? PRE

At what level of LDL-C do safety events increase as reported in recent trials?

A) LDL-C < 100 mg/dL

B) LDL-C < 70 mg/dL

C) LDL-C < 50 mg/dL

D) LDL-C < 20 mg/dL

E) No level of LDL-C has been shown to be unsafe

? PRE

Which of the following LDL-C-lowering medication(s) has been shown to reduce cardiovascular events when added to statin therapy?

A) PCSK9 inhibitors, ezetimibe, niacin

B) PCSK9 inhibitors, ezetimibe

C) Fenofibrate, PCSK9 inhibitors, ezetimibe

D) Fenofibrate, niacin, ezetimibe, PCSK9 inhibitors

E) None

? PRE

According to the 2018 Cholesterol Guidelines, when identifying ASCVD patients at very high risk of recurrent events, which of these is NOT considered a high-risk condition?

A) History of prior PCI or CABG

B) Chronic kidney disease (eGFR 15-59 ml/min/1.73m^2)

C) Stable angina

D) Current smoking

E) All are considered high-risk conditions

Non-Statin Therapy for LDL-c Reduction: Examining the Evidence

TY GLUCKMAN, MD

MEDICAL DIRECTOR, CENTER FOR CARDIOVASCULAR ANALYTICS, RESEARCH, AND DATA SCIENCE

PROVIDENCE HEART INSTITUTE

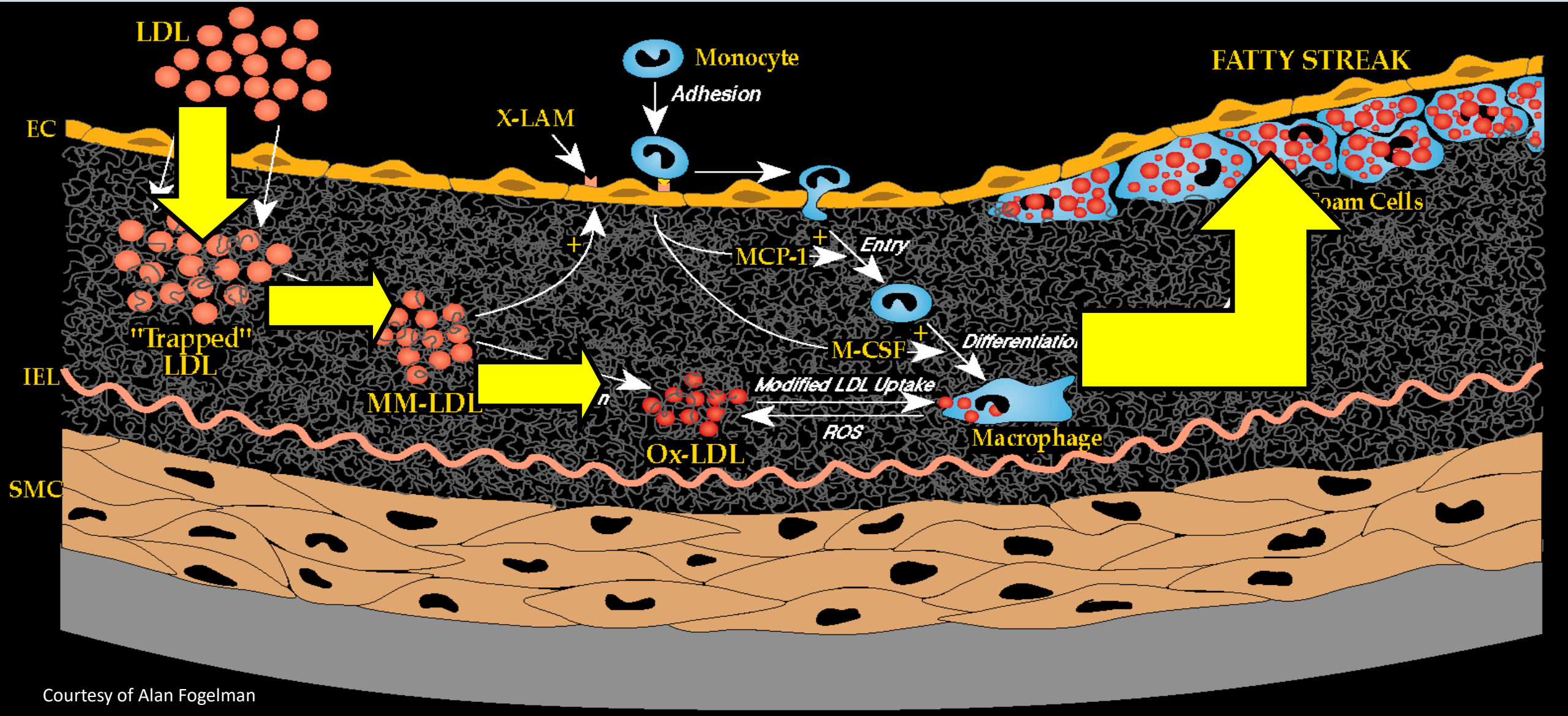
PROVIDENCE ST. JOSEPH HEALTH

PORTLAND, OREGON

Ty Gluckman, MD: Disclosure Information

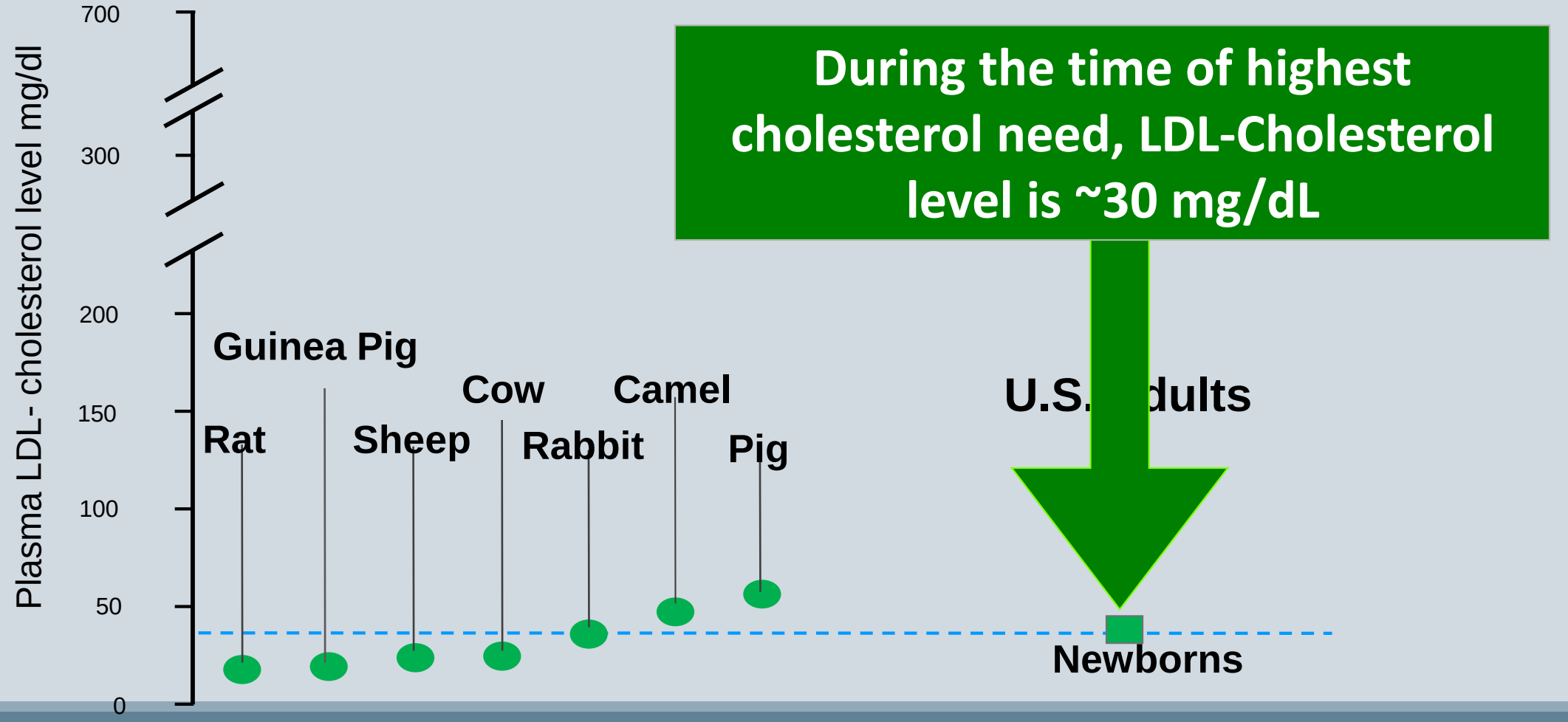
Consultant: AbbVie Inc./Teva Pharmaceuticals

LDL-c is central to atherosclerosis



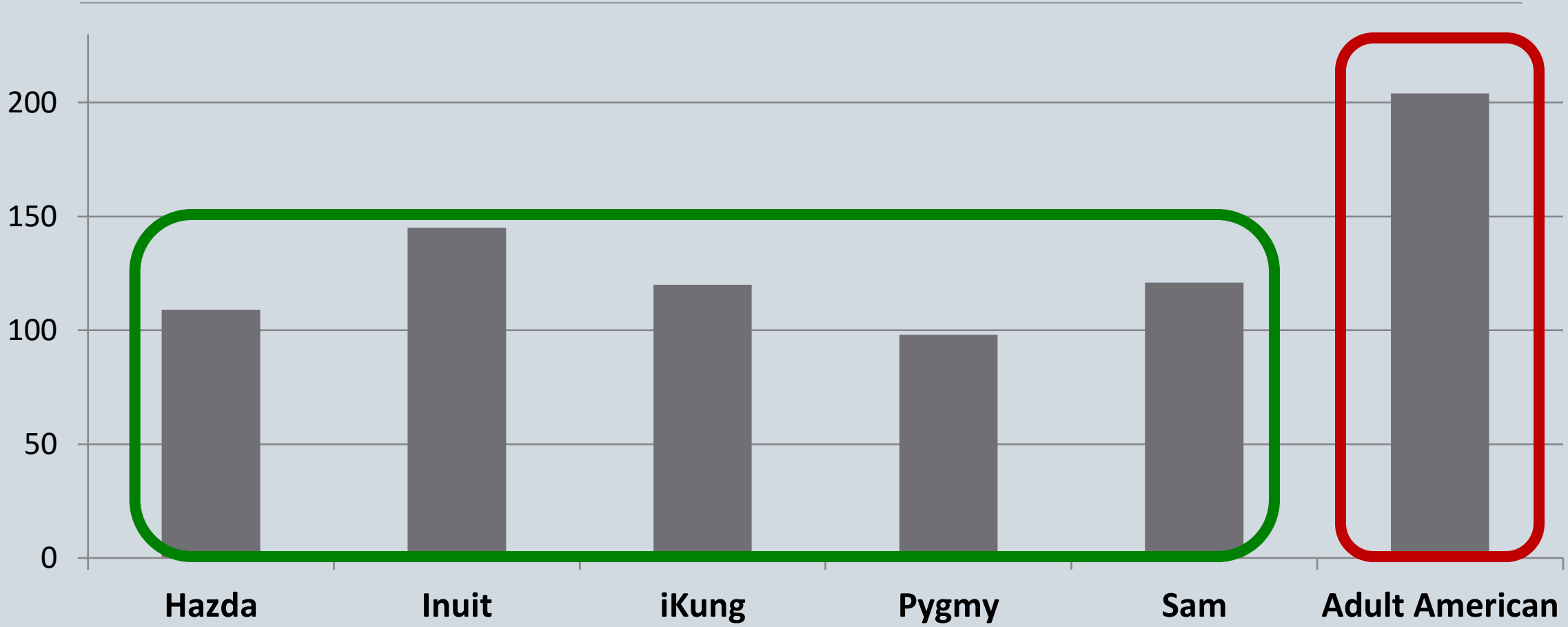
Courtesy of Alan Fogelman

LDL-c levels in today's society are too high



Adapted from O'Keefe J, Jr et al. J Am Coll Cardiol. 2004;43(11):2142-2146.

What is Desirable Cholesterol?



Adapted from O'Keefe J, Jr et al. J Am Coll Cardiol. 2004;43(11):2142-2146.

2013 ACC-AHA Cholesterol Guidelines

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Neil J. Stone, Jennifer Robinson, Alice H. Lichtenstein, C. Noel Bairey Merz, Conrad B. Blum, Robert H. Eckel, Anne C. Goldberg, David Gordon, Daniel Levy, Donald M. Lloyd-Jones, Patrick McBride, J. Sanford Schwartz, Susan T. Shero, Sidney C. Smith, Jr, Karol Watson and Peter W.F. Wilson

Circulation. published online November 12, 2013;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

ACC/AHA Statin Benefit Groups

Secondary Prevention Clinical ASCVD	• Age ≤ 75: High-intensity statin • Age > 75: Moderate-intensity statin
Primary Prevention LDL-C ≥ 190 mg/dL	• High-intensity statin
Diabetes Mellitus	• 10-yr risk < 7.5%: Moderate-intensity statin • 10-yr risk ≥ 7.5%: High-intensity statin
Primary Prevention ≥ 7.5% 10-yr ASCVD risk	• Consider moderate or high intensity statin

Stone NJ et al. Circulation. 2014;129:S1-45.

Intensity of Statin Therapy

HIGH RISK PATIENT	MODERATE RISK PATIENT	LOW RISK PATIENT
High Intensity Statin	**Moderate Intensity Statin**	**Low Intensity Statin**
Daily dose lowers LDL-c ≥50%	Daily dose lowers LDL-c 30% -49%	Daily dose lowers LDL-c <30%
Atorvastatin (40†)-80 mg **Rosuvasatin 20** *(40)* **mg**	Atorvastatin 10 (*20)* mg Rosuvastatin *(5)* 10 mg Simvastatin 20-40 mg Pravstatin 40 *(80)* mg Lovastatin 40 mg (80 mg) *Fluvastatin XL 80 mg* Fluvastatin 40 mg bid *Pitavastatin 1-4 mg*	*Simvastatin 10 mg* Pravastatin 10-20 mg Lovastatin 20 mg *Fluvastatin 20-40 mg*

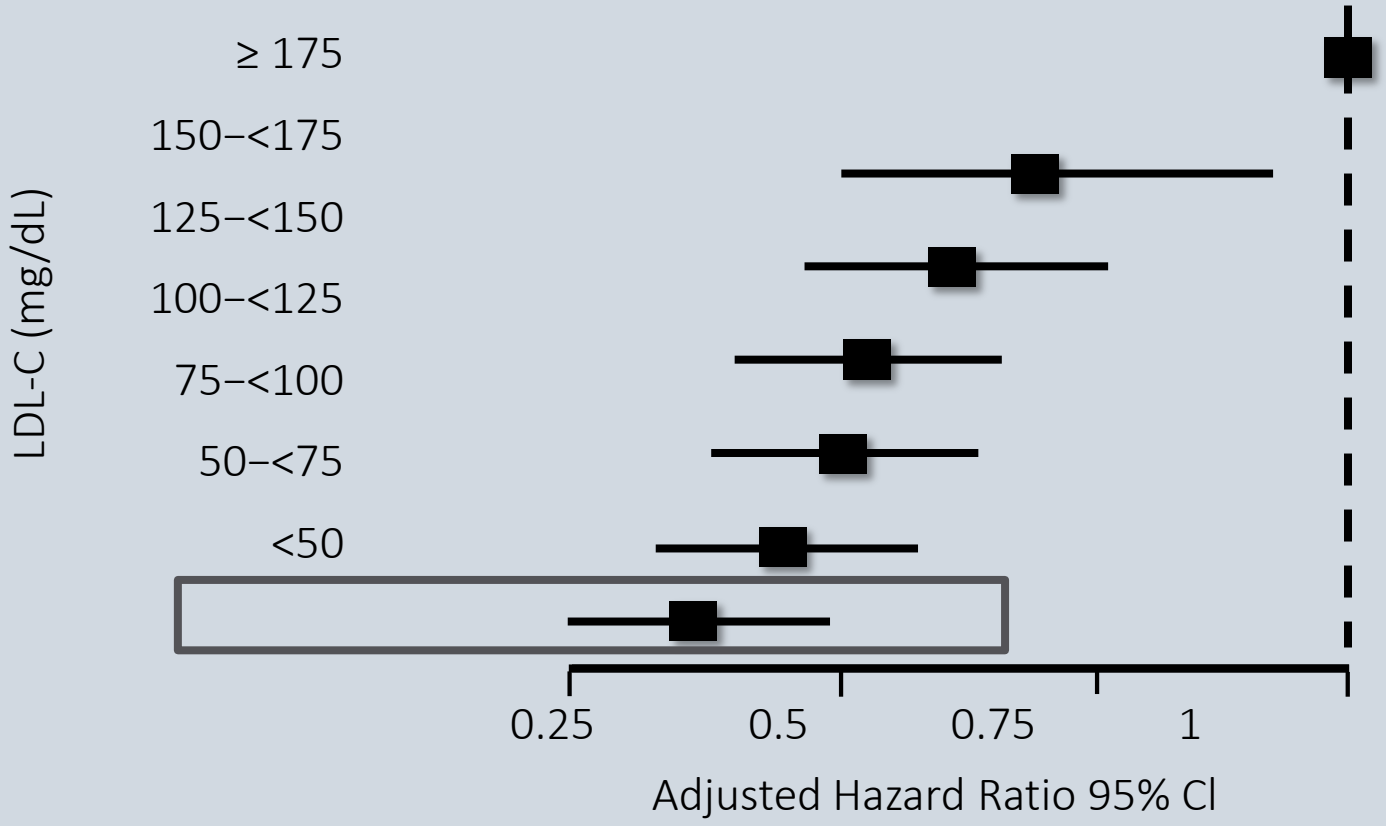
Grundy SM et al. J Am Coll Cardiol. Nov. 8, 2018. † Evidence from 1 RCT only

The intensity of statin should match the intensity of risk

Rationale for Pushing LDL-C Even Lower

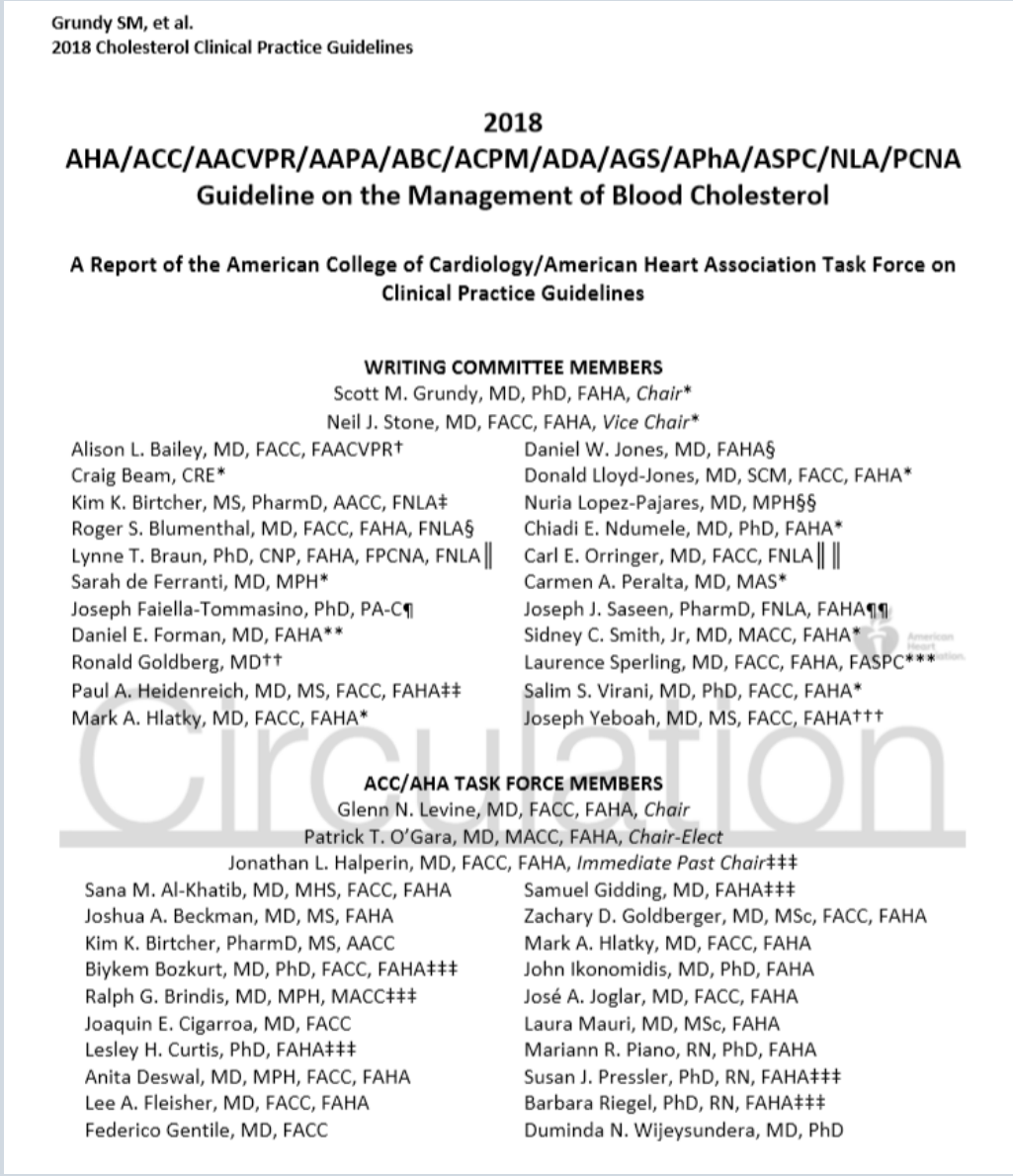
LDL-C Levels and Risk of CV Events

Meta-analysis of 38,153 patients from 8 randomized statin trials



Boekholdt SM et al. *J Am Coll Cardiol.* 2014;64:485-494.

2018 Blood Cholesterol Guidelines



2018
AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA
Guideline on the Management of Blood Cholesterol

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

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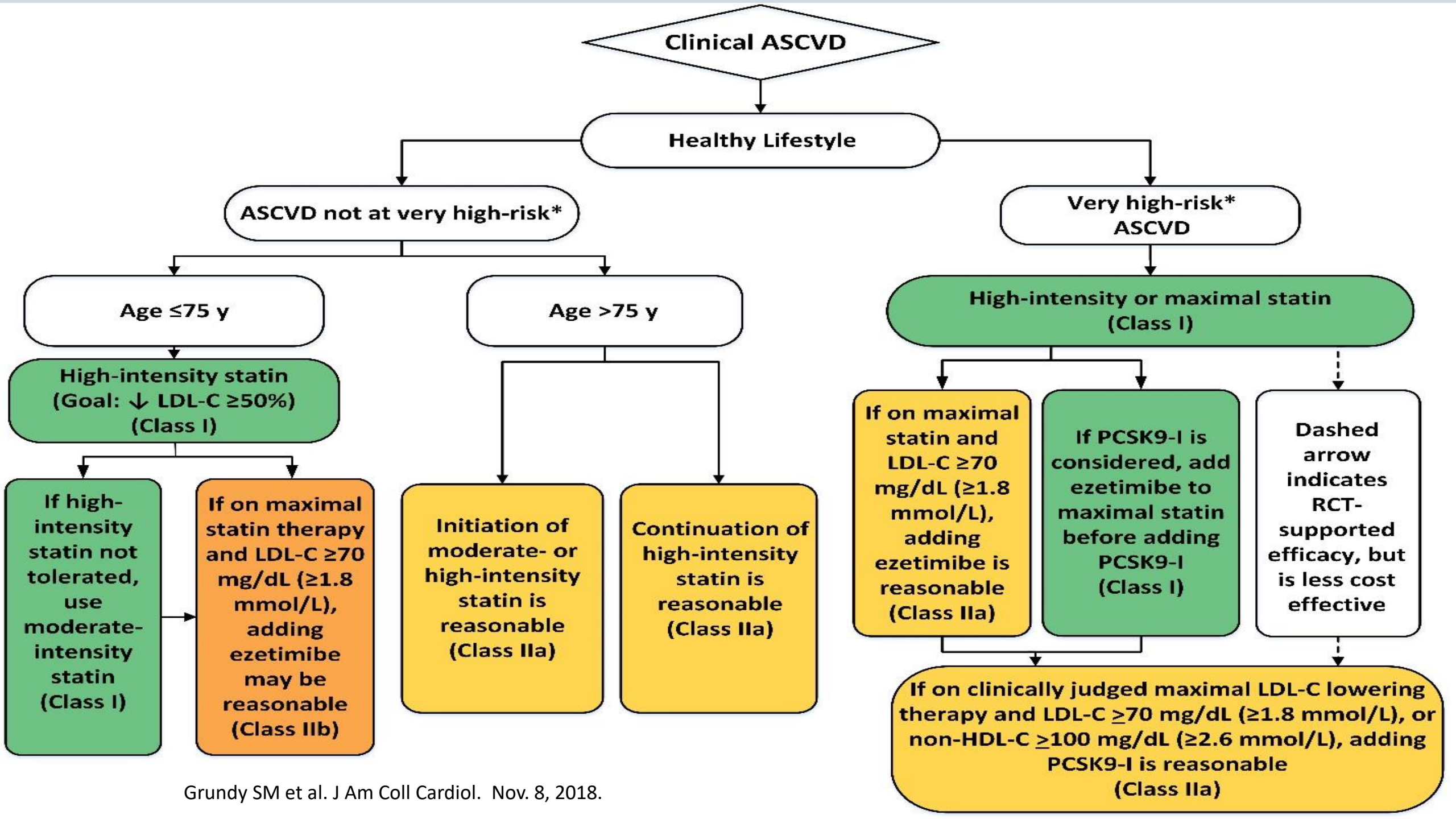
Grundy SM et al. J Am Coll Cardiol. Nov. 8, 2018.



Grundy SM et al. J Am Coll Cardiol. Nov. 8, 2018.

The very high risk Patient

Major ASCVD Events
Recent ACS (within the past 12 months)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic PAD (claudication with ABI <0.85, or previous revascularization or amputation)
High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior CABG or PCI outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL) despite max statin therapy and ezetimibe
History of congestive HF

Grundy SM et al. *J Am Coll Cardiol.* Nov. 8, 2018.

2018 ACC-AHA Blood Cholesterol Guidelines

In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL to consider addition of nonstatins to statin therapy

Intensity of Statin Therapy

VERY HIGH RISK PATIENT	HIGH RISK PATIENT	MODERATE RISK PATIENT	LOW RISK PATIENT
High Intensity Statin	**High Intensity Statin**	**Moderate Intensity Statin**	**Low Intensity Statin**
+ nonstatin	Lowers LDL-c ≥ 50%	Lowers LDL-c 30%-49%	Dose lowers LDL-c <30%
Add ezetimibe first **If LDL > 70 mg/dL consider PCSK9**	**Atorvastatin (40†)-80** **Rosuvastatin 20** *(40)*	Atorvastatin 10 *(20) mg* Rosuvastatin *(5)* 10 mg Simvastatin 20-40 mg Pravastatin 40 *(80) mg* Lovastatin 40 mg (80 mg) *Fluvastatin XL 80 mg* Fluvastatin 40 mg bid *Pitavastatin 1-4 mg*	*Simvastatin 10 mg* Pravastatin 10-20 mg Lovastatin 20 mg *Fluvastatin 20-40 mg*

Grundy SM et al. J Am Coll Cardiol. Nov. 8, 2018

† Evidence from 1 RCT only

IMPROVE-IT: Study Design

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125 mg/dL if no prior lipid-lowering Rx
LDL-C 50–100 mg/dL if on prior lipid-lowering Rx

N=18,144

Standard Medical & Interventional Therapy

Simvastatin 40 mg

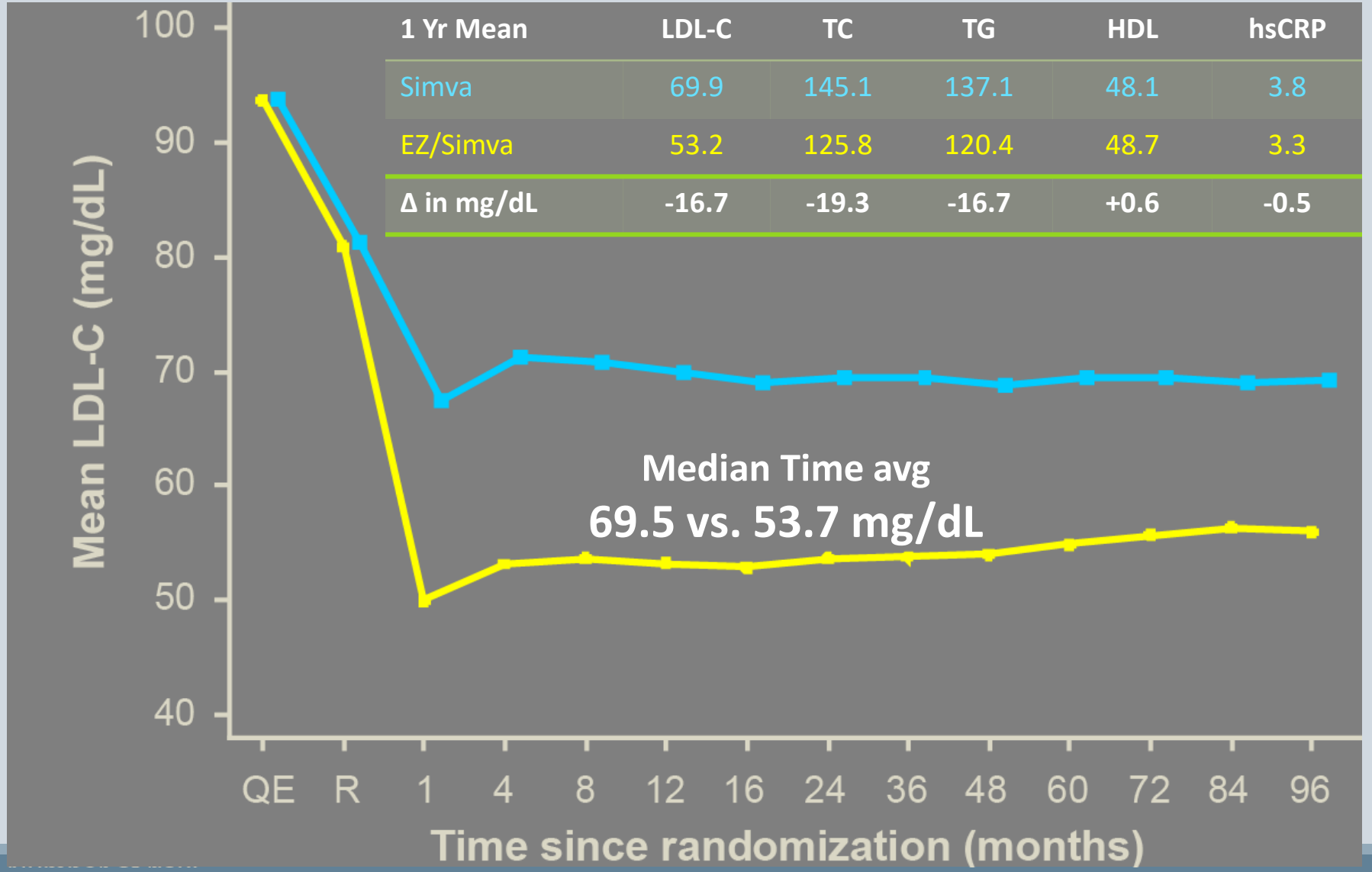
Ezetimibe / Simvastatin 10 / 40 mg

Duration: Median 6 years follow-up **(5314 events)**

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

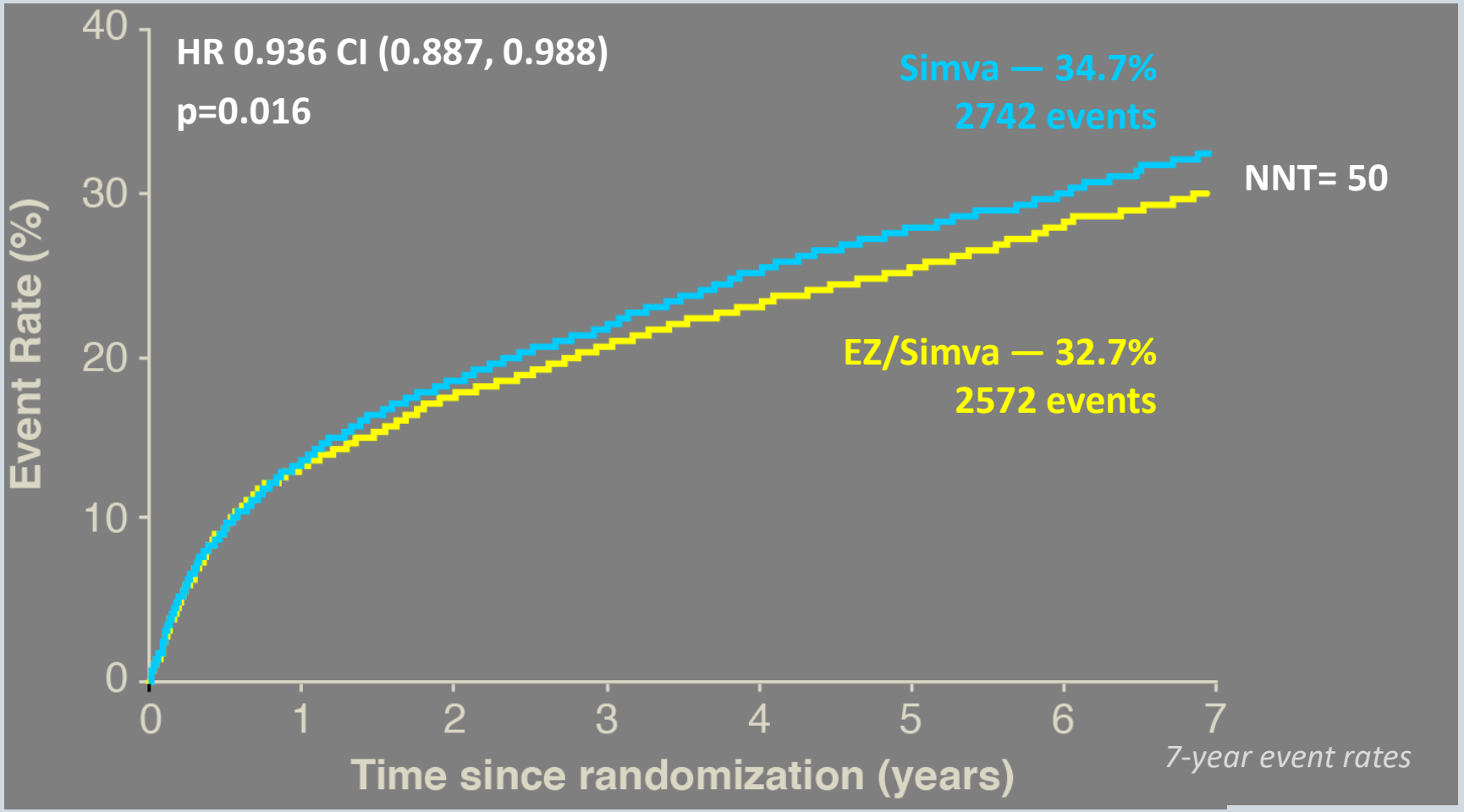
IMPROVE-IT: LDL-C and Lipid Changes



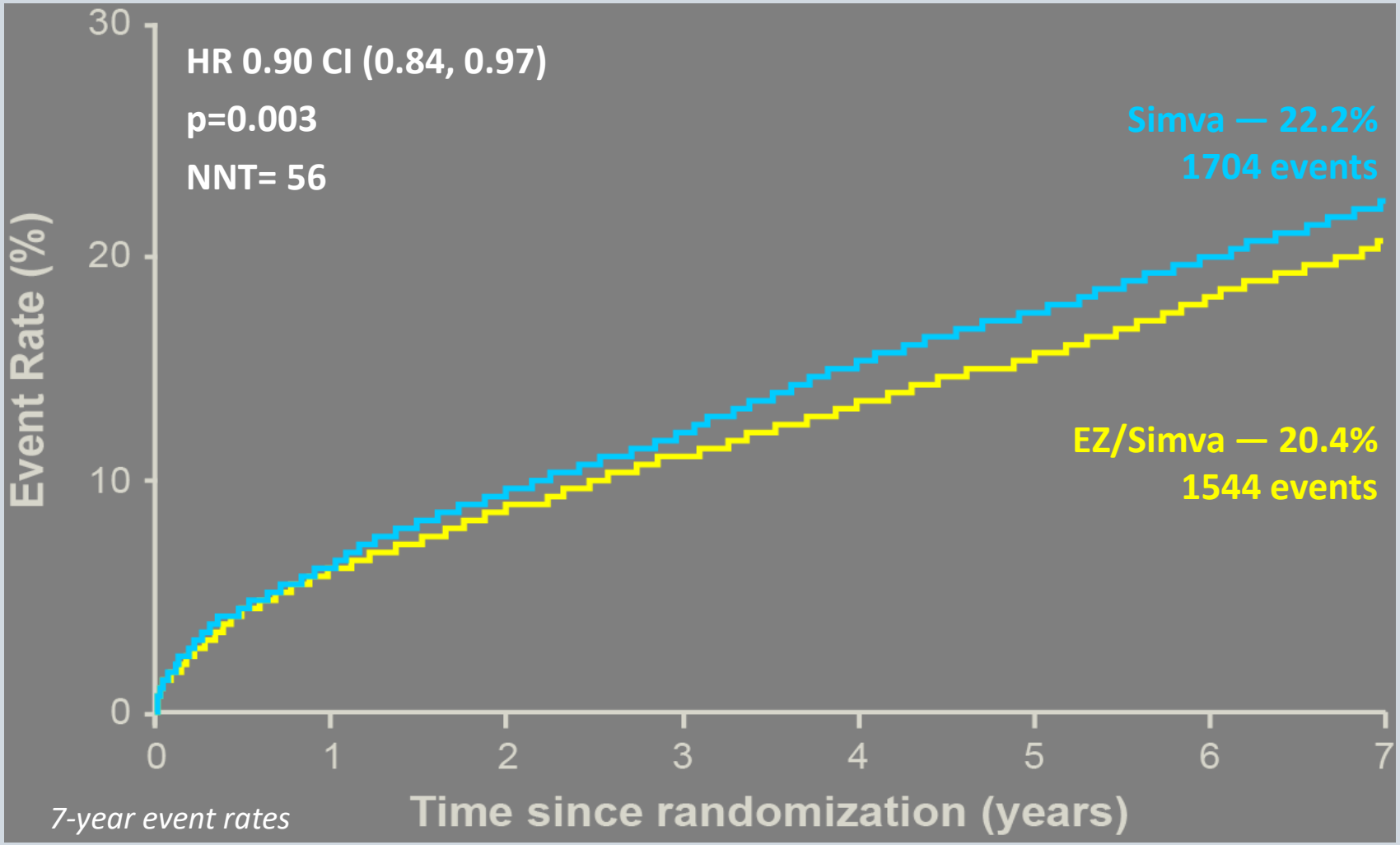
Cannon CP, NEJM 2015;372:2387-97

IMPROVE-IT: Primary Endpoint — ITT

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



IMPROVE-IT: CV Death, Non-fatal MI, or Non-fatal Stroke



Cannon CP et al. *N Engl J Med.*2015;372:2387-97.

IMPROVE-IT: Safety — ITT

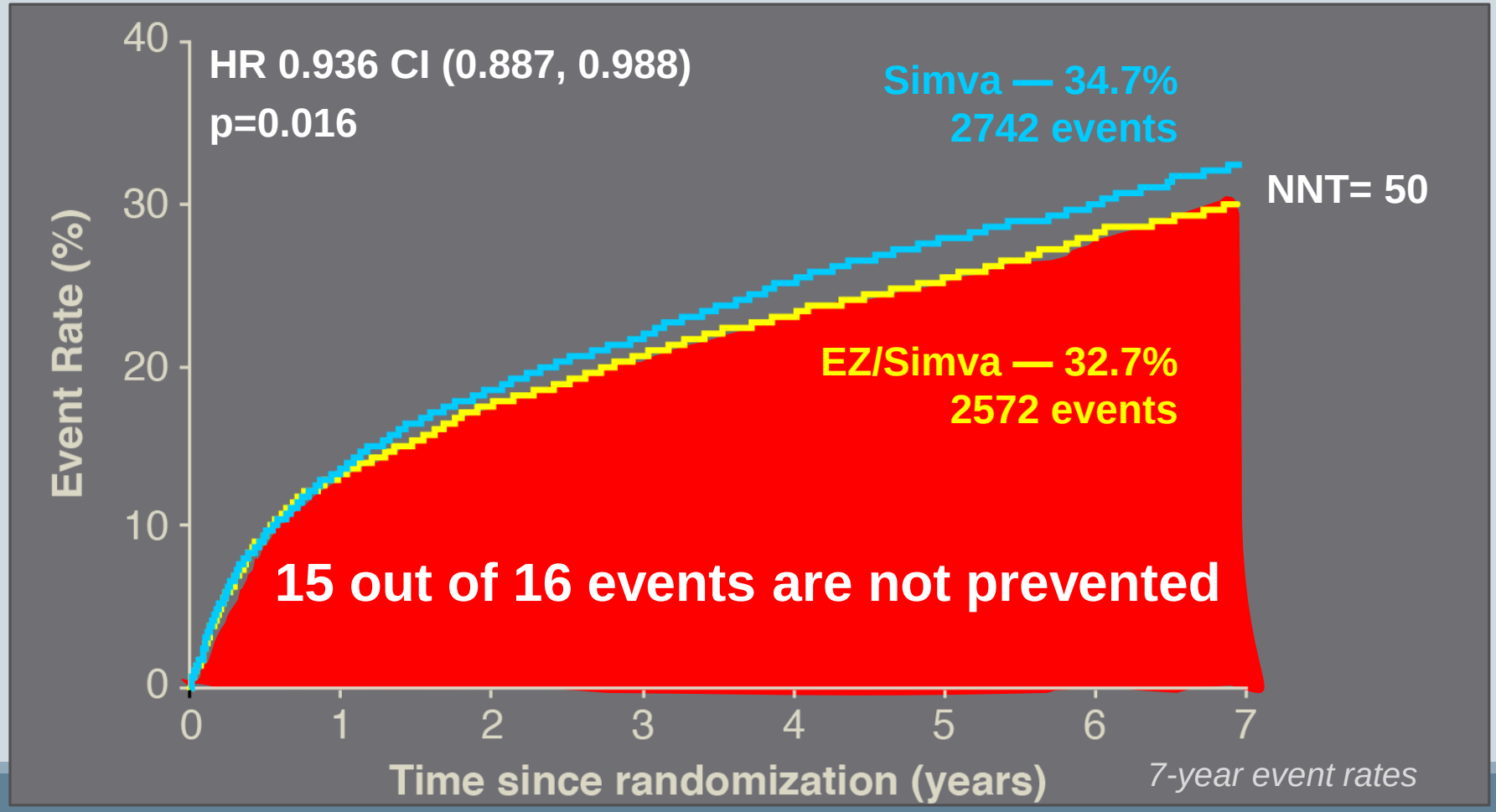
No statistically significant differences in cancer or muscle- or gallbladder-related events

	Simva n=9077 %	EZ/Simva n=9067 %	p
ALT and/or AST≥3x ULN	2.3	2.5	0.43
Cholecystectomy	1.5	1.5	0.96
Gallbladder-related AEs	3.5	3.1	0.10
Rhabdomyolysis*	0.2	0.1	0.37
Myopathy*	0.1	0.2	0.32
Rhabdo, myopathy, myalgia with CK elevation*	0.6	0.6	0.64
Cancer* (7-yr KM %)	10.2	10.2	0.57

** Adjudicated by Clinical Events Committee* *% = n/N for the trial duration*

IMPROVE-IT: Primary Endpoint — ITT

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



Cannon CP, NEJM 2015;372:2387-97

PCSK9 (Proprotein convertase subtilisin/kexin type 9)

A secreted protein which targets the LDL receptor for degradation

Gain of function mutations cause high LDL-C

Loss of function mutations cause low LDL-C

Inhibition lowers LDL-C levels

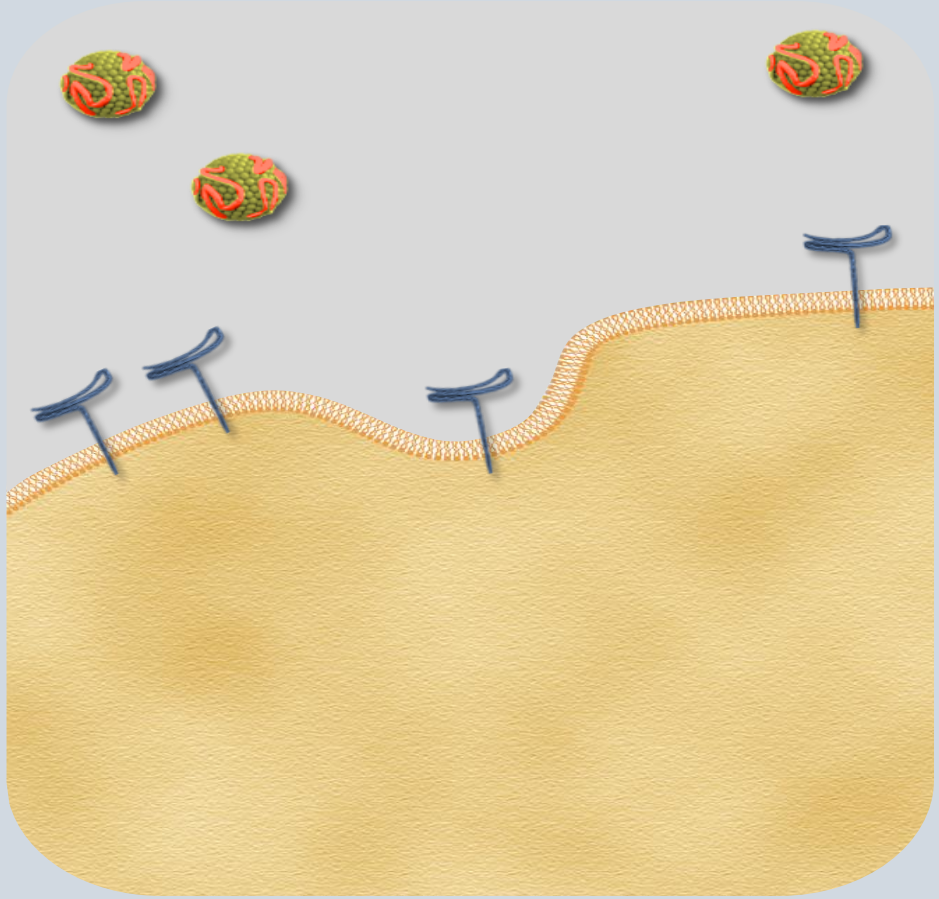
Up-regulated by statin therapy

PCSK9

LDL receptor

LDL

PCSK-9



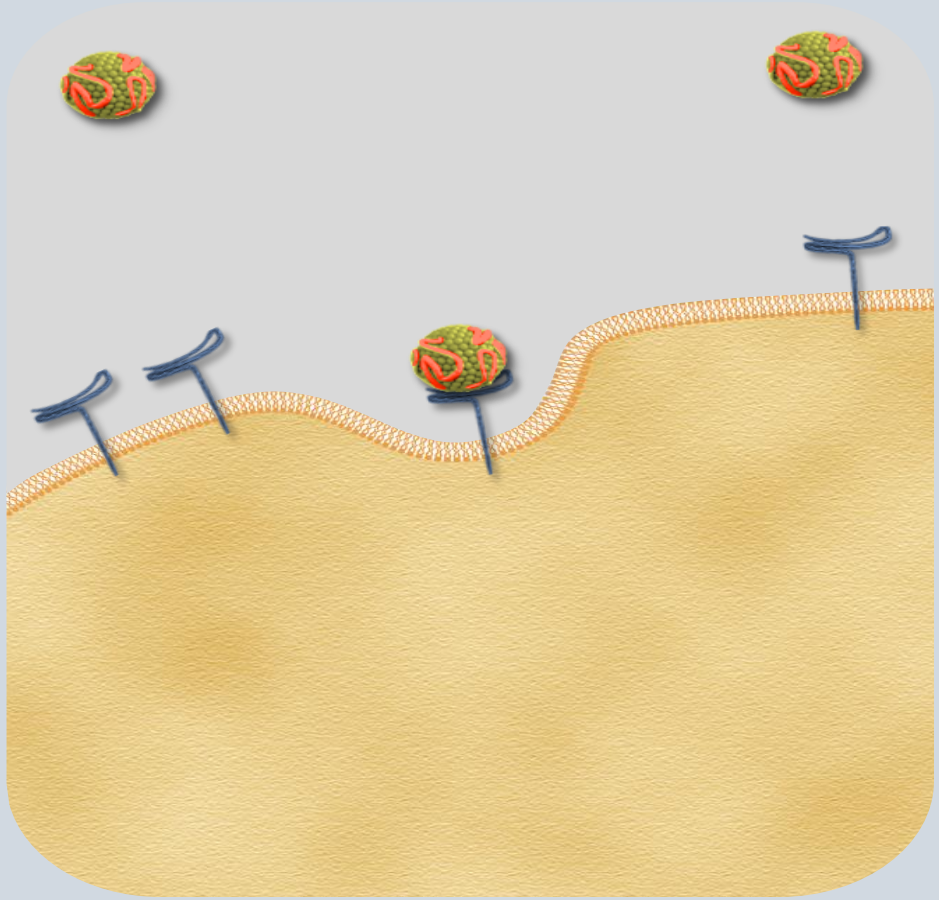
Adapted from Sanofi/Regeneron Pharmaceuticals

PCSK9

LDL receptor

LDL

PCSK-9



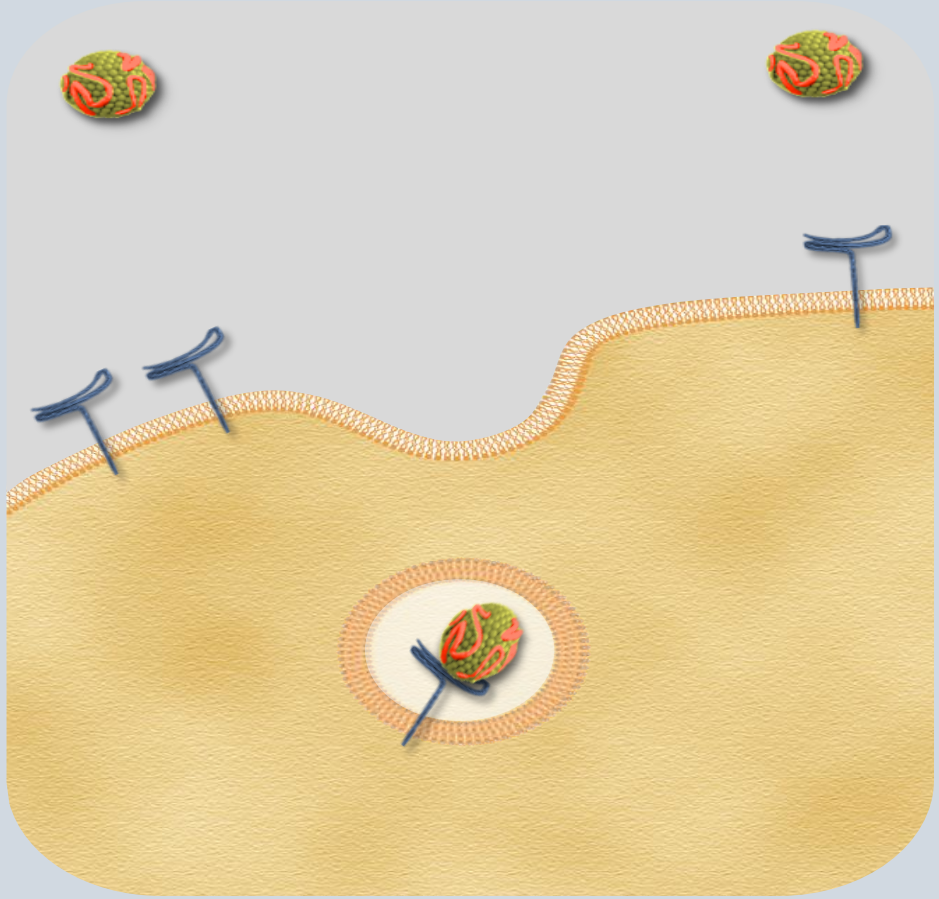
Adapted from Sanofi/Regeneron Pharmaceuticals

PCSK9

LDL receptor

LDL

PCSK-9



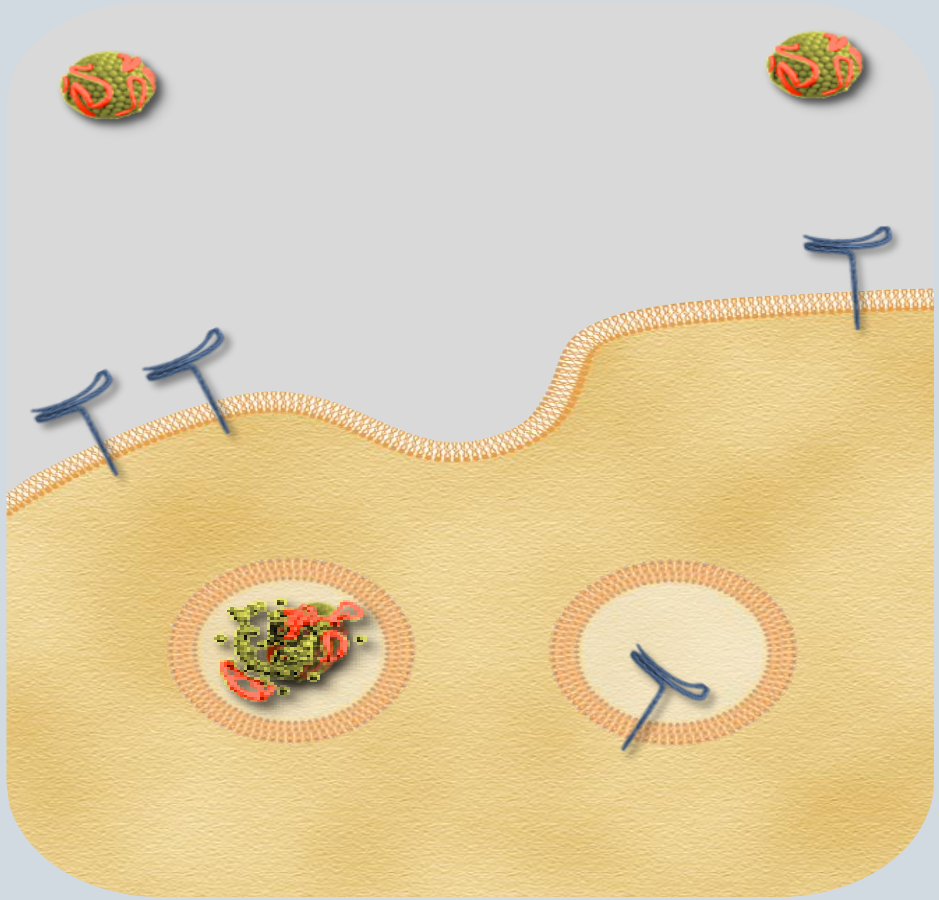
Adapted from Sanofi/Regeneron Pharmaceuticals

PCSK9

LDL receptor

LDL

PCSK-9



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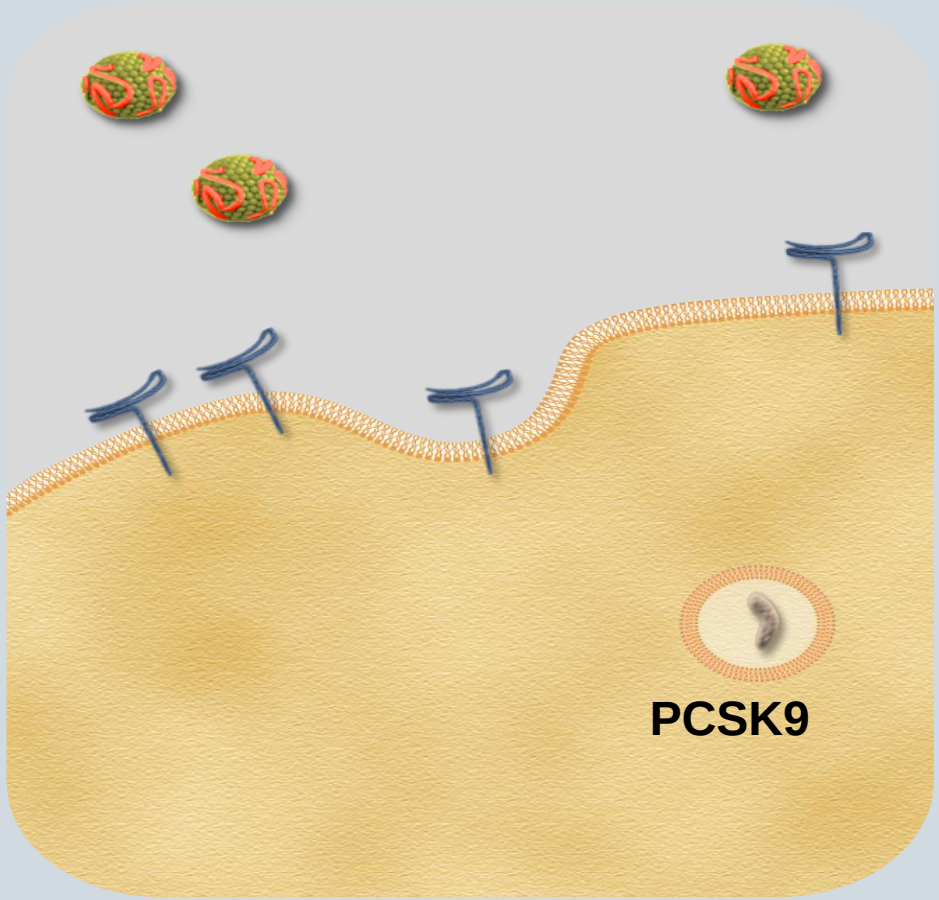
PCSK9

LDL receptor

LDL

PCSK-9



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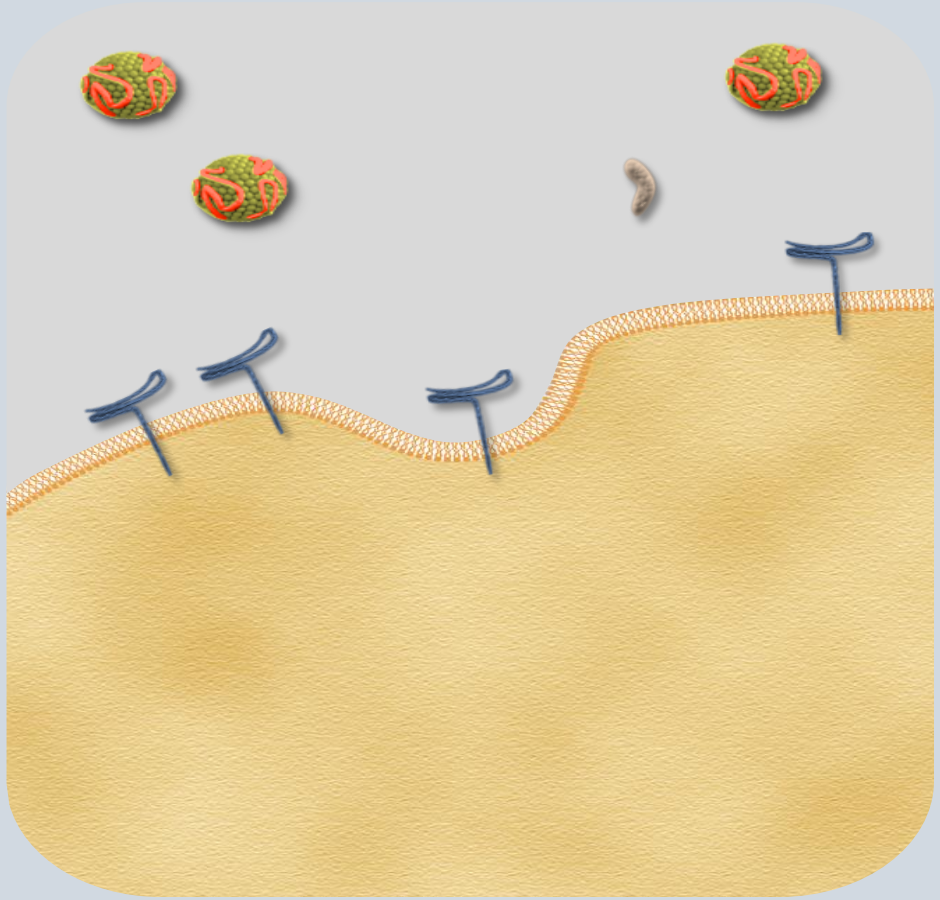
PCSK9

LDL receptor

LDL

PCSK-9



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PCSK9

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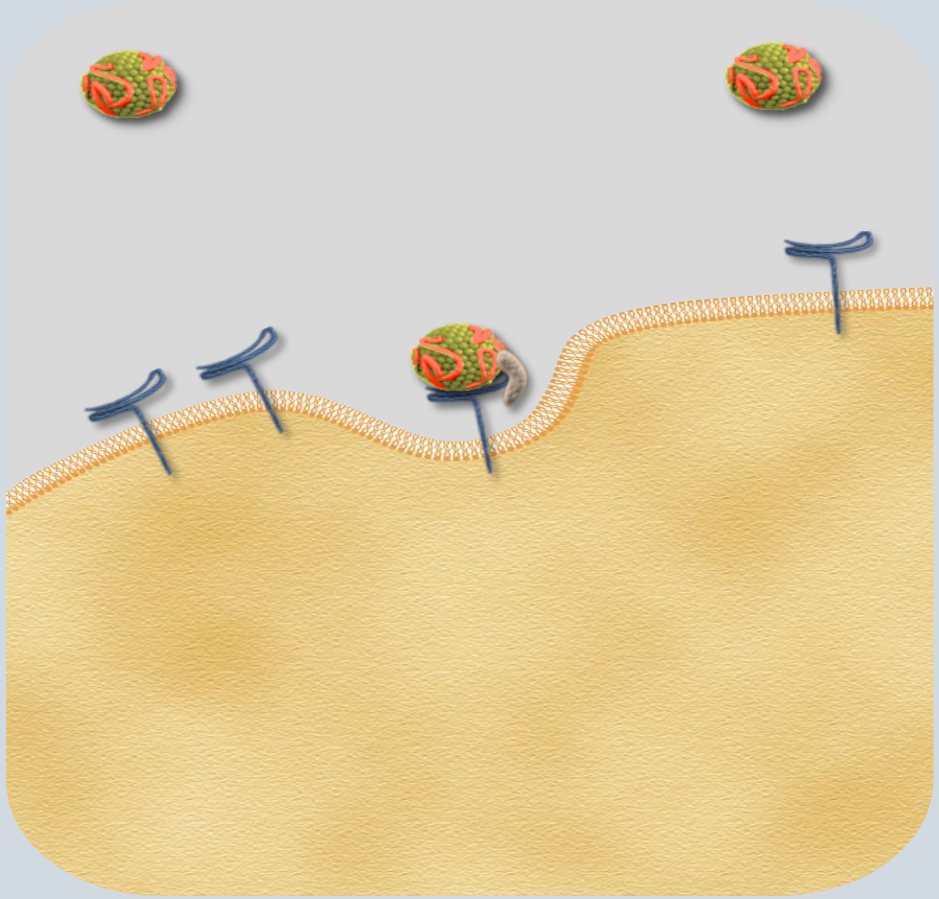

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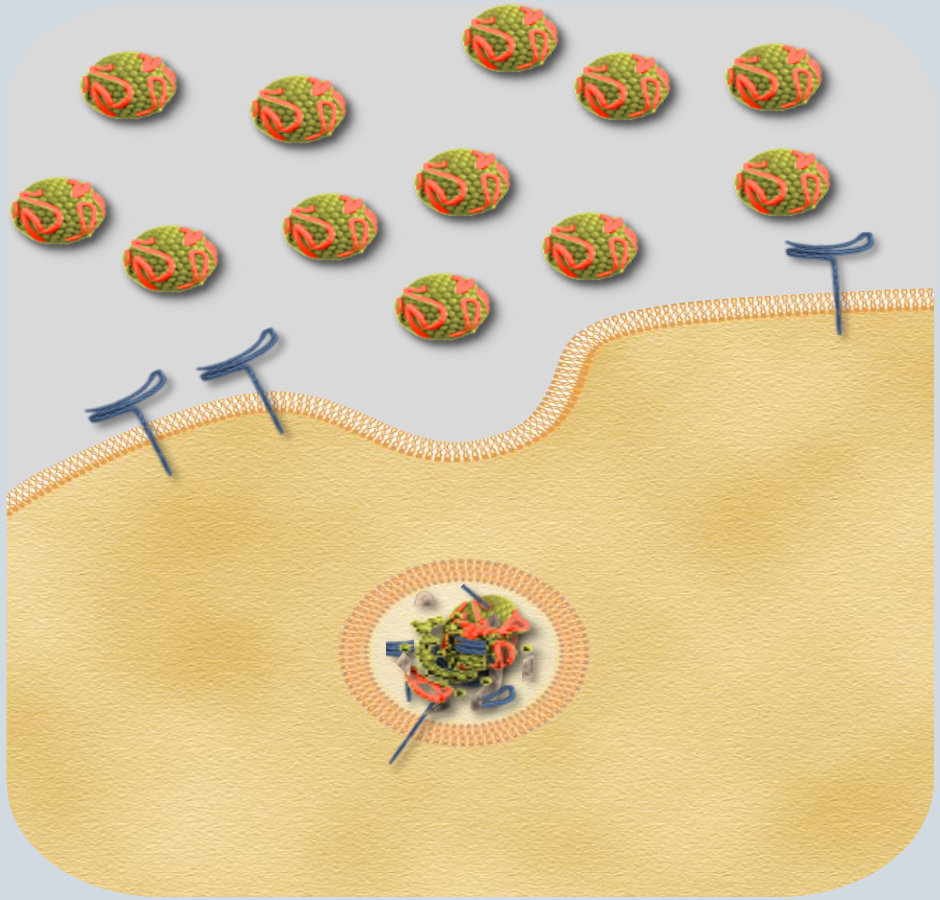
PCSK9

LDL receptor

LDL

PCSK-9



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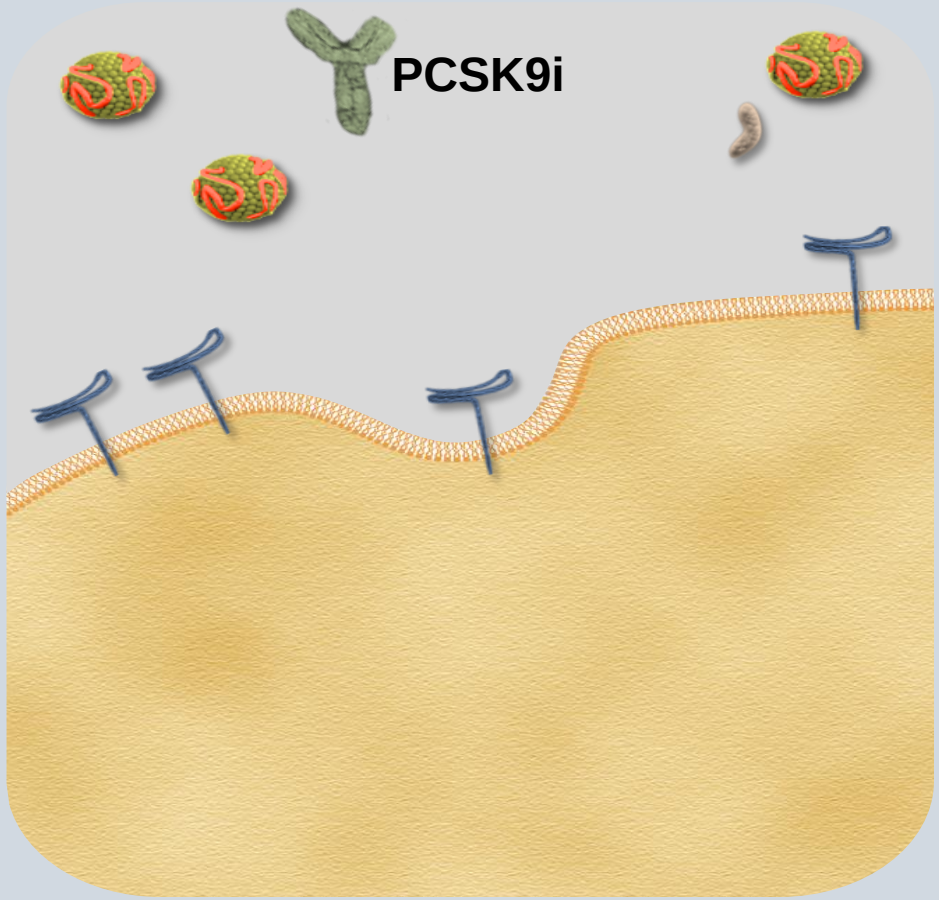
PCSK9

LDL receptor

LDL

PCSK-9



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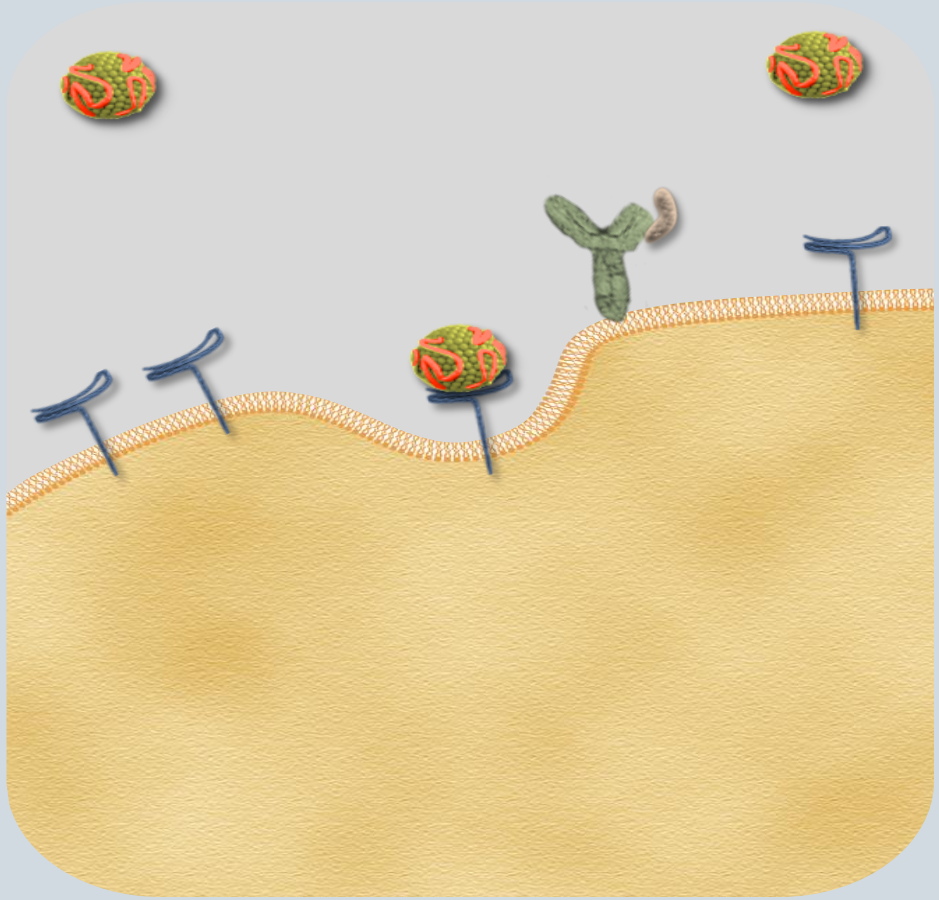
LDL receptor

LDL

PCSK-9



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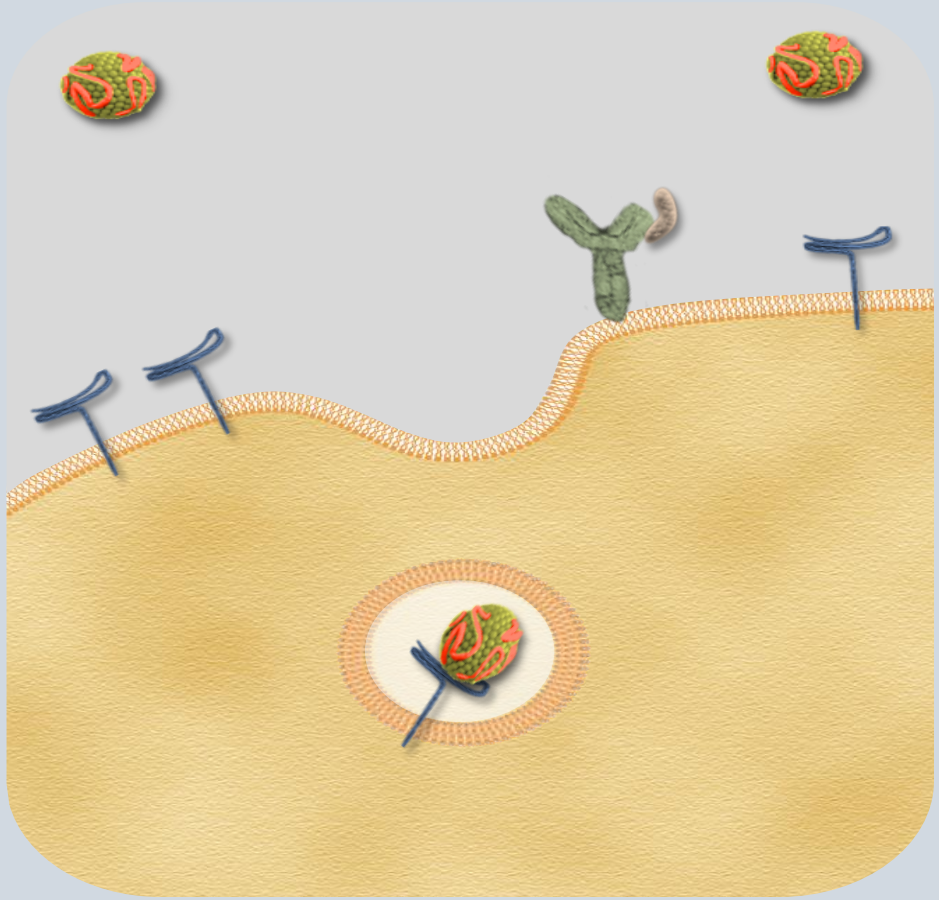

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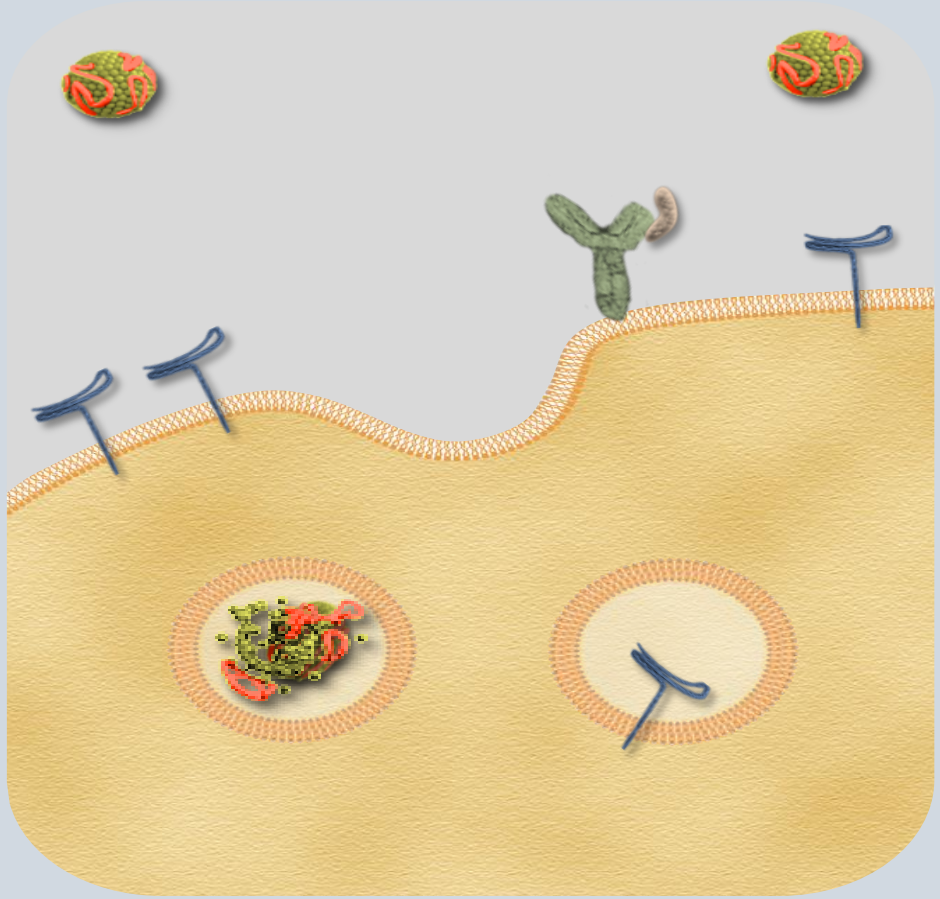
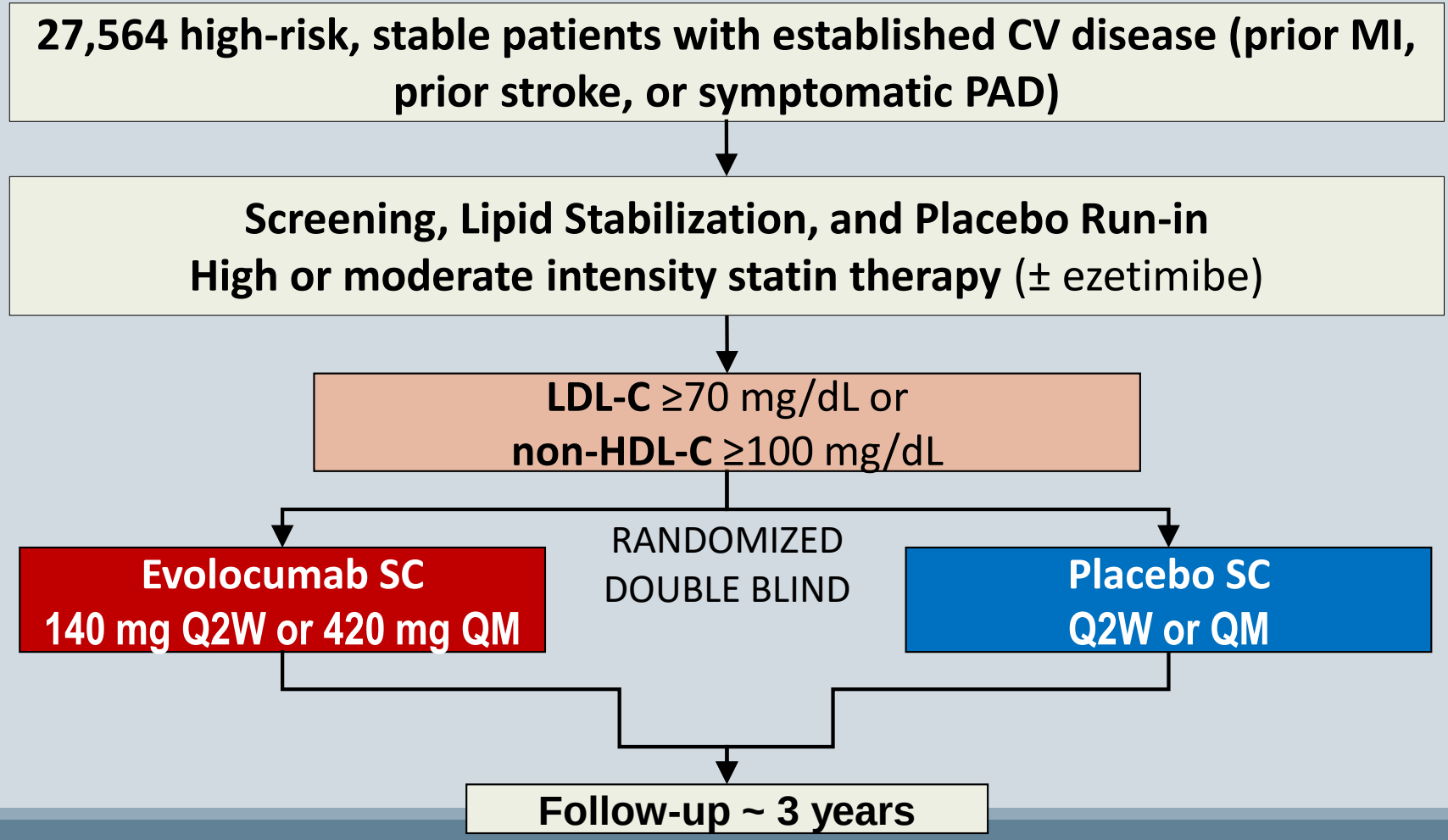


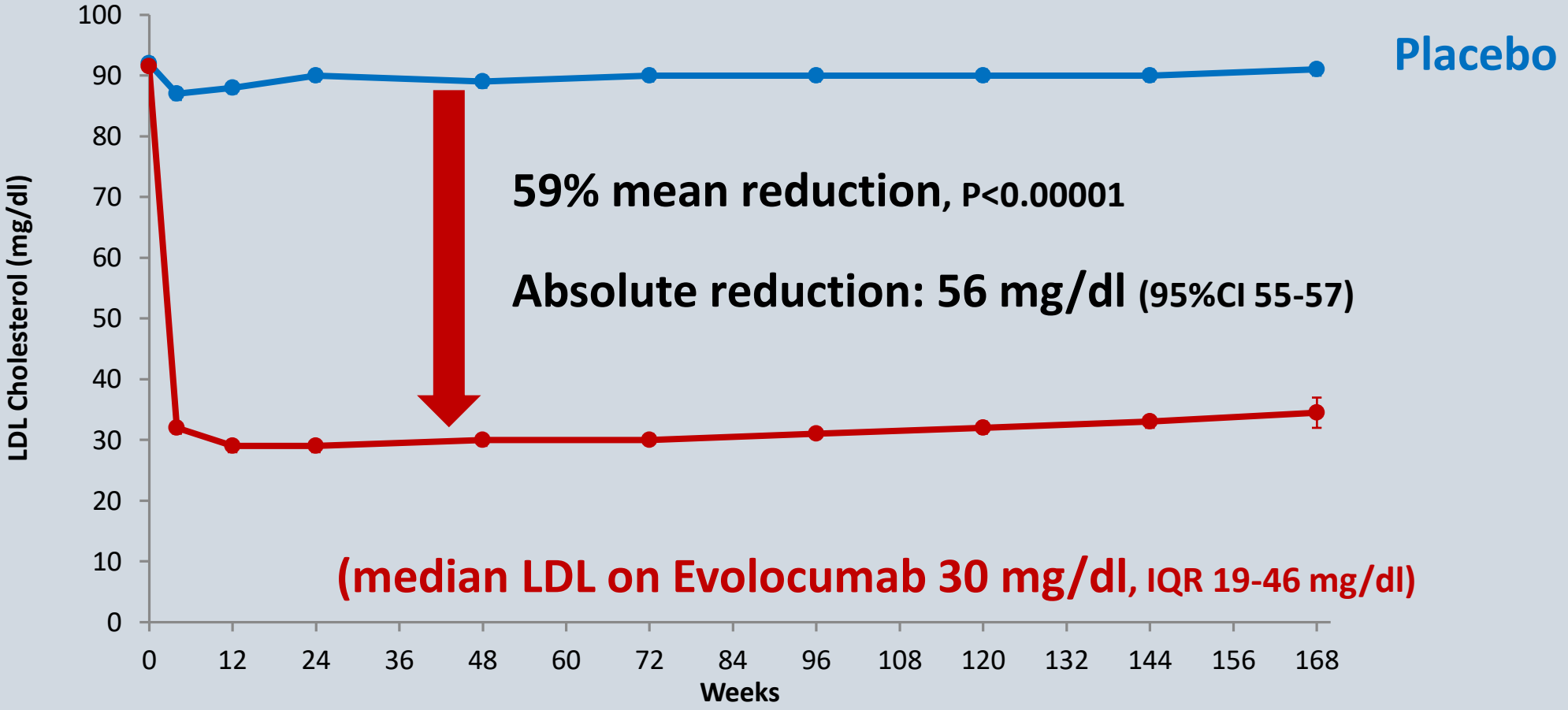
Adapted from Sanofi/Regeneron Pharmaceuticals

Fourier Trial Design - Evolocumab



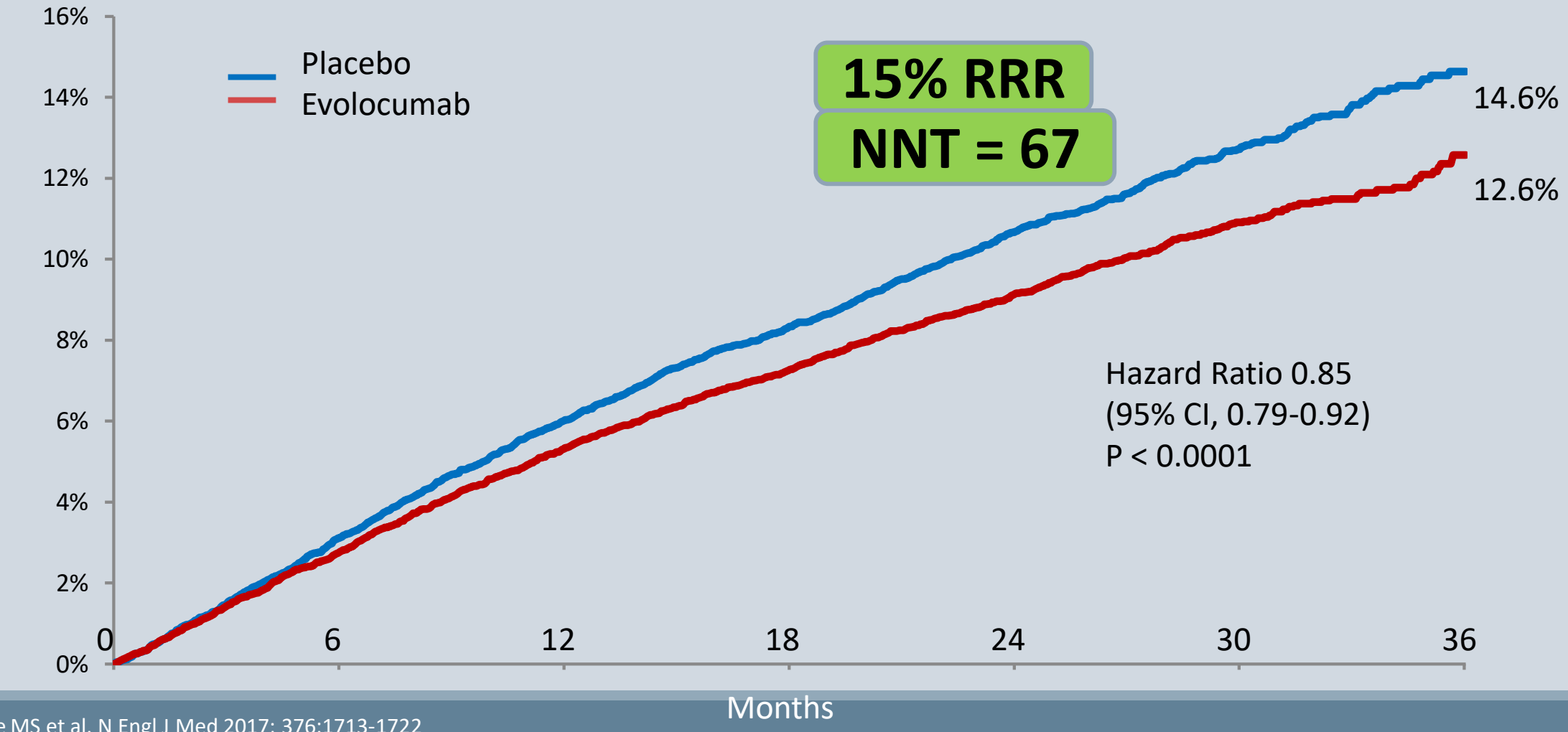
Sabatine MS et al. Am H J 2016; 173: 94-101

Fourier Trial lipid results



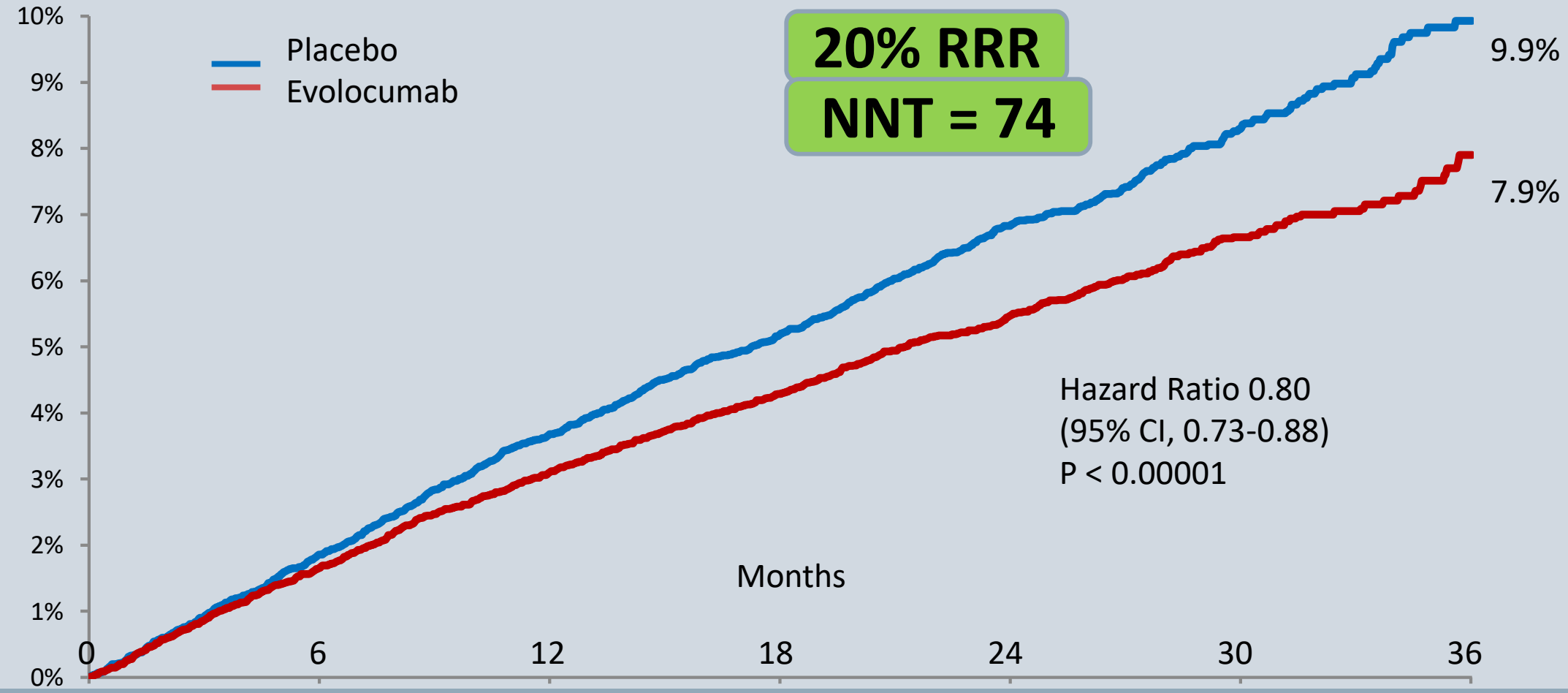
Sabatine MS et al. N Engl J Med 2017; 376:1713-1722

Fourier Trial: Primary Outcome



Sabatine MS et al. N Engl J Med 2017; 376:1713-1722

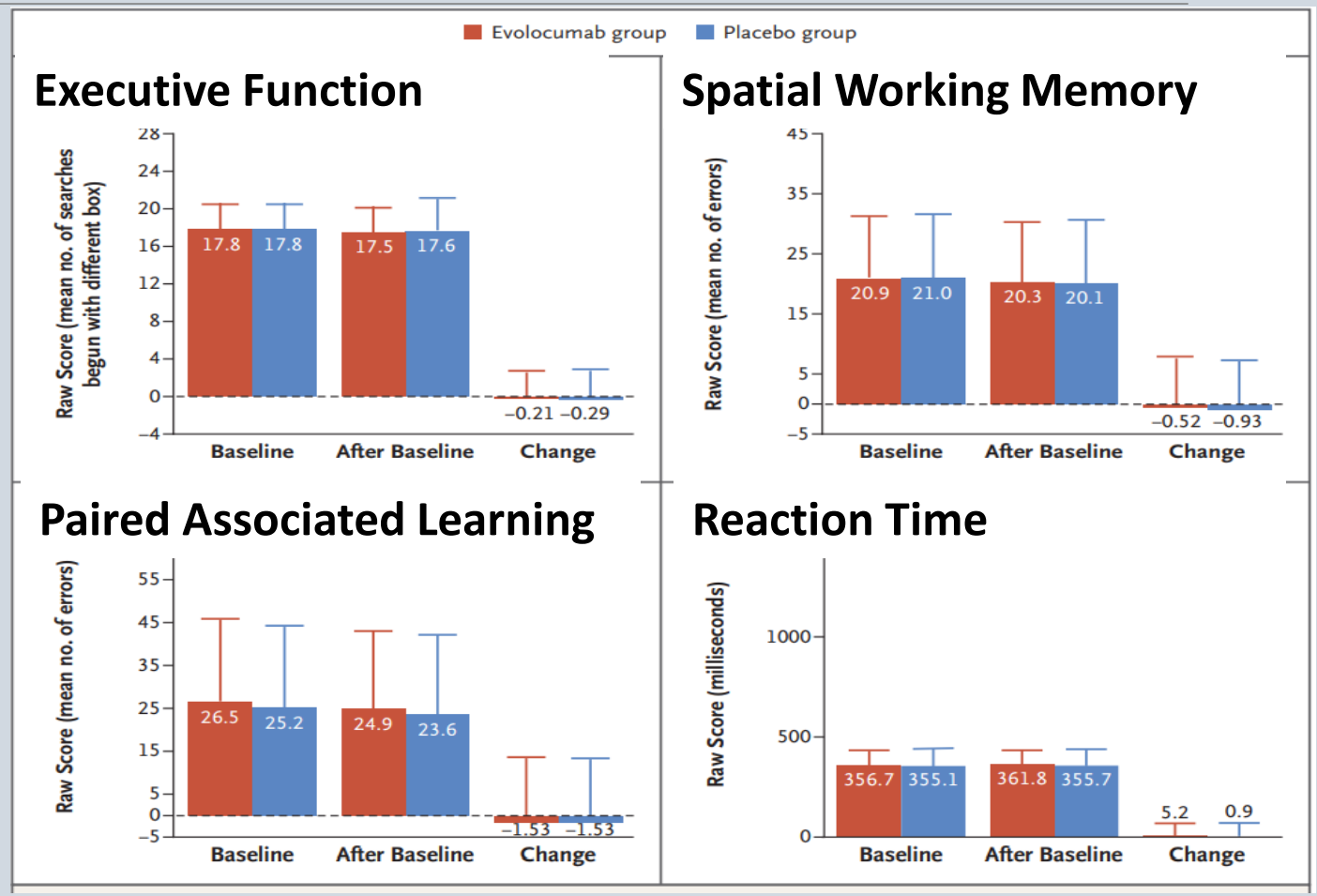
Fourier Trial: MI/Stroke/CV Death



Sabatine MS et al. N Engl J Med 2017; 376:1713-1722

EBBINGHAUS: cognitive function on evolocumab

- Subgroup of FOURIER
  - 1,204 patients
- Cognitive function assessed before and after treatment
  - Stratified by achieved LDL-c
- No differences in cognitive function
  - Regardless of LDL achieved



Giugliano R et al. N Engl J Med 2017;377:633-43.

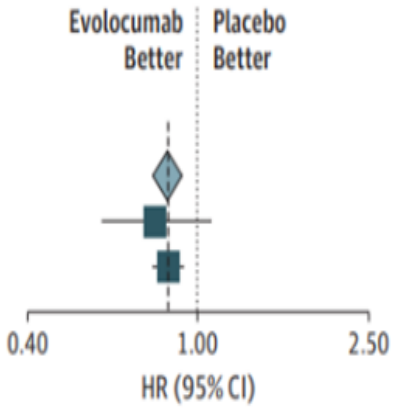
Efficacy of evolocumab regardless of baseline LDL-C or statin intensity

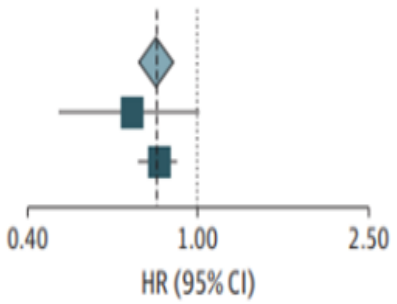
Figure 1. Efficacy Outcomes Stratified by Baseline Low-Density Lipoprotein Cholesterol (LDL-C) Levels and Intensity of Background Statin Treatment

A Efficacy outcomes by baseline LDL-C level

Primary composite end point	HR (95% CI)	P Value for Interaction
All	0.85 (0.79-0.92)	
Baseline LDL-C level, <70 mg/dL	0.80 (0.60-1.07)	.65
Baseline LDL-C level, ≥70 mg/dL	0.86 (0.79-0.92)	

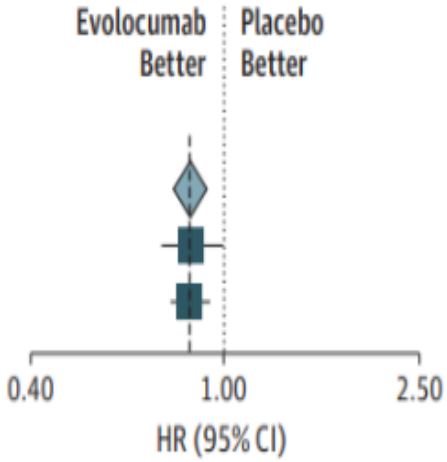
Secondary composite end point	HR (95% CI)	P Value for Interaction
All	0.80 (0.73-0.88)	
Baseline LDL-C level, <70 mg/dL	0.70 (0.48-1.01)	.44
Baseline LDL-C level, ≥70 mg/dL	0.81 (0.73-0.89)	



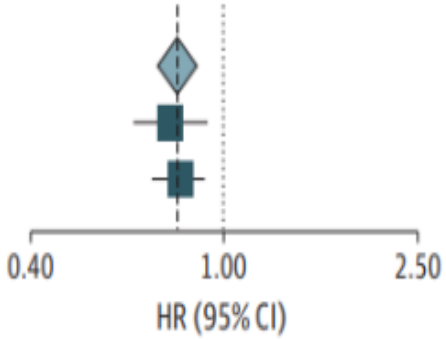


B Efficacy outcomes by potency of background statin

Primary composite end point	HR (95% CI)	P Value for Interaction
All	0.85 (0.79-0.92)	
Maximum intensity statin	0.86 (0.75-0.98)	.88
Less intense statin	0.85 (0.78-0.93)	

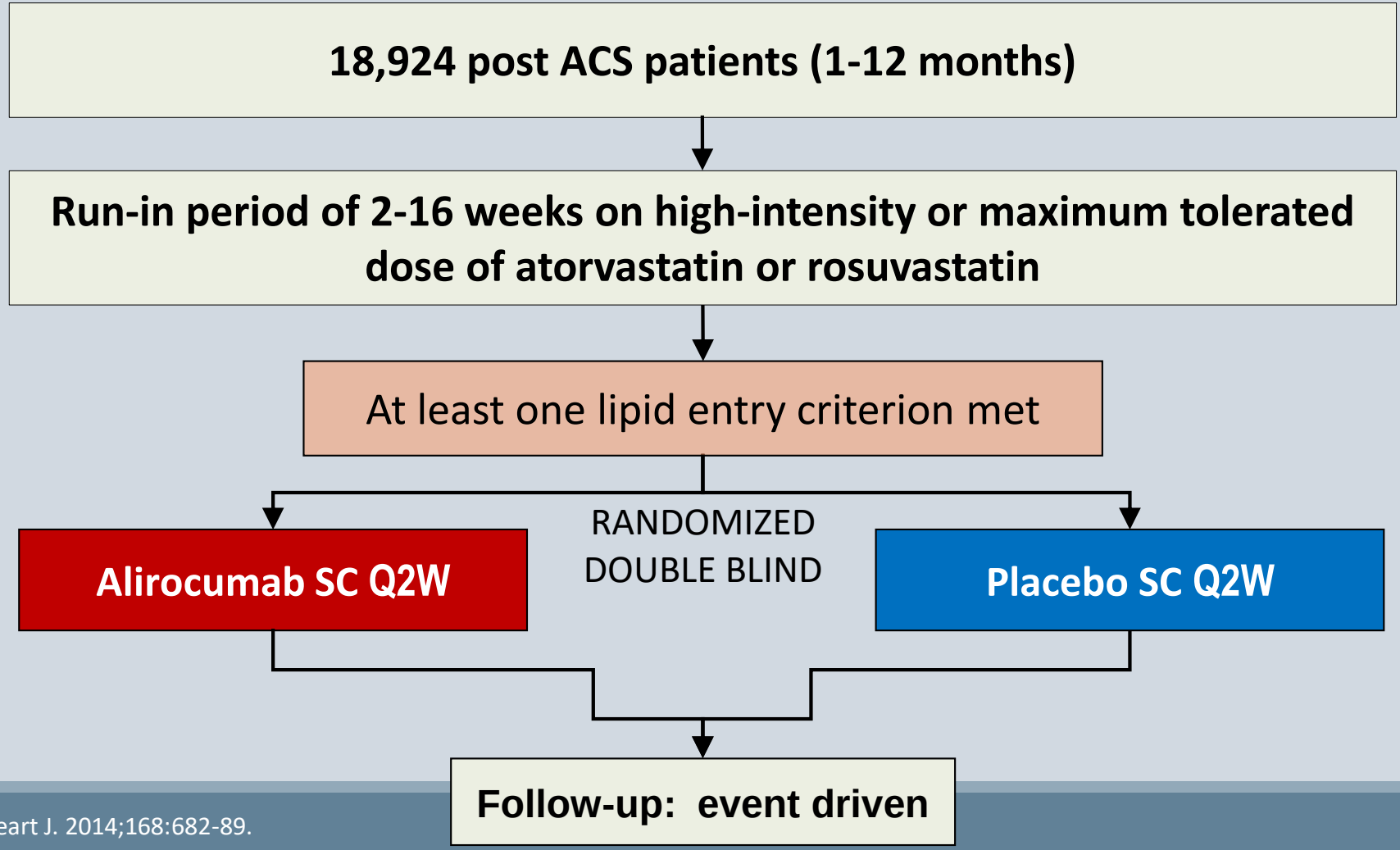


Secondary composite end point	HR (95% CI)	P Value for Interaction
All	0.80 (0.73-0.88)	
Maximum intensity statin	0.78 (0.66-0.92)	.71
Less intense statin	0.81 (0.72-0.90)	



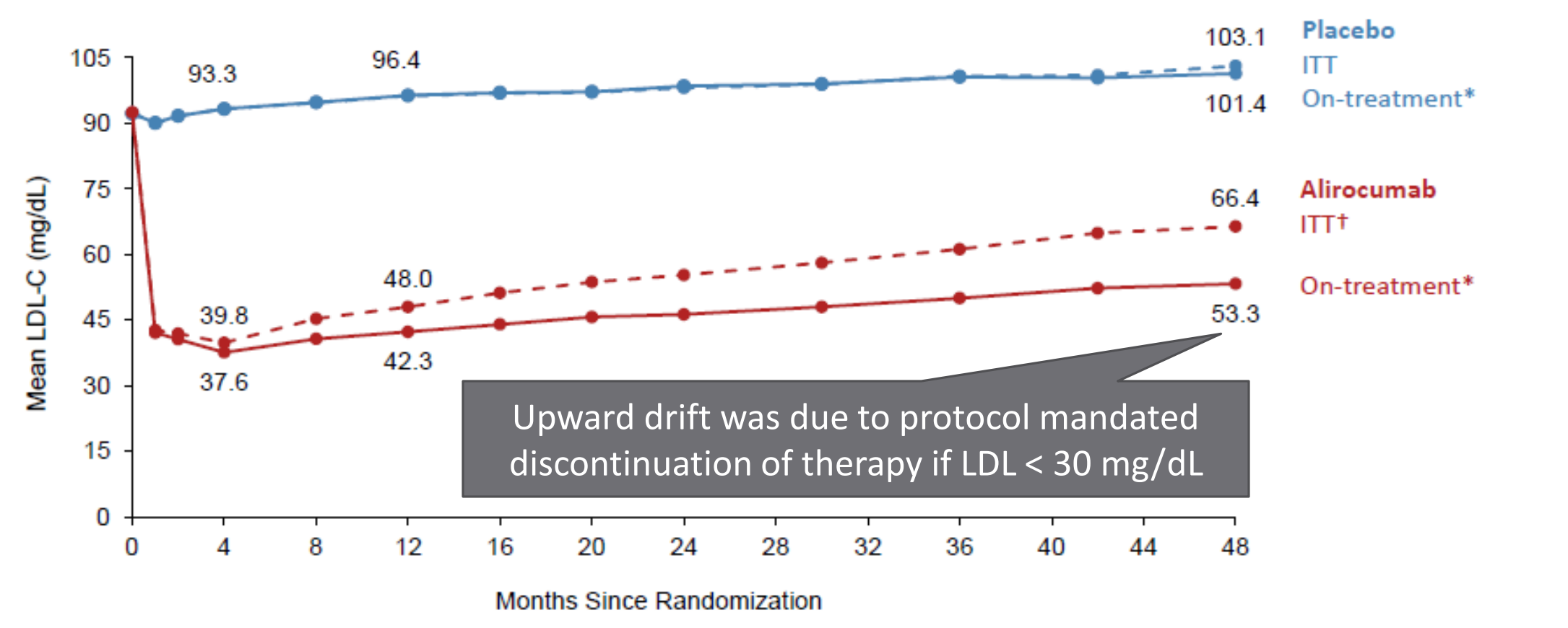
GIUGLIANO RP, ET AL. *JAMA CARDIOL*. 2017;2(12):1385-91.

Odyssey Outcomes Trial



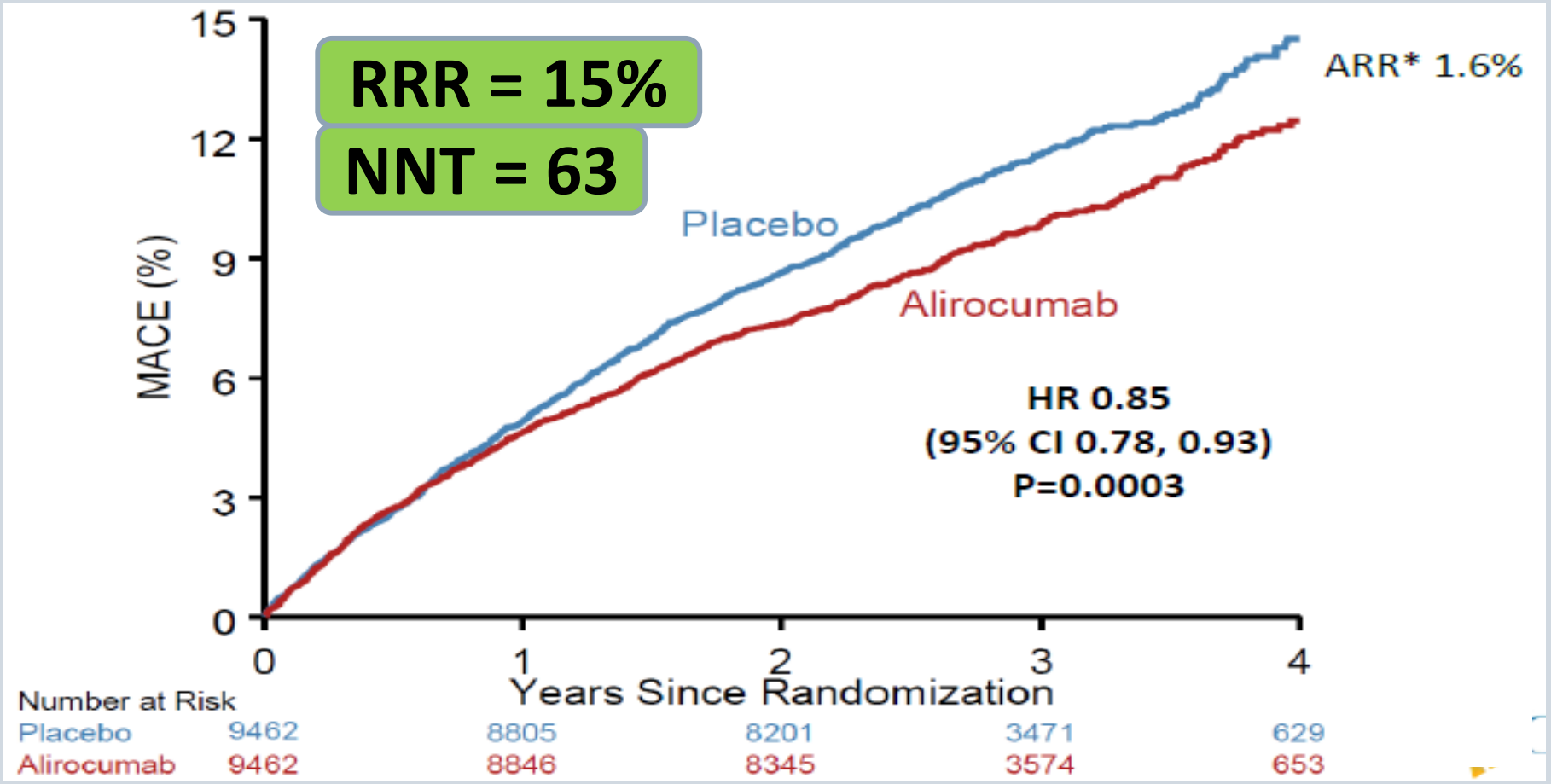
Schwartz GG et al. Am Heart J. 2014;168:682-89.

Odyssey Trial lipid results



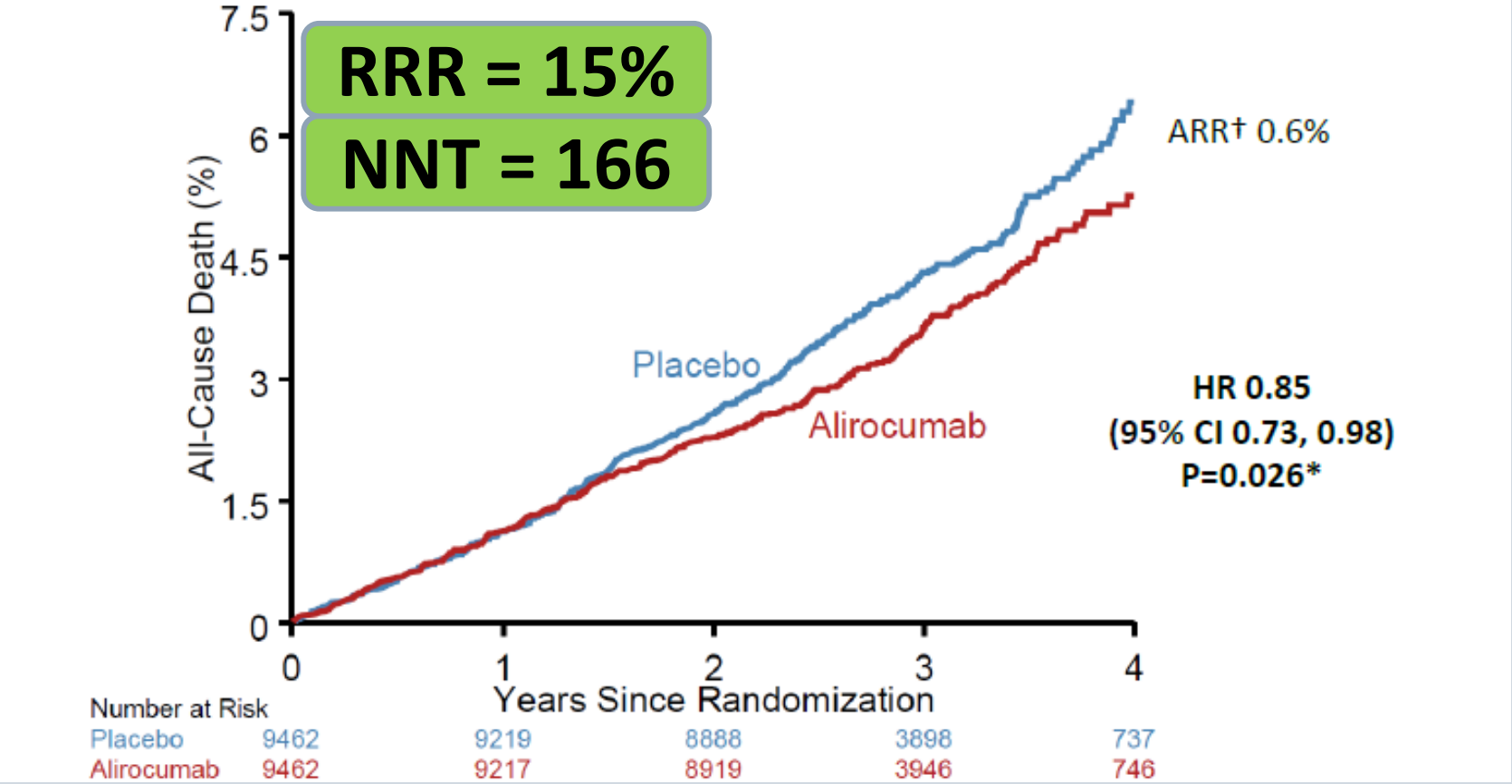
Schwartz GG et. al. N Engl J Med. 2018;379: 2097-2107.

Odyssey Trial – Primary Outcome



Schwartz GG et. al. N Engl J Med. 2018;379: 2097-2107.

Odyssey: All Cause Mortality



Schwartz GG et. al. N Engl J Med. 2018;379: 2097-2107.

Severe Hypercholesterolemia/FH

Patients with LDL ≥ 190 mg/dL with no secondary causes fall into a high risk category for ASCVD EVENTS

Patients with LDL ≥ 190 mg/dL may have familial hypercholesterolemia (FH)

Diagnostic algorithms should be used to make the diagnosis of FH

Statin therapy remains the cornerstone of pharmacologic Rx for patients with FH

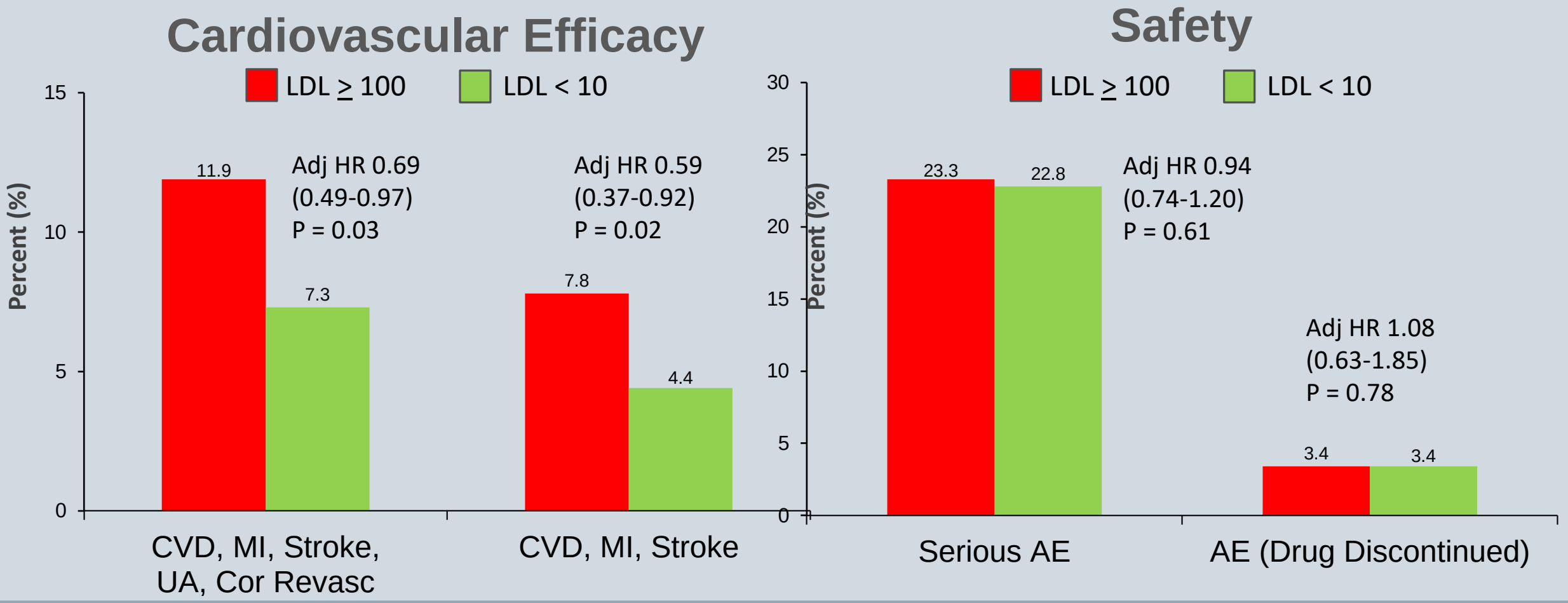
Many patients with FH are not being diagnosed nor treated aggressively enough with statin therapy

Multiple organizations and recommendations/guidelines suggest non-statin therapy in these patients

PCSK9 inhibitors are approved for use in patients with FH and are recommended in the 2018 AHA/ACC Cholesterol Guidelines for use in patients with severe hypercholesterolemia

You will see lower LDL-c levels with PCSK9 inhibitors than you've never seen before

FOURIER Trial—Efficacy and Safety in Patients With LDL-c <10 mg/dL



Giugliano RP, et al. *Lancet*. 2017;390(10106):1962-1971.

Even LDL-c levels < 10 appear to be safe (and efficacious)

Why we need to lower LDL-c even more

If we keep on doing what we've always done...
we'll keep on getting what we've always gotten…