JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 4, NO. 3, 2011

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2010.10.016

Role of Pioglitazone in the Prevention of Restenosis and Need for Revascularization After Bare-Metal Stent Implantation

A Meta-Analysis

Dhavalkumar Patel, MD, MPH,* Brian Walitt, MD, MPH,* Joseph Lindsay, MD,* Robert L. Wilensky, MD†

Washington, DC; and Philadelphia, Pennsylvania

Objectives We performed a meta-analysis to evaluate the impact of pioglitazone in the prevention of in-stent restenosis (ISR) and need for revascularization after bare-metal stent (BMS) implantation.

Background BMS use is associated with a significant incidence of restenosis. Pioglitazone, a thiazolidinedione (TZD), has been shown in small studies to be associated with decreased neointimal formation after BMS implantation.

Methods The meta-analysis included randomized controlled trials that randomized patients undergoing BMS implantation into pioglitazone treatment in combination with standard treatment or standard treatment only. All randomized controlled trials followed patients for 6 months with baseline and follow-up angiographies. The ISR and revascularization rate were considered primary outcomes.

Results We identified 6 eligible studies involving 373 patients (187 in the pioglitazone group and 186 in the control group). Use of pioglitazone was associated with decreased late loss, a larger minimal lumen diameter, and a lower percentage diameter stenosis ($p < 0.01$). The angiographic ISR rate was decreased with pioglitazone ($p < 0.01$), and patients who received pioglitazone were significantly less likely to undergo revascularization ($p < 0.01$). Intravascular ultrasound analysis also demonstrated decreased neointima formation in the pioglitazone group. Subgroup analysis showed significant reduction in ISR and need for revascularization for studies involving only diabetic patients, whereas analysis of the remaining studies demonstrated nonsignificant reduction.

Conclusions This meta-analysis suggests that treatment with pioglitazone is effective in decreasing ISR and need for revascularization after BMS implantation in patients with diabetes. A randomized clinical trial evaluating the hypothesis that administration of pioglitazone reduces restenosis in diabetic patients after BMS implantation seems warranted. (J Am Coll Cardiol Intv 2011;4:353–60)

From the *Washington Hospital Center, Washington, DC; and the †Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania. Dr. Wilensky received research grants from Boston Scientific and GlaxoSmithKline, and he has equity interest in Johnson & Johnson. All other authors have reported that they have no relationships to disclose.

Manuscript received October 18, 2010, accepted October 29, 2010.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 4, NO. 3, 2011
MARCH 2011:353–60

In-stent restenosis (ISR) remains a significant problem after bare-metal stent (BMS) compared with drug-eluting stent (DES) implantation (1). However, the incidence of stent thrombosis, particularly late thrombosis, in DES has led to a recommendation for long-term use of dual antiplatelet therapy after implantations (2). The strategy of long-term use of dual antiplatelet therapy after DES implantation is not, however, without hazards in an unselected patient population with high risk of bleeding (3).

In-stent restenosis in BMS results from neointimal accumulation, a process that is accentuated in diabetic patients (4). Diabetes, multiple stents, small luminal diameter, and length of stent are independent predictors of restenosis, whereas clinical presentations (stable vs. unstable angina) or stenting in infract-related artery does not predict angiographic restenosis (5,6). A variety of pharmacological agents with a potential to limit neointimal tissue development have been studied, and the thiazolidinedione (TZD) family of agents offers promise, because these agents modulate the activity of a wide array of genes and affect several biological processes associated with cellular proliferation and inflammation (7). The TZDs are mainly used for diabetic patients to increase insulin sensitivity and reduce glucose levels. Rosiglitazone and pioglitazone are available in the U.S. for clinical use, whereas troglitazone was withdrawn from the market due to hepatotoxicity. A meta-analysis of 42 studies showed a significant increase in risk of myocardial infarction (MI) from rosiglitazone (8). However, TZDs exhibit different patterns of gene modulation (9) and biological effects (10). For instance, rosiglitazone increases low-density lipoprotein (LDL) cholesterol and also exhibits less favorable effects on high-density lipoprotein (HDL) and triglycerides (TG), whereas pioglitazone favorably affects LDL, HDL, and TG levels (10). Hence, the risk of adverse events associated with rosiglitazone might not predict effects of pioglitazone. Furthermore, pioglitazone has been shown in randomized, placebo-controlled trials and meta-analysis to be associated with decreased rates of death, MI, and stroke (11). In a recent meta-analysis, pioglitazone is shown to be well-tolerated and associated with improvement in glycemic and lipid parameters (12). It is also associated with improvement in glycemic control when added to insulin regimen (13). Thus, pioglitazone is mainly approved for diabetes, but its anti-inflammatory and antiatherogenic properties (14,15) make this drug interesting from a cardiovascular perspective. Importantly, animal and clinical studies indicate an ability of pioglitazone to decrease neointimal hyperplasia after stent implantation (16–24).

Small randomized controlled studies, predominantly involving Asian populations, have examined the effect of TZDs on restenosis and neointimal formation after BMS implantation (16–21,25,26). Previous meta-analysis demonstrated overall benefit of TZDs, both pioglitazone and rosiglitazone, in prevention of ISR and target vessel revascularization (TVR) (25,26). Because troglitazone has not been approved by the U.S. Food and Drug Administration and rosiglitazone has been associated with increased risk of MI (8), we sought to evaluate by means of meta-analysis the potential role of only pioglitazone. Moreover, our meta-analysis also included recently published studies and provides updated information. The goal of the present study is to examine the role of pioglitazone in the prevention of ISR and the need for revascularization after BMS stenting in diabetic and nondiabetic patients.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CHF = congestive heart failure
CI = confidence interval
DES = drug-eluting stent(s)
DM = diabetes mellitus
HbA1c = hemoglobin A1c
HDL = high-density lipoprotein (cholesterol)
ISR = in-stent restenosis
IVUS = intravascular ultrasound
LDL = low-density lipoprotein (cholesterol)
MMP = matrix metalloproteinase
OR = odds ratio
PCI = percutaneous coronary intervention
QCA = quantified coronary angiography
RCT = randomized controlled trial(s)
TG = triglyceride(s)
TVR = target vessel revascularization
TZD = thiazolidinedione

Methods

Study selection. In December 2009, we searched for studies showing the effect of TZDs after stent implantation with PubMed, MEDLINE (Ovid), and the Cochrane Library databases. Abstracts from major cardiology meetings and nonpublished studies were also searched to reduce publication bias. There was no limitation to the language of publication. Search terms used were "pioglitazone," "TZDs," "stent," "coronary," "intravascular ultrasound (IVUS)," "angiography," "atherosclerosis," "restenosis," and "neointima." Only randomized controlled trials (RCTs) that evaluated effects of pioglitazone after BMS implantation were selected for this meta-analysis.

To be included, studies were required to meet the following criteria: 1) prospective and randomized design; 2) Methods section contained clearly defined participant recruitment, follow-up, and other intervention; 3) all randomized patients received—in addition to study medications—recommended post-PCI medical interventions, including beta-blocker, angiotensin-converting enzyme inhibitor, statin, aspirin, and a thienopyridine; 4) diabetes mellitus (DM) was controlled with insulin or other medications in both groups; 5) study included both baseline and follow-up angiography and/or IVUS data; 6) incidence of ISR and/or revascularization rate was reported; and 7) subjects were followed for at least 6 months.

A quality review of each study was performed with the Jadad scoring system (27). All included studies, except the study by Marx et al. (20), were unblinded (although analysis of IVUS and quantified coronary angiography [QCA] was done by technicians blinded to the assigned treatment). Hence, all studies lost 2 points for blinding on the Jadad scale, which led to the overall low score of studies. Studies with at least 2 of 5 points on the Jadad scale were finally selected for this meta-analysis.

Data collection. Data collected from individual studies included: type of study, patient characteristics, year of publication, and type of stent used (Table 1). Demographic variables included age, sex, body mass index, blood pressure, fasting blood sugar, hemoglobin A1c (HbA1c), total cholesterol, LDL, HDL, TG, and smoking status. Use of medications other than pioglitazone was recorded. The frequency of pre-procedural MI, angina and other cardiovascular events was recorded. Variables describing angiographic procedures included were: type of lesions treated, maximum balloon diameter, maximum inflation pressure of balloon, and length of stent. The baseline and follow-up angiographic and IVUS data as well as the incidence of MI, congestive heart failure (CHF), and death within 6 months of the PCI were also collected. Authors of selected studies were contacted to collect unpublished data or verify extracted data.

Outcome. Results of follow-up procedures like IVUS and QCA provided outcome information. Percentage of vessels with angiographic binary stenosis (defined as stenosis more than 50% at the site of stent) and number of patients required to have revascularization (composite outcome of target lesion revascularization and TVR) were considered primary outcomes. Remaining angiographic and IVUS results were secondary outcomes. The QCA results chosen as secondary outcomes included: 1) minimum lumen diameter and percentage stenosis of stented vessels; and 2) change in minimum lumen diameter at the stent site from baseline to follow-up (late loss). The IVUS data were analyzed to determine neointimal growth after BMS implantation. Although individual studies chose different measurements for this analysis, the average neointimal area and neointimal index were used most frequently. Hence, we only included results of average neointimal area (average area of neointima/1-mm section of stent or neointimal volume/length of stent) and neointimal index ([area of neointima/area of vessel wall] $\times$ 100 or [volume of neointima/volume of vessel wall] $\times$ 100) in this meta-analysis. Clinical end points such as incidence of MI, CHF, and death were also considered secondary end points.

Statistical analysis. Comprehensive meta-analysis software (version 2, Biostat, Englewood, New Jersey) was used to perform statistical analysis. Funnel plots were drawn, and their asymmetry was assessed to address possible effect of publication bias. Statistical heterogeneity across studies was evaluated with chi-square test. A p value < 0.1 was considered representative of significant heterogeneity. When a statistically significant heterogeneity was noted, the causes were investigated. Random effects model was used for this meta-analysis. Odds ratio (OR) and 95% confidence interval (CI) were calculated to demonstrate the overall result of the dichotomous data, including ISR and need for revascularization. Weighted difference of means was calculated to

Table 1. Characteristics of Studies Included in the Meta-Analysis

First Author (Study) (Year)	Study Population	Intervention (Pioglitazone Dose and Time of Initiation)	Jadad Score Out of 5	Patients, n	Patients With AMI, n	Age, yrs	Number of Patients With			Baseline/Follow-Up		
							DM	HTN	HLP	HbA1c	Cholesterol	LDL
Takagi et al. (2003)	Type 2 DM	30 mg/6–10 days after PCI	2	PIO:23	15	64.0	23	14	16	6.8/6.5	212/212	134/136
				CONT:21	14	65.0	21	12	16	6.7/6.5	217/208	144/134
Marx et al. (2005)	Non-DM	30 mg/before PCI	4	PIO:26	0	63.4	0	NR	NR*	5.7/5.6	166/178	NR*
				CONT:24	0	60.8	0	NR	NR*	5.6/5.6	182/174	NR*
Nishio et al. (2006)	Type 2 DM	30 mg/2 weeks after PCI	3	PIO:26	18	66.2	26	10	20	7.7/6.0	197/189	122/117
				CONT:28	15	67.5	28	13	17	6.9/6.5	184/185	115/115
Katayama et al. (2007)	Metabolic syndrome	30 mg/after PCI	2	PIO:16	0	60.1	0	12	9†	5.5/5.4	186/185	120/112
				CONT:16	0	61.3	0	14	2	5.4/5.3	194/193	115/115
Kaneda et al. (2009)	Patient with STEMI (DM and non-DM)	15–30 mg/after PCI	2	PIO:48	48	67.0	10	21	20	6.1/5.7	213/197	139/108‡
				CONT:48	48	67.0	10	25	24	5.9/5.7	205/193	116/108
Takagi et al. (POPPS) (2009)	Type 2 DM	30 mg/3 days after PCI	2	PIO:48	24	64.0	48	32	28	7.5/6.8	197/188	119/111
				CONT:49	25	62.4	49	26	29	7.0/6.5	202/184	124/107

All studies have follow-up period of 6 months after bare-metal stent implantation. †Significantly more patients with dyslipidemia in pioglitazone (PIO) group than control (CONT) group. ‡Significantly higher low-density lipoprotein cholesterol (LDL) level at baseline in PIO compared with CONT. Serum cholesterol and LDL values are given in mg/dl. *Number of patients with dyslipidemia and LDL levels was not mentioned, but serum cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were similar in both groups.

AMI = acute myocardial infarction; DM = diabetes mellitus; HbA1c = hemoglobin A1c; HLP = hyperlipidemia; HTN = hypertension; NR = not recorded; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

analyze continuous data obtained from angiographic (minimal lumen diameter, late loss, and percentage stenosis) and IVUS study (average neointimal area and neointimal index). Clinical outcomes, which include frequency of MI, CHF, and death, were analyzed with Fisher exact test.

Results

We identified 36 relevant peer-reviewed articles addressing the effect of TZDs on prevention of ISR and need for revascularization after stent implantation. Fifteen were RCTs. The 2 trials evaluating the effect of troglitazone and 4 evaluating the effect of rosiglitazone were excluded. One study comparing ISR after DES and BMS with pioglitazone was also excluded. Of 2 abstracts that were excluded, 1 did not meet the predetermined inclusion criteria, whereas the other described a subset of an included study. Six RCTs met the predetermined inclusion criteria and were included in this meta-analysis. Table 1 outlines the included studies. The 6 randomized trials included 373 patients, of which 187 were randomly assigned to receive pioglitazone and 186 were randomly assigned to the control arm. In total, 397 lesions were stented—199 in the treatment group, and 198 in the control group.

Baseline characteristics. Randomization within the individual studies led to comparable treatment groups. There were no differences in age, sex, body mass index, blood pressure, fasting blood sugar, HbA1c, total cholesterol, LDL, HDL, TG, and rate of smoking between pioglitazone and control groups. The only exception was the study of Kaneda et al. (17), in which the LDL levels were higher in the pioglitazone group, and the study of Katayama et al. (18), in which pioglitazone group has more patients with dyslipidemia. Angiographic procedures were similarly performed in both groups, and baseline angiographic results including minimal luminal diameter and percentage stenosis were similar. With the exception of the study by Katayama et al. (18), in which beta-blocker was used more frequently in the pioglitazone group, medical therapies were similar in both groups. Overall, pooled analysis of the data with regard to the aforementioned baseline characteristics did not show any significant difference between pioglitazone and control group in this meta-analysis (data not shown).

Outcomes. Results of follow-up angiography are presented in Table 2. By QCA analysis, late loss was less (weighted difference in mean: 0.39 mm, 95% CI: 0.25 to 0.52, $p < 0.01$) and the minimal luminal diameter was greater (weighted difference in mean: 0.27, 95% CI: 0.46 to 0.096, $p < 0.01$) in the pioglitazone-treated groups. Percentage diameter stenosis 6 months after BMS implantation was also significantly lower in the pioglitazone-treated patients (weighted difference in means: 11.97, 95% CI: 7.7 to 16.2, $p < 0.01$). The ISR rate was 18% in pioglitazone groups compared with 40% in placebo-treated patients (OR: 0.26, 95% CI: 0.12 to 0.56, $p < 0.01$, random effects model) (Fig. 1).

Statistical heterogeneity for this analysis was significant ($p < 0.1$) and was addressed by subgroup analysis. Studies were divided into those involving only diabetic patients (with HbA1c >6.5) and the remaining studies (with HbA1c <6.5). Subgroup analysis showed no significant heterogeneity. The ISR for studies including only diabetic patients was 16% in pioglitazone group and 46% in control group ($p < 0.01$), whereas analysis of the remaining studies showed an ISR rate of 19% and 35% in pioglitazone and control group, respectively ($p = 0.1$).

The need for revascularization (composite outcome for target lesion revascularization and TVR) was also lower in pioglitazone-treated patients (13% vs. 31%, OR: 0.3, 95% CI: 0.15 to 0.62, $p < 0.01$, random effects model) (Fig. 2). Statistical heterogeneity was significant for this analysis and

Table 2. Results of Angiographic Data

First Author (Study) (Year)	Total Number PIO/CONT	Minimum Lumen Diameter		Late Loss		Percentage Stenosis	
		PIO	CONT	PIO	CONT	PIO	CONT
Takagi et al. (2003)	23/21	2.0 ± 0.5*	1.5 ± 0.6	NR	NR	32 ± 16*	47 ± 16
Marx et al. (2005)	29/31	2.14 ± 0.46	1.94 ± 0.91	0.88 ± 0.41	1.08 ± 0.85	22.1 ± 12.7*	33.3 ± 23.3
Nishio et al. (2006)	26/28	NR	NR	0.3 ± 0.66*	1.43 ± 1.04	NR	NR
Katayama et al. (2007)	16/16	NR	NR	0.56 ± 0.38*	0.97 ± 0.46	21.5 ± 9.44*	38.6 ± 17.4
Kaneda et al. (2009)	46/45	1.66 ± 0.79	1.53 ± 0.75	0.92 ± 0.87*	1.27 ± 0.73	42 ± 28	48 ± 25
Takagi et al. (POPPS) (2009)	46/40	1.83 ± 0.56	1.57 ± 0.65	0.69 ± 0.52*	1.00 ± 0.49	26.2 ± 16.6*	36.0 ± 23.1
Weighted difference in means (95% CI)							
For DM only studies		0.43 (0.70 to 0.16)*		−0.45 (−0.26 to −0.65)*		−12.1 (−5.8 to −18.4)*	
For other studies		0.16 (0.40 to −0.08)		−0.33 (−0.15 to −0.51)*		−11.85 (−6.1 to −17.6)*	
Overall		0.27 (0.46 to 0.096)*		−0.39 (−0.25 to −0.52)*		−11.97 (−7.7 to −16.2)*	

*$p < 0.05$.
Abbreviations as in Table 1.

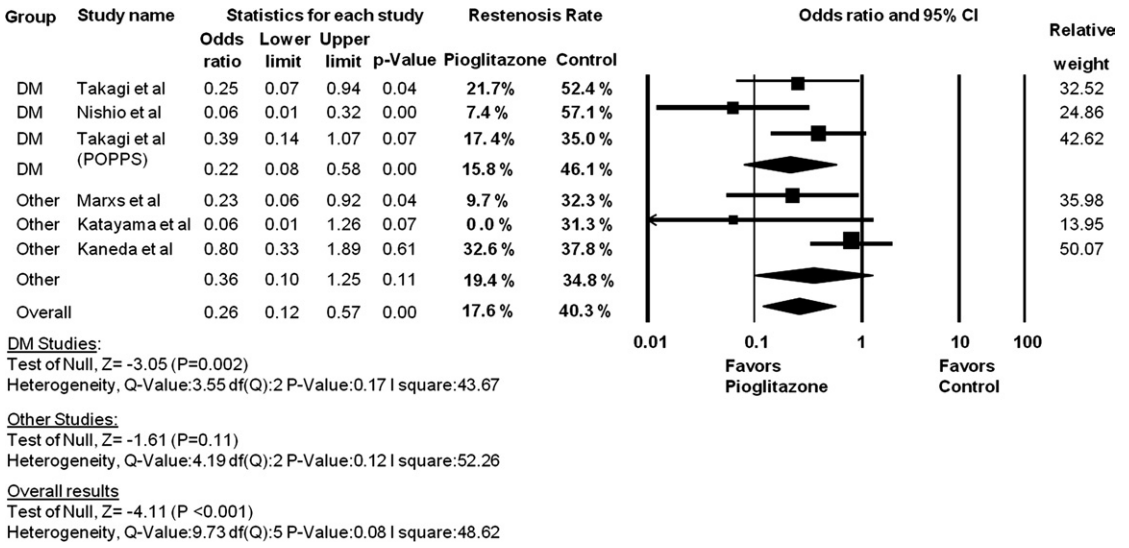

Figure 1. Meta-Analysis for Binary Stenosis

In studies including diabetes mellitus (DM) only, patient rate of binary stenosis was 15.8% in pioglitazone versus 46.1% in control group (p = 0.002). In the remaining studies, binary stenosis for pioglitazone group was 19.4% versus 34.8% in control (p = 0.11). Overall results were in favor of pioglitazone (17.6% vs. 40.3%, p = 0.001). In the studies by Marx et al. (20) and Kaneda et al. (17) restenosis rate was given per lesion. CI = confidence interval; POPPS = Prevention of In-Stent Neointimal Proliferation by Pioglitazone Study.

was again addressed by subgroup analysis. A comparison of revascularization rates for studies including only diabetic patients showed marked reduction in the rate of revascularization with pioglitazone (11% vs. 41%, OR: 0.19, 95% CI: 0.07 to 0.48, p < 0.01) but not in remaining studies (15% vs. 22%, OR: 0.56, 95% CI: 0.19 to 1.68, p = 0.31). Lack of significant reduction of ISR and revascularization rate in nondiabetic studies might be the result of small sample size. Also, the difference between DM-only and non-DM studies seems to be the result of a single study by Kaneda et al.

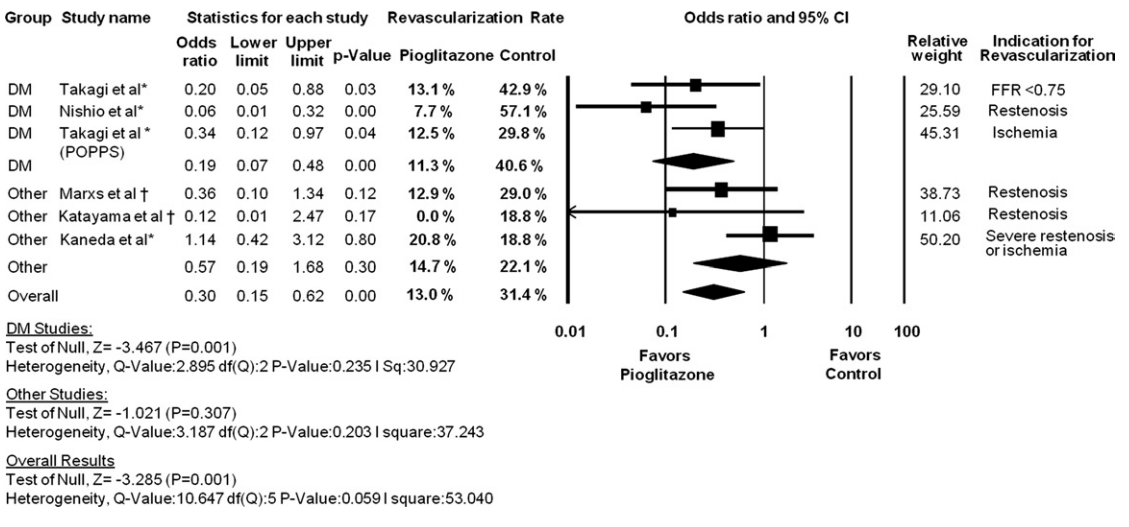

Figure 2. Meta-Analysis for Need for Revascularization

In studies including only diabetic patients, revascularization rate was 11.3% in pioglitazone versus 40.6% in placebo group (p = 0.001). In the remaining studies, benefit of using pioglitazone was not statistically significant (14.7% vs. 22.1%, p = 0.307). Overall, results were in favor of pioglitazone (13.0% vs. 31.4%, p = 0.001). *Revascularization rates reported as target lesion revascularization. †Revascularization rates reported as target vessel revascularization. FFR = fractional flow reserve; other abbreviations as in Figure 1.

Table 3. Results of IVUS Analysis

First Author (Study) (Year)	Number of Patients PIO/CONT	Ave. Neointimal Area		Neointimal Index	
		PIO	CONT	PIO	CONT
Takagi et al. (2003)	23/21	1.7 ± 0.5*	2.8 ± 0.8	28 ± 9*	47 ± 14
Marx et al. (2005)	29/31	2.3 ± 1.1*	3.1 ± 1.6	NR	NR
Nishio et al. (2006)	26/28	NR	NR	NR	NR
Katayama et al. (2007)	16/16	1.28 ± 0.76*	1.9 ± 1.16	13 ± 7*	21 ± 13
Kaneda et al. (2009)	34/32	1.5 ± 0.9*	2.0 ± 0.8	22 ± 13*	28 ± 13
Takagi et al. (POPPS) (2009)	28/28	NR	NR	31.1 ± 14.3*	40.5 ± 12.9
Weighted difference in means (95% CI)					
For DM only studies		−1.11 (−1.49 to −0.71)*		−14.36 (−19.32 to −9.41)*	
For other studies		−0.58 (−0.90 to −0.27)*		−6.85 (−11.59 to −2.12)*	
Over all		−0.78 (−1.03 to −0.54)*		−10.44 (13.87 to −7.01)*	

*$p < 0.05$.

Ave. neointima area = average of area of neointima or neointima volume/length of stent; CI = confidence interval; neointimal Index = (area of neointima/area of vessel wall) × 100 or (volume of neointima/volume of vessel wall) × 100; other abbreviations as in Table 1.

(17). Indeed, analysis after exclusion of a study by Kaneda et al. (17) showed significant reduction of restenosis and revascularization with pioglitazone treatment also for non-DM studies.

The indications for revascularization are shown in Figure 2. Trials that performed revascularization solely on the basis of angiographic restenosis showed similar benefit ($p = 0.003$) of using pioglitazone in prevention of revascularization compared with trials that performed revascularization in the presence of ischemia (clinical symptom, positive stress test, and/or fractional flow reserve <0.75) ($p = 0.004$). In a study by Kaneda et al. (17), revascularization was performed in the presence of either severe restenosis or ischemia, and hence it was excluded from this analysis.

Results of IVUS confirmed the angiographic data (Table 3). Average neointimal formation, measured in 4 studies, demonstrated a significantly lower neointimal area in pioglitazone-treated patients (weighted difference in mean: 0.78, 95% CI: 1.03 to 0.54, $p < 0.01$). Similar results were found for neointimal index (weighted difference in mean: 10.44, 95% CI: 13.87 to 7.02, $p < 0.01$).

Major clinical end points included in this meta-analysis were MI, CHF, and death, results of which are shown in Table 4. There were fewer MIs within 6 months of PCI with pioglitazone, but the difference failed to reach statistical significance, given the low number of events ($p = 0.30$). There was no difference in the incidence of CHF or death. In total, there were 2 deaths reported by Kaneda et al. (17) in the control group. One death was due to noncardiac cause, and 1 was sudden death.

Discussion

The results of this meta-analysis, including RCTs with Jadad score ≥2, indicate a significant clinical benefit in diabetic patients with the addition of pioglitazone to standard medical therapy in reducing the incidence of ISR in BMS at 6 months. Both QCA and IVUS examinations support this conclusion; and the incidence of revascularizia-

Table 4. Results of Clinical Events Including MI, CHF, and Death

First Author (Study) (Year)	Patients (n) PIO/CONT	MI/Unstable Angina		CHF		Death	
		PIO (n)	CONT (n)	PIO (n)	CONT (n)	PIO (n)	CONT (n)
Takagi et al. (2003)	23/21	0	1	0	0	0	0
Marx et al. (2005)	25/23	1*	0	0	0	0	0
Nishio et al. (2006)	26/28	0	1	0	0	0	0
Katayama et al. (2007)	16/16	0	0	0	0	0	0
Kaneda et al. (2009)	48/48	1	3	2	1	0	2†
Takagi et al. (POPPS) (2009)	48/47	1	1	1	2	0	0
Total	184/183	3	6	3	3	0	2

For myocardial infarction (MI), $p = 0.3$ (Fisher exact test). *One patient on intravascular ultrasound examination found to have asymptomatic stent thrombosis. †One patient died due to sudden cardiac death, and one patient died due to pneumonia.

CHF = congestive heart failure; other abbreviations as in Table 1.

tion was also reduced in pioglitazone-treated diabetic patients.

Mechanisms for reduction in ISR by TZDs. Although the precise mechanism of pioglitazone in preventing neointima formation and then ISR remains elusive, it is well-known that cellular proliferation and inflammation are crucial physiological responses to vascular injury secondary to stenting that lead to neointima formation and that pioglitazone affects both. Glucose and lipid levels were not affected, in comparison with the control group, with use of pioglitazone. Thus, suppression of neointimal hyperplasia seems to be the result of direct antiproliferative and anti-inflammatory properties of pioglitazone rather than its metabolic effect.

Pioglitazone has been shown to attenuate the proliferation and migration of vascular smooth muscle cell in vitro (28) and in vivo after balloon angioplasty (29). This antiproliferative effect has been postulated to be a result of decrease in vascular endothelial growth factor expression (29). Furthermore, Little et al. (28) demonstrated that antiproliferative actions of TZDs are enhanced under high glucose conditions in vitro and offer insight into our finding that studies involving diabetic patients demonstrated greater benefit of pioglitazone than the remaining studies. The magnitude of the early inflammatory response also contributes to neointimal growth. In preclinical studies, pioglitazone demonstrated attenuated neointima formation by decreasing expression of inflammatory biomarkers such as matrix metalloproteinase (MMP)-1, MMP-9, monocyte chemoattractant protein-1, and nuclear factor-κB as well as monocyte and macrophage infiltration after vascular injury (22–24). Furthermore, decreased carotid intima-media thickness has been observed clinically with pioglitazone in comparison with glipizide, which was associated with reduced inflammatory cytokines including C-reactive protein, monocyte chemoattractant protein-1, and MMP9 (15). Thus, the anti-inflammatory effects of pioglitazone might have a significant role in containing inflammation and neointimal hyperplasia after stent implantation.

Pioglitazone has been shown to enhance apoptosis, resulting in regression of neointimal hyperplasia (30). An antithrombotic effect of pioglitazone suppresses fibrin formation, the early vascular response leading to neointima formation (31). Moreover, by increasing insulin sensitivity, pioglitazone decreases fasting insulin levels that promote neointimal proliferation after stenting (32). Thus, besides the anti-inflammatory and antiproliferative effects of pioglitazone, other mechanisms might have a significant role in attenuation of neointimal hyperplasia.

Negative cardiovascular outcomes associated with TZDs. Rosiglitazone has been shown, on the basis of a meta-analysis of 42 studies, to be associated with significant increase in the rate of heart attack and cardiovascular mortality (8). Furthermore, a large-scale prospective RCT (RECORD [Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes] trial) led to concern, because the use of rosiglitazone was associated with high risk of CHF (33). In contrast to rosiglitazone, pioglitazone has been found to have positive effects from a cardiovascular standpoint. The PROactive trial (PROspective pioglitAzone Clinical Trial In macroVascular Events) demonstrated significant decrease in all-cause mortality, MI, and stroke with pioglitazone therapy (34). These results have been validated in meta-analysis of 19 studies (11). In that analysis, pioglitazone treatment was associated with low cardiovascular mortality, even though a higher incidence of CHF was noted in the treatment group (11). Similarly, the PERISCOPE trial (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) demonstrated a lower rate of atherosclerosis progression with pioglitazone than glipizide at 18-month IVUS follow-up (35). Pioglitazone might have plaque-stabilizing properties in addition to its antiatherogenic effect. This property might be attributed to a favorable lipid profile (10), a decrease in plaque inflammation (22–24), and an efflux of cholesterol from macrophages (36). Thus, use of pioglitazone after BMS implantation might not only prevent ISR but might also protect against future cardiovascular events.

Study limitations. We performed an extensive search of published reports and included all eligible studies to avoid publication bias. Although a formal test did not show any publication bias, it cannot be ruled out absolutely, due to the small number of trials included in the meta-analysis. Most of the studies predominantly included Asian men as study participants, and it might not be appropriate to generalize these findings. Furthermore, rate of restenosis was measured after 6 months in all studies, and longer follow-up might be required. However, Takagi et al. (16) followed patients for 12 months and demonstrated continuous benefit of using pioglitazone in decreasing the need for revascularization at 12 months. Moreover, all studies included in this meta-analysis started pioglitazone treatment just before or after PCI, and it is not clear whether patients chronically treated with pioglitazone will also benefit from continuation of treatment. Also, all but 1 of the studies included in this meta-analysis used a 30-mg dose of pioglitazone (Kaneda et al. [17] used 15 to 30 mg of pioglitazone). Hence, effect of low dose of pioglitazone on neointima formation and ISR is still not clear. Moreover, we found no difference in the incidence of MI, CHF, or death at 6 months. However, this finding might be limited by lack of long-term follow-up or lack of sufficient power of this meta-analysis to exclude major rare adverse cardiac events.

Conclusions

Pioglitazone is associated with significant reduction in BMS restenosis and in the need for repeat revascularization. Subgroup analysis demonstrated that studies involving only dia-

betic patients (with HbA1c >6.5) showed more benefit from using pioglitazone than the remaining studies (with HbA1c <6.5). A large RCT is warranted to confirm these findings.

Reprint requests and correspondence: Dr. Dhavalkumar Patel, Department of Internal Medicine, Washington Hospital Center, 110 Irving Street Northwest, Washington, DC 20010. E-mail: dhavalkumar.B.Patel@medstar.net.

REFERENCES

1. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.
2. Bavry AA, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. Am J Med 2006;119:1056–61.
3. Lagerqvist B, James SK, Stenestrand U, et al. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. N Engl J Med 2007;356:1009–19.
4. Kornowski R, Mintz GS, Kent KM, et al. Increase restenosis in diabetes mellitus after coronary interventions is due to exaggerated neointimal hyperplasia: a serial intravascular ultrasound study. Circulation 1997;95:1366–79.
5. Kastrati A, Schömig A, Elezi S, et al. Predictive factors of restenosis after coronary stent placement. J Am Coll Cardiol 1997;30:1428–36.
6. Hong SJ, Kim MH, Ahn TH, et al. Multiple predictors of coronary restenosis after drug-eluting stent implantation in patients with diabetes. Heart 2006;92:1119–24.
7. Yki-Järvinen H. Thiazolidinedione. N Engl J Med 2004;351:1106–18.
8. Nissen SE, Wolski K. Effect of rosiglitazone on death and major adverse cardiovascular events in patient with type 2 diabetes mellitus. N Engl J Med 2007;356:2457–71.
9. Hsiao A, Worrall DS, Olefsky JM, Subramaniam S. Variance-modeled posterior inference of microarray data: detecting gene-expression changes in 3T3-L1 adipocytes. Bioinformatics 2004;20:3108–27.
10. Goldberg RB, Kendall DM, Deeg MA, et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care 2005;28:1547–54.
11. Lincoff AM, Wolski K, Nicholls SJ. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 2007;298:1180–8.
12. Rajagopalan R, Xu Y, Abbadessa M, Quartet Study Group. The effect of pioglitazone on glycemic and lipid parameters and adverse events in elderly patients with type 2 diabetes mellitus: a post hoc analysis of four randomized trials. Am J Geriatr Pharmacother 2006;4:123–33.
13. Clar C, Royle P, Waugh N. Adding pioglitazone to insulin containing regimens in type 2 diabetes: systematic review and meta-analysis. PLoS One 2009;4:e6112.
14. Marx N, Duez H, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors and atherogenesis: regulators of gene expression in vascular cells. Circ Res 2004;94:1168–78.
15. Pfützner A, Marx N, Lübben G, et al. Improvement of cardiovascular risk markers by pioglitazone is independent from glycemic control: results from the pioneer study. J Am Coll Cardiol 2005;45:1925–31.
16. Takagi T, Okura H, Kobayashi Y, et al. A prospective, multicenter, randomized trial to assess efficacy of pioglitazone on in-stent neointimal suppression in type 2 diabetes: POPPS (Prevention of In-Stent Neointimal Proliferation by Pioglitazone Study). J Am Coll Cardiol Intv 2009;2:524–31.
17. Kaneda H, Shiono T, Miyashita Y, et al. Efficacy and safety of pioglitazone in patients with ST elevation myocardial infarction treated with primary stent implantation. Heart 2009;95:1079–84.
18. Katayama T, Ueba H, Tsuboi K, et al. Reduction of neointimal hyperplasia after coronary stenting by pioglitazone in nondiabetic patients with metabolic syndrome. Am Heart J 2007;153:e1–7.
19. Nishio K, Sakurai M, Kusuyama T, et al. A randomized comparison of pioglitazone to inhibit restenosis after coronary stenting in patients with type 2 diabetes. Diabetes Care 2006;29:101–6.
20. Marx N, Wöhrle J, Nusser T, et al. Pioglitazone reduces neointima volume after coronary stent implantation: a randomized, placebo-controlled, double-blind trial in nondiabetic patients. Circulation 2005;112:2792–8.
21. Takagi T, Yamamuro A, Tamita K, et al. Pioglitazone reduces neointimal tissue proliferation after coronary stent implantation in patients with type 2 diabetes mellitus: an intravascular ultrasound scanning study. Am Heart J 2003;146:E5.
22. Pakala R, Dilcher C, Baffour R, et al. Peroxisome proliferator-activated receptor y ligand pioglitazone alters neointimal composition in a balloon-denuded and radiated hypercholesterolemic rabbit. J Cardiovasc Pharmacol 2006;48:299–305.
23. Joner M, Farb A, Cheng Q, et al. Pioglitazone inhibits in-stent restenosis in atherosclerotic rabbits by targeting transforming growth factor-B and MCP-1. Arteriosclerosis 2007;27:182–9.
24. Kasai T, Miyauchi K, Yokoyama T, et al. Pioglitazone attenuates neointimal thickening via suppression of early inflammatory response in a porcine coronary after stenting. Atherosclerosis 2008;197:612–9.
25. Rosmarakis ES, Falagas ME. Effect of thiazolidinedione therapy on restenosis after coronary stent implantation: a meta-analysis of randomized controlled trials. Am Heart J 2007;154:144–50.
26. Geng DF, Jin DM, Wu W, Wang Z, Wang JF. Effect of thiazolidinediones on in-stent restenosis in patients after coronary stenting: a meta-analysis of randomized controlled trials. Atherosclerosis 2009; 202:521–8.
27. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
28. Little JP, Osman N, de Dios ST, Cemerlang N, Ballinger M, Nigro J. Anti-proliferative activity of oral anti-hyperglycemic agents on human vascular smooth muscle cells: thiazolidinediones (glitazones) have enhanced activity under high glucose conditions. Cadiovasc Diabetol 2007;6:33.
29. Desouza CV, Gerety M, Hamel FG. Long term effect of a PPAR-gamma agonist, pioglitazone, on neointimal hyperplasia and endothelial regrowth in insulin resistant rats. Vasc Pharmacol 2006;46:188–94.
30. Aizawa Y, Kawabe J, Hasebe N, Takehara N, Kikuchi K. Pioglitazone enhances cytokine-induced apoptosis in vascular smooth muscle cells and reduced intimal hyperplasia. Circulation 2001;104:455–60.
31. Komastu R, Ueda M, Naruko T, Kojima A, Becker AE. Neointimal tissue response at sites of coronary stenting in humans; microscopic, histological and immunohistochemical analyses. Circulation 1998;98:224–33.
32. Li D, Chen K, Sinha N, et al. The effect of PPAR-gamma ligand pioglitazone on platelet aggregation and arterial thrombus formation. Cardiovasc Res 2005;65:907–12.
33. Komajda M, McMurray JJ, Beck-Nielsen H, et al. Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial. Eur Heart J 2010;31:824–31.
34. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study: a randomised controlled trial. Lancet 2005;366:1279–89.
35. Nissen SE, Nicholls SJ, Wolski K, et al. Comparison of pioglitazone vs glimeperide on progression of coronary atherosclerosis in the patient with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA 2008;299:1561–71.
36. Chinetti G, Lestavel S, Bocher V, et al. PPAR-alpha and PPAR-gamma activators induce cholesterol removal from human macrophage foam cells through stimulation of the ABCA1 pathway. Nat Med 2001;7:53–8.

Key Words: neointima ■ pioglitazone ■ restenosis ■ revascularization.