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Relation of Severe Coronary Artery Narrowing to Insulin or Thiazolidinedione Use in Patients With Type 2 Diabetes Mellitus (from the Bypass Angioplasty Revascularization Investigation 2 Diabetes Study)

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Abstract

Patients with diabetes continue to die of coronary artery disease (CAD) at rates 2 to 4 times higher than patients without diabetes, despite advances in treatment of cardiovascular disease. The role of glycemic control therapies, independent of their glucose-lowering effects, on cardiovascular disease is a recurring question. We examined the association of glycemic control therapies with extent of CAD as measured by coronary angiogram obtained at baseline in 1,803 subjects in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial who had type 2 diabetes mellitus, documented moderate to severe CAD, and no previous cardiac revascularization procedures. The association between glycemic control therapy use recorded at baseline and percent coronary artery stenosis and myocardial jeopardy index was analyzed by multiple regression models. Insulin use at study entry was associated with 23% fewer highly stenotic lesions (≥70%) ($p < 0.001$) and a significantly lower myocardial jeopardy index compared with subjects not on insulin, despite a worse cardiac risk factor profile, more unstable angina, and increased inflammatory markers in insulin users. Subjects taking thiazolidinediones (TZDs) for ≥6 months had 17% fewer highly stenotic lesions ($p = 0.02$) and significantly lower C-reactive protein, fibrinogen, and plasminogen activator inhibitor-1 levels compared with those not taking TZDs. In conclusion, this cross-sectional study of patients with type 2 diabetes mellitus and CAD showed that treatment with insulin or TZDs was associated with fewer highly stenotic lesions, independent of disease duration, glycemic control, and other risk factors.

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The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study was undertaken[1] in part to address whether the type of glucose-lowering treatment used could affect cardiovascular disease. BARI 2D is a multicenter, randomized clinical trial of management of adults with type 2 diabetes mellitus (T2DM) and stable coronary artery disease (CAD). One of the hypotheses of BARI 2D is that an "insulin-sensitizing" glycemic treatment strategy compared with an "insulin-providing" strategy will have a favorable effect on mortality and cardiovascular end points.[1] The BARI 2D trial is also testing whether immediate revascularization and intensive medical therapy versus intensive medical therapy of cardiovascular risk factors alone with deferred revascularization, as needed, would affect the same end points. Given the paucity of data on the association of glycemic control therapies and CAD as determined by coronary angiography, we analyzed baseline CAD characteristics of >1,800 BARI 2D subjects in relation to their baseline glucose-lowering therapies.

Methods

The BARI 2D trial design and patient population have been described elsewhere.[2] A total of 2,368 patients with T2DM and CAD documented by angiography were recruited from 49 clinical sites throughout North America, South America, and Europe. In this trial, T2DM was defined by any of these criteria, namely a confirmed (≥2 readings) fasting plasma glucose level >125 mg/dl, random plasma glucose level ≥200 mg/dl, plasma glucose level ≥200 mg/dl 2 hours after ingestion of glucose 75 g, current treatment with oral hypoglycemic agents, or current treatment with insulin and no history of diabetic ketoacidosis. Patients were put on a protocol of intensive medical therapy for CAD and randomized to prompt versus deferred revascularization and to insulin-sensitizing versus insulin-providing treatments for diabetes. All participants signed informed consents. The study and consent forms were approved by institutional review boards at all participating institutions. Data collection for patient history, quality-of-life measurements, physical examination, and laboratory tests have been described previously.[1,2]

CAD variables analyzed included lesions with ≥70% stenosis, lesions with ≥50% to 69% stenosis, and myocardial jeopardy index. Eligibility criteria for BARI 2D required ≥1 coronary artery to have ≥50% stenosis that was physiologically significant and amenable to revascularization. Patients were excluded from the study if angiographic findings indicated a need for immediate revascularization. Angiograms were scored in the BARI 2D core angiographic laboratory and readers were blinded to glycemic control strategies. Lesion severity was first assessed visually for all lesions. Lesions with stenoses ≥50% according to this visual assessment were further measured with calipers to obtain a more precise estimate of percent diameter stenosis. This number was calculated as the ratio of minimum diameter divided by reference diameter, which is an average of proximal and distal diameters of the normal-appearing artery adjacent to the lesion. The myocardial jeopardy index is the percent distal myocardium that is jeopardized by lesions ≥50% in any of the 3 main coronary arteries or their branches and is correlated with 1-year mortality and myocardial infarct size.[3,4]

At baseline, the most current diabetes management regimen was recorded.[2] Insulin use was recorded as none, <3 months, and ≥3 months. Other glycemic medications were grouped as none, <6-month use, and ≥6-month use from data collected as a continuous measurement in units of months. Glycemic medications were categorized into 5 classes as described in Figure 1.

Microvascular disease was defined as a random urine microalbumin/creatinine ratio ≥30 μg/mg[5]; history of photocoagulation for diabetic retinopathy, macular edema, or blindness; and/or peripheral neuropathy with a clinical score >2 on the Michigan Neuropathy Screening Instrument.[6]

Chi-square tests and *t* tests were used to assess statistical significance of observed baseline differences between diabetes therapy groups, where the groups were defined according to use of insulin (≥3 months vs no use) and use of thiazolidinedione (TZD; ≥6 months vs no use). The association between these diabetes therapy groups and CAD indexes was assessed with various statistical models, namely Poisson regression for number of lesions; logistic regressions for presence of lesions with ≥70% and ≥99% stenosis, absence of angina history, and presence of unstable angina; and linear regression for the myocardial jeopardy index, C-reactive protein (log scale), fibrinogen, and plasminogen activator inhibitor-1 (log scale). To control for the potential confounding effect of age, gender, current and previous tobacco use, glycosylate hemoglobin, diabetes duration, hypertension, lipids, and microalbuminuria, we included these variables in each model. To avoid loss of data, missing values were replaced with mean values for each variable with <0.5% missing data.

Results

Association of glycemic control medication with severity of CAD

Patients with no previous revascularization formed the basis of this analysis given the difficulty in determining the severity and significance of vascular lesions in subjects who had previously undergone a revascularization procedure. In this cohort of 1,803 patients with moderately severe but stable CAD, the mean number of highly stenotic lesions (≥70%) per subject was 1.09, and the mean number of lesions with intermediate stenosis (50% to 69%) was 1.50. When this cohort was divided into 5 nonoverlapping medication subgroups, insulin use was associated with fewer highly stenotic lesions but more lesions of intermediate stenosis (Figure 1).

Clinical characteristics of patients using insulin

To pursue the unexpected finding that patients using insulin had fewer highly stenotic lesions, we compared patients who reported insulin use of ≥3-month duration with those not taking insulin at entry (Table 1). Several significant differences were found including that insulin users were more likely to be women and had a longer duration of diabetes, worse glycemic control, and more microvascular complications.

Coronary angiographic analysis

Analysis of coronary angiographic data after adjustment for several variables that could have contributed to observed differences in coronary stenosis associated with insulin use showed that subjects on insulin had 23% fewer highly stenotic lesions compared with subjects not on insulin (Table 2). Another measurement of severity of CAD is maximum stenosis in any vessel. Entry criteria for the BARI 2D study required that ≥1 vessel had ≥50% stenosis, as determined by site investigators. Patients taking insulin were less likely to have highly stenotic lesions (≥70%) and total occlusions (≥99%) as their maximally occluded vessel. Subjects taking insulin also had significantly less myocardium at risk than did those not taking insulin, as measured by the myocardial jeopardy index.

Associations of insulin use with unstable angina, inflammatory markers, and microvascular disease

We analyzed associations of baseline insulin use with several factors that could influence severity or presentation of CAD (Table 2). Despite having fewer highly stenotic lesions, insulin users were more likely to present with unstable angina and had a nonsignificant trend toward fewer patients with no history of angina. Treatment with insulin was also associated with increased markers of inflammation and thrombotic tendency. Insulin users without evidence

of microvascular disease were less likely to have highly stenotic lesions compared with insulin users with microvascular disease.

Associations of TZDs and other glycemic medications with CAD

Neither metformin nor sulfonylurea use at baseline was associated with differences in degree of coronary artery stenosis or myocardial jeopardy index compared with groups not taking those medications. However, subjects reporting TZD use for ≥6 months had 17% fewer highly stenotic lesions compared with those not taking TZDs (Table 3). Analysis of maximum stenosis in any vessel showed that TZD users were less likely to have vessels with total or near-total occlusion. Myocardial jeopardy index was significantly lower for TZD users compared with non-TZD users.

Subjects taking TZDs were 60% more likely to report no history of angina (Table 3) compared with subjects not taking TZDs. In contrast to subjects on insulin at baseline—in whom inflammatory markers were increased—those taking TZDs had significantly lower levels of C-reactive protein, fibrinogen, and plasminogen activator inhibitor-1 activity compared with those not taking TZDs. The 196 subjects on TZDs for ≥6 months had a longer duration of diabetes (11.8 vs 10.0 years, $p = 0.003$), higher body mass index (34.3 vs 31.1 kg/m^2, $p<0.001$), and lower diastolic blood pressure (71 vs 76 mm Hg, $p <0.001$) than the 1,468 subjects not taking TZDs. Eighty-eight subjects reported pioglitazone use and 107 subjects were taking rosiglitazone. No differences in measurements of CAD, angina history, or inflammatory markers were seen in subjects taking pioglitazone versus rosiglitazone.

Recent and combined use of insulin and TZD

About 30% of TZD users were also using insulin and 13% of insulin users had reported TZD use for ≥6 months. However, the association between TZD use and decreased number of highly stenotic lesions remained significant when adjusted for concomitant use of other diabetes drugs, including insulin (data not shown). The combination of insulin and TZD use was associated with fewer highly stenotic lesions than use of either drug alone (Figure 2). We also analyzed the number of highly stenotic lesions in subjects who had recently started insulin (<3 months of treatment) or a TZD (<6 months of treatment). Adjusted odds ratios of these groups were similar to those of groups that had been on those medications for longer periods (data not shown).

Discussion

In this large cohort of patients with T2DM and moderate to severe CAD, those treated with insulin had fewer highly stenotic coronary narrowings and lower myocardial jeopardy indexes compared with those not treated with insulin. Also, subjects treated with TZDs had fewer highly stenotic narrowings compared with those not taking TZDs. These differences remained significant after adjustment for traditional cardiovascular risk factors such as age, gender, lipids, and hypertension. Although insulin use and TZD use were associated with remarkably different levels of inflammatory markers, each drug was independently associated with less severe narrowing of coronary arteries as measured by coronary angiography.

Baseline data of the BARI 2D study permitted an analysis of the association of coronary angiographic measurements with glycemic control and other risk factors in >1,800 diabetic subjects. Although several large population studies have reported differences in cardiovascular mortality associated with oral antidiabetic agents such as metformin and sulfonylureas, [7–9] few studies have assessed the relation of angiographic data to glycemic control therapies. Ravipati et al[10] reported on the number of vessels with diameter stenosis >50% in >300 diabetic patients who presented with de novo chest pain. Patients treated with insulin had the highest

prevalence of 3- and 4-vessel CAD and patients on TZDs had the highest prevalence of 0-vessel disease.[10] In contrast to our data, they did not report degree of stenosis in diseased arteries or adjust for other factors. Another previous study of a smaller cohort of patients with diabetes who were examined with angiography and intravascular ultrasound found that, despite having a longer duration of diabetes, patients treated with insulin had less stenotic plaque and smaller areas of stenosis compared with those not treated with insulin.[11]

Given that coronary angiography is the gold standard for assessing coronary artery stenosis, the finding that insulin use compared with no insulin use at baseline was associated with fewer highly stenotic lesions was unexpected because insulin users had a less desirable cardiac risk factor profile—worse glycemic control, longer duration of diabetes, lower rates of exercise, more obesity, and significantly higher levels of markers of inflammation. However, coronary angiography can assess only the lumen of coronary arteries and therefore its efficacy in outlining diffuse coronary atherosclerosis or presence of vulnerable lesions remains questionable. The high-risk, rupture-prone plaques are not necessarily the severely stenotic plaques, but rather, numerous plaques in a single coronary tree may be more vulnerable to rupture, with inflammation a critical determinant of their stability.[12,13] The specific pathobiology of various plaques in concert with inflammatory findings in our cohorts may explain why insulin users, despite having fewer highly stenotic lesions, were more likely to present with unstable angina pectoris.

Another difficulty of coronary angiography for patients with diabetes is the identified problem of angiographic measurements of reference segments.[14, 15] Adaptive remodeling, i.e., dilatation of an artery proximal to a fixed stenosis, has been described as a compensatory mechanism during atherogenesis and has been found to be decreased in diabetic subjects using insulin.[11] Decreased adaptive remodeling of the proximal reference segment can lead to underestimation of severity of an arterial stenosis detected angiographically.[16] Although available angiographic data did not allow direct verification of this hypothesis, a similar process may have occurred in the BARI 2D cohort. However, the significant decrease in total (≥99%) occlusions with insulin use suggests that decreases in adaptive remodeling or limitations of coronary angiography do not fully explain our findings.

The referral and selection of patients into the BARI 2D trial could also influence the finding of fewer highly stenotic lesions in the group using insulin. Inclusion criteria for the BARI 2D trial included clinically significant CAD amenable to revascularization or intensive medical therapy in patients with diabetes who had undergone coronary angiography. Referral bias may have played a role if treatment with insulin was viewed as a high-risk condition by site investigators, so that only patients with fewer highly stenotic lesions were considered for randomization into this clinical trial. In addition, some unidentified factor associated with insulin use and less severe artery narrowing may have caused selection bias. Survival bias may also have influenced results, favoring enrollment of participants with longstanding, insulin-treated diabetes who were relatively resistant to the severe CAD that might in others have led to an earlier death. In this regard, our finding that insulin users without evidence of microvascular disease had a very low prevalence of highly stenotic lesions (Table 2) would support the idea that they may represent a subset of patients with relative resistance to the long-term detrimental effects of hyperglycemia.

Treatment with TZDs at baseline was also associated with fewer highly stenotic narrowings compared with the group not taking TZDs. The subgroup taking insulin and TZDs had fewer highly stenotic lesions than patients taking either treatment alone, suggesting different mechanisms or factors relating to CAD that might be affected by these 2 therapeutic classes. Clinical characteristics of subjects using TZDs were similar to the larger BARI 2D population, but we have no information regarding reasons for the choice of certain oral hypoglycemic agent

(s) for individual patients. Of note, patients taking TZDs may have been perceived by their physicians to be at low risk for heart failure. Short-term users of TZDs (<6 months) had a similar mean number of highly stenotic lesions as did long-term users (≥6 months), suggesting that the finding of fewer highly stenotic lesions in the TZD group may not be due to a direct action of the drug (data not shown).

Inflammatory markers were significantly lower in subjects taking TZDs, consistent with previous animal and human studies[17–20] and strikingly different from the higher levels in the insulin-using group. TZDs have several positive effects on the vasculature including decreasing vascular inflammation,[21] oxidative stress,[22] and blood pressure,[23] improving endothelial dysfunction,[21] and ameliorating dyslipidemia. [24] TZDs, independent of their glycemic effects, were recently reported to slow the progression of carotid intima—media thickness[25,26] and progression of coronary atherosclerosis as assessed by coronary intravascular ultrasonography. [27] However, a recent meta-analysis has suggested that rosiglitazone may convey a greater risk of myocardial infarction.[28] The enrollment phase of BARI 2D was in 2001 to 2005, before reports associating rosiglitazone with increased risk of myocardial infarction. In BARI 2D, similar coronary angiographic results were found in subjects taking rosiglitazone versus pioglitazone at study entry. However, as discussed earlier, coronary angiography can assess only the lumen of a coronary artery and not future risk of occlusion. Results indicate that long-term outcomes in BARI 2D and other longitudinal randomized clinical trials will require consideration in the context of the potential impact of differences at baseline in randomized groups subjected to different forms of therapy.

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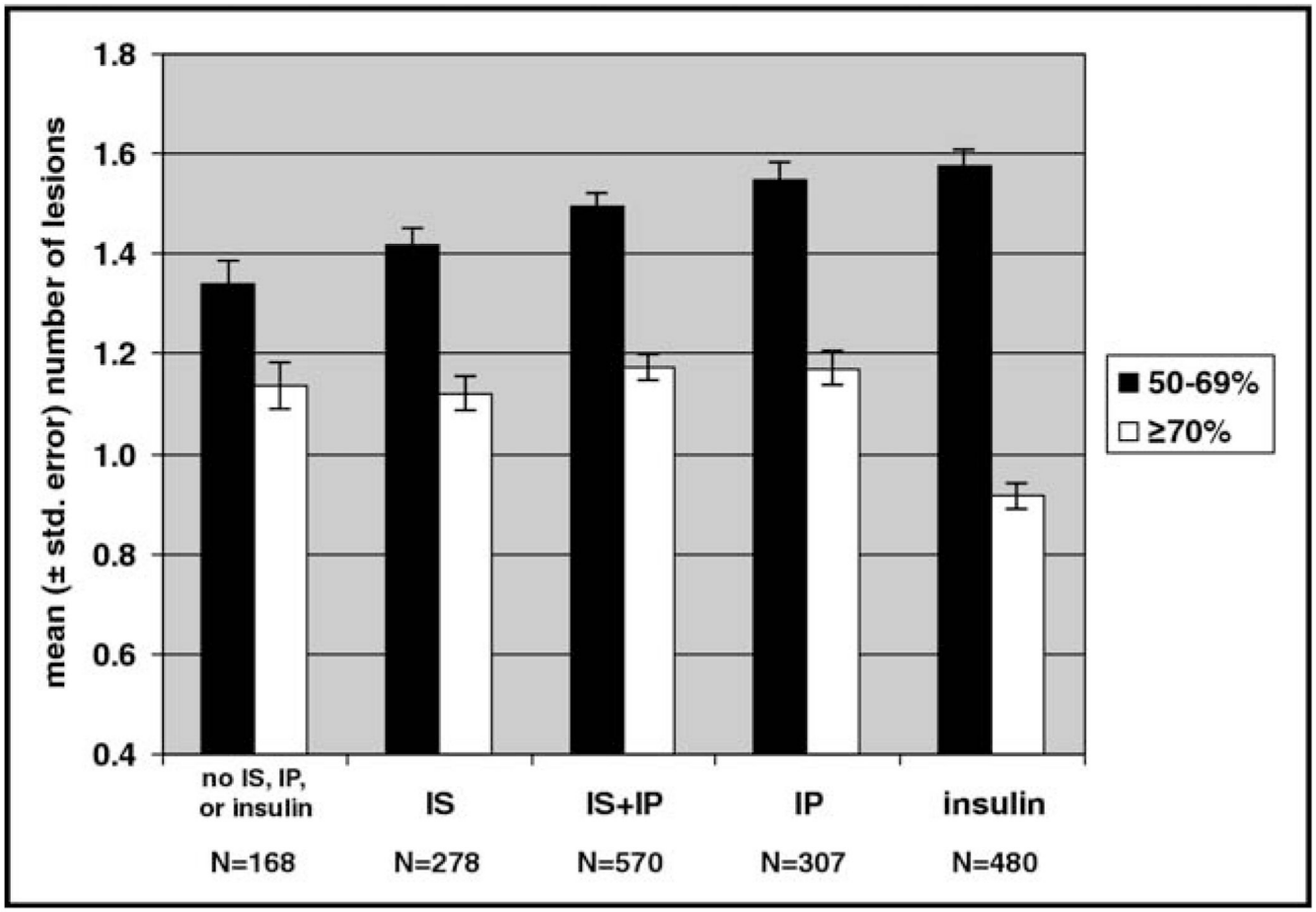

Figure 1.

Glycemic control therapies and 50% to 69% *(black bars)* and ≥70% *(white bars)* stenosis of coronary arteries. The 1,803 patients in the BARI 2D study without previous revascularization were divided into 5 nonoverlapping groups based on their history of glycemic control therapies at baseline—no diabetes medication; insulin sensitizers (ISs), metformin and/or a TZD only; insulin providers (IPs), a sulfonylurea and/or repaglinide and/or nateglinide only; combination of IS and IP medications (IS + IP); and insulin alone or together with any other medication. Degree of stenosis in coronary arteries was determined on entry coronary angiogram at the BARI 2D core angiography laboratory. Data shown are means ± SEMs. For intermediate lesions, the insulin group was significantly different from the no-diabetes medication group ($p = 0.03$). Overall difference among the 5 nonoverlapping medication groups for highly stenotic lesions was significant ($p < 0.001$).

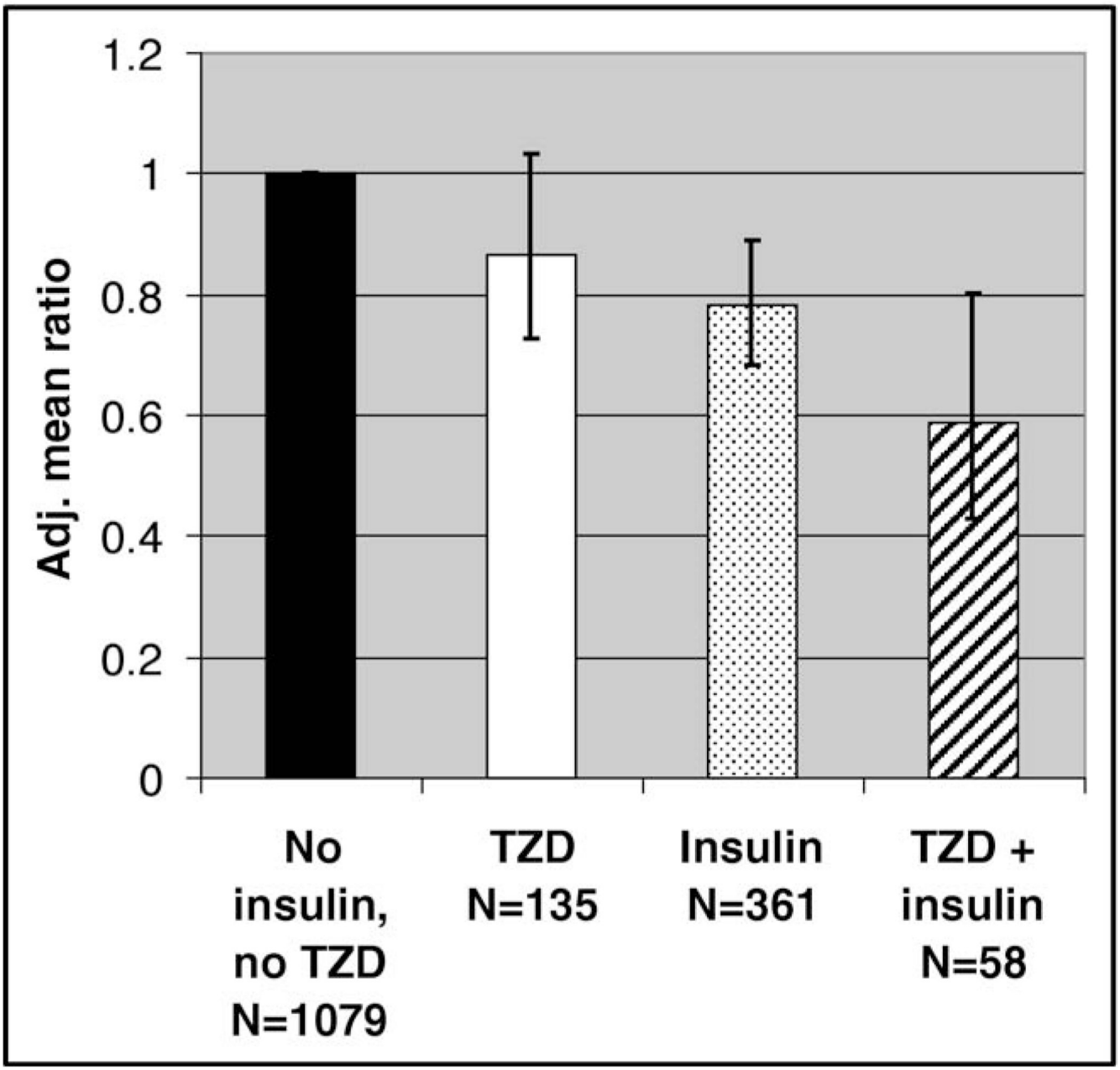

Figure 2.

Joint association between TZD and insulin use and adjusted (Adj.) mean ratios for highly stenotic lesions. Adjusted mean ratios for number of highly stenotic (>70%) lesions were calculated for patients based on insulin and TZD use at baseline. The TZD group included patients who reported TZD use ≥6 months and any other diabetes medications, except insulin. The insulin group included patients who reported insulin use ≥3 months and other diabetes medications, except TZDs. The TZD + insulin group included patients with reported insulin use ≥3 months and TZD use ≥6 months and any other diabetes medications. Data were adjusted for age, gender, tobacco use (current, previous), glycosylated hemoglobin, diabetes duration, hypertension (blood pressure >130/85 mm Hg, >1 antihypertension drug), lipids, and microalbuminuria; 95% confidence intervals *(error bars)* are displayed. The p values for the

insulin and TZD + insulin use groups were <0.001 compared with the no-insulin, no-TZD group.

Table 1

Clinical characteristics at baseline of BARI 2D patients based on insulin use

Variable	No Insulin Use (n = 1,312)	Insulin Use ≥3 mos* (n = 444)	p Value
Mean age (yrs)	62.4	61.9	
Women	26.3%	39.8%	<0.001
Race			
White, non-Hispanic	67.2%	58.1%	<0.001
Black, non-Hispanic	14.3%	23.9%	
Hispanic	13.4%	12.8%	
Asian, non-Hispanic	4.6%	4.5%	
Other	0.4%	0.7%	
Mean diabetes duration (yrs)	8.1	16.5	<0.001
Mean glycosylated hemoglobin†	7.4%	8.3%	<0.001
Diabetes drug use			
TZD	17.8%	18.7%	
TZD use ≥6 mos	10.3%	13.1%	
Metformin	58.7%	42.6%	<0.001
Sulfonylurea	65.5%	21.8%	<0.001
Body mass index (kg/m^2)	31.1	32.9	<0.001
Mean systolic blood pressure (mm Hg)	132	133	
Mean diastolic blood pressure (mm Hg)	75	74	0.005
Mean total cholesterol (mg/dl)†	169	170	
Mean HDL cholesterol (mg/dl)	38	40	0.001
Mean triglycerides (mg/dl)	178	172	
Mean LDL cholesterol (mg/dl)‡	96.7	97.9	
Cigarette smoking			
Never	33.2%	40.5%	0.02
Former	54.0%	47.3%	
Current	12.8%	12.2%	
Mean serum creatinine (mg/dl)	1.03	1.07	0.005
Albumin/creatinine ratio >30 μg/mg	28.5%	45.2%	<0.001
Laser therapy for diabetic retinopathy	1.5%	7.9%	<0.001
Neuropathy: clinical Michigan Neuropathy Screening Instrument >2	47.3%	59.0%	<0.001
Microvascular disease§	59.8%	75.0%	<0.001
Exercise regularly	26.9%	20.4%	0.006
Own health rating (good-excellent)	60.7%	40.5%	<0.001

[*] The 34 patients who reported insulin use of <3 months and the 13 patients (2 insulin users and 11 noninsulin users) without complete data for microvascular disease are not included.

[†] Lipid and glycosylated hemoglobin values were determined by the BARI 2D biochemistry core laboratory. If not available (<5% of cases), then values from local laboratories are used.

[‡] LDL measurements were calculated only when triglycerides were ≤400 mg/dl. For the 2 groups, 95.3% of patients had triglyceride values ≤400 mg/dl.

[§] Patients with any of these 3 conditions, namely urine microalbumin/creatinine ratio >30 μg/mg, history of laser therapy for diabetic retinopathy/ macular edema, or a clinical Michigan Neuropathy Screening Instrument score >2.

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 2

Association between insulin use, indexes of coronary artery disease and inflammation

Indexes of CAD	No Insulin Use (n = 1,312)	Insulin Use ≥3 mos (n = 444)	Adjusted Comparison*		p Value
			Comparison Statistic	Estimate	
Mean no. of lesions with stenosis ≥70%	1.16	0.92	Mean ratio	0.768	<0.001
Mean/no. of patients without unstable angina	1.16/1,218	0.96/393	Mean ratio	0.789	<0.001
Mean/no. patients with unstable angina	1.10/94	0.63/51	Mean ratio	0.588	0.03
Mean/no. of patients without MiVD†	1.14/527	0.61/111	Mean ratio	0.536	<0.001
Mean/no. of patients with MiVD†	1.17/785	1.02/333	Mean ratio	0.856	0.03
Mean no. of lesions with stenosis 50–69%	1.47	1.57	Mean ratio	1.006	0.91
Proportion of patients with maximum stenosis ≥70%	0.66	0.53	Odds ratio	0.569	<0.001
Proportion of patients with maximum stenosis ≥99%	0.41	0.31	Odds ratio	0.659	0.002
Mean myocardial jeopardy index	47.2	44.2	Mean difference	−4.05	0.007
Proportion of patients with no angina history	0.12	0.09	Odds ratio	0.739	0.15
Proportion of patients with unstable angina	0.07	0.11	Odds ratio	1.719	0.01
Mean C-reactive protein (μg/ml) (log scale)‡	0.817	1.151	Mean difference	0.278	<0.001
Mean fibrinogen (mg/dl)§	357.4	390.0	Mean difference	24.55	<0.001
Mean plasminogen activator inhibitor-1 (AU/ml) (log scale)//	2.76	2.65	Mean difference	−0.024	0.55

Logarithmic transformation of inflammatory marker data was used to account for their skewed distribution.

*Adjusted for age, gender, tobacco use (current, previous), glycosylated hemoglobin, diabetes duration, hypertension (blood pressure ≫ 130/85 mm Hg, > 1 antihypertension drug), lipids, and microalbuminuria.

†Analysis repeated in subset of patients without and with MiVD as defined in Table 1.

‡C-reactive protein measurements were available for 1,285 subjects in the no-insulin group and 435 subjects with ≥3 months of insulin use.

§Mean fibrinogen was available for 1,285 subjects in the no-insulin group and 433 subjects with ≥3 months of insulin use.

//Plasminogen activator inhibitor-1 was available for 1,212 subjects in the no-insulin group and 426 subjects with ≥3 months of insulin use.

AU = arbitrary unit; MiVD = microvascular disease.

Table 3

Association between thiazolidinedione use and indexes of coronary artery disease

Indexes of CAD	No TZD Use (n = 1,468)	TZD Use ≥6 mos* (n = 196)	Adjusted Comparison†		p Value
			Comparison Statistic	Estimate	
Mean no. of lesions with stenosis ≥70%	1.12	0.94	Mean ratio	0.832	0.02
Mean/no. of patients without MiVD‡	1.08/528	0.80/69	Mean ratio	0.715	0.02
Mean/no. of patients with MiVD‡	1.14/940	1.02/127	Mean ratio	0.894	0.24
Mean no. of lesions with stenosis 50–69%	1.52	1.45	Mean ratio	0.948	0.41
Proportion of patients with maximum stenosis ≥70%	0.64	0.57	Odds ratio	0.743	0.06
Proportion of patients with maximum stenosis ≥99%	0.40	0.32	Odds ratio	0.696	0.03
Mean myocardial jeopardy index	47.4	43.0	Mean difference	−4.26	0.02
Proportion of patients with no angina history	0.10	0.15	Odds ratio	1.613	0.03
Proportion of patients with unstable angina	0.09	0.08	Odds ratio	0.924	0.78
Mean C-reactive protein (μg/ml) (log scale)§	0.975	0.599	Mean difference	−0.317	<0.001
Mean fibrinogen (mg/dl)//	369.9	346.0	Mean difference	−20.04	0.005
Mean plasminogen activator inhibitor-1 (AU/ml) (log scale)¶	2.76	2.64	Mean difference	−0.119	0.02

*The 126 patients with <6-month history of TZD use and the 13 patients (11 non-TZD users and 2 recent TZD users) without complete data for microvascular disease are not included.

†Adjusted for age, gender, tobacco use (current, previous), glycosylated hemoglobin, diabetes duration, hypertension (blood pressure >130/85 mm Hg, >1 antihypertension drug), lipids, and microalbuminuria.

‡Analysis repeated in subset of patients without and with MiVD as defined in Table 2.

§C-reactive protein measurements were available for 1,433 subjects in the no-TZD group and 194 subjects with ≥6 months of TZD use.

//Mean fibrinogen was available for 1,432 subjects in the no-TZD group and 193 subjects with ≥6 months of TZD use.

¶Plasminogen activator inhibitor-1 was available for 1,357 subjects in the no-TZD group and 193 subjects with ≥6 months of TZD use.

Abbreviations as in Table 2.