Pioglitazone Reduces Neointima Volume After Coronary Stent Implantation
A Randomized, Placebo-Controlled, Double-Blind Trial in Nondiabetic Patients

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Background—Restenosis requiring reintervention limits the long-term success after coronary stent implantation. Thiazolidinediones, like pioglitazone or rosiglitazone, are oral antidiabetic drugs with additional antirestenotic properties. In a randomized, placebo-controlled, double-blind trial, we examined the effect of 6-month pioglitazone therapy on neointima volume after coronary stenting in nondiabetic coronary artery disease patients.

Methods and Results—Fifty nondiabetic patients after coronary stent implantation were randomly assigned to pioglitazone (30 mg daily; pio) or placebo (control) treatment in addition to standard therapy, and neointima volume was assessed by intravascular ultrasound at the 6-month follow-up. Both groups were comparable with regard to baseline characteristics, angiographic lesion morphology, target vessel, and length of the stented segment. In addition, there were no statistical differences in minimal lumen diameter before and after intervention, as well as reference diameter after stent implantation. In this study population of nondiabetic patients, pio treatment did not significantly change fasting blood glucose, fasting insulin, or glycosylated hemoglobin levels, as well as lipid parameters. In contrast, pio treatment significantly reduced neointima volume within the stented segment, with 2.3 ± 1.1 mm³/mm compared with controls (3.1 ± 1.6 mm³/mm; P = 0.04). Total plaque volume (adventitia-lumen area) was significantly lower at follow-up in the pio group (11.2 ± 3.2 mm³/mm) compared with controls (13.2 ± 4.2 mm³/mm; P = 0.04). Moreover, the binary restenosis rate was 3.4% in the pio group versus 32.3% in controls (P < 0.01).

Conclusions—Thus, 6-month treatment with pio significantly reduced neointima volume after coronary stent implantation in nondiabetic patients. These data bolster the hypothesis that antidiabetic thiazolidinediones, in addition to their metabolic effects, exhibit direct antirestenotic effects in the vasculature. (Circulation. 2005;112:2792-2798.)

Key Words: stents ■ thiazolidinediones ■ intima ■ coronary disease ■ diabetes mellitus

Restenosis requiring reintervention is still a limitation of percutaneous coronary angioplasty. Despite the use of stents, the rate of restenosis remains 20% to 30% in all patients, making it a challenging problem in interventional cardiology. Migration and proliferation of medial vascular smooth muscle cells (VSMCs) is the predominant mechanism of neointima formation leading to in-stent restenosis. Various pharmacological strategies, such as the application of antiplatelet or antiinflammatory agents, have been shown to modulate these processes in vitro and were efficient in reducing restenosis in animal models. Still, in clinical trials, most of these attempts did not successfully limit neointima formation after coronary stenting.

Editorial p 2759

Thiazolidinediones (TZDs), like pioglitazone (pio) or rosiglitazone, are a novel class of oral antidiabetic agents currently used to treat patients with type 2 diabetes mellitus. These agents increase insulin sensitivity and, as such, have favorable effects on blood glucose levels and the lipid profile in treated patients. Beyond their metabolic action, TZDs have been shown to exhibit antiinflammatory and antiatherogenic effects in vascular cells in vitro and to limit lesion development in various animal models of arteriosclerosis (reviewed in Marx et al). Moreover, TZDs inhibit VSMC proliferation and migration, 2 critical processes in neointima formation after coronary stenting. Data from rodent models suggest that TZDs limit intimal proliferation after vascular injury, and in clinical studies with type 2 diabetic coronary artery disease (CAD) patients, TZDs have been shown to reduce neointima formation as well as restenosis after coronary stent implantation. Still, it remains unclear to what extent these effects depend on the metabolic action
of these drugs and what might mainly be due to the improve-
ment in glycemic control.

Therefore, we performed a randomized, placebo-
controlled, double-blind trial in nondiabetic CAD patients
and examined by intravascular ultrasound (IVUS) the effect
of 6 months of pio treatment on neointima volume after
coronary stent implantation.

Methods

Study Design and Patient Selection
Fifty nondiabetic patients with angina pectoris and/or exercise-
induced ischemia in the presence of a significant stenosis in a native
coronary artery suitable for stent implantation were included in this
randomized, placebo-controlled, double-blind trial. The nondiabetic
state was assessed by a negative history of diabetes mellitus, no
treatment with antidiabetic drugs, and/or assessment of fasting blood
glucose. All patients were recruited at the Department of Internal
Medicine II, University of Ulm, Ulm, Germany. Exclusion criteria
included the following: diabetes mellitus, acute ST-segment eleva-
tion myocardial infarction (MI), contraindications to treatment with
platelet inhibitors or pio, impaired liver function (aspartate aminotrans-
ferase or alanine aminotransferase 2.5-fold above upper normal
limits), renal insufficiency requiring hemodialysis, pregnancy, sys-
temic inflammatory disease, and life expectancy <6 months. Patients
scheduled for angioplasty were randomized to placebo or pio 30 mg
daily after written, informed consent was obtained. The first dose
was given before the procedure, and treatment was continued until
the 6-month follow-up angiography. Study medication was given in
addition to standard treatments, including aspirin 100 mg/d, β-blockers,
angiotensin-converting enzyme inhibitors, and statins. In addition,
patients received clopidogrel 75 mg/d for at least 4 weeks after
coronary stenting. Patients were seen after 8 weeks for clinical
follow-up and were scheduled for a repeated angiography, including
IVUS, 6 months after the primary intervention. The study was
conducted according to the principles of the Declaration of Helsinki
and was approved by the local ethics committee.

The primary end point of this study was the extent of neointima
volume after 6 months, as assessed by IVUS. A secondary end point
was the mean diameter stenosis of the total segment after 6 months,
as assessed by quantitative coronary angiography (QCA).

Measurement of Inflammatory Biomarkers
Tumor necrosis factor (TNF)-α and soluble CD40L (sCD40L) were
determined by ELISA (R&D Systems) according to the manufactur-
er's protocol. Fibrinogen and C-reactive protein (CRP) were mea-
sured as previously described.18

Angioplasty Procedure and IVUS
All patients were pretreated with at least 500 mg aspirin orally or
intravenously. They received a preangioplasty heparin bolus that was
adjusted according to the activated clotting time (~280 seconds).
Lesions were treated by primary or direct stent implantation and
IVUS guidance to ensure correct stent size and complete strut
apposition. According to the study protocol, patients received only
Express Stents (Boston Scientific Scimed, Inc), but the number of stents
was not limited. Segments were examined by mechanical
IVUS (UltraCross 2.9F, 30 MHz; Boston Scientific Scimed) with
automated pullback at 0.5 mm/s. A coronary segment beginning
5 mm distal to and extending 5 mm proximal to the stented segment
was also analyzed. A computer-based contour-detection program
was used for automated 3-dimensional reconstruction of the seg-
ments (Medis Medical Imaging Systems BV).19 Total vessel volume,
stent volume, and lumen volume were calculated. In the absence of
neointimal formation, lumen volume was delineated by the bound-
aries of the stent struts. Total plaque volume, plaque volume behind
the stent, and neointima formation were calculated as total vessel
volume minus lumen volume, total vessel volume minus stent
volume, and stent volume minus lumen volume, respectively. To
account for differences in stented length, all IVUS parameters were
calculated per millimeter of stent length for the stented segment and
per millimeter of segment length for the proximal and distal adjacent
segment.

Quantitative Coronary Angiography
QCA before and after stent implantation and at follow-up was
performed in the same projections of the treated lesion after
administration of intracoronary glycerol trinitrate. To assess the
minimal luminal diameter, the most severe stenosis in 2 orthogonal
views was measured. Angiographic measurements were done offline
with Pie Medical software version 2.1 (Pie Medical Imaging) as
previously described.20,21

Statistical Analysis
Differences in metabolic parameters between groups and between
treatment time points within a group were analyzed by the Mann-
Whitney U test or Student t test, as appropriate. The primary end
point was neointima volume in the stented segment as determined by
IVUS at the 6-month follow-up. Samples size was calculated on the
basis of results from a previous trial that had examined the effect of
troglitazone on neointima formation in diabetic subjects, with neo-
intima formation in the control group of 3.5 ± 1.8 mm²/mm and in the
troglitazone group of 2.0 ± 0.9 mm²/mm, resulting in 24 lesions per
group to achieve statistical significance (α = 0.05, β = 0.2, 2 tailed).
To account for dropouts and an assumed 80% IVUS-follow-up, we
planned to include 25 patients per group, with an assumed target-
lesion rate of 1.4 per patient. The random allocation sequence was
blocked for every 4 patients. The secondary end point was the mean
diameter stenosis of the total segment after 6 months, as assessed by
QCA. The total segment included edge effects 5 mm proximal and
distal to the stented segment according to trials with brachytherapy.20
Furthermore, the occurrence of major adverse cardiac events, includ-
ing death, MI, and need for reintervention (angioplasty or surgical
revascularization), was analyzed. Group comparisons were done on
a per-lesion basis. To account for repeated assessments within 1
patient, we performed a GEE linear regression (for continuous
outcomes) or a GEE logistic regression (for binary outcomes) to
estimate corrected probability values. Probability values of IVUS
and QCA data were adjusted for established parameters that could
influence follow-up results (reference diameter after procedure,
minimal luminal diameter after procedure, length of stented segment,
and the presence of acute coronary syndrome).22 GEE regression was
performed with the SAS statistical software package (version 8.02
for Unix, SAS Institute Inc). Discrete variables were expressed as
numbers and percentages and compared by the χ² test. Summary
values are expressed as mean ± SD. Skewed data were reported as
median (interquartile range); differences between means of contin-
uous variables were analyzed by t test or the rank-sum test (Statistica
version 6.0, StatSoft Inc). Statistical significance was assumed at the
5% α-error level (P < 0.05).

Results
Clinical Data
Fifty nondiabetic patients with CAD requiring coronary
intervention were enrolled in this study and randomized to
receive either placebo (24 patients) or pio (26 patients)
treatment in addition to standard therapy for CAD. One
patient experienced acute cholecystitis on the day of inter-
vention, and in 1 patient, stent implantation was not success-
ful, leading to exclusion from the study (1 patient in each
group). Both groups did not significantly differ with respect
to baseline characteristics (Table 1), angiographic lesion
morphology, and target vessel. There were no significant
differences in procedural characteristics other than a signifi-
cantly higher maximal inflation pressure in the placebo group
(Table 2). Still, in both groups, high-pressure inflation was
performed, and the groups did not significantly differ with respect to the balloon-to-artery ratio. There were no differences in minimal lumen diameter and reference diameter before and after stent implantation between groups. Stents were implanted in 34 stenoses in the placebo group and in 36 lesions in the pio group (1.5 lesions per patient). One patient in the placebo group (diagnosis of cancer during follow-up) and 4 patients in the pio group were lost to IVUS follow-up (1 patient owing to a diagnosis of cancer, 1 patient refusal of reangiography, and 2 patients withdrawn from the study because of noncompliance; Figure 1). No serious drug-related side effects were observed.

In this study population of nondiabetic patients, pio treatment did not significantly change fasting blood glucose (5.3 [4.9, 5.5] versus 5.4 [4.8, 6.7] mmol/L; \( P = 0.52 \)), fasting insulin (5.1 [3.9, 7.6] versus 7.9 [5.0, 12.1] mmol/L; \( P = 0.08 \)), or glycosylated hemoglobin (HbA1c; 5.6 ±0.3% versus 5.6 ±0.6%; \( P = 0.88 \)) levels compared with placebo at 6 months’ follow-up. In addition, pio did not significantly

### Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=23)</th>
<th>Pioglitazone (n=25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F, n/n</td>
<td>18/5</td>
<td>17/8</td>
<td>0.55</td>
</tr>
<tr>
<td>Age, y</td>
<td>60.8±13.1</td>
<td>63.4±8.5</td>
<td>0.42</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>26.6 (25.1, 30.3)</td>
<td>28 (24.8, 30)</td>
<td>0.98</td>
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<tr>
<td>Blood pressure, systolic mm Hg</td>
<td>120 (120, 130)</td>
<td>120 (113, 130)</td>
<td>0.32</td>
</tr>
<tr>
<td>Blood pressure, diastolic mm Hg</td>
<td>70 (60, 80)</td>
<td>70 (69.5, 80)</td>
<td>0.89</td>
</tr>
<tr>
<td>Smoking</td>
<td>9</td>
<td>15</td>
<td>0.32</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>5.7 (4.9, 6.1)</td>
<td>5.4 (5.0, 5.6)</td>
<td>0.27</td>
</tr>
<tr>
<td>Fasting insulin, µU/mL</td>
<td>9.5 (4.7, 12.2)</td>
<td>6.2 (4.9, 9.6)</td>
<td>0.31</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.6±0.5</td>
<td>5.7±0.4</td>
<td>0.48</td>
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<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.7 (4.2, 5.7)</td>
<td>4.3 (4.1, 5.3)</td>
<td>0.70</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.1 (1.1, 1.2)</td>
<td>1.2 (1, 1.4)</td>
<td>0.35</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.4 (1.2, 1.8)</td>
<td>1.2 (1, 2.2)</td>
<td>0.36</td>
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<td>Previous MI</td>
<td>15</td>
<td>9</td>
<td>0.08</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>1</td>
<td>0</td>
<td>0.80</td>
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<tr>
<td>Unstable angina</td>
<td>6</td>
<td>7</td>
<td>0.99</td>
</tr>
<tr>
<td>Treatment after stenting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>23</td>
<td>25</td>
<td>0.82</td>
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<tr>
<td>Clopidogrel</td>
<td>23</td>
<td>25</td>
<td>0.80</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>22</td>
<td>24</td>
<td>0.99</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>15</td>
<td>18</td>
<td>0.69</td>
</tr>
<tr>
<td>AT1 receptor blocker</td>
<td>0</td>
<td>1</td>
<td>0.80</td>
</tr>
<tr>
<td>Statins</td>
<td>15</td>
<td>19</td>
<td>0.53</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>0</td>
<td>1</td>
<td>0.80</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft; ACE, angiotensin-converting enzyme; and AT1, angiotensin II type 1. Data are mean±SD, median (interquartile range), or n.

### Table 2. Lesion Characteristics and Procedural Data

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Pioglitazone</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>23</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>No. of lesions</td>
<td>34</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Target vessel (coronary artery), n</td>
<td>17</td>
<td>15</td>
<td>0.78</td>
</tr>
<tr>
<td>LAD</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>CX</td>
<td>12</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion type, n</td>
<td></td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>A/B1</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>B2/C</td>
<td>14</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>De novo lesion, %</td>
<td>1.15±0.44</td>
<td>1.11±0.32</td>
<td>0.66</td>
</tr>
<tr>
<td>No. of implanted stents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stented segment, mm</td>
<td>15.0±9.1</td>
<td>16.9±6.8</td>
<td>0.33</td>
</tr>
<tr>
<td>GP IIb/IIIa antagonist, n</td>
<td>3</td>
<td>5</td>
<td>0.56</td>
</tr>
<tr>
<td>No. of inflations</td>
<td>1.8±1.7</td>
<td>1.5±1.1</td>
<td>0.45</td>
</tr>
<tr>
<td>Total inflation time, s</td>
<td>96±105</td>
<td>73±50</td>
<td>0.25</td>
</tr>
<tr>
<td>Maximal inflation pressure, atm</td>
<td>20.4±3.7</td>
<td>17.5±3.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Maximal balloon diameter, mm</td>
<td>3.0±0.4</td>
<td>3.0±0.4</td>
<td>0.95</td>
</tr>
<tr>
<td>Balloon-to-artery ratio</td>
<td>1.1±0.1</td>
<td>1.1±0.1</td>
<td>0.56</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending, CX, circumflex; RCA, right; and GP, glycoprotein. Data are mean±SD.

in the placebo group (diagnosis of cancer during follow-up) and 4 patients in the pio group were lost to IVUS follow-up (1 patient owing to a diagnosis of cancer, 1 patient refusal of reangiography, and 2 patients withdrawn from the study because of noncompliance; Figure 1). No serious drug-related side effects were observed.

In this study population of nondiabetic patients, pio treatment did not significantly change fasting blood glucose (5.3 [4.9, 5.5] versus 5.4 [4.8, 6.7] mmol/L; \( P = 0.52 \)), fasting insulin (5.1 [3.9, 7.6] versus 7.9 [5.0, 12.1] mmol/L; \( P = 0.08 \)), or glycosylated hemoglobin (HbA1c; 5.6 ±0.3% versus 5.6 ±0.6%; \( P = 0.88 \)) levels compared with placebo at 6 months’ follow-up. In addition, pio did not significantly

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**Figure 1.** Flow chart of the study population. Pat indicates patient.
change total cholesterol, HDL cholesterol, or triglyceride levels (Table 3). Moreover, changes in the parameters from baseline to follow-up were not significantly different between the 2 groups (data not shown).

Because TZD treatment has been shown to modulate inflammatory biomarkers of arteriosclerosis, we also measured plasma levels of CRP, fibrinogen, TNF-α, and sCD40L. Only plasma levels of fibrinogen were significantly lowered by pio, but they were also decreased in the placebo group, leading to a nonsignificant difference between the groups at the 6-month follow-up. In addition, pio did not significantly affect plasma levels of CRP, TNF-α, or sCD40L.

**IVUS and Angiographic Data**

IVUS after intervention revealed complete stent apposition to the vessel wall in all lesions. One patient in the pio group had an asymptomatic stent thrombosis of the vessel with 2 stenoses and was not available for follow-up assessment of neointima volume by IVUS. This patient was also excluded from QCA follow-up.

With regard to the primary end point, pio significantly reduced neointima volume within the stented segment compared with placebo (2.3±1.1 mm³/mm in the pio group versus 3.1±1.6 mm³/mm in the placebo group; *P* = 0.04). Moreover, after 6 months, total plaque volume in the stented area was significantly lower in patients treated with pio (11.2±3.2 mm³/mm) compared with controls (13.2±4.2 mm³/mm; *P* = 0.04; Figure 2 and Table 4). Similarly, in the adjacent segments proximal and distal to the stent (edge effects), total plaque volume was significantly lower in the pio compared with the placebo group (Table 4). The effect on neointima volume and total plaque volume remained statistically signif-

**TABLE 3. Metabolic Parameters at Baseline and After 6 Months**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Pio</th>
<th>Placebo</th>
<th>Pio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>5.7 (4.9, 6.1)</td>
<td>5.4 (4.8, 6.7)</td>
<td>0.85</td>
<td>5.4 (5.0, 5.6)</td>
</tr>
<tr>
<td>Fasting insulin, µU/mL</td>
<td>9.5 (4.7, 12.2)</td>
<td>7.9 (5.0, 12.1)</td>
<td>0.85</td>
<td>5.7 (4.7, 9.0)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.6±0.5</td>
<td>5.6±0.6</td>
<td>0.90</td>
<td>5.7±0.4</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.7 (4.2, 5.7)</td>
<td>4.5 (3.7, 5.0)</td>
<td>0.41</td>
<td>4.3 (4.1, 5.3)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.1 (1.0, 1.2)</td>
<td>1.2 (1.0, 1.3)</td>
<td>0.57</td>
<td>1.2 (1.0, 1.4)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.4 (1.2, 1.8)</td>
<td>1.3 (0.9, 2.0)</td>
<td>0.82</td>
<td>1.2 (1.0, 2.2)</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>3.9 (1.3, 5.1)</td>
<td>1.2 (2.5, 5.5)</td>
<td>0.01</td>
<td>2.3 (1.5, 5.5)</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>4.3 (3.4, 4.8)</td>
<td>3.4 (2.7, 4.2)</td>
<td>0.02</td>
<td>4.2 (3.2, 5.3)</td>
</tr>
<tr>
<td>sCD40L, ng/mL</td>
<td>8.7 (6.3, 9.6)</td>
<td>8.5 (6.1, 10.5)</td>
<td>0.90</td>
<td>8.4 (5.6, 11)</td>
</tr>
<tr>
<td>TNF-α, pg/mL</td>
<td>2.7 (1.9, 3.5)</td>
<td>2.6 (1.8, 5.3)</td>
<td>0.9</td>
<td>1.6 (1.2, 2.9)</td>
</tr>
</tbody>
</table>

Data are mean±SD or median (interquartile range). *P* values are for comparison of parameters between time points.

Figure 2. A, Pio reduces neointima volume after coronary stenting in nondiabetic CAD patients, as assessed by IVUS. Bars represent mean±SD of neointimal volume within the stented segment at 6-month follow-up. *P* = 0.04 compared with placebo. B, Effect of pio on total plaque volume after coronary stenting. Bars represent mean±SD of total plaque volume at 6-month follow-up. *P* = 0.04 compared with placebo. C, Cumulative frequency curves of mean and maximal neointimal volumes at follow-up. Patients in the placebo group are shown in black, and patients in the pio group, in red. Solid lines indicate maximal neointima volume, and dotted lines, mean neointima volume. At 6 months, the mean neointima volume in the group that received pio was significantly lower compared with the placebo group (2.3±1.1 vs 3.1±1.6 mm³/mm; *P* = 0.04). In addition, there was a nonsignificant trend toward a reduced maximal neointima volume in the pio group compared with placebo (8.9±1.5 vs 5.0±2.7 mm³/mm; *P* = 0.08).
TABLE 4. IVUS Measurements at 6-Month Follow-Up

<table>
<thead>
<tr>
<th>Lesion Parameters Measured</th>
<th>Placebo (n=31)</th>
<th>Pioglitazone (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proximal</td>
<td>Stent</td>
</tr>
<tr>
<td>Total vessel volume</td>
<td>18.5±6.5</td>
<td>20.0±6.0</td>
</tr>
<tr>
<td>Total plaque volume</td>
<td>10.4±4.0</td>
<td>13.2±4.2</td>
</tr>
<tr>
<td>Plaque behind stent</td>
<td>NA</td>
<td>10.2±4.1</td>
</tr>
<tr>
<td>Stent volume</td>
<td>NA</td>
<td>9.8±2.5</td>
</tr>
<tr>
<td>Neointimal volume</td>
<td>NA</td>
<td>3.1±1.6</td>
</tr>
<tr>
<td>Lumen volume</td>
<td>8.1±3.2</td>
<td>6.8±2.3</td>
</tr>
</tbody>
</table>

NA indicates not applicable. All parameters are given in mm$^3$ per 1-mm stented segment (stent) or per 1-mm vessel segment (proximal and distal). Data are mean±SD.

*P<0.05 for comparison of parameters between groups.

Results of QCA are detailed in Table 5. In the pio group, mean diameter stenosis in the target lesion and the total segment was significantly reduced compared with placebo (percentage of luminal diameter: pio, 22.1±12.7% versus placebo, 37.3±24.2%; P=0.01), leading to a significant reduction in the angiographic restenosis rate by pio treatment (Figure 3). There was a nonsignificant reduction of late loss and late loss index in the pio group compared with placebo. With adjusted GEE linear regression analysis to account for repeated assessments within 1 patient, the effect of pio on mean diameter stenosis and binary restenosis remained significant (P=0.0004 and 0.002, respectively). Moreover, with this analysis, the higher minimal luminal diameter at follow-up (P=0.003 for target lesion and P=0.0004 for the total segment) in the pio group compared with placebo, as well as the effect on late loss (P=0.026 for target lesion and P=0.007 for the total segment) and late loss index (P=0.028 for target lesion and P=0.017 for the total segment), became statistically significant. The effect on restenosis rate was still preserved when analysis included the 1 patient with stent thrombosis and total occlusion of the vessel (target lesion restenosis, 9.7% in the pio group versus 32.3% in the placebo group; P=0.03; total segment restenosis, 9.7% in the pio group versus 38.7% in the placebo group; P=0.01). There were no deaths or MIs during follow-up. Target-vessel revascularization due to restenosis was performed in 9 of 31 (29.0%) lesions in the placebo group compared with 2 of 29 (12.9%) lesions in the pio-treated group (P=0.02).

TABLE 5. QCA Analysis

<table>
<thead>
<tr>
<th>Lesions with follow-up, n</th>
<th>Placebo (n=31)</th>
<th>Pioglitazone (n=29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference diameter, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before procedure</td>
<td>2.82±0.45</td>
<td>2.77±0.43</td>
<td>0.65</td>
</tr>
<tr>
<td>After procedure</td>
<td>3.25±0.48</td>
<td>3.20±0.31</td>
<td>0.66</td>
</tr>
<tr>
<td>Minimal lumen diameter, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before procedure</td>
<td>0.95±0.50</td>
<td>0.74±0.38</td>
<td>0.08</td>
</tr>
<tr>
<td>After procedure</td>
<td>3.02±0.56</td>
<td>3.02±0.32</td>
<td>0.97</td>
</tr>
<tr>
<td>Target lesion at 6 months</td>
<td>1.94±0.91</td>
<td>2.14±0.46</td>
<td>0.29</td>
</tr>
<tr>
<td>Total segment at 6 months</td>
<td>1.83±0.93</td>
<td>2.14±0.46</td>
<td>0.11</td>
</tr>
<tr>
<td>Stenosis, % of luminal diameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before procedure</td>
<td>69.6±13.3</td>
<td>72.7±13.7</td>
<td>0.39</td>
</tr>
<tr>
<td>After procedure</td>
<td>7.8±6.4</td>
<td>6.2±5.4</td>
<td>0.29</td>
</tr>
<tr>
<td>Target lesion at 6 months</td>
<td>33.3±23.3</td>
<td>22.1±12.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Total segment at 6 months</td>
<td>37.3±24.2</td>
<td>22.1±12.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Late loss in target lesion, mm</td>
<td>1.08±0.65</td>
<td>0.88±0.41</td>
<td>0.24</td>
</tr>
<tr>
<td>Late loss in total segment, mm</td>
<td>1.19±0.93</td>
<td>0.88±0.41</td>
<td>0.10</td>
</tr>
<tr>
<td>Late loss index in target lesion</td>
<td>0.60±0.76</td>
<td>0.40±0.19</td>
<td>0.16</td>
</tr>
<tr>
<td>Late loss index in total segment</td>
<td>0.63±0.67</td>
<td>0.40±0.19</td>
<td>0.08</td>
</tr>
<tr>
<td>Binary restenosis, n (%)</td>
<td>10 (32.3)</td>
<td>1 (3.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total segment</td>
<td>12 (38.7)</td>
<td>1 (3.4)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are mean±SD unless otherwise shown.

Figure 3. Cumulative distribution curves for percent stenosis of the luminal diameter in both groups before intervention, after stenting, and at 6-month follow-up. Patients in the placebo group are shown in black, and patients in the pio group, in red. At 6 months, the mean degree of stenosis in the group that received pio was significantly lower compared with the placebo group (22.1±12.7% vs 37.3±24.2% of luminal diameter; P<0.01).
Discussion

The present randomized, placebo-controlled, double-blind trial demonstrates that 6-month treatment with pio reduced neointima volume after coronary stent implantation in nondiabetic CAD patients. Previous studies have shown that TZD treatment reduces restenosis and neointima formation after coronary stenting in patients with type 2 diabetes mellitus.14–17 Although some of the studies analyzed whether this effect was dependent on the glucose-lowering properties of these agents,17 it remained unclear to what extend the favorable results on restenosis were due to improvement in glycemic control or other metabolic parameters. The data presented here suggest that pio directly influences neointima formation independent of its metabolic action. First, our study was conducted in nondiabetic subjects, and we did not find any changes in blood glucose, insulin, or HbA1c levels after 6 months of pio treatment. This is consistent with previous findings that have shown that TZD treatment of nondiabetic subjects does not have an effect on glucose metabolism.23 In addition, we did not find changes in total cholesterol, HDL cholesterol, or triglyceride levels, making it unlikely that the effect on neointima formation resulted from changes in the lipid profile. Still, we did not perform oral glucose tolerance tests in our patients and cannot exclude the possibility that some of the patients might have had impaired glucose tolerance, which may have been influenced by pio treatment. However, the lack of an effect on blood glucose, insulin, or HbA1c levels argues against a causal role of major metabolic effects for the reduction in neointima formation.

The primary end point of this study was the assessment of neointima volume after coronary stenting by IVUS. Both this primary end point and total plaque volume in the stented area and the proximal and distal adjacent segments were significantly lower in the pio-treated patient group compared with patients receiving placebo. In the placebo group, a significantly higher inflation pressure was applied, but in both groups, high-pressure inflation (>14 atm) was performed, and the balloon-to-artery ratio, considered to be an index of coronary injury, was not statistically different in the 2 groups. In addition, in both groups, inflation pressure were not significantly correlated with the primary end point of neointima volume, making the difference in inflation pressure an unlikely explanation for the results observed on neointima volume. Furthermore, there was a nonsignificant trend to higher insulin levels in the placebo group compared with pio-treated patients, potentially reflecting a more insulin-resistant state in the placebo group with an increased risk for the development of restenosis. Because there was a trend to a lower body mass index, a very reliable marker of insulin resistance, in the placebo group, the increased insulin values were most likely due to chance. Moreover, baseline insulin levels were not correlated with neointima volume in both groups. In addition, insulin values fell more in the placebo group than in the pio group during the 6 months of treatment, making it unlikely that the difference at baseline accounted for the effect on neointima formation.

The secondary end point was the mean diameter stenosis of the total segment after 6 months, as assessed by QCA. Our study revealed a significant reduction in mean diameter stenosis of the total segment as well as a significant reduction of in-stent restenosis by pio treatment. This effect was paralleled by a nonsignificant trend to increased minimal luminal diameter, as well as decreased late loss and late loss index in the pio group compared with placebo. Still, when adjusted GEE linear regression analysis was performed to account for repeated assessments within 1 patient, the effect on these parameters was statistically significant.

The data obtained herein are consistent with experimental data on the effect of TZDs on processes involved in neointima formation after coronary stenting, like VSMC migration and proliferation. TZDs are activators of the nuclear transcription factor peroxisome proliferator–activated receptor (PPAR)-γ and, as such, are regulators of gene expression in various cell types. Several groups including our own have demonstrated that PPAR-γ is expressed in VSMCs in vivo and in vitro and that activation of this receptor by TZDs limits both VSMC migration and proliferation.10–12 In addition, very recent experimental data suggest that TZD treatment increases the number of endothelial progenitor cells, a mechanism considered important for endothelialization and reduction of restenosis after coronary stenting.24 Moreover, animal data have shown that TZD treatment reduces intimal hyperplasia after vascular injury.13 Our study extends the knowledge of TZDs’ effects on restenosis by showing that TZD treatment limits neointima volume independent of its metabolic effect in a nondiabetic patient population. These results are in line with previous reports showing that TZDs exhibit direct antiinflammatory and antiatherogenic properties in the vasculature. As such, TZDs reduce serum levels of inflammatory biomarkers, like CRP, fibrinogen, or soluble E-selectin, and modulate endothelial function independent of their metabolic action.25–27 Because inflammatory processes in the vessel wall may also contribute to a reduction in neointima formation, antiinflammatory TZD effects may explain the results observed here. Still, in our study, we did not find significant changes in CRP, fibrinogen, TNF-α, or sCD40L levels after pio treatment compared with placebo. This is most likely due to the small sample size as well as multiple confounding factors, such as hospitalization and the intervention itself, all known to modulate serum levels of these markers.28 However, the lack of a significant effect on inflammatory biomarkers does not exclude the possibility that the antiinflammatory action of pio contributed to the reduction in neointima formation.

Major limitations of the present study are the small sample size in both groups as well as the lack of mechanistic insight of pio’s effect on neointima formation. Therefore, larger studies are needed to further elucidate the antirestenotic effect of TZDs. In addition, such studies should include clinical end points like target-vessel revascularization, which was high (29%) in the placebo group in our study. If larger clinical trials can confirm the beneficial effects of TZD treatment on neointima volume, thus translating into a reduced need for target-vessel revascularization, this treatment with an orally taken drug may be a promising tool to modulate restenosis after stenting. This may also be important with respect to drug-eluting stents, for which the restenosis rate is significantly lower compared with bare metal stents. However, in more complex lesions, the binary restenosis rate is ≈15% and is as high as 31% in small vessels, despite the use of drug-eluting stents, as shown in the TAXUS-V study.29 In these subjects, systemic therapy with TZDs may be combined with drug-eluting stents to further improve clinical
outcomes. In addition, TZD treatment may be used in patients with a history of gastrointestinal or intracranial bleeding who are otherwise unsuitable candidates for stenting with drug-eluting stents because of prolonged combined antplatelet therapy.

Taken together, our study suggests a direct effect of TZD treatment on neointima volume after coronary stent implantation in nondiabetic CAD patients, promoting the concept that PPAR-γ-activating TZDs, independent of their metabolic action, may exhibit direct protective effects in the vasculature. Still, larger clinical trials should replicate these findings and determine whether the effects of TZD treatment on neointima formation also translate into clinical benefits, such as reduction of target-vessel revascularization.

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