# *Aterosclerosi e placca: Alirocumab quali evidenze?*

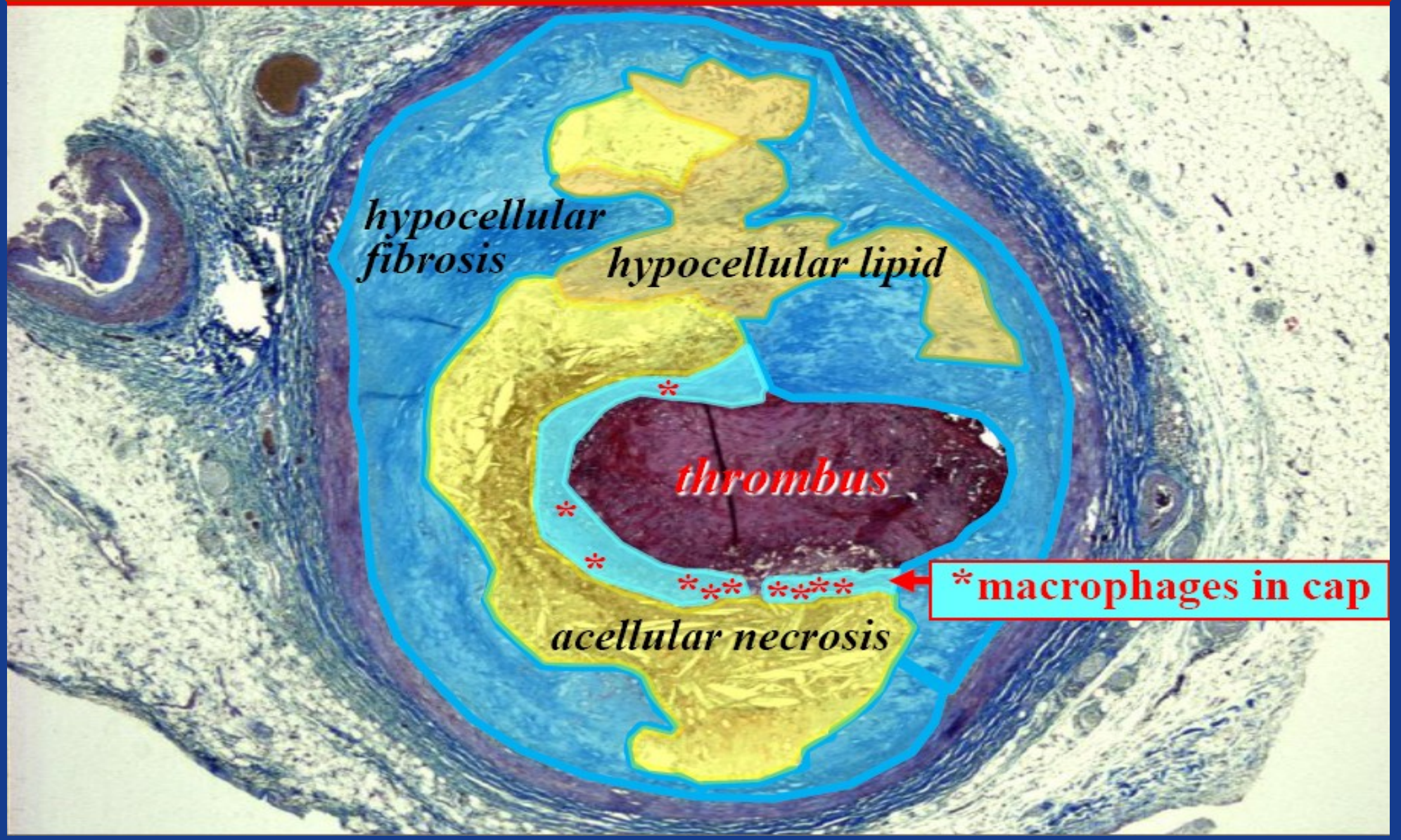
## *Hot Topics in Cardiologia*
## *Napoli, 13-14 Nov 2023*

**F Prati**

**San Giovanni Hospital, Rome**

**and CLI Foundation**

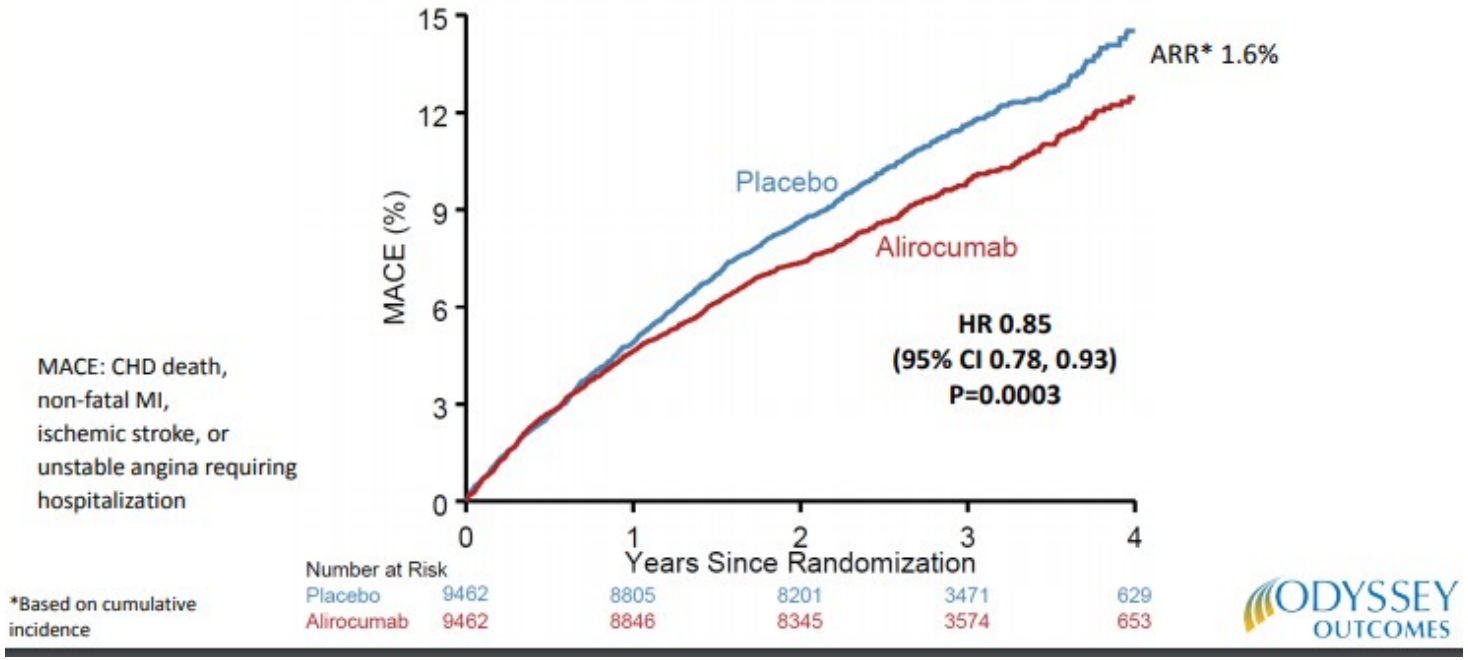
# Identify and measure: Lipid pool, FC thickness, local inflammation



# *Infarto e stroke : ogni mg di Colesterolo LDL conta*

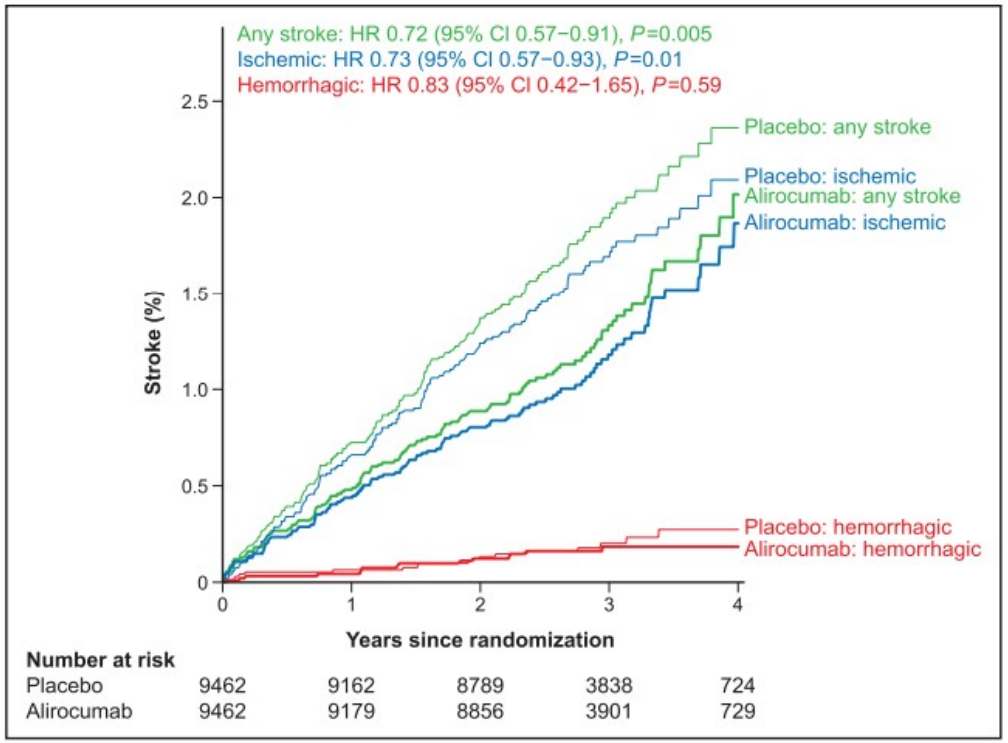
ACC.

## Primary Efficacy Endpoint: MACE




New Engl 2018

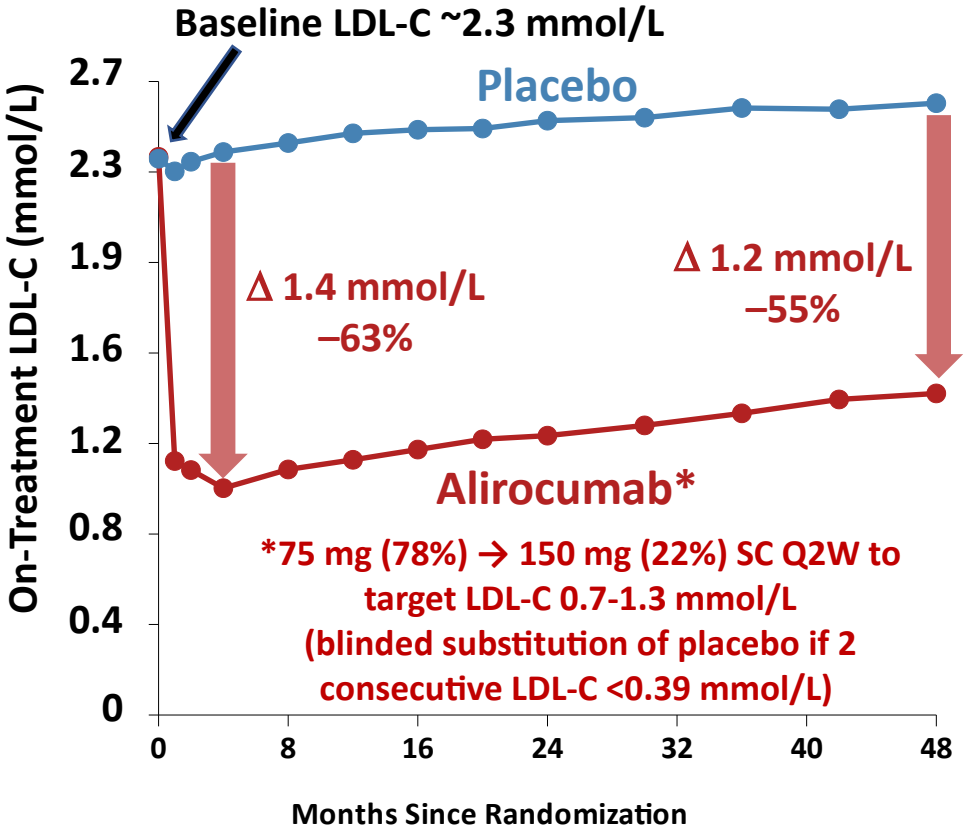
## Stroke



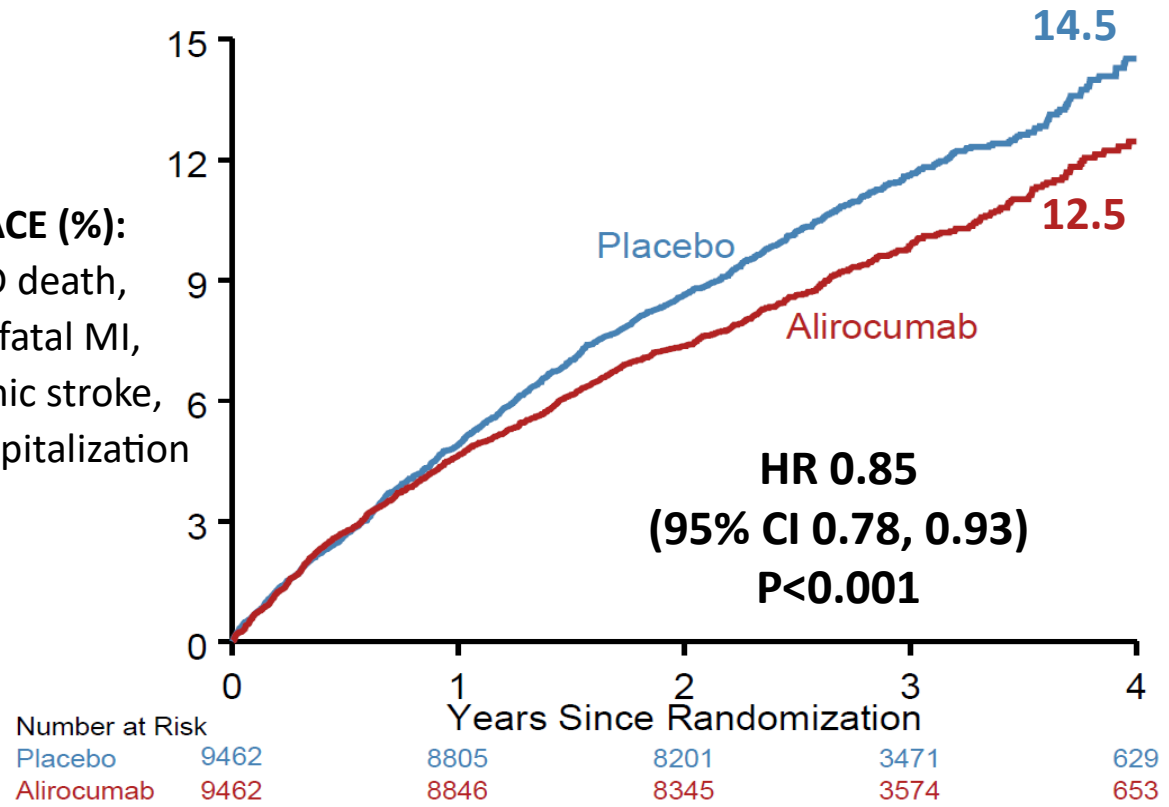

Circulation 2019

# PCSK9 Inhibition with Alirocumab

18,924 patients with recent ACS and LDL-C ≥1.8 mmol/L, non-HDL-C ≥2.6 mmol/L, or ApoB≥0.8 g/L on high-intensity or maximum-tolerated statin

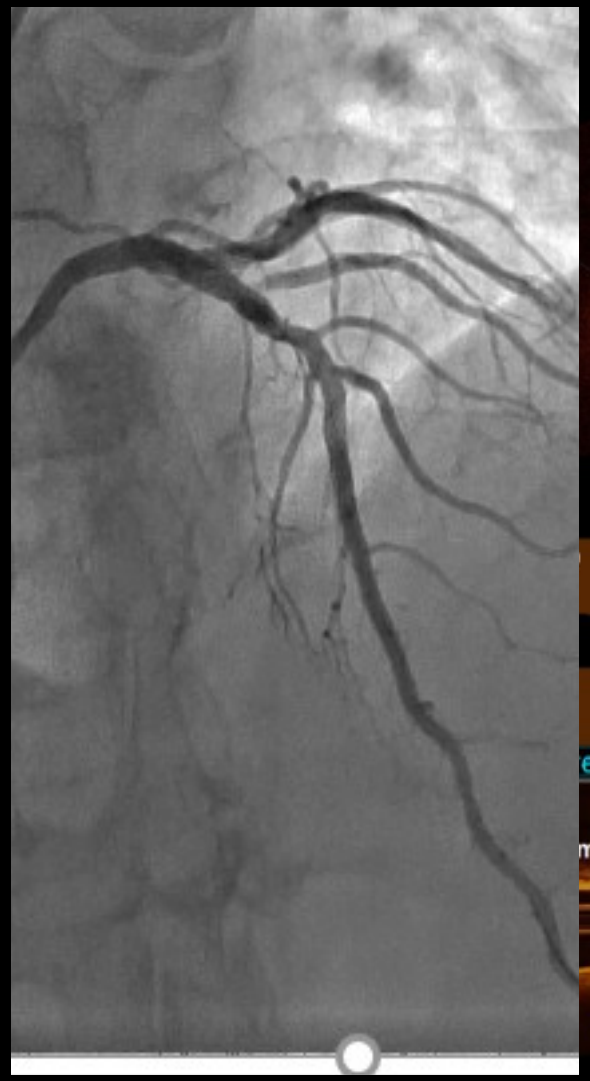


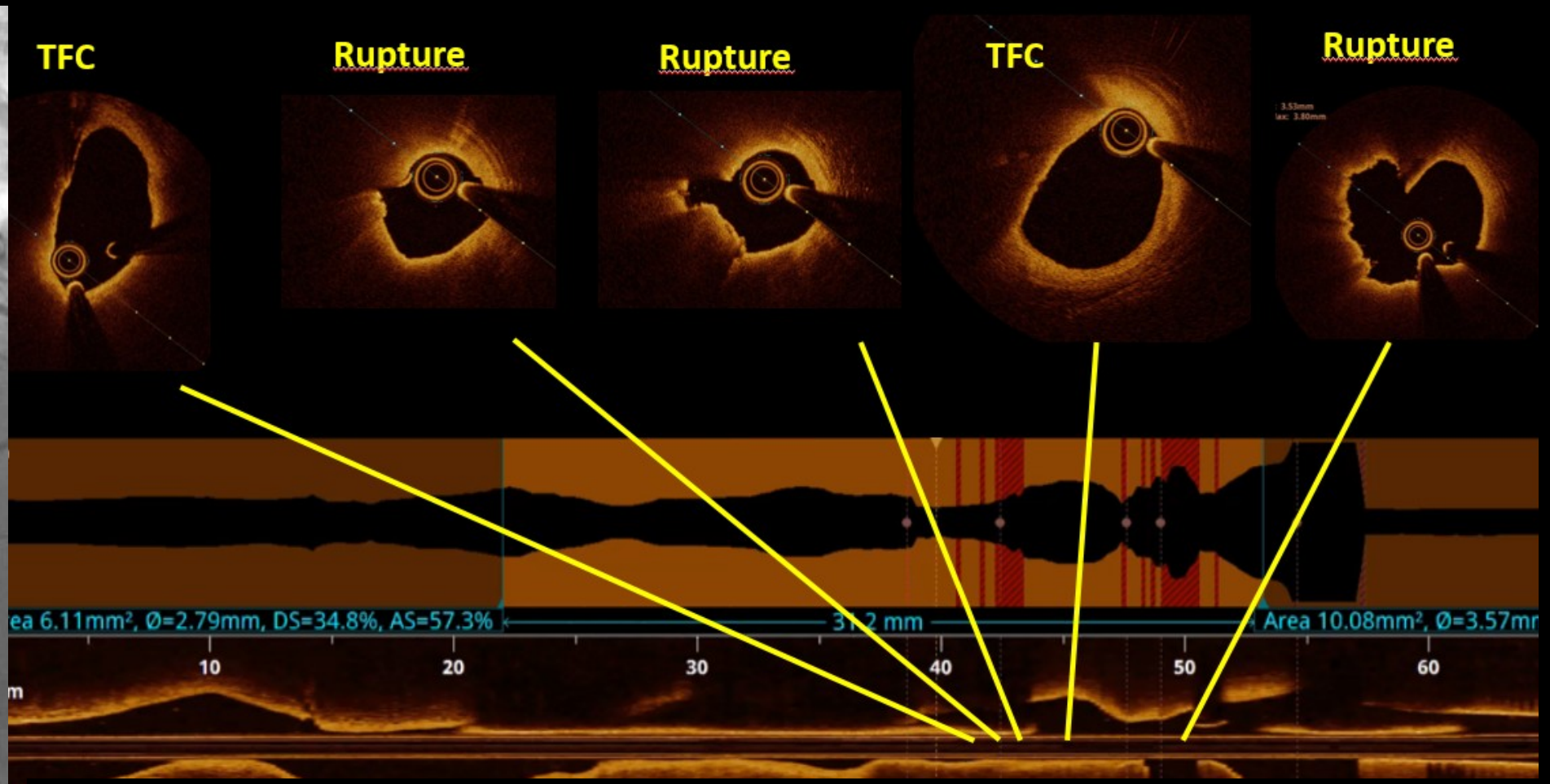

**MACE (%):**
CHD death, non-fatal MI, ischemic stroke, UA hospitalization



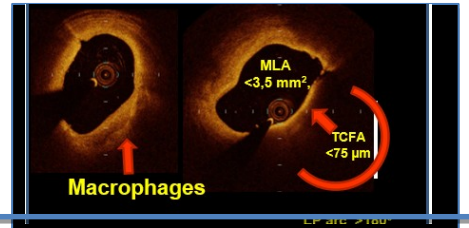
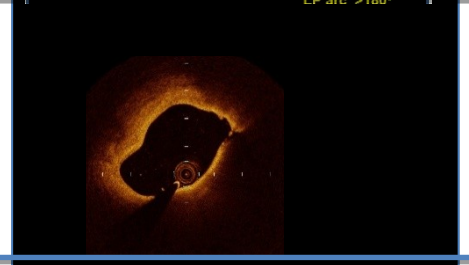
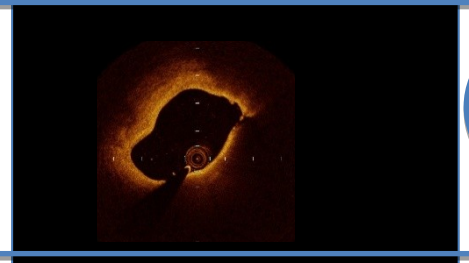
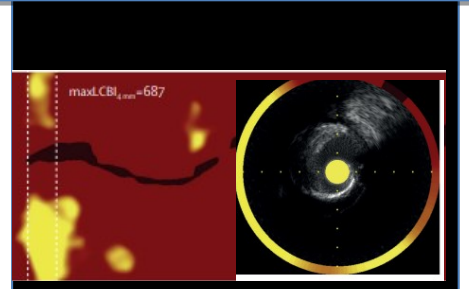
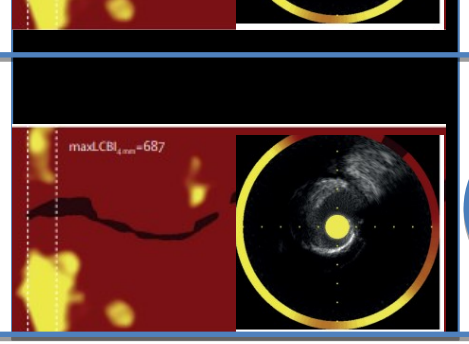

**Schwartz et al *N Engl J Med* 2018;379:2097-107**

- **Lesion at risk : the vulnerable plaque**






# Non culprit ruptured palques: an uncommon anatomy in ACS

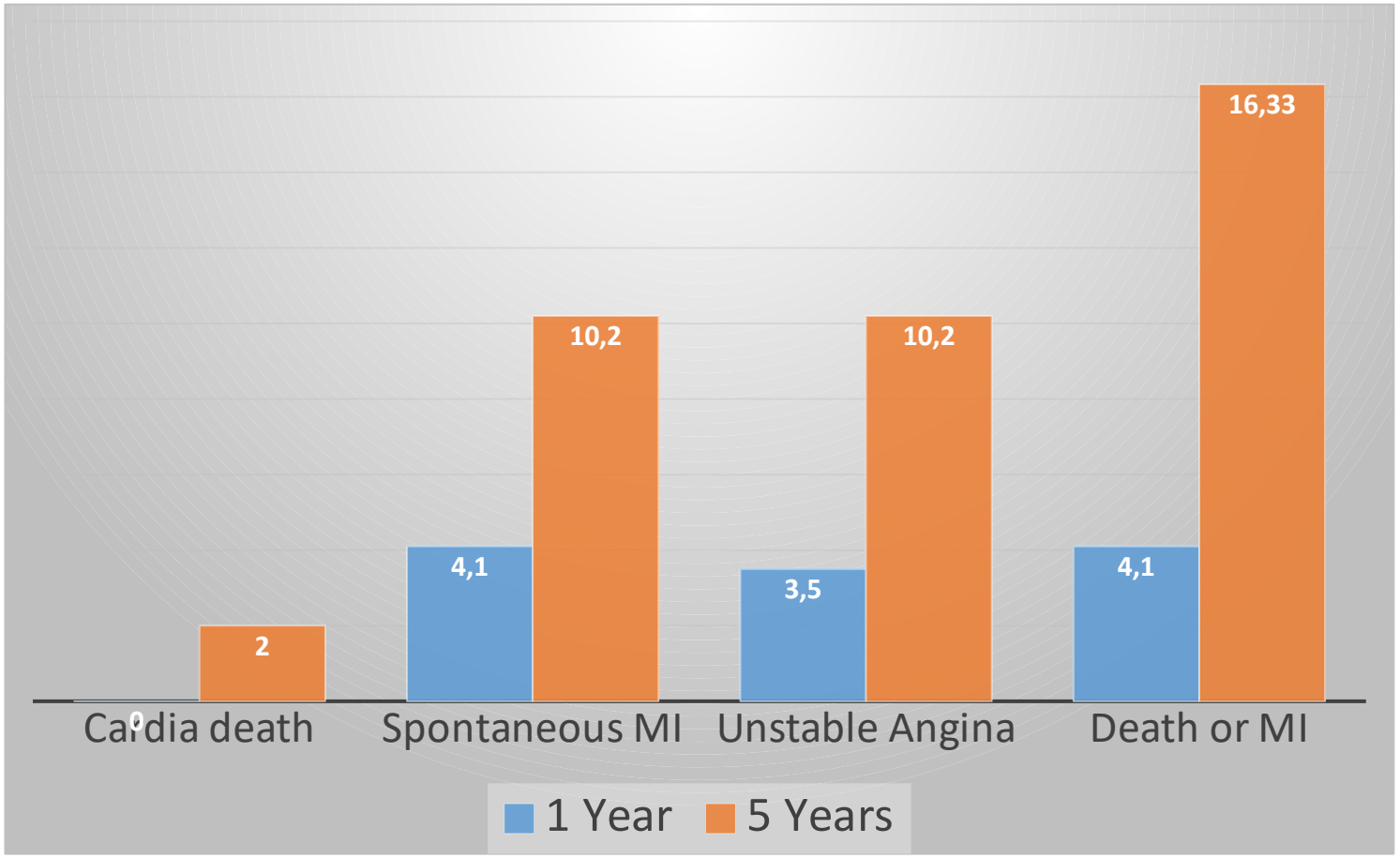
| | | | | | |
|---|---|---|---|---|---|
| CLIMA | Eur. Heart Journal 2019 |  | No FFR | 4 OCT Criteria | CAD + ACS |
| COMBINE | Eur. Heart Journal 2021 |  | FFR Neg. | TFC | Diabetics CAD + ACS |
| PECTUS | JAMA 2023 |  | FFR Neg. | TFC | ACS |
| LRP | Lancet 2019 |  | No FFR. | NIRS-IVUS (LCBI) | ACS |
| PROSPECT II | Lancet 2021 |  | FFR Neg. | NIRS-IVUS (LCBI) | CAD |

- **Number of events in vulnerable lesions**

# COMBINE Study. Clinical end-point at 1 year and 5 years

**TCFA <65µm**

**N=390**




**Fabris et al. Eurointervention 2023**

# Fractional Flow Reserve–Negative High-Risk Plaques and Clinical Outcomes After Myocardial Infarction. PECTUS

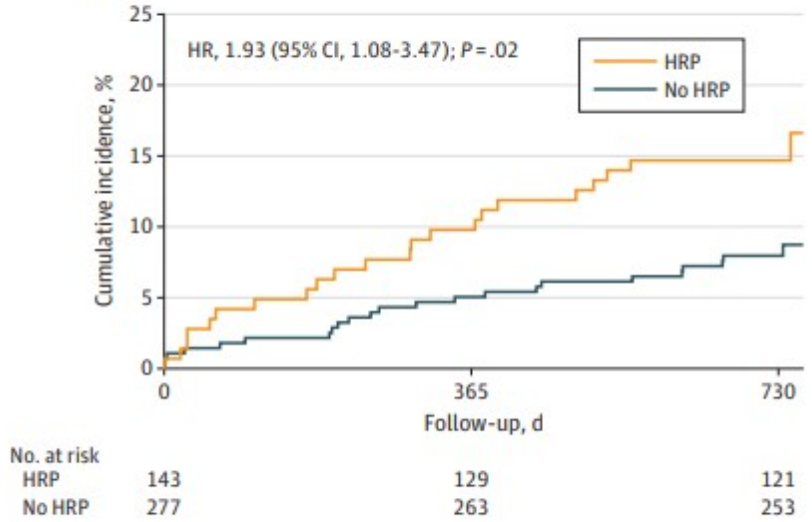
## JAMA 2023

## 420 FFR Negative ACS pts

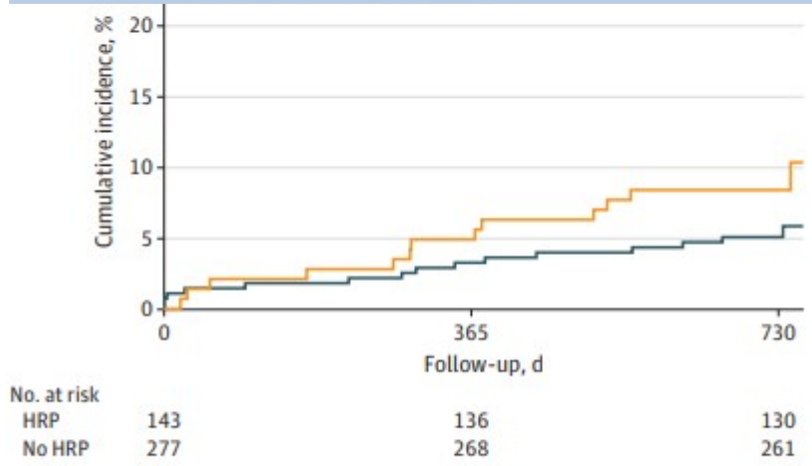
### A high-risk plaque

At least 2 of the following
(1) a lipid arc at least 90°, (2) a fibrous cap thickness less than 65 µm, and (3) either plaque rupture or thrombus presence.

Composite of all-cause mortality, nonfatal MI, or rev.




Composite of all-cause mortality, nonfatal MI, or rev.



- **Rapid changes of plaque morpology in response to treatment**

# Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes

## The MIRACL Study: A Randomized Controlled

**Figure 4.** Risk Ratio Plot

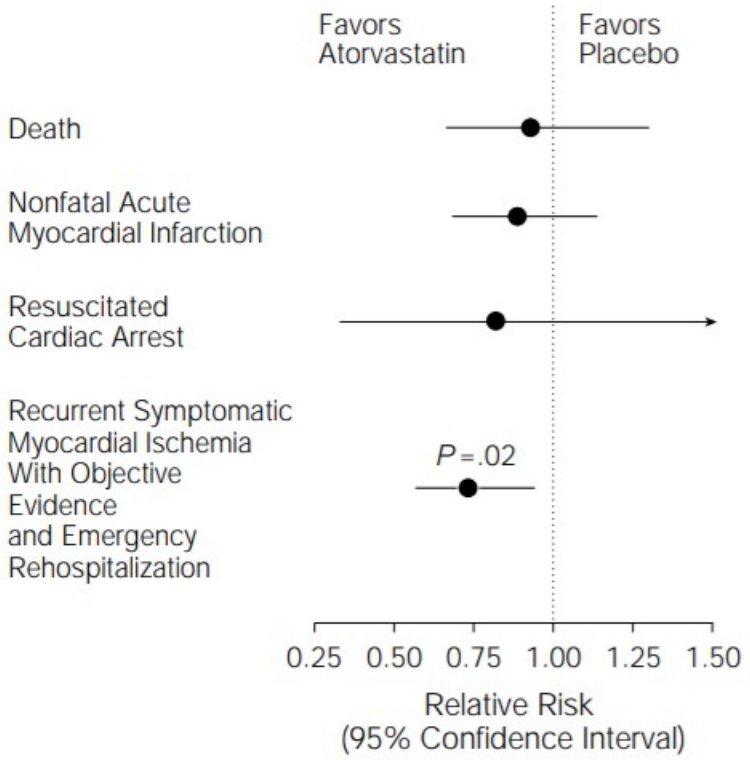
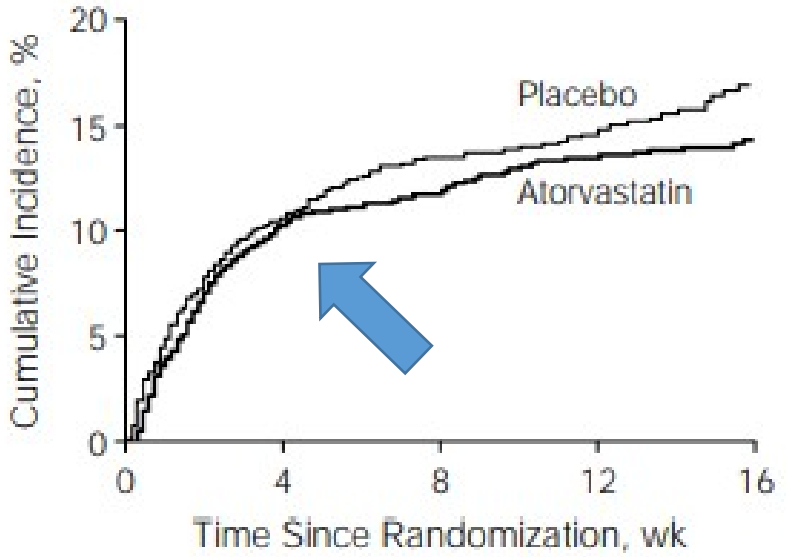



**Figure 3.** Kaplan-Meier Estimates of Primary Outcomes

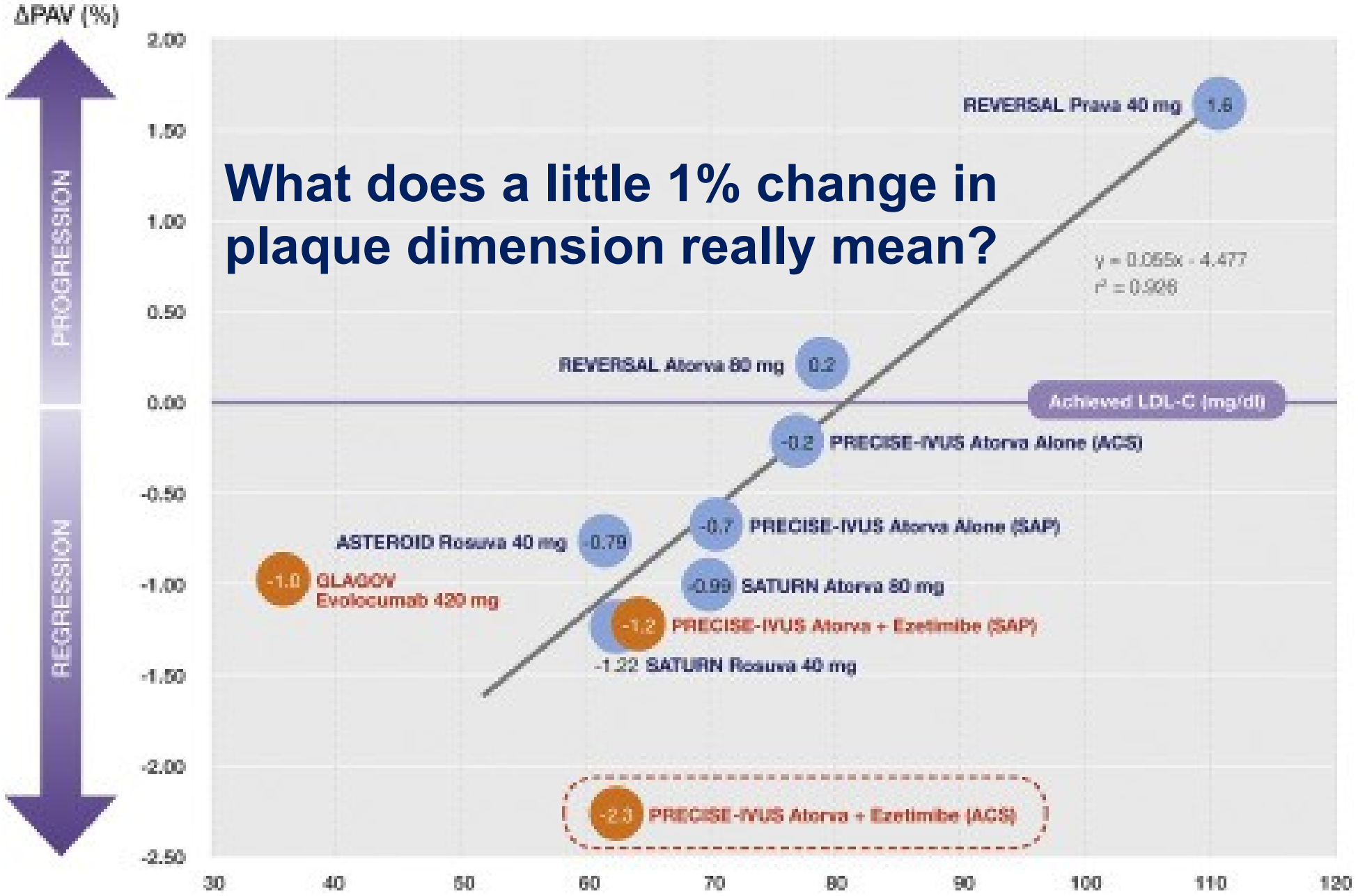



| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Atorvastatin | 1538 | 1381 | 1351 | 1323 | 518 |
| Placebo | 1548 | 1384 | 1338 | 1318 | 473 |

The relative risk of the composite outcome in the atorvastatin group compared with the placebo group was 0.84 (95% confidence interval, 0.70-1.00; $P=.048$), based on a Cox proportional hazards analysis. The decrease in number at risk at 16 weeks reflects the fact that many patients completed the study within the days immediately preceding 16 weeks.

**JAMA 2001**

# What does a little 1% change in plaque dimension really mean?



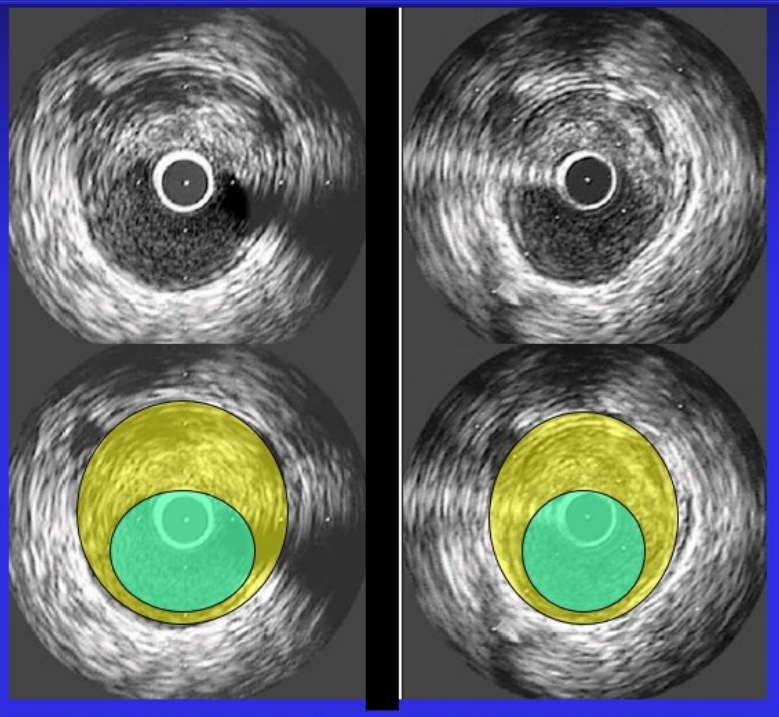
# Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial

,

ASTEROID

**PAV**

**Reduction 1%**



EEM area 16.35 $mm^2$ | EEM area 11.37 $mm^2$

Plaque area 10.16 $mm^2$ | Plaque area 10.81 $mm^2$

Lumen area 6.19 $mm^2$ | Lumen area 5.96 $mm^2$

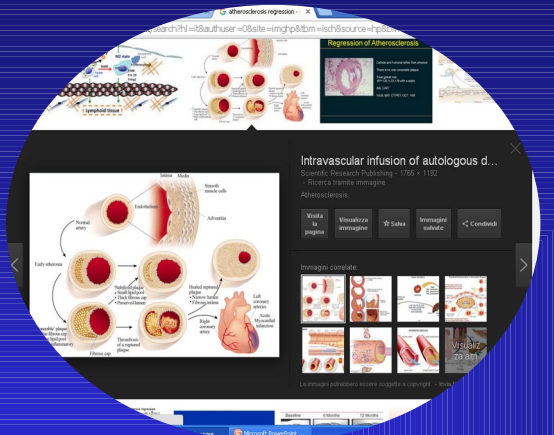
Nissen SE, et al JAMA 2006;295:1556–65.

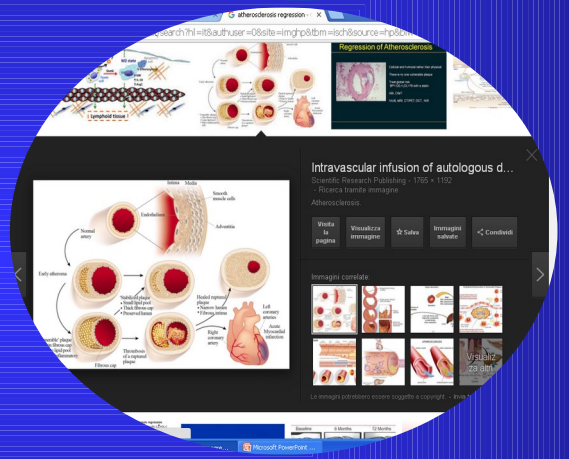
# Therapeutic stabilization of coronary plaques


Progression

Instability

Regression




Original Article

# Assessing the impact of PCSK9 inhibition on coronary plaque phenotype with optical coherence tomography: rationale and design of the randomized, placebo-controlled HUYGENS study

Stephen J. Nicholls, Steven E. Nissen, Francesco Prati, Stephan Windecker, Yu Kataoka, Rishi Puri, Thomas Hucko, Helina Kassahun, Jason Liao, Ransi Somaratne, Julie Butters, Giuseppe Di Giovanni, Stephen Jones, Peter J. Psaltis

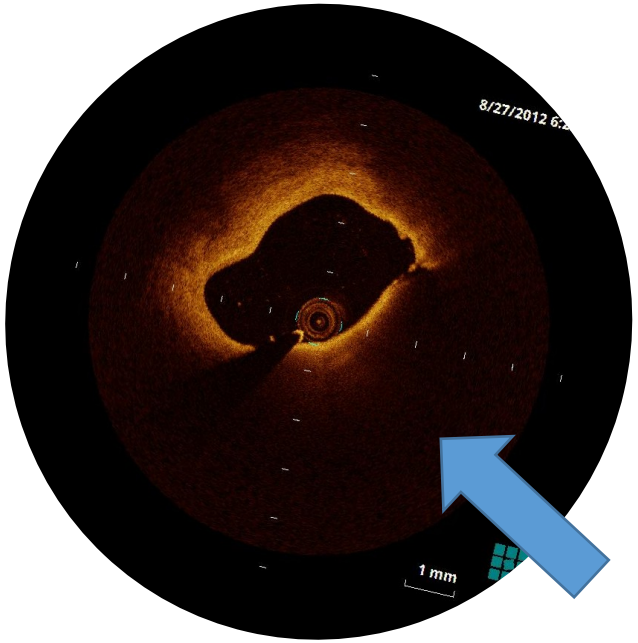
Cardiovascular Diagnosis and Therapy 2021

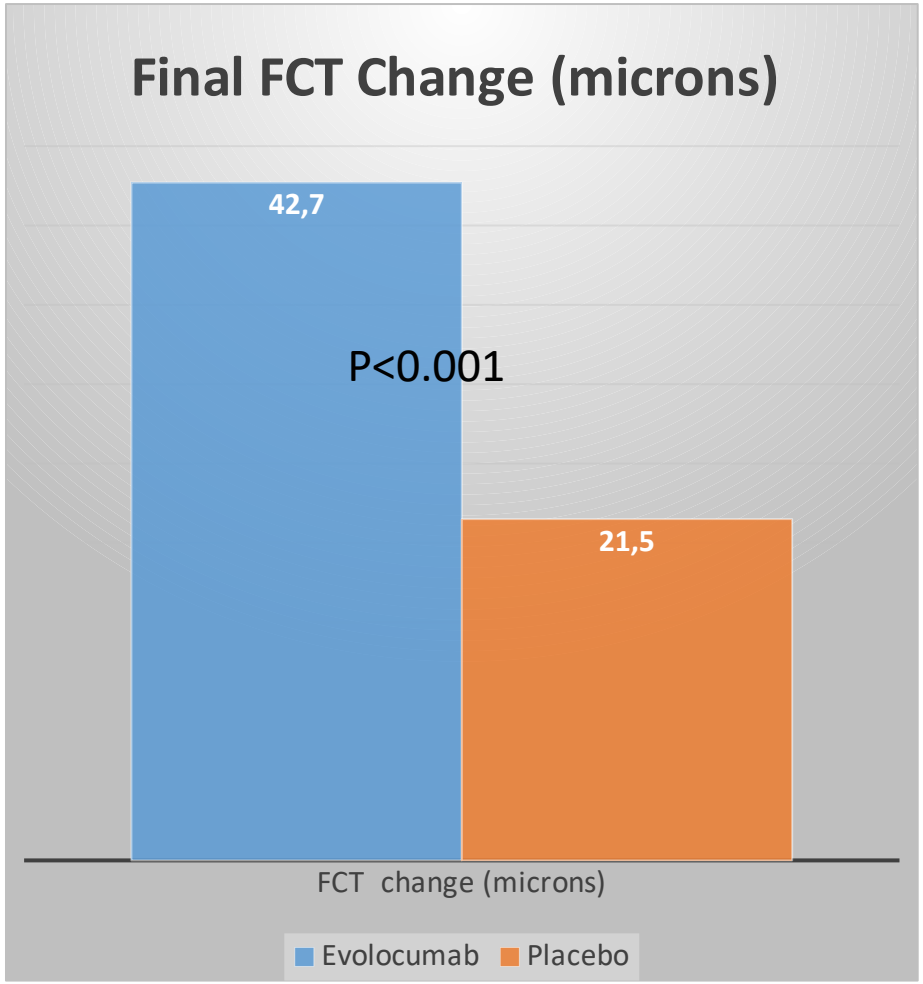
# High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study (HUYGENS)

## Main study end-point: increase in FCT

**Evolocumab group: FCT increased from 56,6 µ to 100,6 m (+ 82%)**

**Placebo group: FCT increased from 54,6 µ to 81,7 (+ 44%)**




JACC Imaging 2021

# Aim

To determine the effect of early administration of 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.

JAMA 2022

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

**Patients with AMI (N-STEMI/STEMI) undergoing successful PCI of the infarct vessel & 2 non-infarct related arteries with non-obstructive lesions (diameter stenosis 20-50%)**

Alirocumab PACMANAMI

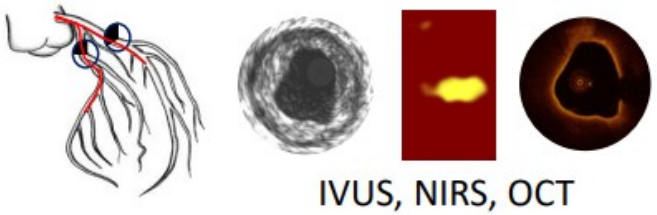
POC

**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

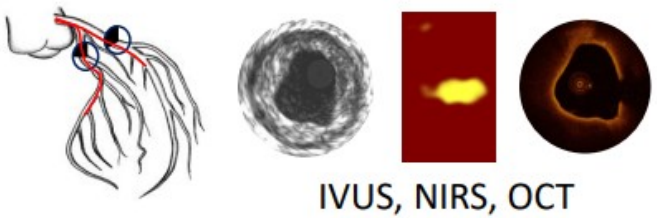
**Alirocumab s.c. 150 mg / 2 weeks + Rosuvastatin 20 mg**

**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.

# Baseline Characteristics

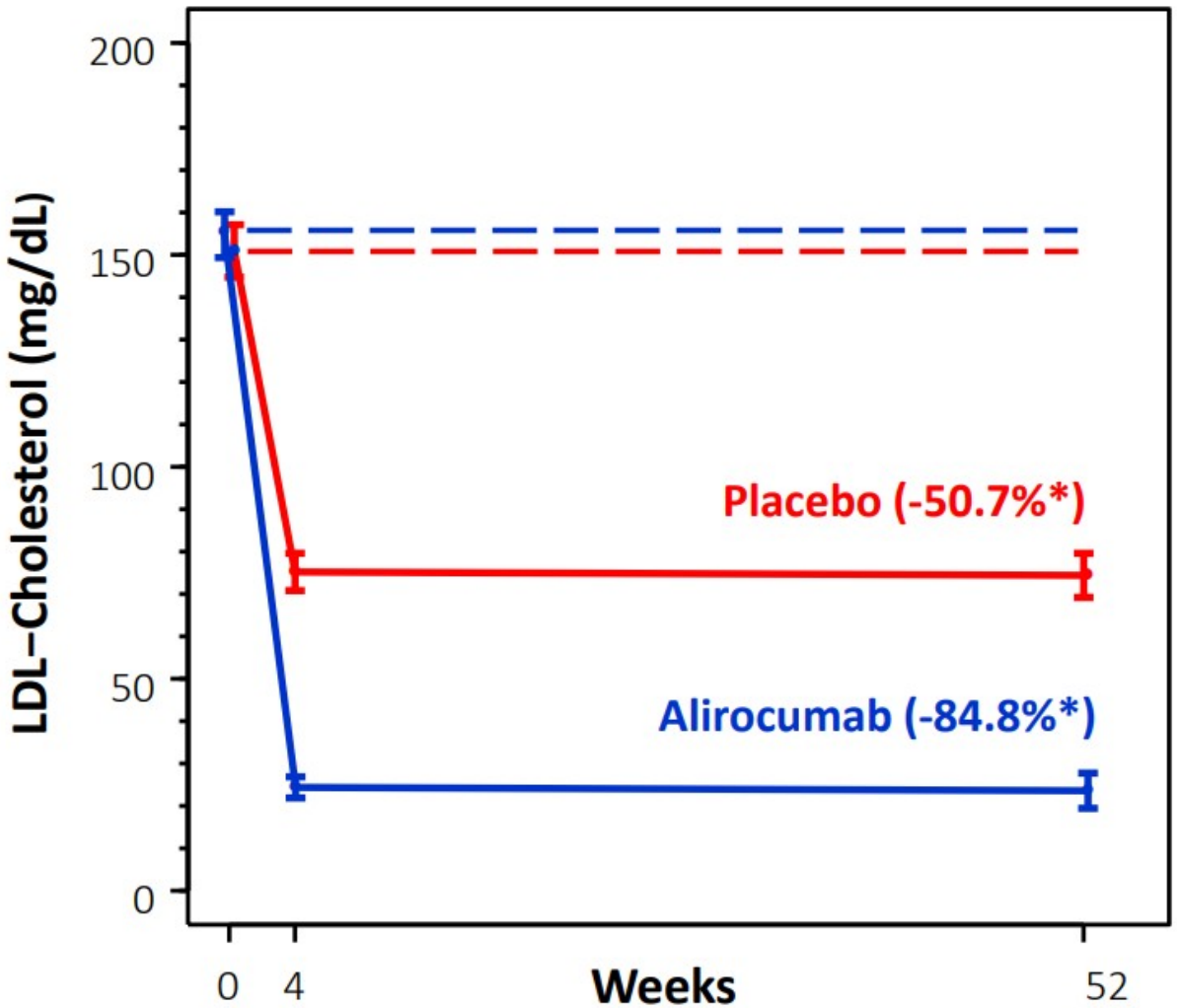
| | Alirocumab (n=148) | Placebo (n=152) |
|---|---|---|
| **Age (y)** | 58.4 (10.0) | 58.6 (9.4) |
| **Women** | 24 (16.2%) | 32 (21.1%) |
| **Body mass index** | 27.3 (4.1) | 28.2 (4.5) |
| **Current smoking** | 77 (52.0%) | 65 (42.8%) |
| **Arterial hypertension** | 60 (40.5%) | 70 (46.1%) |
| **Diabetes 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%) |

JAMA 2022

# 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

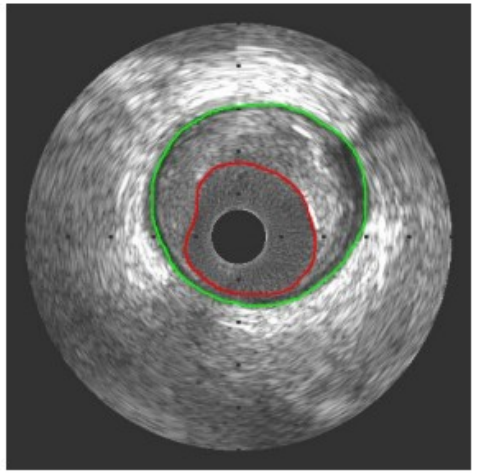


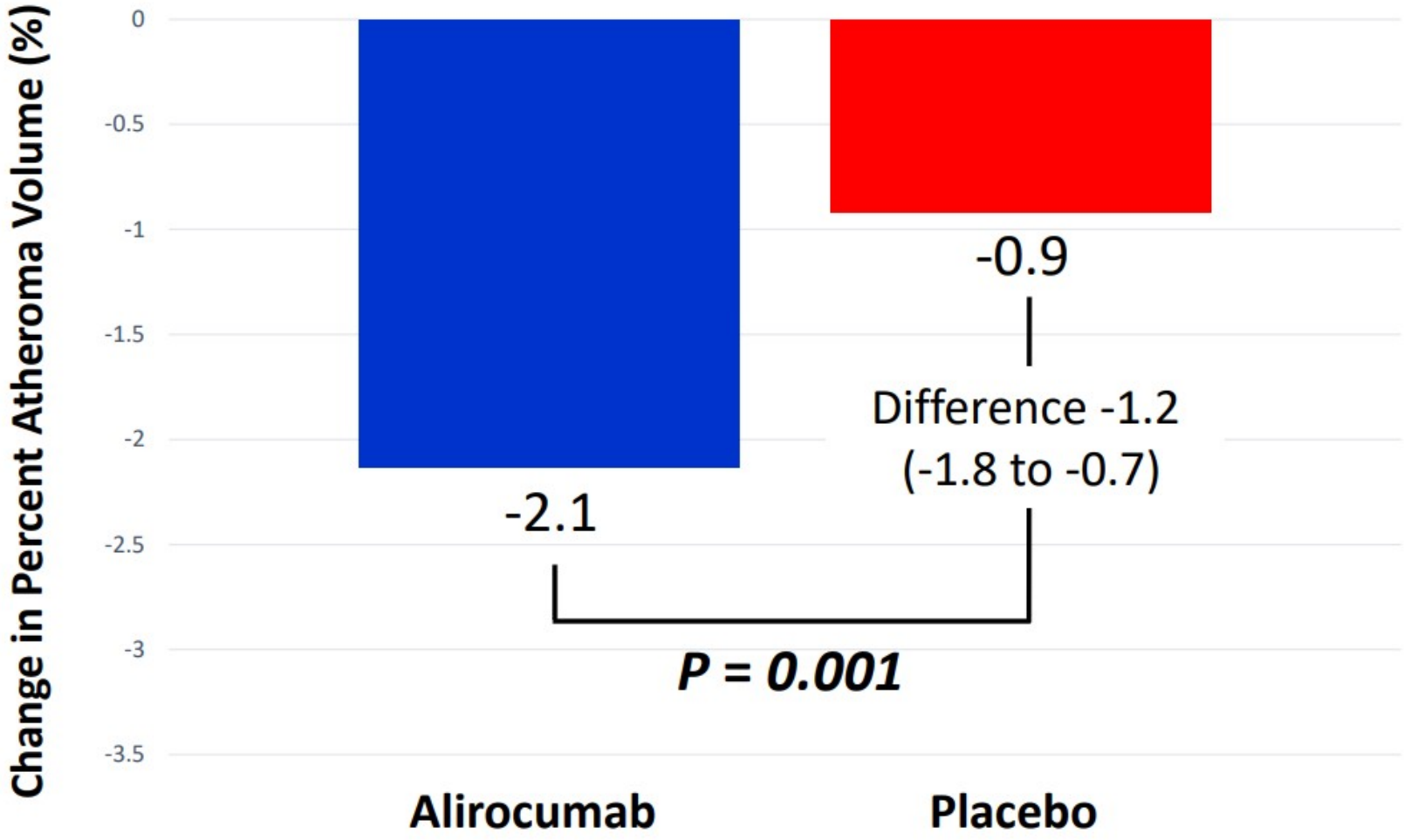

**74.4 (31) mg/dL**
1.9 (0.8) mmol/L

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

* Week 52 vs. Baseline

# Primary EP:
## Change in Percent Atheroma Volume (IVUS)

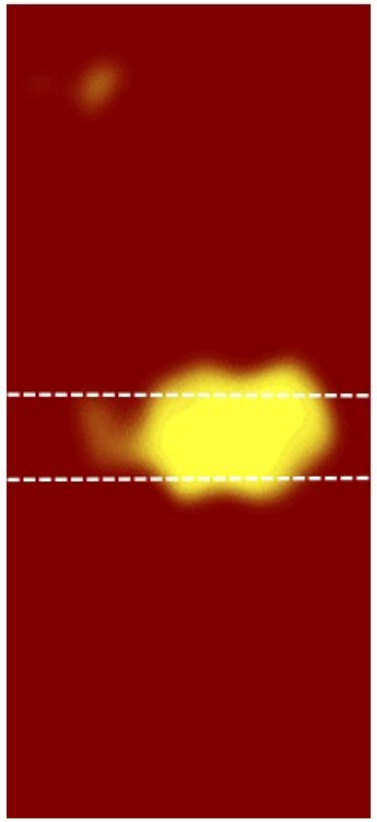


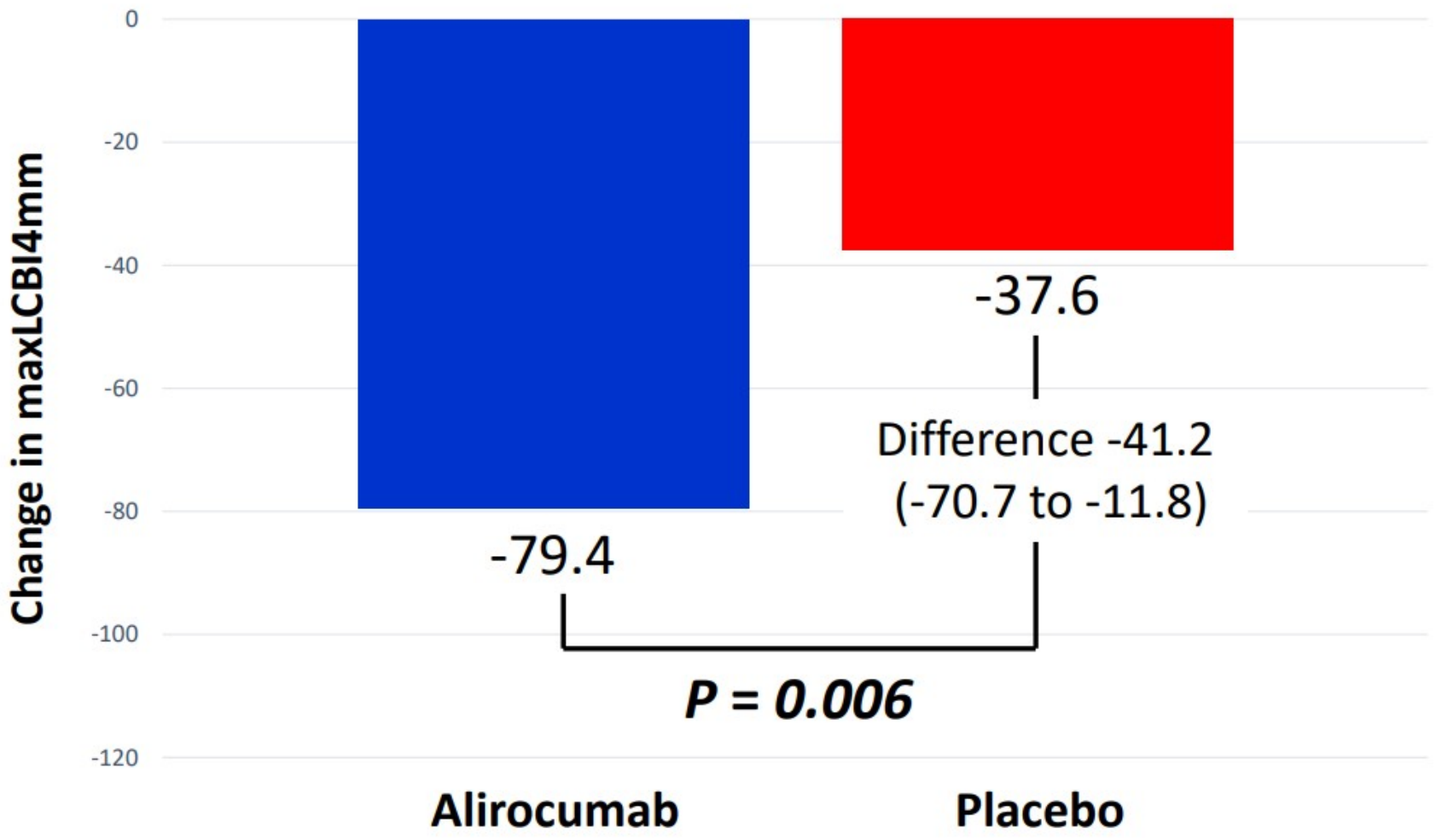



JAMA 2022

# Powered Secondary EP:

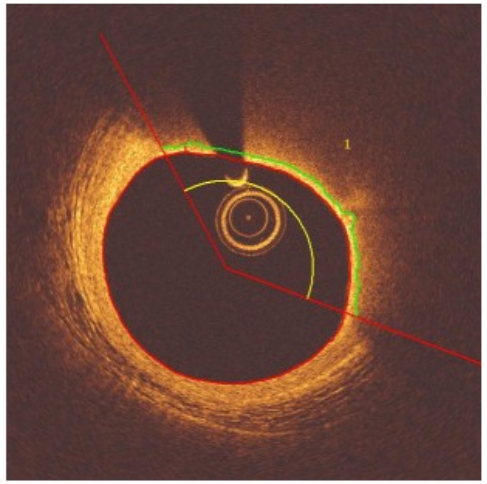
## Change in maxLCBI$_{4mm}$ (NIRS)

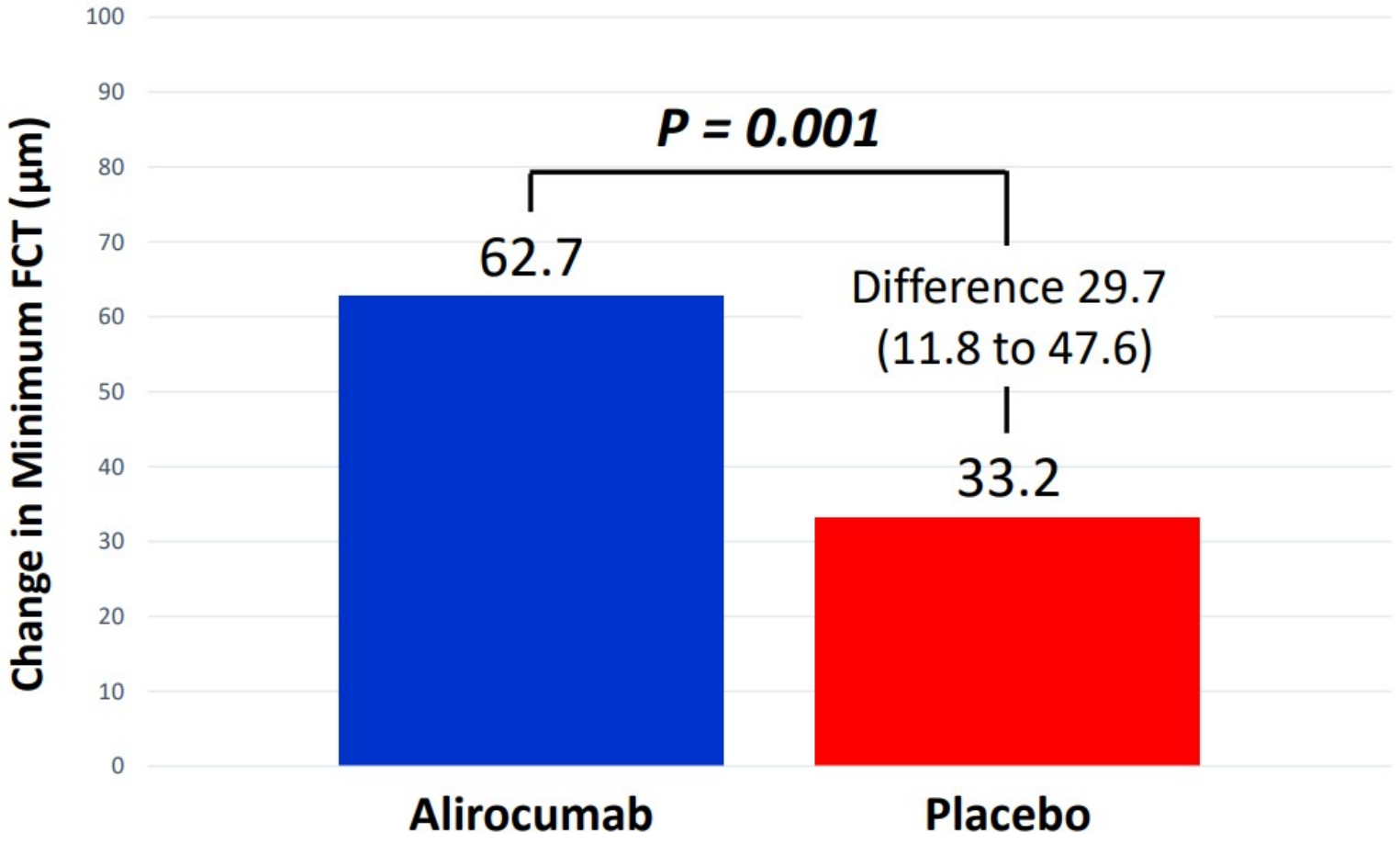





JAMA 2022

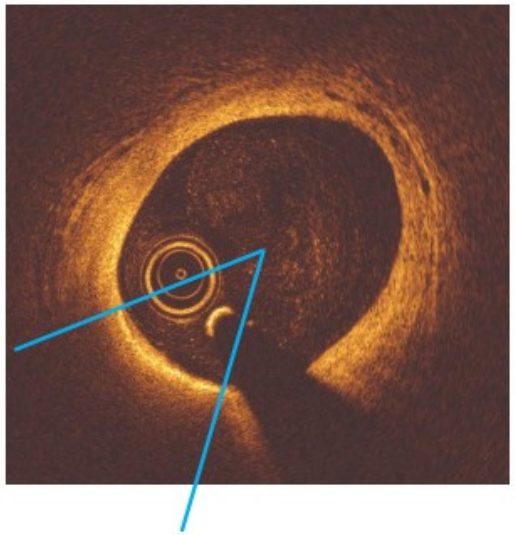
# Powered Secondary EP:
## Change in Minimum FCT (OCT)

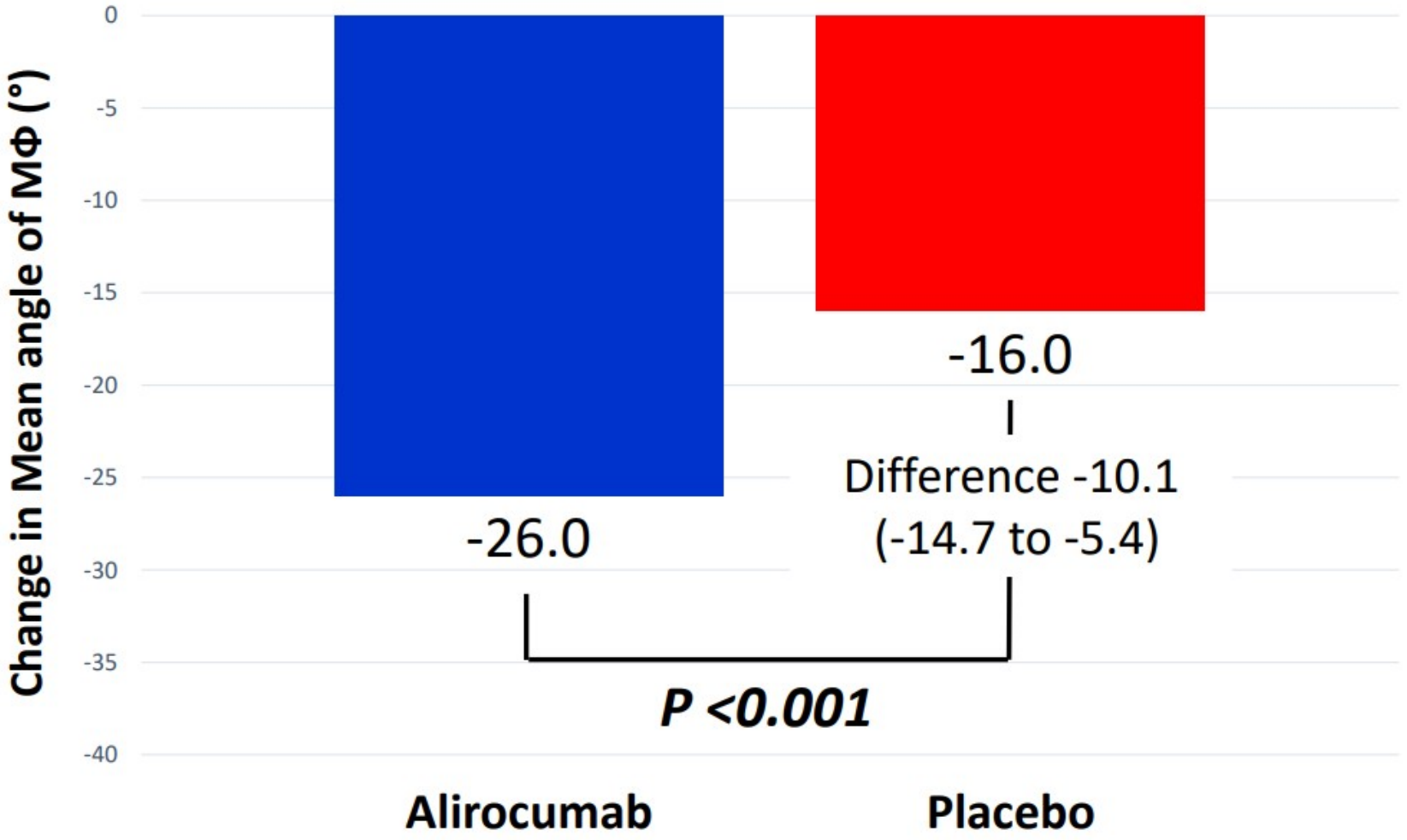





JAMA 2022

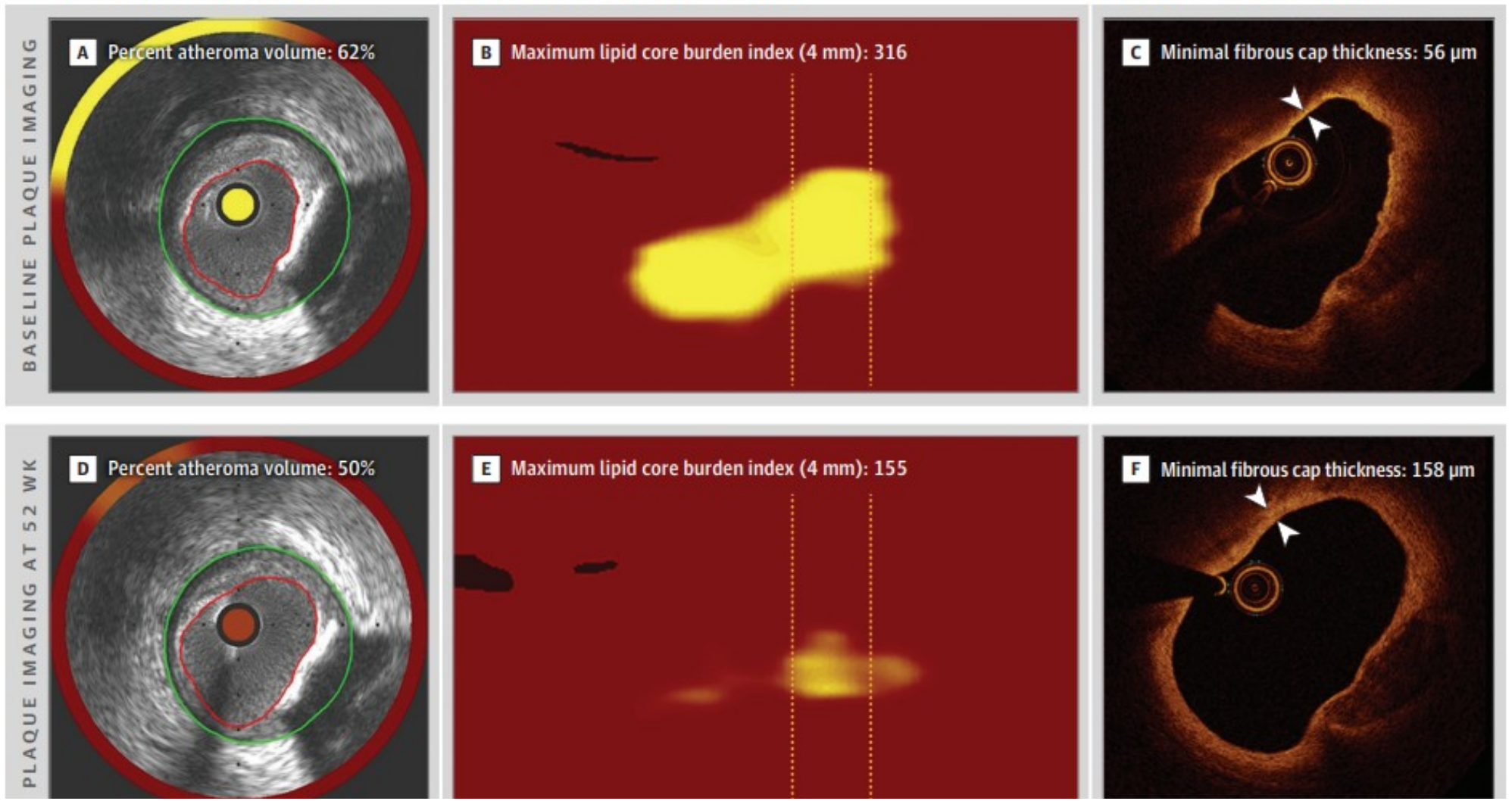
# Prespecified Secondary EP:
## Change in Macrophage Angle (OCT)



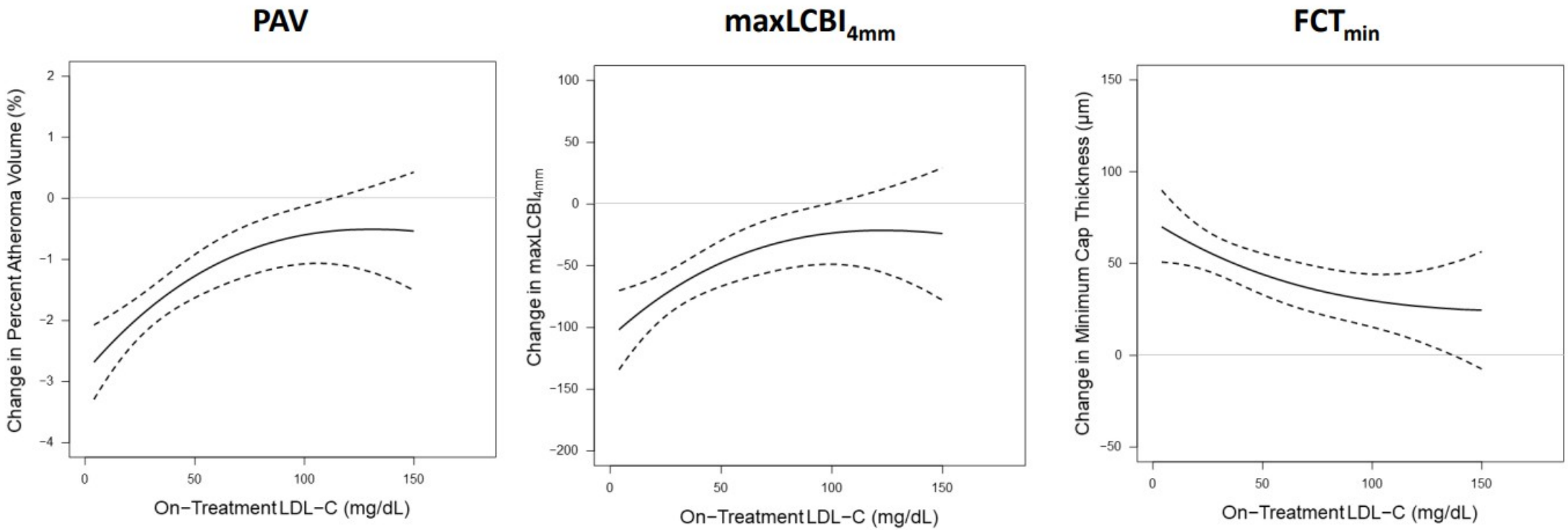



JAMA 2022

**Figure 3. Example of Plaque Regression, Lipid Regression, and Fibrous Cap Thickening in a Trial Patient**



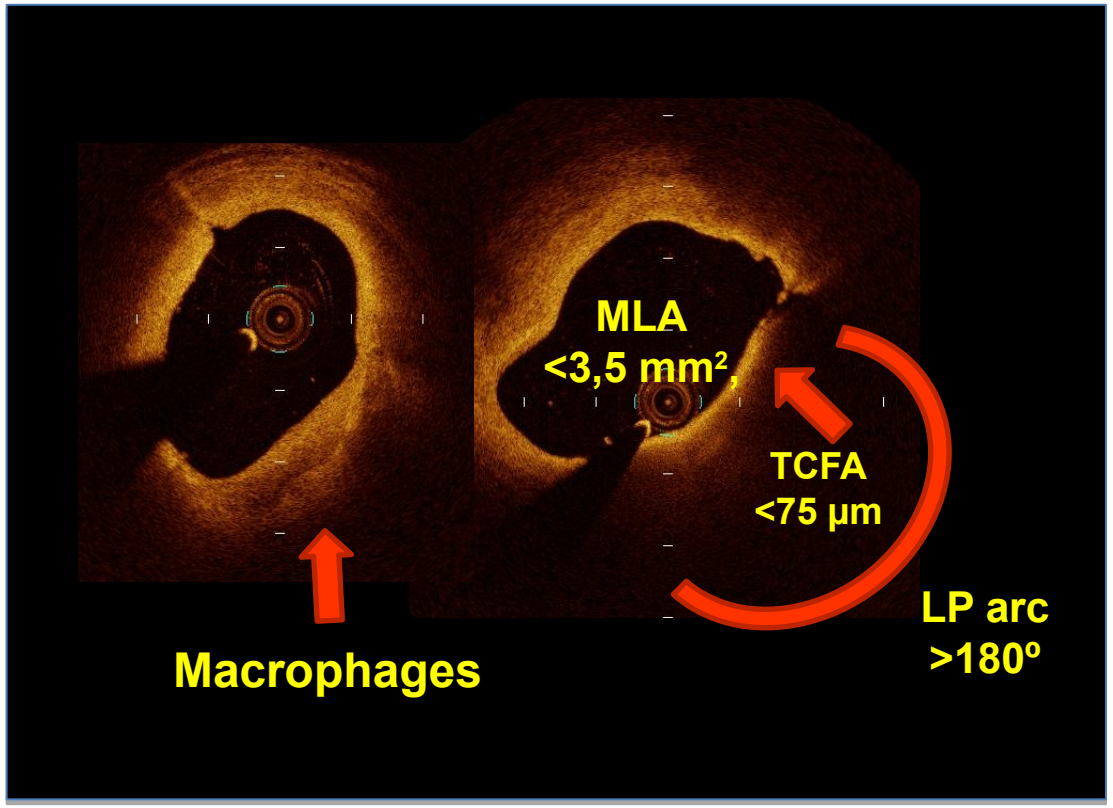
# Relationship Between LDL-C and Endpoints*




* Non-prespecified analysis

# The CLIMA study. Eur Heart Journal 2020

**1003** patients enrolled. Prox. LAD interrogation with OCT. 1 Y FU

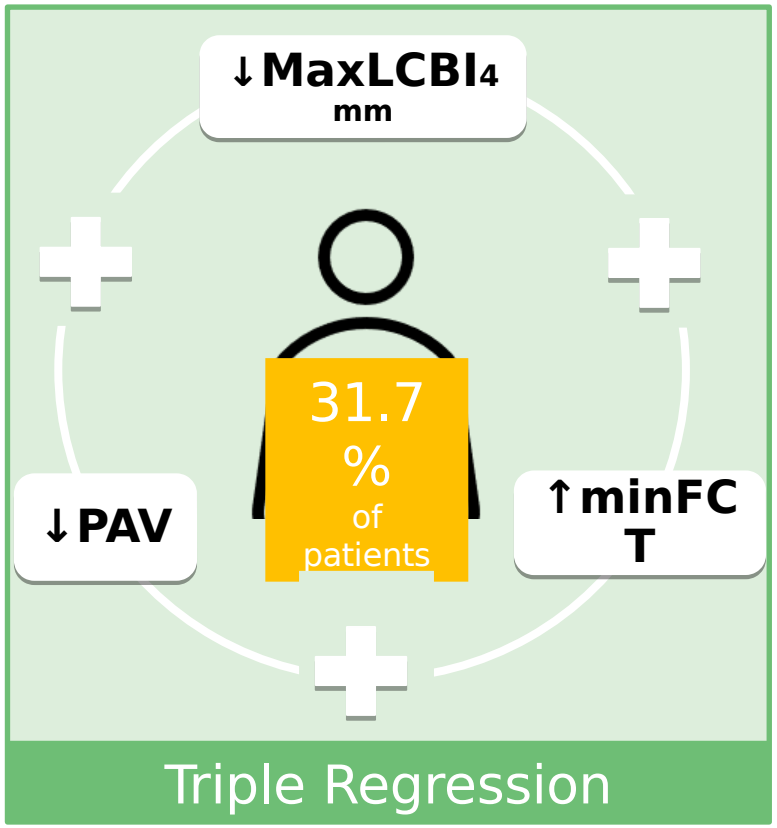


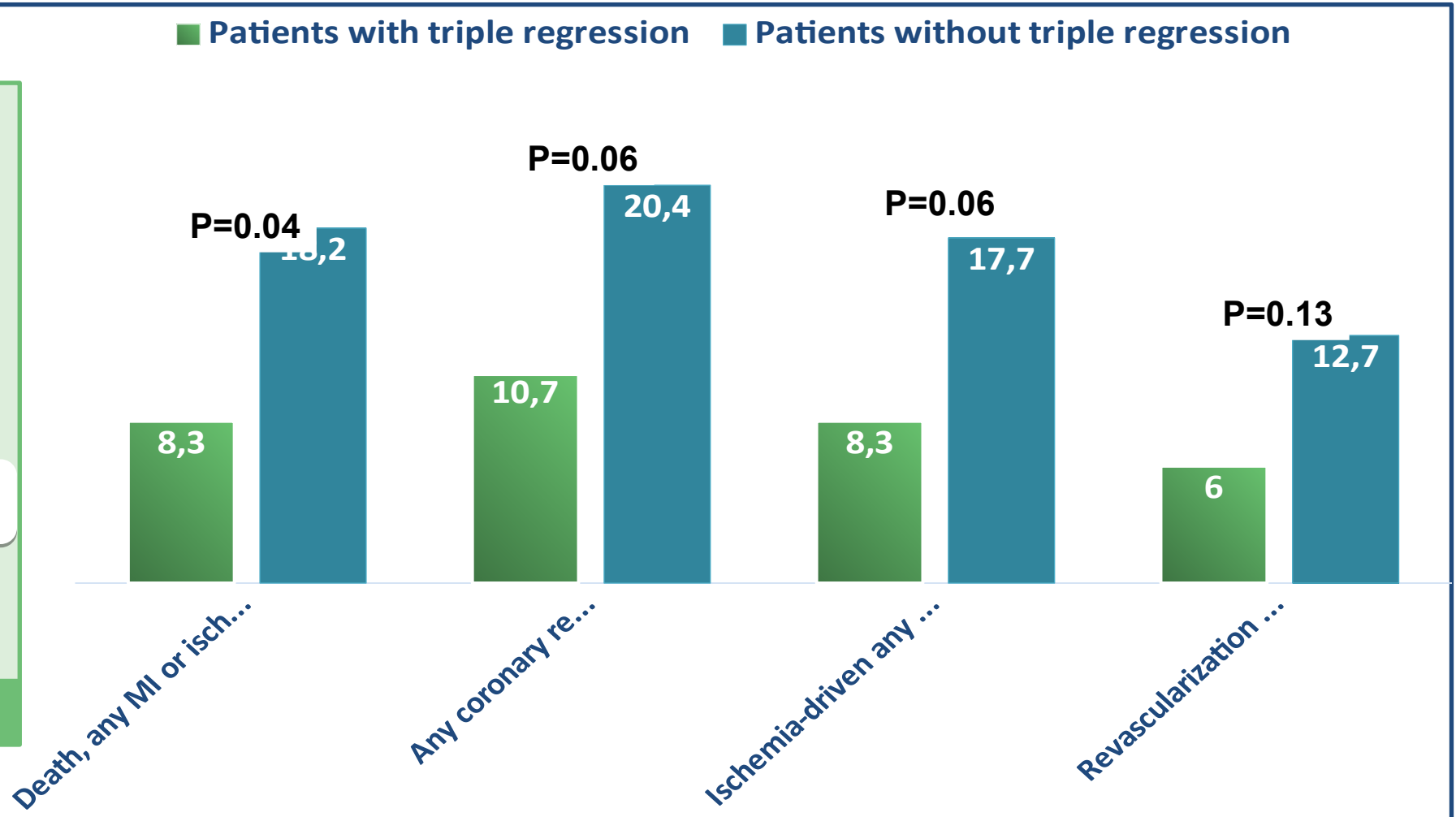

**4 OCT criteria related to hard cardiac end-points (Cardiac Death and target vessel MI)**

**Macrophages**
**LP arc**
**Thin FC**

***All modified by Evolocumab And Alirocumab***

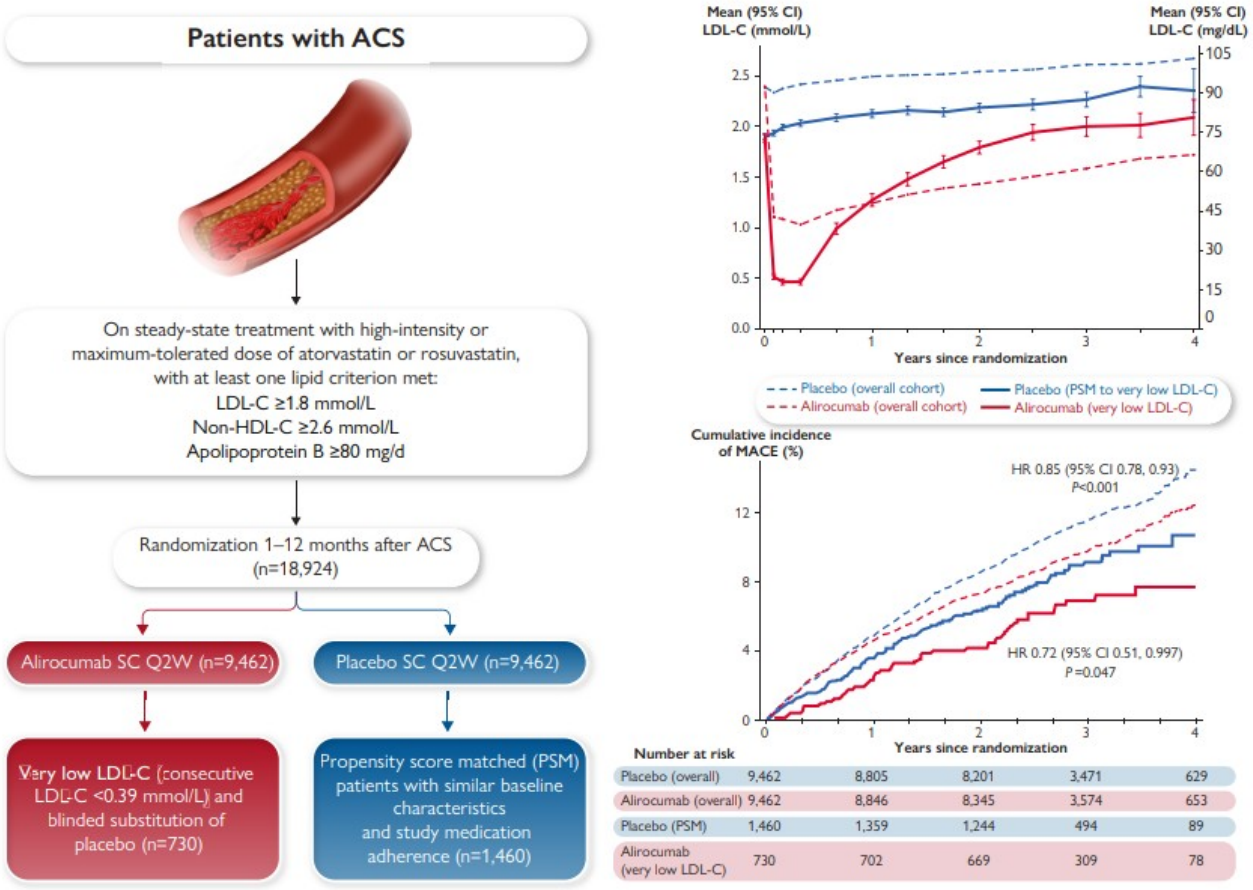
# Events in patient with vs without regression+stabilization of high-risk plaque features




Biccirè et al. JACC 2023; 06468-9.

# Early aggressive LDL lowering treatment










| Number at risk | | | | | |
|---|---|---|---|---|---|
| Placebo (overall) | 9,462 | 8,805 | 8,201 | 3,471 | 629 |
| Alirocumab (overall) | 9,462 | 8,846 | 8,345 | 3,574 | 653 |
| Placebo (PSM) | 1,460 | 1,359 | 1,244 | 494 | 89 |
| Alirocumab (very low LDL-C) | 730 | 702 | 669 | 309 | 78 |

**Transiently achieved very low low-density lipoprotein cholesterol levels by statin and alirocumab after acute coronary syndrome are associated with cardiovascular risk reduction: the ODYSSEY OUTCOMES trial**

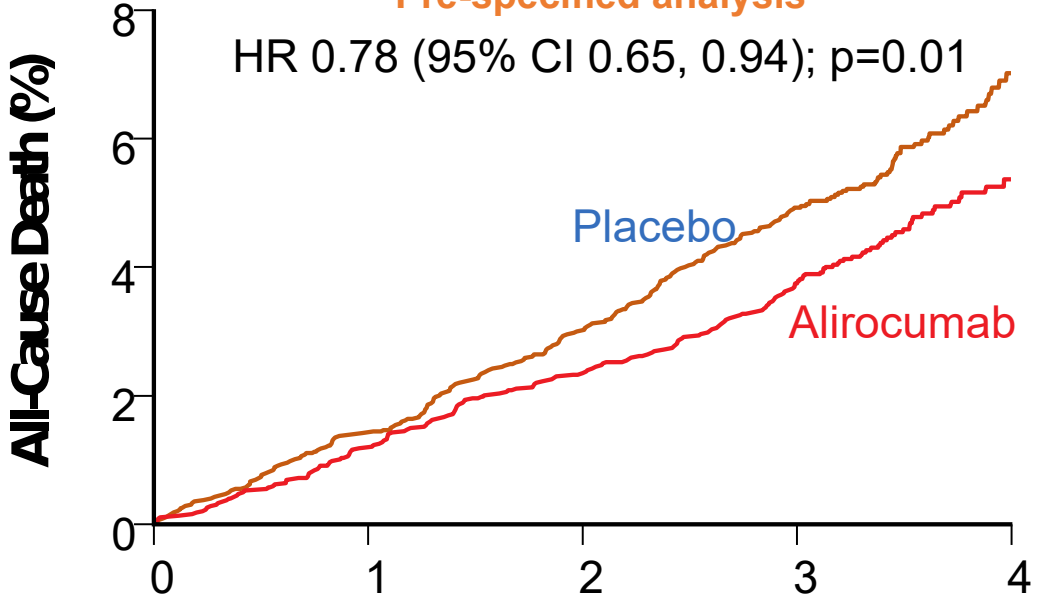
**Gregory G. Schwartz**
**Eupean heart Journal 2023**

# Long-term efficacy, safety and tolerability of alirocumab in 8242 patients eligible for 3-5 years of placebo-controlled observation in the ODYSSEY OUTCOMES trial

## Patients eligible for ≥3 years follow-up

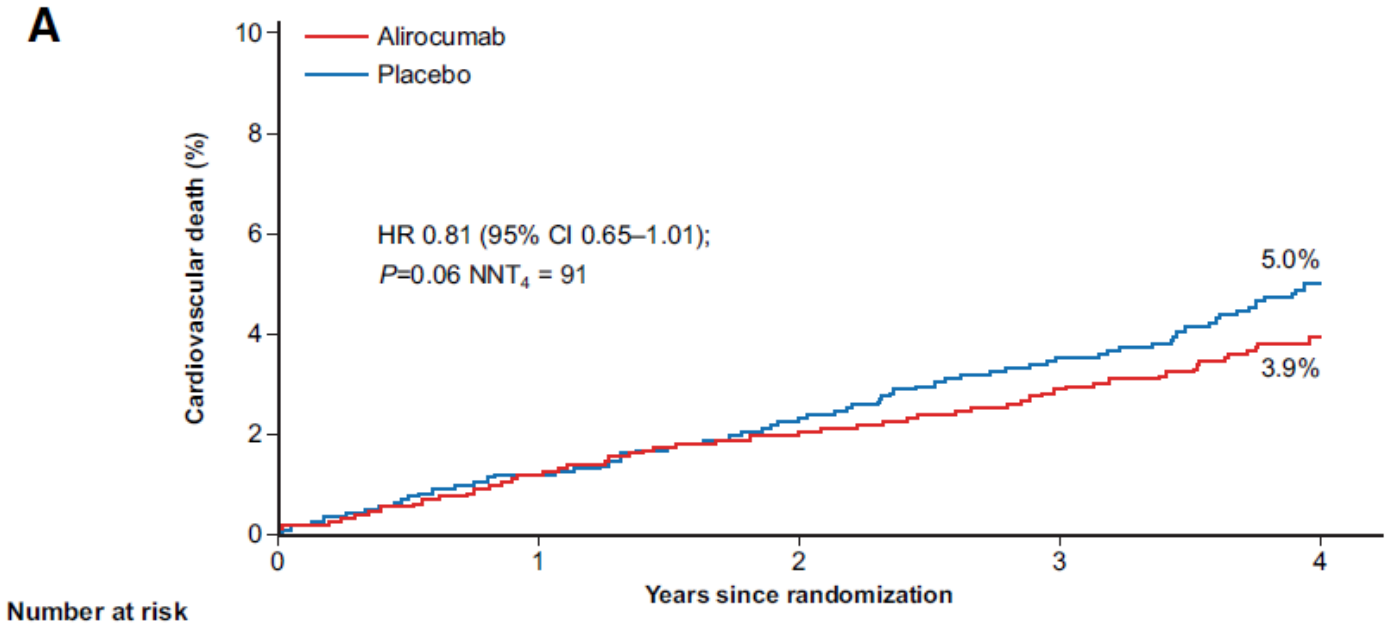
### All-cause Mortality*

*Pre-specified analysis




| Number at risk | | | | | |
|---|---|---|---|---|---|
| Placebo | 4126 | 4061 | 3987 | 3898 | 737 |
| Alirocumab | 4116 | 4059 | 4007 | 3946 | 746 |

Steg et al *Circulation* 2019;140:103-12




| Number at risk | | | | | |
|---|---|---|---|---|---|
| Placebo | 4126 | 4060 | 3986 | 3898 | 737 |
| Alirocumab | 4116 | 4058 | 4007 | 3946 | 746 |

*Goodman et al J Am Heart Assoc.* 2023;12:e029216

La riduzione della mortalità è guidata dalla riduzione della mortalità per cause cardiovascolari

ACC 22

# 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 with alirocumab** and provide a mechanistic rationale in favor of early initiation of very intensive LDL-C lowering in acute MI patients.

# Conclusions

- Plaques with high lipidic content and or features of vulnerablity are related to a worse outcome
- Drugs with high lipid-lowering action, lead to atherosclerosis regression
- PCSK9 inhibitors are the most effective drugs for decreasing LDL Cholesterol level
- There is clinical evidence of a link between lesion regression and clinical benefit
- Plaque regression likely occurs with concomitant changes of plaque vulnerability features

Centro per la Lotta contro l'Infarto - Fondazione Onlus

# INTERCLIMA

CLI Foundation

## study flow chart

**Inclusion criteria:**
- Single intermediate lesion in non culprit vessels of patients with acute coronary syndrome diagnosis
- Life expectancy >3 years
- Age>18 years

**Intermediate lesion in a naïve major coronary segment (Ø ≥2.5 mm) determining stenosis between 40-70%**

**Exclusion criteria:**
- incomplete imaging of the segment of interest (including at least 5 mm at both stenosis edges);
- diffusely segment diseased with more than one lesion (preventing correct adverse event attribution) or significant (>70%) lesion in the same coronary vessel;
- ostial left main or graft conduits involvement;
- prior myocardial infarction or revascularization in the same coronary vessel;
- non-cardiac co-morbid conditions that may result in protocol noncompliance.

**QCA validation and randomization to**
(stratified by LAD localization and center)

Randomization 1:1

**iFR/FFR guidance (770)**

55% DEFER

**Non significant intermediate plaque**
iFR >0.89/FFR >0.80

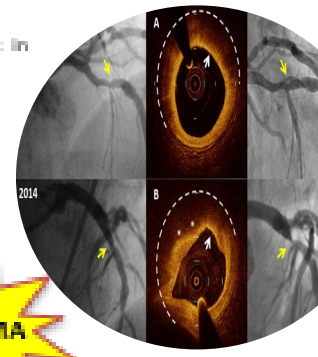
**Significant intermediate plaque**
iFR <0.89/FFR <0.80

**OCT guidance (770)**

12.3% CLIMA

**Not vulnerable plaque**
(Presence of less than 3 CT-defined vulnerability criteria* including fibrous cap thickness <75 µm)

**Vulnerable plaque**
(Presence of at least 3 out the 4 OCT-defined vulnerability criteria* including fibrous cap thickness <75 µm)




**Deferred group**

**Interventional group**

**Target vessel failure[§] with intention-to-treat analyses**

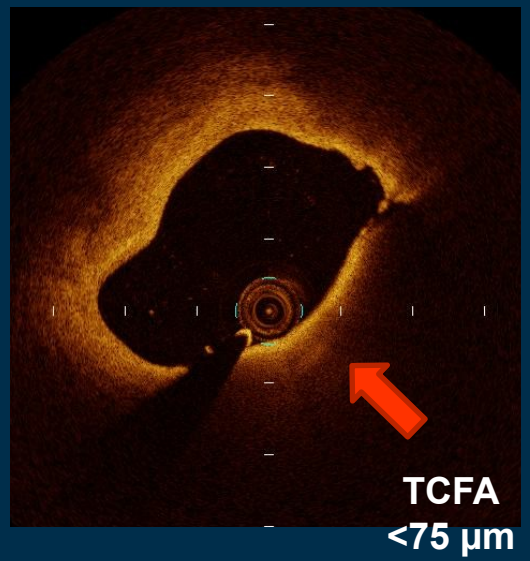
112 events expected

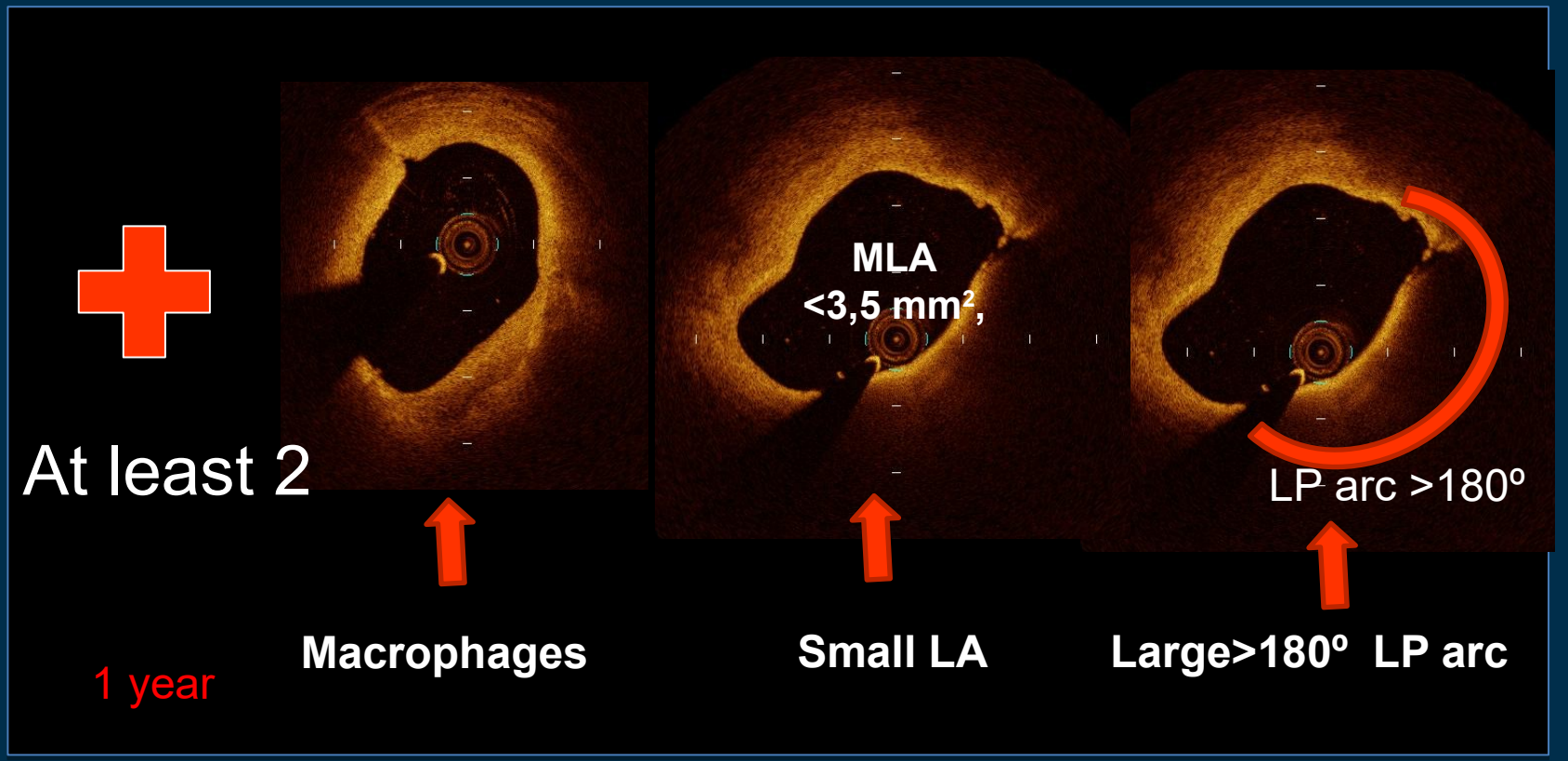
[§]composite of cardiac death, target vessel myocardial infarction

*simultaneous presence of:
MLA <3.5 mm²,
fibrous cap thickness <75 µm,
circumferential lipidic extension >180°,
and macrophage infiltration

# Vulnerability criterion applied in the INTERCLIMA

**Presence of thin FC thickness plus two of the other three vulnerable variables**




**About 15% of patients are supposed to have a vulnerable plaque in the studied vessel**