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Essence-TIMI 73b CCTA Trial:

Effect of APOC3 Inhibition with Olezarsen on Coronary Atherosclerosis

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AMERICAN COLLEGE of CARDIOLOGY

Background

- Triglyceride-rich lipoproteins (TRLs) and the cholesterol they carry, known as remnant cholesterol (RC), are associated with CAD

- Some studies have suggested that TRL particles and remnant cholesterol carry outsized risk compared to LDL particles and LDL-C

- However, whether lowering TRLs and remnant cholesterol favorably modifies coronary atherosclerosis is unclear

Eur Heart J. 2023;44(39):4186.
Arterioscler Thromb Vasc Biol. 2021;41(6):2063.

Apolipoprotein C-III and Olezarsen

- Apolipoprotein C-III (APOC3) is a key regulator of TRL metabolism, and loss-of-function variants in the *APOC3* gene are associated with 39% lower triglyceride levels and a 40% lower lifetime risk of CAD
- Olezarsen is an antisense oligonucleotide targeting APOC3 that:
  - Significantly reduces triglycerides and remnant cholesterol
  - Has minimal effect on LDL-C in moderate hypertriglyceridemia
  - Results in a net reduction in apolipoprotein B
- We investigated the effect of olezarsen on coronary atherosclerosis by CT angiography

N Engl J Med. 2014;371(1):22.
Bergmark B, et al. *N Engl J Med*. 2025;393(13):1279.
Marston N, et al. *N Engl J Med*. 2026;394(5):429.

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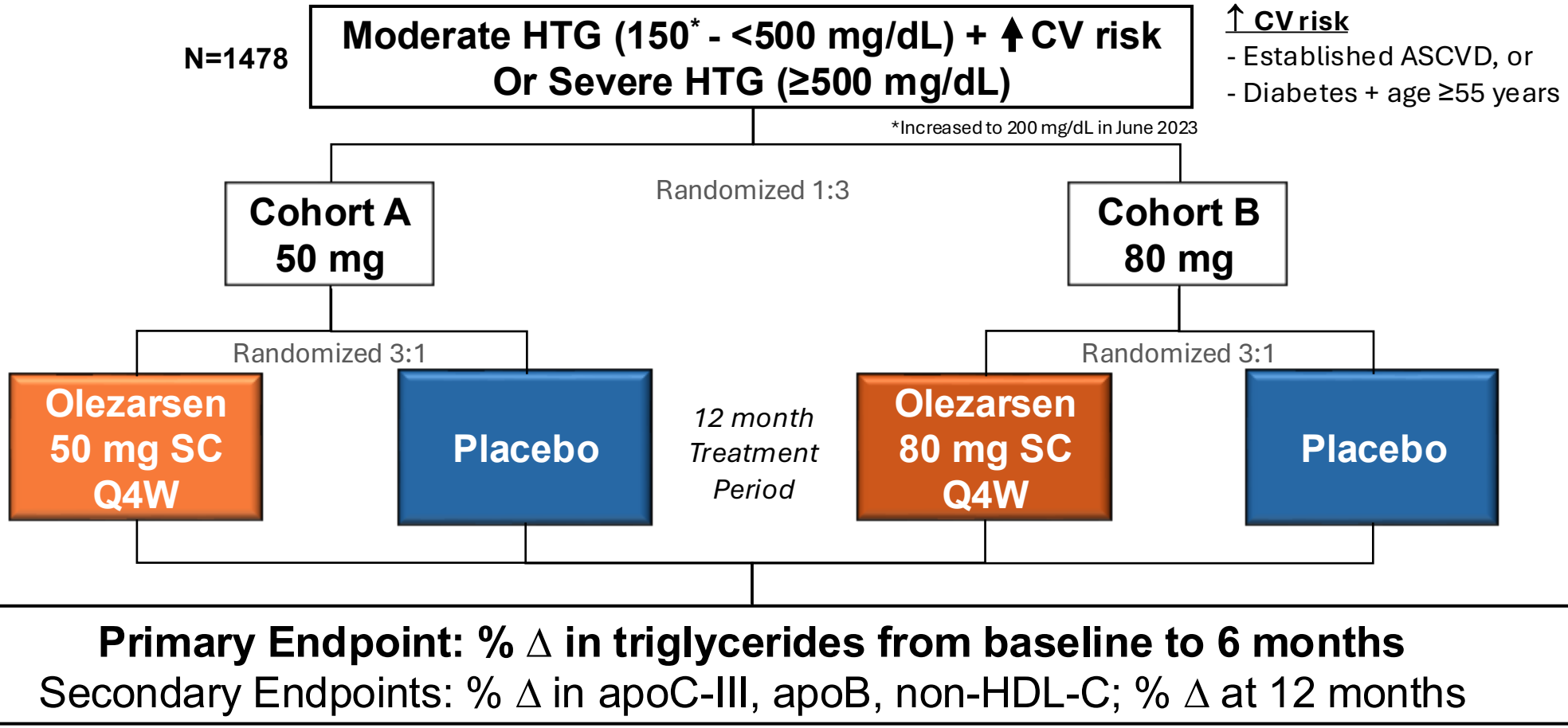

Bergmark B, et al. *N Engl J Med*. 2025;393(13):1279.
Trial funded by Ionis Pharmaceuticals

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Essence-CCTA Substudy

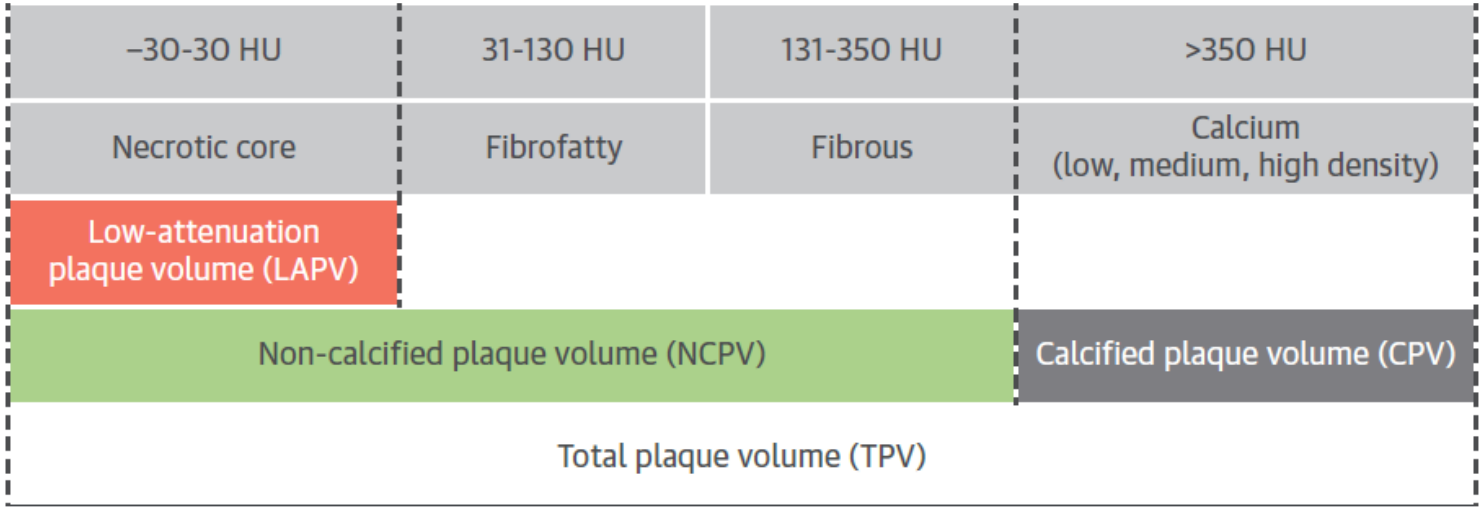
Core Lab
- MGH
- Director, Michael Lu, MD, MPH

Key Inclusion Criterion
- Quantifiable NCPV on baseline CCTA

Follow-up CCTA at 12 months

Imaging Endpoints
- **1° EP:** Pbo-adj % Δ in NCPV
- **Key 2° EP:** LAPV (necrotic core)
- **Other 2° EP's:** fibrofatty, fibrous, calcified, and total plaque volumes

Analytic Approach
- Pooled olezarsen doses
- Needed 400 paired scans to have >80% power to detect a 10% difference between treatment groups (2-sided α of 0.05, SD 30%)



JACC CV Img. 2025;18:912

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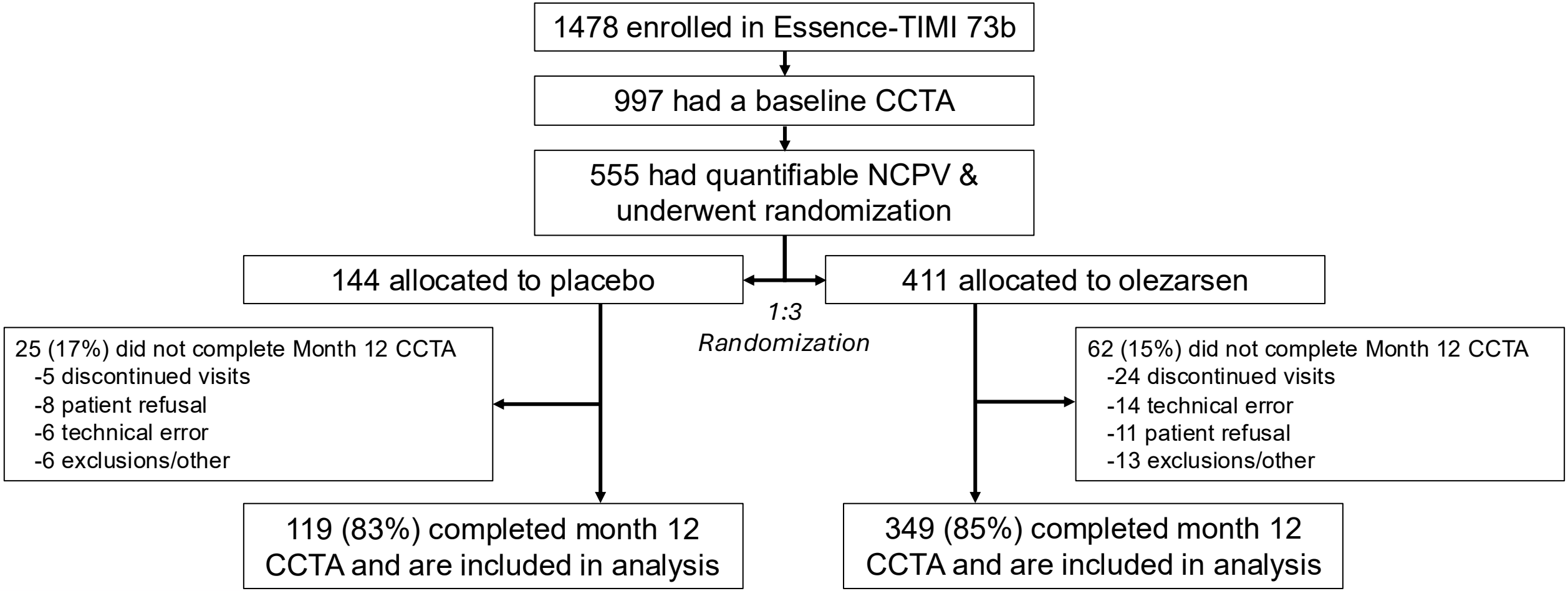
CCTA = coronary computed tomography; HU = Hounsfield units
NCPV = Non-calcified plaque volume; LAP = Low-attenuation plaque volume

Patient Disposition in CCTA Study



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Baseline Characteristics

	Overall N=468
Age (yrs)	63 (56, 70)
Female sex	31%
Race/Ethnicity	
White	93%
Hispanic/Latino	16%
Body Mass Index (kg/m^2)	31 (28, 34)
Coronary Artery Disease	43%
Diabetes mellitus	56%
Any Lipid Lowering Therapy	97%
Statin	79%
Ezetimibe	23%
Omega-3 fatty acid	26%
Fibrates	21%

3:1 randomization to olezarsen

Baseline Lipid Values

Lab Values, mg/dL	Overall N=468
Triglycerides	249 (197–331)
≥500 mg/dL	9%
Non-HDL cholesterol	130 (105–162)
LDL cholesterol	81 (60–109)
Remnant cholesterol	53 (38–76)
VLDL cholesterol	43 (34–57)
Apolipoprotein B	93 (76–111)

All continuous values listed as median (IQR) mg/dL.
Remnant cholesterol was directly measured.

Baseline Plaque Volumes

Plaque Volume (mm^3)	Overall N=468
Non-Calcified	125 (63–213)
Low-Attenuation	4.3 (0.9-14.8)
Calcified	37 (9-102)
Fibrous	107 (53-188)
Fibro-Fatty	5.6 (1.8–13.2)
Total	169 (83-316)

All continuous values listed as median (IQR) mg/dL.

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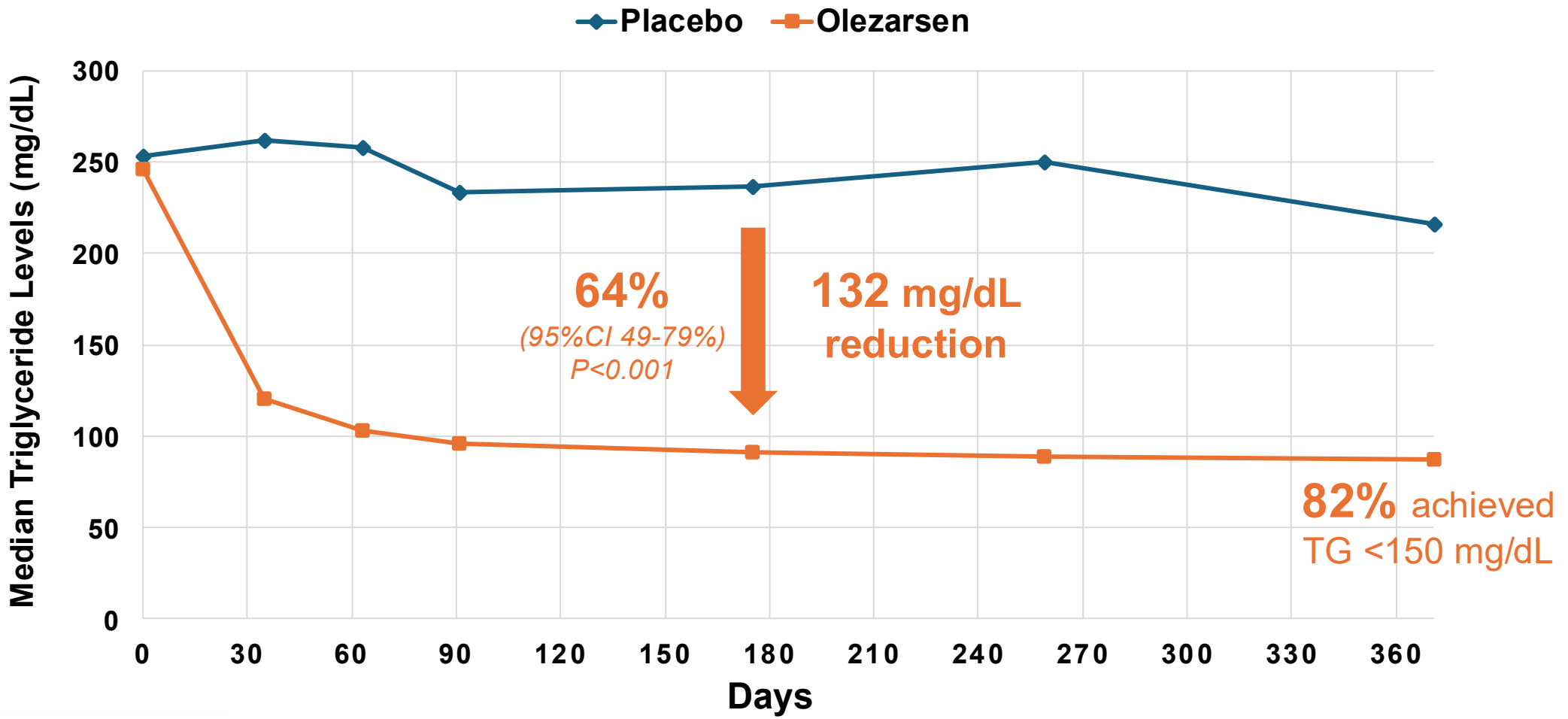
Effect of Olezarsen on Triglyceride Levels



N=468

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Effect of Olezarsen on Other Lipid Measures

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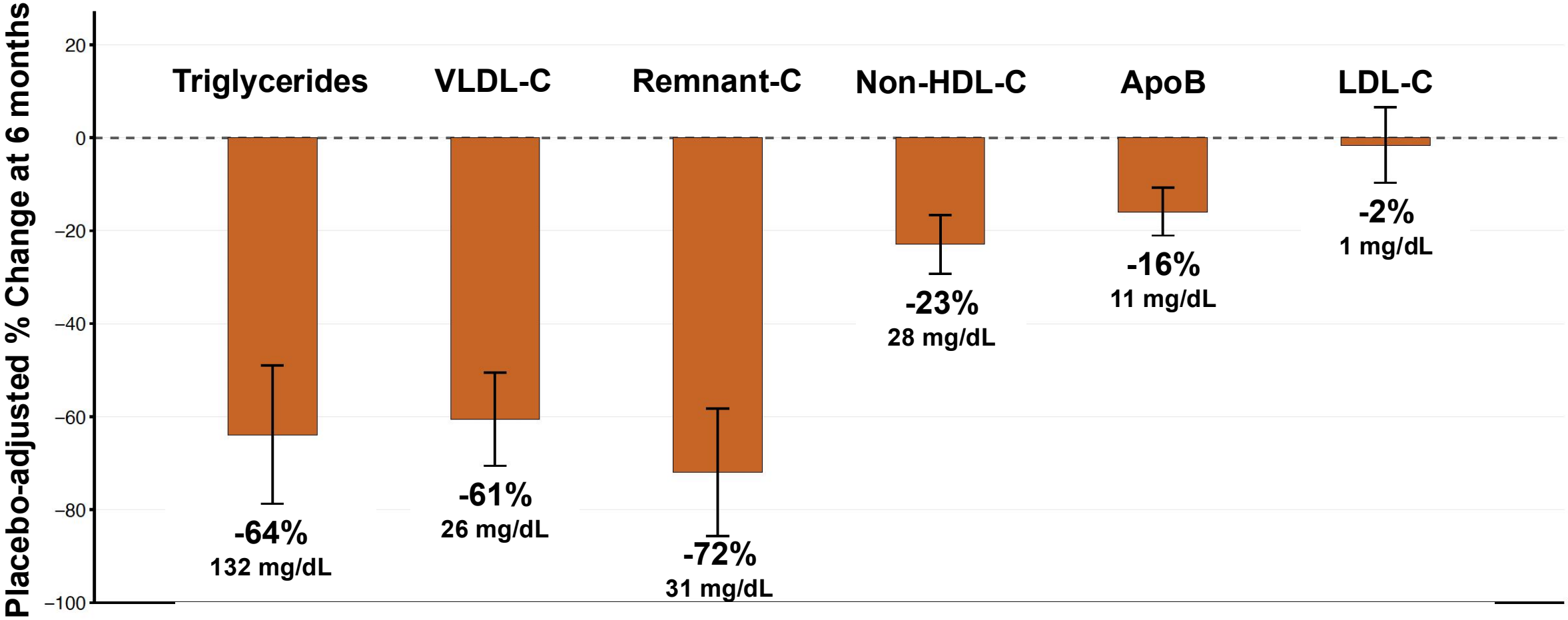

Placebo-adjusted LSM % change
Absolute difference of median changes

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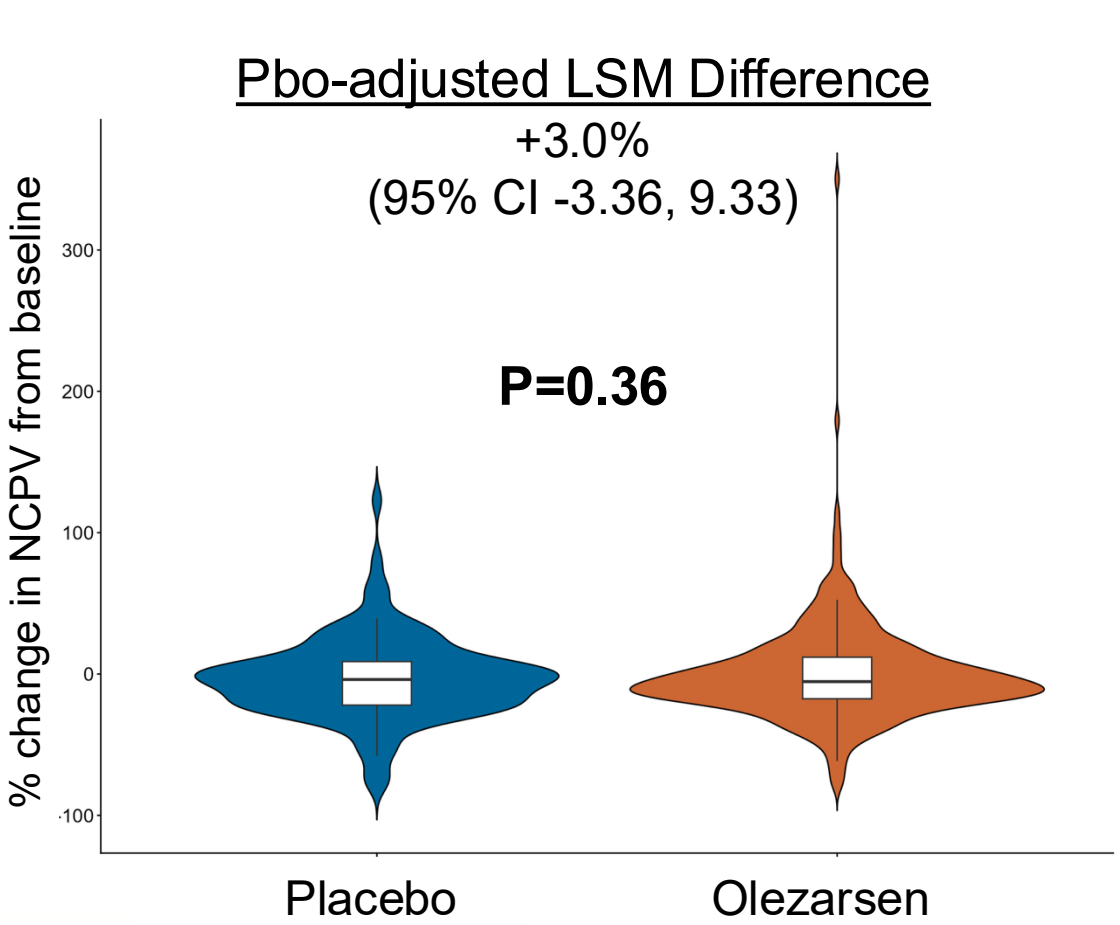
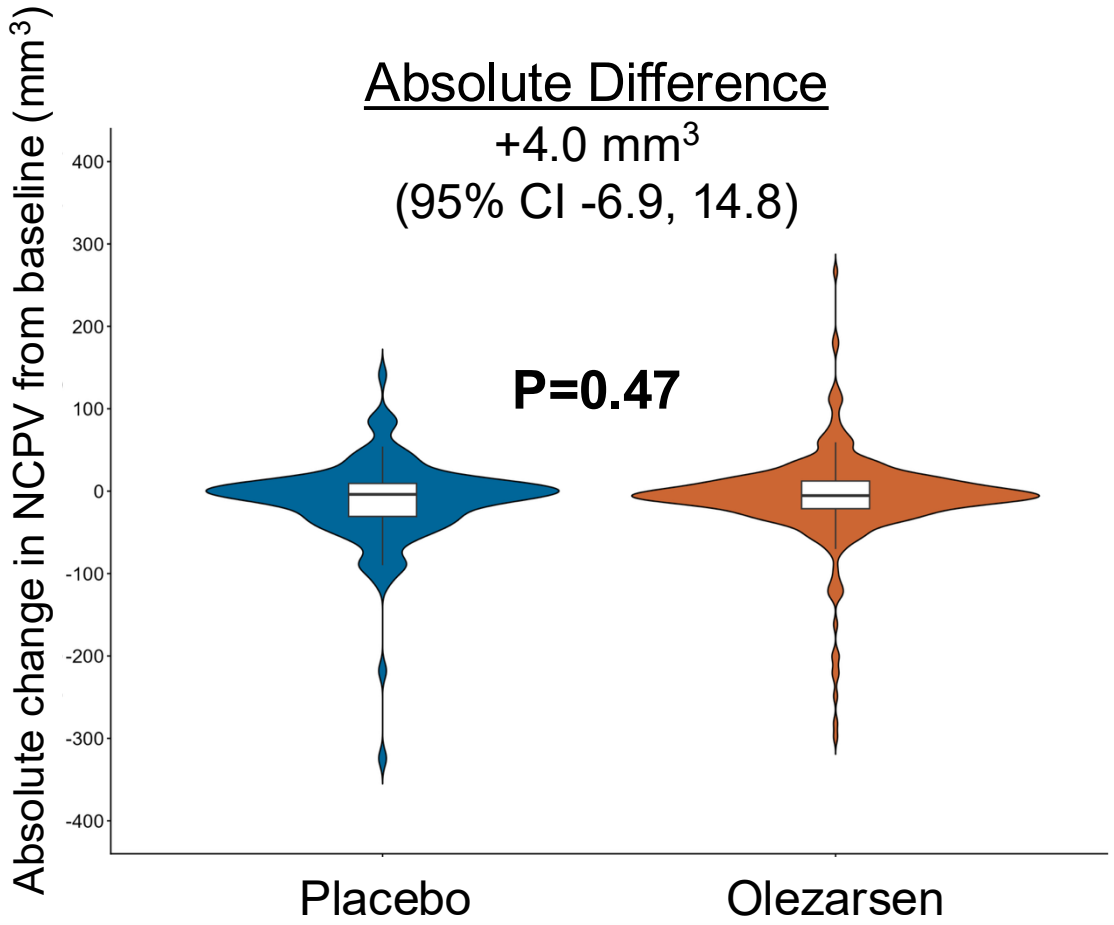
Primary Endpoint: Change in Non-Calcified Plaque Volume





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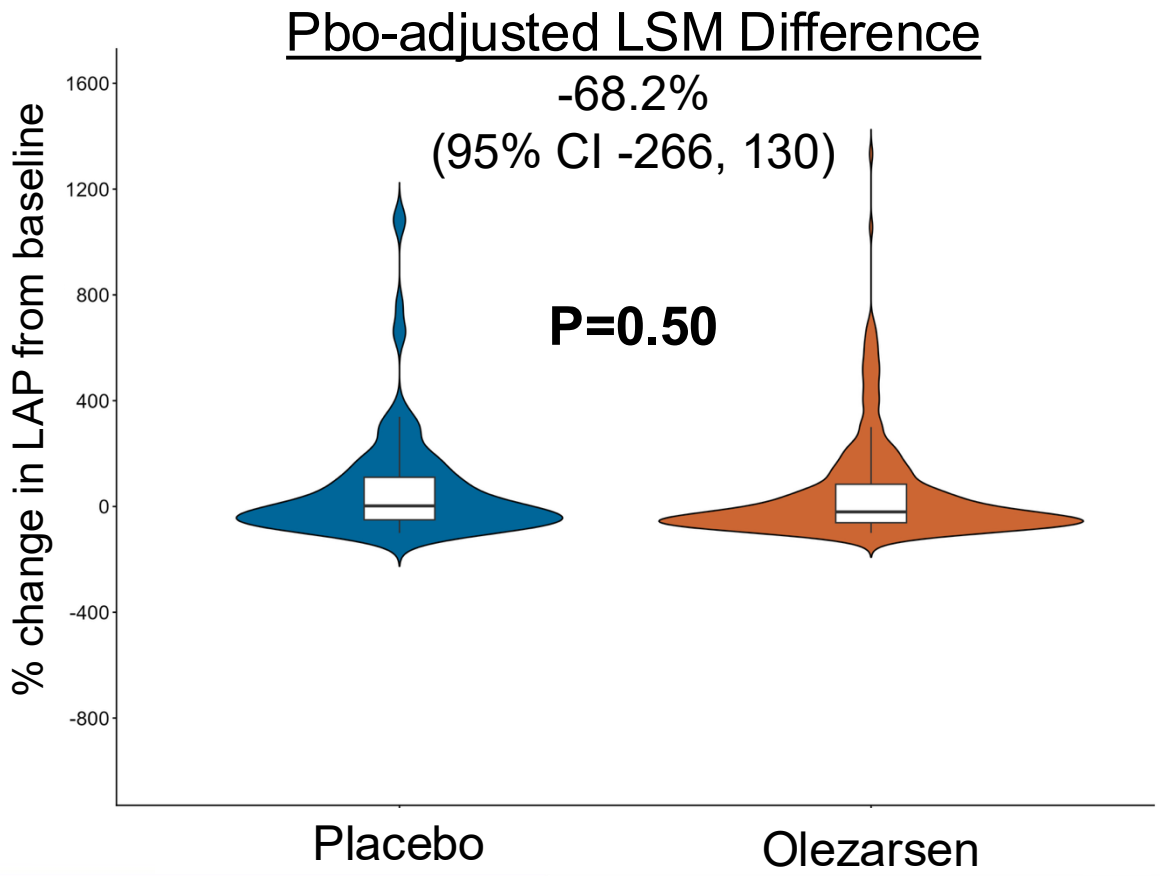
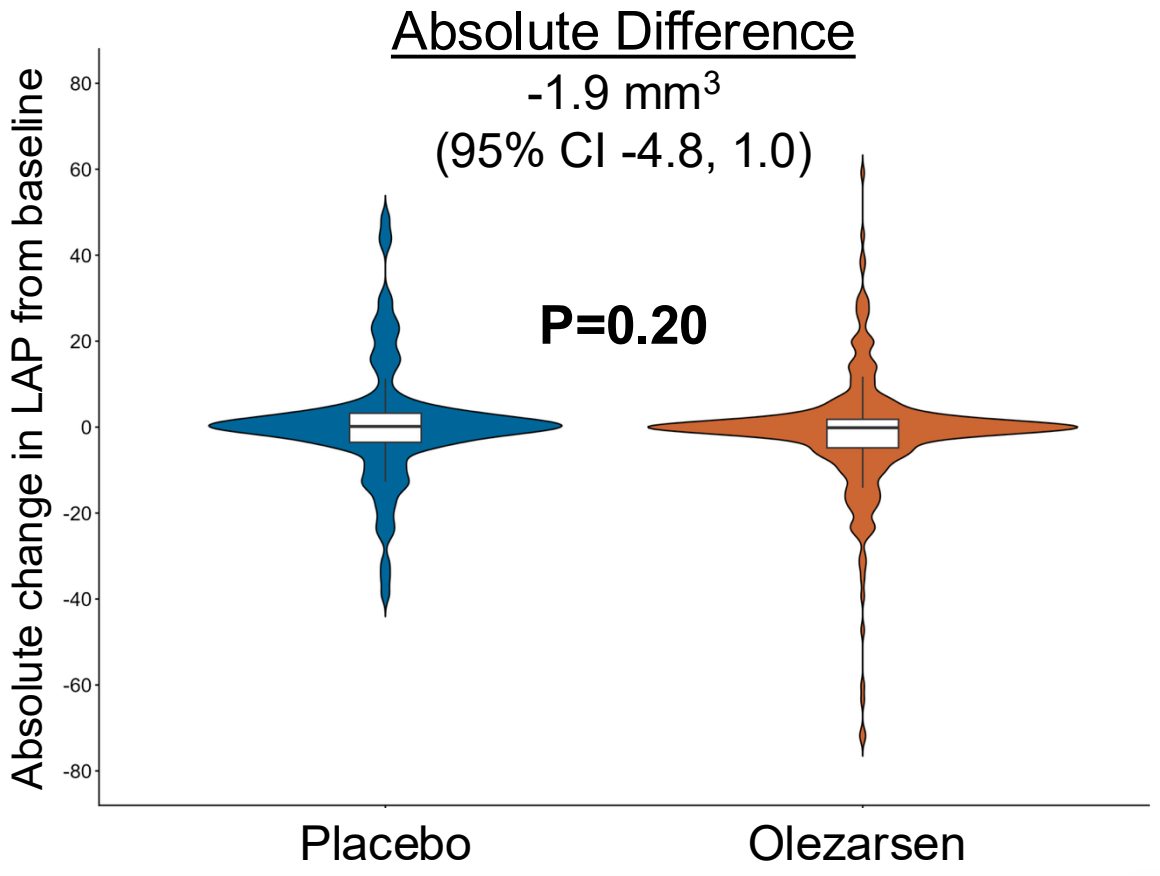
Key Secondary Endpoint: Change in Low Attenuation Plaque Volume





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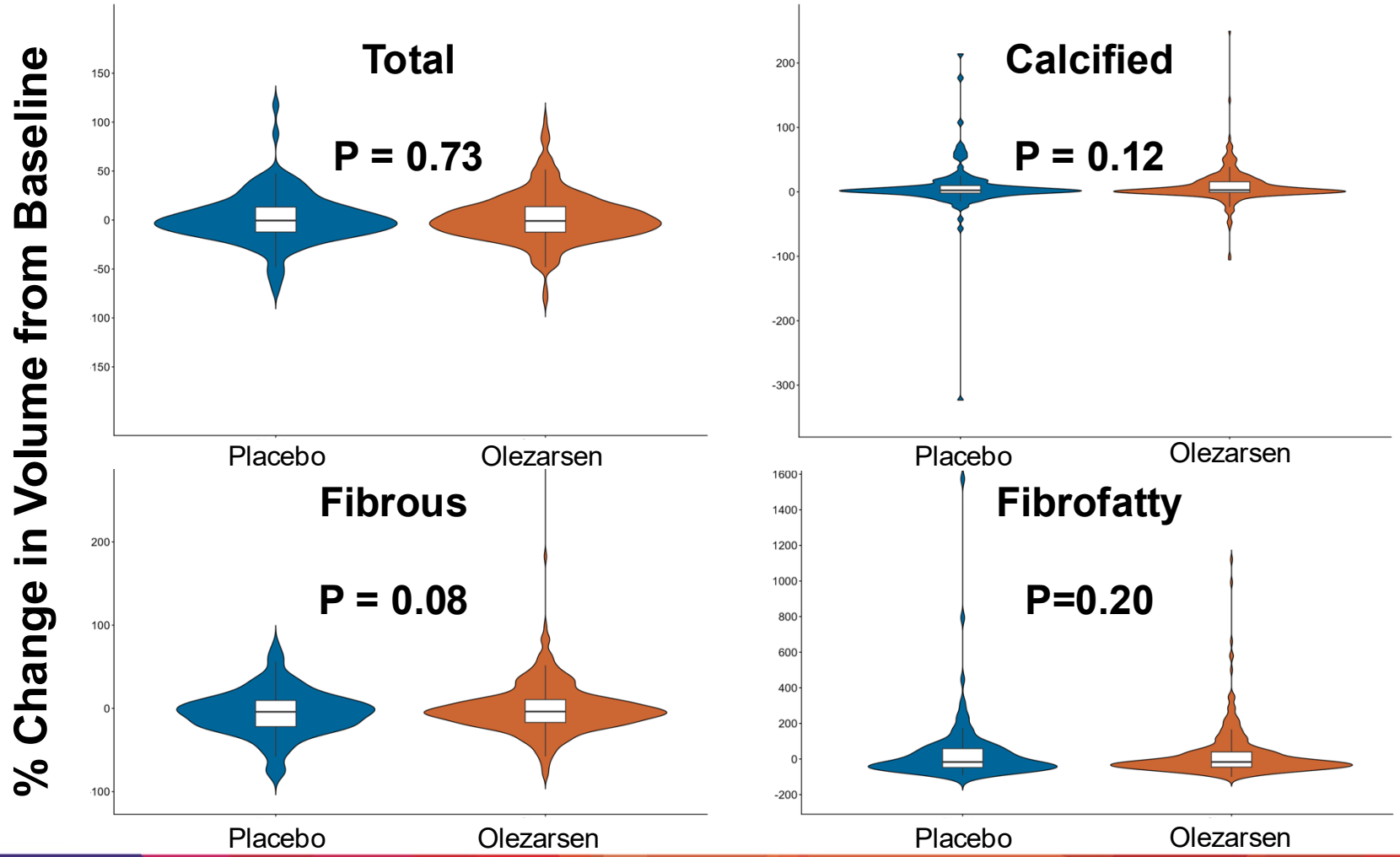
Secondary Plaque Endpoints



Potential Limitations

- Trial duration: Follow up time of 12 months
- Imaging Modality: CCTA vs invasive imaging (IVUS/OCT)
- Population: No significant plaque progression in the placebo group in the setting of significant background lipid lowering therapy

Summary

Among patients with largely moderate hypertriglyceridemia, treatment with olezarsen on top of standard-of-care lipid-lowering therapy:

- Substantially lowered triglycerides and remnant cholesterol levels
- Modestly lowered apolipoprotein B levels
- Did not affect noncalcified coronary plaque volume at 12 months

Conclusion

- These data do not support the hypothesis that reductions in RC and TRL have an outsized cardiovascular benefit compared with reductions in LDL-C and LDL particles
- Nonetheless, genetic epidemiology links lifelong lower ApoC3 levels with a lower risk of coronary artery disease
- Therefore, a cardiovascular outcomes trial would be required to determine if long-term APOC3 inhibition reduces CV events

Circulation

Effect of APOC3 Inhibition with Olezarsen on Coronary Atherosclerosis: Essence–TIMI 73b Imaging Study

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