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ORIGINAL ARTICLE

Effects of the PPARγ agonist pioglitazone on coronary atherosclerotic plaque composition and plaque progression in non-diabetic patients: a double-center, randomized controlled VH-IVUS pilot-trial

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Abstract Despite the advanced therapy with statins, antithrombotics and antihypertensive agents, the medical treatment of coronary artery disease is less than optimal. Therefore, additional therapeutic anti-atherosclerotic options are desirable. This VH-IVUS study (intravascular ultrasonography with virtual histology) was performed to assess the potential anti-atherogenic effect of the PPARγ agonist pioglitazone in non-diabetic patients. A total of 86 non-culprit atherosclerotic lesions in 54 patients with acute coronary syndrome were observed in a 9-month prospective, double-blind, and placebo-controlled IVUS study. Patients were randomized to receive either 30 mg pioglitazone (Pio) or placebo (Plac). As primary efficacy parameter, the change of relative plaque content of necrotic core was determined by serial VH-IVUS analyses. Main secondary endpoint was the change of total plaque volume. In contrast to placebo, in the pioglitazone-treated group, the relative plaque content of necrotic core decreased significantly (Pio -1.3 ± 6.9 % vs. Plac $+2.6 \pm 6.5$ %, $p < 0.01$). In comparison to the placebo group, the plaques in pioglitazone-treated patients showed significantly greater reduction of the total plaque volume (Pio -16.1 ± 26.4 mm^3 vs. Plac -1.8 ± 30.9 mm^3, $p = 0.02$). Treatment with a PPARγ agonist in non-diabetic patients results in a coronary artery plaque stabilization on top of usual medical care.

Keywords Cardiovascular disease · Thiazolidinediones · Intravascular ultrasonography · Atherosclerotic plaque progression, atherosclerotic plaque composition

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Introduction

The vast majority of myocardial infarctions are caused by the rupture of unstable atherosclerotic plaques [1]. Although these "unstable" atherosclerotic lesions are frequently angiographically mild, the histological composition of these plaques predisposes to rupture with subsequent thrombosis of the coronary vessel. Thus, Stone and colleagues identified with the help of VH-IVUS (intravascular ultrasonography with virtual histology) that the most unstable plaques were characterized by IVUS-defined thin-capped fibroatheromas or by an IVUS-defined large plaque burden [2]. These VH-IVUS-determined vulnerable plaques correspond histologically to atherosclerotic lesions, which are characterized by a distinct necrotic core with several cholesterol clefts. The necrotic core is often only

covered by a very thin fibrous cap containing numerous inflammatory cells, macrophages, T lymphocytes and only few smooth muscle cells [3–5]. Because of the pro-inflammatory milieu in these unstable 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 [6, 7]. But Bayturan et al. [8] could show that, despite achieving very low levels of low-density-lipoprotein cholesterol (LDL-C), more than 20 % of patients had an atherosclerotic plaque progression. These data suggested that statin therapy is only one component of successful secondary prevention in patients suffering from coronary artery disease. Therefore, novel anti-atherosclerotic drug therapies would be desirable.

Another potential anti-atherogenic agent is the thiazolidinedione pioglitazone. Pioglitazone is an agonist of peroxisome proliferator-activated receptor γ (PPARγ) used for the treatment of type 2 diabetes [9, 10]. It reduces the levels of different inflammatory markers, such as highly sensitive C-reactive protein (hsCRP), independently of its effect on glycemic metabolism [11]. The PROactive study showed a reduction of composite of all-cause mortality, non-fatal myocardial infarction and stroke in patients with type 2 diabetes under treatment with pioglitazone [12]. 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 [13]. Additionally, pioglitazone stabilized the coronary plaque by reducing the necrotic-core component in patients with type 2 diabetes mellitus [14]. Whether these positive effects on plaque stabilization also exist in non-diabetic patients is unknown.

VH-IVUS (intravascular ultrasonography with virtual histology) is a catheter-based tool, which is widely used to assess atherosclerotic burden [15]. Spectral analyses of IVUS radiofrequency data provide detailed, well-validated information of histological plaque composition [16, 17]. This new imaging technique is very suitable for detecting quantitative changes in coronary plaque composition especially after long-term medical treatment.

The effect of pioglitazone on Plaque Progression-Trial (PPP-Trial) was designed as an VH-IVUS pilot study to evaluate the effect of pioglitazone on atherosclerotic plaque composition and plaque progression in non-diabetic patients. Therefore, the plaque composition was observed using VH-IVUS 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 University Magdeburg and at the Heart Centre, University of Dresden (Trial Registration: clinicaltrialsregister.eu Identifier: 2006-000186-11).

The primary efficacy parameter of this pilot-study was the change of relative plaque content of necrotic core determined with VH-IVUS after a 9-month treatment with pioglitazone compared to placebo.

The main secondary endpoint was the influence of pioglitazone on the total plaque volume of non-culprit coronary artery plaques in non-diabetic patients after acute coronary syndrome. Additionally, geometrical changes of the plaques were measured with various IVUS plaque size parameters. Additionally, the compatibility and prespecified adverse clinical-events of pioglitazone compared to placebo were registered.

Study population and protocol

Eligible subjects were male or female non-diabetic patients 18–80 years of age with unstable angina pectoris (uAP) or non-ST-elevation myocardial infarction (NSTEMI) caused by coronary heart disease requiring stent. In addition to the stented lesion believed to be responsible for the index event at least one further non-culprit hemodynamically insignificant coronary artery plaque (stenosis <50 %) had to be present in the non-culprit vessel. For this reason, only the left coronary vascular bed was used (LAD and RCX) to avoid unnecessary wiring. 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 (TZD). The detailed inclusion and exclusion criteria are listed in Table 1 of the supplements. In case that a patient fulfilled all clinical inclusion criteria and none of the clinical exclusion criteria, a written consent of the patient was obtained and a coronary angiography was performed within 48 h according to the guidelines. As part of the first coronary angiography, a PCI of the target lesion and an intravascular ultrasonography with virtual histology (VH-IVUS) of both the additional non-culprit lesions and the stented target vessel were

Table 1 Baseline characteristics of clinical data

	Pioglitazone	Placebo	*p* value
Total number of patients	27	27	
Age, years (± SD)	59.5 (±10.4)	62.2 (±10.0)	NS
Male sex, no. (%)	21 (77.8)	23 (85.2)	NS
Body-mass index (± SD)	27.7 (±3.7)	27.7 (±3.2)	NS
Current smoking, no. (%)	11 (40.7)	9 (33.3)	NS
Hypertension, no. (%)	22 (81.5)	21 (77.8)	NS
Dyslipidemia, no. (%)	21 (77.8)	21 (77.8)	NS
Previous MI, no. (%)	10 (37.0)	9 (33.3)	NS
Index event, no. (%)			
NSTEMI	6 (22.2)	6 (22.2)	NS
uAP	21 (77.8)	21 (77.8)	NS
Concomitant medications, no (%)			
Anti-platelet agent	27 (100)	27 (100)	NS
Beta-blocker	25 (92.6)	26 (96.3)	NS
ACE-inhibitor	23 (85.2)	20 (74.1)	NS
Angiotensin-receptor blocker	6 (22.2)	7 (25.9)	NS
Atorvastatin 20 mg	27 (100)	27 (100)	NS

Body-mass index, weight in kilograms divided by the square of the height in meters; *MI* myocardial infarction; *NSTEMI* non-ST-elevation myocardial infarction; *uAP* unstable angina pectoris; *NS* not statistically significant

conducted, if patient fulfilled the angiography inclusion criteria. In case of the existence of more than one additional lesion, all present lesions were separately assessed with VH-IVUS. For VH-IVUS examination, after intracoronary administration of 0.1 mg nitro glycerine a commercially available phased-array, 20 MHz-IVUS catheter (Eagle Eye® Gold, IVUS console s5, Volcano Corporation, USA), was placed into the target vessels to a bifurcation of a characteristic side branch distal to the lesions of interest and a motorized catheter pullback (0.5 mm/s) through the vessel to the ostium of left main coronary artery was performed. Based on the bifurcations of the side branches and the ostium of the left main stem, used as fiducial points, the accurate reassessment of the same lesions including the same IVUS pullback lengths at the follow-up IVUS was guaranteed. The obtained VH-IVUS data were stored and analyzed offline in a blinded core laboratory (Laboratory for experimental cardiology, Heart Center Dresden). After completion of all baseline investigations, the enrolled study subjects were randomly assigned either to the pioglitazone group (Pio, $n = 27$) or to the placebo group (Plac, $n = 27$). The pioglitazone group received 30 mg/day 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. Successful 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 in the outpatient clinic were scheduled 2 and 6 months after randomization to confirm the compliance of the patients as well as to verify secondary safety endpoint 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 the first angiography, a second coronary angiography including VH-IVUS of the defined con-culprit lesions and the stented target vessels were performed. Finally, through the 9-month follow-up visit potential adverse events were recorded. A detailed list of all study visits and examinations as well as the detailed description of all measurements are available in the supplements (supplemental table 2).

VH-IVUS imaging analysis

For geometrical IVUS measurement of the gray-scale images, an investigator blinded to patient and visit group, determined the border of lumen and the border to vessel wall for each IVUS image using semiautomatic contour detection software (Fig. 1). The vessel wall boarder was defined as the boundary of the external elastic membrane (EEM). Geometrical data were expressed as cross-sectional areas (CSA, mm^2) for each IVUS image (frame). Volumes were calculated using Simpson's rule (mm^3). Standard measurements for all analyzed plaques obtained: lesion length, number of analyzed IVUS-frames per plaque (N_{frames}), vessel area (EEM_{CSA}), lumen area ($lumen_{csa}$), and plaque $area_{CSA}$. Based on these raw data the following values were calculated for each analyzed plaque: vessel volume, lumen volume, plaque volume, average EEM_{CSA}, average $lumen_{csa}$, average plaque $area_{CSA}$, minimal lumen area, plaque burden $= \Sigma$ (plaque $area_{CSA}/EEM_{CSA} \times 100)/N_{frames}$ and percent atheroma volume (PAV) $= (\Sigma$ plaque $area_{CSA}/\Sigma$ $EEM_{CSA}) \times 100$, mean [2, 3, 8, 18]. In addition, the normalized total atheroma volume (TAV_N) $= \Sigma$ $(EEM_{CSA} - lumen_{csa})/N_{frames}$ *Median number of frames in whole cohort was calculated. This value normalizes the TAV to account the different segment length between the subjects [8, 19]. The plaque eccentricity index (EI) is a measure how pronounced the plaque grows into the vessel lumen and was calculated by dividing the minimum plaque thickness by the maximum plaque thickness [20]. The remodeling index (RI) is a measure of vessel size changing during atherosclerotic plaque progression. In case of an outward increase of the vessel (rising EEM_{CSA}) there is a so-called "positive remodeling", which is associated with coronary plaque rupture. "Negative remodeling" occurs in case of vessel shrinkage (decreased EEM_{CSA}). The remodeling index was calculated by dividing the EEM_{CSA} at

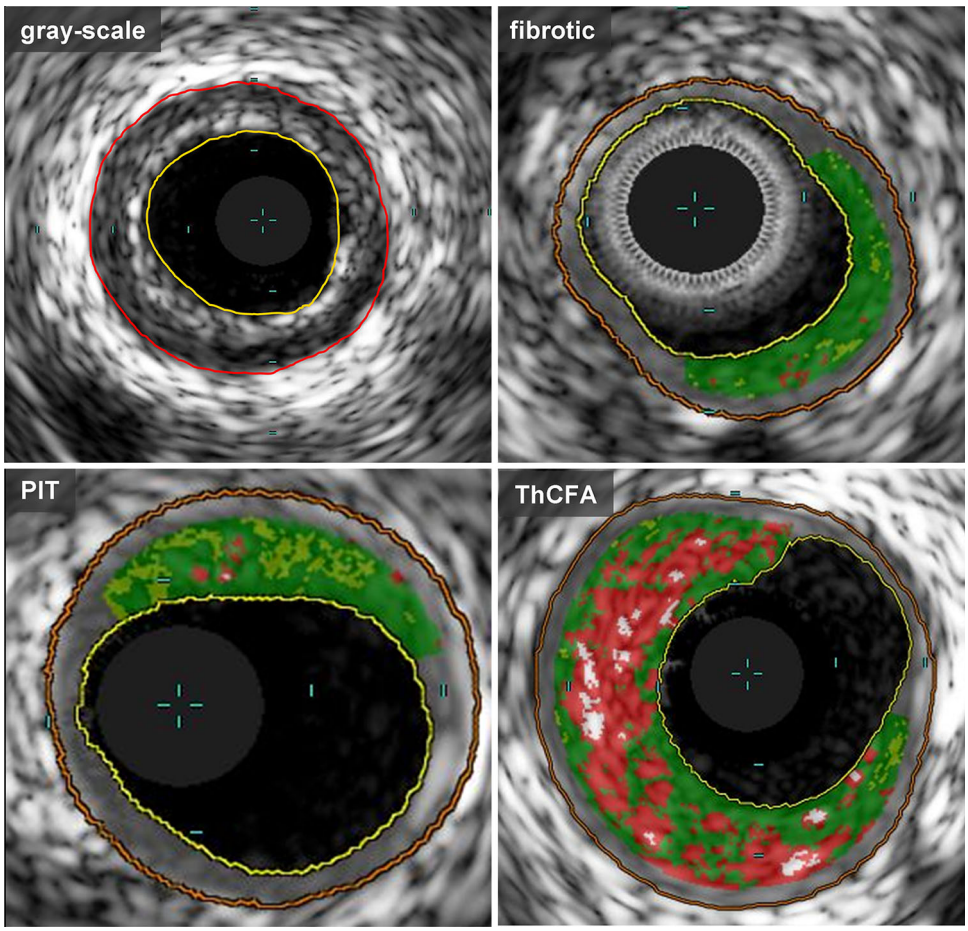

Fig. 1 Plaque classification by VH-IVUS. Gray-scale image: automated contour detection: *red line borders* the EEM_{CSA}, *yellow line borders* $LUMEN_{CSA}$; fibrotic: compositional analysis show mainly fibrotic tissue (FT, *dark green*), <15 % fibro fatty (FF *light green*), <10 % confluent dense calcium (DC, *white*) and <10 % confluent necrotic core (NC, *red*); pathological intimal thickening (PIT): mainly a mixture of FT and FF, <10 % confluent DC and <10 % confluent NC; thick caped fibroatheroma (ThCFA): fibroatheroma with a definable fibrous cap (*green*) and >10 % confluent NC (color figure online)

the plaque site with the greatest plaque diameter by the EEM_{CSA} at the least diseased vessel site within the proximal 10 mm [21]. In case of positive remodeling the index is >1.0, while an index <1.0 indicates a negative RI [3].

On the basis of the VH-IVUS the components of the atherosclerotic plaques were identified as fibrotic tissue (FT), fibrofatty (FF), dense calcium (DC) and necrotic core (NC). The compositional data were expressed as plaque component volume (mm^3) and were calculated as percentage of total plaque volume (supplemental table 3) [22]. Definition of lesion types: lesion types were classified by 2 independent investigators (1 of each participating study center) based on the previous defined plaque composition (supplemental table 3) [2, 23]: pathological intimal thickening (PIT), fibrotic plaque, fibrocalcific plaque, virtual histology intravascular ultrasound-derived thin-capped fibroatheroma (VH-TCFA) and thick-capped fibroatheroma (ThCFA). Atherosclerotic lesions, which had positive criteria for VH-TCFA and ThCFA were defined as VH-TCFA.

Statistical analysis

Due to complete lack of data regarding the treatment of non-diabetic patients with pioglitazone, the PPP trial was designed as a pilot trial. All variables were analyzed of normality with the graphical method of normal probability-quantile plot in combination with the Kolmogorov–Smirnov test. Results of continuous variables are expressed as mean ± standard deviation. Statistical analyses were done using the 2-tailed, unpaired Student's *t* test.

Continuous non-normally distributed data are presented as median (interquartile range). Differences between non-normally distributed variables were compared with the Mann–Whitney *U* test. Level of significance was set to $p < 0.05$. *p* values below 0.05 (0.01/0.001) are indicated by * (**/***). Categorical variables are presented as total number with comparison using Chi-square statistics and Fisher exact test. Significance level was set to $p < 0.05$.

Results

Study population, safety endpoints and vessel baseline characteristics

From March 2007 to September 2010, 54 patients were involved in the prospective, randomized VH-IVUS study. Both treatment groups were well balanced with regard to

the demographics and clinical baseline characteristics (Table 1). There were no relevant differences in age, gender, comorbidities and concomitant medications. No significant differences in the biochemical safety markers and 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 pioglitazone group and 1 in placebo group; recent onset of dyspnoea, 2 in pioglitazone group and 1 in placebo group; recent onset of fatigue, 1 in pioglitazone group and 1 in placebo group; stable angina pectoris, 4 in pioglitazone group and 5 in placebo group.

Overall, a total number of 86 non-culprit lesions were analyzed with gray-scale IVUS and virtual histology (VH-IVUS, Fig. 1) in 54 randomized patients. The detailed baseline vessel characteristics are listed in the supplemental table 4. In both groups about 70 % of the observed lesions were localized in the left anterior descending artery. All other lesions (about 30 %) were situated in the left circumflex artery. The right coronary artery was excluded for reasons mentioned above. There were no significant differences in the vessel characteristics between the 2 treatment groups. The mean lesion lengths in both groups were approximately 25 mm. Also, the initial plaque volume was equal in the pioglitazone group and placebo group (PAV: Pio 49.8 ± 13.4 mm^3 vs. Plac 51.7 ± 14.0 mm^3, $p = 0.54$). Of note, the VH-plaque components were not different in both groups. Fibrotic tissue was the most prevalent component in atherosclerotic plaques (Pio 53.52 ± 33.29 mm^3 vs. Plac 61.96 ± 43.16 mm^3; n.s.) followed by necrotic core (Pio 26.12 ± 21.11 mm^3 vs. Plac 24.78 ± 19.56 mm^3; n.s.), dense calcium (Pio 13.70 ± 15.91 mm^3 vs. Plac 11.12 ± 12.23 mm^3; n.s.) and fibro fatty tissue (Pio 8.04 ± 7.21 mm^3 vs. Plac 11.25 ± 11.01 mm^3; n.s.).

Changes of plaque components after 9 months (primary efficacy parameter)

The change of plaque composition 9 months after treatment with pioglitazone or placebo is illustrated in Fig. 2. In contrast to the placebo group, which revealed a relative increase of NC, in the pioglitazone-treated plaques the relative content of NC decreased (Plac +2.6 ± 6.5 % vs. Pio −1.3 ± 6.9 %, $p = 0.008$). Simultaneously, the placebo-treated plaques showed a significantly elevated reduction of fibrotic (Plac −3.7 ± 7.0 % vs. Pio −0.1 ± 8.2 %, $p = 0.033$) and fibrofatty tissue (Plac −1.4 ± 5.1 % vs. Pio +0.6 ± 3.8 %, $p = 0.045$) in comparison to the pioglitazone plaques. Both treatment groups had similar increased contents of dense calcium (Plac 2.4 ± 5.3 % vs. Pio 0.8 ± 5.2 %, $p = 0.17$).

Serial plaque size analysis (secondary endpoint) by IVUS

The changes of the observed atherosclerotic plaques are summarized in Table 2. At 9-month follow-up the lesion length did not relevantly change in both treatment groups. But in comparison to the placebo group, the plaques in pioglitazone-treated patients showed significantly greater reduction of the total plaque volume [Pio −16.1 ± 26.4 mm^3 vs. Plac −1.8 ± 30.9 mm^3, $p = 0.02$ (Fig. 2)]. This finding was confirmed by other IVUS-values representing the plaque volume. Thus, a reduced PAV (Pio −1.3 ± 11.4 % vs. Plac +1.52 ± 18.9 %), plaque burden (Pio −0.59 ± 3.75 % vs. Plac +0.65 ± 5.47 %) and average plaque CSA (Pio −0.02 ± 0.15 mm^2 vs. Plac +0.10 ± 0.57 mm^2) were determined in the pioglitazone group. Also, when the atheroma volume was normalized to plaque length (TAV_N) the pioglitazone group showed a decreased TAV_N (−0.8 mm^3) after 9 months in comparison to an increased TAV_N (+2.9 mm^3) in the placebo group. After treatment with pioglitazone, the plaques showed nearly no reduction in minimal luminal area (−0.04 mm^2) in contrast to the placebo group, which revealed a noticeable increased minimal luminal area (−0.3 mm^2). No relevant changes of the remodeling index and eccentricity index could be found in both treatment groups.

Lesion types at baseline and after 9 months

The evolution of the lesion types during the 9-month follow-up is illustrated in Fig. 3. At baseline in the pioglitazone group all 42 non-culprit lesions were characterized as VH-ThCFA. In the placebo group there were 42 VH-ThCFAs and 2 PITs at baseline. After 9-month follow-up in the pioglitazone group, 1 VH-ThCFA stabilized into a fibrotic plaque. In the placebo group, 1 PIT evolved into VH-ThCFA.

Discussion

The systemic medical treatment of coronary artery disease remains unsatisfactory despite the advanced therapy with antithrombotics, statins and antihypertensive therapy. Therefore, further pharmacological inhibition of plaque progression is desirable. In this context, the current VH-IVUS study observed for the first time the potential plaque-stabilizing effects of the insulin-sensitizing TZD pioglitazone in non-diabetic patients after acute coronary syndrome.

The salient finding of the PPP-Trial was the significant reduction of the necrotic core within atherosclerotic lesions

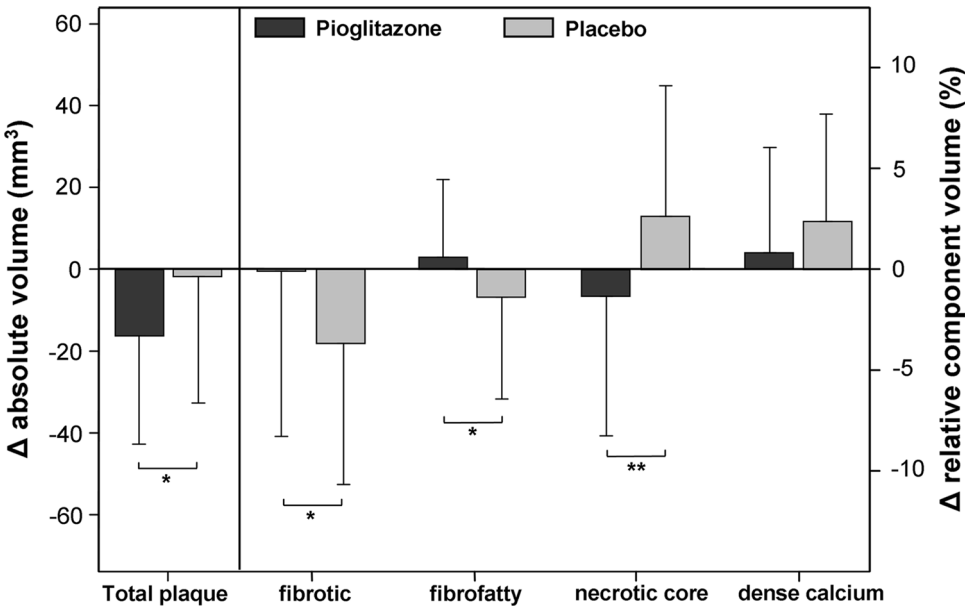

Fig. 2 Change of plaque volume and VH-IVUS plaque components after 9 months. Δ: change from baseline, $*p < 0.05$, $**p < 0.01$

due to the treatment with the PPARγ agonist pioglitazone. Simultaneously, an increase of the fibrofatty components could be detected in the pioglitazone-treated plaques (Fig. 2). In contrast, despite of the medication with antithrombotics, statins and antihypertensive therapy, the necrotic core and dense calcium burden increased while the fibrotic and fibrofatty tissue decreased significantly in the placebo group compared to the pioglitazone group. In this context, a distinct necrotic core (NC) and a high calcification burden (DC) are considered as sign of plaque instability [1, 24]. Conversely, atherosclerotic plaques with a high content of fibrotic (FF) and fibrofatty tissue (FT) are suggested as stable plaques with a lower risk of plaque rupture. It should be noted, that VH-IVUS-measured plaque morphology is not as unequivocally as conventional plaque histology. But with the help of the VH-IVUS the plaque composition can be determined with an accuracy of 80–92 % and a high reproducibility [22, 25–27]. This observation is confirmed by a VH-IVUS trial of Ogasawara et al. In this study, it could be demonstrated that pioglitazone reduces the necrotic core component in diabetic plaques in association with enhanced plasma adiponectin levels [14].

Another finding of the current trial was the significant reduction of the atherosclerotic plaque volume (a difference of -14.3 mm^3) after 9 months of treatment with pioglitazone compared to placebo in non-diabetics. This result is consistent with data of previous VH-IVUS studies in diabetic patients. In the PERISCOPE trial in patients with type 2 diabetes mellitus and coronary artery disease, treatment with pioglitazone resulted in a significant reduction in the percent atheroma volume compared with glimepiride [13]. Other studies have also demonstrated that pioglitazone reduces neointimal tissue proliferation after coronary stent implantation in patients with and without type 2 diabetes mellitus [28, 29].

In addition to the mere quantitative plaque composition, also the localization of the different histological components, especially of the necrotic core, is essential for the stability of the plaques [24]. Thus, based on the location and quantity of the different plaque components the previously described lesion types PIT, fibrotic plaque, fibrocalcific plaque, VH-TCFA and ThCFA were defined [23]. Kubo et al. could demonstrate that atherosclerotic plaques can change their lesion type during the development. In this manner, Kubo and colleagues showed that VH-TCFAs and ThCFAs have a significant plaque progression compared to fibrous or fibrocalcific plaque [23]. Additionally, in the denotative PROSPECT study of Stone et al. the different lesion types were compared with respect to their clinical outcome within a median follow-up period of 3.4 years. In this work, the recurrence of major adverse cardiovascular events caused by non-culprit lesions was associated with the existence of VH-TCFAs [2]. In our current VH-IVUS trial, no VH-TCFAs within the non-culprit lesions could be detected both in the pioglitazone and in the placebo group. The predominant lesion type (98 %) was the thick-capped fibroatheroma (ThCFA). During the 9 months of follow-up, only one pioglitazone-treated ThCFA changed into a fibrotic plaque. In the placebo group only one PIT changed into a ThCFA. Comparable to the present data, also in the work of Kubo et al. the prevalent lesion type was the ThCFA followed by fibrotic and fibrocalcific plaques. Only about 10 % of all lesions were classified as VH-TCFAs in the study of Kubo and colleagues [23]. That only the minority of plaques changed into a more stable lesion type during the treatment with

Table 2 Changes of geometrical vessel data 9 months after treatment with pioglitazone

	Pioglitazone ($n = 42$)	Placebo ($n = 44$)	p value
Lesion length (mm)			
Baseline	24.85 ± 13.74	25.45 ± 15.30	NS
At 9 months	24.41 ± 13.75	25.49 ± 15.14	NS
Difference	−0.45 ± 2.56	0.04 ± 1.98	NS
Vessel volume (mm^3)			
Baseline	368.92 ± 200.01	402.06 ± 277.05	NS
At 9 months	342.11 ± 188.13	391.82 ± 261.87	NS
Difference	−26.82 ± 39.90	−10.24 ± 59.70	NS
Lumen volume (mm^3)			
Baseline	189.07 ± 107.09	211.41 ± 169.15	NS
At 9 months	178.40 ± 104.82	202.93 ± 159.46	NS
Difference	−10.67 ± 23.01	−8.48 ± 41.66	NS
Plaque volume (mm^3)			
Baseline	179.85 ± 104.51	190.65 ± 119.42	NS
At 9 months	163.71 ± 92.26	188.90 ± 114.46	NS
Difference	−16.14 ± 26.44	−1.75 ± 30.87	0.02*
PAV (%)			
Baseline	49.83 ± 13.38	51.65 ± 13.99	NS
At 9 months	48.51 ± 7.33	53.17 ± 16.75	NS
Difference	−1.33 ± 11.39	1.52 ± 18.89	NS
Plaque burden (%)			
Baseline	48.64 ± 7.80	49.28 ± 9.00	NS
At 9 months	48.05 ± 7.64	49.93 ± 9.54	NS
Difference	−0.59 ± 3.75	0.65 ± 5.47	NS
Average vessel CSA (mm^2)			
Baseline	15.47 ± 5.14	16.56 ± 6.06	NS
At 9 months	14.52 ± 4.81	16.04 ± 6.24	NS
Difference	−0.94 ± 2.34	−0.52 ± 2.99	NS
Average lumen CSA (mm^2)			
Baseline	8.29 ± 3.17	8.88 ± 3.77	NS
At 9 months	7.88 ± 4.0	8.26 ± 3.10	NS
Difference	−0.41 ± 2.18	−0.62 ± 2.32	NS
Average plaque CSA (mm^2)			
Baseline	0.21 ± 0.26	0.16 ± 0.37	NS
At 9 months	0.2 ± 0.26	0.26 ± 0.34	NS
Difference	−0.02 ± 0.15	0.10 ± 0.57	NS
Minimal luminal area (mm^2)			
Baseline	5.39 ± 2.70	5.50 ± 2.61	NS
At 9 months	5.34 ± 2.77	5.22 ± 2.28	NS
Difference	−0.04 ± 1.32	−0.28 ± 1.26	NS
TAVn (mm3)			
Baseline	11.21 ± 13.38	10.75 ± 11.52	NS
At 9 months	14.52 ± 4.81	16.04 ± 6.24	NS
Difference	−0.81 ± 7.34	2.85 ± 16.22	NS
Remodeling index			
Baseline	0.71 ± 0.18	0.75 ± 0.24	NS
At 9 months	0.73 ± 0.21	0.74 ± 0.23	NS
Difference	0.02 ± 0.16	−0.01 ± 0.14	NS
Eccentricity index			
Baseline	−0.21 ± 0.17	−0.18 ± 0.21	NS
At 9 months	−0.18 ± 0.22	−0.20 ± 0.21	NS
Difference	0.02 ± 0.13	−0.02 ± 0.12	NS

*$p < 0.05$

pioglitazone can be explained by a too short 9-month follow-up period. It remains speculative if prolonged treatment with pioglitazone is able to cause a relevant plaque evolution into more stable plaque types. All the above-mentioned findings indicate that the treatment with a PPARγ agonist results in a relevant plaque stabilization and in reduction of atherosclerotic plaque size on top of standard medical care, even in patients without type 2 diabetes. However, the exact mechanisms of plaque stabilization are still unclear [2, 23]. Different studies confirmed, that the anti-atherosclerotic effect of pioglitazone cannot solely be explained by its positive effect on glycemia, but also by anti-inflammatory effects of the PPARγ agonist [30–32].

Despite the positive VH-IVUS data of the current trial, it remains uncertain whether pioglitazone is able to prevent hard clinical endpoints due to the reduction of coronary plaque size and plaque stabilization, even in non-diabetics. In the current trial other VH-IVUS parameters like the plaque burden, the eccentricity index (EI) and the remodeling index (RI) were determined as well. All these parameters showed no relevant changes due to the treatment with pioglitazone. Because of these inconsistent results of the IVUS measurements the clinical benefit of the reduction of the plaque volume and the necrotic core remains speculative in this trial. The benefits of the atherosclerotic plaque stabilization have to be balanced with the side effects of pioglitazone treatment. In the current study, both treatment groups revealed the same very low incidence of adverse effects, especially of peripheral edema and angina pectoris. Thus, the treatment with pioglitazone in non-diabetic patients seems to be safety. But because of the known side effects of the glitazones like heart failure, weight gain, peripheral edemas, bone fractures and bladder cancer pioglitazone will probably not be established for the treatment of coronary heart disease in non-diabetics. Nevertheless, the current IVUS trial supports the concept of a systemic anti-inflammatory treatment of coronary heart disease. Maybe different PPAR-activating drugs without the above-mentioned side effects could influence the atherosclerotic plaque progression. Also other anti-inflammatory substances like colchicine seem to be conceivable for the systemic anti-inflammatory treatment [33].

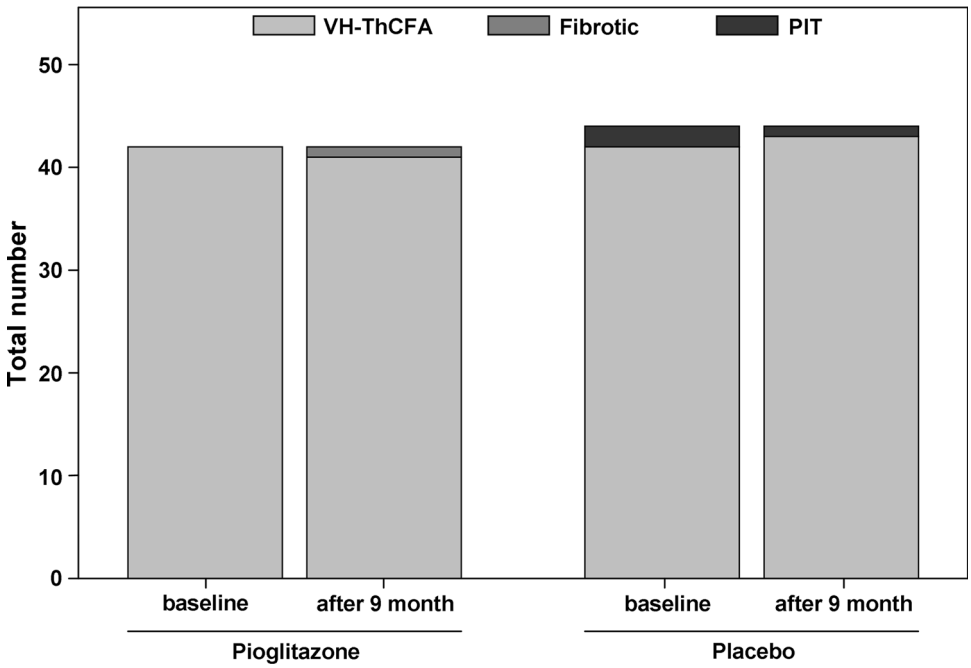

Fig. 3 Change of VH-IVUS Plaque classification after 9 months. At baseline in pioglitazone group all 42 lesions were characterized as VH-ThCFA, in placebo group there were 42 VH-ThCFA and 2 PIT; during follow-up in pioglitazone group 1 VH-ThCFA evolved into fibrotic plaque and in placebo group 1 PIT changed into VH-ThCFA

We recognize that our current study has some limitations. This trial evaluated the effect on coronary atherosclerotic plaque stability and plaque burden. But all these VH-IVUS parameters are only surrogate end points and should not be interpreted as equivalent for the cardiovascular outcome. Further, only patients with a clinically relevant coronary artery disease were included. It is unclear, whether our results are consistent in primary prevention in asymptomatic patients. Another limiting aspect of the study was the relatively small number of patients, so the work should be understood as a pilot study. In this context, the prevalence of side effects of pioglitazone treatment should be further investigated in a larger study population.

Despite these limitations, to the best of our knowledge, the current IVUS study demonstrated, that the treatment with pioglitazone results in a coronary artery plaque stabilization in non-diabetic patients. It is noteworthy that the plaque stabilization and the reduction of plaque size arose on top of usual medical care. These findings highlight the benefit of the treatment with a PPARγ agonist for atherosclerotic plaque stabilization in patients with coronary artery disease.

Whether pioglitazone has similar or different effects on clinical cardiovascular outcome in non-diabetic patients remains speculative, especially in light of recent studies regarding the cardiovascular safety of pioglitazone [12, 13, 34]. Therefore, the anti-atherosclerotic effect of pioglitazone on the cardiovascular outcome in non-diabetics should be investigated in larger outcome trials with longer follow-up period.

Our findings have clinical implications for the development of a novel systemic anti-atherosclerotic therapy.

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Conflict of interest The authors report no conflicts.

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