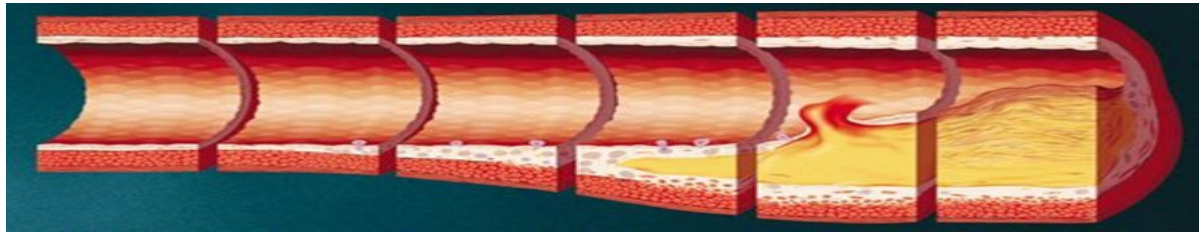
PROGRESSION vs. REGRESSION OF ATEROSCLEROSIS - ARE WE FINALLY THERE?

Elena Izkhakov
Institute of Endocrinology, Diabetes, Metabolism and Hypertension
Tel Aviv Sourasky Medical Center

25.11.2022



Objectives

- Relationship between LDL-C levels and CV events
- New targets for lipid lowering therapies
- Regression of atherosclerotic plaque: from statins to PCSK9i
- Long-term data on safety and efficacy of LDL-C lowering with PCSK9i
- New lipid lowering therapies

Case presentation

- 1996
  - 56 yr old man
  - Post-MI
  - PTCA to LAD
  - Hypertension
    - ENALAPRIL 10mg*2
  - BMI 26
  - HBA1C 5.4
  - Hypercholesterolemia
    - SIMVASTATIN 40mg*1→ CERIVASTATIN 0.4*1

- TC – 231 → 189
- LDL-C – 157 → 118
- HDL-C – 43 → 41
- TG – 157 → 150

Case presentation (cont)

- 2007
- 67 yr old man
- Recently had ACS and CABG
- Hypertension
  - TRITACE 5*1
- BMI 28
  - HBA1C 5.7
  - Hypercholesterolemia
    - ATORVASTATIN 40mg*1 → ATORVASTATIN 80mg*1 + EZETIMIBE 10*1

- TC – 171 → 150
- LDL-C – 102 → 83
- HDL-C – 40 → 39
- TG – 145 → 139

Case presentation (cont)

- 2018
- 78 yr old man
- Rt carotid artery stenosis 95%
- Hypertension
  - TRITACE COMP 5/25*1
  - NORVASC 5*1
- BMI 27.5
  - HBA1C 5.8
  - Hypercholesterolemia
    - ATORVASTATIN 80mg*1 & EZETIMIBE 10mg*1 → + EVOLOCUMAB 140 MG/2M

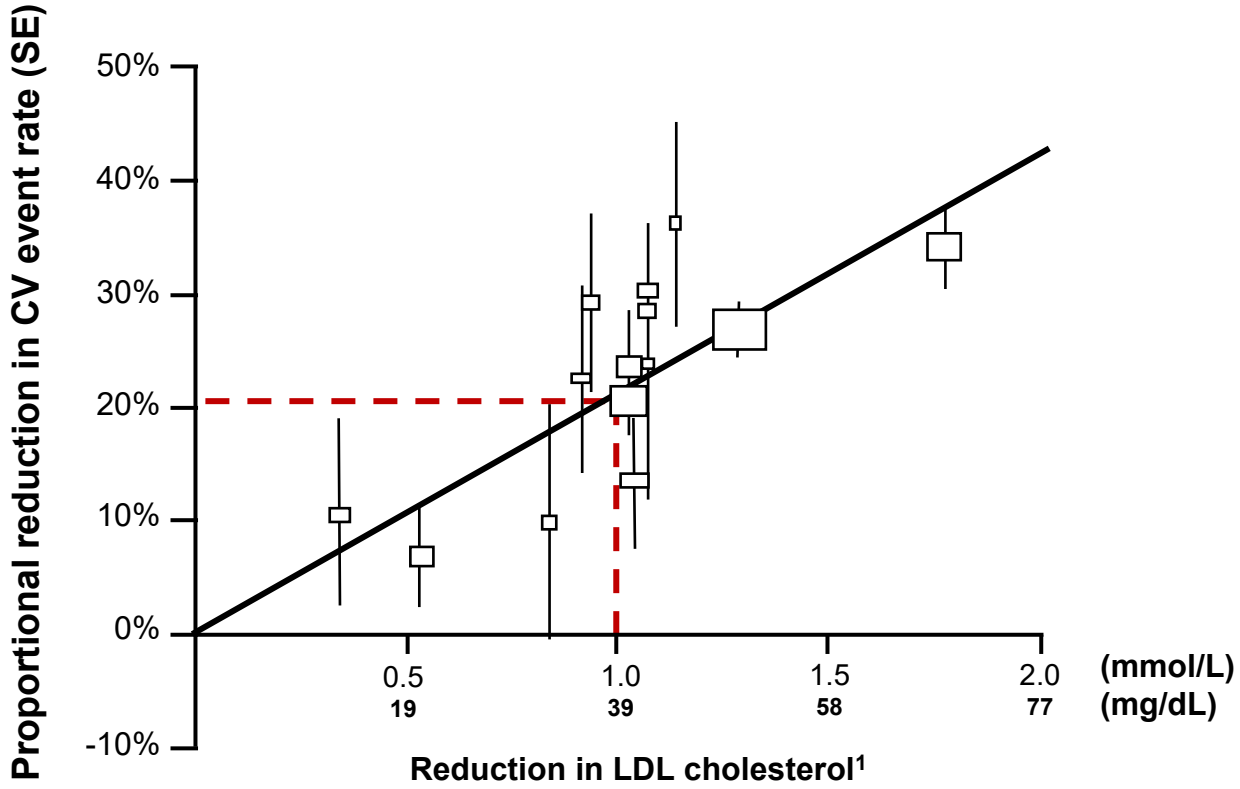
Stenosis regression: 75%, 55%

- TC – 141 → 115 mg/dl
- LDL-C – 79 → 51 mg/dl
- HDL-C – 35 → 36 mg/dl
- TG – 135 → 139 mg/dl
- Non-HDL – 110 → 79 mg/dl
- Apo B100 – 80 → 62 mg/dl
- Lp(a) – 120 mg/dl → 92 mg/dl

CTT line - linear relationship between LDL-C levels and major CV events[1,2]

The Cholesterol Treatment Trialists'(CTT) meta-analysis of 26 studies suggest a linear relationship between LDL-C lowering with statins and CV risk reduction[2]

For every ~40mg/dL reduction in LDL-C, there was a 22% reduction in major CV events at 1 year[2]



Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 26 randomized trials of statins.
Major CV events included myocardial infarction, coronary death, and fatal or non-fatal stroke.

Cholesterol Treatment Trialists' (CTT) Collaborators. *Lancet.* 2005; Cholesterol Treatment Trialists' (CTT) Collaboration. *Lancet*. 2010

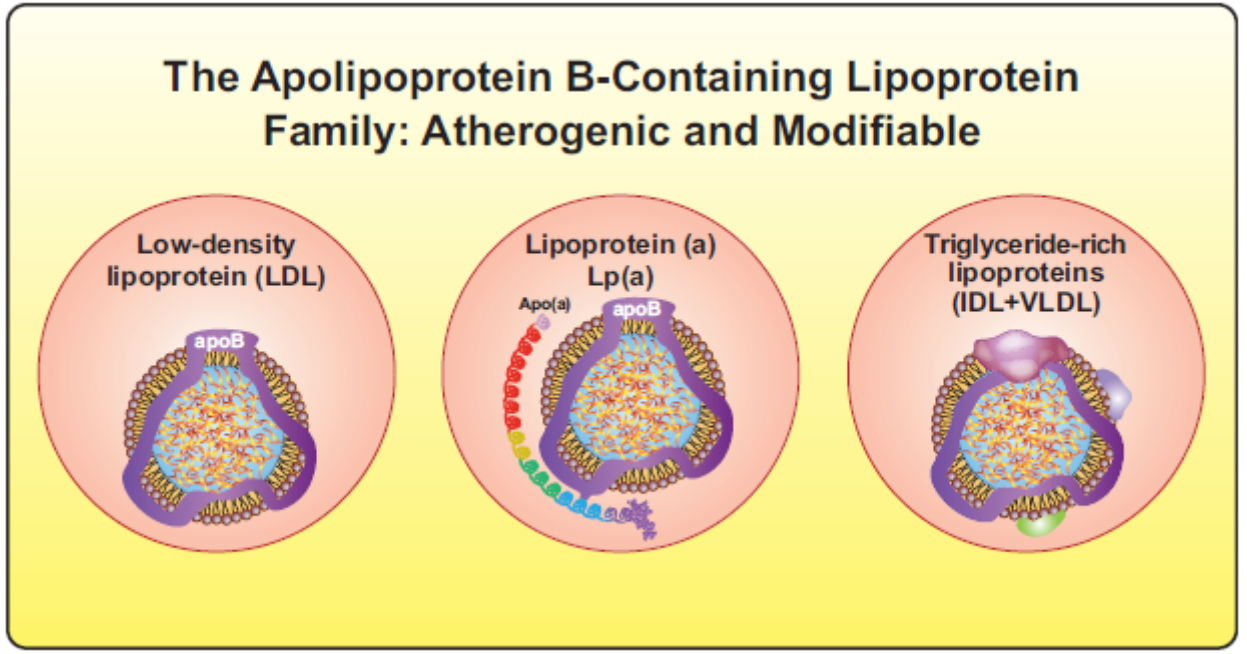
Evidence for efficacy of LDL-lowering therapies down to below 1.4 mmol/L (55 mg/dL)

Source of evidence	Mean reduction in LDL cholesterol; mmol/L [mg/dL]	Outcome	RR (95% CI)
CTT meta-analysis[1] (high-intensity vs standard statin; subgroup <2.0 mmol/L)	1.71 [66] vs 1.32 [50]	MI, CHD death, stroke, coronary revasc.	0.71 (0.56-0.91) [per mmol/L]
IMPROVE-IT[2] (eze plus statin vs statin)	1.55 [70] vs 1.40 [54]	CV death, MI, stroke, UA, coronary revasc	0.94 (0.89-0.99)
FOURIER[3] (evolocumab plus high-dose statin ± eze vs high-dose statin ± eze)	2.37 [92] vs 0.78 [30]	CV death, MI, stroke, UA, coronary revasc	0.85 (0.79-0.92)
ODYSSEY OUTCOMES[4] (alirocumab plus high-dose statin ± eze vs high-dose statin ± eze)	2.37 [92] vs 1.37 [53]	MI, CHD death, stroke, UA	0.85 (0.78-0.93)

[1.] Lancet 2010; 376: 1670-81; [2.] NEJM 2015; 372: 2387-97; [3.] NEJM 2017; 376: 1713-22; [4.] NEJM 2018; 379: 2097-107

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019)

New targets for lipid-lowering therapies



European Heart Journal, 2022

Harefuah. 2021 Jan;160(1):38-44

טבלה מס' 7 - יעדי הטיפול של LDLc

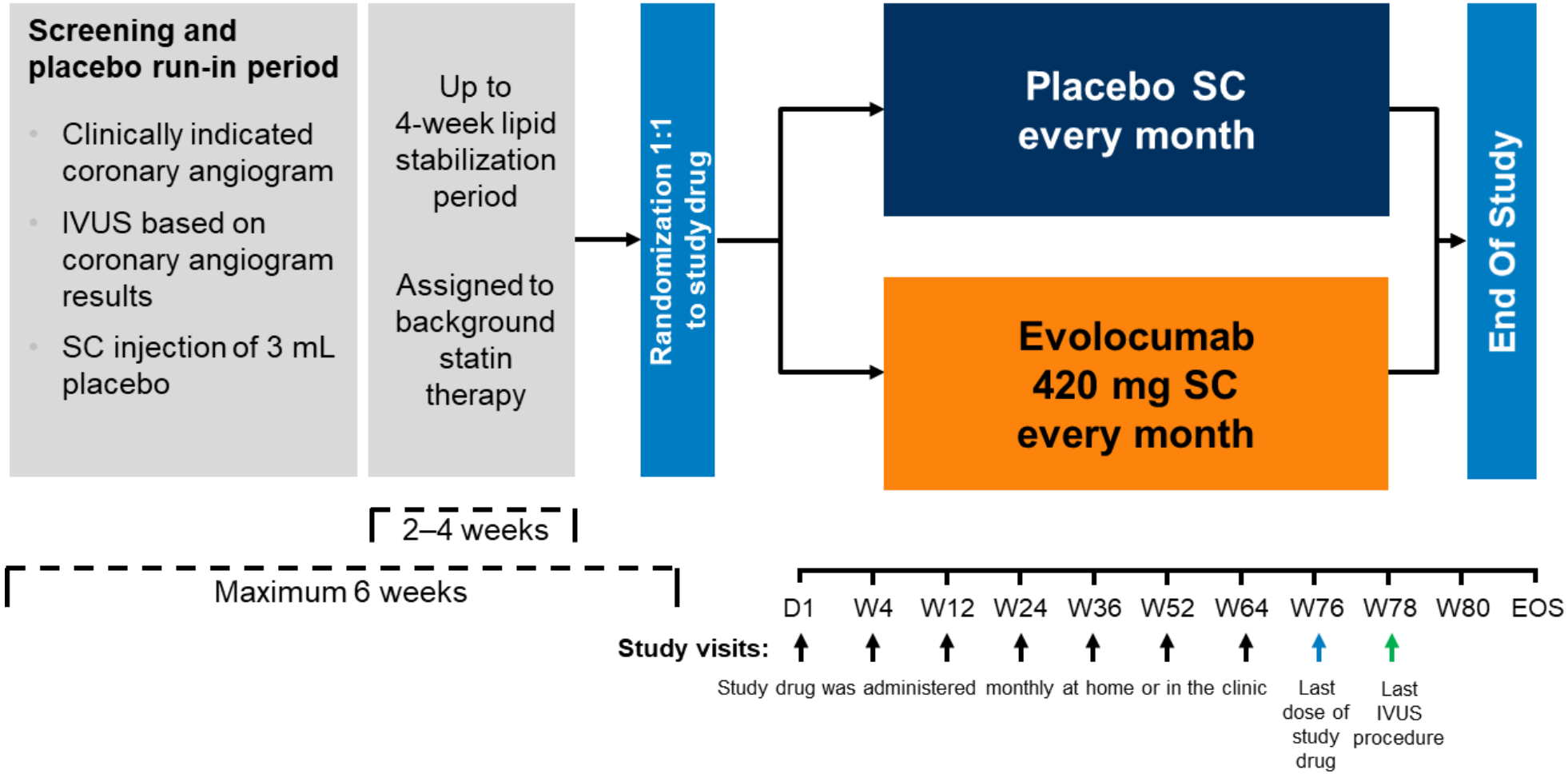
חוזק הוכחה	חוזק המלצה	יעדי טיפול (מ"ג/ד"ל)			% ירידה	דרגת הסיכון לתמותה ב-10 שנים
		apoB	non-HDLc	LDLc		
B	IIb	≤ 130	≤ 170	≤ 140		**נמוכה** [1] • SCORE < 1%
A	IIb	≤ 100	≤ 130	≤ 100		**בינונית** [1] • SCORE 1%-5% • חולי סוכרת צעירים עם משך סוכרת יחסית קצר וללא גורמי סיכון נוספים
A	I	≤ 80	≤ 100	≤ 70	> 50%	**גבוהה** • SCORE 5%-10% • נוכחות גורם סיכון ברמה גבוהה במיוחד • היפרכולסטרולמיה משפחתית ללא גורם סיכון נוסף • סוכרת מעל 10 שנים ו/או עם גורם סיכון נוסף אך ללא פגיעה באיבר מטרה • מחלת כליות כרונית דרגה 3
A	I	≤ 80	≤ 100	≤ 70	> 50%	**גבוהה מאוד** - מניעה ראשונית • SCORE > 10% • סוכרת עם פגיעה באיבר מטרה ו/או 3 גורמי סיכון • סוכרת מסוג I מגיל צעיר עם משך > 20 שנה • מחלת כליות כרונית דרגה 4 • היפרכולסטרולמיה משפחתית עם גורמי סיכון נוספים
B	IIb	≤ 65	≤ 85	≤ 55		
A	I	≤ 65	≤ 85	≤ 55	> 50%	**גבוהה מאוד** - מניעה שניונית • עדות ל-ASCVD (קליני או לפי אמצעי הדמייה)
B	IIb	≤ 50	≤70	≤ 40	> 50%	**גבוהה במיוחד** • חולים עם ASCVD שעברו אירוע וסקולרי נוסף תוך שנתיים למרות טיפול במינון מקסימלי נסבל של סטטין

More stable plaque features were observed within non-obstructive atheromas in patients with very low LDL-C levels on statin treatment

	LDL-C <50 mg/dL (87 plaques)	LDL-C 50–70 mg/dL (81 plaques)	LDL-C 70–100 mg/dL (117 plaques)	LDL-C >100 mg/dL (130 plaques)	*P*
Plaque Microstructures at Lipid Plaques (n=293)					
Fibrous cap thickness (μm)	139.9±93.9	103.1±66.4	92.5±48.5	92.1±47.8	0.001
Plaque rupture, n (%)	1/42 (2.3)	2/46 (4.3)	7/91 (7.6)	12/114 (10.5)	0.17
Thrombus, n (%)	0/42 (0.0)	1/46 (2.1)	2/91 (2.1)	3/114 (2.6)	0.18

Atherosclerosis, 2015

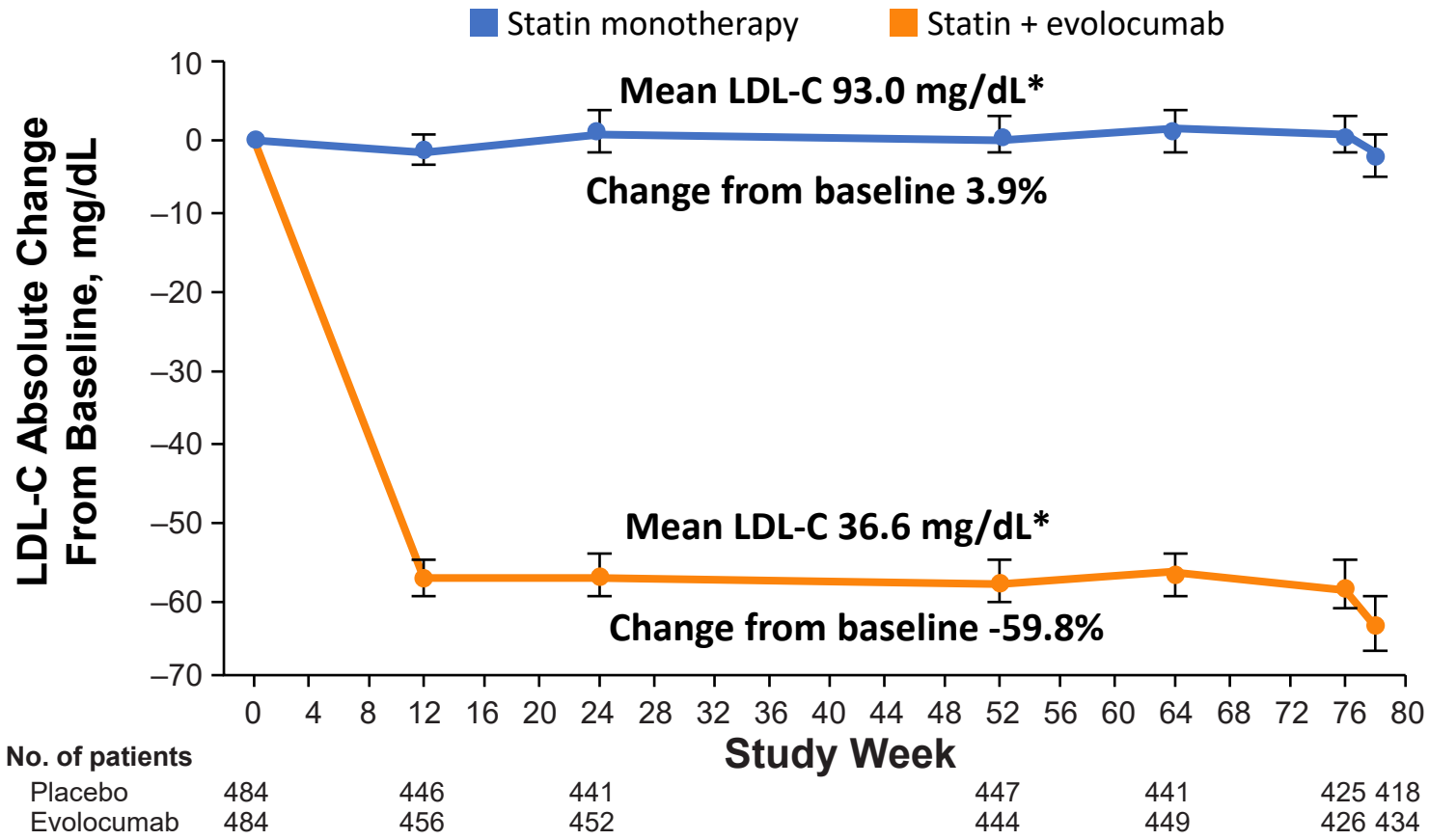
GLAGOV: study design



*Nominal change refers to the actual number, as opposed to percent change
D = day; IVUS = intravascular ultrasound; SC = subcutaneously; W = week.

JAMA, 2016

Mean absolute change in LDL-C

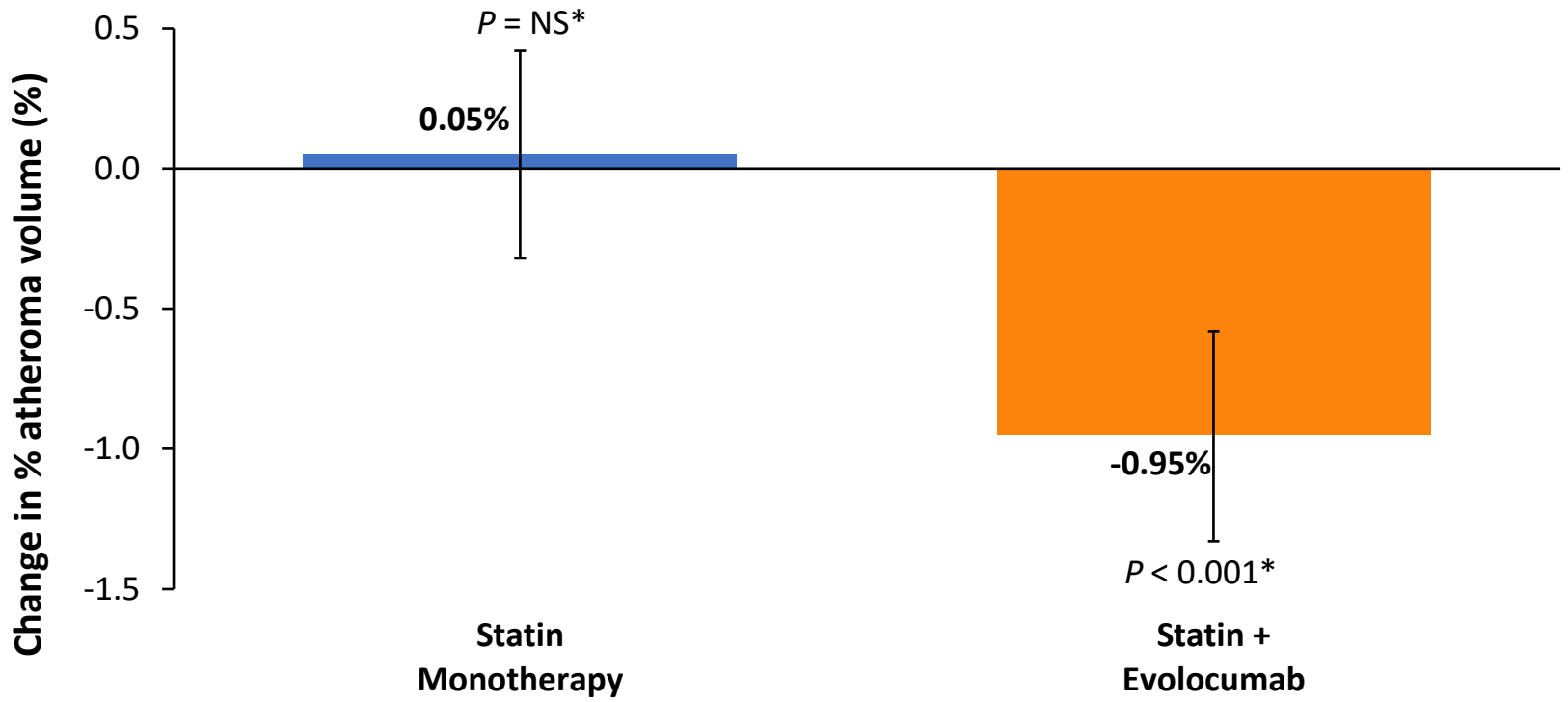


Absolute change for evolocumab-statin group: -56.3 (-59.4 to -53.1); *P* < 0.001

Data shown are Mean (95% CI) *Time-weighted LDL-C; LDL-C = low-density lipoprotein cholesterol

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.
Nissen SE, et al. *American Heart Association Scientific Sessions,* Nov 12 - 16, 2016,
New Orleans, Louisiana. Oral Presentation.

Primary endpoint: nominal change in percent atheroma volume (PAV) from baseline to week 78

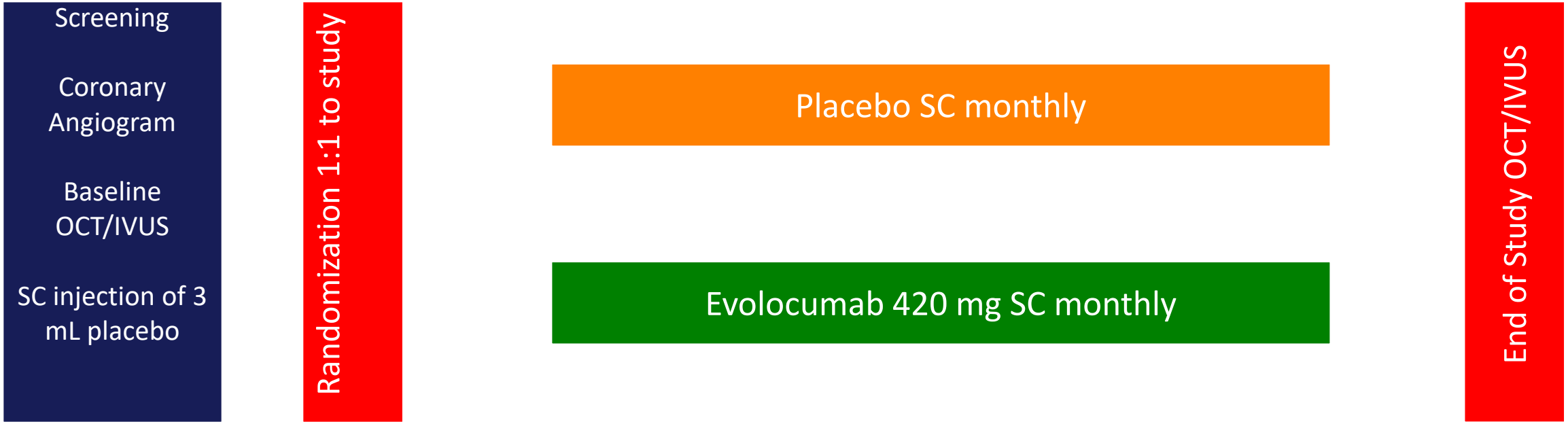


Difference between groups: -1.0% (-1.8 to -0.64); *P* < 0.001

Data shown are least-squares mean (95% CI). PAV = Percent Atheroma Volume
*Comparison versus baseline
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

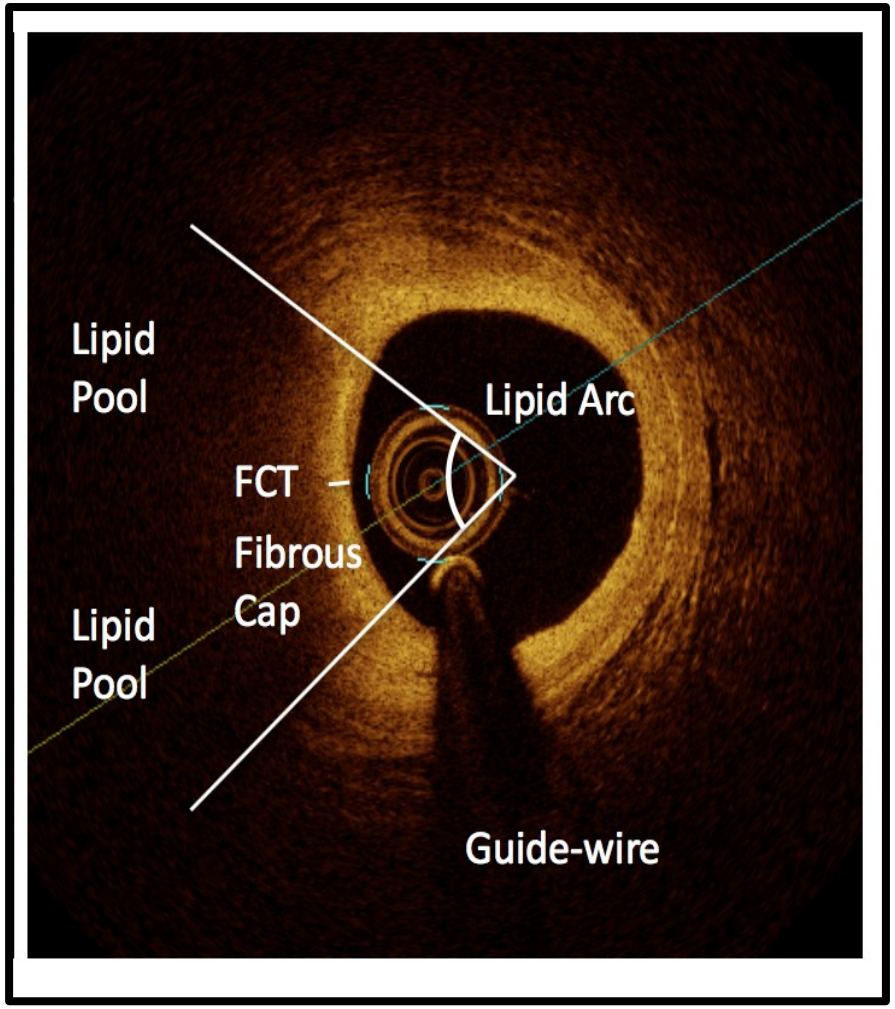
HUYGENS design

161 patients with (i) **NSTEMI**, (ii) angiographic CAD 20-50% stenosis in a target vessel, (iii) LDL-C ≥60 mg/dL on high-intensity, ≥80 mg/dL on low/moderate-intensity or ≥130 mg/dL on no statin at screening, (iv) subsequently treated with maximally tolerated statin and (v) target segment on intracoronary optical coherence tomography (OCT) containing at least one image with a FCT <120 µm and one image with lipid arc >90°



JACC, 2022

Imaging Analysis



- **Primary endpoint: change in minimum FCT anywhere in the segment**
- Secondary endpoints
  - Percent change in minimum FCT
  - Change in average minimum FCT
  - Change in maximum lipid arc
- Plaque analysis: regions containing FCT ≤120μm and lipid arc >90° for ≥3 consecutive images

JACC, 2022

Baseline Demographics and Statin Usage

Characteristic	Placebo (N=81)	Evolocumab (N=80)
Age	60.2	60.9
Male Gender	67.9%	75.0%
BMI kg/m^2	28.0	28.2
Diabetes	17.3%	16.3%
Smoking	59.3%	58.8%
Prior statin use >4 weeks	24.4%	23.2%
Statin use in trial	96.3%	93.8%
High intensity	82.7%	78.8%
Moderate intensity	13.6%	13.8%
Low intensity	0%	1.3%

JACC, 2022

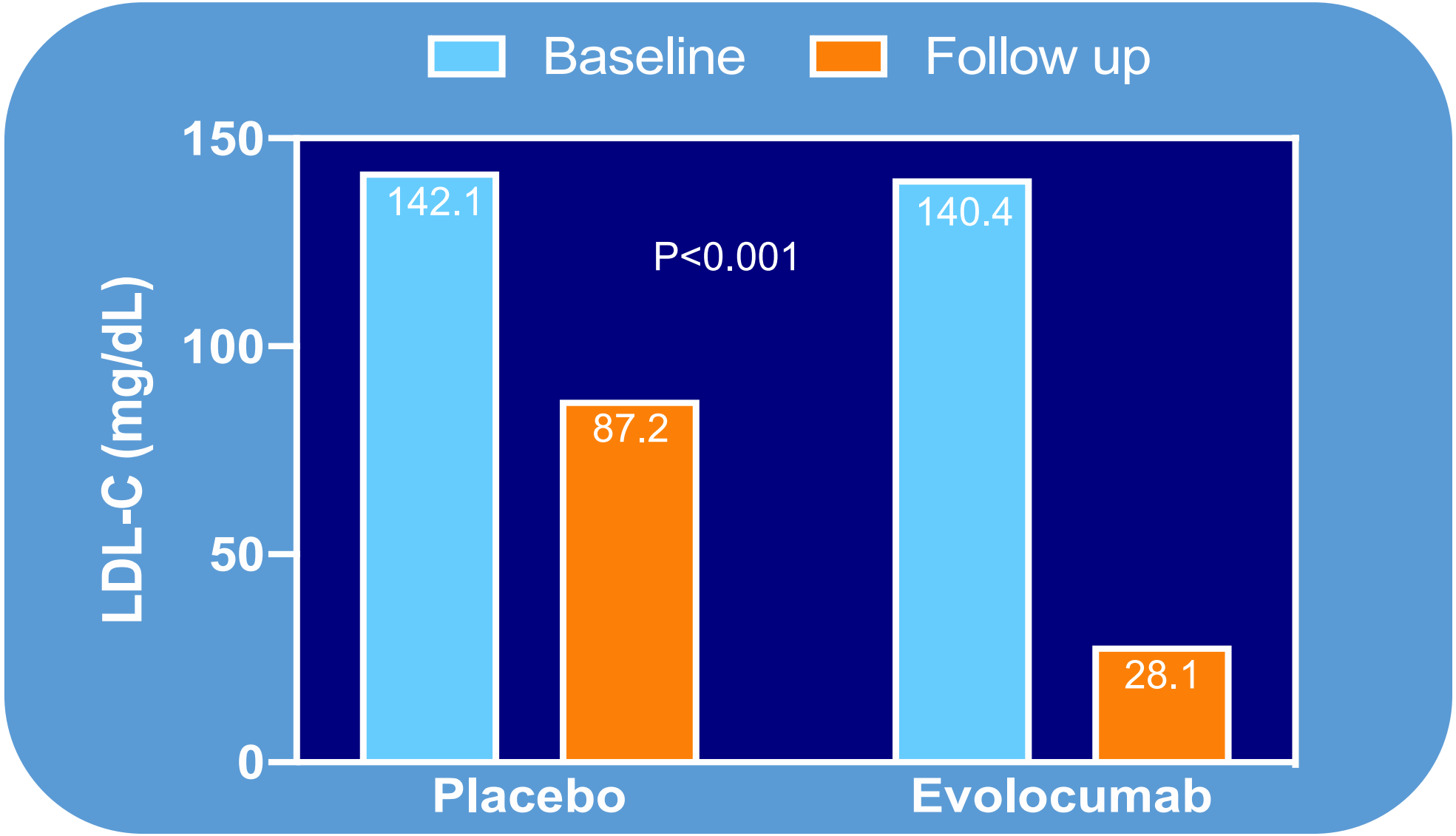
Baseline OCT Measures

	Placebo (n=81)	Evolocumab (n=80)
Minimum FCT (μm)	54.6	56.6
Average min FCT (μm)	133.6	142.3
Maximum lipid arc (°)	224.8	230.2
FCT <65um	71.6%	77.5%
Lipid rich plaque*	91%	90%

*lipid rich plaque defined as 3 consecutive images containing FCT ≤120μm and lipid arc >90°

JACC, 2022

LDL cholesterol



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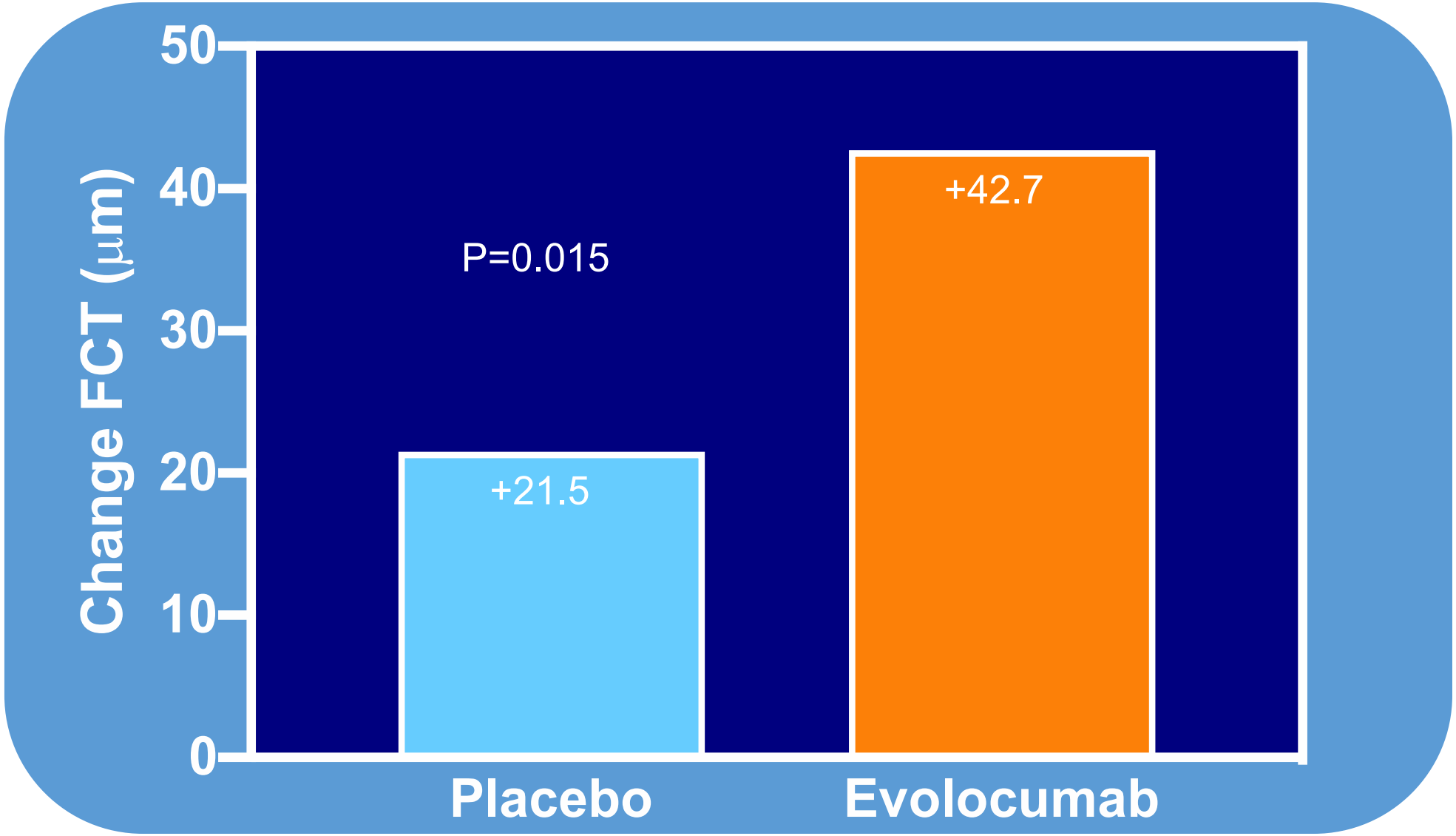
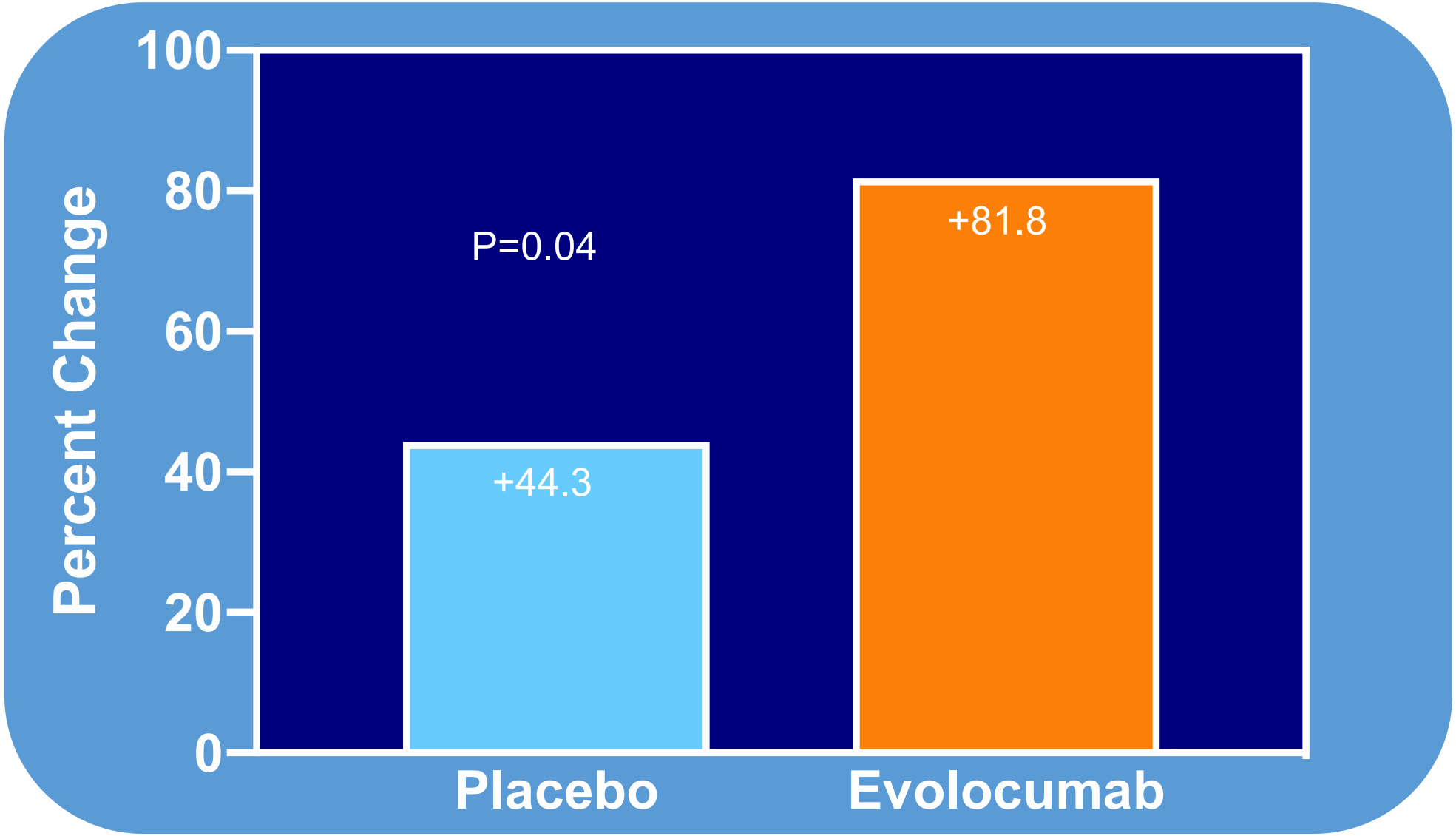
HUYGENS primary endpoint: minimum fibrous cap thickness (FCT)



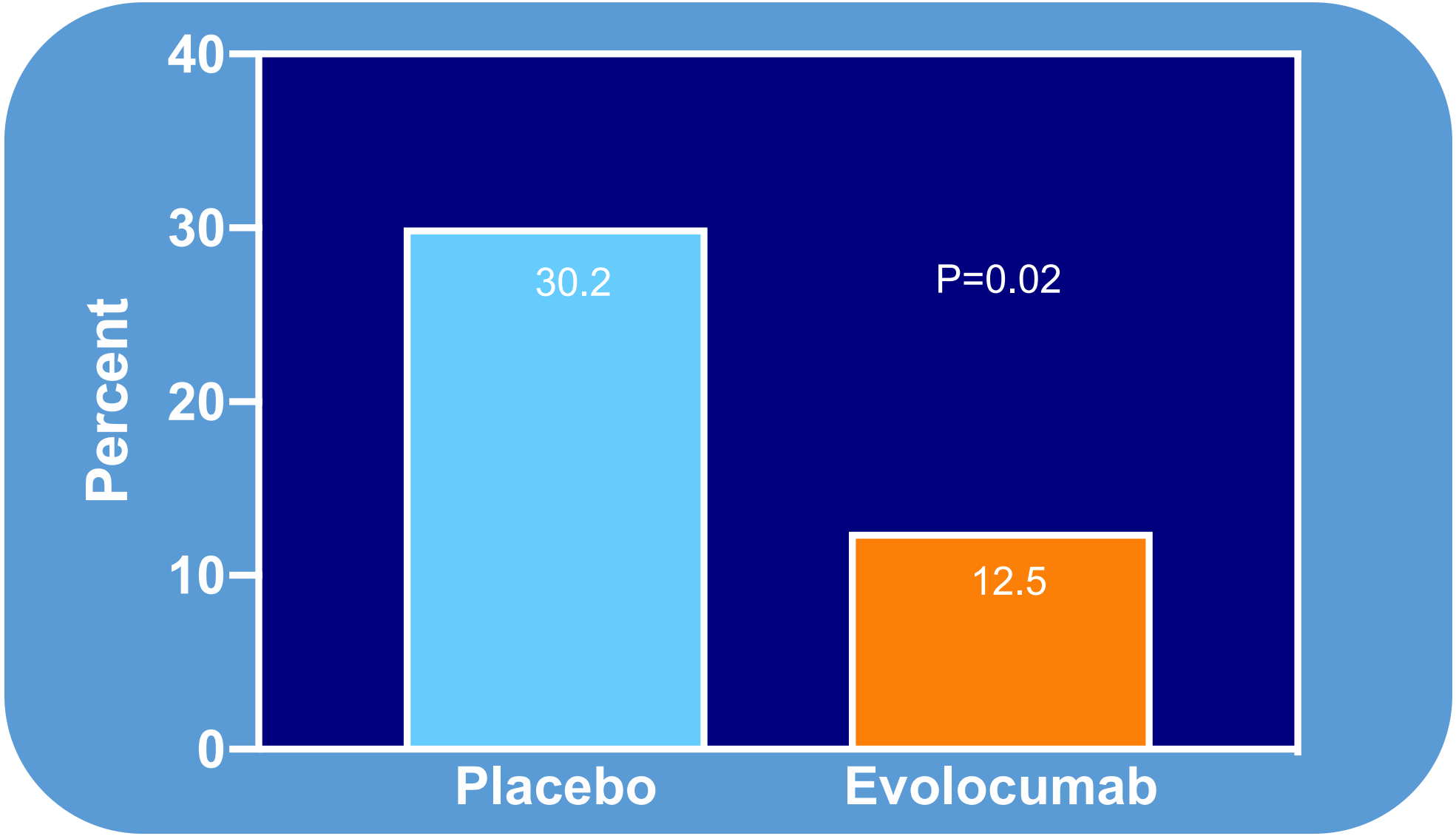
JACC, 2022

HUYGENS secondary endpoint: percent change minimum fibrous cap thickness



JACC, 2022

HUYGENS exploratory endpoint: patients with minimum FCT <65 µm



JACC, 2022

Analysis of regions containing lipid-rich plaque placebo vs evolocumab

- ↓in the maximum lipid arc
  - -31.9 vs -61.9 (P<0.02)
- ↓in the lipid lengs
  - -3.3 vs -5.8 mm (P<0.02)

JACC, 2022

JAMA®

Lorenz Räber, MD, PhD; Yasushi Ueki, MD, PhD; Tatsuhiko Otsuka, MD; Sylvain Losdat, PhD; Jonas D. Häner, MD; Jacob Lonborg, MD; Gregor Fahrni, MD; Juan F. Iglesias, MD; Robert-Jan van Geuns, MD, PhD; Anna S. Ondracek, MSc; Maria D. Radu Juul Jensen, MD, PhD; Christian Zanchin, MD, PhD; Stefan Stortecky, MD; David Spirk, MD; George C. M. Siontis, MD, PhD; Lanja Saleh, PhD; Christian M. Matter, MD; Joost Daemen, MD, PhD; François Mach, MD; Dik Heg, PhD; Stephan Windecker, MD; Thomas Engstrøm, MD, PhD; Irene M. Lang, MD; Konstantinos C. Koskinas, MD, MSc; for the PACMAN-AMI collaborators

Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction
The PACMAN-AMI Randomized Clinical Trial

Published April 3, 2022

Available at jama.com

Patients with AMI (N-STEMI/STEMI) undergoing coronary angiography & successful PCI of the infarct vessel & 2 non-infarct related arteries with non-obstructive lesions

Alirocumab PACMANAMI

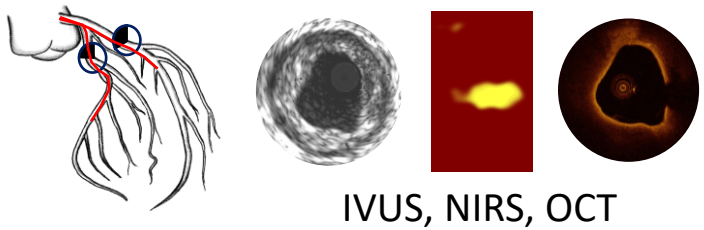
POC

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

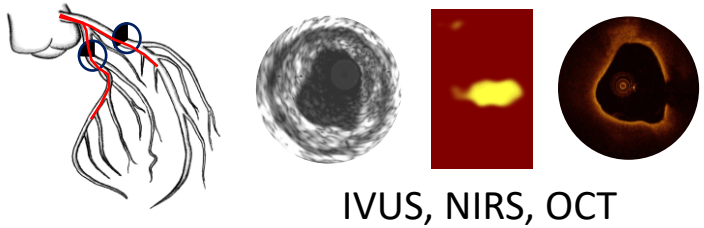
Alirocumab s.c. 150 mg / 2 weeks + Rosuvastatin 20 mg

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

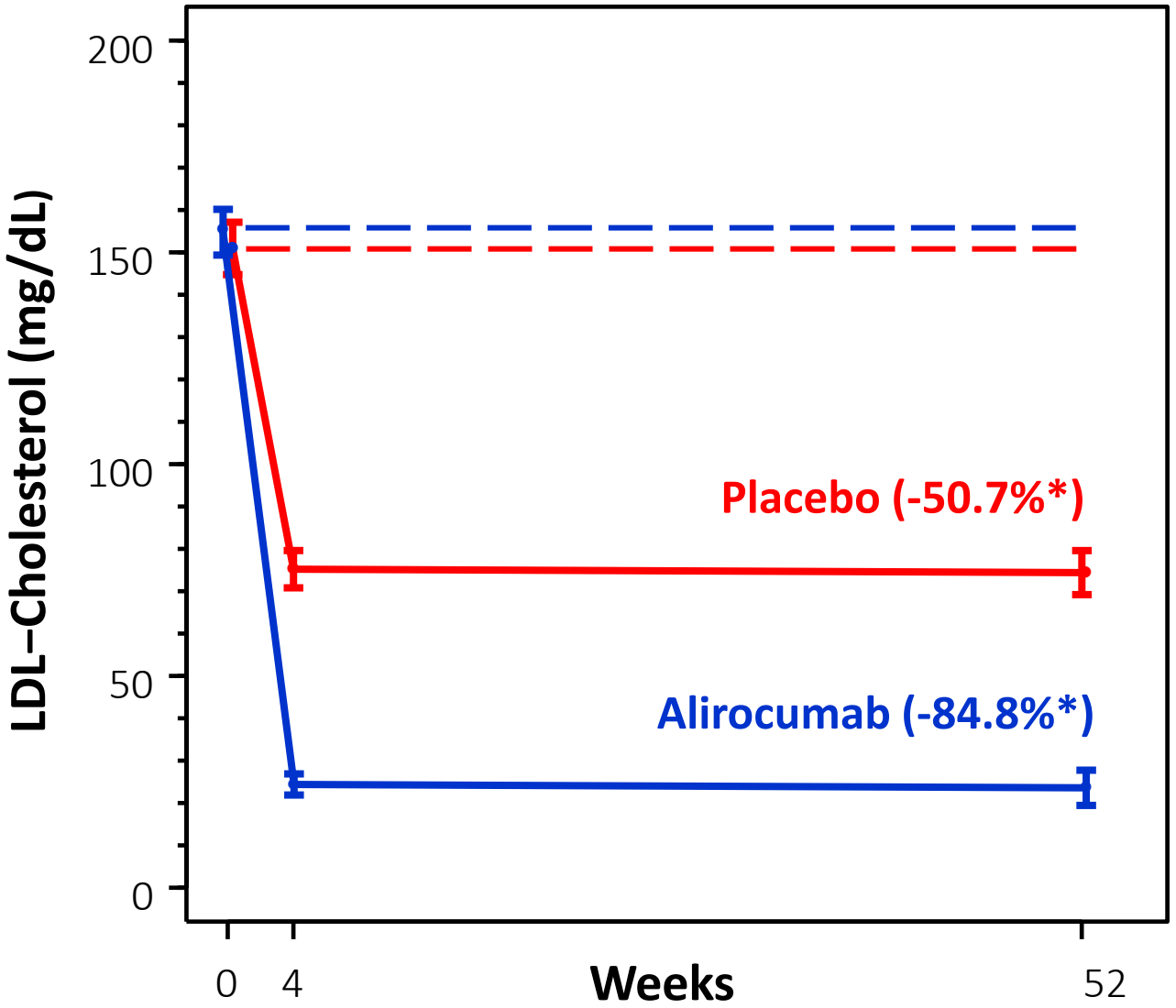
NIRS, Near Infrared Spectroscopy ; OCT, Optical Coherence Tomography)

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

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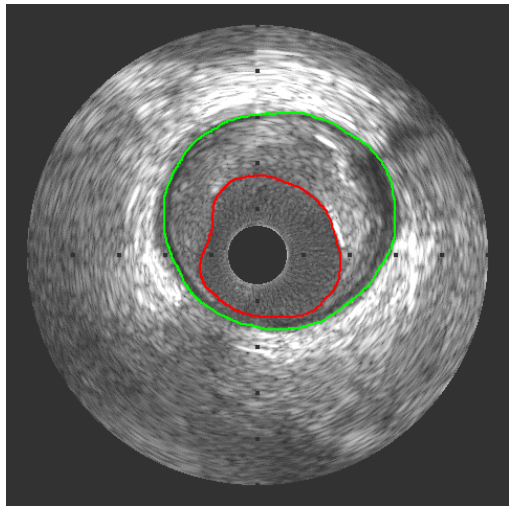
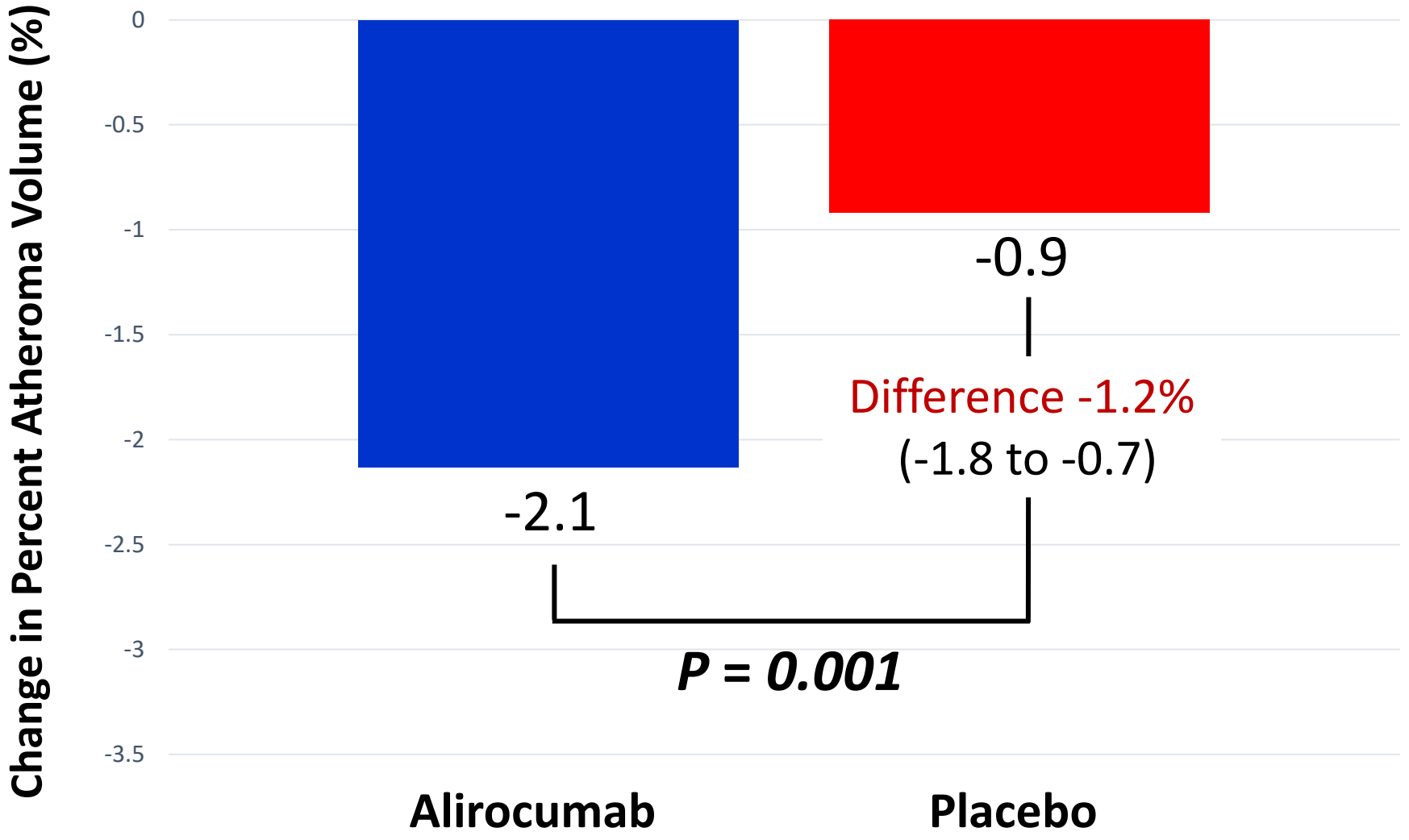
Change in Percent Atheroma Volume (IVUS)





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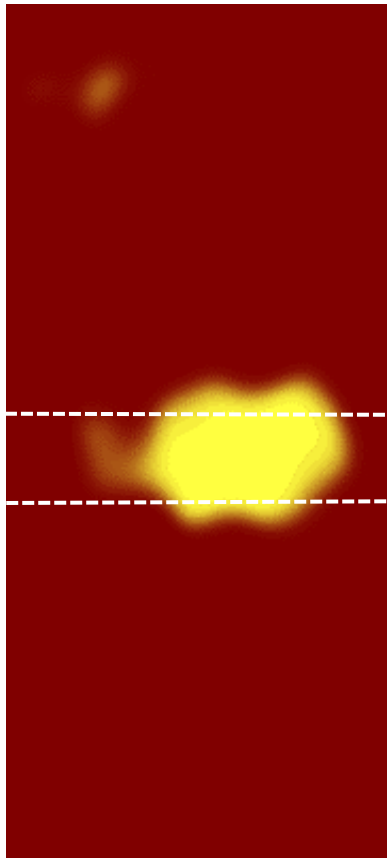
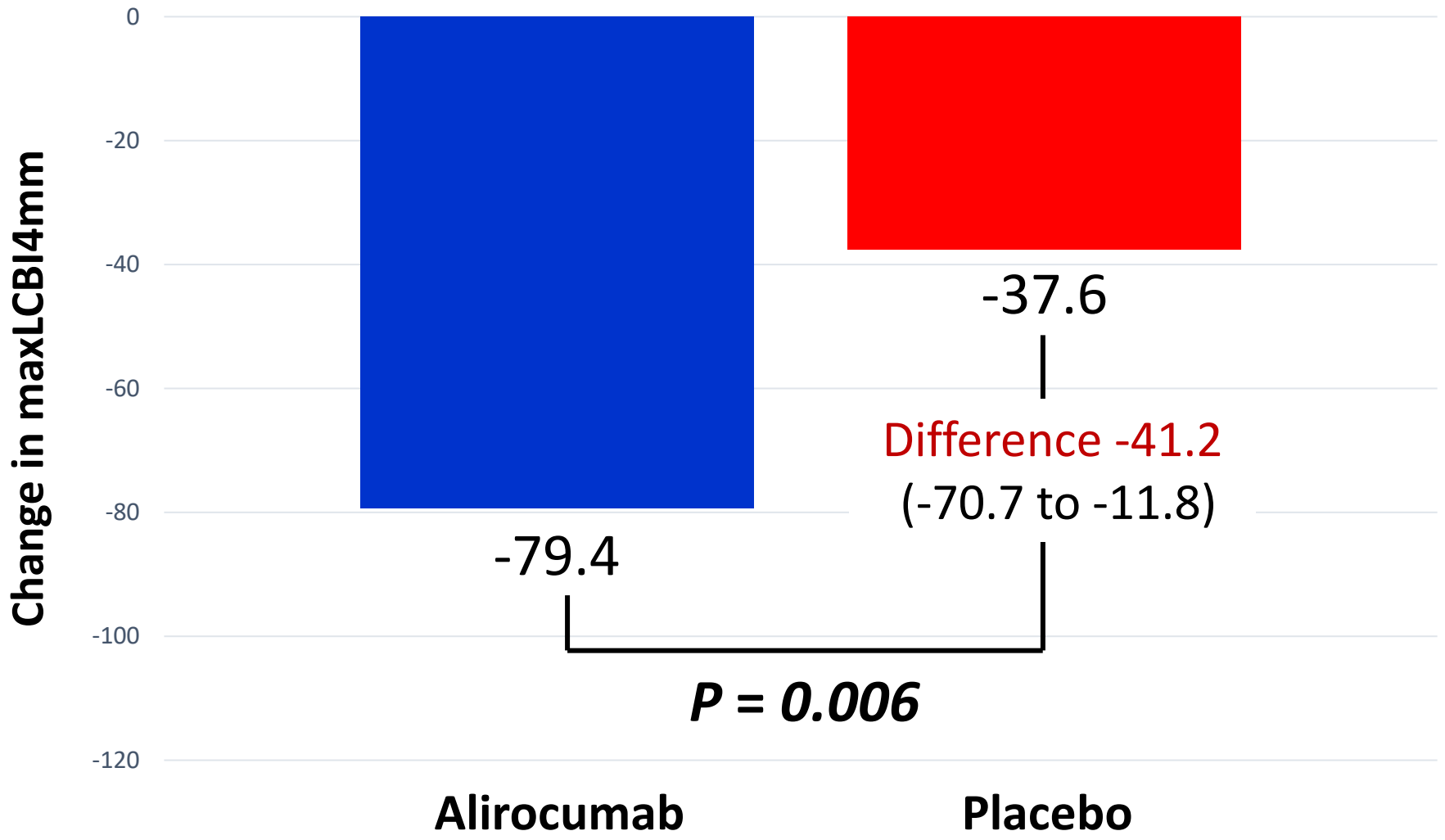
Powered Secondary EP:

Change in maxLCBI$_{4mm}$ (Near Infrared Spectroscopy, NIRS)

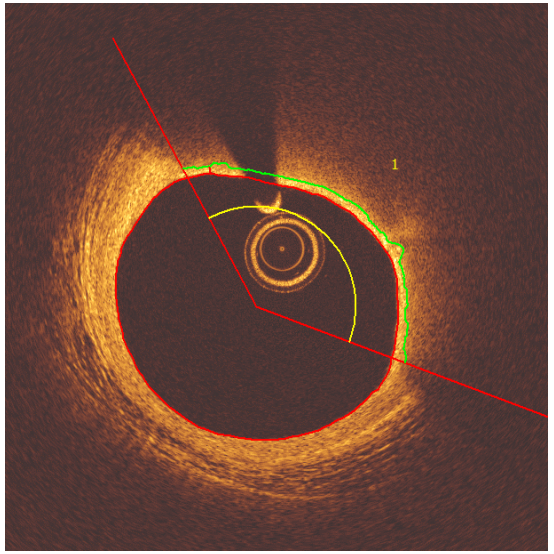


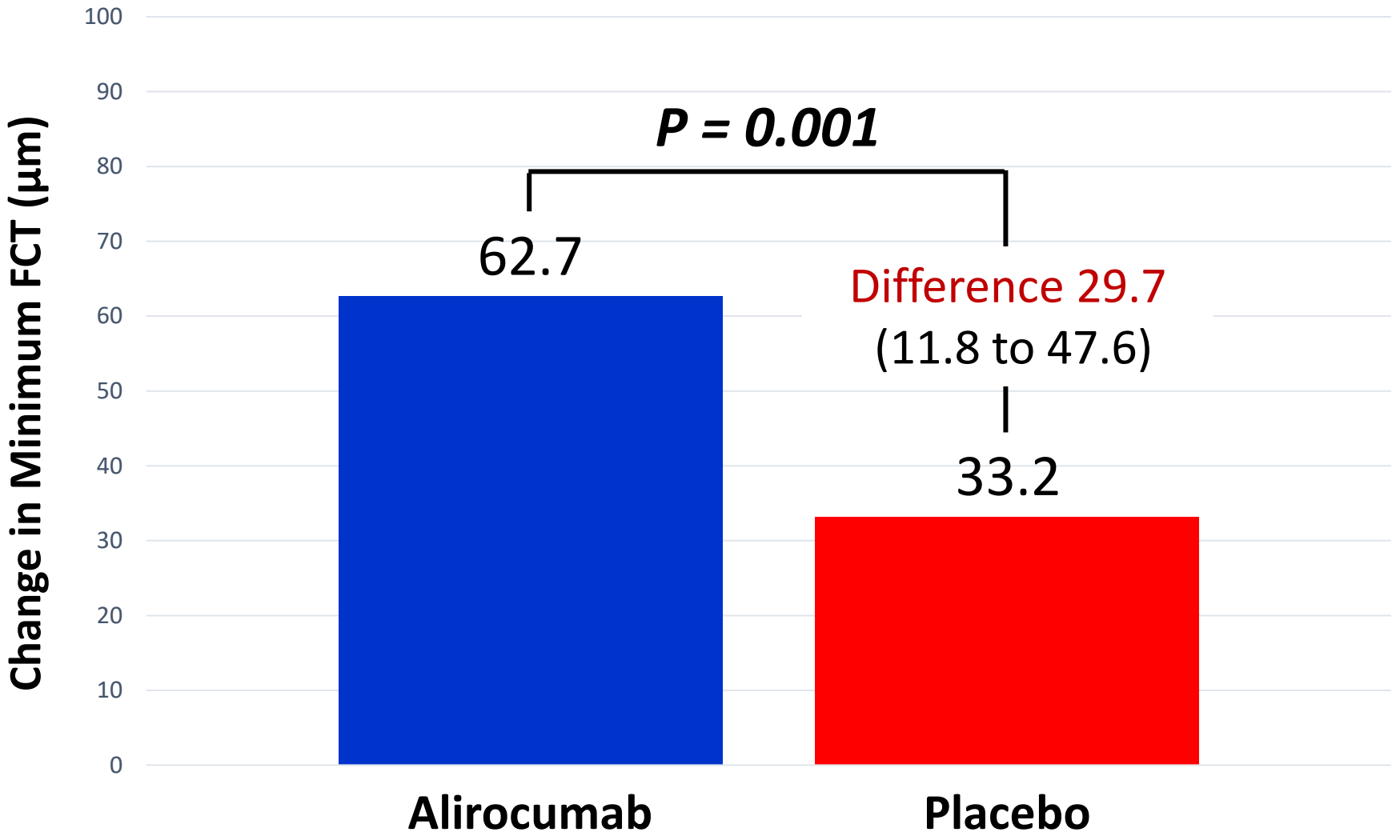


JAMA, 2022

Powered Secondary EP:

Change in minimum fibrous cap thickness (FCT) by Optical Coherence Tomography





JAMA, 2022

Prespecified Clinical Events

	Alirocumab (n=147*)	Placebo (n=151*)	P-value
All-cause death	2 (1.4%)	1 (0.7%)	0.55
Myocardial infarction	2 (1.4%)	3 (2.0%)	0.24
Ischemia-driven revascularization of de novo lesions	**7 (4.8%)**	**17 (11%)**	**0.04**
Stroke	0 (0.0%)	1 (0.7%)	1.00

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

JAMA, 2022

Atherosclerosis 327 (2021) 31–38

Contents lists available at ScienceDirect

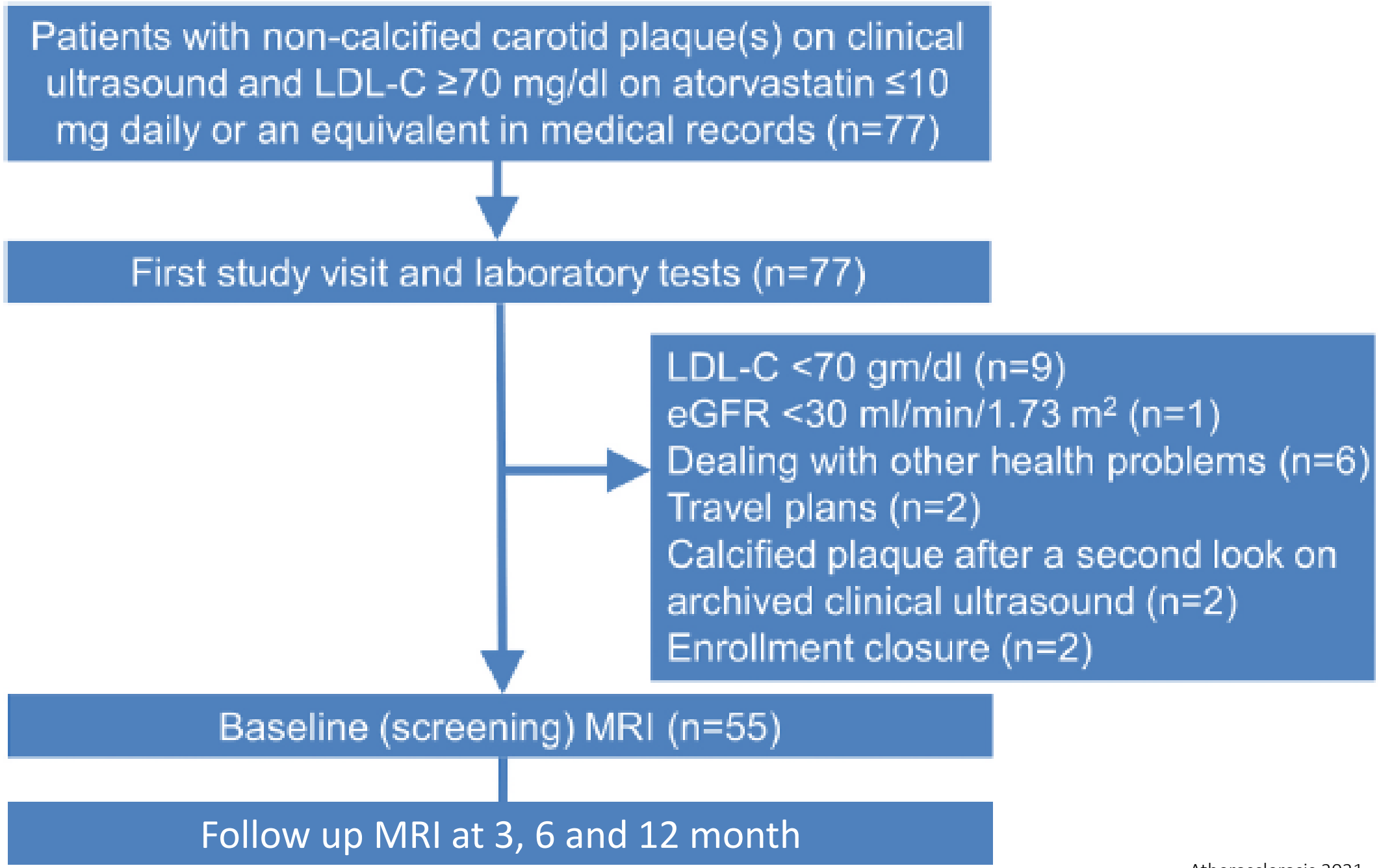
Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

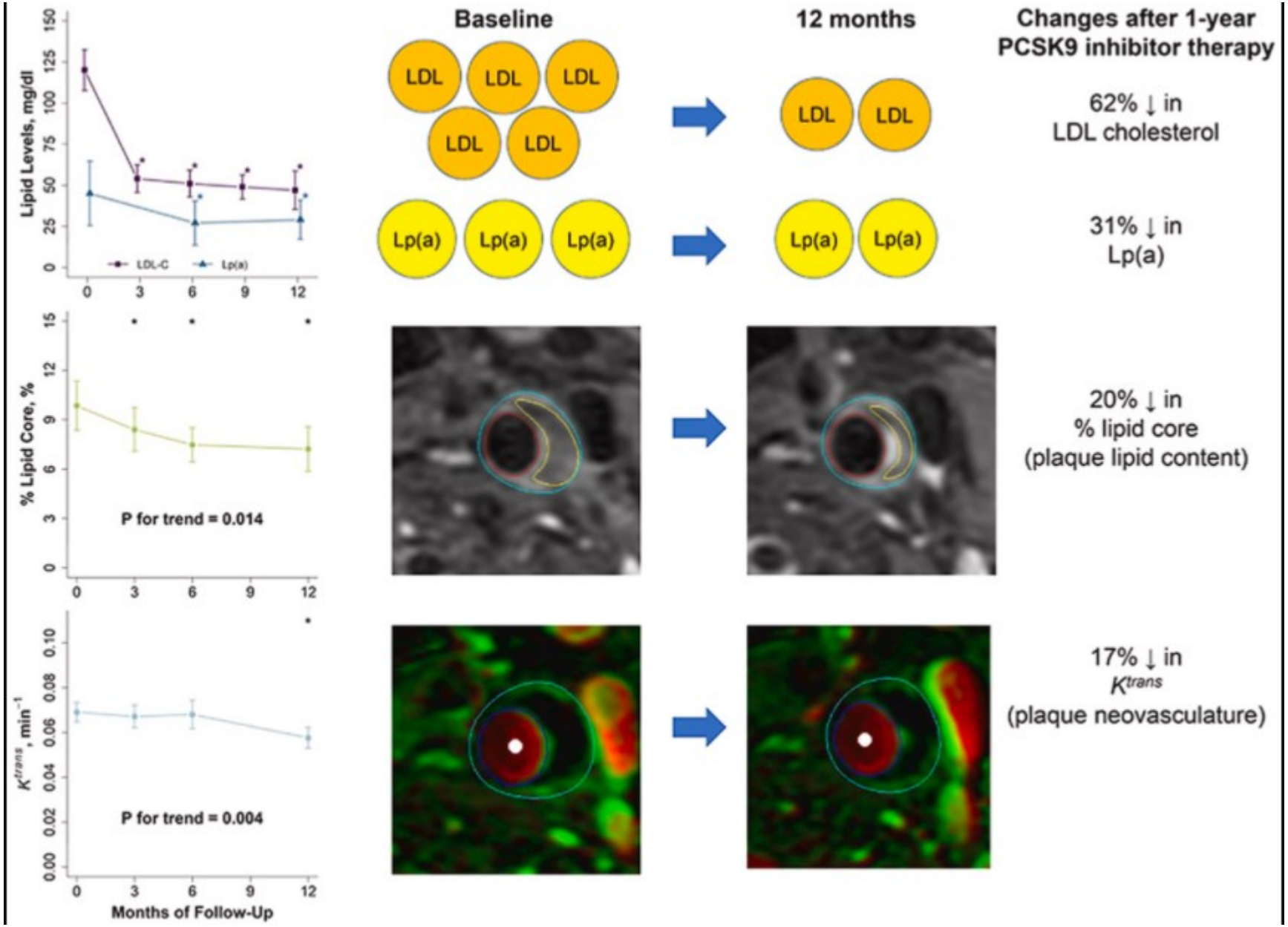
Regression in carotid plaque lipid content and neovasculature with PCSK9 inhibition: A time course study

Norman E. Lepor [a,b,1], Jie Sun [c,*,1], Gador Canton [c], Laurn Contreras [a], Daniel S. Hippe [c], Daniel A. Isquith [c], Niranjan Balu [c], Ilan Kedan [b], Americo A. Simonini [b], Chun Yuan [c], Thomas S. Hatsukami [c], Xue-Qiao Zhao [c]

[a] *Westside Medical Associates of Los Angeles, Beverly Hills, CA, USA*
[b] *Smidt Cedars-Sinai Heart Institute, Los Angeles, CA, USA*
[c] *University of Washington, Seattle, WA, USA*



Atherosclerosis,2021



Atherosclerosis, 2021

Long-Term Evolocumab in Patients with Established Atherosclerotic Cardiovascular Disease:

Primary Results of the FOURIER-OLE (Open-Label Extension) Studies

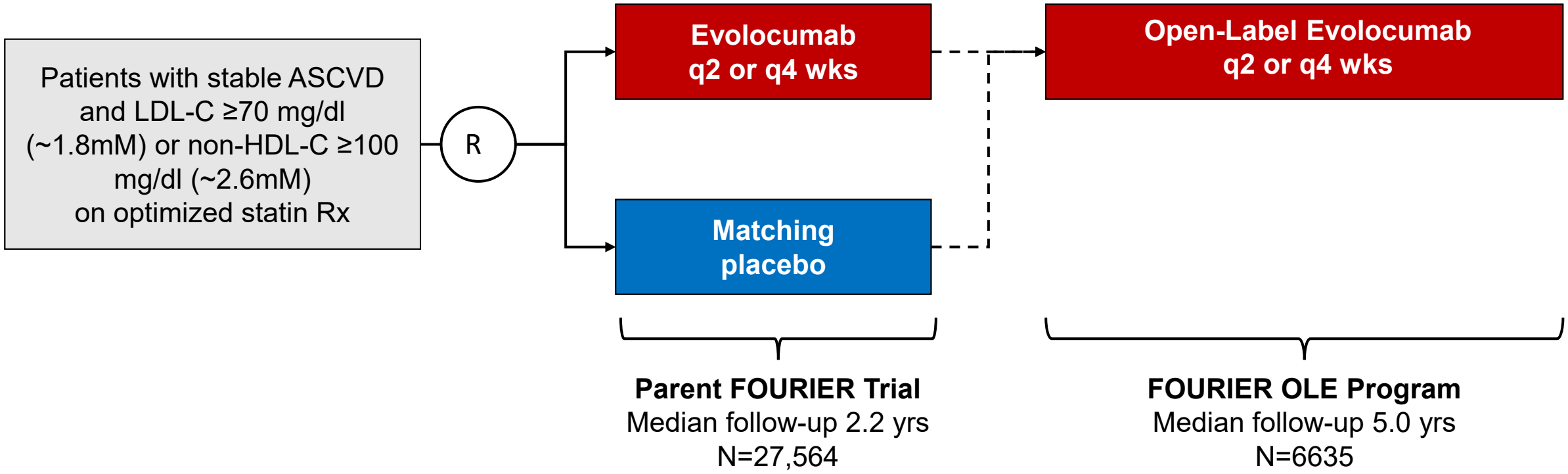
Michelle L. O'Donoghue, Robert P. Giugliano, Sarina Trindade, Dan Atar, Anthony Keech, Julia Kuder, KyungAh Im, Sabina Murphy, Jose H. Flores-Arredondo, J. Antonio G. López, Mary Elliott-Davey, Bei Wang, Maria Laura Monsalvo, Siddique Abbasi, Marc S. Sabatine

On Behalf of the FOURIER-OLE Investigators

AT-REP-0922-00001

This study was funded by Amgen Inc.

Study design



Circulation, 2022

Baseline characteristics of OLE population at randomization

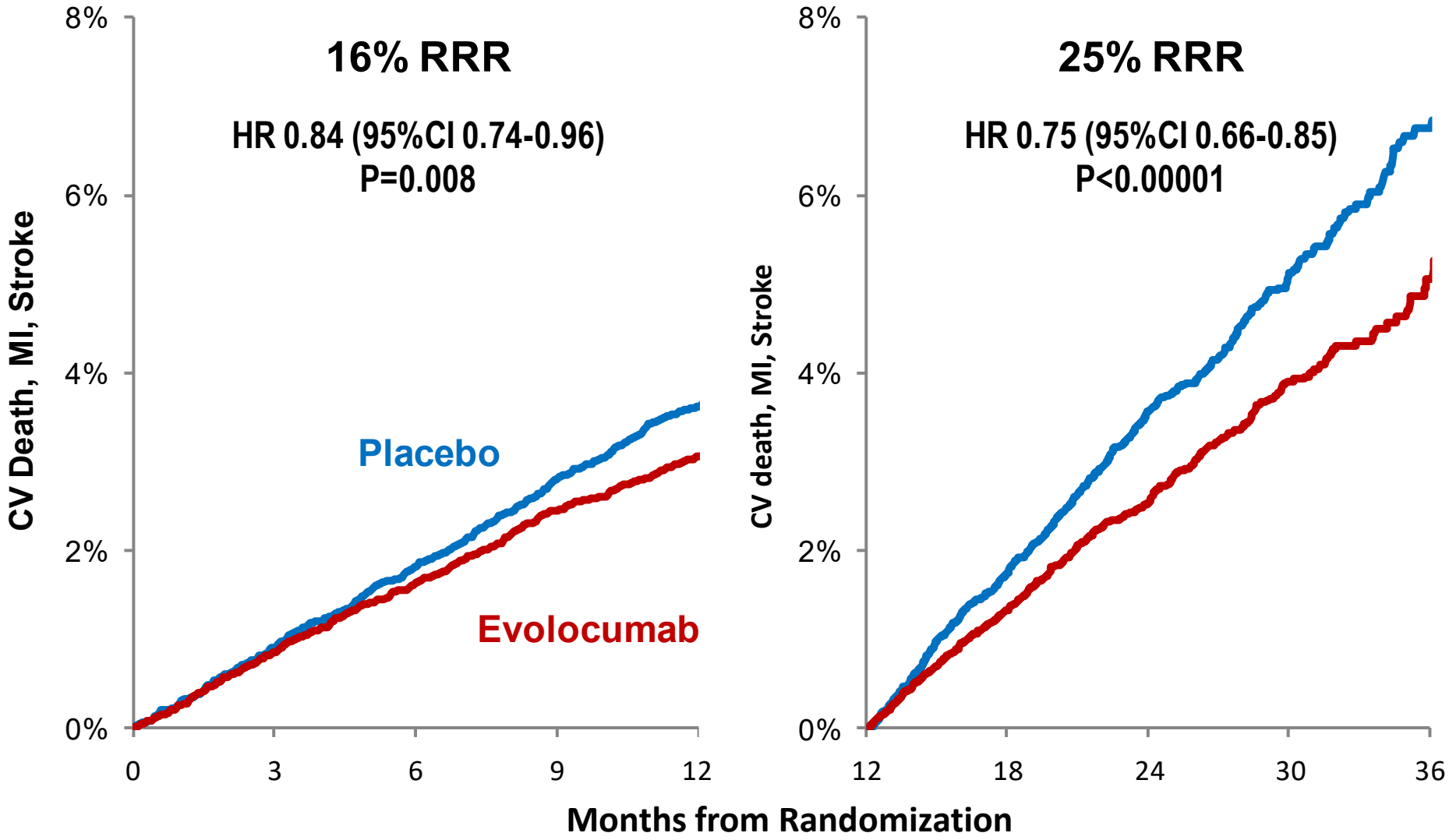
fourier - OLE

		Initial allocation in parent FOURIER trial	
		Placebo (N=3280)	Evolocumab (N=3355)
Demographics	Age (mean, years)	62	62
	Male sex (%)	76	77
	White race (%)	96	95
Region (%)	Europe	66	67
	United States	34	33
Type of athero (%)	Myocardial infarction	84	84
	Non-hemorrhagic stroke	16	16
	Peripheral artery disease	14	15
CV risk factors (%)	Hypertension	85	82
	Diabetes mellitus	35	33
	Current cigarette use	27	26
Meds at time of enrollment in FOURIER (%)	High-intensity statin use	76	77
	Ezetimibe	5.5	6.0
LDL-C at randomization (median, IQR)	mmol/L	2.4 (2.1-2.8)	2.4 (2.1-2.8)
	mg/dl	91 (80-109)	92 (80-108)

All comparisons P>0.05

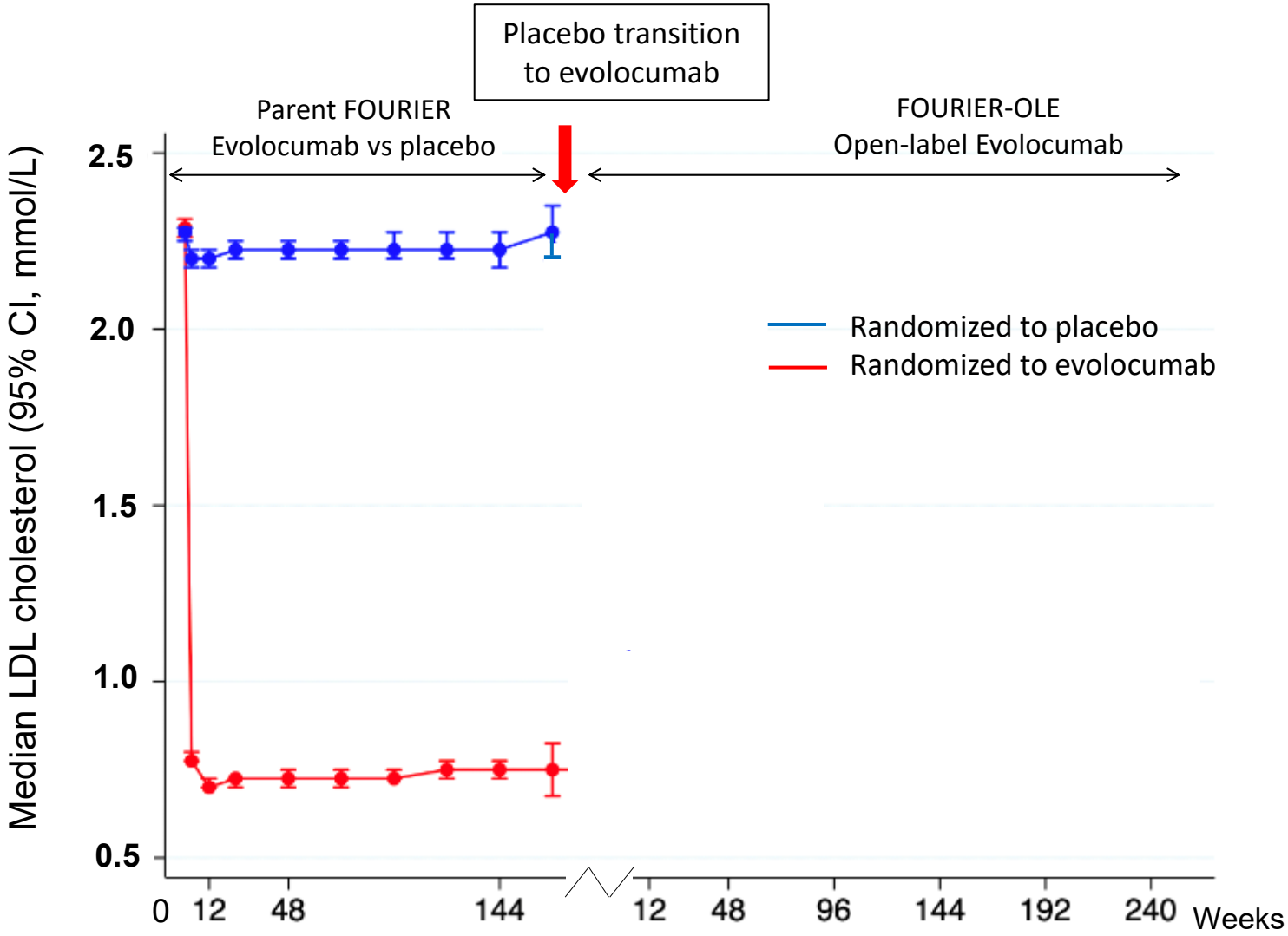
Circulation, 2022

Evolocumab: Evidence of Lag Effect for MACE



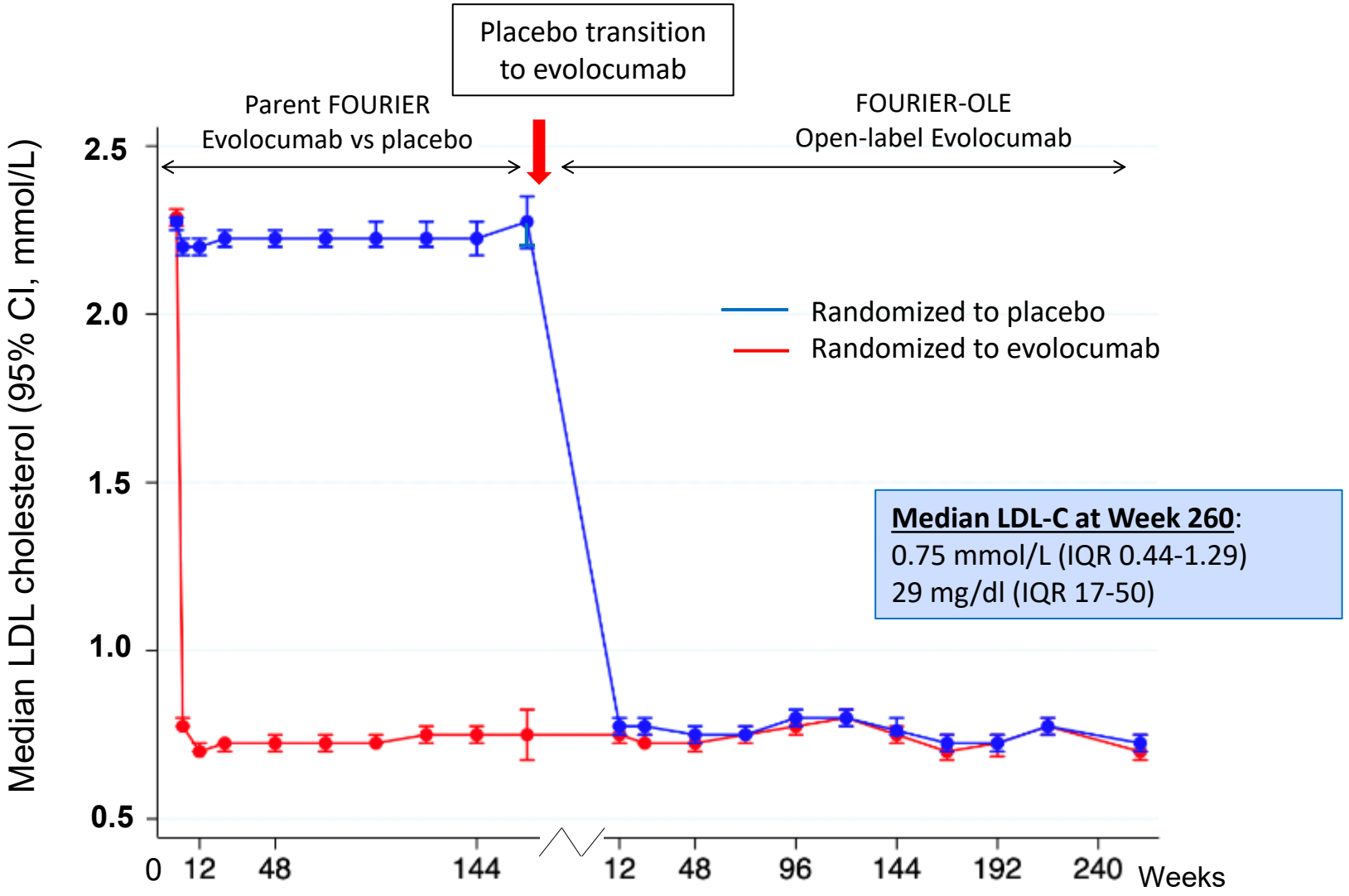
NEJM, 2017

Effect on LDL-C



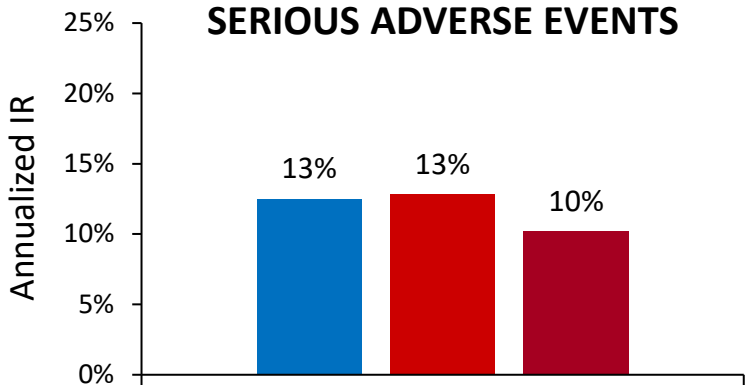
Circulation, 2022

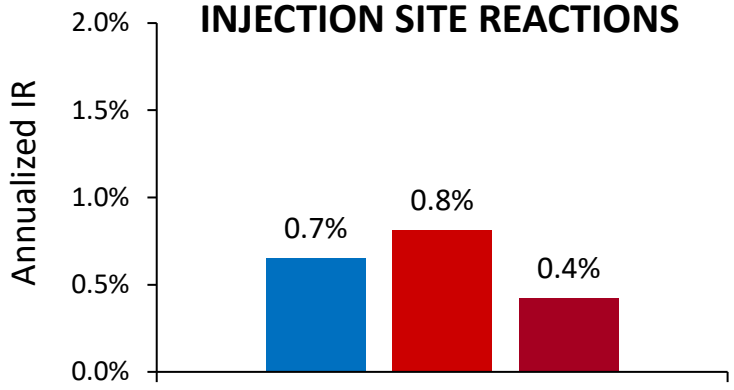
Effect on LDL-C

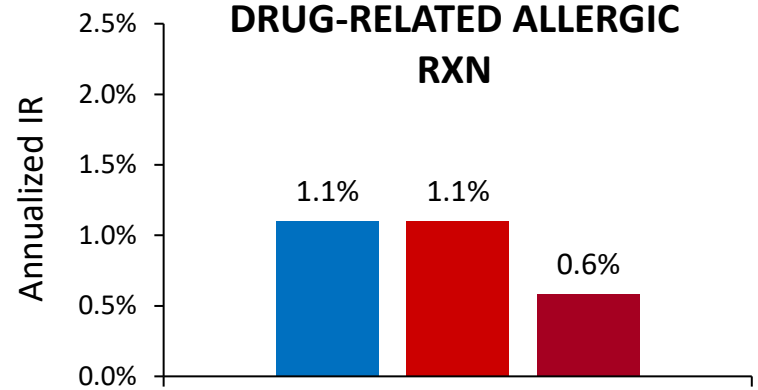


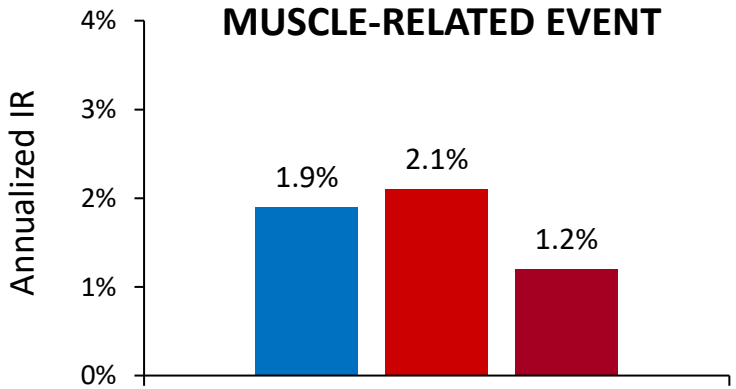
Circulation, 2022

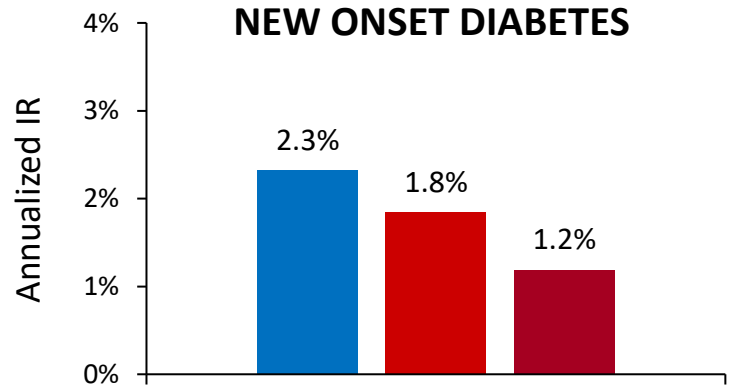
Long-term safety

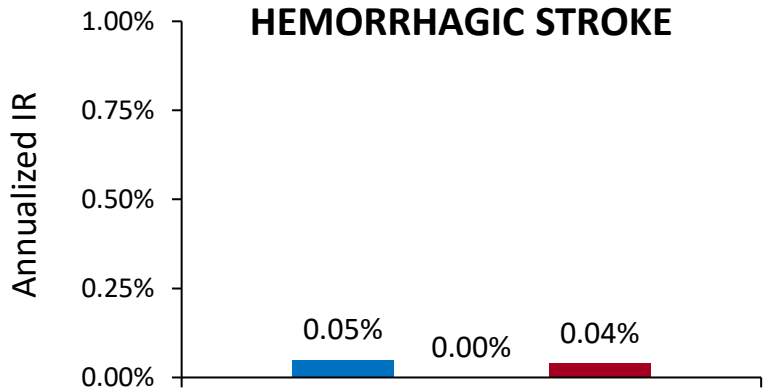








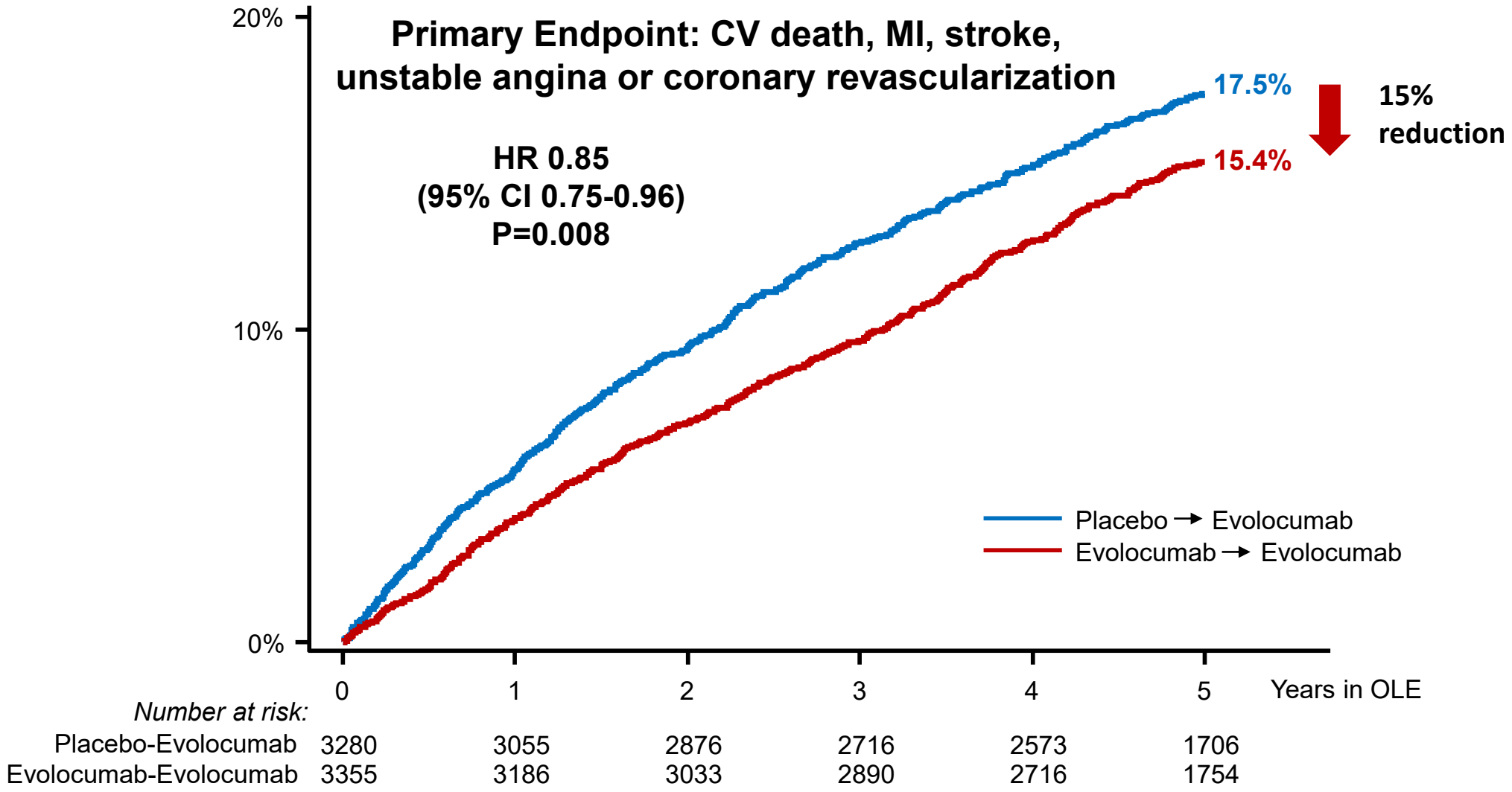




Placebo Phase FOURIER
Evolocumab Phase FOURIER
Evolocumab Phase FOURIER & OLE

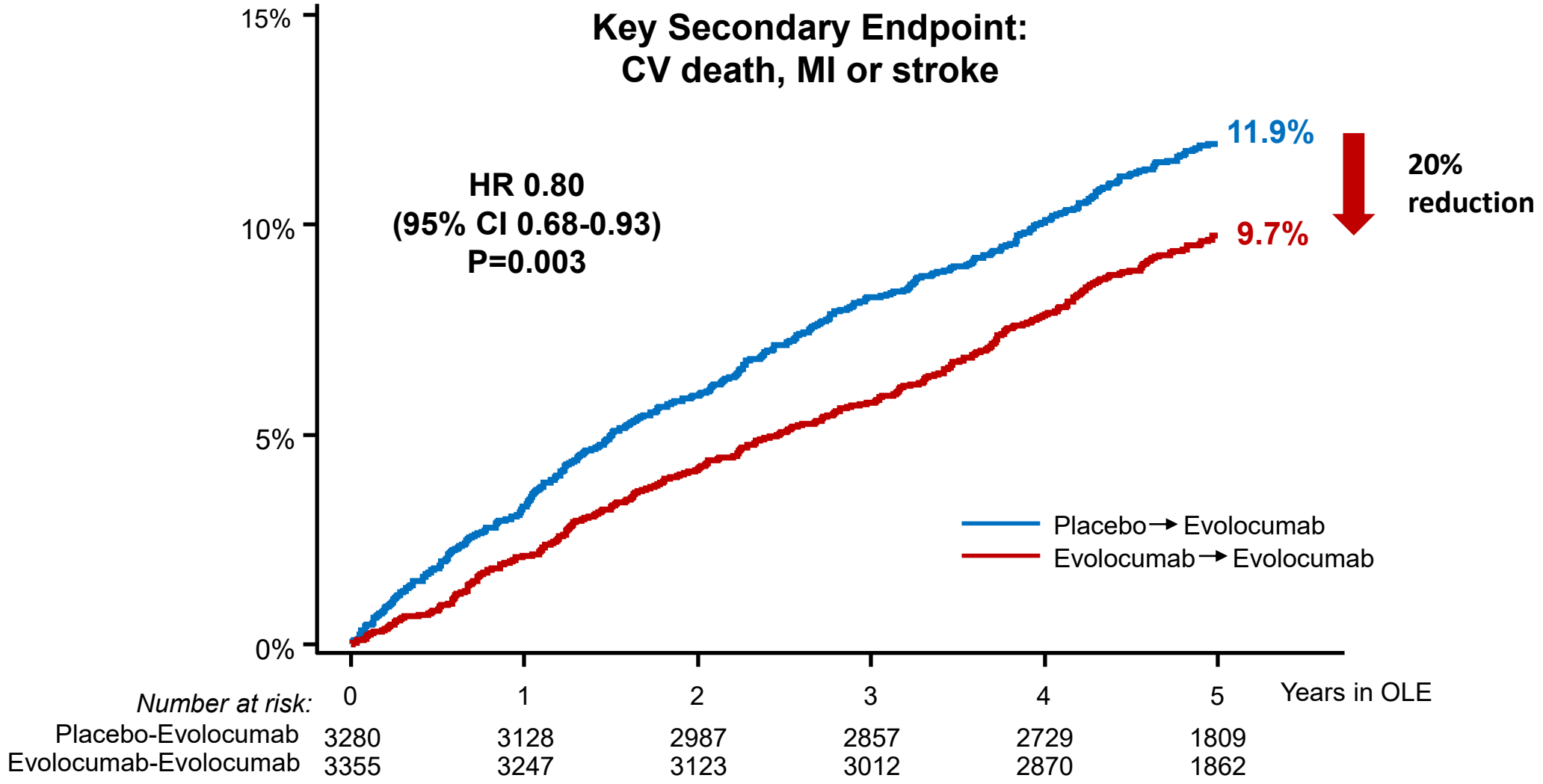
Circulation, 2022

Efficacy during FOURIER-OLE



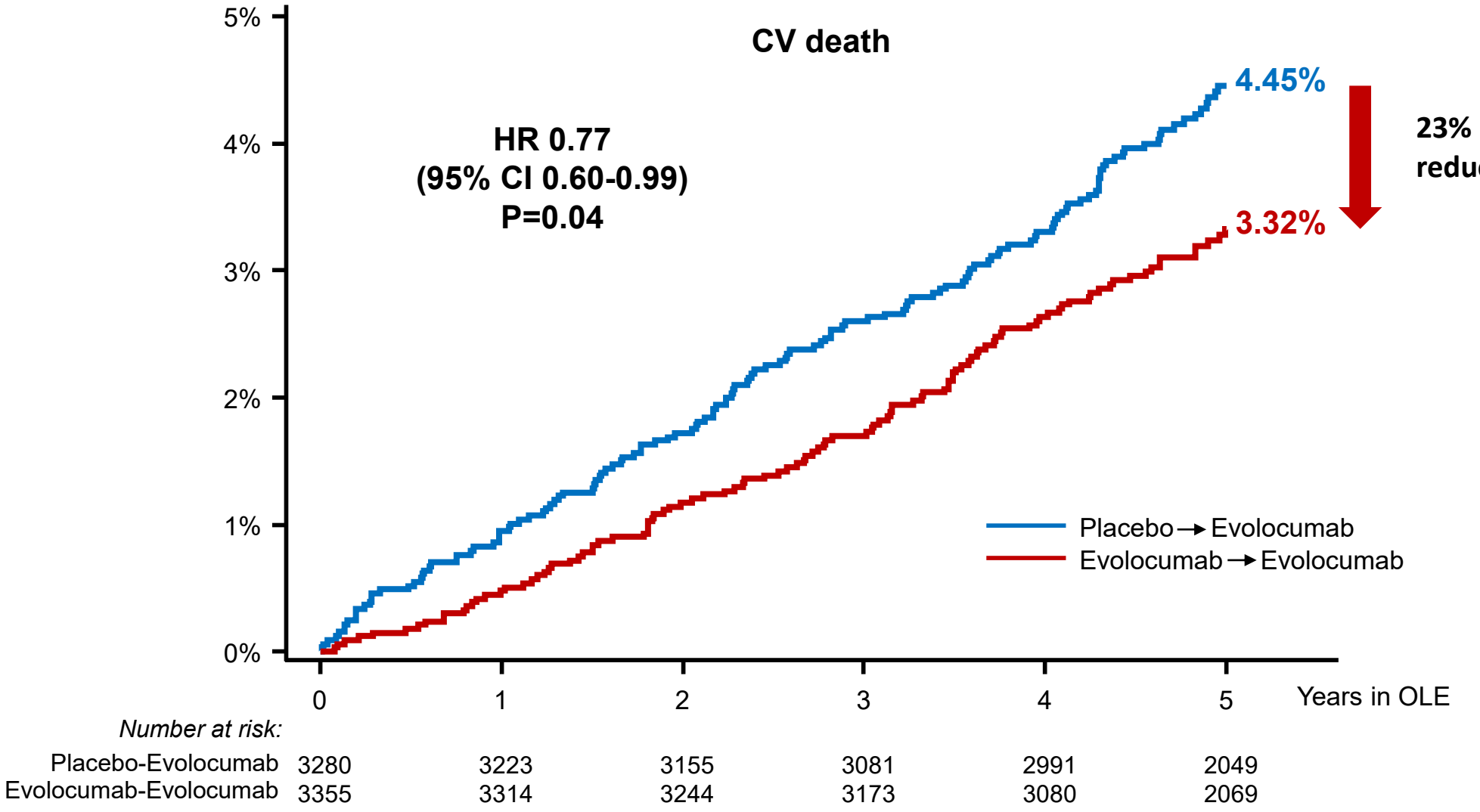
Circulation, 2022

Efficacy during FOURIER-OLE



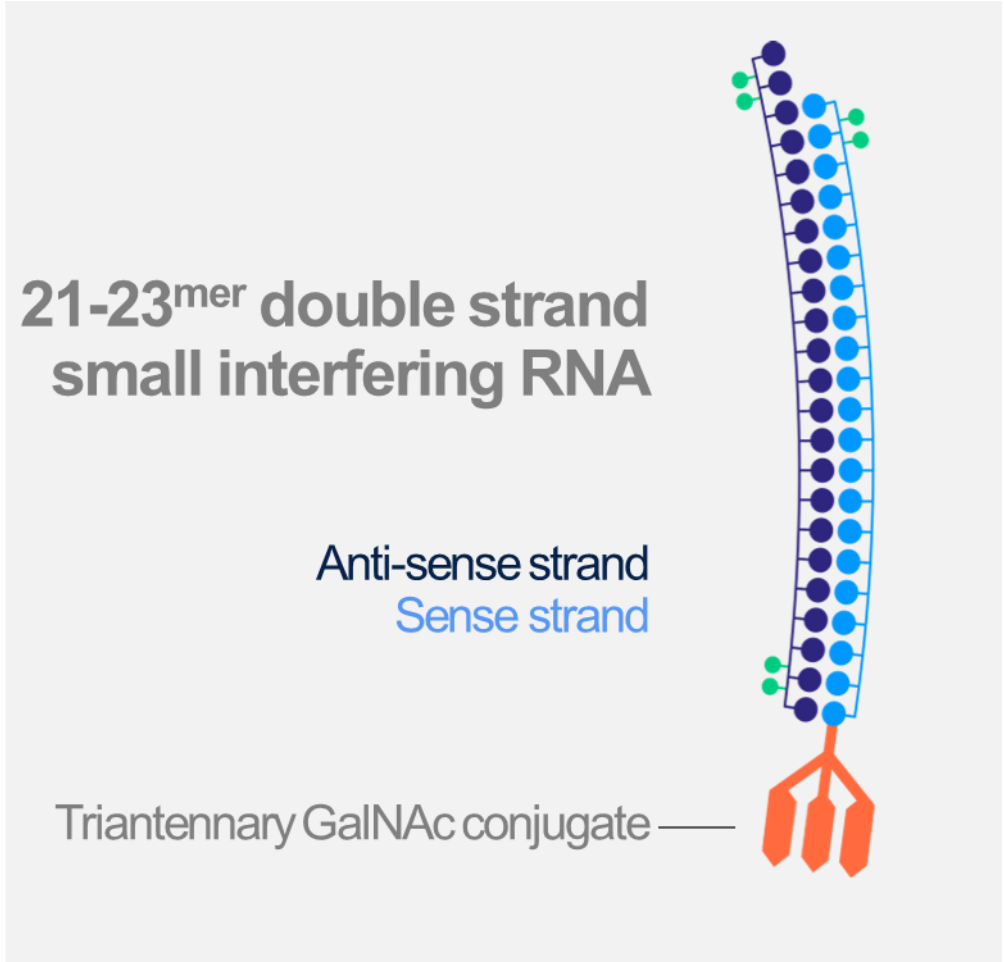
Circulation, 2022

Efficacy during FOURIER-OLE



Circulation, 2022

Inclisiran



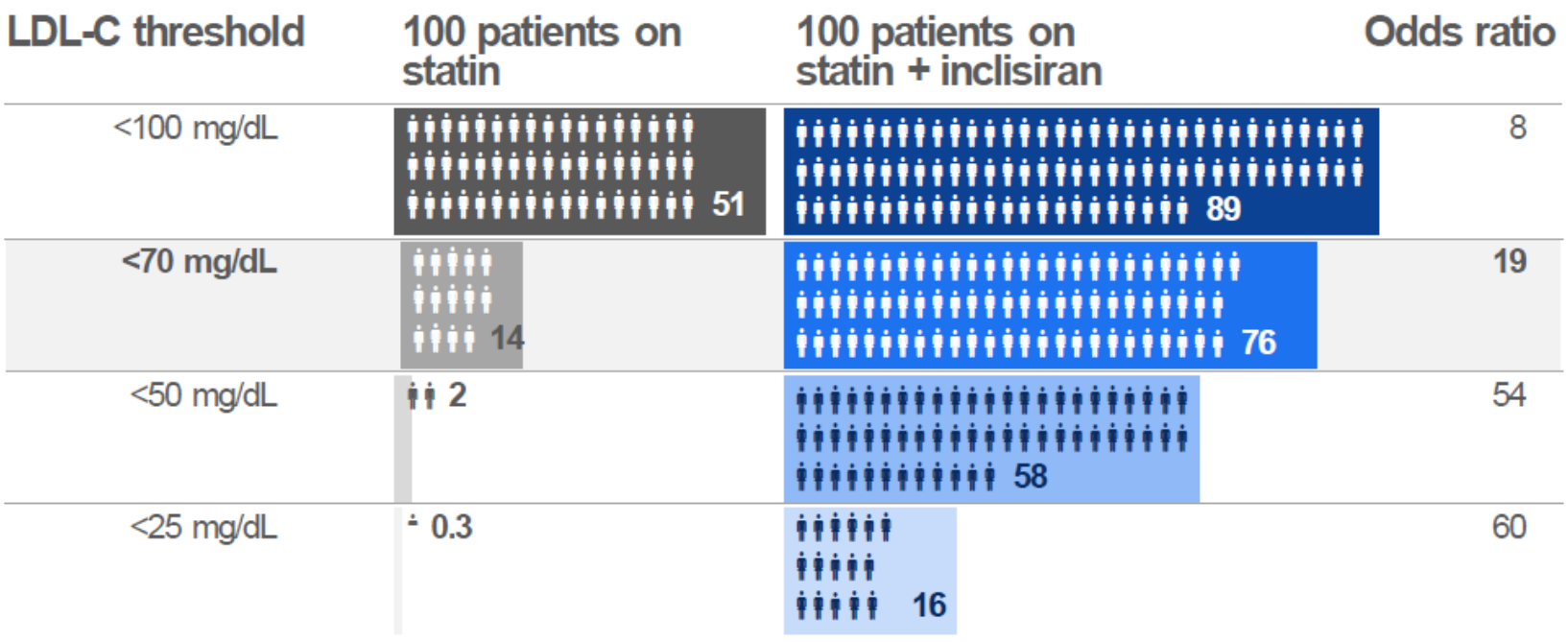
- **Small interfering double-stranded RNA**
- Harnesses the natural process of RNAi
- Nucleotides modified for durability and low immunogenicity
- Distributed to liver due to GalNAc conjugation
- Inhibits production of PCSK9 specifically, durably and potently

JACS, 2014

ORION 9,10,11- Results

ORION Phase III pooled analysis: Efficacy

Likelihood of achieving specific LDL-C thresholds



Likelihood of reaching LDL-C thresholds at Day 510 among patients with available data

Reference:
Wright, R. Scott, and A. ORION. "A pooled analysis of Phase III studies of inclisiran." Data presented at ACC's Scientific Session Together with World Congress of Cardiology, March.
Ray, Kausik K., et al. "Two phase 3 trials of Inclisiran in patients with elevated LDL cholesterol." New England Journal of Medicine 382.16 (2020): 1507-1519.
Raal, Frederick J., et al. "Inclisiran for the treatment of heterozygous familial hypercholesterolemia." New England Journal of Medicine 382.16 (2020): 1520-1530.

ORION Phase III pooled analysis: Efficacy

Effects on other lipid parameters

Percent Change from baseline to day 510 ITT population[1] Imputed values[2]		Placebo N = 1827		Inclisiran N = 1833	p-value
PCSK9	Mean %	+ 14.8	**-83%**	- 68.2	<0.0001
Total cholesterol	Mean %	+ 2.9	**-32%**	- 29.5	<0.0001
Non HDL-C	Mean %	+ 3.6	**-46%**	- 42.8	<0.0001
ApoB	Mean %	+ 1.7	**-42%**	- 40.2	<0.0001
Lp (a) (day 540)	Median %	+ 0.7	**-20%**	- 19.5	<0.0001[3]

1. All patients who were randomized 2: Imputed using a mixed model for repeated measures 3: Non-parametric test; not imputed

Reference:
Wright, R. Scott, and A. ORION. "A pooled analysis of Phase III studies of inclisiran." Data presented at ACC's Scientific Session Together with World Congress of Cardiology, March.
Ray, Kausik K., et al. "Two phase 3 trials of Inclisiran in patients with elevated LDL cholesterol." New England Journal of Medicine 382.16 (2020): 1507-1519.
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ORION Phase III pooled analysis: Exploratory endpoint:
Serious adverse events

Serious treatment emergent adverse events Safety population[1,2]	Placebo N = 1822		Inclisiran N = 1833	
Patients with at least one serious TEAE	**419**	**(23.0%)**	**374**	**(20.4%)**
All cause death	27	(1.5%)	27	(1.5%)
Cancer	6	(0.3%)	4	(0.2%)
New, worsening or recurrent malignancy	49	(2.7%)	44	(2.4%)
TEAEs leading to drug discontinuation	35	(1.9%)	45	(2.5%)

1. Safety population includes all patients who received at least 1 dose of study medication 2. Patients may be counted in more than one category
3. MedDRA-defined CV basket of non-adjudicated terms cardiac death, and any signs or symptoms of cardiac arrest, non-fatal MI and/or stroke

Reference:
Wright, R. Scott, and A. ORION. "A pooled analysis of Phase III studies of inclisiran." Data presented at ACC's Scientific Session Together with World Congress of Cardiology, March.
Ray, Kausik K., et al. "Two phase 3 trials of Inclisiran in patients with elevated LDL cholesterol." New England Journal of Medicine 382.16 (2020): 1507-1519.
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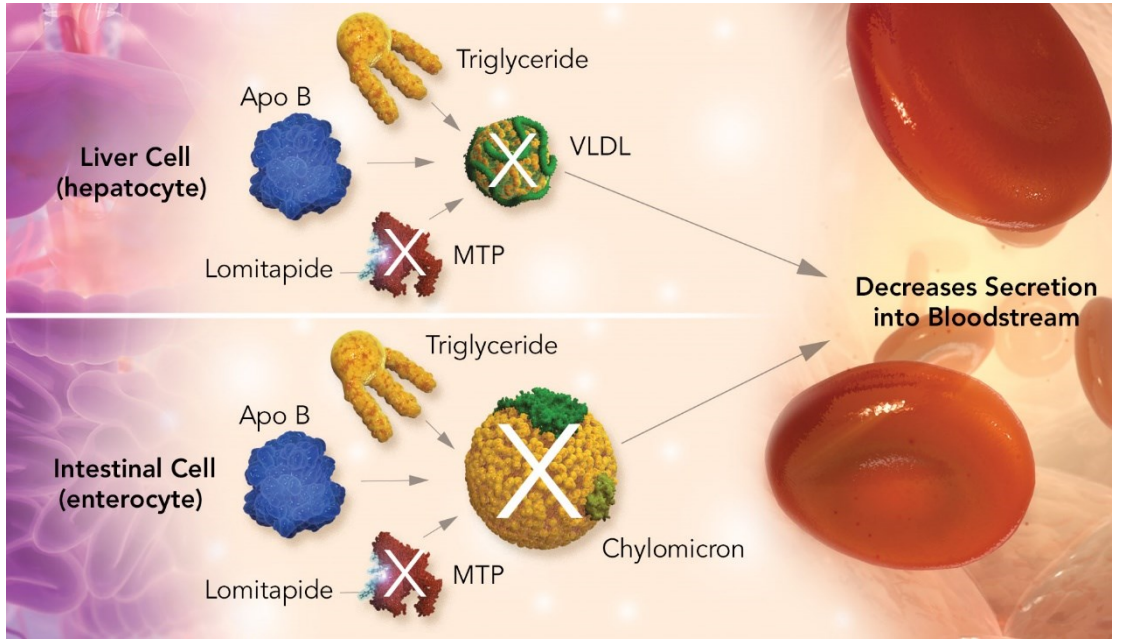
Lomitapide (JUXTAPID)

- Lomitapide is an inhibitor of the microsomal triglyceride transfer protein (MTP), a key protein in the assembly and secretion of apo B-containing lipoproteins in the liver and intestine[1,2]
- Lomitapide acts independently of the LDL-R[3,4]



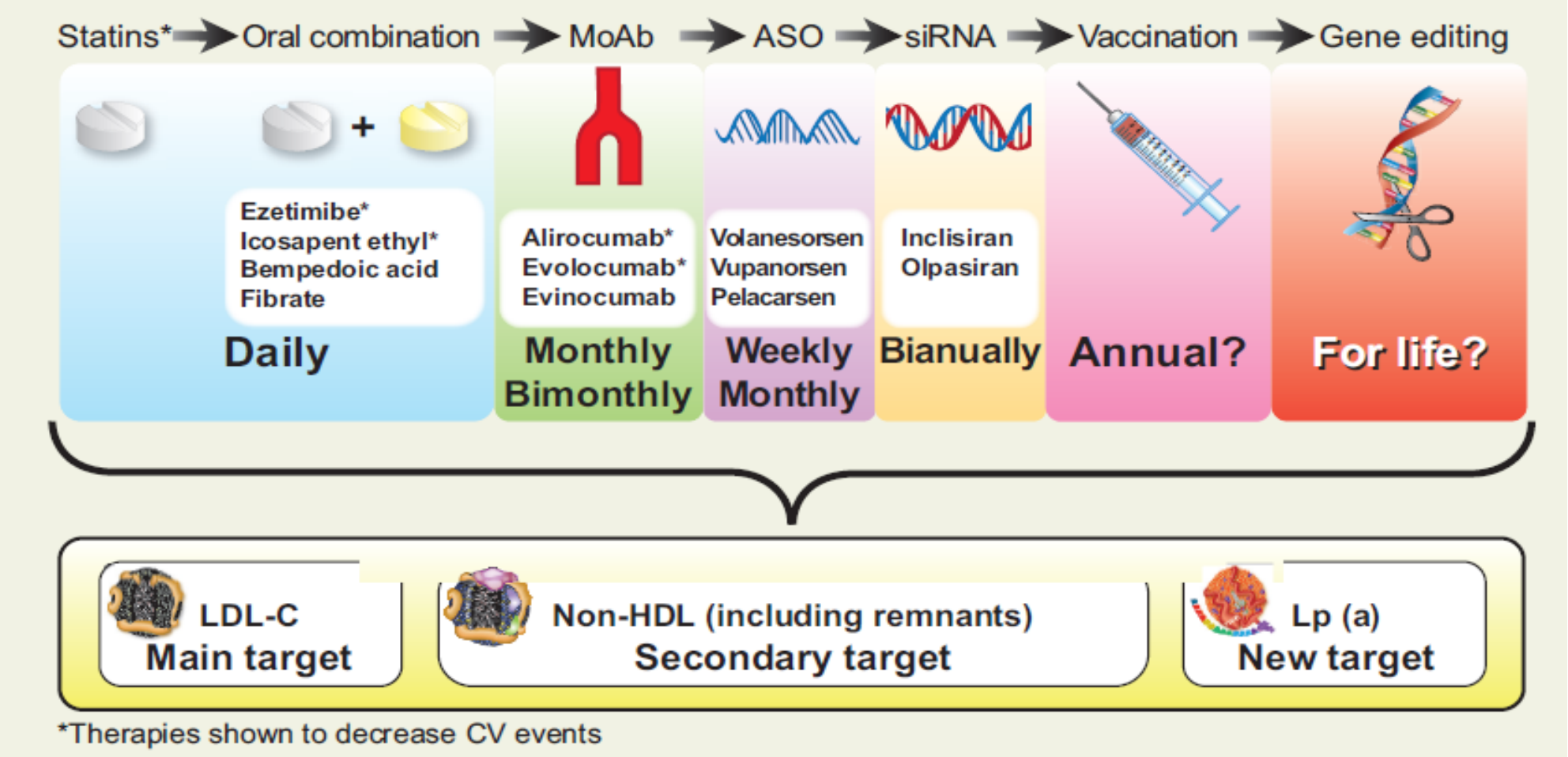
ApoB, apolipoprotein B; LDL-R, low-density lipoprotein receptor; VLDL, very-low-density lipoprotein

1. Lojuxta® (lomitapide) Summary of Product Characteristics.
2. Juxtapid® (lomitapide) capsules US Prescribing Information. Amryt Pharmaceuticals, DAC.
3. Cuchel M, et al. Lancet. 2013;381(9860):40–6
4. Cuchel M, et al. N Engl J Med. 2007;356(2):148–56

Angiopoietin-like protein 3 (ANGPTL3) inhibitor – Evinacumab

- ANGPTL3 is a hepatically secreted protein that inhibits lipoprotein and endothelial lipase
- Evinacumab, an Mab that inhibits ANGPTL3
- ↓LDL-C by 49%
- Evinacumab's unique mechanism of action appears to be independent of LDL-receptor function, which may be particularly valuable in patients with HoFH

Evolution of Lipid Lowering Therapies



ASO, antisense oligonucleotide; MoAb, monoclonal antibodies; siRNA, small-interfering RNA.

European Heart Journal, 2022


THANK
YOU