How Low Your LDL is Safe??

Jose M Garcia Mateo, MD, FACE

Diplomate of the American Board of Endocrinology, Diabetes and Metabolism

Diplomate of the American Board of Clinical Lipidology

SPED President

Disclosure

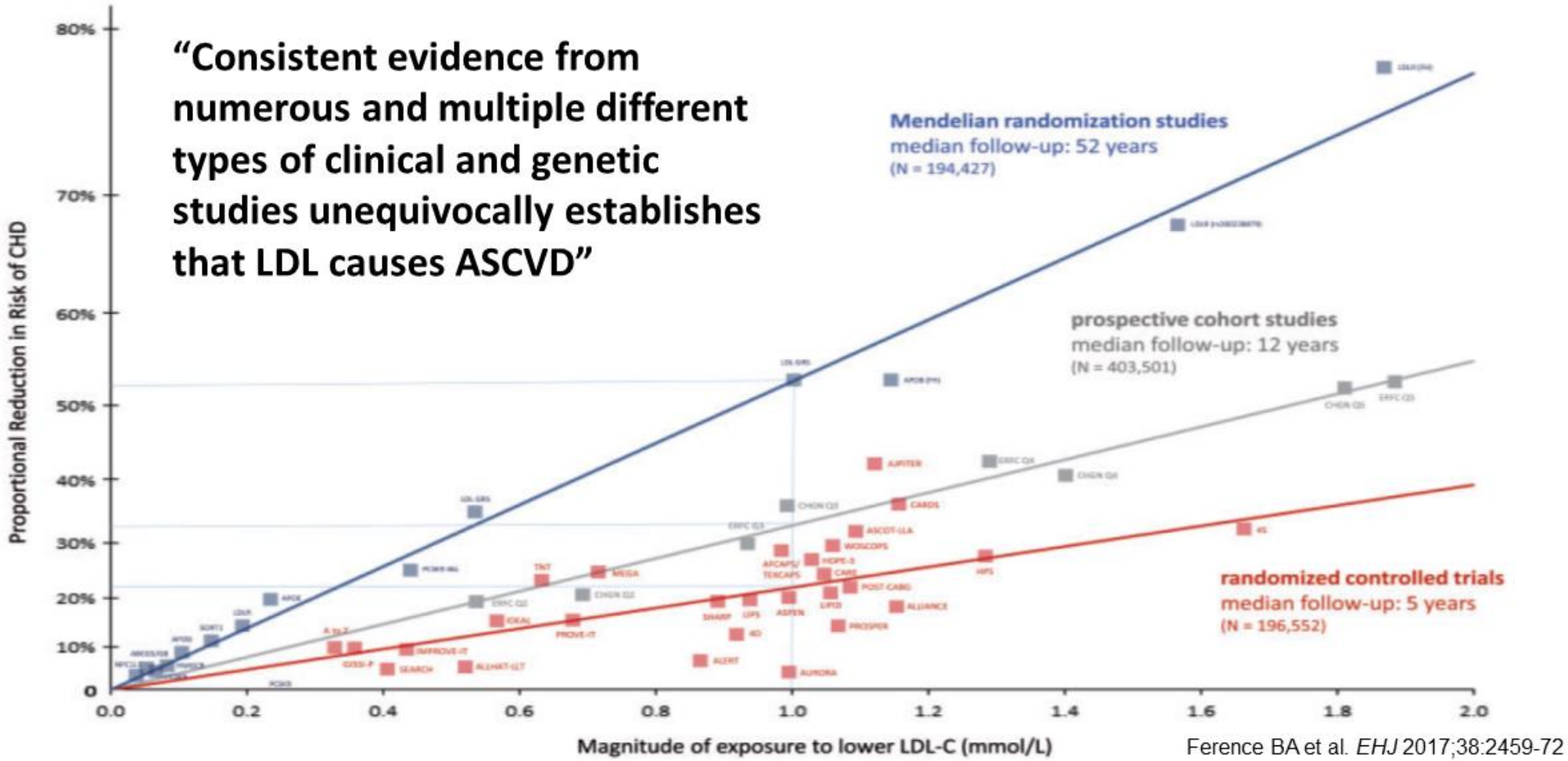
•Dr. Jose M. Garcia Mateo, endocrinologist, declares that he serves as a speaker and consultant for the following pharmaceutical companies: ***Eli Lilly, Astra Zeneca, Sanofi , Amgen, Boehringer Ingelheim, Janseen, Akcea, Abbvie and Merck.***

Objectives

- Review recent advances in lipid lowering therapy resulting in very low LDL levels.
- Evaluate if there is CV benefit from RCT's by further lowering of LDL beyond maximal tolerated statin use.
- Discuss the controversies in safety of very low LDL levels.
- Describe which patients benefit the most from aggressive lipid lowering therapy using a clinical scenario.

Log-linear Association Per Unit Change in LDL-C and the Risk of Cardiovascular Disease

"Consistent evidence from numerous and multiple different types of clinical and genetic studies unequivocally establishes that LDL causes ASCVD"



Ference BA et al. *EHJ* 2017;38:2459-72

NATIONAL LIPID ASSOCIATION

Questions About Low LDL-C

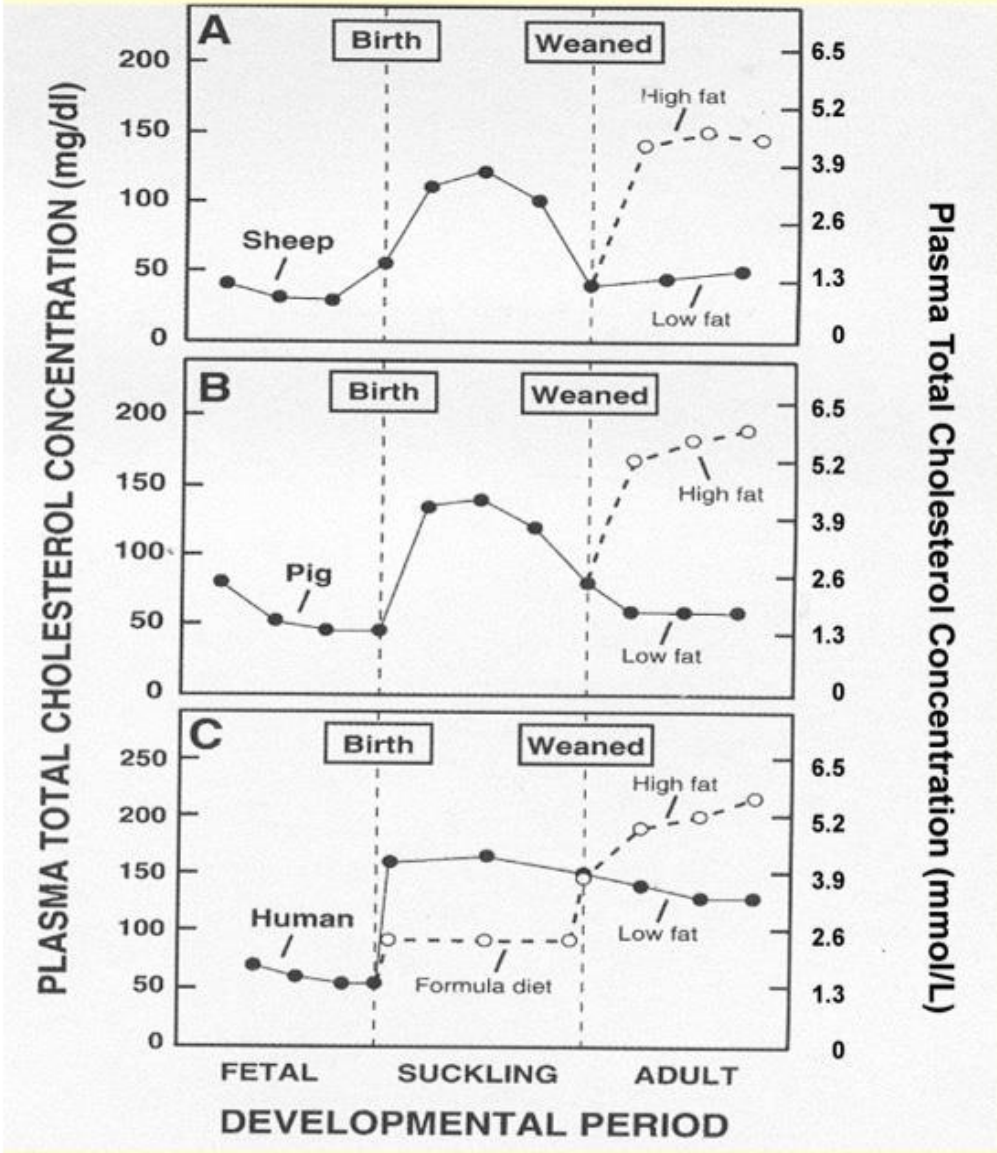
- **Efficacy: Is there a floor to the benefit of LDL-C reduction**
- **Safety: Are very low LDL-C levels safe?**

Low LDL-C is Unsafe

- Early epidemiologic studies showed an association between low cholesterol level and increased risk for cancer, intracranial hemorrhage, and death[1-3]
- Furthermore, studies in canine models raised concerns that supratherapeutic doses of statins may cause brain and optic pathology[4]

1. Kritchevsky SB. *Am J Epidemiol*. 1992;135(5):509-520.
2. Neaton JD. *Arch Intern Med*. 1992;152(7):1490-1500.
3. Tirschwell DL. *Neurology*. 2004;63(10):1868-1875.
4. Berry PH. *Am J Pathol*. 1988;132(3):427-443.

NATIONAL LIPID ASSOCIATION

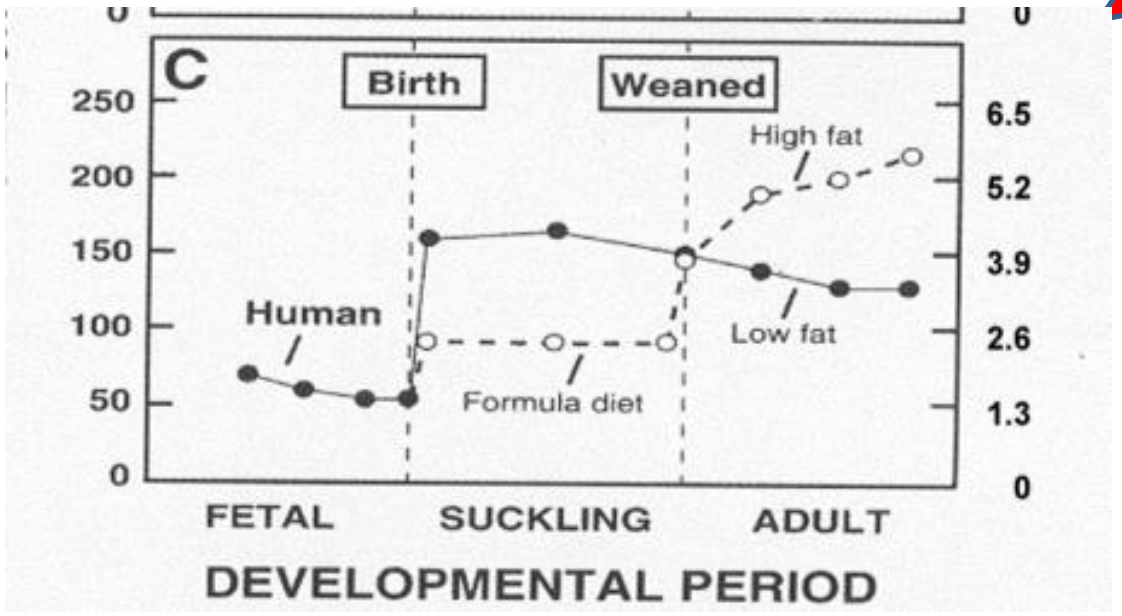


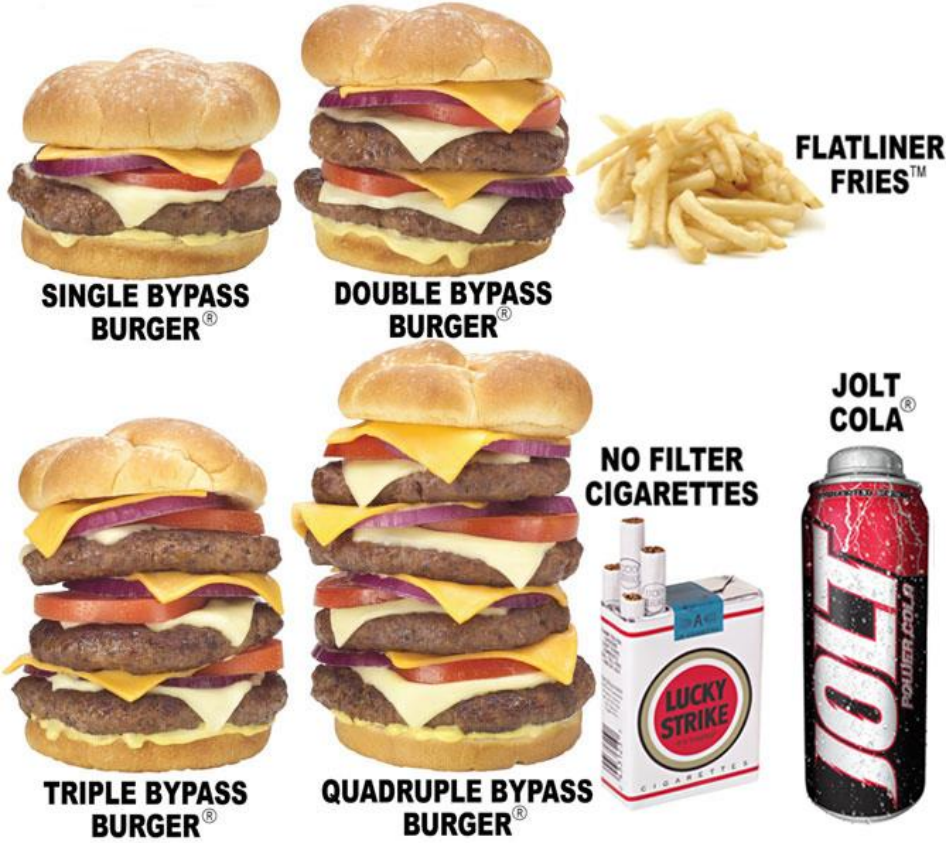
Dietschy JM J Lipid Res 2004:1375-97

Cholesterol levels: what is normal?

- OLD NEWS: Normal lipid levels are primarily determined by diet
- Just prior to birth, human TC is ~ 60 mg/dL
- On breast milk, TC rises to ~ 170 (LDL 100)
- WHY? → Breast milk provides 18 mg chol/d/kg and infant synthesizes 25 mg/d/kg (ingestion rate ~ 70% of synthesis rate).
- Infants on a low cholesterol synthetic formula (2 mg/d/kg = 8% of synthesis rate) see an LDL-C rise by only 40 mg/dL
- After weaning, animals' TC and LDL-c fall dramatically, but humans' LDL, because of a much higher cholesterol and fat intake don't
- Some cultures have diets with < 100 mg/d chol. Their LDLs are < 75. These cultures have virtually no CAD
- Japanese Zen monks have virtually no animal products in diet and LDL = 70 mg/dL

NATIONAL LIPID ASSOCIATION


C
Birth
Weaned
High fat
Human
Low fat
Formula diet
250
200
150
100
50
0
6.5
5.2
3.9
2.6
1.3
0
FETAL
SUCKLING
ADULT
DEVELOPMENTAL PERIOD


SINGLE BYPASS BURGER®
DOUBLE BYPASS BURGER®
FLATLINER FRIES™
TRIPLE BYPASS BURGER®
QUADRUPLE BYPASS BURGER®
NO FILTER CIGARETTES
LUCKY STRIKE
JOLT COLA®
JOLT

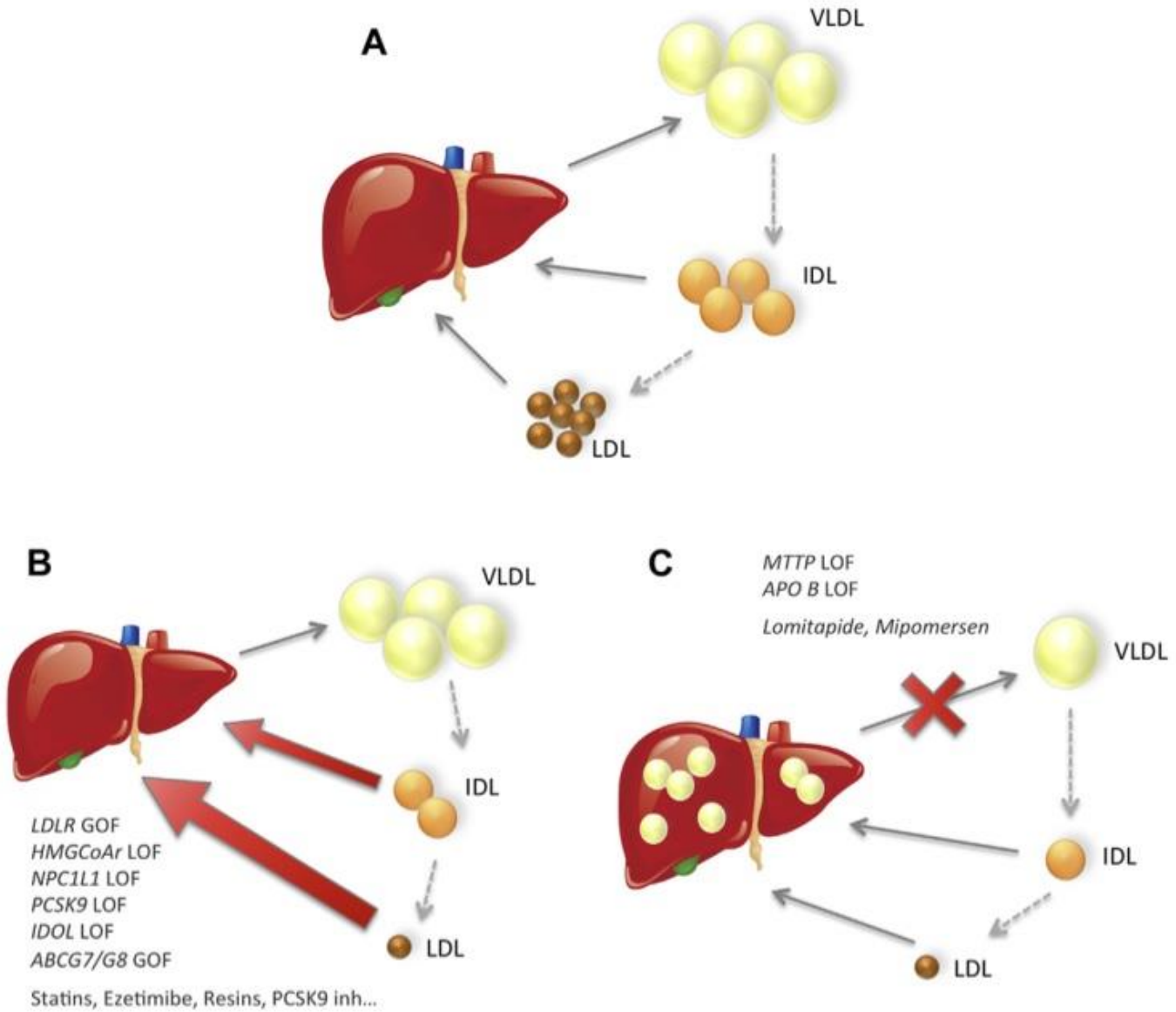
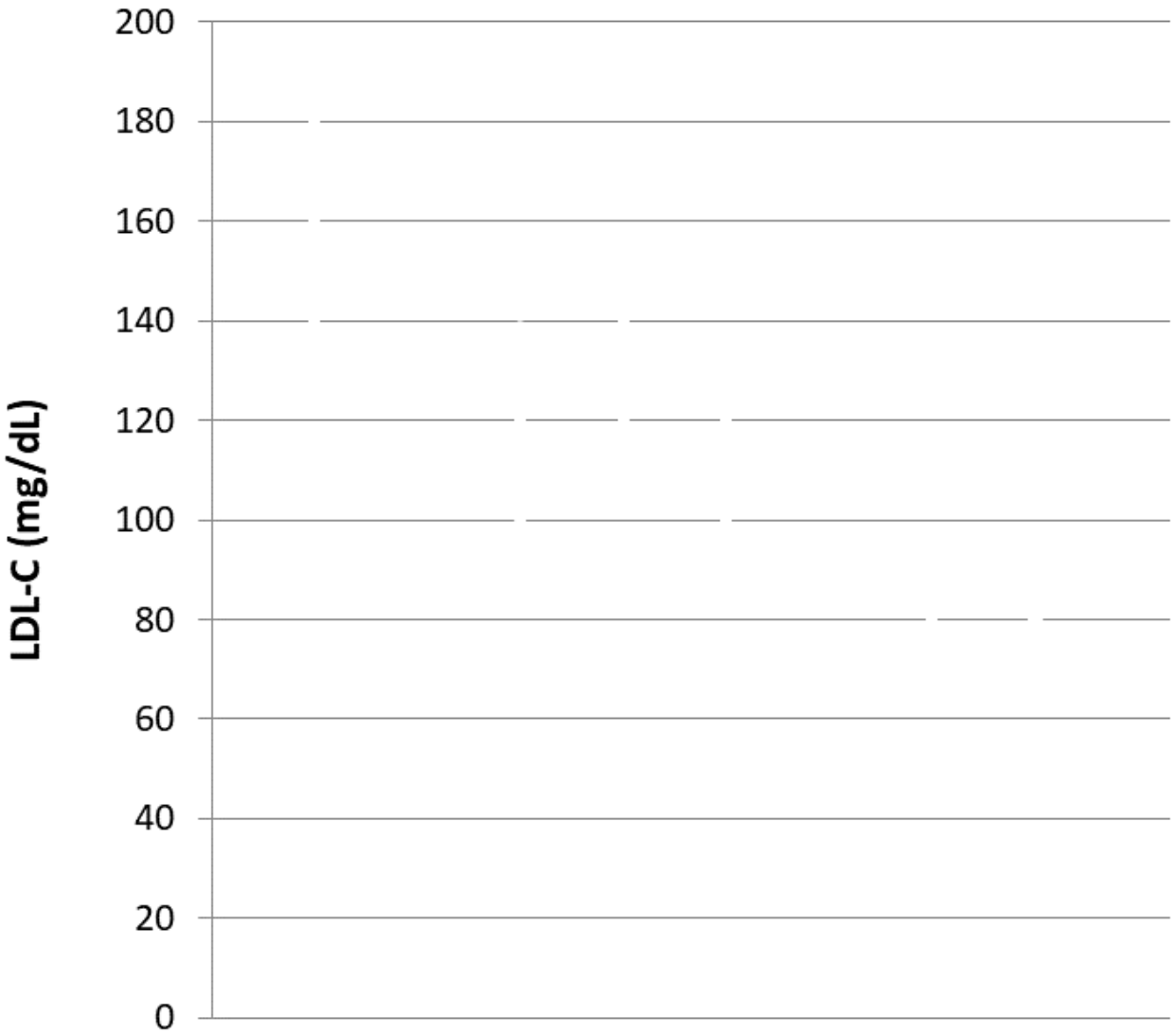


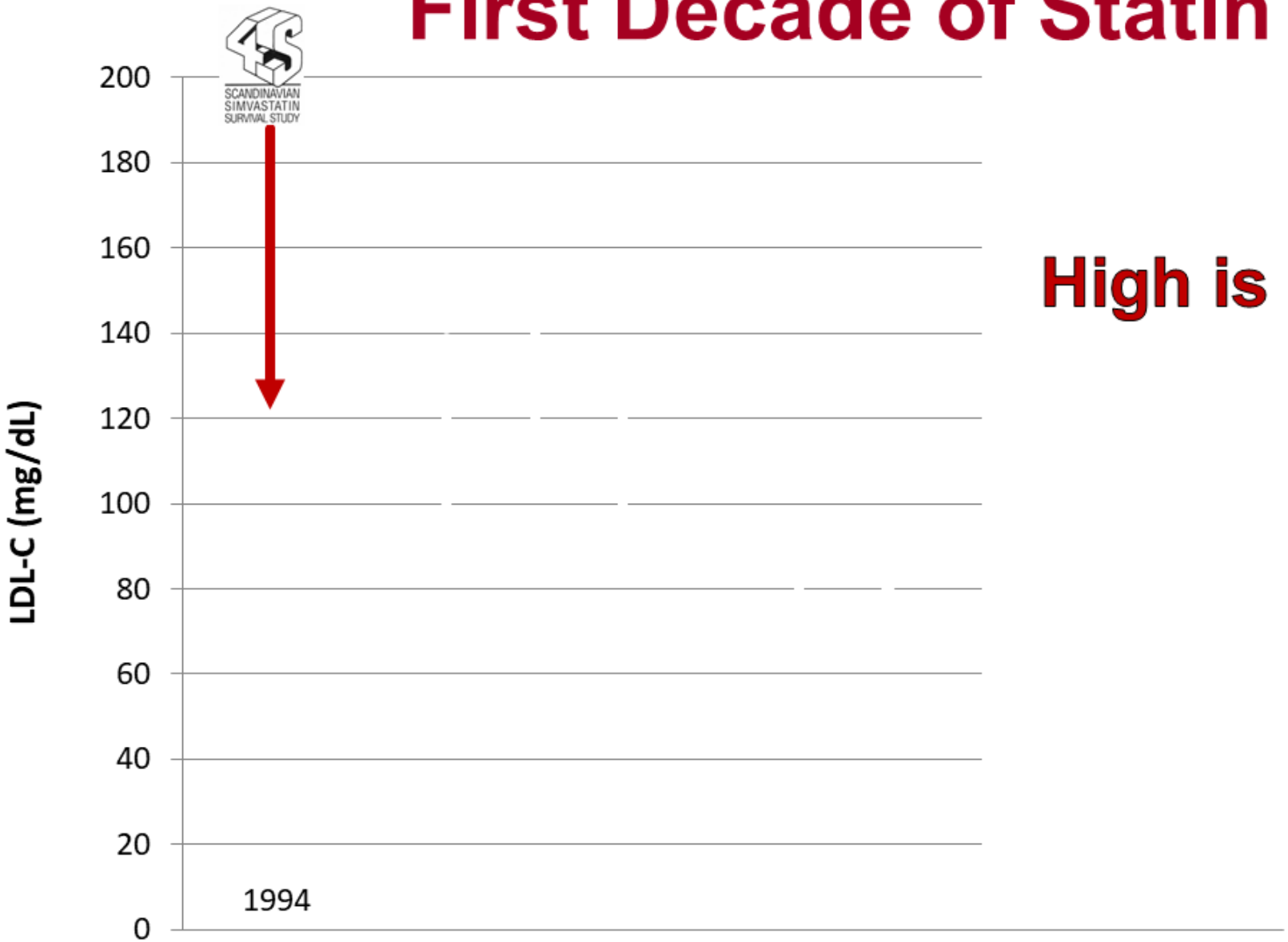
Figure 2 Different pathophysiological mechanisms associated with genetically driven VLDL cholesterol levels. Panel A shows the usual metabolic situation; panel B shows low LDL due to increased lipoprotein clearance. A normal apo B-rich lipoprotein metabolism axis is mantained; panel C shows low LDL due to reduced lipoprotein synthesis. Because of apo B formation inhibition, there is an alteration in fat secretion from the liver (and intestine) producing fatty liver, malabsorption and impacting all lipoprotein cascade. LDL, low-density lipoprotein; VLDL, very low–density lipoprotein; LDLR, LDL-LDL receptor; apo B, apolipoprotein B; IDL, intermediate-density lipoprotein; LOF, loss of function; GOF, gain of function.

First Decade of Statin Trials



NATIONAL LIPID ASSOCIATION

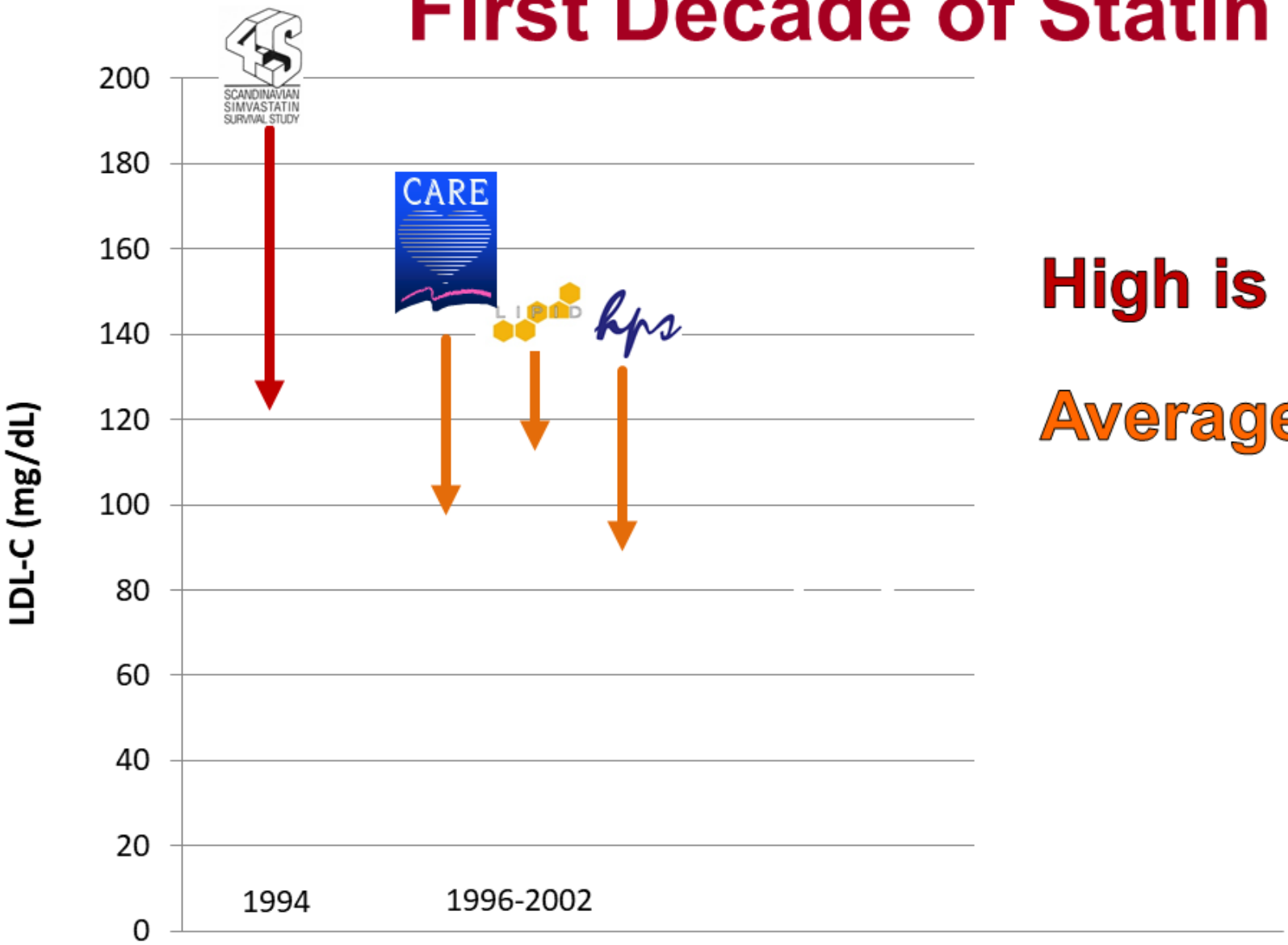
First Decade of Statin Trials



High is bad

NATIONAL LIPID ASSOCIATION

First Decade of Statin Trials

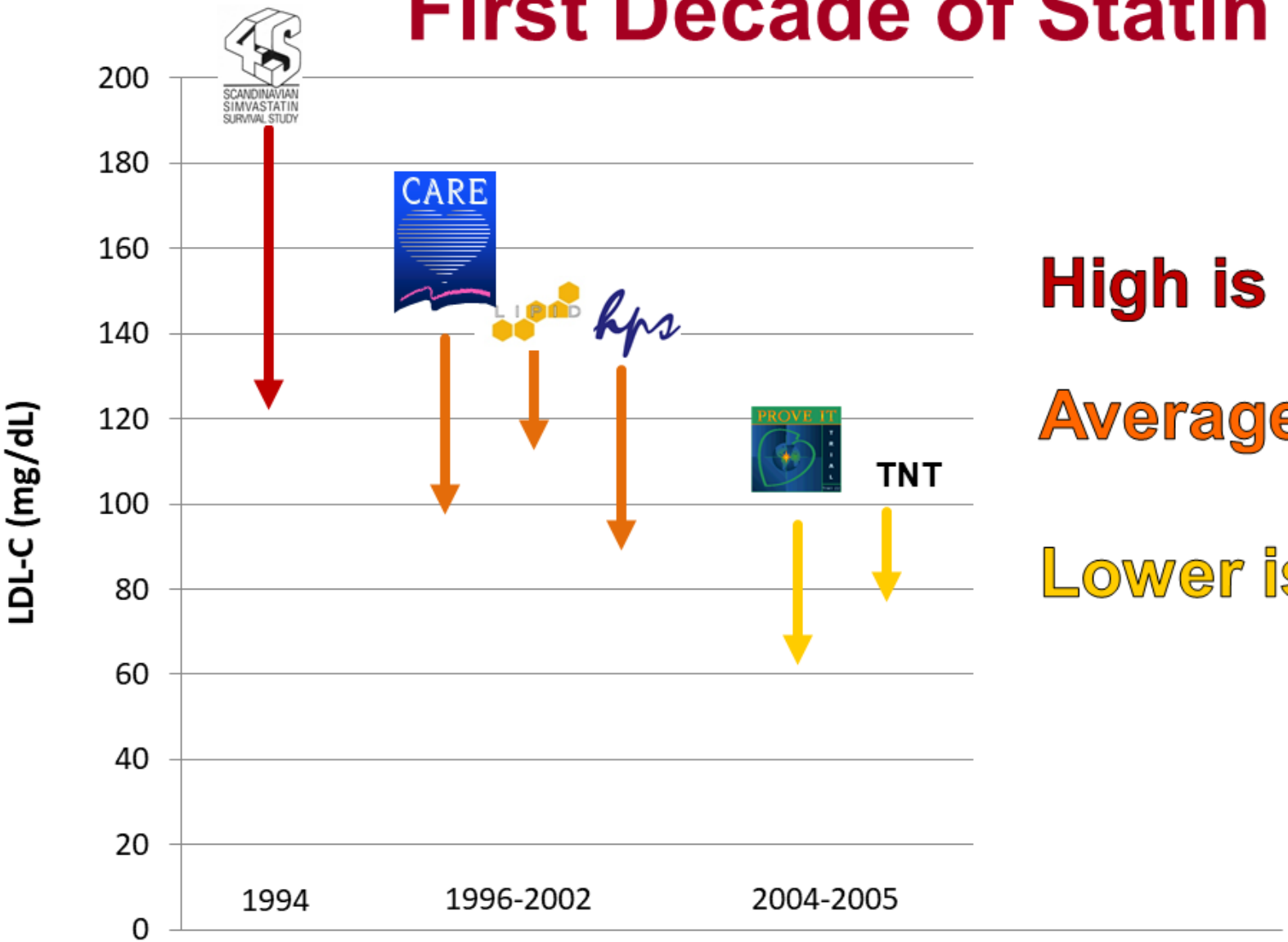


High is bad

Average is not good

NATIONAL LIPID ASSOCIATION

First Decade of Statin Trials



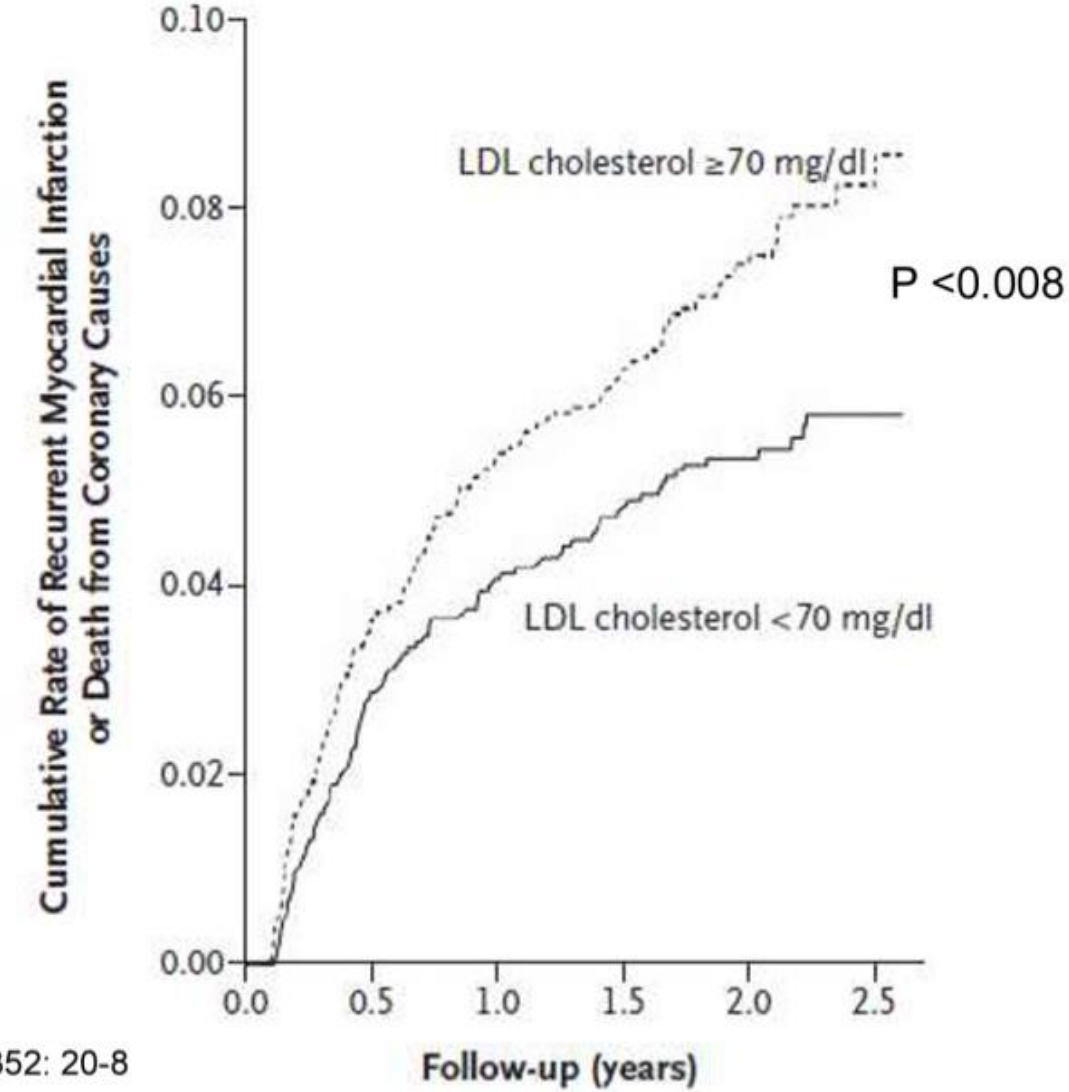
High is bad

Average is not good

Lower is better

NATIONAL LIPID ASSOCIATION

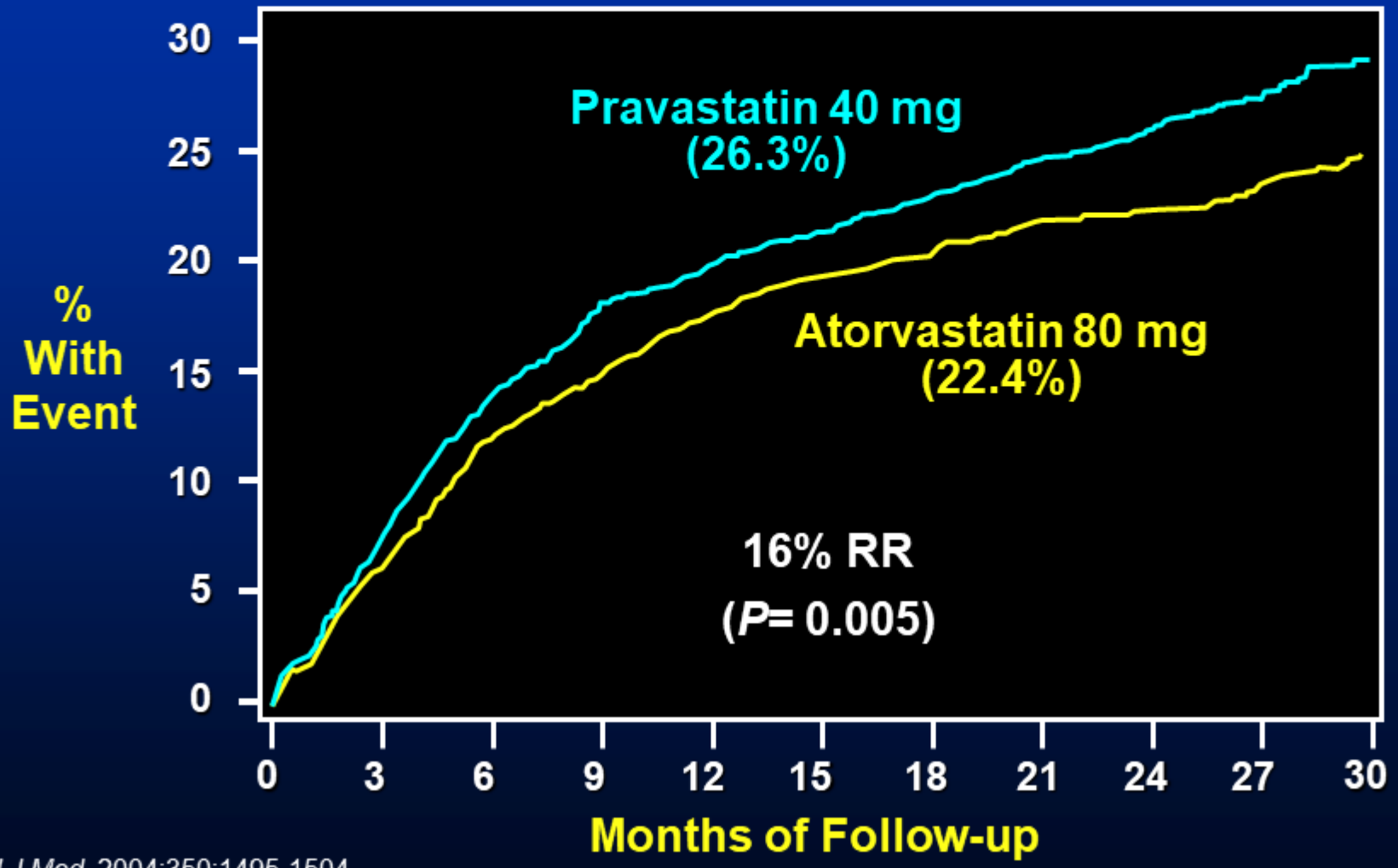
Should We Go Below 70 mg/dL?



Ridker PM, NEJM 2005; 352: 20-8

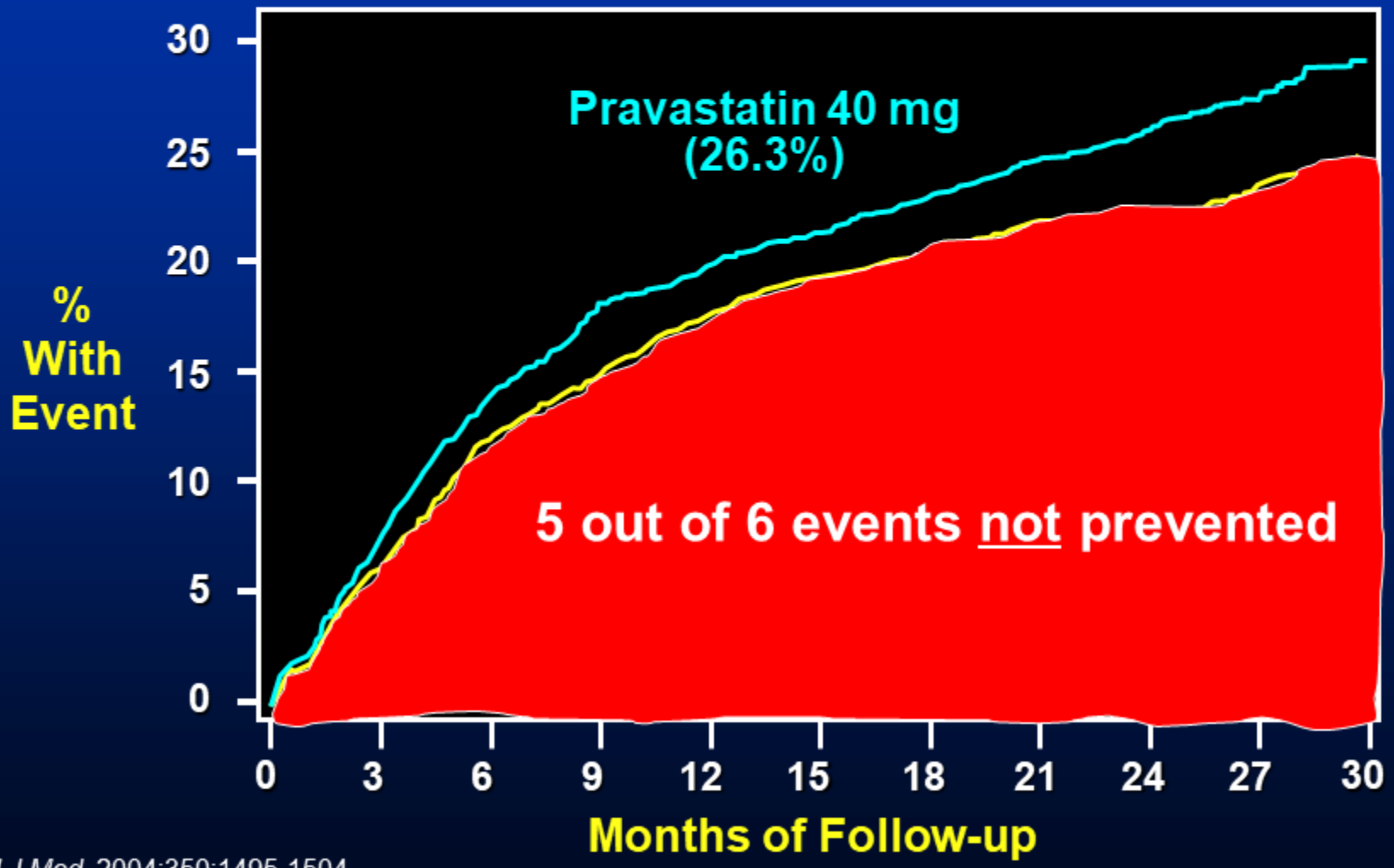
NATIONAL LIPID ASSOCIATION

All-Cause Death or Major CV Events in All Randomized Subjects



Cannon CP, et al. *N Engl J Med.* 2004;350:1495-1504.

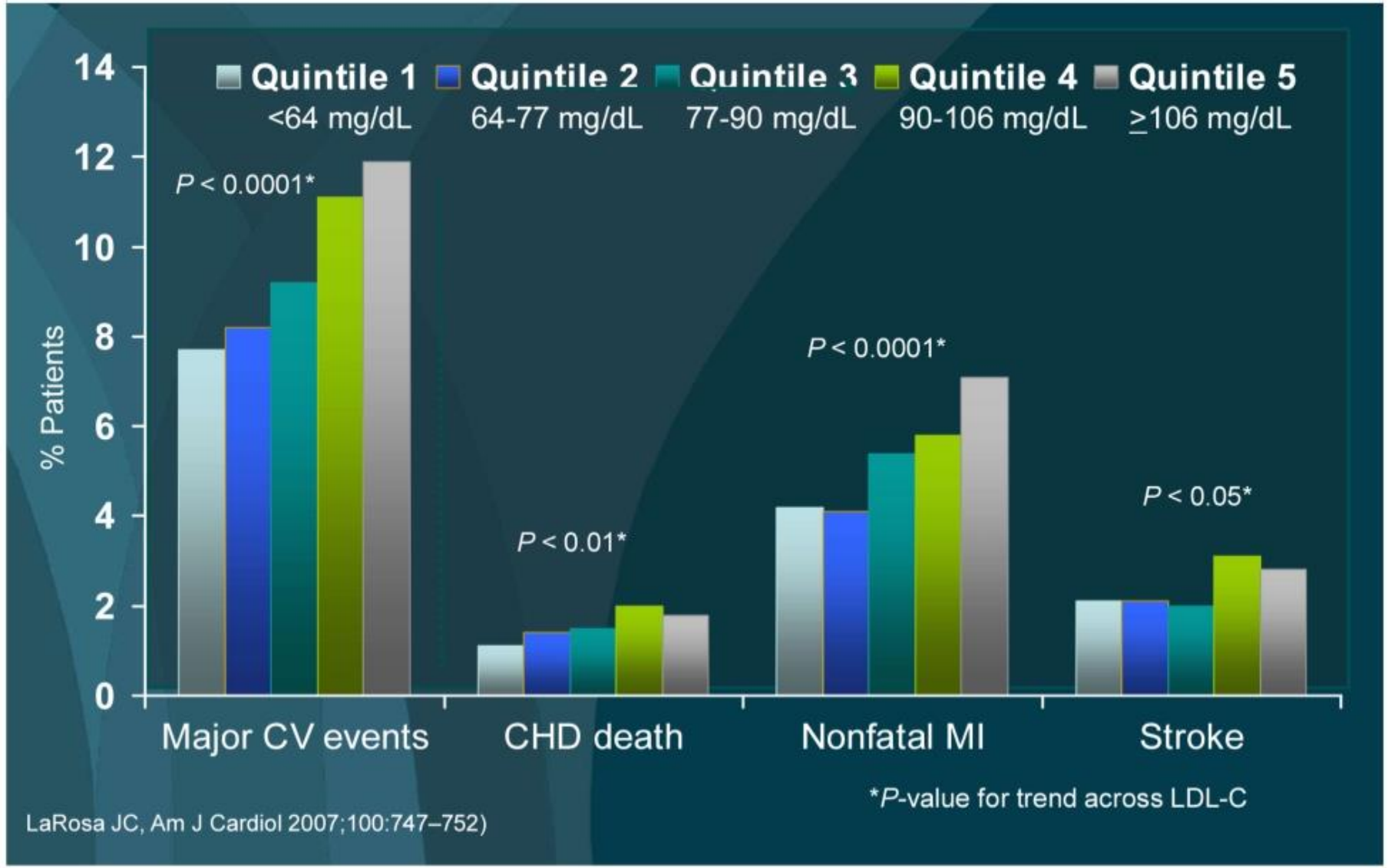
All-Cause Death or Major CV Events in All Randomized Subjects



Cannon CP, et al. *N Engl J Med.* 2004;350:1495-1504.

TNT Is < 64 mg/dL Even Better?

TREATING TO NEW TARGETS



LaRosa JC, Am J Cardiol 2007;100:747–752)

NATIONAL LIPID ASSOCIATION

Adverse Event Profiles Across Quintiles

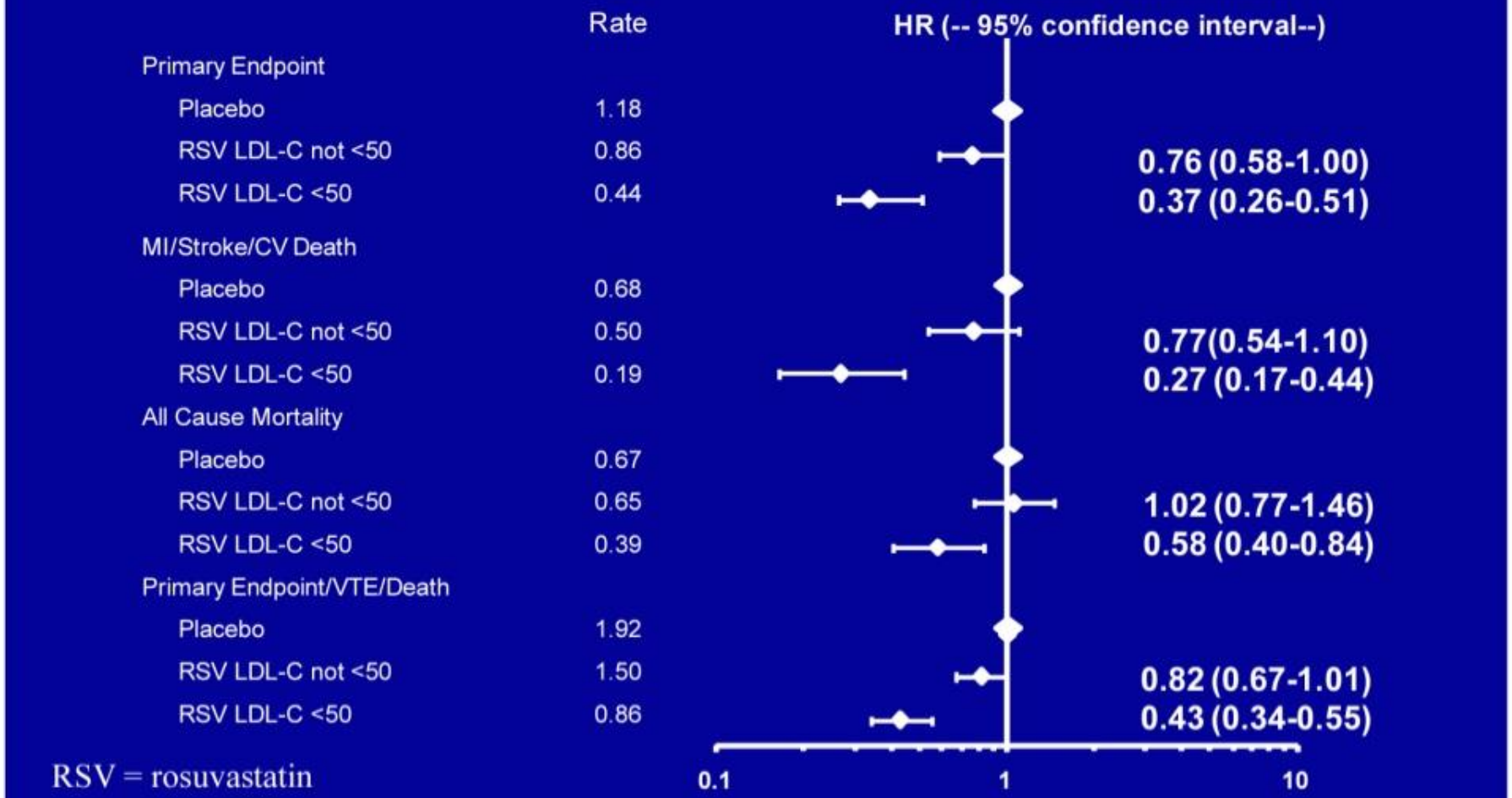
	Number of patients (%)				
	Quintile 1 <64 mg/dL (114/1722)*	Quintile 2 64-<77 mg/dL (529/1403)*	Quintile 3 77-<90 mg/dL (1019/968)*	Quintile 4 90-<106 mg/dL (1515/515)*	Quintile 5 ≥106 mg/dL (1718/266)*
Withdrawals due to treatment-associated AEs	122 (6.6)	107 (5.5)	100 (5.0)	106 (5.2)	143 (7.2)
Treatment-associated myalgia	84 (4.6)	85 (4.4)	93 (4.7)	96 (4.7)	104 (5.2)
Persistent† CPK >10 × ULN	0	0	0	0	0
Persistent† ALT or AST >3 × ULN	20 (1.1)	15 (0.8)	18 (0.9)	8 (0.4)	10 (0.5)

*Number of patients: Atorvastatin 10 mg/atorvastatin 80 mg
†Occurring twice within 4-10 days

LaRosa JC, Am J Cardiol 2007;100:747–752)

NATIONAL LIPID ASSOCIATION

How about < 50 mg/mL?



RSV = rosuvastatin

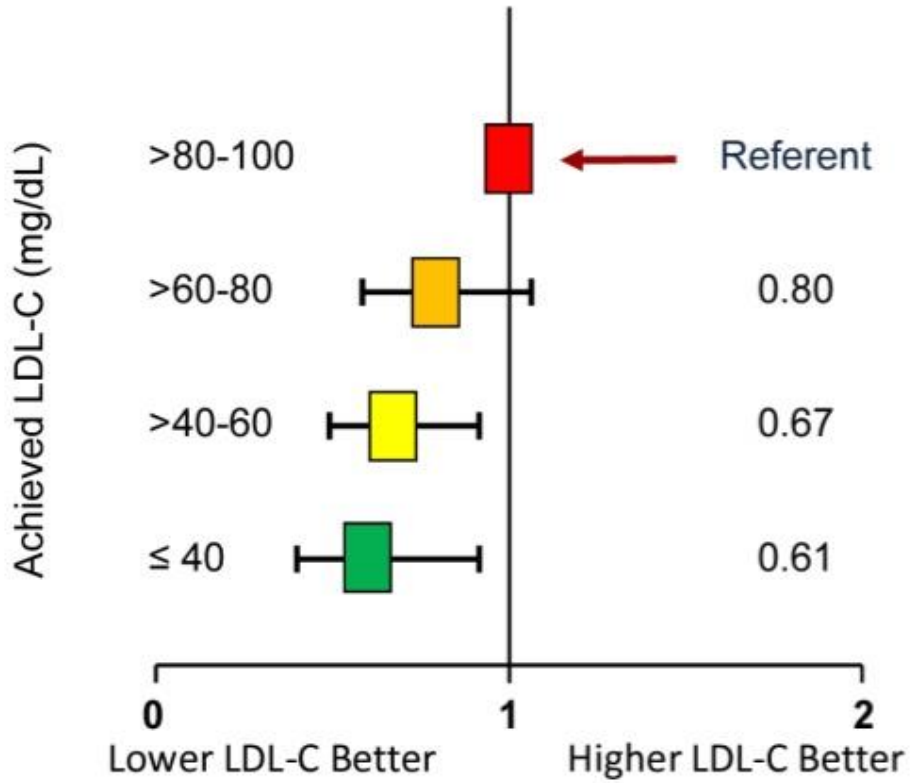
Jupiter Trial, courtesy of PM Ridker

NATIONAL LIPID ASSOCIATION

Are Outcomes Better at <40 mg/dL?

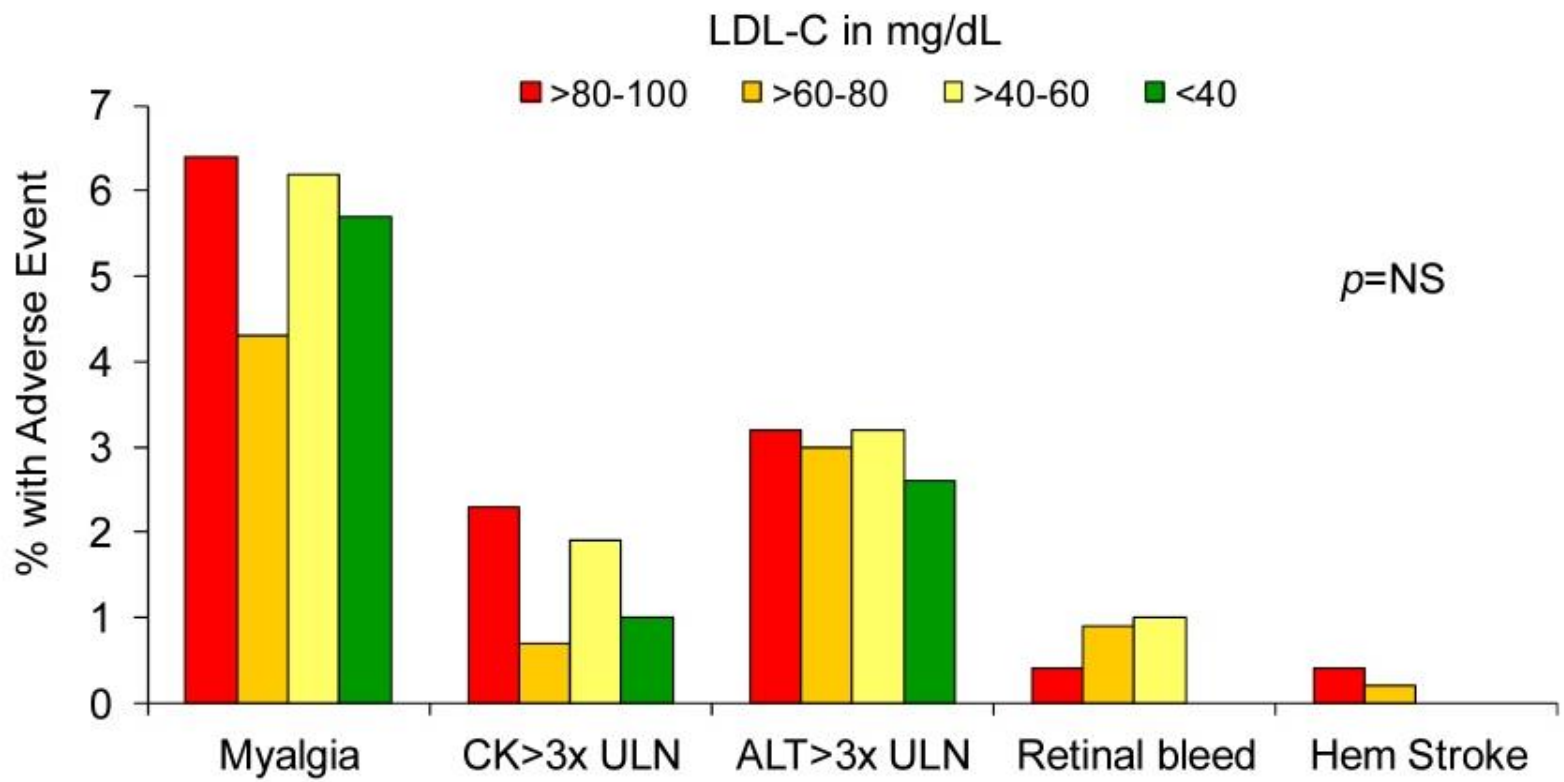
Hazard Ratio for Primary Endpoint (PROVE IT-TIMI 22)

Outcome/events: death, MI, stroke, revascularization and unstable angina requiring hospital admission



Wiviott SD, et al. *J Am Coll Cardiol.* 2005;46:1411-1416.

Is it Safe to Achieve Such Low LDL-C Levels?

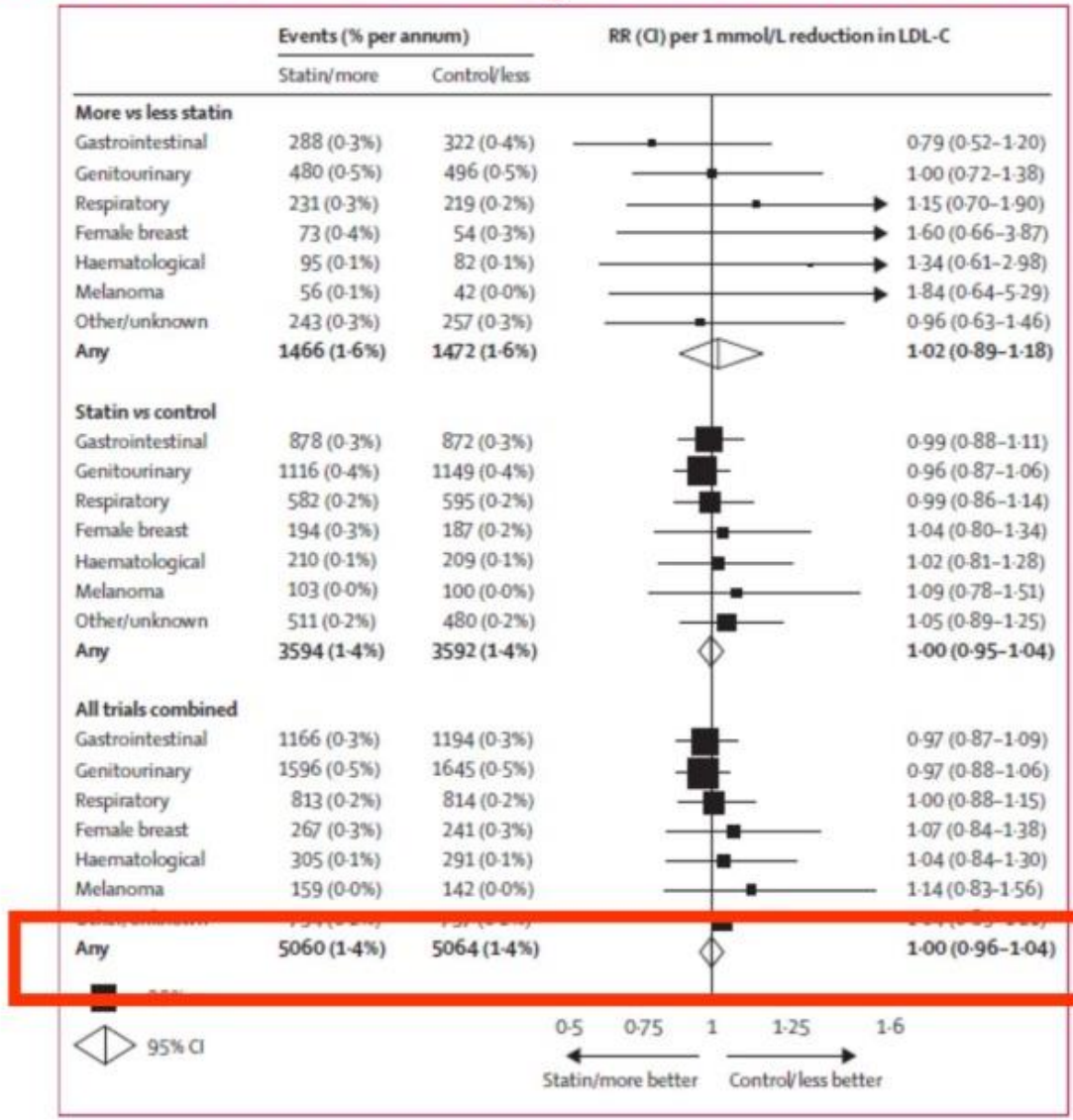


An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Wiviott SD et al. *J Am Coll Cardiol.* 2005;46:1411-1416.

NATIONAL LIPID ASSOCIATION

Cancer Incidence per 1 mM/L LDL Reduction in CTT Cycle #2 Metanalysis



CTT Collaborators
Lancet 2010;
376-1670-81

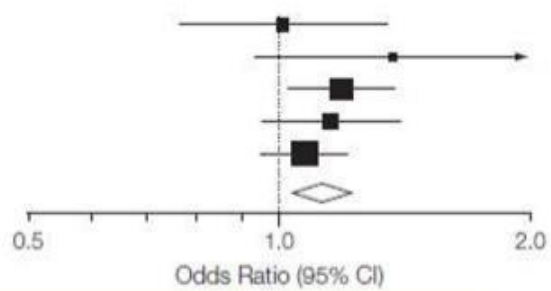
NATIONAL LIPID ASSOCIATION

Risk of Incident Diabetes With Intensive-Dose Compared With Moderate-Dose Statin Therapy

A Meta-analysis

- 5 statin trials: 32752 without baseline DM
- 8.4% new DM: 1449 (intensive) vs 1300 (moderate statin)
- +2.0 cases per 1000 patient-years with intensive statin

Incident Diabetes	Cases/Total, No. (%)		OR (95% CI)
	Intensive Dose	Moderate Dose	
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: $I^2 = 0\%$; $P = .60$			



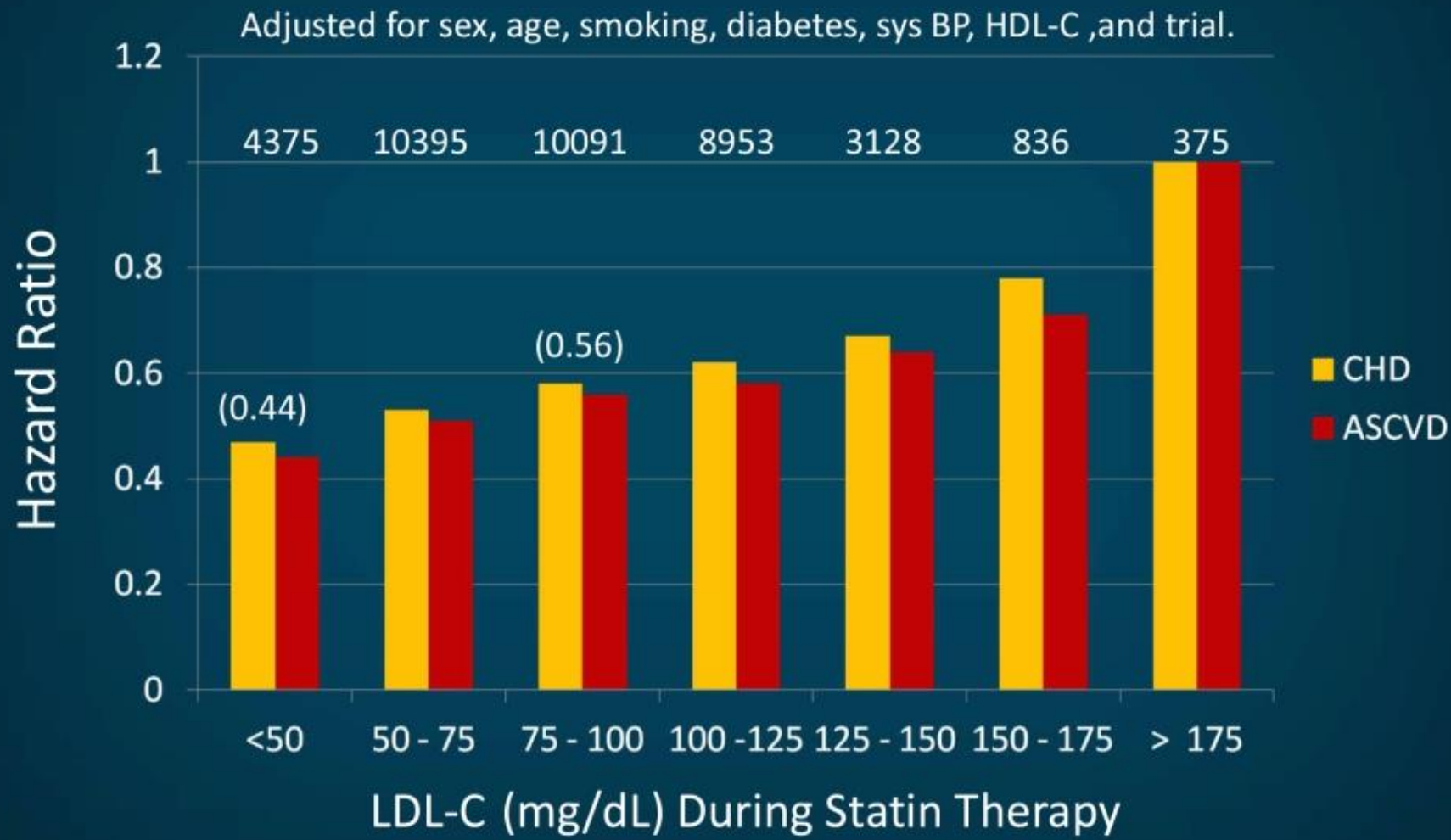
NNH for new DM 498; NNT 155 for CV events

Preiss D et al. *JAMA*. 2011;305:2556-64.

NATIONAL LIPID ASSOCIATION

LDL-C: Residual Risk on Statins

N = 38,253 from 14 DBRCTs



Boekholdt et al. *JACC.* 2014;64(5):485-494.

NATIONAL LIPID ASSOCIATION

Study Design

IMPROVE-IT

N=18,144

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

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

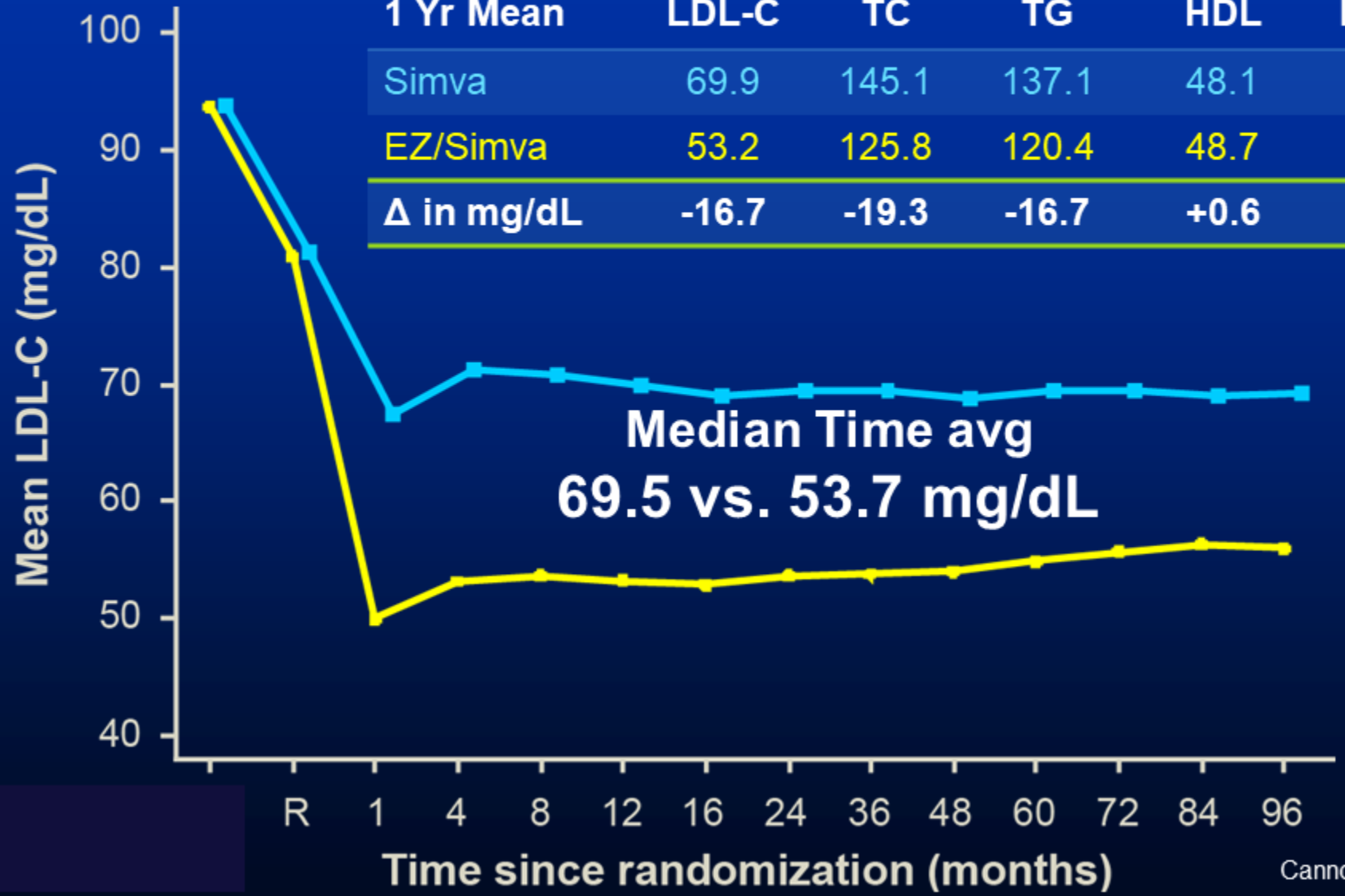
TIMI

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

LDL-C and Lipid Changes

IMPROVE-IT

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5



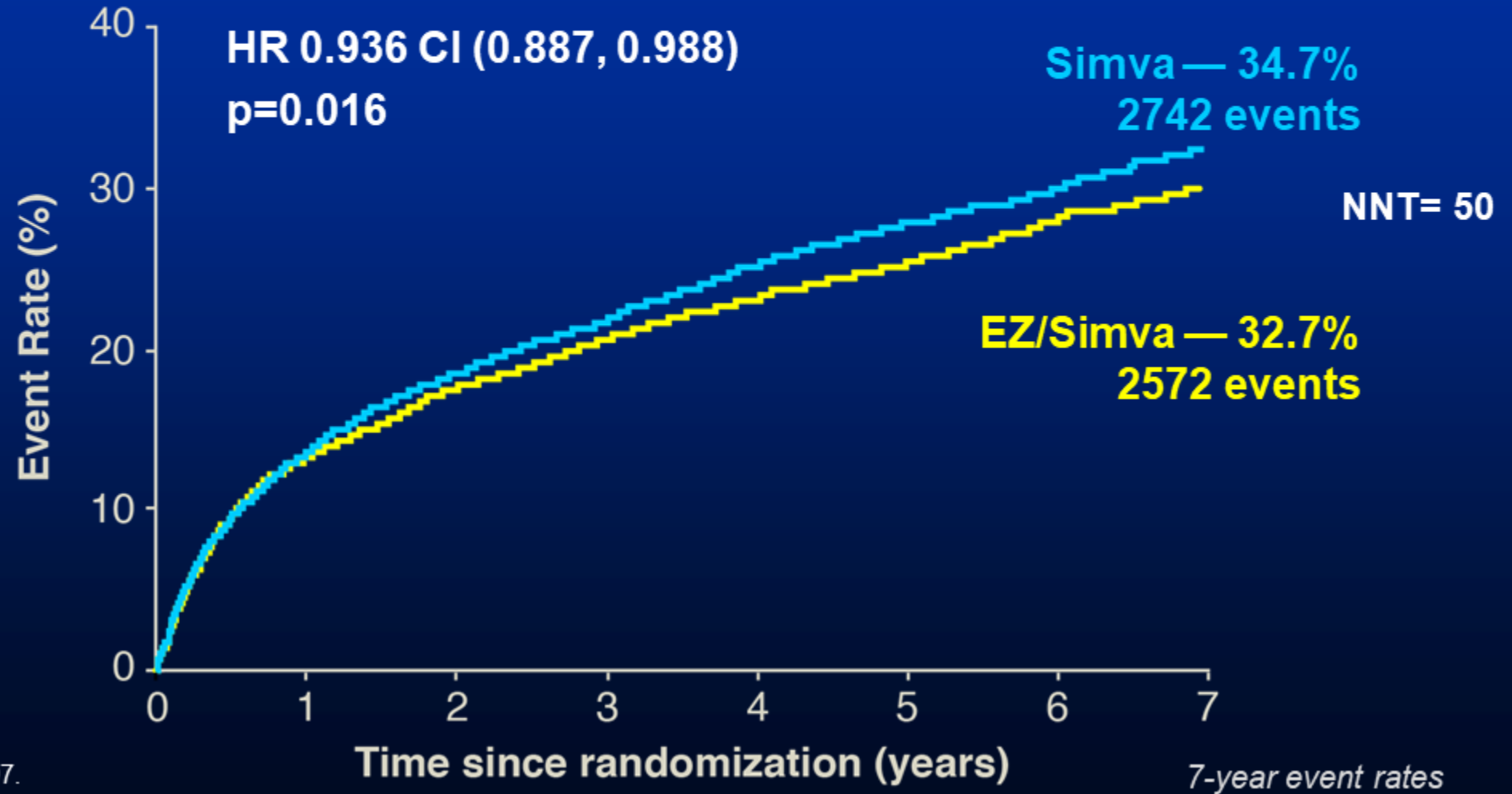
TIMI

Cannon CP, NEJM 2015;372:2387-97

Primary Endpoint — ITT

IMPROVE-IT

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

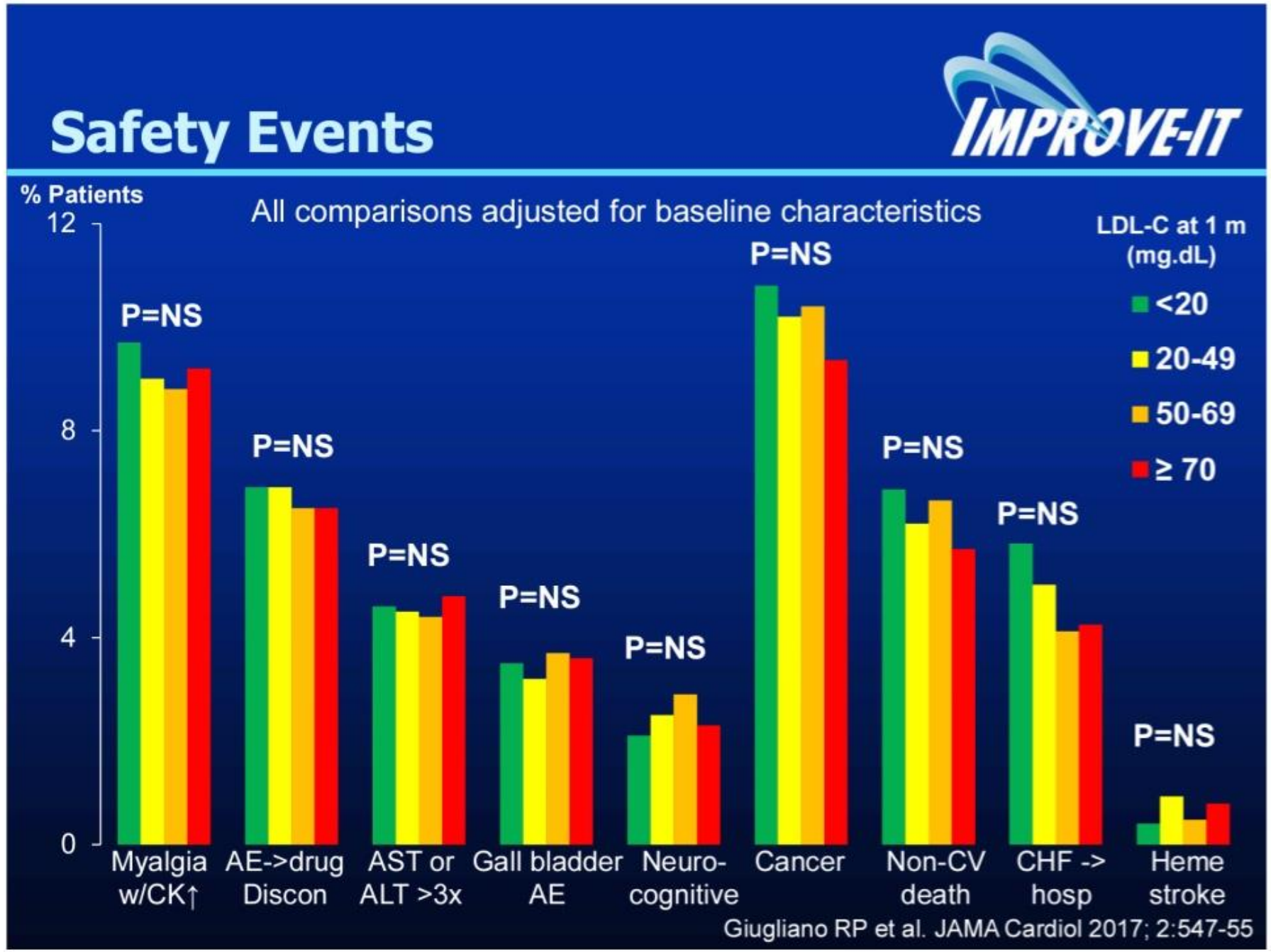


Cannon NEJM 2015;372:2387-97.

7-year event rates

TIMI

Safety Events

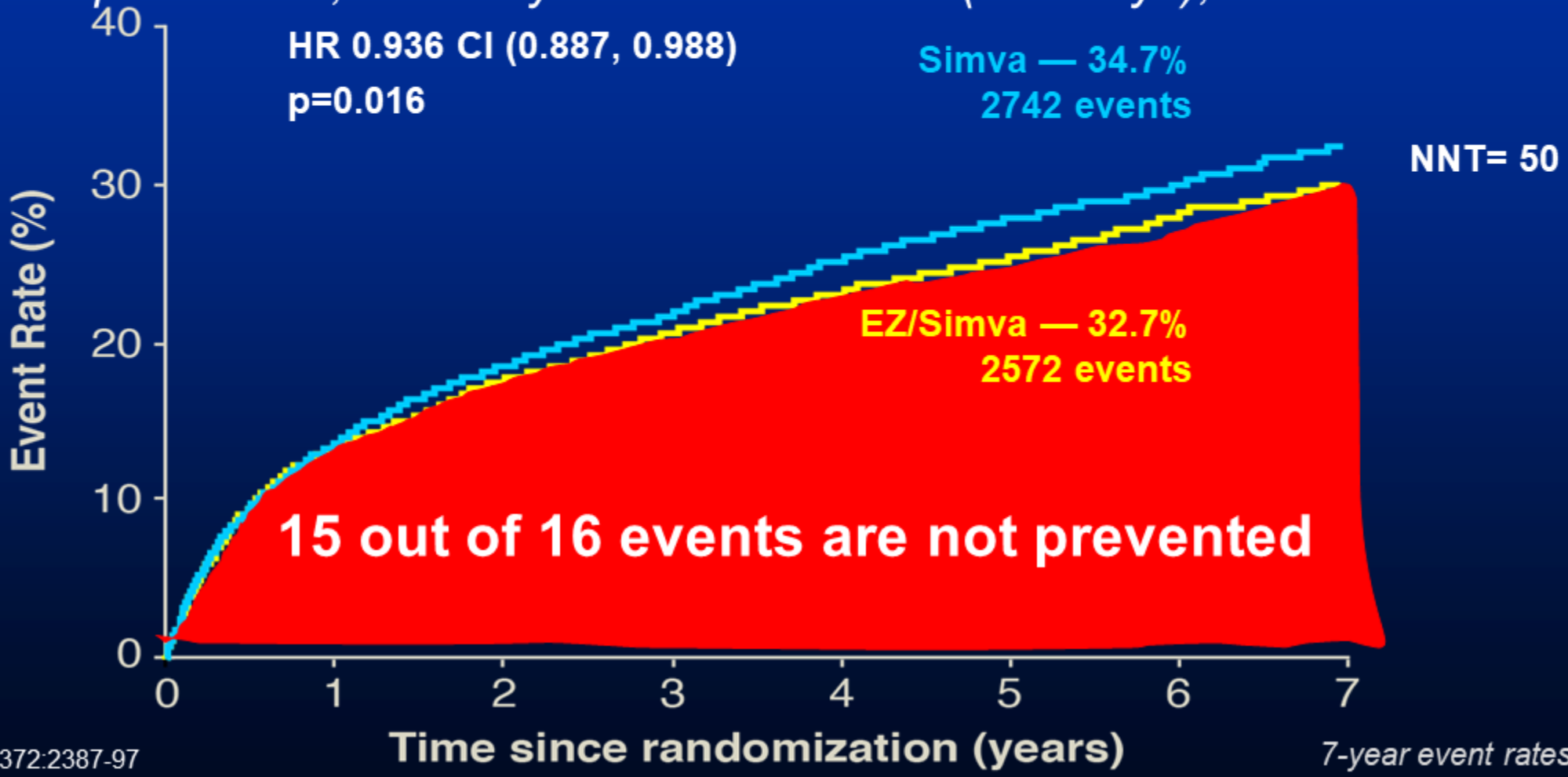


NATIONAL LIPID ASSOCIATION

Primary Endpoint — ITT

IMPROVE-IT

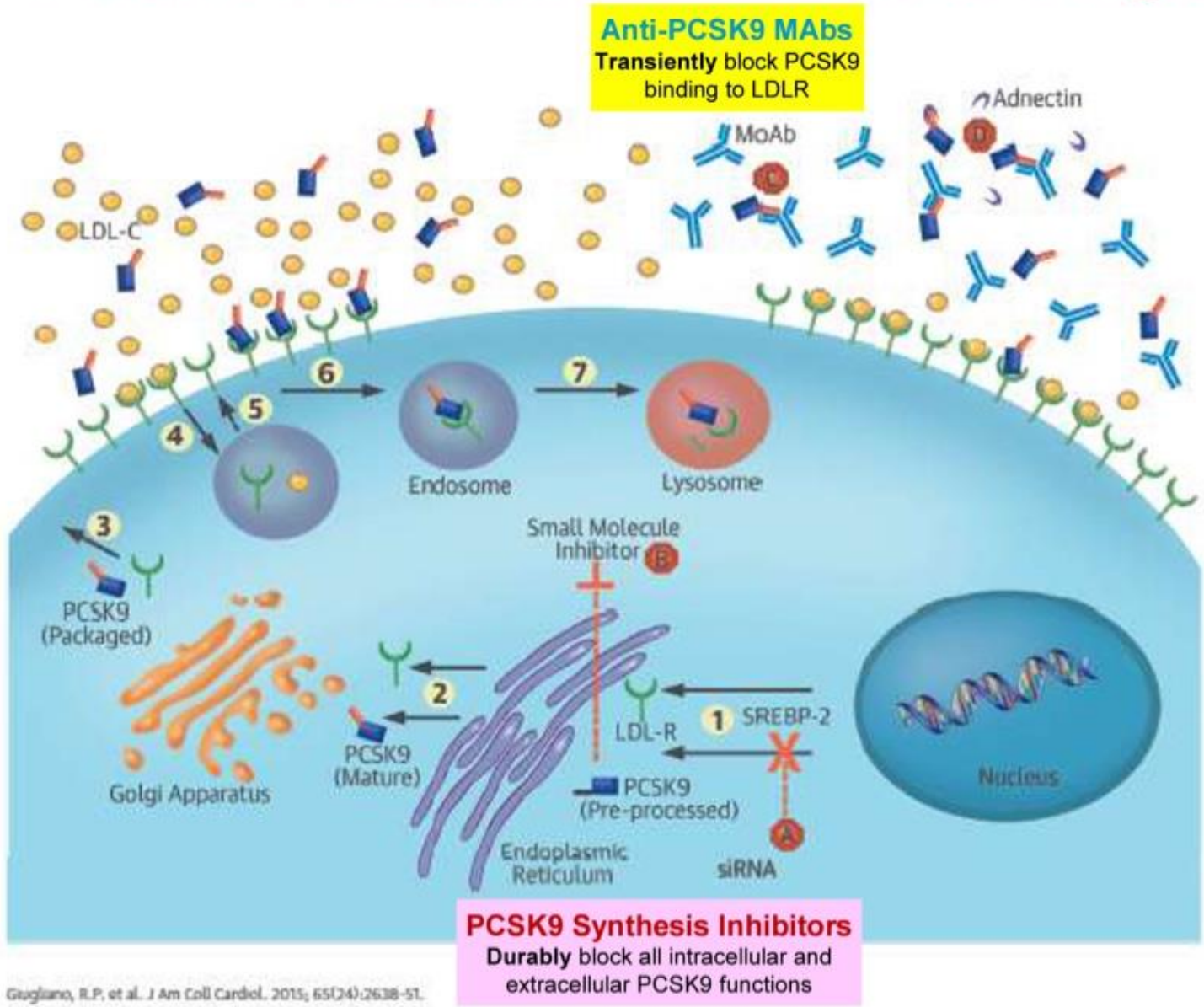
Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



Cannon CP, NEJM 2015;372:2387-97

7-year event rates

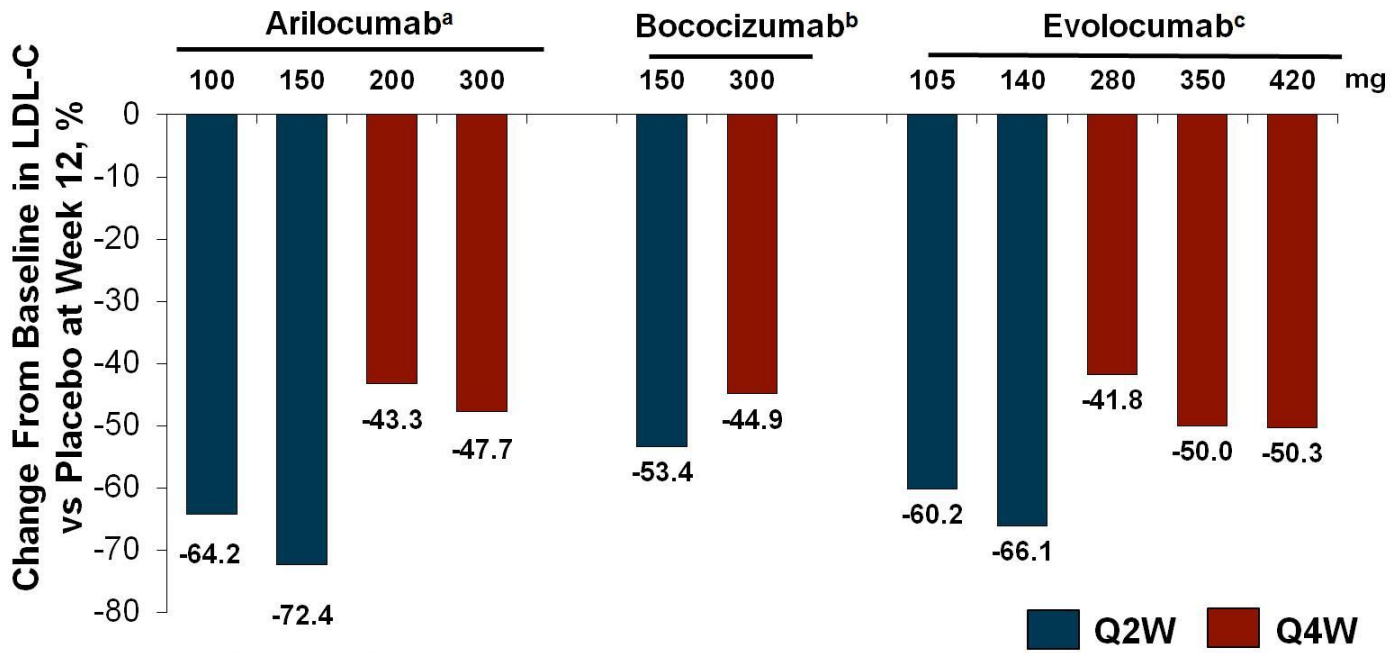
PCSK9 Function and Potential Targets



Giugliano, R.P. et al. J Am Coll Cardiol. 2015; 65(24):2638-51.

NATIONAL LIPID ASSOCIATION

PCSK9 Inhibition in Patients With Hypercholesterolemia Receiving Statin Therapy

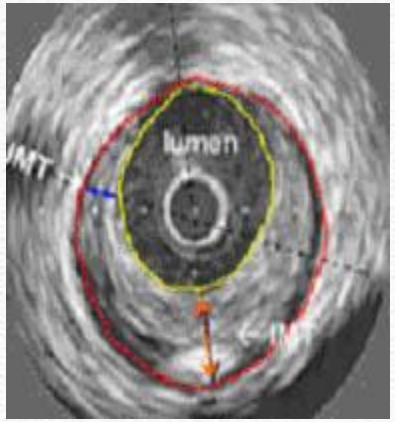


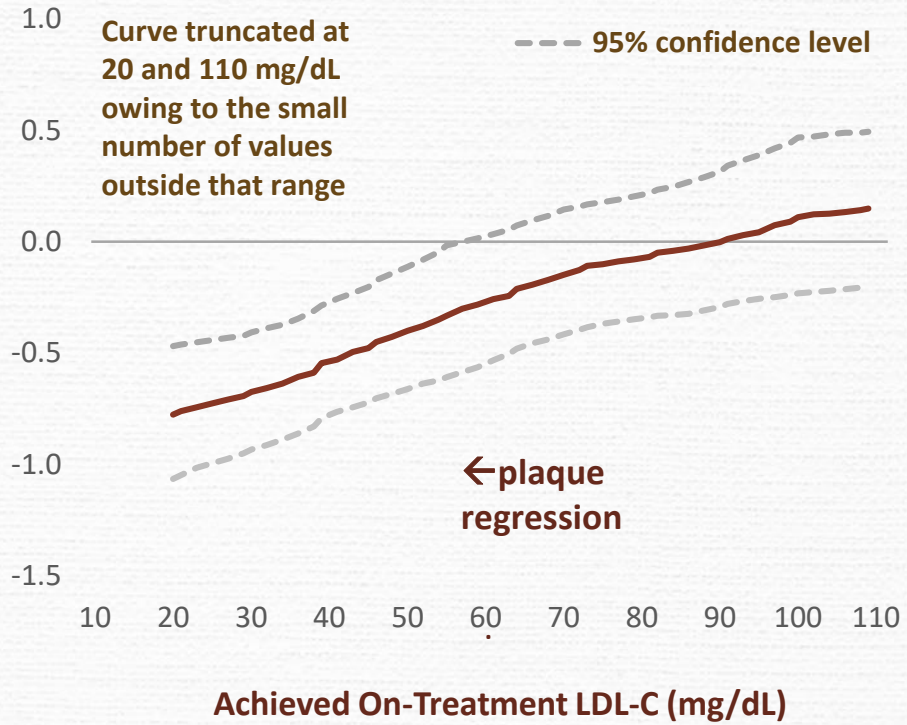
P < .0001 for each comparison.

a. McKenney JM, et al. *J Am Coll Cardiol*. 2012;59:2344-2353[9] b. Ballantyne CM, et al. *J Am Coll Cardiol*. 2014;63:A1374[10]; c. Giugliano RP, et al. *Lancet*. 2012;380:2007-2017.[11]

GLAGOV: Mean On-Treatment LDL-C vs. Change in Percent Atheroma Volume

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





Patients with angiographic CAD were randomized to receive monthly evolocumab (420 mg) (n=484) or placebo (n=484) SQ for 76 weeks, in addition to statins

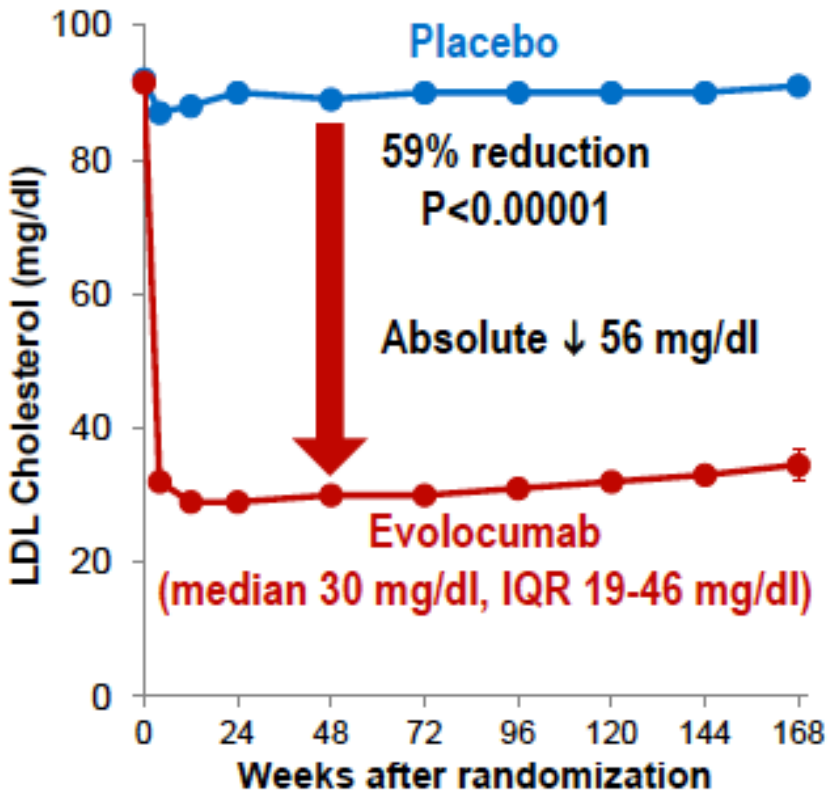
Locally weighted polynomial regression (LOESS) plot demonstrates a linear continuous relationship between achieved LDL-C level and PAV progression/ regression for levels of LDL-C ranging from 110 mg/dL to as low as 20 mg/dL

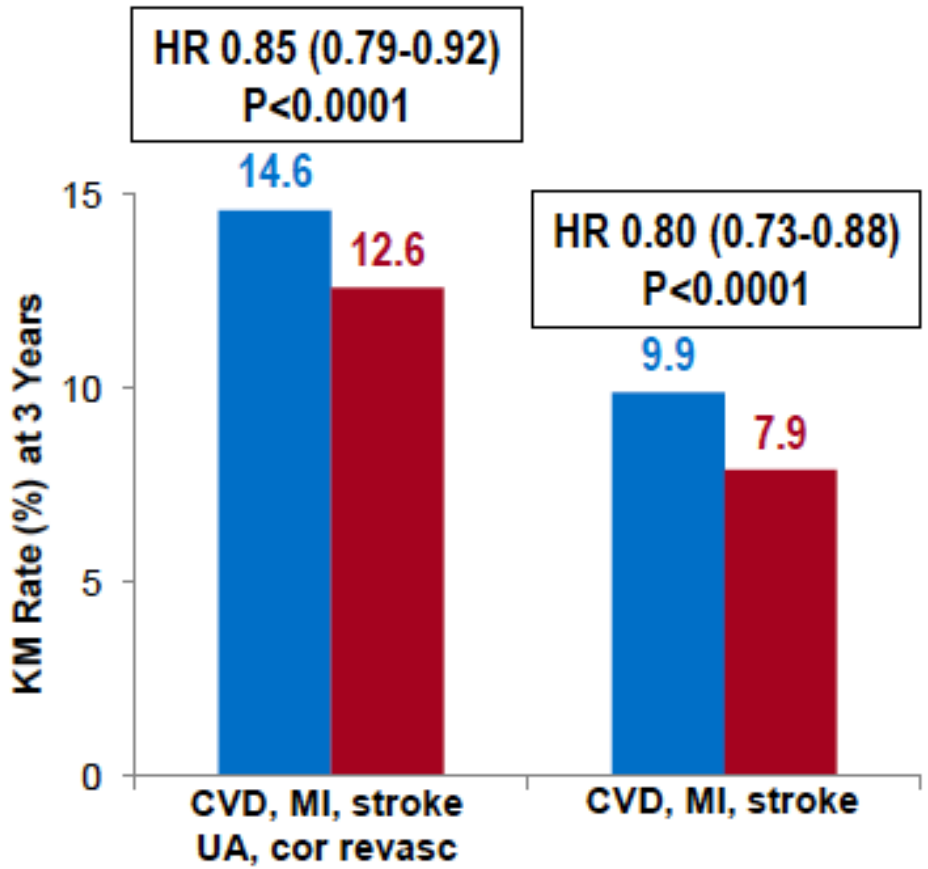
Abbreviations: CAD, coronary artery disease; GLAGOV, Global Assessment of Plaque Regression With a PCSK9 Antibody ;LDL-C, low-density lipoprotein cholesterol; SQ, subcutaneous.

Nicholls SJ. *JAMA*. 2016;316(22):2373-2384.

Summary of Effects of PCSK9i Evolocumab

- 27,564 pts w/ stable ASCVD & LDL-C ≥70mg/dL on a statin
- ↓ LDL-C by 59% down to a median of 30 mg/dl
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated





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

Safety

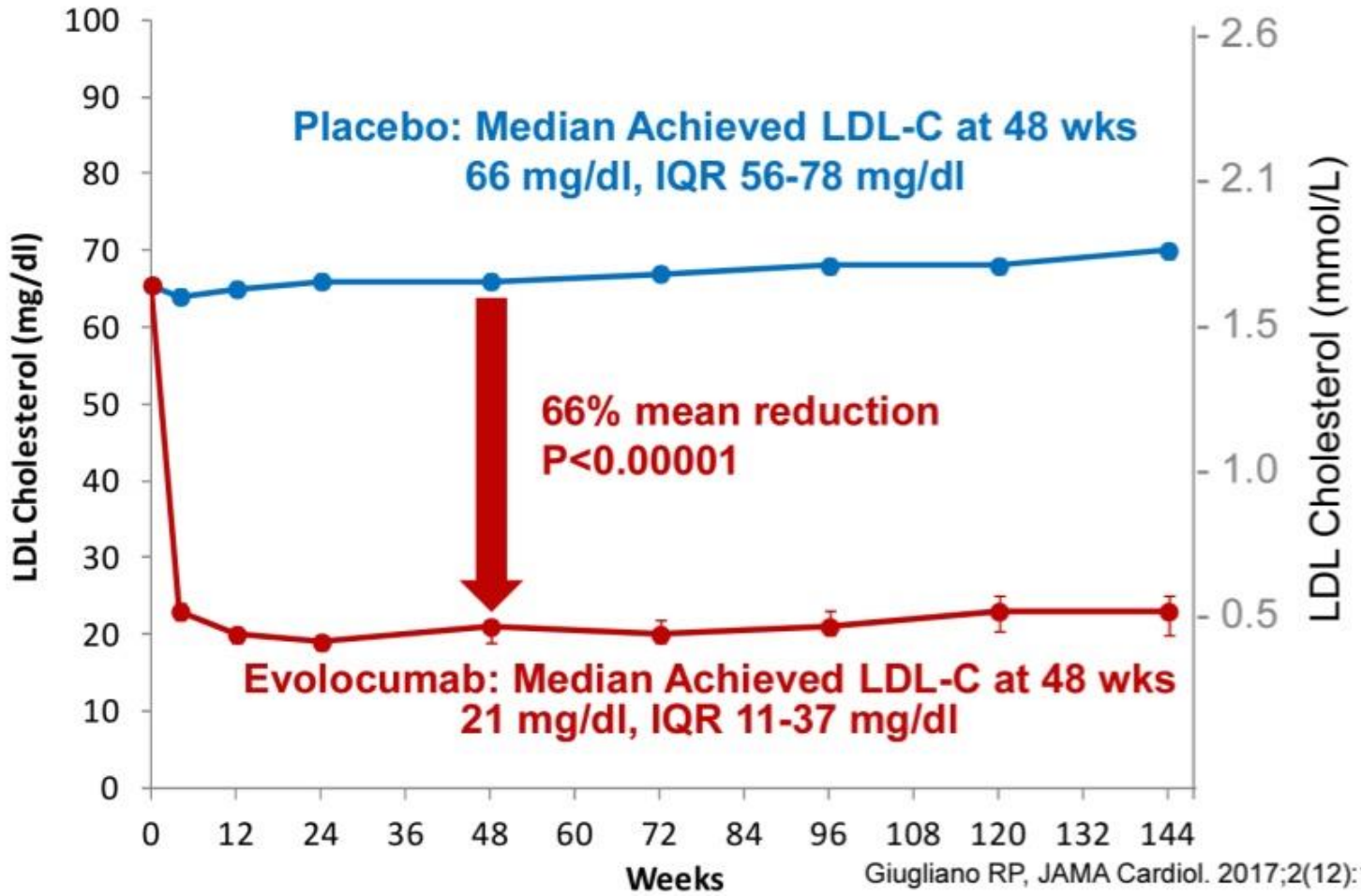
Adverse events (%)	Evolocumab (N=13,769)	Placebo (N=13,756)
Any	77.4	77.4
Serious	24.8	24.7
Allergic reaction	3.1	2.9
Injection-site reaction	**2.1**	**1.6**
Treatment-related & led to d/c of study drug	1.6	1.5
Binding Ab	0.3	n/a
Neutralizing Ab	*none*	n/a
Muscle-related	5.0	4.8
Rhabdomyolysis	0.1	0.1
Cataract	1.7	1.8
Diabetes (new-onset)	8.1	7.7
Neurocognitive	1.6	1.5
Laboratory results (%)		
Aminotransferase >3× ULN	1.8	1.8
Creatine kinase >5× ULN	0.7	0.7

New-onset diabetes assessed in patients without diabetes at baseline; adj by CEC. No significant interactions between baseline LDL-C, evolocumab, and the rates of adverse events.

Sabatine MS et al. *New Engl J Med* 2017;376:1713-22.

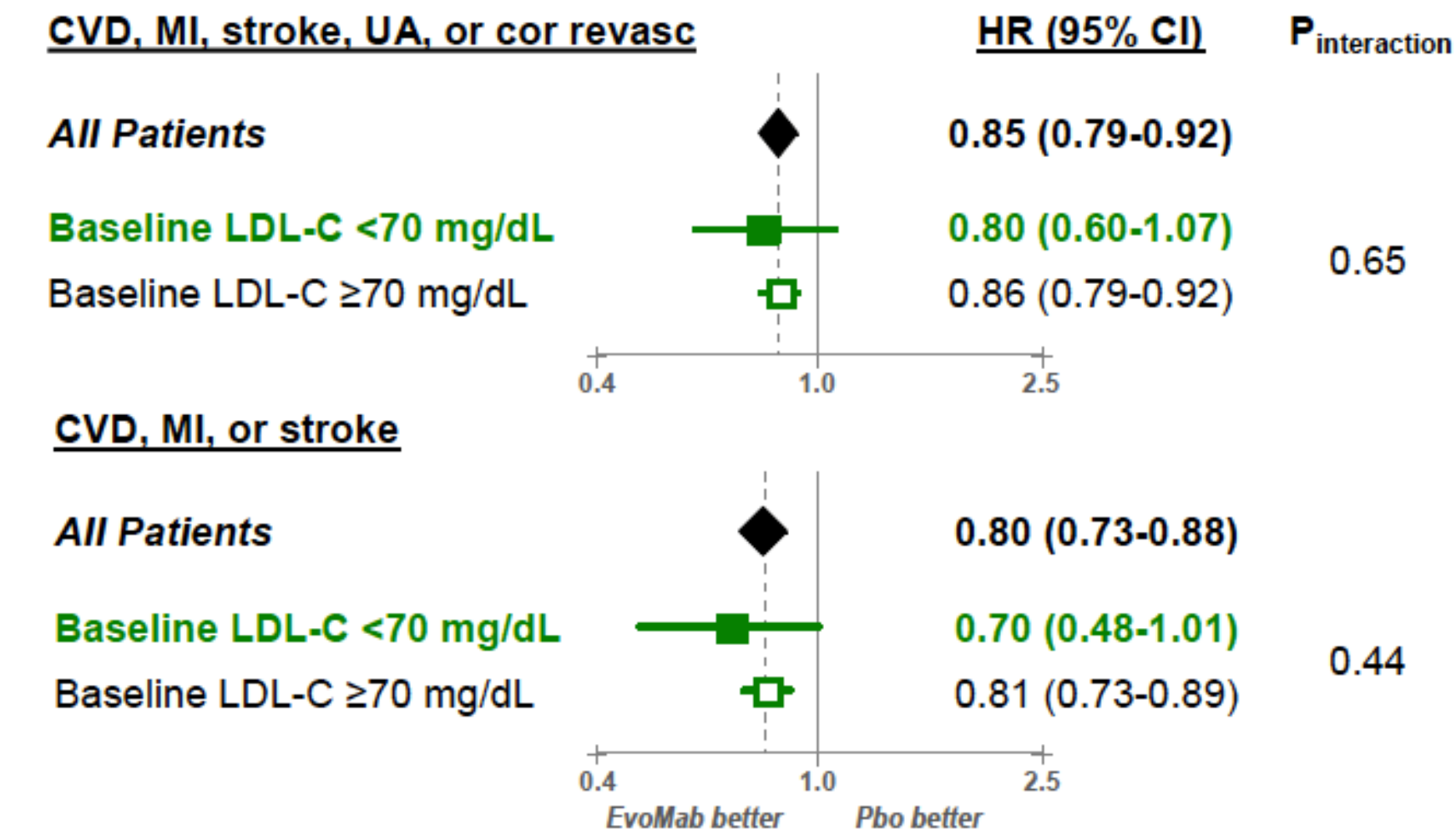
Outcomes in Patients with Low Baseline LDL-C

2034 Pts with Baseline LDL-C <70 mg/dL



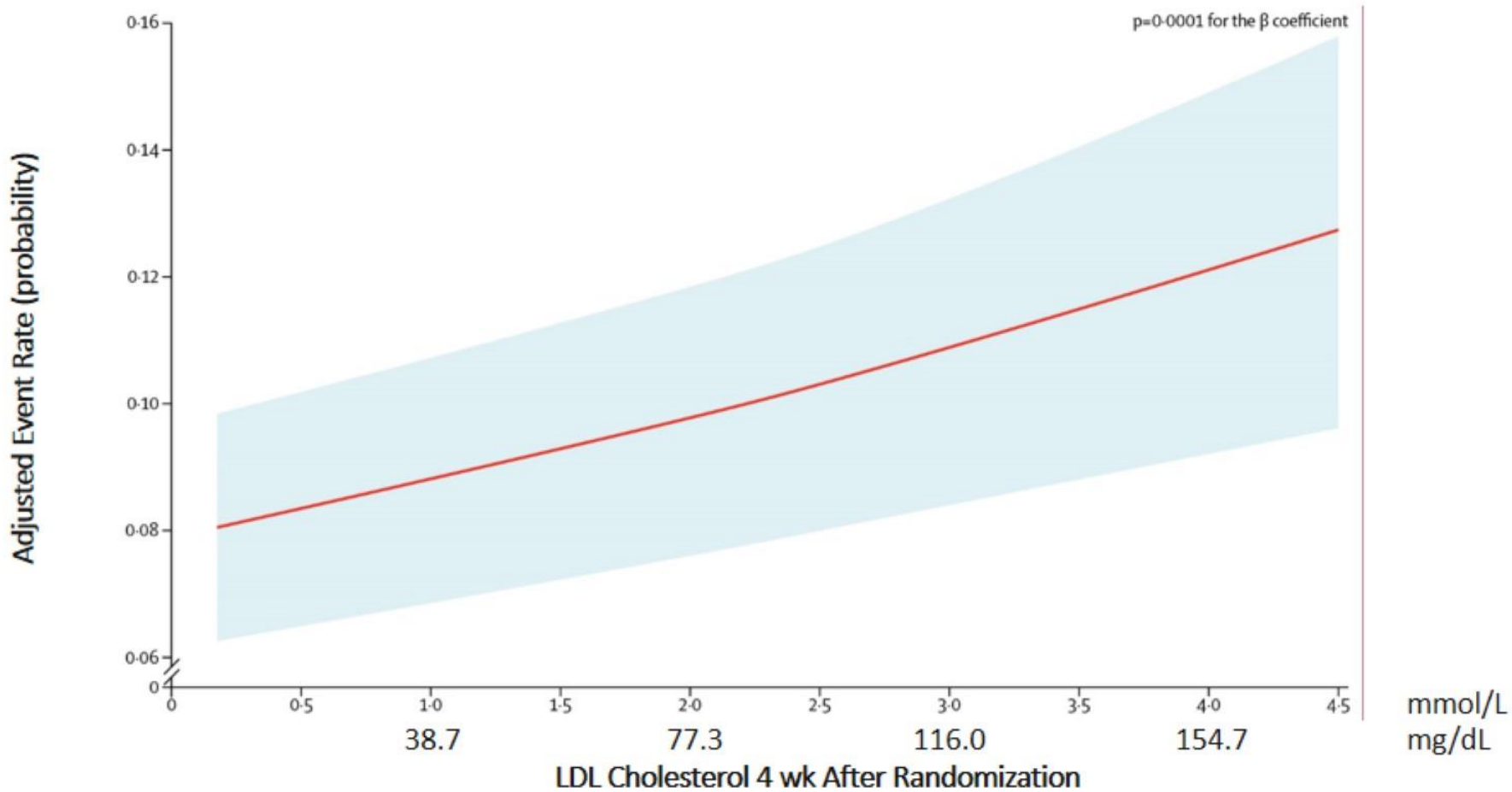
Giugliano RP, JAMA Cardiol. 2017;2(12):1385-91

Clinical Outcomes
by Baseline LDL-C



Giugliano RP et al. and Sabatine MS. *JAMA Cardiol* 2017;2:1385-91

FOURIER: Lower CV Event Rates With Lower LDL-C Levels, as Low as 20 mg/dL (~0.5 mmol/L)



*Relationship between the achieved LDL-C concentration at 4 weeks and the risk of CV death, MI, or stroke. Reprinted from *Lancet*, 390 Giugliano RP et al, Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. 1962-1971, Copyright 2017, with permission from Elsevier

Safety

In patients with baseline LDL-C< 70 mg/dL

No significant interactions between baseline LDL-C, evolocumab, and the rates of adverse events.

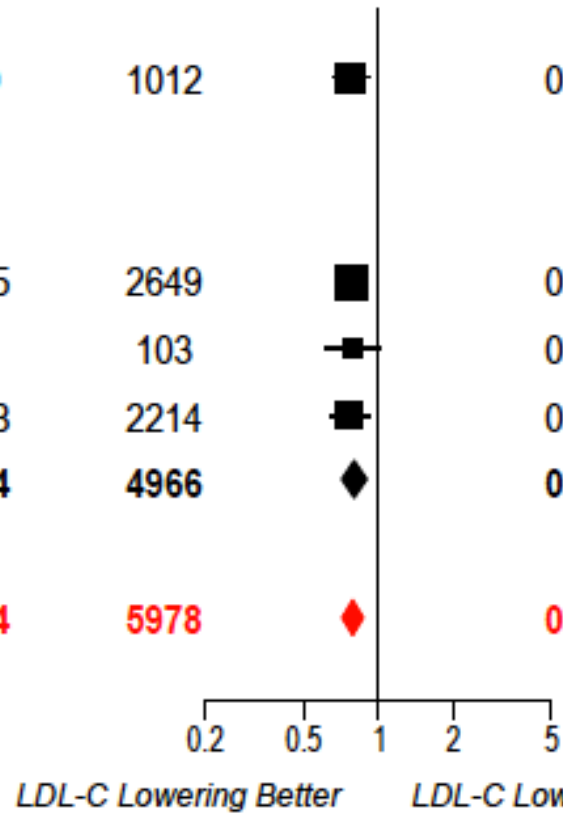
	Evolocumab (N=1030)	Placebo (N=1003)
Adverse events (%)		
Any	79.7	77.9
Serious	26.0	27.3
Allergic reaction	3.8	3.3
Injection-site reaction	2.9	1.6
Treatment-related and led to study drug d/c	1.8	1.9
Muscle-related	4.8	6.0
Cataract	1.8	1.6
Diabetes (new-onset)	8.8	11.2
Neurocognitive	1.7	1.2
Laboratory results (%)		
ALT or AST >3× ULN	2.7	2.3
CK >5× ULN	0.9	0.9

New-onset diabetes assessed in patients without diabetes at baseline

Giugliano RP, JAMA Card 2017;2:1385-91

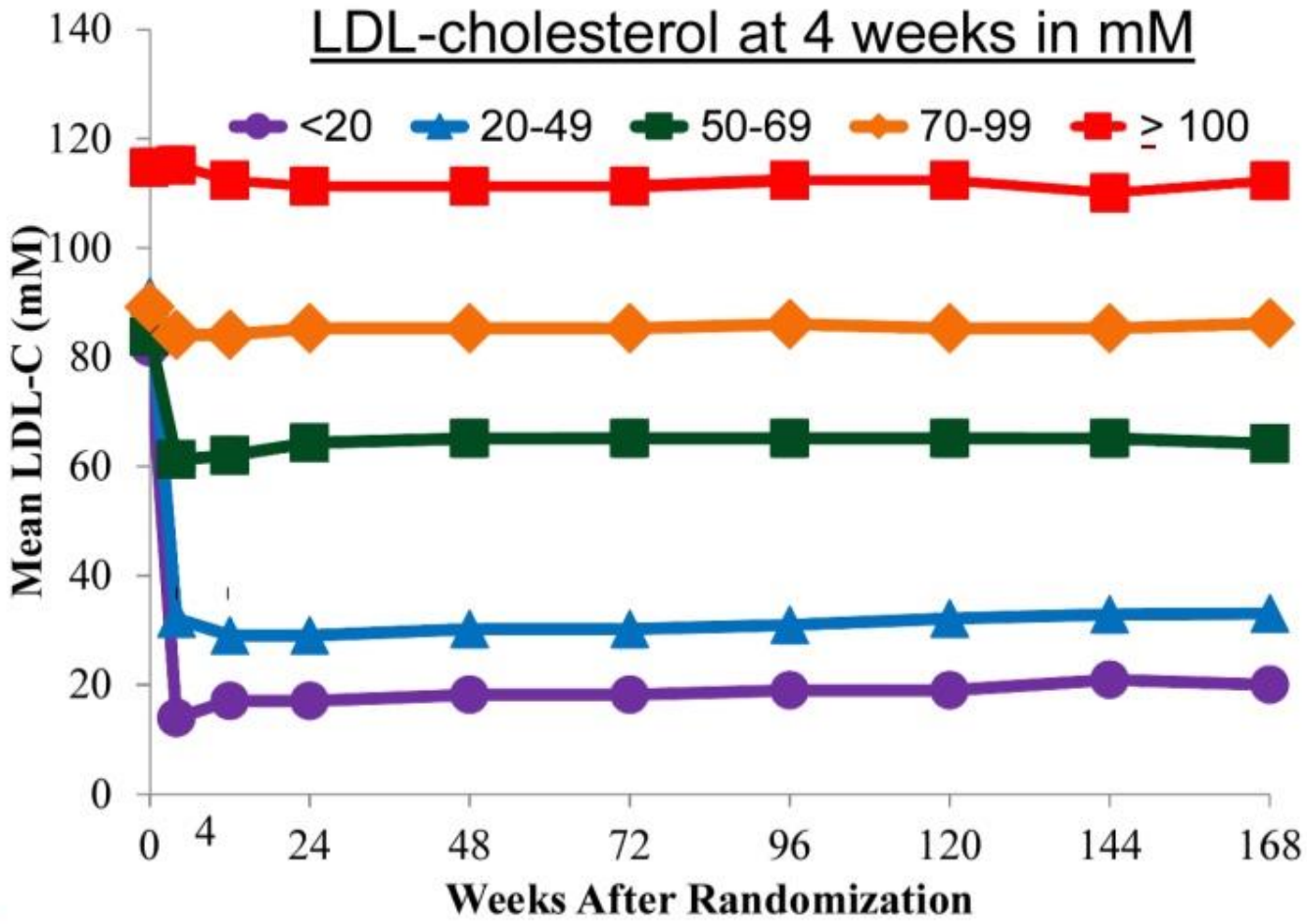
Efficacy of LDL-C Lowering Even When LDL-C ≤70 mg/dL (1.8 mM)

Trial	Starting LDL-C (mg/dl)	Events Expt Arm	Events Ctrl Arm	Major Vascular Events RR (95% CI) per 1 mM ↓ in LDL-C	
Statins					
CTTC <2 mmol/L subgp	66	910	1012	0.78 (0.65-0.94)	
Non-statin LDL-C Lowering					
IMPROVE-IT	70	2455	2649	0.79 (0.67-0.93)	
FOURIER <1.8 mmol/L subgp	66	81	103	0.80 (0.61-1.04)	
REVEAL	63	2068	2214	0.77 (0.63-0.96)	
Summary		**4604**	**4966**	**0.79 (0.70-0.88)**	**P=0.00005**
OVERALL SUMMARY		**5514**	**5978**	**0.79 (0.71-0.87)**	**P=0.000001**



Sabatine MS et al. *JAMA Cardiol* 2018;epub ahead of print

LDL-C Over Time

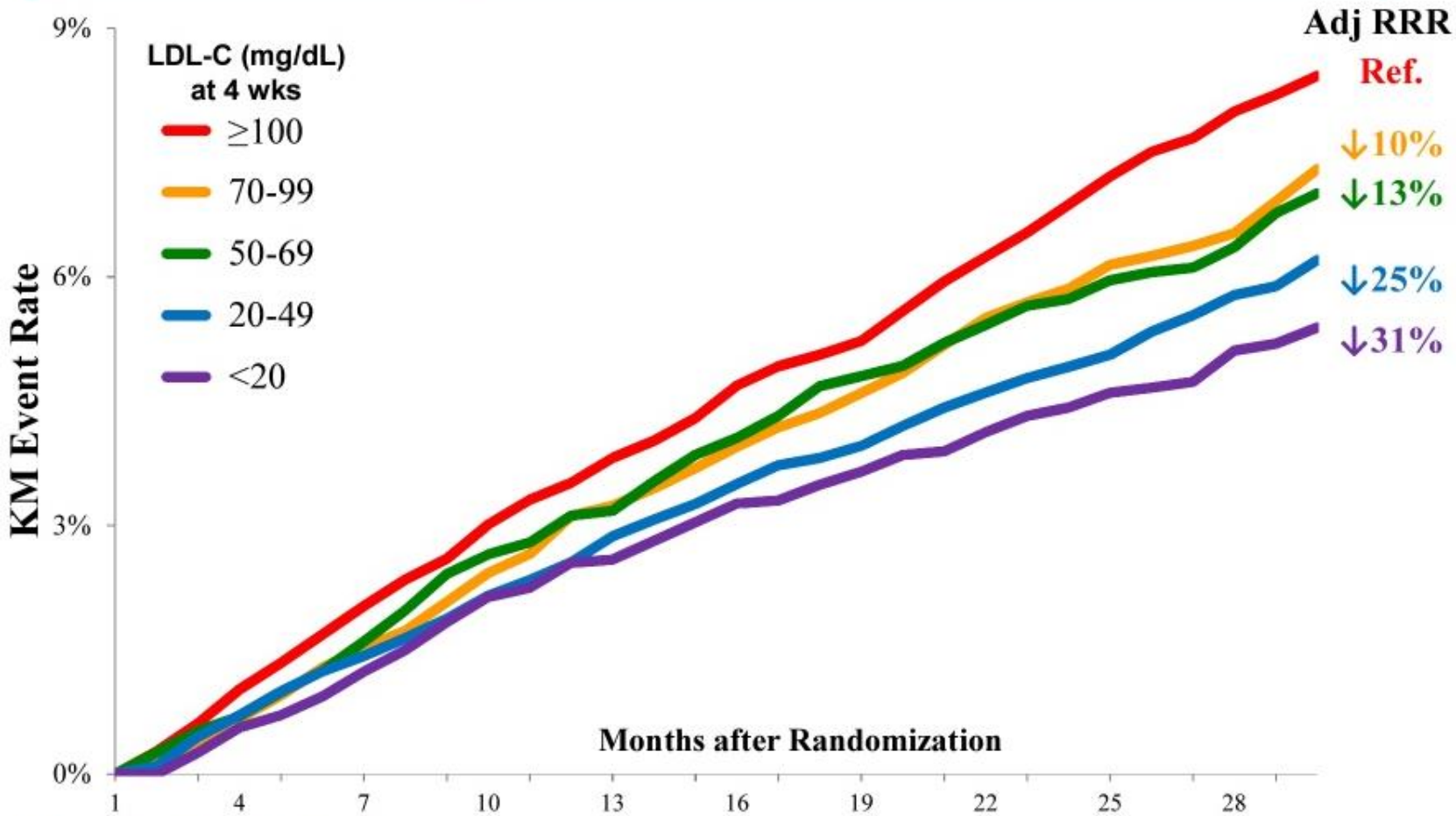


An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

. Giugliano RP, Lancet. 2017;390(10106):1962-71

NATIONAL LIPID ASSOCIATION

CV Death, MI or Stroke by Achieved LDL-C at Month 1



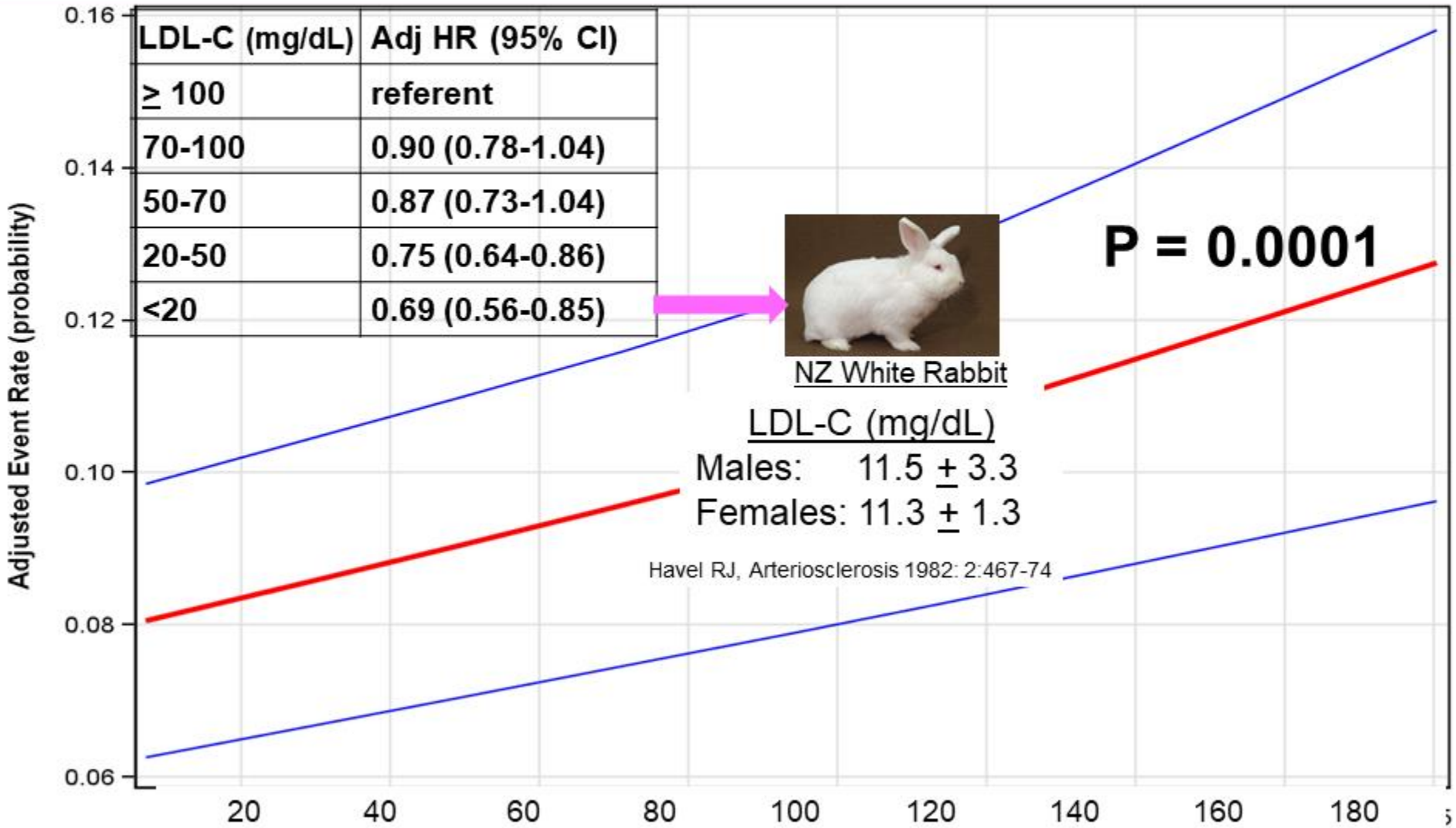
An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Giugliano RP et al, Lancet 2017;390:1962-71)

NATIONAL LIPID ASSOCIATION

CV Death, MI, or Stroke

LDL-C (mg/dL)	Adj HR (95% CI)
≥ 100	referent
70-100	0.90 (0.78-1.04)
50-70	0.87 (0.73-1.04)
20-50	0.75 (0.64-0.86)
<20	0.69 (0.56-0.85)



Giugliano RP et al. Lancet. 2017;390:1962-71.

EVOPACS: Study Design (Evolocumab at Time of ACS)

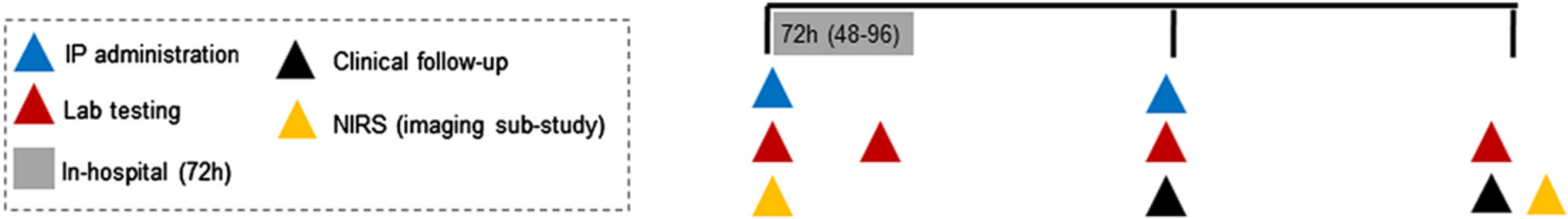
Patients with ACS (n = 308)

- *ACS (NSTEMI / UA <72h, STEMI <24h)*
- *LDL-C ≥1.8 mmol/L (or non-HDL-C ≥2.6 mmol/L) in patients previously on stable treatment with high-intensity statin **OR***
  - *LDL-C ≥2.3 mmol/L (or non-HDL-C ≥3.1 mmol/L) in patients previously on stable treatment with low- or moderate-intensity statin **OR***
  - *LDL-C ≥3.2 mmol/L (or non-HDL-C ≥4.0 mmol/L) in statin-naïve patients or patients not on stable statin regimen*

Randomization 1:1

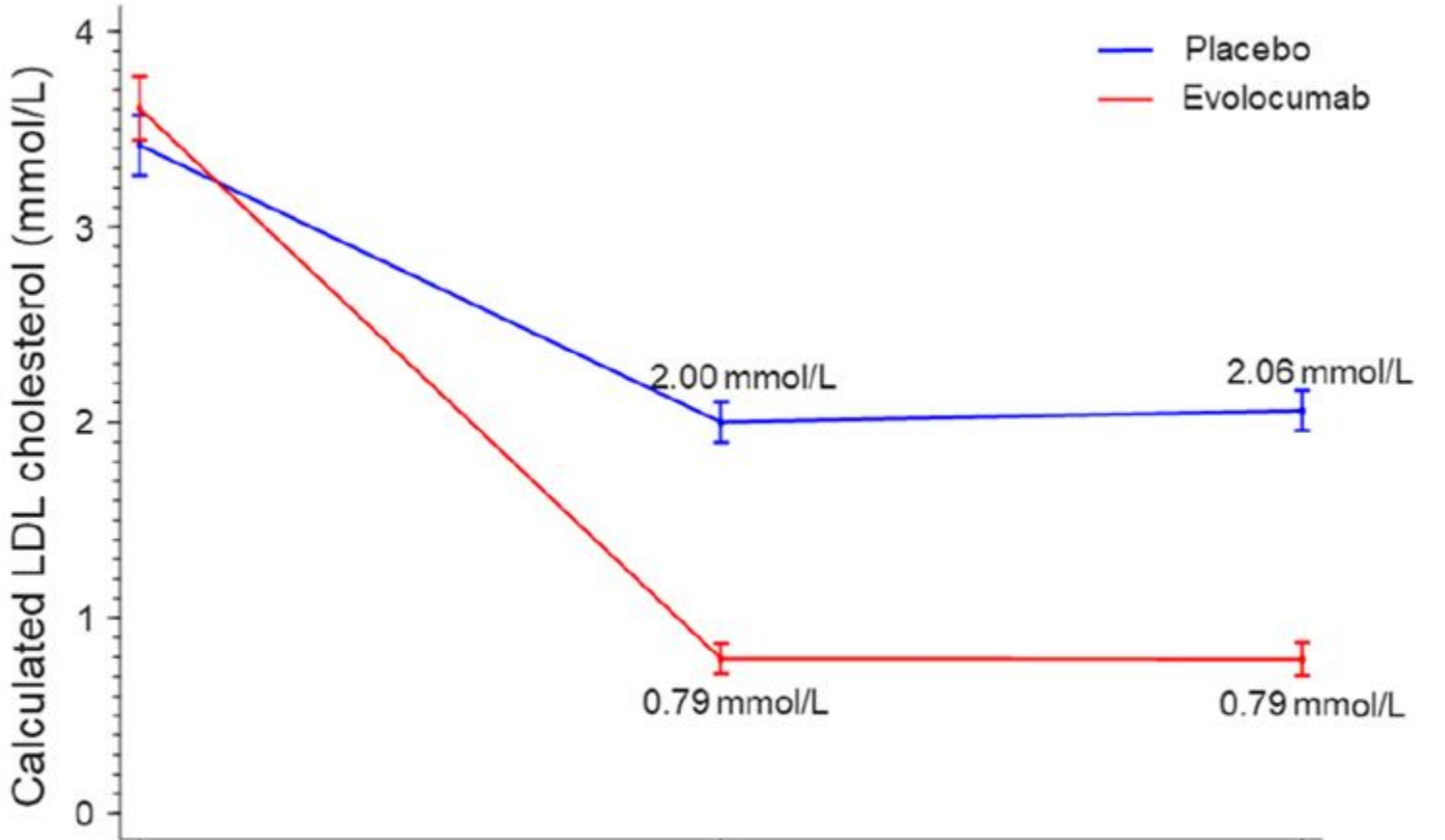
- Evolocumab SC 420mg + Atorvastatin 40mg QD
- Placebo SC + Atorvastatin 40mg QD

End of study



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

EVOPACS: Changes in LDL-C over 8 Weeks



80 mg/dL

31 mg/dL

No. of patients			
Placebo	148	144	149
Evolocumab	146	136	141
Absolute difference (mmol/L)		1.34	1.43
Percentage difference		38.4%	40.7%
P value		<0.001	<0.001

Koskinas KC, JACC 2019
Aug 16 ahead of print.

Presentation of Case

- EH is a 62 yo Caucasian male with a 8 yr history of multivessel CAD.
- Atherosclerotic plaques diffusely distributed in LAD, circumflex, and RCA.
- Well controlled HTN on metoprolol XL 100 mg po qd and ramipril 20 mg po qd.
- Stage 3 CKD with eGFR of 53 ml/min. No albuminuria.
- He is not diabetic and does not have metabolic syndrome.
- Experienced first MI 5 yrs ago along inferior wall, underwent stenting of mid RCA lesion.
- Sustained a STEMI due to a proximal LAD lesion. Presented to ER within minutes of symptom onset and rapid deployment of DES resulted in excellent myocardial salvage. He does not have heart failure.
- Lipid profile prior to anterior wall MI: LDL-C 72 mg/dL, triglycerides 87 mg/dL, HDL-C 58 mg/dL, and non-HDL-C is 82 mg/dL on Rosuvastatin 40 mg/dL and Ezetimibe 10 mg .

NATIONAL LIPID ASSOCIATION

Audience Question:
What LDL-C-Lowering Therapy Would You Recommend?

1) None

2) PCSK9 inhibitor

NATIONAL LIPID ASSOCIATION

Audience Question:

If you recommend a PCSK9 inhibitor,
at what timepoint would you recommend therapy?

1) **Prior to hospital discharge**

2) **1 month**

3) **3 months**

4) **6 months**

5) **12 months**

NATIONAL LIPID ASSOCIATION

Presentation of Case

- Subsequent to the anterior wall MI, the rosuvastatin and ezetimibe were supplemented by 140 mg of evolocumab, every 2 weeks, prior to hospital discharge.
- On follow-up lipid profile revealed an extremely robust, outsized response to the PCSK9 monoclonal antibody therapy. LDL-C was 14 mg/dL, HDL-C was 62 mg/dL, non-HDL-C was 27 mg/dL, and triglycerides were 79 mg/dL.
- The patient is a professor at the Harvard Medical School. He was alarmed by how low his atherogenic lipoprotein burden had become. He had read on the internet that such low LDL-C increased his risk for dementia and hemorrhagic stroke, both of which would interfere with his ability to continue to engage in profound thought. He also did not want to become diabetic!
- He wanted answers!

NATIONAL LIPID ASSOCIATION

QUESTIONS

- Why did you drive my LDL-C so low?

- What is the evidence for this?

NATIONAL LIPID ASSOCIATION

QUESTIONS

- Why did you drive my LDL-C so low?

Recent clinical trials clearly demonstrate that when it comes to LDL-C, LOWER IS BETTER AND LOWEST IS BEST when it comes to ASCVD risk reduction.

- What is the evidence for this?

NATIONAL LIPID ASSOCIATION

Very High-Risk ASCVD

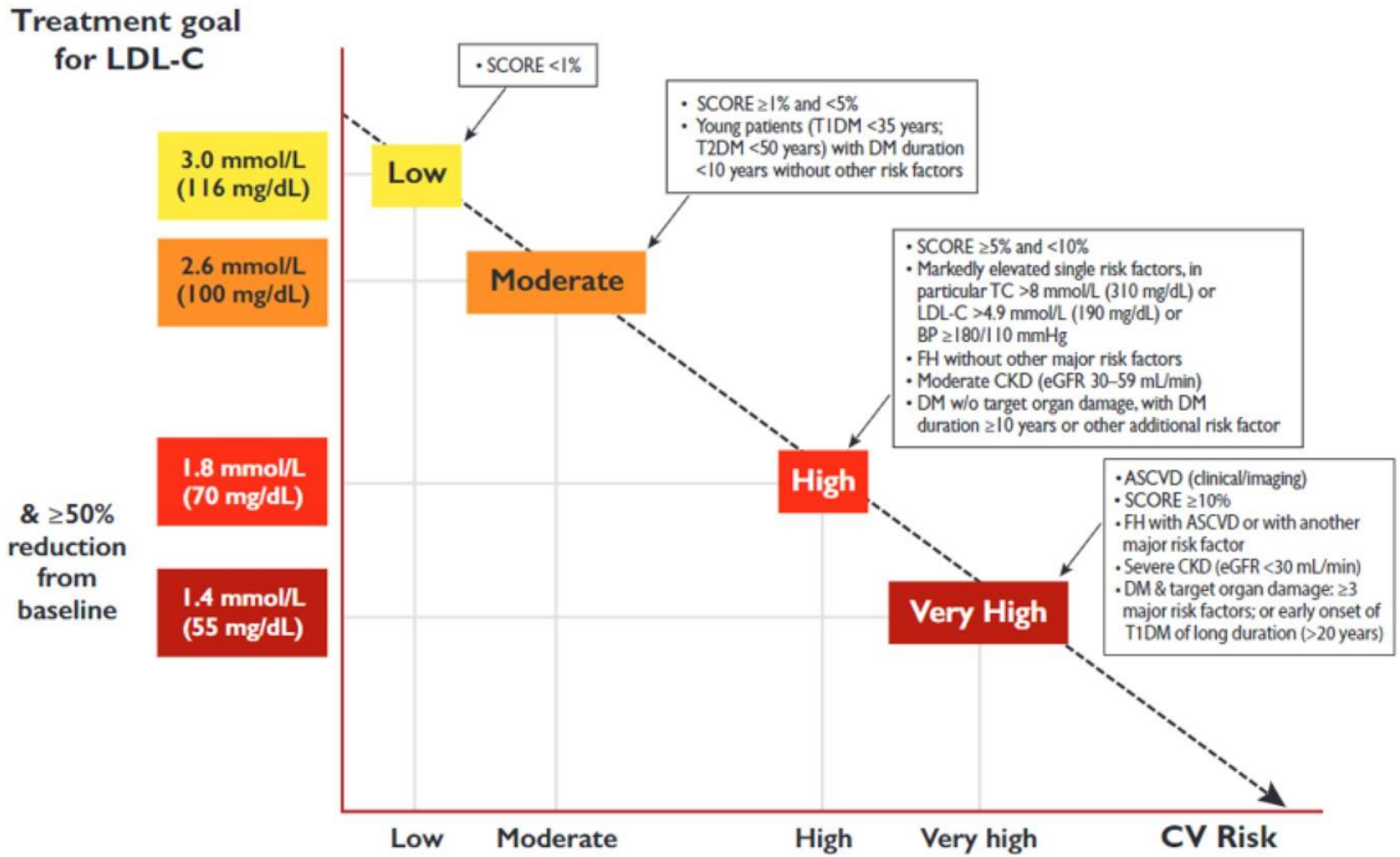
In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy.

- Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.
- In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L).
- In patients at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost- effectiveness is low at mid-2018 list prices.

Grundy S et al. Circulation. 2019;139:e1046-1081.

LDL-C Treatment Goals Per Total ASCVD Risk Categories

ESC
European Society of Cardiology



Mach F, et al. *Eur Heart J*. 2019;00:178. By permission of Oxford University Press.

2019 ESC/EAS Guidelines
New Lipid Targets and Goals

ESC
European Society of Cardiology

Patients with established ASCVD with recurrent event(s) (can be different from first event), while taking maximally tolerated statin therapy:

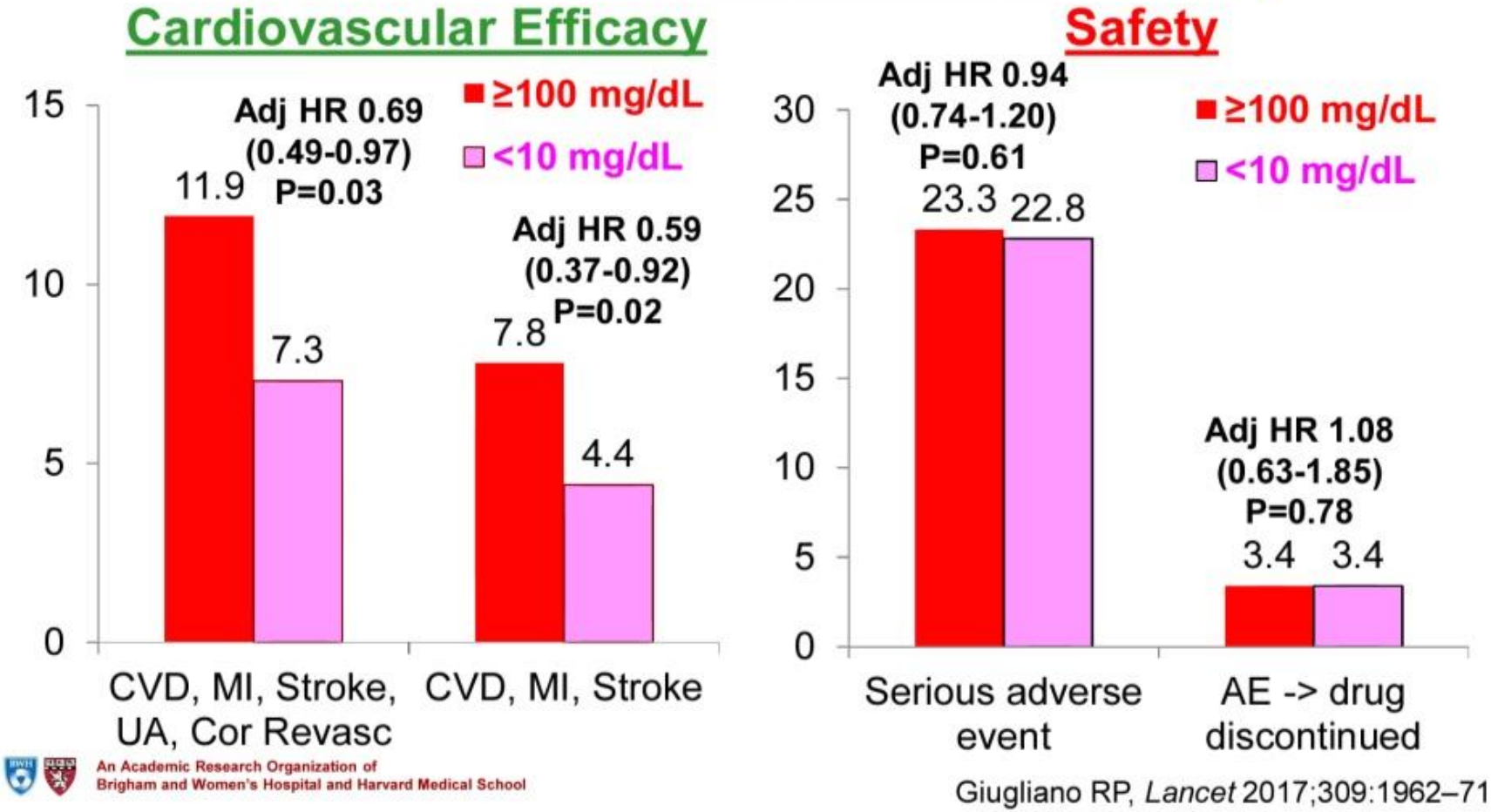
LDL-C Goal: < 1 mmol/L (< 40 mg/dL); Class IIb, Level B

Lower LDL-C is better for patients at very high-risk of recurrent ASCVD events

Mach F, et al. *Eur Heart J*. 2019;00:1-78.

Efficacy and Safety in Pts with *Ultra-Low LDL-C* at 4 wks

N=504: Median LDL-C = 7 mg/dL

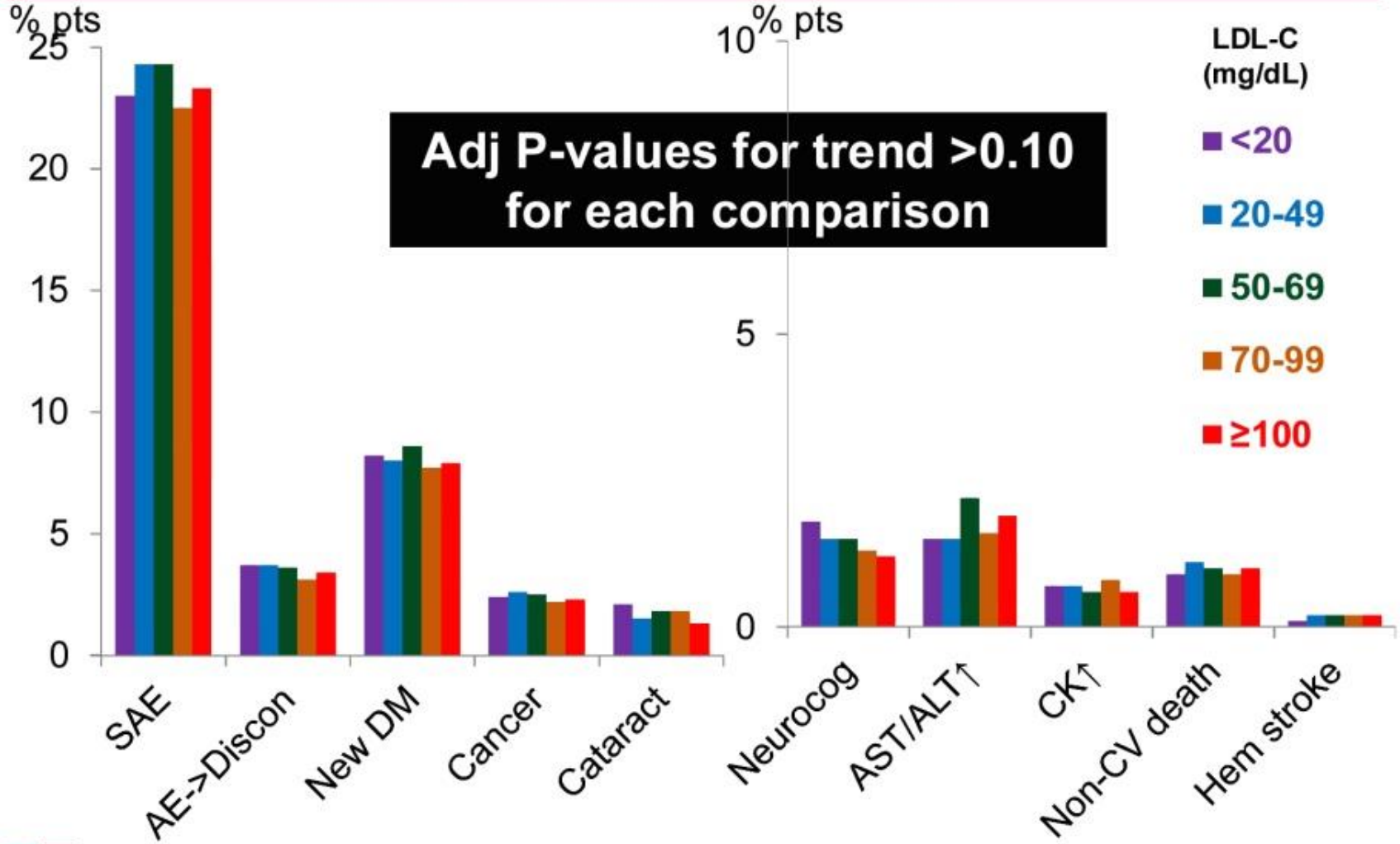


An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Giugliano RP, *Lancet* 2017;309:1962–71

NATIONAL LIPID ASSOCIATION

Safety Events by Achieved LDL-C



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

Giugliano RP et al, *Lancet* 2017;309:1962–71

NATIONAL LIPID ASSOCIATION

QUESTIONS

- What about safety?
- Is there evidence that ultra-low LDL-C induces dementia, hemorrhagic stroke, or other adverse outcomes?

NATIONAL LIPID ASSOCIATION

QUESTIONS

- What about safety?
- Is there evidence that ultra-low LDL-C induces dementia, hemorrhagic stroke, or other adverse outcomes?

- NO!

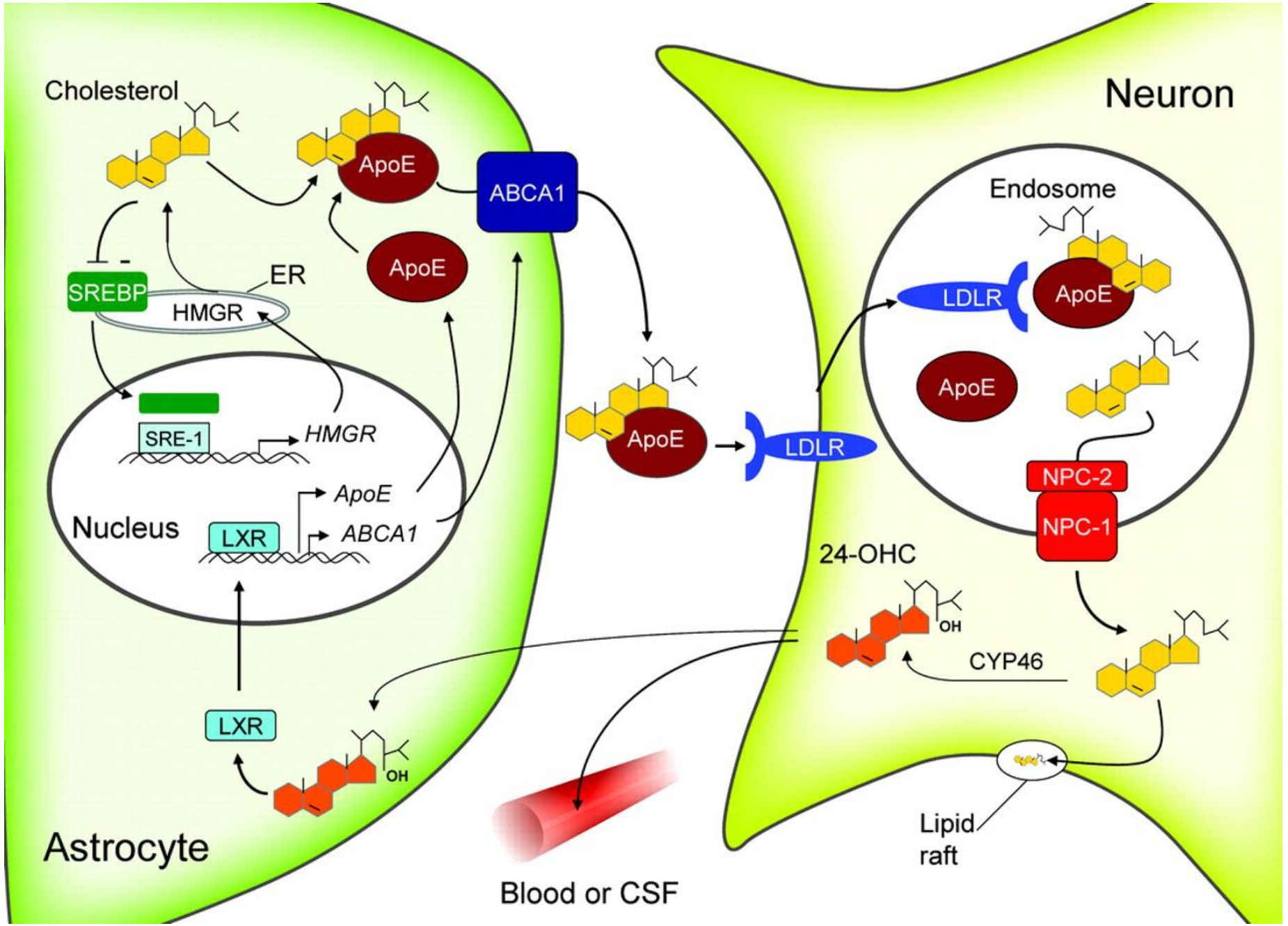
NATIONAL LIPID ASSOCIATION

Cognition and Statins

- Case series and 2 small, 6-month RCTs with statins raised concern regarding cognitive deficits
- In 2012 FDA added risk of adverse cognitive effects to label of all statins
- However analyses from large scale RCTs do not support these findings and 2014 Statin Cognitive Safety Task Force* concluded that statins are not associated with cognitive side effects.

*The National Lipid Association
Rojas-Fernandez CH, et al. *J Clin Lipidol.* 2014;8(3 Suppl):S5-16.

NATIONAL LIPID ASSOCIATION



HALF LIFE OF INTRACEREBRAL CHOLESTEROL IS APROXIMATELY 5 YEARS.

THE BRAIN CAN CARE LESS ABOUT HEPATIC DERIVED LIPOPROTEINS.

NATIONAL LIPID ASSOCIATION

HPS – Results of Testing for Neuropsychiatric Disorders

Measure	Simvastatin	Placebo
Cognitively Impaired*	23.7%	24.2%
Dementia	0.3%	0.3%
Psychiatric Disorder	0.7%	0.7%
Suicide	0.1%	0.1%

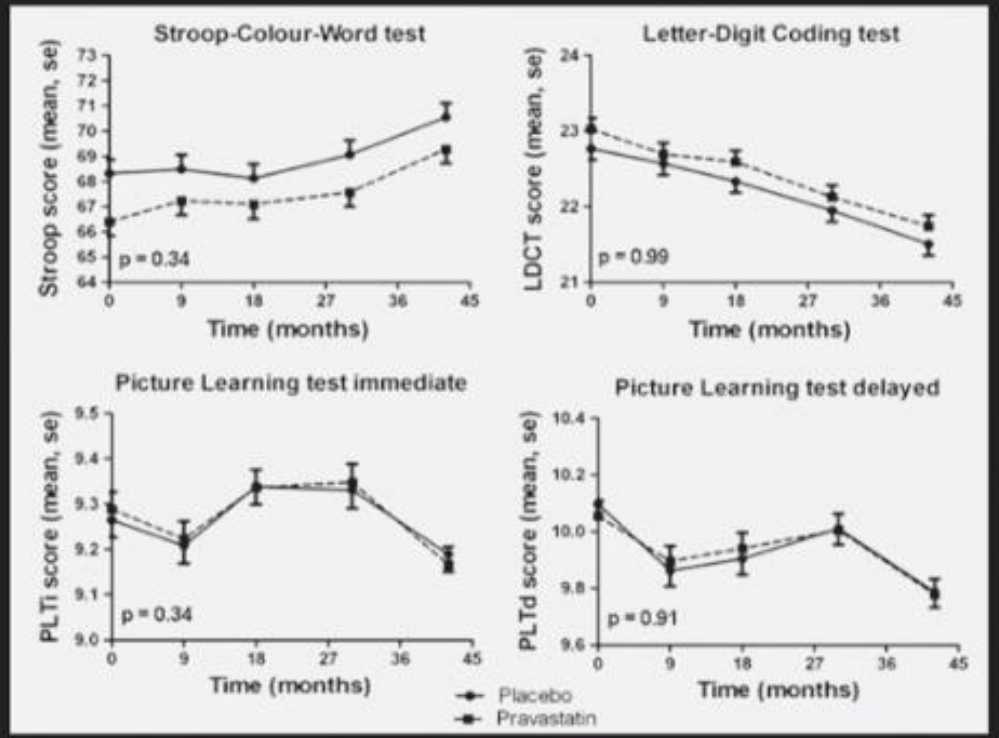
* Telephone Interview for Cognitive Status Questionnaire

Heart Protection Study Collaborative Group. *Lancet.* 2002;360:7-22

NATIONAL LIPID ASSOCIATION

PRAVASTATIN AND COGNITIVE FUNCTION IN THE ELDERLY (PROSPER)

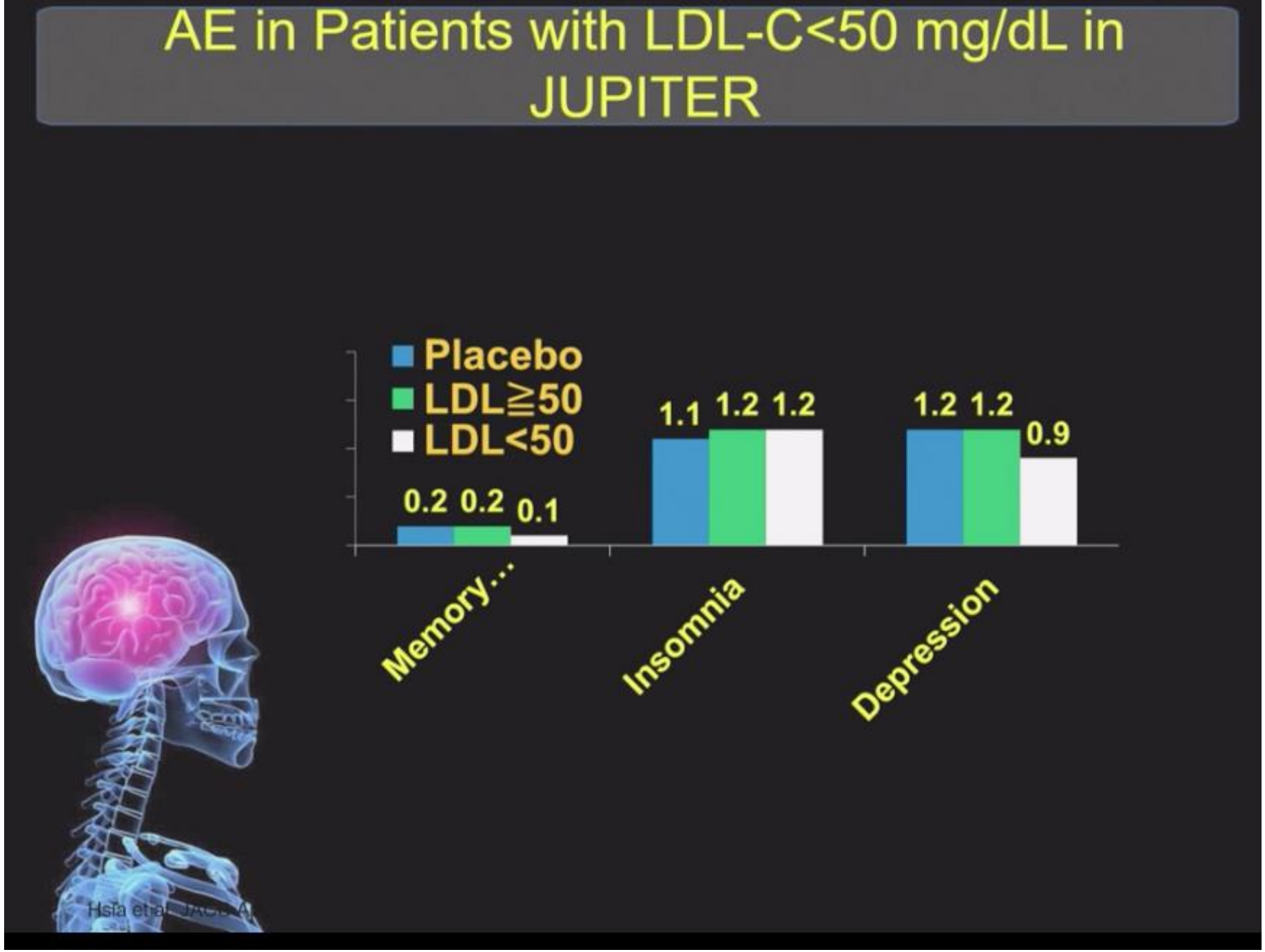
- 5,804 patients, mean age 75.4 y



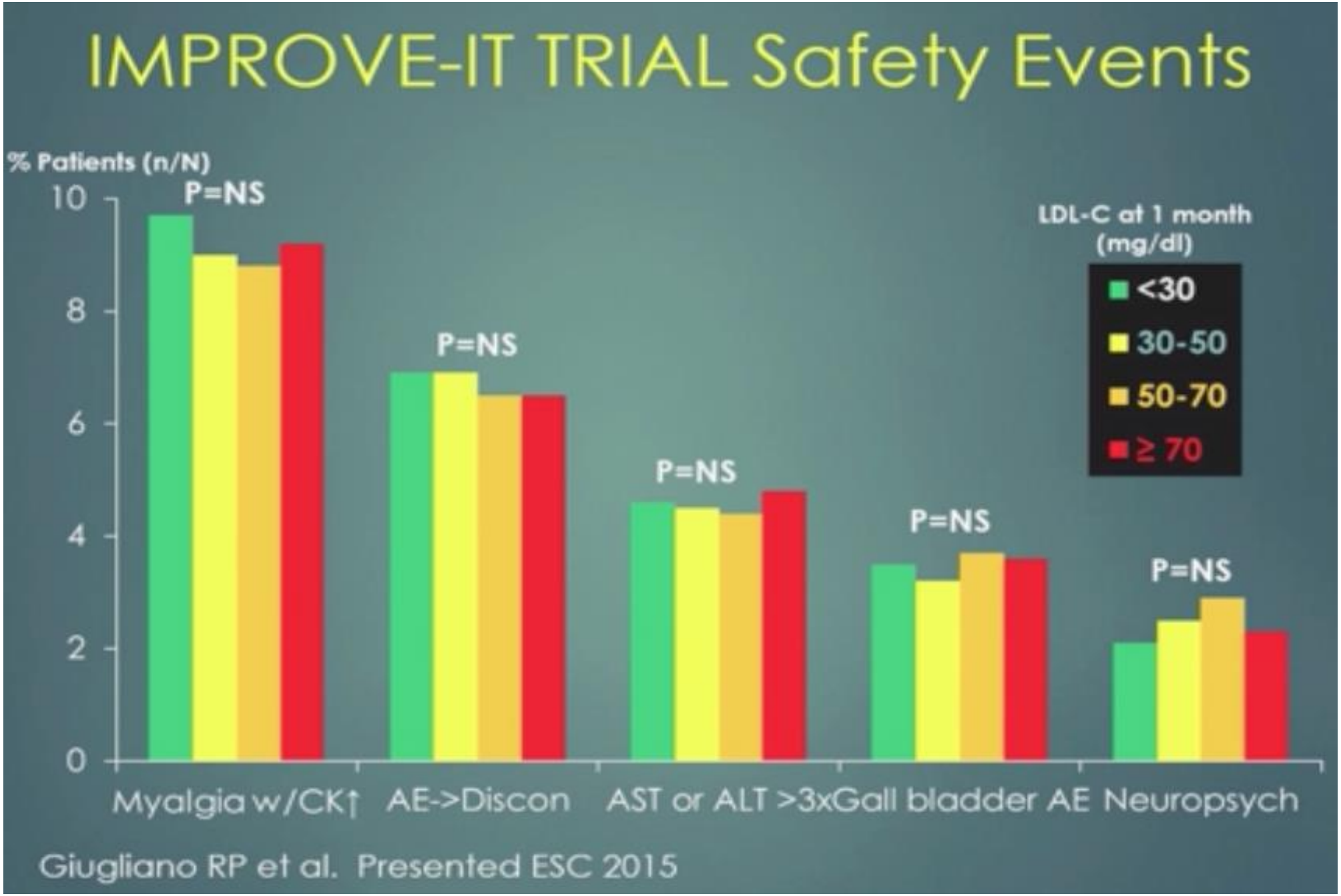
J Neurol. 2010 Jan;257(1):85-90

NATIONAL LIPID ASSOCIATION

AE in Patients with LDL-C<50 mg/dL in JUPITER



IMPROVE-IT TRIAL Safety Events

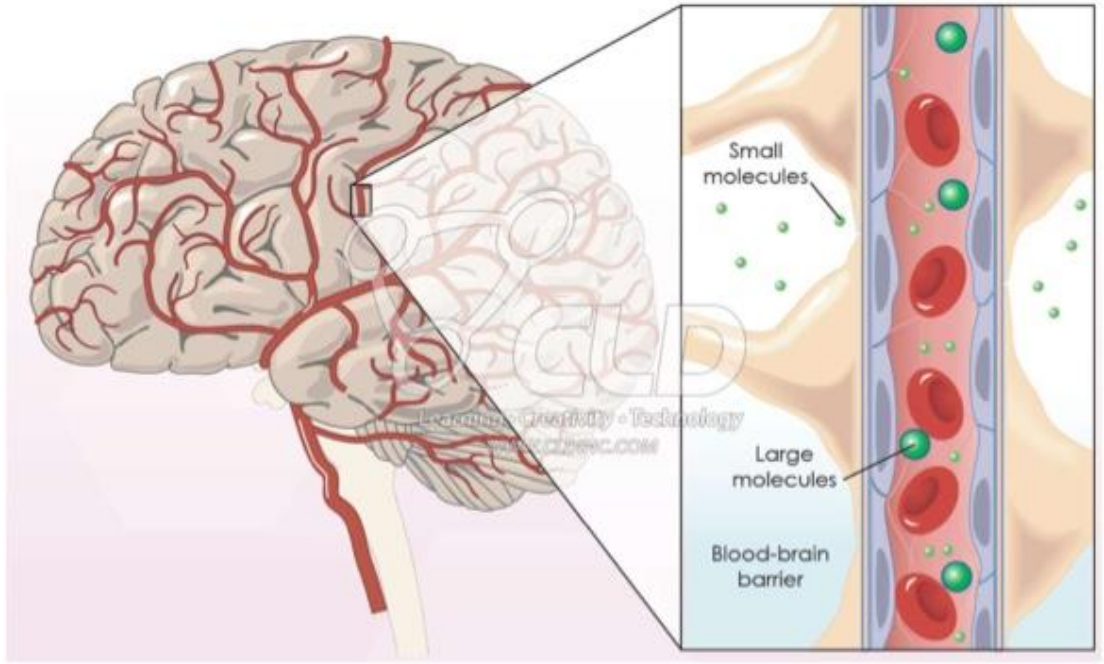


Giugliano RP et al. Presented ESC 2015

NATIONAL LIPID ASSOCIATION

Cognition and PCSK9 Inhibitors

Brain synthesizes cholesterol locally



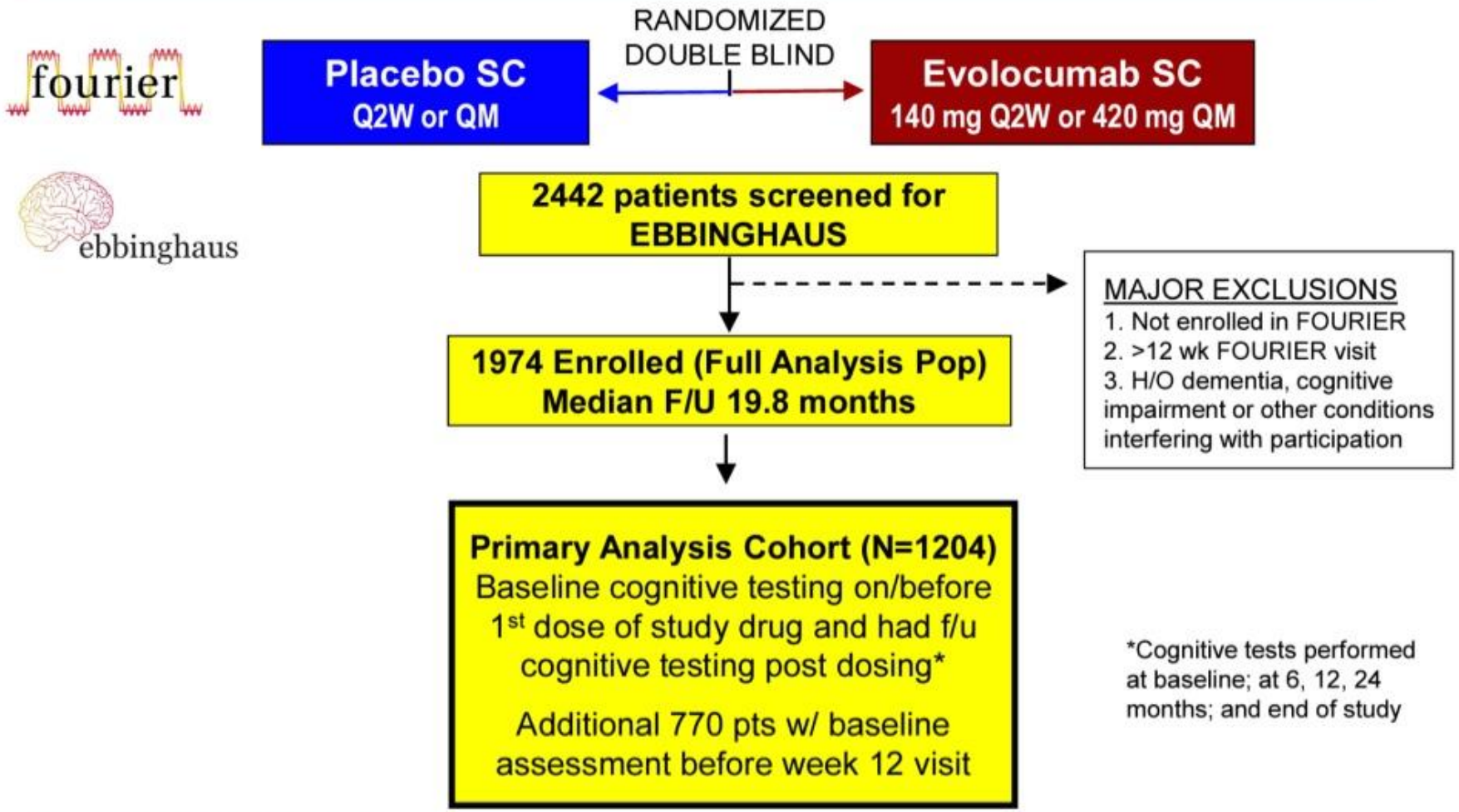
mAb (e.g., evolocumab) are too large to cross the intact blood-brain barrier

Nevertheless meta-analysis* of adverse events from 6 trials in 9581 pts suggested an increased risk with PCSK9 inhibitors: HR 2.3 [1.1, 4.9]

- Event rates low (<1%)
- Unadjudicated, diverse AE terms reported
- Not correlated with LDL-C achieved

*Lipinski MJ, et al. *Eur Heart J.* 2016;37(6):536-545.

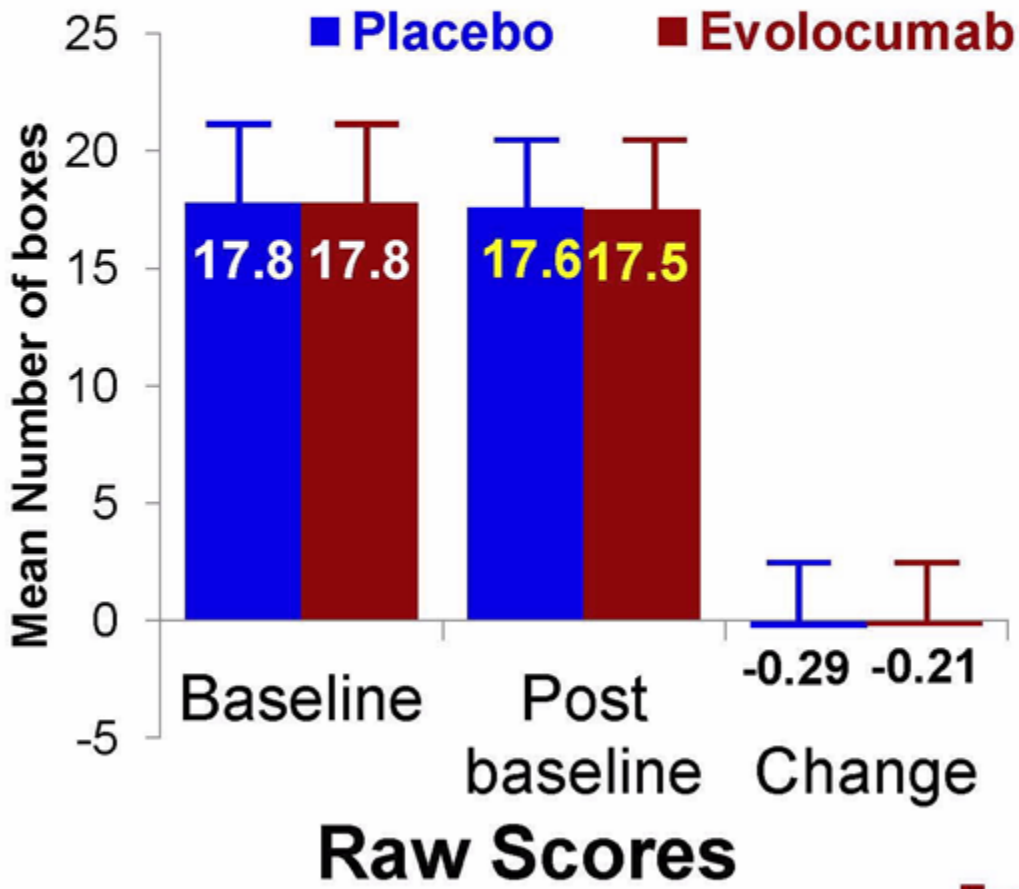
Trial Design



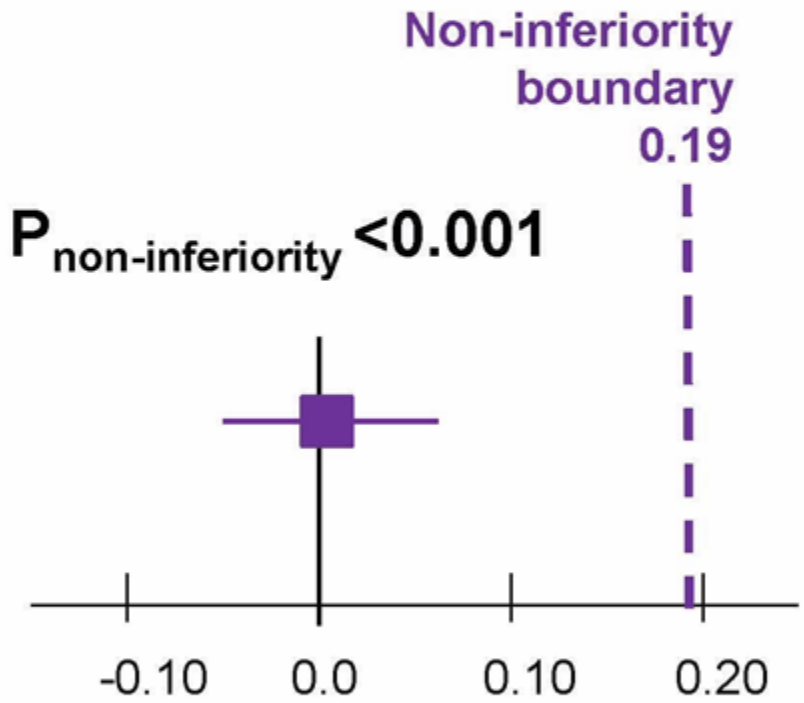
Giugliano RP et al. *Clin Card* 2017;40:59–65

Primary Endpoint

Spatial Working Memory Strategy Index



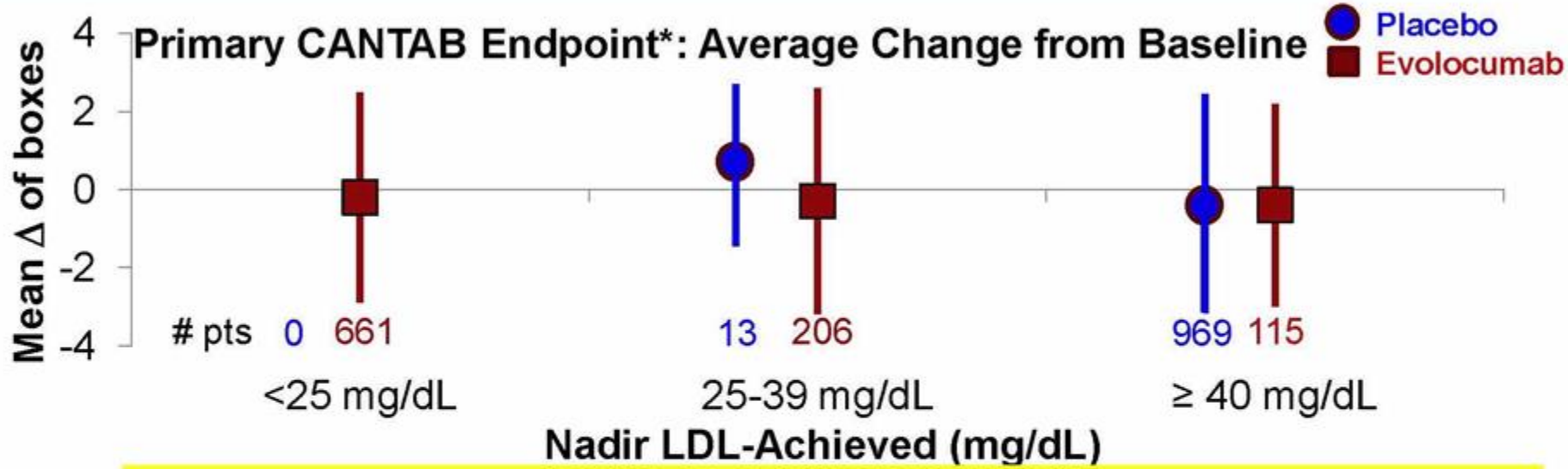
Raw Scores



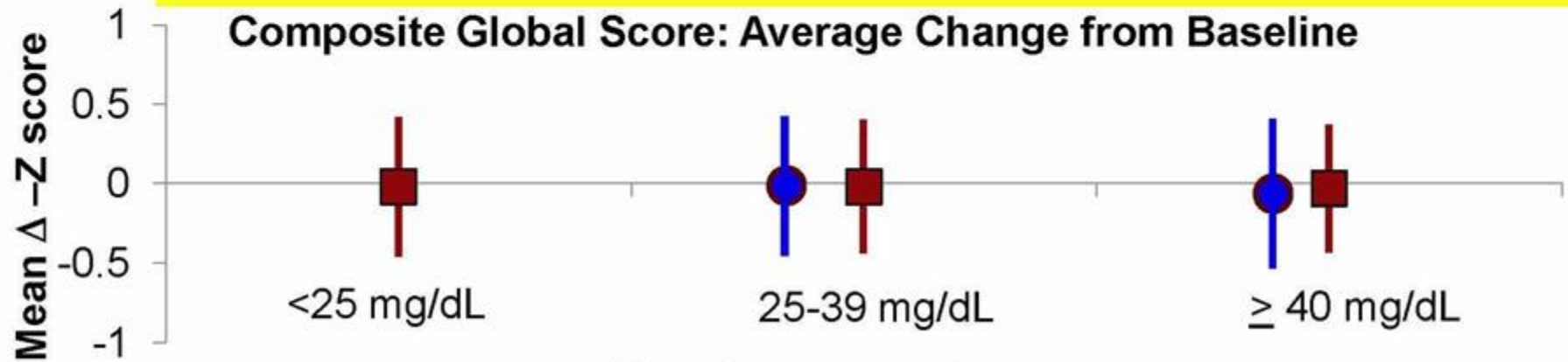
Giugliano RP et al. N Engl J Med. 2017;377:633-43.

P_{NI} is from fixed estimate

Cognitive Assessments by Nadir Achieved LDL-C and Treatment (Full Pop)



P=NS across LDL values achieved and also between treatments



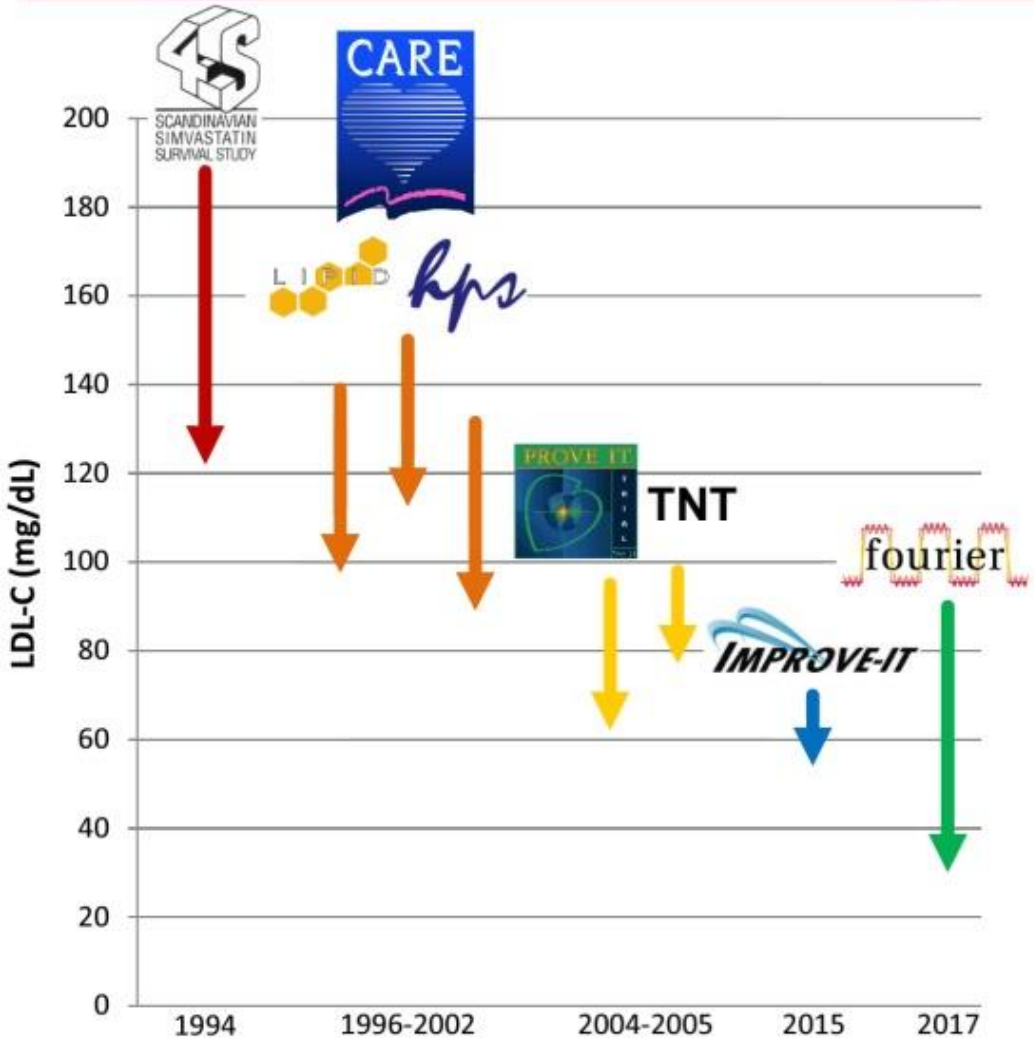
Giugliano RP et al. N Engl J Med. 2017; 377:633-43.

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

Negative score -> improvement
Lower scores are better

*Spatial working memory strategy index of executive function, raw score

A Quarter of a Century of Treating LDL-C



High is bad

Average is not good

Lower is better

Even lower is even better

Lowest is best

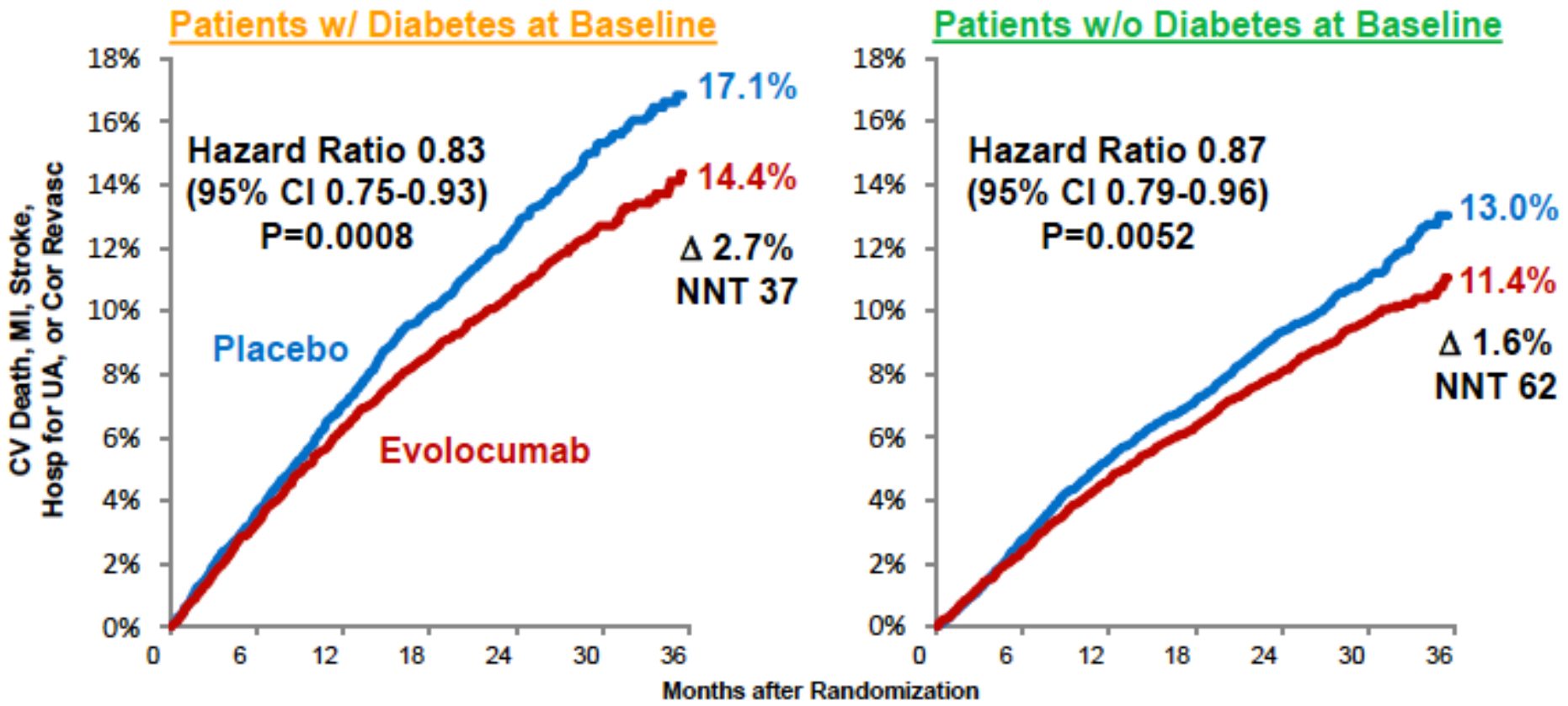
An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

NATIONAL LIPID ASSOCIATION

We now know that low LDL is safe.
BUT, which are the patients that benefit the most from very low LDL lowering with non statin therapy??

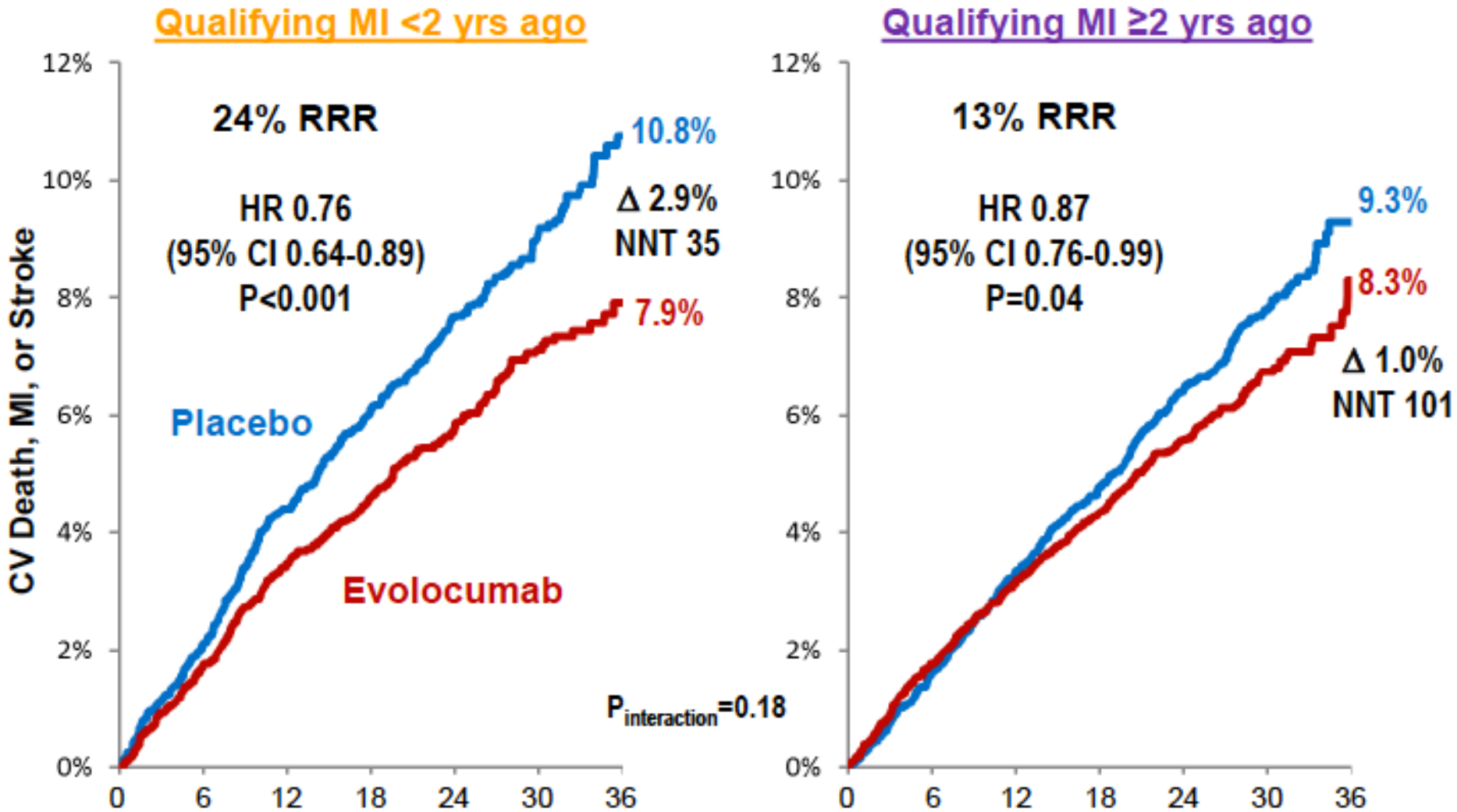
NATIONAL LIPID ASSOCIATION

Clinical Efficacy by Diabetes Status



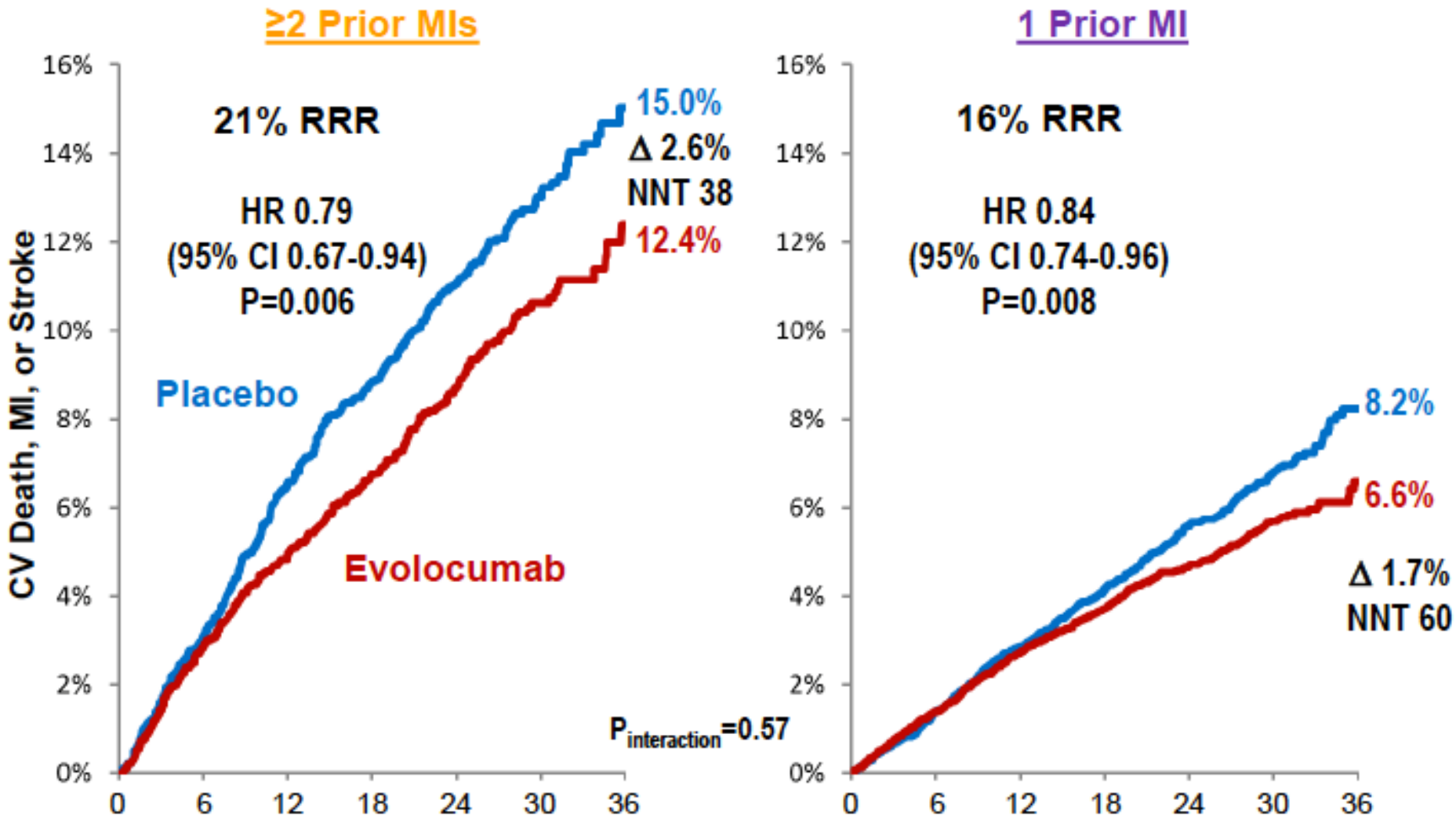
Sabatine MS, Leiter LA et al. *Lancet Diab & Endo* 2017;5;941-50

Benefit of EvoMab Based on Time from Qualifying MI



Sabatine MS et al. *Circulation* 2018;epub ahead of print

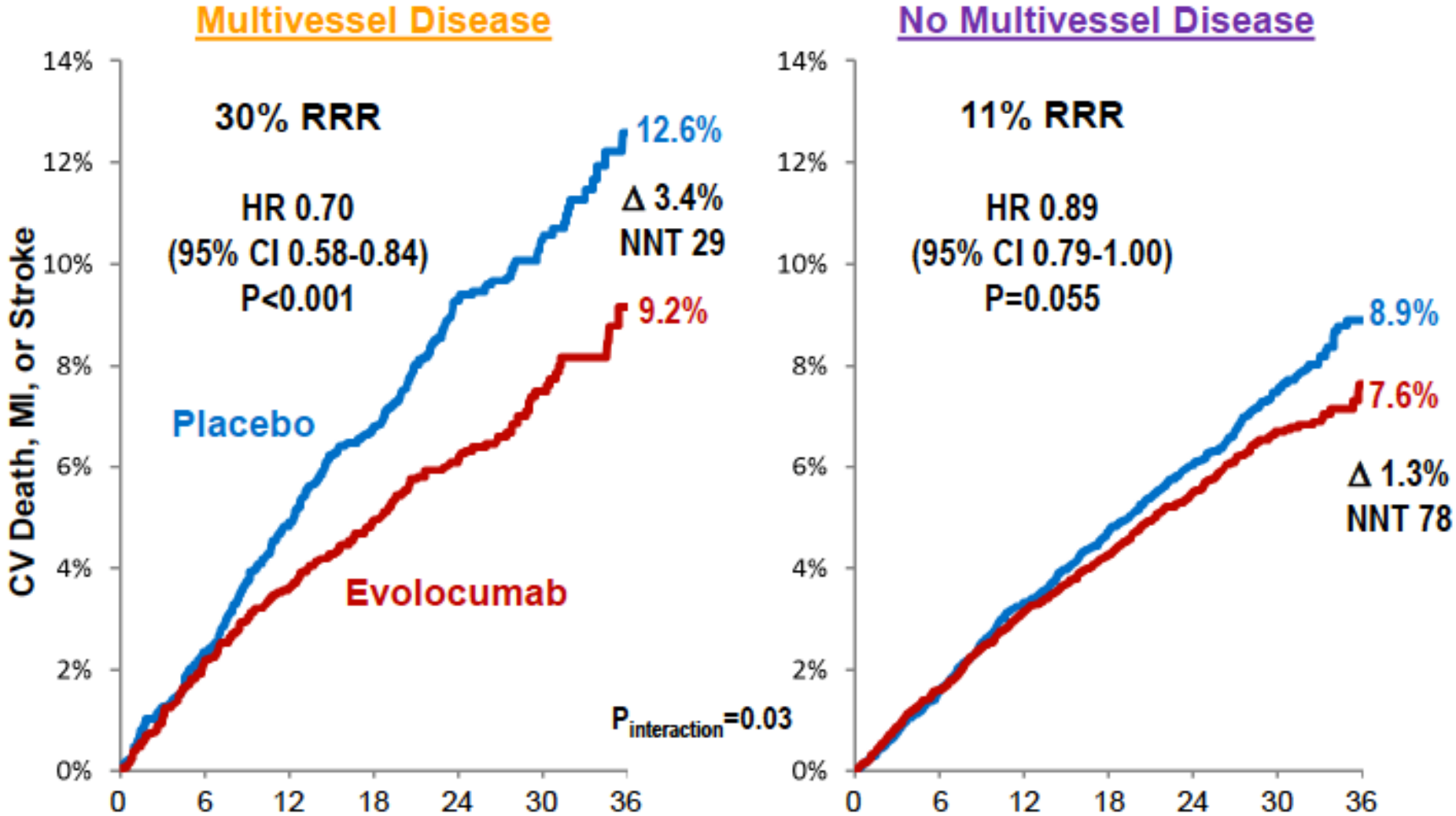
Benefit of EvoMab Based on # of Prior MIs



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

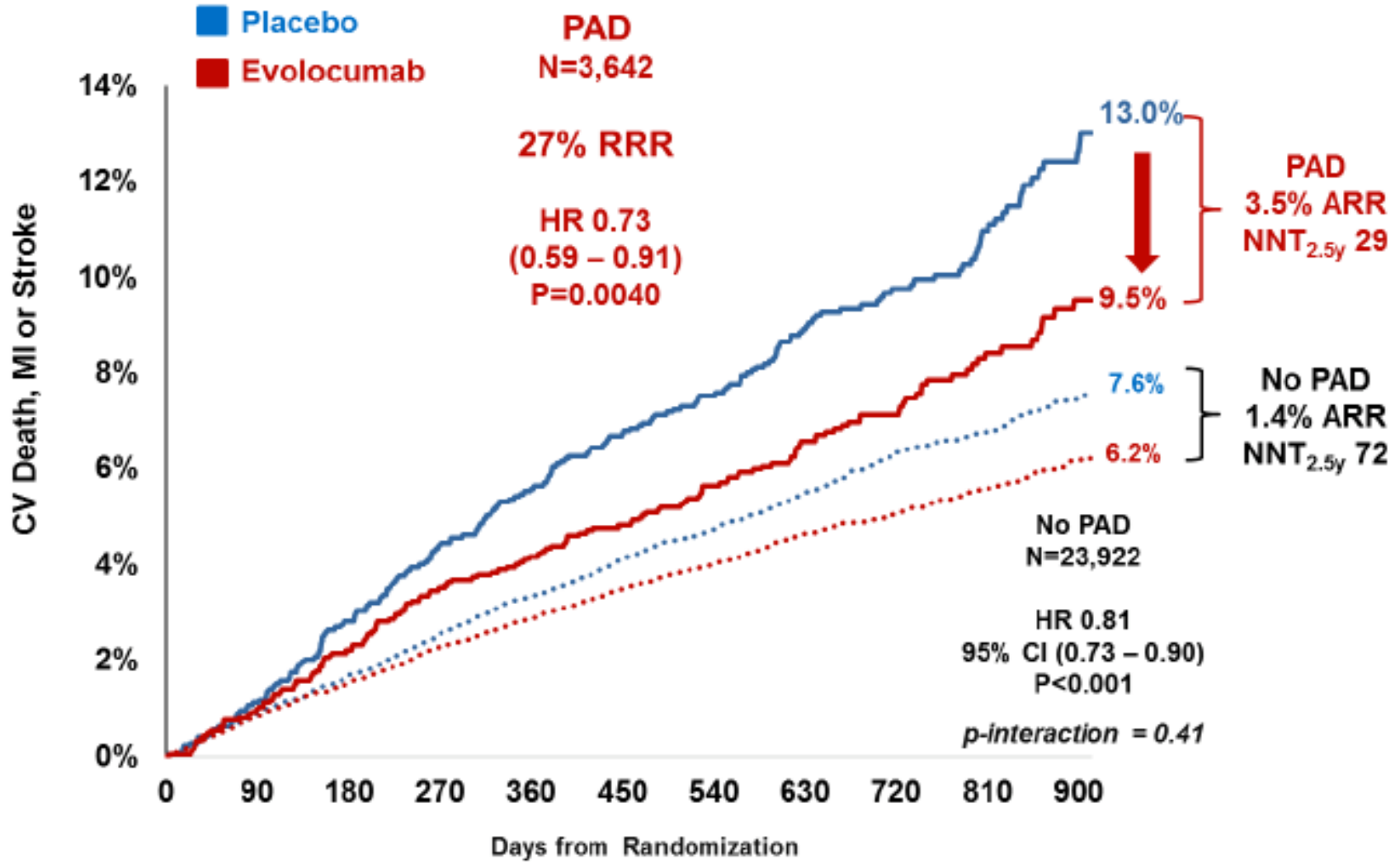
Sabatine MS et al. *Circulation* 2018;epub ahead of print

Benefit of EvoMab Based on Multivessel Disease



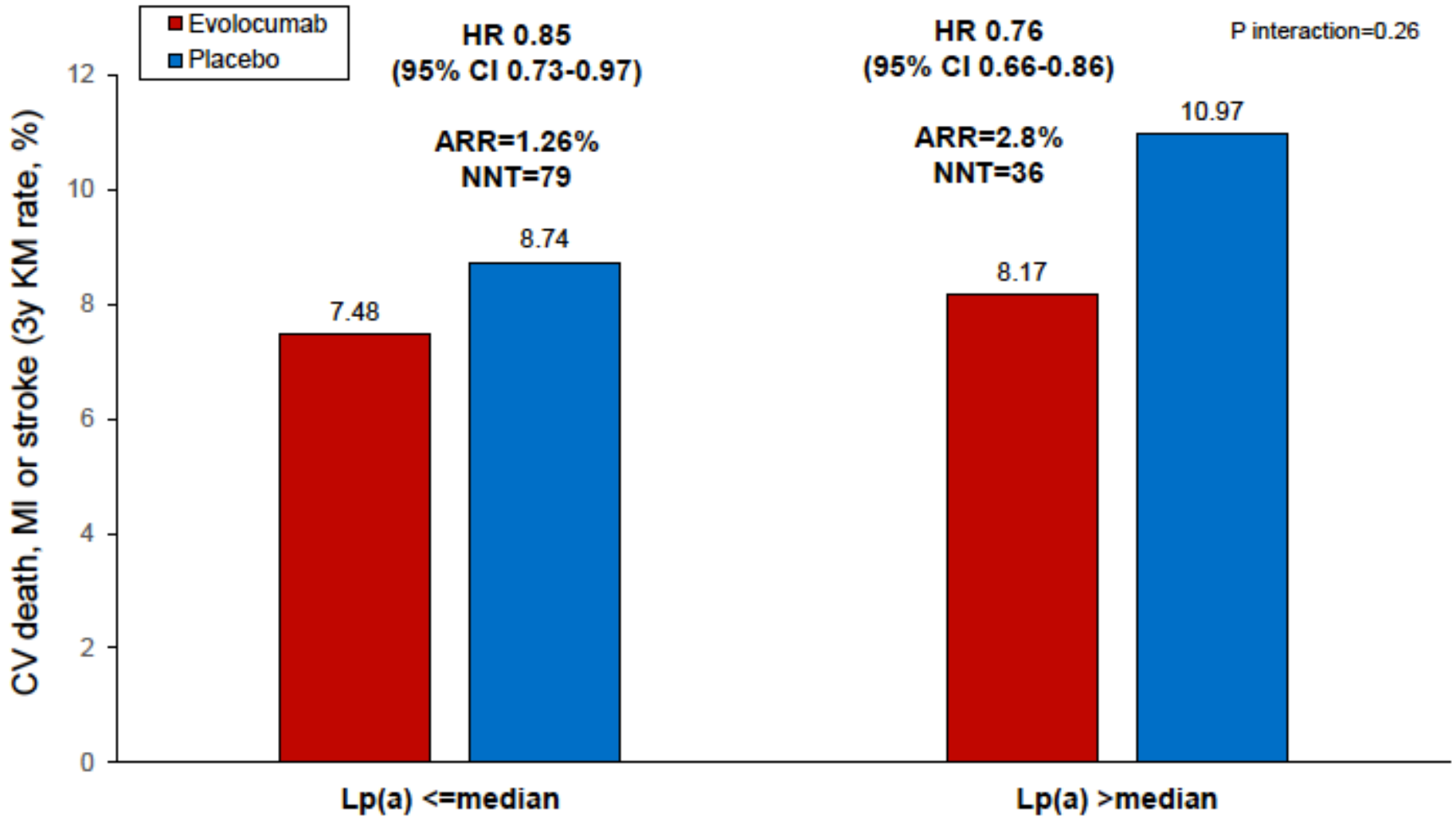
Sabatine. *Circulation* 2018; epub ahead of print

CV Death, MI or Stroke in Patients with and without Peripheral Artery Disease



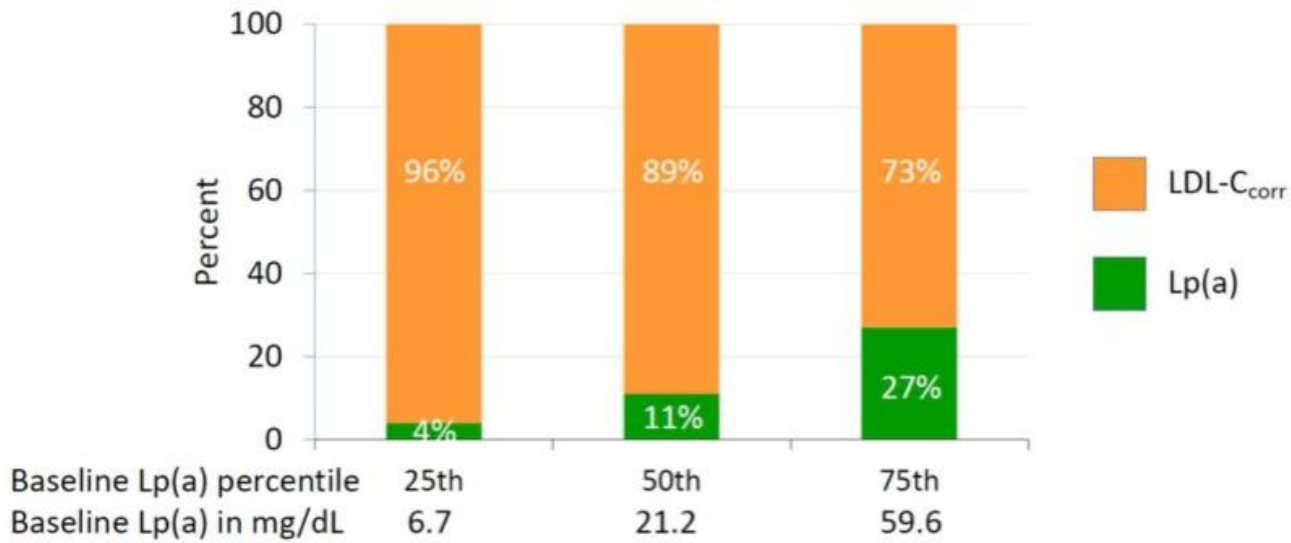
Bonaca MP et al. & Sabatine MS. *Circulation* 2018;137:338-50

Efficacy by Baseline Lp(a)



ODYSSEY OUTCOMES

Proportion of MACE Reduction Attributable to Changes in Lp(a) and Corrected LDL-C



From model with baseline and change in Lp(a), baseline and change in LDL-C_{corr} (Model 2)

Presented by Vera Bittner, ACC19

National Lipid Association Statement

Enhancing the Value of PCSK9 Monoclonal Antibodies by Identifying Patients Most Likely to Benefit

Purpose:

- Update for clinical decision-making based on new information
  - PCSK9 mAb discounting
  - Potential for net ASCVD risk reduction benefit from added LDL-C lowering therapy
    - Systematic review to identify heterogeneity in benefits observed in subgroup analyses

Extremely high risk ≥40% 10-year ASCVD risk

Systematic review subgroups of RCTS Moderate vs high intensity statins, PCSK9 mAbs

ON STATIN THERAPY	
Burden and activity of clinical ASCVD	**Adverse or poorly controlled cardiometabolic risk factors**
EXTREMELY HIGH ATHEROSCLEROTIC BURDEN	**EXTREMELY HIGH RISK FACTORS**
Majority had at least 1 additional adverse or poorly controlled cardiometabolic risk factor	

• Polyvascular clinical ASCVD (coronary heart disease†, ischemic stroke, and symptomatic peripheral arterial disease)
• Symptomatic peripheral arterial disease** in addition to a coronary heart disease† or ischemic stroke
• A clinical ASCVD event (coronary heart disease†, stroke, or symptomatic peripheral arterial disease**) with multi-vessel coronary artery disease defined as ≥40% stenosis in ≥2 large vessels
• Recurrent myocardial infarction within 2 years
	• Heterozygous familial hypercholesterolemia with clinical ASCVD (or coronary artery calcium >100)
	• History of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease** with at least one of:
	  ○ Diabetes
	  ○ LDL-C >100 mg/dl
	  ○ Less than high intensity statin therapy
	  ○ High sensitivity C-reactive protein >3 mg/L
	• Poorly controlled hypertension and clinical ASCVD

† Clinically evident coronary heart disease includes myocardial infarction, history of angina with objective evidence of coronary artery disease (electrocardigraphic, positive stress test, wall motion abnormality on ultrasound, coronary angiographic evidence of significant atherosclerotic lesions), or prior revascularization including coronary artery bypass grafting or percutaneous coronary intervention)

Very high risk 30-39% 10-year ASCVD risk

Systematic review subgroups of RCTS Moderate vs high intensity statins, PCSK9 mAbs

ON STATIN THERAPY	
Burden and activity of clinical ASCVD	**Adverse or poorly controlled cardiometabolic risk factors**
VERY HIGH ATHEROSCLEROTIC BURDEN	**VERY HIGH RISK FACTORS**
Majority had at least 1 additional adverse or poorly controlled cardiometabolic risk factor	
• Recent acute coronary syndrome (only if no subsequent event within 2 years) • Coronary heart disease† and ischemic stroke without symptomatic peripheral arterial disease** • Coronary artery bypass grafting	Clinical ASCVD and one or more of: • Age ≥65 years • Chronic kidney disease • Lipoprotein(a) ≥37 nmol/L • High sensitivity C-reactive protein 1-3 mg/L • Metabolic syndrome with a history of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease** • Smoking

High risk 20-29% 10-year ASCVD risk

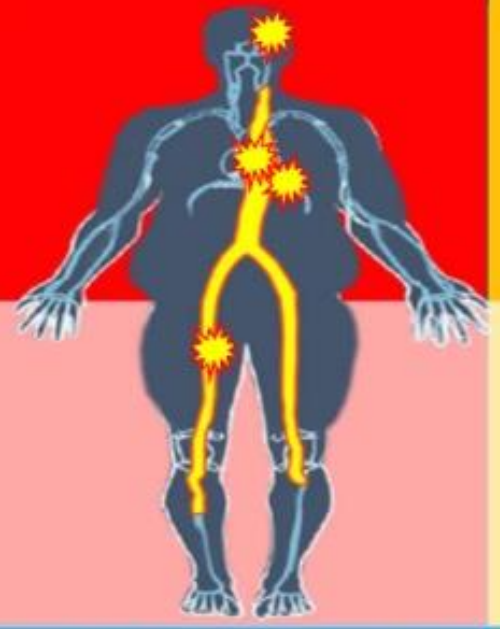
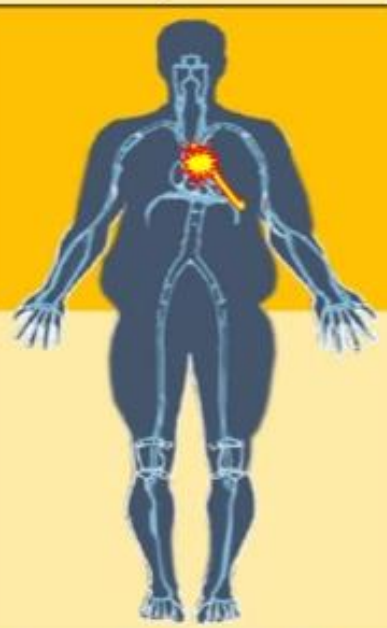
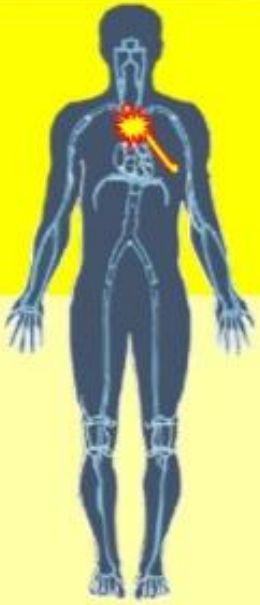
Systematic review subgroups of RCTS Moderate vs high intensity statins, PCSK9 mAbs

ON STATIN THERAPY	
Burden and activity of clinical ASCVD	
HIGH ATHEROSCLEROTIC BURDEN	**WELL-CONTROLLED RISK FACTORS**
<u>High burden (20-29% 10-year ASCVD risk)</u> • Coronary heart disease† only • Ischemic stroke only • Symptomatic peripheral arterial disease only** • Acute coronary syndrome with no subsequent ASCVD event after 2 years	

Did not find heart failure subgroups as in 2018 AHA/ACC Cholesterol Guideline "Very high ASCVD risk" group; Patients with NYHA Class 3 & 4 heart failure excluded from RCTs

NLA Statement: REASONABLE - HIGH VALUE FROM ADDING PCSK9 mAb

ON MAXIMALLY TOLERATED STATIN THERAPY (±ezetimibe)

Extremely High Risk ≥40% 10-year ASCVD risk	Very High Risk 30-39% 10-y ASCVD risk	High Risk 20-29% 10-year ASCVD risk
		
Extensive or active burden of ASCVD Usually with poorly controlled cardiometabolic risk factors	**Less extensive ASCVD & Poorly controlled cardiometabolic risk factors**	**Less extensive ASCVD & Well controlled risk factors**
Less extensive ASCVD & Extremely high risk cardiometabolic risk factors		**Primary prevention HeFH/SGH LDL-C≥220 mg/dl & Poorly controlled cardiometabolic risk factors**
LDL-C ≥70 mg/dl	**LDL-C ≥100 mg/dl**	**LDL-C ≥130 mg/dl**

Robinson JG, et al. J Clin Lipidol 2019; online ahead of print

Conclusions

- With recently approved and forthcoming therapies targeting other aspects of LDL metabolism, it can be reduced to levels not achieved before (<< 40 mg/dL).
- Previous and recent trials with statin and non statin therapies has shown progressive relationship of achieved LDL and CV events, down to LDL-C < 20 mg/dL.
- Despite several concerns and short time period of recent trials there is no excess in safety events with very low achieved LDL-C < 20 mg/dL and even much lower.
- Based on the data and NLA statement, we would advocate targeting an LDL-C < 40 mg/dL in extreme, very high and high risk secondary prevention patients, especially with the use of PCSK9 inhibitors.
- ***THE ONLY SIDE EFFECT OF HAVING A VERY LOW LDL IS LONGEVITY.***

NATIONAL LIPID ASSOCIATION

DON'T FEAR VERY LOW LDL, REMEMBER:


LIPID
SPECIALIST


AMERICAN BOARD OF CLINICAL LIPIDOLOGY
ABCL
EST. 2004

Organizational Awareness & Recognition
NLA Strategic Planning

The NLA Strategic Planning meeting was convened to consider the strategic future direction of the association and related certification boards (ABCL* and ACCL**) with respect to formal recognition as a specialty or sub-specialty of medicine.

***American Board of Clinical Lipidology**

- Certifies physician knowledge and training in Clinical Lipidology
- 767 diplomates as of May 2, 2019

****Accreditation Council for Clinical Lipidology**

- Certifies physicians, nurses, nurse practitioners, physician assistants, pharmacists, registered dietitian/nutritionists, clinical exercise physiologists/specialists and other healthcare professionals knowledge and training in Clinical Lipidology
- 183 CLS as of May 2, 2019

Lipid Specialist Definition

- A Lipid Specialist is defined as a healthcare professional certified by the American Board of Clinical Lipidology (ABCL) or Accreditation Council for Clinical Lipidology (ACCL) specializing in the identification and management of dyslipidemia and related metabolic disorders which lead to atherosclerotic cardiovascular disease (ASCVD) and other morbidities.

Lipid Specialist Benefits

- Consistent nomenclature usage by the NLA, ABCL and ACCL is necessary for recognition.
- Using a single term allows for consistency across multiple disciplines.
- CMS recognition of Lipid Specialists would enable those who can bill for Medicare and Medicaid services to identify themselves Lipid Specialists and be paid for treatment of lipid related services as such.

NATIONAL LIPID ASSOCIATION

SCIENTIFIC SESSIONS

June 4-7

2020

CHICAGO