Newark Beth Israel Medical Center | RWJBarnabas HEALTH

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Lipid Lowering: How Low can you GO?

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Cors at the Shore 2023

Presenter Disclosure Information

DR. MARC COHEN has the following relationships that might materially affect this presentation:

Grant/Research Support: Edwards

Consultant: Getinge

Speakers Bureau: AZ, Sanofi, BI, Janssen, Lilly

Major Stock Shareholder: NONE

2023 Cors at the Shore

Me: What can I do to get healthier, doctor?

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STATINS ON THE INTERNET

- Type statin "benefits" into Google; 655,000 references
- Type statin "risks" into Google; 3,530,000 references
- Patients blinded to drug assignment have the same frequency of adverse muscle events taking placebo or active drug. Gupta, Lancet, 2017, 389:2473

Nissen, Statin Denial, Ann Internal Med 2017: 167: 281

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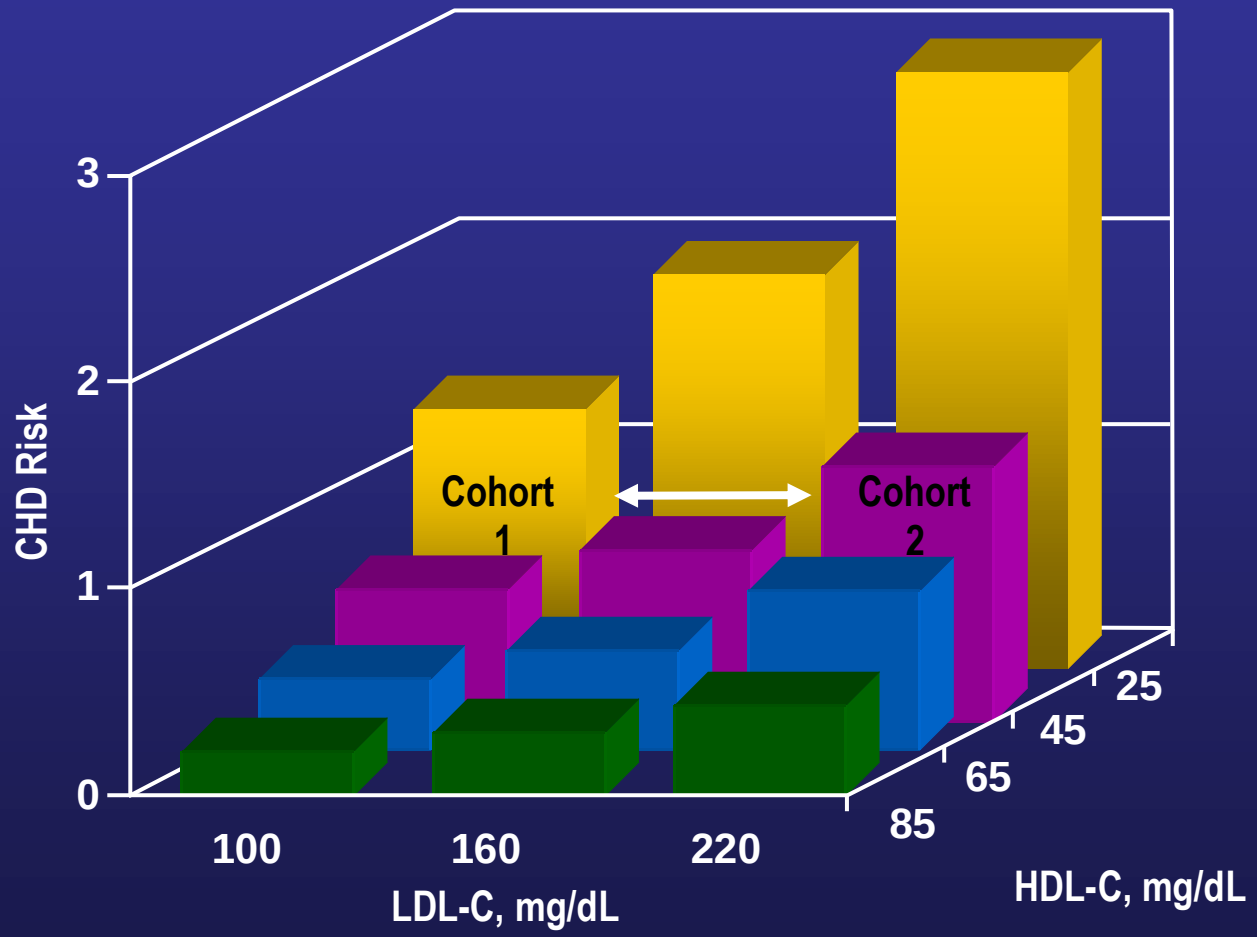
Low HDL-C Increased CHD Risk at All LDL-C Levels: The Framingham Study[1]

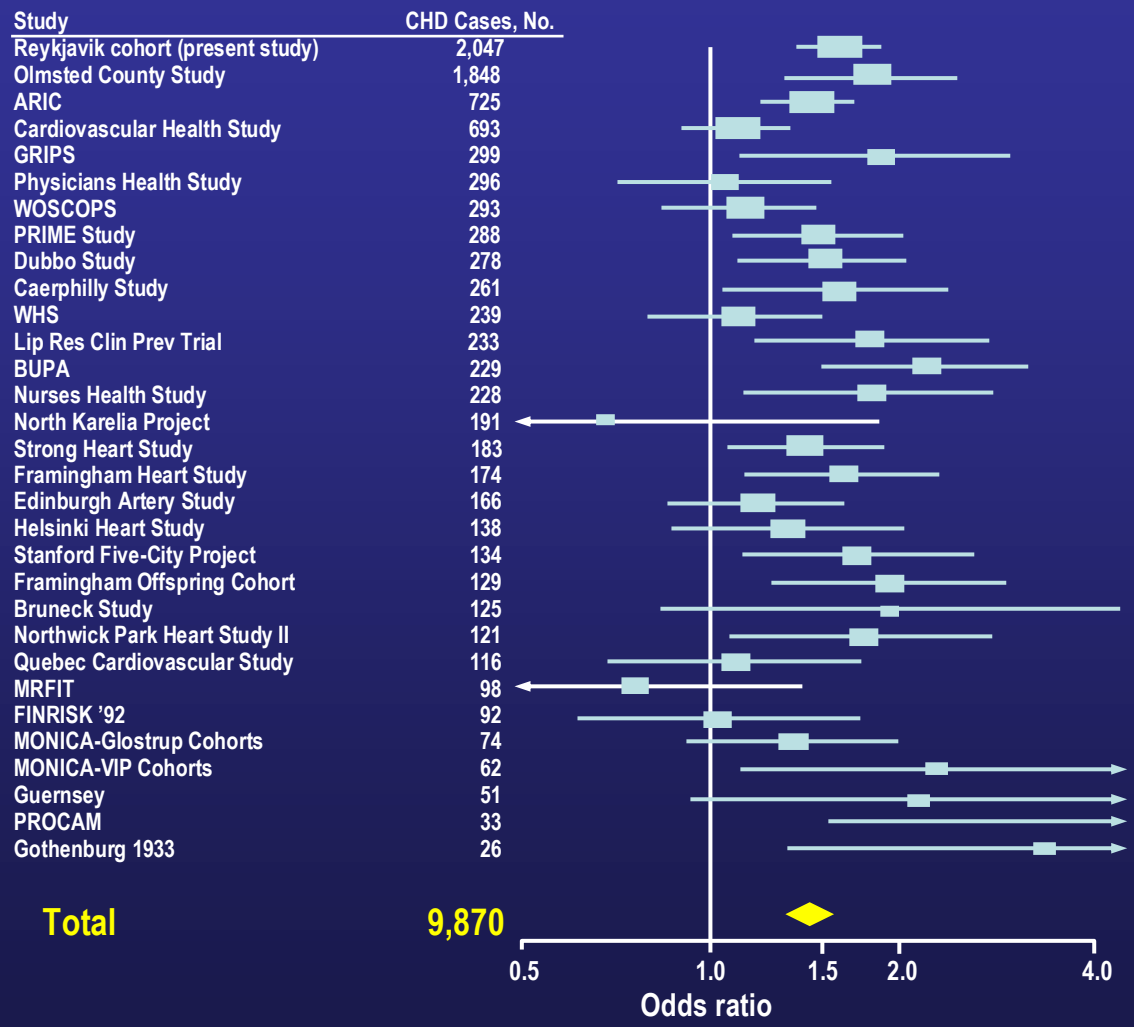
A patient in Cohort 1 having LDL-C = 100 mg/dL and HDL-C = 25 mg/dL would have similar CHD risk as a patient in Cohort 2 having LDL-C = 220 mg/dL and HDL-C = 45 mg/dL.



4-year follow-up to the Framingham Heart Study that evaluated the risk of CHD in men aged 50 to 70 years, according to HDL-C and LDL-C levels.

1. Castelli WP. *Can J Cardiol*. 1988;4(suppl A):5A–10A.

High Lp(a) Levels Were Associated With Increased CHD Risk: Meta-Analysis Results[1]



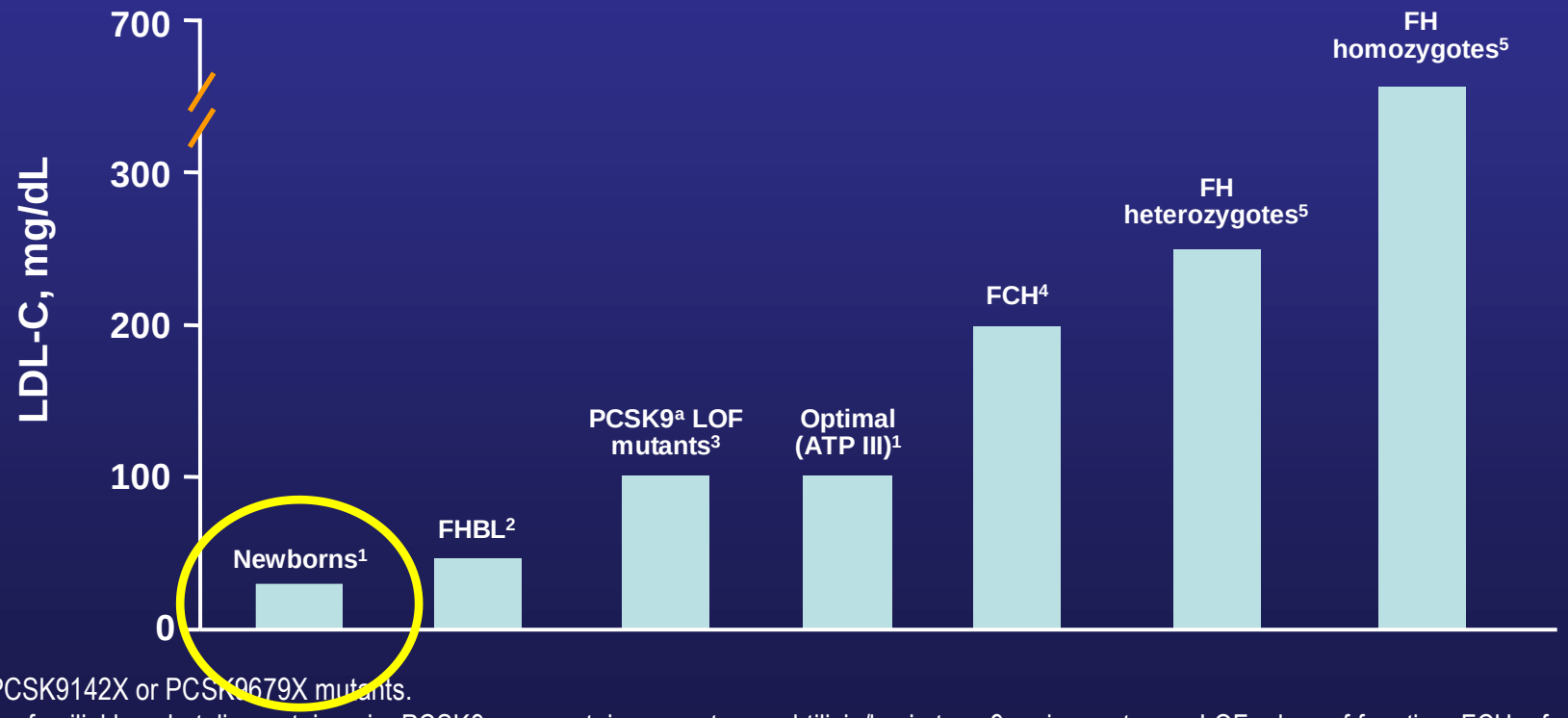
Odds ratios for CHD (top third vs bottom third of the baseline Lp(a) distribution) in each of 31 published prospective studies of Lp(a) in general populations.

Lp(a) = lipoprotein(a)

1. Bennett A et al. *Arch Intern Med*. 2008;168:598–608.

Based on Multiple Sources: LDL-C Levels Vary With Genetic Variants in Cholesterol Metabolism

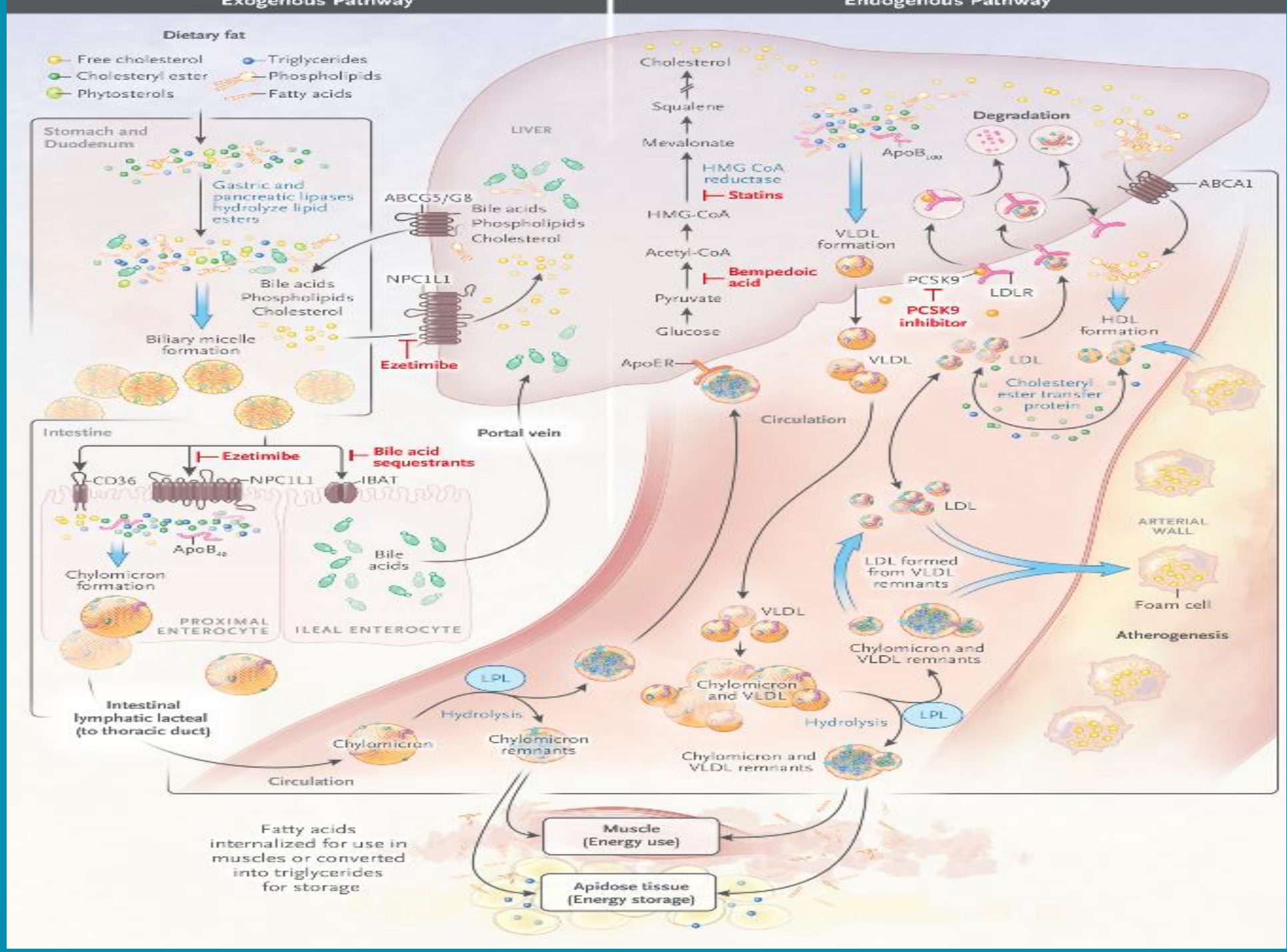
- Individuals with extremely elevated LDL-C display advanced coronary atherosclerosis and premature CHD, even in the absence of other risk factors.[1]
- Individuals with low LDL-C throughout life have decreased CHD risk.[1]



[a]LOF PCSK9142X or PCSK9679X mutants.

FHBL = familial hypobetalipoproteinemia; PCSK9 = proprotein convertase subtilisin/kexin type 9 serine protease; LOF = loss of function; FCH = familial combined hyperlipidemia; FH = familial hypercholesterolemia.

1. NCEP ATP III. *Circulation*. 2002;106:3143–3421; **2.** Glueck CJ et al. *J Lab Clin Med*. 1976;88:941–957; **3.** Cohen JC et al. *N Engl J Med*. 2006;354:1264–1272; **4.** Pauciullo P et al. *Atherosclerosis*. 2009;203:320–324; **5.** Brown MS et al. *Science*. 1986;232:34–47.



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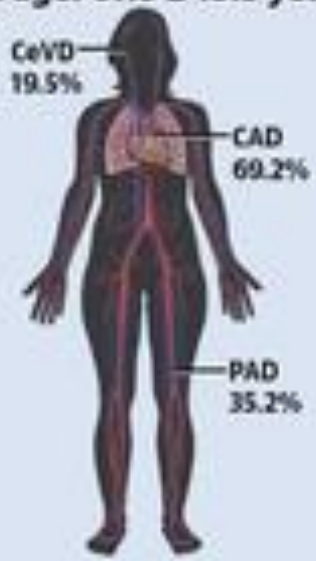
CENTRAL ILLUSTRATION: Statin Use in 601,934 Patients With Atherosclerotic Cardiovascular Disease on January 31, 2019

Study Population

601,934 patients with ASCVD
Mean age: 67.5 ± 13.3 years



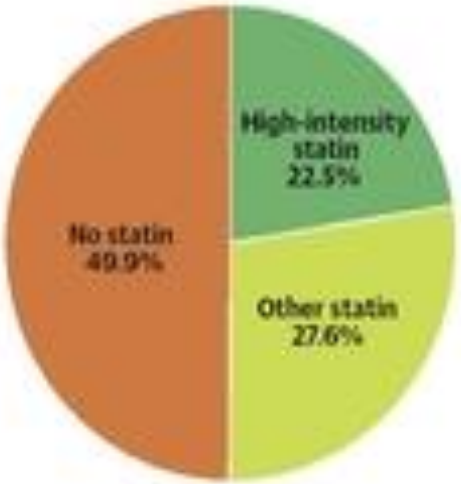
Outcomes

Statin usage on January 31, 2019
± 30 days

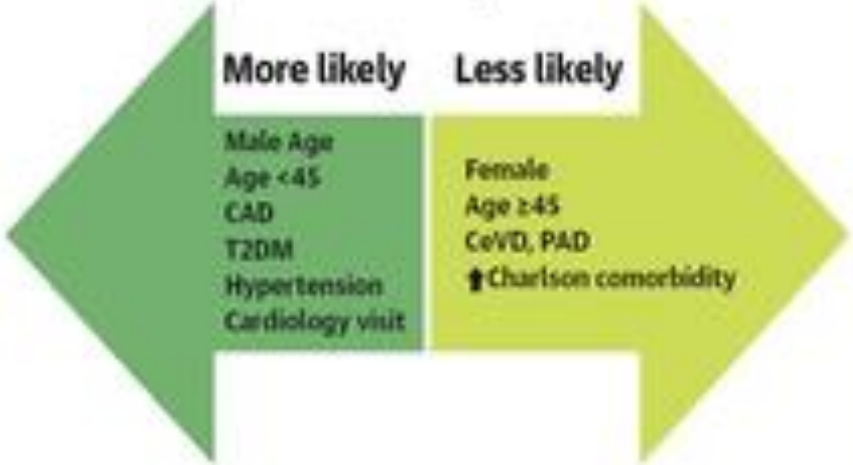
Proportion of days covered

Results

Proportion on high-intensity statin vs other statin vs no statin



Odds of high (vs other) intensity statin use



Proportion of days covered

Nelson AJ, et al. J Am Coll Cardiol. 2022;79(18):1802-1813.

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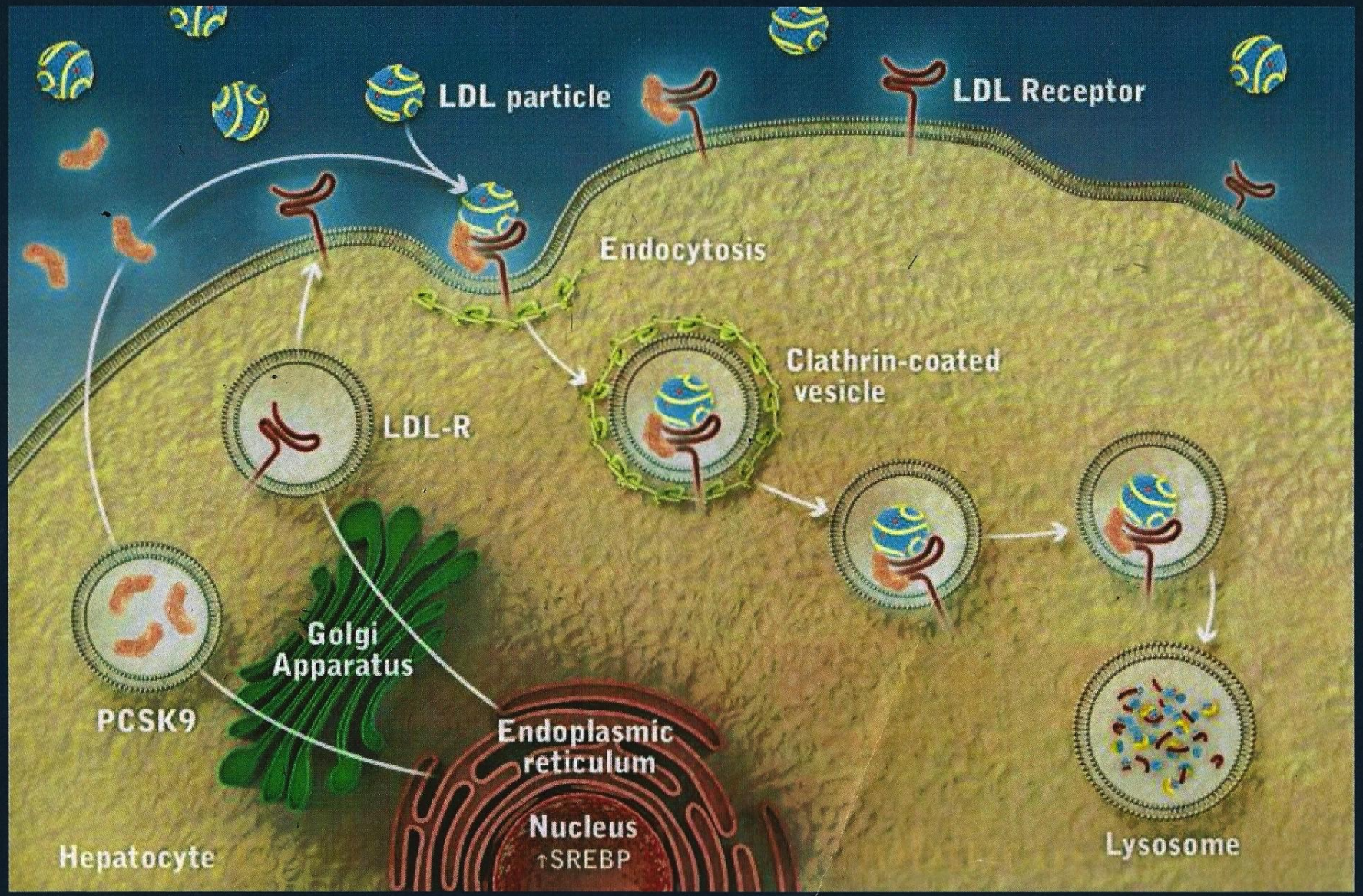
The Role of PCSK9 in the Regulation of LDL Receptor Expression



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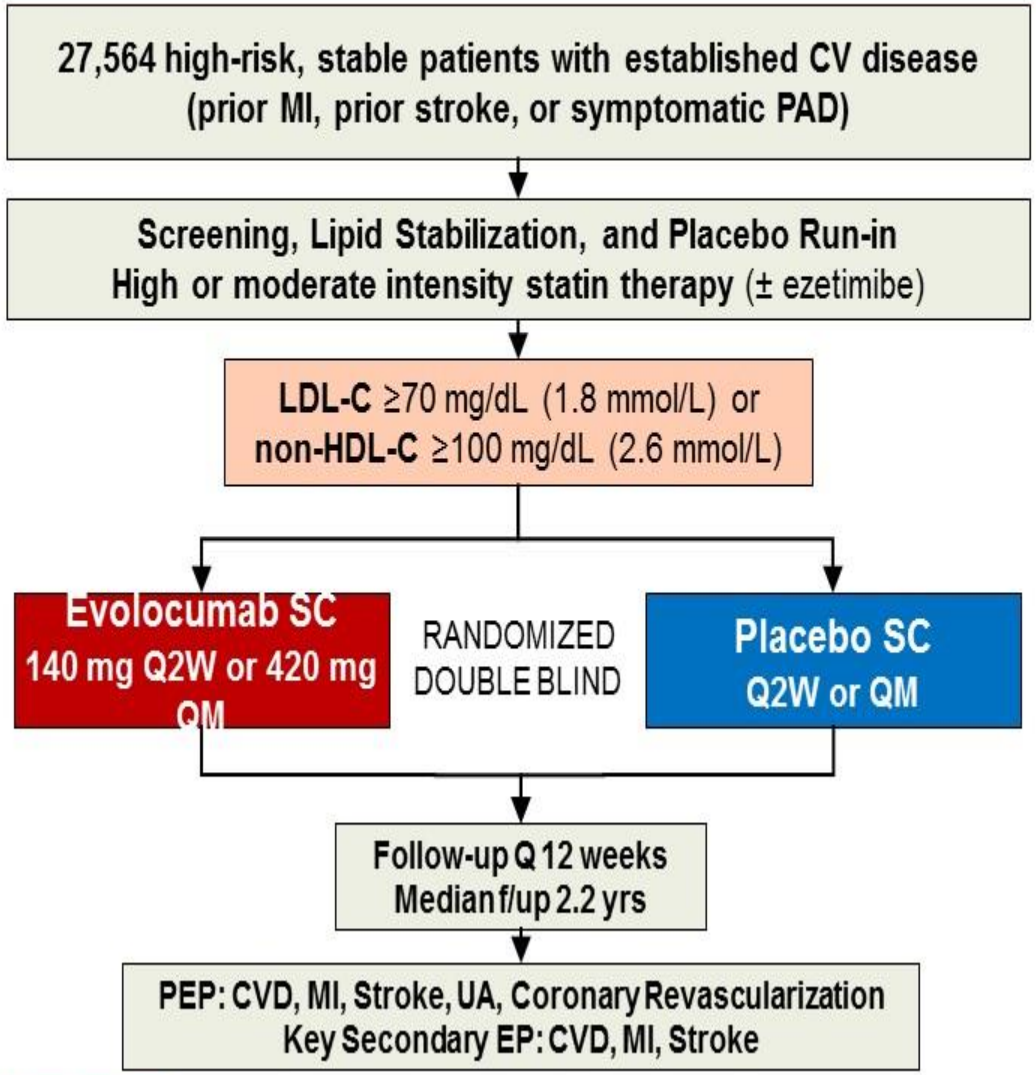
Trial Design



An Academic Research Organization of Brigham and Women's Hospital and Harvard Medical School

Sabatine MS et al. *Am Heart J* 2016;173:94-101

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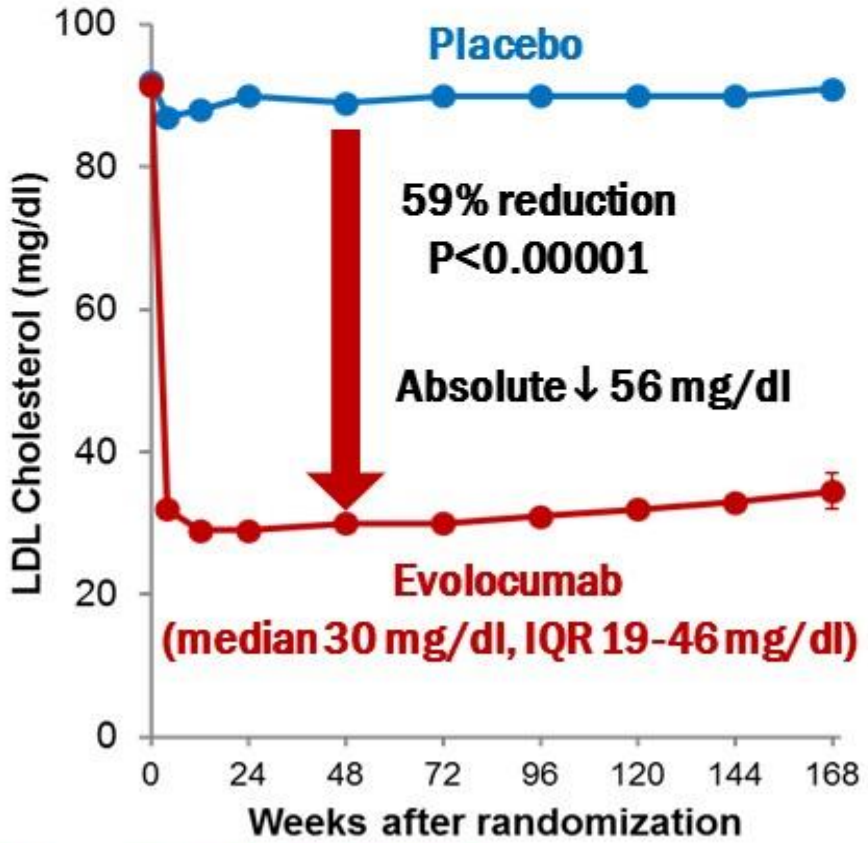
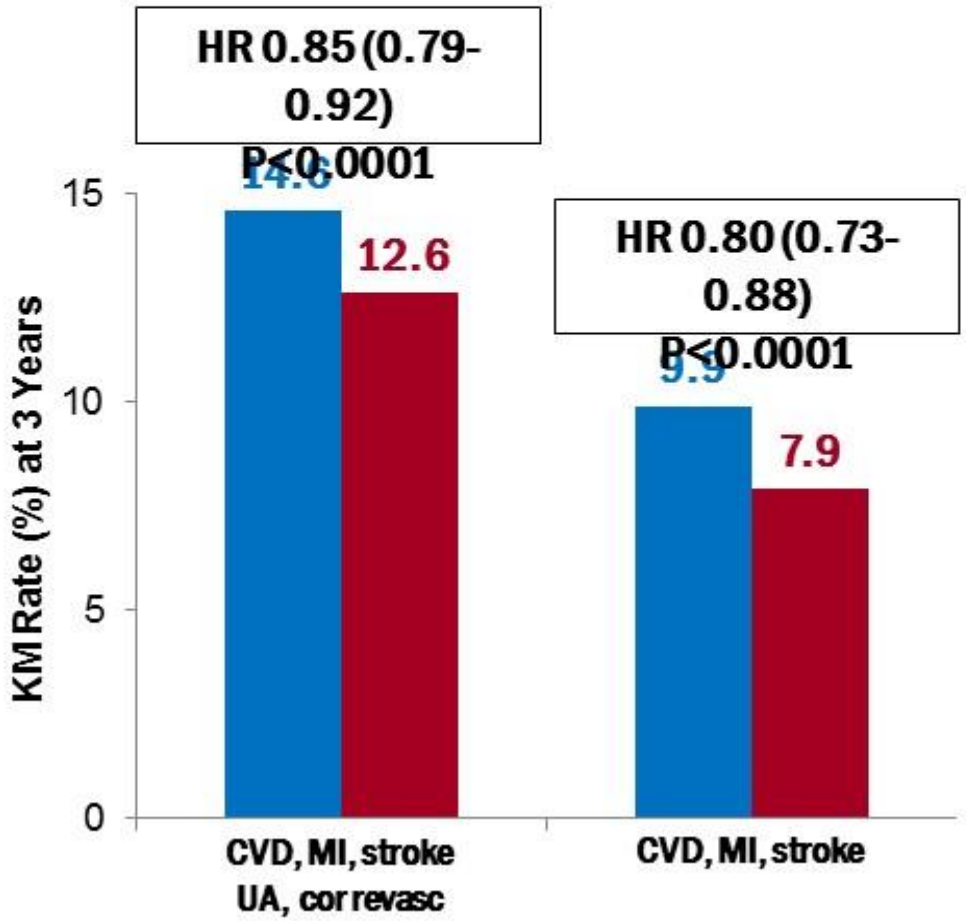
Summary of Effects of PCSK9i Evolocumab

- ↓ LDL-C by 59% to a median of 30 mg/dL
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated





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

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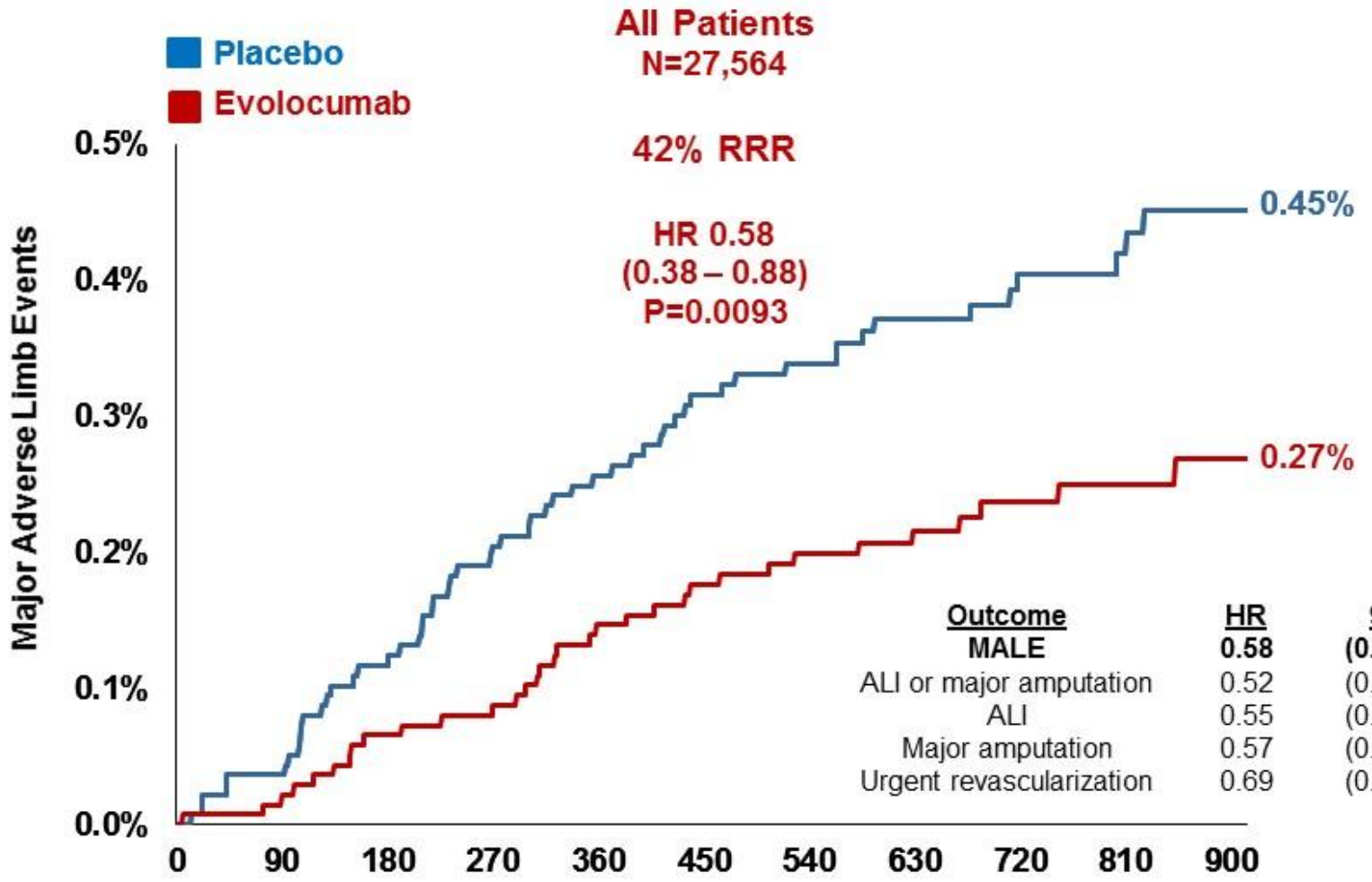
Adverse Events and Laboratory Test Results:
Sabatine, et al. NEJM 2017

Table 3. Adverse Events and Laboratory Test Results.

Outcome	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Adverse events — no. of patients (%)		
Any	10,664 (77.4)	10,644 (77.4)
Serious	3410 (24.8)	3404 (24.7)
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)
Injection-site reaction*	296 (2.1)	219 (1.6)
Allergic reaction	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	228 (1.7)	242 (1.8)
Adjudicated case of new-onset diabetes†	677 (8.1)	644 (7.7)
Neurocognitive event	217 (1.6)	202 (1.5)
Laboratory results — no. of patients/total no. (%)		
Aminotransferase level >3 times the upper limit of the normal range	240/13,543 (1.8)	242/13,523 (1.8)
Creatine kinase level >5 times the upper limit of the normal range	95/13,543 (0.7)	99/13,523 (0.7)

* The between-group difference was nominally significant ($P<0.001$).
† The total numbers of patients were 8337 in the evolocumab group and 8339 in the placebo group, because patients with prevalent diabetes at the start of the trial were excluded.

Major Adverse Limb Events



Outcome	HR	95% CI
MALE	**0.58**	**(0.38–0.88)**
ALI or major amputation	0.52	(0.31–0.89)
ALI	0.55	(0.31–0.97)
Major amputation	0.57	(0.17–1.95)
Urgent revascularization	0.69	(0.38–1.26)

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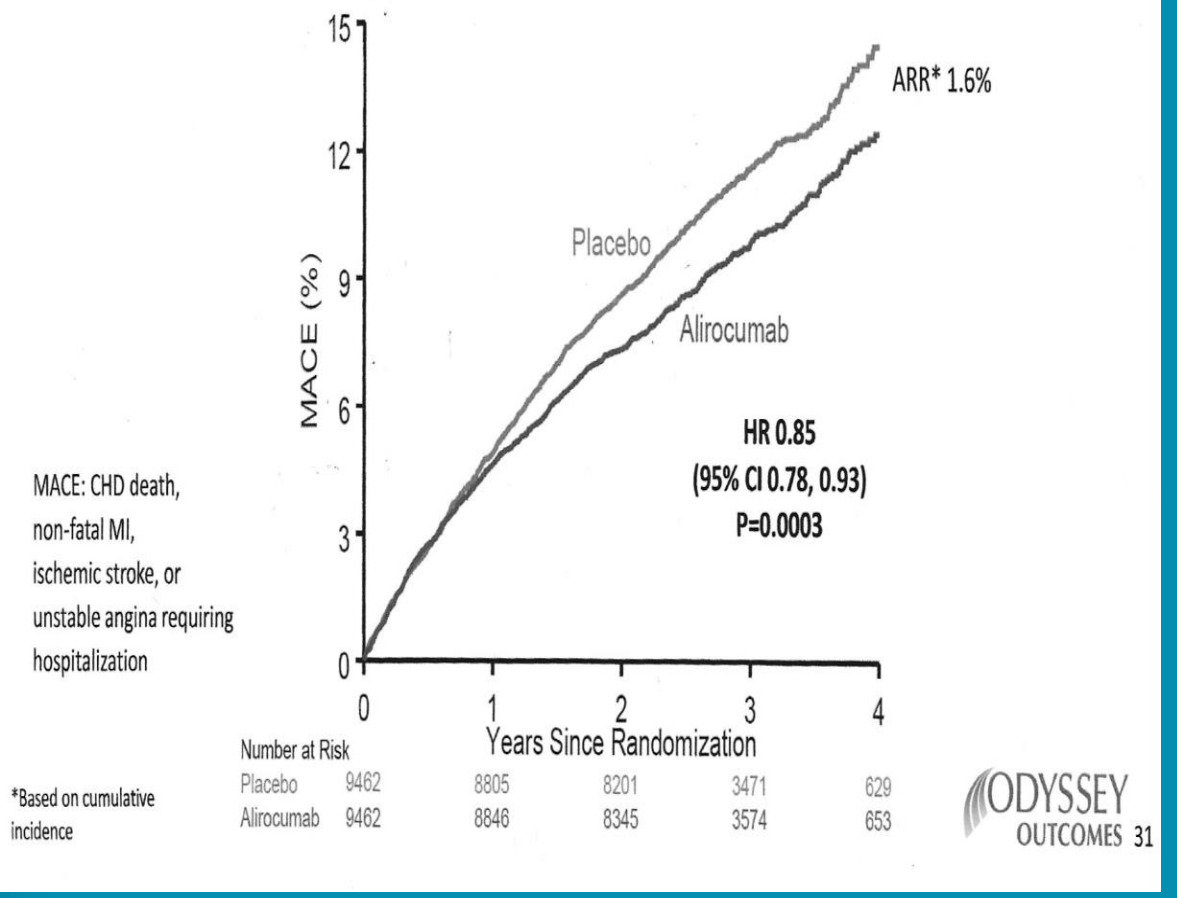
PRIMARY EFFICACY ENDPOINT: MACE



Endpoint, n (%)	Alirocumab (N=2814)	Placebo (N=2815)	Absolute risk reduction (%)	HR (95% CI)
MACE	324 (11.5)	420 (14.9)	3.4	**0.76** (0.65, 0.87)
CHD death	69 (2.5)	96 (3.4)	1.0	**0.72** (0.53, 0.98)
CV death	81 (2.9)	117 (4.2)	1.3	**0.69** (0.52, 0.92)
All-cause death	114 (4.1)	161 (5.7)	1.7	**0.71** (0.56, 0.90)

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ODYSSEY OUTCOMES 4

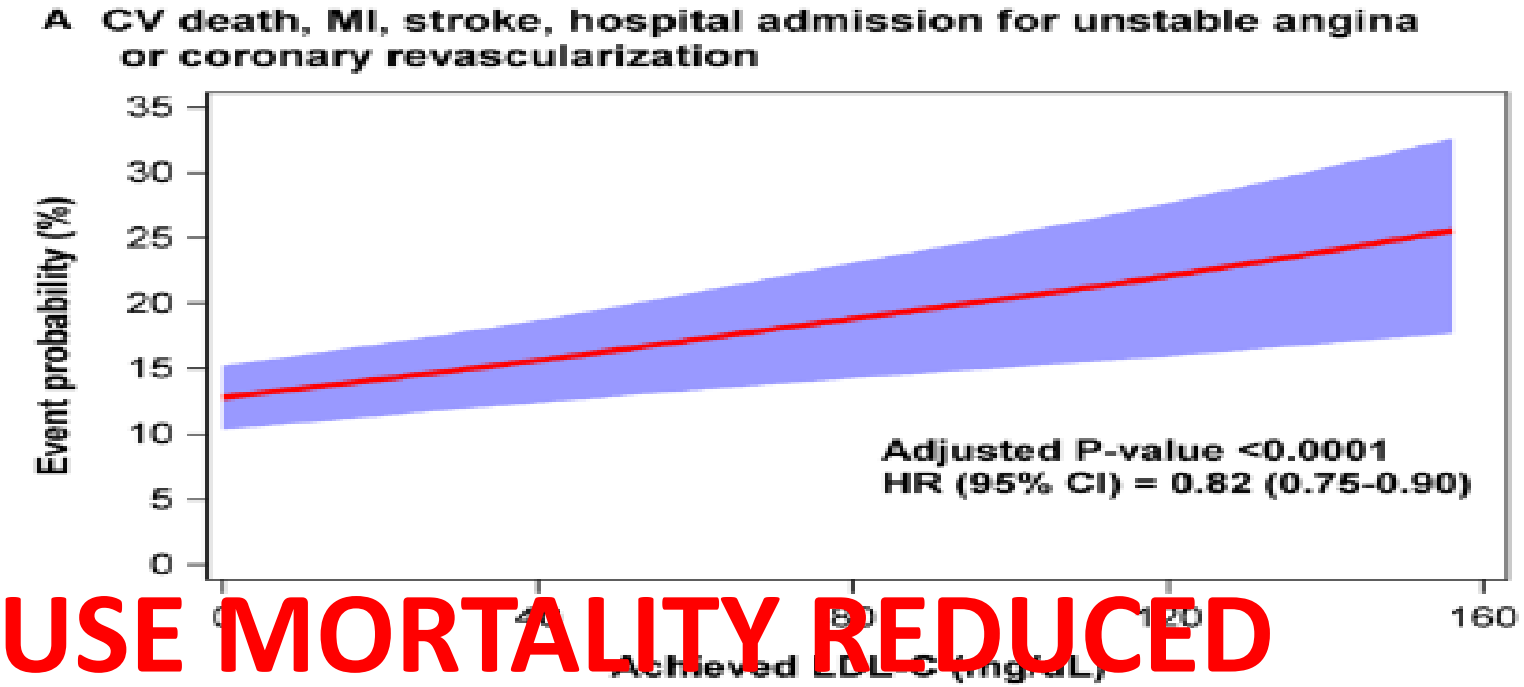
Circulation

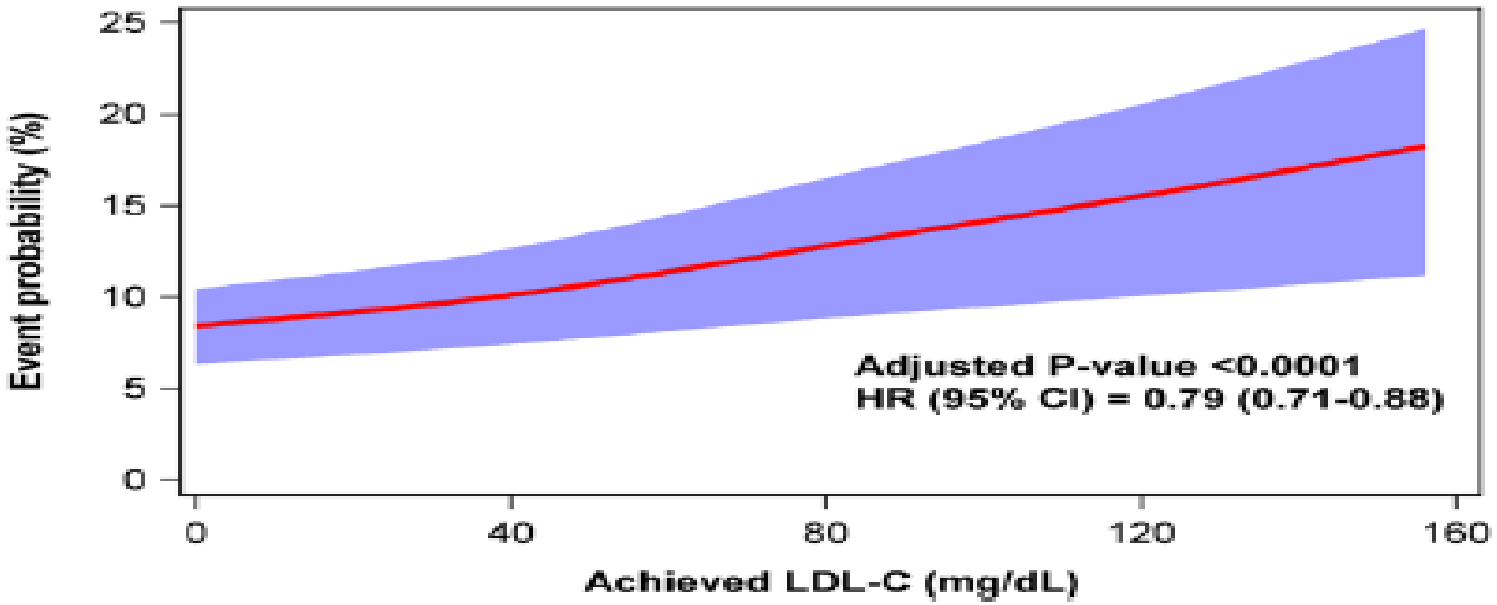
ORIGINAL RESEARCH ARTICLE

Association Between Achieved Low-Density Lipoprotein Cholesterol Levels and Long-Term Cardiovascular and Safety Outcomes: An Analysis of FOURIER-OLE

Prakriti Gaba, MD; Michelle L. O'Donoghue, MD, MPH; Jeong-Gun Park, PhD; Stephen D. Wiviott, MD; Dan Atar, MD; Julia F. Kuder, MA; KyungAh Im, PhD; Sabina A. Murphy, MPH; Gaetano M. De Ferrari, MD; Zbigniew A. Gaciong, MD;

ALL CAUSE MORTALITY REDUCED





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JACC Journals › JACC › Archives › Vol. 81 No. 1

Comparative Effects of Low-Dose Rosuvastatin, Placebo, and Dietary Supplements on Lipids and Inflammatory Biomarkers

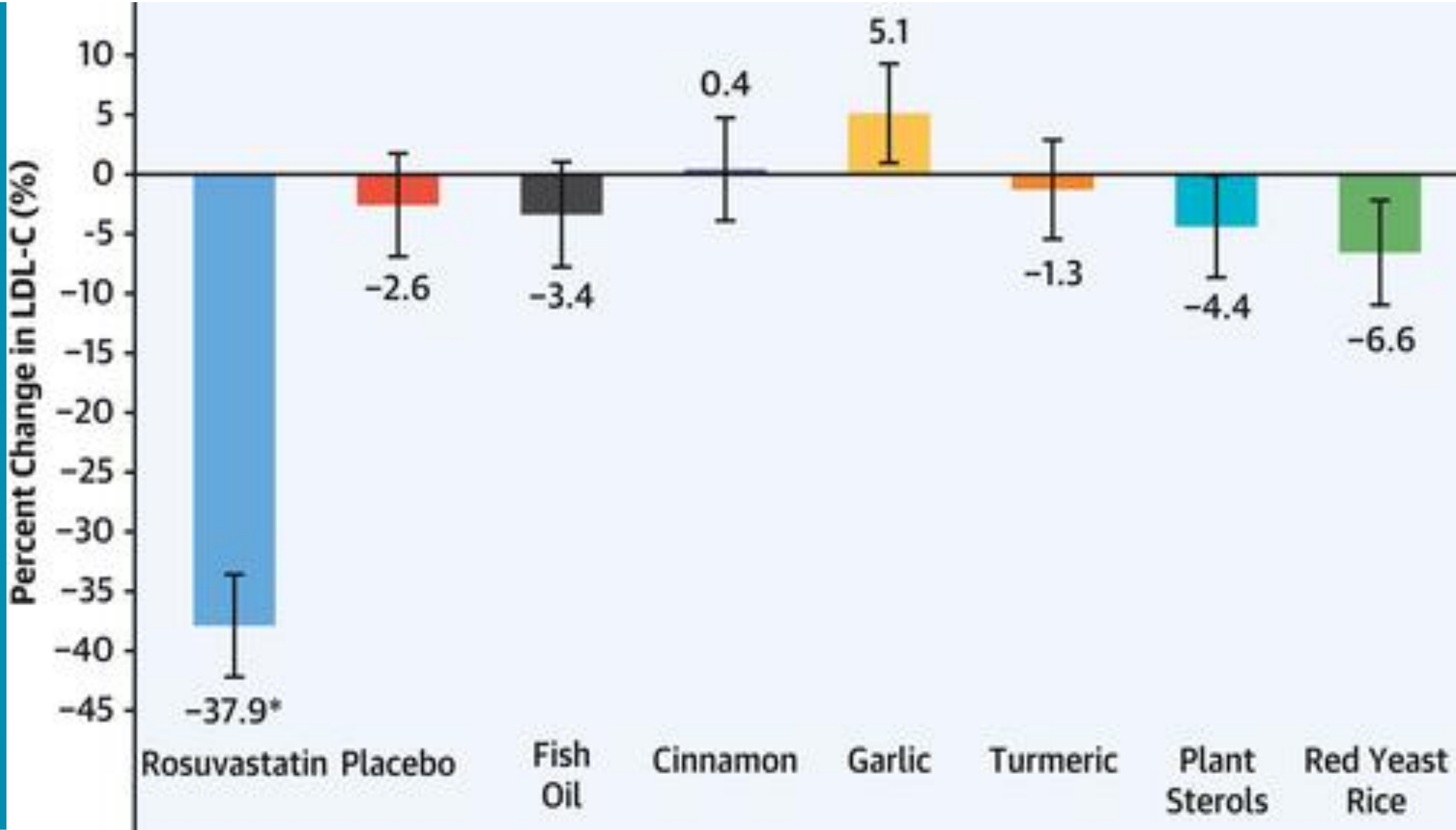
OPEN ACCESS

Original Investigation

Luke J. Laffin, Dennis Bruemmer, Michelle Garcia, Danielle M. Brennan, Ellen McErlean, Douglas S. Jacoby, Erin D. Michos, Paul M Ridker, Tracy Y. Wang, Karol E. Watson, Howard G. Hutchinson, and Steven E. Nissen

J Am Coll Cardiol. 2023 Jan, 81 (1) 1–12

Editorial Comment: Caution Against Rejecting All Dietary Supplements for LDL Cholesterol Reduction*



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