# 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

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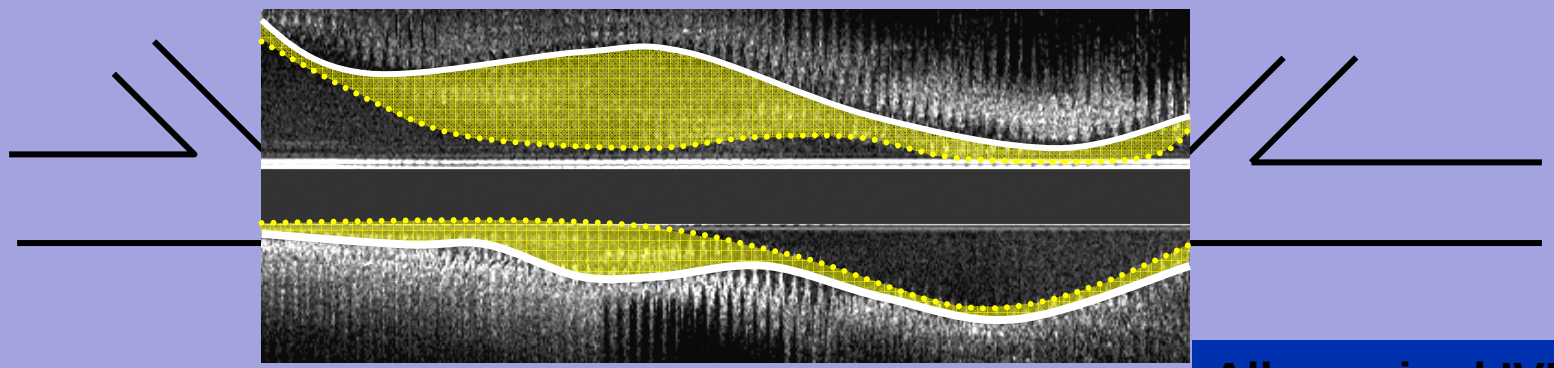
# Methods

- 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

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

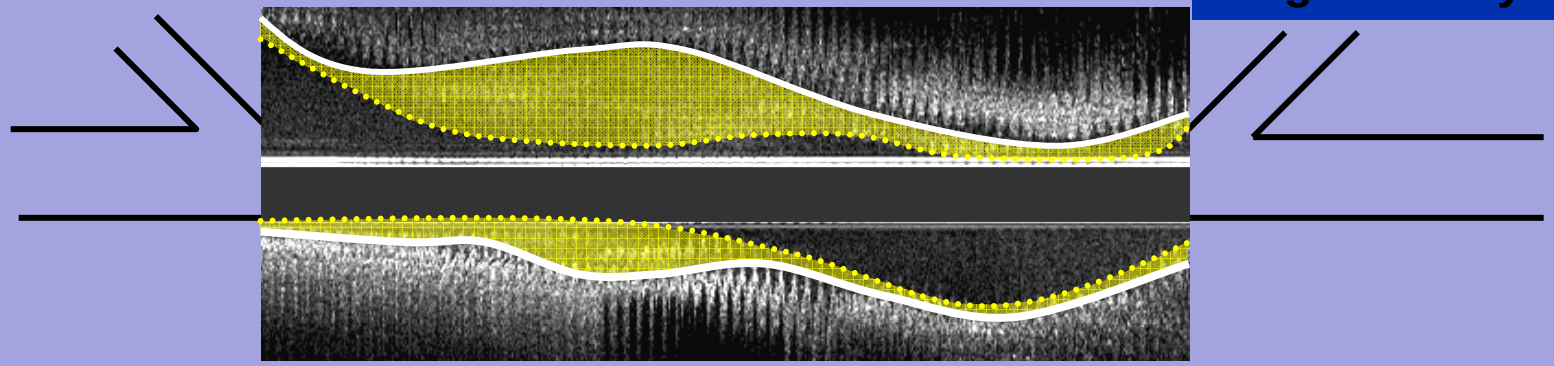
Baseline

**Selection of Region-Of-Interest**



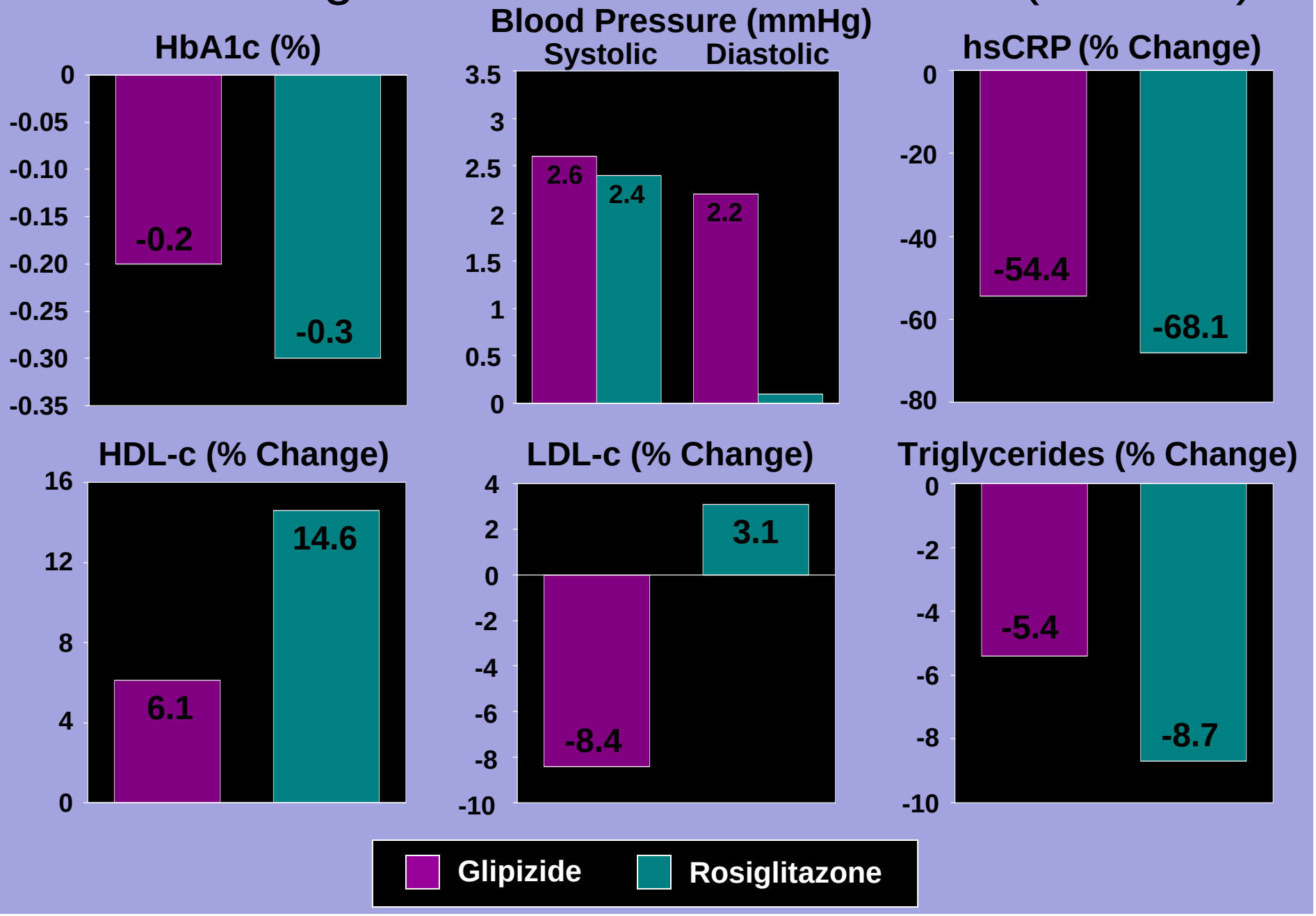
**length of the pullback ~40mm**

18 months



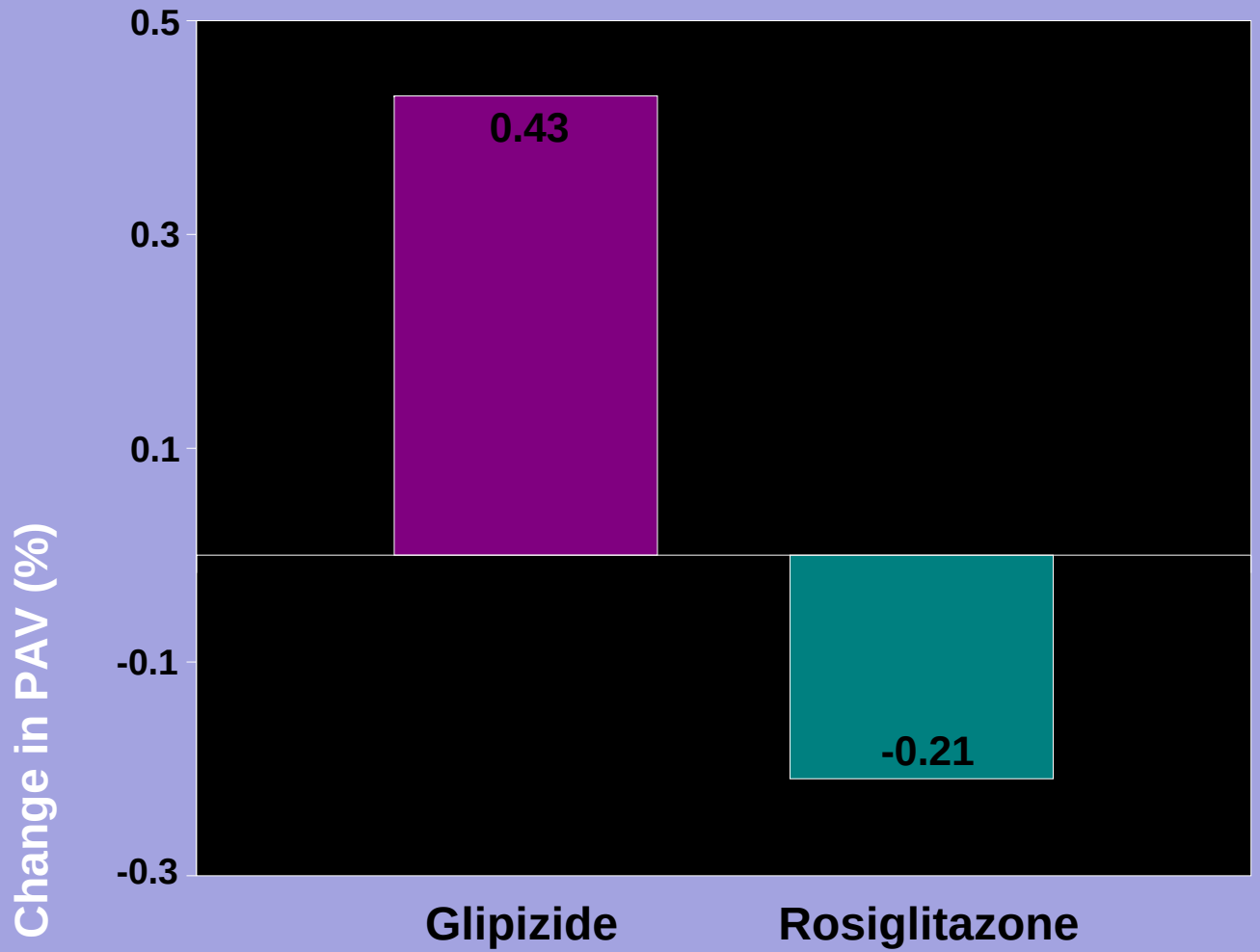
**All acquired IVUS frames were analyzed longitudinally**

# Mean Changes in Selected Parameters (N = 462)

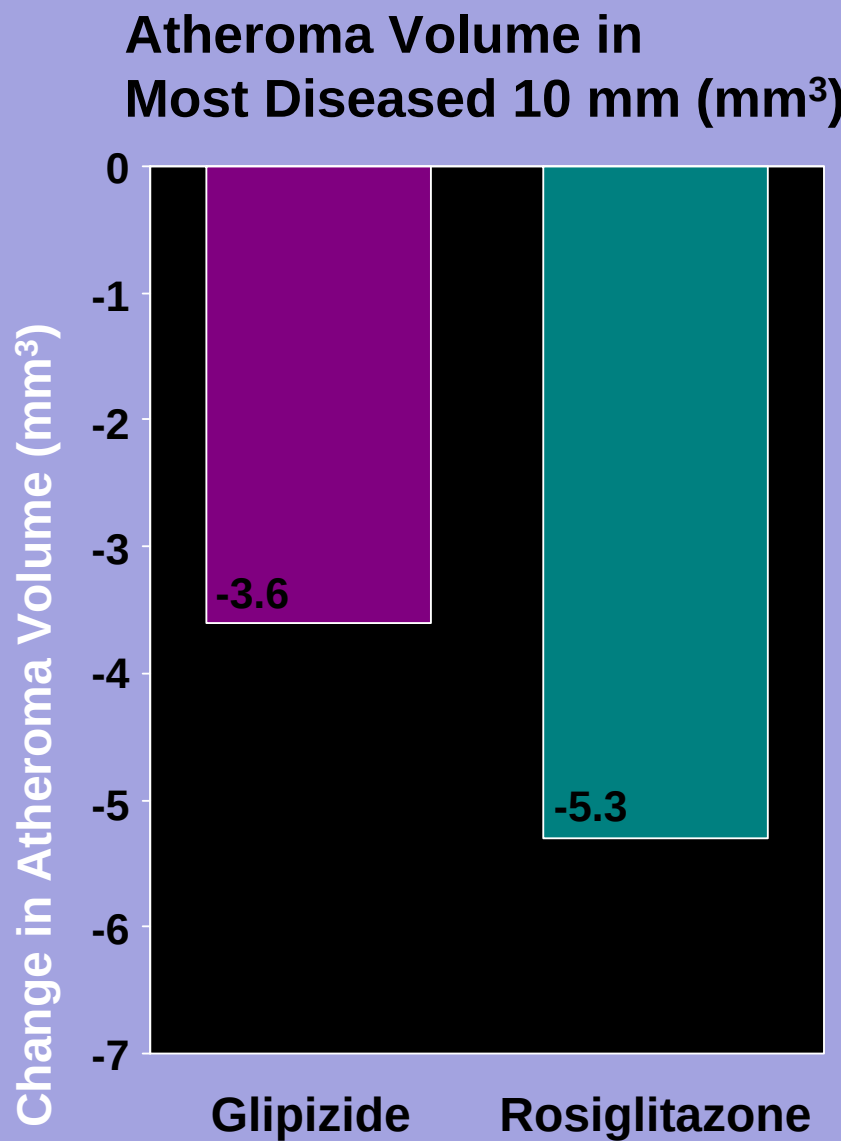


# Primary Endpoint (N = 462)

## Change in Percent Atheroma Volume (%)

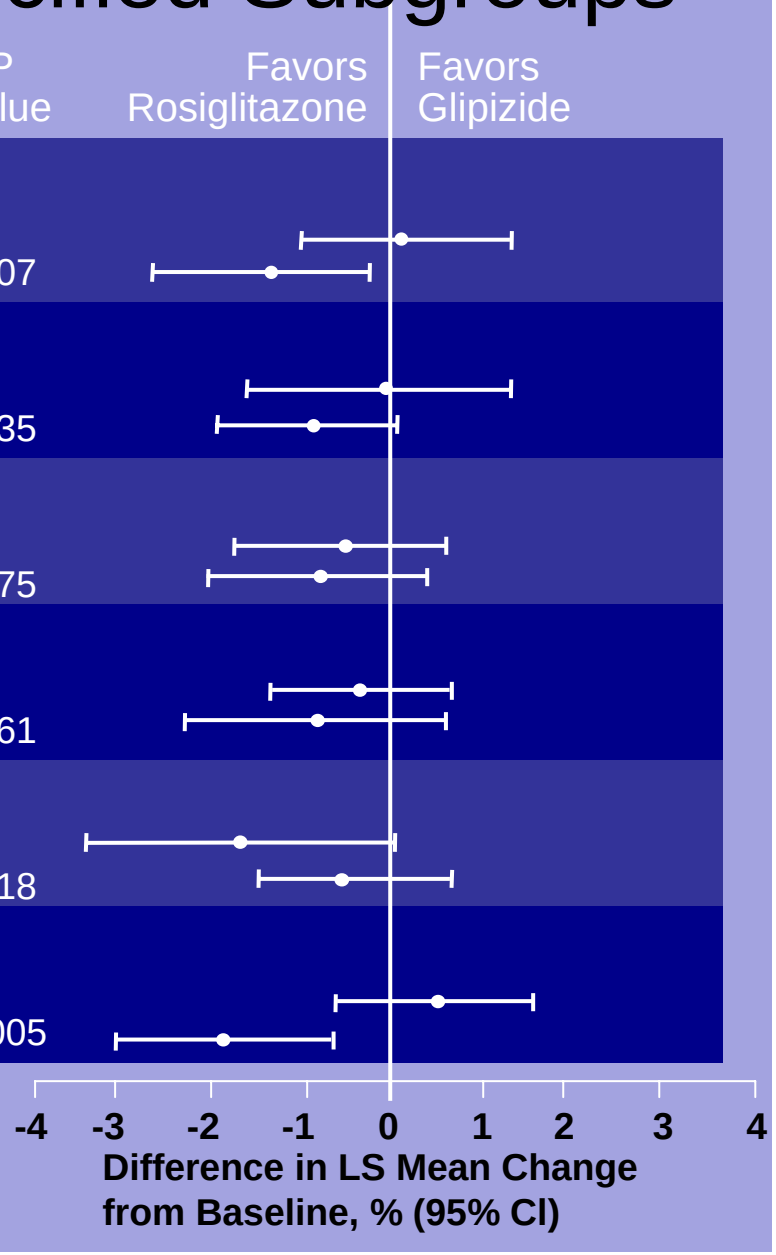


# Key Secondary Endpoints (N = 462)

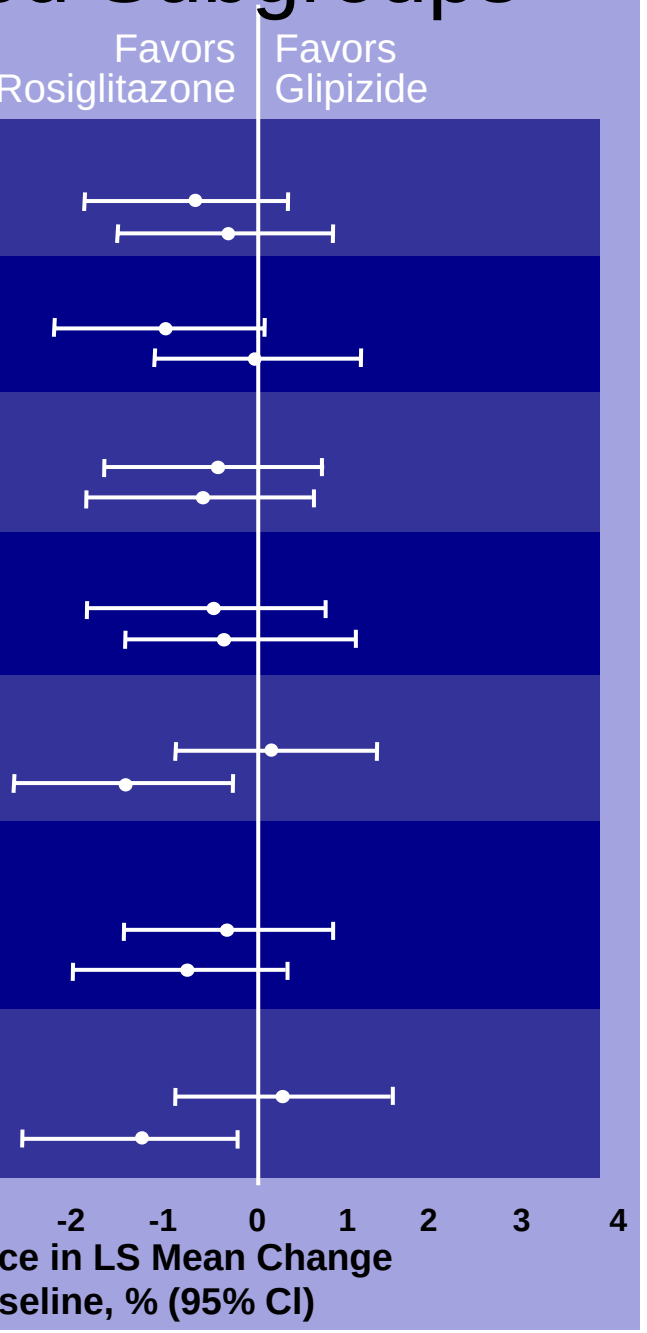
# Change in PAV in Pre-specified Subgroups

| Baseline Characteristics<br>Subgroups | Treatment Difference<br>% (95% CI) | P<br>Value |
|---|---|---|
| Age | | |
| ≤ 60 | 0.12 (-1.06, 1.31) | |
| > 60 | -1.39 (-2.54, -0.25) | 0.07 |
| Sex | | |
| Female | -0.07 (-1.53, 1.39) | |
| Male | -0.91 (-1.90, 0.08) | 0.35 |
| BMI (median = 28.92) | | |
| ≤ Median | -0.55 (-1.72, 0.62) | |
| > Median | -0.82 (-2.00, 0.36) | 0.75 |
| Systolic BP | | |
| ≤ 130 mmHg | -0.39 (-1.41, 0.63) | |
| > 130 mmHg | -0.84 (-2.23, 0.56) | 0.61 |
| Statin Use | | |
| No | -1.60 (-3.27, 0.06) | |
| Yes | -0.31 (-1.24, 0.62) | 0.18 |
| Diabetes Duration (median = 4.86) | | |
| ≤ Median | 0.50 (-0.63, 1.64) | |
| > Median | -1.83 (-2.98, -0.69) | 0.005 |



# Change in PAV in Pre-specified Subgroups

| Baseline Characteristics<br>Subgroups | Treatment Difference<br>% (95% CI) | P<br>Value |
|---|---|---|
| HbA1c (median = 7.10) | | |
| ≤ Median | -0.77 (1.87, 0.33) | |
| > Median | -0.35 (-1.56, 0.87) | 0.61 |
| HDL-c (median = 42.54) | | |
| ≤ Median | -1.10 (-2.28, 0.09) | |
| > Median | -0.02 (-1.21, 1.17) | 0.21 |
| LDL-c (median = 87.01) | | |
| ≤ Median | -0.50 (-1.70, 0.70) | |
| > Median | -0.66 (-1.86, 0.54) | 0.85 |
| Triglycerides (median = 165.04) | | |
| ≤ Median | -0.56 (-1.84, 0.71) | |
| > Median | -0.22 (-1.49, 1.04) | 0.71 |
| hsCRP (median = 5.20) | | |
| ≤ Median | 0.15 (-1.00, 1.31) | |
| > Median | -1.49 (-2.66, -0.32) | 0.05 |
| Percent Atheroma Volume (median = 41.28) | | |
| ≤ Median | -0.43 (-1.59, 0.74) | |
| > Median | -0.87 (-2.03, 0.29) | 0.60 |
| Cardiac Procedure | | |
| Coronary Angiography | 0.13 (-1.03, 1.29) | |
| PCI | -1.38 (-2.52, -0.25) | 0.07 |



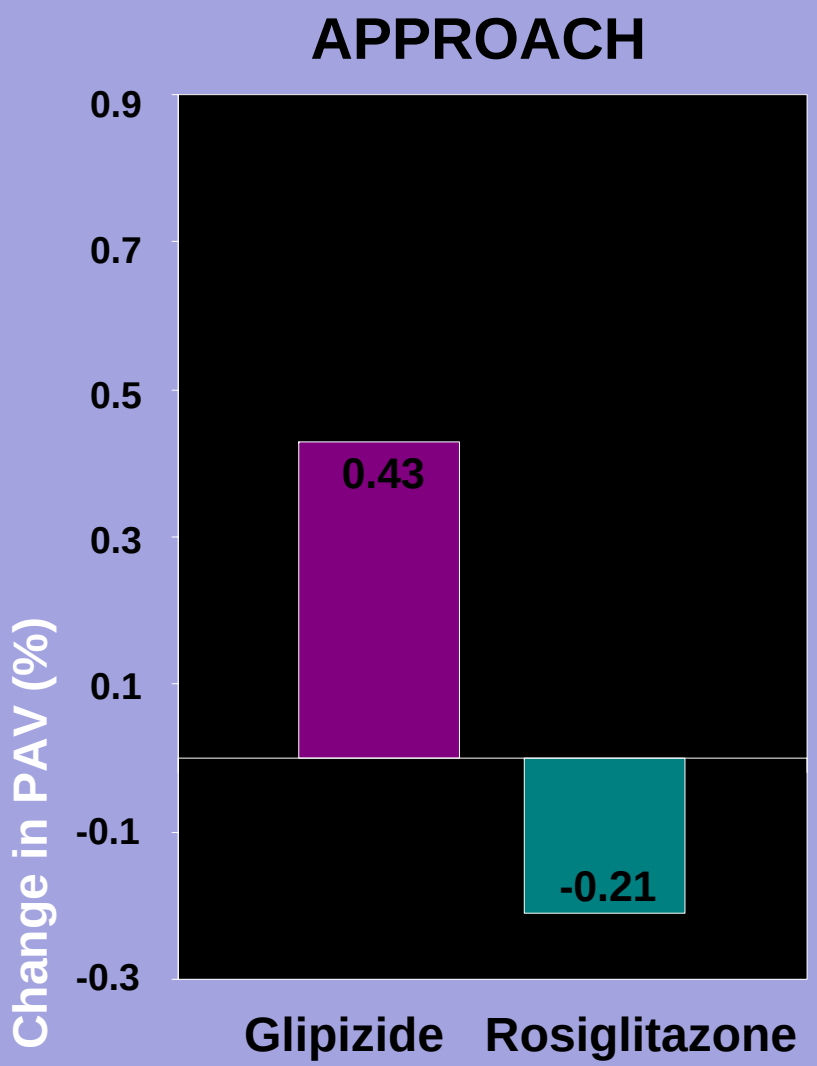
# Adjudicated Cardiovascular Events (N = 672)

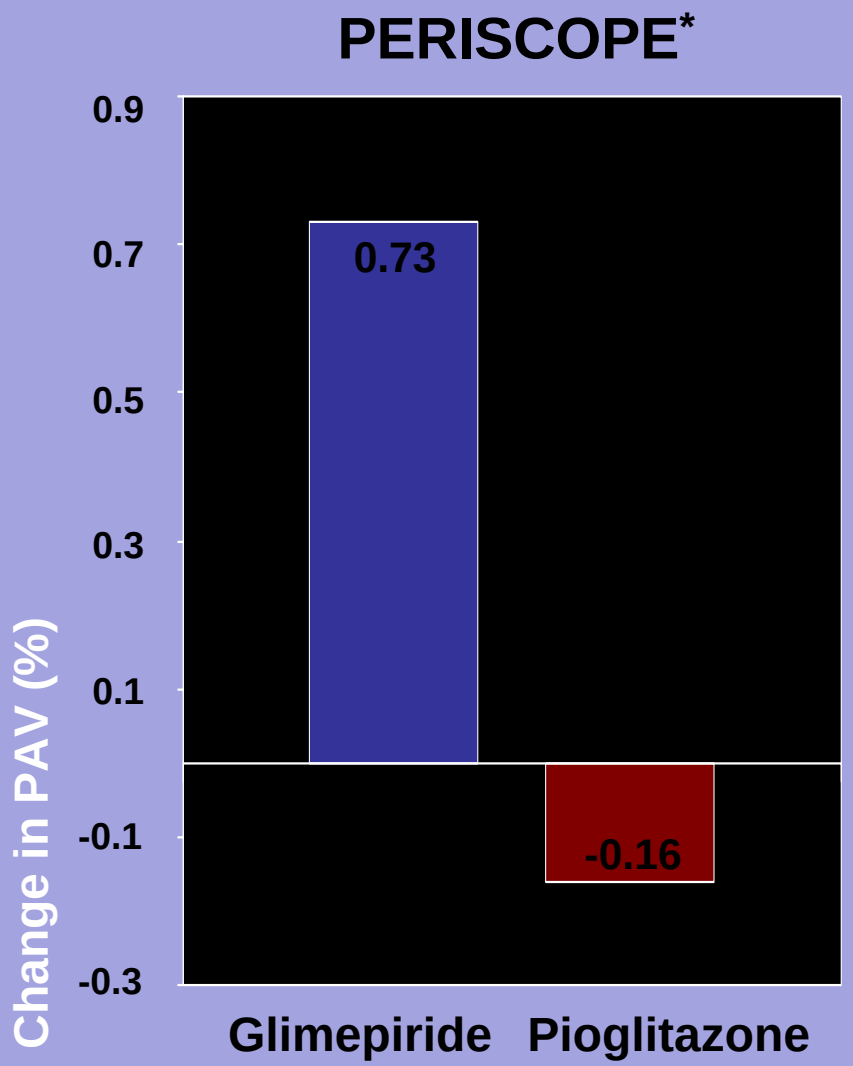
| Patients, n (%) | Glipizide (n = 339) | Rosiglitazone (n = 333) | P value |
|---|---|---|---|
| Composite of all-cause death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for myocardial ischemia | 38 (11.2%) | 39 (11.7%) | 0.58 |
| Composite of CV death, nonfatal MI, 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 | 뿌 |
| 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 |

# Comparison of Primary Endpoints




*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