9.5)	30 / 371 (9.6)	1.08 (0.66, 1.79)	
No	96 / 1588 (7.0)	124 / 1564 (9.1)	0.76 (0.58, 0.99)	0.22
Atrial Fibrillation				
Yes	14 / 134 (11.5)	14 / 130 (12.1)	0.94 (0.45, 1.97)	
No	112 / 1803 (7.0)	140 / 1807 (8.9)	0.80 (0.62, 1.02)	0.70
Hypertension History				
Yes	100 / 1380 (8.2)	125 / 1390 (10.4)	0.80 (0.62, 1.05)	
No	27 / 558 (5.4)	29 / 546 (5.9)	0.89 (0.53, 1.51)	0.71
LDL-cholesterol				
≥2.59 mmol/L	31 / 584 (5.9)	43 / 560 (8.7)	0.68 (0.43, 1.08)	
<2.59 mmol/L	94 / 1334 (8.0)	110 / 1360 (9.4)	0.87 (0.66, 1.14)	0.38
Body Mass Index				
≥30	47 / 825 (6.4)	54 / 858 (7.6)	0.90 (0.61, 1.34)	
<30	79 / 1108 (8.1)	99 / 1073 (10.4)	0.76 (0.57, 1.03)	0.50
Glycated Hemoglobin				
6.5-6.9%**	8 / 116 (8.6)	12 / 129 (9.9)	0.75 (0.30, 1.83)	
5.7%-6.4%	78 / 1150 (7.6)	90 / 1118 (9.5)	0.84 (0.62, 1.14)	
<5.7%	41 / 672 (6.9)	52 / 690 (8.3)	0.79 (0.53, 1.19)	0.96
HOMA >median				
Yes	72 / 976 (8.2)	74 / 957 (8.9)	0.95 (0.69, 1.31)	
No	55 / 963 (6.6)	80 / 980 (9.4)	0.69 (0.49, 0.98)	0.19



* P-value is the test for interaction between treatment and each subgroup unadjusted for multiplicity.
**Participants with HbA1c below the usual target for treatment of 7.0% were permitted to enroll.

Supplemental Figure 2. Risk of Stroke (2004 criteria) by Treatment

Supplemental Table 1. Additional Stroke Outcome Events Meeting 2013 Criteria (n=48)

No.	Treatment	Type	Subtype	NIH Stroke Scale Score			Signs or Symptoms ≥24 hours*	Imaging†
				Baseline	Outcome	Δ		
1	Placebo	Ischemic	Lacunar	0	0	0	Y	N
2	Pioglitazone	Ischemic	Undetermined	2	2	0	N	Y
3	Placebo	Ischemic	Undetermined	4	2	-2	N	Y
4	Placebo	Ischemic	Undetermined	1	1	0	N	Y
5	Pioglitazone	Ischemic	Large vessel	0	0	0	Y	N
6	Placebo	Ischemic	Undetermined	0	0	0	Y	N
7	Pioglitazone	Ischemic	Undetermined	4	0	-4	N/Unc	Y
8	Placebo	Ischemic	Lacunar	0	0	0	Y	N
9	Placebo	Ischemic	Lacunar	1	1	0	Y	Not done
10	Pioglitazone	Ischemic	Large vessel	0	0	0	N	Y
11	Pioglitazone	Ischemic	Undetermined	4	2	-2	Y	N
12	Placebo	Ischemic	Large vessel	2	3	1	Y	N
13	Placebo	Ischemic	Large vessel	0	1	1	N	Y
14	Pioglitazone	Ischemic	Undetermined	2	0	-2	Y	N
15	Placebo	Ischemic	Lacunar	1	1	0	Y	N
16	Placebo	Ischemic	Undetermined	1	0	-1	Y	N
17	Placebo	Ischemic	Undetermined	1	1	0	N	Y
18	Placebo	Ischemic	Cardioembolic	2	1	-1	N	Y
19	Placebo	Ischemic	Undetermined	2	0	-2	Y	N
20	Placebo	Ischemic	Undetermined	2	1	-1	Unc	Y
21	Placebo	Ischemic	Undetermined	2	2	0	N	Y
22	Pioglitazone	Ischemic	Lacunar	9	4	-5	Y	N
23	Pioglitazone	Ischemic	Undetermined	0	0	0	Y	N
24	Pioglitazone	Ischemic	Undetermined	0	0	0	N	Y
25	Placebo	Ischemic	Large vessel	0	--	--	N	Y
26	Placebo	Ischemic	Large vessel	0	0	0	N	Y
27	Placebo	Ischemic	Undetermined	0	0	0	N	Y
28	Placebo	Ischemic	Cardioembolic	0	0	0	N	Y
29	Placebo	Ischemic	Cardioembolic	0	0	0	N	Y
30	Pioglitazone	Ischemic	Undetermined	3	3	0	N	Y
31	Placebo	Ischemic	Lacunar	0	0	0	N	Y
32	Placebo	Ischemic	Cardioembolic	1	9	8	N	Y
33	Placebo	Ischemic	Lacunar	0	0	0	Y	N
34	Placebo	Ischemic	Lacunar	2	0	-2	Y	N
35	Placebo	Ischemic	Large vessel	1	0	-1	N/Unc	Y
36	Placebo	Ischemic	Undetermined	1	0	-1	N	Y
37	Pioglitazone	Ischemic	Lacunar	4	1	-3	Y	N
38	Placebo	Ischemic	Large vessel	0	0	0	N	Y
39	Pioglitazone	Ischemic	Undetermined	0	2	2	Y/N	N/Y
40	Placebo	Ischemic	Undetermined	0	0	0	Y	N
41	Pioglitazone	Ischemic	Cardioembolic	2	1	-1	Y	N
42	Placebo	Ischemic	Undetermined	5	--	--	Y	N
43	Placebo	Ischemic	Undetermined	0	0	0	N	Y
44	Pioglitazone	Ischemic	Large vessel	0	0	0	N	Y
45	Placebo	Ischemic	Large vessel	0	0	0	Y	N
46	Placebo	Ischemic	Undetermined	3	3	0	N	Y
47	Placebo	Ischemic	Undetermined	0	0	0	Y	N
48	Placebo	Undetermined		2	2	0	Y	N

*Acute neurological event with focal signs and symptoms lasting at least 24 hours (consensus opinion of reviewers, Y=yes, N=no, Unc=uncertain).

†CT or MRI indicating a new infarction consistent with signs or symptoms (consensus opinion of reviewers, Y=yes, N=no).

Supplemental Table 2. Risk of Stroke Outcomes (2004 criteria), Overall and by Stroke Type and Subtype[*], by Treatment Group

Stroke Outcome	Pioglitazone (n=1939)			Placebo (n=1937)			Hazard Ratio (95% CI)[§]	P‖
	Events	Pts[†]	Risk[‡]	Events	Pts[†]	Risk[‡]		
Any Stroke[**]	141	127	7.4%	188	154	9.1%	0.82 (0.65, 1.03)	0.09
Hemorrhagic Stroke	17	16	1.0%	19	16	1.0%	1.00 (0.50, 2.00)	1.00
Non-fatal	11	10	0.6%	12	9	0.6%	1.11 (0.45, 2.73)	0.82
Fatal	6	6	0.4%	7	7	0.4%	0.86 (0.29, 2.55)	0.78
Ischemic Stroke	123	113	6.5%	169	143	8.5%	0.78 (0.61, 1.00)	0.05
Non-fatal	117	107	6.3%	158	135	7.9%	0.79 (0.61, 1.01)	0.06
Fatal	6	6	0.3%	11	11	0.8%	0.55 (0.20, 1.47)	0.23
Ischemic Stroke Subtype								
Uncertain	75	71	4.3%	98	86	5.1%	0.82 (0.60, 1.12)	0.22
Large vessel	20	17	0.9%	27	25	1.5%	0.68 (0.37, 1.25)	0.22
Cardioembolic	16	16	0.9%	22	21	1.4%	0.76 (0.40, 1.46)	0.41
Lacunar	10	9	0.5%	17	17	1.0%	0.53 (0.24, 1.19)	0.12
Other defined	2	2	0.1%	5	5	0.3%	0.40 (0.08, 2.07)	0.27

[*]1 fatal event in pioglitazone group was uncertain type and is excluded from analysis by type and subtype.

[†]Number of participants with outcome.

[‡]5-year risk from life-table.

[§]Unadjusted hazard ratios calculated by Cox regression model with corresponding 95% confidence intervals (CI).

‖ Unadjusted P-value from log-rank test.

[**]Results for stroke adjusted for five secondary IRIS outcomes: 95% CI (0.61, 1.10); p-value: 0.19.

*

Supplemental Table 3. Risk of Stroke (2004 criteria) within Subgroups defined by Index Event Type and Subtype[*], by Treatment Group

Subgroup	Pioglitazone Event[†] / N	Risk[‡]	Placebo Event[†]/N	Risk[‡]	Hazard Ratio (95% CI)[§]	P[‖]
Index Event Type[**]						
Ischemic stroke	109 / 1693	7.2%	144 / 1682	9.8%	0.75 (0.58, 0.96)	0.02
Focal stroke	109 / 1670	7.3%	142 / 1660	9.9%	0.76 (0.59, 0.97)	0.03
Non-focal stroke	0 / 23	0.0%	2 / 22	9.5%	--	
TIA	18 / 235	8.9%	10 / 248	4.7%	1.90 (0.88, 4.11)	0.10
Index Event Subtype						
Lacunar	39 / 587	7.7%	40 / 560	8.2%	0.95 (0.61, 1.48)	0.83
Large vessel	28 / 502	6.0%	42 / 505	9.7%	0.65 (0.41, 1.05)	0.08
Cardioembolic	9 / 147	7.2%	18 / 137	14.8%	0.43 (0.19, 0.97)	0.04
Other defined	1 / 38	2.6%	8 / 61	16.8%	0.19 (0.02, 1.49)	0.11
Uncertain	47 / 629	8.5%	43 / 643	7.6%	1.12 (0.74, 1.69)	0.60
Unknown	3 / 36	9.2%	3 / 31	11.0%	0.82 (0.17, 4.07)	0.81

[*]11 participants in pioglitazone group and 7 participants in placebo group had ineligible index events and are excluded from analyses by index event type and subtype; no stroke outcomes occurred in these patients.

[†]Number of participants with stroke outcome.

‡5-year risk from life-table.

[§]Unadjusted hazard ratios calculated by Cox regression model with corresponding 95% confidence intervals (CI).

[‖] Unadjusted P-value from log-rank test.

[**]P-value for test of interaction between index event type and hazard ratio: 0.02.

Supplemental Table 4. IRIS Primary and Secondary Outcomes, using 2013 stroke criteria, by Treatment Group

Outcome	Pioglitazone (N=1939)	Placebo (N=1937)	Hazard Ratio (95% CI)*	P Value†
Primary Outcome	*Number of Participants (%)*			
Stroke or MI	185 (9.5)	254 (13.1)	0.72 (0.59, 0.87)	0.0006
Stroke	133 (6.9)	176 (9.1)		
Fatal	9	13		
Non-Fatal	124	163		
Myocardial Infarction	52 (2.7)	78 (4.0)		
Fatal	7	14		
Non-Fatal	45	64		
Secondary Outcome‡				
Stroke/MI/serious heart failure§	216 (11.1)	273 (14.1)	0.78 (0.65, 0.93)	0.007

*Unadjusted hazard ratios calculated by Cox regression model with corresponding 95% confidence intervals (CI).

†Unadjusted P-value from log-rank test.

‡Only the first event was counted for each participant.

§Serious heart failure is defined as episode resulting in hospitalization or death.

APPENDIX

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