Reducing Cardiovascular Risk with PCSK9 Inhibitors: Addressing Challenges and Improving Outcomes

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Pam Taub, MD: Disclosures

- Consultant: Amgen, Bayer, Boehringer Ingelheim, Edwards, Esperion, Medtronic, Novartis, Novo Nordisk, Sanofi

- Founder and Shareholder of Epirium Bio

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    - Impact of time-restricted feeding (TRF) on glucose homeostasis and mitochondrial function in patients with metabolic syndrome – The TIMET Study
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  - Dysautonomia International Grant (PI: Taub PR)

Marc Sabatine, MD, MPH: Disclosures

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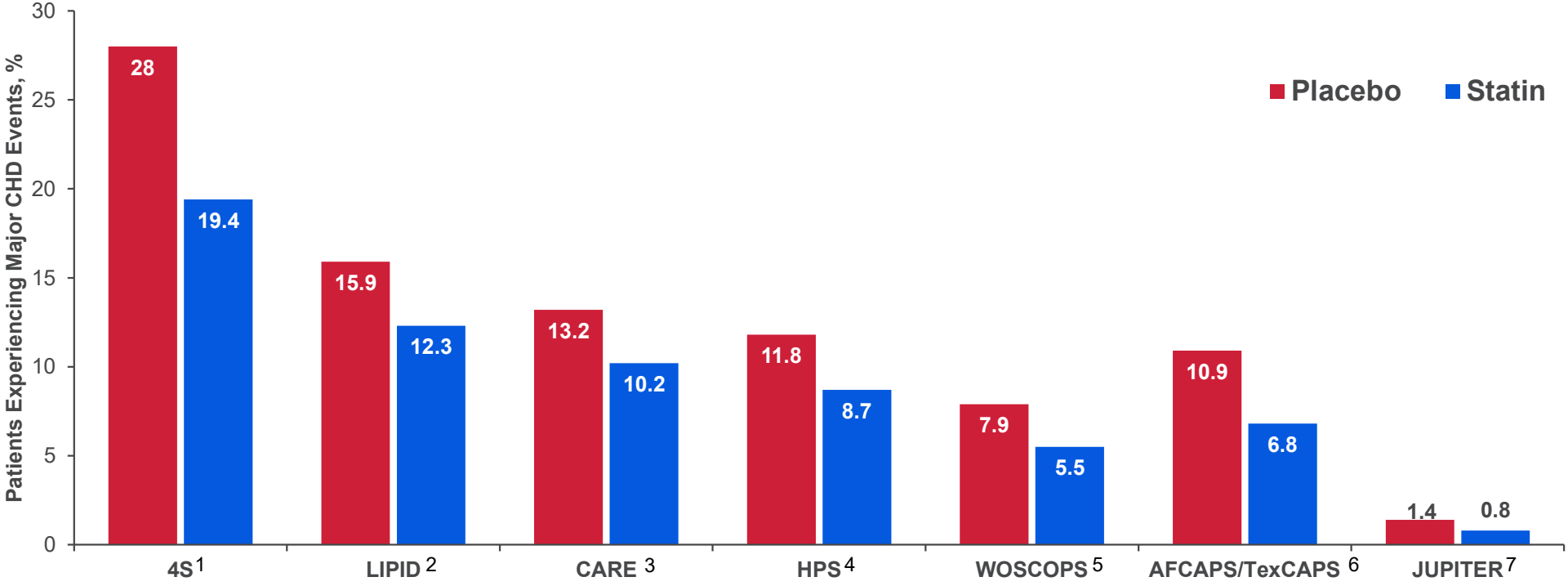
  - Amgen; Anthos Therapeutics; AstraZeneca; Beren Therapeutics; Fibrogen; Merck; Moderna; Novo Nordisk; Silence Therapeutics

Residual CVD Risk in Patients on Statin Therapy

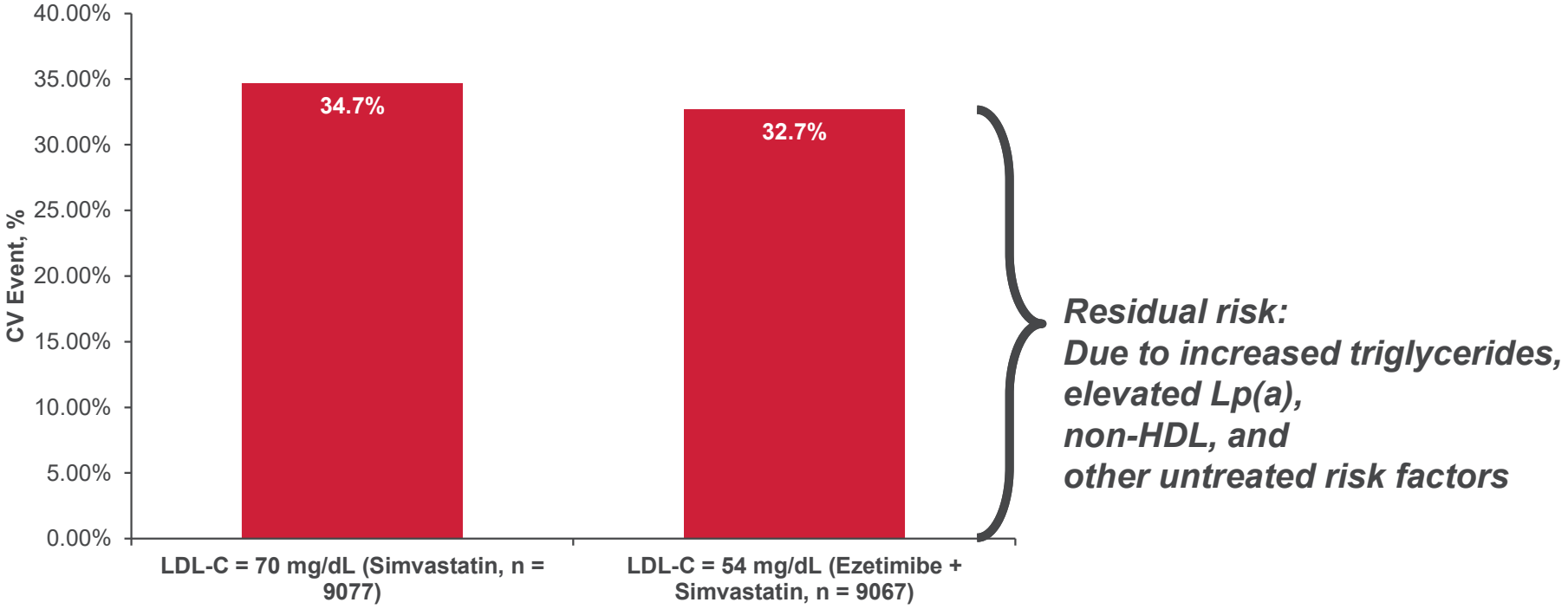
- Despite reduction in ASCVD risk with statin monotherapy, substantial CV risk remains
- This residual CV risk is likely due to suboptimal control of both other risk factors (such as hypertension, diabetes, or smoking) and other lipids (such as triglycerides)



1. 4S Group. *Lancet.* 1994;344:1383-1389. 2. LIPID Study Group. *N Engl J Med.* 1998;339:1349-1357. 3. Sacks FM, et al. *N Engl J Med.* 1996;335:1001-1009.
4. HPS Collaborative Group. *Lancet.* 2002;360:7-22. 5. Shepherd J, et al. *N Engl J Med.* 1995;333:1301-1307. 6. Downs JR, et al. *JAMA.* 1998;279:1615-1622.
7. Ridker PM, et al. *N Engl J Med.* 2008;359:2195-2207.

Residual CVD Risk With Aggressive LDL-C Lowering: IMPROVE-IT Study

- Significant residual risk remains untreated in patients with aggressive LDL-C lowering therapy treatment

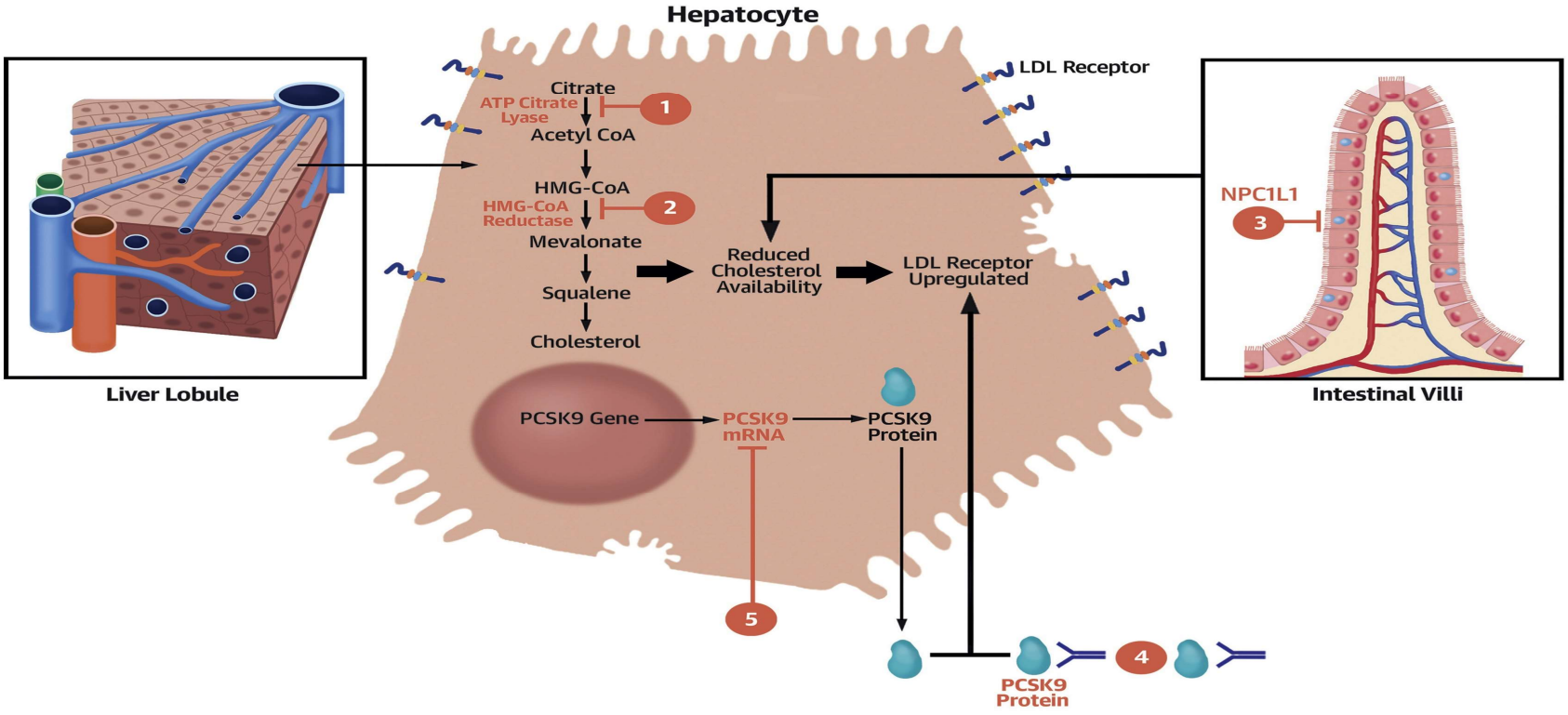


Abbreviations: CV, cardiovascular; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein A.

Cannon CP, et al. *N Engl J Med.* 2015;372:2387-2397.

Review of Mechanism of Action of Non-Statin Agents

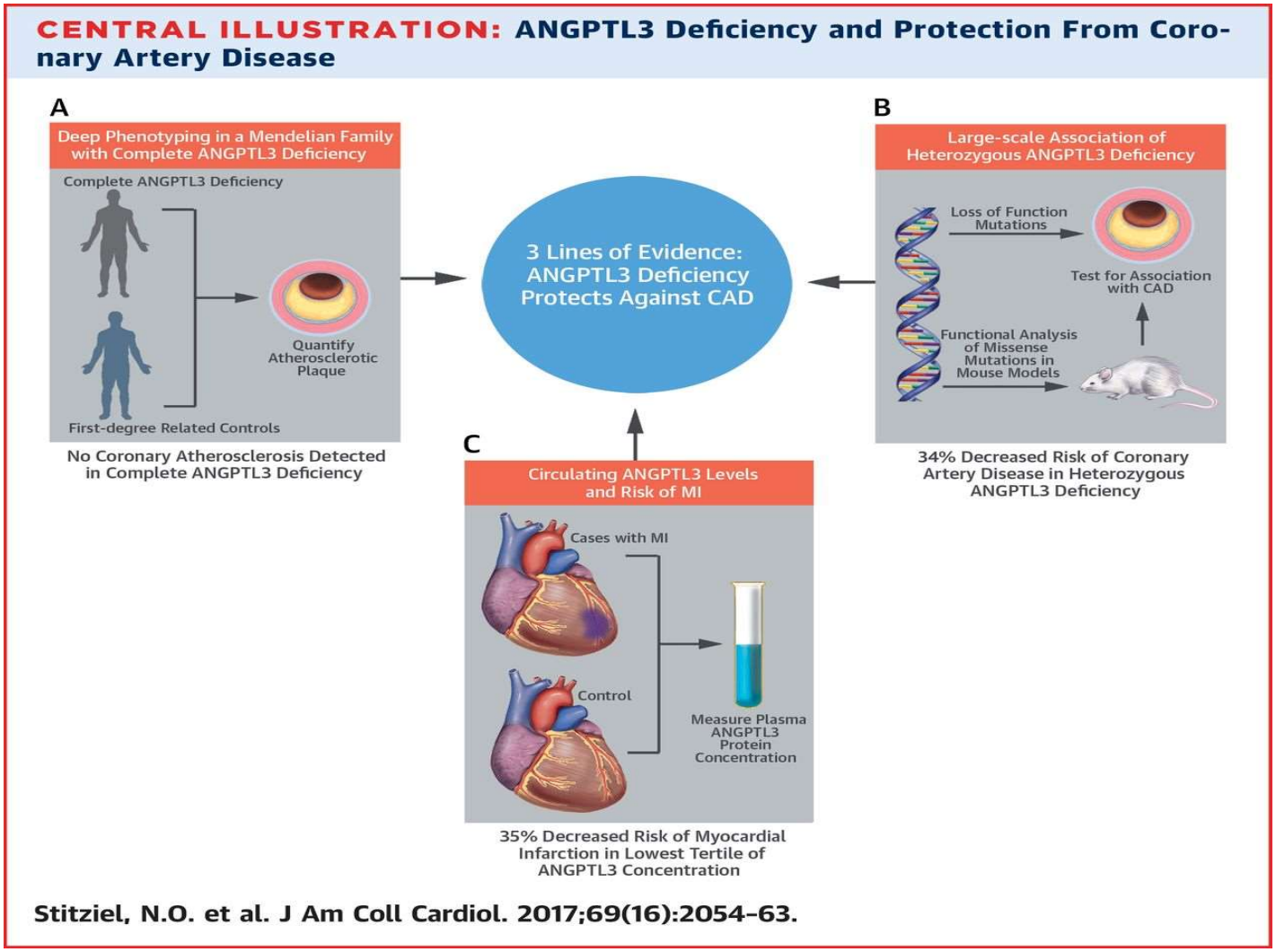
CENTRAL ILLUSTRATION: Schematic Diagram of the Mechanisms of Action of Statins, PCSK9 Inhibitors, PCSK9 Synthesis Inhibitors, and Bempedoic Acid



Preiss, D. et al. J Am Coll Cardiol. 2020;75(16):1945–55.

Comparison of Current Lipid Lowering Agents

	Statin	Ezetimibe	PCSK9 Inhibitor (evolocumab alirocumab)	Bempedoic Acid	Bempedoic Acid + Ezetimibe	PCSK9 small interfering RNA (inclisiran)	ANGPTL3 Inhibitor (evinacumab)
LDL-C Lowering *for non-statin agents LDL lowering is on top of maximally tolerated statin therapy	25-55%	10-18%	50-60%	15-25%	35%	50%	47%
HsCRP Lowering	40%	No change	No change	40%	30%	No change	Data Pending
Triglyceride Lowering	7-30%	7%	10-15%	No change	7%	7-12%	57%
Dosing	Oral	Oral	Injectable	Oral	Oral	Injectable	Injectable
Outcome Study	Positive	Positive	Positive	Pending	Pending	Pending	Pending



A genotype-guided callback study of human “knockouts” for ANGPTL3, which used detailed atherosclerotic phenotyping, demonstrated an absence of coronary atherosclerotic plaque in individuals with complete ANGPTL3 deficiency. (B) Genomic analysis of ANGPTL3 loss-of-function variants, including missense variants that were experimentally found to disrupt ANGPTL3 function, found in up to 180,180 individuals showed a 34% reduction in risk of CAD among loss-of-function variant carriers. (C) Circulating ANGPTL3 protein concentrations were lower in healthy control subjects than in those presenting with a myocardial infarction.

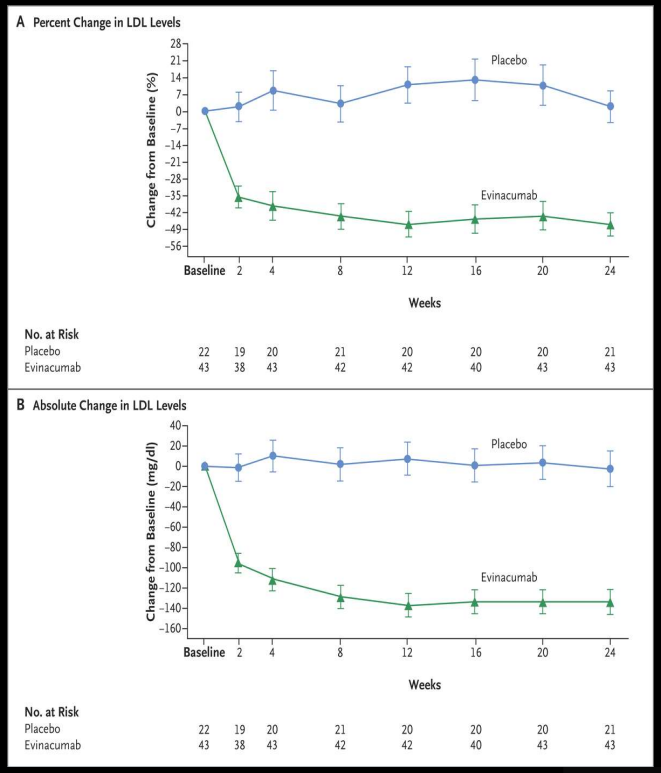
Phase 3 trial in which 65 patients with Homozygous Familial Hypercholesterolemia were randomly assigned to receive an intravenous infusion of evinacumab every 4 weeks or placebo.

Evinacumab group had a relative reduction from baseline in the LDL cholesterol level of 47.1%, as compared with an increase of 1.9% in the placebo group.

Trial patients had good background therapy:
- 94% on statin
- 77% on high-intensity statin
- 77% on PCSK9 inhibitor
- 75% on ezetimibe
- 25% on lomitapide
- 34% on apheresis

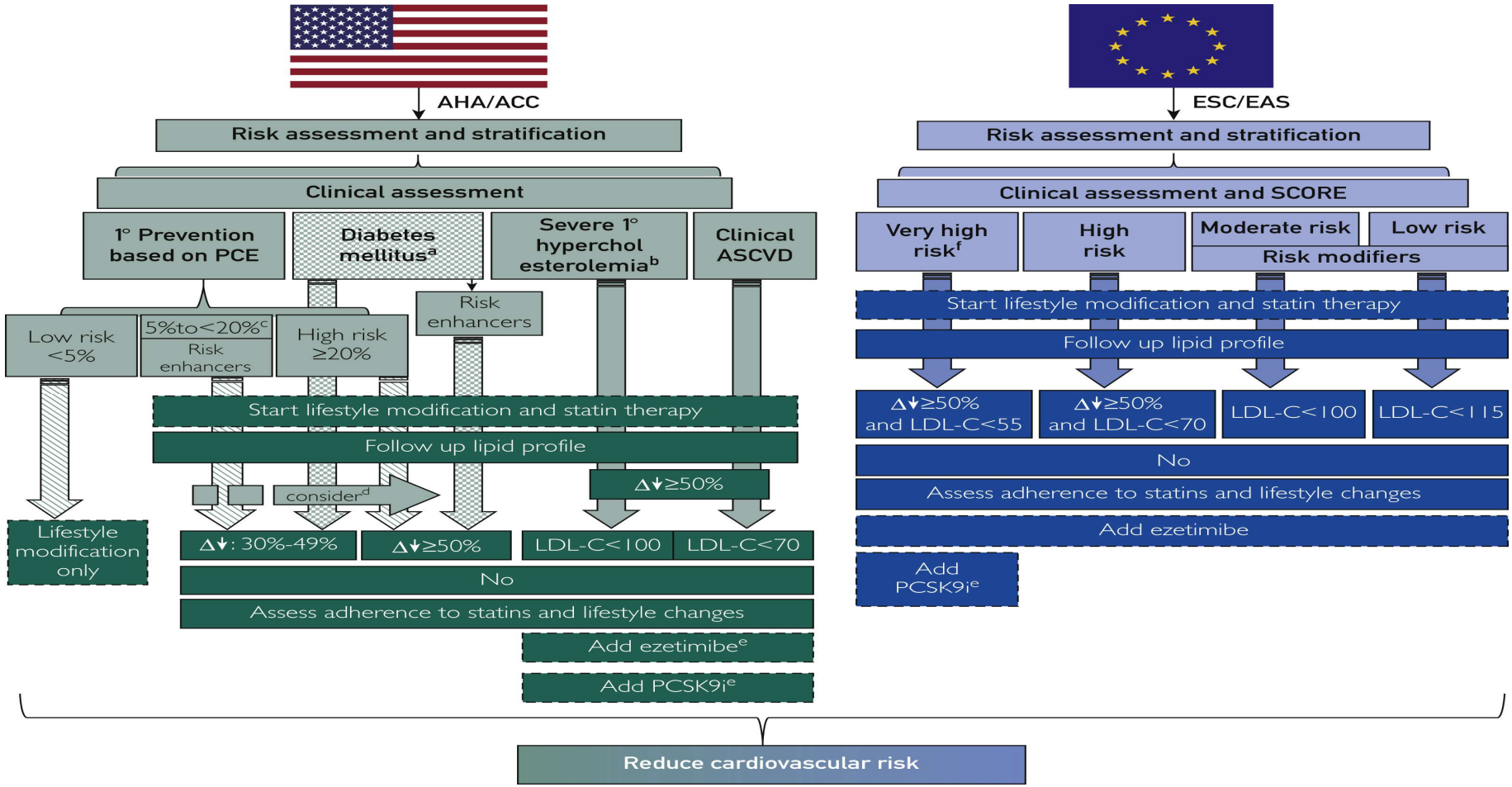
- Recently FDA approved for homozygous familial hypercholesterolemia in February 2021

Changes from Baseline in Low-Density Lipoprotein (LDL) Cholesterol Levels at 24 Weeks.



Least-squares mean percent change (Panel A) and absolute change (Panel B) in calculated LDL choleserol levels from baseline to week 24 in the evinacumab group and the placebo group.

Raal FJ, et al. *N Engl J Med.* 2020;383:711-720.



Singh M, et al. *Mayo Clinic Proceedings* 2020;95:998-1014.

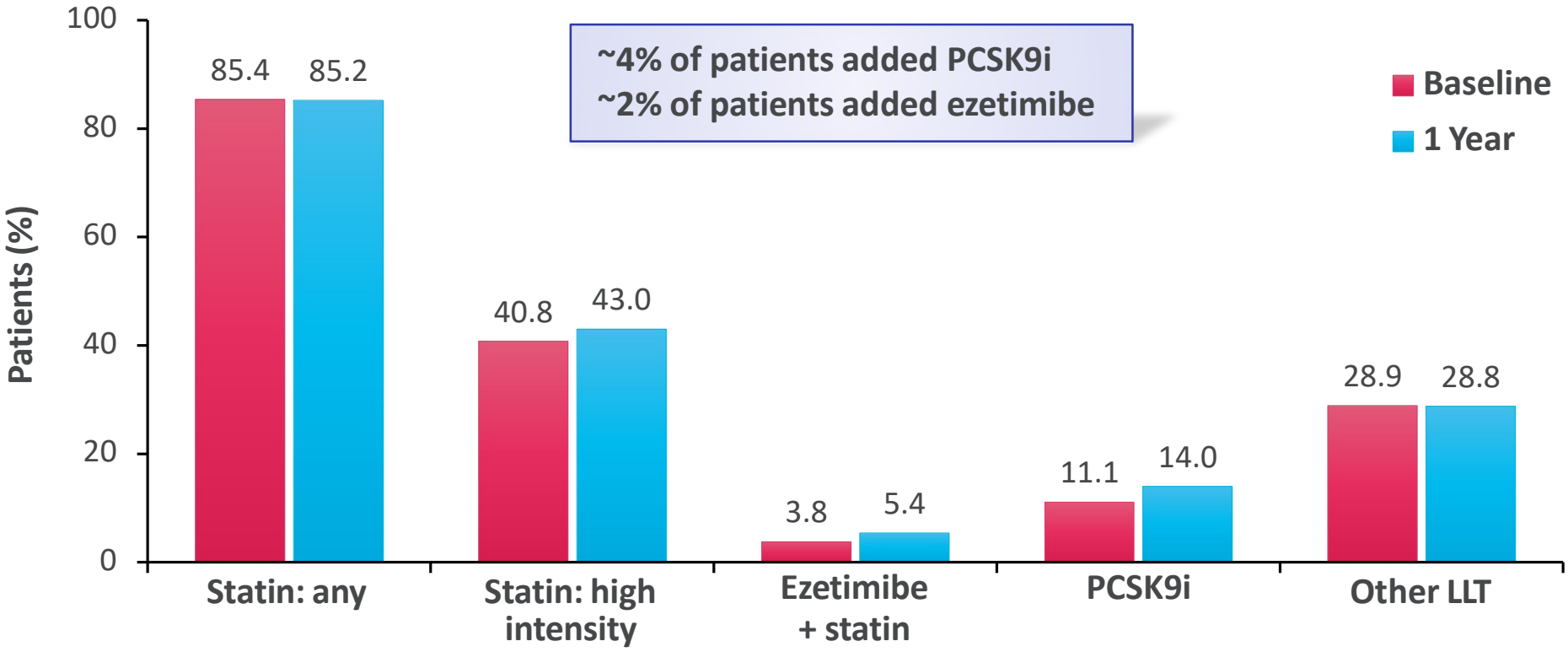
GOULD Registry: High-Risk Patients with ASCVD

- GOULD is a multicenter observational registry that describes LLT patterns among patients with clinical ASCVD and LDL-C ≥ 70 mg/dL (or taking a PCSK9i) in the United States
- 5006 patients enrolled into 3 cohorts:
  - Cohort 1: Patients taking PCSK9i at baseline
  - Cohort 2: Patients with LDL-C ≥ 100 mg/dL
  - Cohort 3: Patients with LDL-C 70–99 mg/dL
- Enrolled patients underwent a 1-year retrospective chart review and baseline interactive phone survey, followed by chart reviews and surveys every 6 months for 2 years
- Patients were enrolled from December 2016 through July 2018

LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor

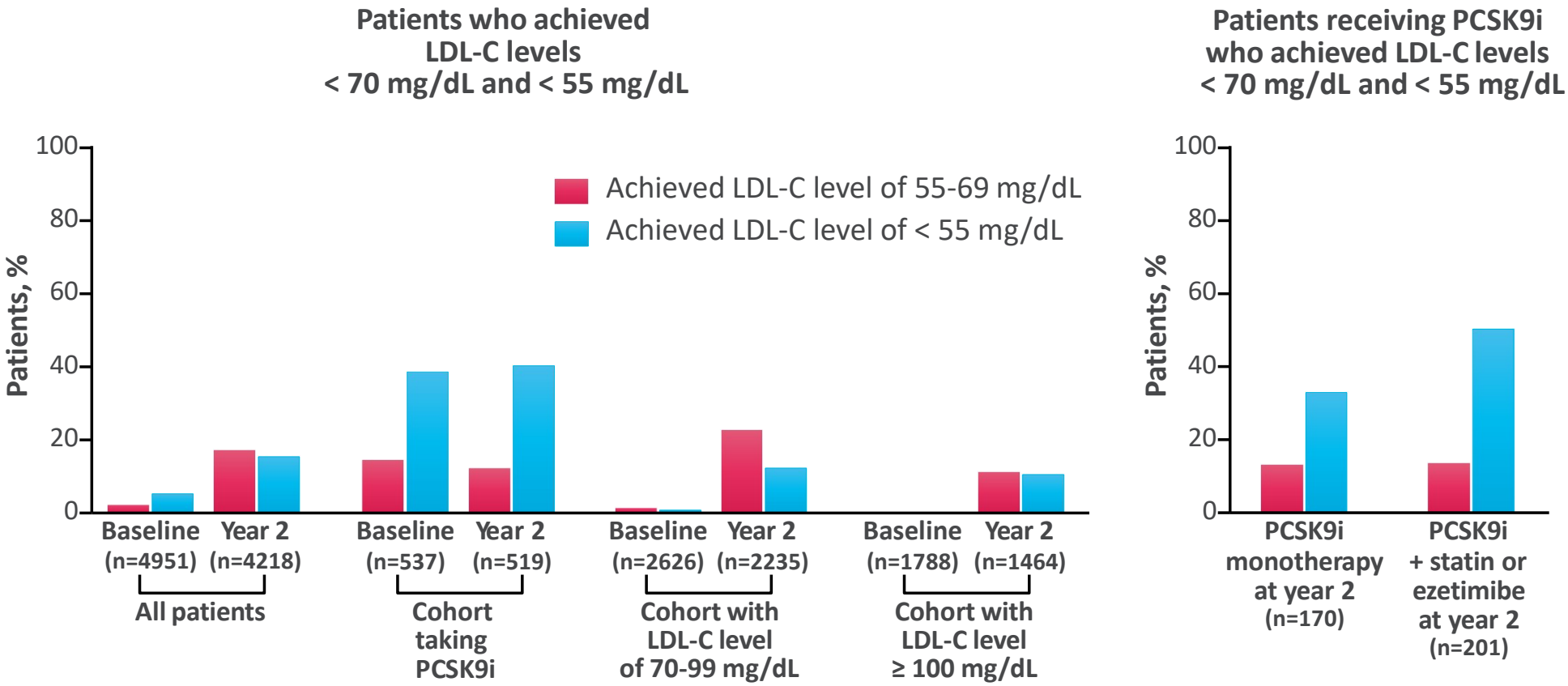
Cannon CP, et al. *Am Heart J.* 2020;219:70-77.

GOULD: At 1 Year, Only 43% of Patients Were on High-Intensity Statin



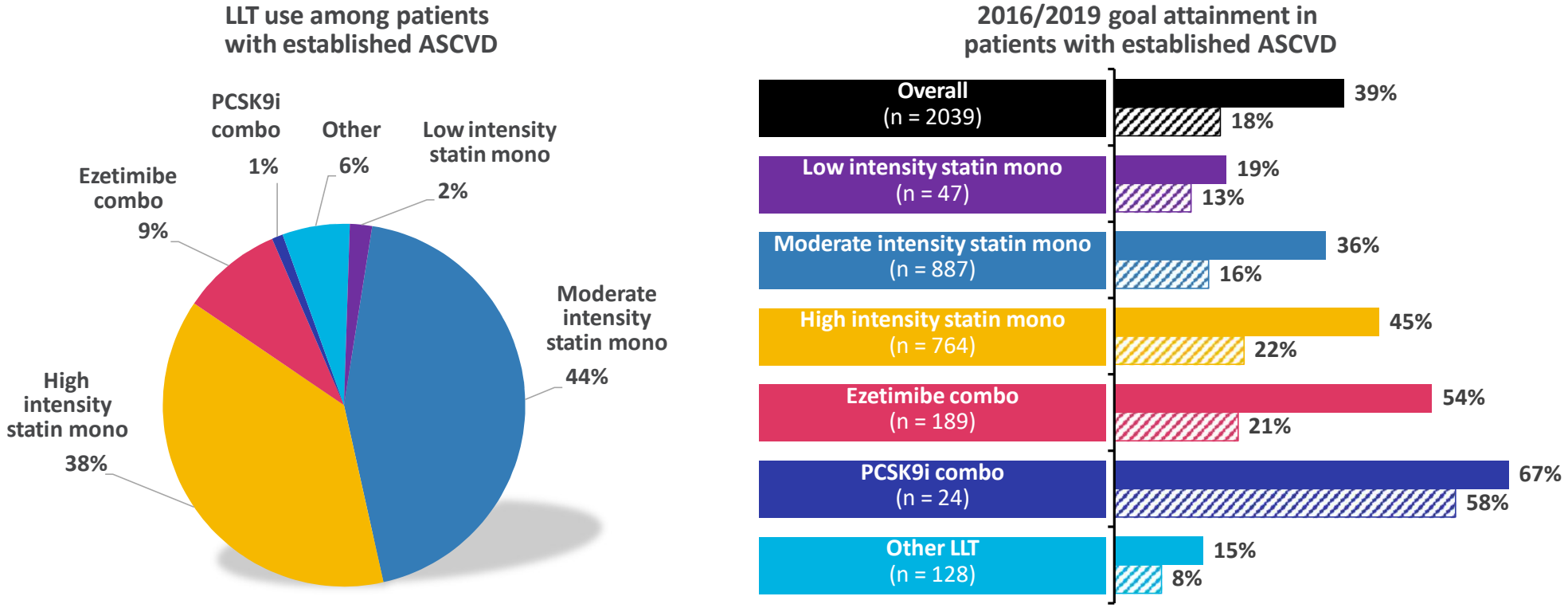
Cannon CP et al. *JAMA Cardiol.* 2021;6(9):1060-1068

GOULD: Getting to Low LDL-C Levels



Cannon CP et al. *JAMA Cardiol.* 2021;6(9):1060-1068.

DA VINCI: In Very High-Risk Patients with Established ASCVD, Goal Attainment was More Likely with Combination Therapy



In very high-risk patients, 2019 goal attainment of 1.4 mmol/L (55 mg/dL) was approximately half that of 2016 (18% vs. 39%)

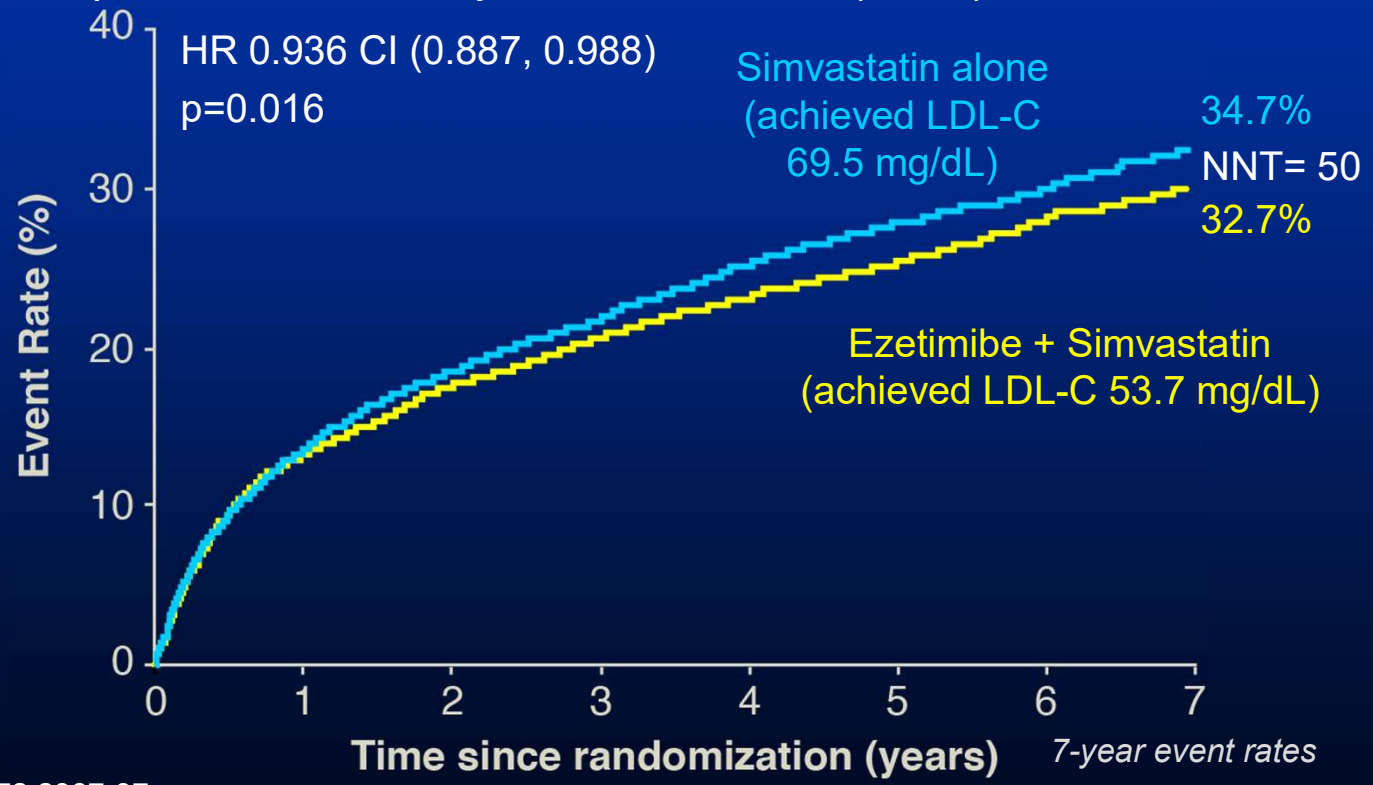
Pie chart shows % of patients receiving each LLT at LDL-C measurement. Bar chart shows % of patients achieving 2016 (solid bars) and 2019 (hashed bars) LDL-C goals. Combo, combination therapy; mono, monotherapy; LLT, lipid-lowering therapy.

Ray KK, et al.*European Journal of Preventive Cardiology* 2020 doi:10.1093/eurjpc/zwaa047

Primary Endpoint — ITT

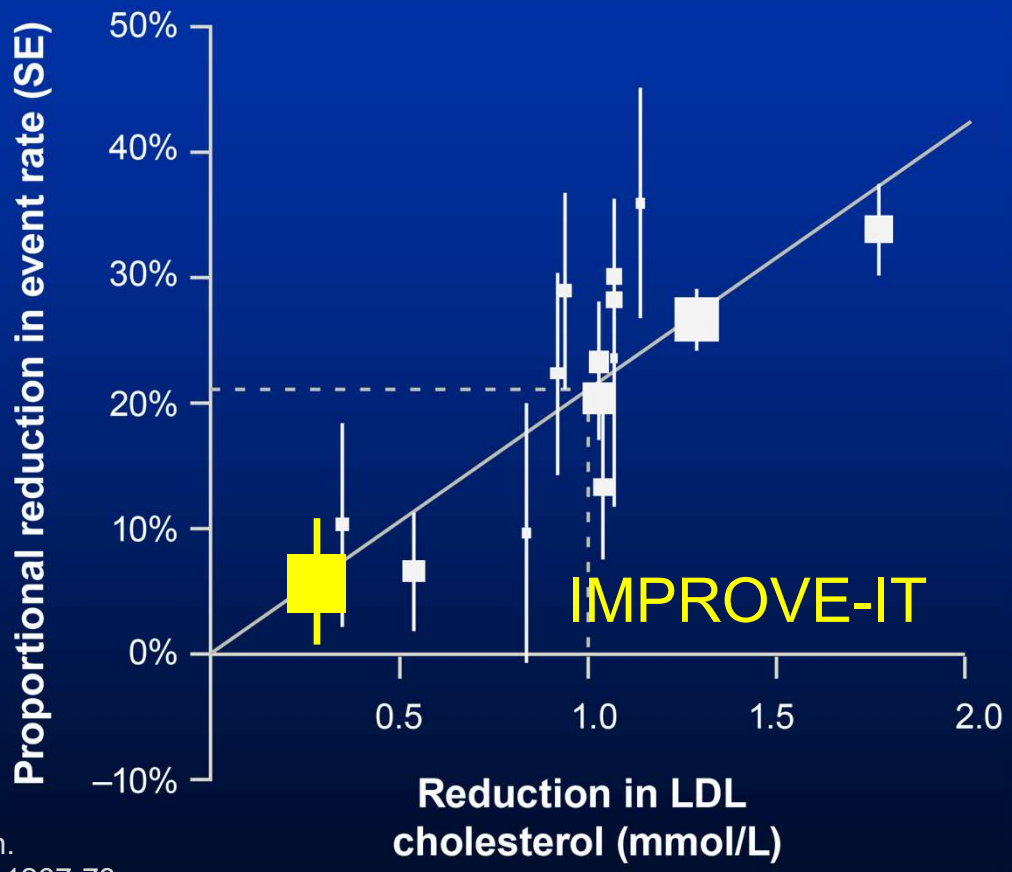
18,144 Patients stabilized post ACS ≤ 10 days

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 d), or stroke



Cannon CP et al. *NEJM* 2015;372:2387-97

IMPROVE-IT vs. CTT: Ezetimibe vs. Statin Benefit

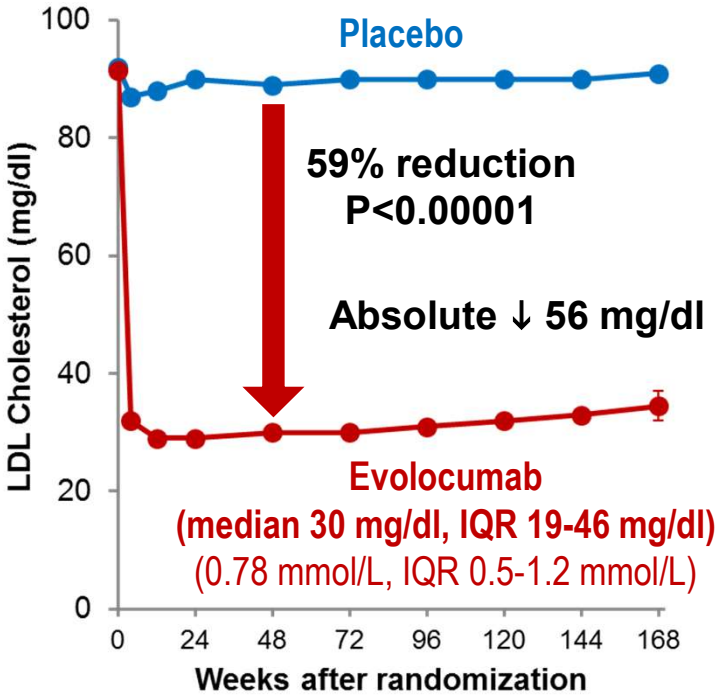


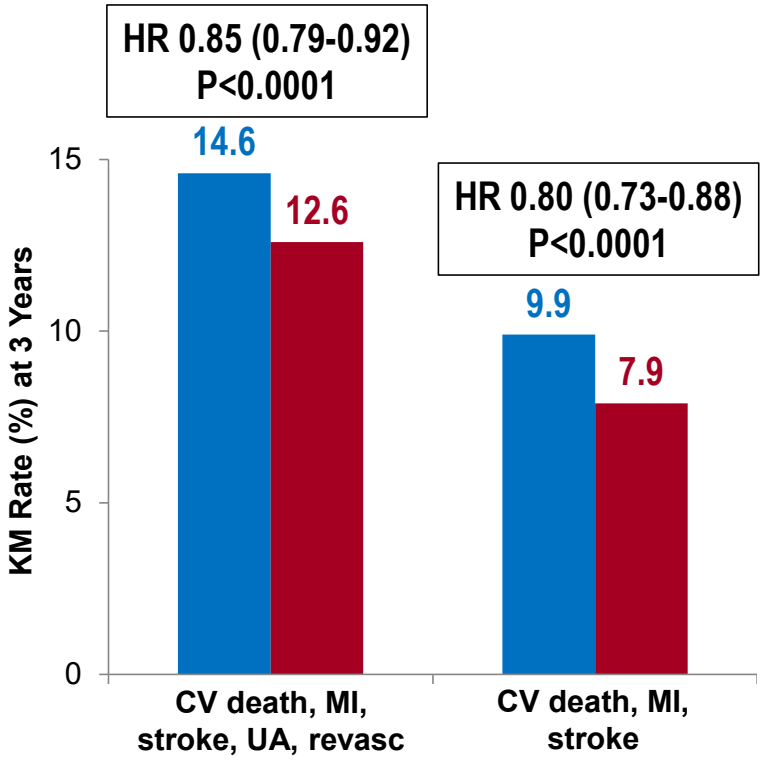
CTT Collaboration.
Lancet 2005; 366:1267-78;
Lancet 2010;376:1670-81.

Using CTT methods: LDL difference between groups using baseline LDL for Pts without blood samples. Endpoint of CV Death, MI, stroke or revasc >30days post Rand. Cox HR reported.

Summary of Effects of PCSK9i with Evolocumab

27,564 Pts w/ prior MI, stroke or PAD on optimized statin therapy





Sabatine MS et al. *NEJM.* 2017;376:1713-22.

Acute Arterial Events

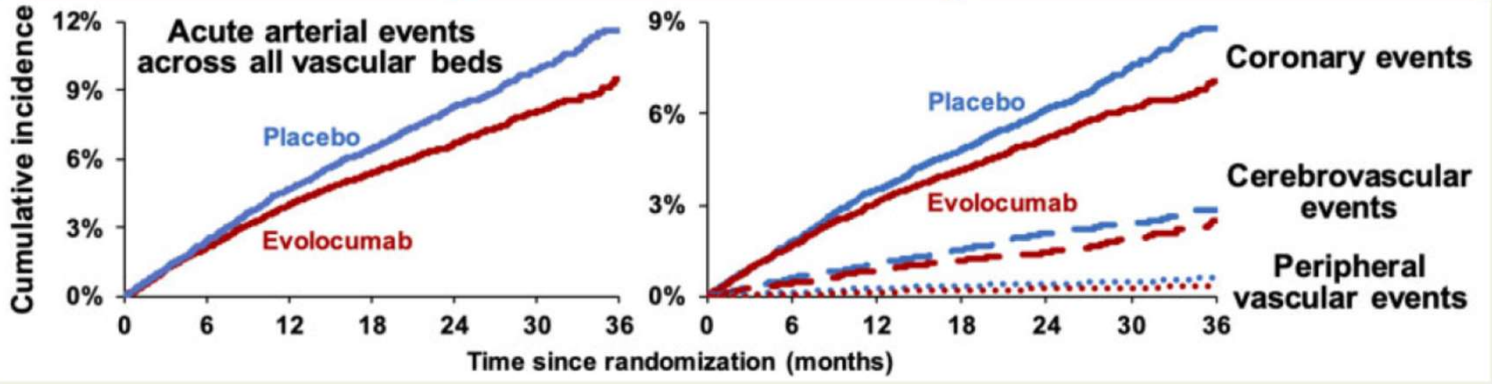
Effect of evolocumab on acute arterial events across all vascular territories

(Acute coronary, cerebrovascular, or peripheral vascular events)

First event: ↓ 19% HR 0.81 (95% CI 0.74-0.88) P<0.001

Total events: ↓ 24% RR 0.76 (95% CI 0.69-0.85) P<0.001

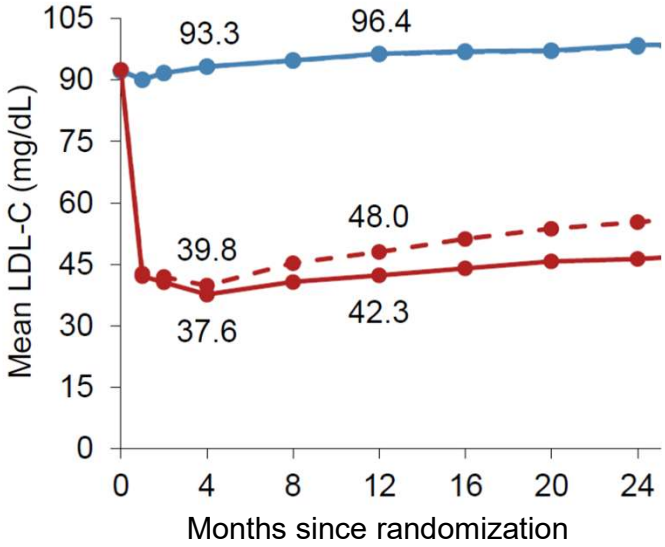
Acute coronary events	Acute cerebrovascular events	Acute peripheral vascular events
(CHD death, MI, or urgent coronary revascularization)	(Ischemic stroke, TIA, or urgent cerebral revascularization)	(ALI, major amputation, or urgent peripheral revascularization)
↓ 17% (First event)	↓ 23% (First event)	↓ 42% (First event)
HR 0.83 (95% CI 0.75-0.91)	HR 0.77 (95% CI 0.65-0.92)	HR 0.58 (95% CI 0.38-0.88)

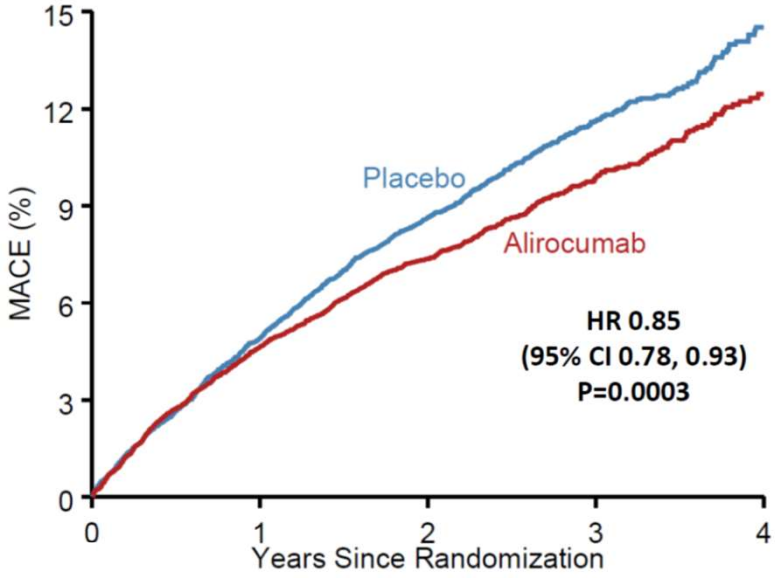


Oyama et al. *EHJ.* 2021;42:4821-9

ODYSSEY OUTCOMES

18,924 patients with ACS 1-12 months earlier





Schwartz GG et al. *NEJM* 2018;379:2097-2107.

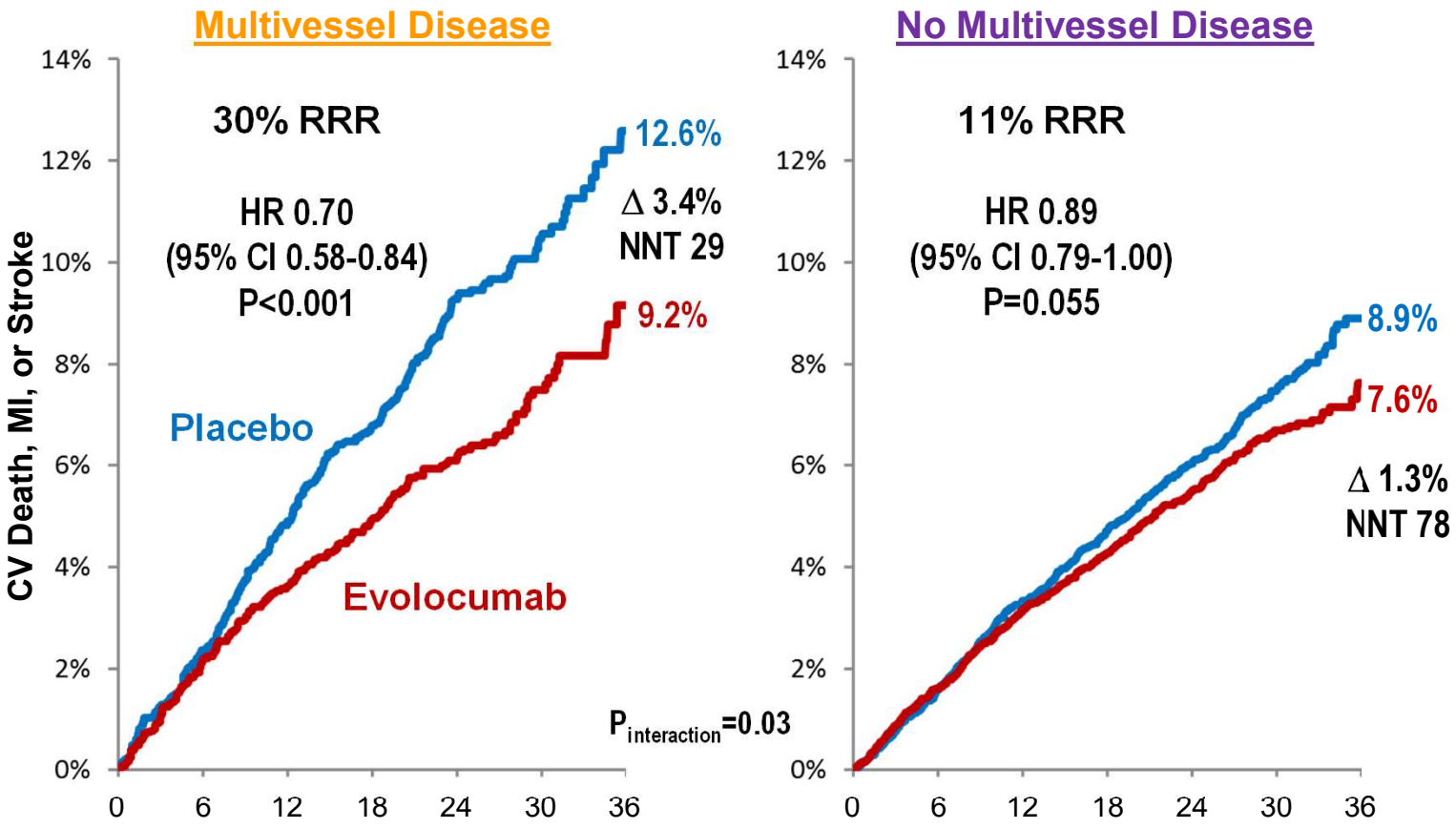
Safety of PCSK9i mAb

	fourier		ODYSSEY OUTCOMES	
	Evolocumab (N=13,769)	Placebo (N=13,756)	Alirocumab (N=9451)	Placebo (N=9443)
Adverse events (%)				
Any	77.4	77.4	75.8	77.1
Serious	24.8	24.7	23.3	24.9
Allergic reaction	3.1	2.9	7.9	7.8
Injection-site reaction	2.1	1.6	3.8	2.1
Led to d/c of study drug	4.6	4.2	3.6	3.4
Myositis	0.7	0.7	0.5	0.5
Elevated aminotransferases	1.8	1.8	2.3	2.4
Cataract	1.7	1.8	1.3	1.4
Diabetes (new-onset)	8.1	7.7	9.6	10.1
Neurocognitive	1.6	1.5	1.5	1.8

Sabatine MS et al. *NEJM* 2017;376:1713-22 & Schwartz GG et al. *NEJM* 2018;379:2097-2107.

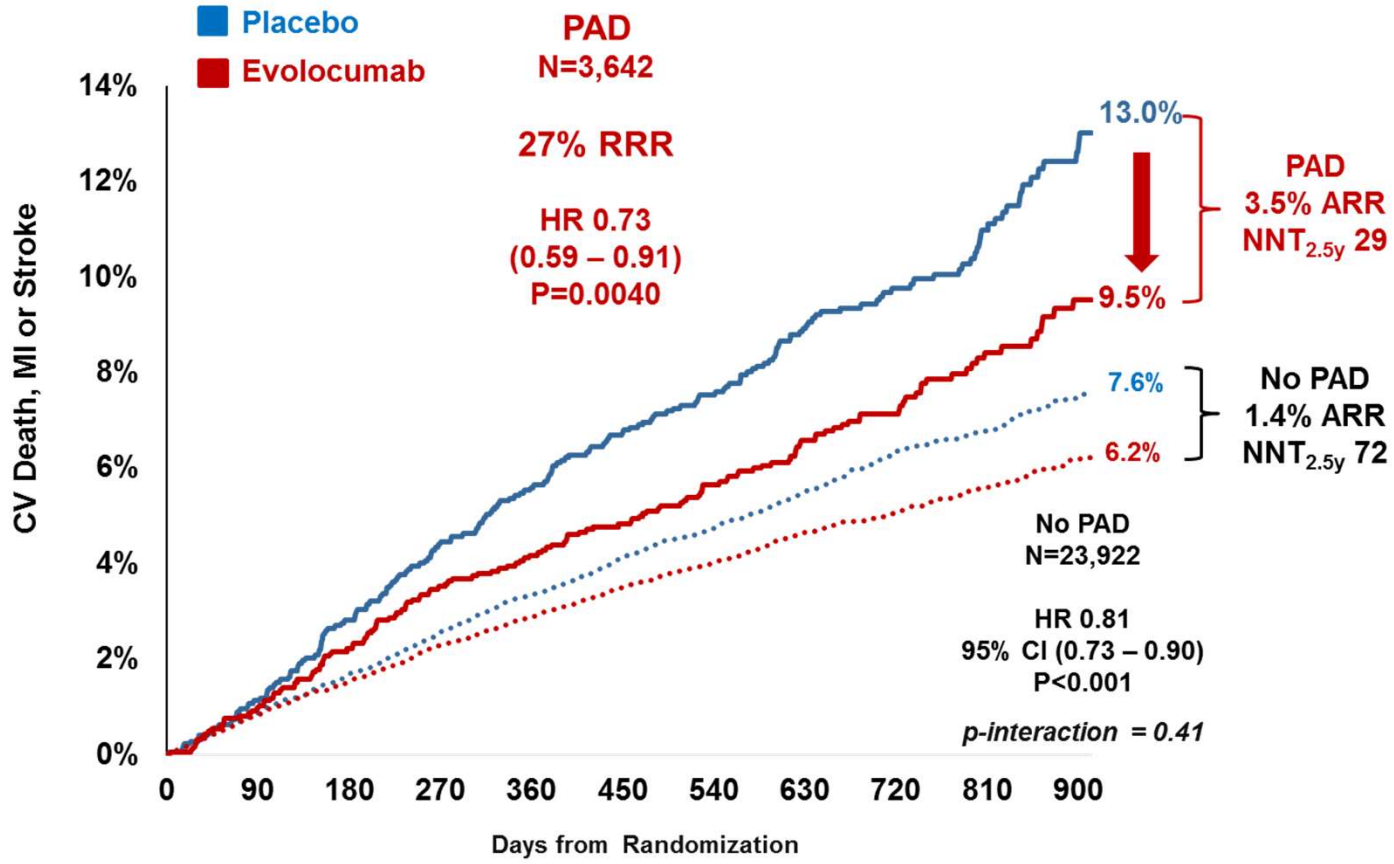
mAb, monoclonal antibodies

Benefit of Evolocumab Based on Multivessel Disease



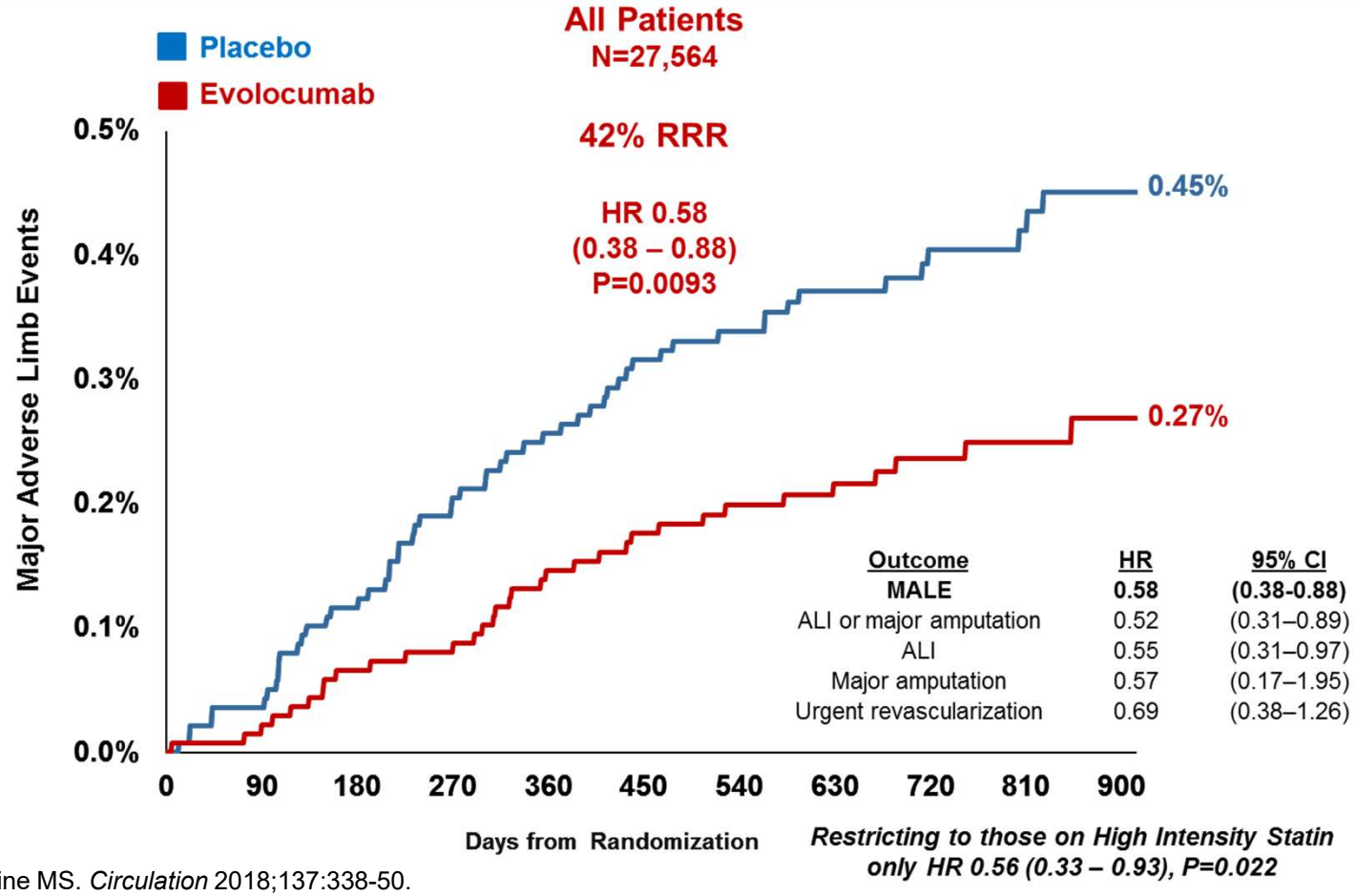
Sabatine M et al. *Circulation.* 2018;138:756-66.

CV Death, MI or Stroke in Patients w/ & w/o Peripheral Artery Disease



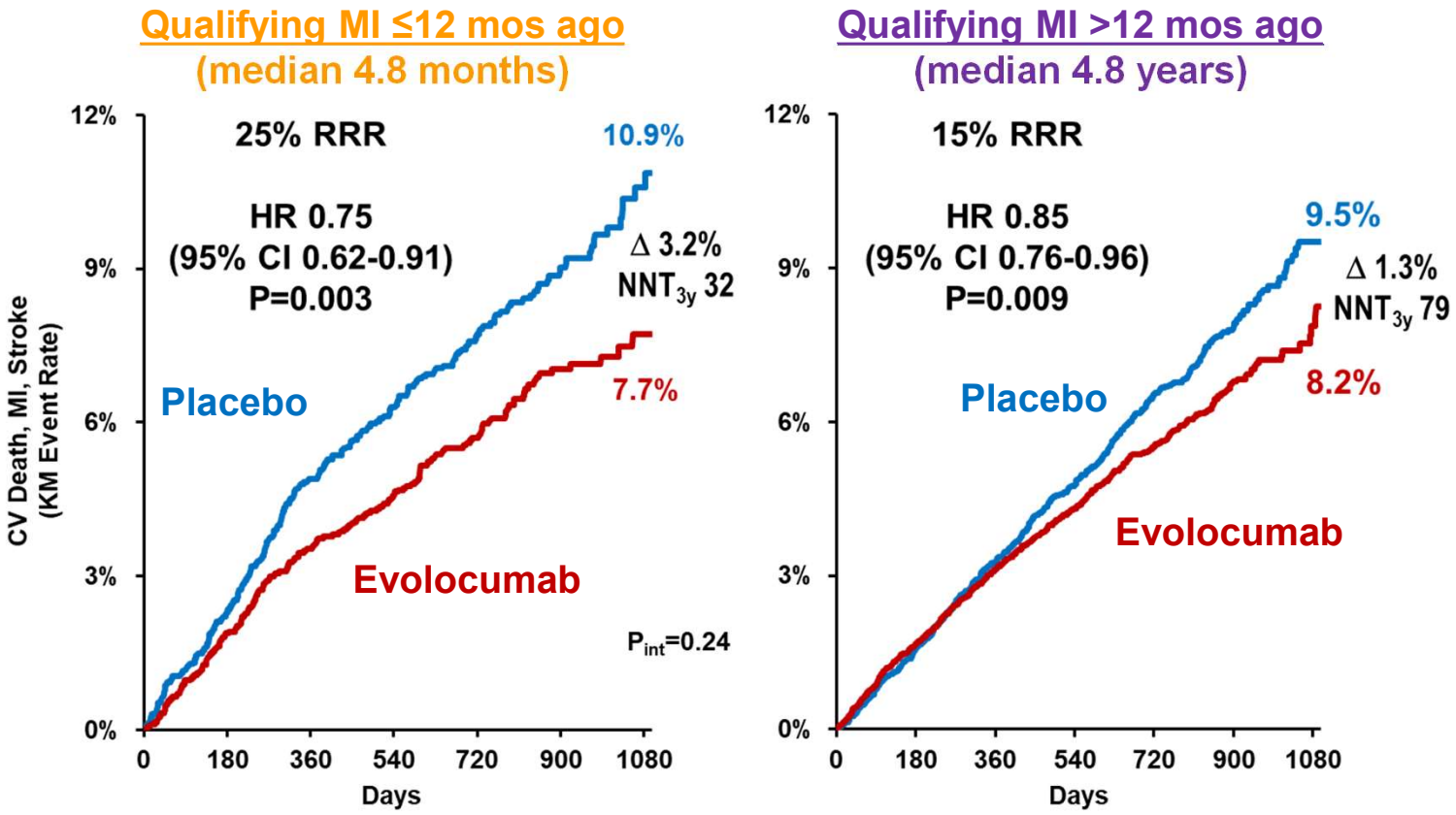
Bonaca MP et al. & Sabatine MS. *Circulation* 2018;137:338-50.

Major Adverse Limb Events



Bonaca MP et al. & Sabatine MS. *Circulation* 2018;137:338-50.

Benefit of Evolocumab Based on Time from Qualifying MI



Gencer B et al. *JAMA Cardiol* 2020;5:952-57.

DOI: 10.1002/clc.23112

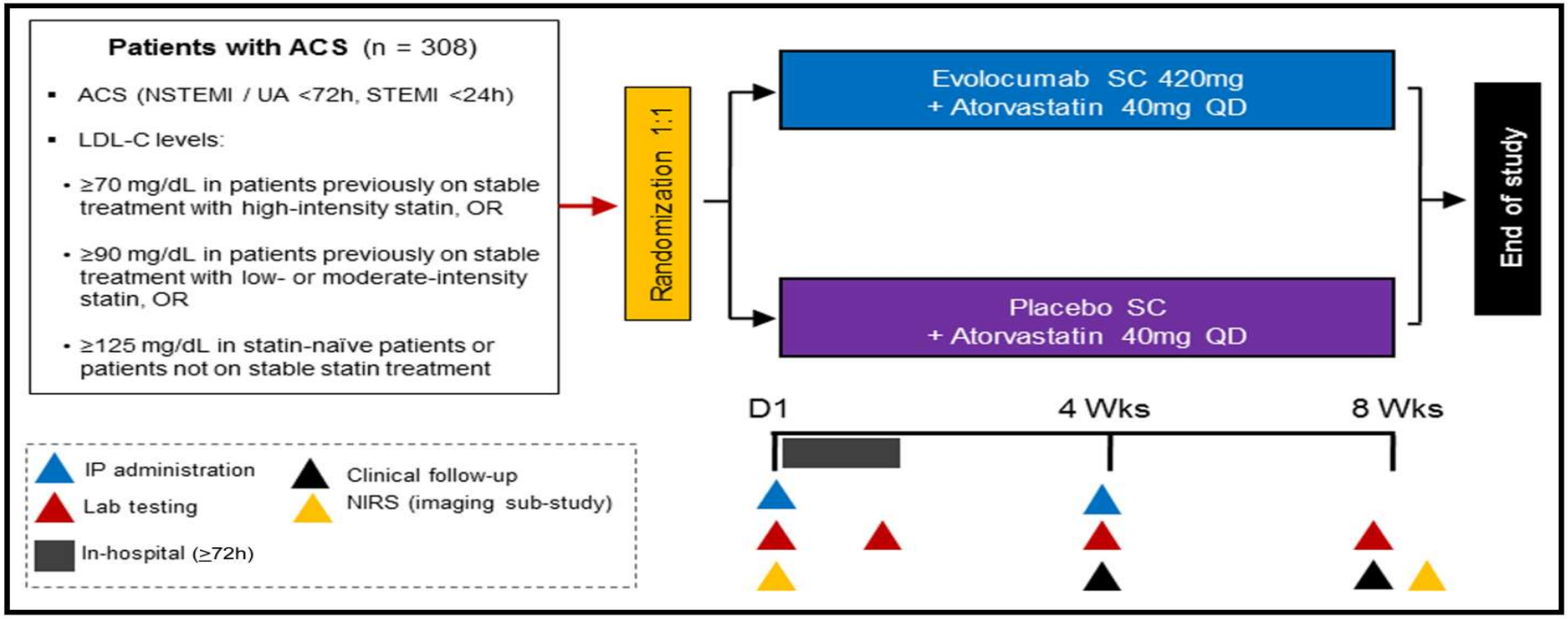
WILEY CLINICAL CARDIOLOGY

TRIAL DESIGNS

Design of the randomized, placebo-controlled evolocumab for early reduction of LDL-cholesterol levels in patients with acute coronary syndromes (EVOPACS) trial

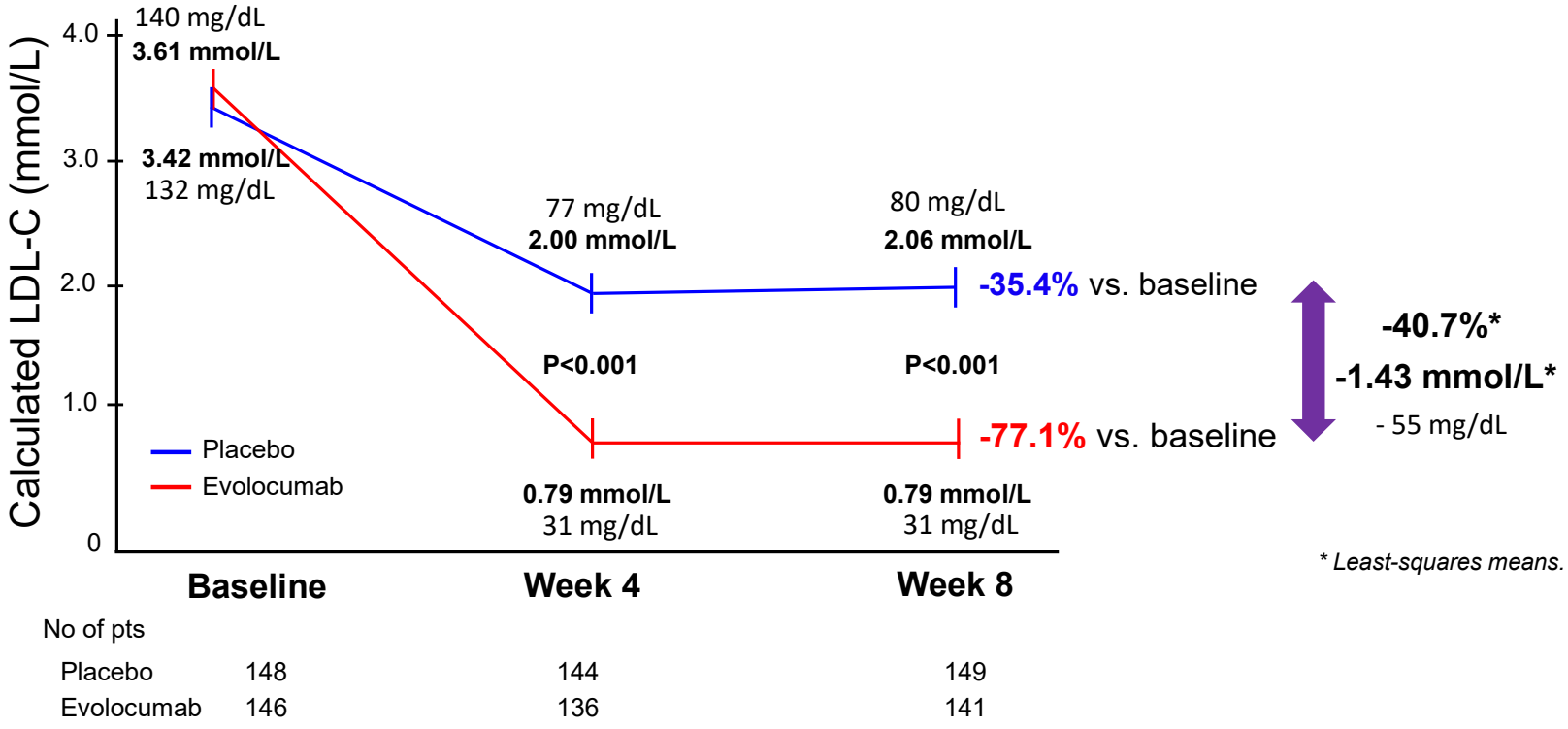
Konstantinos C. Koskinas[1] | Stephan Windecker[1] | Aliki Buhayer[2] | Baris Gencer[3] | Giovanni Pedrazzini[4] | Christian Mueller[5] | Stephan Cook[6] | Olivier Muller[7] | Christian M. Matter[8] | Lorenz Räber[1] | Dik Heg[9] | François Mach[3] | on behalf of the EVOPACS Investigators

EVOPACS



Koskinas KC et al. *Clin Cardiol 2018*;41:1513-20.

Primary endpoint: % Change in LDL-C at 8 Weeks



* *Least-squares means.*

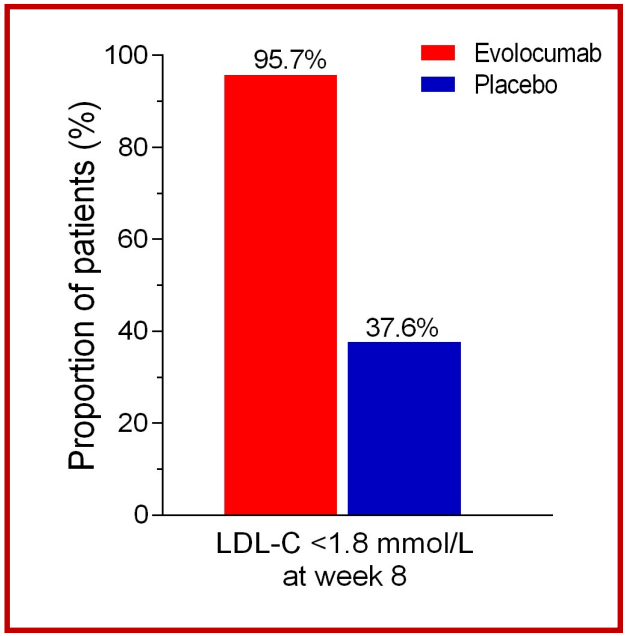
No of pts

Placebo	148	144	149
Evolocumab	146	136	141

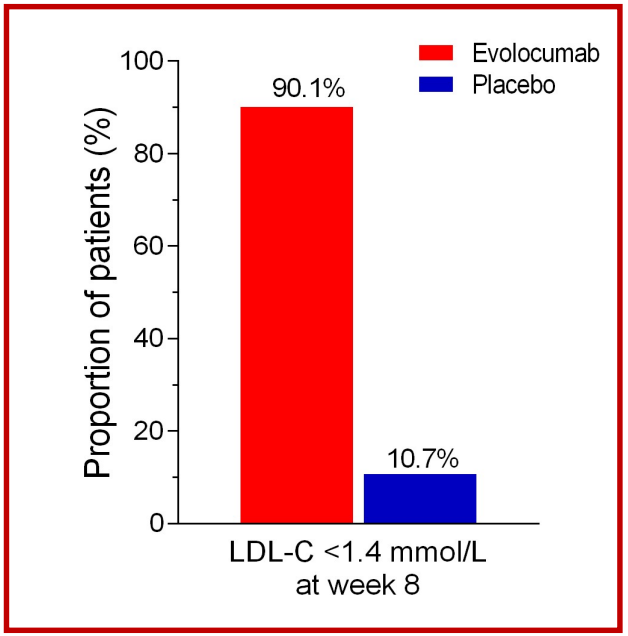
Koskinas KC et al. *J Am Coll Cardiol* 2019;74:2452-62.

Achievement of LDL-C Treatment Targets

LDL-C target **<1.8 mmol/l**
(<70 mg/dl)

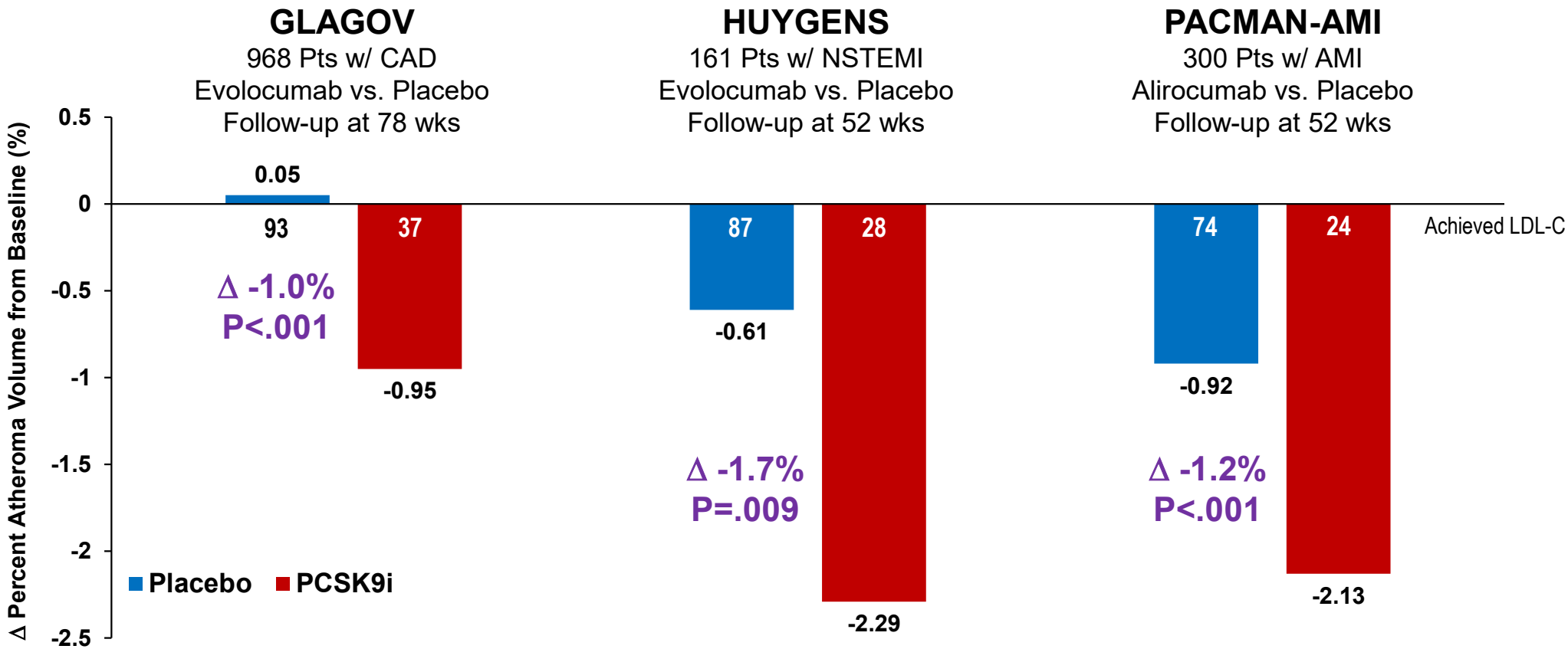


LDL-C target **<1.4 mmol/l**
(<55 mg/dl)



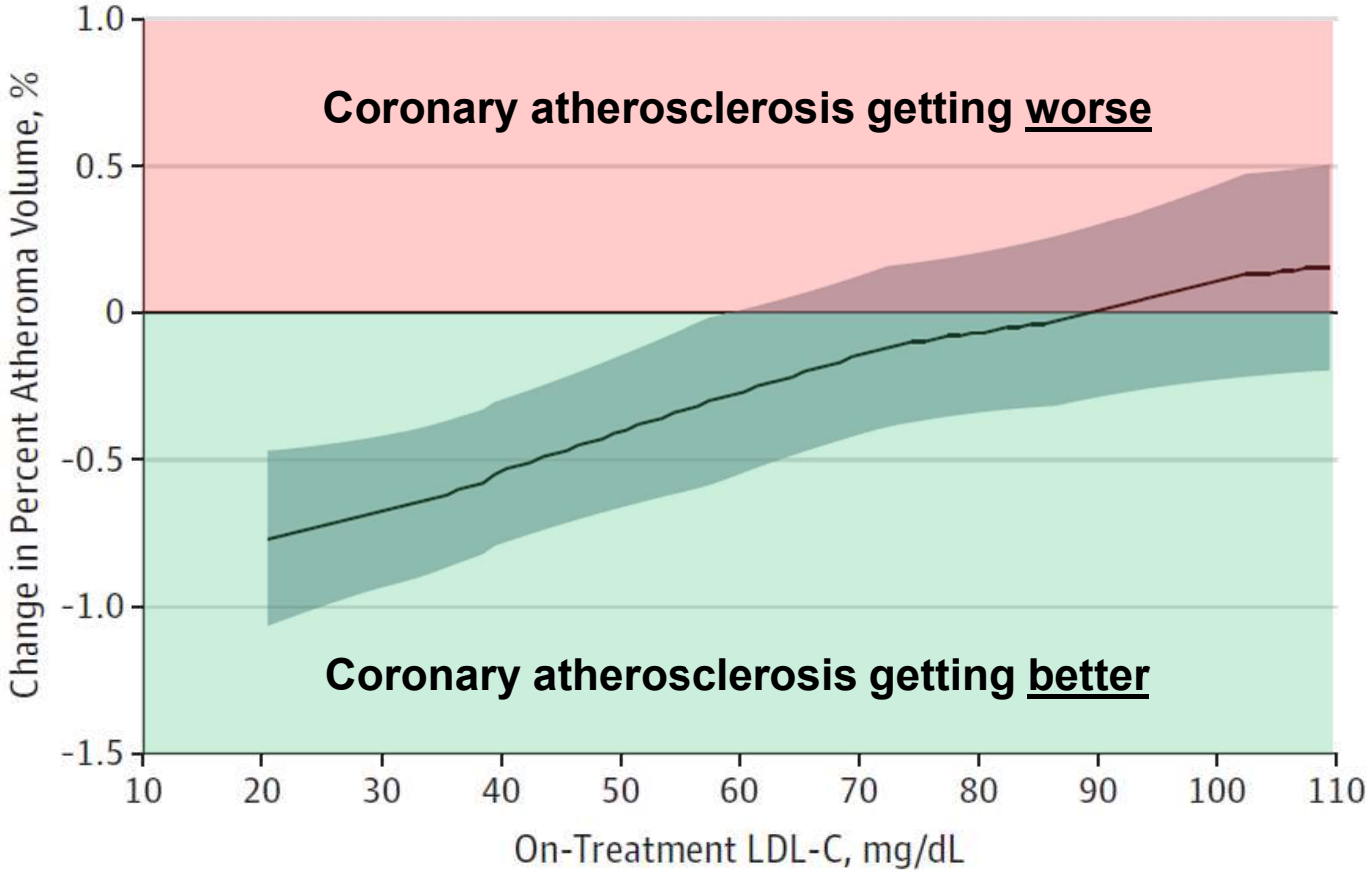
Koskinas KC, et al. *J Am Coll Cardiol* 2019;74:2452-62.

PCSK9i and Plaque Atheroma Volume



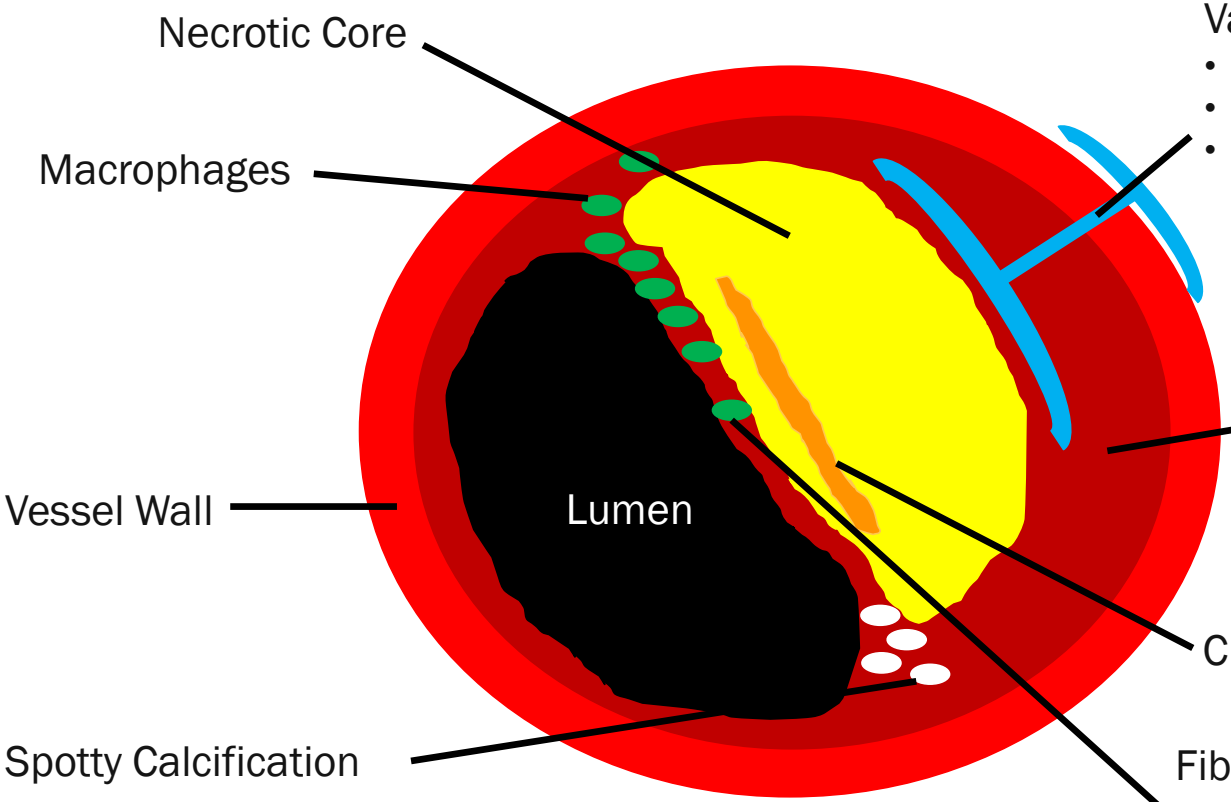
Nicholls SJ et al. *JAMA* 2016;316:2373-84; Nicolls SJ et al. *JACC CV Imaging* 2022 Mar 16 (epub ahead of print); Raber L et al. *JAMA* 2022 April 3 (epub ahead of print).

LDL-C & Coronary Artery Plaque Size w/ PCSK9i



Nicholls SJ et al. *JAMA* 2016;316:2373-84.

Vulnerable Plaque



Vasa Vasorum Proliferation
- Neovascularization
- RBC leak
- Intraplaque hemorrhage

Plaque Burden
Outward remodeling

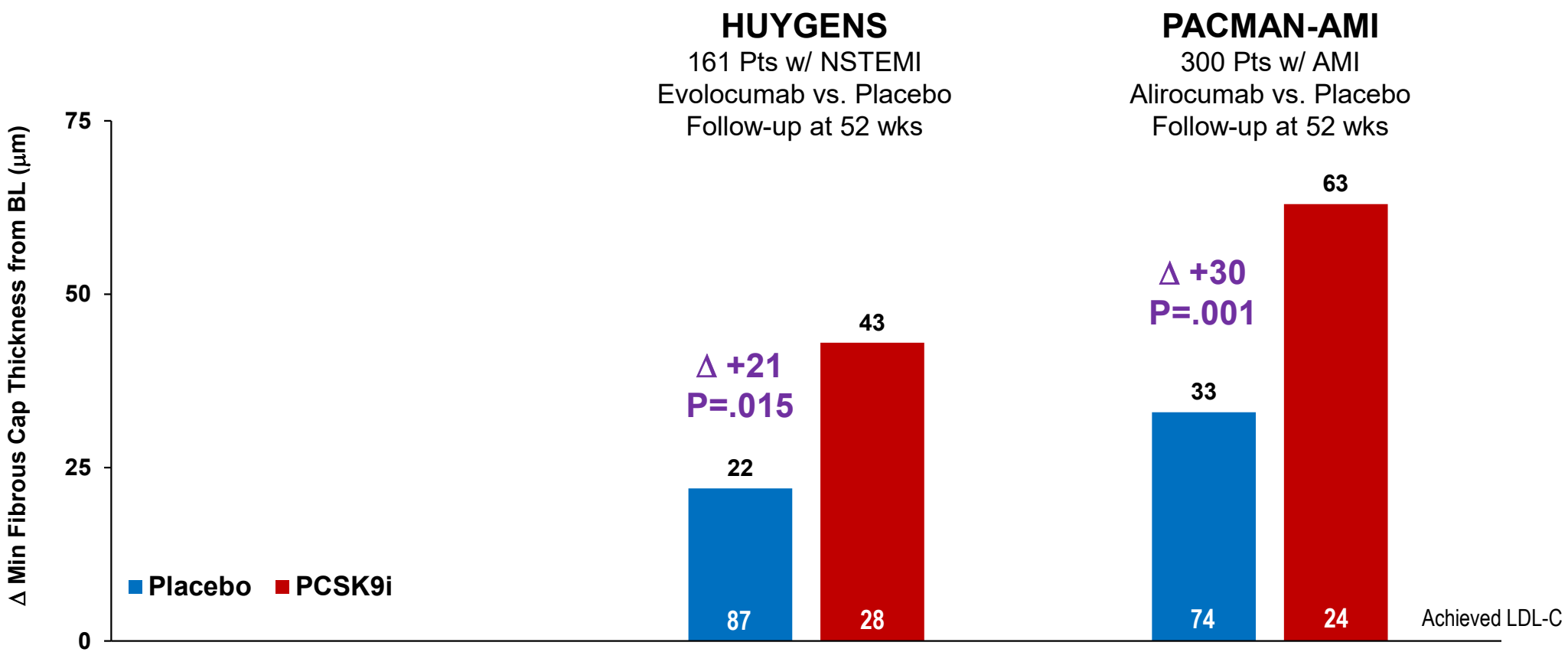
Cholesterol Crystal

Fibrous Cap
- Thin (< 65 um)
- Macrophage infiltration

RBC, red blood cell

Narula J, et al. Nat Clin Prac Cardiovasc Med. 2008;5(suppl 2):S2-S10.

PCSK9i and Minimum Fibrous Cap Thickness



Nicholls SJ et al. *JACC CV Imaging* 2022 Mar 16 (epub ahead of print);
Raber L et al. *JAMA* 2022 April 3 (epub ahead of print).