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Original Article

Different Effects of Thiazolidinediones on Cardiovascular Events among Type 2 Diabetic Patients Implanted with Bare Metal Stents: A Nationwide Study

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SUMMARY

Background: This study aimed to evaluate the effect of thiazolidinediones (TZDs) on re-hospitalization rates for revascularization after bare-metal stent (BMS) implantation.
Methods: Data from the National Health Insurance Research Database (NHIRD), a government-operated, population-based database, were analyzed from March, 2000 to December, 2006. Type 2 diabetes subjects treated with BMS implantations who used TZDs (either rosiglitazone or pioglitazone) were compared with subjects not on TZDs (non-TZD group) to evaluate the risk of readmission for coronary revascularization. Endpoints were acute coronary syndrome (ACS) and readmission for revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery) after 3, 6, and 12 months.
Results: In total, 6911 type 2 diabetes patients were hospitalized for BMS implantation (average follow-up, 294.4 ± 108.9 days). Rosiglitazone treatment in patients who received BMSs was associated with a higher risk of re-hospitalization for revascularization at 6 and 12 months (hazard ratio (HR) = 1.33; 95% CI: 1.08–1.64 and HR = 1.20 95% CI: 1.01–1.43). However, there were no significant differences between the pioglitazone and non-TZD groups.
Conclusion: The use of rosiglitazone in type 2 diabetes patients after BMS implantation may increase the risk of re-hospitalization for revascularization. Our study suggests that rosiglitazone should be used cautiously in diabetes patients with BMS implantation.

1. Introduction

Cardiovascular (CV) disease is the leading cause of death in patients with type 2 diabetes mellitus (DM). Diabetes patients are also at increased risk of target vessel revascularization (TVR) after coronary stenting.[1] Coronary stenting is associated with significantly higher in-stent restenosis (ISR) rates in type 2 DM patients (32.8%), compared with non-DM patients (23.8%).[2] The use of medical therapy to prevent readmission for revascularization and acute coronary syndrome (ACS) after coronary stent deployment is a challenging issue in interventional cardiology.

Thiazolidinediones (TZDs), which act as peroxisome proliferator-activated receptor (PPAR) -γ agonists, are insulin-sensitizing agents that improve glucose tolerance and insulin sensitivity in type 2 DM patients.[3] Pioglitazone and rosiglitazone are commercially available TZDs used to treat type 2 diabetes.[4] Compared with pioglitazone, rosiglitazone poses a higher risk of myocardial infarction (MI).[5] TZDs also increase the risk of heart failure.[6] In addition, these drugs appear to have significant direct vascular effects.[7] PPARs are a family of three nuclear hormone receptors, PPARα, -δ, and -γ. PPARs inhibit growth factor-stimulated vascular smooth muscle cell proliferation and migration and reduce the production of pro-inflammatory cytokines, which have an important role in causing vessel narrowing after mechanically-induced coronary injury.[8,9] A meta-analysis of five randomized, controlled trials (RCTs) [which included 235 patients who underwent coronary stent implantation (and received 6-months of pioglitazone or rosiglitazone therapy)] showed that TZD therapy resulted in reduced ISR rates and fewer repeat revascularization procedures in patients who had undergone coronary stent implantation.[10] Another meta-analysis involving 366 patients indicated that TZD therapy can prevent ISR in diabetes patients undergoing coronary stenting.[11]

Pioglitazone is effective in decreasing ISR rates and reducing the incidence of revascularization after bare-metal stent (BMS) implantation as shown in a meta-analysis involving 373 diabetes patients.[12] In contrast, rosiglitazone did not lower ISR rates or lumen loss or decelerate angiographic progression of non-culprit coronary artery lesions in type 2 DM.[13,14] However, the CV effects of TZDs for patients with BMS implantation has been partially evaluated.

This study aimed to examine the effects of pioglitazone, rosiglitazone, and non-TZDs on re-hospitalization for revascularization or ACS in type 2 diabetes Taiwanese patients after BMS implantation.

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2. Materials and methods

2.1. Study design and patient population

Due to the retrospective nature of the study, informed consent was waived. A retrospective cohort study was performed over an approximately 7-year observational period (from March 2000 to December 2006). using the National Health Insurance Research Database (NHIRD). The NHIRD contains comprehensive information such as demographic data, dates of clinical visits, diagnostic codes, details of prescriptions, and expenditure amounts, as described previously.[15] The NHIRD covers 99.7% of the population (nearly 23 million people) in Taiwan. The same dataset of diabetes patients extracted from NHIRD and a similar protocol were utilized in a previous study.[16] A total of 8,776 patients were analyzed using the following criteria: (1) underwent bare-metal stent (BMS) placement between March 1, 2001, and December 31, 2005; (2) had a diagnosis of type 2 DM (ICD-9-CM codes 250.x0 and 250.x2) before the first BMS deployment; and (3) had at least one prescription for a hypoglycemic agent during a 1-year period prior to the first placement. A subject's entry date was defined as the date of discharge after the first BMS implantation. Each subject was followed-up for 1 year after the entry date. Anti-diabetic medication could only be prescribed when patients fulfilled any one of following: 1) a fasting plasma glucose level $\geq$ 126 mg/dL; 2) a plasma glucose $\geq$ 200 mg/dL two hours after a 75 g oral glucose load as in a glucose tolerance test; or 3) symptoms of high blood sugar and casual plasma glucose $\geq$ 200 mg/dL or glycosylated hemoglobin (HbA1c) $\geq$ 6.5% under benefit package of NHI. Patients were excluded if (1) they did not have an ambulatory visit or receive a hypoglycemic agent within 90 days after the entry date; (2) they needed revascularization, experienced ACS, or were lost to enrollment within 7 days after the entry date; (3) they were prescribed rosiglitazone and pioglitazone at the same time; or (4) the admission length of stay exceeded 3 months. A total of 6,911 subjects were included in this analysis. The study subjects were classified into three groups (rosiglitazone, pioglitazone, and non-TZD groups) based on the antidiabetic agents they received within 90 days after the entry date.

2.2. Outcomes and covariates

Outcomes of this study included time to event and a censoring indicator. Time to event represents the number of days from the entry date to the date of the earliest of the following events: (1) the end of the observation or (2) the occurrence of target events, including revascularization (including percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery) or ACS (ICD-9-CM co 410.xx, 411.xx, and 414.9). Repeat revascularization was defined as PCI (ICD-9-CM codes 36.0–36.09) and CABG (ICD-9-CM codes 36.1–36.19). The observational period began at the cohort entry date and continued until the first occurrence of any major adverse cardiac event or up to 1 year of follow-up. If the earliest event was the occurrence of a target event, the record was not censored. We calculated the defined daily dose (DDD) for each individual over the entire observation period (from the cohort entry to the end date) to estimate the dose-response effect.[15,17] Individuals were classified into two equally-sized groups, low or high dose group, based on the mean of DDD values.

2.3. Statistical analysis

We used the Chi-Squared test to examine the association between the three groups (rosiglitazone, pioglitazone, non-TZD groups) and binary/categorical variables, and ANOVA between drug types and continuous variables. A Cox proportional hazards model was used to estimate the association between the exposure to TZDs and the risk of cardiac events. The propensity score adjustment was used to balance the distribution of confounders and adjust the selection bias.

The associations were expressed as hazard ratios (HRs) with 95% confidence intervals. Two-sided p-values less than 0.05 were considered statistically significant. The Cox proportional hazard model was used to investigate dose-response association among subjects continuing the same drug before and after the entry date while adjusting by the DDD level (low vs. high dose) and other covariates. Covariates were included in the Cox proportional hazard model (see Supplementary Appendix I). All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

2.4. Ethical approval

This study protocol was approved by the Institutional Review Board established by Taipei Veterans General Hospital (TVGH) (No 201006015IC). One of the authors, CFH, worked at National Yang Ming University and sent this protocol to TVGH before he was transferred to I Shou University.

3. Results

The study population consisted of 6,911 patients (average age, 65.41 years $\pm$ 10.18 years; male gender, 62.19% of patients). These 6,911 patients who received BMS were divided into three groups, 775 patients in the rosiglitazone group, 322 in the pioglitazone group, and 5,814 in non-TZD group. Patients in the non-TZD group were older than those in either the rosiglitazone or the pioglitazone group. Compared with either TZD group, the non-TZD group had a higher proportion of patients with a history of hypertension, CHF, MI, sulfonylurea and insulin ticlopidine use; a smaller proportion of patients were on a lipid-lowering agent, and clopidogrel, and these had a higher Carlson comorbidity index. Compared with the non-TZD group, the rosiglitazone group had a lower proportion of more than one stent deployment (see Supplementary Appendix II, Table 1).

The crude incidence rate of readmission for revascularization or ACS events was lower in the non-TZD group than in the TZD groups (rosiglitazone and pioglitazone). Across all events (readmission for revascularization or ACS), the non-TZD group had the lowest crude incidence rate of major adverse cardiac events of any group (Table 1).

After multivariate adjustment for revascularization within 3 months, 6 months, and 1 year after the index date, the rosiglitazone group had a significantly higher risk of revascularization within 6 months, and 1 year (HR = 1.33, 95% CI, 1.08–1.64; HR = 1.20, 95% CI, 1.01–1.43, respectively) compared with the non-TZD group. The rosiglitazone group also had a significantly higher risk of cardiac events within 6 months and 1 year (HR = 1.30, 95% CI: 1.07–1.60; HR = 1.19, 95% CI: 1.00–1.41, respectively) than did the non-TZD group. However, there were no significant differences between the pioglitazone and non-TZD groups (Table 2). For the effect of the dose-response parameters on the need for coronary revascularization, there were no significant differences between the two drug groups (rosiglitazone and pioglitazone, respectively) (Table 3). Figures 1–3 show the survival analysis details for readmission for revascularization or ACS and their association with exposure to rosiglitazone, pioglitazone, and no exposure to TZDs after BMS deployment.

Table 1
Patients follow-up, events, and incidence rate in patients with type 2 DM after BMS implantation.

	Rosiglitazone (N = 775)	Pioglitazone (N = 322)	Non-TZD (N = 5,814)
Revascularization or ACS Readmission			
Events (%), n			
3 months	87 (11.23)	29 (9.01)	557 (9.58)
6 months	205 (26.45)	72 (22.36)	1,245 (21.41)
12 months	282 (36.39)	107 (33.23)	1,837 (31.60)
Revascularization			
Events (%), n	265 (34.19)	101 (31.37)	1,720 (29.58)
Incidence rate per person-year	0.45	0.40	0.38
ACS			
Events (%), n	77 (9.94)	25 (7.76)	415 (7.14)
Incidence rate per person-year	0.13	0.10	0.09
Revascularization or ACS			
Events (%), n	282 (36.39)	107 (33.23)	1,837 (31.60)
Incidence rate per person-year	0.48	0.42	0.41

Abbreviation: BMS, bare-metal stent; TZD, thiazolidinedione; ACS, acute coronary syndrome; DM, diabetes mellitus.

Table 2
Effect of exposure to TZD (rosiglitazone, pioglitazone) versus non-TZD after BMS implantation.

	Revascularization		ACS		Revascularization or ACS	
	Adjusted HR* (95% CI)	p-value	Adjusted HR* (95% CI)	p-value	Adjusted HR* (95% CI)	p-value
3 months						
Non-TZD						
Rosiglitazone	1.28 (0.91–1.78)	0.15	1.47 (0.86–2.50)	0.16	1.28 (0.94–1.74)	0.12
Pioglitazone	1.23 (0.77–1.96)	0.39	0.90 (0.36–2.24)	0.82	1.19 (0.77–1.85)	0.44
6 months						
Non-TZD						
Rosiglitazone	1.33 (1.08–1.64)	0.01*	1.44 (0.97–2.14)	0.07	1.30 (1.07–1.60)	0.01*
Pioglitazone	1.13 (0.85–1.52)	0.40	1.31 (0.72–2.35)	0.37	1.08 (0.81–1.44)	0.59
12 months						
Non-TZD						
Rosiglitazone	1.20 (1.01–1.43)	0.04*	1.36 (0.98–1.88)	0.07	1.19 (1.00–1.41)	0.04*
Pioglitazone	1.13 (0.89–1.43)	0.32	1.38 (0.86–2.21)	0.19	1.10 (0.87–1.39)	0.41

* $p < 0.05$. ** $p < 0.01$.
Abbreviation: as Table 1; HR, hazard ratio.

Table 3
Hazard ratios by drug type and defined daily dose (DDD) derived from Cox proportional hazard models.

	Rosiglitazone (n = 775)		Pioglitazone (n = 322)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Two-level DDD (Low vs. High)				
Crude HR	1.00 (0.79–1.26)	0.98	1.39 (0.95–2.03)	0.09
Adjusted HR[#]	0.89 (0.70–1.14)	0.35	1.26 (0.82–1.94)	0.29

* $p < 0.05$. ** $p < 0.01$.
HR, hazard ratio.

4. Discussion

We found that type 2 diabetes patients who received rosiglitazone therapy were more likely to undergo re-hospitalization for revascularization within one year after stenting compared with patients who received pioglitazone therapy or non-TZD therapy after adjusting for other CV risks. In addition, pioglitazone did not increase the risk of adverse cardiac events in our study.

In a meta-analysis of 48 trials, rosiglitazone significantly increased the risk of MI.[18,19] Among patients with type 2 diabetes, use of rosiglitazone modestly but significantly increased the incidence of major cardiac events compared with pioglitazone.[5] Rosiglitazone had a higher risk of MI than did sulfonylurea, metformin, or pioglitazone.[20] A retrospective cohort study from a large health care insurer in the US showed that compared with rosiglitazone, pioglitazone achieved a 22% reduction in the hospitalization rate for MI in patients with type 2 DM.[21] Our results are consistent with these previous studies suggesting a more neutral effect for pioglitazone and potential relative adverse CV outcome for rosiglitazone. A meta-analysis involving 178 patients over seven trials showed that pioglitazone significantly decreased the risk of the need for target vessel revascularization (TVR) following PCI, but rosiglitazone did not.[22] Another meta-analysis of five trials which included 235 patients indicated that those taking either pioglitazone or rosiglitazone therapy were less likely to develop ISR or to undergo TVR.[10] Although previous studies using fewer patient numbers than ours have demonstrated that TZDs lower angiographic restenosis,[12,23–25] other studies have shown the opposite results.[13,14] Our study differed from previous studies as it only focused on diabetes patients treated with BMSs. In addition, several clinical trials designed to test BMSs used a specific and limited population to assess the effects of TZDs after stent implantation. Thus, results from such

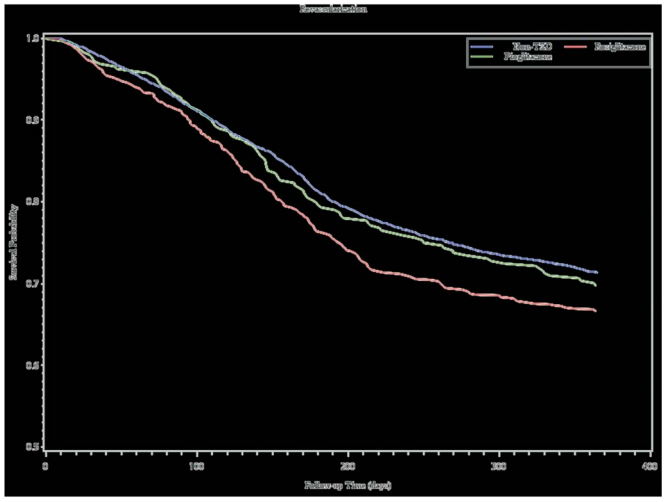

Figure 1. Kaplan–Meier plots of hospitalization for revascularization in patients with rosiglitazone, pioglitazone, and non-TZD use after BMS implantation.

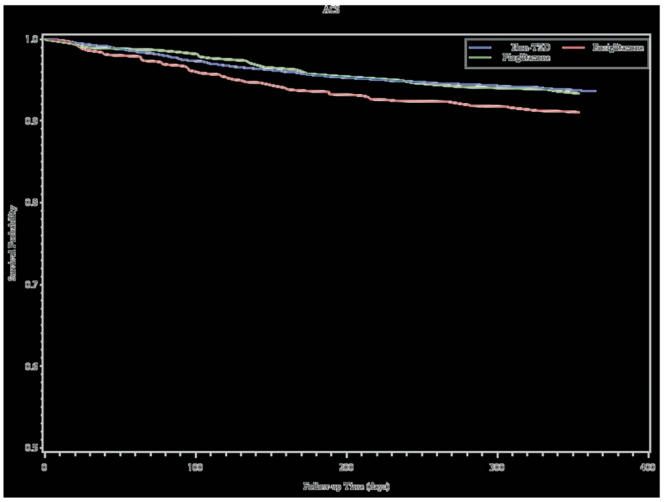

Figure 2. Kaplan–Meier plots of hospitalization for acute coronary syndrome in patients with rosiglitazone, pioglitazone, and non-TZD use after BMS implantation.

studies might not reflect real-world conditions and have limited scope for generalization. When evaluating outcomes, it is important to consider the complex interplay between the stent, the drugs, and comorbid conditions. Our population-based study using the NHIRD had adjusted possible potential confounders of CV events among patients with diabetes and BMS implantation.

4.1. Mechanism

Several mechanisms may explain the results observed in patients undergoing TZD treatment and include both a change in glycemic control and dyslipidemia. Compared with rosiglitazone, pioglitazone has more beneficial effects on low-density lipoprotein, high-density lipoprotein, and triglycerides.[26,27] These findings suggest that rosiglitazone and pioglitazone may be associated with different degrees of risk of having an MI. These differences may be partly explained by their different affinity of TZD for the PPARα subtype of receptors on effect of the blood lipid profile. Therefore, these two TZDs may have different effects on the severity and mortality of CV disease. In addition, an increased risk of heart failure and fluid retention was found in patients treated with rosiglitazone in the RECORD trial.[28] Fluid overload increases left ventricular wall stress which increases myocardial oxygen demand and provokes myocardial ischemia in patients with coronary artery disease. The third and final mechanism involves a direct effect of PPAR-γ activation on the arterial wall. Pioglitazone therapy had a significantly lower rate of coronary atherosclerosis progression than rosiglitazone.[29] In addition, rosiglitazone did not reduce progression of coronary atherosclerosis or percentage atheroma volume compared with glipizide. Rosiglitazone, in contrast to pioglitazone, does not retard progression of coronary atherosclerosis in patients with type 2 DM over a similar treatment period.[30] Compared with rosiglitazone, a significant decrease in inflammation biomarker levels such as C-reactive protein and tumor necrosis factor-α brought about by pioglitazone may contribute to a reduction in risk of CV events.[31]

4.2. Study limitations

This study had several limitations. Firstly, the details regarding lesion characteristics (i.e., location, diameter, and length), vessel size, cause of mortality and smoking status were not available in the

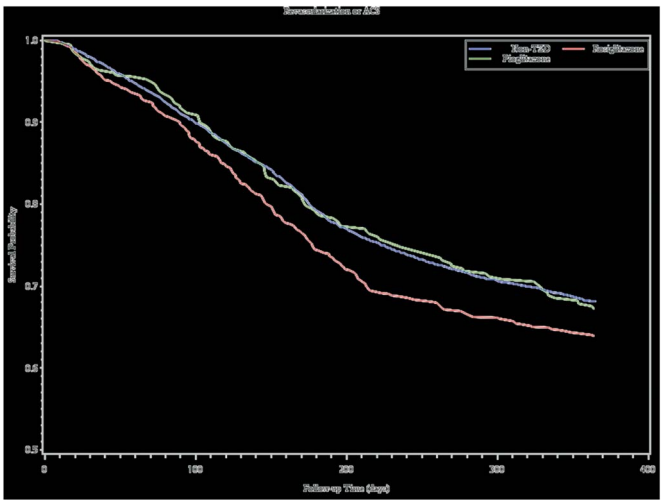

Figure 3. Kaplan–Meier plots of hospitalization for revascularization or acute coronary syndrome in patients with rosiglitazone, pioglitazone, and non-TZD use after BMS implantation.

NHIRD. Although this analysis could not assess the true frequency of events involving the target vessel, it was designed to provide overall CV outcomes with respect to the interactions between the disease and the device or drugs used. Secondly, the claims database did not contain patients' clinical biomarkers, such as HbA1c levels, the reasons why patients were prescribed TZDs, and certain demographic characteristics (such as body weight) which are necessary to control for any selection bias in the use of TZDs. Thirdly, the percentage of insulin use was higher in the rosiglitazone group and may have influenced glycemic control. Our data did not include serial changes in HbA1c level. However, we were able to include some variables related to outcomes in our models which were not reported in other studies, including comorbid conditions and drug use before and after the entry date.

4.3. Clinical implications

Based on this study involving patients with BMS implantation who underwent TZD treatment, our results showed that continued use of rosiglitazone may lead to a greater number of adverse cardiac events compared with either pioglitazone or non-TZD antidiabetic

medication. Rosiglitazone is not currently restricted by the U.S. Food and Drug Administration for patients with type 2 diabetes who cannot control their diabetes on other medications.[32] Our findings can help physicians to balance these CV risks and benefits against those of alternative antidiabetic agents such as dipeptidyl peptidase-4 inhibitorsthat may or may not be safer than TZDs.

In conclusion, rosiglitazone is associated with a significantly increased risk of re-hospitalization for revascularization after BMS implantation. Our study would lead to a recommendation to exercise a degree of caution in the use of rosiglitazone in patients who have had implantation of a BMS.

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Appedix I

1. Covariates entered to Cox-proportional hazard model included age, sex, comorbidities and DM drug use in 1 year before entry date (hypertension, hyperlipidemia, congestive heart failure, myocardial infarction, renal disease, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease liver disease, cancer, percutaneous coronary intervention, and history of coronary artery bypass graft; rosiglitazone, pioglitazone, metformin, sulfonylurea, insulin), drug use after discharge (metformin, sulfonylurea, insulin, β-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, lipid-lowering agents, and aspirin), and the intensity of the use of medical services during the index hospitalization, including the number of days spent in the hospital and the number of stents received.

Appedix II

Table 1
Characteristics of diabetes mellitus patients who had received BMS implantation, stratified by medication taken within 3 months after BMS implantation.

	Rosiglitazone		Pioglitazone		Non-TZD		p-value
	n	%	n	%	n	%	
	775	11.21	322	4.66	5,814	84.13	
Age, mean ± SD, year	64.18 ± 9.72		64.54 ± 9.52		65.62 ± 10.26		< 0.001**
Sex							
Female	302	38.97	130	40.37	2,181	37.51	0.46
Male	473	61.03	192	59.63	3,633	62.49	
Medical history in prior 1 year							
Hypertension	584	75.35	222	68.94	4,427	76.14	0.01*
Hyperlipidemia	112	14.45	37	11.49	720	12.38	0.22
Congestive heart failure	178	22.97	60	18.63	1,437	24.72	0.03*
Myocardial infarction	240	30.97	103	31.99	2,185	37.58	< 0.001**
PCI	755	97.42	314	97.52	5,675	97.61	0.95
CABG	8	1.03	1	0.31	79	1.36	0.22
DM drug use in prior 1 year							
Rosiglitazone	556	71.74	59	18.32	466	8.02	< 0.001**
Pioglitazone	22	2.84	170	52.80	160	2.75	< 0.001**
Metformin	610	78.71	247	76.71	4,238	72.89	< 0.01**
Sulfonylurea	667	86.06	287	89.13	5,198	89.40	0.02*
Insulin	190	24.52	63	19.57	947	16.29	< 0.001**
Characteristics of index hospitalization							
Inpatient for ≤ 7 days	144	18.58	74	22.98	1,626	27.97	< 0.001**
Use TZDs	421	54.32	170	52.80	165	2.84	< 0.001**
Stent no. > 1	140	18.06	77	23.91	1,329	22.86	< 0.01**
Drug use during the follow-up period							
Metformin	551	71.10	208	64.60	3,931	67.61	0.07
Sulfonylurea	618	79.74	269	83.54	4,975	85.57	< 0.001**
Insulin	171	22.06	69	21.43	807	13.88	< 0.001**
β-blocker	544	70.19	229	71.12	4,049	69.64	0.82
Calcium channel blocker	420	54.19	160	49.69	3,209	55.19	0.14
ACEI/ARB	578	74.58	242	75.16	4,357	74.94	0.97
Lipid lowering agents	565	72.90	221	68.63	3,402	58.51	< 0.001**
Antiplatelet agents							
Aspirin	672	86.71	274	85.09	5,003	86.05	0.77
Ticlopidine	90	11.61	17	5.28	861	14.81	< 0.001**
Clopidogrel	674	86.97	298	92.55	4,780	82.22	< 0.001**
Charlson comorbidity index, mean (SD)	1.18 ± 1.29		1.07 ± 1.23		1.25 ± 1.39		0.03*

* $p < 0.05$. ** $p < 0.01$.

Abbreviation: BMS, bare-metal stent; TZD, thiazolidinedione; ACS, acute coronary syndrome; PCI: percutaneous coronary intervention; CABG, coronary artery bypass graft; DM, diabetes mellitus; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker.