Recent ACC/AHA Guidelines on Lipids: Already Getting Older From IMPROVE-IT to PCSK9 Inhibitors

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BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

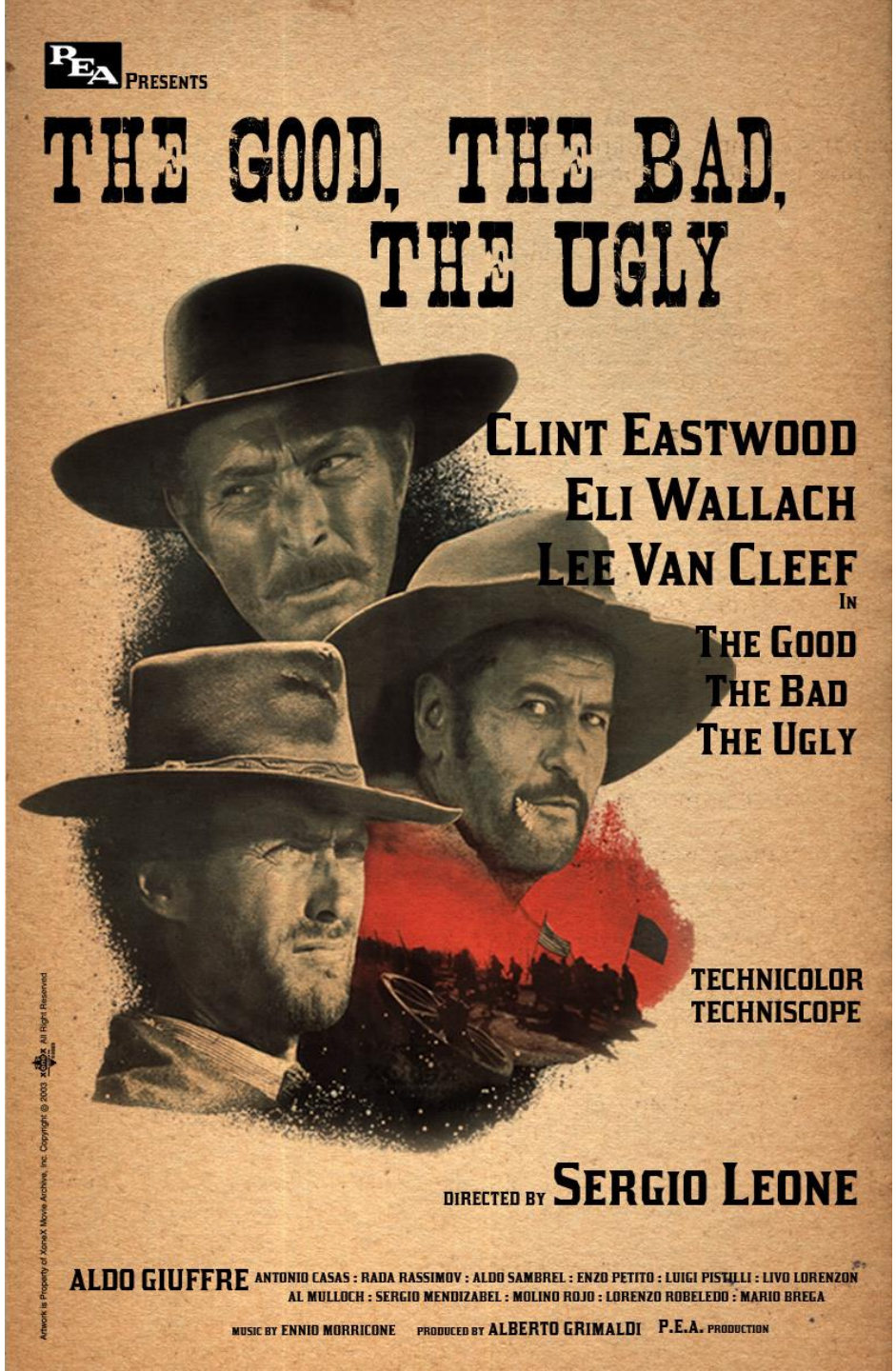
2013 ACC/AHA Cholesterol Guidelines

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


PEA PRESENTS
THE GOOD, THE BAD, THE UGLY
CLINT EASTWOOD
ELI WALLACH
LEE VAN CLEEF
IN
THE GOOD
THE BAD
THE UGLY
TECHNICOLOR
TECHNISCOPE
DIRECTED BY SERGIO LEONE
ALDO GIUFFRE ANTONIO CASAS : RADA RASSIMOV : ALDO SAMBREL : ENZO PETITO : LUIGI PISTILLI : LIVO LORENZON
AL MULLOCH : SERGIO MENDIZABEL : MOLINO ROJO : LORENZO ROBELEDO : MARIO BREGA
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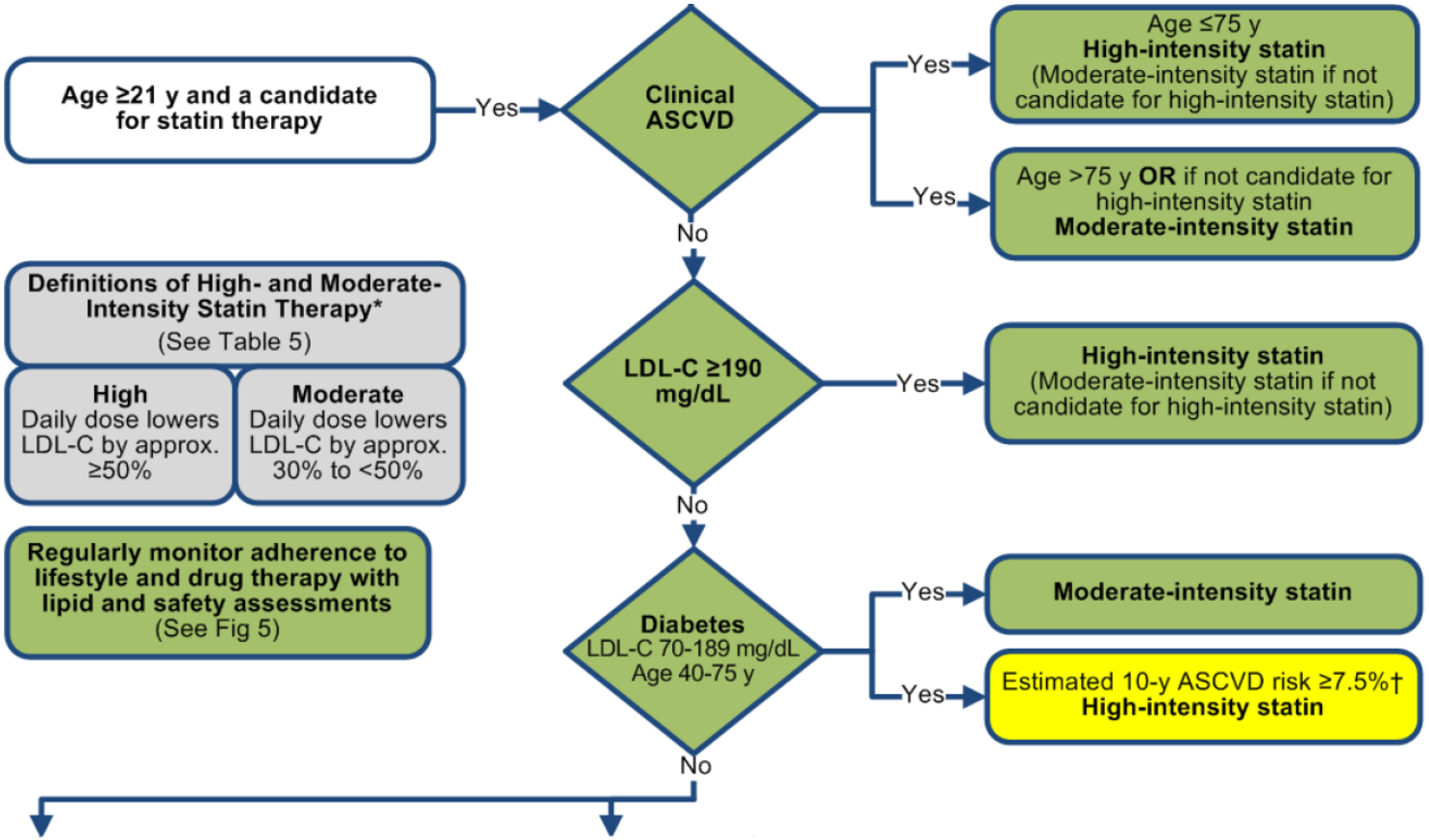
2013 ACC/AHA Cholesterol Guidelines

The Good:

Recommend high-intensity statin therapy for patients at high risk



2013 ACC/AHA Cholesterol Guidelines

The (Seemingly) Bad:

No LDL-C goals

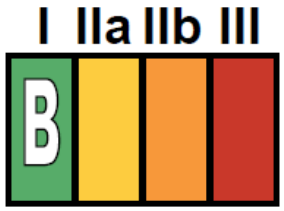
"… given the absence of data on titration of drug therapy to specific goals, no recommendations are made for or against specific LDL-C … goals"

No value for drugs other than statins

"Clinicians treating high-risk patients who have less-than-anticipated response to statins … may consider the addition of a nonstatin cholesterol-lowering therapy … preferentially drugs that have been shown in RCTs to provide ASCVD risk-reduction …"

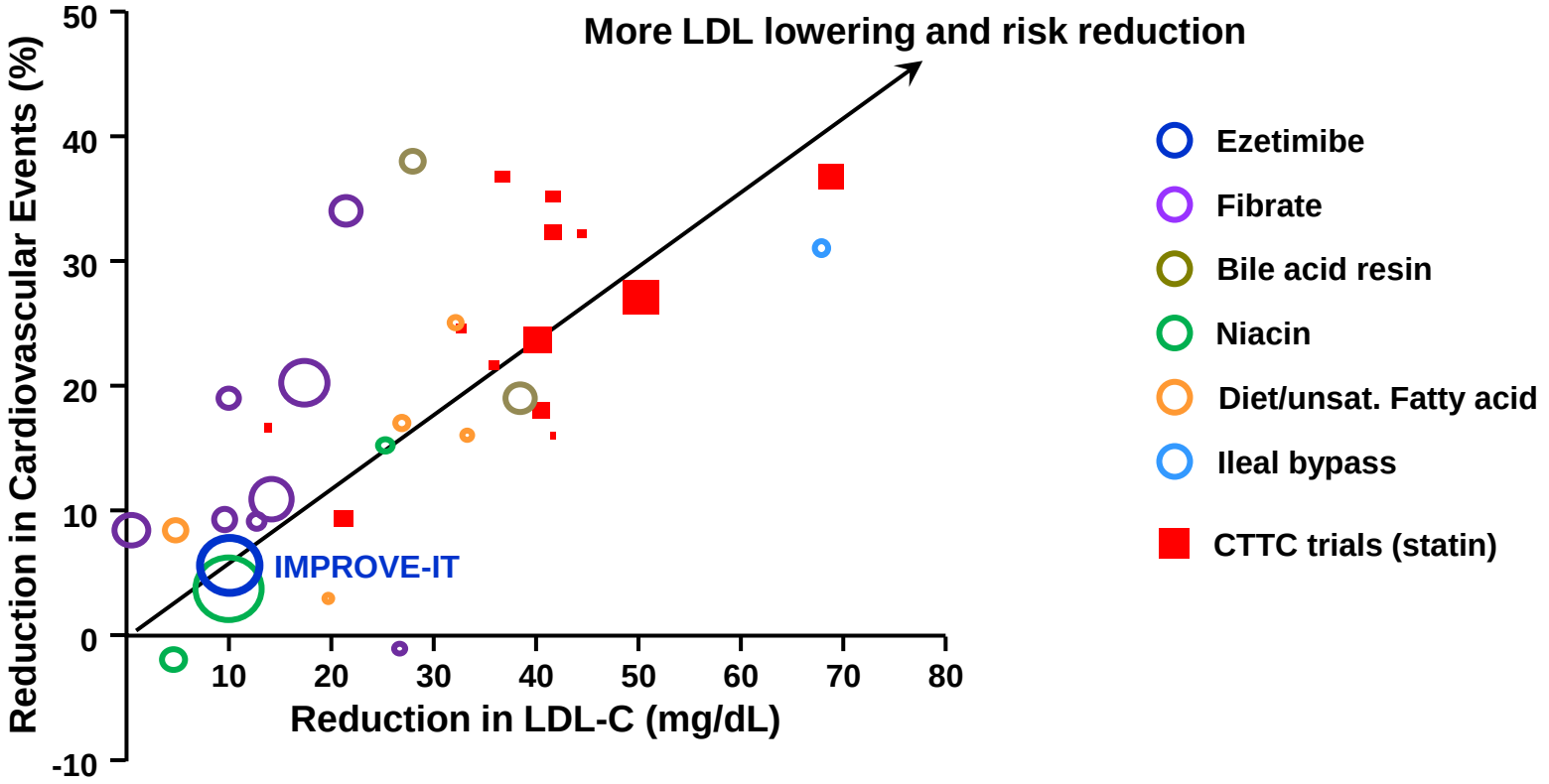
2013 ACC/AHA Cholesterol Guidelines

The Ugly (controversy):

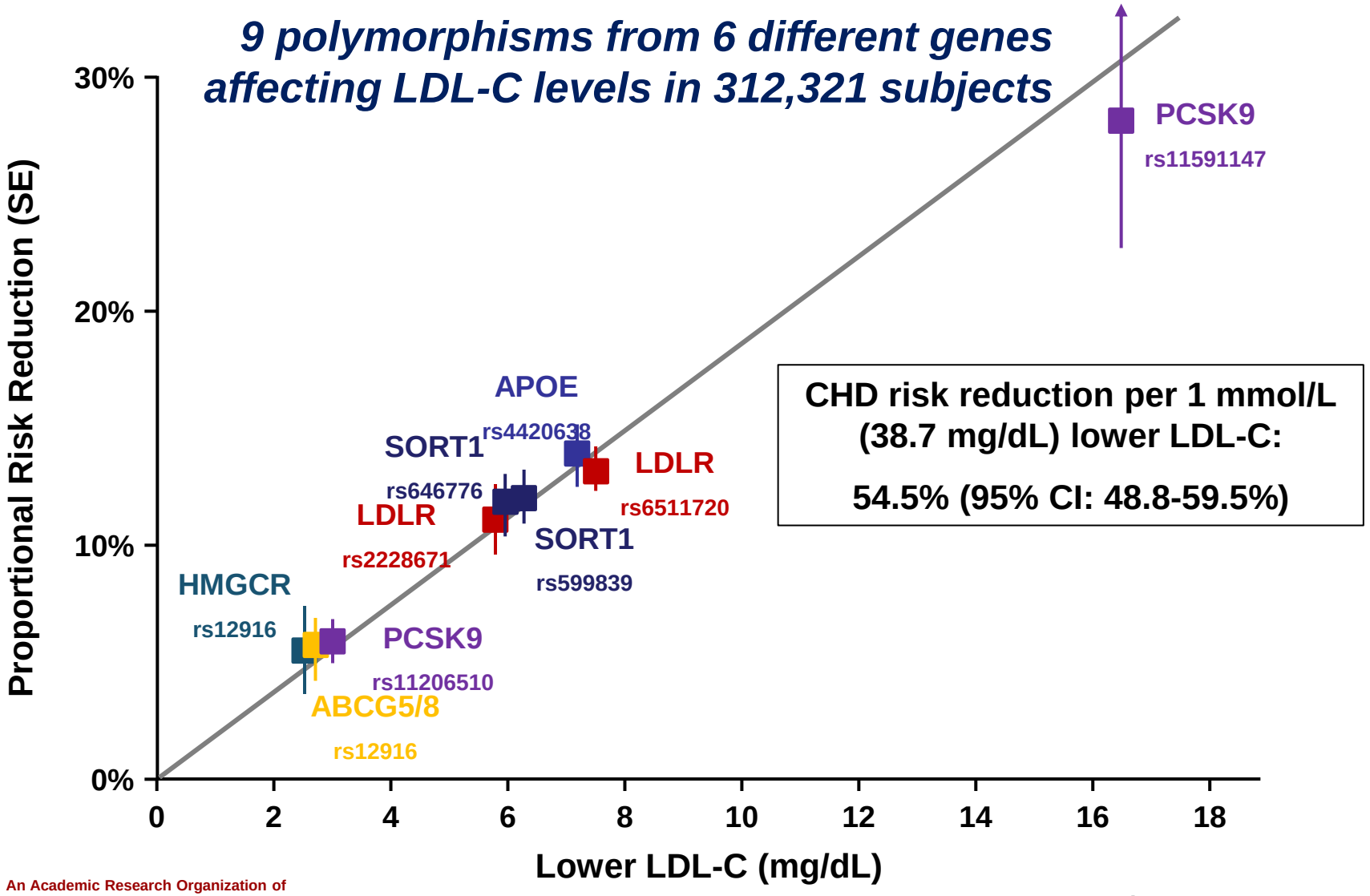


The Pooled Cohort Equations should be used to estimate 10-year ASCVD‖ risk for individuals with LDL-C 70 to 189 mg/dL without clinical ASCVD* to guide initiation of statin therapy for the primary prevention of ASCVD.

Effect of Absolute Reduction in LDL-C on Relative Risk Reduction in CV Events

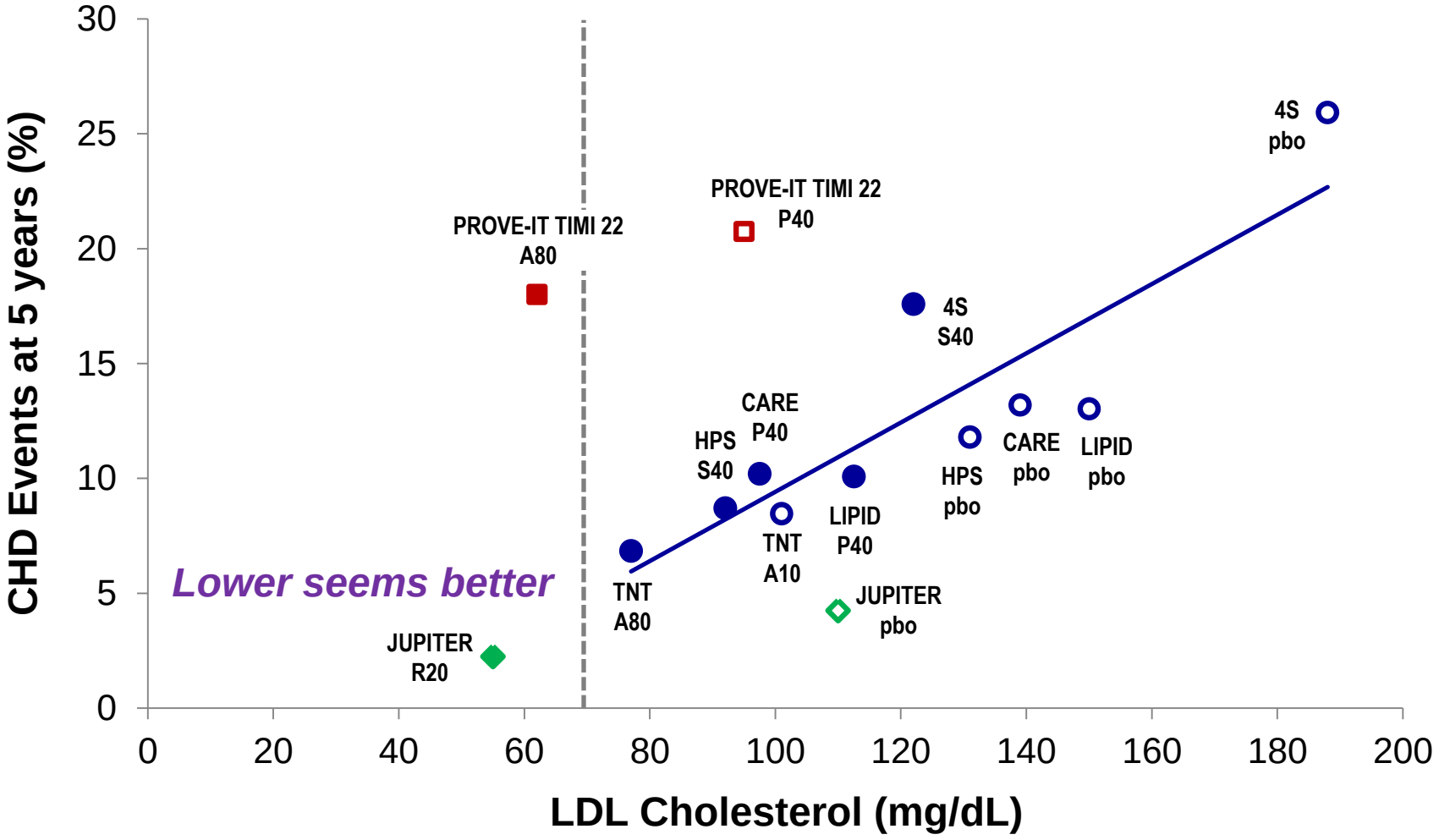


Lower Risk of Cardiovascular Events via Multiple Genetic Variants Affecting LDL-C



Ference BA et al. JACC 2012;60:2631–9

LDL Cholesterol & Coronary Events

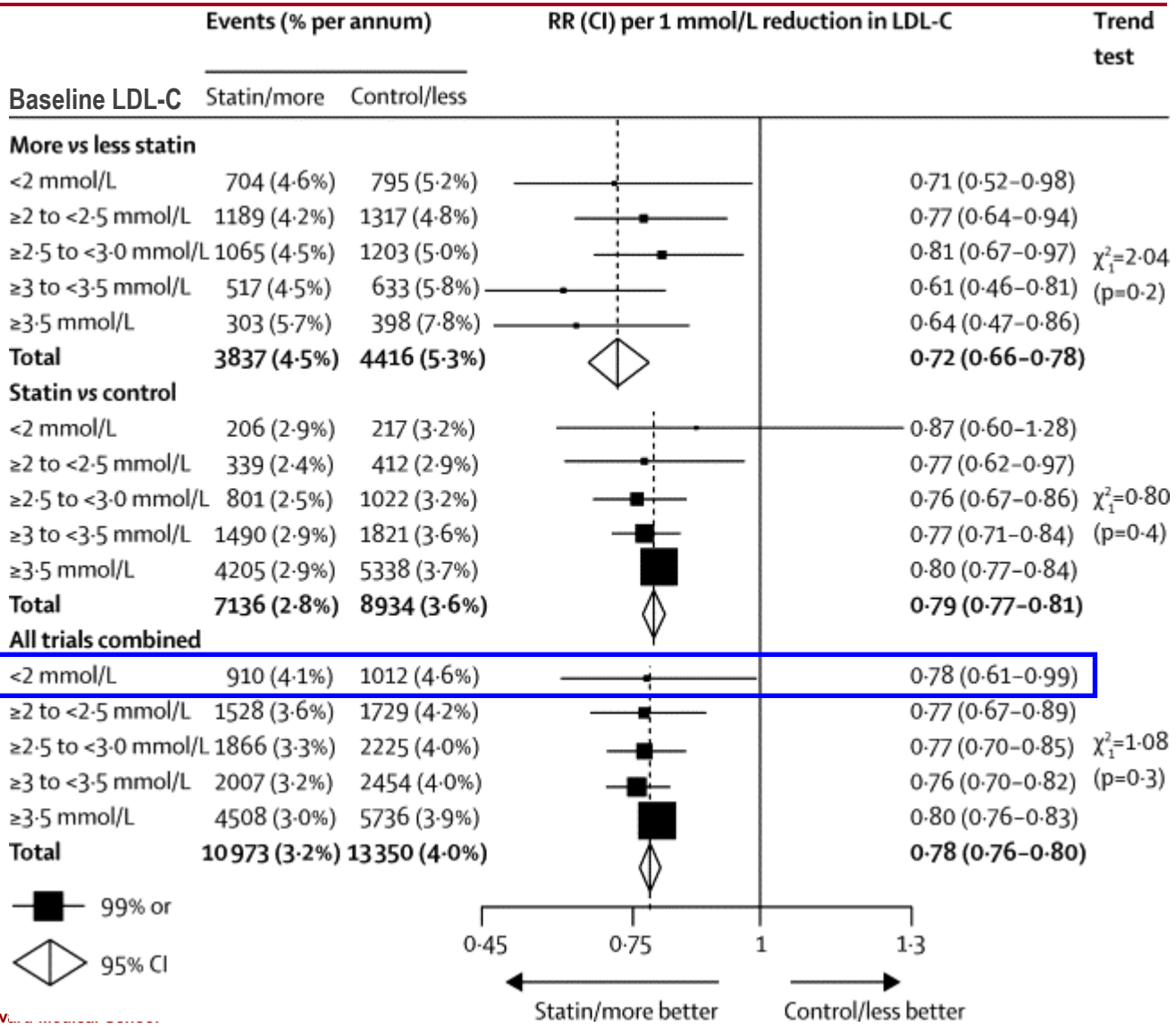


Meta-analysis Supporting Benefit of Lowering LDL-C, Even When Starting "Low"

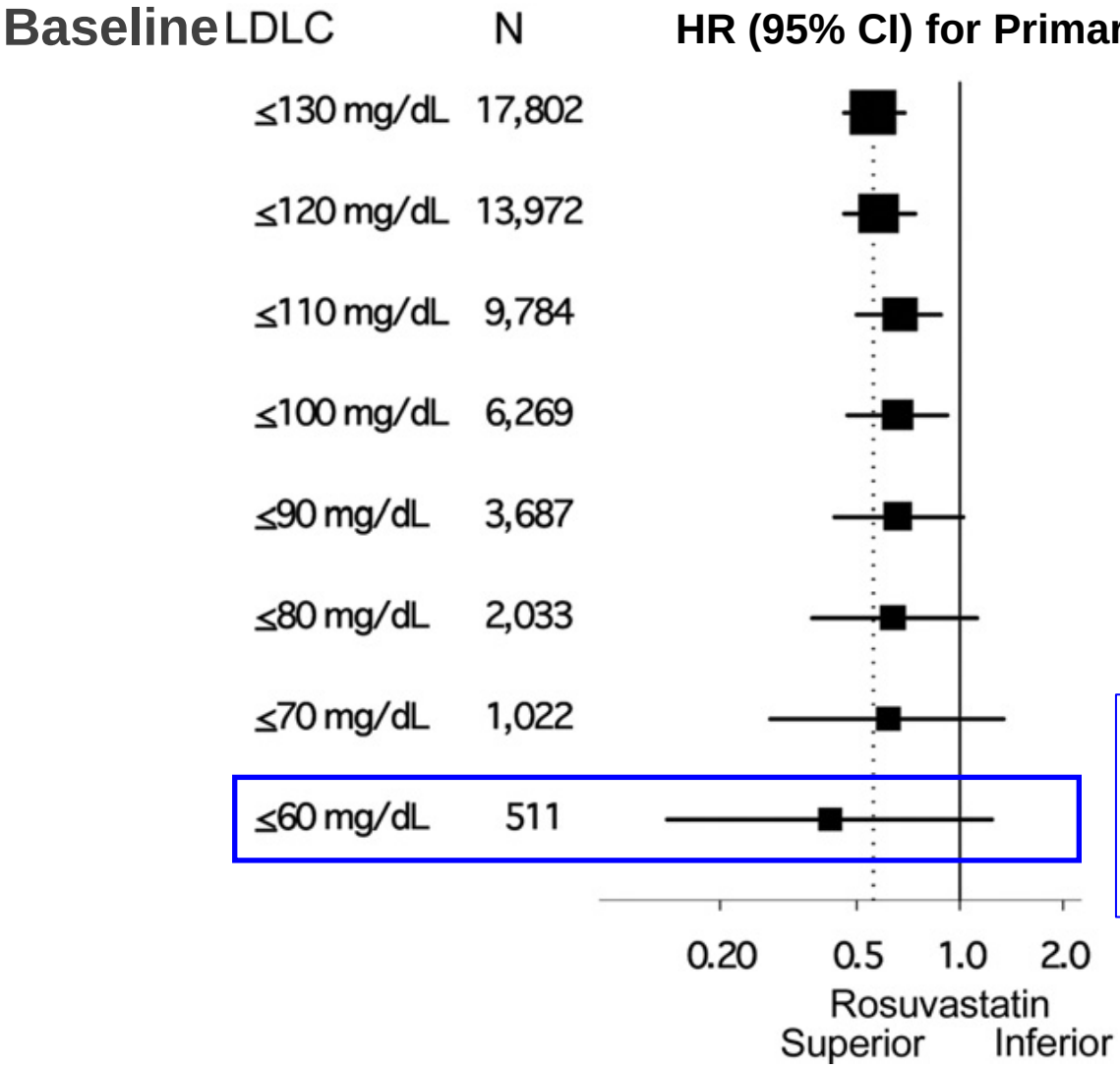
>160,000 pts

CTT Cycle #2
***Lancet* 2010;**
376:1670-81

Benefit similar even if starting with LDL-C <77 mg/dL



Risk Reduction in JUPITER by Baseline LDL-C



Overall in trial, rosuvastatin reduced LDL-C by 50%, suggesting achieved LDL-C of ≤30 mg/dL in this subgroup

Hsia J et al. *JACC* 2011; 57:1666-75

Study Design

IMPROVE-IT

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

*3.2mM
**2.6mM

N=18,144

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

90% power to detect ~9% difference

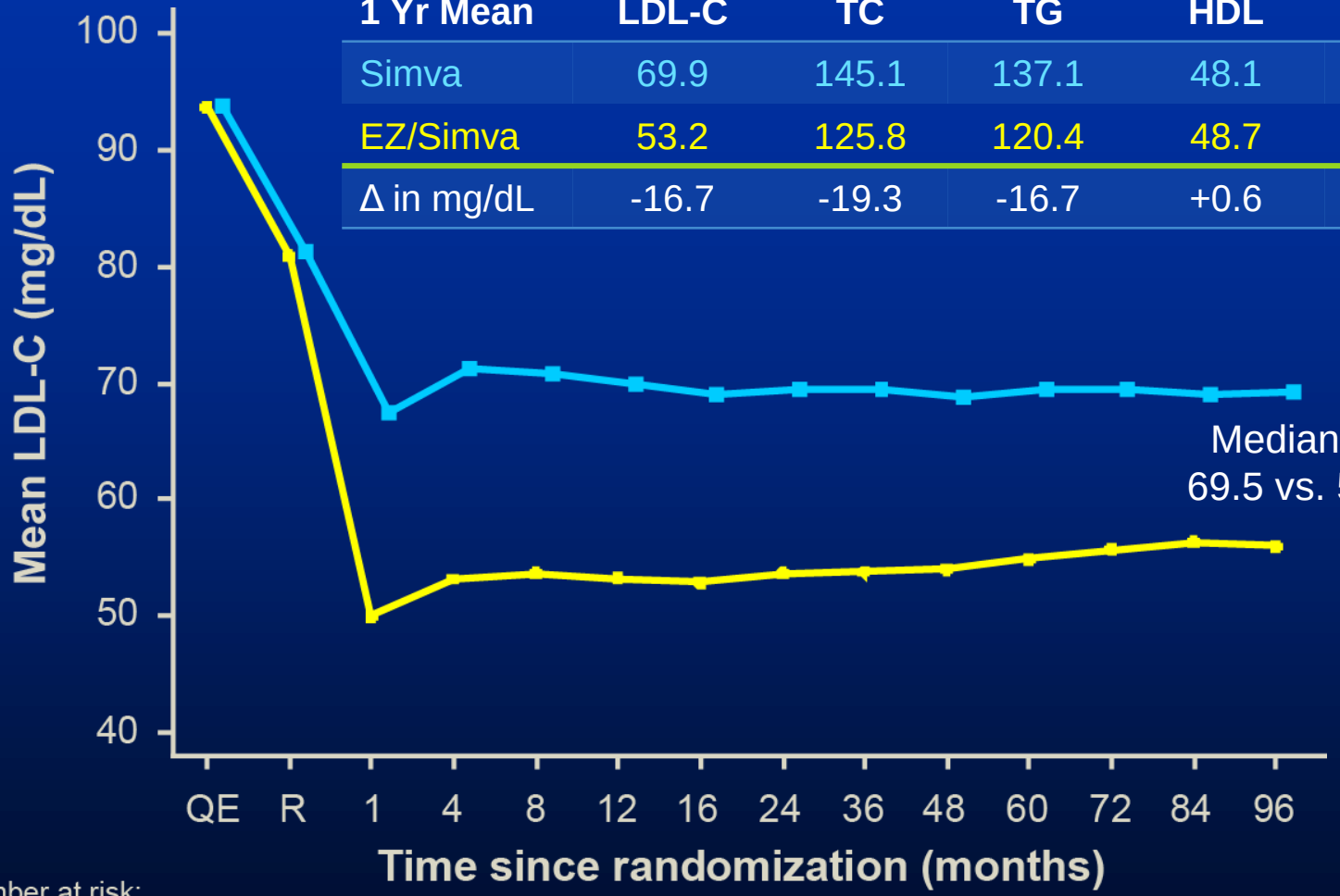
Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

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

LDL-C and Lipid Changes

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



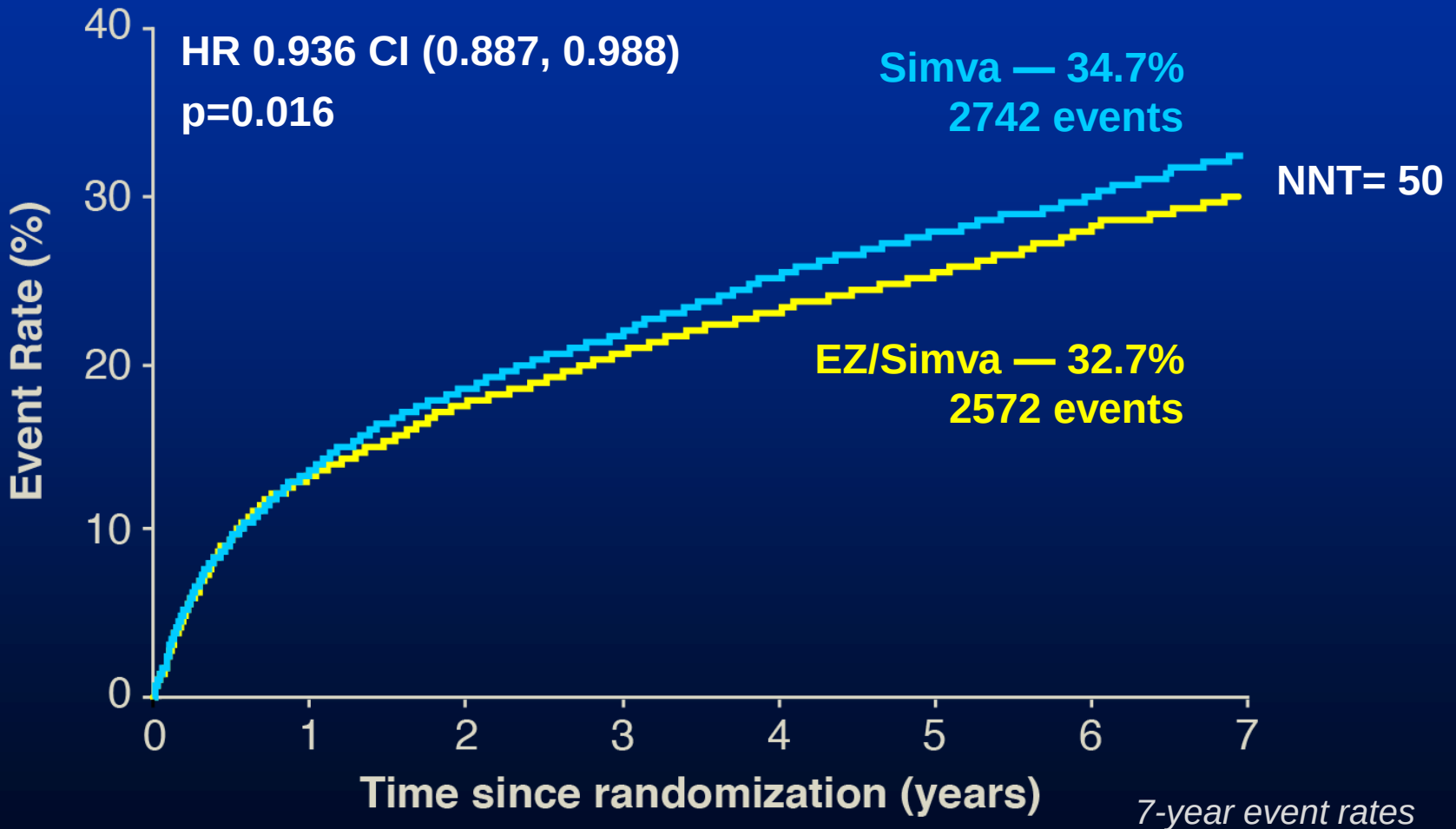
Median Time avg
69.5 vs. 53.7 mg/dL

Number at risk:

EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

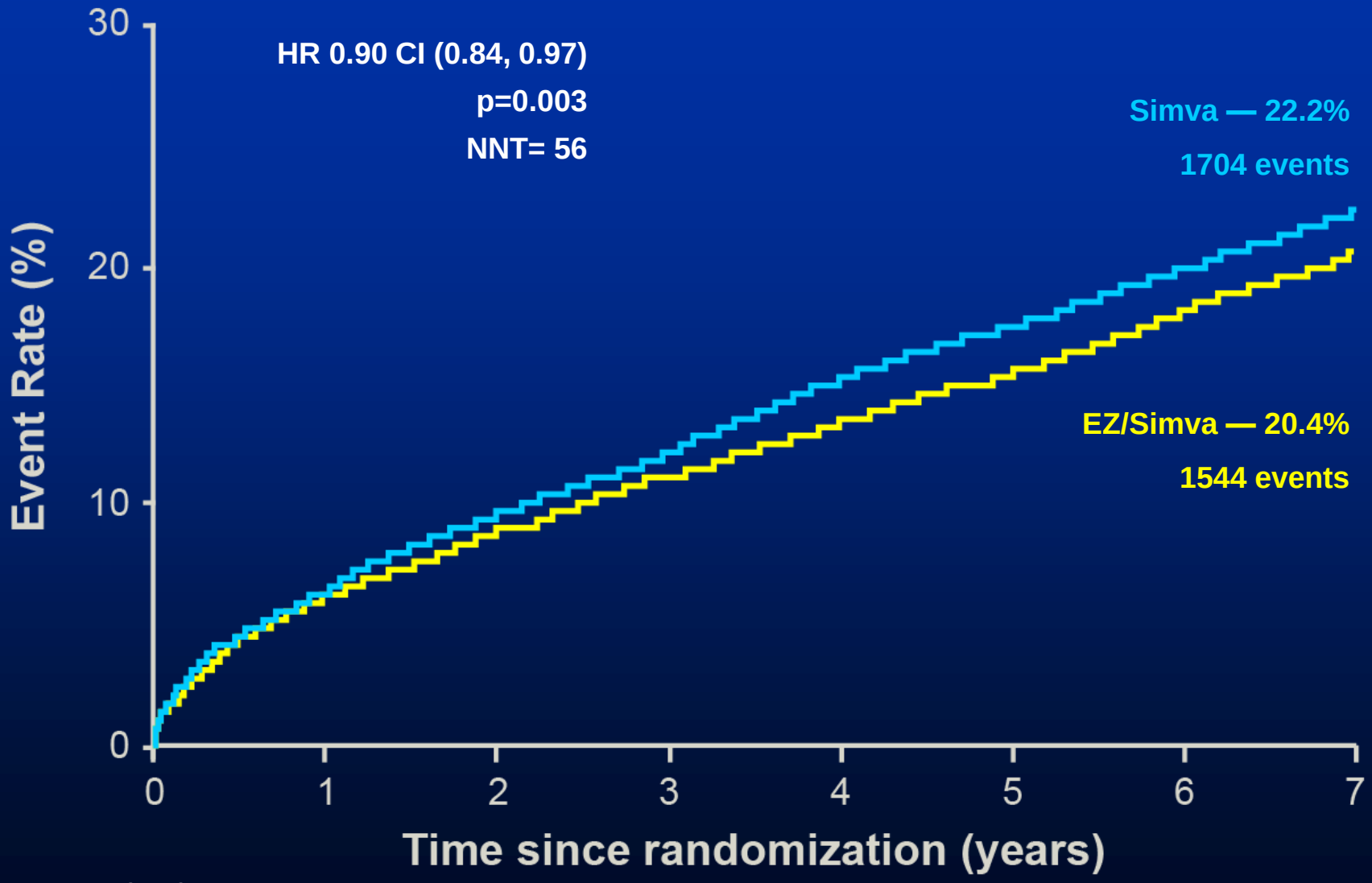
Primary Endpoint — ITT

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



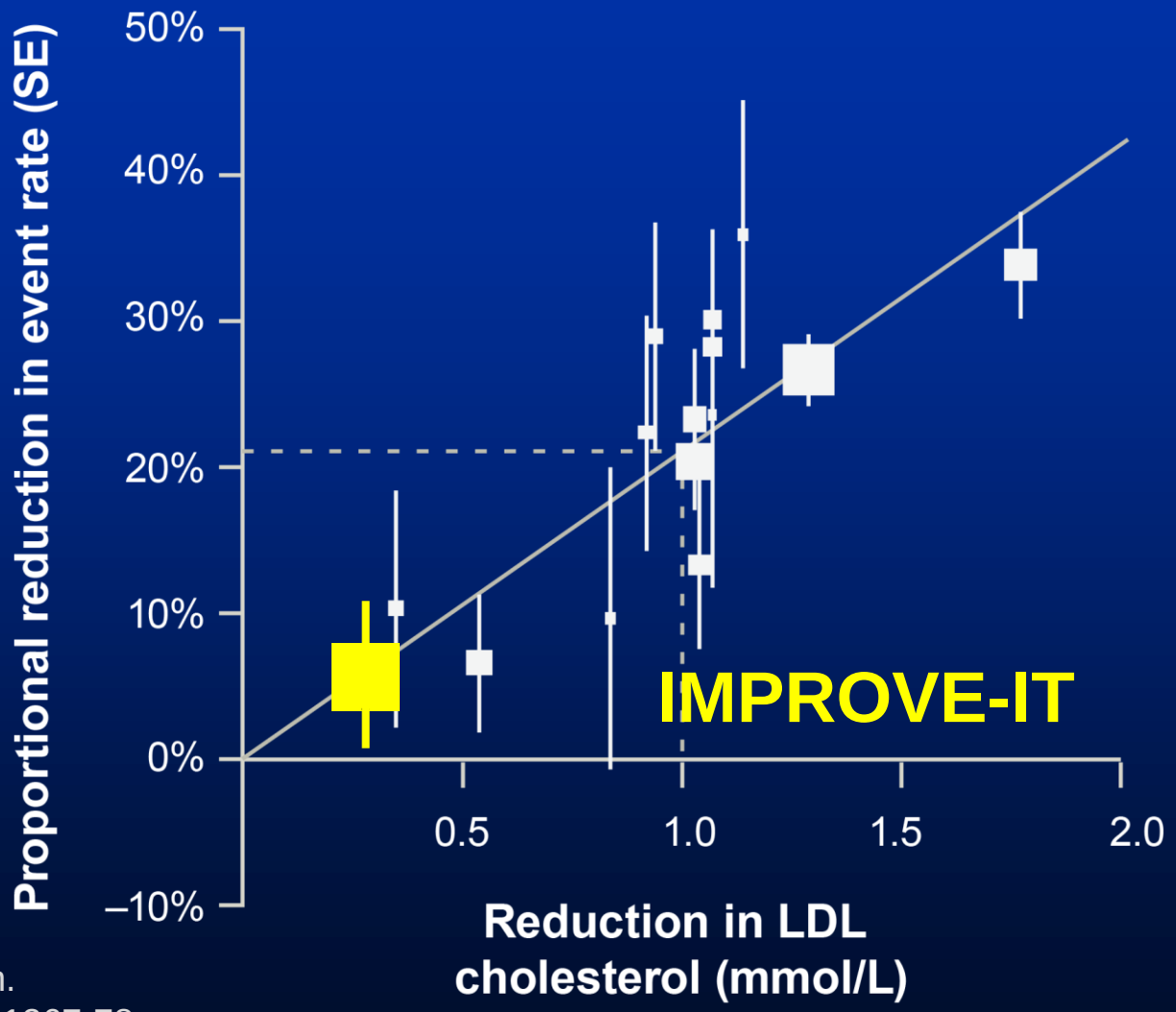
7-year event rates

CV Death, Non-fatal MI, or Non-fatal Stroke



7-year event rates

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.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) Mutations

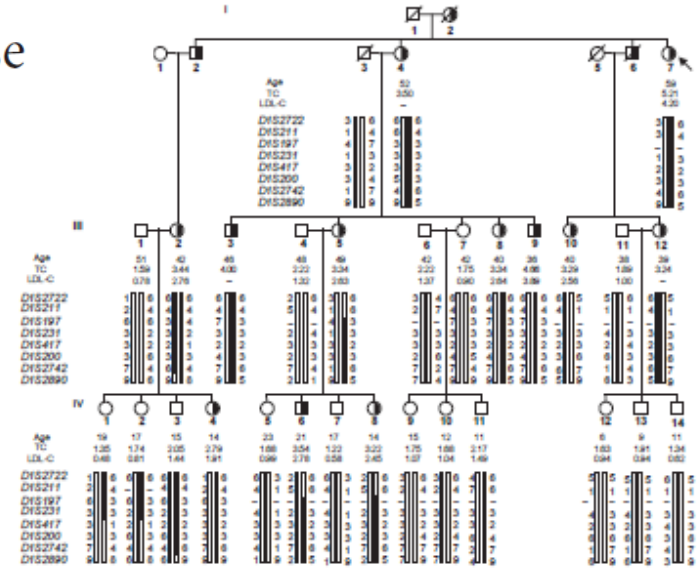
nature

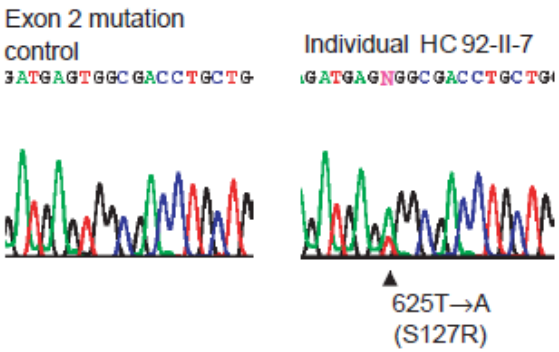
Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

Affected family members with:

- **Total chol in 90th percentile**
- **Tendon xanthomas**
- **CHD, Early MI**
- **Stroke**

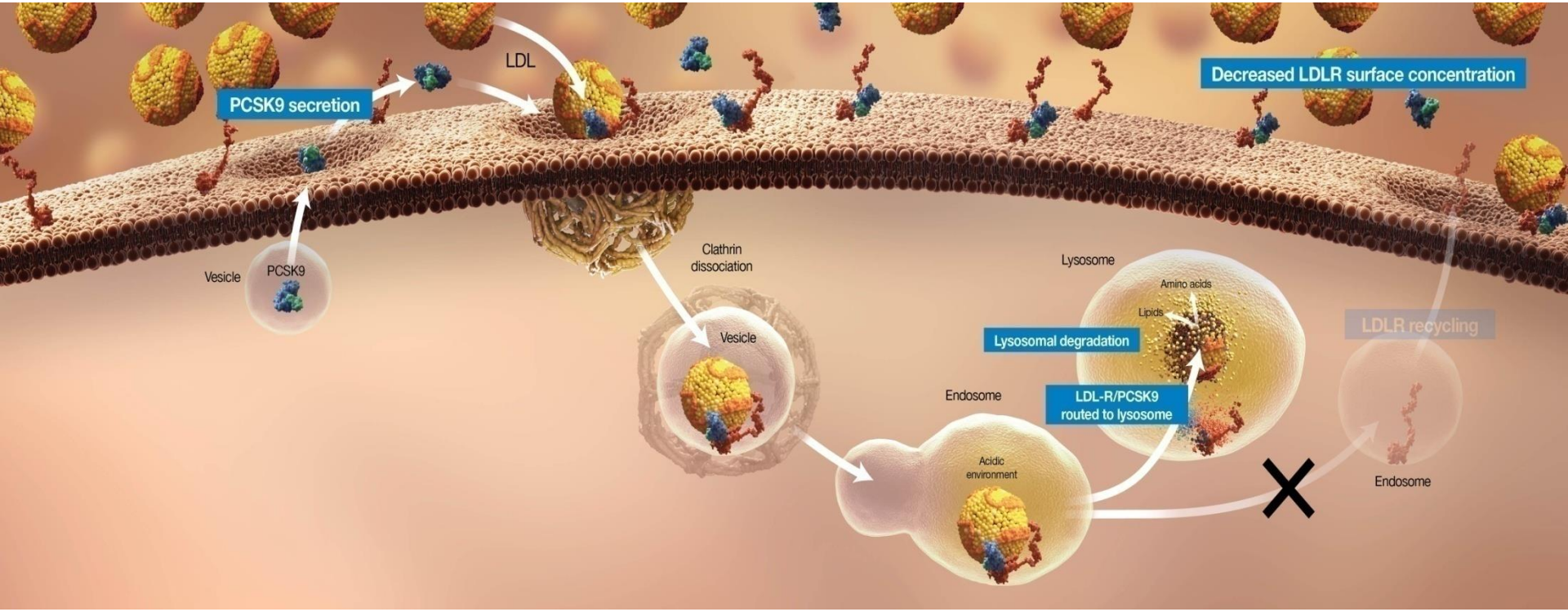
Family HC92 Pedigree





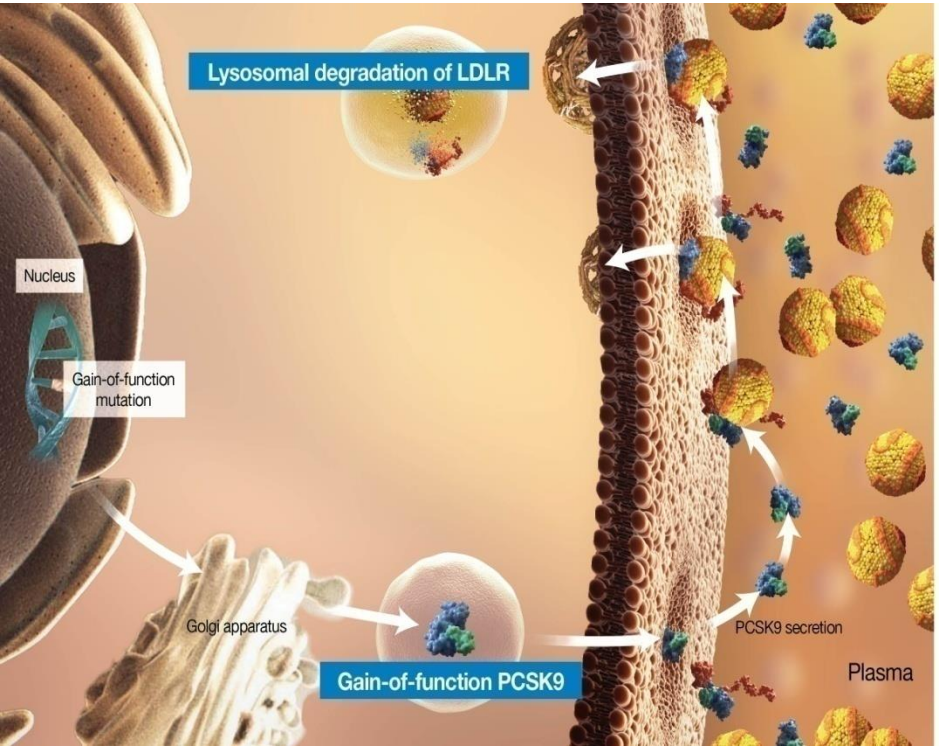
Abifadel M, et al. *Nature Genet*. 2003;34:154-156.

PCSK9 Regulates the Surface Expression of LDL-Rs by Targeting Them for Lysosomal Degradation



Qian YW, et al. *J Lipid Res*. 2007;48:1488-1498.
Horton JD, et al. *J Lipid Res*. 2009;50:S172-S177.
Zhang DW, et al. *J Biol Chem.* 2007;282:18602-18612.

PCSK9 Mutations



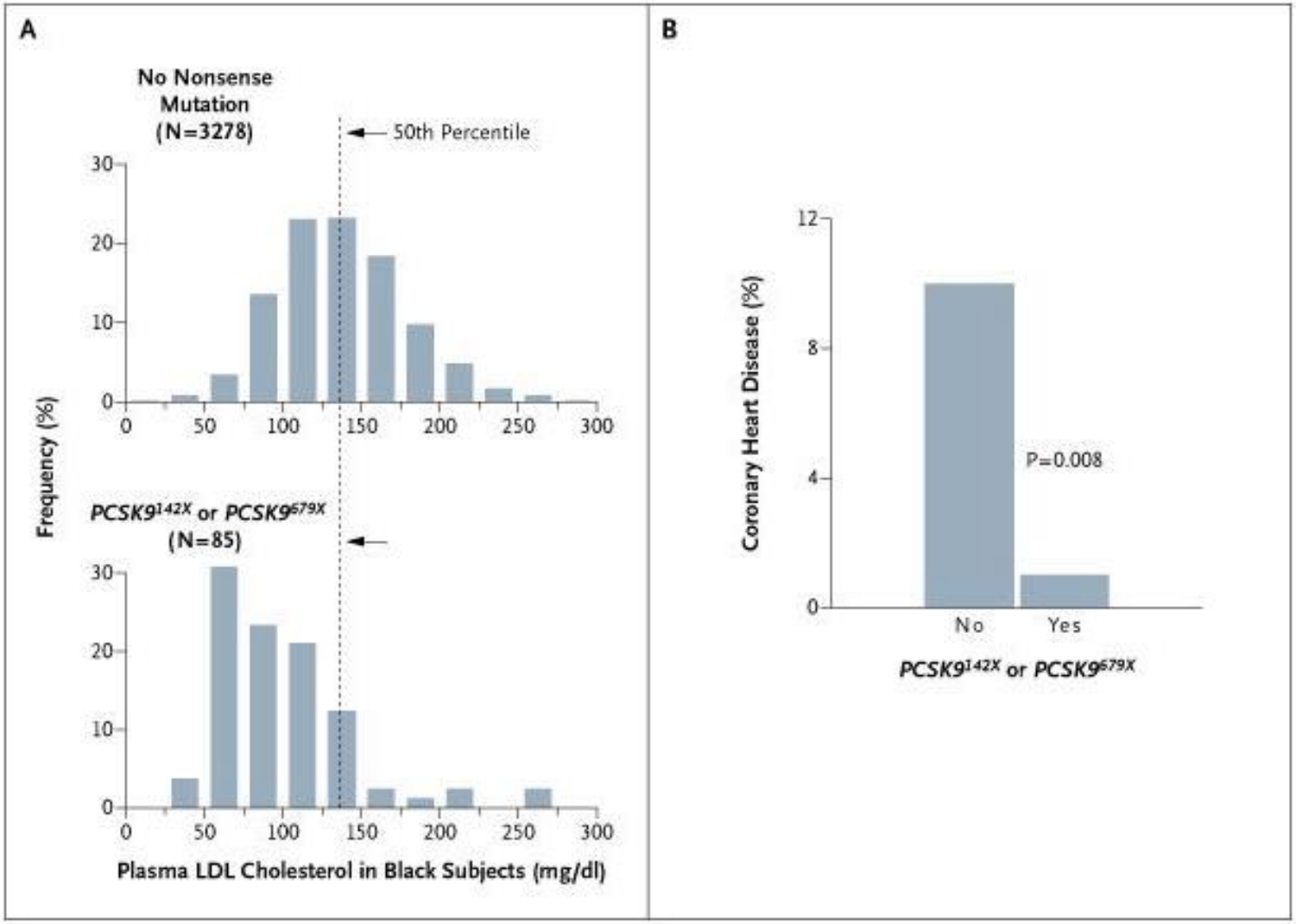
PCSK9 Gain-of-Function Mutations

↓ hepatic LDL receptors

↑ circulating LDL-C

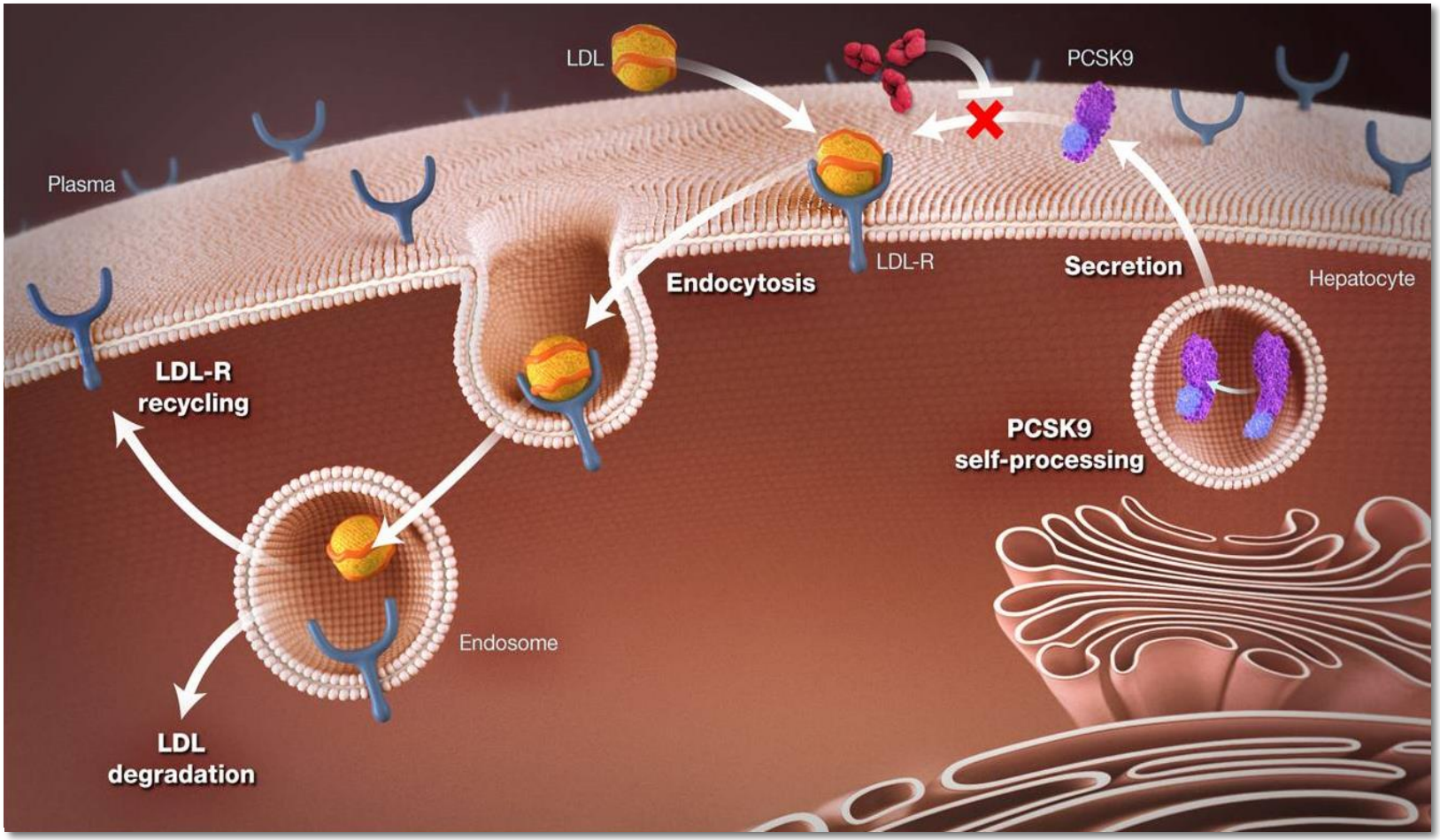
Familial hypercholesterolemia phenotype

PCSK9 Loss-of-Function Mutations: Effect of Lifelong Low LDL-C on CHD



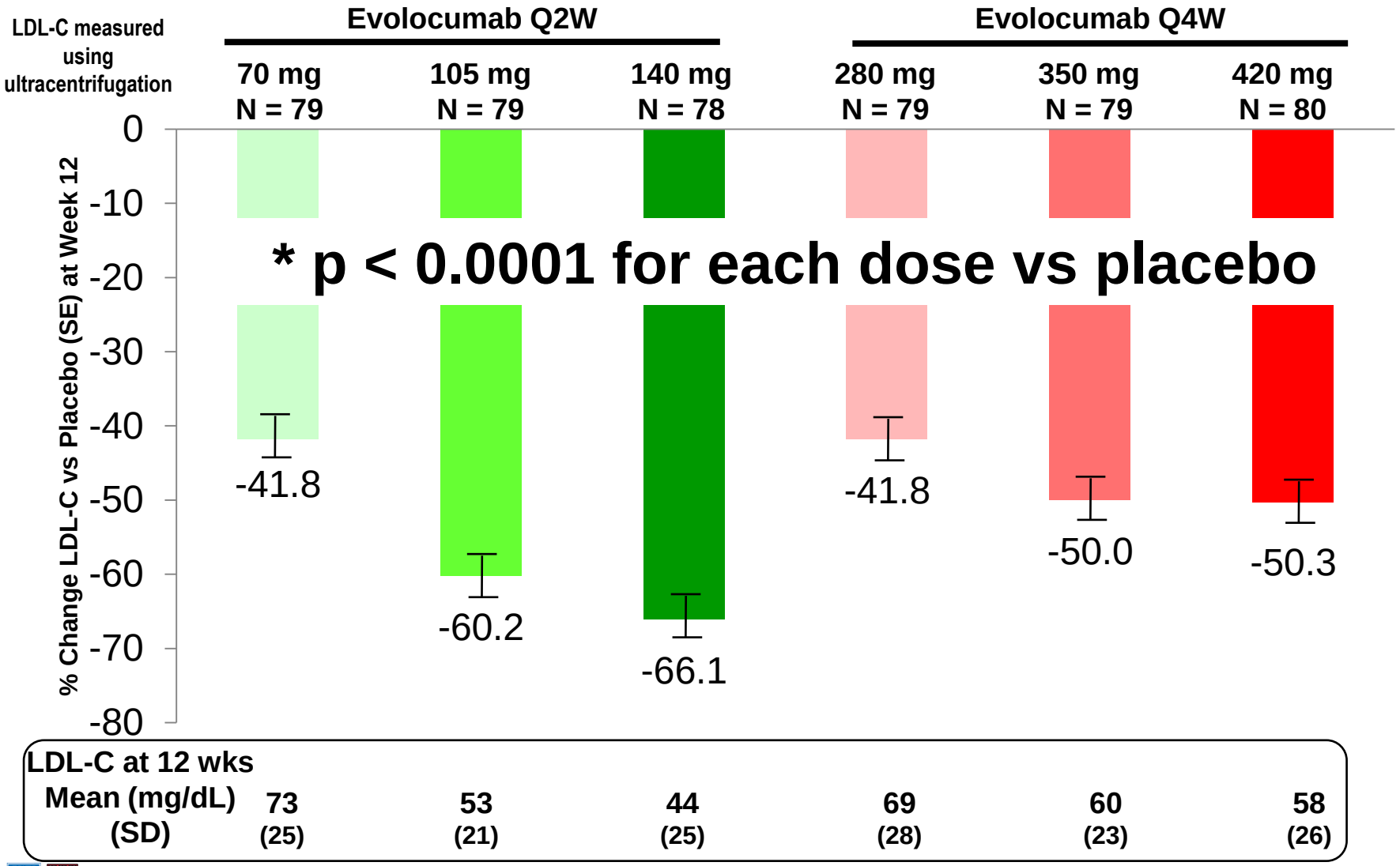
Cohen JC et al. *NEJM*. 2006;354:1264–1272

PCSK9 Inhibition with a Monoclonal Antibody



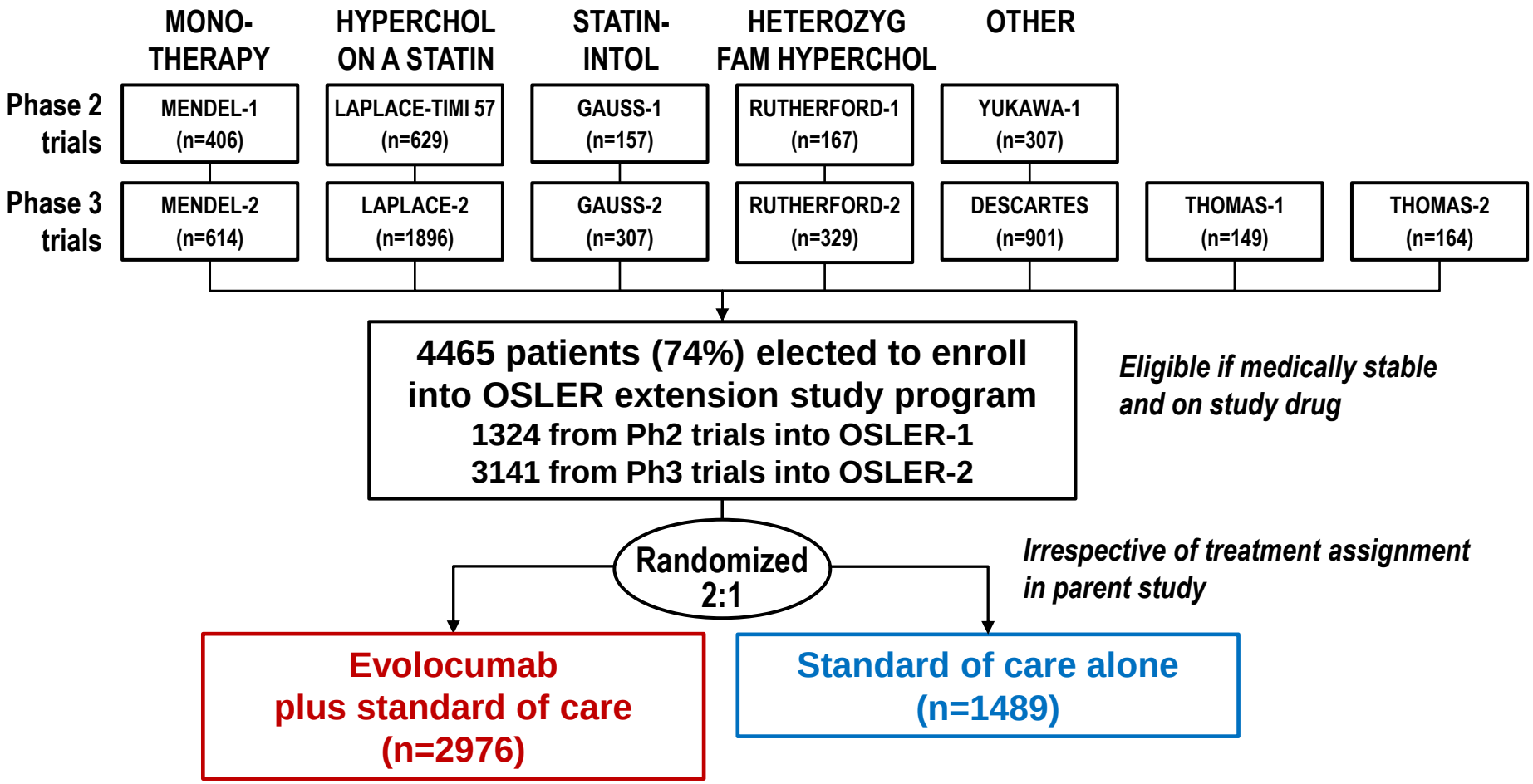
Qian YW, Schmidt RJ, Zhang Y, et al. *J Lipid Res*. 2007;48:1488-1498
Horton JD, Cohen JC, Hobbs HH. *J Lipid Res*. 2009;50(suppl):S172-S177
Rashid S et al. *PNAS* 2005;102:5374-5379
Chan JC, Piper DE, Cao Q, et al. *Proc Natl Acad Sci U S A.* 2009;106:9820-9825

LDL-C Reduction in 631 Patients w/ Hypercholesterolemia on Statins



Giugliano RP et al. and Sabatine MS. *Lancet* 2012;380:2007-17.

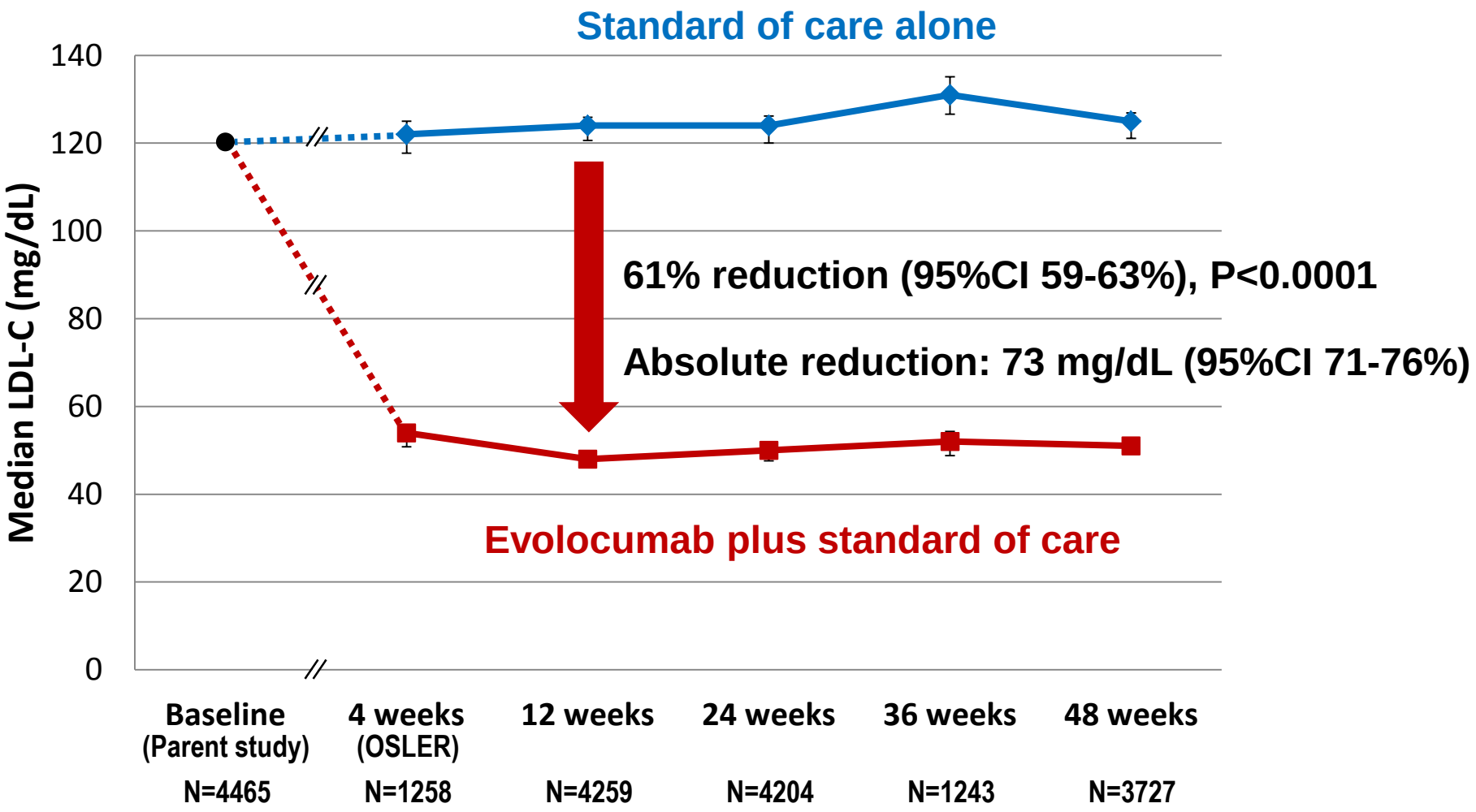
OSLER Program



Median follow-up of 11.1 months (IQR 11.0-12.8)
7% discontinued evolocumab early
96% completed follow-up

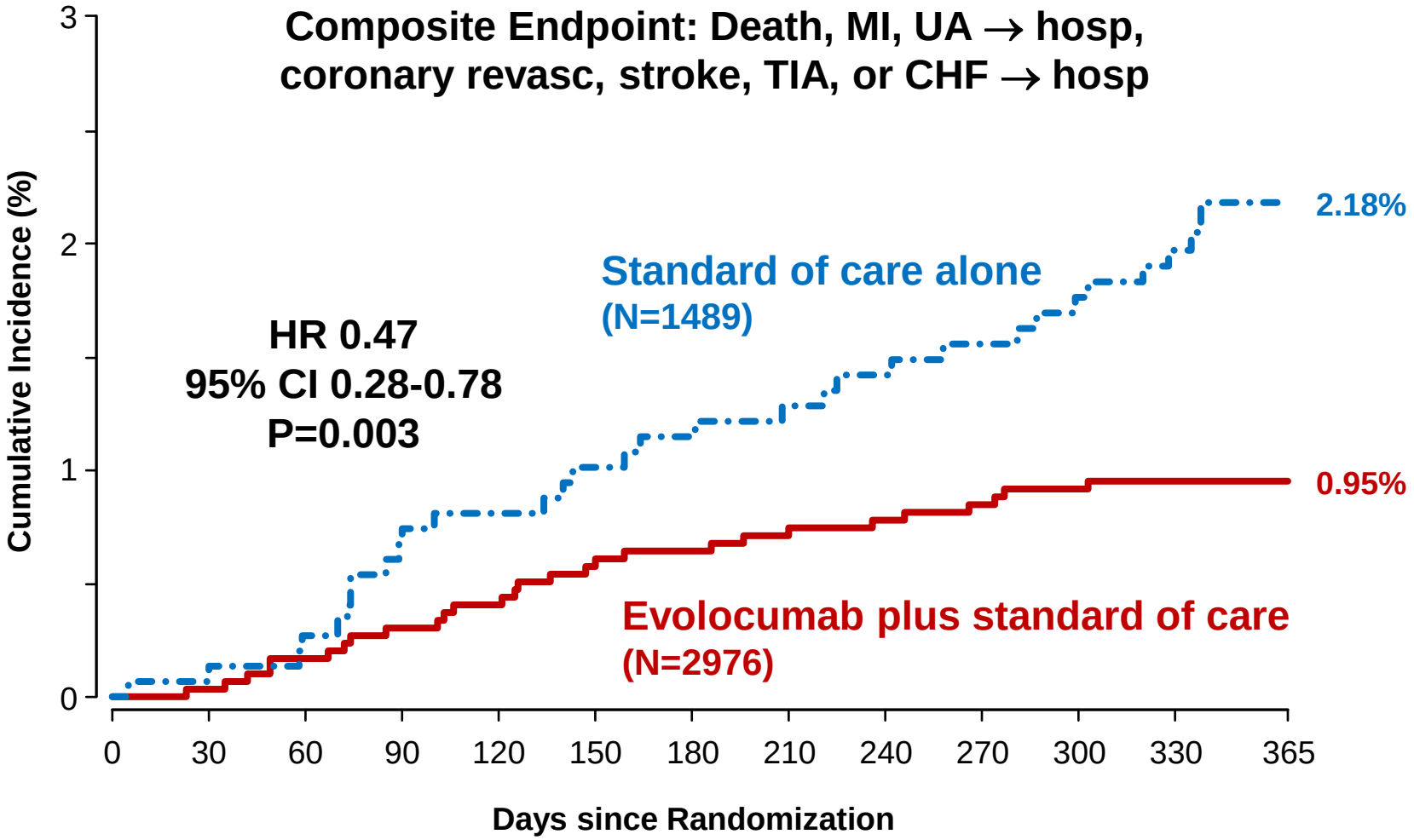
Trial Sponsor: Amgen

LDL Cholesterol



Sabatine MS et al. *NEJM* 2015;epub ahead of print

Cardiovascular Outcomes



Sabatine MS et al. *NEJM* 2015;epub ahead of print

Safety

	Evolocumab + stnd of care (N=2976)	Standard of care alone (N=1489)
Adverse events (%)		
Any	69.2	64.8
Serious	7.5	7.5
Leading to discontinuation of evolocumab	2.4	n/a
Injection-site reactions	4.3	n/a
Muscle-related	6.4	6.0
Neurocognitive	0.9	0.3
Laboratory results (%)		
ALT or AST >3×ULN	1.0	1.2
Creatine kinase >5×ULN	0.6	1.2

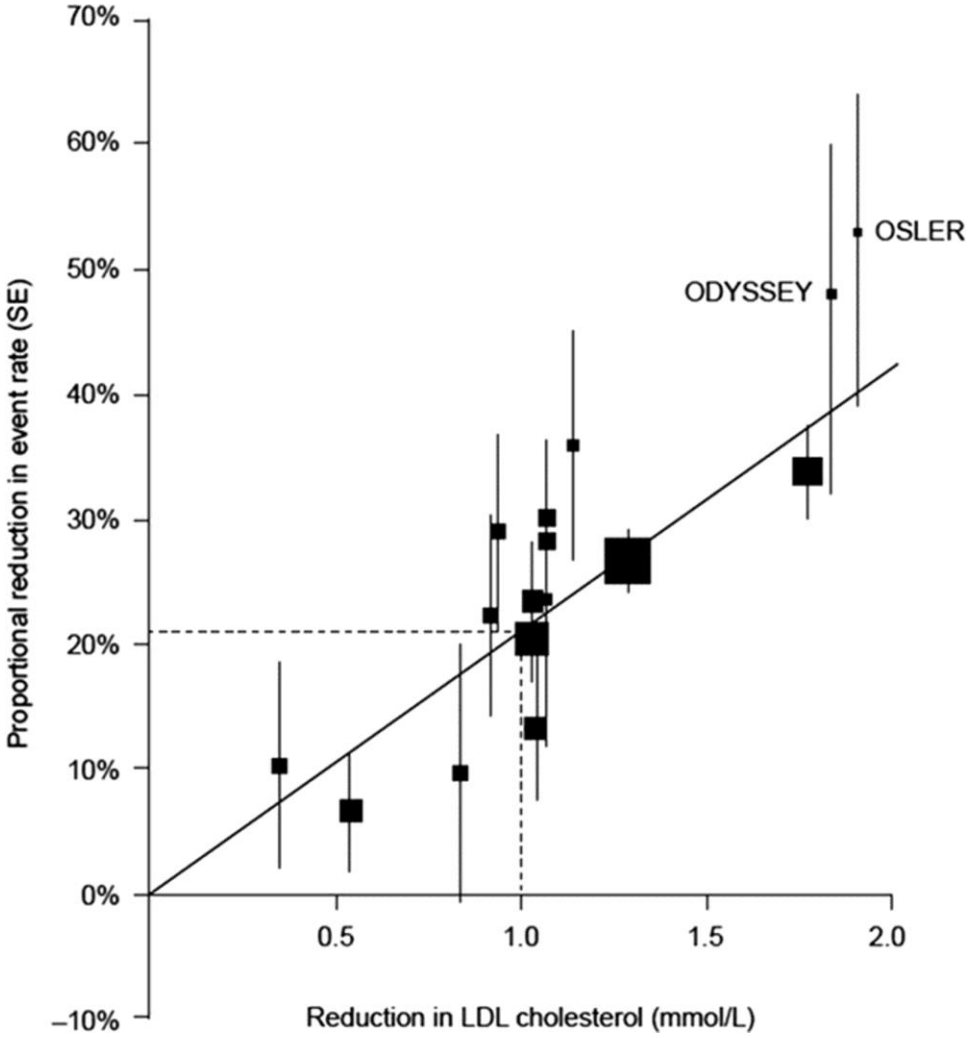
Sabatine MS et al. *NEJM* 2015;epub ahead of print

Adverse Events by Achieved LDL-C

	Evolocumab subjects stratified by minimum achieved LDL-C				All EvoMab (n=2976)	Stnd of Care Alone (n=1489)
	<25 mg/dL (n=773)	25 to <40 mg/dL (n=759)	<40 mg/dL (n=1532)	≥40 mg/dL (n=1426)		
Adverse Events (%)						
Any	70.0	68.1	69.1	70.1	69.2	64.8
Serious	7.6	6.9	7.2	7.8	7.5	7.5
Muscle-related	4.9	7.1	6.0	6.9	6.4	6.0
Neurocognitive	0.5	1.2	0.8	1.0	0.9	0.3
Lab results (%)						
ALT/AST >3×ULN	0.9	0.8	0.8	1.3	1.0	1.2
CK >5×ULN	0.4	0.9	0.7	0.5	0.6	1.2

Sabatine MS et al. *NEJM* 2015;epub ahead of print

Relationship between reduction in LDL-C and Relative Risk Reduction in CV events



Waters DD and Hsue PY. *Circulation Research*.2015;116:1643-1645

FDA Approval

Evolocumab (REPATHA) is indicated as an adjunct to diet and:

1. Maximally tolerated statin therapy for treatment of adults with
   a) Heterozygous familial hypercholesterolemia (HeFH) or
   b) Clinical atherosclerotic cardiovascular disease (CVD),

   ***who require additional lowering of LDL-C*.**
2. Other LDL-lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C

Alirocumab (PRALUENT) is indicated as an adjunct to diet and:

1. Maximally tolerated statin therapy for treatment of adults with
   a) Heterozygous familial hypercholesterolemia (HeFH) or
   b) Clinical atherosclerotic cardiovascular disease (CVD),

   ***who require additional lowering of LDL-C*.**

Cardiovascular Outcomes Trials of PCSK9 Inhibitors

	Alirocumab (SAR236553 /REGN727)	Evolocumab (AMG 145)	Bococizumab (RN 316)	
Sponsor	Sanofi / Regeneron	Amgen	Pfizer	
Trial	**ODYSSEY Outcomes**	**FOURIER**	**SPIRE I**	**SPIRE II**
Sample size	18,000	27,500	12,000	6,300
Patients	4-52 wks post-ACS	MI, stroke or PAD	High risk of CV event	
Statin	Evid-based med Rx	Atorva ≥20 mg or equiv	Lipid-lowering Rx	
LDL-C (mg/dL)	≥70	≥70	70-99	≥100
PCSK9i Dosing	Q2W	Q2W or Q4W	Q2W	
Endpoint	CHD death, MI, ischemic stroke, or hosp for UA	1°: CV death, MI, stroke, hosp for UA, or cor revasc Key 2°: CV death, MI, or stroke	CV death, MI, stroke, or urgent revasc	
Completion	2016-2017	Before end of 2016	2017	

Conclusions

- **Patients at high risk should be treated with high-intensity statin therapy**
- **To date, no floor has been identified beyond which lowering LDL-C does not provide clinical benefit**
- **The benefits of lower LDL-C are seen with a variety of pharmacologic interventions and genetic variants**
- **We now have data that ezetimibe reduces CV events**
- **PCSK9 inhibitors reduce LDL-C by ~60% and we have preliminary data that they reduce CV events**