Results of the MILANO-PILOT Study

Effect of Infusion of ApoA-I_{Milano} HDL Mimetic on Coronary Atherosclerosis in Acute Coronary Syndrome Patients

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Disclosure

Consulting: AstraZeneca, Amgen, Anthera, Boehringer Ingelheim, CSL Behring, Eli Lilly, Esperion, Merck, Takeda, Roche, Kowa, LipoScience, Novartis, Sanofi-Regeneron.

Clinical Trials: Amgen, Anthera, AstraZeneca, Eli Lilly, Novartis, Cerenis, The Medicines Company, Resverlogix, InfraReDx, Roche, Sanofi-Regeneron, LipoScience.

The MILANO-PILOT study was sponsored by The Medicines Company.

Background

- Epidemiological studies suggest that high-density lipoproteins (HDL) protect against cardiovascular disease.
- However, HDL-cholesterol raising agents have not proven to reduce cardiovascular events in recent clinical trials.
- Infusing a HDL mimetic containing the naturally occurring variant ApoA-I_{Milano} (ETC-216) promoted plaque regression in a small intravascular ultrasound (IVUS) reported in 2003.
- Following refinements in the manufacturing process, the mimetic MDCO-216 was found to be well tolerated and produced expected increases in cholesterol efflux capacity.

Objective of Study

To perform a pilot proof of concept study to determine whether five infusions of a HDL mimetic containing ApoA-I_{Milano} (MDCO-216) at a dose of 20 mg/kg would provide a signal suggesting an impact on coronary atherosclerosis in patients with a recent acute coronary syndrome.

Trial Leadership

Steven E. Nissen MD
Study Co-Chair

Stephen J. Nicholls MBBS PhD
Study Co-Chair

Executive Committee

Christie Ballantyne MD (USA)

Wouter Jukema MD PhD (Netherlands)

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Wolfgang Koenig MD (Germany)

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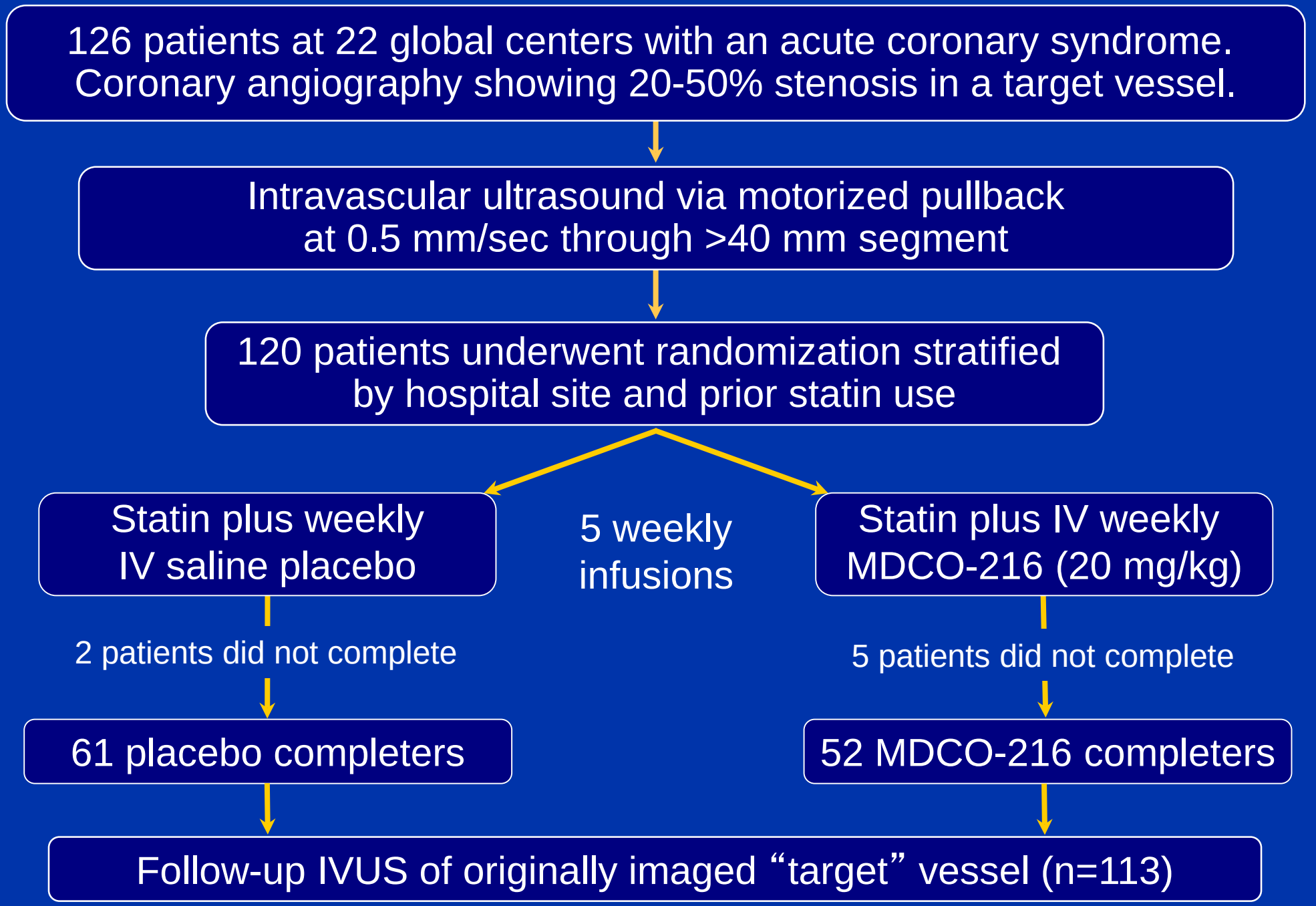

126 patients at 22 global centers with an acute coronary syndrome.
Coronary angiography showing 20-50% stenosis in a target vessel.
Intravascular ultrasound via motorized pullback
at 0.5 mm/sec through >40 mm segment
120 patients underwent randomization stratified
by hospital site and prior statin use
Statin plus weekly
IV saline placebo
5 weekly
infusions
Statin plus IV weekly
MDCO-216 (20 mg/kg)
2 patients did not complete
5 patients did not complete
61 placebo completers
52 MDCO-216 completers
Follow-up IVUS of originally imaged “target” vessel (n=113)

Baseline Demographics and Statin Usage

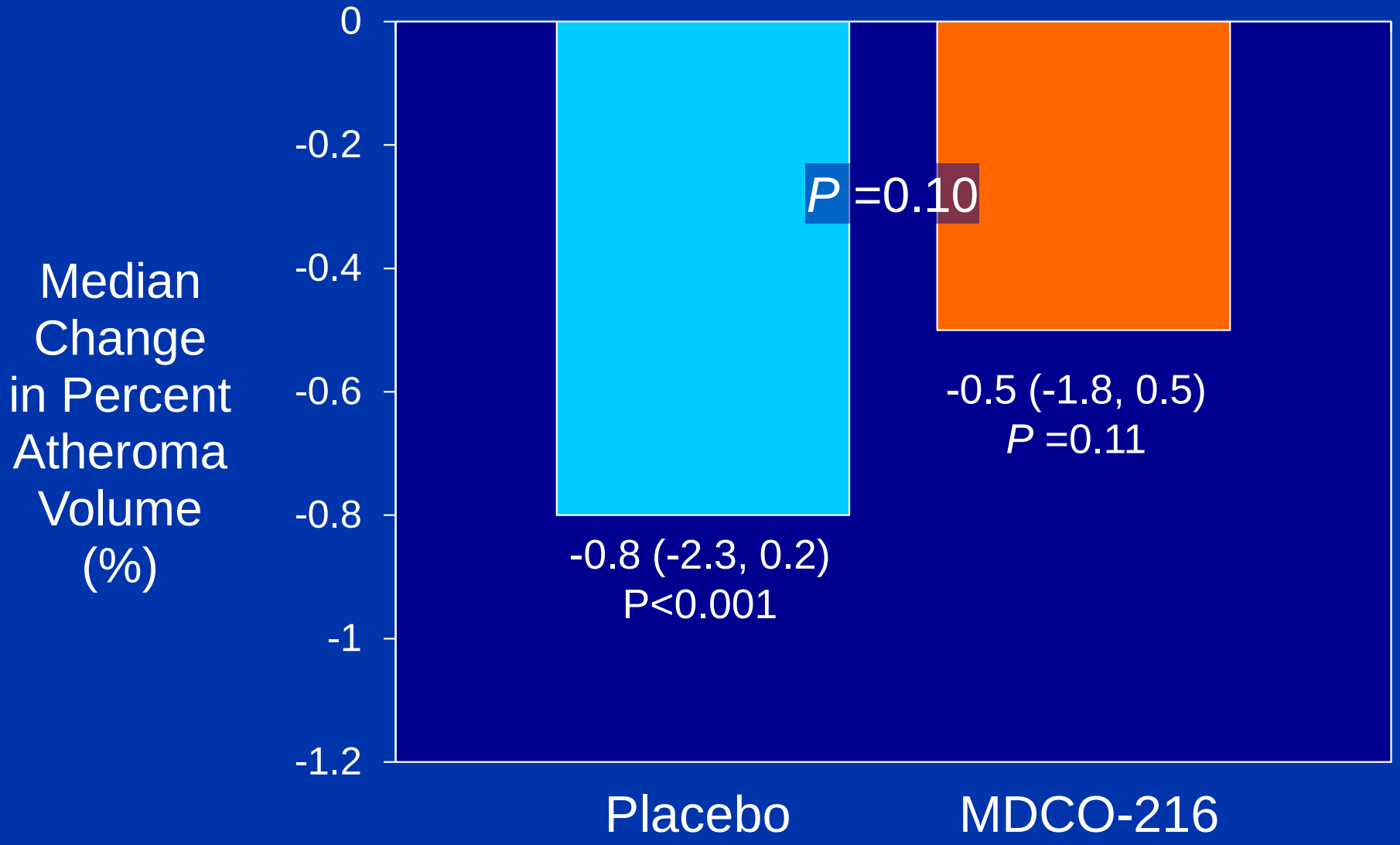
Characteristic	Placebo (N=61)	MDCO-216 (n=52)	P value
Age	61.4	62.2	0.68
Male Gender	73.8%	76.9%	0.70
BMI kg/m^2	28.1	29.4	0.50
Hypertension	56.7%	74.5%	0.05
Diabetes	20.0%	17.6%	0.75
Smoking	31.1%	38.5%	0.69
Baseline statin use	52.5%	48.1%	0.72
High intensity statins	44.3%	44.2%	0.99
Baseline LDL-C	76.0 mg/dL	87.0 mg/dL	0.15
Baseline HDL-C	41.0 mg/dL	44.0 mg/dL	0.62

Percent Change in Biochemical Parameters

Characteristic	Placebo	MDCO-216	P Value
LDL cholesterol	-19.0%	-21.2%	0.49
HDL cholesterol	+8.0%	-7.8%	<0.001
Free cholesterol	-8.7%	-14.8%	0.27
Triglycerides	-8.4%	-5.1%	0.81
Apolipoprotein B	-17.2%	-13.7%	0.87
Apolipoprotein A-I	+5.6%	-5.3%	<0.001
hsCRP	-62.1%	-53.9%	0.51

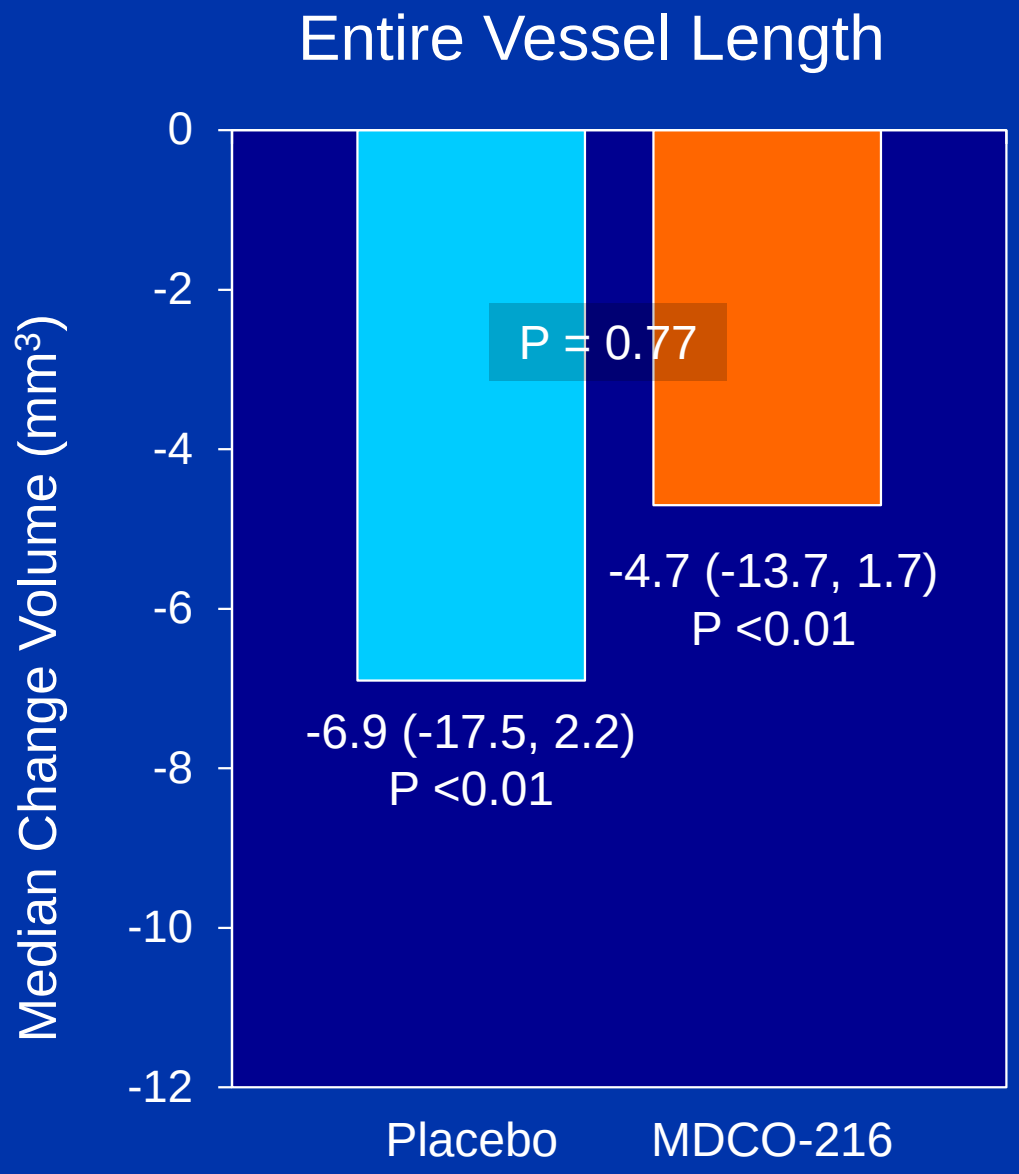
HDL: high-density lipoprotein; hsCRP: high-sensitivity C-reactive protein; LDL: low-density lipoprotein

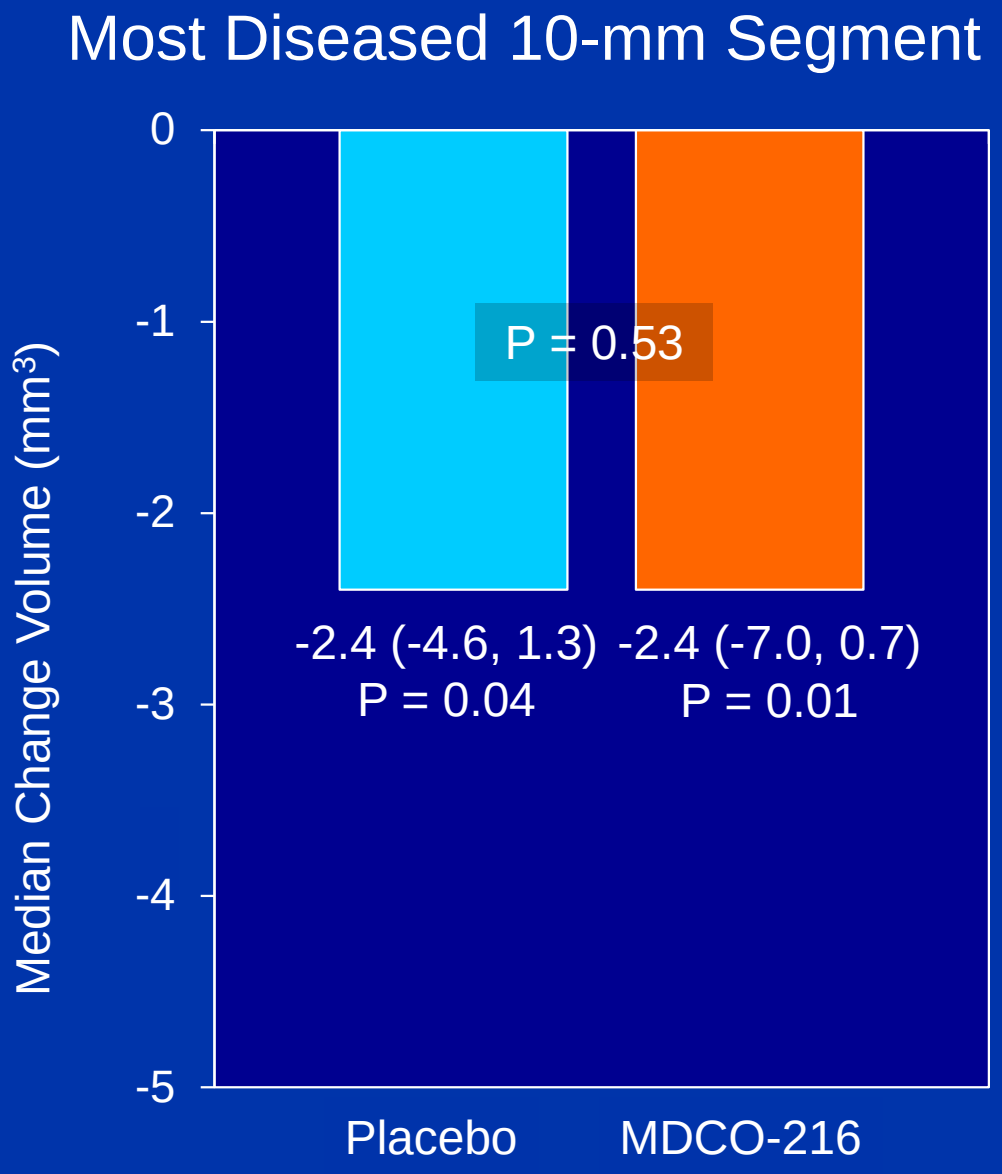
Primary Endpoint: Percent Atheroma Volume



Results expressed as median (interquartile range)

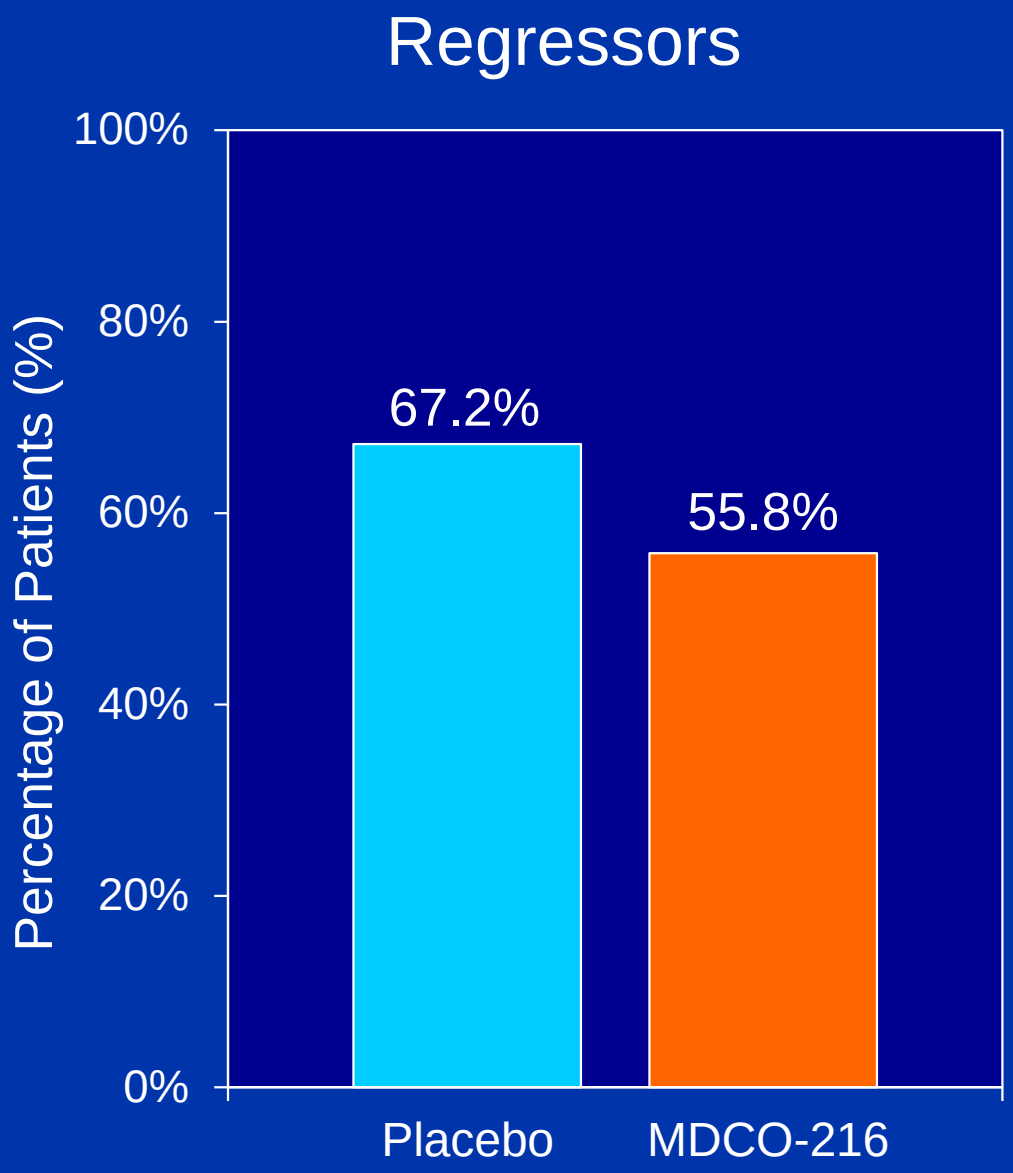
Secondary Endpoint: Total Atheroma Volume

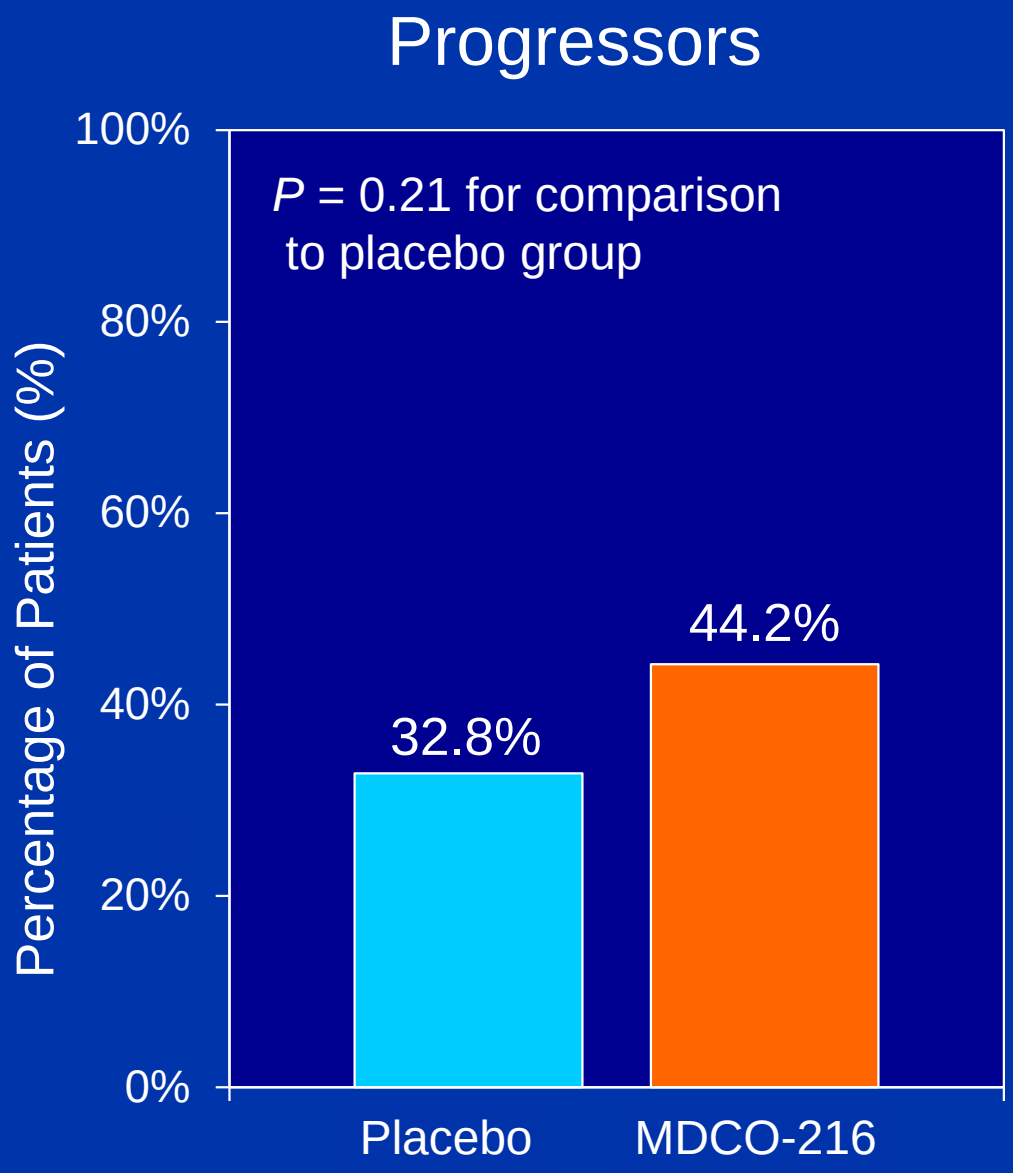




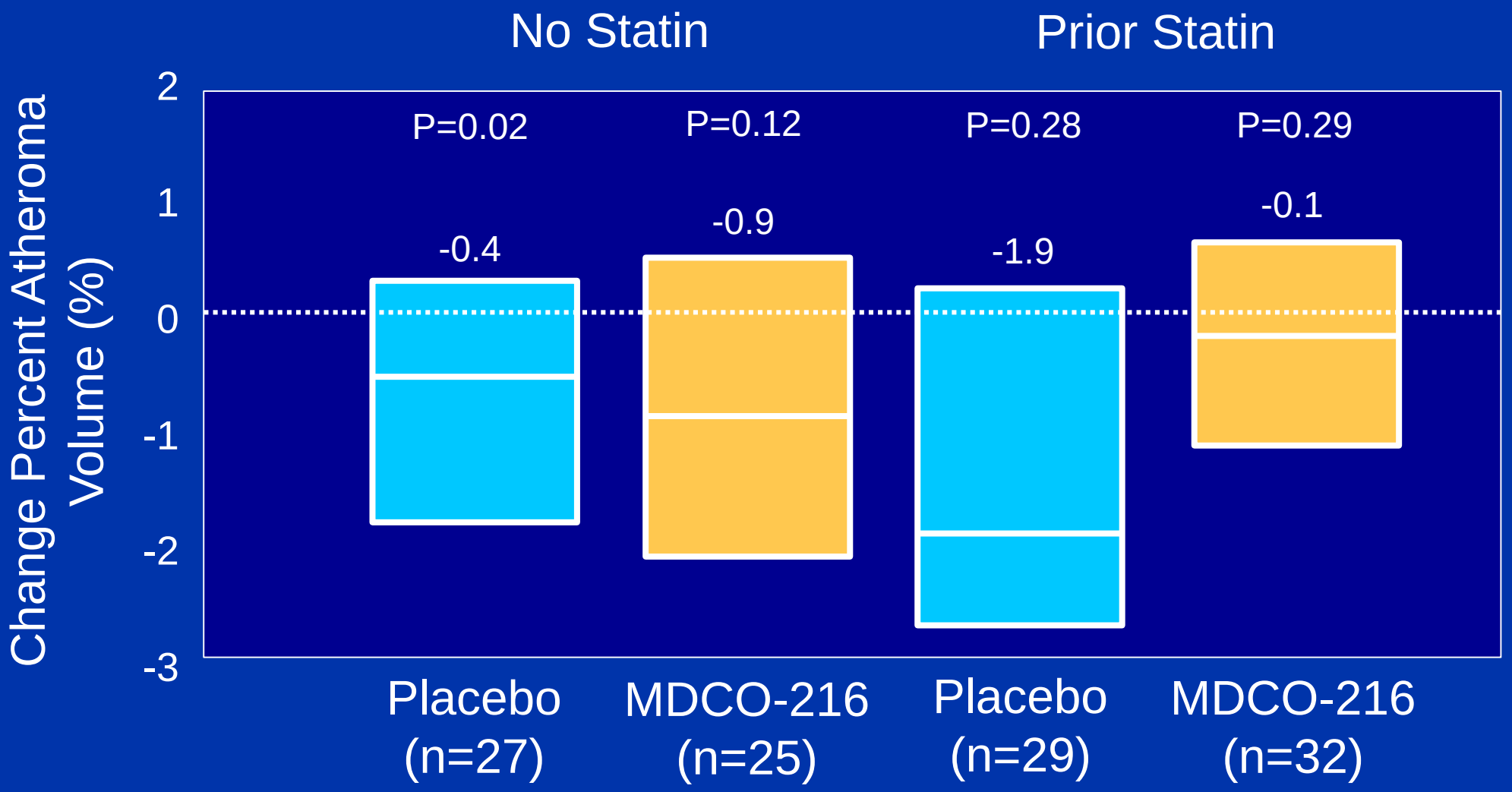
Results expressed as median (interquartile range)

Percent of Patients Showing Regression in PAV



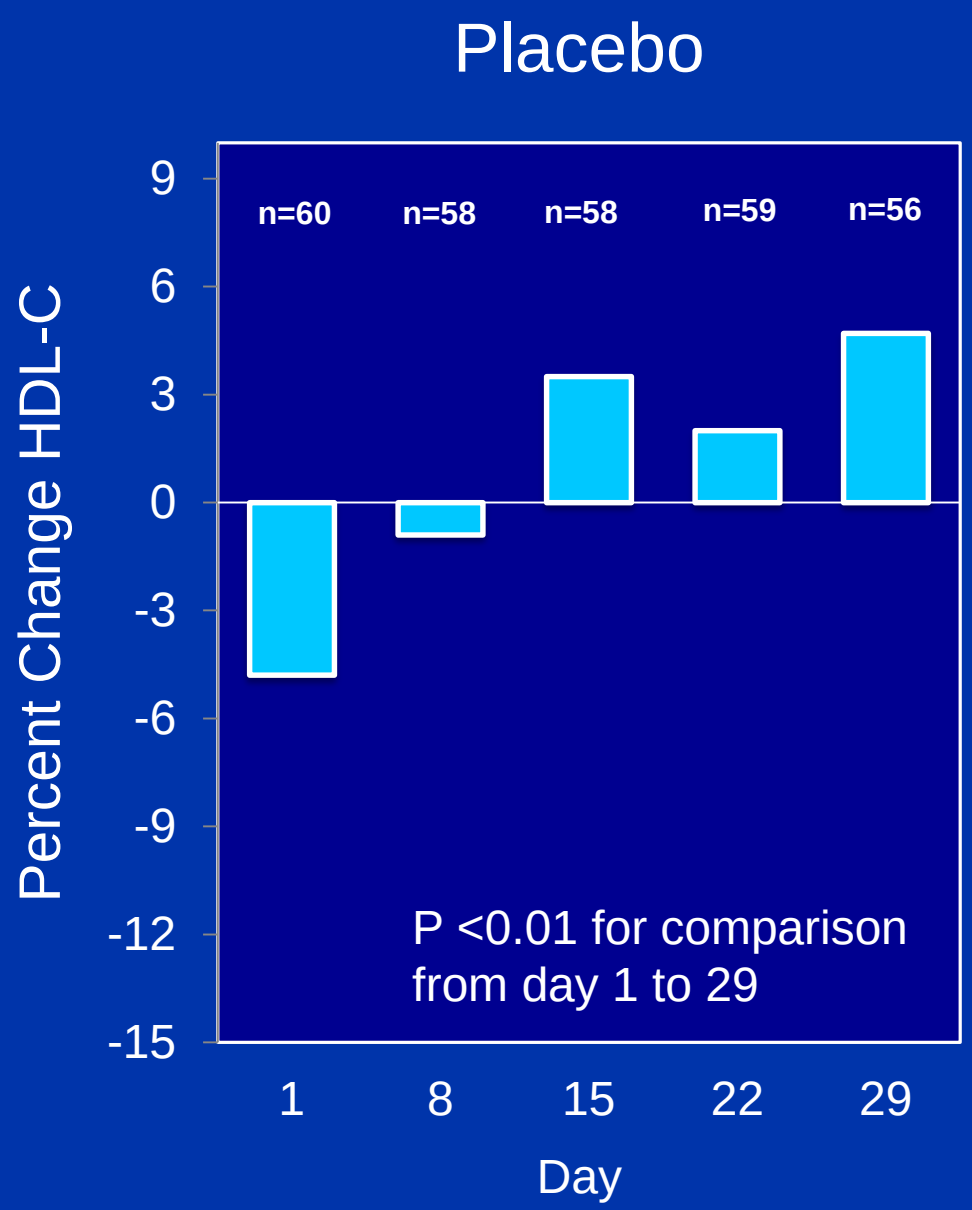


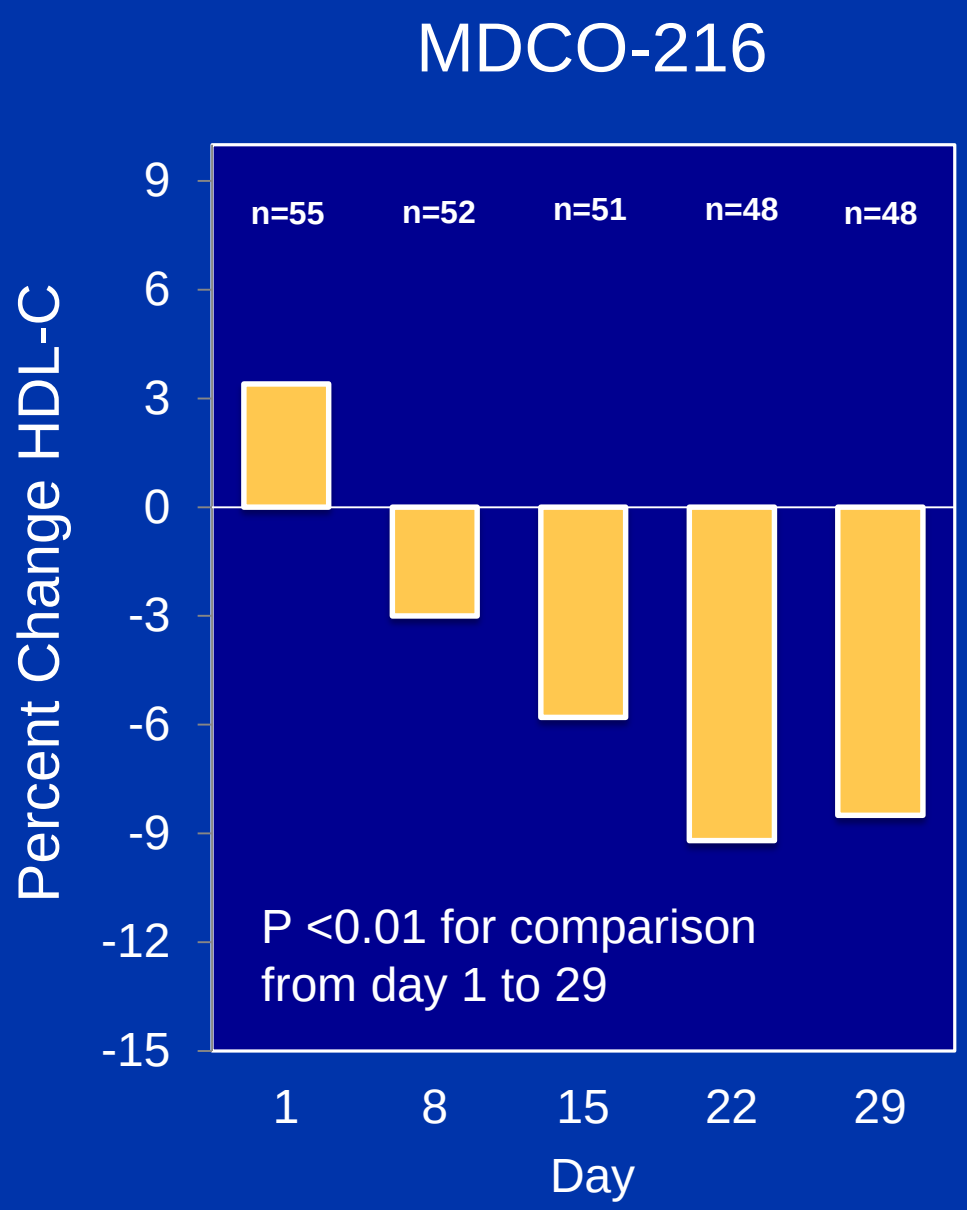
Exploratory Analysis: Effect of Prior Statin Use



Results expressed as median (interquartile range)

Percent Change in HDL-Cholesterol Post Infusion





Adverse Clinical Events and Safety Findings

Event	Placebo (N-64)	MDCO-216 (n=58)	P Value
ALT/AST >2x ULN	1.7%	1.7%	1.0
Total Bilirubin >2x ULN	0%	1.7%	0.49
CK >5x ULN	1.7%	0%	1.0
Change creatinine	+2.0%	-0.2%	0.23
Change glucose	+4.6%	+2.2%	0.84
Serious adverse events	10.9%	17.2%	0.32
Adverse events of special interest*	4.7%	15.5%	0.05
Infusion site reactions	3.1%	6.9%	0.34

ALT: alanine transaminase; AST: aspartate transaminase; CK: creatine kinase; ULN: upper limit of normal

*acute renal failure, infusion reaction, thromboembolic event, non-infectious hepattits, liver abnormalities requiring investigation

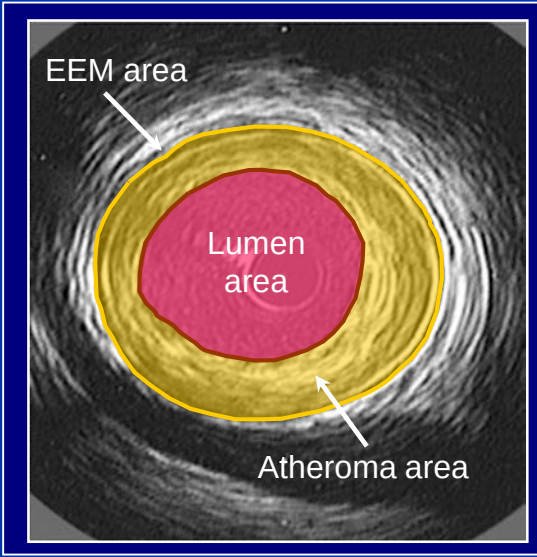
Conclusions

- Five infusions of MDCO-216 were well tolerated.
- HDL-C levels *increased* post-infusion in placebo patients and *decreased* with MDCO-216 as expected.
- However, MDCO-216 did not produce a significant effect on coronary disease progression measured by IVUS.
- These results occurred on a background of contemporary therapy in the post ACS setting.
- The findings from this pilot study do not provide the evidence required to proceed with further development.

Some Final Thoughts

- Favorable effects of HDL infusions in several prior imaging studies provided support for targeting HDL to favorably impact coronary atherosclerosis.
- However, the failure to demonstrate benefit with MDCO-216 in the setting of contemporary medical therapy will raise further skepticism that targeting HDL will prove protective.
- HDL mimetics differing in composition from MDCO-216 and a CETP inhibitor continue to undergo clinical evaluation.
- Unless one of these new agents demonstrates clinical benefits, the HDL modulation story may soon end.

Intravascular Ultrasound Efficacy Parameters



$$\text{Change in Percent Atheroma Volume} = \frac{\sum_n \text{Atheroma}_{CSA}}{\sum_n \text{EEM}_{CSA}}\ (\text{Month 24}) - \frac{\sum_n \text{Atheroma}_{CSA}}{\sum_n \text{EEM}_{CSA}}\ (\text{baseline})$$

$$\text{Normalized Atheroma Volume} = \frac{\sum_n \text{Atheroma}_{CSA} - \sum_n \text{Lumen}_{CSA}}{\text{Number of slices in patient's pullback}} \times \text{Median number of slices in all pullbacks}$$

$$\text{Change in Atheroma Volume} = \text{Atheroma Volume}\ (\text{Month 24}) - \text{Atheroma Volume}\ (\text{baseline})$$

Ultrasound Determination of Atheroma Area

Precise Planimetry of EEM and Lumen Borders