Pioglitazone for Secondary Stroke Prevention
A Systematic Review and Meta-Analysis

Meng Lee, MD; Jeffrey L. Saver, MD; Hung-Wei Liao, MD; Chun-Hsien Lin, MD; Bruce Ovbiagele, MD

Background and Purpose—Pioglitazone reduced major vascular events after ischemic stroke in a recent randomized controlled trial. The purpose of this study was to conduct a meta-analysis of randomized controlled trials to evaluate the effect of pioglitazone therapy in reducing the risk of recurrent stroke in stroke patients.

Methods—Pubmed, EMBASE, Medline, and Cochrane Central Register of Controlled Trials from 1966 to March 2016 were searched to identify relevant studies. We included randomized controlled trials that included comparison of pioglitazone versus control and trials in which quantitative estimates of the hazard ratio and 95% confidence interval for recurrent stroke associated with pioglitazone therapy among stroke patients were reported. Hazard ratios with 95% confidence intervals were used as a measure of the association between use of pioglitazone and risks of recurrent stroke (ischemic and hemorrhagic) and major vascular events (nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death) after pooling data across trials. Between-study heterogeneity was assessed using the I² statistic.

Results—Three randomized controlled trials with 4980 participants were identified. Use of pioglitazone in stroke patients with insulin resistance, prediabetes, and diabetes mellitus was associated with lower risk of recurrent stroke (hazard ratio 0.68; 95% confidence interval, 0.50–0.92; P=0.01) and future major vascular events (hazard ratio 0.75; 95% confidence interval, 0.64–0.87; P=0.0001). There was no heterogeneity across trials. There was no evidence of an effect on all-cause mortality and heart failure.

Conclusions—Pioglitazone reduces recurrent stroke and major vascular events in ischemic stroke patients with insulin resistance, prediabetes, and diabetes mellitus. (Stroke. 2017;48:388-393. DOI: 10.1161/STROKEAHA.116.013977.)

Key Words: diabetes mellitus ■ insulin resistance ■ pioglitazone ■ prediabetic state ■ secondary prevention

Patients with ischemic stroke or transient ischemic attack (TIA) remain at increased risk for recurrent stroke and future vascular events despite the effectiveness of current preventive therapies and a temporal decline in stroke incidence.1–3 New preventive strategies to further improve outcomes after ischemic stroke or TIA are needed.

Disorders of glucose metabolism are highly prevalent among patients with stroke and TIA,4–6 and diabetes mellitus is associated with increased risk for recurrent ischemic stroke.7–9 However, oral antidiabetic drugs have not been associated with reduced stroke events,10 and intensive glycemic control does not seem to prevent risk of stroke in diabetic patients.11 Similar to statin drugs, which have potent vascular protective properties that go beyond their primary action of cholesterol lowering, it is conceivable that hypoglycemic agents with pleiotropic properties may better at reducing vascular events than traditional hypoglycemic drugs. Pioglitazone is a peroxisome proliferator–activated receptor γ agonist that, in addition to its primary effect on glycemic control, exerts potential beneficial effects on inflammation, fat distribution, lipid and protein metabolism, and vascular endothelial function.12–15 The IRIS trial (Insulin Resistance Intervention After Stroke) found that among patients without diabetes mellitus who had insulin resistance along with a recent history of ischemic stroke or TIA, the risk of combined stroke or myocardial infarction was lower among patients who received pioglitazone than among those who received placebo, but differences in recurrent stroke alone did not reach statistical significance.16 The objective of this study was to use the totality of the published literature to qualitatively and quantitatively evaluate the risk of recurrent stroke in stroke patients with abnormal glucose metabolism receiving pioglitazone therapy, by conducting a systematic review and meta-analysis of randomized controlled trials.

Methods

This study was performed in accordance with the recommendations of the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).17

Received May 3, 2016; final revision received November 4, 2016; accepted November 14, 2016.

From the Department of Neurology, Chang Gung University College of Medicine, Chang Gung Memorial Hospital, Chiayi, Taiwan (M.L., C.-H.L.); Stroke Center, Geffen School of Medicine, University of California, Los Angeles (J.L.S.); Jia-Yi Clinic, Taoyuan, Taiwan (H.-W.L.); and Department of Neurology, Medical University of South Carolina, Charleston (B.O.).

Guest Editor for this article was Tatjana Rundek, MD, PhD.

Correspondence to Bruce Ovbiagele, MD, Department of Neurology, Medical University of South Carolina, 96 Jonathan Lucas St, CSB 301, MSC 606 Charleston, SC 29425. E-mail ovibes@musc.edu

© 2016 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.116.013977

388
Data Sources and Searches
We searched Pubmed (1966 to March 4, 2016), EMBASE and Medline (1980 to March 4, 2016), and the Cochrane Central Register of Controlled Trials with the terms pioglitazone or actos and stroke or cerebrovascular disease or cerebral ischemia or myocardial infarction or coronary heart disease or coronary artery disease or cardiovascular disease or macrovascular disease. There were no language restrictions. We also reviewed the Introduction and Discussion sections of retrieved trials and relevant review articles to identify additional trials.

Study Selection
Criteria for inclusion of a study were as follows: (1) randomized controlled trial design; (2) comparison of pioglitazone with control (eg, placebo or other glucose-lowering agents); and (3) reporting on quantitative estimates of the hazard ratio (HR) and 95% confidence interval (CI) for recurrent stroke associated with pioglitazone therapy among stroke patients. We excluded trials if they did not enroll patients with a documented history of stroke or the outcome of stroke was not a prespecified and adjudicated major (primary or secondary) end point. Participants of any age or of either sex were included. One investigator (M.L.) developed selection criteria and conducted literature search. Another investigator (H.-W.L.) assessed these criteria and independently checked the enrolled trials. Discrepancies were resolved by discussion with a third investigator (B.O.) and by referencing the original report.

Data Extraction and Quality Assessment
All data from eligible studies were extracted by 2 independent investigators according to a standard protocol. Recorded data variables were trial name, year of publication, country of origin, eligibility criteria, mean age, proportion of women in the study, baseline characteristics, duration of follow-up, and number of participants and events for each group. We assessed study quality using the Cochrane risk-of-bias algorithm (www.cochrane.org/training/cochrane-handbook).18

Data Synthesis and Analysis
The primary efficacy outcome analyzed was any recurrent stroke (ischemic or hemorrhagic). The secondary efficacy outcome was any major vascular event, defined as the composite of nonfatal stroke, nonfatal myocardial infarction, and vascular death. Safety outcomes were all-cause mortality and heart failure.

HR with 95% CI, adjusted for multiple comparisons, was used as a measure of the association between pioglitazone versus control and risk of stroke. In each study, we converted these values by using their natural logarithms, and we calculated the SEs from these logarithmic numbers and their corresponding 95% CIs. For the statistical analysis, we combined log HRs and SEs using the inverse variance approach. We used a random-effects model and explored for sources of inconsistency (I²) and heterogeneity. We considered study-level estimates to be heterogeneous if the χ² test was significant (P<0.10) or the I² statistic was >50%. The Cochrane Collaboration’s Review Manager Software Package (RevMan 5.3) was used for this meta-analysis.

Results
The literature review identified 11 articles for detailed assessment, among which 5 were excluded because of no patients with a history of stroke being enrolled, 2 were excluded because stroke was not a prespecified and adjudicated major end point, and 1 was excluded because it was derived from the same study population as another report. Our final analysis included 3 randomized controlled trials that enrolled 4980 individuals, with 2488 participants (50%) randomly assigned to the pioglitazone group and 2492 participants (50%) to the control group (Figure 1).16,19,20 The study design and patient baseline characteristics of these randomized controlled trials are shown in Table 1. Analyzed data were abstracted from whole trials that enrolled only stroke or TIA patients (2 trials)16,19 and a separately reported subgroup of stroke patients (1 trial).20,21 One trial included patients with insulin resistance and having their fasting glucose <126 mg/dL and hemoglobin A1c <7%,19 another trial included patients with impaired glucose tolerance or newly diagnosed diabetes mellitus,19 and a third trial included patients with diabetes mellitus.20 The number of participants ranged from 120 to 3876.16 The median study duration was 4.4 years (ranged from 2.8 to 4.8 years).16

Risk-of-bias assessment of included trials was reported in Table 2. The results from the PROactive trial (Prospective Pioglitazone Clinical Trial in Macrovascular Events) had high risks of selection bias and reporting bias because the data were derived from a subgroup of patients with cerebrovascular disease.20,21 The results from the J-SPIRIT trial (Juntendo Stroke Prevention Study in Insulin Resistance and Impaired Glucose Tolerance) had high risks of performance bias because it was an open, nonblinded study.19

Clinical End Points
The primary efficacy end point of recurrent stroke was reported in all 3 trials, whereas the remaining end points were reported only in the 2 trials. For the outcome of recurrent stroke, pooled results from the random-effects model showed that pioglitazone was associated with reduced risk of recurrent stroke (HR, 0.68; 95% CI, 0.50–0.92; P=0.01; Figure 2). There was no substantial heterogeneity across trials (P=0.14; I²=49%). The estimates from the fixed-effects model (HR, 0.70; 95% CI, 0.58–0.86; P=0.0004) were similar to those of the random-effects model. For the secondary efficacy outcome of all major vascular events, pooled results from the random-effects model showed that pioglitazone was associated with reduced risk (HR, 0.75; 95% CI, 0.64–0.87; P=0.0001). There was no heterogeneity among trials (P=0.74; I²=0%).

For the 2 safety outcomes, there was no evidence of an effect on all-cause mortality (HR, 0.94; 95% CI, 0.79–1.12; P=0.48) and heart failure (HR, 1.21; 95% CI, 0.81–1.80; P=0.54).

Figure 1. Flow of study selection. CENTRAL indicates Cochrane Central Register of Controlled Trials.
In this meta-analysis comprising 3 randomized controlled trials, enrolling \( \approx 5000 \) stroke patients with evidence of abnormal glucose metabolism (ie, diabetes mellitus, prediabetes, insulin resistance), we found that adding pioglitazone to standard therapy was associated with a 32% risk reduction of recurrent stroke and a 25% risk reduction of major cardiovascular events. There was no evidence of an effect on all-cause mortality and heart failure.

One of the challenges with directly translating the results of the IRIS trial into clinical practice has been that in IRIS patients were classified as having insulin resistance on the basis of the HOMA-IR index \( 16 \). Although this measurement is relatively easy to perform, a component of it (plasma insulin level) is not globally standardized, and the test itself has to be done \( \approx 2 \) weeks after the index stroke or TIA meaning that there is a potential opportunity lost to prevent early recurrent events and a real risk of delaying or not getting this screening test done once the patient gets into the community. Our current results, which include data from studies beyond just IRIS, as well as the association of prediabetes with greater future risk of stroke, \( 22 \) suggest that perhaps more globally standardized tests of abnormal glucose metabolism, which can be readily obtained during the index stroke or TIA hospitalization such as hemoglobin A\(_1c\), might be used to promptly and consistently identify patients with abnormal glucose metabolism without frank diabetes mellitus who might benefit from pioglitazone treatment \( 23 \).

Although how pioglitazone specifically decreases vascular events is uncertain, several mechanism of pioglitazone may contribute to reduce recurrent stroke risk in stroke patients with insulin resistance or diabetes mellitus. Pioglitazone is effective for improving insulin sensitivity, reducing C-reactive protein concentration and triglyceride, increasing high-density lipoprotein cholesterol, enhancing cholesterol efflux capacity, and lowering blood pressure \( 16,24,25 \). Pioglitazone, as compared with placebo, reduces the risk of conversion of impaired glucose tolerance to diabetes mellitus \( 26 \). Pioglitazone, as compared with glimepiride, slows the progression of carotid intima–media thickness and coronary atherosclerosis among diabetic patients \( 27,28 \). However, the observed cardiovascular benefits of

### Table 1. Characteristics of Included Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>IRIS(^a)</th>
<th>J-SPIRIT(^a)</th>
<th>PROactive(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publication year</td>
<td>2016</td>
<td>2015</td>
<td>2007</td>
</tr>
<tr>
<td>Country</td>
<td>International</td>
<td>Japan</td>
<td>European countries</td>
</tr>
<tr>
<td>Population</td>
<td>Ischemic stroke or TIA, age ( \geq 40 ) y, insulin resistance, excluded patients with fasting glucose ( \geq 126 ) mg/dL or Hba1c ( \geq 7.0% )</td>
<td>Ischemic stroke or TIA, age ( \geq 20 ) y, IGT or newly diagnosed DM</td>
<td>Subgroup of people with previous stroke, age 35 to 75 y, DM (9 y since diagnosis of DM)</td>
</tr>
<tr>
<td>Active/control</td>
<td>Pioglitazone/placebo</td>
<td>Pioglitazone/diet or other treatment</td>
<td>Pioglitazone/placebo</td>
</tr>
<tr>
<td>Sample size, pioglitazone/control</td>
<td>1939/1937</td>
<td>63/57</td>
<td>486/498</td>
</tr>
<tr>
<td>Stroke events, pioglitazone/control</td>
<td>127/154</td>
<td>4/7</td>
<td>27/51</td>
</tr>
<tr>
<td>Recurrent stroke rate, %, pioglitazone/control</td>
<td>6.5/8.0</td>
<td>6.3/12.3</td>
<td>5.6/10.2</td>
</tr>
<tr>
<td>Women, %</td>
<td>35</td>
<td>24</td>
<td>39</td>
</tr>
<tr>
<td>Age, y</td>
<td>63.5 (10.6)</td>
<td>68.5 (40–89)</td>
<td>62.3 (7.5)</td>
</tr>
<tr>
<td>Baseline Hba1c, %</td>
<td>5.8 (0.4)</td>
<td>6.0 (0.4)</td>
<td>8.1 (1.4)</td>
</tr>
<tr>
<td>Baseline fasting glucose, mg/dL</td>
<td>98.3 (10.0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>BMI</td>
<td>30.0 (5.5)</td>
<td>24.2 (3.3)</td>
<td>30.8 (4.8)</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin, %</td>
<td>82.5</td>
<td>46.0</td>
<td>32.0</td>
</tr>
<tr>
<td>Antiplatelet, %</td>
<td>92.2</td>
<td>84.5</td>
<td>83.0</td>
</tr>
<tr>
<td>Anticoagulant, %</td>
<td>11.5</td>
<td>15.8</td>
<td>NA</td>
</tr>
<tr>
<td>Median follow-up, y</td>
<td>4.8</td>
<td>2.8</td>
<td>2.9</td>
</tr>
<tr>
<td>Changes from baseline to year 1 or final visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hba1c change, %, active/control</td>
<td>NA</td>
<td>(-0.06/0.07)</td>
<td>NA</td>
</tr>
<tr>
<td>Fasting glucose change, mg/dL, active/ control</td>
<td>(-3.0/1.4)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Definition of major vascular events in this meta-analysis</td>
<td>Myocardial infarction+stroke</td>
<td>NA</td>
<td>Nonfatal stroke+nonfatal myocardial infarction+vascular death</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; DM, diabetes mellitus; Hba1c, hemoglobin A\(_1c\); IGT, impaired glucose tolerance; IRIS, Insulin Resistance Intervention After Stroke; J-SPIRIT, Juntendo Stroke Prevention Study in Insulin Resistance and Impaired Glucose Tolerance; NA, not available; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; and TIA, transient ischemic attack.

Discussion

In this meta-analysis comprising 3 randomized controlled trials, enrolling \( \approx 5000 \) stroke patients with evidence of abnormal glucose metabolism (ie, diabetes mellitus, prediabetes, insulin resistance), we found that adding pioglitazone to standard therapy was associated with a 32% risk reduction of recurrent stroke and a 25% risk reduction of major cardiovascular events. There was no evidence of an effect on all-cause mortality and heart failure.

One of the challenges with directly translating the results of the IRIS trial into clinical practice has been that in IRIS patients were classified as having insulin resistance on the basis of the HOMA-IR index (homeostatic model assessment-estimated insulin resistance) \( 16 \). Although this measurement is relatively easy to perform, a component of it (plasma insulin level) is not globally standardized, and the test itself has to be done \( \approx 2 \) weeks after the index stroke or TIA meaning that there is a potential opportunity lost to prevent early recurrent events and a real risk of delaying or not getting this screening test done once the patient gets into the community. Our current results, which include data from studies beyond just IRIS,
pioglitazone cannot be simply explained by a class effect by thiazolidinediones. Another agent in this class, rosiglitazone, has been associated with an increased risk of cardiovascular events in several meta-analyses.29,30

There are several limitations in this study. First, meta-analysis may be biased when the literature search fails to identify all relevant trials or the selection criteria for including a trial are applied in a subjective manner. To minimize these risks, we performed thorough searches across multiple literatures and trial databases and used explicit criteria for study selection, data abstraction, and data analysis. Second, there were only 3 relevant randomized controlled trials, and the results of this meta-analysis were dominated by IRIS trial.16 The data from PROactive trial30 were derived from a subfraction of patients having previous stroke in a randomized trial. This limits the interpretability of the pooled results. Also, only 6% of patients in IRIS trial had diabetes mellitus, and pioglitazone reduced new-onset diabetes mellitus substantially in this trial.16 Because it may be too late for a hypoglycemic agent to have an effect on macrovascular events once diabetes mellitus is

Table 2. Risk-of-Bias Assessment of Included Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>IRIS16 (selection bias)</th>
<th>J-SPIRIT19 (selection bias)</th>
<th>PROactive20 (selection bias)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Other potential bias</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
</tr>
</tbody>
</table>

IRIS indicates Insulin Resistance Intervention After Stroke; J-SPIRIT, Juntendo Stroke Prevention Study in Insulin Resistance and Impaired Glucose Tolerance; and PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events.

Figure 2. Hazard ratios with 95% confidence intervals (CI) for recurrent stroke in randomized controlled trials on efficacy of treatment with pioglitazone. IRIS indicates Insulin Resistance Intervention After Stroke; J-SPIRIT, Juntendo Stroke Prevention Study in Insulin Resistance and Impaired Glucose Tolerance; and PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events.
established, another large-scale randomized controlled trial to explore the effect of pioglitazone on stroke patients with diabetes mellitus may be warranted. Third, because some potential adverse effects, such as fracture and weight gain, were only reported in one of the trials in this meta-analysis,15 we did not report it in our analysis. However, these potential adverse effects need to be taken into consideration when weighing the risk–benefit profile of pioglitazone. Fourth, the populations and frequency of medication use, especially statins, differed across trials. The variation in frequency of statin use among trials likely reflected the fact that the benefit of statin use in secondary stroke prevention was not well established until SPARCL trial (Stroke Prevention by Aggressive Reduction in Cholesterol Levels)11 published in 2006. Increased statin use in more recent trials are likely to reduce the recurrent stroke risk thereby possibly making the efficacy of active treatment drugs less obvious. Although the effect size differed among trials, there was no heterogeneity, probably because the statistical power was too low. Because our study was a study-level meta-analysis, the issues mentioned above may not be well settled. Individual-level pooled analyses of relevant trials could provide additional insights. Fifth, the definition of the secondary outcome, major vascular events, differed between 2 available studies. One study16 reported composite of myocardial infarction and stroke, whereas another20 reported nonfatal myocardial infarction, nonfatal stroke, and vascular death as major vascular events. Because fatal myocardial infarction and fatal stroke are likely the major components of vascular death, the end points categorized as major vascular events between 2 available studies may not be substantially different. Finally, although these results are largely confirmatory, given the paucity of available evidence about the role of antidiabetic drugs for secondary stroke prevention in patients with abnormal glucose metabolism, as noted by the prevailing secondary stroke prevention guidelines,32 and the potential challenges with regularly obtaining HOMA index tests in routine practice, especially at times beyond the period of highest risk of stroke recurrence, a formal meta-analysis to broadly support or refute this therapeutic strategy in these patients was probably warranted.

In conclusion, this meta-analysis of randomized trial data indicates that pioglitazone may reduce risk of recurrent stroke and major vascular events in ischemic stroke and TIA patients with insulin resistance, prediabetes, and type 2 diabetes mellitus. There was no evidence of an effect on all-cause mortality and heart failure.

Sources of Funding
This study was founded by grants from Ministry of Science and Technology Taiwan (MOST104-2314-B-182-019 and MOST105-2028-B-182-008-MY2). The sponsors played no role in the study design, data collection and analysis, or decision to submit the article for publication.

Disclosures
None.

References
Lee et al. Pioglitazone and Recurrent Stroke Prevention


Pioglitazone for Secondary Stroke Prevention: A Systematic Review and Meta-Analysis
Meng Lee, Jeffrey L. Saver, Hung-Wei Liao, Chun-Hsien Lin and Bruce Ovbiagele

Stroke. 2017;48:388-393; originally published online December 20, 2016;
doi: 10.1161/STROKEAHA.116.013977
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/48/2/388

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/