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Effects of the Peroxisome Proliferator-Activated Receptor-γ Agonist Pioglitazone on Peripheral Vessel Function and Clinical Parameters in Nondiabetic Patients: A Double-Center, Randomized Controlled Pilot Trial

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For editorial comment see p. 162

Key Words
Cardiovascular disease · Peroxisome proliferator-activated receptor-γ agonist · Pioglitazone · Pulse wave analysis · Intima-media thickness · Retinal vessel function

Abstract
Objective: Despite the advanced therapy with statins, antithrombotics, and antihypertensive agents, the medical treatment of atherosclerotic disease is less than optimal. Therefore, additional therapeutic antiatherosclerotic options are desirable. This pilot study was performed to assess the potential antiatherogenic effect of the peroxisome proliferator-activated receptor-γ agonist pioglitazone in nondiabetic patients. ***Methods:*** A total of 54 nondiabetic patients were observed in a prospective, double-blind, placebo-controlled study. Patients were randomized to pioglitazone or placebo. The following efficacy parameters were determined by serial analyses: artery pulse wave analysis and carotid-femoral pulse wave velocity (PWV), static and dynamic retinal vessel function, and the common carotid intima-media thickness (IMT). The main secondary endpoint was the change in different biochemical markers. ***Results:*** After 9 months, no relevant differences could be determined in the two treatment groups in PWV (pioglitazone 14.3 ± 4.4 m/s vs. placebo 14.2 ± 4.2 m/s), retinal arterial diameter (pioglitazone 112.1 ± 23.3 µm vs. placebo 117.9 ± 21.5 µm) or IMT (pioglitazone 0.85 ± 0.30 mm vs. placebo 0.79 ± 0.15 mm). Additionally, there were no differences in the change in biochemical markers like cholesteryl ester transfer protein, low-density lipoprotein cholesterol, high-sensitivity C-reactive protein or white blood cell count. ***Conclusions***: Treatment with a peroxisome proliferator-activated receptor-γ agonist in nondiabetic patients did not improve the function of large and small peripheral vessels (PPP Trial, clinicaltrialsregister.eu: 2006-000186-11).

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Introduction

Atherosclerosis is a chronic systemic disease that is mainly caused by a chronic inflammation of the arterial walls [1]. This widespread disease affects the large arteries like the aorta as well as the small vessels like the retinal vessels and causes pathological vessel wall stiffness. Thus, increased aortic stiffness is a strong independent predictor of all-cause and mainly cardiovascular mortality [2]. Thereby, the chronic local vessel wall inflammation is triggered by numerous inflammatory cells like macrophages and T lymphocytes [3, 4]. Because of this proinflammatory milieu in atherosclerotic plaques, a systemic anti-inflammatory drug therapy for plaque stabilization is promising. For example, it could be demonstrated that statin administration led to stabilization of atherosclerotic lesions [5, 6]. However, Bayturan et al. [7] were able to show that, despite achieving very low levels of low-density lipoprotein (LDL) cholesterol, more than 20% of patients had atherosclerotic plaque progression. These data suggested that statin therapy is only one component of successful secondary prevention in patients suffering from atherosclerosis. Therefore, novel antiatherosclerotic drug therapies would be desirable.

Another potential antiatherogenic agent is the thiazolidinedione pioglitazone. Pioglitazone is an agonist of peroxisome proliferator-activated receptor-γ used for the treatment of type 2 diabetes [8, 9]. It reduces the levels of different inflammatory markers, such as high-sensitivity C-reactive protein (hsCRP), independently of its effect on glycemic metabolism [10]. The PROactive study could show a reduction of a composite of all-cause mortality, nonfatal myocardial infarction and stroke in patients with type 2 diabetes under treatment with pioglitazone [11]. In the PERISCOPE trial, treatment with pioglitazone resulted in a significantly lower rate of progression of coronary atherosclerosis compared with glimepiride in patients with type 2 diabetes [12]. A previous study demonstrated a stabilization of coronary artery plaques and a delay of plaque size progression in nondiabetic patients [13]. Whether these positive effects on systemic plaque stabilization also exist in nondiabetic patients is unknown.

The Pioglitazone on Plaque Progression Trial (PPP Trial) evaluated the effect of pioglitazone on vessel wall function of large and small arteries as well as clinical and laboratory data as surrogate parameters for atherosclerotic plaque progression in nondiabetic patients. Therefore, carotid intima-media thickness (IMT), static and dynamic retinal vessel analysis, and pulse wave velocity (PWV) were measured before and after administration of pioglitazone for 9 months.

Methods

Study Design

The Dresden PPP Trial was a double-blind, placebo-controlled, double-center study performed in compliance with the guidelines for good clinical practice and the Declaration of Helsinki. The study was approved by the institutional ethics committee at each participating site and written informed consent was obtained from each patient prior to enrollment in the study. All data were collected, managed and analyzed at the Department of Cardiology of the University Magdeburg and at the Heart Centre, University of Dresden (clinicaltrialsregister.eu Identifier: 2006-000186-11).

The main observed clinical efficacy parameters of this pilot study were the change in (1) artery pulse wave analysis and carotid-femoral PWV, (2) static and dynamic retinal vessel analysis, (3) measure of the common carotid IMT and (4) body weight and blood pressure. The secondary efficacy endpoint was the influence of pioglitazone on different biochemical markers like cholesteryl ester transfer protein (CETP) concentration and activity, white blood cell count, and hsCRP.

Study Population and Protocol

Eligible subjects were male or female nondiabetic patients 18–80 years of age with unstable angina pectoris or non-ST-elevation myocardial infarction caused by coronary heart disease requiring a stent. The main exclusion criteria were the presence of overt diabetes mellitus, ST-elevation myocardial infarction and a known intolerance to pioglitazone or previous treatment with thiazolidinediones. The detailed inclusion and exclusion criteria are listed in table 1 of the supplements. When a patient fulfilled all clinical inclusion criteria and none of the clinical exclusion criteria, written consent of the patient was obtained and a coronary angiography was performed within 48 h according to the guidelines. After the angiography, all of the above-mentioned baseline blood samples were drawn and baseline clinical data were measured. The obtained baseline data were stored and analyzed in a core laboratory (Heart Center Dresden). After completion of all baseline investigations, the enrolled study subjects were randomly assigned either to the pioglitazone group (n = 27) or to the placebo group (n = 27). The pioglitazone group received 30 mg/day of pioglitazone in addition to the standard medical treatment. The additional medication after the index event could be adjusted by the responsible physician, with the exception of the lipid-lowering therapy, which was given in a fixed dose of 20 mg of atorvastatin in both treatment groups. Successfully enrolled and randomized patients entered the observation phase of the study and medical treatment with pioglitazone or placebo was continued for up to 9 months. Two follow-up visits at the outpatient clinic were scheduled 2 and 6 months after randomization to confirm patient compliance as well as to verify secondary safety endpoints and the compatibility of the study medication. Safety assessments included 12-lead ECG, clinical laboratory parameters, and physical examination. At the final follow-up visit 9 months after randomization, all biochemical markers and clinical data were obtained for a second time. Finally, at the 9-month follow-up visit, potential adverse events were recorded. A detailed list of all study visits and examinations is available in table 2.

Artery Pulse Wave Analysis and Carotid-Femoral PWV

For the pulse wave analysis, radial artery pressure waveforms were sampled with a tonometer (Millar Tonometer; Millar Instru-

Table 1. Baseline patient characteristics and clinical data

	Pioglitazone	Placebo	p
Total number of patients	27	27	
Age, years	59.5±10.4	62.2±10.0	n.s.
Male	21 (77.8)	23 (85.2)	n.s.
BMI	27.7±3.7	27.7±3.2	n.s.
Current smoking	11 (40.7)	9 (33.3)	n.s.
Hypertension	22 (81.5)	21 (77.8)	n.s.
Dyslipidemia	21 (77.8)	21 (77.8)	n.s.
Previous MI	10 (37.0)	9 (33.3)	n.s.
Index event			
NSTEMI	6 (22.2)	6 (22.2)	n.s.
uAP	21 (77.8)	21 (77.8)	n.s.
Concomitant medications			
Antiplatelet agent	27 (100)	27 (100)	n.s.
β-Blocker	25 (92.6)	26 (96.3)	n.s.
ACE inhibitor	23 (85.2)	20 (74.1)	n.s.
Angiotensin receptor blocker	6 (22.2)	7 (25.9)	n.s.
Atorvastatin 20 mg	27 (100	27 (100)	n.s.

Values are means ± SD or n (%). MI = Myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; uAP = unstable angina pectoris; n.s. = not statistically significant.

ments, Houston, Tex., USA) and calibrated to the current systemic blood pressure. The obtained peripheral waveforms were processed with the SphygmoCor System (AtCor Medical, Australia) to calculate an averaged aortic pulse waveform with the help of a previously validated generalized transfer function [12]. Based on the calculated aortic pulse waveform, the augmentation pressure, a measure of arterial stiffness and the central pulse pressure (central systolic blood pressure – central diastolic blood pressure) were determined. Finally, the aortic augmentation index, defined as the ratio of augmentation pressure to the central pulse pressure (augmentation pressure/central pulse pressure × 10), was calculated [13]. The augmentation index indicates the size of the increase or decrease in pulse height as a result of the reflected pulse wave expressed in percent. To measure the carotid-femoral PWV, distance from the femoral recording site to the carotid recording site was determined at the body surface. Afterwards, ECG-triggered pulse wave recordings were performed sequentially at the femoral and carotid arteries using an arterial tonometer adjusted to systemic blood pressure, which was measured directly before the PWV analysis. PWV was calculated based on the determined propagation time from the femoral waveform to the carotid waveform and the distance between the two recording sites.

Static and Dynamic Retinal Vessel Analysis

Digital fundus imaging and retinal vessel analysis were performed with the Dynamic Vessel Analyzer (DVA; IMEDOS GmbH, Jena, Germany) as described previously [14, 15]. In short, 30 min after initiation of mydriasis using 1% tropicamide eye drops, each participant underwent 7-field fundus photography using the Visualis system (IMEDOS, FF450plus, 535–561 nm, 30° image, 1,840 × 1,360 pixels). The arterial and venous diameters were measured. Subsequently, dynamic vessel analysis was performed allowing noninvasive evaluation of microvascular func-

Table 2. Changes in clinical and laboratory values after treatment with pioglitazone

	Pioglitazone	Placebo	p
Body weight, kg			
Baseline	83.1±11.3	84.5±11.8	n.s.
At 9 months	85.5±11.9	83.2±12.7	n.s.
Difference	2.4±6.2	−1.0±5.7	0.04*
Systolic blood pressure, mm Hg			
Baseline	136.3±19.5	135.7±22.0	n.s.
At 9 months	132.4±19.7	130.6±21.2	n.s.
Difference	−3.8±27.9	−5.5±23.8	n.s.
Diastolic blood pressure, mm Hg			
Baseline	79.5±11.4	77.1±13.5	n.s.
At 9 months	76.6±10.3	76.6±10.0	n.s.
Difference	−2.9±14.0	−0.7±18.0	n.s.
Triglycerides, mmol/l			
Baseline	1.6±0.9	1.4±0.6	n.s.
At 9 months	1.4±0.7	1.5±1.1	n.s.
Difference	−0.2±0.8	0.1±0.8	n.s.
Total cholesterol, mmol/l			
Baseline	5.0±1.0	4.8±1.4	n.s.
At 9 months	4.8±1.1	4.3±0.9	n.s.
Difference	−0.2±1.4	−0.4±1.3	n.s.
LDL cholesterol, mmol/l			
Baseline	3.1±1.0	3.1±1.1	n.s.
At 9 months	2.8±1.0	2.5±0.6	n.s.
Difference	−0.3±1.1	−0.5±1.0	n.s.
HDL cholesterol, mmol/l			
Baseline	1.3±0.3	1.2±0.3	n.s.
At 9 months	1.4±0.3	1.3±0.3	n.s.
Difference	0.1±0.3	0.1±0.4	n.s.
CETP activity, pmol/ng CETP/h (mean ± SEM)			
Baseline	4.68±0.67	4.48±0.63	n.s.
After 3 months	5.07±0.58	4.57±0.59	n.s.
CETP concentration, ng/ml (mean ± SEM)			
Baseline	15.58±4.20	12.91±2.83	n.s.
After 3 months	13.02±2.98	14.74±3.56	n.s.
hsCRP, mg/l (median [25–27%])			
Baseline	2.7 [1.1–6.2]	1.8 [1.3–4.0]	n.s.
At 9 months	1.8 [0.5–2.7]	1.2 [0.6–1.4]	n.s.
Difference	−0.5 [−1.6 to −1.0]	−0.9 [−3.5 to 0.4]	n.s.
White blood cell count, Gpt/l (median [25–75%])			
Baseline	7.1 [5.6–10.4]	8.5 [5.9–9.6]	n.s.
At 9 months	6.1 [5.0–7.6]	7.2 [5.3–8.3]	n.s.
Difference	−0.7 [−1.9 to 2.0]	−1.3 [−2.6 to 0.1]	n.s.
Glycated hemoglobin, %			
Baseline	5.7±0.4	5.7±0.5	n.s.
At 9 months	5.7±0.4	5.8±0.4	n.s.
Difference	−0.02±0.34	−0.1±0.31	n.s.
Aspartate aminotransferase, μkat/l			
Baseline	0.64±0.47	0.66±0.83	n.s.
At 9 months	0.42±0.10	0.53±0.45	n.s.
Difference	−0.21±0.45	−0.13±0.55	n.s.
Alanine aminotransferase, μkat/l			
Baseline	0.57±0.33	0.58±0.81	n.s.
At 9 months	0.41±0.18	0.42±0.19	n.s.
Difference	−0.16±0.31	−0.16±0.75	n.s.
Creatinine, μmol/l			
Baseline	85.6±27.6	83.8±10.3	n.s.
At 9 months	91.1±25.0	86.5±15.6	n.s.
Difference	5.4±18.3	2.7±12.6	n.s.

Values are means ± SD unless otherwise indicated. n.s. = Not statistically significant. * $p < 0.05$.

tion by measuring the diameter of retinal arterioles and venules continuously. For this analysis, after a baseline recording of 30 s, three periods of flicker light stimulation (20-second duration) interrupted by steady fundus illumination (50-second duration) was performed. Baseline vessel diameters were obtained by averaging the baseline records. The peak dilation was defined as the largest vessel diameter at the end of each flicker stimulation, averaged across three flicker periods. Changes in ocular vessel diameters were expressed as percent change over baseline values.

Measurement of the Common Carotid IMT

IMT measurement was performed while the patient was lying in the supine position. IMT was determined in the common carotid artery 10 mm proximal to the bifurcation at the transducer far vessel wall using a Phillips iE33™ ultrasound machine with a linear transducer. The maximum end-diastolic IMT measurements were performed bilaterally at three different scanning angles with the help of digital callipers. The six tracings were then averaged to calculate the mean IMT.

Laboratory Studies

CETP concentration and activity were determined from the patients at two time points (study begin and after 3 months of treatment). CETP activity was measured from conserved serum samples with a CETP activity fluorometric assay kit (Abcam, ab65383) according to the manufacturer's protocol on a Synergy HT (BioTek) multimode plate reader under the usage of a fluorescent excitation filter 485 nm/20 nm and an emission filter 528 nm/20 nm. CETP concentration within the serum was measured with a CETP ELISA kit (Abnova, KA1152) from the same serum samples. Concentration, activity, and normalized activity were calculated according to the supplier's standards.

Statistical Analysis

All variables were analyzed for normality with the graphical method of normal probability-quantile plot in combination with the Kolmogorov-Smirnov test. Results of continuous variables are expressed as means ± SD. Statistical analyses were done using a 2-tailed, unpaired Student's t test.

Continuous nonnormally distributed data are presented as medians (interquartile ranges). Differences between nonnormally distributed variables were compared with the Mann-Whitney U test. The level of significance was set to $p < 0.05$. Categorical variables are presented as total numbers with comparisons using χ^2 and Fisher's exact tests.

Results

Study Population, Safety Endpoints, and Vessel Baseline Characteristics

From March 2007 to September 2010, 54 patients were involved in the prospective, randomized study. Both treatment groups were well balanced concerning demographics and clinical baseline characteristics (table 1). There were no relevant differences in age, gender, comorbidities, or concomitant medications.

Clinical and Biochemical Outcome after 9 Months

The clinical and biochemical outcome data are summarized in table 2. The body weight in pioglitazone patients increased significantly by 2.4 kg, whereas the control patients revealed a weight loss of 1 kg. The systolic and diastolic blood pressures decreased equally in both treatment groups. The biochemical markers creatinine, aspartate aminotransferase, and alanine aminotransferase showed no relevant changes after 9 months in both treatment groups. As markers of systemic inflammation, white blood cell count and hsCRP were determined. Both inflammation markers declined slightly in both treatment groups after 9 months. However, no significant differences of these inflammation markers could be detected between the pioglitazone group and the placebo group. Further, no relevant changes in levels of triglycerides, total cholesterol, LDL cholesterol, and high-density lipoprotein (HDL) cholesterol as common values of lipid metabolism could be observed in either treatment group. Additionally, CETP concentration and activity were determined. It is supposed that a reduction in CETP activity inhibits the atherosclerotic plaque development by increasing the plasma level of HDL cholesterol. However, after treatment with pioglitazone, no relevant changes in CETP concentration and activity could be measured compared to controls. Finally, the glycated hemoglobin level was not affected after treatment with pioglitazone.

No significant differences in the safety endpoints between the two treatment groups were observed. Thus, the incidences of adverse events were similar among the groups after 9 months: peripheral edema = 1 in the pioglitazone group and 1 in the placebo group; recent onset of dyspnea = 2 in the pioglitazone group and 1 in the placebo group; recent onset of fatigue = 1 in the pioglitazone group and 1 in the placebo group, and stable angina pectoris = 4 in the pioglitazone group and 5 in the placebo group.

Clinical Function of Noncoronary Vessels at Baseline and after 9 Months

To investigate the influence of the therapy with pioglitazone on the arterial stiffness in 'large' vessels, analysis of artery pulse wave and carotid-femoral PWV were performed at baseline and after 9 months. In these examinations, no relevant changes in PWV and augmentation index were found in either the pioglitazone group or the placebo group (table 3). As an additional parameter for the development of atherosclerosis in the 'large' vessels, the common carotid IMT was determined. After 9 months, no relevant difference in the IMT was deter-

mined in either of the treatment groups. The mean IMT was 0.8 mm in both groups at baseline and after 9 months (table 3). To examine the changes in microcirculation under treatment with pioglitazone, static and dynamic retinal vessel analysis were performed (table 3). In static retinal vessel analysis, no significant differences were observed in either the arterial diameters (pioglitazone 112.1 ± 23.3 μm vs. placebo 117.9 ± 21.5 μm) or in the venous diameter (pioglitazone 166.8 ± 23.8 μm vs. placebo 161.9 ± 20.6 μm) after 9 months. In the dynamic analysis, the arterial diameter change was equal in the placebo and in the pioglitazone groups as well.

Table 3. Noncoronary vessel function 9 months after treatment with pioglitazone

	Pioglitazone	Placebo	p
Common carotid IMT, mm			
Baseline	0.87±0.34	0.80±0.14	n.s.
At 9 months	0.85±0.30	0.79±0.15	n.s.
Difference	0.01±0.17	−0.01±0.13	n.s.
Artery pulse wave analysis and carotid-femoral PWV			
Aortic augmentation index, %			
Baseline	26.3±10.2	19.9±11.8	n.s.
At 9 months	23.1±10.4	24.9±9.8	n.s.
Difference	−0.7±2.3	5.6±12.1	n.s.
PWV, m/s			
Baseline	12.9±3.5	13.9±3.6	n.s.
At 9 months	14.3±4.4	14.2±4.2	n.s.
Difference	0.46±2.10	0.72±2.10	n.s.
Static and dynamic retinal vessel analysis			
Retinal arterial diameter, μm			
Baseline	116.7±16.3	114.9±18.2	n.s.
At 9 months	112.1±23.3	117.9±21.5	n.s.
Difference	−4.7±31.9	3.0±14.7	n.s.
Retinal venous diameter, μm			
Baseline	162.8±31.0	147.1±19.0	n.s.
At 9 months	166.8±23.8	161.9±20.6	n.s.
Difference	4.0±15.2	14.8±25.0	n.s.
Arterial diameter change, %			
Baseline	1.78±3.32	2.54±4.69	n.s.
At 9 months	1.89±0.49	0.81±2.40	n.s.
Difference	0.11±3.42	−1.73±6.28	n.s.

Values are means ± SD.

Discussion

The systemic medical treatment of atherosclerosis remains unsatisfactory despite advanced therapy with antithrombotics, statins, and antihypertensive therapy. Therefore, further pharmacological inhibition of this systemic disease is desirable. In this context, the current study observed for the first time the potential antiatherosclerotic effects of the insulin-sensitizing thiazolidinedione pioglitazone in nondiabetic patients.

The salient finding of the clinical part of the PPP Trial was that the additional treatment with pioglitazone was not able to influence the function of peripheral vessels as important clinical surrogate parameters for the cardiovascular outcome. In the current trial, no relevant changes in the IMT could be determined after pioglitazone treatment. In contrast, the Chicago trial showed that compared with glimepiride, pioglitazone slowed down the progression of carotid IMT in type 2 diabetic patients over a treatment period of 18 months even though the absolute values were very low (difference between both groups: –0.013 mm) [16]. This could be explained either by the follow-up period being too short or by the normal glycemic metabolism in the current trial. Next, the aortic stiffness was observed with the help of PWV and the augmentation index, which are strong independent predictors of all-cause and cardiovascular mortality [2]. Also, these surrogate parameters did not differ significantly after treatment with pioglitazone. Finally, microvascular function was examined with the help of static and dynamic vessel analysis. In these analyses, pioglitazone treatment did improve endothelial function in retinal vessels.

Different studies have shown that the antiatherosclerotic effect of pioglitazone cannot solely be explained by its positive effect on glycemia [16–18]. For that reason, we hypothesized that atherosclerotic plaque regression is partially attributable to lipid-modulating effects, anti-inflammatory effects or a combination of these effects. However, the current data showed no relevant changes in the levels of triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, and the inflammatory markers such as white blood cell count and hsCRP after 9 months of pioglitazone treatment.

These results are contradictory to previous studies, which postulated a positive influence on lipid metabolism in type 2 diabetes patients. Thus, a previous study investigated the effect of pioglitazone and another thiazolidinedione rosiglitazone on dyslipidemia in 802 diabetic patients. In this trial, the administration of pioglitazone compared with rosiglitazone was associated with significant improvements in triglycerides, HDL cholesterol, and LDL particle concentration independent of glycemic control [17]. These positive effects of pioglitazone on diabet-

ic dyslipidemia were confirmed in the Chicago trial [16]. On the other hand, a previous study with nondiabetic patients could not find any changes in lipid parameters after treatment with pioglitazone, similar to the current nondiabetic study population [19]. Additionally, in the present trial, no relevant change in CETP concentration and activity could be measured after treatment with pioglitazone compared to controls. It is thought that a reduction of CETP activity increases the plasma level of HDL cholesterol [20, 21]. Next, the anti-inflammatory component of pioglitazone, which has often been described, could explain its antiatherosclerotic effect [10, 22, 23]. Also in the current trial the white blood cell count and hsCRP were found to be decreased after pioglitazone treatment. However, a significant difference between the two treatment groups could not be detected because of the large variation of these inflammatory markers. Possibly, a measurement of further cytokine levels like IL-1, IL-6, or TNF-α could better prove the anti-inflammatory effect of pioglitazone. On the other hand, the acute coronary syndrome itself, as it was required in the inclusion criteria of the current trial, could influence all inflammatory markers more than the underlying chronic coronary artery disease. In summary, based on the current study, the antiatherosclerotic effect of pioglitazone in peripheral vessels in nondiabetic patients remains speculative.

It is noteworthy that the current study has some limitations. The current trial was not primarily designed to investigate the clinical outcome after treatment with pioglitazone in nondiabetics. Further, the follow-up period of the current trial was too short to investigate the clinical outcome. Thus, the benefit of pioglitazone on the cardiovascular morbidity and mortality in nondiabetic patients remains uncertain despite the unchanged surrogate parameter. Further, only patients with a clinically relevant coronary artery disease were included. It is unclear whether our results are consistent in primary prevention of atherosclerosis. Another limitation of the study was the relatively small number of patients, so the work should be understood as a pilot study. An additional limitation of the study was that the concomitant medication with atorvastatin and antiplatelet agents may influence the vessel function on top of pioglitazone, which could lead to a masking effect of pioglitazone action. Despite these limitations, to the best of our knowledge, the current study did not show any relevant changes in the vessel wall function after treatment with pioglitazone in nondiabetics.

Whether pioglitazone influences the clinical cardiovascular outcome in nondiabetic patients remains speculative, especially in light of recent studies regarding the cardiovascular safety of pioglitazone. Therefore, the antiatherosclerotic effect of pioglitazone on the cardiovascular outcome in nondiabetics should be investigated in larger outcome trials with longer follow-up periods.

Our findings have clinical implications for the development of a novel systemic antiatherosclerotic therapy.

Conflict of Interest

The authors report no conflicts of interest. This work was supported by Takeda Pharmaceutical Company Ltd., by the DFG (Deutsche Forschungsgemeinschaft, German Research Foundation) and SFB 854 (Sonderforschungsbereich, collaborative research center).

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