October 28, 2023,
Sue Gross Auditorium,
UCI Susan & Henry Samueli
College of Health Sciences,
UCI School of Medicine, Irvine, CA

Low Density Lipoprotein Cholesterol (LDL-C): Earlier, Lower, and Longer, is Better, and Safe

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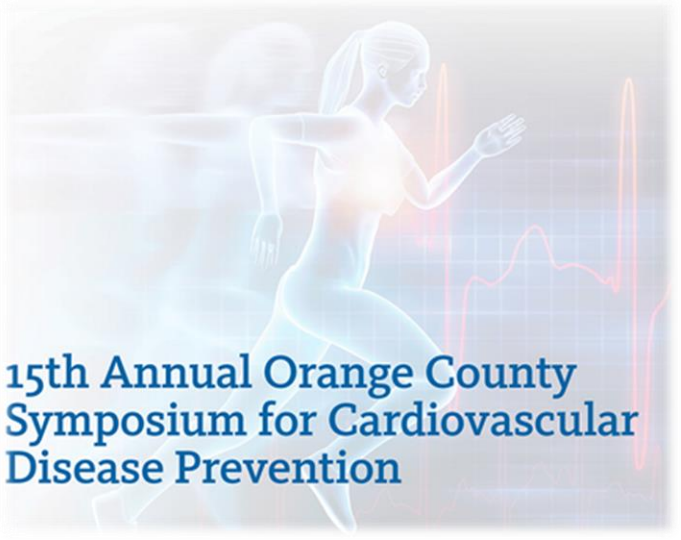


2022 – 2023
Faculty Disclosures*

Dr. Paul D. Rosenblit reported the following relevant financial relationships with commercial interests:

Clinical Research Site Trials: **Ionis(Akcea), Novo Nordisk, Novartis**

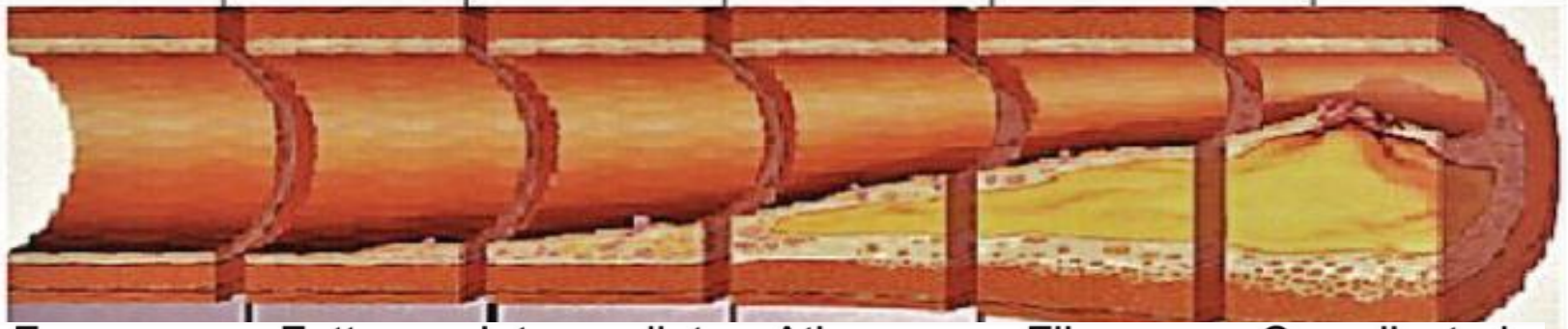
15th Annual ORANGE COUNTY SYMPOSIUM CAPRDIOVACULAR PREVENTION:
October 28, 2023, Sue Gross Auditorium, UCI Susan & Henry Samueli College of Health Sciences, UCI School of Medicine, Irvine, CA

Low Density Lipoprotein Cholesterol (LDL-C): Earlier, Lower, and Longer, is Better, and Safe

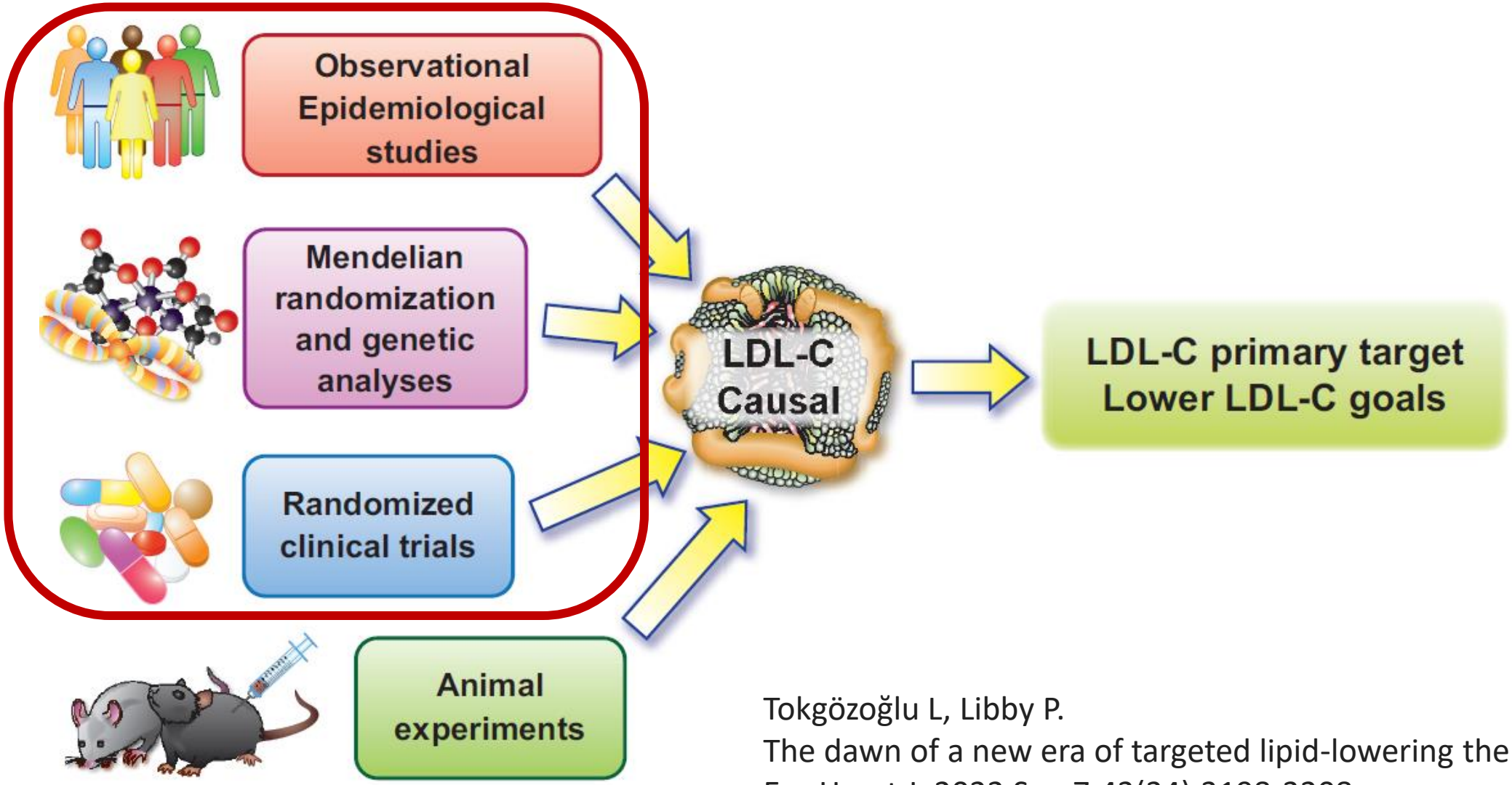
Objectives:

- **Review the clinical trial and atherosclerosis imaging study support for lower goals of therapy when targeting LDL-C.**
- **Discuss the safety of lipid-lowering**
- **Suggest concept that not only lower, but earlier and longer, is better.**

The Stages of the Progression of Atherosclerosis

Clinical findings	Asymptomatic		Asymptomatic or Symptomatic		
Growth mechanism	Growth is mainly with lipid deposition			Proliferation of smooth muscle cells and increase of collagen	Thrombosis and /or hematoma
Onset of time	From first decade	From Third decade		From fourth decade	
Phases of progression of Atherosclerosis	 Foam Cell / Fatty Streak / Intermediate Lesions / Atheroma / Fibrous Plaque / Complicated Lesion/Rupture				
Main Histology of the progression	***First lesion:*** -Normal Histology - Macrophage migration -Isolated foam cells	***Fatty Streak:*** -Mainly intracellular lipid deposition	***Intermediate phases:*** -New fatty streaks -Intracdlular Lipid deposition and lipid pools	***Atheroma:*** -New fatty streaks -Intracellular and Extracellular lipid accumulation	***Fibroatheroma:*** -New fatty streaks -Single or multiple lipid cores -Fibrotic and calcific layers	***Complicated Lesions:*** -Disrupted surface (ulcerated plaque) -Thrombosis -Hematoma and hemorrhage

Multiple Lines of Evidence Showing Low-density Lipoprotein Cholesterol is Causal for Cardiovascular Disease



Tokgözoğlu L, Libby P.
The dawn of a new era of targeted lipid-lowering therapies.
Eur Heart J. 2022 Sep 7;43(34):3198-3208.
doi: 10.1093/eurheartj/ehab841.

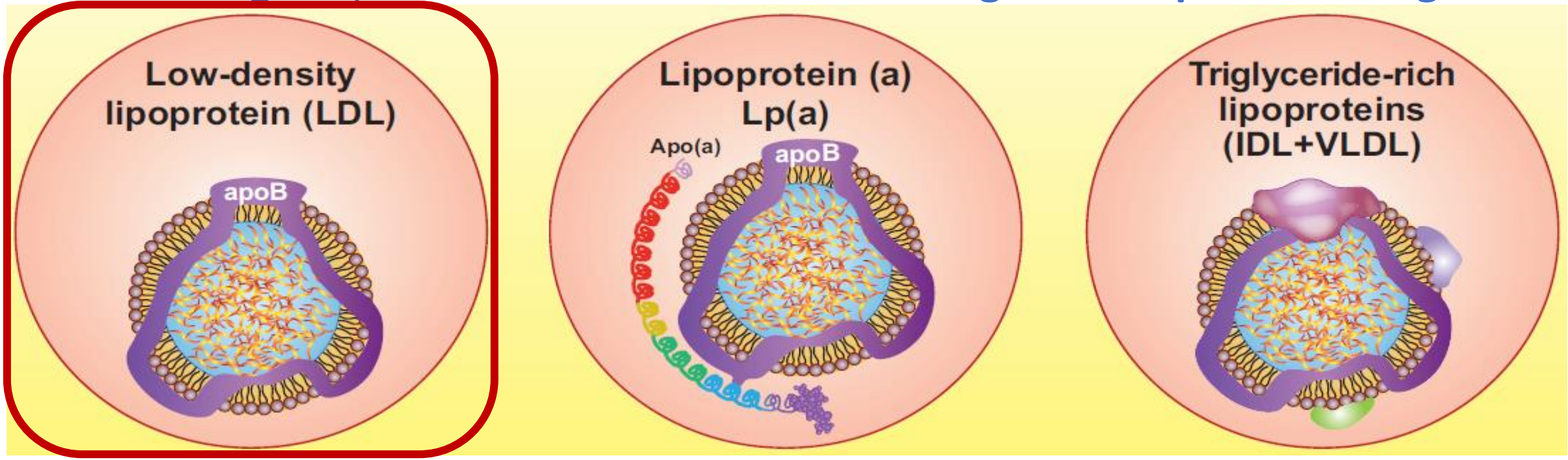
Criteria for Atherosclerotic Cardiovascular Disease (ASCVD) Causality: ApoB Cholesterol Containing Lipoproteins [VLDL, their remnants, IDL, LDL, & Lp(a)]

From 'Cholesterol Hypothesis' to 'Lipoprotein Cholesterol Principle'

Criterion	Summary of the evidence
1. Plausibility	LDL and other apolipoprotein (apo) B-containing lipoproteins (VLDL, their remnants, IDL and Lp(a)) are directly implicated in the initiation and progression of ASCVD; experimentally-induced elevations in plasma LDL and other apoB-containing lipoproteins lead to atherosclerosis in all mammalian species studied.
2. Strength	Monogenic and polygenic-mediated lifelong elevations in LDL lead to markedly higher lifetime risk.
3. Biological gradient	Monogenic lipid disorders, prospective cohort studies, Mendelian randomization studies, & randomized intervention trials uniformly demonstrate a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL & risk of ASCVD
4. Temporal sequence	Monogenic lipid disorders & Mendelian randomization studies demonstrate that exposure to ↑ LDL precedes the onset of ASCVD
5. Specificity	Mendelian randomization studies and randomized intervention trials both provide unconfounded randomized evidence that LDL is associated with ASCVD independent of other risk factors
6. Consistency	>200 studies involving >2 million participants with >20 million person-years of follow-up & >150,000 CV events consistently demonstrate a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD
7. Coherence	Monogenic lipid disorders, prospective cohort studies, Mendelian randomization studies, and randomized intervention trials all show a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD
8. Reduction in risk with intervention	>30 randomized trials involving >200,000 participants and >30,000 ASCVD events evaluating therapies specifically designed to lower LDL (including statins, ezetimibe, and PCSK9 inhibitors) consistently demonstrate that reducing LDL cholesterol (LDL-C) reduces the risk of ASCVD events proportional to the absolute reduction in LDL-C

Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Borén J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskinen MR, Tokgözoglu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano AL. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017 Aug 21;38(32):2459-2472. doi: 10.1093/eurheartj/ehx144

The Apolipoprotein B-Containing Lipoprotein Family: Atherogenic, Modifiable and Treatment Targets for Lipid-Lowering



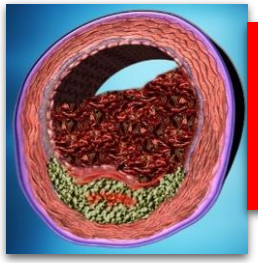
	Low-density lipoprotein (LDL)	Lipoprotein (a) Lp(a)	Triglyceride-rich lipoproteins (IDL+VLDL)
Therapies: Current & Emerging	**ATP citrate lyase inhibitor: Bempedoic acid** **NPC1L1 inhibitor: Ezetimibe** **PCSK9 inhibitors: Mabs, SiRNA** **HMGCoA Inhibitor: Statins** **Bile Acid Sequestrants** **PCSK9 inhibitors: Oral**	**PCSK9 inhibitors: -Mabs, -siRNA** **Pelacarsen ASO** **Olpasiren siRNA** **Zerlasiran siRNA**	**NPC1L1 inhibitor: Ezetimibe** **PCSK9 inhibitors: Mabs, SiRNA** **HMGCoA Inhibitor: Statins** **APOC3 Olezarsen ASO** **APOC3 Volanesorsen ASO** **ARO-APOC3 siRNA** **ANGPLT3 Evinacumab (FH approved)**

Adapted from:

Tokgözoğlu L, Libby P. The dawn of a new era of targeted lipid-lowering therapies. Eur Heart J. 2022 Sep 7;43(34):3198-3208. doi: 10.1093/eurheartj/ehab841.

Primary/Secondary ASCVD Prevention of At-Risk Individuals

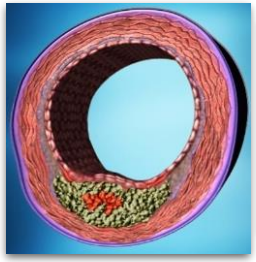
***Reduce Fundamental Atherogenic Cholesterol-containing Lipoprotein Particles**
How aggressive the management, i.e., How low the targeted LDL-C goal?



Secondary Prevention
- Prior Events or Multimorbidity
- Prior Event (or CHD risk Equivalent)

Very High risk, Extreme risk

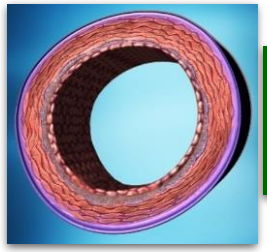
What is best way to identify 'Subclinical Disease'?



Primary Prevention
- Disease
- No Prior Event, YET!

High, Very-High, Extreme risk

Who is at-risk to develop disease over their lifetime?
At what age start? Is lower LDL-C necessary?



Primary Prevention
- No Disease

Low, Moderate, Intermediate 10-yr risk (High Lifetime risk?)

"Primary prevention of any disease is more effective if started sooner."

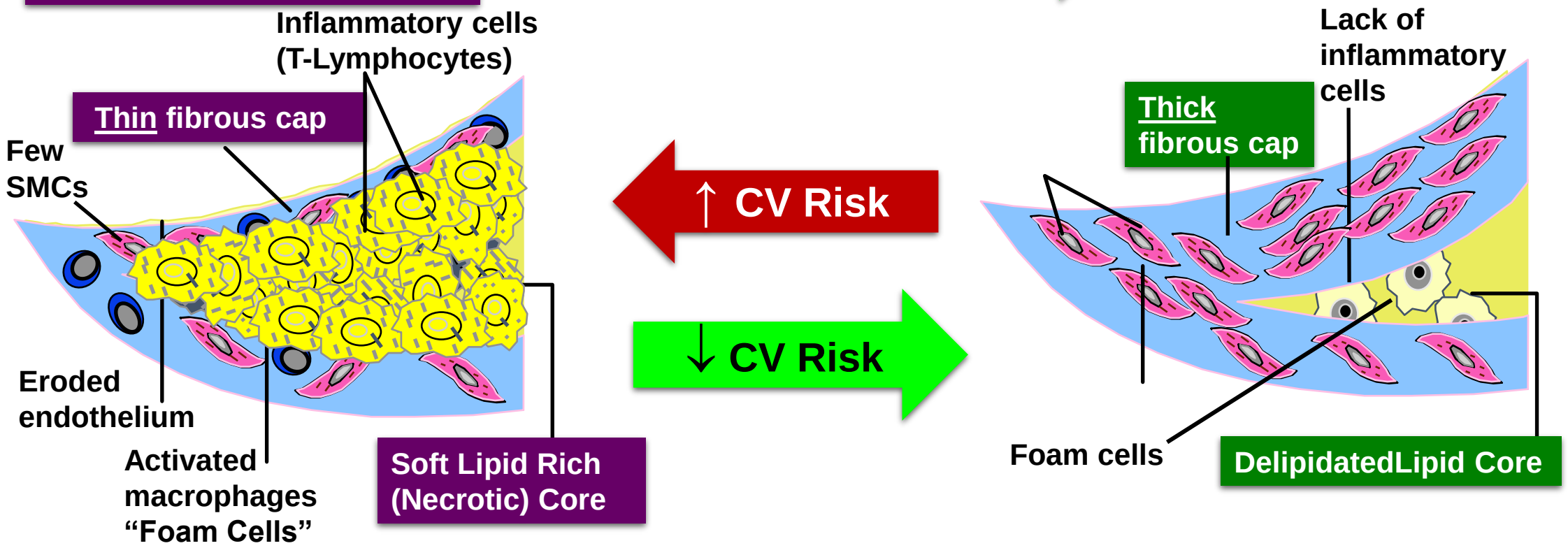
PDR

ASCVD: Characteristics of Unstable and Stable Plaque

Unstable (Clinical Events)

Regression / Stabilization

Stable

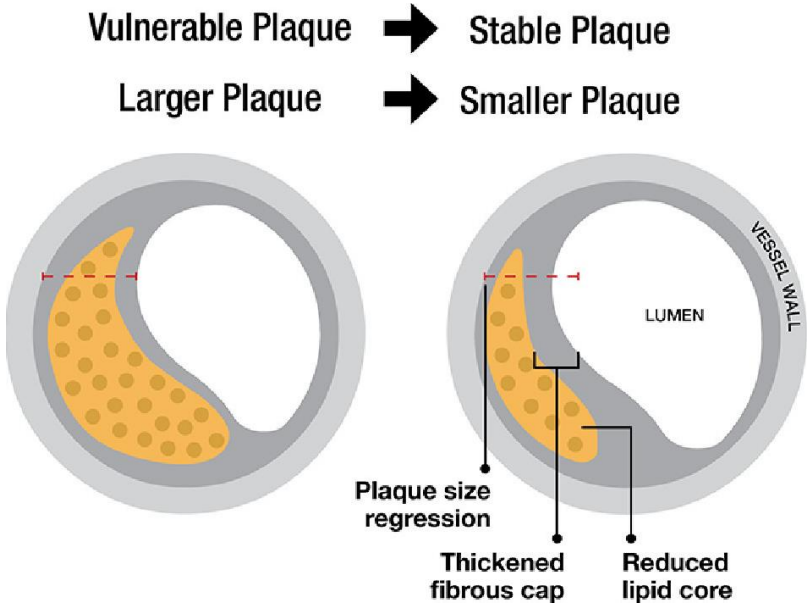


Unstable plaques have a thin fibrous cap & are 'vulnerable' (i.e., at greater risk for rupture); the lipid-rich core may represent the majority of the plaque volume.

In stable plaques, a thick fibrous cap may represent >70% of plaque volume. It stabilizes the plaque and prevents it from undergoing rupture.

Studies of Vascular and Intravascular Imaging Modalities Integrated into Clinical Trials have Complemented and Supported the Benefits of Targeted Atherogenic Lipoprotein-Lowering and Determining Goals of Therapy

Post-morbid Histology



Non-Invasive Procedures

Carotid Ultrasound
Carotid Intimal-medial Thickness (CIMT)

Magnetic Resonance Imaging (MRI) Studies

Computer Tomography
Coronary Artery Calcium (CAC) scoring

CT Angiography (CTA)

Invasive Procedures

Quantitative Coronary Angiography (QCA)

Intravascular Ultrasound (IVUS)

Optical Coherence Tomography (OCT)

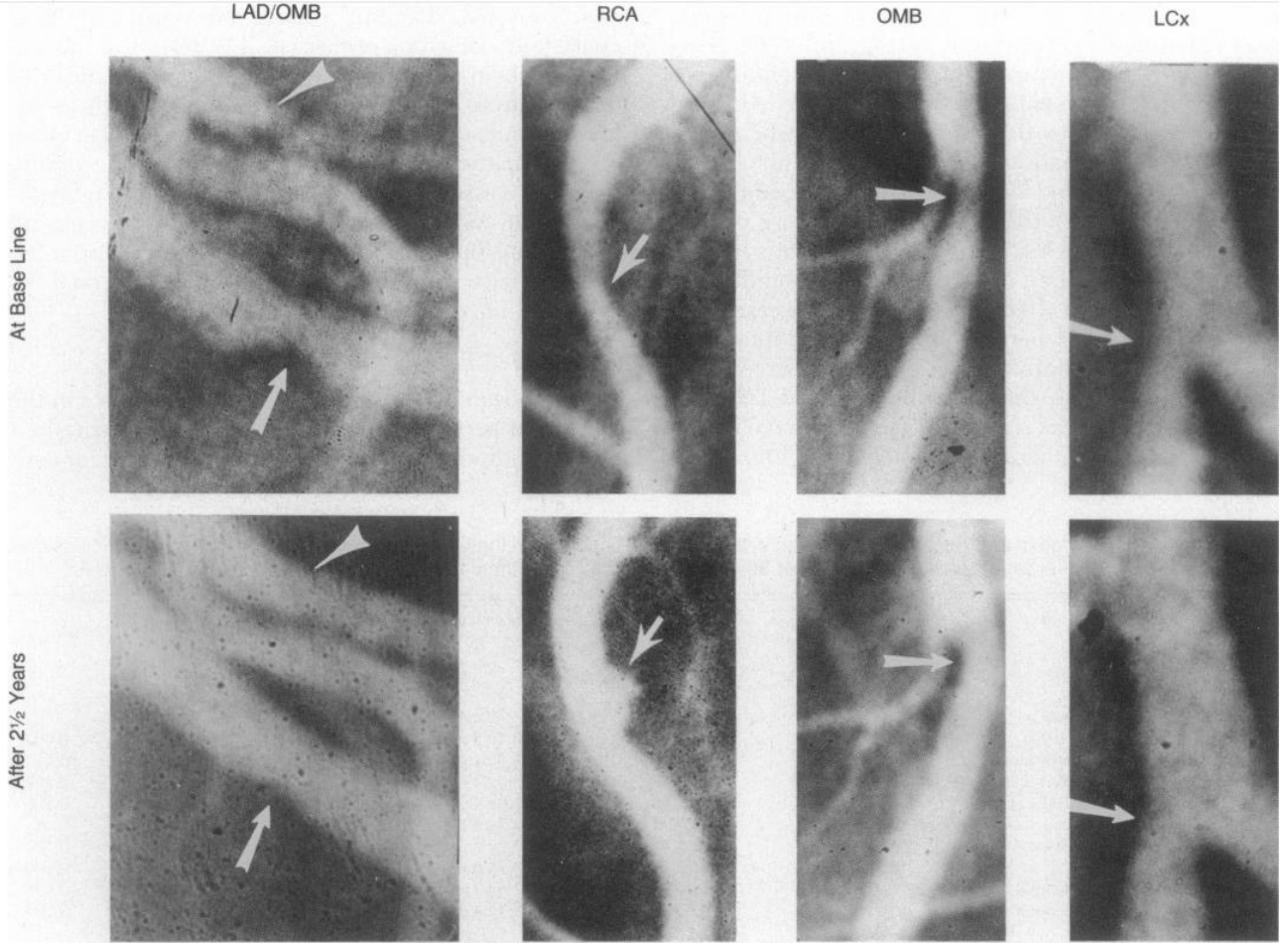
Near Infra-red Spectroscopy (NIRS)

Di Giovanni G, Nicholls SJ.
Intensive lipid lowering agents and coronary atherosclerosis: Insights from intravascular imaging.
Am J Prev Cardiol. 2022 Jul 1;11:100366.
doi: 10.1016/j.ajpc.2022.100366.

Quantitative Coronary Arteriography

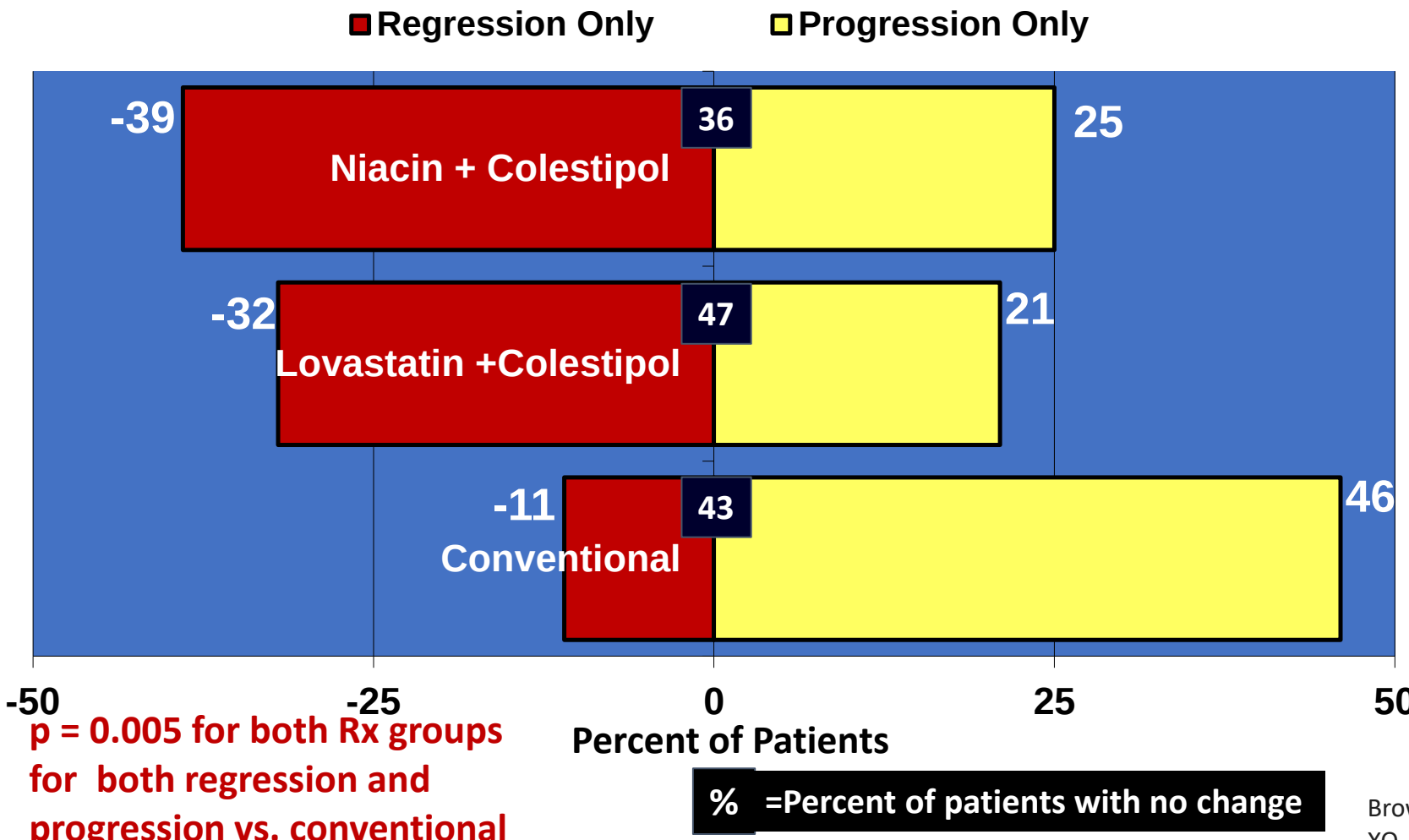
Brown BG, Bolson E, Frimer M, Dodge HT. **Quantitative coronary arteriography**: estimation of dimensions, hemodynamic resistance, and atheroma mass of coronary artery lesions using the arteriogram and digital computation. **Circulation. 1977** Feb;55(2):329-37. doi: 10.1161/01.cir.55.2.329.

Describes an objective method for analysis of a diseased coronary arterial segment. It represents a significant improvement over those methods described above because:
1) it deals at a fundamental level with the magnification and distortion inherent in cineangiography;
2) it uses perpendicular cine projections to construct a 3-dimensional, true-scale representation of the diseased arterial segment; and
3) it computes other potentially important parameters of lesion severity.
The precision of the method is evaluated, and examples of its clinical applications are given.



Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin JT, Kaplan C, Zhao XQ, Bisson BD, Fitzpatrick VF, Dodge HT. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B.
N Engl J Med. 1990 Nov 8;323(19):1289-98. doi: 10.1056/NEJM199011083231901.

Familial Atherosclerosis Treatment (2.5 yrs) Study (FATS) *: Effect of Intensive Lipid-lowering Therapy on Coronary Atherosclerosis, Assessed by Quantitative Arteriography, Demonstrates Lesion Regression and Luminal Diameter Improvement and Coincident Reduction in Coronary Events



p = 0.005 for both Rx groups for both regression and progression vs. conventional

Lipid Effects:			CVEs RR%
LDL-C	HDLC	TG	
-32%	43%	-29%	2/48 -80% p=0.01
-46%	15%	-9%	3/46 -70% p=0.01
-7%	5%	15%	10/52 ----

Males (n=146, <63 yo), Apo B >125 mg/dl, FH+CAD, angiographic CAD (avg. severity stenosis 34%; mandatory 1 vessel >50% or 3 vessels >30% stenosis)

Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin JT, Kaplan C, Zhao XQ, Bisson BD, Fitzpatrick VF, Dodge HT.
Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B.
N Engl J Med. 1990 Nov 8;323(19):1289-98.
doi: 10.1056/NEJM199011083231901.

CLAS: 4.0-year F/U Secondary Prevention Study of Colestipol/Niacin vs. Placebo Evaluating Changes in Carotid Intimal-Media Thickness (CIMT)

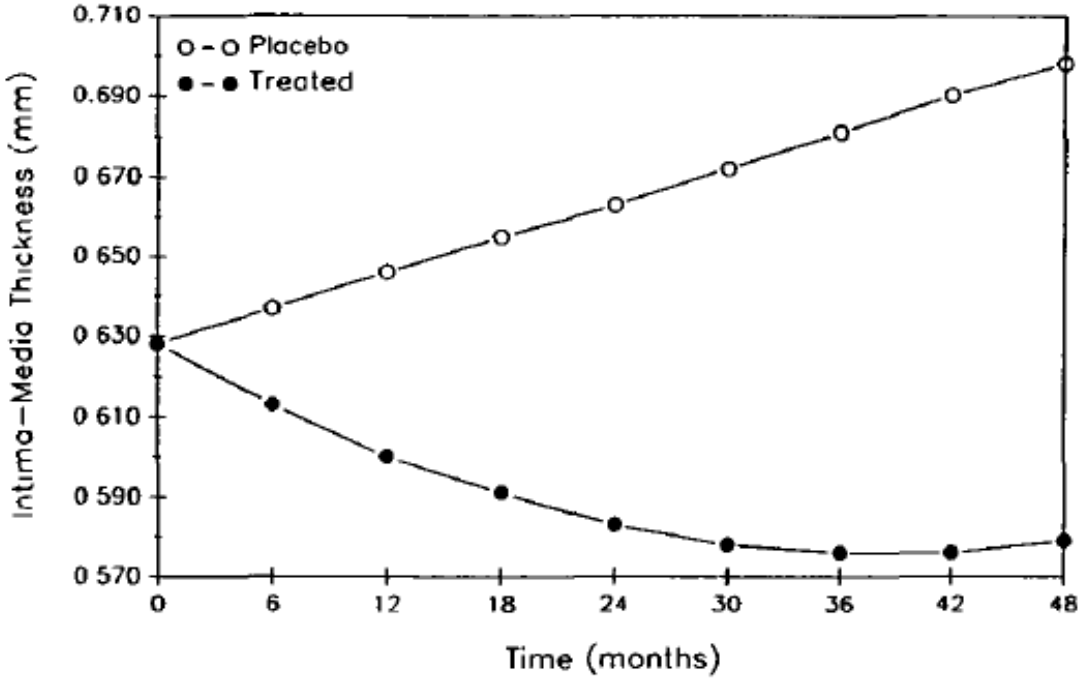


FIG 7. Graph showing temporal characteristics of intima-media thickness change with colestipol-niacin therapy and placebo over a 48-month period in the CLAS study.

- **In the Placebo group, CIMT progressively increased over the 4-year study period at a rate of +0.018 mm per year.**
- **In the Niacin-Colestipol group, CIMT decreased at a rate of -0.036 mm per year over the 1st 3.2 study years and then plateaued over the remaining year.**

Blankenhorn DH, Selzer RH, Crawford DW, Barth JD, Liu CR, Liu CH, Mack WJ, Alaupovic P.
Beneficial effects of colestipol-niacin therapy on the common carotid artery.
Two- and four-year reduction of intima-media thickness measured by ultrasound.
Circulation. 1993 Jul;88(1):20-8. doi: 10.1161/01.cir.88.1.20.

2001 Evidence* Supportive of Targeted LDL-C Goal <100 mg/dL

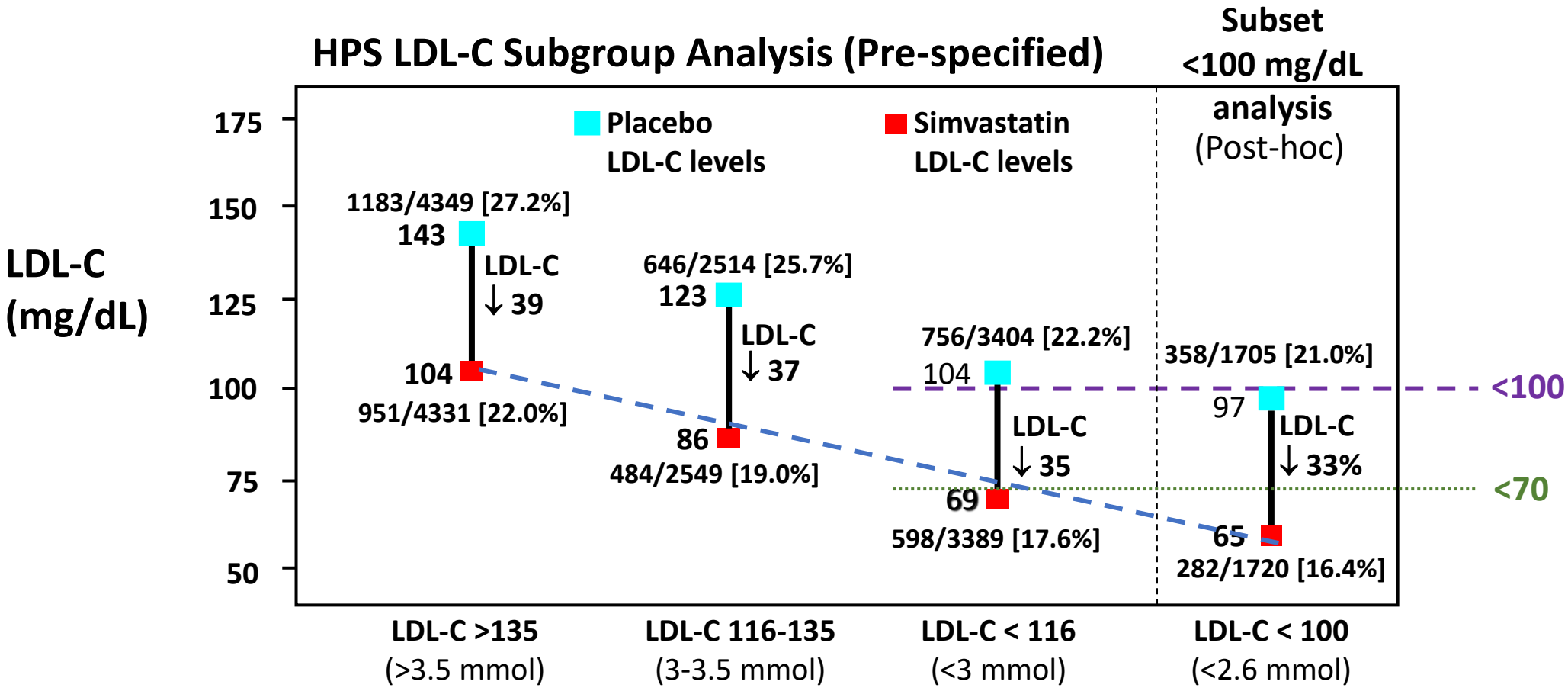
2001 ATP III*: RCTs that Provided Evidence of Improved Outcomes when Targeted LDL-C was <100 mg/dL for Highest Risk Patients

Trial Analysis	Randomized Clinical Trial, RCT	Mean LDL-C, mg/dL, achieved
Level 1A RCT(statin)	CARE MIRACL (ACS) AVERT MARS	72 77 95 93
Level 1A RCT(combination)	CLAS (Niacin + Colestipol) * HATS (Niacin + Simvastatin)* FATS-Extension (Niacin + Colestipol + Lovastatin) * POST-CABG (Lovastatin+Cholestyramine	97 75 84 98
Quantitative Coronary Arteriography (QCA)	MARS CLAS (Niacin + Colestipol) * HATS	93 97 75
Carotid Intimal Medial Thickness(CIMT)	MARS CLAS (Niacin + Colestipol) *	93 97

***2001 ATP III Update**: National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-3421.

What was the basis for “<70 mg/dL” becoming the “Optional Goal” when Targeting LDL-C for Lowering CHD risk in the 2004 ATP III Update?

Heart Protection Study (HPS): Effects of Fixed Dose Statin by Prespecified LDL-C 'Subgroups' and a Post-hoc 'Subset' and Lack of Evidence for LDL-C Threshold



Relative Risk Reduction of Major Vascular Events: 19% | 23% | 21% p<0·0001 | 25% p=0.0006

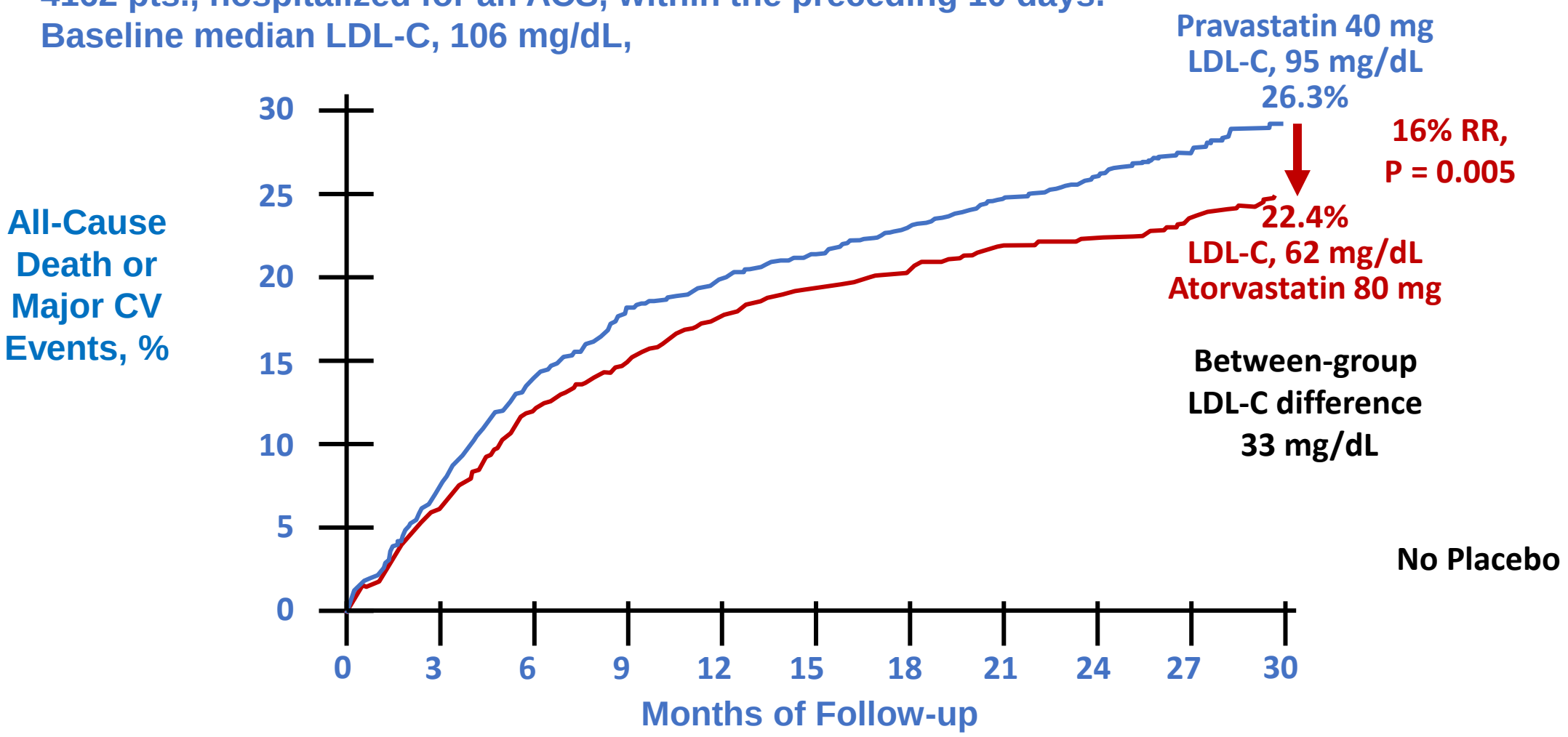
Results <u>suggest</u> that it is important to treat CHD patients with a fixed dose of a statin who are at high risk of developing subsequent cardiac events despite baseline LDL-C levels.

N=6,793 → N=3,425

Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002 Jul 6;360(9326):7-22. doi: 10.1016/S0140-6736(02)09327-3.

PRavastatin Or AtorVastatin Evaluation and Infection Therapy (PROVE-IT)-TIMI 22: All-Cause Death or Major CV Events in All Randomized Subjects, 30 mos. (mean 24 mos.) F/U

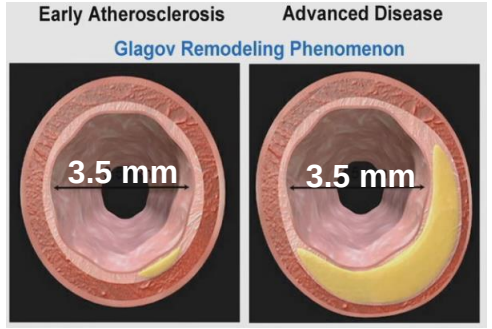
4162 pts., hospitalized for an ACS, within the preceding 10 days.
Baseline median LDL-C, 106 mg/dL,



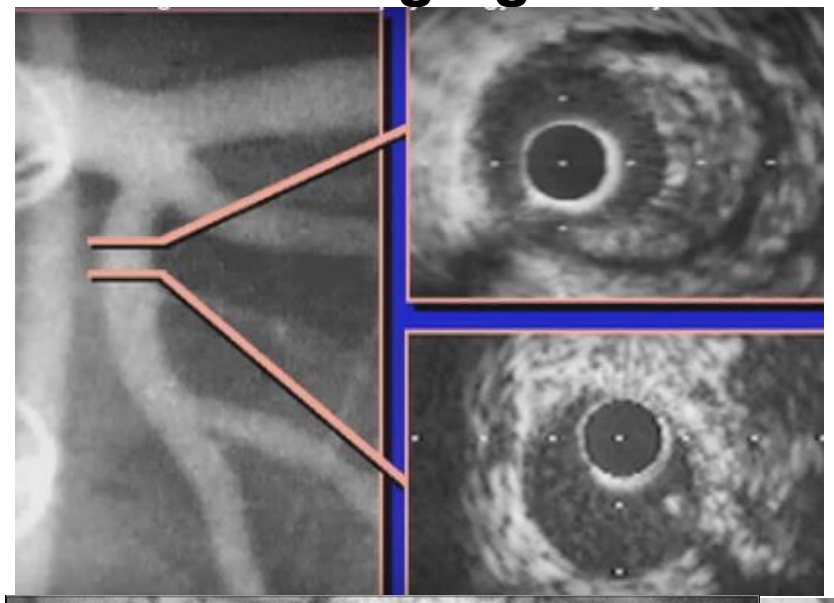
Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004 Apr 8;350(15):1495-504. doi: 10.1056/NEJMoa040583.

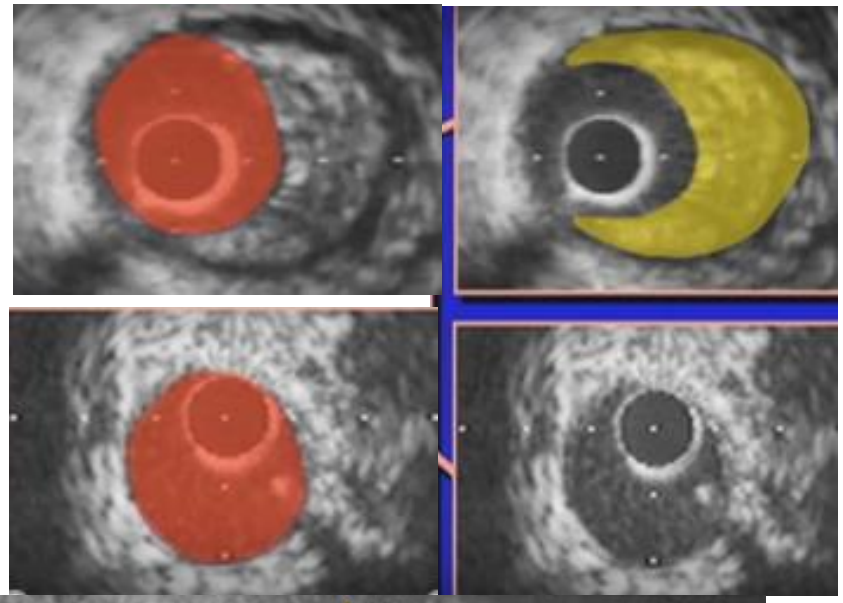
Role of Intravascular Ultrasound

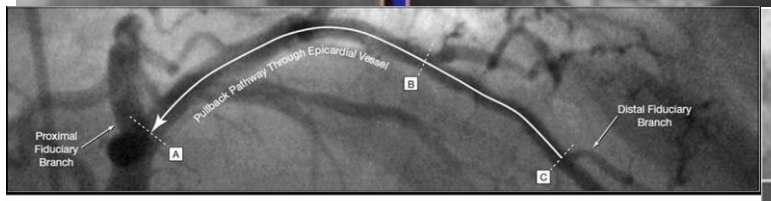
Atherosclerosis is not an arterial luminal disease, but rather an arterial wall disease with compensatory expansion and remodeling to maintain normal lumen and blood flow
S. Glagov circa 1987

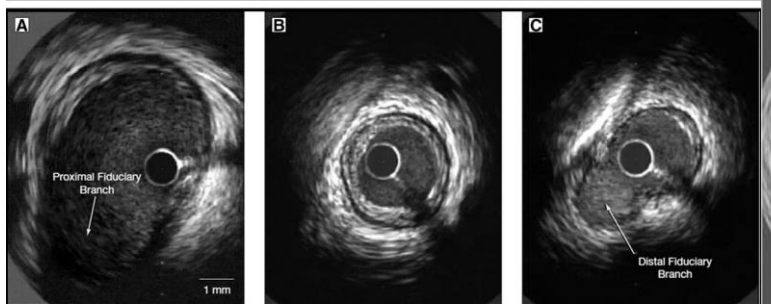


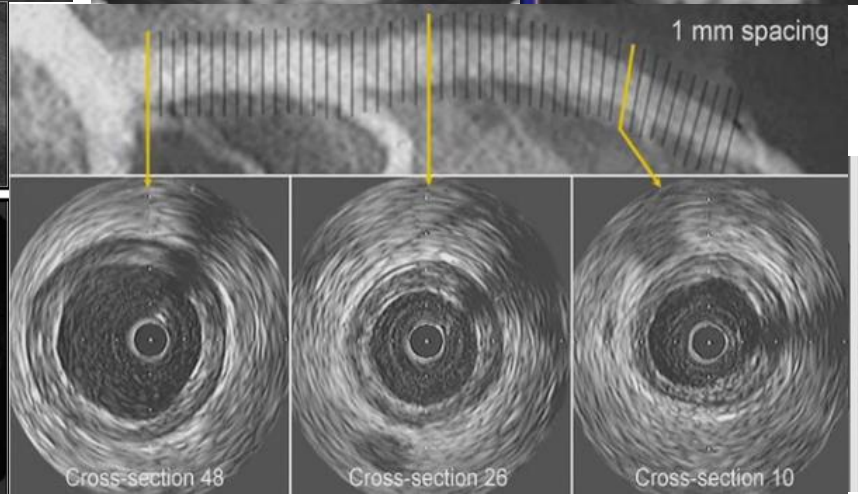
'Normal' Angiogram

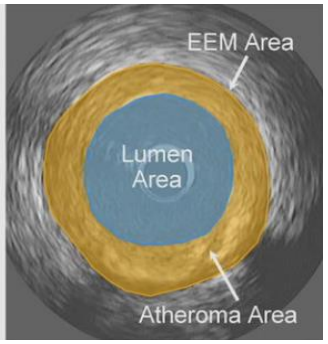




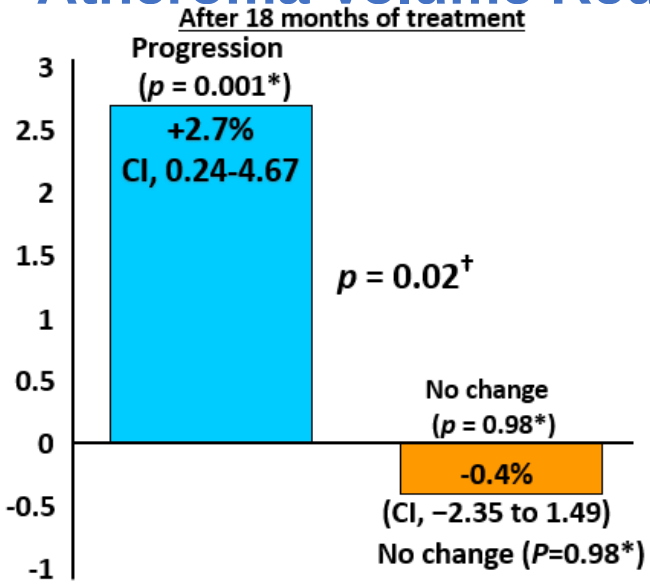






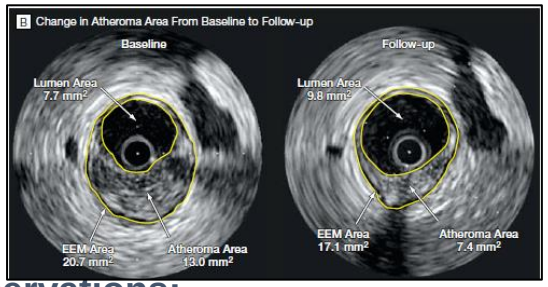


Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL): Atheroma Volume Reduction Correlated to %LDL Change and Achieved LDL-C Level

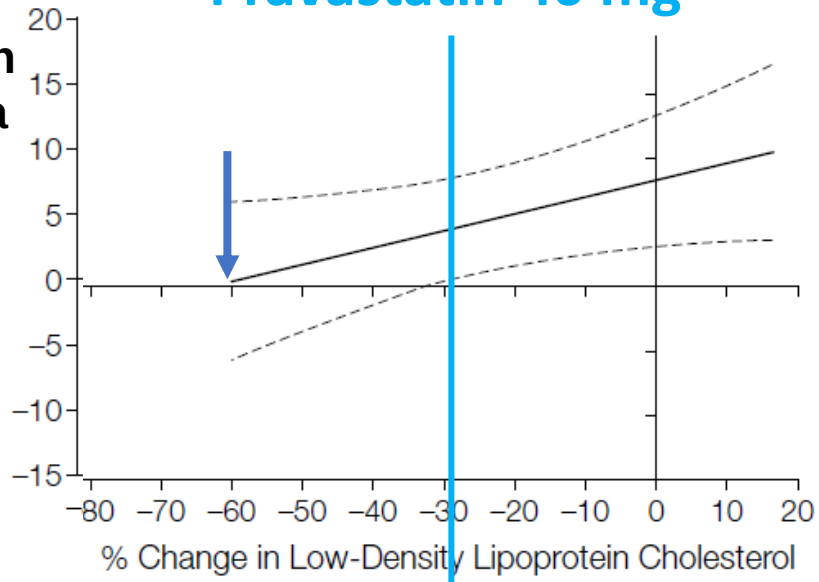


Change in Atheroma Volume, mm^3

No Placebo



Pravastatin 40 mg

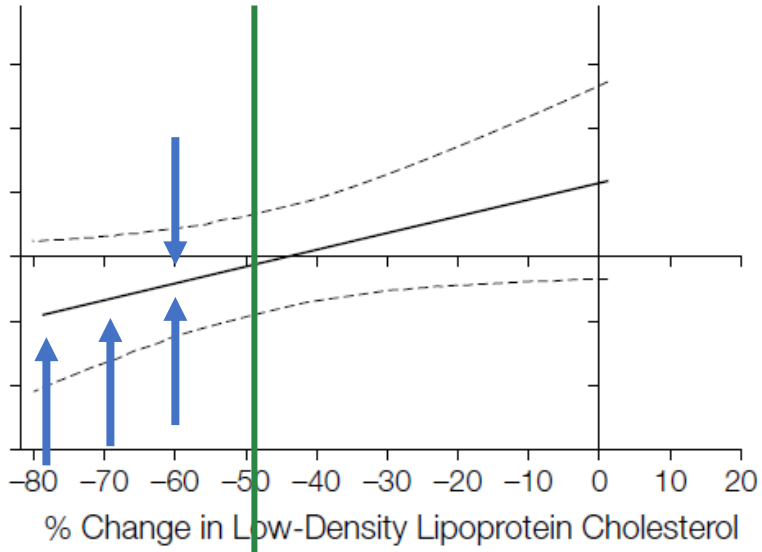


30 45 60 75 90 105 120 135 150

110 ← ↓25%,150 mg/dl

Achieved LDL-C, mg/dL

Atorvastatin 80 mg



30 45 60 75 90 105 120 135 150

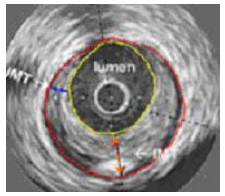
79 ←↓46%, 150 mg/dL

Achieved LDL-C, mg/dL

Selected key observations:

1. For each 10% (15 mg/dL) reduction in LDL-C level, a 1% reduction in atheroma volume was yielded after the 18-month treatment duration.
2. 'Progression' continues below the NCEP ATP III 2001 recommended LDL-C <100 mg/dL.
3. 'Progression' stopped with LDL-C <80 mg/dL in the atorva group, but lower in prava group.
4. 'Regression' is 'continuous' as LDL reductions exceeding >50%-70% LDL-C reduction or LDL-C levels continuously drop well below 75 mg/dL, even below 45 mg/dL.
5. 'Regression' occured with high-intensity statin, but not with the moderate-intensity statin.

Linear Regression Analysis



Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, Crowe T, Howard G, Cooper CJ, Brodie B, Grines CL, DeMaria AN; REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA. 2004 Mar 3;291(9):1071-80. doi: 10.1001/jama.291.9.1071.

2004 ATP III Update*: RCTs that Provided Evidence of Improved Outcomes when Targeted LDL-C was <70 mg/dL for Highest Risk Patients

2004 Evidence* Supportive of Targeted LDL-C Goal <70 mg/dL

Trial Analysis	RCT	LDL-C, mg/dL, achieved
Level 1A RCT	PROVE-IT * (Atorva 80 vs. Prava 40)	62
RCT Subgroup Analyses: Prespecified or Post-hoc	HPS ** - lowest tertile - sub-group <100 mg/dL	 69 65
Imaging: Coronary IVUS trial, Arterial Volume (PAV) % changes by linear regression analysis (LRA)	REVERSAL *** (Atorva 80 vs. Prava 40) Mean 73 mg/dL	LRA 83→30

*__2004 ATP III Update__: Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004 Jul 13;110(2):227-39. doi: 10.1161/01.CIR.0000133317.49796.0E.

Rosenblit PD. Lowering Targeted Atherogenic Lipoprotein Cholesterol Goals for Patients at "Extreme" ASCVD Risk. Curr Diab Rep. 2019 Nov 21;19(12):146. doi: 10.1007/s11892-019-1246-y. .

PROVE-IT: Cannon CP, Braunwald E, McCabe CH, Rader DJ, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004 Apr 8;350(15):1495-504. doi: 10.1056/NEJMoa040583.
HPS: Heart Protection Study Collaborative Group. **MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial**. Lancet. 2002;360:7–22.
REVERSAL: Nissen SE, Tuzcu EM, Schoenhagen P, et al. **Effect of intensive compared with moderate lipid lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial.** JAMA. 2004;291:1071–80.

√

Intensive LDL-C Goals for High-Risk and Highest Patients

Recommended LDL-C treatment goals

ATP III Update 2004

<100 mg/dL: Patients with CHD or CHD risk Equivalents* (10-year risk >20%)
<70 mg/dL: "Therapeutic option" for "very high-risk patients"

<100 mg/dL

<70 mg/dL

2006 AHA/ACC guidelines for patients with CHD*,[2]

<100 mg/dL: Goal for all patients with CHD†,
<70 mg/dL: "Reasonable goal" for "all patients with CHD"†,[2]

2006 AHA/ACC Update

* **And other forms of atherosclerotic disease.[2]**

† Factors that place a patient at **very high risk:**
established CV plus: multiple major risk factors (especially diabetes); severe and poorly controlled risk factors (eg, cigarette smoking); metabolic syndrome (triglycerides [TG] ≥200 mg/dL + non–HDL-C ≥130 mg/dL with HDL-C <40 mg/dL); and **acute coronary syndromes (ACS)**

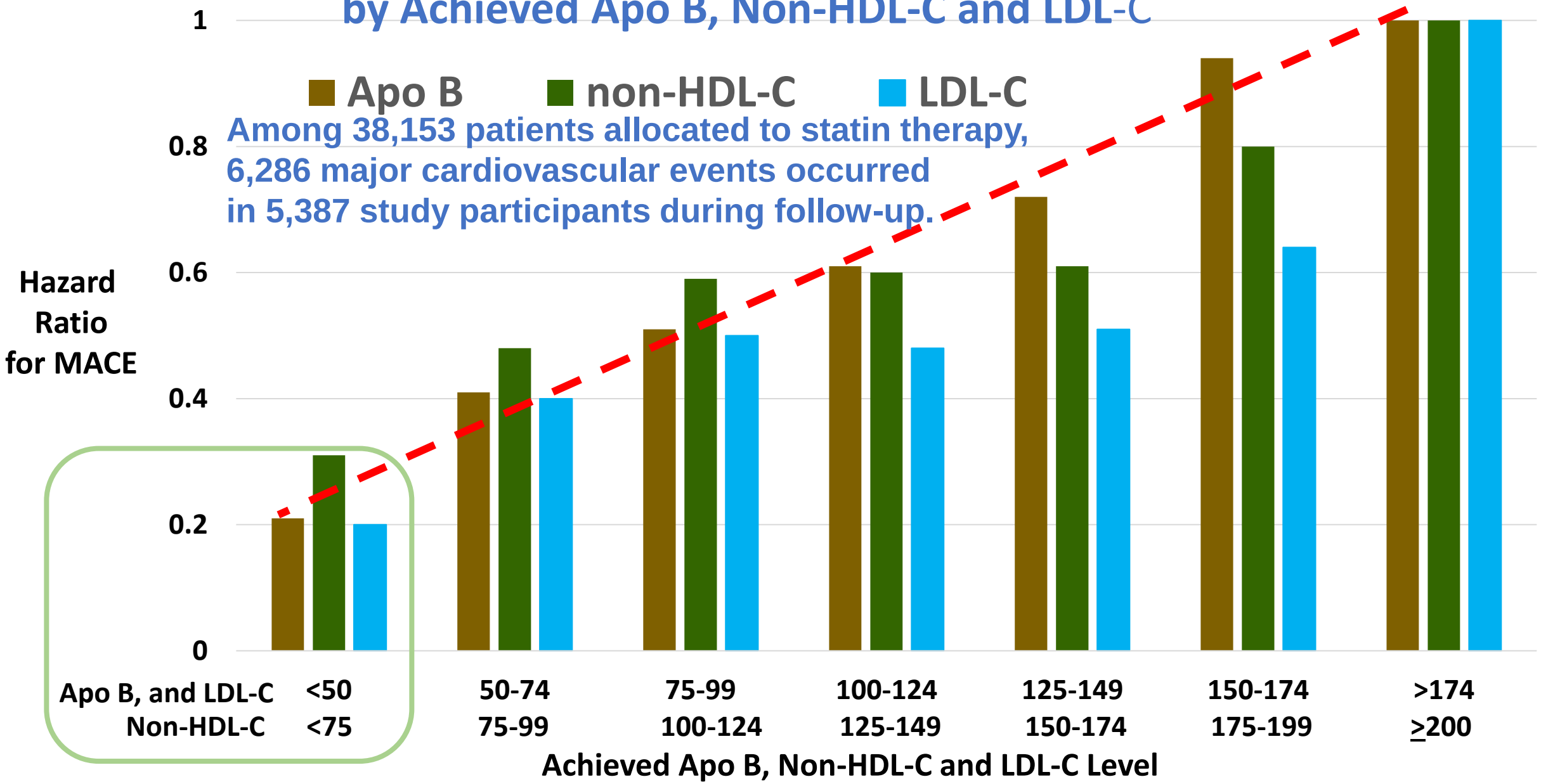
"If it is not possible to attain LDL-C <70 mg/dL, because of a high baseline LDL-C, it generally is possible to achieve LDL-C reductions of >50% with more intensive LDL-C–lowering therapy, including drug combinations."

Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. **Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines.** Circulation. 2004 Jul 13;110(2):227-39. doi: 10.1161/01.CIR.0000133317.49796.0E.

Smith SC Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, Grundy SM, Hiratzka L, Jones D, Krumholz HM, Mosca L, Pasternak RC, Pearson T, Pfeffer MA, Taubert KA; AHA/ACC; National Heart, Lung, and Blood Institute. **AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update**: endorsed by the National Heart, Lung, and Blood Institute. Circulation. 2006 May 16;113(19):2363-2372. doi: 10.1161/CIRCULATIONAHA.106.174516.

What was the basis for “<55 mg/dL” becoming the “Goal of Therapy” when Targeting LDL-C for Lowering to Reduce ASCVD risk in the 2017 AACE Guidelines and Algorithm?

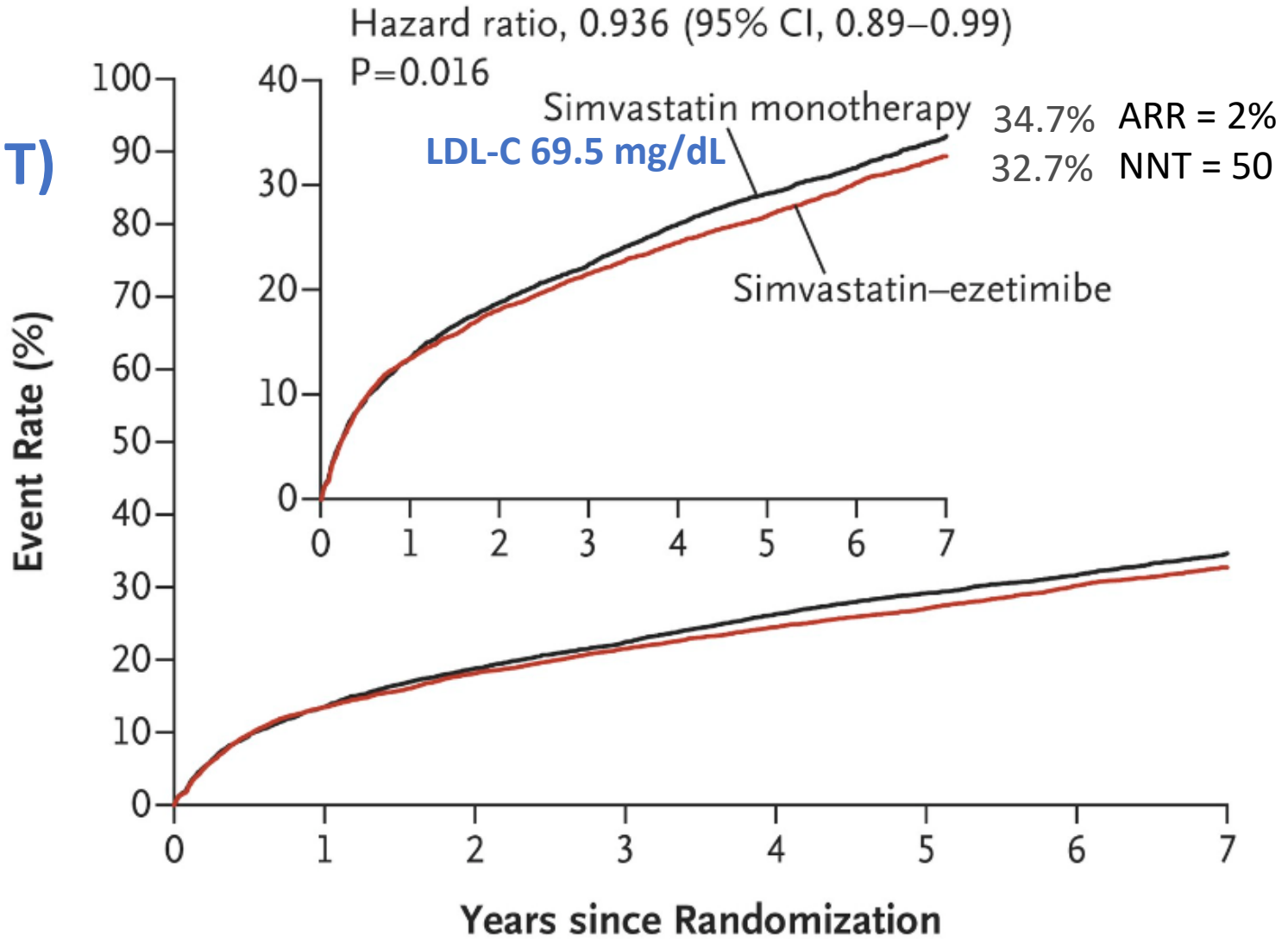
Hazard Ratio for Major Cardiovascular Events, MACE, by Achieved Apo B, Non-HDL-C and LDL-C



Boekholdt SM, Hovingh, GK, Mora S, et al. JACC. 2014;64(5):485-494.

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) Kaplan–Meier Curves for the Primary Efficacy End Point.

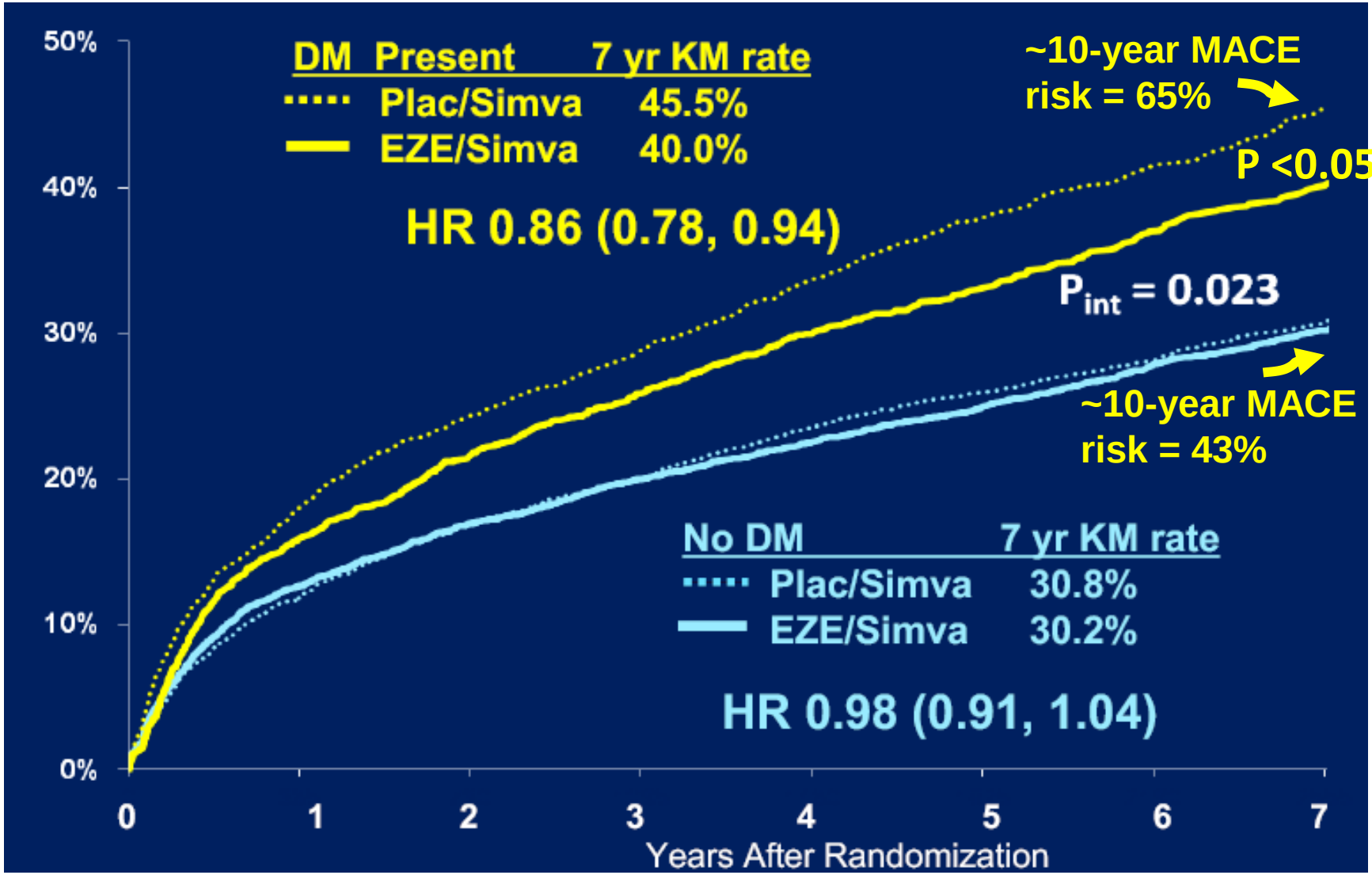
CVD death,
nonfatal MI,
nonfatal stroke,
unstable angina requiring hospital admission, or
coronary revascularization occurring at least 30 days after randomization),
in the intention-to-treat population



No. at Risk								
Simvastatin–ezetimibe	9067	7371	6801	6375	5839	4284	3301	1906
Simvastatin	9077	7455	6799	6327	5729	4206	3284	1857

Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators.
Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes.
N Engl J Med. 2015 Jun 18;372(25):2387-97.
doi: 10.1056/NEJMoa1410489.

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT): Pre-specified Subgroup by Diabetes Status



Diabetes Present

Relative Risk Reduction

RRR = 14%

Absolute Risk Reduction

ARR = 5.5%

7-yr (6-yr median) NNT = 18

Diabetes Not Present

RRR = 2%

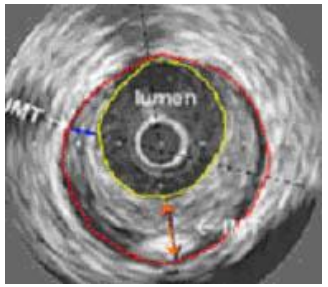
ARR = 0.6%

7-yr (6-yr median) NNT = 166

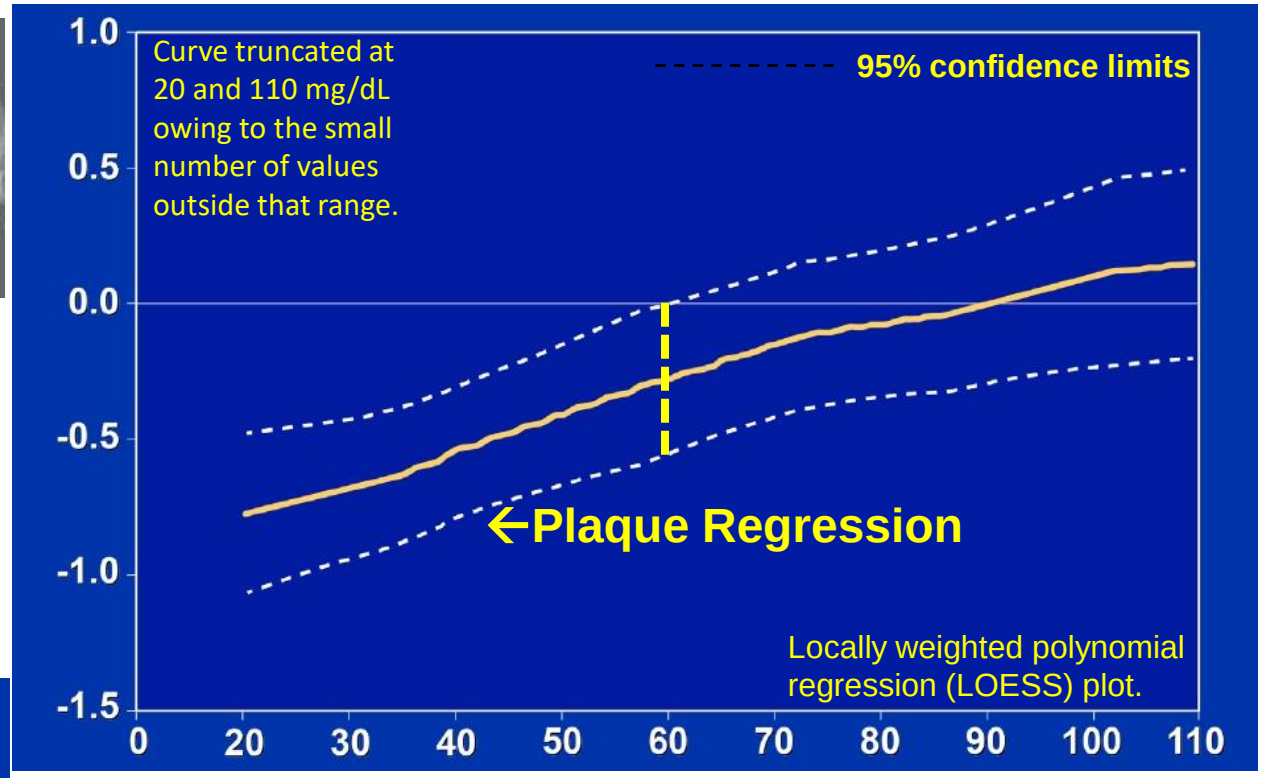
Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators.
Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes.
N Engl J Med. 2015 Jun 18;372(25):2387-97.
doi: 10.1056/NEJMoa1410489

GLAGOV: 1.5 years F-U Mean On-Treatment LDL-C vs. Change in PAV,

The GLAGOV multicenter, double-blind, placebo-controlled, randomized clinical trial (enrollment 5/2013 to 1/2015) conducted at 197 academic & community hospitals in 6 continents, enrolling patients (n=968, mean age 59.8 yrs, 27.8% female) with coronary angiographic CAD.

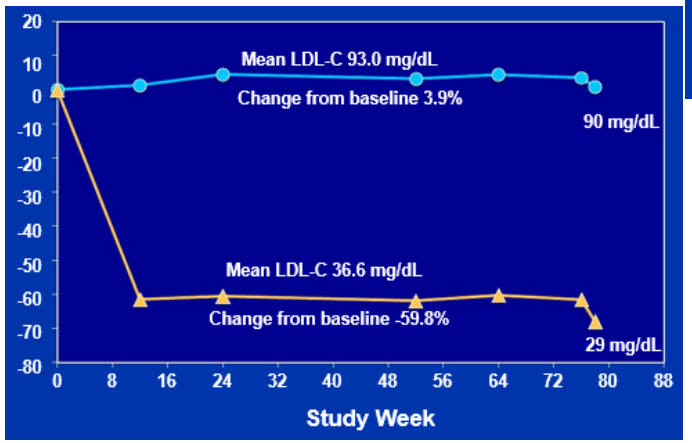


Change Percent Atheroma Volume, PAV (%)



Achieved On-Treatment LDL-C (mg/dL)

LDL-C Change from Baseline (mg/dL)



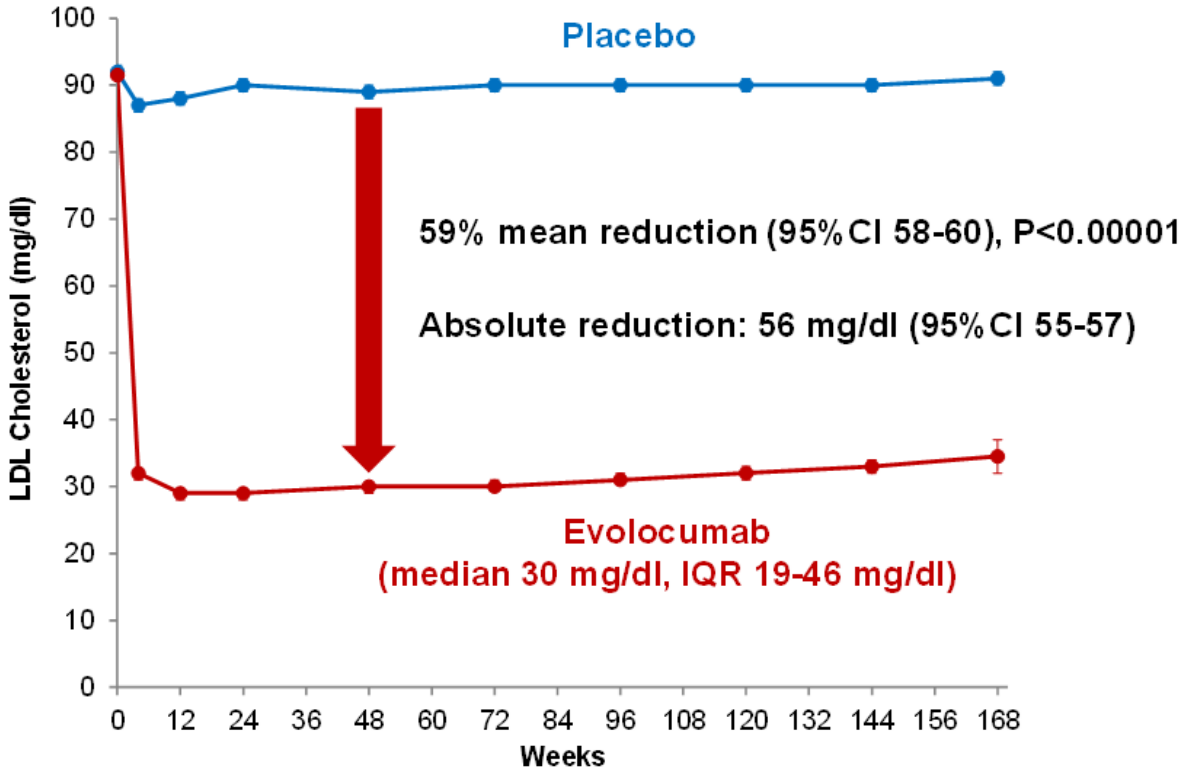
Patients with angiographic CAD on mod- to high- intensity statin with LDL-C > 80 mg/dL (or LDL-C 60-80 mg/dL if with multiple risk factors), were randomized to receive Monthly evolocumab(420mg) (n = 484) or placebo (n = 484) via subcutaneous injection for 76 weeks.

A linear continuous relationship between achieved LDL-C level and PAV progression / regression for levels of LDL-C ranging from 110 mg/dL to as low as 20mg/dL.

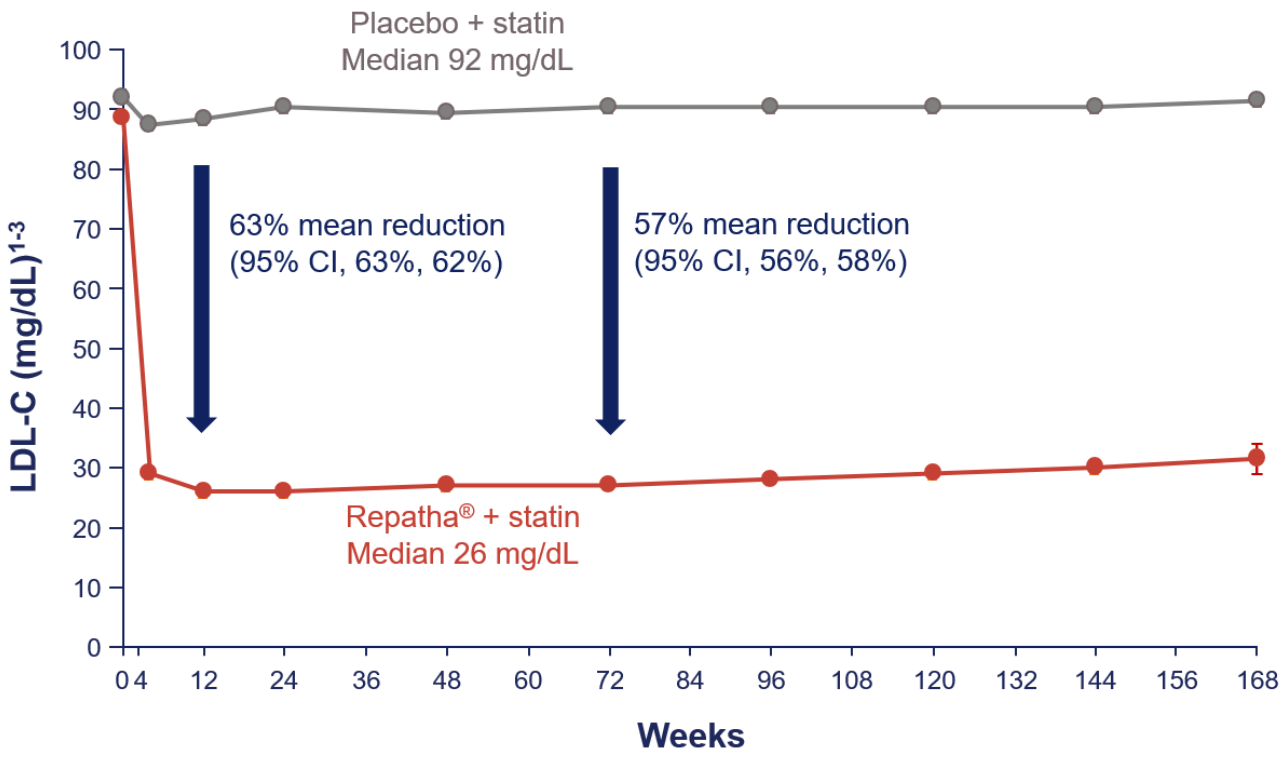
Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, Koenig W, Somaratne R, Kassahun H, Yang J, Wasserman SM, Scott R, Ungi I, Podolec J, Ophuis AO, Cornel JH, Borgman M, Brennan DM, Nissen SE. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. JAMA. 2016 Dec 13;316(22):2373-2384. doi: 10.1001/jama.2016.16951.

FOURIER: Efficacy in LDL-C Lowing

Intention-to-Treat (ITT) Analysis



On-Treatment Analysis

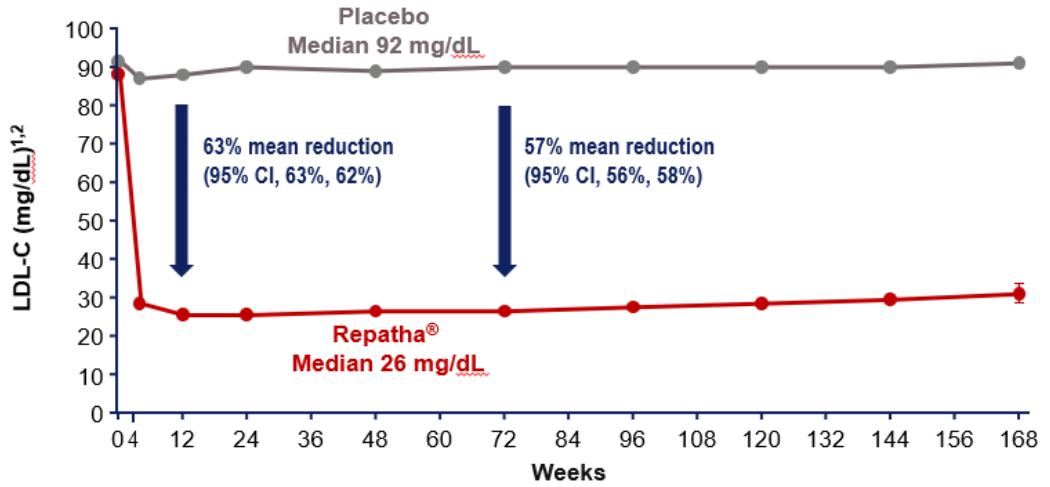


A fixed cohort of 11,077 patients who:

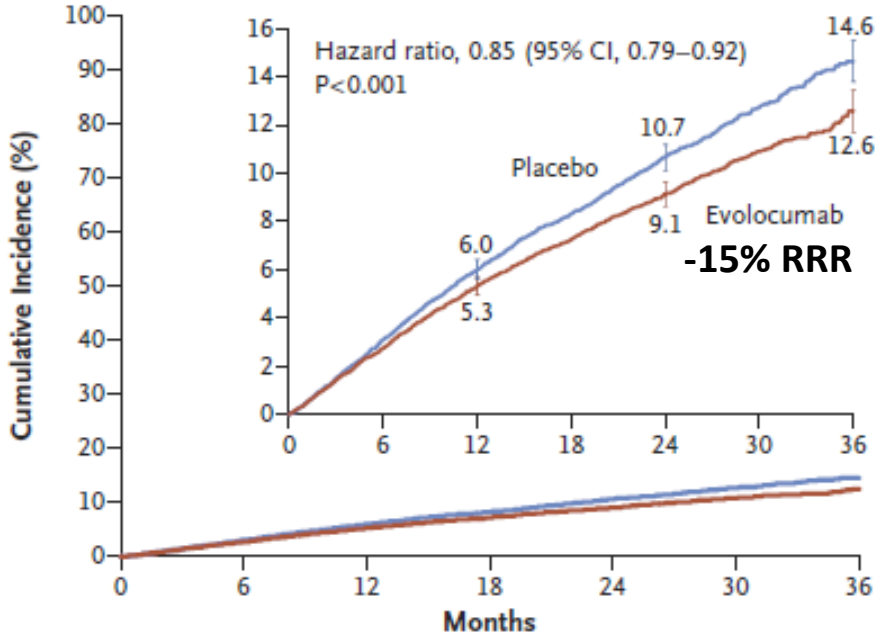
- **had all measurements through 120 weeks,**
- **did not discontinue study drug, and**
- **did not change concomitant background lipid lowering therapy.**

Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. for the FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376(18):1713–22. https://doi.org/10.1056/NEJMoa1615664.

FOURIER Further Cardiovascular OUtcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk

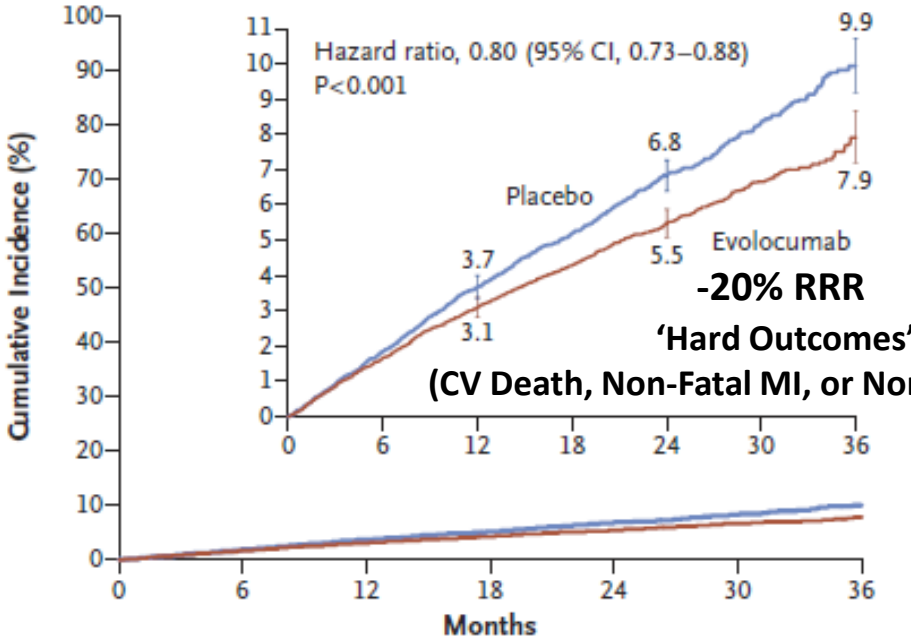


A Primary Efficacy End Point



No. at Risk							
Placebo	13,780	13,278	12,825	11,871	7610	3690	686
Evolocumab	13,784	13,351	12,939	12,070	7771	3746	689

B Key Secondary Efficacy End Point



No. at Risk							
Placebo	13,780	13,449	13,142	12,288	7944	3893	731
Evolocumab	13,784	13,501	13,241	12,456	8094	3935	724

2017 AACE Algorithm: RCTs that Provided Evidence of Improved Outcomes when Targeted LDL-C was <55 mg/dL for Highest Risk Patients

2017 Evidence* Supportive of Targeted LDL-C Goal <55 mg/dL

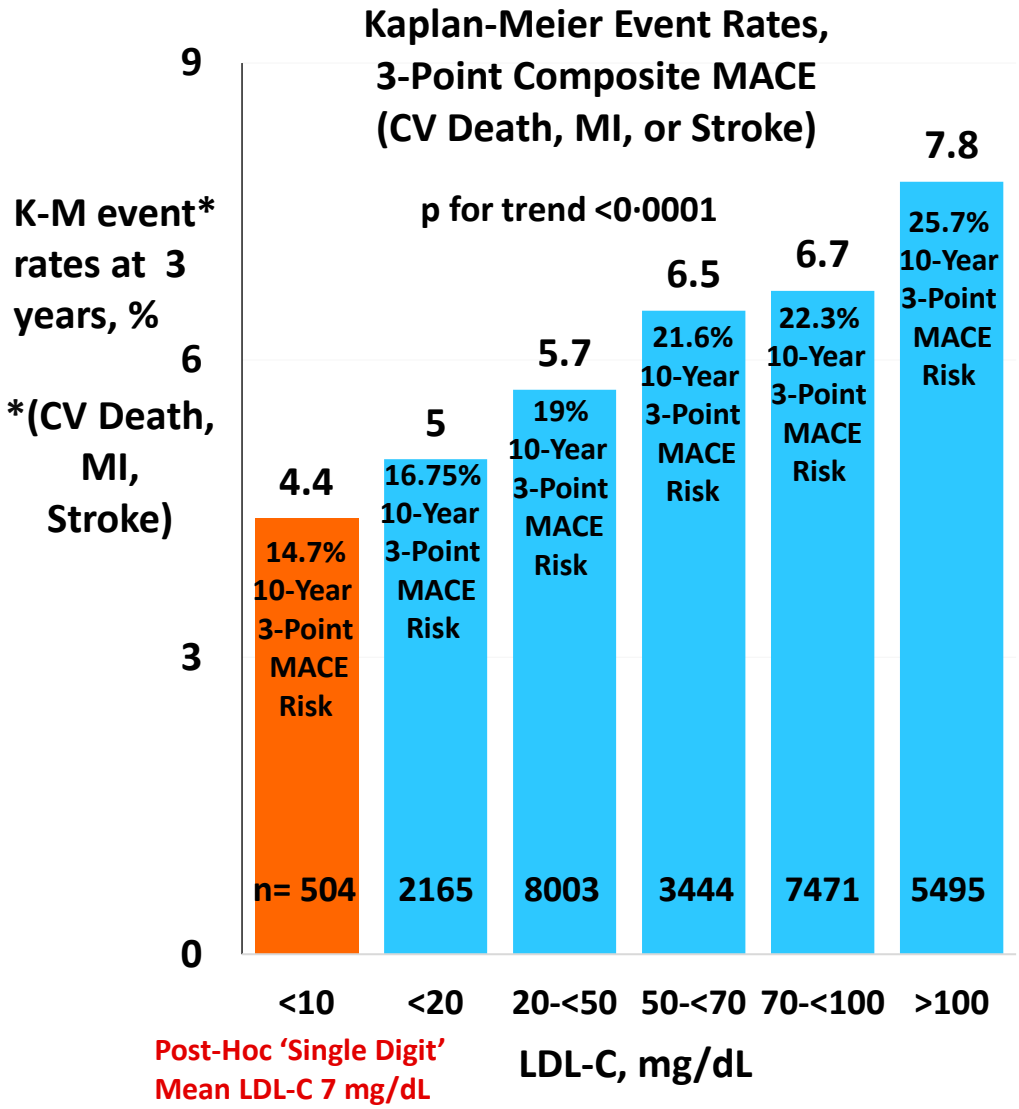
Trial Analysis	RCT	LDL-C, mg/dL, achieved
Level 1A RCT	IMPROVE-IT *	53.5
	FOURIER	30
Subgroup Analyses: Prespecified or Post-hoc	PROVE-IT TNT VA Palo Alto Healthcare JUPITOR	40 54 40 44
Meta-analysis RCT Statin Trials	8 Statin RCTs -divided by Quartiles -divided by Septiles	Q1(<62)mean 49 S1, <50
Imaging: Coronary IVUS trial, Percent Arterial Volume (PAV)	GLAGOV	mean 36.6
Imaging: Coronary IVUS trial, PAV changes by linear regression analysis (LRA)	REVERSAL *** Mean 73 mg/dL	LRA 83→30

Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al. **2017 AACE/ACE** Guidelines American Association of Clinical Endocrinologists and American College of Endocrinology **Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease**. Endocr Pract. 2017;23(Supplement 2):1–87.

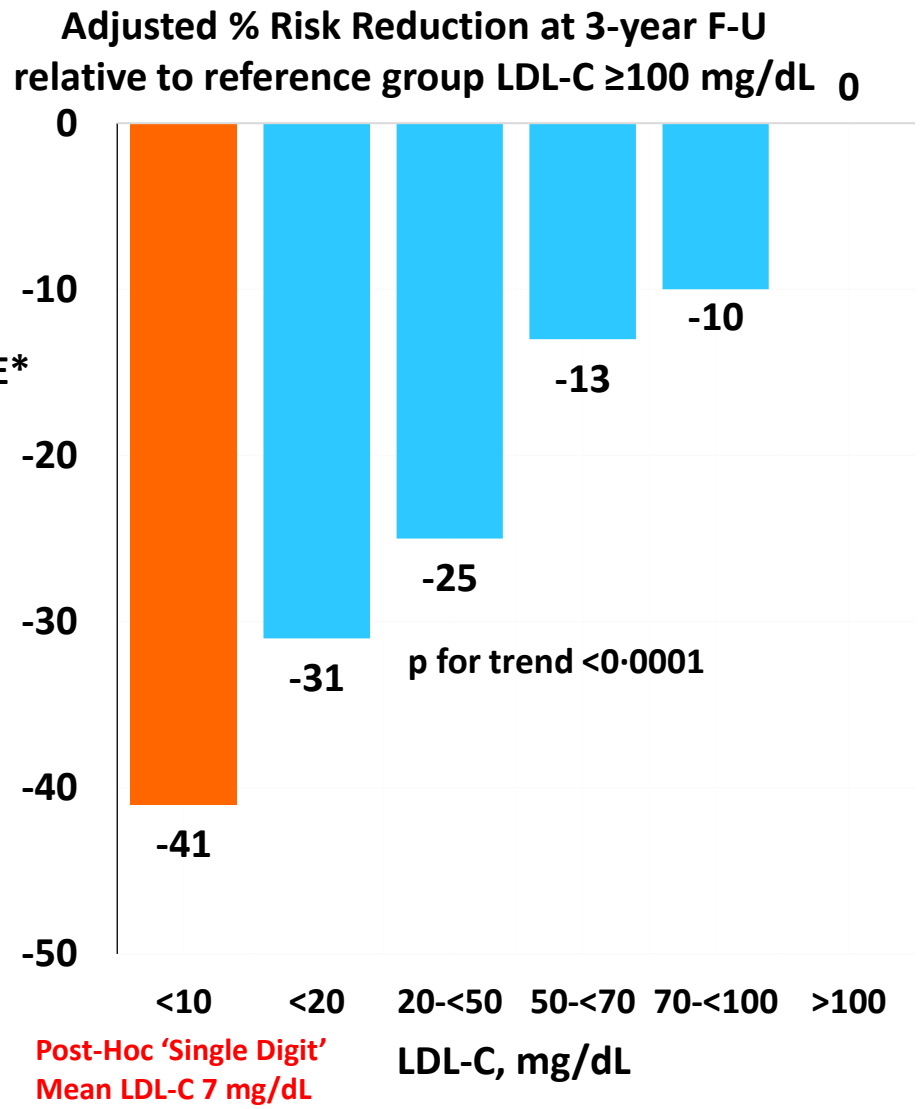
Rosenblit PD. **Lowering Targeted Atherogenic Lipoprotein Cholesterol Goals for Patients at 'Extreme' ASCVD Risk**. Current Diabetes Reports. 2019;19(12):146:1-18.

Can Patients Benefit from Targeting an LDL-C to an Even Lower Goal, i.e., <30 mg/dL ?

FOURIER: *Prespecified Analysis and a Post-Hoc Analysis* of the Relationship Between the Achieved LDL-C Level at 4 weeks and the Risk of the Secondary Efficacy Composite* Endpoints



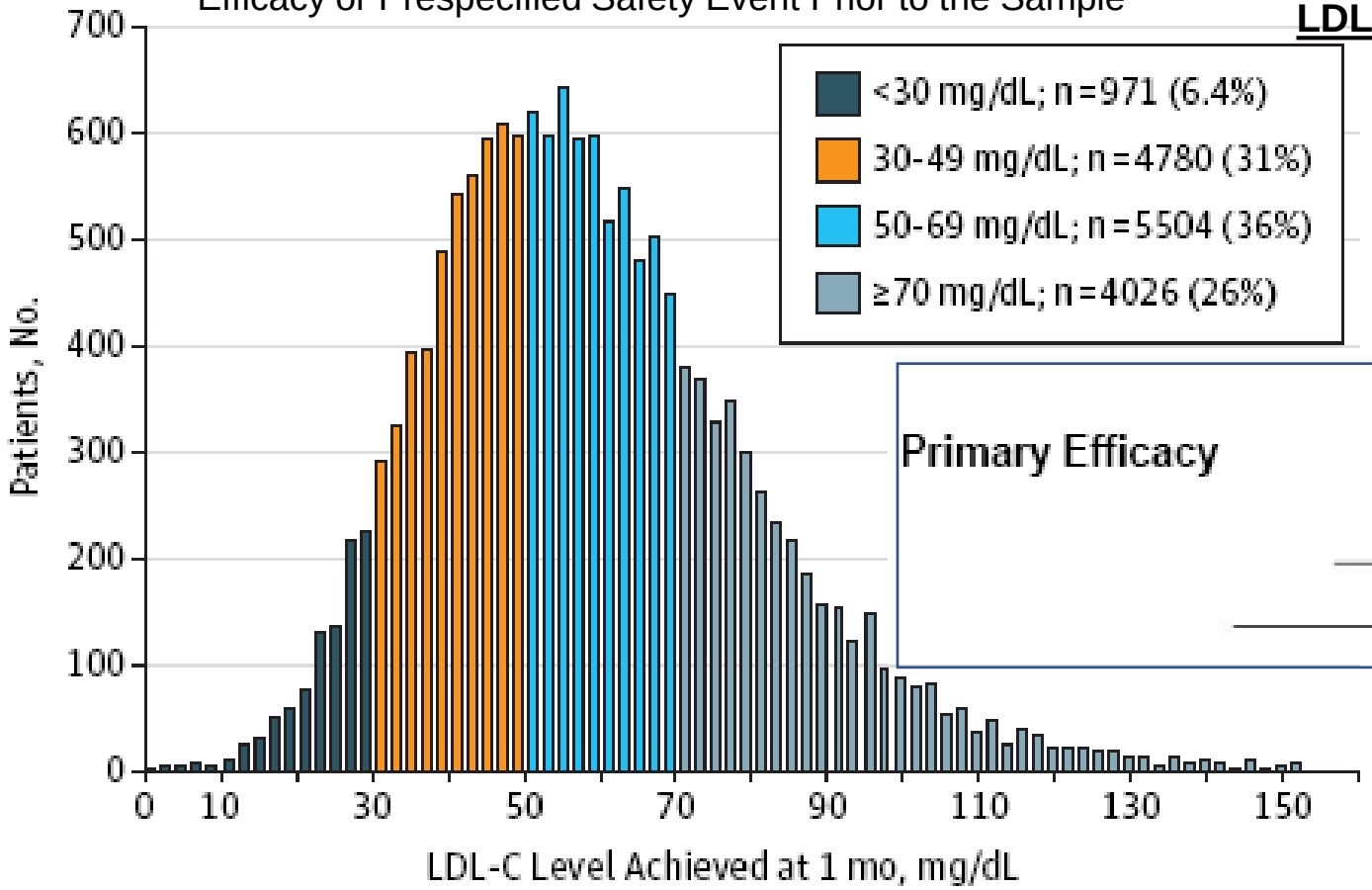
Patient Background Hx
Clinical ASCVD (100%)
Single morbidity
= 'Very-high' risk (85%)
= 10-year MACE* risk >20%
Polyvascular Disease (15%) or Diabetes (40%) = 'Extreme' risk
= 10-year MACE* risk >30%
Standard-of-care management
ACEi or ARB 78.4%
Beta Blocker 75.8%
Aspirin, P2Y12, or DAPT 93%
Statin 99.7% (LDL=92 mg/dL]



Giugliano RP, Pedersen TR, Park JG, De Ferrari GM, Gaciong ZA, Ceska R, Toth K, Gouni-Berthold I, Lopez-Miranda J, Schiele F, Mach F, Ott BR, Kanevsky E, Pineda AL, Somaratne R, Wasserman SM, Keech AC, Sever PS, Sabatine MS; for the FOURIER Investigators. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. Lancet. 2017;390(10106):1962-1971..doi: 10.1016/S0140-6736(17)32290-0.

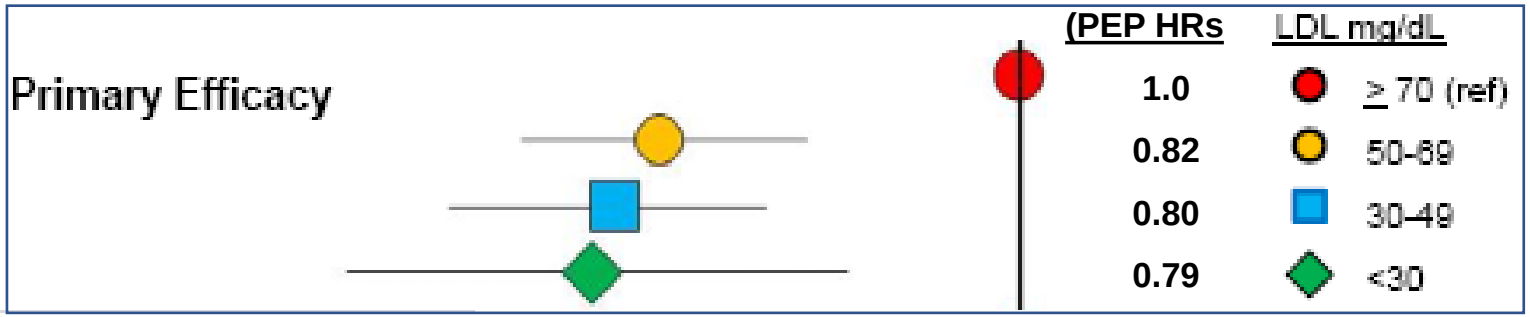
IMPROVE-IT: Very Low LDL-C Levels (<30 mg/dL)

Distribution of Achieved Calculated LDL-C Level
at 1 Month Among Patients Who Did Not Have a Primary Efficacy or Prespecified Safety Event Prior to the Sample



Time-Weighted Mean LDL-C 4-72 months	
<30 mg/dL; n=971 (6.4%)	34.4 mg/dL
30-49 mg/dL; n=4780 (31%)	48.3 mg/dL
50-69 mg/dL; n=5504 (36%)	63.3 mg/dL
≥70 mg/dL; n=4026 (26%)	79.9 mg/dL

The adjusted risk of the primary efficacy (PEP) composite (CV death, major coronary events*, or stroke) was significantly (21%) lower in patients achieving an LDL-C level <30 mg/dL at 1 month (adjusted hazard ratio, 0.79; 95% CI, 0.69-0.91; *P* = 0.001) compared with ≥70 mg/dL.



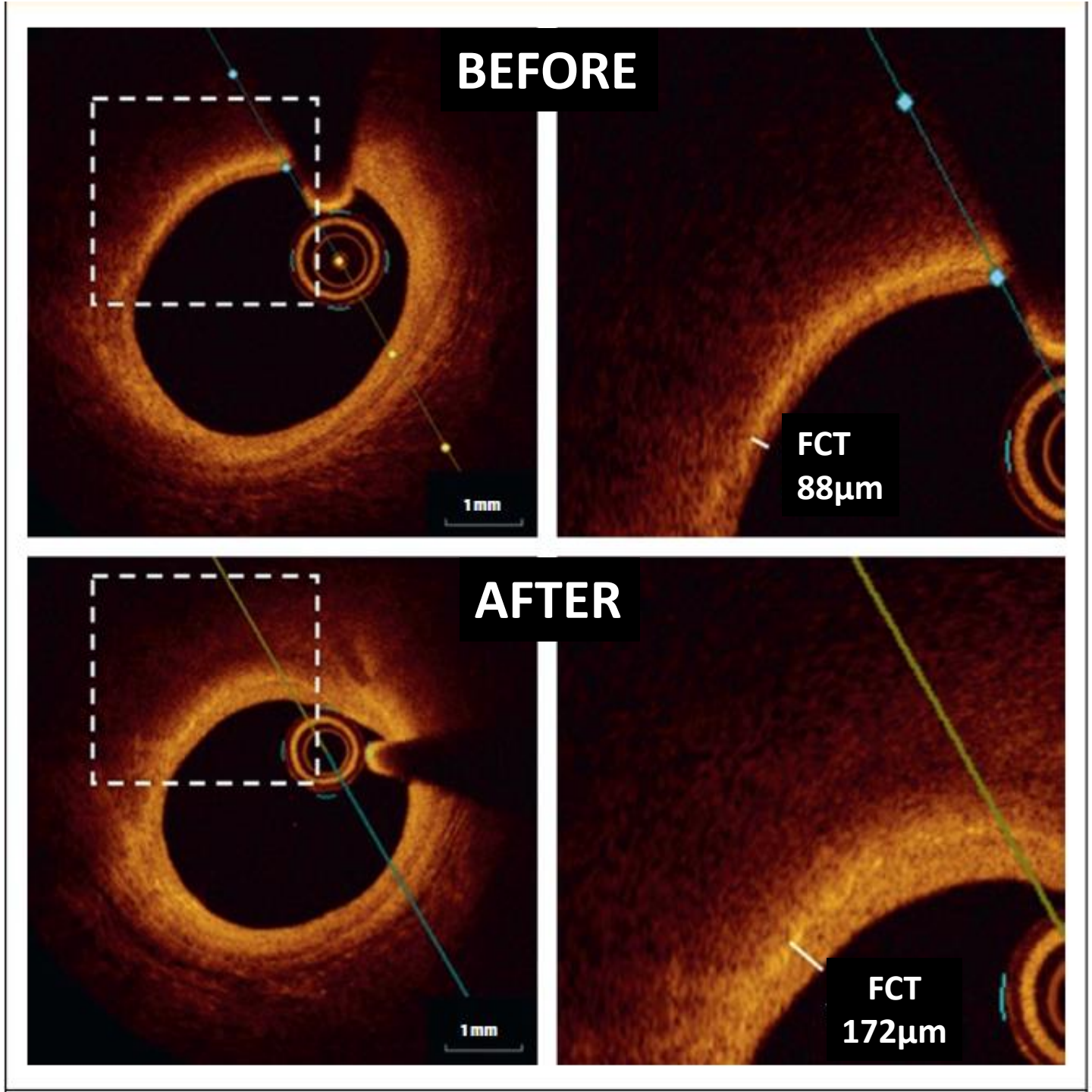
*myocardial infarction (MI), unstable angina requiring hospitalization (UA), coronary revascularization > 30 days after randomization (revasc),

Giugliano RP, Wiviott SD, Blazing WA, De Ferrari GM, Park J-G, Murphy SA, White JA, Tershakovec AM, Cannon CP, Braunwald E. Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol A Prespecified Analysis of the IMPROVE-IT Trial. JAMA Cardiol. 2017;2(5):547-555 & Suppl. doi:10.1001/jamacardio.2017.0083

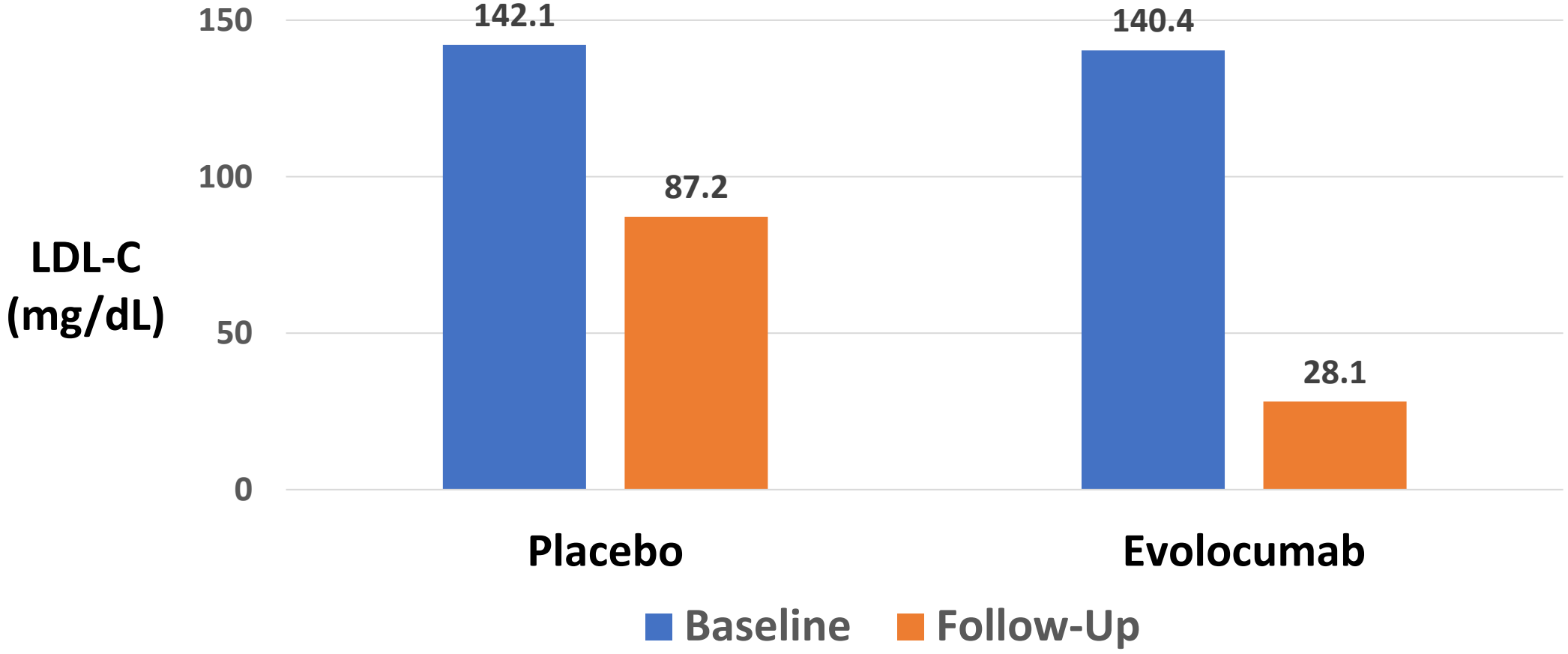
High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study (HUYGENS)

Effect of Evolocumab on Coronary Plaque Phenotype and Burden in Statin-Treated Patients Following Myocardial Infarction Evaluating Measures of Plaque Composition by Optical Coherence Tomography (OCT)

Nicholls SJ, Kataoka Y, Nissen SE, Prati F, Windecker S, Puri R, Hucko T, Aradi D, Herrman JR, Hermanides RS, Wang B, Wang H, Butters J, Di Giovanni G, Jones S, Pompili G, Psaltis PJ.
Effect of Evolocumab on Coronary Plaque Phenotype and Burden in Statin-Treated Patients Following Myocardial Infarction.
JACC Cardiovasc Imaging. 2022 Jul;15(7):1308-1321.
doi: 10.1016/j.jcmg.2022.03.002.

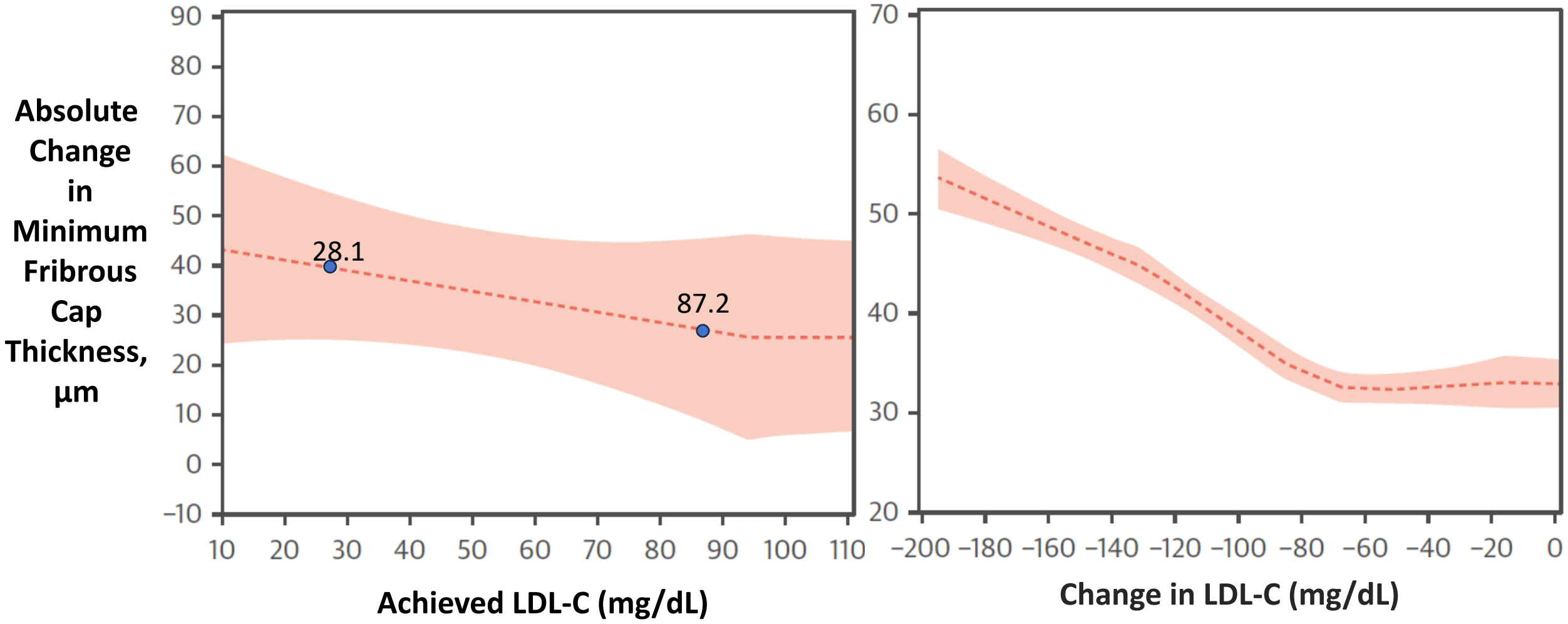


High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study (HUYGENS): Effect of Evolocumab on in Statin-Treated Patients Following Myocardial Infarction



Nicholls SJ, Kataoka Y, Nissen SE, Prati F, Windecker S, Puri R, Hucko T, Aradi D, Herrman JR, Hermanides RS, Wang B, Wang H, Butters J, Di Giovanni G, Jones S, Pompili G, Psaltis PJ. Effect of Evolocumab on Coronary Plaque Phenotype and Burden in Statin-Treated Patients Following Myocardial Infarction. JACC Cardiovasc Imaging. 2022 Jul;15(7):1308-1321. doi: 10.1016/j.jcmg.2022.03.002.

LOESS Plot for Change in Minimum Fribrous Cap Thickness FCT versus Achieved LDL-C (mg/dL) Change in LDL-C (mg/dL)



Nicholls SJ, Kataoka Y, Nissen SE, Prati F, Windecker S, Puri R, Hucko T, Aradi D, Herrman JR, Hermanides RS, Wang B, Wang H, Butters J, Di Giovanni G, Jones S, Pompili G, Psaltis PJ. Effect of Evolocumab on Coronary Plaque Phenotype and Burden in Statin-Treated Patients Following Myocardial Infarction. JACC Cardiovasc Imaging. 2022 Jul;15(7):1308-1321. doi: 10.1016/j.jcmg.2022.03.002.

RCTs that Provided Evidence of Improved Outcomes when Targeted LDL-C was <30 mg/dL for Highest Risk Patients; Further Validating the AACE Guideline 'Extreme Risk' Targeted LDL-C Goal <55 mg/dL (No Lower Limit)

Reduced CV Outcomes Achieved with LDL-C Level <30 mg/dL

Trial Analysis	RCT	LDL-C, mg/dL, achieved
Level 1A Large RCT	FOURIER (stable CAD)	<30 (median 26)
Subgroup Analysis Prespecified or Post-hoc	IMPROVE-IT (ACS) FOURIER (stable CAD)	<30 <20 <10 (7)
Imaging: Coronary IVUS trial, Percent Arterial Volume (PAV) changes by linear regression analysis (LRA)-post-hoc LOESS plot	8 Statin IVUS trials GLAGOV (stable CAD) mean 36.6	LRA 93→15 LRA 90→20

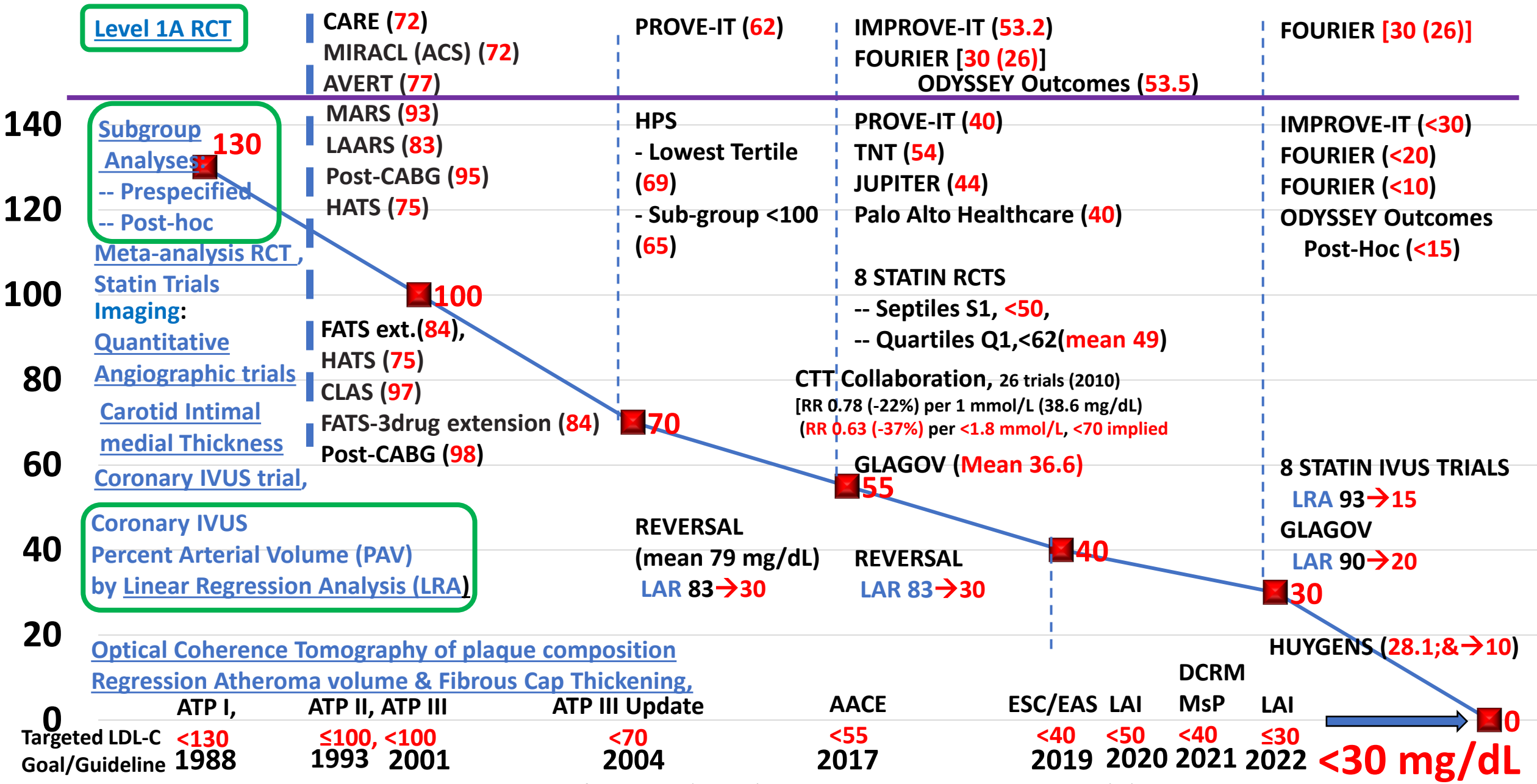
Reviewed: Rosenblit PD. Lowering Targeted Atherogenic Lipoprotein Cholesterol Goals for Patients at 'Extreme' ASCVD Risk. Current Diabetes Reports. 2019;19(12):146:1-18.

Subgroup Analysis-Post-hoc	ODYSSEY* (ACS)(median 8.3 mos. after randomization) before substitution of PBO	30 (<15)

*Schwartz G, Szarek M, Li QH, Chiang CE, Diaz R, Hagstrom E, Huo Y, Jukema YW, Lecorps G, Moryusef A, Pordy R, White HD, Yusoff K, Zeiher AM, Steg BG. Eur Heart J. Oct. 2019;40(Supp1):Abstract: P1226.

Imaging: OCT	Huygens	28.5

Lower Achieved LDL-C (mg/dL) & Greater Reduction of CV Outcomes among Highest Risk



Rosenblit PD. Lowering Targeted Atherogenic Lipoprotein Cholesterol Goals for Patients at 'Extreme' ASCVD Risk. Current Diabetes Reports. 2019;19(12):146:1-18.

Wong ND, Puri R, Mehta V, Duell PB. When is it Appropriate to Lower Low Density Lipoprotein-Cholesterol Levels to <30 mg/dL? Am J Cardiol. 2021 Oct 15;157:142-144. doi: 10.1016/j.amjcard.2021.06.041.

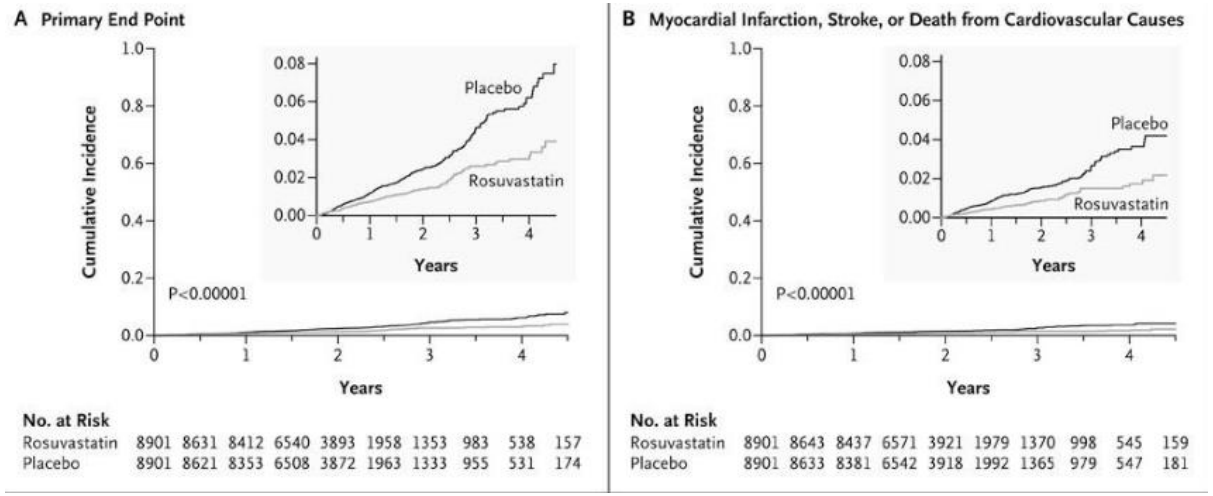
JUPITER

Justification for the **U**se of Statins in **P**revention: an **I**ntervention **T**rial Evaluating **R**osuvastatin

17,802 apparently healthy men and women

LDL-C levels <130 mg/dL and hs-CRP ≥2.0 mg/dL

Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008 Nov 20;359(21):2195-207. doi: 10.1056/NEJMoa0807646.



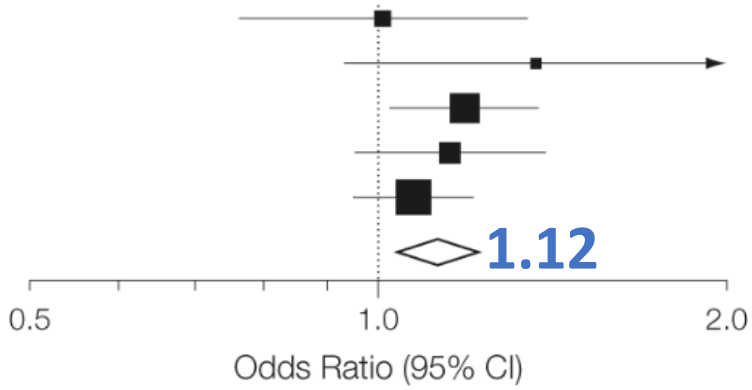
Median follow-up period of 1.9 years (maximum, 5.0)
44% RRR in Primary endpoint (p<0.00001)
47% RRR in MI, Stroke or Death (p<0.00001)

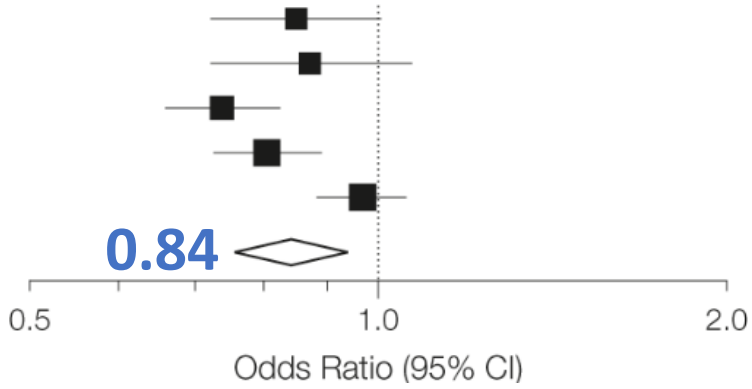
Statins and Diabetes

	Rosuvastatin (N=8901)	Placebo (N=8901)	P Value
Laboratory values‡			
Creatinine, >100% increase from baseline — no. (%)	16 (0.2)	10 (0.1)	0.24
Glomerular filtration rate at 12 mo — ml/min/1.73 m²			0.02
Median	66.8	66.6	
Interquartile range	59.1–76.5	58.8–76.2	
Alanine aminotransferase >3× ULN on consecutive visits — no. (%)	23 (0.3)	17 (0.2)	0.34
Glycated hemoglobin at 24 mo — %			0.001
Median	5.9	5.8	
Interquartile range	5.7–6.1	5.6–6.1	
Fasting glucose at 24 mo — mg/dl			0.12
Median	98	98	
Interquartile range	91–107	90–106	
>Trace of glucose in urine at 12 mo — no. (%)	36 (0.5)	32 (0.4)	0.64
Other events			
Newly diagnosed diabetes (physician-reported) — no. (%)	270 (3.0)	216 (2.4)	0.01
Hemorrhagic stroke — no. (%)	6 (0.1)	9 (0.1)	0.44

Meta-analysis of New-Onset Diabetes and First Major Cardiovascular Events in 5 Large Trials Comparing Intensive-Dose to Moderate Dose Statin Therapy

	Cases/Total, No. (%)		
	Intensive Dose	Moderate Dose	OR (95% CI)
Incident Diabetes			
PROVE IT–TIMI 22,[18] 2004	101/1707 (5.9)	99/1688 (5.9)	1.01 (0.76-1.34)
A to Z,[17] 2004	65/1768 (3.7)	47/1736 (2.7)	1.37 (0.94-2.01)
TNT,[15] 2005	418/3798 (11.0)	358/3797 (9.4)	1.19 (1.02-1.38)
IDEAL,[16] 2005	240/3737 (6.4)	209/3724 (5.6)	1.15 (0.95-1.40)
SEARCH,[5] 2010	625/5398 (11.6)	587/5399 (10.9)	1.07 (0.95-1.21)
Pooled odds ratio	**1449/16 408 (8.8)**	**1300/16 344 (8.0)**	**1.12 (1.04-1.22)**
Heterogeneity: $I^2 = 0\%$; $P = .60$			
Incident CVD			
PROVE IT–TIMI 22,[18] 2004	315/1707 (18.4)	355/1688 (21.0)	0.85 (0.72-1.01)
A to Z,[17] 2004	212/1768 (12.0)	234/1736 (13.5)	0.87 (0.72-1.07)
TNT,[15] 2005	647/3798 (17.0)	830/3797 (21.9)	0.73 (0.65-0.82)
IDEAL,[16] 2005	776/3737 (20.8)	917/3724 (24.6)	0.80 (0.72-0.89)
SEARCH,[5] 2010	1184/5398 (21.9)	1214/5399 (22.5)	0.97 (0.88-1.06)
Pooled odds ratio	**3134/16 408 (19.1)**	**3550/16 344 (21.7)**	**0.84 (0.75-0.94)**
Heterogeneity: $I^2 = 74\%$; $P = .004$			





Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, DeMicco DA, Barter P, Cannon CP, Sabatine MS, Braunwald E, Kastelein JJ, de Lemos JA, Blazing MA, Pedersen TR, Tikkanen MJ, Sattar N, Ray KK.
Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis.
JAMA. 2011 Jun 22;305(24):2556-64. doi: 10.1001/jama.2011.860.

6.5 fewer CVD events/1000 pt-yrs
2 cases of New-onset DM/1000 pt-yrs

National Lipid Association (NLA) Expert Panel.
An Assessment by the Statin Diabetes Safety Task Force: 2014 update.

Statin use is associated with **a modest, but statistically significant, overall increase in the odds for new-onset diabetes (~10%** compared with placebo or usual care). **Intensive-dose statin therapy is associated with an increase in risk for new-onset diabetes of ~12%** compared with standard dose statin therapy.

US Food and Drug Administration in 2012 added a statement to the labels of statin medications indicating that increases in glycated hemoglobin (HbA1C) and fasting glucose levels have been reported with statin use.

Statin therapy is effective for reducing MACE rates in patients at lower and higher risk for diabetes as well as among those with prevalent diabetes, in both primary and secondary prevention. Randomized trial data indicate that **several major CV events are prevented for each excess case of diabetes associated with statin use**.

Statins should continue to be recommended for reducing CVD event risk in appropriate patients with and without diabetes or risk factors for diabetes.

Lifestyle modification should be emphasized to all patients recommended for statin therapy to help lessen not only their cardiovascular risk, but also to attenuate any modest increase in diabetes risk.

Maki KC, Ridker PM, Brown WV, Grundy SM, Sattar N,
The Diabetes Subpanel of the National Lipid Association Expert Panel.
An assessment by the Statin Diabetes Safety Task Force: 2014 update.
J Clin Lipidol. 2014 May-Jun;8(3 Suppl):S17-29. doi: 10.1016/j.jacl.2014.02.012.

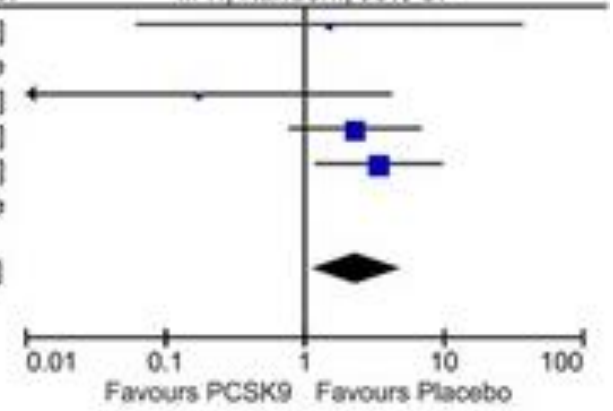
Cognition and PCSK9 Inhibitors

Neurocognitive Adverse Events

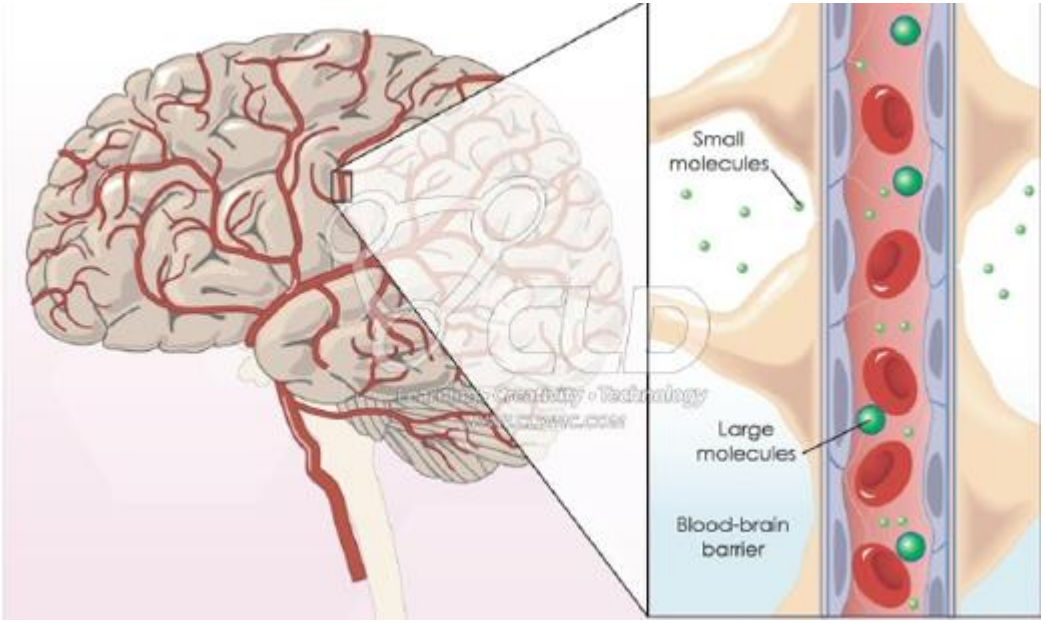
Study or Subgroup	PCSK9 Events	PCSK9 Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
LAPLACE-2	1	1117	0	558	5.3%	1.50 [0.06, 36.90]
MENDEL-2	0	306	0	154		Not estimable
ODYSSEY COMBO I	0	207	1	107	5.3%	0.17 [0.01, 4.24]
ODYSSEY LONG TERM	18	1550	4	788	43.3%	2.30 [0.78, 6.83]
OSLER 2	27	2976	4	1489	46.0%	3.40 [1.19, 9.73]
RUTHERFORD 2	0	220	0	109		Not estimable
Total (95% CI)		**6376**		**3205**	**100.0%**	**2.34 [1.11, 4.93]**
Total events	46		9			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.11$, df = 3 (P = 0.38); $I^2 = 4\%$

Test for overall effect: Z = 2.25 (P = 0.02)



Brain synthesizes Cholesterol locally



mAbs (i.e., Evolocumab or Alirocumab) are too large to cross the intact blood-brain barrier

Nevertheless, meta-analysis* of adverse events from 2 out of 6 PCSK9i trials totaling 9,581 pts suggested an increased risk with PCSK9 inhibitors: HR 2.3 [1.1, 4.9]

- **Event rates low (<1%)**
- **Events were unadjudicated and diverse AE terms reported**
- **Not correlated with LDL-C achieved**

Giugliano RP, Mach F, Zavitz K, Kurtz C, Schneider J, Wang H, Keech A, Pedersen TR, Sabatine MS, Sever PS, Honarpour N, Wasserman SM, Ott BR; EBBINGHAUS Investigators. Design and rationale of the EBBINGHAUS trial: A phase 3, double-blind, placebo-controlled, multicenter study to assess the effect of evolocumab on cognitive function in patients with clinically evident cardiovascular disease and receiving statin background lipid-lowering therapy-A cognitive study of patients enrolled in the FOURIER trial. Clin Cardiol. 2017 Feb;40(2):59-65. doi: 10.1002/clc.22678.

EBBINGHAUS

Executive Committee: Robert P. Giugliano (Chair), François Mach, Brian R. Ott

TIMI Study Group Marc S. Sabatine (Chairman), Marc P. Bonaca (Safety Desk), Sabina Murphy (Director of Stats)
Kelly Im (Assoc Dir Stats), Estella Kanevsky

Cambridge Cognition: Kenton Zavitz (non-voting member of EC)

Sponsor: Amgen

Participating Countries (N=30)

1,974 patients enrolled (free of history of dementia, cognitive impairment or other condition interfering with participation)

In patients with known CVD on background statin followed for 20 months

1. No differences between evolocumab vs. placebo
   A. A battery of cognitive tests
   B. Patient-reported everyday cognition
   C. Adverse cognitive events reported by MD
2. No evidence of differences in cognitive tests by achieved nadir LDL-C, even <25 mg/dL

Gencer B, Mach F, Guo J, Im K, Ruzza A, Wang H, Kurtz CE, Pedersen TR, Keech AC, Ott BR, Sabatine MS, Giugliano RP; FOURIER Investigators. Cognition After Lowering LDL-Cholesterol With Evolocumab. J Am Coll Cardiol. 2020 May 12;75(18):2283-2293. doi: 10.1016/j.jacc.2020.03.039.

Aggressive LDL-C Lowering and the Brain: Impact on Risk for Dementia and Hemorrhagic Stroke: A 2023 Scientific Statement From the American Heart Association

- Scientific statement objective: to evaluate contemporary evidence that either supports or refutes the conclusion that aggressive LDL-C-lowering or lipid-lowering exerts toxic effects on the brain, leading to cognitive impairment or dementia or hemorrhagic stroke.
- The writing group used literature reviews, references to published clinical and epidemiology studies, clinical and public health guidelines, authoritative statements, and expert opinion to summarize existing evidence and to identify gaps in current knowledge.
- Although some retrospective, case control, and prospective longitudinal studies suggest that statins and LDL-C lowering are associated with cognitive impairment or dementia, the preponderance of observational studies and data from randomized trials do not support this conclusion.
- Risk of hemorrhagic stroke associated with statin therapy in patients without a history of cerebrovascular disease is nonsignificant; achieving very low LDL-C levels does not increase that risk.
- Data reflecting the risk of hemorrhagic stroke with lipid-lowering treatment among patients with a history of hemorrhagic stroke are not robust and require additional focused study.

Goldstein LB, Toth PP, Dearborn-Tomazos JL, Giugliano RP, Hirsh BJ, Peña JM, Selim MH, Woo D; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Peripheral Vascular Disease; and Stroke Council. Aggressive LDL-C Lowering and the Brain: Impact on Risk for Dementia and Hemorrhagic Stroke: A Scientific Statement From the American Heart Association. Arterioscler Thromb Vasc Biol. 2023 Oct;43(10):e404-e442. doi: 10.1161/ATV.0000000000000164.

NLA Statin Muscle Symptom Taskforce (2014) Definition of Statin Associated Muscle Symptoms (SAMS) and Estimated Prevalence.

Myalgia (5-25% in observational studies)—unexplained muscle discomfort often described as "flu-like" symptoms with normal CK level. The spectrum of myalgia symptoms includes the following:

- Muscle aches
- Muscle soreness
- Muscle stiffness
- Muscle tenderness
- Muscle cramps with or shortly after exercise (not nocturnal cramping)

Myopathy (1/1000)—muscle weakness (not attributed to pain; and not necessarily associated with elevated CK)

Myositis—muscle inflammation by skeletal muscle biopsy and/or magnetic resonance imaging

Myonecrosis—CK muscle enzyme elevations

- Mild > 3 X baseline or ULN CK adjusted for age, race, and sex
- Moderate ≥ 10 X baseline or ULN CK adjusted for age, race, and sex
- Severe ≥ 50 X baseline or ULN CK adjusted for age, race, and sex

Clinical rhabdomyolysis (1/10,000)—myonecrosis with myoglobinuria or acute renal injury (increase in creatinine ≥0.5 mg/dL)

Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA, The National Lipid Association's Muscle Safety Expert Panel.
An assessment by the Statin Muscle Safety Task Force: 2014 update.
J Clin Lipidol. 2014 May-Jun;8(3 Suppl):S58-71.
doi: 10.1016/j.jacl.2014.03.004.

Risk factors for Statin Associated Muscle Symptoms (SAMS)[6,13,22]

Demographics	Genetics	Comorbid conditions	Social	Drugs*
Older age, Female sex, Asian ethnicity**, Low body weight.	Family history of SAMS Known pathogenic variants in genes involved in statin metabolism (testing not routinely recommended).	Hypothyroidism, including post-treatment of hyperthyroidism, Vitamin D deficiency, Musculoskeletal disease, Immunologic disease, Chronic kidney disease, Organ or electrolyte dysfunction.	New exercise routine, Strenuous exercise, Alcohol use, Cocaine and other stimulants.	Fibrates (especially gemfibrozil), Colchicine, Immunosuppressants, Antiarrhythmics, Antivirals, Antibiotics, Antifungals, Antiseizures, Other inhibitors of statin clearance.

* Either through direct myotoxic effects or drug-drug interactions with statins.

** Especially for high dose rosuvastatin.

Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA, The National Lipid Association's Muscle Safety Expert Panel.
An assessment by the Statin Muscle Safety Task Force: 2014 update.
J Clin Lipidol. 2014 May-Jun;8(3 Suppl):S58-71.
doi: 10.1016/j.jacl.2014.03.004.

Estimates of the Frequency of SAMS and Pharmacologic SAMS in General Statin-treated Populations

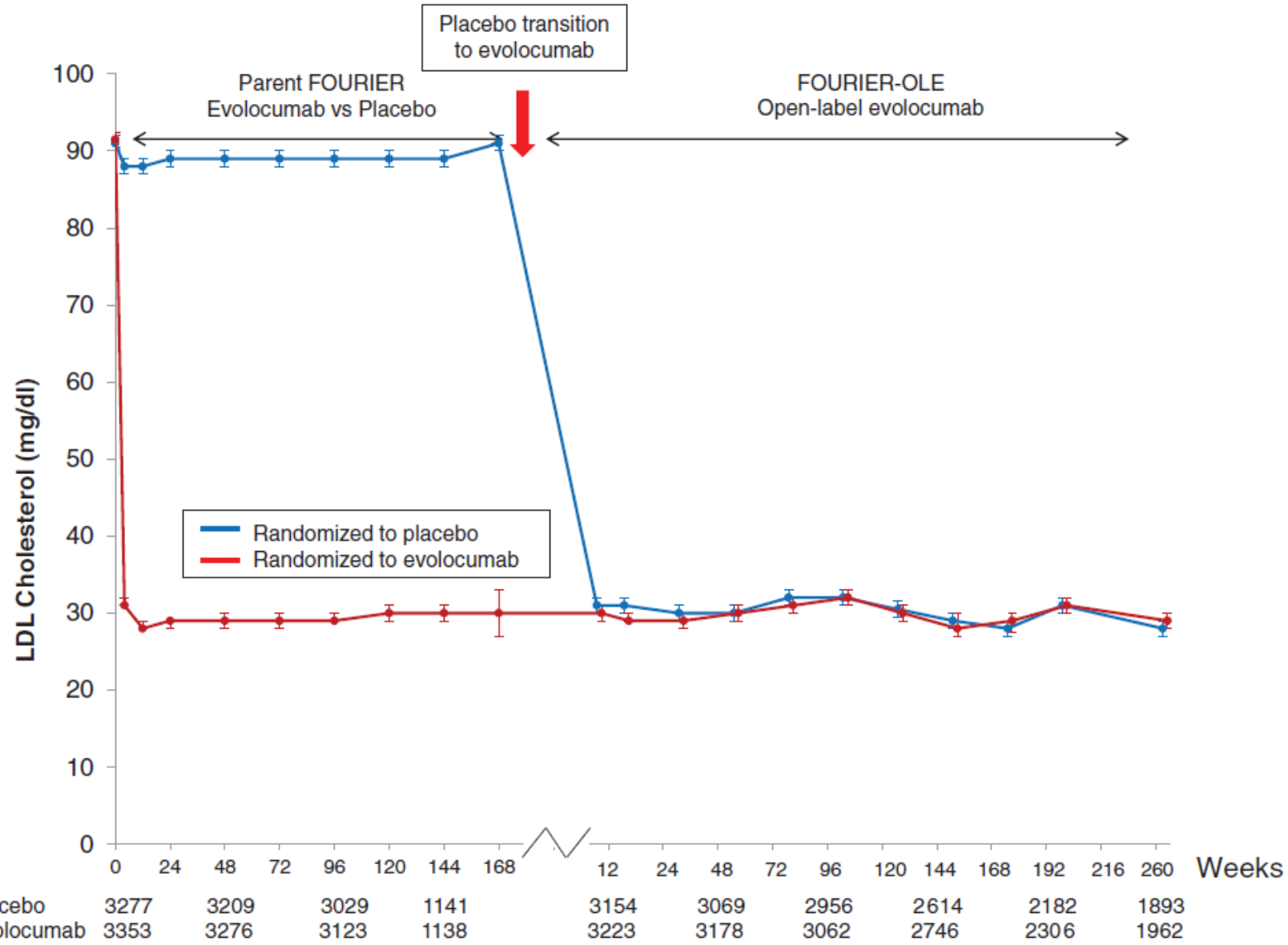
Source	Type of evidence	Frequency estimate	Comments
Frequency of SAMS			
Lipid disorders clinic in New Zealand[25] 1991 n=110	First 110 patients treated in the clinic with simvastatin	**13.6%**	Clinical experience prior to widescale internet use and prior to social media. 15 patients (13.6%) reported muscle aches they attributed to statin therapy. 5 patients (4.5%) withdrew from therapy due to suspected side effects.
Academic clinician estimate (James Shepherd) [26] 1995	Early clinical experience	**~5%**	Prior to widescale internet use and prior to social media.
PRIMO[17] 2005, n=7,924	Nationwide observational survey of high-dosage statin use	**10.5%**	Symptoms solicited by questionnaire. 97% of those reporting symptoms had statin treatment adjustment. Results varied by statin, from 5.1% with fluvastatin-XL to 18.2% with simvastatin.
USAGE[28,] 2012, n=10,138	Internet survey of a registered consumer panel of current or former statin users	**Up to 25%**	25% of current statin users reported muscle symptoms with concern for statin side-effects, although only 19% switched or stopped statins due to all side-effect concerns.
Frequency of pharmacologic SAMS*			
STOMP[27] ,2013, n=468	Parallel group RCT among statin-naïve subjects, muscle symptoms as primary outcome	**4.8%**	Endpoint of new unexplained muscle pain regardless of severity, resolved after study drug cessation, and confirmed in additional randomized crossover trial. Marginal significance (p = 0.05) for statin effect.
Large scale statin randomized trials[23] 2016, n>150,000	Meta-analysis of tertiary RCT endpoints	**Up to 0.5-1.0%**	The meta-analysis makes an unstated assumption that statins do not improve muscle symptoms in any patient subset. In addition, recruitment bias may have excluded patients with previous statin myalgia or those more likely to experience muscle symptoms.
CTT Collaboration[24] 2022, n=154,664	Meta-analysis of individual patient level data from 23 RCTs	**0.5% 0.7% (year 1)**	The same limitations stated above for the 2016 meta-analysis[23] also apply here. Any muscle pain or weakness occurred in 27.1% of statin users versus (vs) 26.6% of those on placebo RR 1.03 (95% CI 1.01-1.06). After one year there was no significant excess of first reported SAMS events. SAMS was more prevalent with higher intensity statin regimens than lesser intensive regimens [RR 1.08 (95% CI 1.04-1.13) vs 1.03 (95% CI 1.00-1.05)] compared with placebo.

PRIMO, Prédiction du Risque Musculaire en Observationnel survey; STOMP, Effect of Statins on Skeletal Muscle Function and Performance trial; USAGE, Understanding Statin Use in America and Gaps in Patient Education survey; CI, confidence interval; CTT, Cholesterol Treatment Trialists'; RCT, randomized controlled trial; RR, relative risk; SAMS, statin-associated muscle symptoms. ∗ Pharmacologic SAMS refers specifically to muscle symptoms that are caused by the statin.

Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA, The National Lipid Association's Muscle Safety Expert Panel.
An assessment by the Statin Muscle Safety Task Force: 2014 update. J Clin Lipidol. 2014 May-Jun;8(3 Suppl):S58-71. doi: 10.1016/j.jacl.2014.03.004.

LDL-C Lowering Earlier and Longer

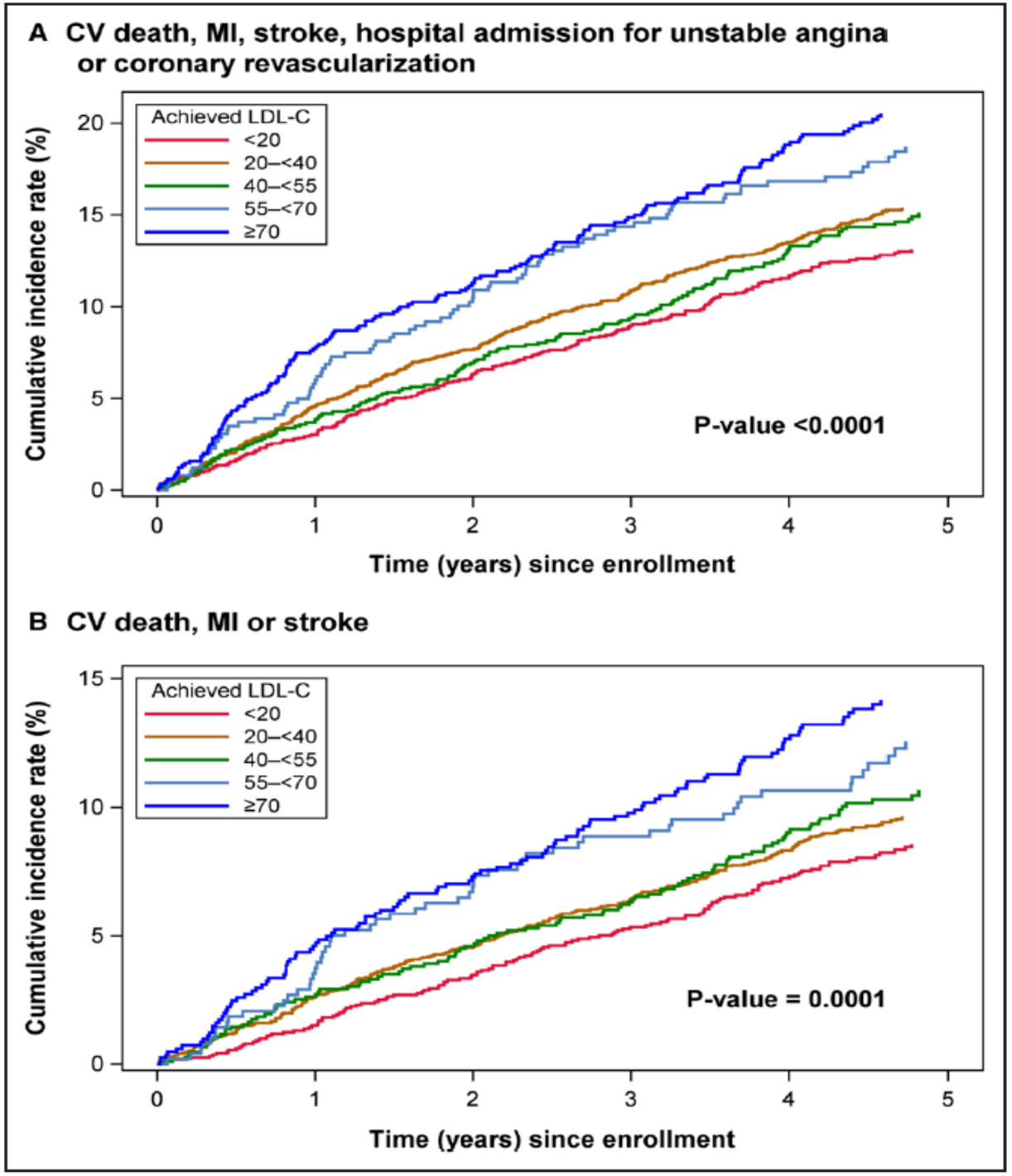
Median (95% CI) LDL-C concentration by randomized treatment arm during the parent FOURIER and FOURIER-OLE trials.



O'Donoghue ML, Giugliano RP, Wiviott SD, Atar D, Keech A, Kuder JF, Im K, Murphy SA, Flores-Arredondo JH, López JAG, Elliott-Davey M, Wang B, Monsalvo ML, Abbasi S, Sabatine MS.
Long-Term Evolocumab in Patients With Established Atherosclerotic Cardiovascular Disease.
Circulation. 2022 Oct 11;146(15):1109-1119. doi: 10.1161/CIRCULATIONAHA.122.061620.

Cumulative Incidence Rates of Cardiovascular Outcomes in FOURIER-OLE.

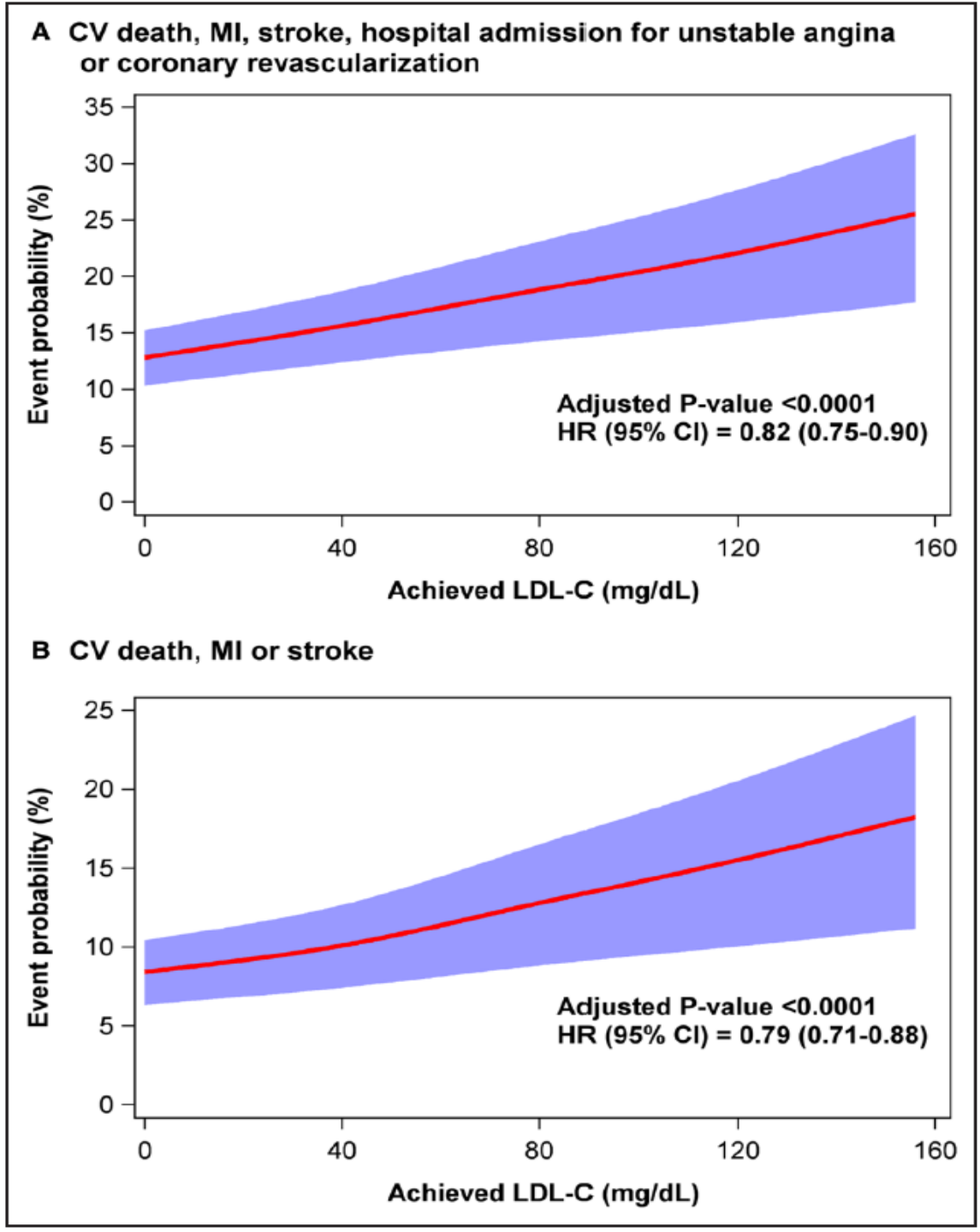
In patients with ASCVD, long-term achievement of lower LDL-C levels, down to <20 mg/dL (<0.5 mmol/L), was associated with a lower risk of cardiovascular outcomes with no significant safety concerns.



Gaba P, O'Donoghue ML, Park JG, Wiviott SD, Atar D, Kuder JF, Im K, Murphy SA, De Ferrari GM, Gaciong ZA, Toth K, Gouni-Berthold I, Lopez-Miranda J, Schiele F, Mach F, Flores-Arredondo JH, López JAG, Elliott-Davey M, Wang B, Monsalvo ML, Abbasi S, Giugliano RP, Sabatine MS.
Association Between Achieved Low-Density Lipoprotein Cholesterol Levels and Long-Term Cardiovascular and Safety Outcomes: An Analysis of FOURIER-OLE. Circulation. 2023 Apr 18;147(16):1192-1203.
doi: 10.1161/CIRCULATIONAHA.122.063399.

Continuous Relationship Between Achieved LDL-C Level and the Primary and Key Secondary Cardiovascular Efficacy Outcomes in FOURIER-OLE.

In patients with ASCVD, long-term achievement of lower LDL-C levels, down to <20 mg/dL (<0.5 mmol/L), was associated with a lower risk of cardiovascular outcomes with no significant safety concerns.



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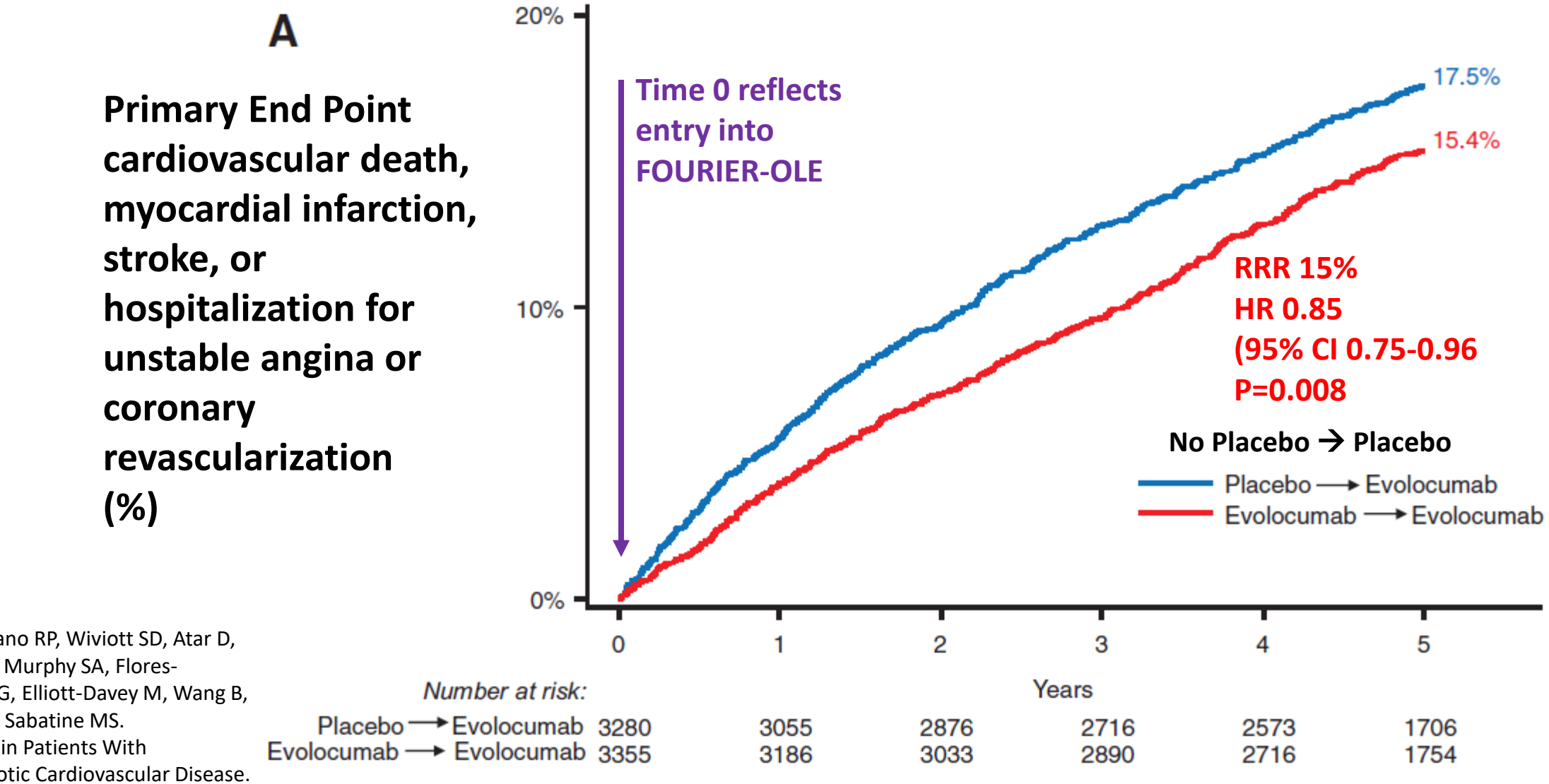
Association Between Achieved Low-Density Lipoprotein Cholesterol Levels and Long-Term Cardiovascular and Safety Outcomes: An Analysis of FOURIER-OLE.
Circulation. 2023 Apr 18;147(16):1192-1203.
doi: 10.1161/CIRCULATIONAHA.122.063399.

Kaplan-Meier curves for Primary End Point in FOURIER during the FOURIER-OLE (FOURIER Open-Label Extension): Primary End Point

A

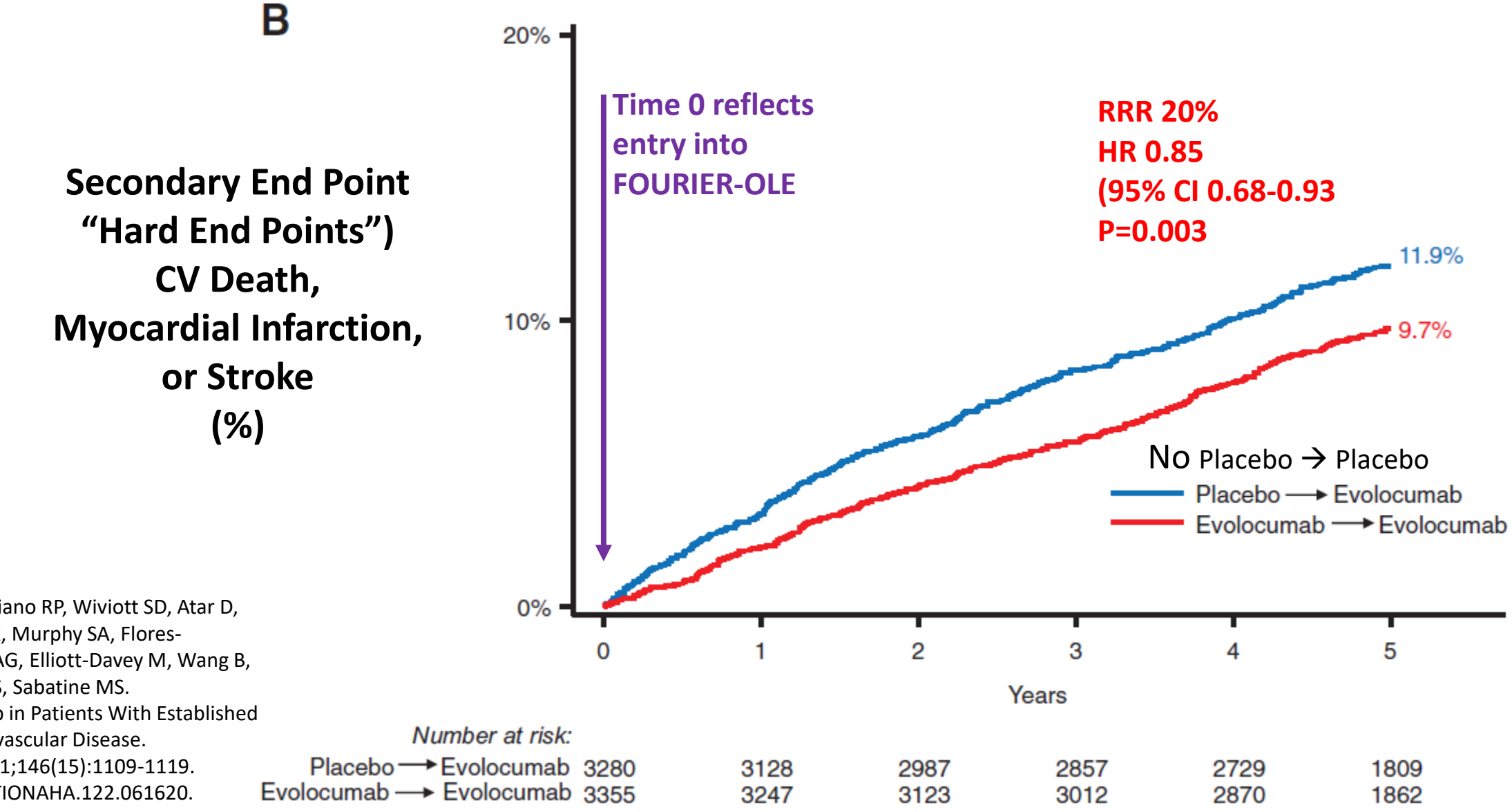
Primary End Point cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina or coronary revascularization (%)



O'Donoghue ML, Giugliano RP, Wiviott SD, Atar D, Keech A, Kuder JF, Im K, Murphy SA, Flores-Arredondo JH, López JAG, Elliott-Davey M, Wang B, Monsalvo ML, Abbasi S, Sabatine MS. Long-Term Evolocumab in Patients With Established Atherosclerotic Cardiovascular Disease. Circulation. 2022 Oct 11;146(15):1109-1119. doi: 10.1161/CIRCULATIONAHA.122.061620.

Kaplan-Meier curves for Primary End Point in FOURIER during the FOURIER-OLE (FOURIER Open-Label Extension): Secondary End Point

Secondary End Point
"Hard End Points")
CV Death,
Myocardial Infarction,
or Stroke
(%)



O'Donoghue ML, Giugliano RP, Wiviott SD, Atar D, Keech A, Kuder JF, Im K, Murphy SA, Flores-Arredondo JH, López JAG, Elliott-Davey M, Wang B, Monsalvo ML, Abbasi S, Sabatine MS.
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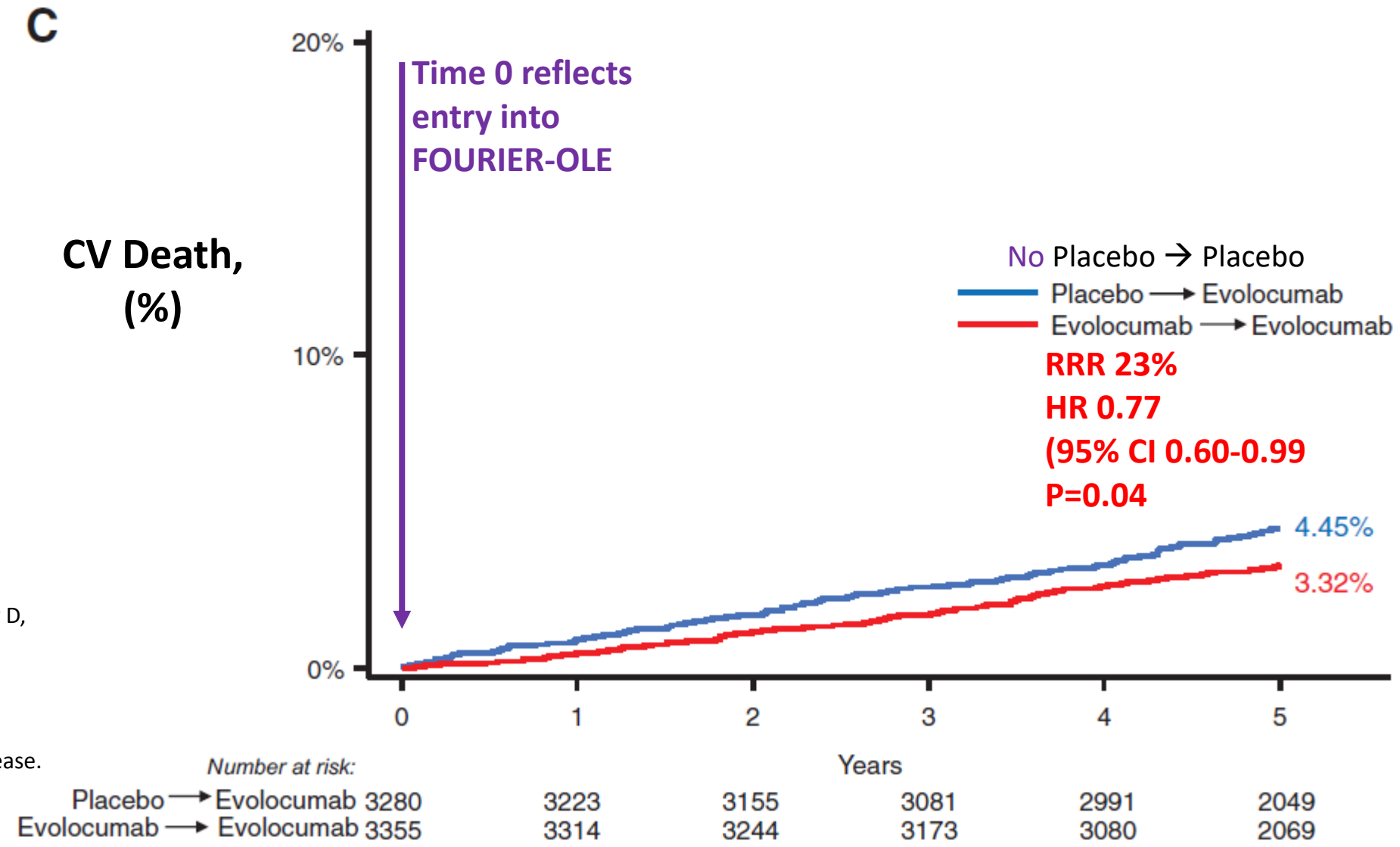
Circulation. 2022 Oct 11;146(15):1109-1119.
doi: 10.1161/CIRCULATIONAHA.122.061620.

Kaplan-Meier curves for Primary End Point in FOURIER during the FOURIER-OLE (FOURIER Open-Label Extension): Cardiovascular Death



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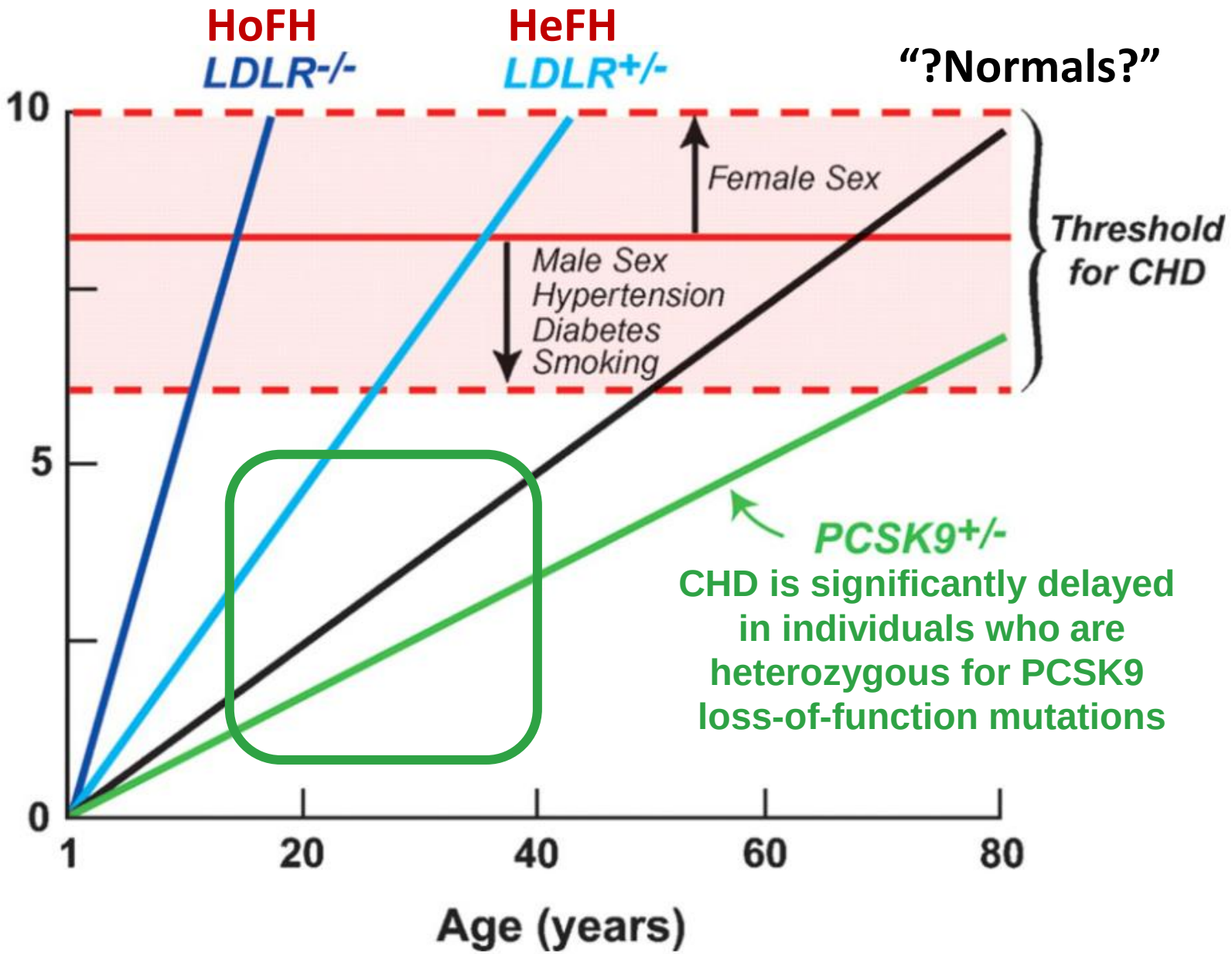
What was Observed in the FOURIER to FOURIER Open-Label Extension(FOURIER-OLE)?

Long-term LDL-C lowering with evolocumab was associated with persistently low rates of adverse events for >8 years that did not exceed those observed in the original placebo arm during the parent study and led to further reductions in cardiovascular events compared with delayed treatment initiation.

Conclusion: For Best Results (i.e., best risk reduction) Lowest is Best and Treat Early and Longer!

Relationship Between Cumulative LDL-C Exposure and Age at Which ASCVD Events Manifest



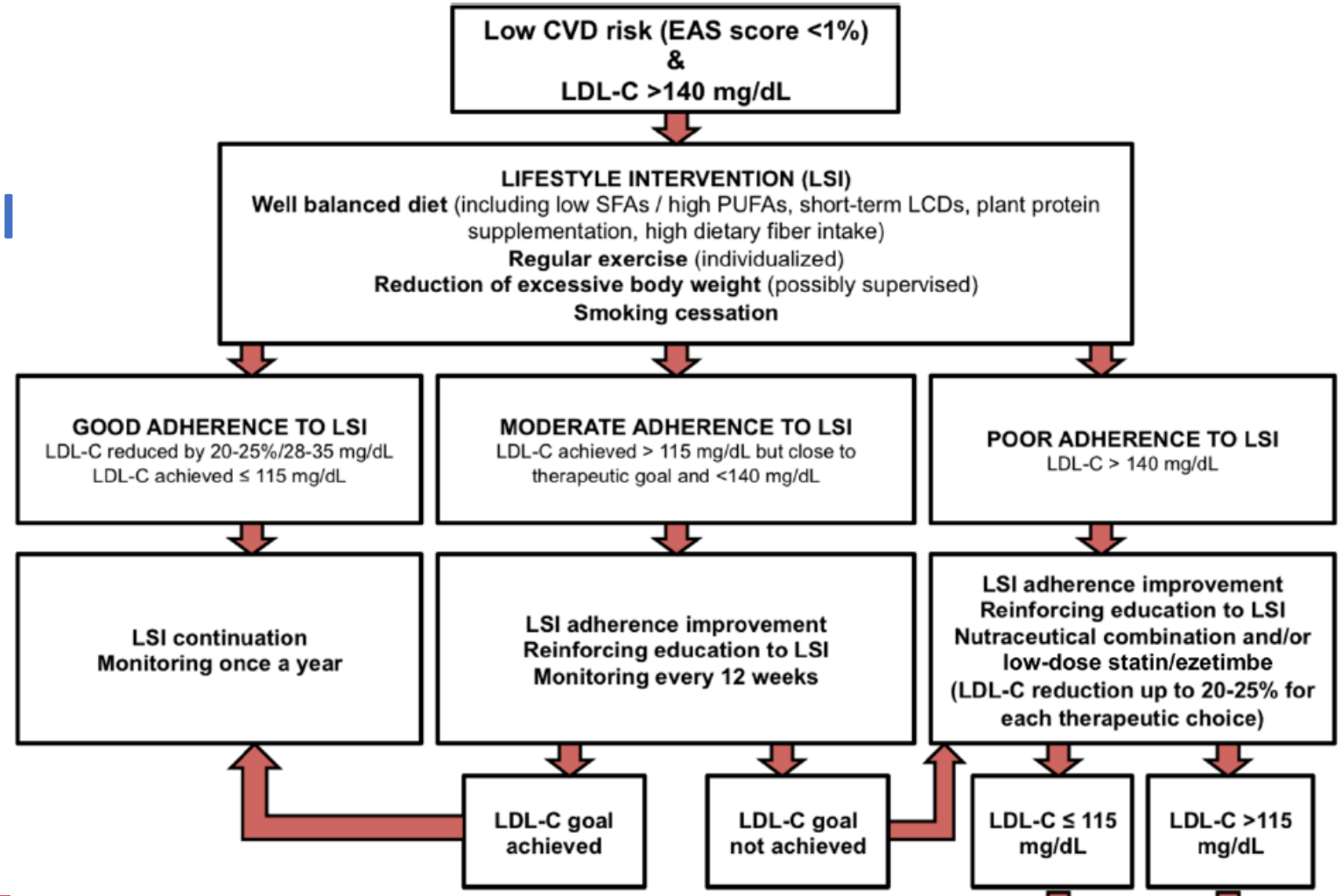
Cumulative LDL-C (grams/dL-years)

"Would modest reductions in plasma levels of LDL-C starting at an earlier age enhance the benefit of cholesterol-lowering therapy?"

Horton JD, Cohen JC, Hobbs HH.
PCSK9: a convertase that coordinates LDL catabolism.
J Lipid Res. 2009 Apr;50 Suppl(Suppl):S172-S177.
doi: 10.1194/jlr.R800091-JLR200.

2020 Recommendations Endorsed by the 80-Member International Lipid Expert Panel (ILEP; ilep.eu):

Proposed Approach to the Management of CV risks in Individuals with Low (EAS score < 1%) 10-year ASCVD risk, but elevated LDL-C (> 140 mg/dL, 3.6 mmol/L) to Achieve Targeted LDL-C Goal <115 mg/dL (<3.0 mmol/L)



Penson PE, Pirro M, Banach M. LDL-C: lower is better for longer-even at low risk. BMC Med. 2020 Oct 8;18(1):320 (1-6). doi: 10.1186/s12916-020-01792-7.

Early Intervention

Regarding

…the war against coronary artery disease.
It can be prevented.
In fact, clinical trials with the statins have shown remarkable decreases in both coronary heart disease mortality and also total mortality.

Decreasing LDL by 25% is enough to lower coronary heart disease mortality by 30–40%, and that is the result of only 5 or 6 years of intervention.
It seems reasonable to extrapolate and expect even greater reductions if treatment is started earlier in life
and continued not for just 5 years but for decades.

Steinberg D.
Thematic review series: the pathogenesis of atherosclerosis.
An interpretive history of the cholesterol controversy: part I.
J Lipid Res. 2004 Sep;45(9):1583-1593.
doi: 10.1194/jlr.R400003-JLR200.

Daniel Steinberg, MD, PhD
(1923–2015)

one of a few founders of the modern fields of cholesterol and atherosclerosis.

When Targeting LDL-C for Lowering

High is Bad

Average is not Good

Lower is Better

Even Lower is Even Better

Lowest is Best,

now down to 20-25 mg/dL

Marc S. Sabatine, MD, MPH (Chairman)
& Robert P. Giugliano, MD, SM (a Senior Investigator) of the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Boston,
at Brigham and Women's Hospital

"Lower Longer is Better"

Peter Libby
Mallinckrodt Professor of Medicine
at Harvard Medical School

…a level of LDL-cholesterol in plasma of 25 mg/dL would be sufficient to nourish body cells with cholesterol

Michael S. Brown and Joseph L Goldstein
from Nobel Prize Lecture, Stockholm, Sweden, 1985.

How to Live to Age 100 Years Before Developing Clinical Coronary Artery Disease: A Suggestion

In reference to one's

"predicted threshold for CHD?:

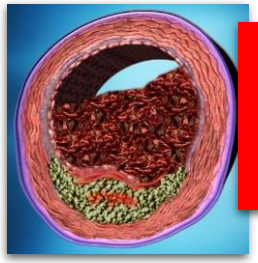
Horton JD, Cohen JC, Hobbs HH. PCSK9: a convertase that coordinates LDL catabolism. J Lipid Res. 2009 Apr;50 Suppl(Suppl):S172-7. doi: 10.1194/jlr.R800091-JLR200.

Braunwald provocatively suggests

"the potential of initiating pharmacologic therapy to lower LDL-C by ≈50% at age 30 years, to delay reaching this threshold until very late in life."

Braunwald E. How to live to 100 before developing clinical coronary artery disease: a suggestion. Eur Heart J. 2022 Jan 31;43(4):249-250. doi: 10.1093/eurheartj/ehab532.

Summary: Primary/Secondary ASCVD Prevention of At-Risk Individuals with Life-Time, Lipid / Lipoprotein Aggressive Management* Goals



How aggressive the management?

Secondary Prevention
- Prior Events or Multimorbidity
- Prior Event (or CHD risk Equivalent)

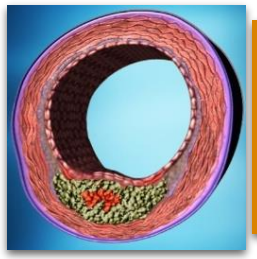
Very High risk
Extreme risk

Long-term Aggressive CVD risk(i.e., Lipid*) Management

LDL-C
<130 mg/dL 1988
≤100 mg/dL 1993
<100 mg/dL 2001
<70 mg/dL 2004
<55 mg/dL 2017
<40 mg/dL 2019
<30 mg/dL 2022

Ultimate GOALS:

Lipid Pool-Delipidation
Maximize Regression
Fibrous Cap Thickening
Stabilize Plaque
Slowed 'Quiescent' Progression
No 2nd Clinical Event



What is best way to identify Subclinical Disease?

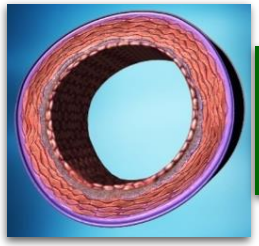
Primary Prevention
- Disease (CHD risk Equivalent)
- No Prior Event, YET!

High, Very-High, Extreme risk

CAC

	CAC score	LDL-C
Moderate risk:	1-99	<70 mg/dL
High risk:	100	<55 mg/dL
Very-High risk:	300	<40 mg/dL
Extreme risk:	1000	<30 mg/dL

Lipid Pool-Delipidation
Maximize Regression
Fibrous Cap Thickening
Stabilize Plaque
Slowed 'Quiescent' Progression
No 1st Clinical event



Who is at-risk to develop disease? At what age start?

Primary Prevention
- No Disease

Low or Moderate 10-yr risk, High Lifetime risk?

LDL-C
<100 mg/dL
(if Diabetes, <70 mg/dL)

Prevent Plaque Formation
Normal Vascular Aging or
Slowed 'Quiescent' Progression
No 1st Clinical Event

"Primary prevention of any disease is more effective if started sooner."
Claudio Napoli, MD, PhD, Second University of Naples

*Reduce Fundamental Atherogenic Cholesterol-containing Lipoprotein Particles

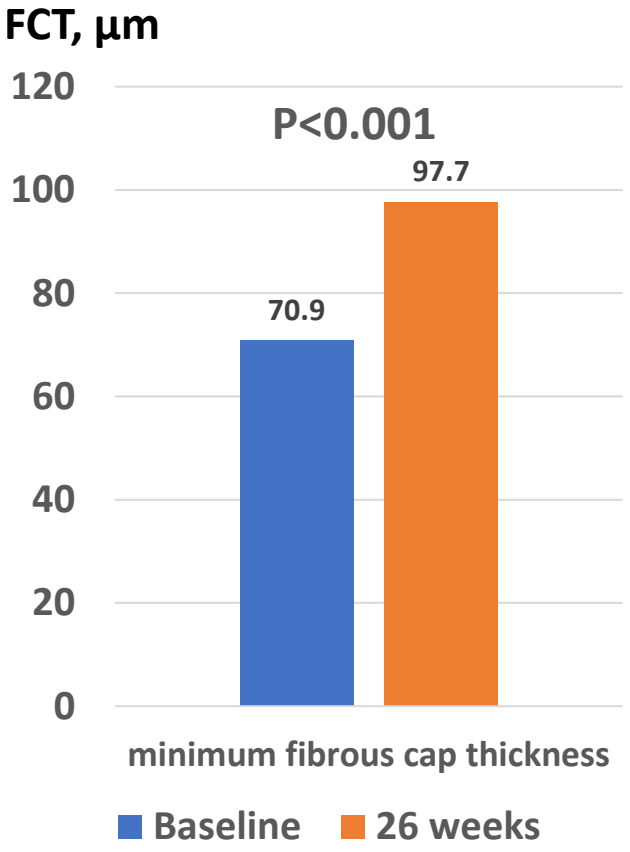
PDR

Thank you


15th Annual Orange County
Symposium for Cardiovascular
Disease Prevention

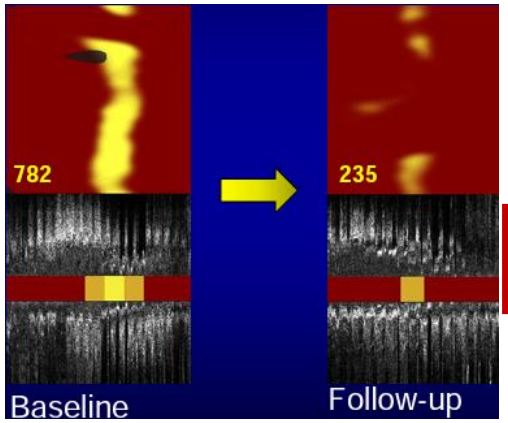
YELLOW III: Effect of '26-week' Evolocumab Therapy on 3 Coronary Plaque Characteristics in 129 patients with Stable CAD.

Baseline LDL-C 96.8 mg/dL; at 26-weeks F-U LDL-C 39.1 mg/dL



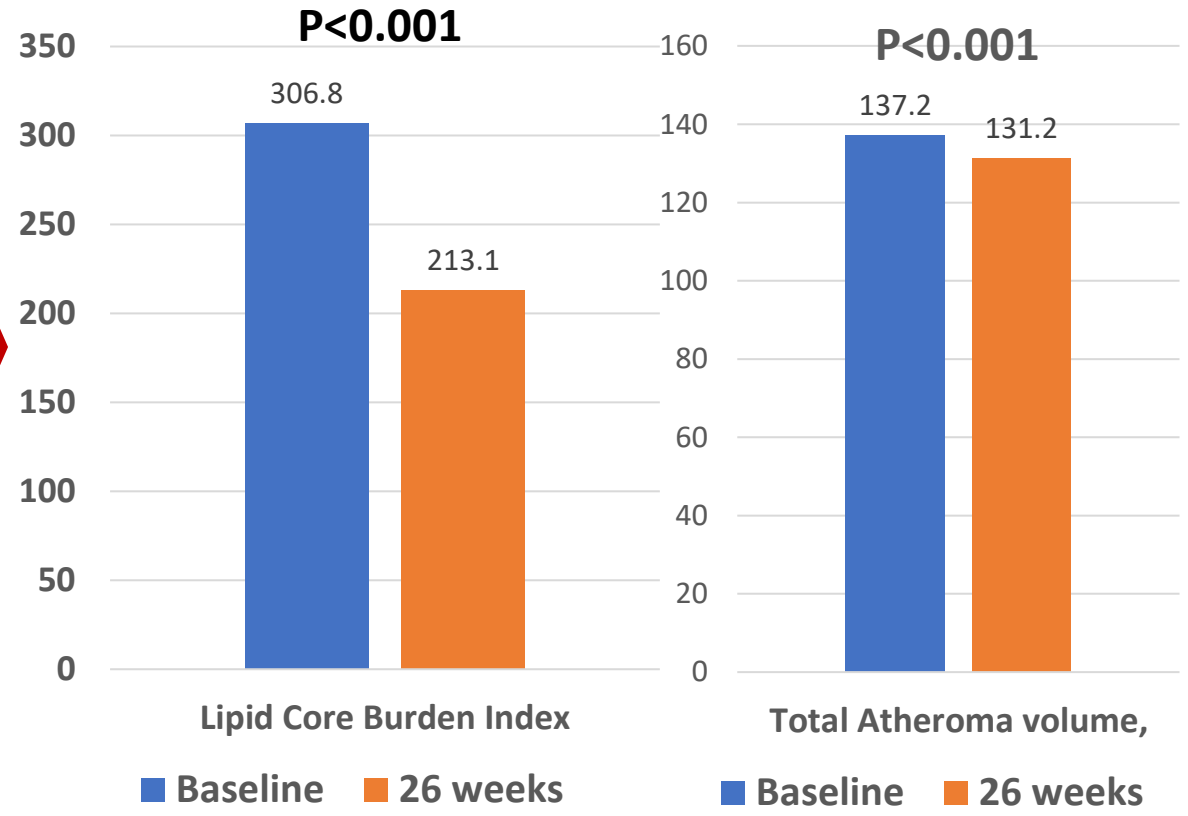
80% has increase in Fibrous cap;
But 20% had no change
in cap thickness.
(i.e., No Improvement)

Near-infrared spectroscopy (NIRS)



MaxLCBI4mm
Reduction (NIRS)

high-risk vulnerable plaque [Thin-Cap, TCFA] lesion patients was reduced from 48% to 13% (absolute 35% reduction)



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