Effect of Rosiglitazone Versus Glipizide on Progression of Coronary Atherosclerosis in Patients with Type 2 Diabetes and Coronary Artery Disease

The APPROACH Trial

Assessment on the Prevention of Progression by Rosiglitazone On Atherosclerosis in Diabetes Patients with Cardiovascular History

Richard Nesto MD, Christopher Cannon MD, Hertzel Gerstein MD MSc, Robert Ratner MD, Patrick Serruys MD PhD, Gerrit-Anne van Es PhD, Nikheel Kolatkar MD MPH, Barbara Kravitz MS, Allen Wolstenholme PhD, Andrew Zalewski MD PhD, Peter Fitzgerald MD PhD

Disclosures

APPROACH Steering Committee:

Richard Nesto, MD – Speakers Bureau: GlaxoSmithKline, Takeda; Advisor: GlaxoSmithKline

Christopher Cannon, MD – Grants: Accumetrics, AstraZeneca, Bristol-Myers Squibb/Sanofi Partnership, GlaxoSmithKline, Merck, Merck/Schering Plough Partnership; Advisor/Equity: Automedics Medical Systems

Hertzel Gerstein, MD MSc – Honoraria: AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Lilly, Merck, Novo Nordisk, Sanofi-Aventis; Grants: GlaxoSmithKline, King, Merck, Novo Nordisk, Sanofi-Aventis

Robert Ratner, MD – Grants: AstraZeneca, Bayhill Therapeutics, Boehringer Ingelheim, GlaxoSmithKline, Merck, Novo Nordisk, Pfizer, Takeda, Veralight; Advisor: Amylin, AstraZeneca, Eli Lilly, GlaxoSmithKline, Lifescan, Novo Nordisk, Roche, Sanofi-Aventis, Sirtris, Takeda, Tethys; Stock (> $10,000 value): Abbott, Johnson & Johnson, Merck

Patrick Serruys, MD PhD – Honoraria: GlaxoSmithKline

Gerrit-Anne Van Es, PhD – Employment: Cardialysis; Honoraria: GlaxoSmithKline

Andrew Zalewski, MD PhD – Employment and stock: GlaxoSmithKline

Peter Fitzgerald, MD PhD – Honoraria: GlaxoSmithKline

Additional Authors:

Barbara Kravitz, MS; Nikheel Kolatkar, MD MPH; Allen Wolstenholme, PhD – Employment and stock: GlaxoSmithKline

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Background

- Diabetes is a strong risk factor for CV events and atherosclerosis
- TZDs (rosiglitazone and pioglitazone) lower glucose, BP, inflammatory markers, and improve lipid profile, endothelial function, and carotid IMT
- TZDs may therefore reduce progression of coronary atherosclerosis compared to other antidiabetic drugs
- This study was designed to assess the effect of rosiglitazone (insulin sensitizer) vs glipizide (insulin secretagogue) on IVUS measures of atherosclerosis in native coronary arteries

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Methods

- Multicenter, double-blind RCT of rosiglitazone vs glipizide (19 countries, 92 centers)
- ***Key eligibility criteria:***
  - Clinically indicated angiography or PCI
  - ≥1 plaque and 10–50% narrowing in a non-intervened coronary
  - Type 2 diabetes with HbA1c 6.6–8.5%, on 0, 1 or 2 oral agents
  - No CABG, valvular heart disease, EF <40%, CHF, renal disease, liver disease or uncontrolled BP
- ***Endpoints:***
  - Primary:
    - Change in percent atheroma volume
  - Key Secondary:
    - Change in normalized total atheroma volume
    - Change in atheroma volume in the most diseased 10 mm segment

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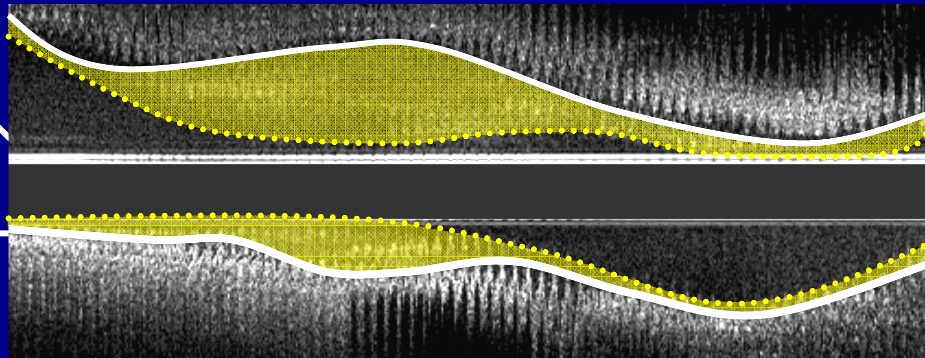
IVUS Analysis was Performed by a Blinded Core Lab (Cardialysis, Rotterdam, The Netherlands)

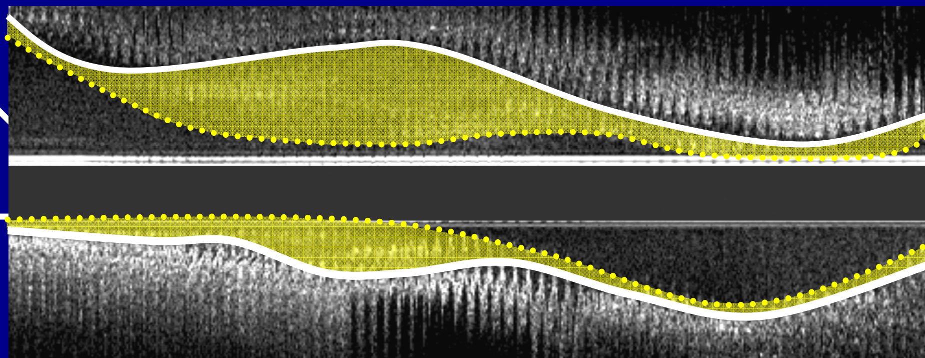
Selection of Region-Of-Interest

Baseline



← length of the pullback ~40mm →

18 months



All acquired IVUS frames were analyzed longitudinally

Methods

- Randomized to blinded rosiglitazone titrated to 8 mg/d or glipizide titrated to 15 mg/d
- Metformin or insulin could be added after 3 months as needed targeting HbA1c ≤ 7%
- Other CV risk factors were treated according to regional guidelines and clinical judgment
- Sample size calculations showed that N ≥ 634 randomized [412 pairs of IVUS measurements] would give 90% power to detect a primary outcome difference of 1.6% (with SD of 5% and non-completion of 35%)
- Data are presented for patients with an evaluable baseline and final IVUS at 18 months (N = 462/672; 69%)

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Baseline Characteristics (N = 672)

	N = 672
Age (years)	61
Male (%)	68
BMI (kg/m^2)	30
Median diabetes duration (years)	4.8
Prior MI (%)	24
Diabetes meds 0/1/2 (%)	18/54/28

	N = 672
HbA1c (%)	7.2
LDL (mg/dL)	90
HDL (mg/dL)	43
TG (mg/dL)	161
BP (mmHg)	129*/76
hsCRP (mg/L)	5.1
Creatinine (mg/dL)	1.0*

*$P < 0.05$
BP: glipizide 131/76, rosiglitazone 128/75
Creatinine: glipizide 0.98, rosiglitazone 1.02

Balanced between rosiglitazone and glipizide, except as noted

Baseline Medications (N = 672)

	Glipizide (n = 339)	Rosiglitazone (n = 333)
Aspirin	82.3%	84.1%
Other antiplatelet	57.5%	58.9%
Beta-blocker	65.8%	72.4%
ACE inhibitor or ARB	70.2%	71.2%
Statin	77.3%	74.5%
Fibrate or other lipid-lowering agent	7.1%	10.2%

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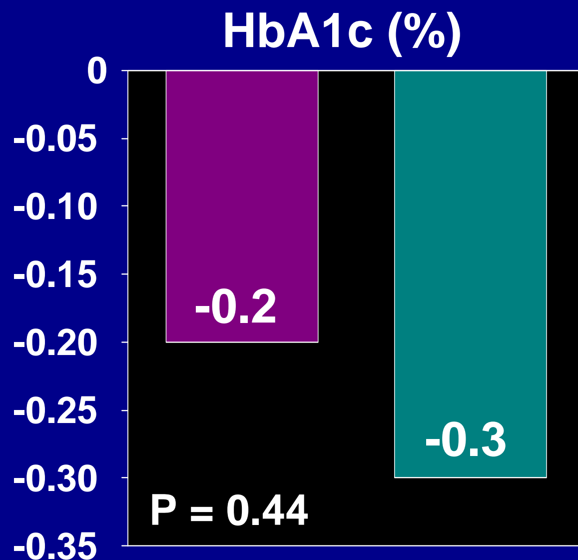
$P > 0.05$ for all comparisons

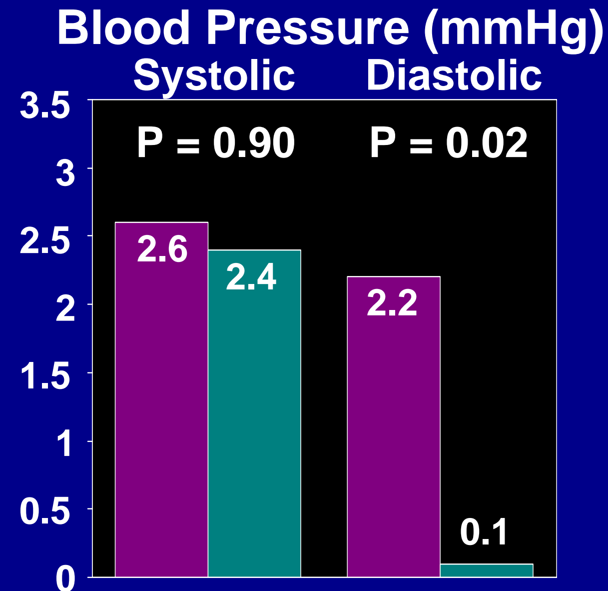
Final Visit Medication Use (N = 462)

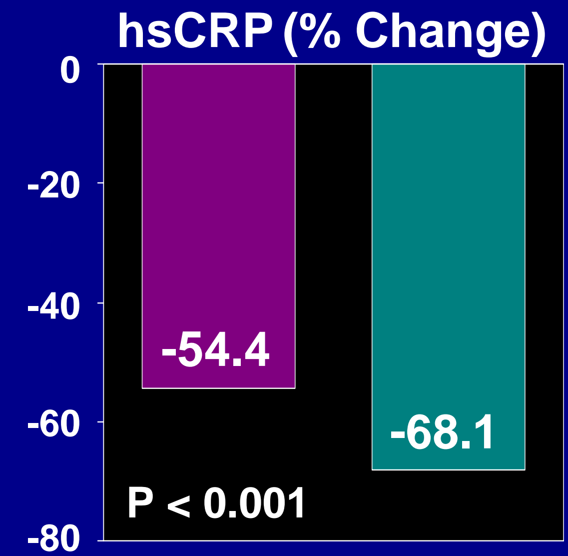
	Glipizide (n = 229)	Rosiglitazone (n = 233)
Aspirin	83.0%	85.4%
Other antiplatelet	40.6%	35.2%
Beta-blocker	66.4%	67.8%
ACE inhibitor or ARB	72.5%	75.5%
Nitrates	34.1%	32.6%
Statin	78.2%	81.5%
Fibrate or other lipid-lowering agent	11.8%	15.0%
Metformin	66.8%	65.2%
Insulin	9.2%	6.0%

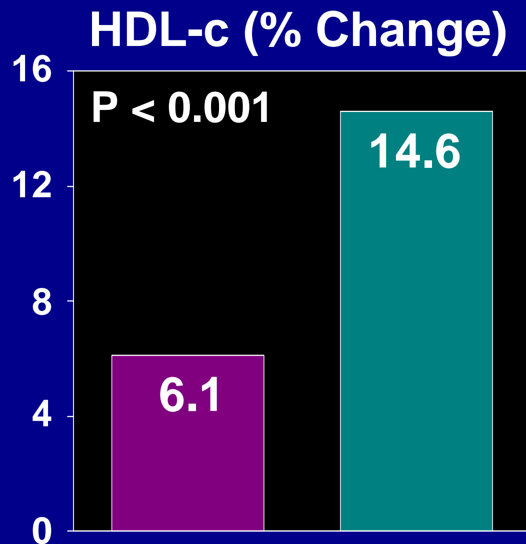
$P > 0.05$ for all comparisons

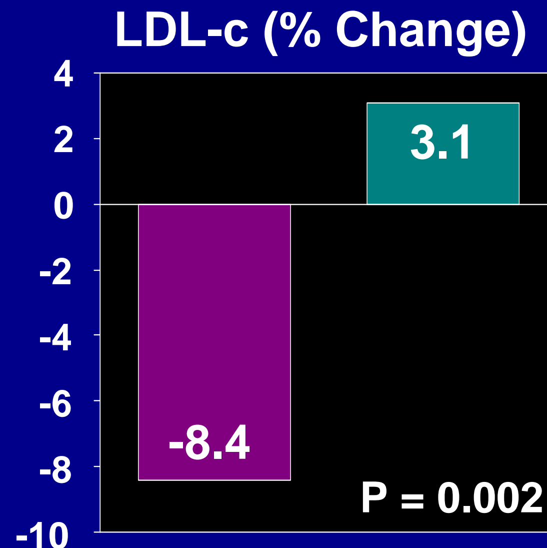
Mean Changes in Selected Parameters (N = 462)

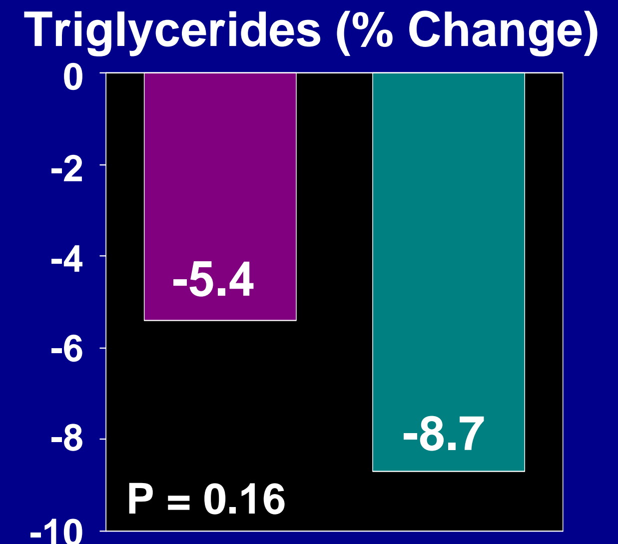












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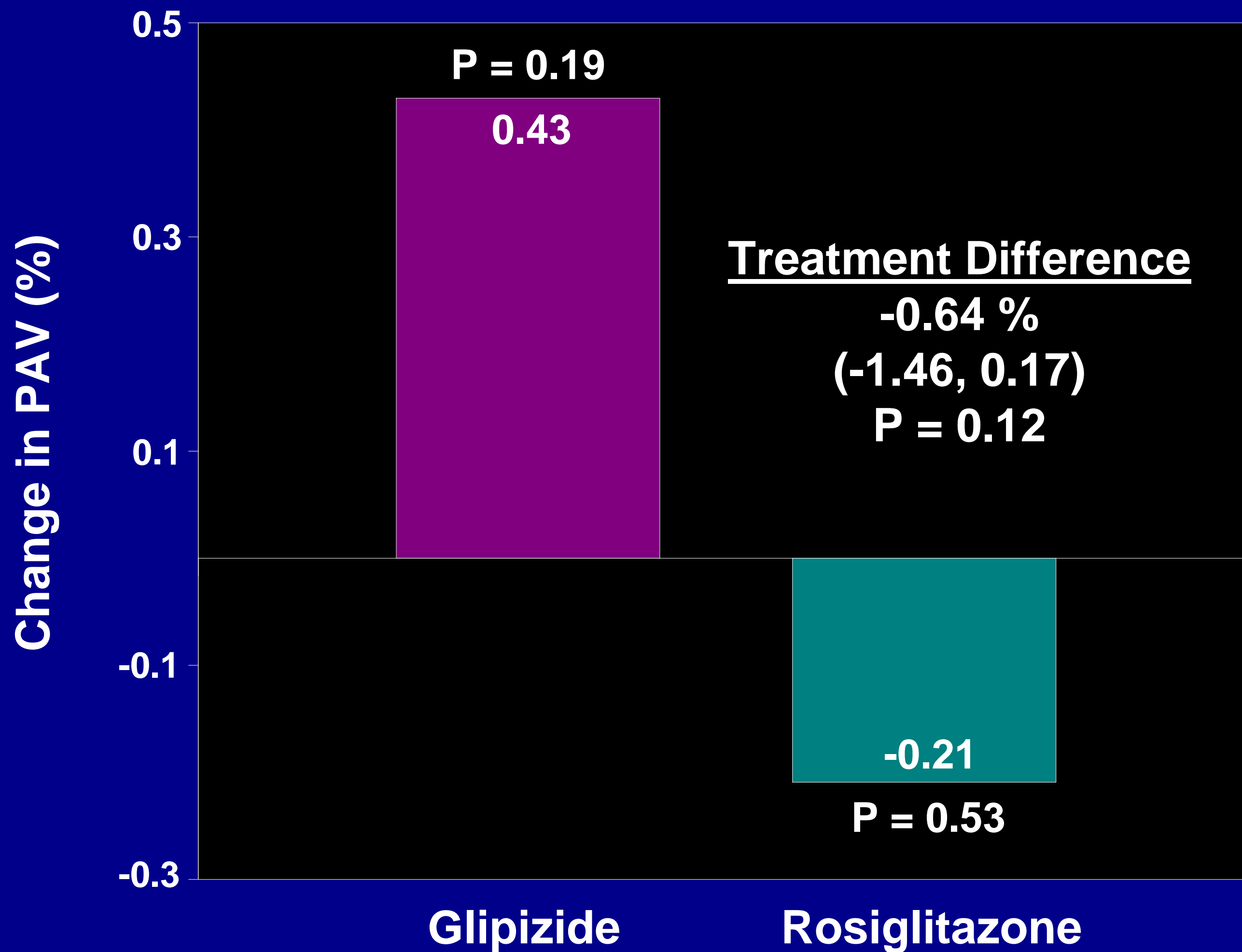
Glipizide Rosiglitazone

Primary Endpoint (N = 462)
Change in Percent Atheroma Volume (%)



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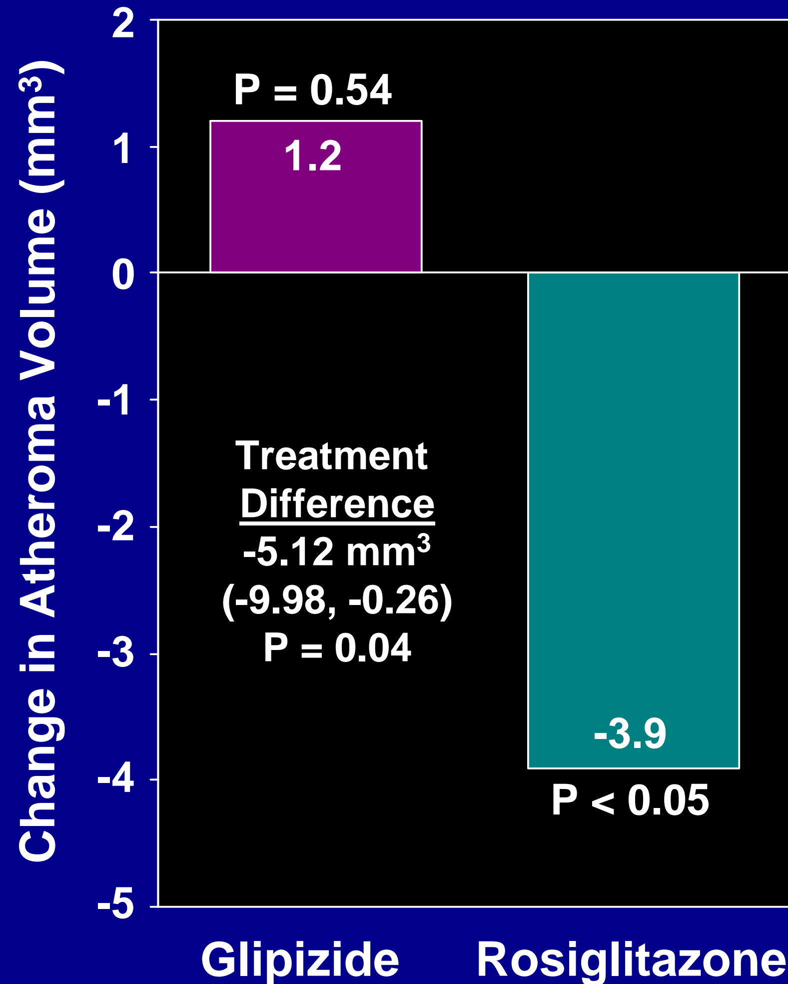
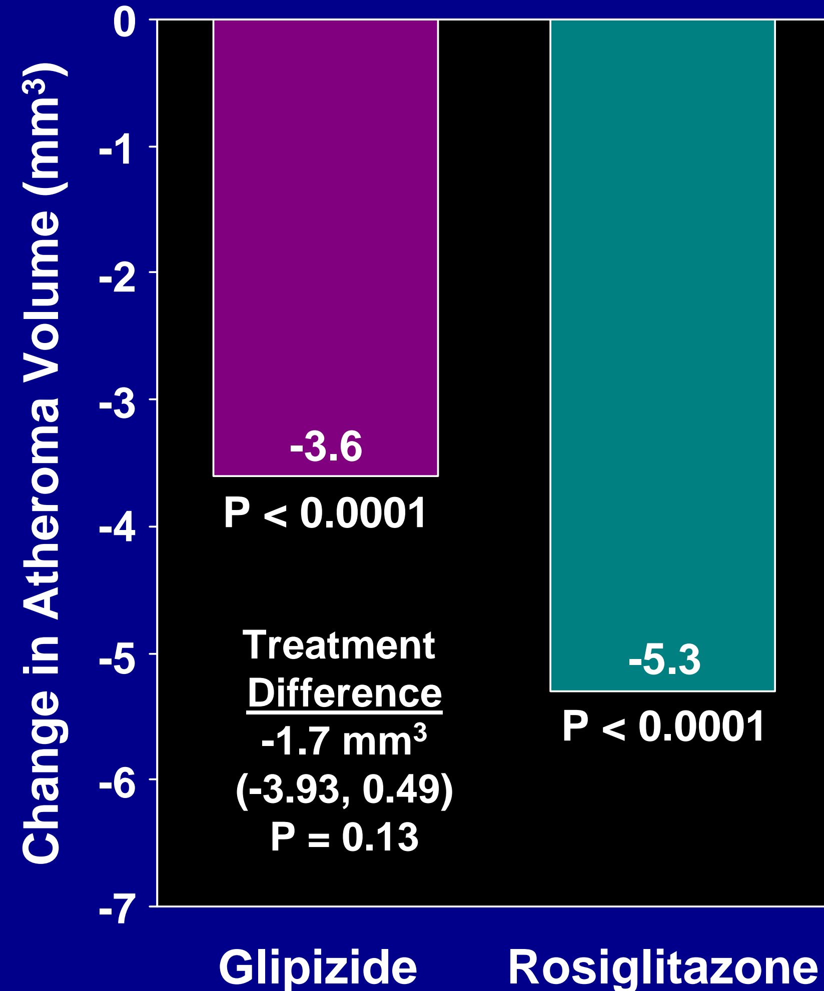
Key Secondary Endpoints (N = 462)





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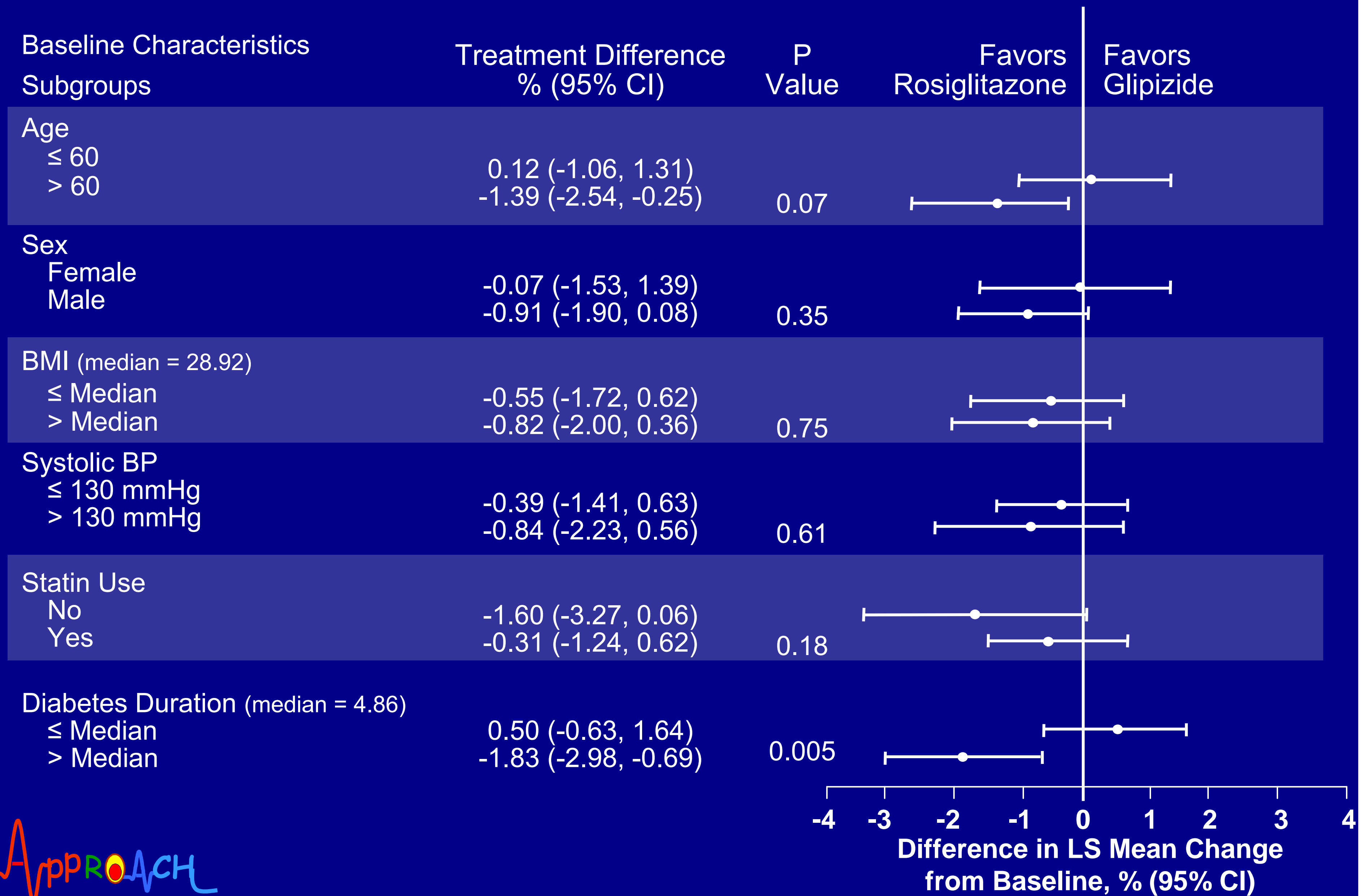
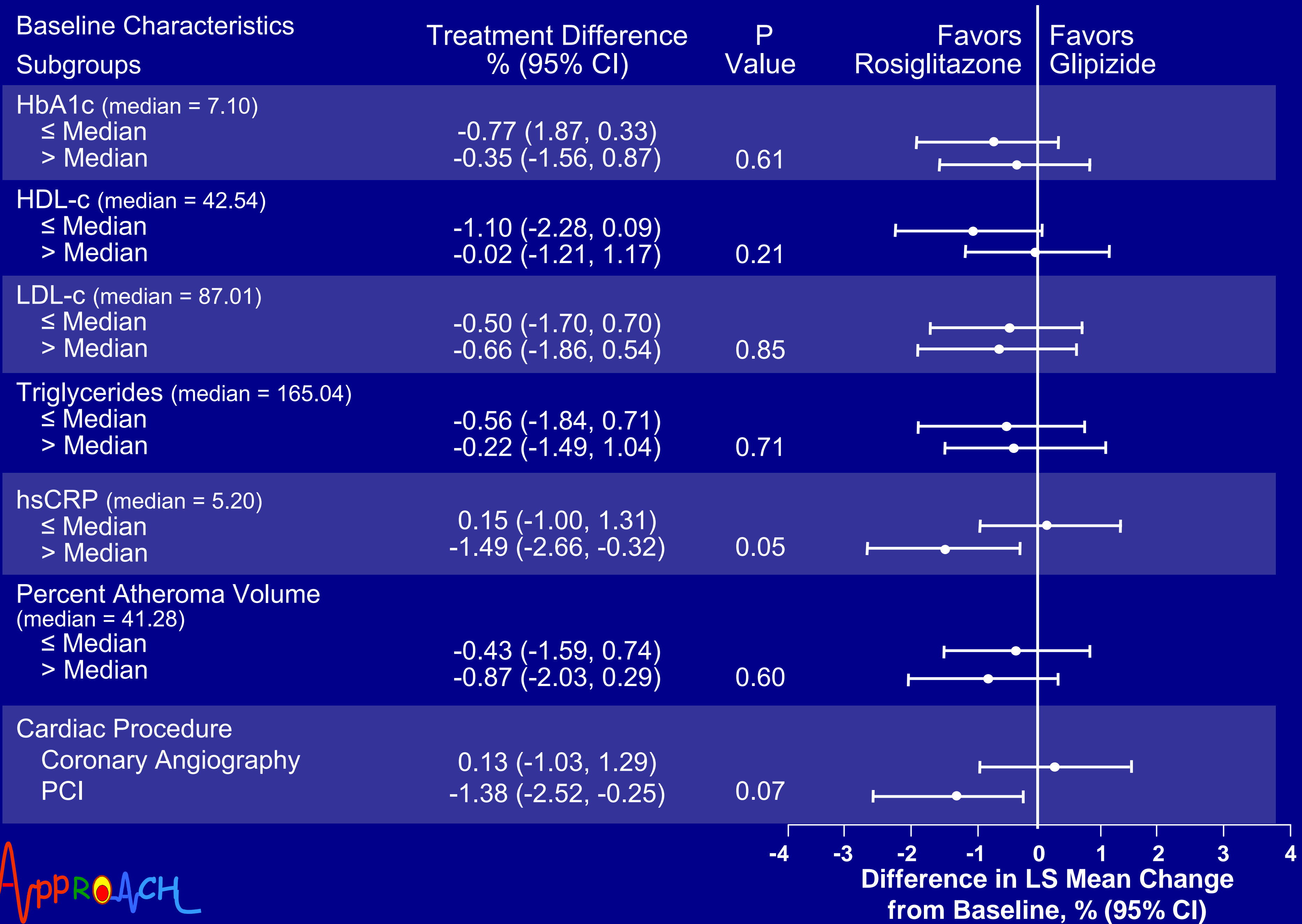
Change in PAV in Pre-specified Subgroups




Change in PAV in Pre-specified Subgroups
Baseline Characteristics Subgroups
Treatment Difference % (95% CI)
P Value
Favors Rosiglitazone
Favors Glipizide
HbA1c (median = 7.10)
≤ Median
> Median
-0.77 (1.87, 0.33)
-0.35 (-1.56, 0.87)
0.61
HDL-c (median = 42.54)
≤ Median
> Median
-1.10 (-2.28, 0.09)
-0.02 (-1.21, 1.17)
0.21
LDL-c (median = 87.01)
≤ Median
> Median
-0.50 (-1.70, 0.70)
-0.66 (-1.86, 0.54)
0.85
Triglycerides (median = 165.04)
≤ Median
> Median
-0.56 (-1.84, 0.71)
-0.22 (-1.49, 1.04)
0.71
hsCRP (median = 5.20)
≤ Median
> Median
0.15 (-1.00, 1.31)
-1.49 (-2.66, -0.32)
0.05
Percent Atheroma Volume (median = 41.28)
≤ Median
> Median
-0.43 (-1.59, 0.74)
-0.87 (-2.03, 0.29)
0.60
Cardiac Procedure
Coronary Angiography
PCI
0.13 (-1.03, 1.29)
-1.38 (-2.52, -0.25)
0.07
-4 -3 -2 -1 0 1 2 3 4
Difference in LS Mean Change from Baseline, % (95% CI)
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Adjudicated Cardiovascular Events (N = 672)

Patients, n (%)	Glipizide (n = 339)	Rosiglitazone (n = 333)	P value
Composite of all-cause death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for myocardial ischemia	38 (11.2%)	39 (11.7%)	0.58
Composite of CV death, nonfatal MI, nonfatal stroke	10 (2.9%)	14 (4.2%)	0.31
All-cause death	7 (2.1%)	8 (2.4%)	0.72
Cardiovascular death	3 (0.9%)	4 (1.2%)	0.50
Myocardial infarction			
Non-fatal	6 (1.8%)	7 (2.1%)	0.71
Fatal	1 (0.3%)	1 (0.3%)	0.89
Stroke			
Non-fatal	1 (0.3%)	5 (1.5%)	0.13
Fatal	0	0	–
Coronary revascularization	27 (8.0%)	26 (7.8%)	0.82
Hospitalization for myocardial ischemia	7 (2.1%)	11 (3.3%)	0.25
Congestive heart failure	3 (0.9%)	8 (2.4%)	0.14

Other Adverse Events (N = 672)

Patients, n (%)	Glipizide (n = 339)	Rosiglitazone (n = 333)	P value
Bone Fracture	2 (< 1%)	6 (2%)	0.17
Peripheral Edema	24 (7%)	29 (9%)	0.48
Weight Gain, mean change from baseline	1.4 kg	2.6 kg	0.02
Hemoglobin Decrease > 3 g/dL	10 (3%)	26 (8%)	0.01
Hypoglycemia	96 (28%)	27 (8%)	< 0.0001
Severe Hypoglycemia (requiring external assistance)	3 (< 1%)	0 (0%)	0.25
Angina Pectoris	35 (10%)	31 (9%)	0.69
ALT > 3 x Upper Limit of Normal	3 (< 1%)	2 (< 1%)	1.00

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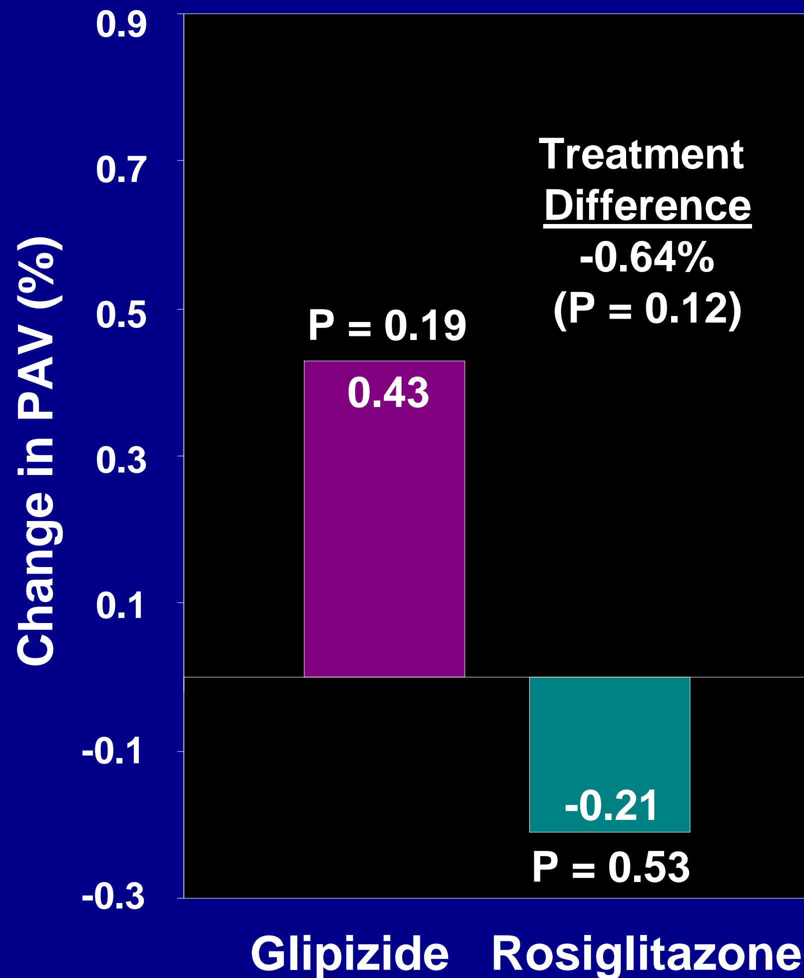
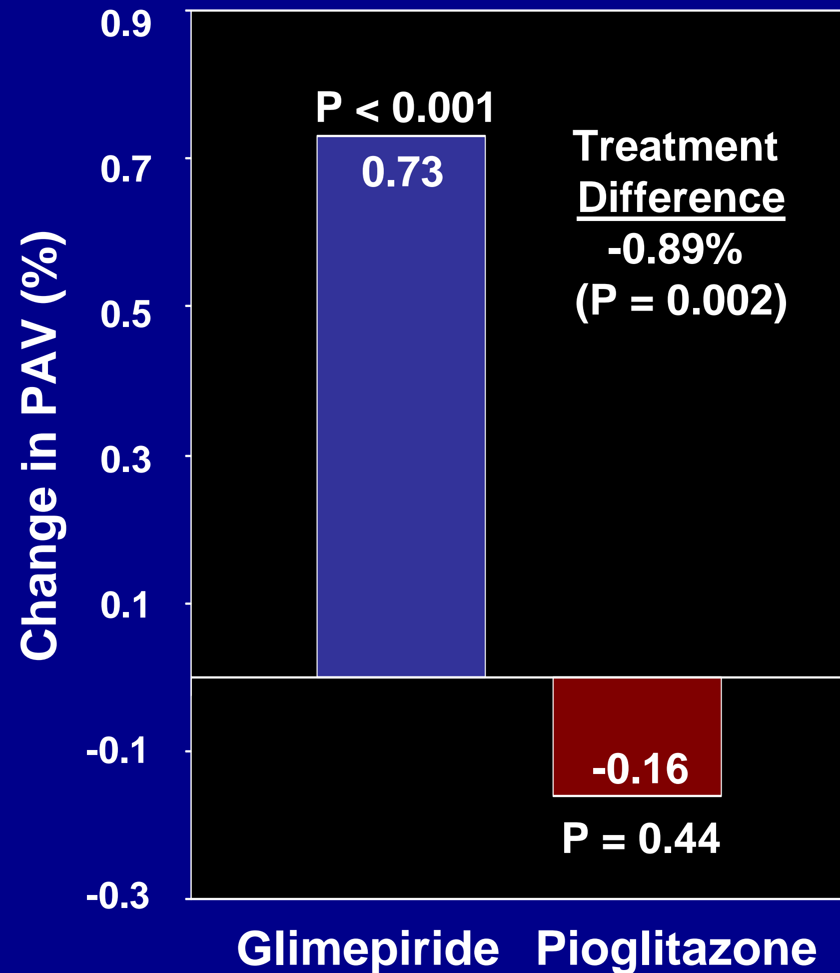
Comparison of Primary Endpoints





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*Nissen et al. *JAMA*. 2008;299:1561-1573.

Conclusions

- This study did not show a statistically significant difference in percent atheroma volume for rosi-glitazone compared to glipizide (p=0.12)
- Rosiglitazone did show a favorable effect on the normalized total atheroma volume compared to glipizide (p=0.04)
- Pre-specified subgroup analyses raise the hypothesis that rosiglitazone may have a greater anti-atherosclerotic effect in patients with more advanced diabetes
- There were no significant differences in major cardiovascular events

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Acknowledgements

- We thank the patients and the study staff without whom this study would not have been possible

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Supplemental Slides

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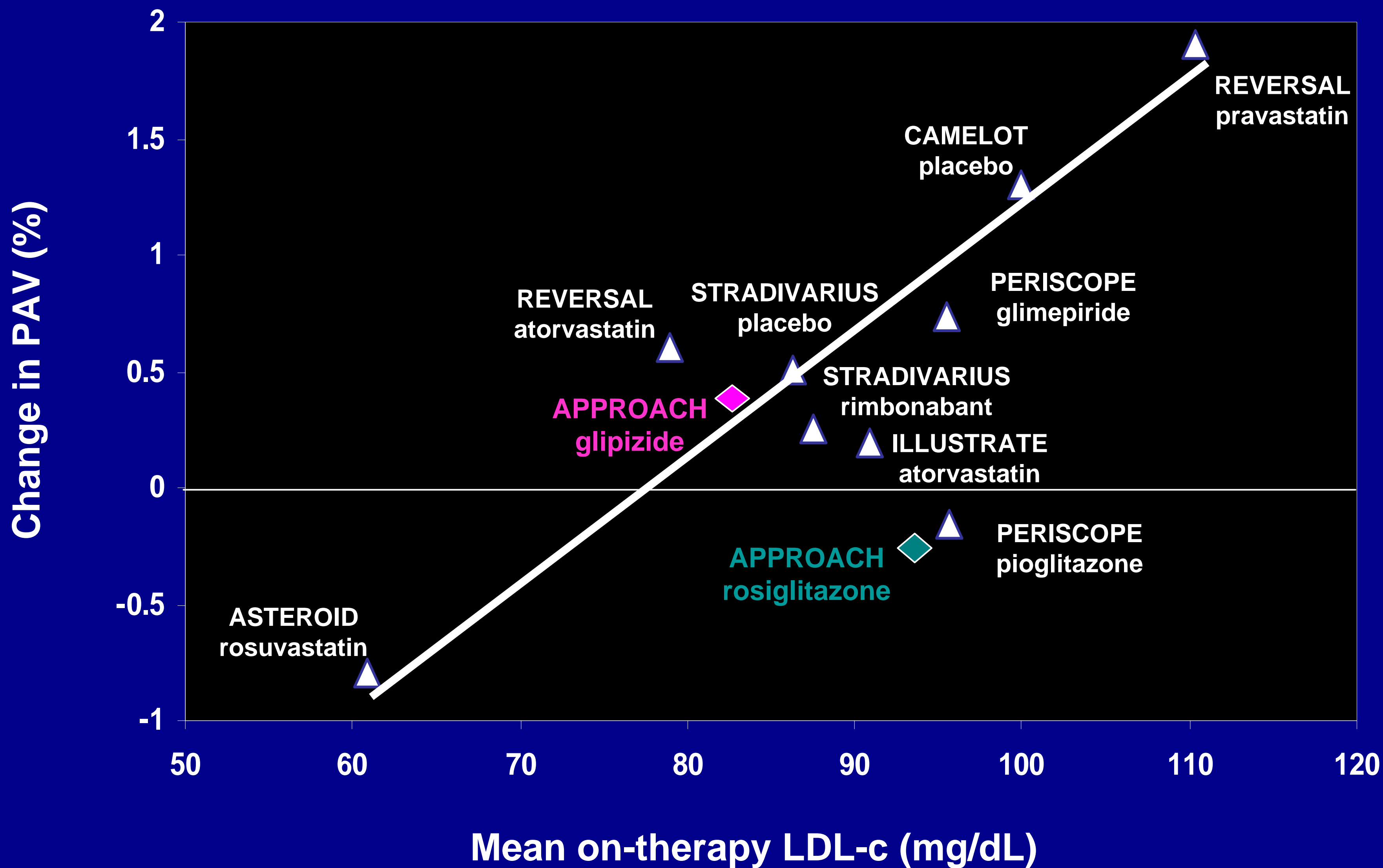
Other IVUS Trials



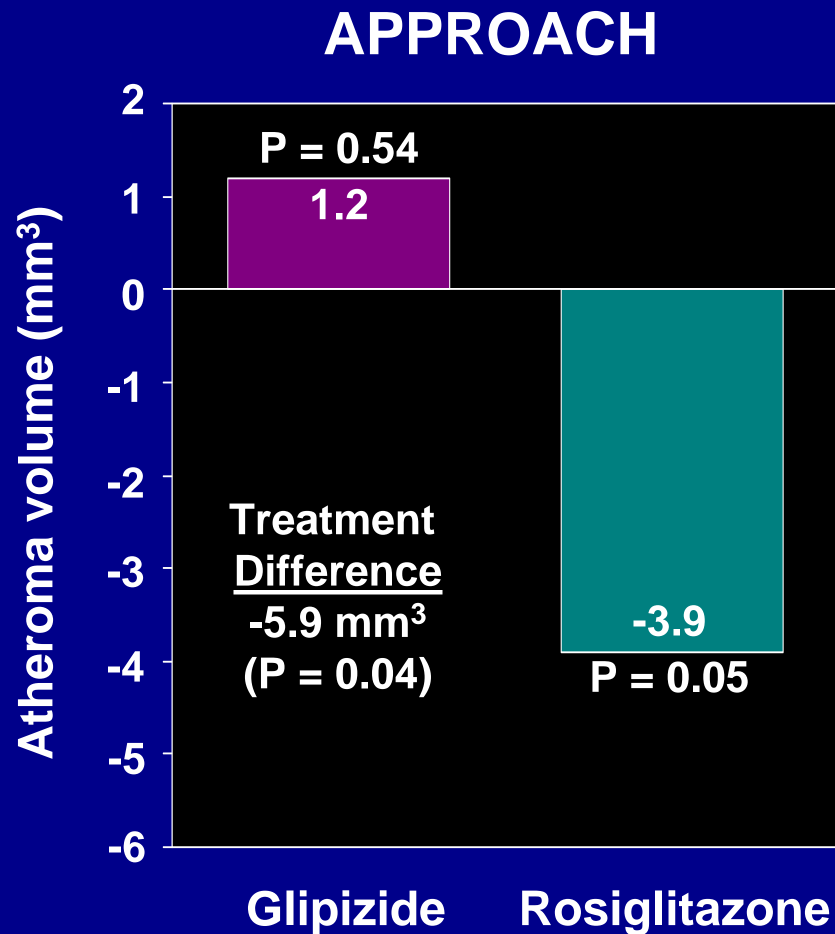
IVUS Trials of TZDs in Patients with Diabetes

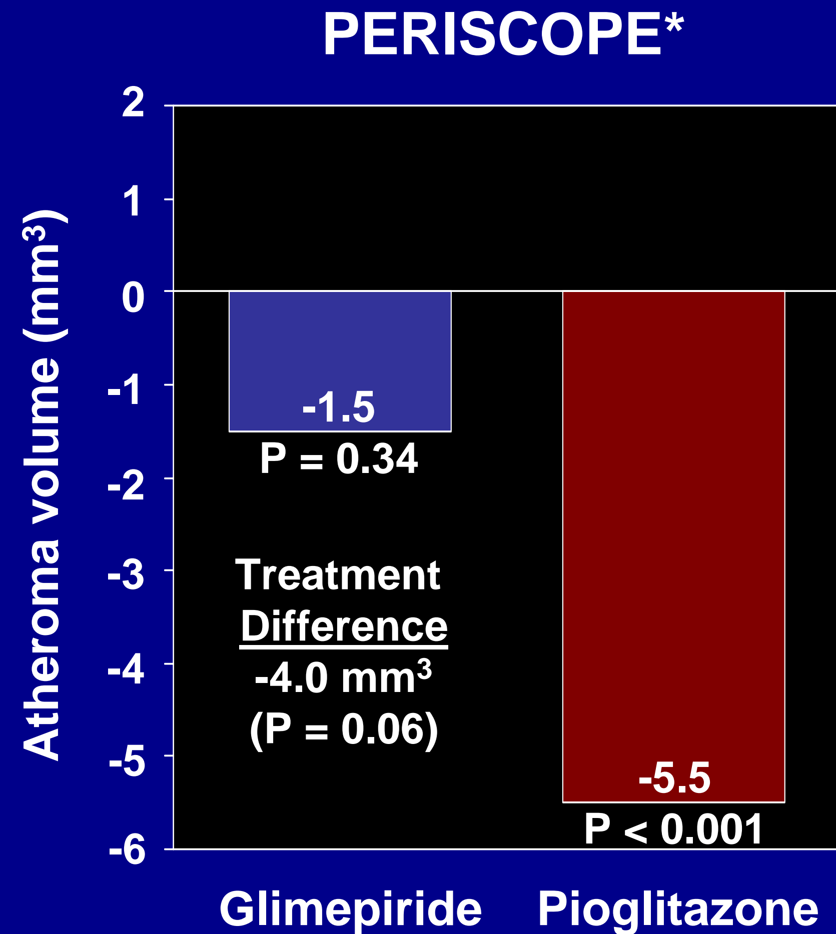
Measurement	Rosiglitazone (APPROACH)		Pioglitazone (PERISCOPE*)	
	Baseline	Change	Baseline	Change
Percent atheroma volume	40.4 (11.8)	-0.21 (-.86, 0.44)	40.6 (8.4)	-0.16 (-0.57, 0.25)
Normalized TAV	226.1 (100.6)	-3.9 (-7.82, -0.02)	207.5 (83.8)	-5.5 (-8.67, -2.38)
Atheroma volume in the most diseased 10 mm segment	71.0 (30.0)	-5.3 (-0.70, -3.51)	62.7 (28.1)	-2.0 (-3.33, -0.67)
HbA1c, mean (SD), %	7.1 (0.8)	-0.2 (-0.4, -0.2)	7.4 (1.0)	-0.55 (-0.68,-0.42)
SBP, mean (SD), mmHg	127.6 (16.9)	2.3 (0.1, 4.6)	127.8 (16.6)	0.1 (-1.4,1.5)
DBP, mean (SD), mmHg	74.7 (10.3)	0.2 (-1.2, 1.6)	75.7 (10.7)	-0.9 (-1.7, -0.01)
Weight, mean (SD), kg	82.0 (17.9)	2.6 (1.8, 3.4)	94.3 (19.5)	3.6 (2.8, 4.4)
LDL, mean (SD), mg/dL	90.9 (36.8)	2.8 (-2.4, 7.9)	93.5 (30.7)	2.1 (-1.5,5.8)
HDL, mean (SD), mg/dL	42.5 (10.9)	6.2 (4.8, 7.6)	40.8 (11.5)	5.7 (4.4, 7.0)
TG, median [IQR], mg/dL	163.7 [123.9-214.2]	-14.2 (-23.0, -2.7)	139 [104-198]	-16.3 (-27.7, -11.0)
Fasting insulin, median [IQR], µU/mL	13.0 [8.6-19.9]	-6.5 (-10.4, -2.5)	21.0 [16.0-33.0]	-5.0 (-7.0,-4.0)
BNP median [IQR], pg/mL	22 [11-54]	3.0 (0.0, 6.0)	22.0 [11-52]	8.0 (5.0, 10.5)
hsCRP median [IQR], mg/L	4.7 [2.2-10.5]	-3.2 (-4.0, -2.4)	2.6 [1.2-6.5]	-1.0 (-1.5, -0.8)

*Nissen et al. *JAMA*. 2008;299:1561-1573.

Comparison of Secondary Endpoints

Normalized Total Atheroma Volume (mm^3)





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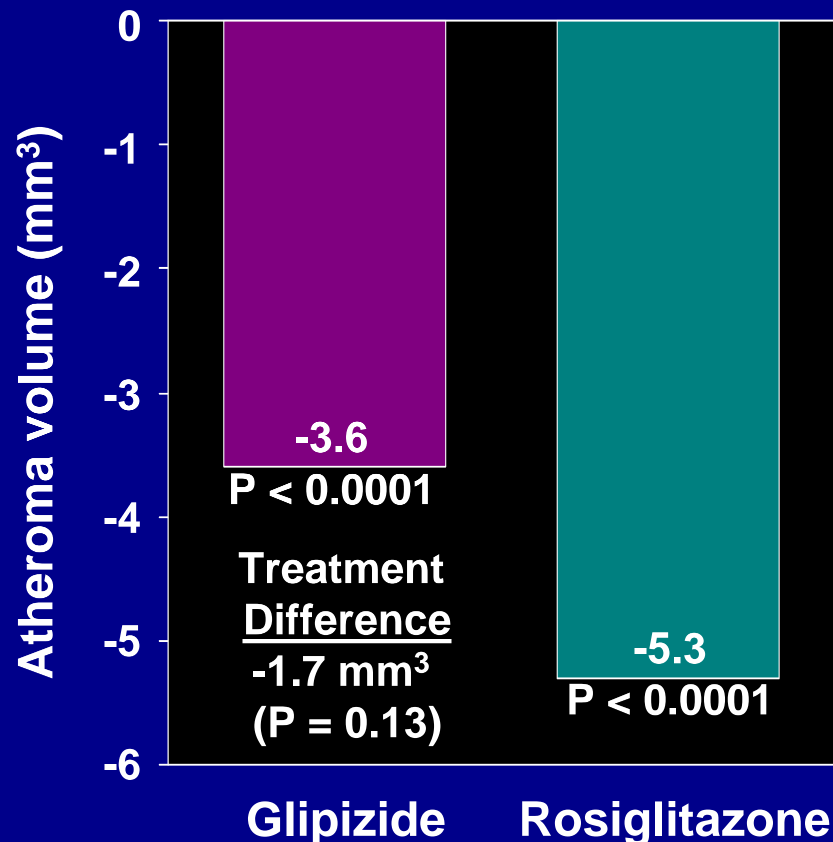
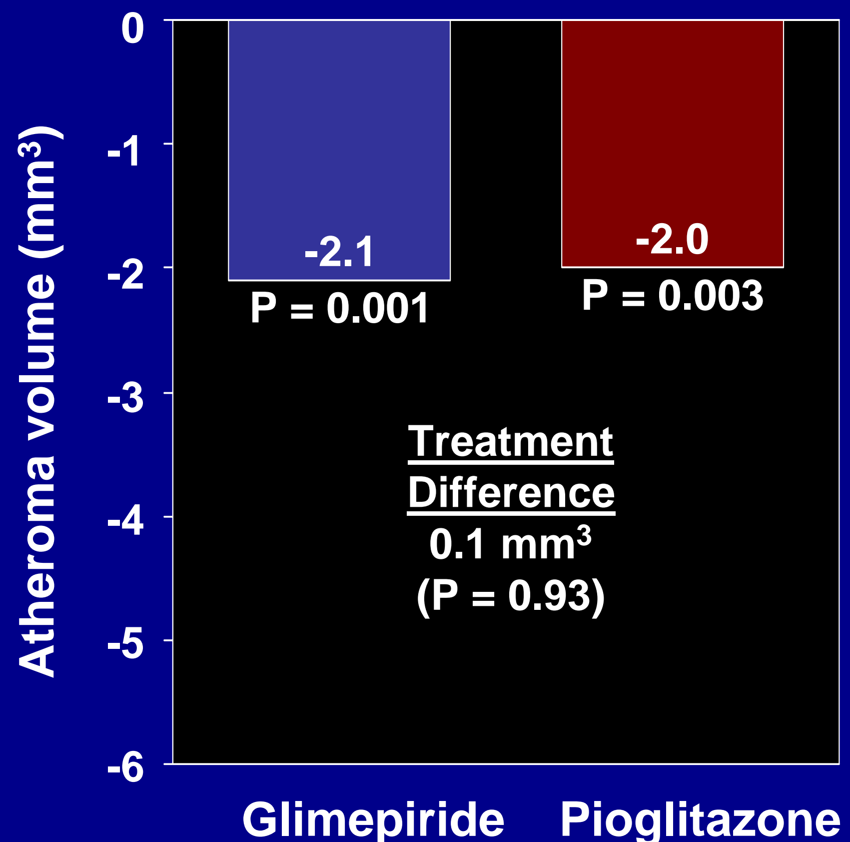
*Nissen et al. *JAMA*. 2008;299:1561-1573.

Comparison of Secondary Endpoints

Atheroma Volume in the Most Diseased 10 mm (mm^3)





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