Effects of Alirocumab on Coronary Atherosclerosis in Patients with Acute Myocardial Infarction:

The PACMAN-AMI Randomized Clinical Trial

Lorenz Räber, MD PhD, on behalf of the PACMAN AMI investigators

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Background

- Coronary plaques responsible for acute myocardial infarction (AMI) frequently feature large plaque burden and lipid rich pool covered by a thin fibrous cap. Intracoronary imaging enables visualization of high-risk plaque characteristics.

- Alirocumab is a PCSK9i that lowers LDL-C and has shown to reduce major cardiovascular events in stabilized ACS patients. These patients remain at increased risk of recurrent atherothrombotic events due to high-risk plaque characteristics, particularly in non-infarct related vessels.

- The effect of alirocumab on high-risk plaque characteristics administered early after ACS remains largely unknown.

Aim

To determine the effect of early administration of the PCSK9i alirocumab on top of high-intensity statin therapy on coronary plaque characteristics, assessed by 2-vessel serial multi-modality intracoronary imaging (IVUS, NIRS, and OCT) in patients with AMI throughout 52 weeks.

IVUS, intravascular ultrasound; NIRS, near infrared spectroscopy; OCT, optical coherence tomography

Patients with AMI (N-STEMI/STEMI) undergoing coronary angiography & successful PCI of the infarct vessel & 2 non-infarct related arteries with angiographic evidence of atherosclerosis (20-50% DS)

Alirocumab PACMAN AMI

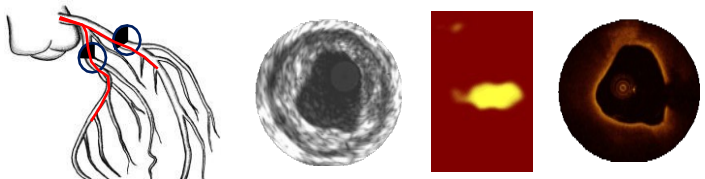
POC

No statin, LDL >125 mg/dL (>3.2 mmol/L)

On Statin, LDL >70 mg/dL (>1.8 mmol/L)

Enrollment of 300 Patients

Baseline



IVUS, NIRS, OCT

Baseline blood sampling

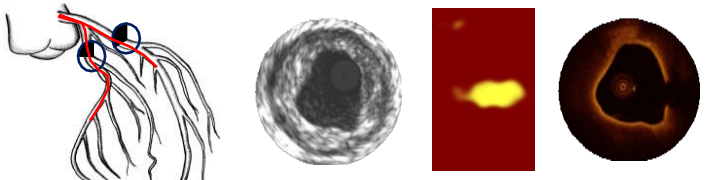
Alirocumab s.c. 150 mg / 2 weeks + Rosuvastatin 20 mg

R 1:1

Placebo s.c. / 2 weeks + Rosuvastatin 20 mg

Initiated <24 hrs after PCI

52 weeks

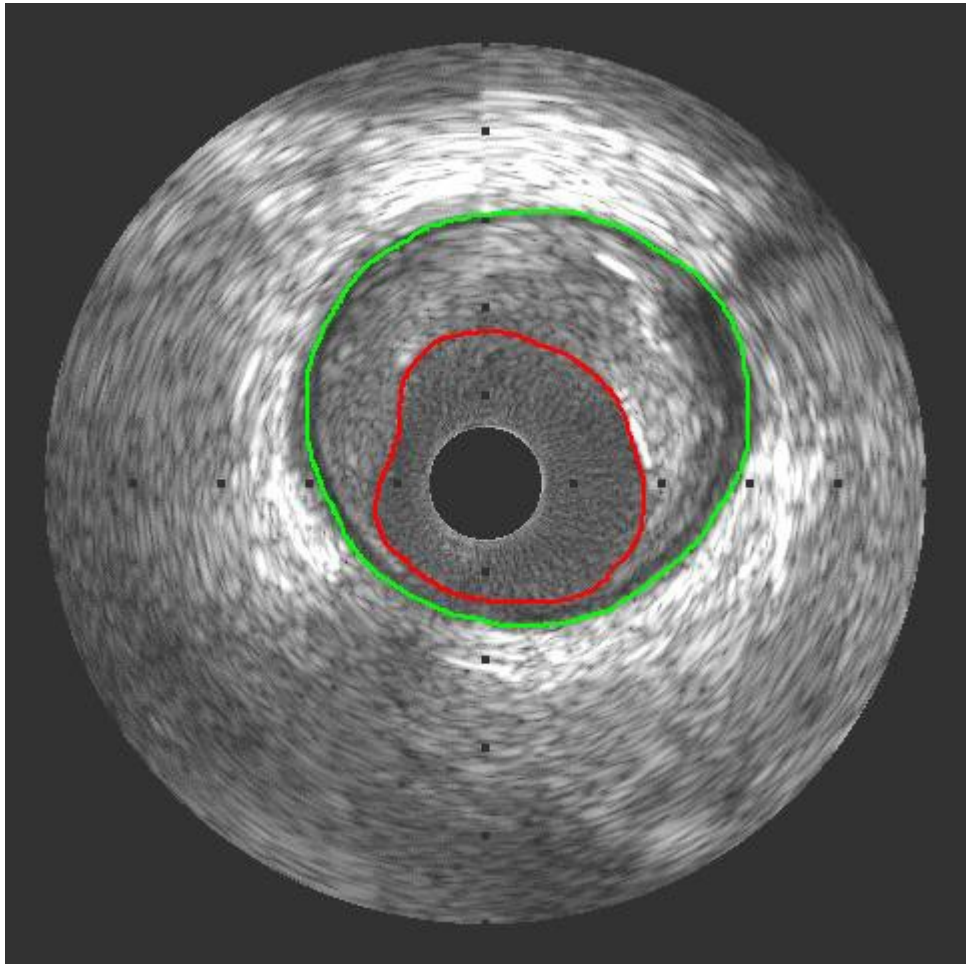


IVUS, NIRS, OCT

Blood sampling 4 weeks
3 visits, 4 phone calls
Blood sampling 52 weeks

Am Heart J 2021;238:33-44.

Primary Endpoint

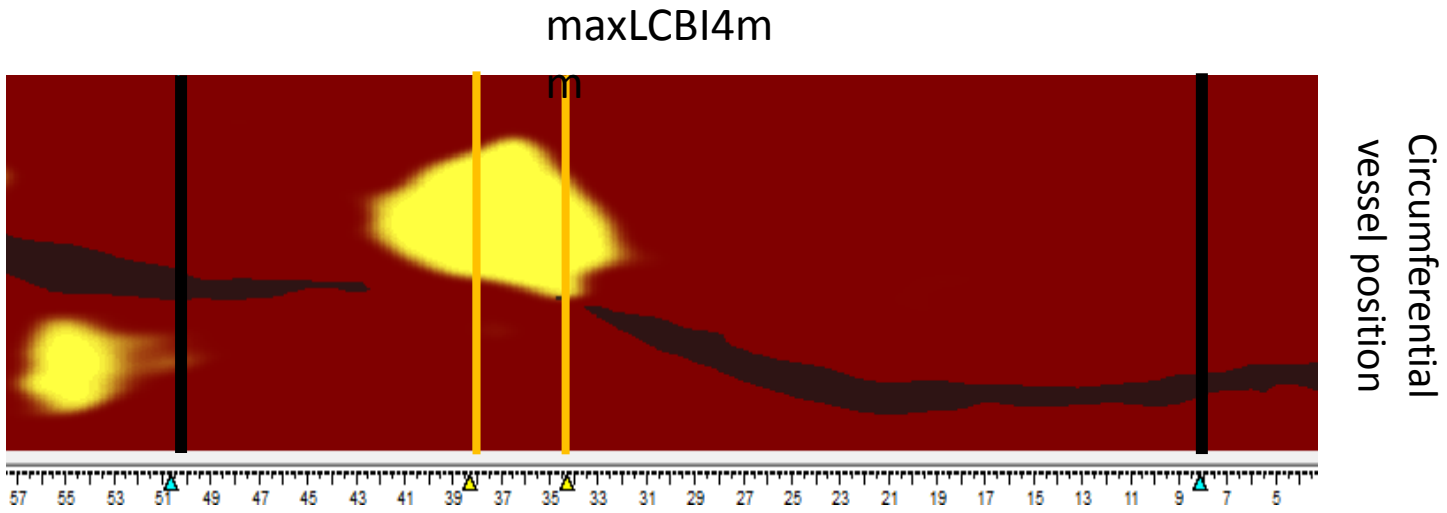


Analysis interval: 1 mm
Obtained by NIRS-IVUS catheter

$$PAV = \frac{\Sigma(EEMCSA - LumenCSA)}{\Sigma EEMCSA} \times 100$$

Change in **percent atheroma volume** (PAV) by **greyscale IVUS**

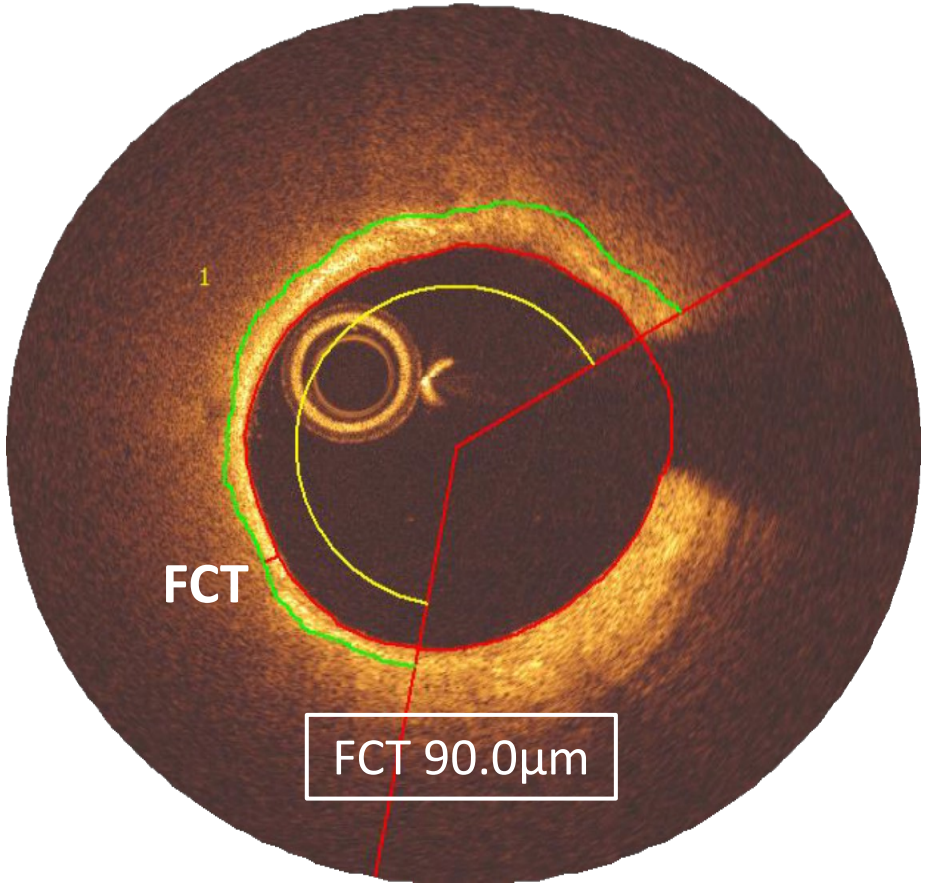
Powered Secondary Endpoint



maxLCBI4mm=
a measure of lipid probability at the 4 mm with maximal lipid load of a vessel imaged by NIRS

Change in **maximal lipid-core burden index** (maxLCBI4mm) by **NIRS**

Powered Secondary Endpoint

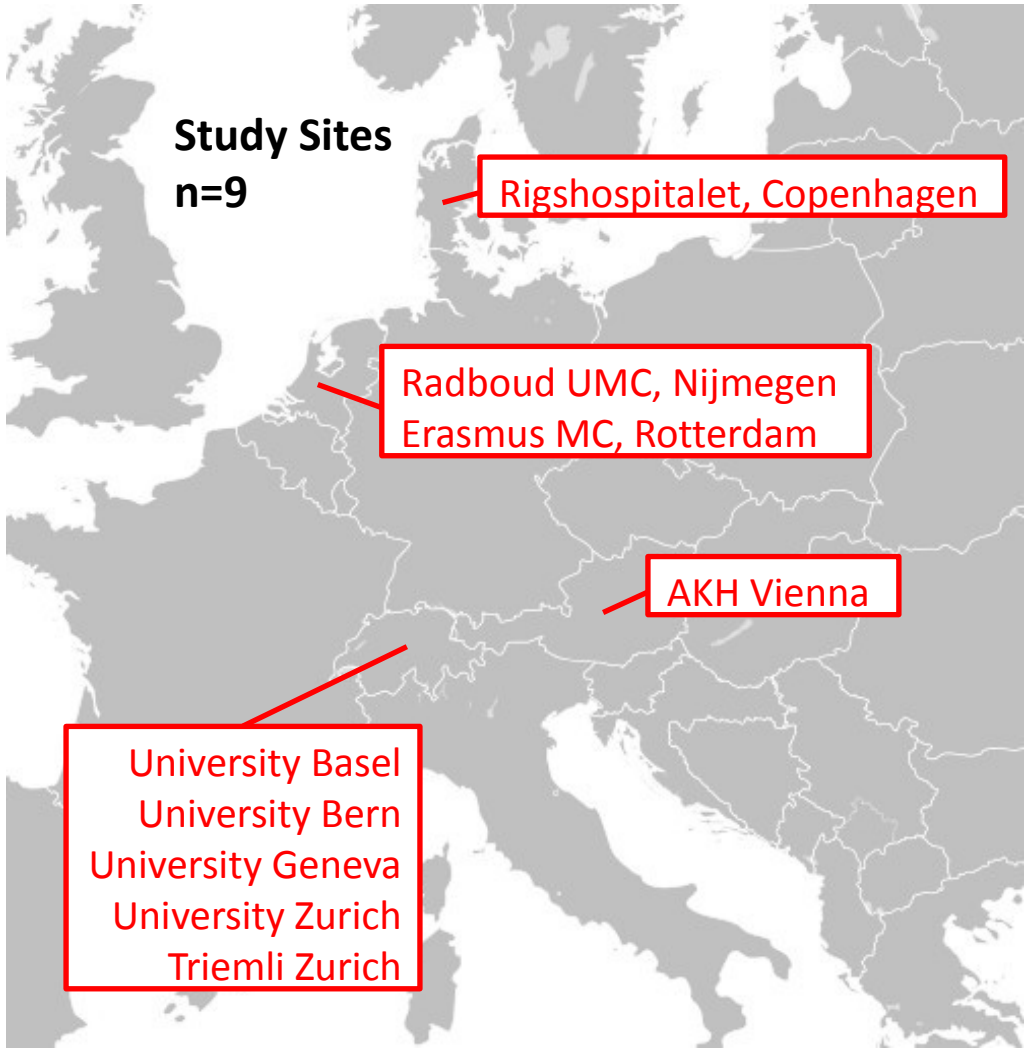


Analysis interval: 0.4 mm
Method: semiquantitative software assisted FCT tracing

FCTmin = minimal fibrous cap thickness anywhere in lipid rich plaques imaged by OCT

Change in **minimal fibrous cap thickness** (FCTmin) by **OCT**

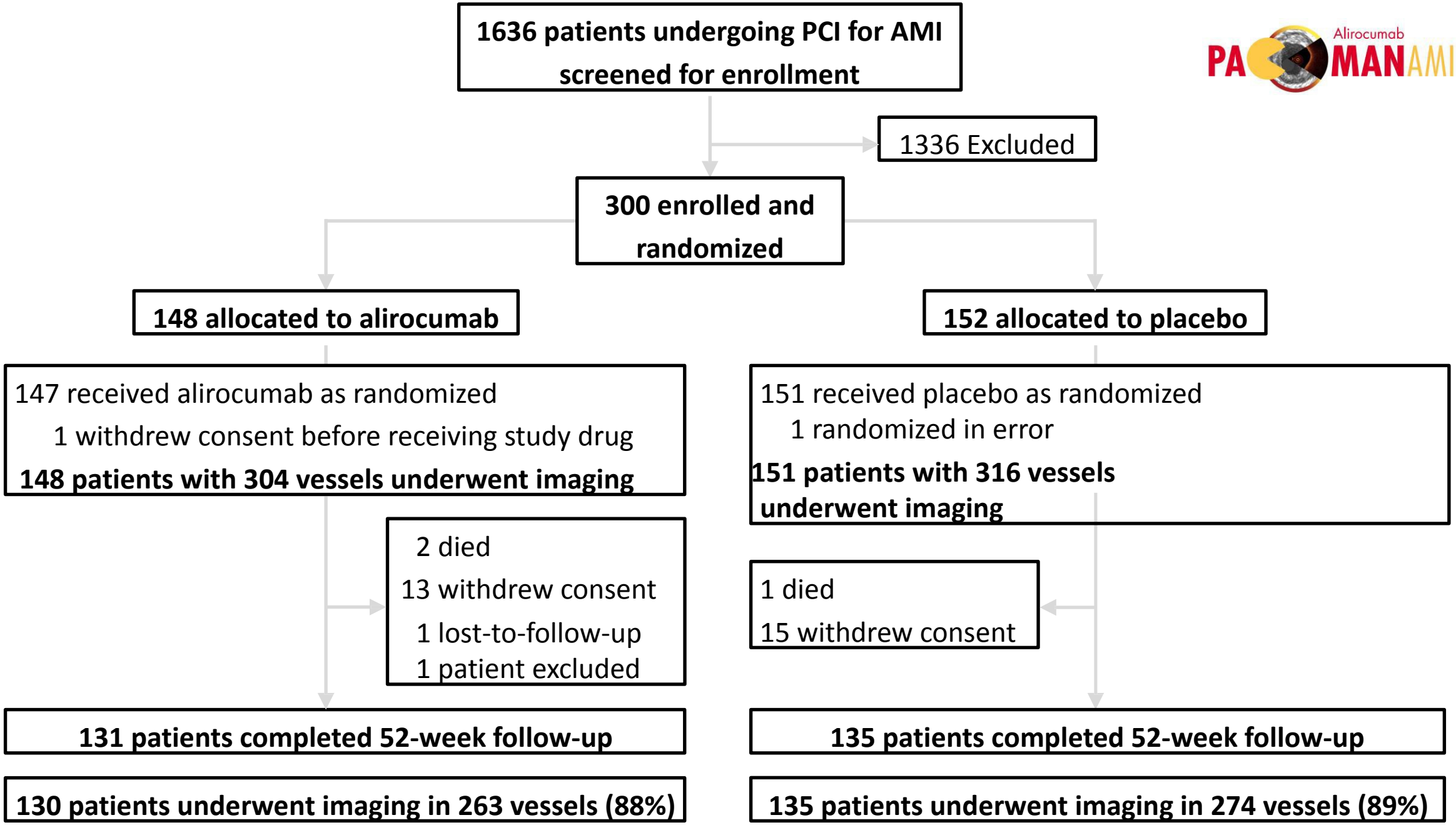
Study Organization



Study chair **Principal investigator Steering committee**	Lorenz Räber, MD PhD Konstantinos C. Koskinas, MD MSc Francois Mach, MD
Corelab IVUS, NIRS	Cardialysis, Rotterdam, NL
Corelab OCT	Bern University Hospital, CH
Statistical analysis	Sylvain Losdat, MSc Dik Heg, MSc CTU Bern, CH
Drug labelling	Hospital Pharmacy, Bern University Hospital
DSMB	Christian Müller, MD, Basel (Chair) Kurt Huber, MD, Vienna David Conen, MD MPH, Hamilton,
CA	Patrick Badertscher, MD, Basel
CEC	Niklas Millauer, MD, Bern, CH Roberto Galea, MD, Bern, CH

Power Calculation

Primary EP	PAV difference 1.0%, SD 3.4% Intra-class correlation coefficient 0.435 Two vessels per patient, attrition rate 10% 294 patients provide 80% power with two-sided α of 0.05
Secondary EP	95% power for LCBImax4mm and 85% power for FCTmin
Analysis	For 1° & 2nd EP, gatekeeping procedure was applied, the 1°EP was first tested at an alpha level of 0.05. If the P value was <0.05, the significance level was equally split between the two powered 2nd EPs using Bonferroni correction (significance level set to 0.025).


1636 patients undergoing PCI for AMI screened for enrollment
1336 Excluded
300 enrolled and randomized
148 allocated to alirocumab
152 allocated to placebo
147 received alirocumab as randomized
1 withdrew consent before receiving study drug
148 patients with 304 vessels underwent imaging
2 died
13 withdrew consent
1 lost-to-follow-up
1 patient excluded
151 received placebo as randomized
1 randomized in error
151 patients with 316 vessels underwent imaging
1 died
15 withdrew consent
131 patients completed 52-week follow-up
135 patients completed 52-week follow-up
130 patients underwent imaging in 263 vessels (88%)
135 patients underwent imaging in 274 vessels (89%)

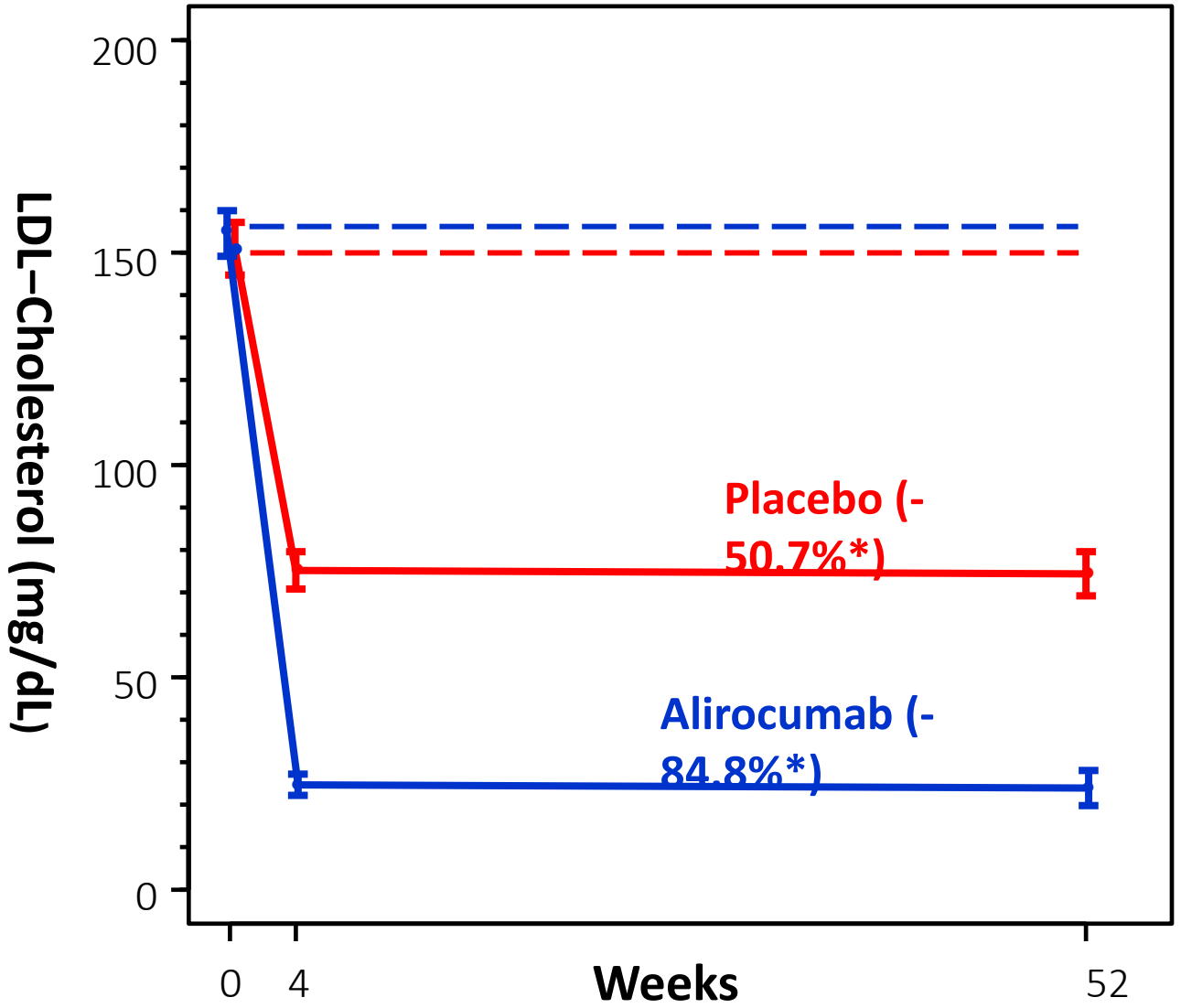
Baseline Characteristics

	Alirocumab (n=148)	Placebo (n=152)
Age (y)	58.4 (10.0)	58.6 (9.4)
Women	24 (16.2%)	32 (21.1%)
Body mass index	27.3 (4.1)	28.2 (4.5)
Current smoking	77 (52.0%)	65 (42.8%)
Arterial hypertension	60 (40.5%)	70 (46.1%)
Diabetes mellitus	12 (8.1%)	19 (12.5%)
Statin	17 (11.5%)	20 (13.2%)
High-intensity statin	11 (7.4%)	9 (5.9%)
Type of AMI		
N-STEMI	70 (47.3%)	72 (47.4%)
STEMI	78 (52.7%)	80 (52.6%)

Change in LDL-C, mean (SD)

154.8 (31) mg/dL
4.00 (0.8) mmol/L

150.9 (36) mg/dL
3.9 (0.9) mmol/L

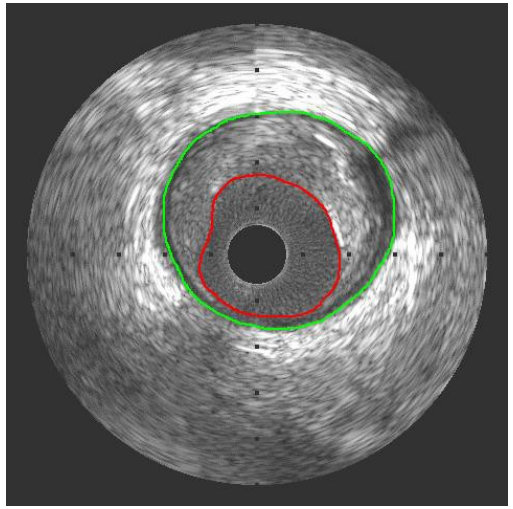


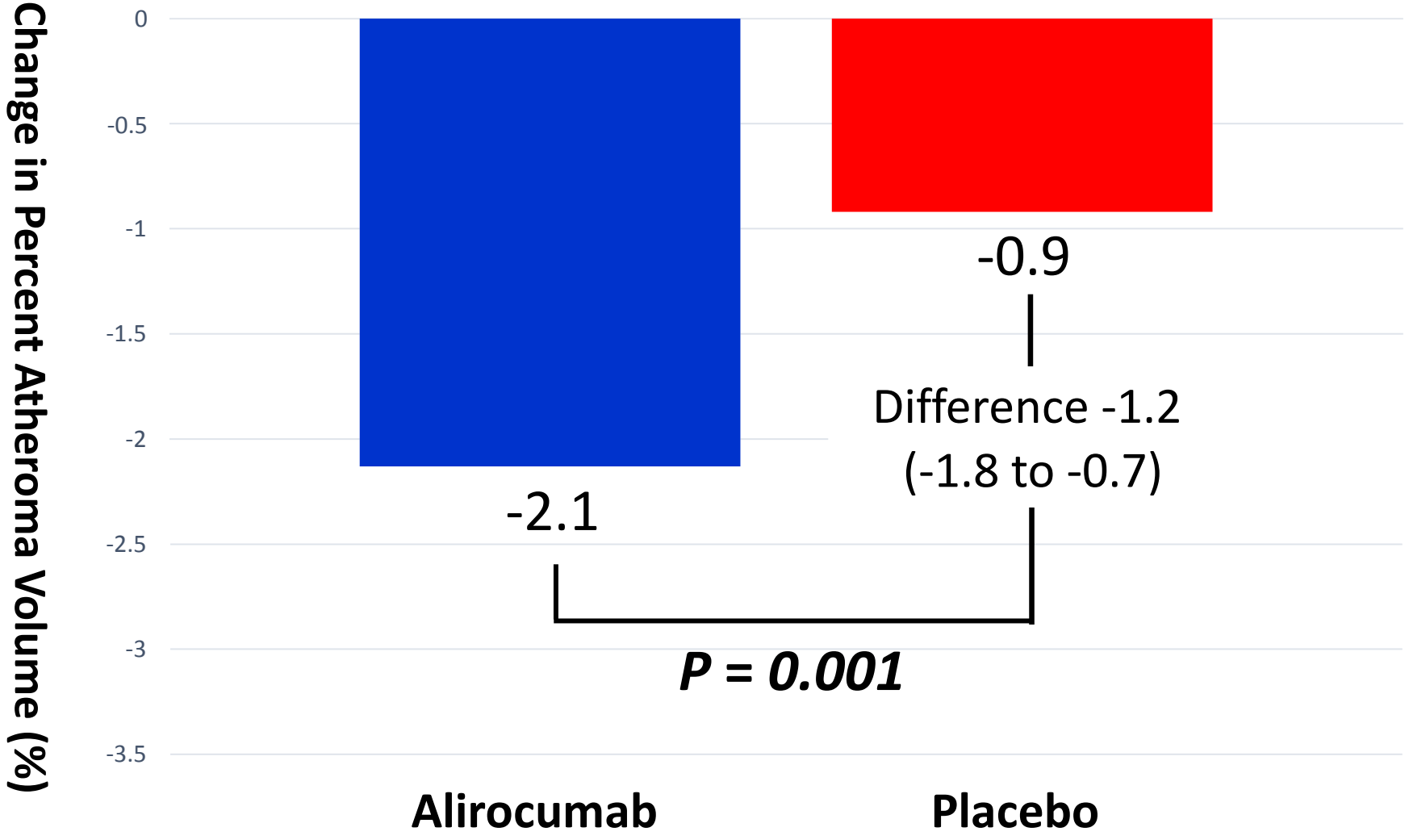
74.4 (31) mg/dL
1.9 (0.8) mmol/L

23.6 (24) mg/dL
0.6 (0.6) mmol/L

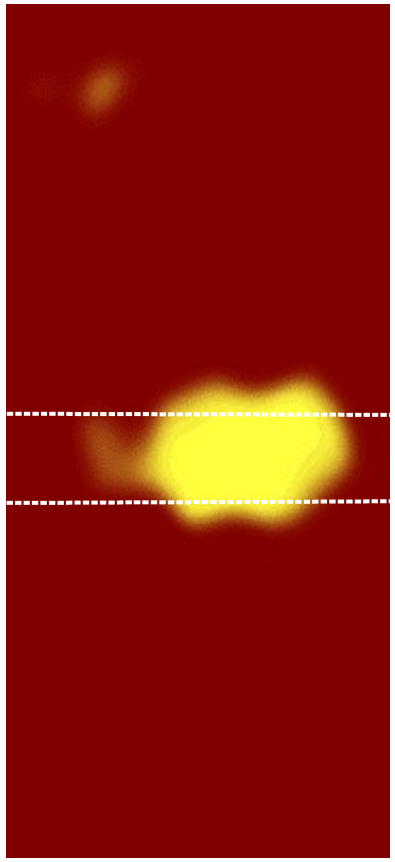
* Week 52 vs. Baseline

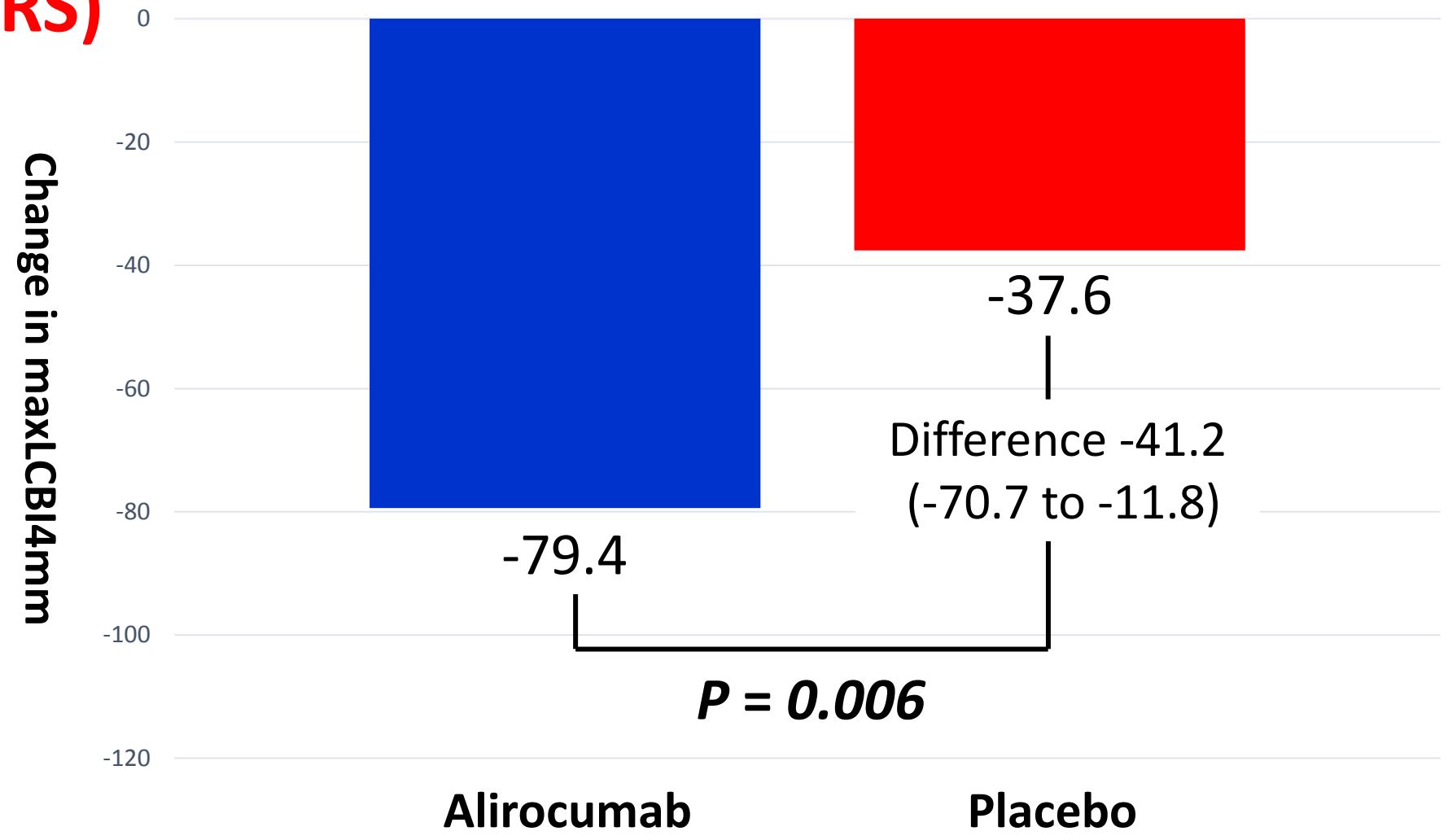
Primary EP:
Change in Percent Atheroma Volume (IVUS)



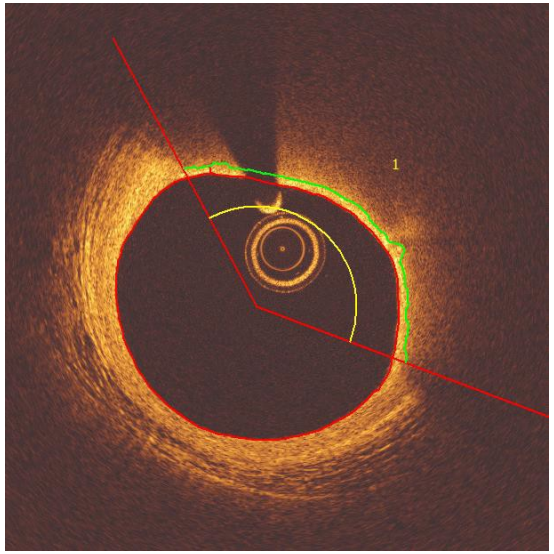


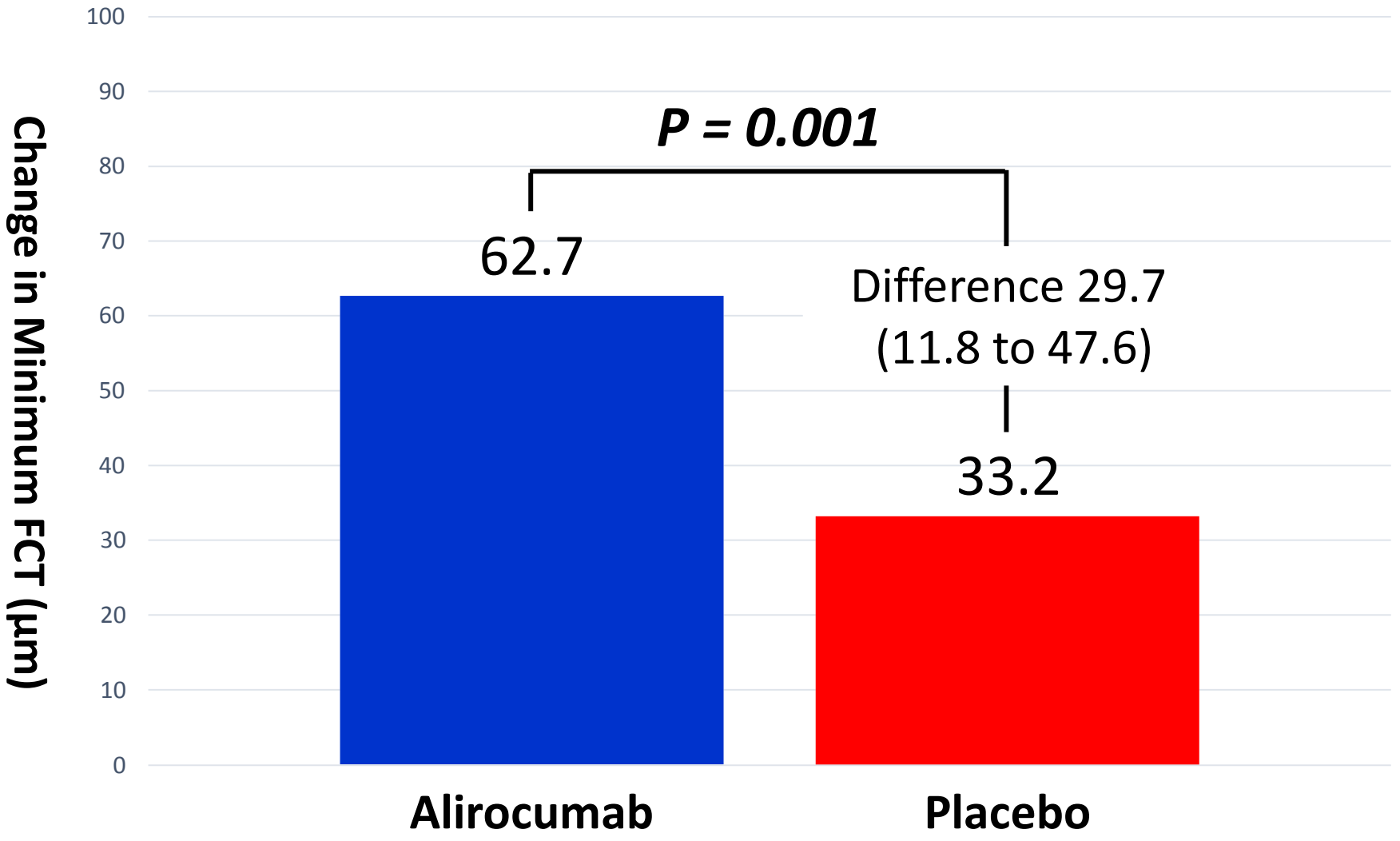
Powered Secondary EP: Change in maxLCBI4mm (NIRS)



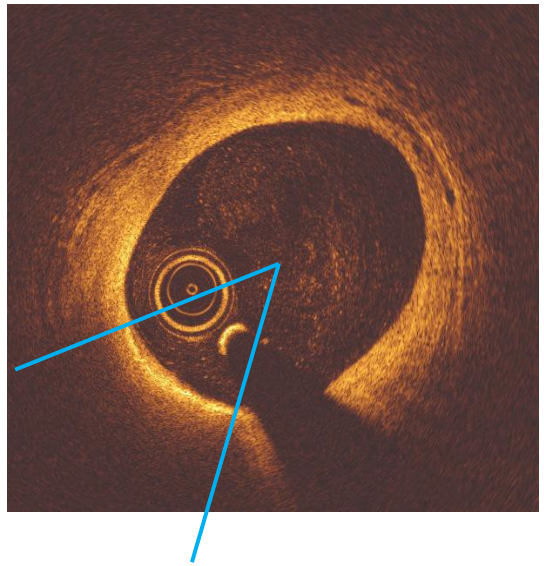


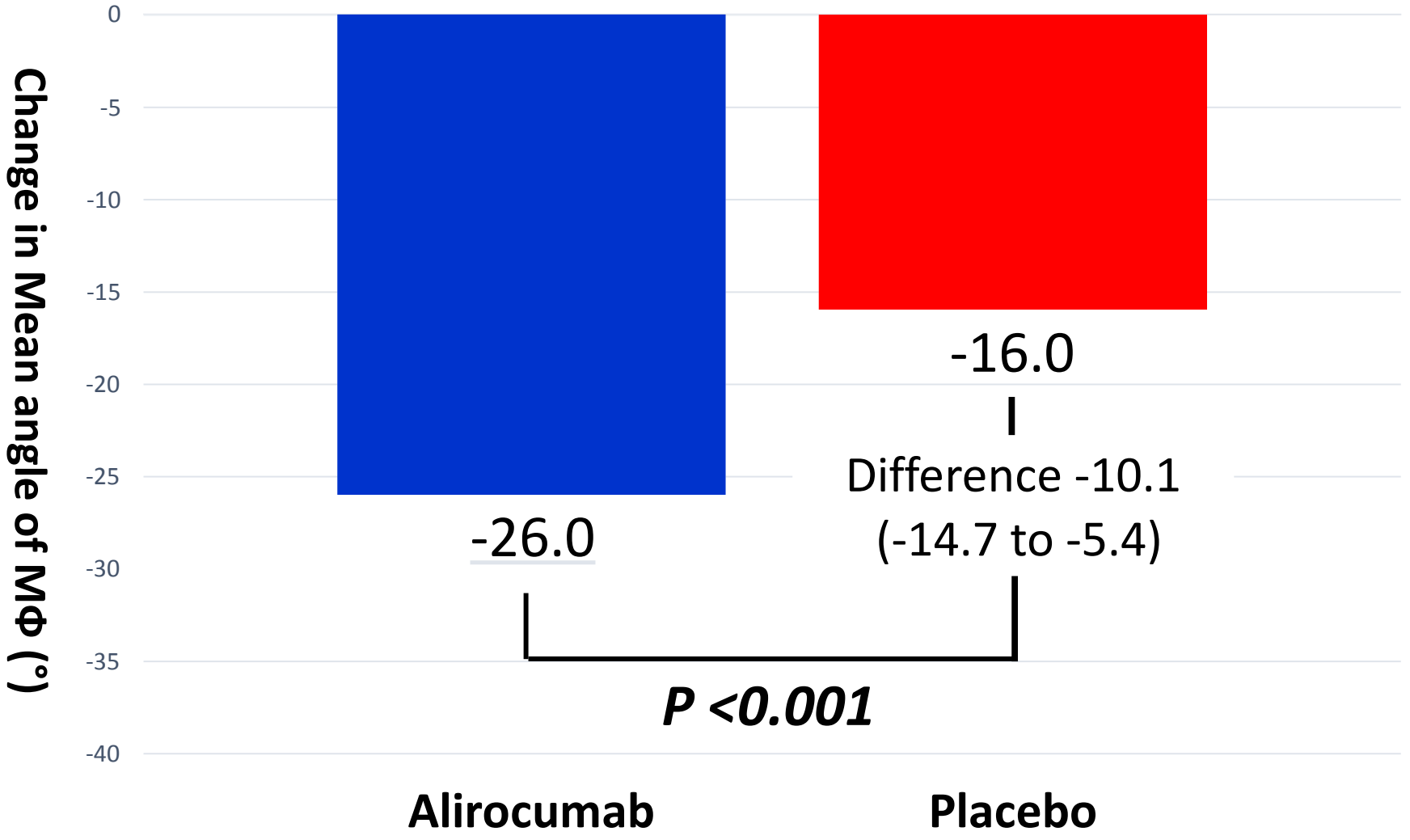
Powered Secondary EP: Change in Minimum FCT (OCT)





Prespecified Secondary EP: Change in Macrophage Angle (OCT)

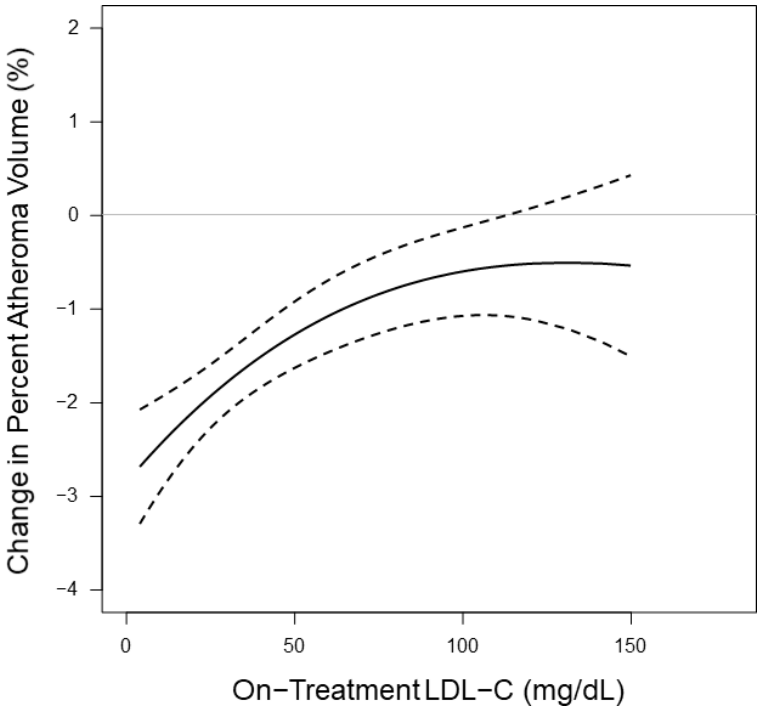




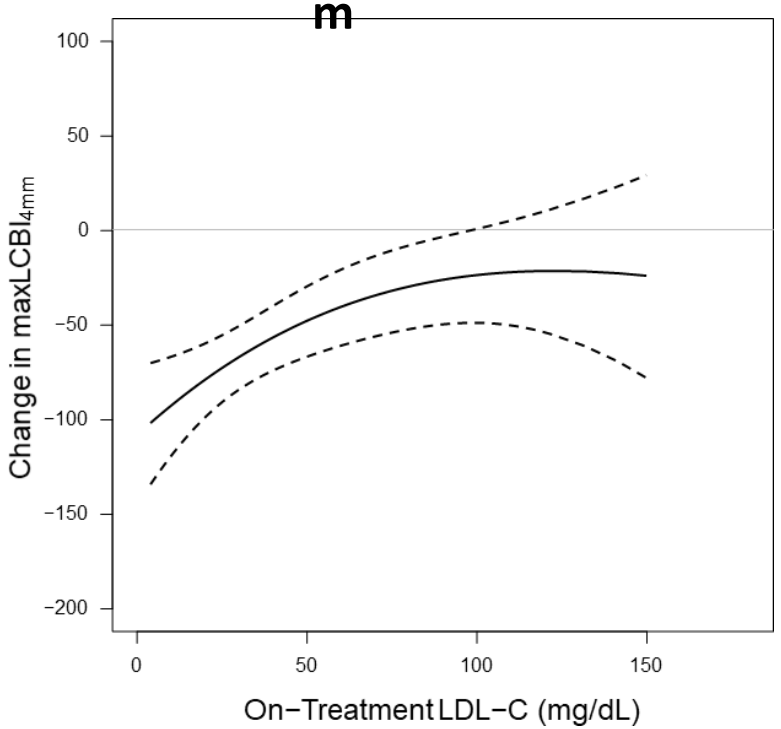
Relationship Between LDL-C and Endpoints*

Alirocumab PACMANAMI

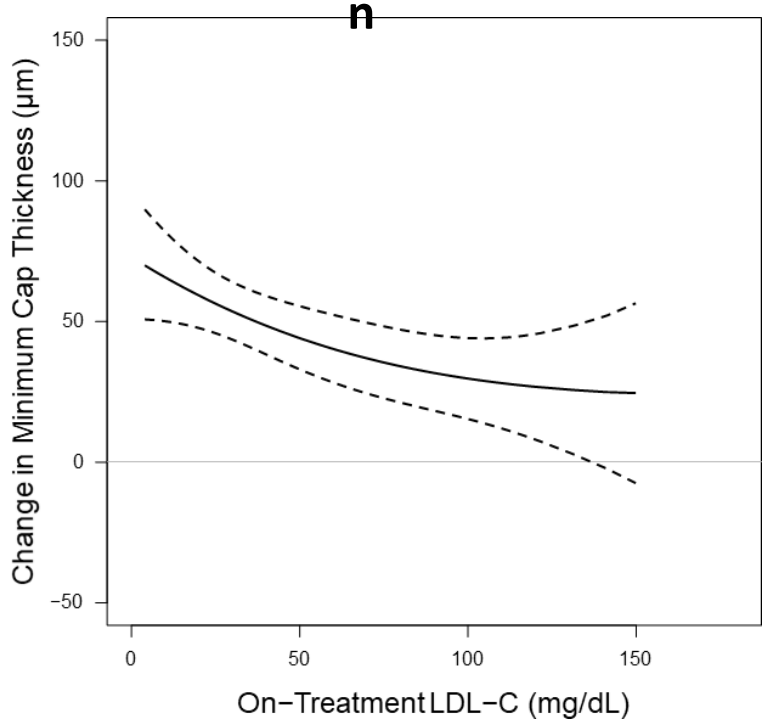
PAV



maxLCBI4mm

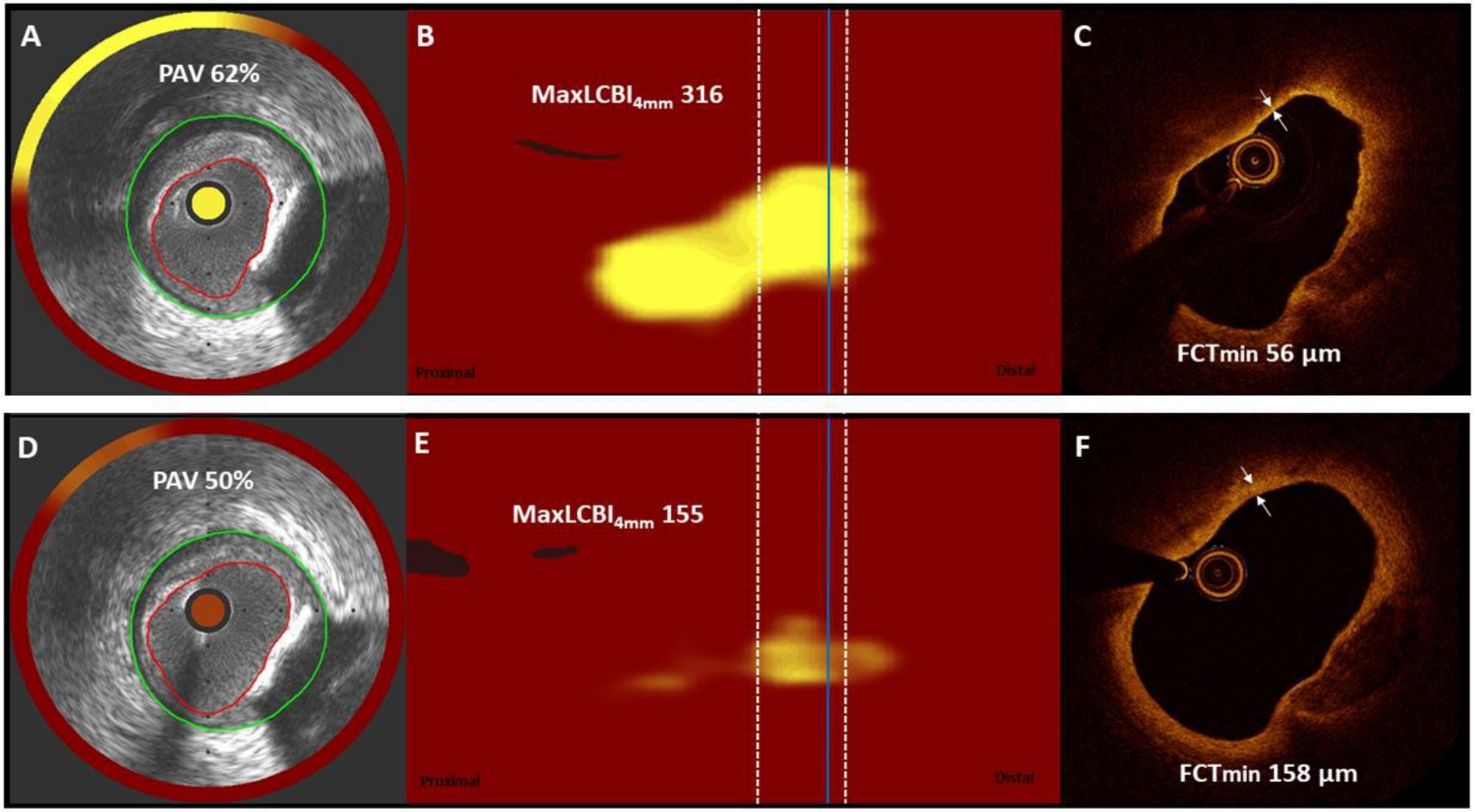


FCTmin



* Non-prespecified analysis

Case Example Alirocumab & Statin Group



Prespecified Adverse Events and Safety Findings

	Alirocumab (n=147*)	Placebo (n=151*)
Any adverse event	104 (71%)	110 (73%)
Serious adverse event	47 (32%)	50 (33%)
Adverse events resulting in study drug discontinuation	2 (1.4%)	0 (0.0%)
Adverse events of special interest		
Local injection site reaction	9 (6.1%)	5 (3.3%)
General allergic reaction	5 (3.4%)	0 (0.0%)
Neurocognitive event	3 (2.0%)	0 (0.0%)
ALT increase > 3x ULN	1 (0.7%)	0 (0.0%)

* Includes patients who received at least one dose of the study drug

Conclusions

Compared with placebo, alirocumab initiated in the setting of acute AMI on top of high-intensity statin therapy resulted in greater decrease in PAV, larger reduction in lipid burden and higher increase in minimal fibrous cap thickness after

52 weeks of treatment.

These findings indicate incremental coronary plaque regression, lipid core reduction and plaque stabilization and provide a mechanistic rationale in favor of early initiation of very intensive LDL-C lowering in the setting of acute MI.