PERISCOPE

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

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Background and Objectives

- Cardiovascular disease is the leading cause of death in patients with diabetes.
- Few studies have compared outcomes for diabetes medications beyond their glucose lowering efficacy.
- We sought to compare coronary disease progression measured by intravascular ultrasound for two alternative treatment strategies:
  - Glimepiride (an insulin secretagogue)
  - Pioglitazone (an insulin sensitizer)

Methods

- Patients selected with type 2 diabetes undergoing angiography for clinical indications.
- Baseline intravascular ultrasound (IVUS) performed to determine atheroma volume.
- 543 patients randomized to glimepiride 1-4mg or pioglitazone 15-45mg titrated to maximally tolerated dose by 16 weeks.
- After 18 months, IVUS of the originally examined coronary artery performed in 360 participants.

Baseline Patient Characteristics (n=543)

	Glimepiride (n=273)	Pioglitazone (n=270)
Age (years)	59.7	60.0
Male gender	65.9%	68.9%
White	80.6%	83.3%
DM duration (years)	5.9	5.8
Weight (kg)	92.8	94.2
BMI	32.0	32.1
Hypertension	91.6%*	83.3%*
Current Smoker	19.4%†	11.5%†

*P = 0.002 †P = 0.01

Baseline Medications (n=543)

	Glimepiride (n=273)	Pioglitazone (n=270)
Aspirin	91.9%	89.6%
ß-blocker	77.3%	75.9%
ACEi or ARB	83.9%	80.4%
Statin	82.0%	81.5%
Metformin	63.7%	65.2%
Insulin	23.1%	18.1%

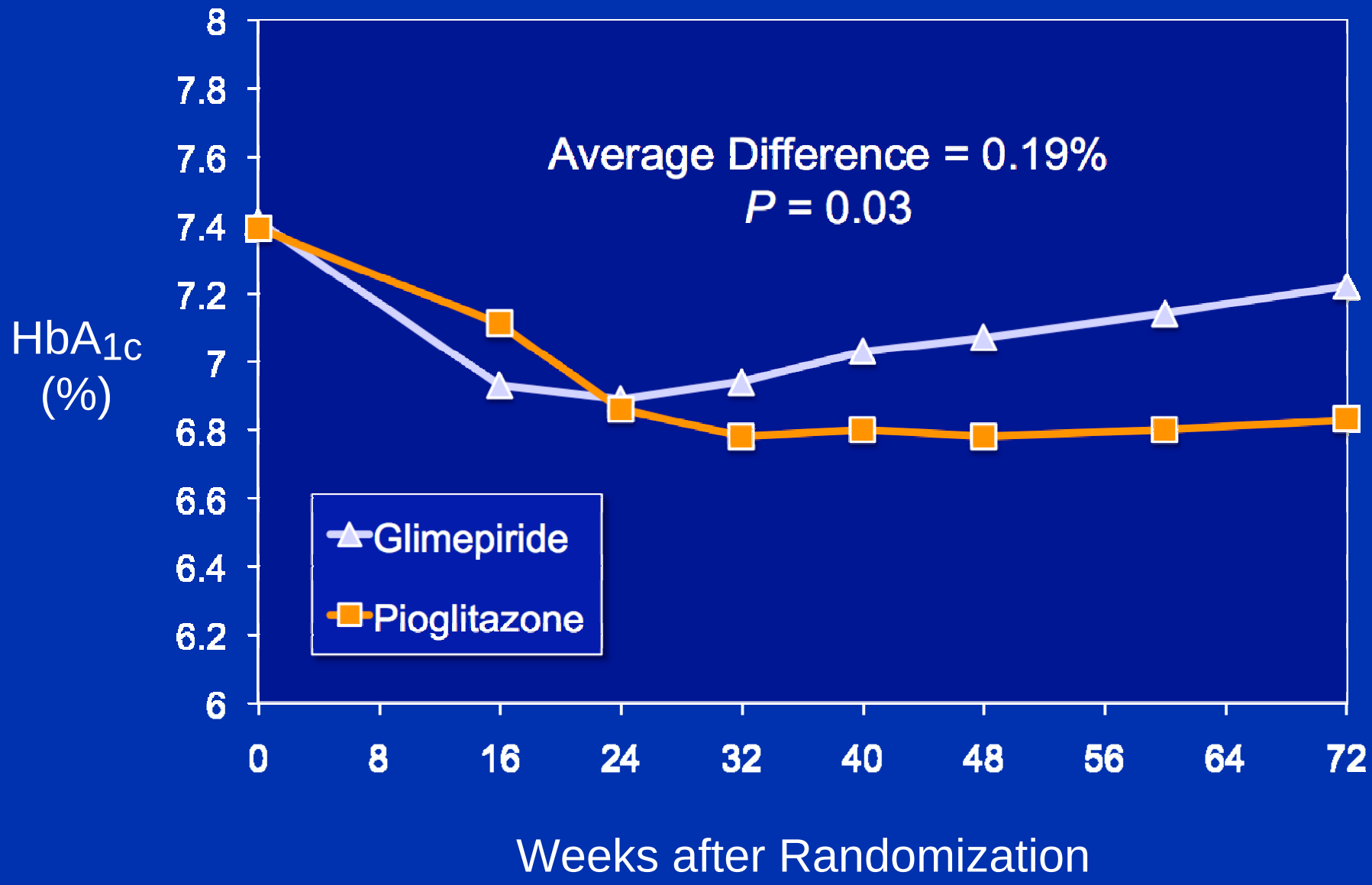
Baseline Laboratory Values & Blood Pressure*

	Glimepiride (n=181)	Pioglitazone (n=179)
HbA_{1c} (%)	7.4	7.4
LDL-cholesterol (mg/dL)	94.4	93.5
HDL-cholesterol (mg/dL)	43.4†	40.8
Triglycerides (mg/dL)	145	139
hsCRP (mg/L)	3.0	2.6
Systolic BP (mmHg)	128.6	127.8
Diastolic BP (mmHg)	75.2	75.7

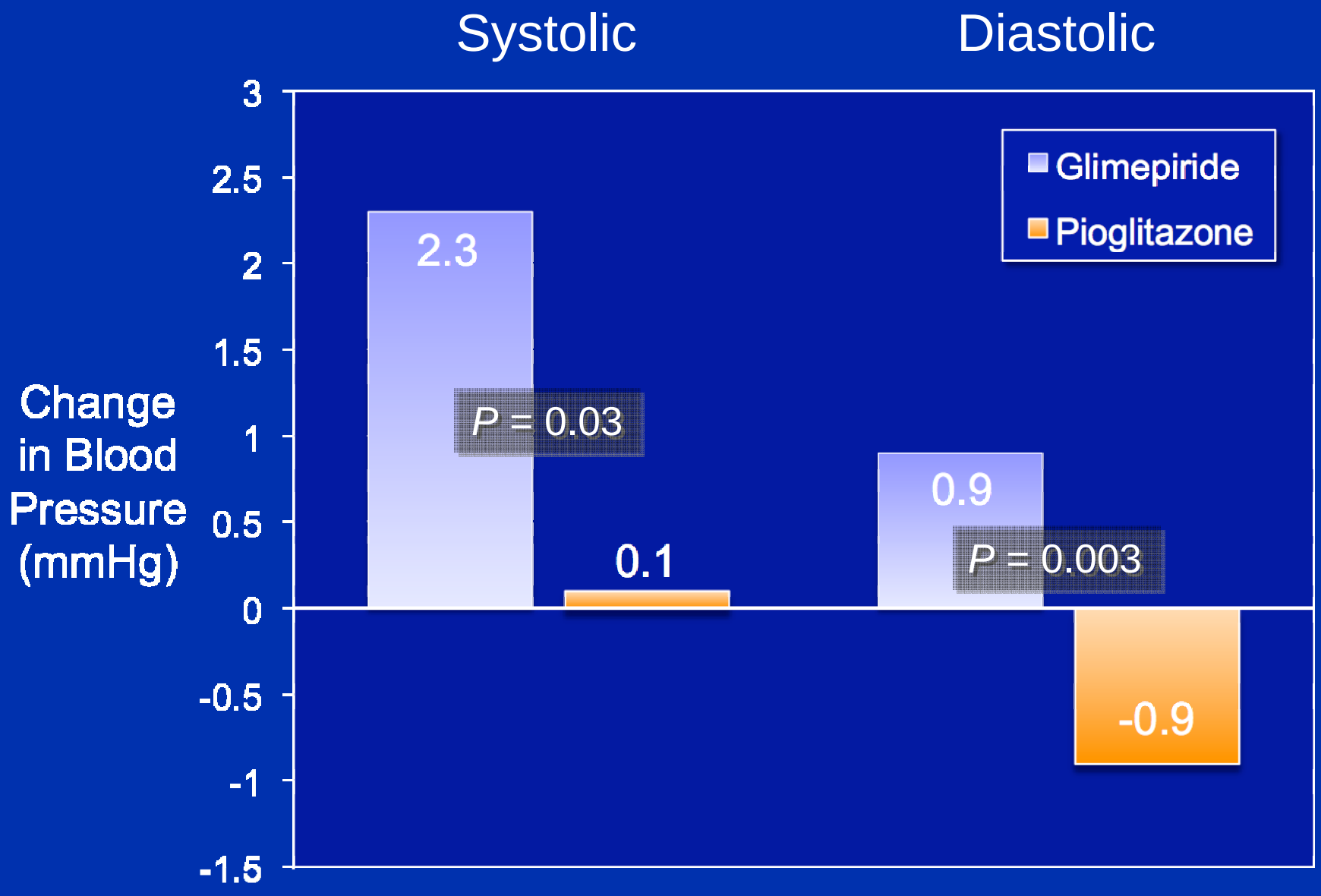
*N=360 (patients with both baseline and final IVUS)

†*P* = 0.05

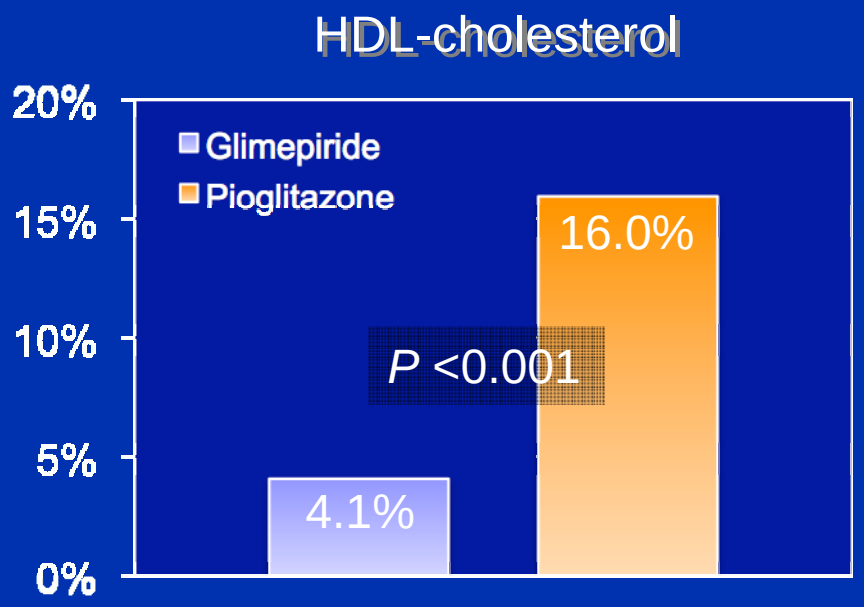
Glycohemoglobin Levels during the Trial

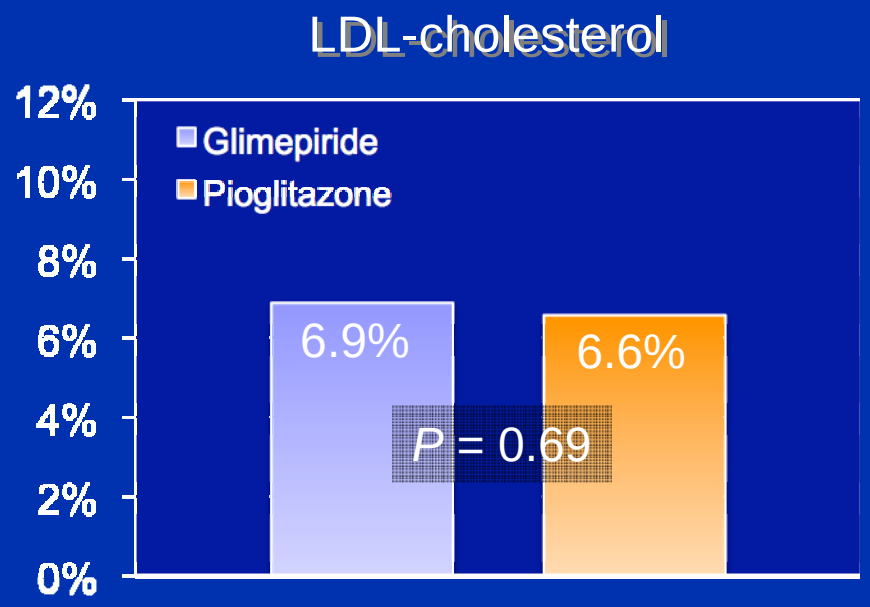


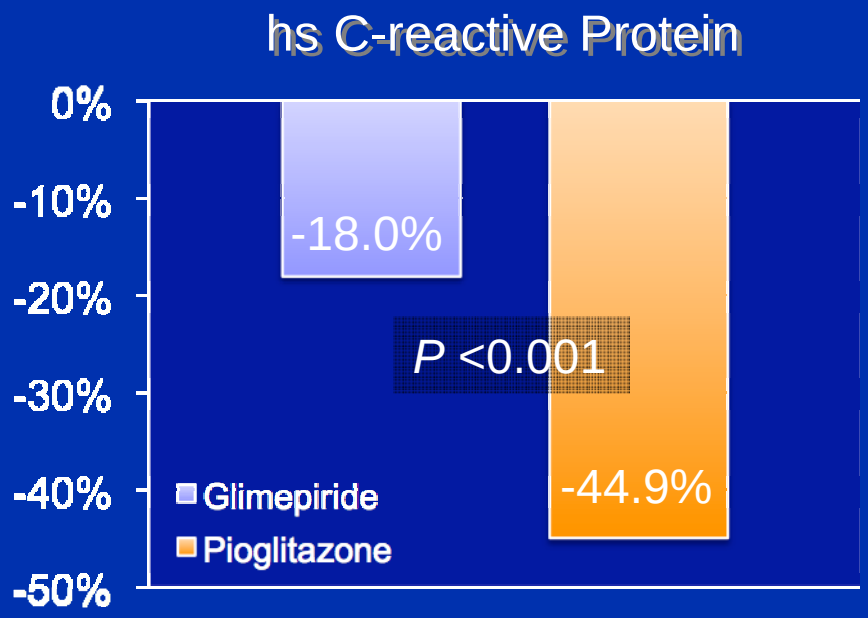
Mean Changes in Blood Pressure (n = 360)

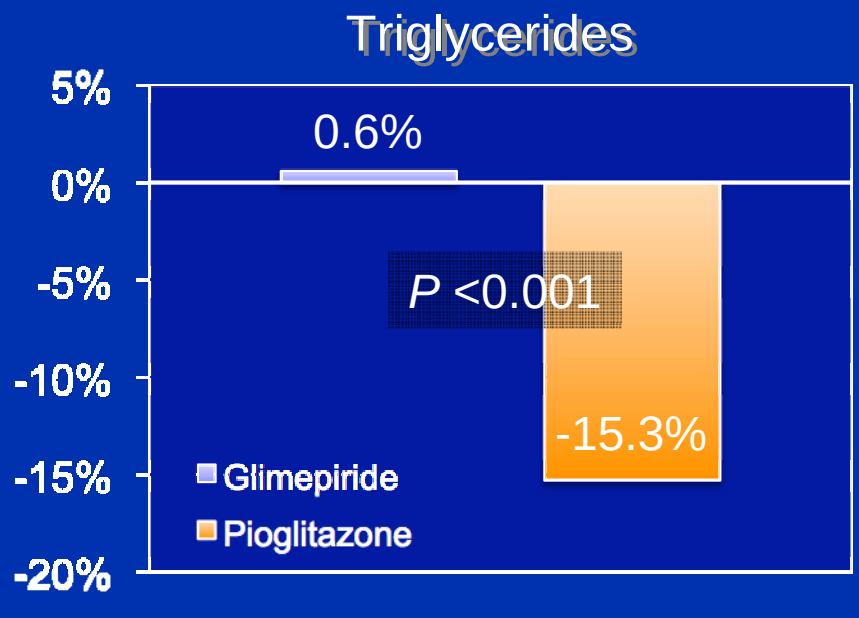


Percentage Changes: Biochemical Parameters



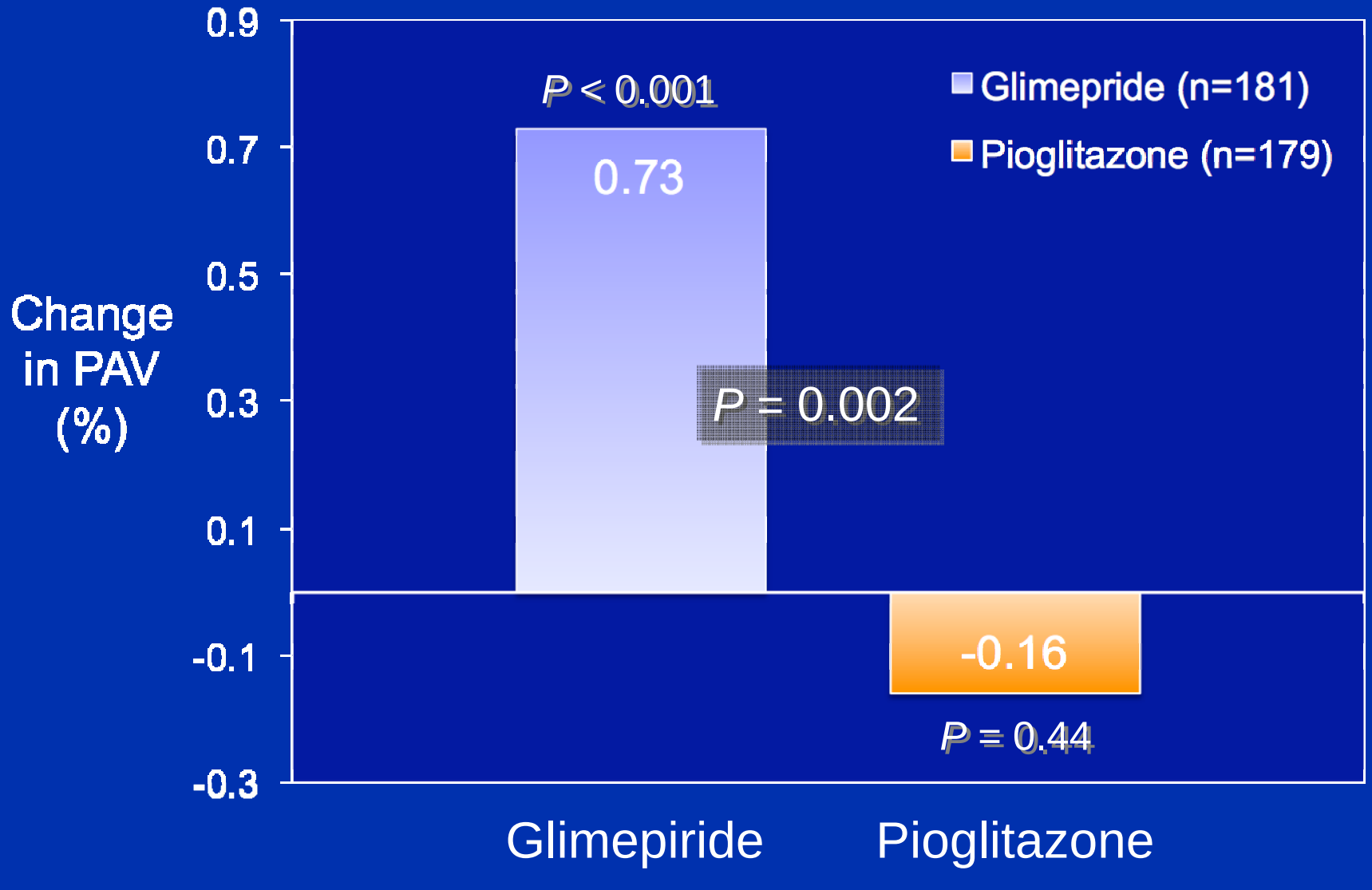




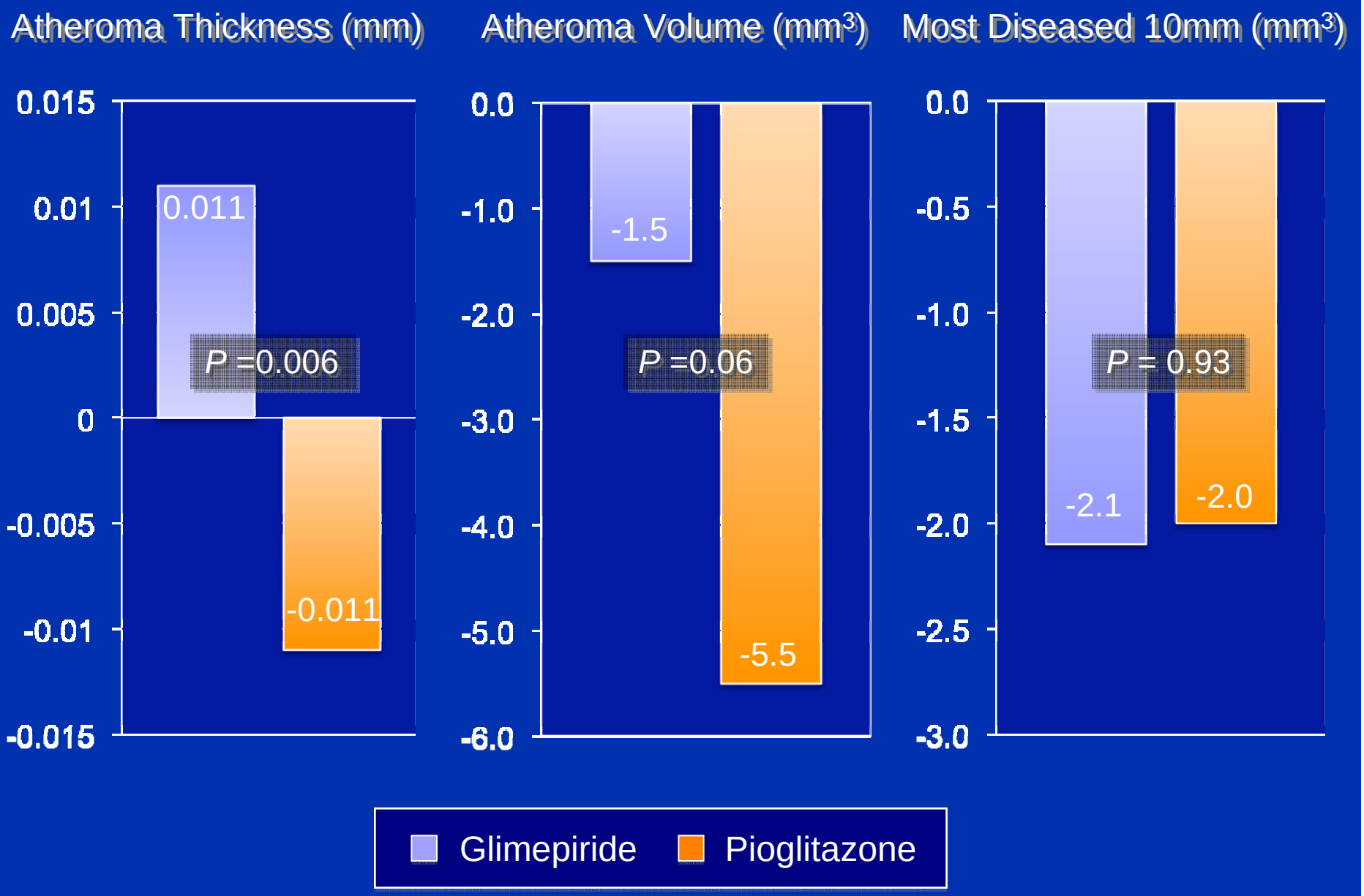


Primary Efficacy Parameter

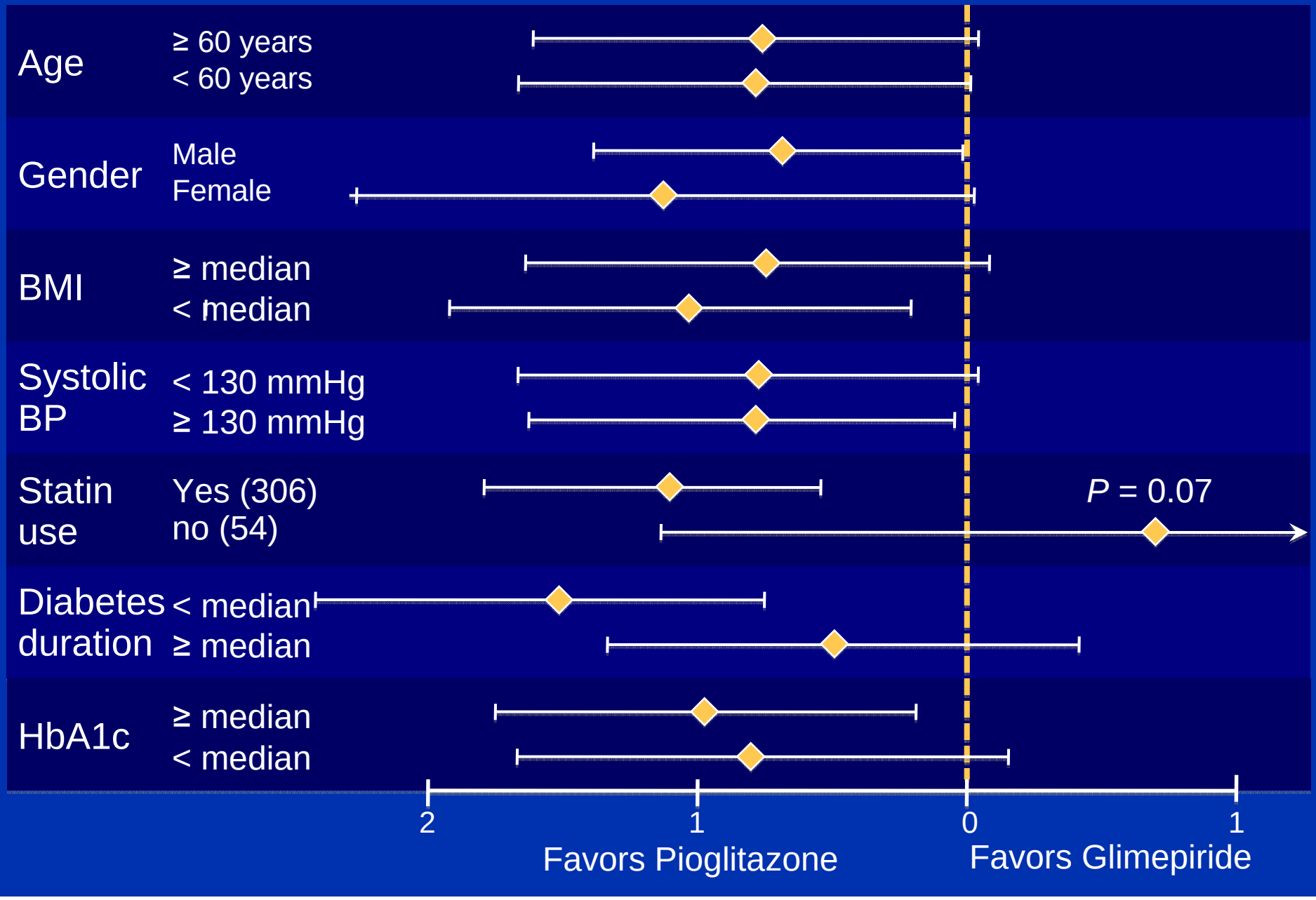
Change in Percent Atheroma Volume (%)



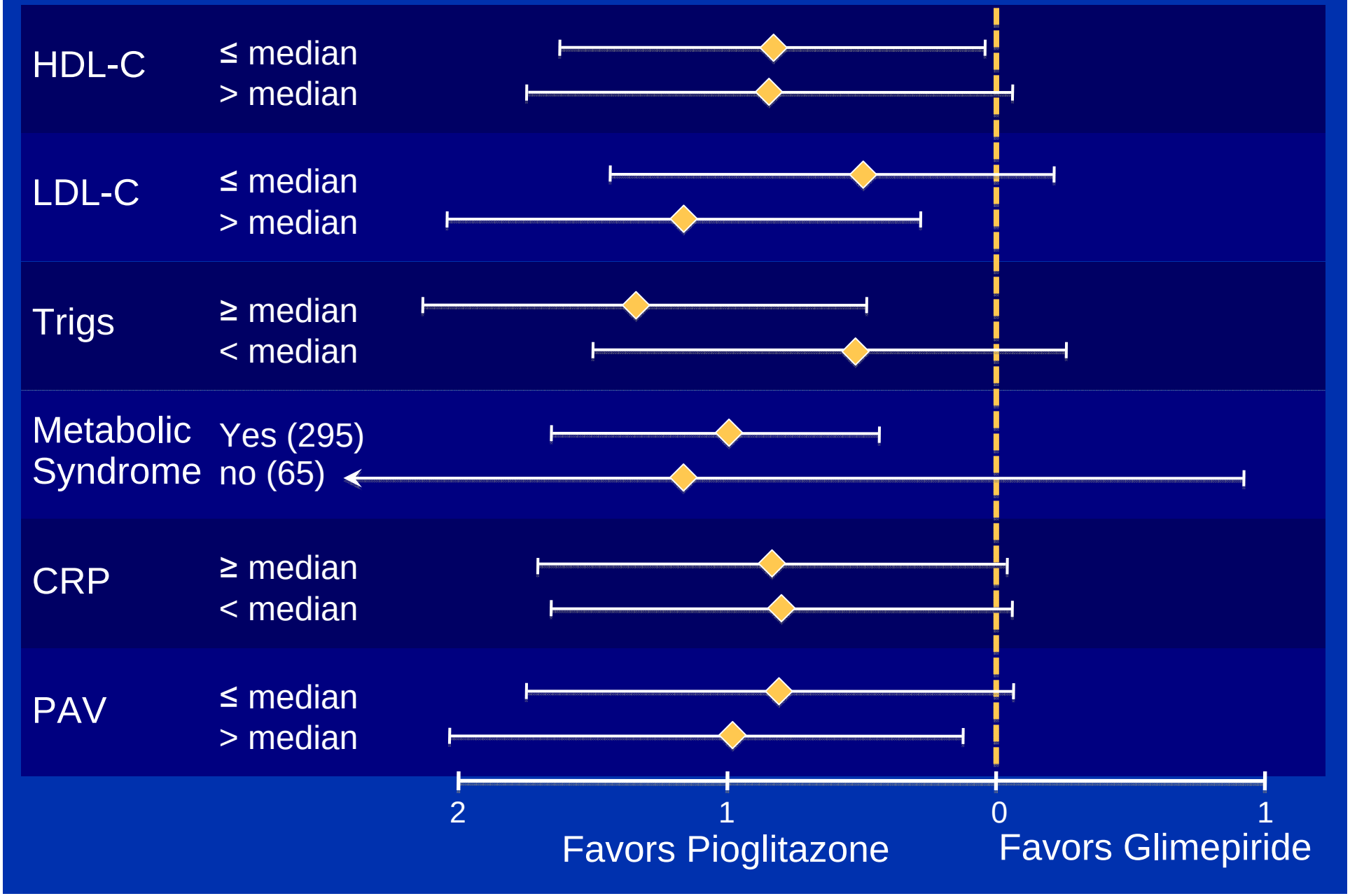
Intravascular Ultrasound: Secondary Endpoints



Change in PAV in Pre-specified Subgroups



Change in PAV in Exploratory Subgroups



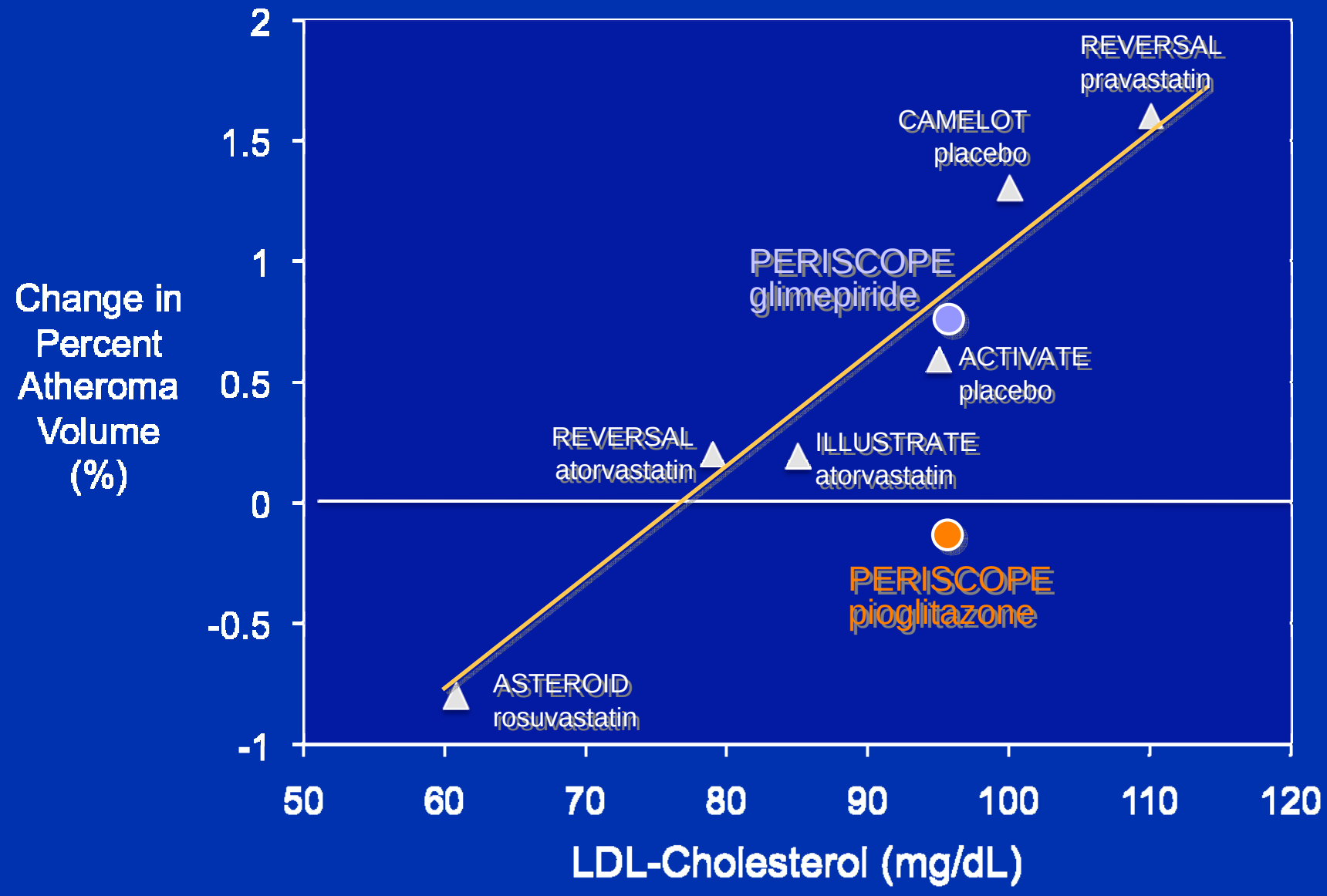
Adjudicated Major Cardiovascular Events

	Glimepiride (n=273)	Pioglitazone (n=270)
Composite of CV death, nonfatal MI, or nonfatal stroke	2.2%	1.9%
Cardiovascular death	0.4%	1.1%
Nonfatal myocardial infarction	1.5%	0.7%
Nonfatal stroke	0.4%	0%
Non-cardiovascular death	0.4%	0%
Hospitalization for unstable angina	0.7%	1.5%
Coronary revascularization	11.0%	10.7%
Hospitalization for CHF	1.8%	1.5%

Other Adverse Effects

	Glimepride (n=273)	Pioglitazone (n=270)	*P* value
Hypoglycemia	37.0%	15.2%	<0.001
Edema	11.0%	17.8%	0.02
Angina	12.1%	7.0%	0.05
BUN >30 mg/dL	4.8%	10.7%	0.01
Creatinine > 2.0 mg/dL	0.7%	1.1%	0.69
Hypertension	8.8%	4.8%	0.07
Bone Fractures	0%	3.0%	0.004
Change in Body Weight	+1.6kg	+3.6kg	<0.001

PERISCOPE: Comparison to Other Trials



Conclusions

- Pioglitazone, on a background of optimal medical therapy, prevented progression of coronary atherosclerosis, *P* = 0.002 compared with glimepiride.
- Compared with glimepiride, pioglitazone produced similar, although more durable, glucose-lowering.
- Pioglitazone favorably affected BP, raised HDL-C (16.0% vs. 4.1%), lowered triglycerides (-15.3% vs. +0.6%) and reduced hsCRP (-44.9% vs. -18.0%).
- Hypoglycemia and angina were more common with glimepiride treatment; edema, fractures and weight gain more frequent with pioglitazone treatment.

ORIGINAL CONTRIBUTION

JAMA-EXPRESS

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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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

Some Final Thoughts

There exist few comparative effectiveness trials examining endpoints other than glycemic control for anti-diabetic medications.

Given the recent controversy about the effects of diabetes treatments on cardiovascular disease, we urgently must close this knowledge gap.

We hope the PERISCOPE trial will encourage further studies examining alternative diabetes management strategies, particularly clinical outcomes trials.

Backup Slides

Changes in Laboratory Values and BP

	Glimepiride (n=181)	Pioglitazone (n=179)	*P* value
HbA_{1c}	-0.36%	-0.55%	0.03
LDL-cholesterol	+6.9%	+6.6%	0.69
HDL-cholesterol	+4.1%	+16.0%	<0.001
Triglycerides	+0.6%	-15.3%	<0.001
hsCRP	-18.0%	-44.9%	<0.001
Systolic BP	+2.3 mmHg	+0.1 mmHg	0.03
Diastolic BP	+0.9 mmHg	-0.9 mmHg	0.003

Other Biomarkers: Insulin Levels and BNP