Effect of on Oral Agent Inducing ApoA-I Synthesis on Progression of Coronary Atherosclerosis: Results of the ASSURE Study

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Disclosures

- Research support: AstraZeneca, Amgen, Anthera, Eli Lilly, Novartis, Resverlogix, InfraReDx, Roche and LipoScience

- Consulting and honoraria: AstraZeneca, Eli Lilly, Anthera, Omthera, Merck, Takeda, Resverlogix, Sanofi-Aventis, CSL Behring, Esperion, Boehringer Ingelheim

- ASSURE was sponsored by Resverlogix

Steering Committee

- Steven Nissen (Chair)
- Stephen Nicholls (Principal Investigator)
- Christie Ballantyne
- Philip Barter
- Bryan Brewer
- John Kastelein
- Jan Johansson (non-voting)

Background

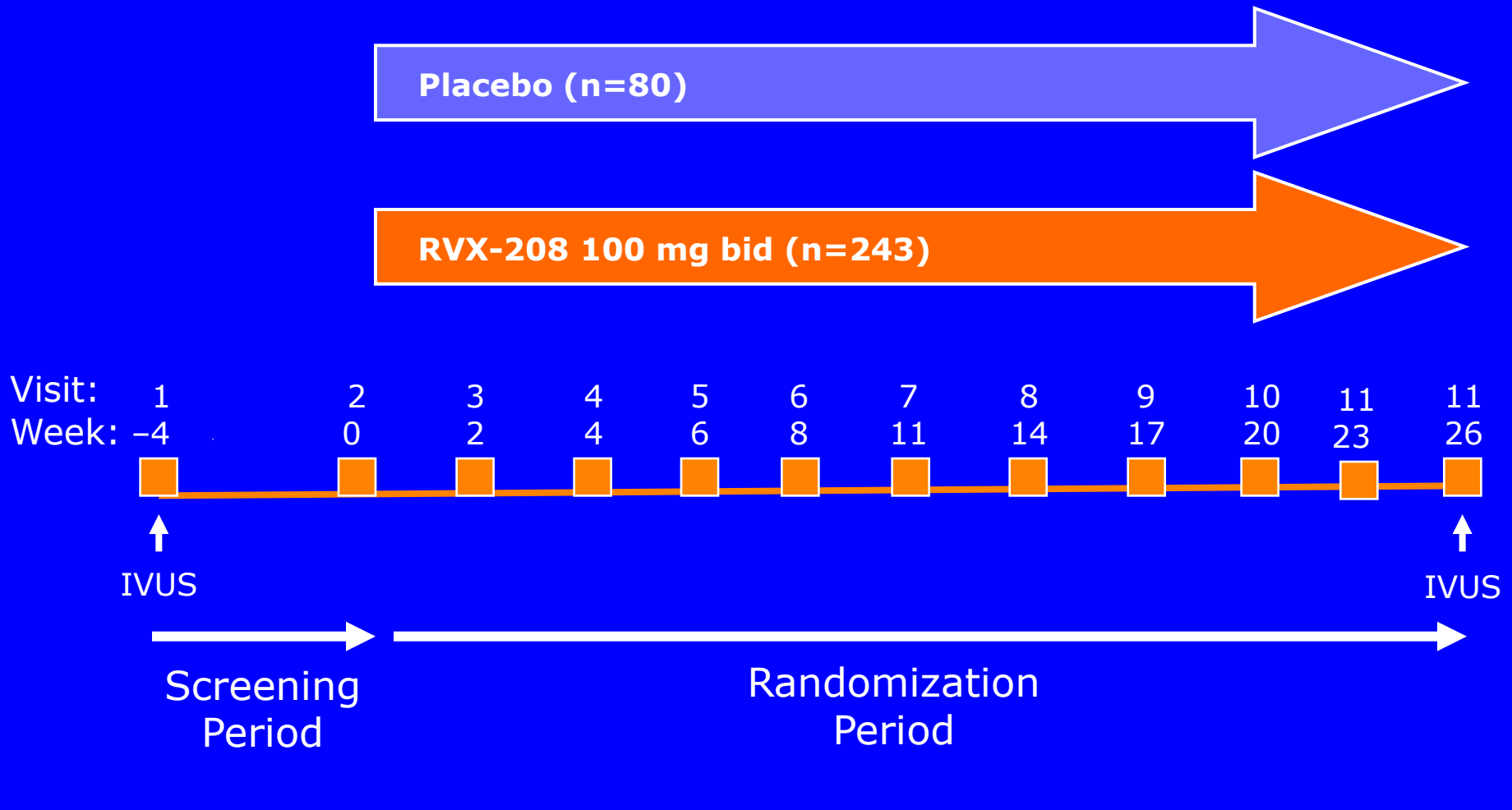
- There remains considerable interest in the development of novel agents that promote the biological activity of HDL.
- Induction of synthesis of apoA-I is a novel therapeutic approach to the generation of functional HDL particles
- The bromodomain and extra-terminal (BET) protein inhibitor, RVX-208, induces apoA-I synthesis, with favorable effects on HDL related measures and cholesterol efflux.
- The impact of RVX-208 on atherosclerotic plaque in humans has not been investigated.

Objective

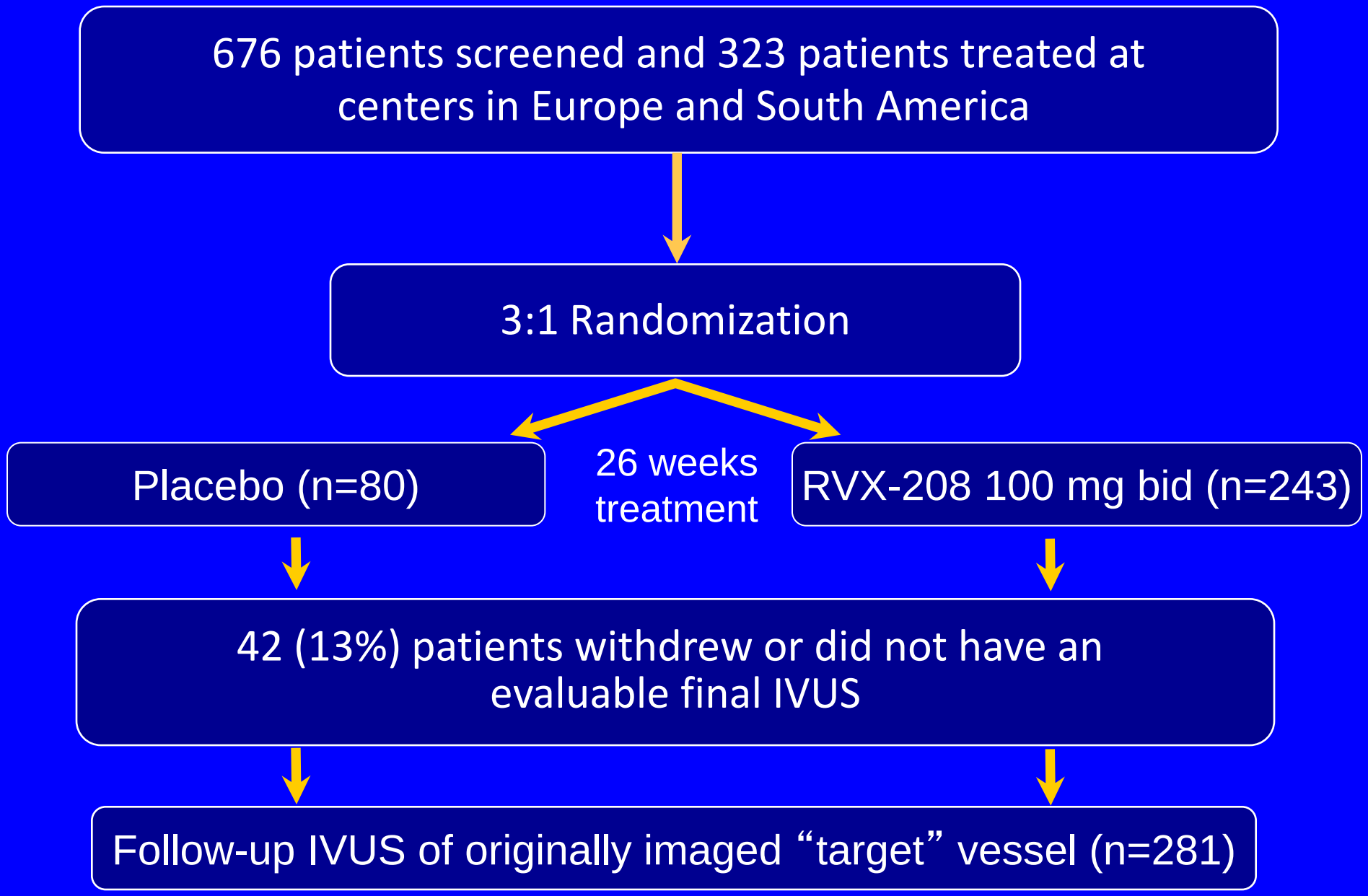
To evaluate the early effects of RVX-208 100 mg bid on progression of coronary atherosclerosis compared to baseline assessed by intravascular ultrasound when administered for 26 weeks to patients with coronary disease and low HDL-C levels.

ASSURE Study Design

323 patients with symptomatic CAD (angiographic stenosis >20%) and low HDL-C levels



ASSURE Trial: Flow of Patients



Clinical Characteristics

Parameter	Placebo (n=80)	RVX-208 (n=243)
Mean age in years	57.6	58.3
Males	71.3%	77.8%
Median Body Mass Index	30.5	30.0
History of Hypertension	86.3%	79.4%
History of Diabetes	28.8%	31.3%
Prior myocardial infarction	40.0%	40.3%
Prior statin use	78.8%	83.5%
Concomitant Medications		
Aspirin	83.8%	85.6%
Beta-blocker	73.8%	80.7%
ACE inhibitor	46.3%	42.0%

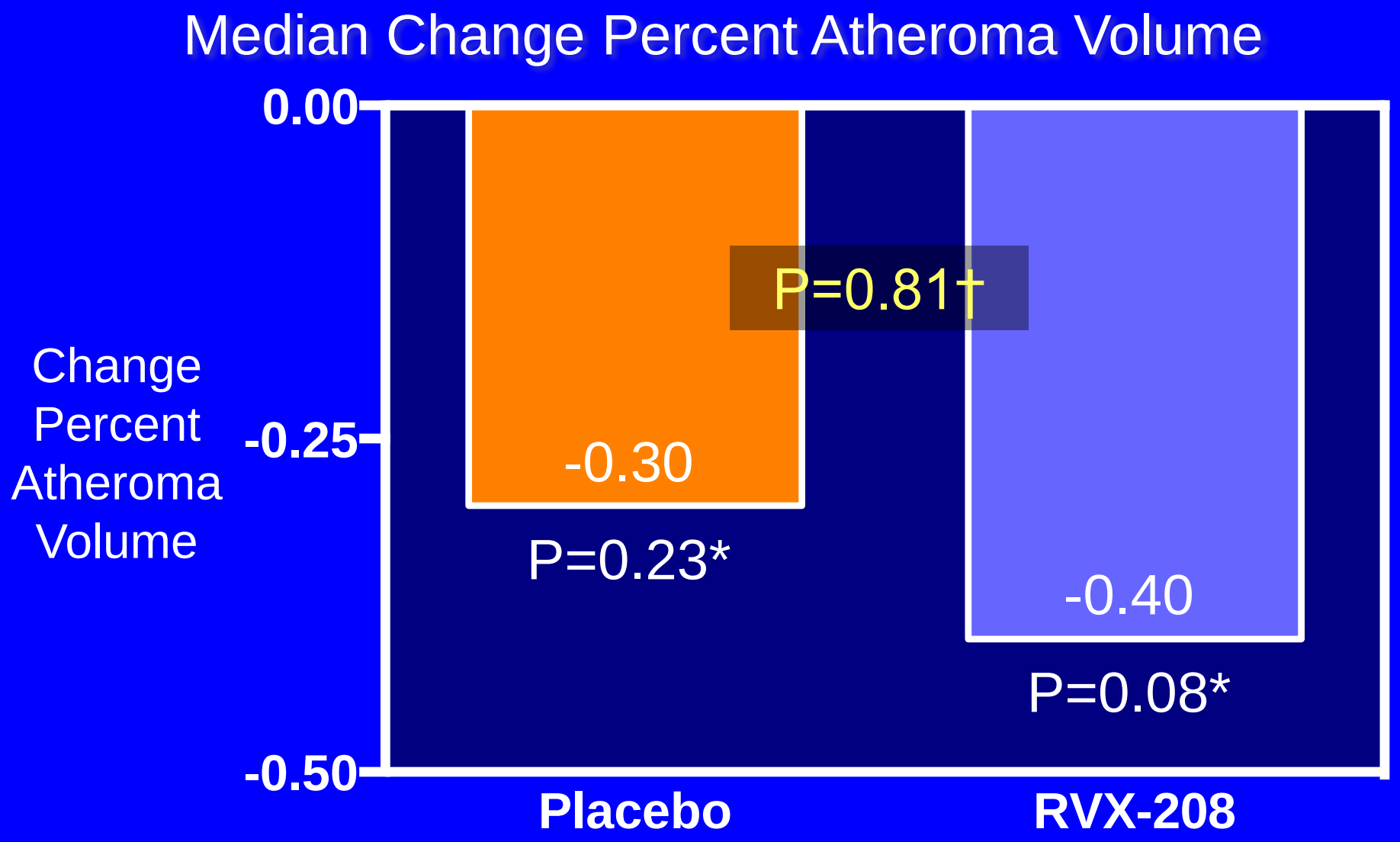
Baseline Laboratory and Plaque Measures

Parameter	Placebo (n=80)	RVX-208 (n=243)	P Value
LDL-C (mg/dL)	96.5	98.1	0.69
HDL-C (mg/dL)	39.0	39.0	0.97
Triglycerides (mg/dL)	132.5	135.0	0.98
ApoA-I (mg/dL)	115.0	118.0	0.45
Total HDL particles (μmol/L)	25.4	26.2	0.12
Large HDL particles (μmol/L)	2.1	2.3	0.93
Plaque Measures			
Percent atheroma volume	36.2	38.1	0.11
Total atheroma volume (mm^3)	154.8	199.9	<0.001
Atheroma volume most diseased 10-mm segment (mm^3)	50.7	61.6	0.05

Change in Biochemical Parameters

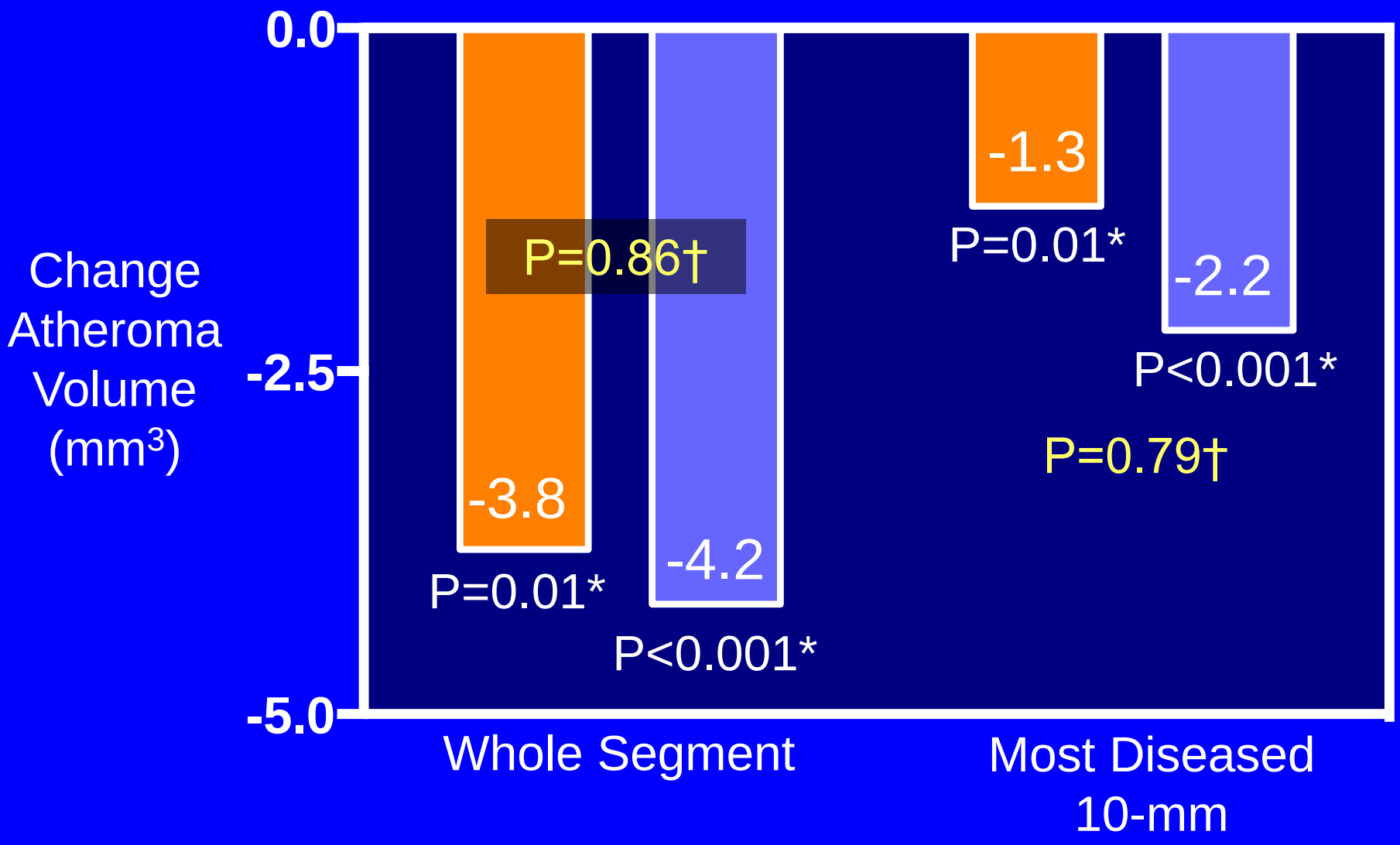
Parameter	Placebo (n=80)		RVX-208 (n=243)		P Value Between Groups
	Change	P Value	Change	P Value	
LDL-C	-17.6%	<0.001	-16.0%	<0.001	0.56
HDL-C	7.7%	<0.001	10.9%	<0.001	0.32
ApoA-I	10.6%	<0.001	12.8%	<0.001	0.18
ApoB	-11.5%	<0.001	-6.1%	<0.001	0.23
Total HDL	6.3%	<0.001	10.0%	<0.001	0.13
Large HDL	38.0%	<0.001	38.1%	<0.001	0.69
hsCRP	-33.8%	0.08	-32.7%	<0.001	0.65

Primary IVUS Efficacy Parameter



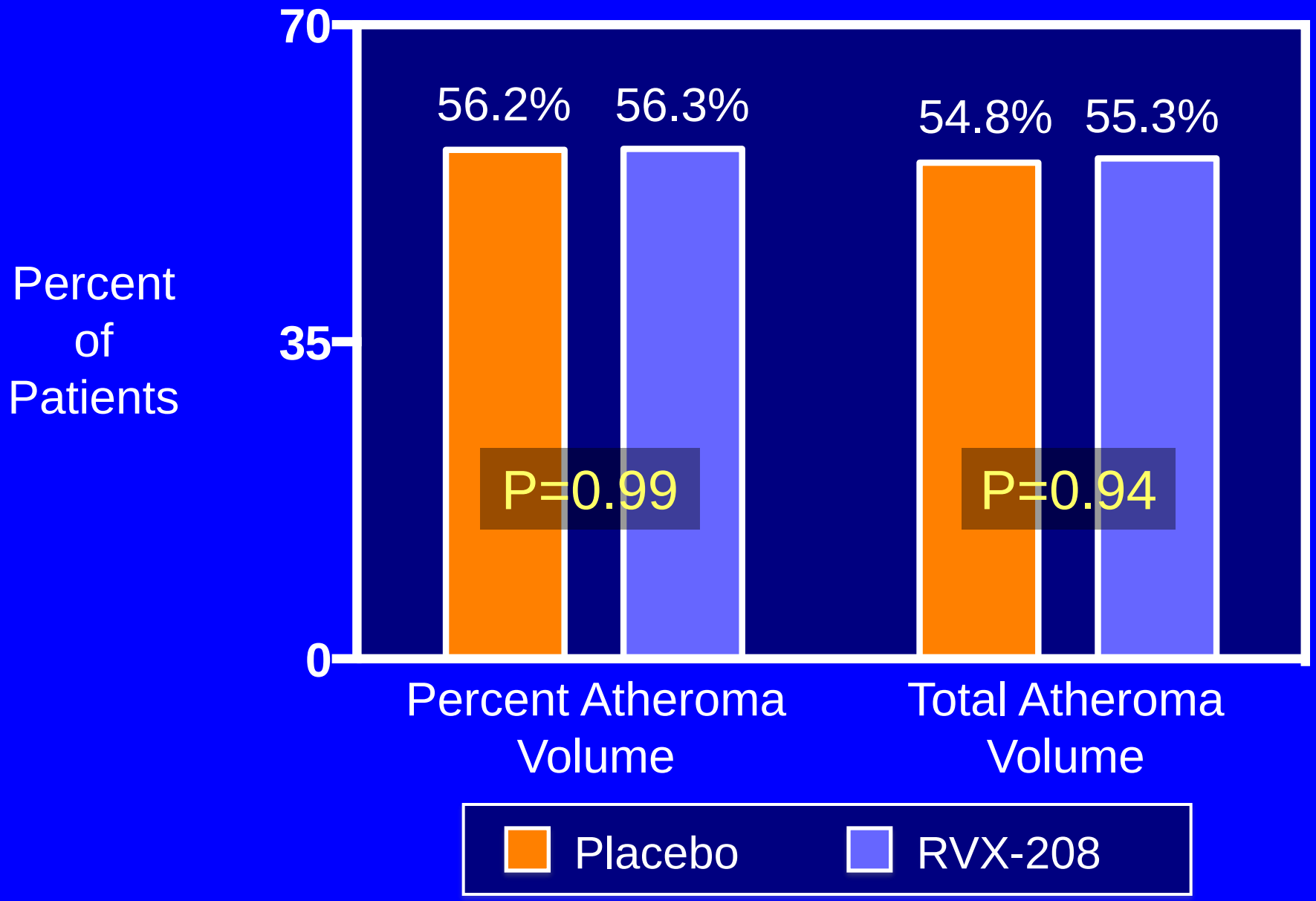
* Primary endpoint: comparison from baseline † comparison between groups.

Secondary IVUS Efficacy Parameters

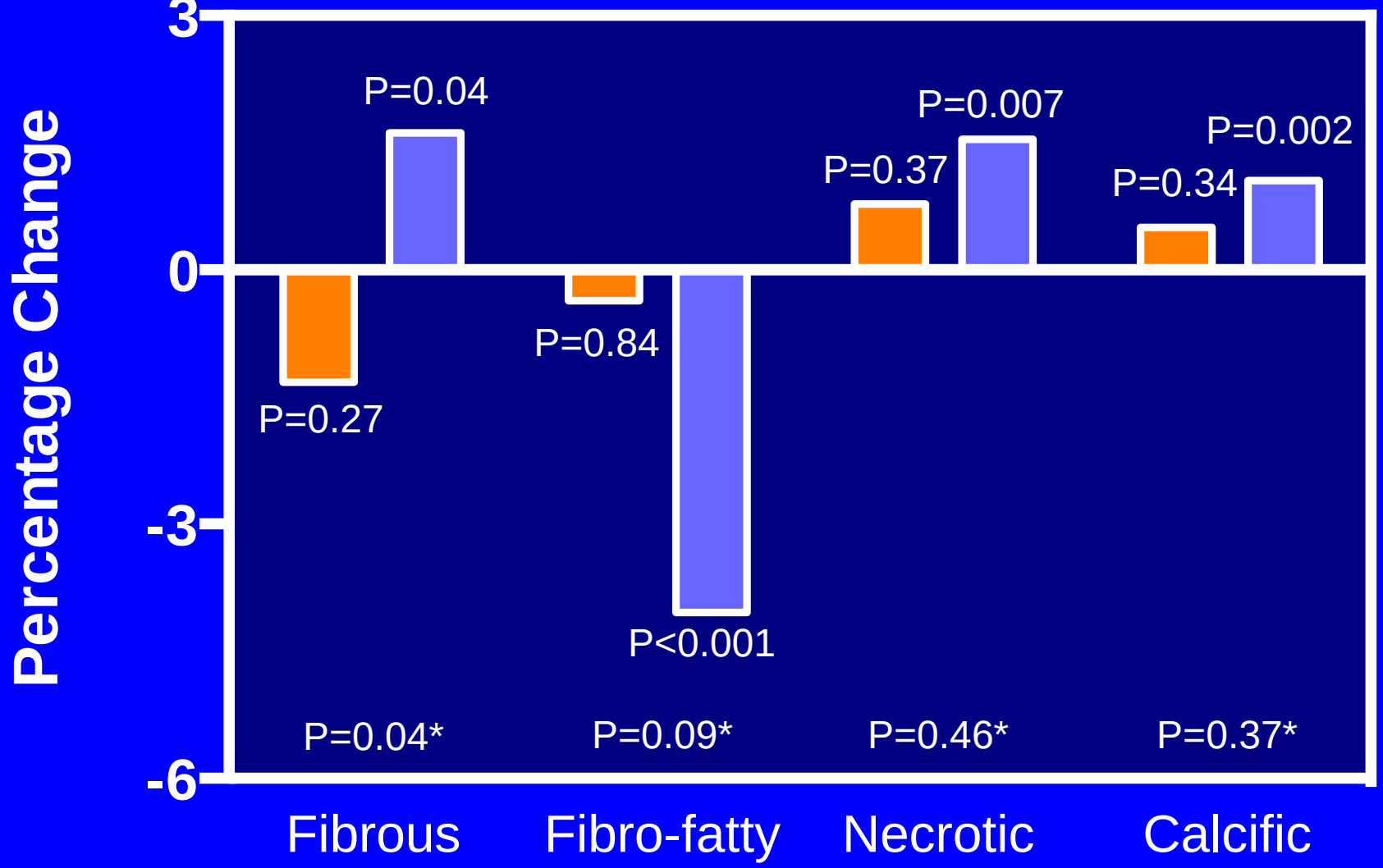


† comparison between groups.
* comparison from baseline

Fraction of Patients Exhibiting Regression



Exploratory Analysis: Plaque Composition



Expressed as LS mean change
P values for comparison with baseline
*P value for comparison with placebo

Adverse Clinical and Biochemical Events

Parameter	Placebo (n=80)	RVX-208 (n=243)	P Value
Cardiovascular events	13.8%	7.4%	0.09
ALT/AST >3x ULN	0%	7.1%	0.009
Bilirubin >2x ULN	0%	0%	1.00
CK >3x ULN	0%	1.3%	0.58
Creatinine >1.5x ULN	0%	0.9%	1.00

Conclusions

- Increases in HDL-C and apoA-I and a decrease in LDL-C compared with baseline with RVX-208 did not differ from the placebo group.
- For the primary endpoint, a trend to regression with RVX-208 was observed.
- For the secondary endpoints, regression of all IVUS measures with RVX-208 did not differ from placebo.
- RVX-208 administration was associated with liver enzyme elevations as previously observed.

A Final Thought

- Potentially protective properties of HDL has stimulated an immense search for a new therapeutic agent for patients with CAD.
- Administration of RVX-208 for 26 weeks did not produce an incremental benefit on atherosclerotic plaque compared with placebo.
- The search for benefit of RVX-208 and an effective HDL targeted therapy continues.