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Research Paper

Cardiovascular Outcomes in Patients With Previous Myocardial Infarction and Mild Diabetes Mellitus Following Treatment With Pioglitazone
Reports of a Randomised Trial From The Japan Working Group for the Assessment Whether **P**ioglitazone **P**rotects DM Patients **A**gainst **R**e-Infarction (PPAR Study)

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ABSTRACT

Background: Secondary prevention in patients with myocardial infarction (MI) is critically important to prevent ischaemic heart failure and reduce social burden. Pioglitazone improves vascular dysfunction and prevents coronary atherosclerosis, mainly via anti-inflammatory and antiatherogenic effects by enhancing adiponectin production in addition to antihyperglycemic effects, thus suggesting that pioglitazone attenuates cardiovascular events in patients with mild (HbA1c levels < 6·5%) diabetes mellitus (DM). Therefore, we evaluated the effects of pioglitazone on cardiovascular events in patients with both previous MI and mild DM.
Methods: In this multicentre, prospective, randomised, open, blinded-endpoint trial, we randomly assigned 630 patients with mild DM with a history of MI to undergo either DM therapy with (pioglitazone group) or without (control group) pioglitazone. DM was diagnosed using the 75-g oral glucose tolerance test, and mild DM was defined if HbA1c level was <6·5%. The primary endpoint was the composite of cardiovascular death and hospitalisation caused by acute MI, unstable angina, coronary revascularisation (including percutaneous coronary intervention and cardiac bypass surgery), and stroke.
Findings: HbA1C levels were 5·9 and 5·8% ($p = 0·71$) at baseline and 6·0 and 5·8% ($p < 0·01$) at 2 years for the control and pioglitazone groups, respectively.
The primary endpoint was observed in 14·2% and 14·1% patients in the control and pioglitazone groups during two years (95% confidential interval (CI):0.662–1·526, $p = 0·98$), respectively; the incidence of MI and cerebral infarction was 0·3% and 2·2% (95%CI: 0·786–32·415, $p = 0·09$) and 1·0% and 0·3% (95%CI: 0·051–3·662, $p = 0·44$), respectively. Post-hoc analyses of the 7-year observation period showed that these trends were comparable (21·9% and 19·2% in the control and pioglitazone groups, 95%CI: 0.618–1·237, $p = 0·45$).
Interpretation: Pioglitazone could not reduce the occurrence of cardiovascular events in patients with mild DM and previous MI.

1. Introduction

Recently, there have been several advances in the treatment of cardiovascular disorders [1]; however, heart failure (HF) remains a major cause of increased morbidity and mortality [2]. The most common cause of HF is myocardial infarction (MI) owing to impaired cardiac function or recurrence of MI [3]. Therefore, preventing the recurrence of MI is crucial for preventing HF in these patients, along with prognostic treatment of chronic HF [4,5]. Type II diabetes mellitus (DM), which is often complicated by ischaemic heart disease [6,7] constitutes a strong risk factor for arteriosclerotic disease [8]. Pioglitazone is one of the effective drugs used to treat DM [9], which may merit DM-induced cardiovascular disorders by lowering blood glucose levels. Furthermore, pioglitazone exhibits anti-inflammatory and anti-atherogenic effects in animals and humans [10–14]. However, the effects of pioglitazone on cardiovascular outcomes are not conclusive [15–17] partially owing to differences in vascular and heart effects [16,18], combination of other drugs for DM [15], and comorbidity with

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Research in Context

Evidence Before This Study

There have been many lines of evidence as to whether the treatment of diabetes mellitus (DM) decreases the occurrence of the cardiovascular events, and the consensus at present is that the blood-glucose lowering using the drugs for DM is not enough to prevent the cardiovascular events, and the additional cardioprotective property of the drugs for the DM is necessary. Pioglitazone is one of such drugs of DM; pioglitazone affects PPARγ and increases adiponectin production, which may merit the cardiovascular dysfunction on the top of its blood-glucose lowering effect. Therefore, pioglitazone may be beneficial for the prevention of cardiovascular events in patients with previous myocardial infarction (MI) and mild DM. However, the effects of pioglitazone on cardiovascular outcomes are not conclusive partially owing to comorbidity with DM, such as MI. Although the sub-analysis of this PROactive study showed that pioglitazone reduces the recurrence of MI in patients with moderate DM with an HbA1c level > 7.0% compared with placebo, this fact does not necessarily guarantee the effectiveness of supplemental treatment with pioglitazone in patients with both previous MI and well-controlled DM in reducing the occurrence of cardiovascular events. Since recurrent cardiovascular events in patients with previous MI are critical in the cardiovascular practice, we need the evidence as to whether pioglitazone decreases the cardiovascular events in DM patients. Therefore, we conducted a multicentre, prospective, randomised, open blinded-endpoint (PROBE) study to evaluate the effects of supplemental treatment with pioglitazone on cardiovascular events in patients with mild DM and previous MI.

Added Value of This Study

The present study showed that pioglitazone did not prevent the occurrence of cardiovascular events, such as cardiovascular death and hospitalisation caused by acute MI, unstable angina, coronary revascularisation including percutaneous coronary intervention and cardiac bypass surgery, and stroke in patients with mild DM with previous MI, and observed that pioglitazone did not decrease the incidence of the primary endpoint of cardiovascular composite events. This indicates that pioglitazone may be unable to induce cardiovascular protection beyond the blood glucose-lowering effects at least for patients with previous MI, although several basic investigations showed the cardioprotective sequences. This study hints that the fruitful results of the basic research cannot be necessarily extended to the clinical medicine. The other important observation of the present study reveals that pioglitazone increases the deleterious adverse actions such as bladder cancers or heart failure.

Implications of All the Available Evidence

Although the present study concluded that pioglitazone could not reduce the occurrence of cardiovascular events in patients with mild DM and previous MI, we understand that mild DM or previous MI independently increases the occurrence of the cardiovascular events, and thus the cardiovascular death, indicating that we should treat such patients appropriately to improve the quality and quantity of life and decrease the social burden. To achieve the cardiovascular protection, we need to apply all of the previous evidence for the correction of blood pressure, lipid profiles and the inhibition of either renin-angiotensin or sympathetic nerve systems, use of aspirin on the top of blood-glucose lowering without hypoglycemia to treat the patients with DM. Since recent large scale trials using SGLT2 inhibitors show the reduction of cardiovascular events in patients with DM, it would be important to test whether SGLT2 inhibitors inhibit cardiovascular events in patients with MI and DM.

DM, such as MI [15,17,19,20]. Furthermore, the difference of glucose controls in some clinical trials used placebo for pioglitazone may make the differences in the clinical outcomes. Indeed, although the sub-analysis of this PROactive study showed that pioglitazone reduces the recurrence of MI in patients with moderate DM with an HbA1c level > 7.0% compared with placebo [21], this fact does not necessarily guarantee the effectiveness of supplemental treatment with pioglitazone in patients with both previous MI and well-controlled DM in reducing the occurrence of cardiovascular events.

Therefore, we conducted a multicentre, prospective, randomised, open blinded-endpoint (PROBE) study to evaluate the effects of supplemental treatment with pioglitazone on cardiovascular events in patients with mild DM and previous MI. We defined mild DM as a HbA1c level < 6·5% to minimise the confounding blood glucose-lowering effects of pioglitazone, with compliance of the guidelines of the Japanese DM Society.

2. Methods

2.1. Study Design

The **P**ioglitazone **P**rotects DM Patients **A**gainst **R**e-Infarction (PPAR) study was a multicenter, prospective, randomised (1:1), open blinded endpoint (PROBE) study conducted across 106 hospitals and clinics in Japan. The trial has been registered with Clinicaltrials.gov (No. NCT00212004) and UMIN (No C0000000091).

2.2. Participants

We recruited patients with clinically overt MI and DM. Inclusion criteria were as follows: 1) age between 20 and 79 years, 2) fasting plasma glucose levels ≥126 mg/dL or 2-h 75-g oral glucose tolerance test (OGTT) value ≥200 mg/dL, and 3) HbA1c levels <6·5% (47·5 IFCC). As for DM, we enrolled the previously diagnosed DM patients or newly diagnosed DM patients by the confirmation of the condition 2) in two different days.

Patients with DM with previous MI were randomly allocated to receive either 1) pioglitazone or 2) any DM drug other than pioglitazone such as sulfonylurea (SU) agents on the top of lifestyle modification of weight reduction, appropriate diet, regular exercise. If good glycemic control is not maintained in either group, the additional drugs can be administered.

The target number of patients for recruitment was 720 and the target number of cardiovascular events for the primary endpoints was 81, and the compulsory period for follow-up was 2 years to assess clinical events to reach a firm conclusion. We extended the follow-up period to the time of the last patient out from 2 years to approximately 7 years to strengthen the conclusion of this study.

The exclusion criteria were as follows: acute MI occurring within the last 7 days; patients with NYHA symptoms of II-IV or with left ventricular ejection fraction ≤40%; suspected type I DM; patients with scheduled coronary angioplasty or history of coronary artery bypass graft surgery; patients with severe liver or kidney injury, history of allergy or drug hypersensitivity, arteriosclerosis obliterans with Fontaine stage III or worse, inability to understand and/or comply with study medications, procedures and/or follow-up or any conditions that may render the patient unable to complete the study in the opinion of the investigator.

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All patients provided written informed consent. The study protocol was approved by the institutional review boards and the ethics committees of all the involved hospitals. The study was performed following the principles of the Declaration of Helsinki and the Japanese ethical guidelines for clinical research.

2.3. Randomisation and Masking

All patients were randomly assigned (1:1) through a web-based central randomisation system using computer-generated random numbers (NTT Data, Tokyo, Japan) to undergo either pharmacologic intervention with pioglitazone (pioglitazone group) or non-pharmacologic or pharmacological interventions using SUs or additional drugs other than pioglitazone (control group). We used permuted blocked randomisation. This study was open-labelled, and allocation was unmasked to the patients and investigators; however, the event adjudication committee and the data and safety monitoring board were blinded to the study characteristics.

2.4. Procedures

Participants in the pioglitazone group were administered a pioglitazone tablet (15 mg) once a day. The dosage of pioglitazone was reduced to half or quarter of the original dosage if side effects, such as oedema, occurred. Otherwise, the dose of pioglitazone was increased to 30 mg/day. Participants assigned to the control group were treated with diet and exercise therapy or SUs or additional drugs other than pioglitazone.

Diet or exercise therapy was strengthened by expert nutritionists and/or physical therapists besides the attending physicians if DM exacerbated in patients in any of the groups. Concomitant use of SUs was permitted if the strengthened non-pharmacological therapies could no longer improve DM. Body weight, blood pressure, results of 75-g OGTT, HbA1c levels, serum triglyceride, and total cholesterol levels, plasma BNP levels, left ventricular ejection fraction (LVEF), LV diastolic parameter (E/A) and LV deceleration time by echocardiography were measured, and medications were documented at baseline and at 24 months. All data were compiled at the data center in the NTT Data (Tokyo, Japan) and G-ONE (Osaka, Japan).

2.5. Outcomes

The primary outcome was the time until the first cardiovascular composite endpoint of death from cardiovascular death, hospitalisation due to nonfatal MI, nonfatal unstable angina [22], treatment with coronary revascularisation (percutaneous coronary intervention or coronary artery bypass graft) and cerebral infarction. Secondary outcomes were an all-cause death, each factor of the primary endpoints, DM progression (HbA1c levels >7·0%) and worsening of renal function (serum creatine levels ≥2·5 mg/dL or increase in serum creatine levels by ≥2 mg/dL).

2.6. Statistical Analysis

The sample size was calculated based on the estimated occurrence of the composite primary endpoint following 24 months of the study period. The sample size was originally calculated 3000 (1500 each for the pioglitazone and control groups) using the preliminary and uncertain information of our clinical database because no data were available for the cardiovascular event rate for previous MI patients with mild DM. Therefore, we conducted an interim data review while the treatment assignments to patients were still blinded to the principle investigators, statistician and data managers. Since the cardiovascular events for the primary endpoints occurred more than we expected, we recalculated

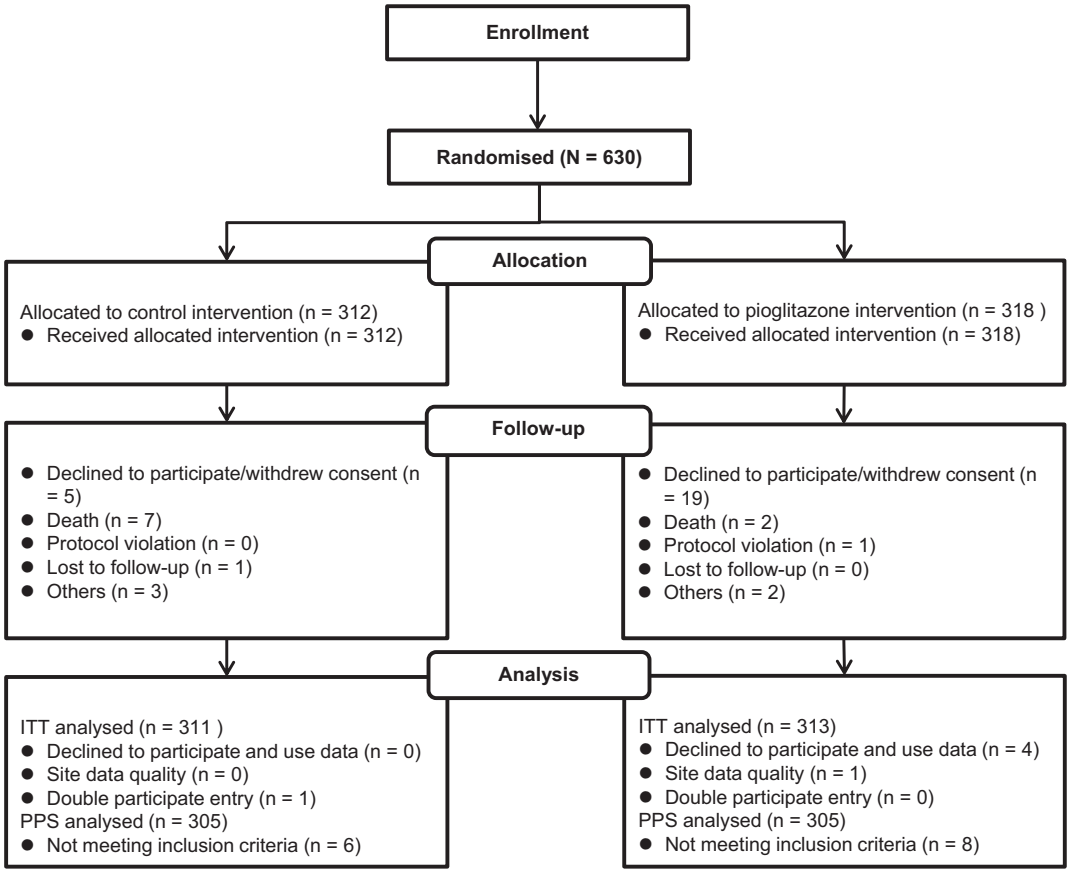

Fig. 1. Trial profile of the PPAR study.

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Table 1
Baseline characteristics of patients.

	Time (min)	Unit	Control group N = 311	Pioglitazone group N = 313
Male		%; n	85.2%; 265	86.3%; 270
Age (years)		Mean ± SD; n	66.0±9.1; 311	66.0 ±10.1; 13
BMI		Mean ± SD; n	24.8±3.2; 309	24.8 ± 3.3; 312
Blood glucose level (mg/dL)	0	Median (25%–75%); n	111.0 (98.0–122.0); 309	110.0 (98.0–122.0); 309
	30		187.0 (166.5–207.0); 220	186.0 (169.0–209.5); 220
	60		237.0 (211.0–256.0); 245	237.0 (212.0–260.0); 247
	120		231.0 (213.0–259.0); 309	230.0 (211.0–254.0); 309
Insulin level (μg/dL)	0	Median (25%–75%); n	7.0 (4.7–10.0); 288	6.9 (4.5–9.8); 278
	30		27.0 (17.6–43.0);191	29.2 (18.8–47.0); 176
	60		43.2 (28.5–74.5); 199	49.0 (29.5–83.2); 190
	120		75.6 (47.1–119.7); 282	75.4 (45.7–126.4); 270
Time from previous MI		Median (25%–75%); n	83.0 (13.0–1213.0); 309	80.0 (15.0–1198.0); 313
Hypertension		%; n	78.3%; 238	79.4%; 244
Dyslipidemia		%; n	81.2%; 246	81.4%; 249
Smoking		%; n	59.9%; 181	57.4%; 174
Stroke		%; n	3.3%; 10	5.9%; 18
Arteriosclerosis (ASO)		%; n	3.6%; 11	3.9%; 12

Values are presented as mean (±SD, interquartile range, n or % as appropriate). Abbreviations: BMI, body mass index.

the sample size and the required number of events. If we assumed the event-free survival rates at 24 months of 83.2% and 90.6% in the control and pioglitazone groups (hazard ratio: 1.863) [23–26], we calculated the total required events number of 81 and a sample size of 330 subjects per group to detect the treatment effect with 80% power at the significance level 0.05 by using two-sided log-rank test (Collett approximation). When patients lost to follow-up were assumed to reach up to 8%, we estimated the total sample size of 720 subjects (360 per group). Then we decided to terminate the patient enrollment when 720 subjects were enrolled or the number of cardiovascular events exceeded 81.

Efficacy analysis was based on the intention-to-treat (ITT) principle. Continuous data were presented as median with interquartile range (IQR), where IQRs were presented in terms of 25th and 75th percentiles. Categorical data were presented as frequencies (%). Event-free survival for the primary composite event was calculated from the date of randomisation to composite endpoints, whichever occurred first. Data concerning patients who were alive and did not experience events were censored at their last date of follow-up. The event-free survival curves were estimated using the Kaplan–Meier method. Between-group differences in survival were assessed using the log-rank test. HRs with 95% confidence interval (CI) were calculated using Cox proportional hazard regression, including those for the subgroup analyses. The proportional hazards assumption was graphically investigated based on the Schoenfeld residuals over time. The primary outcomes were also analyzed based on the per-protocol set (PPS) population to assess the robustness of the conclusion from the ITT analysis. All tests were two-sided, and $p < 0{\cdot}05$ was considered statistically significant. All analyses were performed using the statistical analysis software SAS, version 9·3 for Windows (SAS Institute, Cary, NC, USA).

2.7. Role of the Funding Source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or in the writing of the report. The corresponding author had full access to all the data in the study at the end of the study and had final responsibility for the decision to submit for publication.

3. Results

Fig. 1 presents the trial profile. We enrolled 630 patients between May 2005 and June 2014 until we obtained more than 81 cardiovascular events of the primary endpoints, and we ended this study when the cardiovascular events became more than 81. Of these, 6 patients were excluded from the ITT population owing to withdrawal of informed consent, inappropriate enrolment, and low-quality site data. Fourteen patients were excluded from the PPS population owing to failure to meet the entry criteria. Thus, 624 and 610 participants were included in the ITT and PPS populations, respectively. Table 1 presents the baseline characteristics of the patients. The follow-up period was at least 2 years in both groups. The median follow-up durations were

Table 2
Data of blood pressure, blood chemistry, and echocardiogram at the time of entry.

			Control group N = 311	Pioglitazone group N = 313
Systolic BP	(mm Hg)	Median (25%–75%); n	128.0 (114.0–140.0); 303	125.0 (115.0–136.0); 306
Diastolic BP	(mm Hg)	Median (25%–75%); n	74.0 (66.0–80.0); 303	74.0 (65.0–80.0); 306
HbA1c	(%)	Mean±SD; n	5.9±0.4; 288	5.8±0.4; 292
Creatinine levels	(mg/dL)	Mean± SD; n	0.9±0.2; 280	0.9±0.2; 288
Total cholesterol levels	(mg/dL)	Mean±SD; n	177.6±36.3; 251	174.0±35.9; 265
Triglyceride levels	(mg/dL)	Median (25%–75%); n	133.0 (95.0–193.0); 276	123.0 (87.0–174.5); 284
HDL cholesterol levels	(mg/dL)	Mean±SD; n	47.1±12.4; 272	48.5±14.2; 281
BNP levels	(pg/mL)	Median (25%–75%); n	48.1 (23.1–110.0); 199	52.1 (22.2–114.7); 194
LV diastolic dimension	(mm)	Mean±SD; n	49.4±6.5; 190	49.2±6.8; 233
LV systolic dimension	(mm)	Mean±SD; n	33.8±7.8; 186	33.3±6.8; 220
E/A ratio		Median (25%–75%); n	0.8 (0.7–1.0); 162	0.8 (0.7–0.9); 196
LV deceleration time	(ms)	Mean±SD; n	216.9±4.8; 163	215.9±63.1; 195
LV ejection fraction	(%)	Mean±SD; n	57.4±11.6; 179	58.2±11.8; 214

Values are presented as mean (±SD, interquartile range, n or % as appropriate).
Abbreviations: BP, blood pressure; LV, left ventricular; E/A, peak early diastolic LV filling velocity/peak atrial filling velocity ratio.

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Table 3
Data of blood pressure, blood chemistry, and echocardiogram at two years after entry.

			Control group N = 311	Pioglitazone group N = 313
Systolic BP	(mm Hg)	Median (25%–75%); n	126.5 (118.0–140.0); 254	128.0 (118.0–136.0); 250
Diastolic BP	(mm Hg)	Median (25%–75%); n	72.5 (68.0–80.0); 254	70.0 (65.0–80.0); 250
HbA1c	(%)	Mean ± SD; n	6.0 ± 0.5; 241	5.8 ± 0.4; 243
Creatinine levels	(mg/dL)	Mean ± SD; n	0.9 ± 0.7; 236	0.9 ± 0.3; 234
Total cholesterol levels	(mg/dL)	Mean ± SD; n	170.8 ± 31.9; 207	170.7 ± 30.2; 206
Triglyceride levels	(mg/dL)	Median (25%–75%); n	124.0 (84.5–163.0); 232	110.0 (76.0–159.0); 229
HDL cholesterol levels	(mg/dL)	Mean ± SD; n	50.5 ± 12.4; 235	53.7 ± 14.3; 233
BNP levels	(pg/mL)	Median (25%–75%); n	27.5 (16.1–50.1); 166	53.0 (22.5–90.5); 169
LV diastolic dimension	(mm)	Mean ± SD; n	49.9 ± 7.0; 176	50.4 ± 6.8; 181
LV systolic dimension	(mm)	Mean ± SD; n	33.9 ± 8.2; 171	34.6 ± 8.0; 176
E/A ratio		Median (25%–75%); n	0.8 (0.6–0.9); 156	0.8 (0.7–1.0); 162
LV deceleration time	(ms)	Mean ± SD; n	227.9 ± 57.0; 157	220.4 ± 63.1; 167
LV ejection fraction	(%)	Mean ± SD; n	59.3 ± 11.4; 170	59.4 ± 11.8; 177

Values are presented as mean (±SD, interquartile range, n or % as appropriate).
Abbreviations are similar to those in Table 2.

1813.0 days (25%–75%; 1120·5, 2520·0 days) for 624 patients, and 1848·0 days (25%–75%; 1127·0, 2499·0 days) and 1778.0 days (25%–75%; 1110·0, 2535·0 days) for the control (n = 311) and the pioglitazone (n = 313) groups, respectively.

Tables 2 and 3 present data concerning blood pressure, laboratory investigations, and echocardiography at the time of entry and 2 years after, respectively. Although blood pressure, HbA1c levels, total and HDL cholesterol levels, and BNP levels were not significantly altered, changes in blood HbA1c levels in the pioglitazone group (0·0% ± 0·4%; n = 223) were slightly lower ($p < 0·01$) than those in the control group (0·1 ± 0·5; n = 230). The major dose of pioglitazone was 15 mg (55% of the pioglitazone group), and the ratio of the patients treated with 30 mg of pioglitazone was 14%. The compliance rate was >80% in 87% and 68% of the patients in the pioglitazone group at 1–3 months and 2 years after enrolment. Table 4 presents the concomitant drugs used at the time of entry and 2 years after. Most patients were administered renin–angiotensin inhibitors and blockers, statins, beta-blockers, and anti-coagulant drugs, because the patients had previous MI. Fig. 2 and Table 5 indicate that pioglitazone did not decrease the frequency of the cardiovascular composite endpoints. This result was comparable with the primary outcome assessed using the PPS population. Table 6 shows the results of subgroup analysis and no significant deviation of the primary endpoints according to subgroups. Fig. 3 indicates that the results were identical even if the observational period was increased to up to almost 7 years, thus showing that pioglitazone did not improve the occurrence probability of cardiovascular outcomes.

In addition to the severe adverse events detected as primary and secondary endpoints (Table 5), the frequencies of additional adverse events in the control and pioglitazone groups were 123 vs. 127 events. The major detailed adverse events were as follows: gastrointestinal disorders (7 vs. 8 events); hepatic disorders (2 vs. 2 events); respiratory disorders (2 vs. 4 events); benign and malignant disorders (11 vs. 5 events), including bladder cancer (1 vs. 0 events); metabolic, endocrine, and nutritional disorders (20 vs. 15 events), including hypoglycaemia (1 vs. 0 events); nervous system disorders (9 vs. 2 events); ophthalmological disorders (3 vs. 2 events); infectious disorders (4 vs. 6 events); renal and urinary disorders (2 vs. 4 events); cardiac disorders (41 vs. 51 events), including HF (2 vs. 7 events); vascular disorders (5 vs. 5 events) and oedema (2 vs. 10 events) in the control and pioglitazone groups, respectively.

4. Discussion

Here, we tested the hypothesis that pioglitazone prevents the occurrence of cardiovascular events, such as secondary prevention in patients with mild DM with previous MI, and observed that pioglitazone did not decrease the incidence of the primary endpoint of cardiovascular composite events. Further, we found that sex, age, body mass index, history of hypertension, dyslipidaemia, and arteriosclerosis or treatment with statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and beta-blockers did not affect primary outcomes. Similarly, no effect was observed with respect to the secondary endpoints, although pioglitazone, slightly but significantly, improved the severity of DM based on the HbA1c levels. Thus, pioglitazone did not provide any substantial and significant benefits for cardiovascular clinical outcomes in patients with both previous MI and mild DM. Although the negative results of the present study may shed light on the secondary prevention of MI, several issues need to be considered while interpreting the results.

First of all, the present study seems to contradict the results of either PROactive [16] or IRIS studies [17] In the PROactive study, the results were neutral for the primary outcomes and positive for the main secondary endpoints; In the IRIS study, the results were positive for the primary outcome, but neutral for each component of the primary outcome. However, the hypotheses and protocols of those studies are different from that of the present study. The HbA1c levels in the PROactive study were higher (7.9% vs 7.8% in the placebo and pioglitazone groups)

Table 4
Concomitant drugs at the time of entry and at two years after entry.

		Control group, N = 311	Pioglitazone group, N = 313
At the time of entry			
ACEI-ARB	%; n	76.2%;237	76.4%;239
Statin	%; n	80.7%;251	84.0%;263
Ca-blocker	%; n	33.1%;103	30.4%;95
Beta-blocker	%; n	59.5%;185	55.9%;175
Diuretics	%; n	15.4%;48	16.3%;51
Anti-platelet drugs	%; n	92.9%;289	92.7%;290
Anti-coagulant drugs	%; n	10.0%;31	7.0%;22
Vasodilators	%; n	17.7%;55	17.3%;54
Anti-ulcer drugs	%; n	68.8%;214	61.7%;193
Nicorandil	%; n	21.5%;67	16.0%;50
2 years after			
ACEI-ARB	%; n	63.0%;196	61.0%;191
Statin	%; n	72.4%;225	69.0%;216
Ca blocker	%; n	33.4%;104	27.8%;87
Beta-blocker	%; n	48.6%;151	46.0%;144
Diuretics	%; n	13.2%;41	15.3%;48
Anti-platelet drugs	%; n	81.4%;253	75.7%;237
Anti-coagulant drugs	%; n	7.4%;23	5.4%;17
Vasodilators	%; n	13.2%;41	11.5%;36
Anti-ulcer drugs	%; n	59.2%;184	51.4%;161
Nicorandil	%; n	15.4%;48	12.8%;40

Values are presented as mean (n or % as appropriate).
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; Ca blocker, calcium channel blocker.

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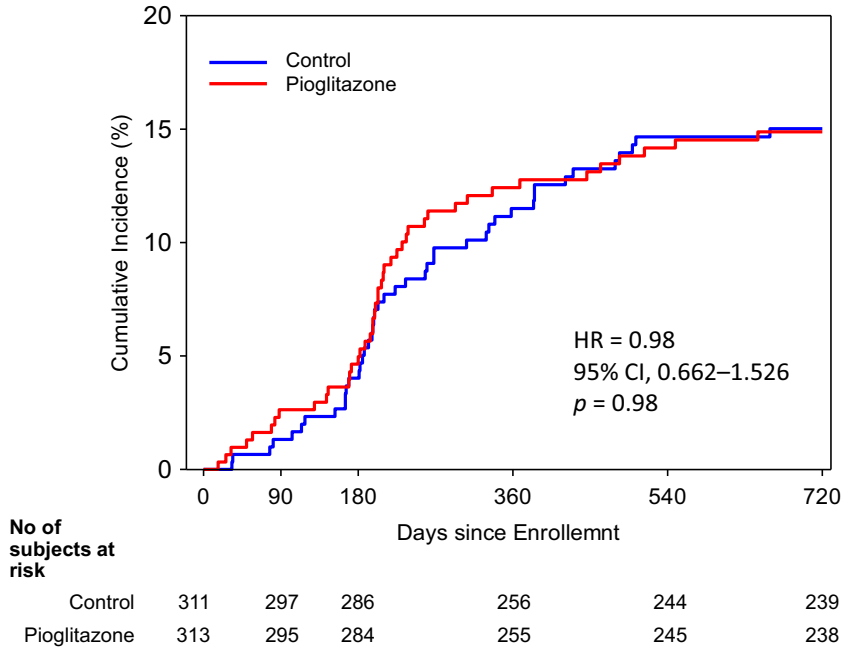

Fig. 2. Effects of pioglitazone on composite cardiovascular events of primary endpoints for 2 years in patients with mild DM and history of MI using ITT analysis.

than those in the present study (5·9% vs 5·8% in the comparator and pioglitazone groups). Indeed, the PROACTIVE study had beneficial effects on secondary cardiovascular events in severely diseased persons, since pioglitazone was the more effective in the most seriously affected patients. Because the PROactive study was designed to use placebo, the HbA1c levels decreased by 0·8% and by 0·3% in the pioglitazone and placebo groups, respectively. However, in the present study, pioglitazone did not further decrease the HbA1c levels (5.8%) because of the following factors: 1) we enrolled patients with mild DM with HbA1c levels <6·5% and 2) the target HbA1c level after the onset of the study was <6·3%, and other anti-DM drugs were decreased or withdrawn when pioglitazone was additionally administered in the pioglitazone group. The PROactive study investigated both blood glucose-lowering and pleotropic effects of pioglitazone in patients with moderate or severe DM, whereas in this study, we mainly observed the pleotropic effects of pioglitazone while maintaining the blood glucose levels at an almost constant level. We observed no pleotropic cardiovascular protective effects of pioglitazone in patients with previous MI with mild DM.

The PROactive study also enrolled patients with not only previous MI but also macrovascular diseases, such as coronary artery disease and sympathetic peripheral arterial obstructive diseases, thus making the results of the outcome different from those of the present study. However, the sub-analysis [21] of the PROactive study, wherein the enrolled patients were limited to those with previous MI showing identical results with those of the PROactive study, suggested that the difference between the PROactive and present studies is not attributable to the basal cardiovascular diseases but to the differences of HbA1c controls attributable to the use of placebo or comparators.

On the other hand, the HbA1c levels in the IRIS study are similar to those observed in our study; the mean HbA1c level at baseline is 5·8%. However, the differences between the IRIS and PPAR studies were the basal diseases; >80% of the patients had a history of stroke, the other patients had a history of transient ischaemic attack in the IRIS study, and 100% of the patients had previous MI in the present study. The IRIS study showed positive results for the primary endpoint (stroke + MI); however, the results were negative for each endpoint of stroke or MI

Table 5
Effects of pioglitazone on composite cardiovascular events of the primary endpoints for two years in patients with mild DM and history of MI.

		Control group N = 311	Pioglitazone group N = 313	HR (95%CI)	Wald p-Value
Composite	% (n)	14.2% (44)	14.1% (44)	1.005 (0.662, 1.526)	0.98
Cardiovascular death	% (n)	0.2% [1]	0% (0)		
MI	% (n)	0.3% [1]	2.2% [7]		
Unstable angina	% (n)	1.0% [3]	1.9% [6]		
Coronary revascularization	% (n)	11.5% (36)	9.6% [30]		
Cerebral infarction	% (n)	1.0% [3]	0.3% [1]		
All-cause death	% (n)	2.3% [7]	1.6% [5]	0.722 (0.229, 2.274)	0.58
Cardiovascular death	% (n)	0.2% [1]	0% (0)	0.334 (0.004, 30.794)	0.64
MI	% (n)	0.3% [1]	2.2% [7]	5.049 (0.786, 32.415)	0.09
Unstable angina	% (n)	1.0% [3]	1.9% [6]	1.876 (0.477, 7.380)	0.37
Coronary revascularization	% (n)	12.9% (40)	13.7% (43)	1.083 (0.704,1.666)	0.72
Cerebral infarction	% (n)	1.0% [3]	0.3% [1]	0.431 (0.051, 3.662)	0.44
ACS (MI + unstable angina)	%(n)	1.3% [4]	4.2% [13]	3.058 (1.020, 9.165)	0.05

		Control N = 311	Poglitazone N = 313	OR (95%CI)	Chisq p-Value
Progression of diabetes mellitus	% (n)	7.1% [22]	3.8% [15]	1.497 (0.767, 2.919)	0.23
Worsening of renal function	% (n)	0.6% [2]	0.3% [1]	1.683 (0.220, 12.859)	0.56

Values are presented as mean (95% confidential interval (CI), n or % as appropriate). Abbreviations: MI, myocardial infarction; ACS, acute coronary syndrome.

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Table 6
Subgroup analysis of the effects of pioglitazone on composite cardiovascular events of the primary endpoints for two years in patients with mild DM and history of MI.

		Control group	Pioglitazone group	HR (95%CI)	Wald p-Value	p-Value for interaction
Overall		14.2%(44/311)	14.1%(44/313)	1.005 (0.662, 1.526)	0.98	
Sex	Male	14.0%(37/265)	14.4%(39/270)	1.048 (0.668, 1.643)	0.84	0.63
	Female	15.2%(7/46)	11.6(5/43)	0.781 (0.248, 2.454)	0.67	
Age (years)	<65	10.9%(15/138)	12.4%(17/137)	1.164 (0.581, 2.331)	0.67	0.61
	≥65	16.8%(29/173)	15.3%(27/176)	0.922 (0.546, 1.557)	0.76	
Body mass index	<25	14.7%(26/177)	15.3%(26/170)	1.050 (0.610, 1.808)	0.86	0.90
	≥25	12.9%(17/132)	12.7%(18/142)	0.990 (0.510, 1.920)	0.98	
Hypertension	No	16.7%(11/66)	14.5%(9/62)	0.966 (0.401, 2.331)	0.94	0.95
	Yes	13.9%(33/238)	13.9%(34/244)	1.000 (0.619, 1.614)	1.00	
Dyslipidemia	No	21.1%(12/57)	17.5%(10/57)	0.858 (0.371, 1.985)	0.72	0.71
	Yes	13.0%(32/246)	13.3%(33/249)	1.032 (0.635, 1.678)	0.90	
Arteriosclerosis	No	14.4%(42/291)	14.7%(43/293)	1.040 (0.680, 1.592)	0.86	0.22
	Yes	18.2%(2/11)	0.0%(0/12)	0.172 (0.004, 7.108)	0.35	
Statin	No	16.7%(10/60)	12.0%(6/50)	0.704 (0.257, 1.931)	0.50	0.44
	Yes	13.6%(34/251)	14.6%(38/263)	1.090 (0.686, 1.731)	0.72	
ACEI—ARB	No	9.5% (7/74)	8.1%(6/74)	0.894 (0.300, 2.658)	0.84	0.81
	Yes	15.6%(37/237)	15.9%(38/239)	1.026 (0.652, 1.613)	0.91	
Beta-blocker	No	14.3%(18/126)	9.4%(13/138)	0.664 (0.326, 1.355)	0.26	0.14
	Yes	14.1%(26/185)	17.7%(31/175)	1.285 (0.763, 2.164)	0.35	

Values are presented as mean (95% confidential interval (CI), n or % as appropriate). Abbreviations are similar to those in Table 4.

and acute coronary syndrome. Similarly, the present study showed that pioglitazone did not improve any secondary endpoint of MI, unstable angina and coronary revascularisation, which is similar to the effects of pioglitazone on secondary endpoints, although the criteria for the enrolment of patients with either stroke or MI were different.

Finally, pioglitazone may be unable to induce cardiovascular protection beyond the blood glucose-lowering effects [27], at least for patients with previous MI, although several basic investigations showed cardioprotective sequences [28]. The discrepant results of the previous basic research and the present clinical trial may be explained by the following: 1. the pleotropic effects of pioglitazone are not potent enough to mediate cardiovascular protection against patients with mild DM and previous MI partially due to the relatively low dose of pioglitazone with minimal influence for the lipid profile; 2. pioglitazone cannot eliminate hidden risks, such as genetic background and social stress, behind the previous MI, because, in addition to ordinary risks, such as DM, smoking and hypertension, previous MI is a very potent risk factor for the occurrence of cardiovascular events [29]; 3. basic research based on biology may not preproduce the clinical trial based on statistics; 4. in patients with MI, pioglitazone may have deleterious effects, such as worsening of HF due to pioglitazone-induced fluid retention in patients with HF; 5. this study was conducted via the PROBE method [25], i.e. the patients were not blinded to the group they were enrolled in owing to limitations in the budget; 6. the mean time from MI in this study is 80 months, which has implications for modifiable risk compared with earlier events and 7. In Japan, metformin is not so often used for the treatment of DM, which may deviate the present results compared with the results of other countries.

Most of all, the use of PROBE method in the present study may have led the patients allocated to the control group to try to improve their

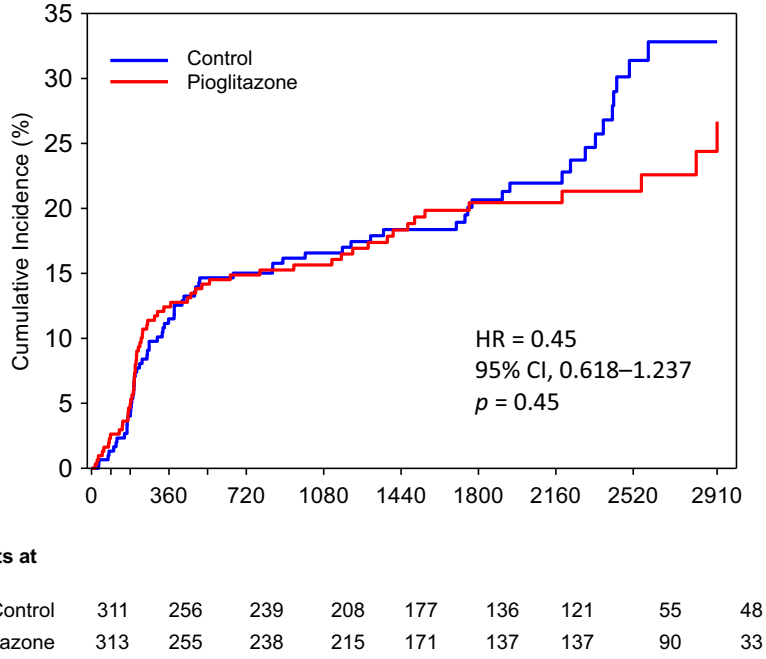

Fig. 3. Effects of pioglitazone on composite cardiovascular events of the primary endpoints for approximately 7 years until the end of the study in patients with mild DM and history of MI using ITT analysis.

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mild DM by better adhering to exercise or diet to reduce the risk of cardiovascular events [26]. Indeed, patients in both groups were followed-up and prescribed every 1–3 months owing to the rule of the Japanese medical insurance. At each visit, blood tests, including testing of the plasma glucose level, were performed, and both diet and physical activity were assessed in all enrolled patients. Therefore, we cannot deny this possibility; however, a 20-year follow-up from the original Da Qing Diabetes Prevention Study showed that although lifestyle changes could produce long-term reduction in the incidence of type 2 DM, the effects on cardiovascular events was at its best modest [30]. Finally, the cardiovascular event rate may be too low in the Japanese population to demonstrate the effect of treatment. Furthermore, we followed up the patients up to 2 years and this duration seems to be too short to observe the metabolic effects of pioglitazone. However, we followed the patients until 7 years as a post-hoc test and observed no change in the results.

Although the risk for recurrent MI in patients with previous MI is 4–5 times higher than that in patients with no history of MI in Finland [29], we do not have sufficient data of morbidity or mortality in Japanese MI patients with and without mild DM. If there is no difference of the morbidity or mortality in MI patients with and without mild DM in Japan, the treatment with pioglitazone would not decrease the occurrence of cardiovascular events in patients with both mild DM and previous MI, and the present study may just follow this scenario.

Taken together, we conclude that pioglitazone could not reduce the occurrence of cardiovascular events in patients with mild DM and previous MI, however we need to follow up such patients carefully treating with the drugs for DM.

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The Role of Each Author in This Manuscript

Study concept and design: Kitakaze; Acquisition, analysis, or interpretation of data: Asakura, Asanuma, and Kim; Drafting of the manuscript: Kitakaze; Critical revision of the manuscript for important intellectual content: Asakura and Hamazaki; Statistical analysis: Hamasaki; Obtained funding: Kitakaze; Administrative, technical, or material support: Asakura, Asanuma and Kim, and All; The data enrollment: All, Study supervision: Asakura and Kitakaze.

Conflict of Interest

Dr. Asakura reports grants from Acterion Pharmaceutical Japan, grants from Boehringer Ingelheim Japan, Inc., personal fees from Otsuka Pharmaceutical Co., Ltd., personal fees from Sanofi K.K., personal fees from Bayer Yakuhin, Ltd., personal fees from MSD K.K., personal fees from Takeda Pharmaceutical Company Limited, personal fees from ONO PHARMACEUTICAL CO., LTD., personal fees from Mitsubishi Tanabe Pharma Corporation, personal fees from DAIICHI SANKYO COMPANY, LIMITED, personal fees from Pfizer Japan Inc., personal fees from Astellas Amgen Biopharma, outside the submitted work.

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Dr. Takase reports grants from Japan Heart Foundation, during the conduct of the study; personal fees from MSD, personal fees from Astellas Pharma, personal fees from AstraZeneca, personal fees from Ono Pharmaceutical, personal fees from Sanwa kakagu kenkyusho, personal fees from Medical View, personal fees from Medical Tribune, personal fees from Kowa Pharmaceutical, personal fees from Sanofi, personal fees from Shionogi, personal fees from Daiichi-Sankyo, personal fees from Sumitomo Dainippon, personal fees from Takeda Pharmaceutical, personal fees from Toa Eiyo, personal fees from Nippon Boehringer Ingelheim, personal fees from Novartis Pharma, personal fees from Bayer Yakuhin, personal fees from Pfizer, personal fees from Fujifilm Ri Pharma, personal fees from Bristol-Myers, personal fees from Mochida.

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Dr. Sawada reports grants from Japan Heart Foundation, during the conduct of the study; personal fees from Pfizer, personal fees from Takeda Pharmaceutical, personal fees from Bayer Yakuhin.

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Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Appendix A

The following investigators and institutions participated in the PPAR study:

Department of Cardiology, Hiroshima City Hospital, Hiroshima, Japan (Y Nakama); Division of Cardiology, Yokohama City University Medical Center, Kanagawa, Japan (K Tsukahara); Department of Clinical Medicine & Development, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan (M Kitakaze); Department of Cardiology, Higashi Takarazuka Satoh Hospital, Hyogo, Japan (Y Higashino); Department of Cardiology, Saitama Prefecture Cardiovascular and Respiratory Center, Saitama, Japan (T Ishikawa); Division of Cardiology, Department of Medicine, Showa University Hospital, Tokyo, Japan (S Koba); Department of Cardiology, Cardiovascular Center, Veritas Hospital, Hyogo, Japan (M Tsujimoto); Division of Cardiology, Fujisawa City Hospital, Kanagawa, Japan (H Himeno); Department of Internal Medicine, St. Luke's International Hospital, Heart Center, Tokyo, Japan (Y Nishi); Department of Cardiology, Iwatsuki-minami Hospital, Saitama, Japan (Y Maruyama); Department of Cardiology, Hokko Memorial Hospital, Hokkaido, Japan (T Ookusa); Department of Internal Medicine, Nihon University School of Medicine, Tokyo, Japan (S Yoda); Division of Cardiology, Showa University Fujigaoka Hospital, Kanagawa, Japan (H Suzuki); Department of Cardiovascular Medicine, Tokyo Medical University Ibaraki Medical Center, Ibaraki, Japan (S Okubo); Department of Cardiology, International Goodwill Hospital, Kanagawa, Japan (M Shimizu); Department of Cardiology, Kameda Medical Center, Chiba, Japan (Yuji Hashimoto); Department of Cardiology, Fukui General Clinic, Fukui, Japan (K Satake); Department of Cardiology, Fukui Prefectural Hospital, Fukui, Japan (S Fujino); Department of Cardiology, Fukui University Hospital, Fukui, Japan (H Uzui); Department of Cardiology, Osaka Railway Hospital, Osaka, Japan (J Nariyama); Department of Cardiology, Rinku General Medical Center, Osaka, Japan (Y Nagai); Department of Cardiology, Tokyo Rinkai Hospital, Tokyo, Japan (T Kohno); Department of Internal Medicine, Fukui Cardiovascular Center, Fukui, Japan (S Mizuno); Department of Cardiology, Fukuyama City Hospital, Hiroshima, Japan (M Nakahama); Division of Cardiology, Ishikawa Prefectural Central Hospital, Ishikawa, Japan (H Kanaya); Department of Cardiology, Nagoya University, Aichi, Japan (T Murohara); Department of Cardiology, Kanagawa Cardiovascular and Respiratory Center, Kanagawa, Japan (K Fukui); Department of Internal Medicine, Enshu Hospital, Shizuoka, Japan (H Takase); Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medical Sciences, Aichi, Japan (N Ohte); Department of Cardiology, Kitasato University Medical Center, Saitama, Japan (T Shiono); Division of Cardiology, Osaka General Medical Center, Osaka, Japan (M Fukunami); Department of Cardiology, Saiseikai Yokohama City Southern Hospital, Kanagawa, Japan (T Endo); Department of Cardiology, Hadano Red Cross Hospital, Kanagawa, Japan (R Sawada); Department of Cardiology, Sakurabashi Watanabe Hospital, Osaka, Japan (K Fujii); Department of Internal Medicine, Takeuchi Clinic, Hyogo, Japan (M Takeuchi); Division of Cardiology, Uwajima City Hospital, Ehime, Japan (S Ikeda); Department of Cardiology, Kawasaki Municipal Tama Hospital, Kanagawa, Japan (K Mizuno); Department of Cardiovascular Division, Kansai Rosai Hospital, Hyogo, Japan (M Uematsu); Department of Cardiovascular Medicine, Shinrakuen Hospital, Niigata, Japan (T Matsubara); Department of Cardiovascular Medicine, Almeida Memorial Hospital, Ooita, Japan (S Yano); Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Miyagi, Japan (J Takahashi); Division of Cardiology, Komatsu Municipal Hospital, Ishikawa, Japan (K Ueda); Department of Cardiology, Kinoshita Clinic, Hiroshima, Japan (Y Kinoshita); Department of Cardiology, Nishinomiya Watanabe Cardiovascular Center, Hyogo, Japan (K Tamita); Department of Internal Medicine, Hoetsu Hospital, Tokushima, Japan (H Hayashi); Department of Cardiology, Shizuoka General Hospital, Shizuoka, Japan (O Doi); Division of Cardiology, Department of Cardiology, National Hospital Organization Ureshino Medical Center, Saga, Japan (T Muroya); Department of Cardiology, Kawasakisaiwai Hospital, Kanagawa, Japan (Y Tsukamoto); Department of Cardiology, National Hospital Organization Kanazawa Medical Center, Ishikawa, Japan (M Sakagami); Department of Cardiology, Pulmonology, Hypertension and Nephrology, Ehime University Graduate School of Medicine, Ehime, Japan (J Higaki); Division of Cardiology, Tsuchiya General Hospital, Hiroshima, Japan (T Sakuma); Department of Cardiology, Tokai University Hachioji Hospital, Tokyo, Japan (M Takigawa); Department of Cardiology, Hitachi Ltd. 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Appendix B. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eclinm.2018.09.006.

References

[1] Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 2014;63(12):1123–33.
[2] Jessup M, Brozena S. Heart failure. N Engl J Med 2003;348(20):2007–18.
[3] Braunwald E, Bristow MR. Congestive heart failure: fifty years of progress. Circulation 2000;102(20 Suppl 4):Iv14–23.
[4] Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet 2002;360(9335):752–60.
[5] Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002;347(18):1397–402.
[6] White HD, Chew DP. Acute myocardial infarction. Lancet 2008;372(9638):570–84.
[7] Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60(24):e44-164.
[8] Libby P, Aikawa M. Stabilization of atherosclerotic plaques: new mechanisms and clinical targets. Nat Med 2002;8(11):1257–62.
[9] Yki-Jarvinen H. Thiazolidinediones. N Engl J Med 2004;351(11):1106–18.
[10] Marx N, Duez H, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors and atherogenesis: regulators of gene expression in vascular cells. Circ Res 2004;94(9):1168–78.
[11] Marx N, Schonbeck U, Lazar MA, Libby P, Plutzky J. Peroxisome proliferator-activated receptor gamma activators inhibit gene expression and migration in human vascular smooth muscle cells. Circ Res 1998;83(11):1097–103.
[12] Law RE, Meehan WP, Xi XP, et al. Troglitazone inhibits vascular smooth muscle cell growth and intimal hyperplasia. J Clin Invest 1996;98(8):1897–905.
[13] Agarwal R. Anti-inflammatory effects of short-term pioglitazone therapy in men with advanced diabetic nephropathy. Am J Physiol Ren Physiol 2006;290(3):F600–5.
[14] Mazzone T, Meyer PM, Feinstein SB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. JAMA 2006;296(21):2572–81.
[15] Vaccaro O, Masulli M, Nicolucci A, et al. Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial. Lancet Diabetes Endocrinol 2017;5(11):887–97.
[16] Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366(9493):1279–89.
[17] Kernan WN, Viscoli CM, Furie KL, et al. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med 2016;374(14):1321–31.
[18] Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 2007;298(10):1180–8.
[19] Kernan WN, Viscoli CM, Dearborn JL, et al. Targeting pioglitazone hydrochloride therapy after stroke or transient ischemic attack according to pretreatment risk for stroke or myocardial infarction. JAMA Neurol 2017;74(11):1319–27.
[20] de Jong M, van der Worp HB, van der Graaf Y, Visseren FLJ, Westerink J. Pioglitazone and the secondary prevention of cardiovascular disease. A meta-analysis of randomized-controlled trials. Cardiovasc Diabetol 2017;16(1):134.
[21] Erdmann E, Dormandy JA, Charbonnel B, Massi-Benedetti M, Moules IK, Skene AM. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. J Am Coll Cardiol 2007;49(17):1772–80.
[22] Miyauchi K, Morino Y, Tsukahara K, Origasa H, Daida H. The PACIFIC (Prevention of AtherothrombotiC Incidents Following Ischemic Coronary attack) Registry: Rationale and design of a 2-year study in patients initially hospitalised with acute coronary syndrome in Japan. Cardiovasc Drugs Ther 2010;24(1):77–83.
[23] Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA 2003;290(4):486–94.
[24] Li L, Evans SR, Uno H, Wei LJ. Predicted interval plots (PIPS): a graphical tool for data monitoring of clinical trials. Stat Biopharm Res 2009;1(4):348–55.
[25] Hansson L, Hedner T, Dahlof B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. Blood Press 1992;1(2):113–9.
[26] Yates T, Haffner SM, Schulte PJ, et al. Association between change in daily ambulatory activity and cardiovascular events in people with impaired glucose tolerance (NAVIGATOR trial): a cohort analysis. Lancet 2014;383(9922):1059–66.
[27] Reynolds K, Goldberg RB. Thiazolidinediones: beyond glycemic control. Treat Endocrinol 2006;5(1):25–36.
[28] Giannini S, Serio M, Galli A. Pleiotropic effects of thiazolidinediones: taking a look beyond antidiabetic activity. J Endocrinol Investig 2004;27(10):982–91.
[29] Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339(4):229–34.
[30] Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet 2008;371(9626):1783–9.

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