Effects of Pioglitazone on Macrovascular Events in Patients with Type 2 Diabetes Mellitus at High Risk of Stroke: The PROFIT-J Study

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*Aim: The present study evaluated the effects of pioglitazone treatment on the incidence of primary cardiovascular events in Japanese subjects with type 2 diabetes mellitus at high risk of stroke.

Methods: A prospective, multicenter, randomized, open label, comparative study was conducted among diabetic patients recruited from 50 medical institutions nationwide. A total of 522 patients with hypertension and/or dyslipidemia who had one or more silent cerebral infarcts, advanced carotid atherosclerosis or microalbuminuria at baseline were randomly treated with (n=254) or without pioglitazone (n=268) and observed for a medium of 672 days. The hypertension and dyslipidemia were concurrently treated according to the respective treatment guidelines. The primary outcome was the time to the first occurrence of a composite of all-cause death, nonfatal cerebral infarction and nonfatal myocardial infarction.

Results: Treatment with pioglitazone resulted in significant reductions in the levels of HbA1c, diastolic blood pressure and LDL-cholesterol and a significant increase in the levels of HDL-cholesterol. The pioglitazone non-users exhibited a significant reduction in the LDL-cholesterol levels alone. Primary events were registered during the study period in nine patients in the pioglitazone group and 10 patients in the non-pioglitazone group. The difference in the cumulative incidence of the primary outcome was not significant between the two groups (1.8% per year).

Conclusions: Pioglitazone therapy produces immediate and effective improvements in glycemic control, diastolic blood pressure and lipid profiles. While this study was too underpowered to determine the effects of pioglitazone on the incidence of cardiovascular events, the results indicated that two years of pioglitazone treatment did not produce any statistically significant reductions in the rate of primary cardiovascular events.


Key words: Pioglitazone, Primary prevention, Mortality-macrovascular events, Diabetes mellitus
Introduction

The incidence of diabetes has been increasing worldwide due to lifestyle and dietary changes. Chronic hyperglycemia in patients with diabetes causes serious complications, including micro- and macrovascular diseases, such as advanced life-threatening ischemic heart disease and stroke. Importantly, the incidence of macrovascular diseases is expected to increase in association with the increased prevalence of diabetes.

According to a 4-year follow-up study, risk factors for stroke in patients with type 2 diabetes include an older age, previous history of cardiovascular disease or stroke and microvascular complications. Carotid artery atherosclerosis is another risk factor for stroke, as well as silent cerebral infarction and carotid artery stenosis, in patients with type 2 diabetes, such that the presence of a common carotid intima-media thickness (IMT) of $>1$ mm increases the risk of silent cerebral infarction four times compared to its absence.

The longevity of patients with diabetes depends considerably on the development of macroangiopathy. However, early studies of glucose-lowering therapy demonstrated that neither primary nor secondary stroke can be prevented by intensive glucose control in patients with type 2 diabetes. In addition, although two long-term follow-up studies suggested the importance of blood glucose control with respect to the prevention of macrovascular disease, the primary prevention of vascular diseases, including stroke, with the administration of glucose-lowering agents has thus so far not been validated in patients with type 2 diabetes.

Thiazolidinediones are ligands of the nuclear transcription factor, peroxisome-proliferator-activated receptor γ. Several preclinical studies have indicated that thiazolidinediones have protective effects against the development of atherosclerosis. However, meta-analyses have reported an increased cardiovascular risk associated with rosiglitazone use. On the other hand, one meta-analysis of the use of pioglitazone and cardiovascular safety showed a significant 18% reduction in the risk of a composite of cardiovascular outcomes. In addition, pioglitazone therapy has been found to slow the progression of carotid atherosclerosis compared with glimepiride. Furthermore, in a subanalysis of the PROactive study, treatment with pioglitazone significantly reduced the incidence of secondary stroke by 47% in type 2 diabetics with a history of stroke.

The present study was designed to examine the effects of pioglitazone therapy on the incidence of primary events of macrovascular disease and mortality (all-cause death, nonfatal cerebral infarction and nonfatal myocardial infarction) in Japanese patients with type 2 diabetes at high risk of stroke with a history of one or more silent cerebral infarcts, advanced carotid atherosclerosis or albuminuria treated between August 2007 and December 2011.

Materials and Methods

Eligibility and Study Design

The Primary prevention of high risk Type 2 diabetes in Japan (PROFIt-J) trial was a prospective, multicenter, randomized, open label, comparative study of type 2 diabetic patients at high risk of stroke carried out at 50 medical institutions nationwide. Patients, both men and women, who had been diagnosed with type 2 diabetes were recruited, excluding those with a glycated hemoglobin A1c (HbA1c) level of more than 10.5% (the NGSP value for HbA1c was calculated using the Japanese Diabetes Society formula, and the HbA1c level was expressed as the NGSP value in the text). Patients with diabetes mellitus were enrolled if they fulfilled one or more of the following three criteria: 1) silent cerebral infarction identified on MRI according to the 2007 guidelines; 2) carotid artery atherosclerosis (a mean common carotid artery IMT of $\geq 1$ mm), as measured according to the procedure described previously by Yamasaki et al.; and 3) albuminuria (a urinary albumin/creatinine ratio (ACR) of $\geq 100$ mg/g creatinine in a casual urine sample).

The subjects ranged from 55 to 85 years old. In addition to diabetes, they also had hypertension and/or dyslipidemia, or treated with anti-hypertensive medications or lipid-lowering agents. The exclusion criteria included the presence or history of cardiac failure, severe hepatic dysfunction (an ALT $\geq 100$ or viral hepatitis), severe renal dysfunction (a serum creatinine $>2.5$ mg/dL), documented dementia, history of documented cerebral infarction, cerebral hemorrhage, transient ischemic attack, myocardial infarction, angina pectoris before study entry, or previous use of thiazolidinediones within the last 8 weeks of study entry.

Eligible patients were stratified into 16 bins according to age at baseline (less than or older than 65...
years), the HbA1c level (less or higher than 7.7), a body mass index (BMI) of less or higher than 23.5 kg/m² and insulin use (yes or no). The subjects were then randomly assigned to either the pioglitazone group or non-pioglitazone group. All patients were treated under the intent-to-treat principle for three years. The pioglitazone group started with a daily dose of 15 mg pioglitazone, which was then increased up to 45 mg/day for men and 30 mg/day for women. When the HbA1c level could not be controlled to <6.9%, other glucose-lowering drugs were added to the treatment regimen. Among the patients who were not treated with pioglitazone, antidiabetic drugs, excluding pioglitazone, were used to reduce the HbA1c level to <6.9%. Hyper-tension and hyperlipidemia were concurrently treated according to the respective treatment guidelines. The study protocol was approved by the institutional review board and/or ethics committee of each Hospital/University. All patients provided their written informed consent. Instructional materials and behavioral counseling for diet therapy were given to each patient.

This study was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN000000846).

**Study Outcomes and Measured Parameters**

The primary outcome of this study was the time to the first occurrence of any of a composite of all-cause death, nonfatal stroke or nonfatal myocardial infarction. The secondary outcome was the incidence of cerebral infarction, transient ischemic attack (TIA), cerebral hemorrhage, myocardial infarction, angina pectoris, percutaneous coronary intervention/coronary bypass surgery (PCI/CABG) and acute coronary syndrome, excluding myocardial infarction.

Urinary ACR was conducted as scheduled. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the supine position. The HbA1c, low-density lipoprotein cholesterol (LDL-cholesterol), high-density lipoprotein cholesterol (HDL-cholesterol) and triglyceride (TG) level were directly measured at 0, 6, 12, 24 and 36 months during the observation period. Adverse effects, such as hypoglycemia, peripheral edema, heart failure and hepatic dysfunction, related to the use of pioglitazone and other diabetic drugs were examined at each visit.

**Statistical Analysis**

The Hisayama Study reported that macrovascular events occur at a frequency of 11.6 events per 1,000 patients with diabetes per year. The recruited subjects had at least two more risk factors for future cardiovascular events, one of which represented the presence of atherosclerosis or related tissue damage, which are considered to be higher risk factors than other general risk factors. A previous study demonstrated that patients with diabetes and two more risk factors exhibit an almost three-fold increased risk of cardiovascular events compared to patients with diabetes only. Therefore, the incidence of the primary outcome in this study was estimated to be 10% over a follow-up period of three years among the subjects not treated with pioglitazone and to diminish by 40% among the patients treated with pioglitazone. Assuming a power of 85% and statistical significance of <0.05, the calculated sample size of one arm was 720. Therefore, the estimated sample size was 1,000 for each arm of the study.

The mean values are expressed as the mean ± SD. Differences in categorical variables between the two groups were evaluated using Fisher’s exact test, while differences in continuous variables between the two groups were assessed using the unpaired *t*-test. In the survival analysis, the last date of survival was defined by the date of occurrence of the first event or the date of patient withdrawal.

Chronological changes in the variables were evaluated after excluding patients with missing entry data. A two-way repeated measured analysis of variance was performed in each group. If the differences in the chronological changes or the values observed between the two groups were significant, the mean values were evaluated using Dunnert’s multiple comparison test.

The cumulative incidence of each event was calculated using the Kaplan-Meier method. Kaplan-Meier curves were evaluated according to the log-rank test. The hazard ratio was calculated according to the Cox proportional hazard model. A *p* value of <0.05 was considered to be significant in all analyses. All statistical analyses were performed using the R 2.15.1 software program (R Foundation For Statistical Computing, Wien, Austria).

**Results**

A pre-designed interim analysis performed on October 2011 showed that the estimated incidence of primary outcome was 3.6% during an average intervention period of 562 days, with a forecasted three-year incidence of 5.4%. The latter rate was almost half that predicted in the study protocol. The incidence of primary outcome was less than half of 12% for three years, which was reported in a follow-up study of Japanese type 2 diabetic patients with advanced atherosclerosis of the carotid artery, urinary microalbumin-
lowed. The mean duration of follow-up until the interim analysis was 557 days in the pioglitazone group \( (n=234) \) and 598 days in the non-pioglitazone group.

The baseline characteristics of the study subjects are shown in Table 1. The mean age and proportion of men were similar between the pioglitazone and non-pioglitazone groups. The HbA1c, LDL-cholesterol, HDL-cholesterol and triglyceride levels were also similar between the two groups. Furthermore, the mean systolic/diastolic blood pressure, urinary albumin ACR and creatinine level were similar between the two groups. There were no differences in the use of sulfonylureas, α-glucosidase inhibitors, biguanides, glinides, insulin or dipeptidyl peptidase-4 inhibitors at study entry between the two groups (Table 1). A significantly smaller proportion of patients in the pioglitazone group used antihypertensive medications than those in the non-pioglitazone group \( (p=0.0321) \); however, no such differences were noted with respect to the use of lipid-lowering drugs.

The composite endpoint of all-cause death, non-fatal cerebral infarction and nonfatal myocardial

Table 1. Baseline characteristics of the participating patients

<table>
<thead>
<tr>
<th></th>
<th>Pioglitazone group ( (n=234) )</th>
<th>Non-pioglitazone group ( (n=247) )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (%)</td>
<td>148/234 (63.2)</td>
<td>163/247 (66.0)</td>
<td>0.5673</td>
</tr>
<tr>
<td>Age (year)</td>
<td>69.0 ± 6.9</td>
<td>68.9 ± 7.3</td>
<td>0.8473</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.6 ± 8.7</td>
<td>160.3 ± 8.4</td>
<td>0.3979</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.9 ± 11.4</td>
<td>62.4 ± 10.0</td>
<td>0.6067</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>24.2 ± 3.3</td>
<td>24.3 ± 3.3</td>
<td>0.8034</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>87.1 ± 8.2</td>
<td>87.6 ± 8.8</td>
<td>0.5468</td>
</tr>
<tr>
<td>Duration of diabetes mellitus (years)</td>
<td>11.1 ± 8.8</td>
<td>11.5 ± 9.0</td>
<td>0.6268</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.43 ± 0.84</td>
<td>7.43 ± 0.97</td>
<td>0.9764</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>136.0 ± 16.8</td>
<td>136.1 ± 15.1</td>
<td>0.9730</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>77.3 ± 11.1</td>
<td>76.0 ± 10.6</td>
<td>0.2158</td>
</tr>
<tr>
<td>Urinary albumin-creatinine ratio (mg/g Cr)</td>
<td>222.7 ± 619.1</td>
<td>223.5 ± 521.4</td>
<td>0.9883</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>115.4 ± 30.7</td>
<td>113.2 ± 27.0</td>
<td>0.4197</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>54.8 ± 14.7</td>
<td>54.0 ± 14.5</td>
<td>0.5218</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>140.8 ± 77.0</td>
<td>140.8 ± 76.0</td>
<td>0.9970</td>
</tr>
<tr>
<td>Glucose-lowering agents used at study entry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonylurea (%)</td>
<td>105/231 (45.4)</td>
<td>116/247 (47.0)</td>
<td>0.7832</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors (%)</td>
<td>91/231 (39.4)</td>
<td>79/247 (32.0)</td>
<td>0.1041</td>
</tr>
<tr>
<td>Biguanide (%)</td>
<td>75/231 (32.5)</td>
<td>73/247 (29.6)</td>
<td>0.5527</td>
</tr>
<tr>
<td>Glinide (%)</td>
<td>29/231 (12.6)</td>
<td>43/247 (17.4)</td>
<td>0.1596</td>
</tr>
<tr>
<td>Insulin (%)</td>
<td>16/231 (6.9)</td>
<td>16/247 (6.5)</td>
<td>0.8569</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 inhibitors (%)</td>
<td>0/231 (0.0)</td>
<td>1/247 (0.4)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Other drugs for cardiovascular diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive agents (%)</td>
<td>131/234 (56.0)</td>
<td>162/247 (65.6)</td>
<td>0.0321</td>
</tr>
<tr>
<td>Lipid-lowering agents (%)</td>
<td>96/234 (41.0)</td>
<td>114/247 (46.2)</td>
<td>0.2707</td>
</tr>
</tbody>
</table>

uria (>30 mg/g creatinine) or two or more risk factors, such as hypertension, dyslipidemia and obesity. Furthermore, the low incidence observed in this study was similar (1.7% for one year) to that of Japanese type 2 diabetic subjects free of a history of previous cardiovascular events (JPAD study). Moreover, the Kaplan-Meier curve showed no significant differences in the primary or secondary endpoints between the two groups \( (p=0.9914) \). From an ethical point of view, the data and safety monitoring committee recommended the discontinuation of this study.

Ultimately, a total of 522 diabetic patients (254 patients in the pioglitazone group and 268 patients in the non-pioglitazone group) were recruited from 50 medical institutions nationwide, comprising 165 patients with silent cerebral infarction, 204 patients with advanced carotid atherosclerosis and 173 patients with microalbuminuria. After excluding eight participants (six treated with pioglitazone and two treated without pioglitazone) who withdrew their consent after entry and 33 participants with a lack of follow-up data, the remaining 234 patients treated with pioglitazone and 247 patients treated without pioglitazone were followed.
ysis indicated no differences in the cumulative incidence of the primary outcome between the two groups (HR: 1.053, 95% CI: 0.427-2.593, \( p = 0.9114 \), according to the log-rank test).

With regard to the secondary outcome, three infarction occurred in a total of nine patients (one, three and five events, respectively) in the pioglitazone group and 10 patients (two, four and four events, respectively) in the non-pioglitazone group during the intervention period (Fig. 1A). The Kaplan-Meier analysis indicated no differences in the cumulative incidence of the primary outcome between the two groups (HR: 1.053, 95% CI: 0.427-2.593, \( p = 0.9114 \), according to the log-rank test).
In the pioglitazone group, the mean HDL-cholesterol level was significantly higher at six months (59.5 ± 15.9 mg/dL) relative to the baseline value (54.8 ± 14.7 mg/dL, \( p = 0.012 \)) and remained elevated during the 24-month treatment period. In comparison, this parameter did not change significantly in the non-pioglitazone group (Fig. 3A). In both groups, the LDL-cholesterol levels were significantly lower at 24 months than at baseline (pioglitazone: 107.0 ± 26.1 vs 115.4 ± 30.8 mg/dL, non-pioglitazone: 105.4 ± 26.4 vs 113.2 ± 27.0 mg/dL, respectively, Fig. 3B). In both groups, no significant changes were noted in the serum triglyceride levels (Fig. 3C). The patients in the pioglitazone group showed a significant reduction in diastolic blood pressure throughout the intervention period, although no such changes were observed in systolic blood pressure. In the non-pioglitazone group, no significant changes were observed in either systolic or diastolic blood pressure. Furthermore, there were no significant changes in body weight, BMI or abdominal circumference in either group.

The mean urinary ACR decreased from 223 ± 620 at baseline to 201.7 ± 412 at 24 months (\( n = 116 \)) in the pioglitazone group. In contrast, this parameter increased from 223 ± 521 at baseline to 343 ± 913 at 24 months (\( n = 148 \)) in the non-pioglitazone group.

**Fig. 2.** Changes in glycated hemoglobin in the pioglitazone and non-pioglitazone groups.

The difference in HbA1c between each time point and baseline was evaluated using paired Dunnett’s \( t \)-test, while the differences between the two groups were examined using Welch’s \( t \)-test. The vertical bars represent the standard deviation.
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However, these changes were not significant, and there were no significant differences between the two groups.

A total of 39 adverse events were registered in 33 patients (rate: 14.1%) in the pioglitazone group, compared with 13 events in 10 patients (5.3%) in the non-pioglitazone group \( (p=0.0001) \). These events included peripheral edema \( (n=12) \) and cancer \( (n=3) \) in the pioglitazone group and cancer \( (n=5) \) and cataracts \( (n=3) \) in the non-pioglitazone group. One patient in the non-pioglitazone group died from rectal cancer during the observation period.

Fig. 3. Changes in blood lipid profiles in the pioglitazone and non-pioglitazone groups.

The differences in the blood lipid profile between each time point and baseline were evaluated using paired Dunnett’s t-test, while the differences between the two groups were tested using Welch’s t-test. The vertical bars represent the standard deviation.
Discussion

In a recent multicenter study, we reported the effectiveness of pioglitazone in reducing the intima-media thickness of the common carotid artery in Japanese subjects with type 2 diabetes for up to three years. Based on these results, we designed the present study to examine the effects of pioglitazone on macrovascular diseases (all-cause death, nonfatal cerebral infarction and nonfatal myocardial infarction) in Japanese patients with type 2 diabetes at high risk of stroke. However, this study was clearly too underpowered to definitively prove the effectiveness of pioglitazone in reducing macrovascular disease due to the small sample size. On the other hand, during the 24-month intervention period, treatment with pioglitazone significantly reduced the levels of glycated hemoglobin, diastolic blood pressure and LDL cholesterol and significantly increased the level of HDL cholesterol. In contrast, the LDL cholesterol level was the only parameter to show a significant improvement in the non-pioglitazone group. Some of the positive effects of pioglitazone identified in the present study were also previously reported by our group, including the effects on glycated hemoglobin and HDL cholesterol. Other researchers have also reported that pioglitazone therapy results in a significant reduction of systolic blood pressure in type 2 diabetic patients.

Comparing pioglitazone with rosiglitazone, a previous study reported that treatment with pioglitazone increases the LDL cholesterol level, although the increase is lower than that achieved with rosiglitazone. In addition, pioglitazone therapy has been reported to decrease triglycerides, while rosiglitazone increases triglycerides. Furthermore, the HDL cholesterol level has been reported to increase more significantly following treatment with pioglitazone than with rosiglitazone. In the present study, we found a similar trend with respect to the effects on lipid profiles following pioglitazone treatment.

The present multicenter intervention study demonstrated a discrepancy between risk reduction and the final outcome, i.e., improvements in several risk factors in patients treated with pioglitazone, with no differences in the incidence of cardiovascular events. What is the reason for this discrepancy? One explanation is that significant risk reduction for two years might be insufficient to manifest a significant difference in the primary and secondary outcomes. At baseline, the mean HbA1c level was 7.4%, with a mean systolic blood pressure of 136 mmHg and a mean LDL cholesterol of 114 mg/dL. These values were lower than those reported in the PROactive Study. In the present study, treatment with pioglitazone resulted in a reduction of HbA1c to 6.9% at 24 months, which was smaller than that reported in a previous study (0.9%)<sup>27</sup>. Therefore, these improvements may not culminate in a significant reduction in the incidence of cardiovascular events.

Another possibility is that a larger proportion of patients in the non-pioglitazone group required additional glucose-lowering drugs, which may have resulted in a reduction in the frequency of cardiovascular events comparable to that observed in the pioglitazone group. With regard to the glucose-lowering drugs used in the present cohort, the proportion of patients in the non-pioglitazone group treated with biguanides increased significantly from 40.1% at the start of the study to 50.8% at 24 months (p<0.05). In contrast, this proportion decreased from 31.6% to 28.1% in the pioglitazone group. Several studies have shown that metformin, a representative biguanide, reduces the rate of cardiovascular events in patients with type 2 diabetes<sup>28</sup>. In addition, a meta-analysis demonstrated that treatment with acarbose, an α-glucosidase inhibitor, reduces cardiovascular events in type 2 diabetics<sup>29</sup>. In the present study, the proportion of patients treated with α-glucosidase inhibitors increased from 39% at baseline to 44% at 24 months in the non-pioglitazone group, although the change was not statistically significant.

The third possibility is that the present study included patients at high risk of stroke, but without a previous history of stroke. In fact, we enrolled diabetic patients who met one or more of the three entry criteria: silent cerebral infarction, advanced carotid atherosclerosis (an IMT of ≥ 1.0 mm) or albuminuria (an ACR of >100 mg/g creatinine). Evidence suggests that these conditions are associated with an increased frequency of cardiovascular events. Indeed, in the subanalysis of the PROactive study, treatment with pioglitazone was found to be significantly reduce the incidence of secondary stroke by 47% in the type 2 diabetes patients with a previous history of stroke<sup>11</sup>. However, that subanalysis also showed that pioglitazone therapy reduced the incidence of the primary outcome by only 6% (p=0.350) and did not decrease the incidence of primary stroke (HR=1.06). Taken together, the results of the subanalysis of the PROactive study and our present findings suggest that the risk of primary stroke in the present study is comparable to that observed in patients without a previous history of stroke rather than those with a previous history of stroke in the PROactive study.

In conclusion, the present study indicated that treatment with pioglitazone produces immediate and
effective improvements in glycemic control, blood pressure and lipid profiles in type 2 diabetic patients at high risk of stroke, compared with non-pioglitazone medications. The observed incidence of all-cause death, nonfatal cerebral and myocardial infarction decreased to a low level (1.8% per year), which is comparable with that observed in Japanese type 2 diabetics without a history of cardiovascular disease. However, our results indicate that the favorable effects of two years of treatment with pioglitazone did not translate into a reduction in the incidence of primary cardiovascular events relative to that observed with treatment with other agents.

Acknowledgments

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Conflicts of Interest

TY has received lecture fees from AstraZeneca, Shionogi, Dainippon Sumitomo Pharm and Takeda Pharmaceutical Co. and research funds from AstraZeneca and Dainippon Sumitomo Pharm. HW has received lecture fees from Boehringer Ingelheim, Sanofi-Aventis, Ono Pharmaceutical Co., Novartis Pharmaceuticals, Eli Lilly, Sanwakagaku Kenkyusho, Daiichi Sankyo Inc., Takeda Pharmaceutical Co., MSD, Dainippon Sumitomo Pharm. and Kowa Co. and research funds from Boehringer Ingelheim, Pfizer, Mochida Pharmaceutical Co. Sanofi-Aventis, Novo Nordisk Pharma, Novartis Pharmaceuticals, Sanwakagaku Kenkyusho, Terumo Corp. Eli Lilly, Mitsubishi Tanabe Pharma, Daiichi Sankyo Inc., Takeda Pharmaceutical Co., MSD, Shionogi, Pharma, Dainippon Sumitomo Pharma, Kissei Pharma and AstraZeneca. MM has received lecture fees from Sanofi-Aventis, Novo Nordisk Pharma, Novartis Pharmaceuticals and Mitsubishi Tanabe Pharma and research funding from Terumo Corp. Nikkiso Corp. RK has received lecture fees from AstraZeneca, Dainippon Sumitomo Pharm., Novartis Pharmaceuticals, Eli Lilly, Boehringer Ingelheim, Daiichi Sankyo Inc., MSD, AstraZeneca and Shionogi.

Appendix

Organizing Committee: Ryuzo Kawamori (Chair), Yoshimitu Yamasaki, Hirotaka Watada, Munehide Matsuhisa

Event Ascertainment Committee: Masayasu Matsumoto, Shunsuke Otsuki, Kazuo Kitagawa, Masafumi Kitakaze

Data and safety monitoring committee: Masayasu Matsumoto, Masafumi Kitakaze

Medical expert for the epidemiological analysis: Tutomo Yamazaki

Participants in the Profit-J study group:


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