Original Article

Effects of Pioglitazone for Secondary Stroke Prevention in Patients with Impaired Glucose Tolerance and Newly Diagnosed Diabetes: The J-SPIRIT Study

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Aim: Prediabetes is an independent risk factor for future stroke. However, no effective treatment has yet been established for the recurrence of stroke in patients with prediabetes. Here we investigated the effects of pioglitazone, a potent peroxisome proliferator-activated receptor-gamma agonist, for the reduction of recurrent stroke in patients with prediabetes.

Methods: Participants were patients who had a symptomatic ischemic stroke or transient ischemic attack (TIA) without a history of type 2 diabetes mellitus and who were diagnosed to have IGT or newly diagnosed diabetes by a 75-g oral glucose tolerance test. These patients were randomized to either receive or not receive pioglitazone. The primary endpoint was a recurrence of ischemic stroke.

Results: A total of 120 patients were enrolled in the study. Sixty-three patients received pioglitazone and 57 were enrolled in the control group that did not receive pioglitazone. The majority of patients (68.3%) were prescribed 15 mg of pioglitazone, while the remaining patients (31.7%) were treated with 30 mg of pioglitazone. Over a median follow-up period of 2.8 years, treatment with pioglitazone was found to be associated with a lower rate of the primary endpoint (recurrence of stroke) than that observed in the control group [event rate 4.8% pioglitazone vs 10.5% control, hazard ratio 0.62, 95% confidence interval 0.13–2.35, p=0.49]. However, differences were not statistically significant.

Conclusions: While this study was too underpowered to determine the effect of pioglitazone, the result failed to show beneficial effects in patients of ischemic stroke or TIA with impaired glucose tolerance and newly diagnosed diabetes.


Key words: Prediabetes, Stroke prevention, Pioglitazone

Introduction

Stroke is a leading cause of mortality1), and if affected patients survive, they still generally require support for daily life. Type 2 diabetes is a strong risk factor for stroke, and the number of stroke patients with comorbid diabetes has been increasing2). Patients with diabetes have a two-to-three-fold increased risk of cerebrovascular events compared with those without diabetes3-5). Moreover, the short-term prognosis of stroke patients with diabetes is significantly worse compared with that of patients without diabetes6, 7), and the long-term prognosis of stroke survivors with diabetes is also poor8). In addition to the increasing
incidence of diabetes, the number of cases with prediabetic conditions, such as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), has also been increasing13,14, and these are also considered to be important risk factors for cardiovascular events15.

For example, the DECODE study demonstrated that the presence of newly diagnosed diabetes (new DM) and IGT, as detected by the 75-g oral glucose tolerance test (OGTT), increased the risk of cardiovascular death12. The Funagata study showed that not only diabetes but also IGT was an independent risk factor for cardiovascular disease, whereas the IFG level was not a risk factor13. A high incidence of these types of prediabetic conditions among symptomatic stroke patients has been reported from both Asian and Western populations14-17. These prediabetic conditions were also correlated with a poor outcome after stroke7,18 and increased the risk of recurrence19. Thus, prediabetes is an important target to prevent the recurrence of stroke and to decrease the incidence of cardiovascular events. Although glycemic control for stroke survivors is suggested in several stroke prevention guidelines, the level of evidence is still low. Several mega studies have been performed to evaluate the efficacy of strict glycemic control for preventing cardiovascular events, but these failed to demonstrate positive results20. However, pioglitazone, an agonist of peroxisome proliferator-activated receptor gamma, reduced cardiovascular events in high-risk patients with type 2 diabetes in the PROActive study21. Furthermore, pioglitazone significantly attenuated the risk of stroke recurrence in a subgroup analysis from PROActive study populations22. We previously reported the effects of pioglitazone on macrovascular events in Japanese patients with type 2 diabetes mellitus at a high risk of stroke (PROFIT-J Study)23. However, the effects of pioglitazone for preventing stroke recurrence in patients with IGT or new DM remains unclear. Here we report the effects of pioglitazone for preventing stroke recurrence in stroke survivors with prediabetes.

**Materials and Methods**

**Study Design**

The Juntendo Stroke Prevention study in Insulin Resistance and Impaired glucose Tolerance (J-SPIRIT) study was designed as a prospective, randomized, open-label, comparative controlled, multicenter trial. Four stroke centers in or near Tokyo (Juntendo University Hospital, Juntendo University Urayasu Hospital, Juntendo University Shizuoka Hospital, and Juntendo Tokyo Koto Geriatric Medical Center) participated in the study. The research protocol was approved by the ethics committee of Juntendo University Hospital. The patients, all of whom had a history of symptomatic ischemic stroke or transient ischemic attack (TIA) without known type 2 diabetes (HbA1c ≥ 6.5% or a causal blood glucose ≥ 200 mg/dl) and no history of treatment for diabetes, underwent the 75-g OGTT to evaluate them for abnormal glucose metabolism (AGM). The patients diagnosed as having AGM, such as those with IGT or new DM, were randomly assigned to either pioglitazone treatment (pioglitazone 15–45 mg) or a matching control group (diet or other treatments except for pioglitazone). The exclusion criteria were that the index stroke was a hemorrhagic stroke; females of child-bearing potential; patients with active cancer; patients with other causes of stroke, such as cerebral artery dissection or associated collagen disease; and patients with an abnormal coagulation status. Patients with severely impaired renal or liver function, hypersensitivity to the study drug, planned surgery, or any other condition judged inappropriate for inclusion in the study by the physician were also excluded. Eligible patients were stratified into two groups on the basis of age and gender and were matched to subjects with IGT and new DM and were randomized to either receive or not receive pioglitazone. Written informed consent was obtained from all participants in this study. The first participant was recruited in December 2005, and the last participant was randomized in May 2011. A total of 120 participants were enrolled, and the maximum intervention period was 5 years.

This study was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN 000013499).

**Study Population**

We recruited male and female patients who were 20 years of age or older and who had experienced a non-disabling ischemic stroke (modified Rankin Scale ≤ 3) or TIA. To screen for AGM, patients who had never been diagnosed with type 2 diabetes mellitus and who had no history of treatment for type 2 diabetes underwent the 75-g OGTT. The interpretation of OGTT results was based on the World Health Organization definition24 and also on the concept of IFG included in the American Diabetes Association criteria25.

In brief, the patients were classified on the basis of whether they had diabetes when they had a fasting plasma glucose (FPG) level of ≥ 126 mg/dL or when the plasma glucose level at 2 h after OGTT was ≥ 200 mg/dL. IGT was defined as an FPG level of < 126 mg/dL and a 2-h OGTT plasma glucose level of
140–199 mg/dL. Patients with IFG had FPG levels
of 110–125 mg/dL and 2-h OGTT plasma glucose
levels of <140 mg/dL. Patients with normal glucose
tolerance (NGT) had an FPG level of <110 mg/dL
and a 2-h OGTT plasma glucose level of <140 mg/dL.

**Patient Characteristics**

The demographic data, including age, sex, BMI,
medical history, and blood pressure, were recorded.
Ischemic stroke was classified into three categories:
non-cardioembolic, cardioembolic, and TIA. The details
of the antithrombotic therapy and use of antihyper-
tensive medications or statins were obtained. Par-
ticipants were also examined for their full blood chem-
istry and lipid profiles and regarding their HbA1c level.

**Clinical Evaluation and Outcome Measures**

The primary end point was the recurrence of
ischemic stroke. Cerebrovascular events were consid-
ered to be definite lesions related to neurological symp-
toms and signs, which correlated with a new lesion on
CT or MRI. The secondary endpoints consisted of
primary endpoint, TIA, hemorrhagic stroke, any cause
of stroke, and all causes of death. The definition of
TIA was tissue based and indicated any transient neu-
rological deficit with negative findings on diffusion-
weighted imaging. All participants were followed up
every 2 or 4 months until the end of the trial (the
maximum follow-up duration was 5 years). The dose
of pioglitazone was left to the physicians’ discretion.
Patients were withdrawn from the trial if they experi-
enced any cardiovascular events corresponding to pri-
mary or secondary outcomes or when the trial treat-
ment was suspended for more than 3 consecutive
months. Follow-up data were collected from partici-
pants who were followed up for at least 3 months, and
these data were assessed around the period of the last
clinical evaluation.

**Statistical Analysis**

Previous data showed a higher recurrence rate of
stroke, and 12% of patients with IGT and 18% of
patients with DM had a recurrence of stroke during
the 2.6-year study period\(^ {19} \). Recent Asian data also
showed that the recurrence rate after a 1-year follow-
up period to be 8.2% in cases with impaired glucose
level\(^ {18} \). These data indicated that the recurrence
rate of stroke in cases with IGT and new DM would
be expected to be higher than the rates recently
reported in Japanese patients with symptomatic ischemic stroke or TIA\(^ {20, 27} \). Therefore, the incidence of
the primary outcome in this study was estimated to be
10% over a follow-up period of 2 years among sub-
jects not treated with pioglitazone and was expected to
diminish by 50% among patients treated with piogli-
tazone. Assuming a power of 80% and a statistical sign-
ificance of <0.05, the calculated sample size of one
arm was 435. Therefore, the estimated sample size was
450 for each arm of the study.

All primary and secondary outcome measures
were analyzed using an intention-to-treat analysis. We
used the \( \chi^2 \) test to compare the frequency distribu-
tions of categorical variables between the two groups.
Continuous variables were compared using Student’s
t-test or the Mann–Whitney \( U \) test, as appropriate,
after normality distribution testing. We compared the
time to first vascular event for the primary and sec-
ondary end points using the Kaplan–Meier method
and log-rank test. Hazard ratios (HRs) and their 95%
confidence intervals (CIs) were calculated using the
Cox proportional hazard model. Missing data were
imputed using the last value carried forward. The data
for patients who were lost to follow-up or who with-
drew were censored at the time of the last visit. The
JMP Version 9.0 software program (SAS Inc. Cary,
NC, USA) was used for data analysis.

**Results**

A total of 120 participants were enrolled in this
study (Fig. 1), and their characteristics are described in
Table 1. The mean age of participants was 68.4
years, and less than 30% were females. Among the
enrolled participants, 79.1% had experienced a non-
cardioembolic stroke, 14.2% had a cardioembolic stroke,
and 6.7% experienced a TIA, and there were
no significant differences in stroke subtypes between
the groups (Table 1). The majority (90.8%) of index
strokes and TIA had developed within 1 year before
allocation. There were no significant differences in the
baseline characteristics of patients, such as the LDL-
C, triglycerides, or HbA1c levels, between the groups.
However, HDL-C levels were significantly lower in the
control group than in the pioglitazone group
(Table 1). The prevalence of IGT and new DM was
not significantly different between the groups, and the
use of antithrombotics, statins, and antihypertensive
medications was also not different between the groups.
The majority of patients (68.3%, 43/63) in the piogli-
tazone arm were prescribed 15 mg of pioglitazone,
while the remaining patients (31.7%) were prescribed
30 mg of pioglitazone. None of the patients were
treated with 45 mg of pioglitazone. Although systolic
and diastolic blood pressure values in the pioglitazone
arm were significantly decreased between the baseline
and follow-up examinations, there were no significant
During the study period, 15 (23.8%) participants in the pioglitazone group discontinued the study medication regimen due to adverse effects. The causes of pioglitazone discontinuation included five cases of limb edema, two cases of drug-related rashes, two cases of cytopenia, one case of complications of heart failure, one case of chest discomfort, one case of general discomfort, one case of heart palpitations, one case of sleepiness, and one case of bladder cancer. Furthermore, five (7.9%) patients were not contactable in the pioglitazone group, whereas two (3.4%) patients withdrew their consent and eight (14.0%) patients were not contactable in the control group during the study period.

**Discussion**

We aimed to demonstrate the effects of pioglitazone for the secondary prevention of ischemic stroke in this study. However, this study was too underpowered to definitively prove the effectiveness of pioglitazone in reducing the stroke recurrence, recurrence of any strokes or TIA, or for reducing the all-cause of death in patients with IGT and new DM due to the small sample size. Because we could not increase the number of cases enrolled, we could not reach a pre-
tolerance during a median follow-up period of 34 months in this study.

Vermeer et al. assessed the association between IGT and stroke recurrence on the basis of non-fasting glucose levels\textsuperscript{19). In their report, 12% of patients with IGT and 18% of patients with diabetes experienced a recurrence of stroke during the study period. The adjusted risk of stroke recurrence in patients with IGT was nearly double of that in patients with normal glucose levels (HR, 1.8; 95% CI, 1.1–3.0) during the 2.6-year follow-up period\textsuperscript{19). In contrast, a recent study

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
<th>Pioglitazone (n=63)</th>
<th>Control (n=57)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, %</td>
<td>22.20%</td>
<td>26.30%</td>
<td>0.6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.1 (48–82)</td>
<td>68.8 (40–89)</td>
<td>0.69</td>
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<tr>
<td>BMI</td>
<td>23.8 ± 3.4</td>
<td>24.7 ± 3.1</td>
<td>0.12</td>
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<tr>
<td>Hypertension (%)</td>
<td>50 (79.4%)</td>
<td>48 (84.2%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>27 (42.9%)</td>
<td>25 (43.9%)</td>
<td>0.91</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>35 (55.6%)</td>
<td>32 (56.1%)</td>
<td>0.95</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.99 ± 0.38</td>
<td>5.91 ± 0.37</td>
<td>0.23</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>118.8 ± 40.6</td>
<td>115.9 ± 28.0</td>
<td>0.66</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>55.3 ± 14</td>
<td>48.6 ± 11.1</td>
<td>0.005</td>
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<tr>
<td>Triglycerides (mg/dl)</td>
<td>140.8 ± 91.5</td>
<td>130.4 ± 46.2</td>
<td>0.44</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>140.7 ± 17.7</td>
<td>137.7 ± 14.7</td>
<td>0.32</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78.9 ± 10.9</td>
<td>77.4 ± 11.2</td>
<td>0.46</td>
</tr>
<tr>
<td>75-g OGTT (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired glucose tolerance (%)</td>
<td>40 (63.5%)</td>
<td>42 (73.7%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Newly diagnosed diabetes (%)</td>
<td>23 (36.5%)</td>
<td>15 (26.3%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Subtype of ischemic stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-cardiogenic (%)</td>
<td>50 (79.4%)</td>
<td>45 (78.9%)</td>
<td>0.96</td>
</tr>
<tr>
<td>cardiogenic (%)</td>
<td>11 (17.5%)</td>
<td>6 (10.5%)</td>
<td>0.28</td>
</tr>
<tr>
<td>TIA (%)</td>
<td>2 (3.2%)</td>
<td>6 (10.5%)</td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Previous AP (%)</td>
<td>1 (1.6%)</td>
<td>5 (8.8%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Previous Stroke (%)</td>
<td>4 (6.4%)</td>
<td>8 (14.0%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Antithrombotic treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPT (%)</td>
<td>49 (77.8%)</td>
<td>45 (79.0%)</td>
<td>0.88</td>
</tr>
<tr>
<td>DAPT (%)</td>
<td>2 (3.2%)</td>
<td>5 (8.8%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Anticoagulant (%)</td>
<td>12 (19.1%)</td>
<td>7 (12.3%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Anticoagulant + antiplatelet (%)</td>
<td>3 (4.8%)</td>
<td>1 (1.8%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Combined medical therapy</td>
<td></td>
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<td></td>
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<tr>
<td>Statin (%)</td>
<td>29 (46.0%)</td>
<td>24 (42.1%)</td>
<td>0.67</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ARB (%)</td>
<td>34 (54.0%)</td>
<td>36 (63.2%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Calcium antagonist (%)</td>
<td>26 (41.3%)</td>
<td>28 (49.1%)</td>
<td>0.39</td>
</tr>
<tr>
<td>β-blocker (%)</td>
<td>2 (3.2%)</td>
<td>6 (10.5%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Diuretic agent (%)</td>
<td>3 (4.8%)</td>
<td>3 (5.3%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Pioglitazone 15 mg (%)</td>
<td>43 (68.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone 30 mg (%)</td>
<td>20 (31.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

defined sample size within the deadline.

The risk of stroke was previously reported to be significantly increased by 1.26-fold in patients with IGT or combined glucose tolerance and IFG in a meta-analysis of 15 prospective cohort studies\textsuperscript{28). The existence of abnormal glucose tolerance, as assessed by the standard OGTT, has been shown to be a strong predictor of future cardiovascular events after myocardial infarction\textsuperscript{11). The incidence of non-fatal stroke was 1.8% (1/55) in patients with NGT but was increased to 4.4% (5/113) in patients with abnormal glucose tolerance during a median follow-up period of 34 months in this study.

Vermeer et al. assessed the association between IGT and stroke recurrence on the basis of non-fasting glucose levels\textsuperscript{19). In their report, 12% of patients with IGT and 18% of patients with diabetes experienced a recurrence of stroke during the study period. The adjusted risk of stroke recurrence in patients with IGT was nearly double of that in patients with normal glucose levels (HR, 1.8; 95% CI, 1.1–3.0) during the 2.6-year follow-up period\textsuperscript{19). In contrast, a recent study
effects of antidiabetic treatment for the prevention of stroke recurrence in patients who presented with IGT or new DM.

Pioglitazone has been shown to reduce the risk of conversion from IGT to diabetes by 72% \(^{29}\). Furthermore, a daily dose of 45 mg of pioglitazone has been reported to improve insulin sensitivity and decrease the concentration of hs-CRP during 3 months of treatment in stroke survivors without diabetes but with impaired insulin sensitivity \(^{30}\). Another report demonstrated that metformin treatment improved IGT in patients with a recent TIA or minor ischemic stroke \(^{31}\). However, none of these studies demonstrated the efficacy of these pharmacological treatments for preventing stroke recurrence. We were also unable to find a significant impact of pioglitazone to prevent the recurrence of ischemic stroke in this study. All participants in our study received strict cardiovascular risk control, such as blood pressure-lowering or lipid-lowering treatments (Table 2). These might have influenced the efficacy of pioglitazone in this study.

Our present study showed that the 1-year recurrence rate of ischemic stroke during the first year was 5.0% in the overall population. This recurrence rate is higher than that in the EVEREST registry, which showed a 3.81% recurrence rate in the 1-year follow-up period in patients with recent non-cardioembolic stroke \(^{26}\). However, our study enrolled patients with not only ischemic stroke but also TIA. A recent observational study (J-STARS-Longitudinal) showed that there was a recurrence rate of 8.9% during the median observation period of 568 days when patients with both ischemic stroke and TIA were included in the population \(^{27}\). Furthermore, an Asian registry study (ACROSS China) demonstrated that the 1-year recurrence rate was 8.2% among patients with impaired glucose regulation with ischemic stroke. Therefore, the recurrence rate of ischemic stroke and TIA in patients with IGT and new DM remains unclear. Further studies are needed to clarify this issue.

There have been few studies that assessed the effects of antidiabetic treatment for the prevention of stroke recurrence in patients who presented with IGT or new DM.

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Only one case with a recurrent stroke in the non-pioglitazone arm had a cardioembolic infarction due to atrial fibrillation (AF, Table 4). However, the PT-

| Table 2. Changes in the clinical parameters after treatment with pioglitazone (12 months) |
|---------------------------------|------------|------------|-----------------|
|                                | Pioglitazone | Control    | \(p\) Value Between Groups |
| HbA1c                          |             |            |                  |
| Baseline                       | 5.99 ± 0.38 | 5.91 ± 0.37| 0.23             |
| 12 months                      | 5.93 ± 0.37 | 5.98 ± 0.54| 0.61             |
| \(p\) value vs. baseline       | 0.38        | 0.46       |                  |
| LDL-C                          |             |            |                  |
| Baseline                       | 118.8 ± 40.6| 115.9 ± 28.0| 0.66            |
| 12 months                      | 102.5 ± 23.0| 109.8 ± 25.3| 0.18            |
| \(p\) value vs. baseline       | 0.03*       | 0.26       |                  |
| HDL-C                          |             |            |                  |
| Baseline                       | 55.3 ± 14.0 | 48.6 ± 11.1| 0.005*          |
| 12 months                      | 57.4 ± 11.5 | 52.3 ± 11.7| 0.05*           |
| \(p\) value vs. baseline       | 0.43        | 0.11       |                  |
| TG                             |             |            |                  |
| Baseline                       | 140.8 ± 91.5| 130.4 ± 46.2| 0.44            |
| 12 months                      | 121.6 ± 64.4| 139.2 ± 87.4| 0.3             |
| \(p\) value vs. baseline       | 0.5         | 0.26       |                  |
| SBP, mmHg                      |             |            |                  |
| Baseline                       | 140.7 ± 17.9| 137.7 ± 14.7| 0.32            |
| 12 months                      | 128.0 ± 16.3| 135.5 ± 17.0| 0.04*           |
| \(p\) value vs. baseline       | 0.0003*     | 0.5        |                  |
| DBP, mmHg                      |             |            |                  |
| Baseline                       | 78.9 ± 10.9 | 77.4 ± 11.2| 0.46            |
| 12 months                      | 71.2 ± 12.1 | 73.9 ± 10.7| 0.28            |
| \(p\) value vs. baseline       | 0.0011*     | 0.12       |                  |
INR in this case was 1.98 at recurrence, which was within the recommended ranges in the Japanese guidelines for anticoagulant treatment for elderly Japanese with AF\(^\text{22}\). Thus, the selection or adjustment of oral antithrombotics did not seem to have a major influence on the risk of recurrent cerebrovascular events.

Our study is associated with several potential limitations that may decrease its value. Because of the limited number of enrolled patients, we did not find any statistically significant evidence of the efficacy of pioglitazone for preventing recurrent stroke. A sub-analysis of the PROactive study demonstrated that pioglitazone significantly reduced the rate of recurrent stroke by 47% in type 2 diabetes with a previous history of stroke compared with non-pioglitazone treatment\(^\text{22}\). Our study also showed a 38% decrease in recurrent ischemic stroke, which was similar to the findings of the PROactive study. However, this value was not significant given the small number of cases included in the study. Thus, a large number of randomized prospective studies are needed to confirm the effects of pioglitazone for stroke survivors with prediabetes.

Second, many of the participants (71.4%) were prescribed low-dose pioglitazone (15 mg) in our study, and the results did not show a significant improvement in the glycemic status or lipid profile, except for a blood pressure-lowering effect, compared with the

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**Table 3.** Primary and secondary events (ITT)

<table>
<thead>
<tr>
<th>Event</th>
<th>Pioglitazone (+)</th>
<th>Control (-)</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence of ischemic stroke (%)</td>
<td>3 (4.8%)</td>
<td>6 (10.5%)</td>
<td>0.62</td>
<td>0.13–2.35</td>
<td>0.49</td>
</tr>
<tr>
<td>TIA (%)</td>
<td>0</td>
<td>1 (1.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke (%)</td>
<td>1 (1.6%)</td>
<td>1 (1.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal stroke (%)</td>
<td>2 (3.2%)</td>
<td>6 (10.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal stroke (%)</td>
<td>2 (3.2%)</td>
<td>1 (1.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any stroke (%)</td>
<td>4 (6.3%)</td>
<td>7 (12.3%)</td>
<td>0.66</td>
<td>0.17–2.18</td>
<td>0.5</td>
</tr>
<tr>
<td>Any stroke and TIA (%) (Ischemic or hemorrhagic stroke, and TIA)</td>
<td>4 (6.3%)</td>
<td>8 (14.0%)</td>
<td>0.58</td>
<td>0.15–1.86</td>
<td>0.37</td>
</tr>
<tr>
<td>Any stroke, TIA, and all-cause of death (%)</td>
<td>5 (7.9%)</td>
<td>10 (17.5%)</td>
<td>0.61</td>
<td>0.19–1.71</td>
<td>0.35</td>
</tr>
</tbody>
</table>

---

**Fig. 2.** Kaplan–Meier curves and hazard ratios for the time to recurrence of ischemic stroke.
no pioglitazone group, indicating that this dose may have been too low to exert sufficient preventive effects. Pioglitazone has been shown to reduce the blood pressure and has several possible mechanisms by which it exerts blood pressure-lowering effects, such as reducing insulin resistance, inhibiting the secretion of vasoactive agents, and increasing the transcription of genes encoding proteins that cause vasodilation\(^3\)). To confirm mechanisms underlying the effects of pioglitazone, the development of a fixed titration protocol is warranted.

Third, we did not monitor patients for markers of inflammation, coagulation, or endothelial function. Pioglitazone has also been shown to reduce proinflammatory gene and protein expression from both monocytes and lymphocytes in patients with IGT\(^3\)). Other

---

**Table 4.** Recurrent cerebrovascular events in each group

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Index stroke</th>
<th>Recurrent stroke</th>
<th>Fatal stroke</th>
<th>OGTT</th>
<th>Antithrombotics</th>
<th>PT-INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-pioglitazone</td>
<td>74</td>
<td>M</td>
<td>SVO</td>
<td>ATI</td>
<td>no</td>
<td>IGT</td>
<td>Cilostazol</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>M</td>
<td>SVO</td>
<td>TIA</td>
<td>no</td>
<td>IGT</td>
<td>Cilostazol</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>M</td>
<td>BAD</td>
<td>ICH</td>
<td>no</td>
<td>IGT</td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>M</td>
<td>UE</td>
<td>ATI</td>
<td>no</td>
<td>DM</td>
<td>Cilostazol</td>
</tr>
<tr>
<td></td>
<td>77</td>
<td>M</td>
<td>SVO</td>
<td>ATI</td>
<td>no</td>
<td>IGT</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>F</td>
<td>ATI</td>
<td>UE</td>
<td>no</td>
<td>IGT</td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>F</td>
<td>CE (AF)</td>
<td>CE (AF)</td>
<td>yes</td>
<td>DM</td>
<td>Warfarin</td>
</tr>
<tr>
<td></td>
<td>74</td>
<td>F</td>
<td>SVO</td>
<td>ATI</td>
<td>no</td>
<td>DM</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>72</td>
<td>M</td>
<td>TIA</td>
<td>ATI</td>
<td>no</td>
<td>IGT</td>
<td>Cilostazol</td>
</tr>
<tr>
<td></td>
<td>77</td>
<td>F</td>
<td>SVO</td>
<td>Other</td>
<td>no</td>
<td>DM</td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>66</td>
<td>M</td>
<td>CE (AF)</td>
<td>ICH</td>
<td>yes</td>
<td>IGT</td>
<td>Warfarin</td>
</tr>
<tr>
<td></td>
<td>74</td>
<td>F</td>
<td>SVO</td>
<td>ATI</td>
<td>no</td>
<td>IGT</td>
<td>Cilostazol</td>
</tr>
</tbody>
</table>

---

**Fig. 3.** Kaplan–Meier curves and hazard ratios for the time to any stroke, TIA, and all-cause of death.
studies have demonstrated that pioglitazone improved the endothelial dysfunction in patients with diabetes\textsuperscript{35, 36}. These pleiotropic effects may play an important role in reducing the recurrence of ischemic stroke and should be examined in future studies.

Fourth, 23.8% of the participants in the pioglitazone group discontinued the study medication regimen due to adverse effects. We did not observe hypoglycemia, which was the most prevalent adverse event in the PROactive study, in any of our patients\textsuperscript{37}. The most common adverse events were edema, which occurred in 7.9% (5 in 63) of the patients in the pioglitazone arm. In the PROactive study, 26.4% of the patients in the pioglitazone arm and 15.1% of the patients in the control group showed edema\textsuperscript{37}. Other adverse events were relatively rare, and their relationship to the treatment remains unclear. Because our study was not placebo controlled, we could not confirm any relationship between the use of pioglitazone and adverse effects in this study. Only one case showed bladder cancer in the pioglitazone arm (1.6%, 1 of 63). This case was prescribed 15 mg of pioglitazone for 22 months and discontinued the pioglitazone thereafter. The risk of bladder cancer in case with taking pioglitazone is still controversial\textsuperscript{38, 39}. One retrospective study assessing the association between the risk of bladder cancer and use of pioglitazone in Japanese patients with type 2 diabetes showed a 1.36% (9 of 663) risk of bladder cancer and a non-significant overall increase in the risk of bladder cancer (HR, 1.75; 95% CI, 0.89–3.45)\textsuperscript{40}. Although the risk of bladder cancer and the use of pioglitazone in our study showed a similar trend to the previous report, a further analysis of this issue will be needed.

In conclusion, the findings of this study demonstrated that pioglitazone did not significantly reduce the number of recurrent ischemic strokes in patients with IGT and new DM. While this study was too underpowered to determine the effect of pioglitazone, the result failed to show beneficial effects. Larger studies examining the effects of pioglitazone are needed to determine whether pioglitazone is able to reduce the risk of recurrence of ischemic stroke.

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Conflicts of Interest/Disclosures
R.T. has received lecture fees from Boehringer Ingelheim, Sanofi-Aventis, Novartis Pharmaceuticals, Takeda Pharmaceutical Co., Ltd., Bristol-Myers Squibb, Otsuka Pharmaceutical Co., Ltd., Bayer, Astellas Pharma Inc., Shionogi & Co., Ltd.


R.K. has received lecture fees from AstraZeneca, Boehringer Ingelheim, MSD, Novartis Pharmaceuticals, Sanofi-Aventis, and Takeda Pharmaceutical Co.

Abbreviations

AF; atrial fibrillation, ATI; atherothrombotic infarction, BAD; branch atheromatous disease, CE; cardiogenic embolism, ICH; intracranial hemorrhage, SVO; small vessel occlusion, TIA; transient ischemic attack, UE; undetermined etiology

References


