Results of the GLAGOV Trial

Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound

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Disclosure

Consulting: Many companies

Clinical Trials: Abbvie**,** Amgen, AstraZeneca, Cerenis, Eli Lilly, Esperion, Takeda, Novo Nordisk, The Medicines Company, and Pfizer.

Companies are directed to pay any honoraria directly to charity. No personal reimbursement is accepted for directing or participating in clinical trials.

Background

- Prior intravascular ultrasound (IVUS) trials have shown that statins slow progression or induce regression of coronary disease in proportion to the magnitude of LDL-C reduction.
- No other LDL-lowering therapy has shown regression in an IVUS trial.
- The lowest LDL-C achieved in prior trials was approximately 60 mg/dL. Effects of lower levels remain unknown.
- PCSK9 inhibitors incrementally lower LDL-C when added to statins, allowing achievement of very low LDL-C levels, however, no data exist describing effects on progression.

Trial Leadership

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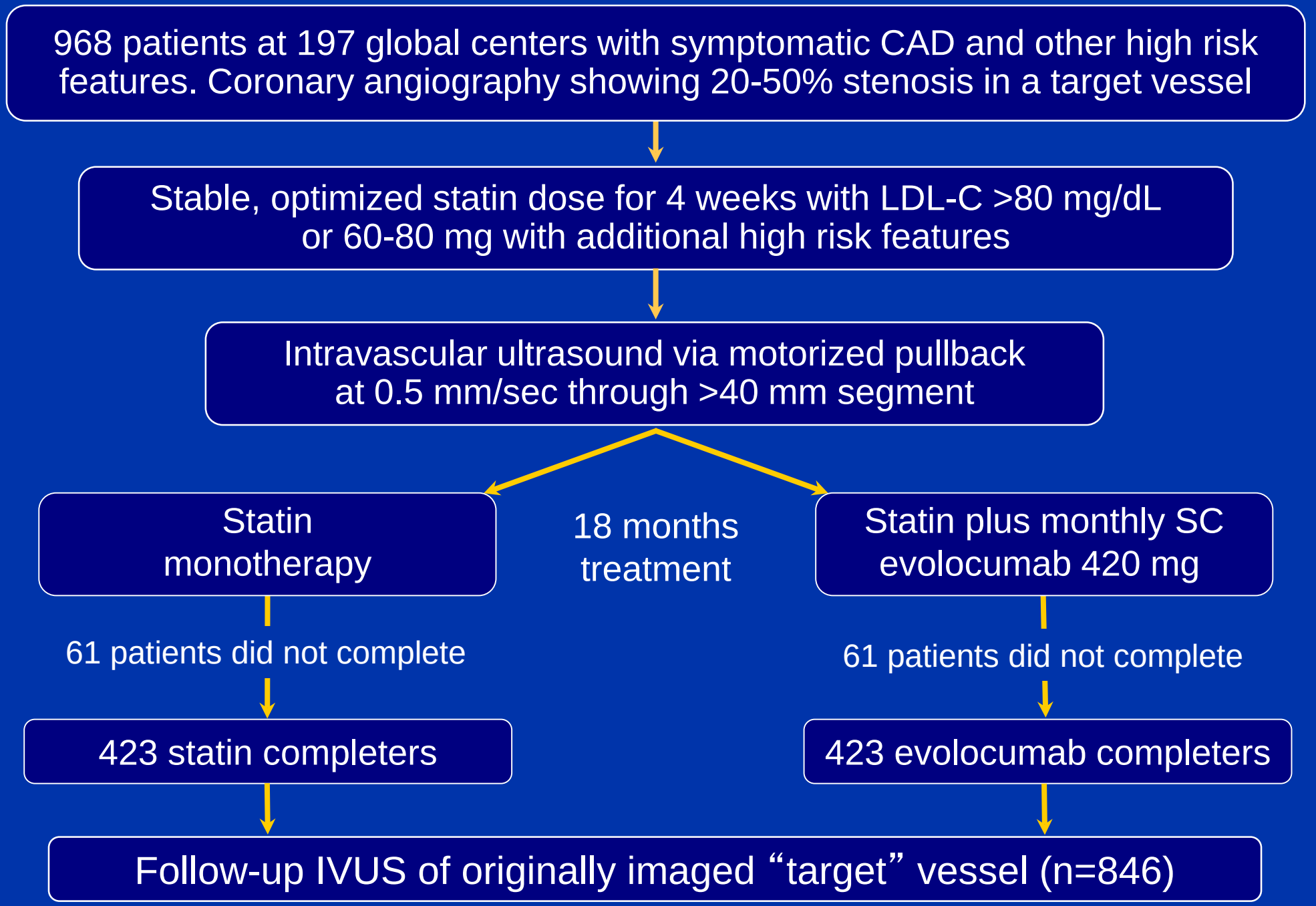
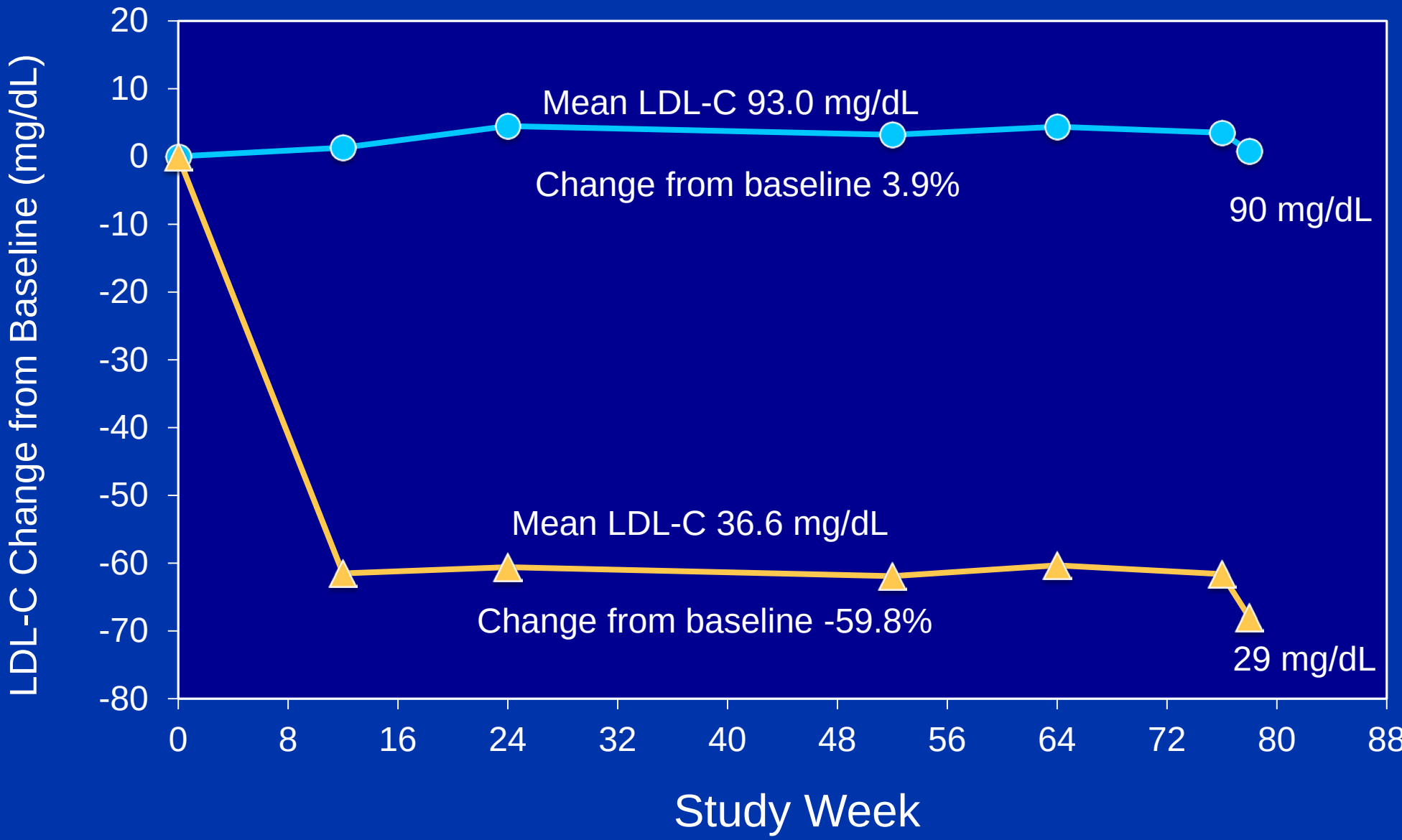

968 patients at 197 global centers with symptomatic CAD and other high risk features. Coronary angiography showing 20-50% stenosis in a target vessel
Stable, optimized statin dose for 4 weeks with LDL-C >80 mg/dL or 60-80 mg with additional high risk features
Intravascular ultrasound via motorized pullback at 0.5 mm/sec through >40 mm segment
Statin monotherapy
18 months treatment
Statin plus monthly SC evolocumab 420 mg
61 patients did not complete
61 patients did not complete
423 statin completers
423 evolocumab completers
Follow-up IVUS of originally imaged “target” vessel (n=846)

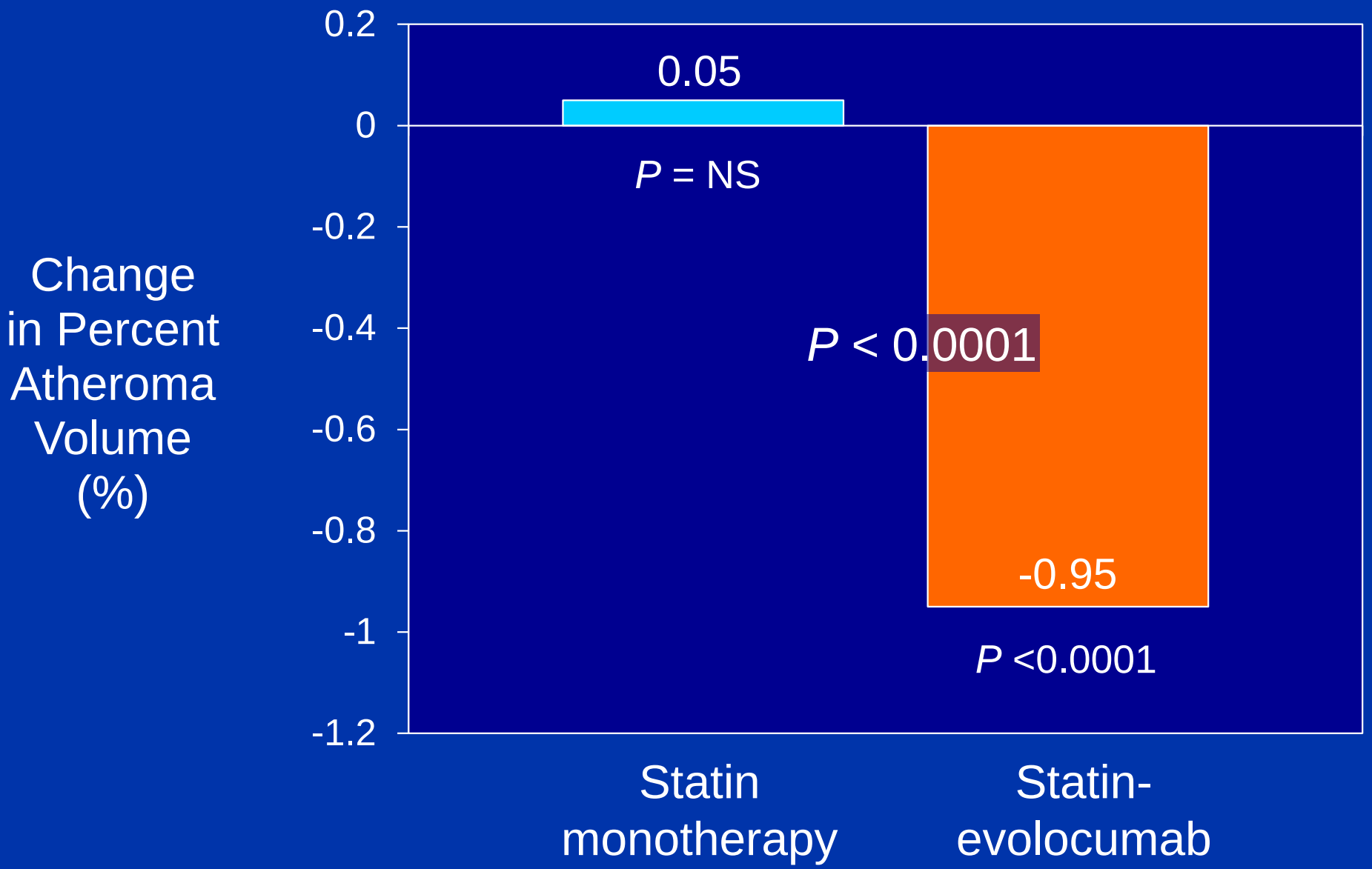
Baseline Demographics and Statin Usage

Characteristic	Placebo (N-484)	Evolocumab (N=484)
Age	59.8	59.8
Male Gender	72.3%	72.1%
BMI kg/m^2	29.5	29.4
Diabetes	21.5%	20.2%
Smoking	23.3%	25.6%
Baseline statin use	98.3%	98.8%
High intensity	59.9%	57.9%
Moderate intensity	38.2%	40.5%
Low intensity	0.2%	0.4%
Baseline LDL-C	92.4 mg/dL	92.6 mg/dL

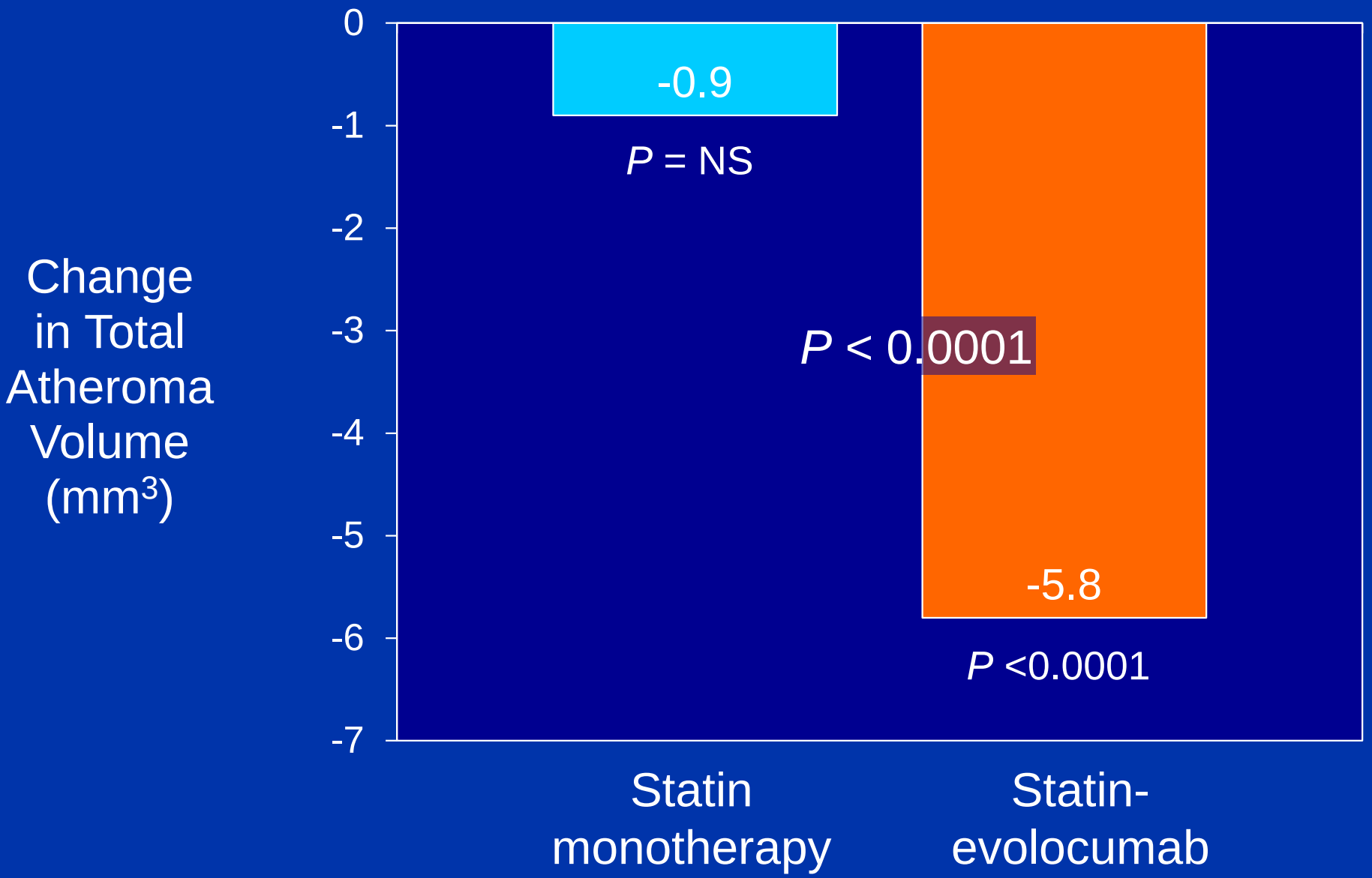
Percent Change in LDL-C During Treatment



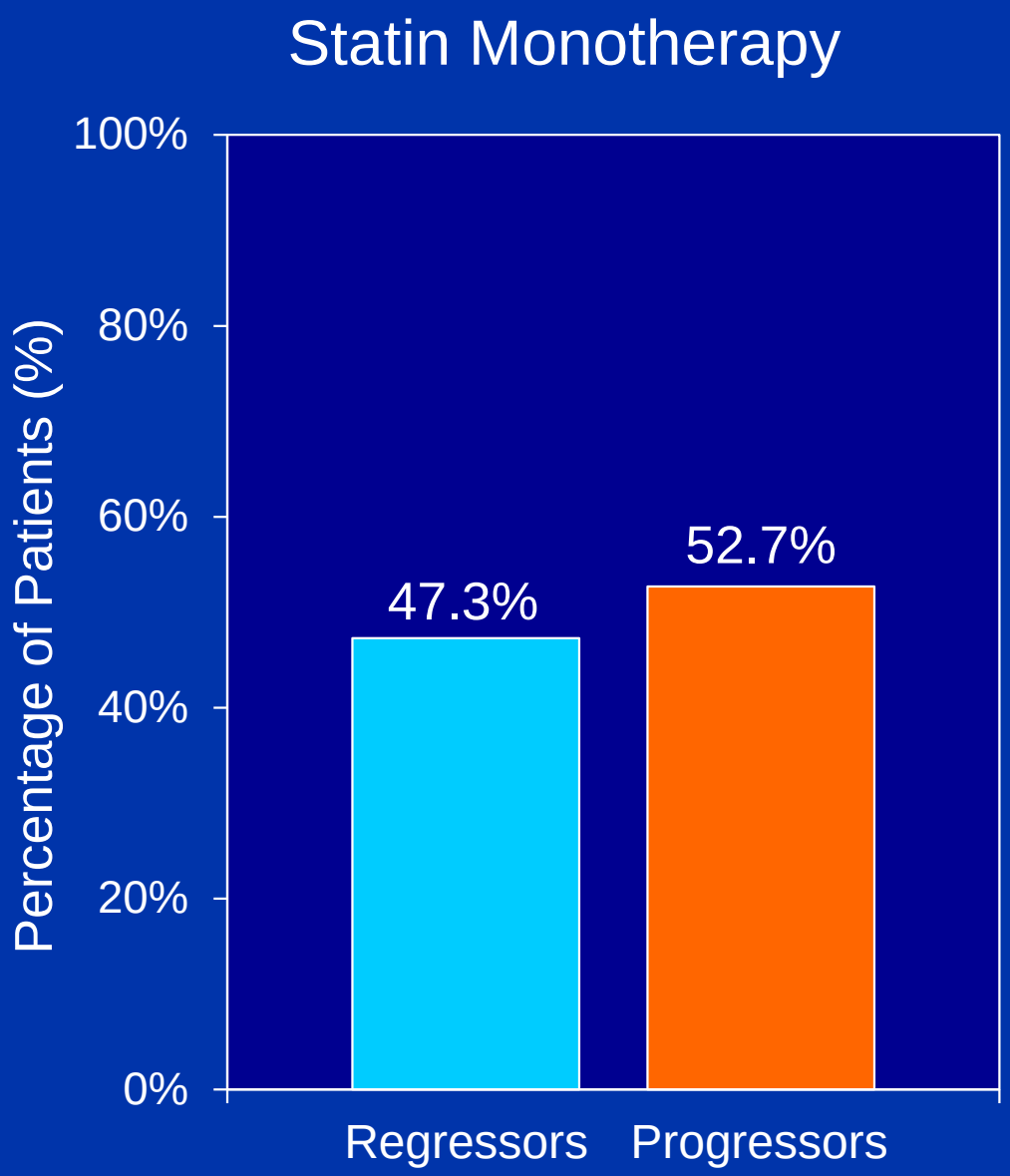
Primary Endpoint: Percent Atheroma Volume

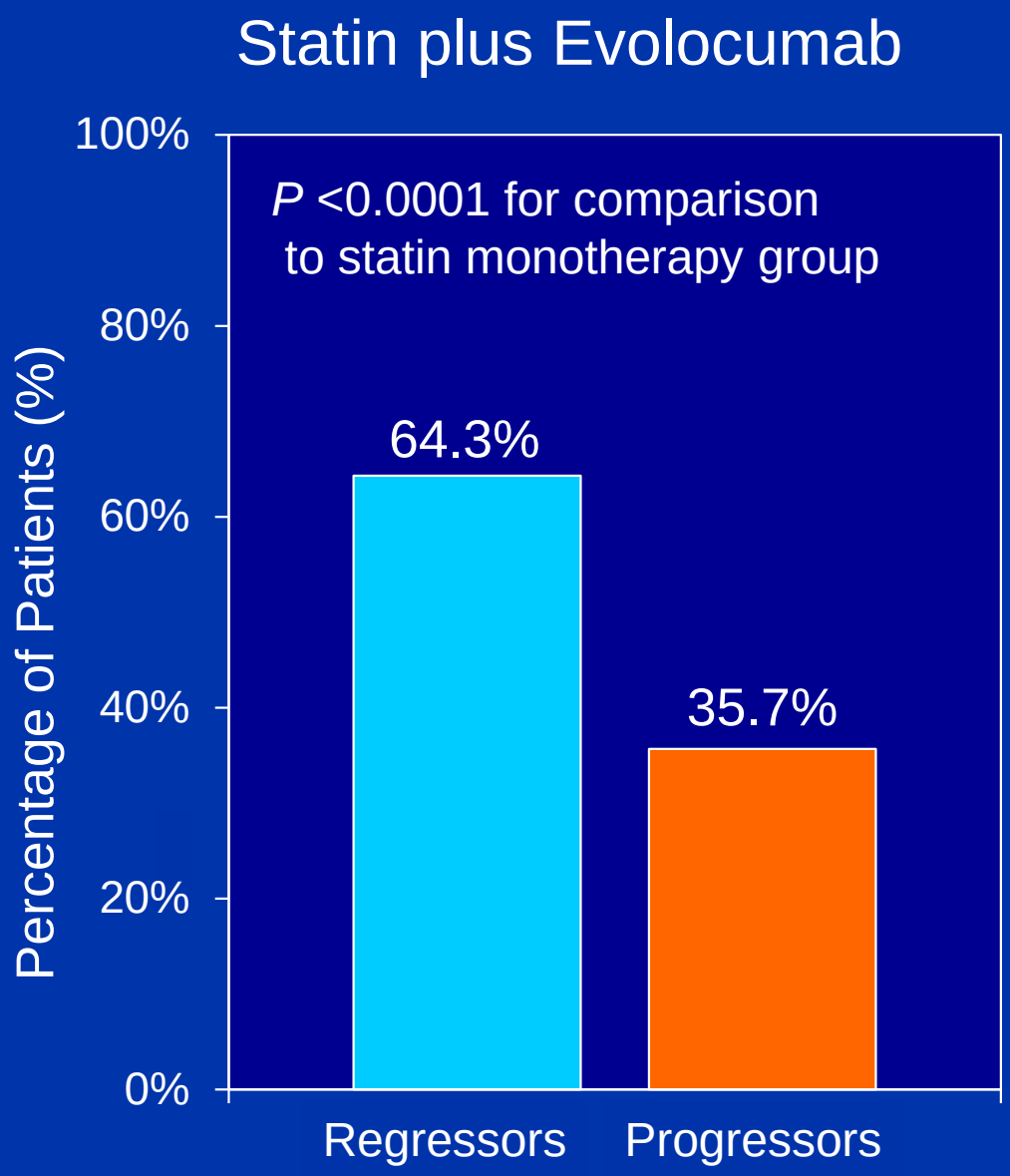


Secondary Endpoint: Total Atheroma Volume

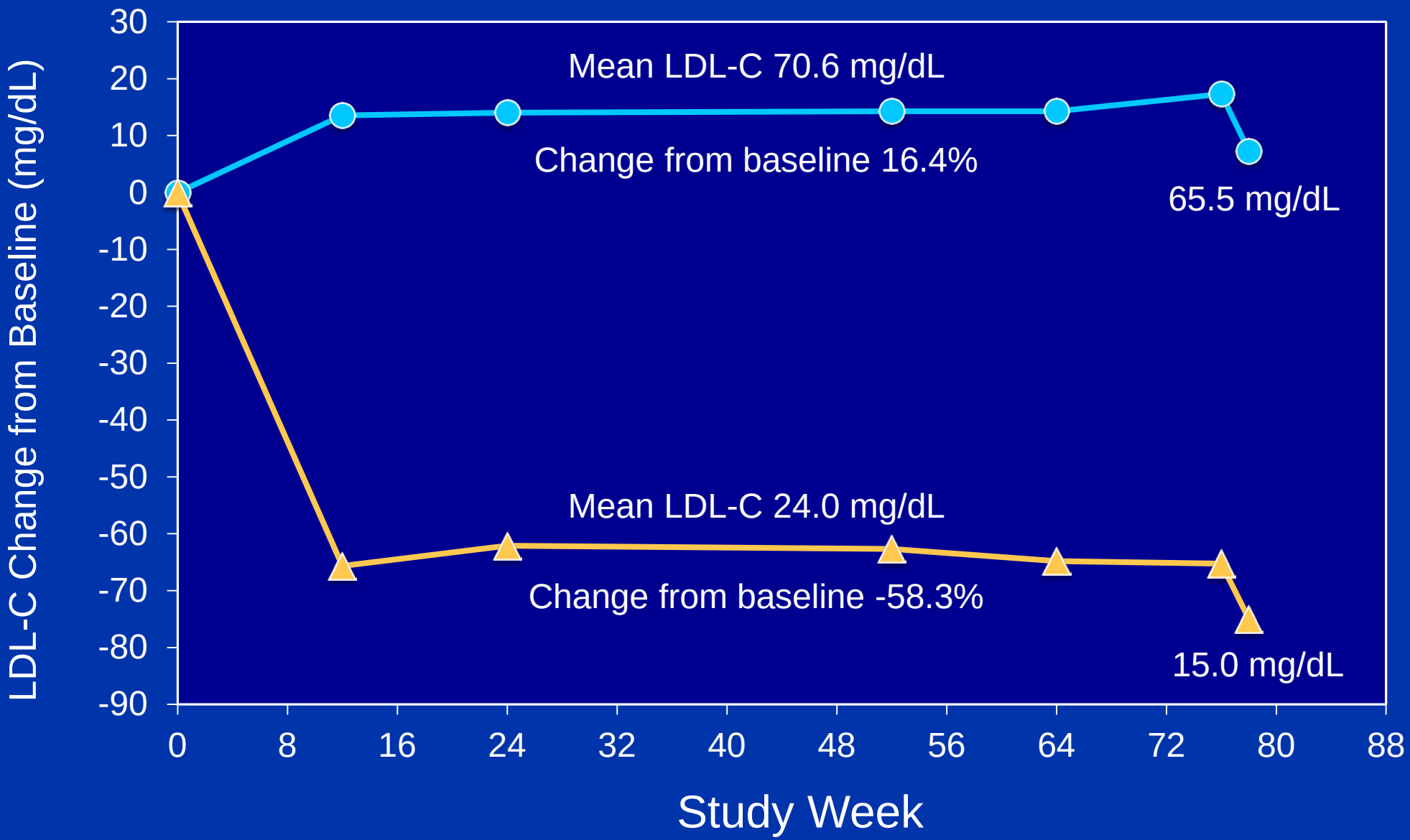


Percent of Patients Showing Regression in PAV





Exploratory Subgroup: Baseline LDL-C <70 mg/dL



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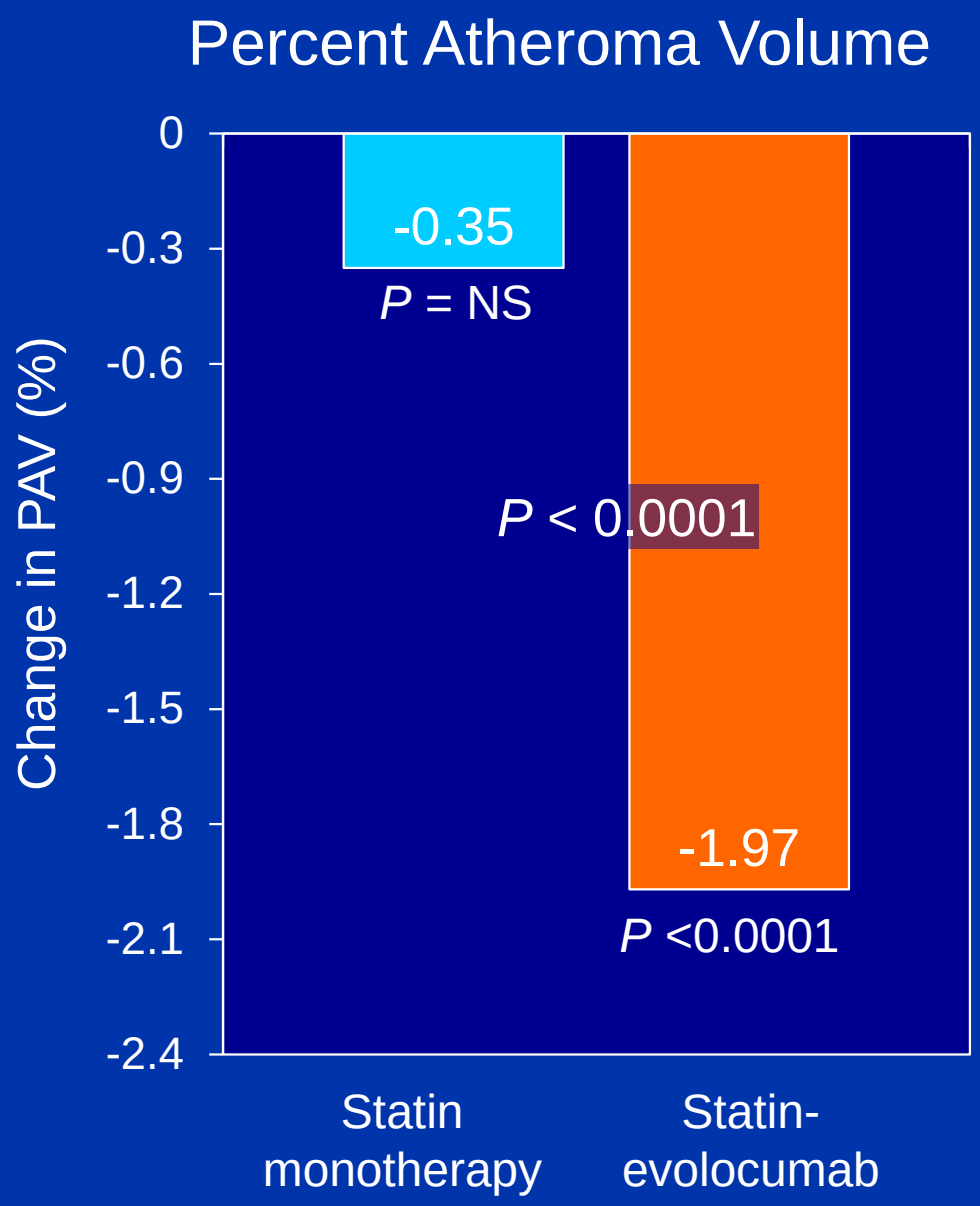
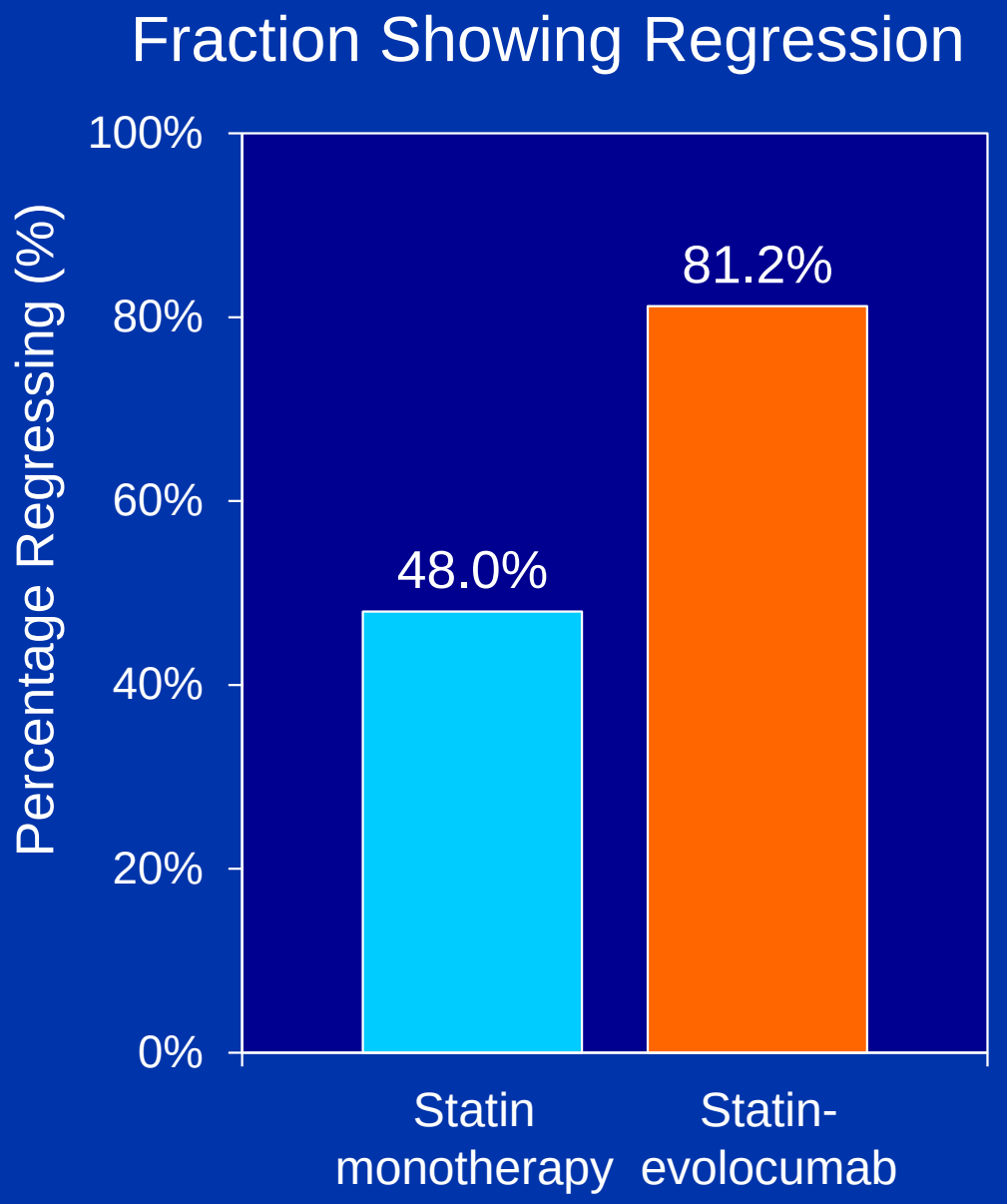
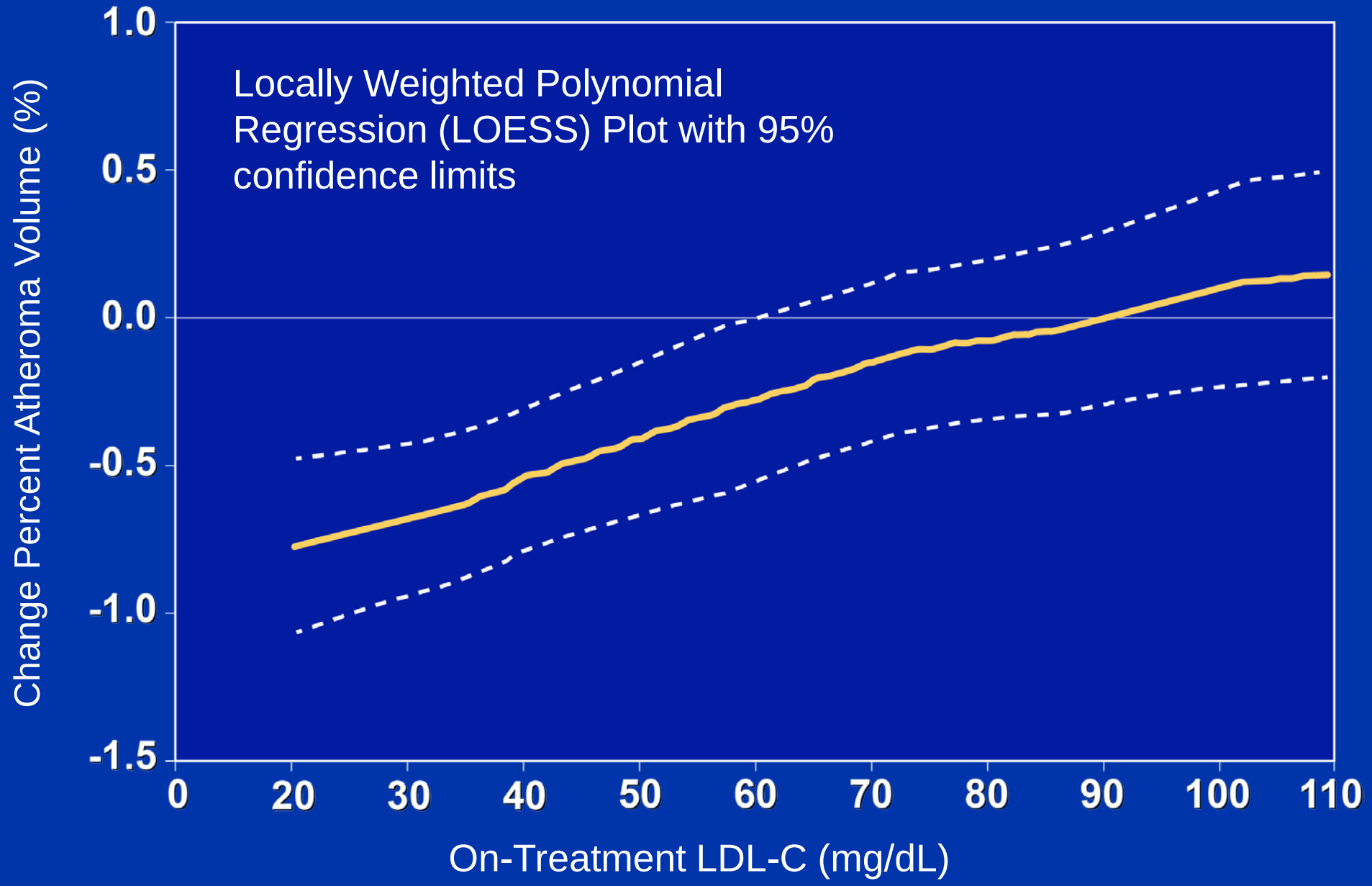
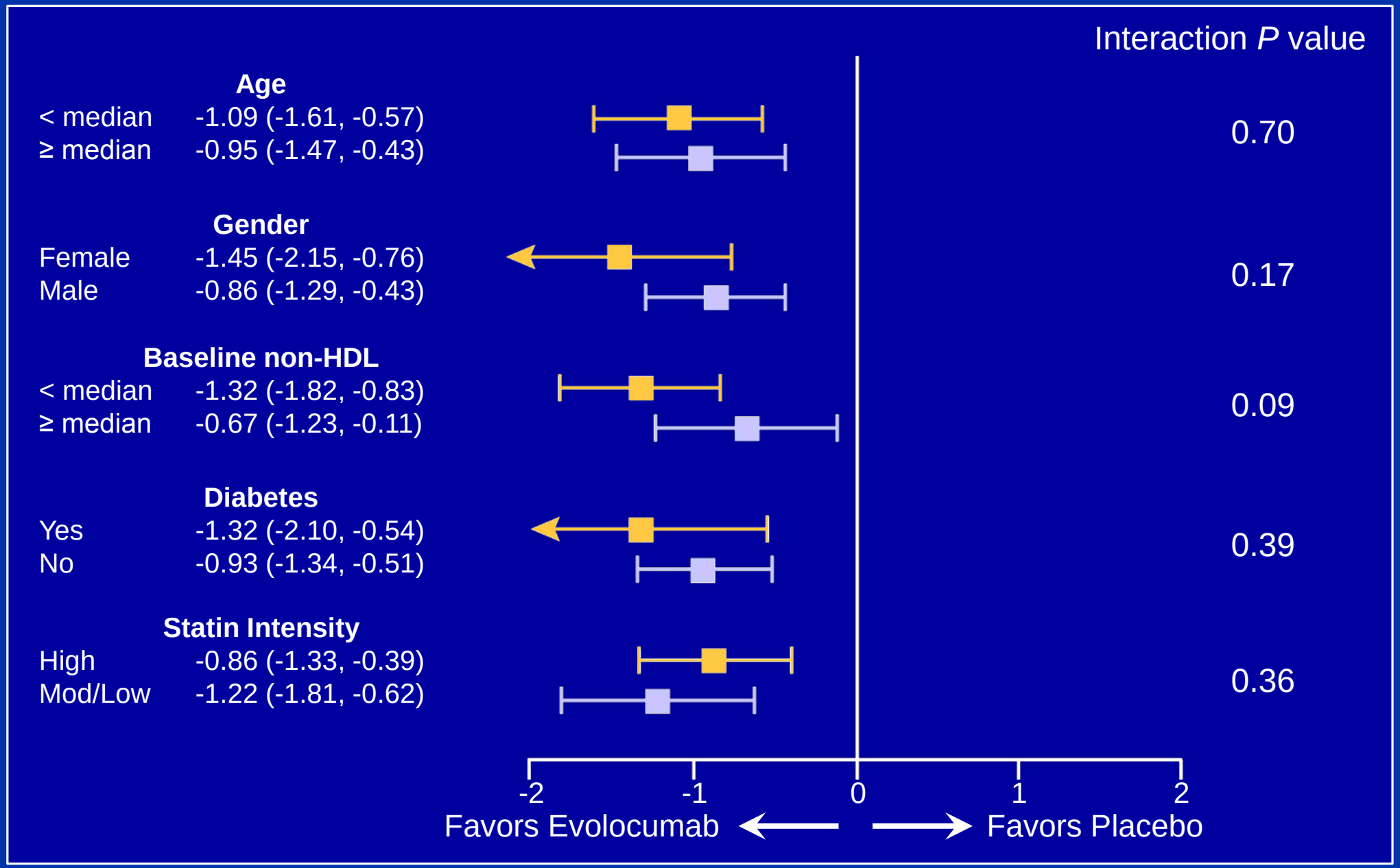




Mean On-Treatment LDL-C vs. Change in PAV



Interaction: Selected Prespecified Subgroups (PAV)



Adverse Clinical Events and Safety Findings

Event	Placebo (N=484)	Evolocumab (N=484)
Death	0.8%	0.6%
Nonfatal MI	2.9%	2.1%
Nonfatal Stroke	0.6%	0.4%
Hosp. for Unstable Angina	0.8%	0.6%
Coronary Revascularization	13.6%	10.3%
First Major Cardiovascular Event	15.3%	12.2%
Injection site reactions	0%	0.4%
Anti-evolocumab binding antibody	NA	0.2%
Neutralizing antibodies	NA	0%
Neurocognitive events	1.2%	1.4%
New onset diabetes	3.7%	3.6%
Myalgia	5.8%	7.0%

Limitations

- The GLAGOV trial assessed a select group of patients with coronary disease presenting for a clinically-indicated angiogram treated for only 18 months:

- Although retention was better than previous IVUS studies, 13% of patients did not have a follow up examination.

- IVUS is a useful measure of disease activity, but the critical determination of benefit and risk will require completion of large outcomes trials currently underway.

Conclusions-1

- In statin-treated patients with symptomatic coronary disease, addition of evolocumab, 420 mg monthly for 18 months:
  - Achieved LDL-C levels averaging 36.6 mg/dL compared with 93 mg/dL for a statin alone.
  - Produced regression, mean change in PAV of -0.95% compared with +0.05% in statin-only patients, (P<0.0001).
  - Induced regression in a greater percentage of patients, 64% vs. 47% (P<.0.0001).
- Post hoc analysis showed a incremental benefit for combination therapy at LDL-C levels as low as 20 mg/dL

Conclusions-2

- Benefits of combination therapy were observed in patients with baseline LDL-C below the lowest levels recommended by global guidelines (<70 mg/dL).
- No safety issues were identified at the mean LDL-C levels of 36.6 mg/dL achieved in the trial:
  - No excess in new onset diabetes, myalgia, or neurocognitive adverse effects.
  - However, the sample size of the trial was modest, providing limited power for safety assessments.

Research

JAMA | Original Investigation

Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients

The GLAGOV Randomized Clinical Trial

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IMPORTANCE Reducing levels of low-density lipoprotein cholesterol (LDL-C) with intensive statin therapy reduces progression of coronary atherosclerosis in proportion to achieved LDL-C levels. Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors produce incremental LDL-C lowering in statin-treated patients; however, the effects of these drugs on coronary atherosclerosis have not been evaluated.

OBJECTIVE To determine the effects of PCSK9 inhibition with evolocumab on progression of coronary atherosclerosis in statin-treated patients.

DESIGN, SETTING, AND PARTICIPANTS The GLAGOV multicenter, double-blind, placebo-controlled, randomized clinical trial (enrollment May 3, 2013, to January 12, 2015) conducted at 197 academic and community hospitals in North America, Europe, South America, Asia, Australia, and South Africa and enrolling 968 patients presenting for coronary angiography.

INTERVENTIONS Participants with angiographic coronary disease were randomized to receive monthly evolocumab (420 mg) (n = 484) or placebo (n = 484) via subcutaneous injection for 76 weeks, in addition to statins.

MAIN OUTCOMES AND MEASURES The primary efficacy measure was the nominal change in percent atheroma volume (PAV) from baseline to week 78, measured by serial intravascular ultrasonography (IVUS) imaging. Secondary efficacy measures were nominal change in normalized total atheroma volume (TAV) and percentage of patients demonstrating plaque regression. Safety and tolerability were also evaluated.

RESULTS Among the 968 treated patients (mean age, 59.8 years [SD, 9.2]; 269 [27.8%] women; mean LDL-C level, 92.5 mg/dL [SD, 27.2]), 846 had evaluable imaging at follow-up. Compared with placebo, the evolocumab group achieved lower mean, time-weighted LDL-C levels (93.0 vs 36.6 mg/dL; difference, −56.5 mg/dL [95% CI, −59.7 to −53.4]; $P < .001$). The primary efficacy parameter, PAV, increased 0.05% with placebo and decreased 0.95% with evolocumab (difference, −1.0% [95% CI, −1.8% to −0.64%]; $P < .001$). The secondary efficacy parameter, normalized TAV, decreased 0.9 mm^3 with placebo and 5.8 mm^3 with evolocumab (difference, −4.9 mm^3 [95% CI, −7.3 to −2.5]; $P < .001$). Evolocumab induced plaque regression in a greater percentage of patients than placebo (64.3% vs 47.3%; difference, 17.0% [95% CI, 10.4% to 23.6%]; $P < .001$ for PAV and 61.5% vs 48.9%; difference, 12.5% [95% CI, 5.9% to 19.2%]; $P < .001$ for TAV).

CONCLUSIONS AND RELEVANCE Among patients with angiographic coronary disease treated with statins, addition of evolocumab, compared with placebo, resulted in a greater decrease in PAV after 76 weeks of treatment. Further studies are needed to assess the effects of PCSK9 inhibition on clinical outcomes.

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Supplemental content

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Some Final Thoughts

LDL is now universally accepted as the major driver of atherosclerosis, however, the question of how far to reduce lipid levels has remained a moving target.

In medical school, we were taught that a “normal” total cholesterol was any value <300 mg/dL.

Over 4 decades, evidence has accumulated suggesting that optimal LDL-C levels for patients with coronary disease may be much lower than commonly achieved.

While we await large outcome trials for PCSK9 inhibitors, the GLAGOV Trial provides intriguing evidence that clinical benefits may extend to LDL-C levels as low as 20 mg/dL.