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Comparison of Pioglitazone vs Glimepiride on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes

The PERISCOPE Randomized Controlled Trial

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ALTHOUGH MANAGEMENT OF glucose levels represents one of the principal treatment goals of diabetes therapy, it has been difficult to demonstrate a favorable effect of improved glycemic control on the macrovascular complications of this disease.^{1,2} No antidiabetic regimen has demonstrated the ability to reduce the progression of coronary atherosclerosis. Accordingly, there is little evidence to support a preference of one class of glucose-lowering medication over any other as a means to reduce atherosclerotic disease burden.³ Sulfonylureas have been available for decades, lower blood glucose by acting as insulin secretagogues, and represent one of the most

For editorial comment see p 1603.

Context No antidiabetic regimen has demonstrated the ability to reduce progression of coronary atherosclerosis. Commonly used oral glucose-lowering agents include sulfonylureas, which are insulin secretagogues, and thiazolidinediones, which are insulin sensitizers.

Objective To compare the effects of an insulin sensitizer, pioglitazone, with an insulin secretagogue, glimepiride, on the progression of coronary atherosclerosis in patients with type 2 diabetes.

Design, Setting, and Participants Double-blind, randomized, multicenter trial at 97 academic and community hospitals in North and South America (enrollment August 2003-March 2006) in 543 patients with coronary disease and type 2 diabetes.

Interventions A total of 543 patients underwent coronary intravascular ultrasonography and were randomized to receive glimepiride, 1 to 4 mg, or pioglitazone, 15 to 45 mg, for 18 months with titration to maximum dosage, if tolerated. Atherosclerosis progression was measured by repeat intravascular ultrasonography examination in 360 patients at study completion.

Main Outcome Measure Change in percent atheroma volume (PAV) from baseline to study completion.

Results Least squares mean PAV increased 0.73% (95% CI, 0.33% to 1.12%) with glimepiride and decreased 0.16% (95% CI, -0.57% to 0.25%) with pioglitazone ($P = .002$). An alternative analysis imputing values for noncompleters based on baseline characteristics showed an increase in PAV of 0.64% (95% CI, 0.23% to 1.05%) for glimepiride and a decrease of 0.06% (-0.47% to 0.35%) for pioglitazone (between-group $P = .02$). Mean (SD) baseline HbA_{1c} levels were 7.4% (1.0%) in both groups and declined during treatment an average 0.55% (95% CI, -0.68% to -0.42%) with pioglitazone and 0.36% (95% CI, -0.48% to -0.24%) with glimepiride (between-group $P = .03$). In the pioglitazone group, compared with glimepiride, high-density lipoprotein levels increased 5.7 mg/dL (95% CI, 4.4 to 7.0 mg/dL; 16.0%) vs 0.9 mg/dL (95% CI, -0.3 to 2.1 mg/dL; 4.1%), and median triglyceride levels decreased 16.3 mg/dL (95% CI, -27.7 to -11.0 mg/dL; 15.3%) vs an increase of 3.3 mg/dL (95% CI, -10.7 to 11.7 mg/dL; 0.6%) ($P < .001$ for both comparisons). Median fasting insulin levels decreased with pioglitazone and increased with glimepiride ($P < .001$). Hypoglycemia was more common in the glimepiride group and edema, fractures, and decreased hemoglobin levels occurred more frequently in the pioglitazone group.

Conclusion In patients with type 2 diabetes and coronary artery disease, treatment with pioglitazone resulted in a significantly lower rate of progression of coronary atherosclerosis compared with glimepiride.

Trial Registration clinicaltrials.gov Identifier: NCT00225277

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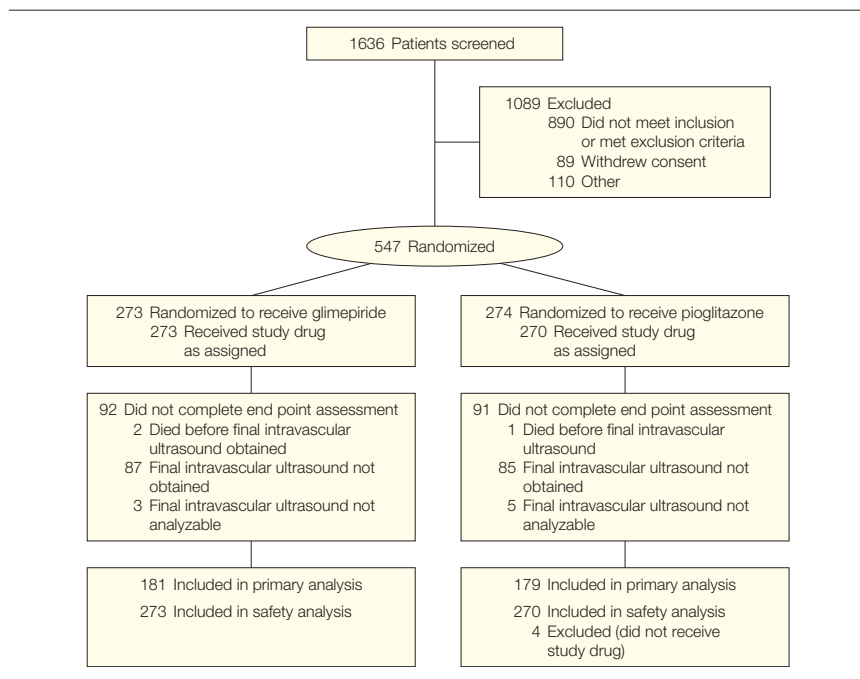
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commonly-used classes of antidiabetic therapy. Thiazolidinediones (TZDs) are a relatively new class of antidiabetic agents that reduce glucose pri-

Author Affiliations and a List of the PERISCOPE Investigators appear at the end of this article.

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Figure 1. Flow of Patients Through the Trial



marily by increasing insulin sensitivity in peripheral tissues.⁴

These 2 approaches to management of hyperglycemia have important differences in their metabolic and physiological effects.³ Two TZDs are currently marketed: pioglitazone and rosiglitazone. Both agents reduce inflammatory biomarkers, while pioglitazone also produces greater elevations of high-density lipoprotein cholesterol (HDL-C) and reduces triglyceride levels.⁵ In separate randomized clinical trials, pioglitazone decreased the rate of progression of carotid intimal medial thickness and showed some evidence for a reduction in adverse cardiovascular outcomes.^{6,7} The effects of sulfonylureas on cardiovascular disease have been controversial.⁸ However, the majority of recent analyses suggest a neutral effect for this class of agents on cardiovascular outcomes.^{1,3}

We compared the effects of these 2 widely used, but distinctly different, classes of oral hypoglycemic agents on the rate of progression of coronary atherosclerosis. We used intravascular ultrasonography (IVUS) because this imaging modality is considered an ac-

curate and reliable approach to evaluating the effect of therapies on progression of coronary atherosclerosis.⁹ Pioglitazone was selected to represent the TZD class and glimepiride chosen as representative of the sulfonylurea class. The goal of this study was to directly compare the effectiveness of these 2 alternative approaches, an insulin-providing vs an insulin-sensitizing strategy, in reducing progression of atherosclerosis in patients with type 2 diabetes and coexisting coronary artery disease.

METHODS

Study Design

The PERISCOPE Trial (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) was a prospective, randomized, multicenter, double-blind clinical trial (FIGURE 1). The study was designed by the Cleveland Clinic Coordinating Center for Clinical Research (C5 Research) in collaboration with the sponsor. The institutional review boards of participating centers approved the protocol and all participants provided written informed con-

sent. Participants aged 35 to 85 years were eligible if they had a baseline glycosylated hemoglobin (HbA_{1c}) level of 6.0% to 9.0% (if taking a glucose-lowering medication) or 6.5% to 10% (if not currently receiving drug therapy). Patients were required to have coronary angiography performed for clinical indications that demonstrated at least 1 angiographic stenosis with at least 20% narrowing. A “target vessel” for IVUS examination was required to have less than 50% obstruction throughout a 40-mm or longer segment.

Patients were excluded for type 1 diabetes, if they were taking 3 or more antidiabetic medications, or if they had received any TZD within the past 12 weeks. Other major exclusion criteria were a serum creatinine level of >2.0 mg/dL, triglyceride level of more than 500 mg/dL, uncontrolled hypertension (blood pressure >160/100 mm Hg despite therapy), active liver disease, or a left main coronary artery stenosis of more than 50%. Each of these exclusion criteria was selected to exclude patients who might not complete a full 18 months of treatment after randomization. All diabetic medications, including insulin, were permitted during the study with the exception of a TZD, sulfonylurea, or other insulin secretagogue. An independent committee blinded to treatment assignment centrally adjudicated adverse cardiovascular events.

Titration of Study Drug

If the patient was taking a sulfonylurea or other insulin secretagogue prior to randomization, the drug was discontinued. Participants naive to glucose-lowering therapy at screening or taking less than glimepiride, 2 mg/d (or the equivalent dosage of another sulfonylurea), took 15 mg of pioglitazone or 1 mg of glimepiride. For those taking 2 mg/d or more of glimepiride (or the equivalent) or metformin monotherapy, the starting dosage was 30 mg of pioglitazone or 2 mg of glimepiride. If fasting capillary blood glucose measurements exceeded 140 mg/dL at sub-

sequent visits, the study drug was increased to the next level (2 mg or 4 mg for glimepiride or 30 mg or 45 mg for pioglitazone). Study drug was titrated to the maximum dose by 16 weeks, if tolerated. Metformin, insulin, or both could be added or increased in dosage at the discretion of the investigator to achieve the target HbA_{1c} level of less than 7.0%. If a patient experienced hypoglycemic symptoms, other glucose-lowering therapies were reduced to maintain maximal dosages of study medication.

Randomization and Allocation Concealment

The patients and all study personnel were blinded to treatment assignment. The randomization was performed using an interactive voice-response system that used a block size of 4. The study specified a balanced (1:1) treatment allocation stratified according to diabetes treatment status at the time of randomization (treatment-naïve or <2 mg/d of glimepiride or equivalent vs ≥2 mg/d of glimepiride or equivalent, metformin monotherapy, or sulfonylurea-metformin combination therapy).

Intravascular Ultrasound Examination and Measurement

Patients underwent coronary angiography and the operator selected a coronary vessel for intravascular ultrasound (IVUS) examination. The methods for IVUS image acquisition and measurement have been described in prior publications.¹⁰⁻¹⁶ Briefly, the operator was instructed to select the longest and least angulated epicardial coronary artery for IVUS examination. The ultrasound probe was passed over a guidewire into the distal vessel just beyond a side branch, which served as a reference point. Subsequently, a motor drive was engaged that withdrew the ultrasonic transducer at 0.5 mm/s. The examination was screened for image quality in the core laboratory and only patients meeting prespecified image quality requirements were eligible for randomization.

A follow up IVUS examination was performed after 18 months of treatment in all patients who provided informed consent, regardless of whether they continued to take the study drug (modified intent-to-treat population). If a patient required cardiac catheterization for a clinical indication between 12 and 18 months, a follow-up IVUS examination was performed to avoid exposing patients to the risk of an additional catheterization at study completion.

The follow-up IVUS examination was performed in the same coronary segment imaged during baseline examination. The motorized pullback was initiated at the same side branch originally selected during the baseline examination to ensure that the same segment was imaged during follow-up. Using digitized images, personnel blinded to clinical characteristics and treatment assignments performed measurements for cross-sections spaced at 1.0-mm intervals. For each analyzed cross-section, the operator measured the area of the external elastic membrane (EEM) and the lumen. The accuracy and reproducibility of this method has been reported previously.¹⁷

Calculation of Efficacy Parameters

The primary efficacy parameter, change in percent atheroma volume (PAV), was calculated as previously described.¹⁰⁻¹⁶

$$PAV = \left(\frac{\sum (EEM_{CSA} - LUMEN_{CSA})}{\sum EEM_{CSA}} \right) \times 100$$

where EEM_{CSA} is the external elastic membrane cross-sectional area and LUMEN_{CSA} is the luminal cross-sectional area.

Several secondary IVUS efficacy parameters were prespecified, including the change in average maximum atheroma thickness, computed by measuring the maximum thickness of the atheroma in each cross section, then averaging these values for the entire artery. The secondary efficacy parameter "normalized total atheroma volume" was calculated as the average atheroma area per cross section multi-

plied by the median number of matched cross-sections in pullbacks for all patients completing the trial. This procedure adjusts for pullbacks with differing numbers of measured cross-sections, resulting in an equal weighting of each individual patient in computing efficacy results. An additional secondary efficacy parameter, change in atheroma volume in the most diseased 10-mm subsegment, was calculated by first determining the 10 contiguous cross-sections with the greatest atheroma volume at baseline, then comparing atheroma volume at follow-up for these same cross-sections.

PAV was selected as the primary efficacy parameter because this end point has exhibited the lowest variability in multiple previous IVUS trials for a diverse range of therapeutic interventions.^{10-12,14-16}

Statistical Methods

For continuous variables with a normal distribution, the mean and 95% confidence intervals (CIs) are reported. For variables not normally distributed, median and interquartile ranges are reported and 95% CIs around median changes were computed using bootstrap resampling. Intravascular ultrasonography efficacy parameters were analyzed using analysis of covariance and reported as least square means and 95% CIs using a linear model that included treatment group, pooled center, and baseline values as covariates. All *P* values are 2-sided and not adjusted for multiple testing. *P* values of ≤.05 were considered significant. A sensitivity analysis was performed using a multiple imputation procedure (PROC MI and ANALYSE in SAS version 9.1; SAS Institute Inc, Cary, North Carolina) to impute the IVUS end points for patients who did not have a follow-up IVUS performed.

For the primary efficacy parameter, change in PAV, the sample size was selected to provide 90% power at a 2-sided α of .05 to detect a treatment difference of 1.8% assuming a 5.0% standard deviation. A treatment difference of 1.8% and standard deviation of 5.0% was based on the differences between

Table 1. Baseline Demographic Characteristics and Medications at the Time of Randomization

	Glimepiride (n = 273)	Pioglitazone (n = 270)	P Value ^a
Age, mean (SD), y	59.7 (9.1)	60.0 (9.4)	.64
Men, No. (%)	180 (65.9)	186 (68.9)	.39
Race, No. (%) ^b			
White	220 (80.6)	225 (83.3)	.17
Black	27 (9.9)	30 (11.1)	
Asian	16 (5.9)	12 (4.4)	
Native American	10 (3.7)	3 (1.1)	
Ethnicity, No. (%)			
Hispanic	71 (26)	63 (23.3)	.21
Weight, mean (SD), kg	92.8 (18.5)	94.2 (19.7)	.28
BMI, mean (SD)	32.0 (5.2)	32.1 (5.3)	.91
Smoking status, No. (%)			
Current	53 (19.4)	31 (11.5)	.01
Past	119 (43.6)	147 (54.4)	.44
Never	99 (36.4)	89 (33.0)	.42
Duration of disease, median (IQR), mo			
Diabetes	71.0 (30.0-131.0)	70.0 (27.0-129.0)	.74
Coronary disease	8.0 (1.0-56.0)	9.0 (1.0-50.0)	.90
Hypertension, No. (%)	250 (91.6)	225 (83.3)	.002
Prior myocardial infarction, No. (%)	70 (25.6)	83 (30.7)	.08
Medication use, No. (%)			
Aspirin	251 (91.9)	242 (89.6)	.29
β-Blocker	211 (77.3)	205 (75.9)	.84
ACE inhibitor or ARB	229 (83.9)	217 (80.4)	.30
Statin	224 (82.0)	220 (81.5)	.87
Other lipid-lowering agent	17 (6.2)	13 (4.8)	.50
Metformin	174 (63.7)	176 (65.2)	.69
Insulin	63 (23.1)	49 (18.1)	.09

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; IQR, interquartile range.

^aComparisons were made after controlling for pooled center.

^bSelf-report by participant by selecting options from a list.

the 2 active therapies in patients with diabetes in a previous trial comparing moderate and intensive lipid-lowering therapies.¹¹ Approximately 330 patients with evaluable IVUS examinations at baseline and follow-up were required. Assuming a dropout rate of 25%, randomization of approximately 440 randomized individuals was anticipated. Due to an observed dropout rate of approximately 35% during study conduct, the enrollment target was increased to 540 patients. Analyses were performed using SAS version 8.2 (SAS Institute Inc).

To convert creatinine to μmol/L, multiply values by 88.4; C-reactive protein to nmol/L, multiply by 9.524; triglycerides to mmol/L, multiply by 0.0113; blood glucose to mmol/L, multiply by 0.0555; HDL-C and low-

density lipoprotein cholesterol (LDL-C) to mmol/L, multiply by 0.0259; and insulin to pmol/L, multiply by 6.945.

RESULTS

Patient Population

Between August 5, 2003, and March 31, 2006, 547 patients were randomized and 543 received study drug at 97 centers in North America and South America, 273 in the glimepiride group and 270 in the pioglitazone group. Evaluable baseline and follow-up IVUS examinations were available in 360 patients (66%), 181 in the glimepiride group and 179 in the pioglitazone group. The disposition of patients in the trial is shown in Figure 1.

Most demographic characteristics and baseline medications were similar in both treatment groups (TABLE 1). How-

ever, despite randomization, small, but statistically significant imbalances were observed for 2 characteristics. Patients randomized to receive glimepiride were more likely to report a history of hypertension, although baseline blood pressures were similar between treatment groups (TABLE 2). Patients randomized to receive pioglitazone were more likely to be former smokers, whereas patients randomized to receive glimepiride were more likely to be current smokers. Race and ethnicity were self-reported by selecting options from a list and were collected to determine whether these characteristics influenced the response of patients to the study treatments. Characteristics were similar in the 360 patients who completed the trial and the 183 patients who did not (data not shown).

A high percentage of patients received concomitant medications of established value in prevention of cardiovascular complications of diabetes. Greater than 80% of patients were receiving an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, more than 75% were receiving a β-blocker, approximately 90% were taking aspirin, and nearly 90% were receiving lipid-lowering therapy. The mean titrated daily dosage of glimepiride was 2.9 mg, and the mean titrated dosage of pioglitazone was 37.4mg.

Laboratory Results

Table 2 summarizes laboratory values, body weight, and blood pressures for the 360 patients who had evaluable IVUS examinations at both baseline and follow-up. FIGURE 2 shows changes during the course of the trial for HbA_{1c} levels, fasting plasma glucose, HDL-C, and high-sensitivity C-reactive protein. At baseline, in both treatment groups, mean HbA_{1c} concentration was 7.4%, LDL-C averaged approximately 95 mg/dL, HDL-C was slightly higher than 40 mg/dL, and fasting triglycerides was about 145 mg/dL. Blood pressure averaged approximately 128/75 mm Hg. There were no major differences in laboratory values for patients randomized to the 2

Table 2. Baseline and On-Treatment Vital Signs and Laboratory Values in Participants Completing the Trial (n = 360)^a

Parameters	Glimepiride (n = 181)	Pioglitazone (n = 179)	P Value ^b
Baseline Values			
HbA _{1c} , mean (SD), %	7.4 (1.0)	7.4 (1.0)	.76
Fasting blood glucose, mean (SD), mg/dL	148.0 (43.4)	147.2 (41.0)	.77
Fasting insulin levels, median (IQR), μU/mL	22.5 (15.5 to 32.0)	21.0 (16.0 to 33.0)	.52
Cholesterol, mean (SD), mg/dL			
Total	163.8 (38.0)	160.8 (35.7)	.47
LDL	94.4 (32.9)	93.5 (30.7)	.89
HDL	43.4 (13.9)	40.8 (11.5)	.05
Fasting triglycerides, median (IQR), mg/dL	145 (104 to 216)	139 (104 to 198)	.28
C-reactive protein, median (IQR), mg/L	3.0 (1.3 to 5.2)	2.6 (1.2 to 6.5)	.57
Brain-type natriuretic peptide, median (IQR), pg/mL	24.0 (11 to 42)	22.0 (11 to 52)	.60
Blood pressure, mean (SD), mm Hg			
Systolic	128.6 (17.1)	127.8 (16.6)	.95
Diastolic	75.2 (9.4)	75.7 (10.7)	.45
Weight, mean (SD), kg	93.3 (18.5)	94.3 (19.5)	.65
Average Values During Treatment^c			
HbA _{1c} , mean (SD), %	7.0 (1.0)	6.9 (0.9)	.04
Fasting blood glucose, mean (SD), mg/dL	147.9 (33.8)	139.3 (29.1)	.01
Fasting insulin levels, median (IQR), μU/mL ^d	26.5 (16.0 to 36.0)	16.0 (12.0 to 23.0)	<.001
Cholesterol, mean (SD), mg/dL			
Total	165.9 (35.7)	164.5 (35.9)	.95
LDL	96.1 (30.4)	95.6 (28.9)	.82
HDL	43.7 (12.4)	46.8 (11.7)	.03
Fasting triglycerides, median (IQR), mg/dL	152 (108 to 220)	119 (87 to 166)	<.001
C-reactive protein, median (IQR), mg/L ^d	2.2 (1.1 to 4.1)	1.2 (0.7 to 3.1)	<.001
Brain-type natriuretic peptide, median (IQR), pg/mL	22.6 (11.5 to 41.2)	32.4 (17.0 to 67.3)	<.001
Blood pressure, mean (SD), mm Hg			
Systolic	130.5 (11.9)	128.1 (11.1)	.07
Diastolic	75.9 (6.7)	74.5 (7.4)	.05
Weight, mean (SD), kg ^d	94.9 (19.1)	97.8 (21.1)	.16
Change From Baseline^{e,f,g}			
HbA _{1c} level, LS mean (95% CI), %	-0.36 (-0.48 to -0.24)	-0.55 (-0.68 to -0.42)	.03
Fasting blood glucose, LS mean (95% CI), mg/dL	0.41 (-3.66 to 4.48)	-8.5 (-12.73 to -4.27)	.003
Fasting insulin levels, median (95% CI), μU/mL, [% change] ^d	1.33 (-0.5 to 5.0) [8.5]	-5.0 (-7.0 to -4.0) [-28.3]	<.001
Cholesterol, LS mean (95% CI), mg/dL [% change]			
Total	1.16 (-2.9 to 5.3) [3.1]	2.5 (-3.3 to 8.3) [4.4]	.39
LDL	1.1 (-2.4 to 4.6) [6.9]	2.1 (-1.5 to 5.8) [6.6]	.69
HDL	0.9 (-0.3 to 2.1) [4.1]	5.7 (4.4 to 7.0) [16.0]	<.001
Fasting triglycerides, median (95% CI), mg/dL [% change]	3.3 (-10.7 to 11.7) [0.6]	-16.3 (-27.7 to -11.0) [-15.3]	<.001
C-reactive protein, median (95% CI), mg/L [% change] ^d	-0.4 (-0.9 to -0.2) [-18.0]	-1.0 (-1.5 to -0.8) [-44.9]	<.001
Brain-type natriuretic peptide, median (95% CI), pg/mL	0.58 (-2.0 to 4.5)	8.0 (5.0 to 10.5)	.001
Blood pressure, median (95% CI), mm Hg			
Systolic	2.3 (0.9 to 3.7)	0.1 (-1.4 to 1.5)	.03
Diastolic	0.9 (0.1 to 1.7)	-0.9 (-1.7 to -0.01)	.003
Weight, median (95% CI), kg ^d	1.6 (0.8 to 2.4)	3.6 (2.8 to 4.4)	<.001

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CI, confidence interval; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; LS, least squares.

SI conversion factors: To convert C-reactive protein to nmol/L; multiply by 9.524; fasting blood glucose to mmol/L, multiply by 0.0555; fasting insulin to pmol/L, multiply by 6.945; HDL, LDL, and total cholesterol to mmol/L, multiply by 0.0259; and triglycerides to mmol/L, multiply by 0.0113.

^aAll participants with a baseline and follow-up intravascular ultrasound examination who contributed to the primary efficacy parameter were included in this analysis.

^bP values for average follow-up values were generated from a 2-way analysis of variance model with terms for baseline, treatment, and pooled center.

^cMean (SD) or median (IQR) average postrandomization values.

^dLast observation carried forward.

^eLeast-square means for absolute and percentage change (%) were estimated using a 2-way analysis of variance with terms for treatment, pooled center and baseline value.

^fFor laboratory parameters with a nonnormal distribution (fasting insulin, triglycerides, and C-reactive protein), percentage change was estimated using the logarithm of the ratio of follow-up value to baseline value as the dependent variable.

^g95% CIs around medians were calculated using bootstrap resampling.

treatment groups, although patients randomized to glimepiride had a slightly higher mean HDL-C level, 43.4 mg/dL compared with 40.8 mg/dL for pioglitazone ($P = .05$).

During the first 24 weeks of the trial, HbA_{1c} values were reduced comparably in the 2 treatment groups, but subsequently diverged, with average postrandomization values slightly lower in the pioglitazone group, 6.9% compared with 7.0% in the glimepiride group ($P = .04$; Table 2 and Figure 2). The mean HDL-C levels increased from baseline significantly more in the pioglitazone treatment group, 5.7 mg/dL (95% CI, 4.4 to 7.0 mg/dL; 16.0%) compared with 0.9 mg/dL (95% CI, -0.3 to 2.1 mg/dL; 4.1%) for the glimepiride group, ($P < .001$; Table 2 and Figure 2). Changes from baseline in median levels of both triglycerides, -16.3 mg/dL (95% CI, -27.7 to -11.0 mg/dL; 15.3%)

vs 3.3 mg/dL (95% CI, -10.7 to 11.7 mg/dL; 0.6%) and high-sensitivity C-reactive protein, -1.0 mg/L (95% CI, -1.5 to -0.8 mg/L; 44.9%) vs -0.4 mg/L (95% CI, -0.9 to -0.2 mg/L; 18%) showed more favorable effects in the pioglitazone group compared with the glimepiride group ($P < .001$ for both comparisons). Glimepiride increased median fasting insulin levels by 1.33 μ U/mL (95% CI, -0.5 to 5.0 μ U/mL; 8.5%), whereas pioglitazone reduced median fasting insulin levels by 5.0 μ U/mL (95% CI, -7.0 to -4.0 μ U/mL; 28.3%; $P < .001$).

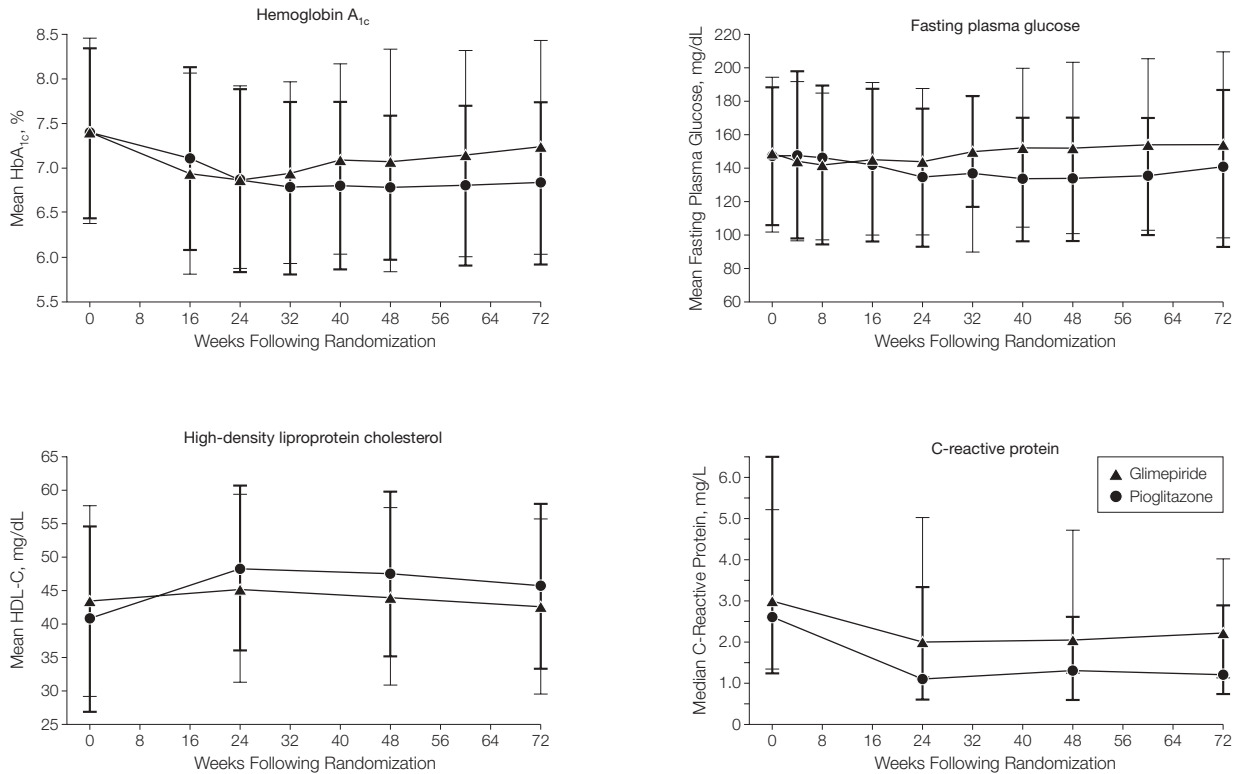
Systolic blood pressure increased in both treatment groups, but the median increase was smaller in the pioglitazone group, 0.1 (95% CI, -1.4 to 1.5 mm Hg) compared with the glimepiride group, 2.3 (95% CI, 0.9 to 3.7 mm Hg; $P = .03$). Compared with glimepiride, pioglitazone treatment was

associated with greater mean weight gain, 3.6 kg (95% CI, 2.8 to 4.4 kg) vs 1.6 kg (0.8 to 2.4 kg; $P < .001$), and an increase in brain-type natriuretic peptide levels, 8.0 pg/mL (95% CI, 5.0 to 10.5 pg/mL) vs 0.58 pg/mL (95% CI, -2.0 to 4.5 pg/mL; $P = .001$; Table 2).

IVUS Results

TABLE 3 summarizes the results for the primary and secondary IVUS efficacy parameters. The primary efficacy measure, least square mean change in percent atheroma volume, increased 0.73% (95% CI, 0.33% to 1.12%) in the glimepiride group ($P < .001$ for change from baseline) and decreased 0.16% (95% CI, -0.57% to 0.25%) in the pioglitazone group ($P = .44$ for change from baseline; between-treatment groups, $P = .002$). Analysis of the primary end point adjusting for baseline differences in smok-

Figure 2. Changes in Mean Hemoglobin A_{1c}, Fasting Plasma Glucose Levels, High-Density Lipoprotein Cholesterol, and C-Reactive Protein During the Trial (n = 360)



SI conversion factors: To convert C-reactive protein to nmol/L, multiply by 9.524; fasting plasma glucose to mmol/L, multiply by 0.0555; high-density lipoprotein cholesterol to mmol/L, multiply by 0.0259; and triglycerides to mmol/L, multiply by 0.0113. Error bars indicate standard deviations for the hemoglobin A_{1c}, glucose, and high-density lipoprotein cholesterol panels and interquartile range for the C-reactive protein panel.

ing did not significantly alter the results. A secondary efficacy measure, change in maximum atheroma thickness increased in the glimepiride group, 0.011 mm (95% CI, -0.0002 to 0.022 mm) and decreased in the pioglitazone group, -0.011 mm (95% CI, -0.022 to 0.0004 mm; between groups, $P = .006$). Another secondary IVUS parameter, normalized total atheroma volume, showed a greater reduction for pioglitazone compared with glimepiride: -5.5 mm^3 (95% CI, -8.67 to -2.38 mm^3) vs -1.5 mm^3 (95% CI, -4.50 to 1.54 mm^3) that did not reach statistical significance ($P = .06$), with a significant within-group decrease from baseline for the pioglitazone group ($P < .001$) and no change for the glimepiride group ($P = .34$). A secondary efficacy measure, change in the 10 mm of the most diseased segment showed no difference between the 2 treatment groups. FIGURE 3 shows a consistent treatment effect across multiple prespecified and exploratory subgroups with no statistical heterogeneity.

IVUS Results Imputing Noncompleters

Because of the relatively high rate (34%) of noncompletion of patients randomized in the trial (ie, no analyzable IVUS), a sensitivity analysis was performed in which values for the primary and secondary end points were imputed for each randomized patient not completing the trial. The imputation technique assigned changes in these efficacy end points for each noncompleter based on the patient's baseline characteristics, including demographics, laboratory values, and baseline atheroma volumes. The resulting analyses are shown in TABLE 4. For the primary efficacy parameter, PAV, the glimepiride group showed a mean increase of 0.64% (95% CI, 0.23% to 1.05%) vs -0.062% (95% CI, -0.47% to 0.35%) for the pioglitazone group ($P = .02$). Although all P values for IVUS efficacy parameters were reduced in statistical significance using the imputed results, the overall interpretation of the study was not altered.

Clinical Outcomes and Adverse Events

TABLE 5 shows centrally adjudicated clinical outcomes, investigator-reported adverse events, laboratory abnormalities, and reasons for discontinuing drug therapy during the trial. An independent committee blinded to treatment assignment centrally adjudicated major adverse cardiovascular events. Adjudicated end points included cardiovascular and noncardiovascular death, nonfatal myocardial infarction and stroke, hospitalization for unstable angina or congestive heart failure, and coronary revascularization. The investigators reported other listed adverse events, including hypoglycemia, angina pectoris, peripheral edema, hypertension, and bone fractures.

The frequency of major adverse cardiovascular events was similar in both treatment groups, although the trial was not powered to detect differences in morbidity and mortality. Among investigator-reported adverse events, hypo-

Table 3. Baseline, Follow-up, and Change From Baseline in Intravascular Ultrasound End Points

	Glimepiride (n = 181)		Pioglitazone (n = 179)		P Value ^a
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Baseline Examination					
Percent atheroma volume, % ^b	40.3 (8.9)	40.3 (34.7 to 45.9)	40.6 (8.4)	40.3 (34.1 to 46.0)	.54
Maximum atheroma thickness, mm ^c	0.82 (0.26)	0.80 (0.64 to 0.98)	0.81 (0.25)	0.79 (0.61 to 1.00)	.94
Normalized total atheroma volume, ^c mm ³	219.8 (95.2)	197.8 (148.1 to 277.7)	207.5 (83.8)	190.9 (147.6 to 254.5)	.27
Atheroma volume in 10-mm most diseased segment, ^c mm ³	64.7 (31.5)	62.1 (40.9 to 86.6)	62.7 (28.1)	59.4 (43.6 to 78.7)	.59
Follow-up Examination					
Percent atheroma volume, % ^b	41.0 (9.0)	40.5 (35.2 to 46.9)	40.5 (8.5)	40.5 (33.6 to 46.3)	.73
Maximum atheroma thickness, mm ^c	0.83 (0.26)	0.81 (0.64 to 0.99)	0.80 (0.24)	0.76 (0.62 to 0.97)	.39
Normalized total atheroma volume, ^c mm ³	217.7 (95.3)	192.6 (150.9 to 278.3)	200.8 (81.6)	184.5 (144.6 to 248.4)	.13
Atheroma volume in 10-mm most diseased segment, ^c mm ³	62.4 (31.2)	57.8 (39.5 to 83.1)	60.0 (27.5)	57.9 (39.7 to 77.8)	.62
Nominal Change From Baseline					
	LS Mean (95% CI)	P Value Change From Baseline	LS Mean (95%CI)	P Value Change From Baseline	P Value ^d
Percent atheroma volume, % ^b	0.73 (0.33 to 1.12)	<.001	-0.16 (-0.57 to 0.25)	.44	.002
Maximum atheroma thickness, mm ^c	0.011 (-0.0002 to 0.022)	.054	-0.011 (-0.022 to 0.0004)	.06	.006
Normalized total atheroma volume, ^c mm ³	-1.5 (-4.50 to 1.54)	.34	-5.5 (-8.67 to -2.38)	<.001	.06
Atheroma volume in 10-mm most diseased segment, ^c mm ³	-2.1 (-3.33 to -0.84)	.001	-2.0 (-3.33 to -0.67)	.003	.93

Abbreviation: CI, confidence interval; IQR, interquartile range; LS, least squares.

^a P values for baseline and average follow-up values were generated from a 2-way analysis of variance model with terms for treatment and pooled center.

^bPrimary efficacy parameter.

^cSecondary efficacy parameter.

^d P values from 2-way analysis of variance with terms for treatment and pooled center and baseline value as covariates.

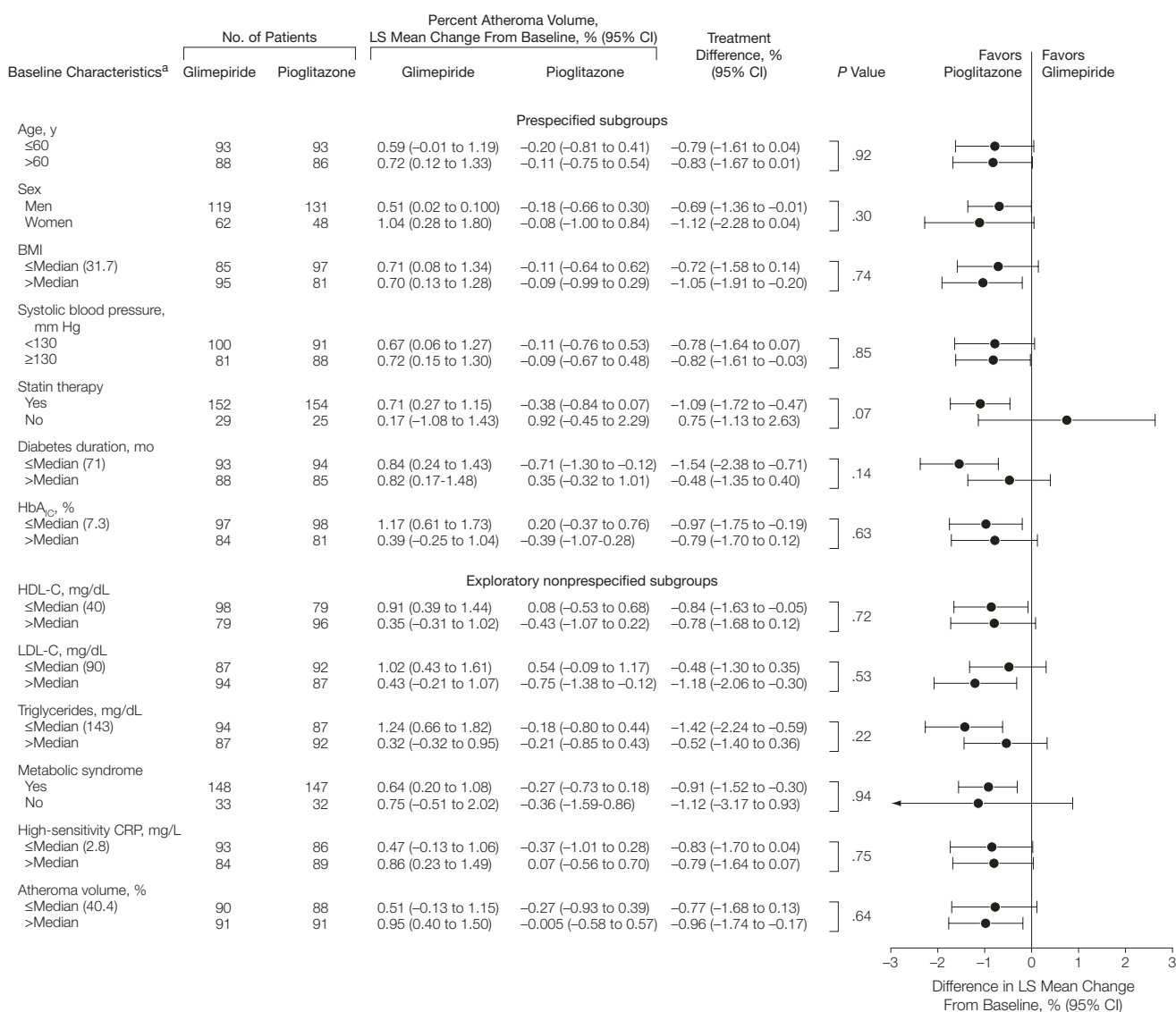
glycemia was more common in the glimepiride group 37.0% vs 15.2% ($P < .001$) and edema more common in the pioglitazone group, 17.8% vs 11% ($P = .02$). Angina pectoris was reported in 12.1% of glimepiride-treated patients and 7.0% of pioglitazone-treated patients ($P = .05$). In the pioglitazone group, fractures occurred in 3.0% of patients compared with none in the glimepiride group

($P = .004$). Decreases in hemoglobin were more common in the pioglitazone group ($P = .01$). An increase in fractures and reductions in hemoglobin level are both effects previously observed with TZD therapy. More patients randomized to pioglitazone had an increase in blood urea nitrogen levels ($P = .009$), but there were no differences in incidence of elevations in creatinine (Table 5).

COMMENT

Atherosclerosis in patients with diabetes is particularly aggressive, characterized by higher cardiovascular event rates and a greater severity of coronary obstructive disease.¹⁸⁻²¹ Cardiovascular disease represents the ultimate cause of death in approximately 75% of patients with diabetes.²² Accordingly, defining the optimal strategy for management of coronary disease in the diabetic

Figure 3. Primary Efficacy Parameter (Percent Atheroma Volume) in Prespecified Subgroups



P values for subgroup interaction were generated from a 2-way analysis of variance model with terms for treatment and pooled center and baseline value. BMI indicates body mass index, calculated as weight in kilograms divided by height in meters squared; CI, confidence interval; CRP, C-reactive protein; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LS, least squares.
^aMedian values are shown in parentheses.

Table 4. Change From Baseline in Intravascular Ultrasound End Points Using Imputed Values for Noncompleters

	Least Squares Mean Change From Baseline				Between-Group P Value ^a
	Glimepiride (n = 273)		Pioglitazone (n = 270)		
	LS Mean (95% CI)	P Value (Change From Baseline) ^a	LS Mean (95% CI)	P Value (Change From Baseline) ^b	
Percent atheroma volume, % ^b	0.64 (0.23 to 1.05)	.003	-0.062 (-0.47 to 0.35)	.77	.02
Maximum atheroma thickness, mm ^c	0.008 (-0.002 to 0.019)	.12	-0.011 (-0.023 to 0.001)	.07	.01
Normalized total atheroma volume, ^c mm ³	-1.37 (-4.37 to 1.62)	.37	-5.35 (-9.47 to -1.22)	.01	.14
Atheroma volume in 10-mm most diseased segment, ^c mm ³	-2.11 (-3.37 to -0.85)	.002	-2.52 (-3.73 to -1.31)	<.001	.66

Abbreviations CI, confidence interval, LS, least squares.

^aP values from 2-way analysis of variance with terms for treatment, pooled center, and baseline value as covariates.

^bPrimary efficacy parameter.

^cSecondary efficacy parameter.

population has important public health implications. Although cardiovascular disease represents a critical source of morbidity and mortality, there exist few data to support the preference of any specific glucose-lowering regimen to prevent these complications.³ Since the introduction of sulfonylureas nearly 50 years ago, several additional classes of oral hypoglycemic agents have been introduced. We sought to clarify the effects on coronary disease progression for 2 of these classes, a sulfonylurea, an insulin secretagogue, and a TZD, an insulin sensitizer, 2 diametrically opposite strategies for management of hyperglycemia.

The observation of a significant benefit for pioglitazone treatment represents, to our knowledge, the first demonstration of the ability of any hypoglycemic agent to slow the progression of coronary atherosclerosis in patients with diabetes. Evidence for a slowing of disease progression has proven a very challenging end point in recent years with the prominent failure of several promising approaches.^{15,16} Many observers have attributed the difficulty in further reducing atherosclerosis progression using novel therapies to the effectiveness of contemporary medical management, including statins and antihypertensive agents. In the current study, a high percentage of patients received optimal treatment with nearly 90% of patients receiving lipid-lowering therapy. Average LDL-C levels and blood pressures during treatment were below the current guideline targets. HbA_{1c} levels were con-

sistent with good diabetes management ($\leq 7.0\%$). Thus, pioglitazone showed the ability to further reduce disease progression on a background of contemporary medical therapy.

There are several potential explanations for these findings. The sulfonylurea, glimepiride, could have increased the rate of disease progression or alternatively, pioglitazone could have exerted an antiatherosclerotic effect, or both. We think that a proatherogenic effect of glimepiride is unlikely. Low-density lipoprotein cholesterol levels are highly predictive of coronary progression rates in IVUS trials. The rate of progression of atherosclerosis observed in the glimepiride treatment group is consistent with results in other IVUS trials for patients treated to comparable LDL-C levels.¹¹⁻¹⁶ However, the rate of progression in the pioglitazone group was substantially lower than might be expected for a population with observed LDL-C levels, particularly considering that prior IVUS studies have demonstrated a higher rate of coronary disease progression in patients with diabetes compared with those who do not have diabetes.²³

The precise mechanism for the observed antiatherosclerotic effect of pioglitazone remains uncertain. It seems unlikely that the small differences in HbA_{1c} levels between treatment groups (0.19%) could explain the observed differences in the rate of disease progression. Studies of glycemic management in type 2 diabetes have failed to show reduc-

tions in the incidence of macrovascular disease from much larger decreases in HbA_{1c} levels than observed in PERISCOPE.^{24,25} In the United Kingdom Prospective Diabetes Study (UKPDS), intensive therapy achieved a HbA_{1c} level of 7.0% vs 7.9% for standard therapy but showed no reduction in macrovascular complications.²⁵ Recently, the intensive treatment arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was stopped by the data monitoring committee because the intensive treatment group (median HbA_{1c} level 6.4%) showed increased mortality compared with the standard treatment group (median HbA_{1c} levels 7.5%).²⁶

The HbA_{1c} levels observed in the PERISCOPE trial were approximately midway between the intensive and the standard treatment groups in ACCORD and were similar to the intensive treatment group in UKPDS. Moreover, a post hoc exploratory analysis examining outcomes based on whether patients reached an HbA_{1c} of 7% or lower showed that the achieved HbA_{1c} level was not an important mediator of the atherosclerosis progression rate (P value for interaction = .74). Accordingly, it seems unlikely that a 0.19% difference in HbA_{1c} levels could explain the observed benefits of pioglitazone on disease progression.

Alternatively, differences between these 2 treatments in nonglycemic effects seem more likely to explain the observed outcomes. Diabetes promotes

atherosclerosis in the setting of profound metabolic and physiologic effects. Adverse metabolic effects include abnormalities in lipid metabolism, an increased incidence of hypertension, promotion of coagulation, and increased systemic inflammation.²⁷ Several biomarkers associated with atherosclerosis progression were favorably affected by pioglitazone, including

a 16% increase in HDL-C, and substantial reductions in both triglyceride levels (15%) and C-reactive protein levels (45%). A more favorable effect on blood pressure was also observed. Pioglitazone also significantly reduced fasting-serum insulin levels. Insulin resistance, resulting in hyperinsulinemia, is associated with adverse cardiovascular outcomes.²⁸ Accordingly, it re-

mains theoretically possible that an insulin-sensitizing therapy confers independent antiatherosclerotic benefits over an insulin-providing treatment strategy. These hypotheses will be explored in subsequent post hoc analyses of the current trial.

It cannot be assumed that the observed benefits of pioglitazone represent a “class effect” of TZDs. The only

Table 5. Clinical End Points, Adverse Events, Laboratory Abnormalities, and Reasons for Discontinuing Participation (Safety Population, n = 543)

	No. (%) of Patients		P Value
	Glimepiride (n = 273)	Pioglitazone (n = 270)	
Centrally Adjudicated Cardiovascular Events^a			
Composite of cardiovascular death, nonfatal MI, or nonfatal stroke	6 (2.2)	5 (1.9)	.78
Composite of cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, or congestive heart failure	13 (4.8)	11 (4.1)	.70
Composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary or carotid revascularization, hospitalization for unstable angina, or congestive heart failure	41 (15.0)	40 (14.8)	.95
Cardiovascular death	1 (0.36)	3 (1.1)	.37
Noncardiovascular death	1 (0.36)	0 (0.0)	>.99
Nonfatal MI	4 (1.5)	2 (0.7)	.69
Nonfatal stroke	1 (0.36)	0 (0.0)	>.99
Hospitalization for unstable angina	2 (0.7)	4 (1.5)	.45
Coronary revascularization	30 (11.0)	29 (10.7)	.93
Hospitalization for congestive heart failure	5 (1.8)	4 (1.5)	>.99
Investigator-Reported Adverse Events			
Hypoglycemia	101 (37.0)	41 (15.2)	<.001
Angina pectoris	33 (12.1)	19 (7.0)	.05
Peripheral edema	30 (11.0)	48 (17.8)	.02
Hypertension	24 (8.8)	13 (4.8)	.07
Bone fracture	0 (0)	8 (3.0) ^c	.004
Central Laboratory Abnormalities			
ALT >3 × ULN	3 (1.1)	2 (0.7)	>.99
Serum urea nitrogen >30 mg/dL	13 (4.8)	29 (10.7)	.009
Creatinine >2.0 mg/dL	2 (0.7)	3 (1.1)	.69
Hematocrit decrease >20%	3 (1.1)	8 (3.0)	.12
Hemoglobin decrease >3 g/dL	2 (0.7)	11 (4.1)	.01
Reasons for Discontinuation of Drug Therapy (n = 192)^b			
Adverse event	34 (12.5)	30 (11.1)	.63
Lack of efficacy	1 (0.4)	4 (1.5)	.21
Lost to follow-up	6 (2.2)	4 (1.5)	.75
Study termination at site	9 (3.3)	7 (2.6)	.63
Protocol violation	3 (1.1)	6 (2.2)	.34
Voluntary withdrawal by participant	34 (12.5)	40 (14.8)	.42
Investigator's discretion	8 (2.9)	6 (2.2)	.60
Total Not Completing the Trial	95 (34.8)	97 (35.9)	.78

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; MI, myocardial infarction ULN, upper limit of normal.

SI conversion factors: To convert ALT to $\mu\text{kat/L}$, multiply by 0.0167; creatinine to $\mu\text{mol/L}$, multiply by 76.25; urea nitrogen to mmol/L , multiply by 0.357;

^aAdverse events were collected for 30 days following each participant's last dose.

^bThis represents patients who discontinued before the final visit (week 172) regardless of whether a final intravascular ultrasound was obtained.

^cSix women, 2 men; location: foot, 2; humerus, 2; lower limb, 2; malleolar, 1; metacarpal, 1; facial, 1; rib, 1; upper limb, 1; wrist, 1 (total number >8, because of multiple fractures in the same patient).

other agent in the class, rosiglitazone, increases LDL-C approximately 18%, and exhibits less favorable effects on other biomarkers, including HDL-C and triglycerides.^{5,29} In addition, rosiglitazone has been associated with an increased risk of myocardial infarction or other ischemic events in several meta-analyses, whereas a similar meta-analysis of pioglitazone showed a reduction in the risk of adverse cardiovascular outcomes.^{30,31} Furthermore, a well-controlled randomized trial in another vascular bed, the carotid artery, demonstrated an absence of progression of intimal medial thickness for pioglitazone-treated patients and progression in glimepiride-treated patients.⁷ A placebo-controlled clinical outcomes trial investigating pioglitazone reported a reduction in major adverse cardiovascular events that did not reach conventional levels of statistical significance (hazard ratio, 0.90; 95% CI, 0.80-1.02; $P = .095$), but showed a significant reduction in the composite of death, myocardial infarction, and stroke (hazard ratio, 0.84; 0.72-0.98, $P = .027$).⁶

The benefits of any therapy must always be evaluated in the context of treatment-emergent adverse effects. In the current study, both regimens were well tolerated but exhibited a different pattern of adverse effects. Hypoglycemia was more prevalent in the glimepiride group and edema more common in the pioglitazone group, but neither case resulted in a difference in rates of discontinuation of therapy (Table 5). Fractures occurred in 3.0% of pioglitazone-treated patients and none of the glimepiride-treated patients. Patients gained weight on both regimens, but the weight gain was approximately 2 kg greater in the pioglitazone group. There were no observed differences in major cardiovascular morbidity or mortality, although the trial was not powered to assess clinical outcomes. We therefore conclude reduced atherosclerosis progression was associated with a reasonable safety profile, generally comparable with glimepiride, although there were distinct differences in the types of adverse effects for the 2 drugs.

We recognize that the current study has limitations. The withdrawal rate of patients in this trial (35%) was higher than for most recent IVUS studies.^{11,12,14-16} We attribute the higher drop-out rate to the difficulty of maintaining patients on complex antidiabetic regimens for the course of the trial. This observation is consistent with the approximate 30% withdrawal rate in a contemporary, noninvasive diabetes trial of the same duration and using the same comparators.⁷ The demographic and laboratory characteristics of completers and noncompleters were similar and a post hoc sensitivity analysis imputing efficacy values for noncompleters did not alter interpretation of the trial. Intravascular ultrasonography evaluates the effect of therapies on the change in atherosclerotic disease burden, not morbidity and mortality. The magnitude of the differences in progression rates observed in the current trial are similar to the results reported for other beneficial therapies, such as statins or blood pressure-lowering agents.^{11,12,14} However, clinical outcomes trials, not surrogate end point studies, are the preferred approach to the determination of the benefits of any therapeutic intervention, particularly in the context of the current controversy regarding the cardiovascular effects of TZDs. Unfortunately, few current trials are comparing clinical outcomes for alternative antidiabetic therapies. A recently announced large comparative trial of several diabetes therapies, including rosiglitazone, will not report findings until 2014.³²

Despite these limitations, the current study provides potentially useful insights into the cardiovascular effects of these 2 diabetes treatment strategies. The findings of the PERISCOPE study support the conclusion that treatment with the insulin-sensitizing TZD, pioglitazone compared with glimepiride can prevent the progression of atherosclerosis in patients with type 2 diabetes during 18 months of treatment. Patients randomized to pioglitazone exhibited a lower rate of progression of coronary atherosclerosis across a wide

array of prespecified and exploratory subgroups. These findings may have important implications for defining the optimal strategy for management of patients with type 2 diabetes and coronary atherosclerosis.

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Independent Statistical Analysis: An independent statistical analysis was conducted by Kathy Wolski, MPH, from the Department of Cardiovascular Medicine at the Cleveland Clinic Foundation. Ms Wolski received the trial database from the sponsor, which included all the raw data, not just derived datasets; and independently computed the IVUS efficacy parameters, safety measures, laboratory parameters, and demographic variables. Ms Wolski is employed by the Cleveland Clinic Cardiovascular Coordinating Center, which received compensation from the sponsor for conducting the trial, including reimbursement for statistical services.

An additional independent statistical analysis was performed by Bo Hu, PhD, from the Department of Quantitative Health Sciences at Cleveland Clinic. Dr Hu is also an adjunct assistant professor in the Department of Statistics at Case Western Reserve University. Dr Hu received the entire trial database and independently confirmed Ms Wolski's findings. Dr Hu received compensation from the coordinating center, but not from the sponsor, for statistical services. The results reported in this article are based on the independent analyses.

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