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## Thiazolidinediones and Risk of Atrial Fibrillation Among Patients with Diabetes and Coronary Disease

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### Abstract

**BACKGROUND:** We sought to determine whether insulin-sensitizing therapy (thiazolidinediones or metformin) decreased the risk of developing atrial fibrillation compared with insulin-providing therapy (insulin, sulfonylurea, or a meglitinide). Thiazolidinediones are insulin sensitizers that also decrease the inflammatory response. Because inflammation is a risk factor for atrial fibrillation, we hypothesized that treating diabetes with thiazolidinediones might decrease the risk of developing atrial fibrillation.

**METHODS:** The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial enrolled patients with type 2 diabetes and documented coronary artery disease. All patients were randomized to insulin-sensitizing therapy or insulin-providing therapy.

**RESULTS:** A total of 2319 patients entered the study, with 1160 assigned to the insulin-sensitization strategy and 1159 assigned to the insulin-provision strategy. Over a median follow-up of 4.2 years, 90 patients (3.9%) developed new-onset atrial fibrillation. In the intention-to-treat analysis, the incidence of atrial fibrillation was 8.7 per 1000 person-years in patients assigned to insulin sensitization compared with 9.5 in patients assigned to insulin provision with a hazard ratio (HR) of 0.91 (95% confidence interval [CI], 0.60–1.38,  $P = .66$ ). In a time-varying exposure analysis, the incidence rate per 1000 person-years was 7.2 while exposed to thiazolidinediones and 9.7 while not exposed to thiazolidinediones with an adjusted HR of 0.80 (95% CI, 0.33–1.94,  $P = .62$ ). In a subset of patients matched on propensity to receive a thiazolidinediones, the HR was 0.75 (95% CI, 0.43–1.30,  $P = .30$ ).

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\*A full listing of the Bypass Angioplasty Revascularization Investigation 2 Diabetes Study Group can be found in the Supplementary Appendix, at [NEJM.org](https://doi.org/10.1016/j.nejm.2009.360.2503-15) (*N Engl J Med.* 2009;360:2503-15).

Authorship:

All authors had access to the data and played a role in writing this manuscript.

**Conflicts of Interest:** None.

**CONCLUSIONS:** We did not find a significant reduction of atrial fibrillation incidence with use of thiazolidinediones.

### Keywords

Atrial fibrillation; Diabetes mellitus; Insulin providers; Insulin sensitizers; Thiazolidinediones

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## INTRODUCTION

Patients with type 2 diabetes mellitus (diabetes) are at increased risk of atrial fibrillation, and patients with the combination of atrial fibrillation and diabetes are at particularly increased risk of stroke.<sup>1-4</sup> The potential mechanisms underlying the predisposition for atrial fibrillation in patients with diabetes are not fully understood, but microvascular coronary disease accompanied by elevated C-reactive protein, inflammation, and oxidative stress on the endothelium, all present in both diabetes and atrial fibrillation, could play a role.<sup>5-12</sup> In addition, increased left atrial size is known to be associated with increased risk of atrial fibrillation, and diabetes is known to induce an increase in left atrium size independent of hypertension and diastolic function.<sup>13-15</sup> Finally, diabetes causes neural remodeling in the atrium, characterized by both parasympathetic and sympathetic denervation, which in itself could engender atrial fibrillation.<sup>16</sup> Interventions that alter these processes might reduce the risk of atrial fibrillation in patients with diabetes.

Thiazolidinediones are insulin sensitizers that belong to the class of peroxisome proliferator-activated receptor gamma activators. Binding to this transcription factor alters glucose and lipid homeostasis, increases sensitivity to insulin, decreases the inflammatory response, and reduces levels of resistin.<sup>17-20</sup> Elevated levels of serum resistin have been shown to be significantly associated with higher rates of incident atrial fibrillation.<sup>20</sup> Thiazolidinediones reduce glucose levels in patients with diabetes, but they have also been associated with worsening heart failure, which prompted the US Food and Drug Administration to apply a black box warning on rosiglitazone and pioglitazone, the only thiazolidinediones still available in the United States after withdrawal of troglitazone.<sup>21</sup> International guidelines recommend thiazolidinediones as a second-line treatment option for diabetes.<sup>22</sup>

It has been hypothesized that the use of thiazolidinediones could prevent atrial fibrillation through their anti-inflammatory effects and other mechanisms,<sup>23-26</sup> but empirical evidence for this potential effect is scant. The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial provides a unique opportunity to test whether treatment with thiazolidinediones decreases the risk of developing atrial fibrillation, because it randomized patients to a strategy of insulin sensitization, which included the use of thiazolidinediones, or a strategy of insulin provision to treat diabetes.

## METHODS

The BARI 2D trial design has been described in detail.<sup>27</sup> Briefly, BARI 2D enrolled patients with type 2 diabetes mellitus who had documented coronary artery disease of sufficient severity to warrant consideration of revascularization. Patients were excluded if they had heart failure symptoms equal to New York Heart Association class III or IV, an indication

for immediate coronary revascularization, a creatinine level  $>2.0$  mg/dL ( $177 \mu\text{mol/L}$ ), a glycohemoglobin (HbA1C) level  $>13.0\%$ , hepatic dysfunction, coronary artery bypass graft surgery within 12 months, or prior percutaneous coronary intervention. The institutional review boards at the University of Pittsburgh and at each participating site approved the protocol, and all patients provided written informed consent.

Patients in the BARI 2D trial were randomized in a 2-by-2 factorial design to (1) an insulin-sensitizing therapy or an insulin-provision strategy; and (2) to prompt coronary revascularization with optimal medical therapy or optimal medical therapy alone. Insulin-sensitizing therapy was defined as treatment with a thiazolidinedione or metformin, and insulin-provision therapy was defined as treatment with insulin, sulfonylurea, or a meglitinide. If the HbA1C level could not be maintained at less than  $8.0\%$  using the protocol-assigned drugs, patients assigned to insulin-sensitizing therapy were allowed use of an insulin-providing drug and vice versa. A total of 2368 participants were enrolled at 49 international clinical sites between January 1, 2001, and March 31, 2005. Treatment continued until the 6-year visit or December 1, 2008.

Most patients were already on treatment with a glucose-lowering drug at entry into BARI 2D, with 240 patients receiving rosiglitazone and 204 patients receiving pioglitazone at baseline. After random assignment to the insulin-sensitization versus insulin-provision groups, medical therapy was adjusted by the site diabetes specialist in accordance with the study protocol with the goal of achieving a target HbA1C level of  $<7.0\%$ . Patients assigned to the insulin-provision strategy who were taking a thiazolidinedione at study entry ( $19.4\%$ ) were generally tapered off the thiazolidinedione over the first 6 months. Current medication use and discontinuation for thiazolidinediones, and for rosiglitazone and pioglitazone in particular, were recorded at trial entry and at each follow-up visit. These data were used to determine the on-treatment thiazolidinediones intervals and coincident events.

## Outcomes

The primary outcome of interest of this investigation was the new onset of atrial fibrillation after randomization. Because atrial fibrillation was not a predefined study end point, we used data from electrocardiograms (ECGs) systematically recorded according to the trial protocol at baseline, 3 months, and each annual follow-up visit to identify atrial fibrillation. The protocol also required ECGs to be collected before and after revascularization procedures, and during evaluation for suspected myocardial infarction. The BARI 2D ECG Core Laboratory at the University of St Louis determined the rhythm for each submitted ECG and specifically noted the presence of atrial fibrillation. Atrial fibrillation types were classified by the timing of the electrocardiography recording as “baseline atrial fibrillation,” “postoperative atrial fibrillation,” or “new-onset atrial fibrillation.” All patients with baseline atrial fibrillation were excluded from the study cohort.

In a sub-study of the Economic outcomes of the BARI 2D trial, 2005 patients were contacted every 3 months by the BARI 2D Economics Core Laboratory at Stanford University to collect data on health care use and costs.<sup>28</sup> For patients enrolled in the BARI 2D Economics sub-study, International Classification of Diseases 9th or 10th Revision codes with atrial fibrillation were available from collected for hospitalizations from some of the

included sites. A hospitalization was categorized as an atrial fibrillation hospitalization if the primary or a secondary International Classification of Diseases 9th Revision code was 427.3 or if the primary International Classification of Diseases 10th Revision code was 148. The only hospital providing International Classification of Diseases 10th Revision codes did not provide secondary codes. Analyses using these data were censored at the end of follow-up in the economics sub-study, which was earlier than that of the main BARI 2D trial.

## Statistical Analyses

We conducted 3 types of analyses: (1) an intention-to-treat-analysis, based on random assignment to the insulin-sensitization versus insulin-provision strategies; (2) a treatment received analysis, using time-updated information on thiazolidinedione status (prescription from the prior study visit); and (3) a propensity score-matched analysis based on 1:1 matching using a propensity for thiazolidinedione use. Subgroup analyses including only the economics sub-study patients were conducted using both an intention-to-treat approach and a propensity score-matched analysis.

Patient characteristics were compared according to insulin-sensitization or insulin-provision assignment status and by early thiazolidinedione use (yes or no). Early thiazolidinedione use was defined as maintenance of baseline thiazolidinedione use at 6 months or any new initiation of thiazolidinediones use within the first 6 months, as previously described.<sup>29</sup> Categorical data were presented as counts with percentages, and statistical differences were tested using chi-square tests and Fisher exact tests where appropriate. Continuous variables were presented as mean with standard deviations for normally distributed data and as medians with interquartile range for non-normally distributed data. Statistical differences were tested using Student *t* test and Wilcoxon rank-sum test where appropriate.

Crude incidence rates of new-onset atrial fibrillation were calculated per 1000 person-years by assigned treatment and by thiazolidinedione status. The relative risk for new-onset atrial fibrillation were estimated using hazard ratios (HRs) with 95% confidence intervals (CIs) using Cox proportional regression analyses. A *P* value <.05 was considered as statistically significant.

A Cox proportional hazards regression model with time-varying exposures was used to assess the association of current thiazolidinedione use with atrial fibrillation. Risk for the detection of atrial fibrillation at a visit was modeled as a function of whether or not a patient used thiazolidinedione between the previous and current visits. The time-varying analysis was adjusted for sex, age, US patient status, duration of diabetes, history of hypercholesterolemia, hypertension, myocardial infarction, heart failure, stroke or transient ischemic attack, prior coronary revascularization, sitting 60-second pulse, body mass index, level of activity, cigarette smoking category, low-density lipoprotein cholesterol, HbA1c, statin, angiotensin-converting enzyme inhibitor, and angiotensin II inhibitors.

Propensity scores were constructed using a logistic regression model developed to predict which patients assigned to the insulin-sensitization strategy would receive a thiazolidinedione within 6 months compared with patients assigned to the insulin-sensitization group who did not receive a thiazolidinedione within 6 months. The variates

included in the propensity score were sex, age, country (United States or other), duration of diabetes, history of hypercholesterolemia, hypertension, myocardial infarction, heart failure, stroke or transient ischemic attack, prior coronary revascularization, sitting 60-second pulse, body mass index, level of activity, cigarette smoking category, low-density lipoprotein cholesterol, HbA1c, statin, angiotensin-converting enzyme inhibitor, and angiotensin II inhibitors. Patients with missing values in these variables were not included in the matched analysis. Patients who received a thiazolidinedione in the insulin-sensitization group were then matched 1:1, without replacement, based on the propensity score with patients randomly assigned to the insulin-provision strategy who did not receive a thiazolidinedione within 6 months, using a greedy matching algorithm, with a caliper distance of 0.02. The matched analysis was performed to compare patients receiving thiazolidinedione from the insulin-sensitization group with patients from the insulin-provision group, who would have been likely to receive thiazolidinedione if they had been randomized to the insulin-sensitization group instead of insulin-provision group.

In the subgroup analysis of 2005 patients from the economics sub-study, risk of atrial fibrillation was investigated as both an intention-to-treat analysis and a propensity score-matched analysis using a similar approach as in the main analyses.

## RESULTS

### Cohort Summary

Of the 2368 patients enrolled in the BARI 2D study, 31 had atrial fibrillation at study baseline and 18 had no follow-up time, yielding a final study population of 2319 patients, 1160 of whom were assigned to the insulin-sensitization strategy and 1159 of whom were assigned to insulin-provision strategy (Figure 1). The 2 groups had similar baseline demographics, medical history, and laboratory values (Table 1), as expected by randomization.

### Intention-to-Treat Analysis

A total of 90 patients (3.9%) developed new-onset atrial fibrillation based on ECG Core Laboratory classification over a median follow-up of 4.2 years (interquartile range, 3.9–5.3 years), 43 patients assigned to the insulin-sensitization strategy and 47 assigned to the insulin-provision strategy. Post-operative atrial fibrillation after a revascularization procedure developed in an additional 27 patients (15 in the insulin-sensitization strategy group and 12 in the insulin-provision strategy group), which was not classified as new-onset atrial fibrillation in this study. The incidence rate of new-onset atrial fibrillation was 8.7 per 1000 person-years in patients assigned insulin sensitization, compared with 9.5 in patients assigned to insulin provision (Figure 2). In the intention-to-treat analysis, the relative risk of atrial fibrillation was 9% lower in the insulin-sensitization group, with an HR of 0.91 (95% CI, 0.60–1.38,  $P = .59$ ).

### Thiazolidinedione Time-Varying Exposure

Patients in BARI 2D were exposed to a thiazolidinedione for 3418 years (34%) of the 10,006 person-years of follow-up. New-onset atrial fibrillation developed in 29 patients while

exposed to thiazolidinedione, an incidence rate of 7.2 (95% CI, 4.8–10.7) per 1000 person-years, and in an additional 61 patients while not exposed to a thiazolidinedione, equivalent to an incidence rate of 9.7 (95% CI, 7.6–12.4). The unadjusted HR was 0.73 (95% CI, 0.46–1.18,  $P = .20$ ), and the adjusted HR was 0.80 (95% CI, 0.33–1.94,  $P = .62$ ) (Figure 2).

### Propensity Score-Matched Analyses

The propensity score developed with a logistic regression model to identify the thiazolidinedione users in the insulin-sensitization group had good predictive properties, with a C-statistic of 0.78. In the matched analysis, 663 patients entered each group with a 98.8% propensity score match between the 2 groups. A nonstatistically significant decreased risk of atrial fibrillation was found in the thiazolidinedione group (22 patients) compared with the nonthiazolidinedione group (27 patients), with an HR of 0.75 (95% CI, 0.43–1.30,  $P = .30$ ) (Table 2).

### Subgroup Analysis from the economics Sub-Study

After excluding 29 patients with baseline atrial fibrillation, 1976 patients entered the economic sub-study, 995 (50.4%) assigned to the insulin sensitization strategy and 981 (49.6%) assigned to the insulin provision strategy. Of the 118 cases of new-onset atrial fibrillation, 42 (36%) came from hospital discharge diagnosis, 57 (48%) came from ECG, and 19 (16%) came from both discharge diagnosis and ECG. In the intention-to-treat analysis, assignment to the insulin-sensitization strategy decreased risk of atrial fibrillation with an HR of 0.89 (95% CI, 0.62–1.28,  $P = .54$ ) compared with the insulin-provision strategy, and in the matched analysis thiazolidinedione decreased risk of atrial fibrillation with an HR of 0.79 (95% CI, 0.49–1.26,  $P = .32$ ) compared with matched patients who did not receive a thiazolidinedione; thus, none of the results were significant (Table 2).

## DISCUSSION

Atrial fibrillation is a common, serious clinical problem among patients with diabetes and coronary disease. This analysis of the BARI 2D randomized trial suggests that the incidence of atrial fibrillation might be 20% to 25% lower in patients treated with an insulin-sensitizing thiazolidinedione, but the confidence limits on these observations were very wide, and the trial lacked the statistical power to establish or exclude a clinically important effect of thiazolidinediones on atrial fibrillation, because of the relatively low incidence of documented atrial fibrillation (<1% per year).

The potential of thiazolidinediones to lower the risk of developing atrial fibrillation has been suggested by a few earlier studies. In a Danish nationwide cohort study, a decreased risk of atrial fibrillation with thiazolidinedione of 24% was found in 108,624 patients with diabetes.<sup>30</sup> This was similar to the study by Chao et al,<sup>25</sup> who reported a 30% lower risk of developing atrial fibrillation with the use of thiazolidinediones in a nationwide, observational study of 12,065 patients with diabetes (HR, 0.69; 95% CI, 0.49–0.91;  $P = .03$ ). The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) randomized controlled trial comparing pioglitazone with placebo for the treatment of diabetes was not designed to test differences in atrial fibrillation,<sup>31</sup> but noted that it

developed in 42 patients (1.6%) assigned to proglitazone compared with 51 patients (1.9%) assigned to placebo (rate ratio, 0.82,  $P = .37$ ).<sup>31</sup> The difference between the 2 register-based studies finding a reduced risk of atrial fibrillation with thiazolidinedione and the PROactive study and the BARI 2D study is both the design of the studies, register versus randomized controlled trial, and the size of the cohorts. Atrial fibrillation was also a predefined end point in the 2 register-based studies whereas in this study and in the PROactive trial atrial fibrillation was not a predefined endpoint but identified in post hoc analyses.

The effect of thiazolidinedione on the risk of developing atrial fibrillation has also been investigated in patients after cardiac procedures.<sup>23,24</sup> A study of 188 patients with diabetes who underwent cardiothoracic surgery, 40 of whom were treated with a thiazolidinedione, reported a lower risk of developing postoperative atrial fibrillation, with an adjusted odds ratio of 0.80 (95% CI, 0.32–1.99,  $P = .63$ ). The risk of recurrent atrial tachycardia after catheter ablation was investigated in diabetic patients who were randomized to pioglitazone versus no treatment: Pioglitazone decreased the risk of atrial tachycardia recurrence, with an odds ratio of 0.32 (95% CI, 0.12–0.86,  $P = .02$ ).

A decreased thiazolidinedione use was seen after the black-box warnings restrictions, although these restrictions subsequently were lifted by the Food and Drug Administration, because there was no convincing evidence from the RECORD trial that myocardial infarction risk was higher, thiazolidinediones never regained their popularity. However, because of the possible beneficial effects, such as lower atrial fibrillation rates, there may be reasons for more widespread use.

## LIMITATIONS

The BARI 2D was not designed to investigate the risk of atrial fibrillation and therefore did not monitor patients systematically for its development, such as with long-term ECG monitors. This could explain to some extent the low number of patients with atrial fibrillation at baseline and the low number of cases of new-onset atrial fibrillation found in the study. A little more than half of the patients assigned to the insulin sensitization strategy received a thiazolidinedione, and most of the remaining patients received metformin. Consequently, the intention-to-treat comparison between randomized diabetes management strategies includes many patients in both arms who did not receive a thiazolidinedione, which diluted this study's ability to document an effect of thiazolidinediones on atrial fibrillation. We attempted to overcome this limitation by developing a propensity score model to identify which patients assigned to the insulin-sensitization strategy were prescribed a thiazolidinedione instead of metformin or other medications. In this subset, there was a stronger signal of an effect of the randomized assignment on atrial fibrillation (HR, 0.75 in the matched patients vs 0.91 in the entire population), but the confidence limits were again wide because relatively few outcome events were documented.

## CONCLUSIONS

Our findings suggest no significant reduction of atrial fibrillation incidence with the use of thiazolidinediones. Larger studies with closer ECG monitoring are warranted among patients

at increased risk of atrial fibrillation to provide a more conclusive evaluation of whether thiazolidinediones might reduce the risk of atrial fibrillation.

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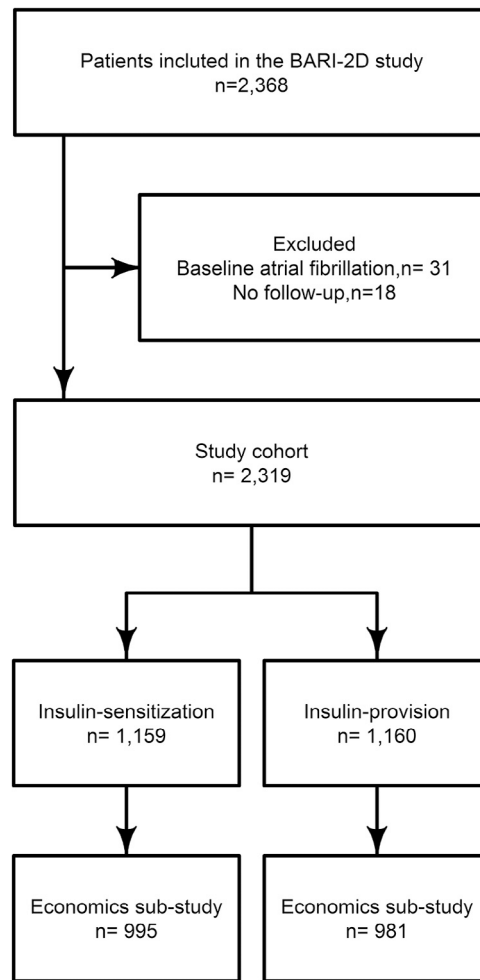
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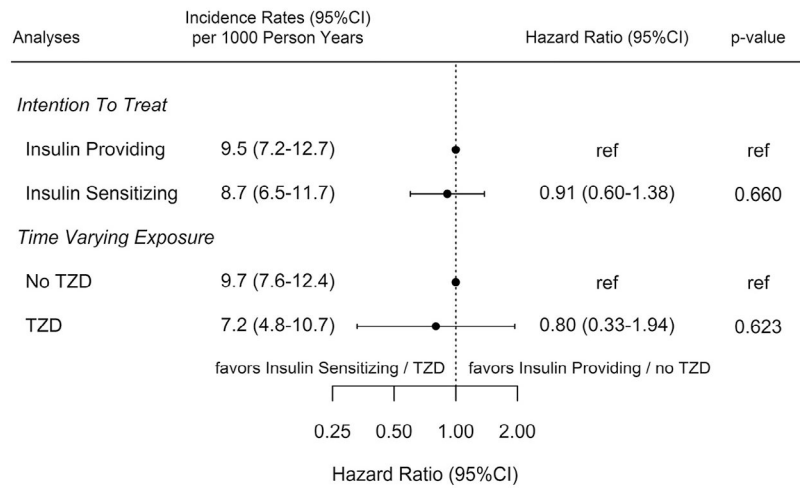
**CLINICAL SIGNIFICANCE**

- A total of 2319 patients with coronary disease were randomized to insulin-sensitization therapy (thiazolidinediones or metformin) or insulin-provision therapy (insulin, sulfonylurea, or a meglitinide).
- The incidence rate of new-onset atrial fibrillation was 8.7 per 1000 person-years in patients assigned to insulin sensitization compared with 9.5 in patients assigned to insulin provision.
- This gave a 20% to 25% lower risk of atrial fibrillation in patients treated with an insulin-sensitizing thiazolidinedione compared with insulin-provision therapy. This finding was not significant.



**Figure 1.** Flowchart of intention-to-treat analysis. BARI-2D = Bypass Angioplasty Revascularization Investigation 2 Diabetes.

### Risk of Atrial Fibrillation



**Figure 2.** Incidence rates and HRs of atrial fibrillation. The time-varying exposure analysis was adjusted for US patients’ status, duration of diabetes, history of hypercholesterolemia, hypertension, myocardial infarction, heart failure, stroke or transient ischemic attack, prior coronary revascularization, sitting 60-second pulse, body mass index, level of activity, cigarette smoking category, low-density lipoprotein cholesterol, HbA1c, statin, angiotensin-converting enzyme inhibitor, and angiotensin II inhibitors. CI = confidence interval; TZD = thiazolidinedione.

Table 1

## Baseline Characteristics by Random Treatment Assignment

	Insulin Sensitization	Insulin Provision	P Value
n	1159	1160	
Demographics			
Female, n (%)	349 (30.1)	346 (29.8)	.92
Age (mean $\pm$ SD)	61.8 (9.1)	61.9 (8.6)	.82
Non-US patient, n (%)	435 (37.5)	427 (36.8)	.75
Medical Insurance (%)			.87
Medicare	301 (26.1)	293 (25.3)	
Other public	504 (43.6)	503 (43.5)	
Private	298 (25.8)	313 (27.1)	
None/self-pay	52 (4.5)	47 (4.1)	
Medical history			
Duration of diabetes in years (median [IQR])	8.3 [3.8–14.8]	9.1 [3.7–15.7]	.15
History of CHF, n (%)	72 (6.3)	72 (6.2)	1.00
History of hypercholesterolemia, n (%)	924 (80.8)	950 (83.0)	.19
History of stroke/TIA, n (%)	114 (9.9)	111 (9.6)	.85
History of hypertension, n (%)	929 (81.1)	960 (83.8)	.09
History of hypoglycemia, n (%)	229 (20.0)	270 (23.6)	.04
History of MI, n (%)	374 (32.8)	361 (31.6)	.55
Prior coronary revascularization, n (%)	265 (22.9)	279 (24.1)	.53
Physical exam			
Serum creatinine mg/dL (mean ( $\pm$ SD))	1.0 (0.3)	1.1 (0.3)	.47
Sitting diastolic BP, mm Hg (mean ( $\pm$ SD))	74.6 (11.4)	74.6 (11.1)	.98
Sitting systolic blood pressure, mm Hg (mean ( $\pm$ SD))	131.7 (19.8)	131.9 (20.3)	.88
ABI <0.90, n (%)	213 (20.5)	226 (21.5)	.63
Sitting 60-sec pulse (mean ( $\pm$ SD))	68.5 (10.7)	67.9 (10.5)	.12
BMI, kg/m <sup>2</sup> (median [IQR])	30.9 [27.6–34.7]	30.9 [27.6–34.8]	.94
Lifestyle			
Level of activity, n (%)			.55

	Insulin Sensitization	Insulin Provision	P Value
Sedentary	258 (22.4)	251 (21.8)	
Mild	488 (42.3)	468 (40.7)	
Moderate/strenuous	407 (35.3)	431 (37.5)	
Cigarette Smoking Category, n (%)			.12
Never smoked	403 (34.8)	363 (31.4)	
Former smoker	607 (52.4)	654 (56.6)	
Current smoker	148 (12.8)	138 (11.9)	
Core Lab Measures from the Biochemistry Laboratories			
HDL, mg/dL (mean (±SD))	37.9 (10.0)	38.5 (10.6)	.22
LDL mg/dL (mean (±SD))	95.6 (33.9)	96.92 (33.0)	.35
Total cholesterol, mg/dL (median [IQR])	163 [140–190]	167 [144–193]	.08
Triglycerides cholesterol, mg/dL (median [IQR])	147 [101–221]	149 [108–219]	.34
HbA1c % (median [IQR])	7.3 [6.4–8.6]	7.3 [6.5–8.5]	.51
Core lab measures from the ECG Core Laboratory			
Presence of abnormal Q-waves, n (%)	227 (20.2)	195 (17.3)	.10
Abnormal ST depression, n (%)	179 (17.0)	180 (17.1)	.98
Abnormal T-waves, n (%)	448 (42.5)	446 (42.4)	1.00
Abnormal LVEF, n (%)	203 (18.1)	182 (16.2)	.26
Medications			
Insulin, n (%)	316 (27.3)	329 (28.4)	.58
Biguanide, n (%)	634 (54.8)	620 (53.5)	.56
Thiazolidinedione, n (%)	224 (19.4)	213 (18.4)	.58
Sulfonylurea, n (%)	625 (54.0)	611 (52.7)	.56
Statin, n (%)	866 (74.9)	861 (74.4)	.82
Beta-blocker, n (%)	860 (74.4)	825 (71.3)	.10
Calcium channel blockers, n (%)	346 (29.9)	383 (33.1)	.11
Nonsublingual nitrate, n (%)	369 (32.0)	357 (30.8)	.58
ACE inhibitor, n (%)	738 (63.8)	755 (65.3)	.49
Angiotensin receptor blocker, n (%)	172 (14.9)	163 (14.1)	.63
Aspirin, n (%)	1022 (88.6)	1016 (87.9)	.62
Antiplatelet therapy (nonaspirin), n (%)	232 (20.1)	219 (18.9)	.52

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	<b>Insulin Sensitization</b>	<b>Insulin Provision</b>	<b>P Value</b>
Diuretic, n (%)	440 (38.0)	450 (38.9)	.70

ABI = ankle-brachial index; ACE = angiotensin-converting enzyme; BMI = body mass index; CHF = congestive heart failure; ECG = electrocardiogram; HbA1c = glycohemoglobin; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SD = standard deviation; TIA = transient ischemic attack.

**Table 2**

## Matched Analysis and Cost-Effectiveness Study

<b>BARI 2D Cohort Propensity Score-Matched Analysis*</b>	<b>HR (95% CI)</b>	<b>P Value</b>
Thiazolidinedione users in the insulin sensitization group compared with nonthiazolidinedione users in the insulin provision group as reference*	0.75 (0.43–1.30)	.30
<b>Economics sub-study</b>	<b>HR (95% CI)</b>	<b>P Value</b>
Insulin sensitization vs insulin provision intention to treat	0.89 (0.62–1.28)	.54
Thiazolidinedione users in the insulin sensitization group compared with nonthiazolidinedione users in the insulin providers group as reference matched analysis*	0.79 (0.49–1.26)	.32

BARI 2D = Bypass Angioplasty Revascularization Investigation 2 Diabetes; CI = confidence interval; HR = hazard ratio.

\* Matched by propensity score based on country (United States or other), duration of diabetes, history of hypercholesterolemia, hypertension, myocardial infarction, heart failure, stroke or transient ischemic attack, prior coronary revascularization, sitting 60-second pulse, body mass index, level of activity, cigarette smoking category, low-density lipoprotein cholesterol, HbA1c, statin, angiotensin-converting enzyme inhibitor, and angiotensin II inhibitors.