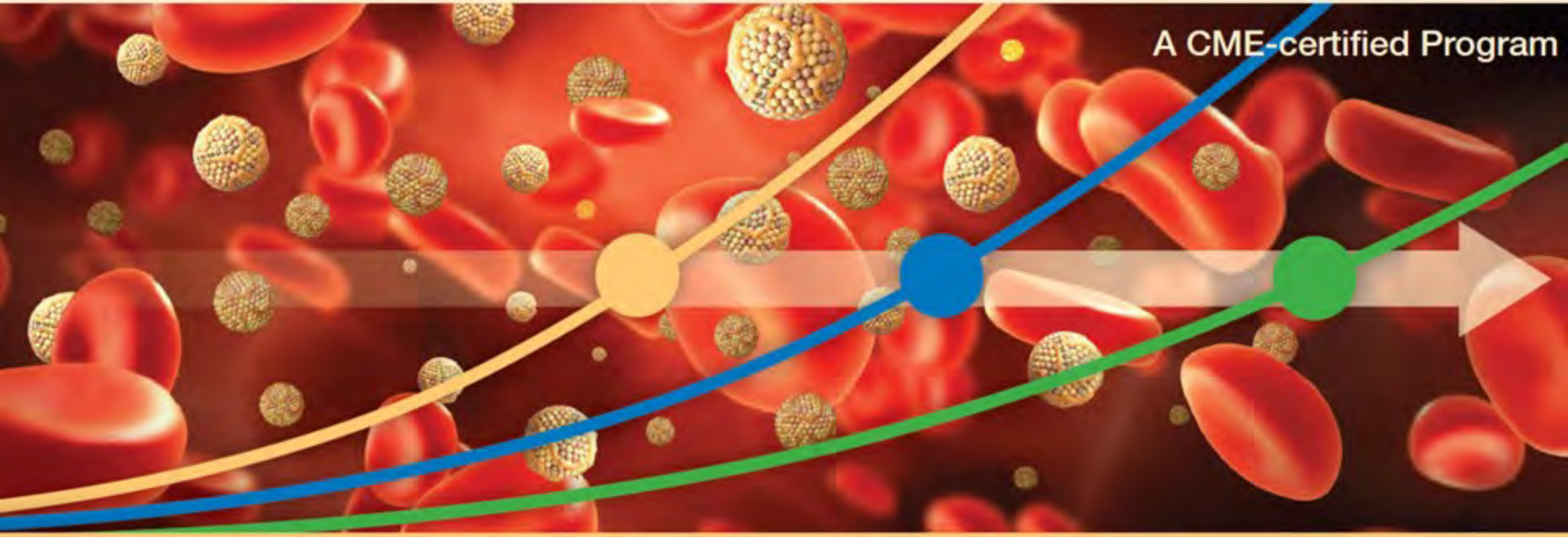
Managing Severe or Resistant Hypercholesterolemia

The Next Generation of LDL-C Lowering Agents



Jointly provided by the Potomac Center for Medical Education and Rockpointe

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Disclosures

Faculty and Steering Committee Disclosures

The faculty and steering committee reported the following relevant financial relationships that they or their spouse/partner have with commercial interests:

Michael Miller, MD, FACC, FAHA: *Consultant/Independent Contractor:* Pfizer: *National Coordinator:* SPIRE

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Non-faculty Disclosures

Non-faculty content contributors and/or reviewers reported the following relevant financial relationships that they or their spouse/partner have with commercial interests:

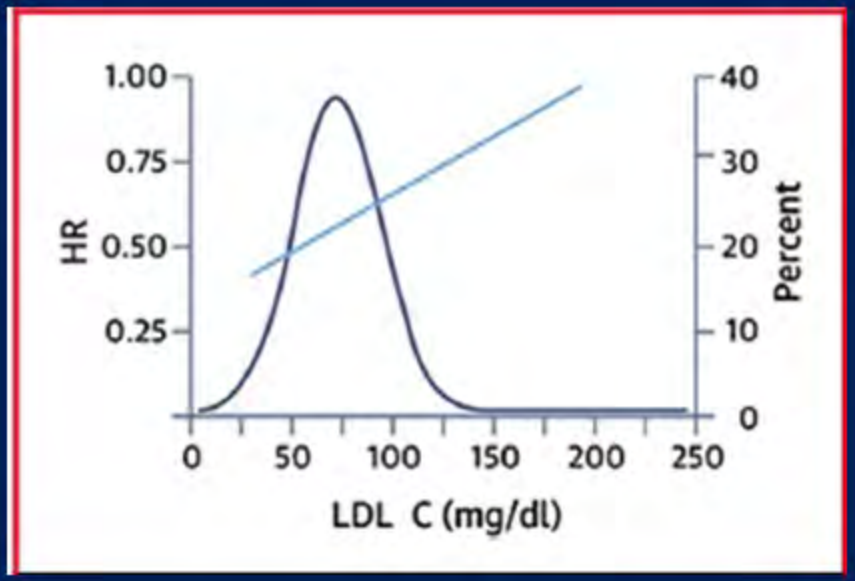
Barry Watkins, PhD; Blair St. Amand; Jay Katz, MA, CHCP; Lindsay Scott, PT, DPT, ATC: Nothing to disclose.

LDL-C

Metabolism and Pathobiology

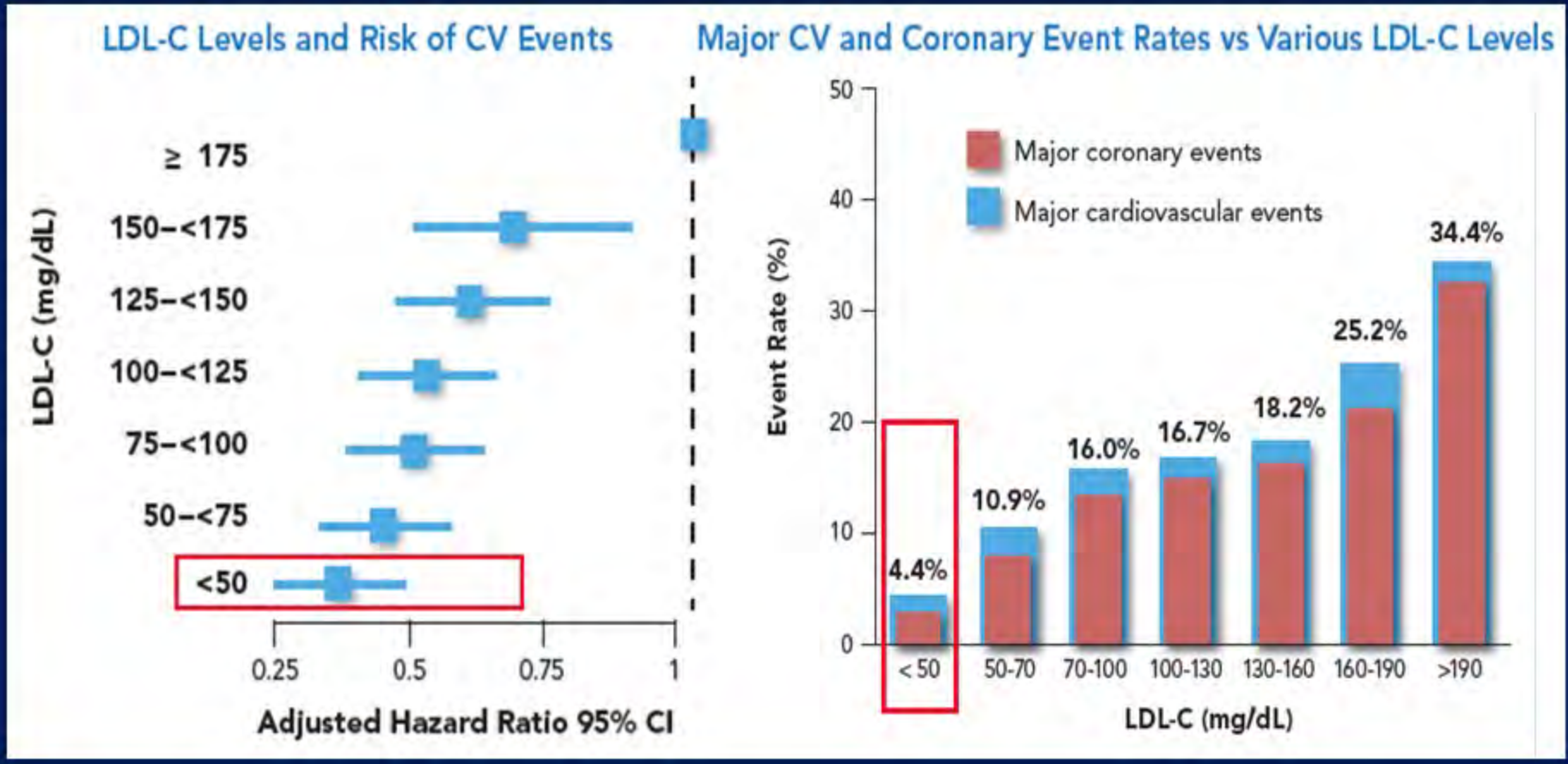
CONCLUSIONS The reductions of LDL-C, non-HDL-C, and apoB levels achieved with statin therapy displayed large interindividual variation. Among trial participants treated with high-dose statin therapy, >40% did not reach an LDL-C target <70 mg/dl. Patients who achieve very low LDL-C levels have a lower risk for major cardiovascular events than do those achieving moderately low levels. (J Am Coll Cardiol 2014;64:485–94) © 2014 by the American College of Cardiology Foundation.

When LDL-C is reduced to 50 mg/dL or lower, the risk for CV events is reduced ***by more than half.***



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

Mean Attained LDL-C on Statin Therapy and Risks of Secondary Cardiovascular Events



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

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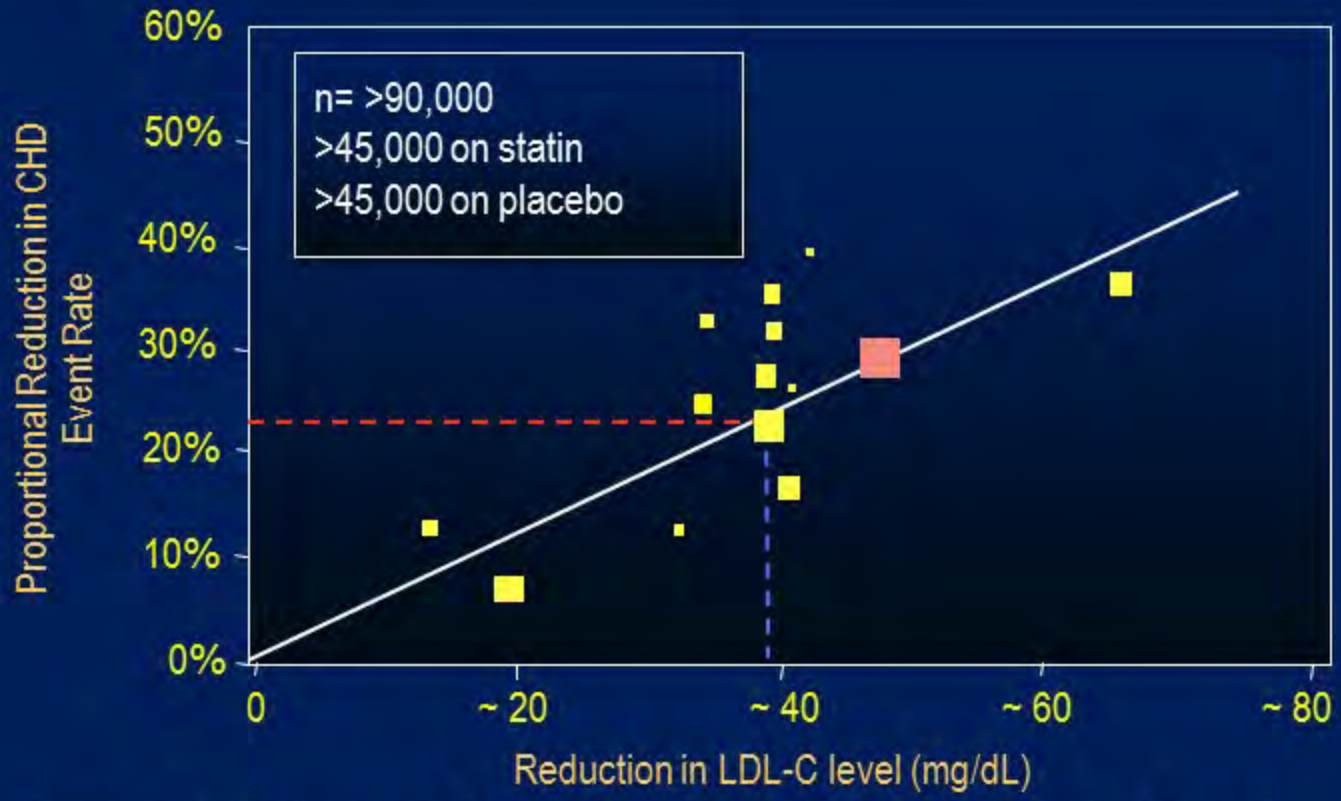
Relation Between Reduction in Incidence of Major CVD Events and Mean Absolute LDL-C

*Reduction at Year 1**



1 mmol/L reduction in LDL-C results in 20% reduction in CVD risk at 1 year

***Meta-analysis of 14 statin trials (CTT collaborators)**

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

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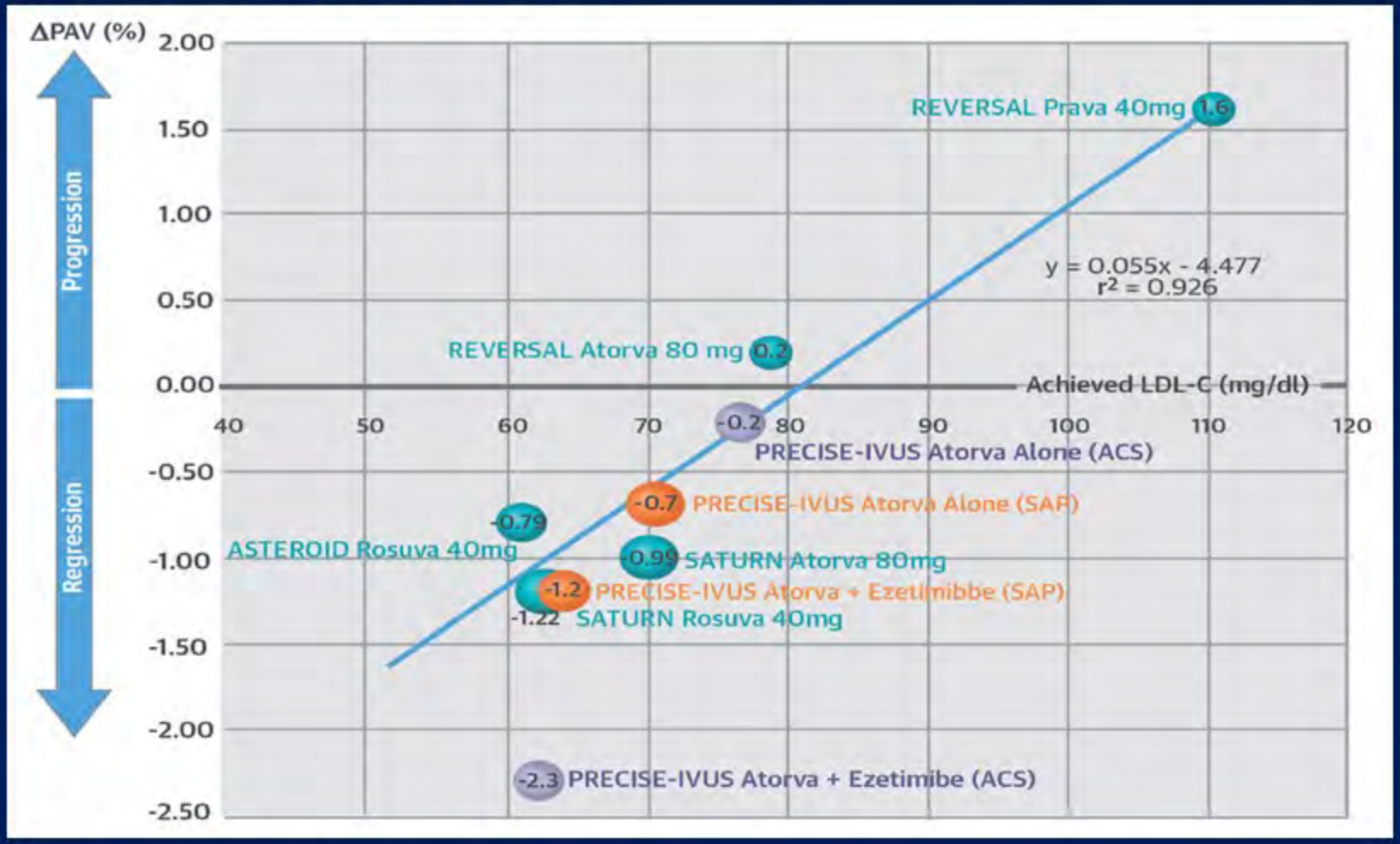
PRECISE-IVUS

Median Change in % Atheroma Volume (PAV) Relates to Achieved LDL-C Levels



Tsujita K et al. *J Am Coll Cardiol.* 2015;66:495-507.

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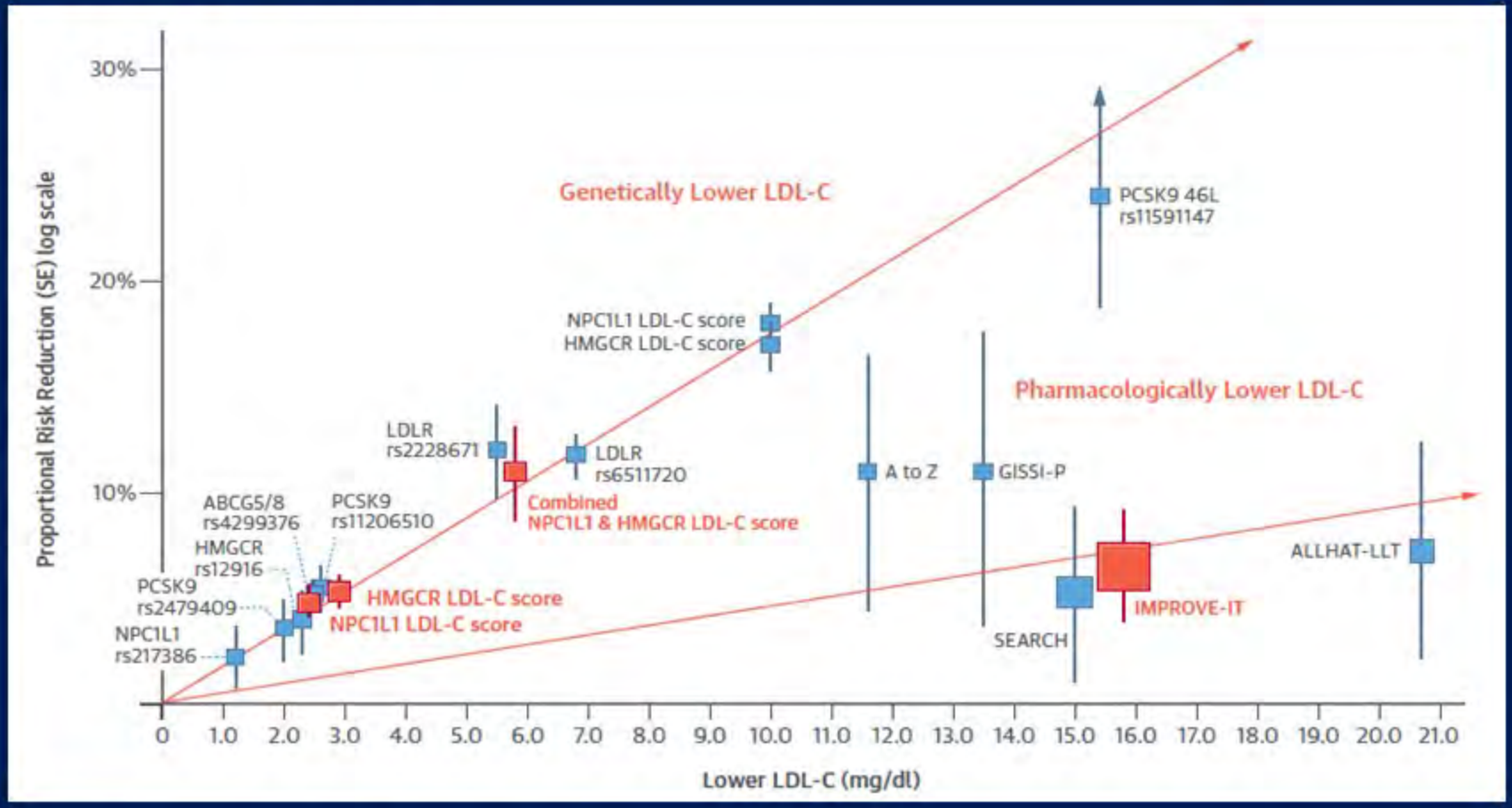
Cholesterol Metabolism

Targets for LDL-C Lowering

Genetically and *Pharmacologically* Mediated Reduction of LDL-C Lowers Risk of Coronary Heart Disease



Ference BA et al. *J Am Coll Cardiol.* 2015;65:1552-1561.

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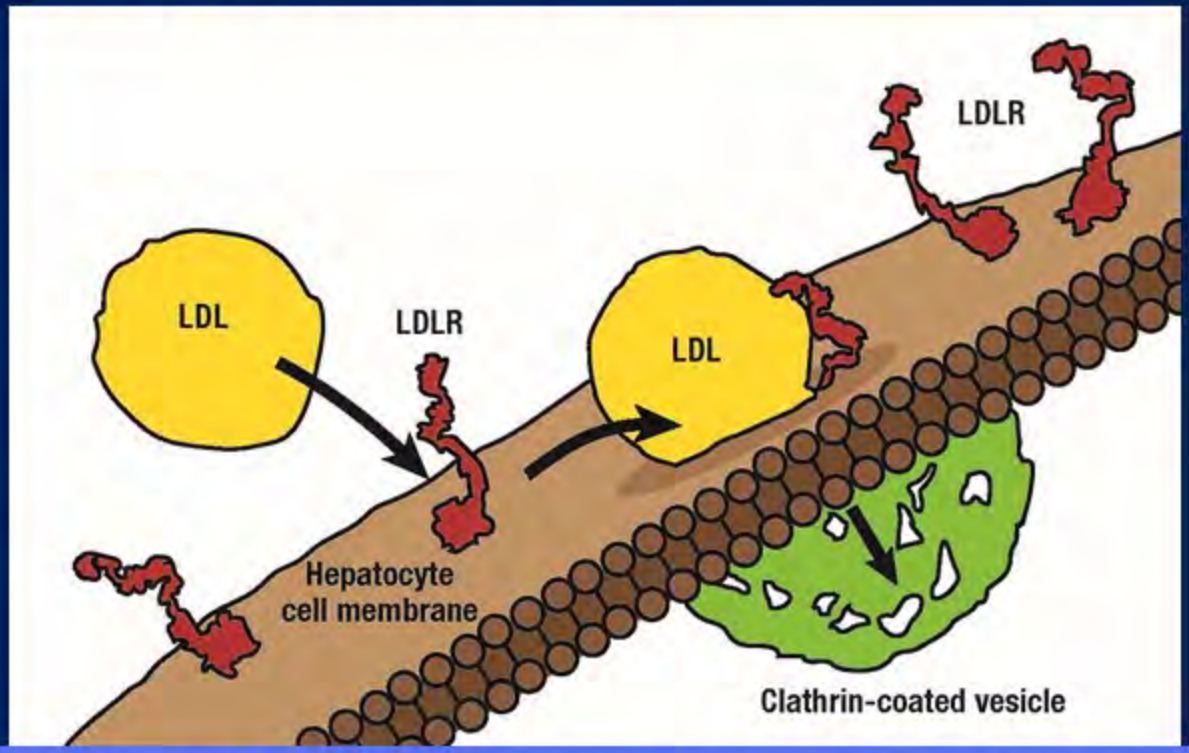
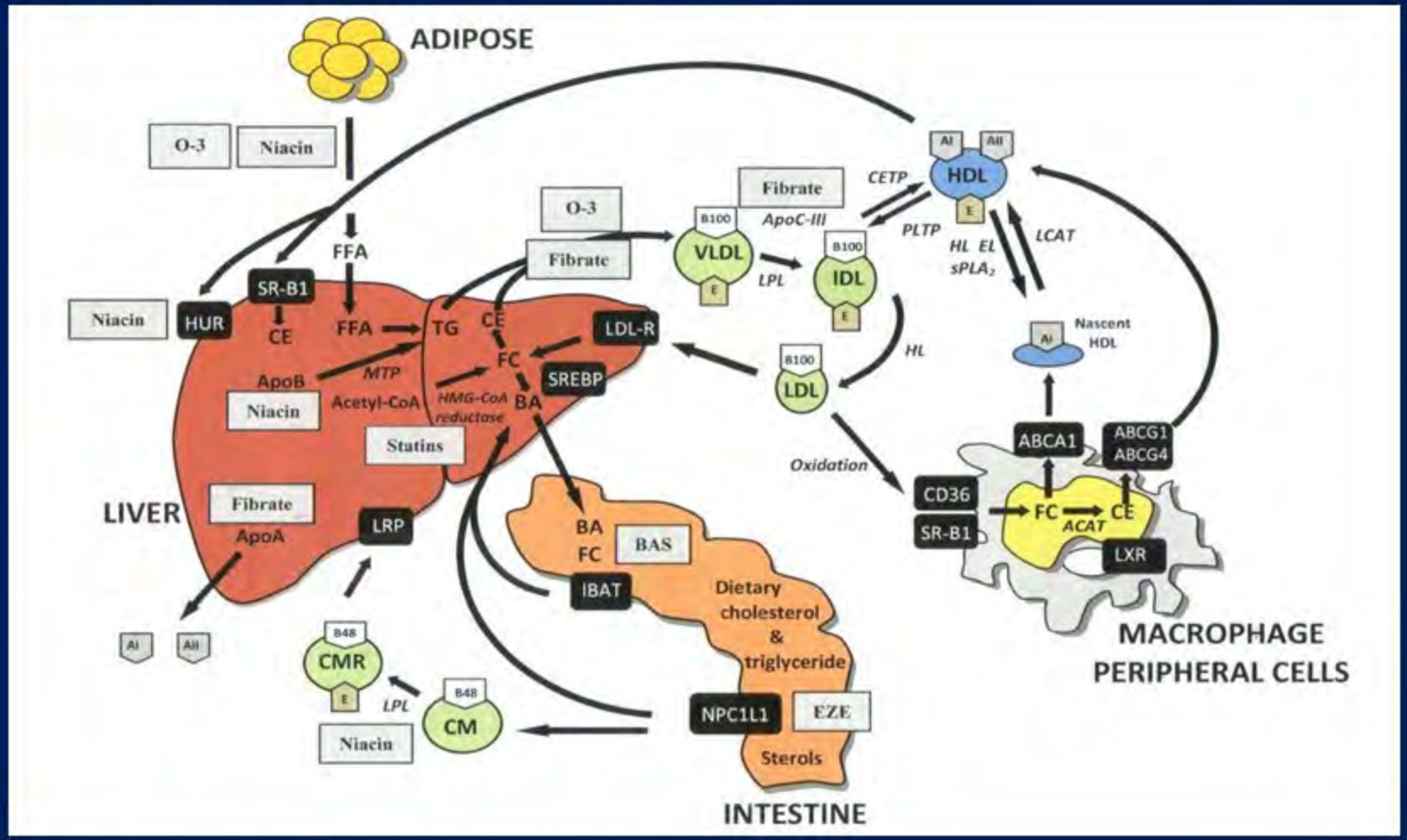
Hepatic LDL Receptors Play a Central Role in Cholesterol Homeostasis



- The LDL/LDLR complex is internalized into the hepatocyte via clathrin-coated vesicles, thereby removing LDL from the blood[1-3]
- Affinity of hepatic LDLR for apoB on LDL enables LDLRs to clear plasma LDL effectively[4]

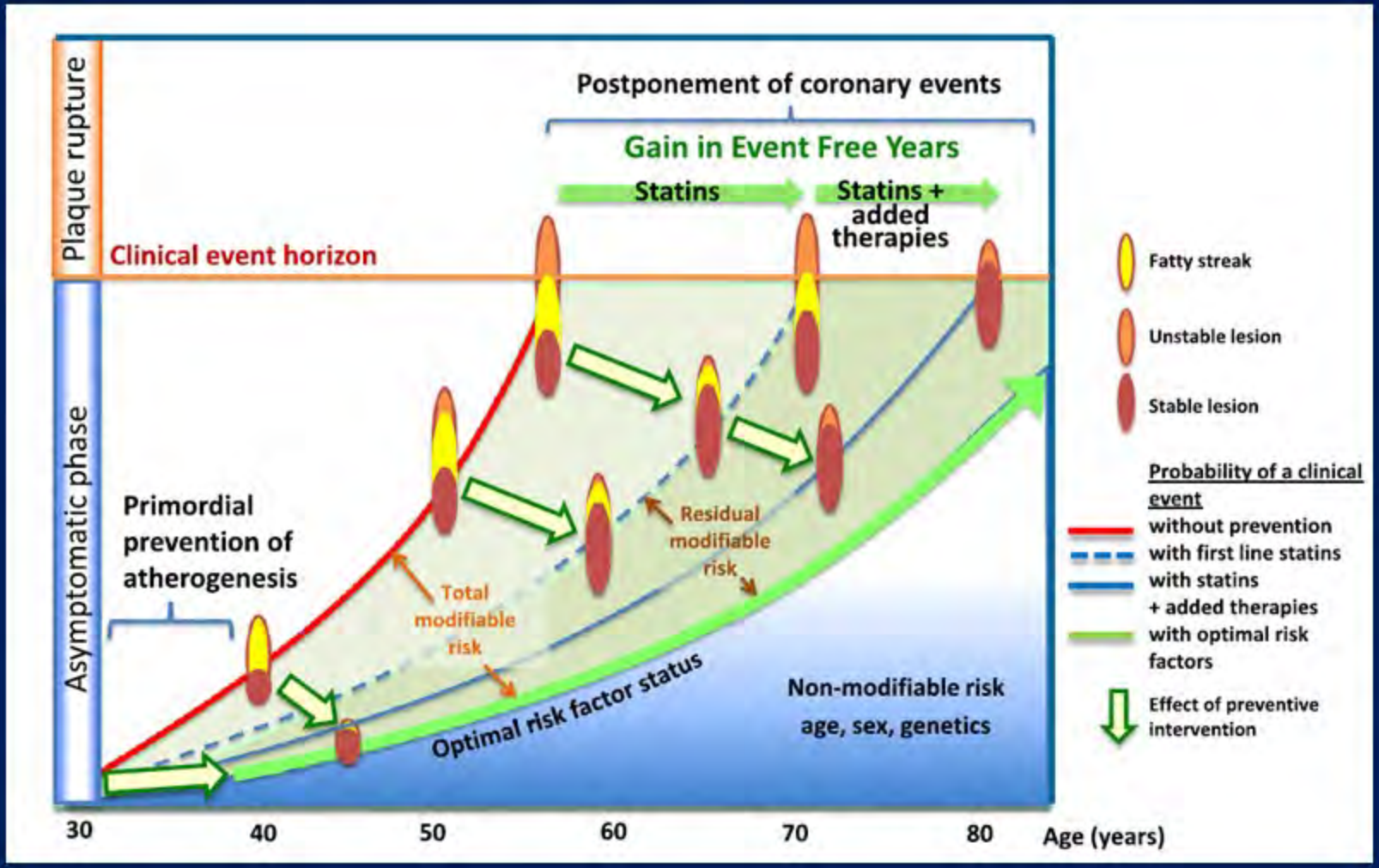
1. Brown MS, Goldstein JL. *Proc Natl Acad Sci USA.* 1979;76:3330-3337.
2. Goldstein JL, Brown MS. *Arterioscler Thromb Vasc Biol.* 2009;29:431-438.
3. Brown MS, Goldstein JL. *J Lipid Res.* 2009;50:S15-S27.
4. Brown MS, Goldstein JL. *Science.* 1986;232:34-47.

Mechanisms of Drug Actions in Lipoprotein Metabolism



Kwiterovich PO. *Johns Hopkins Textbook of Dyslipidemia*; 2013.

Disease Trajectories in CVD Prevention



Packard CJ et al. *Vasc Pharmacol.* 2015;71:37-39.

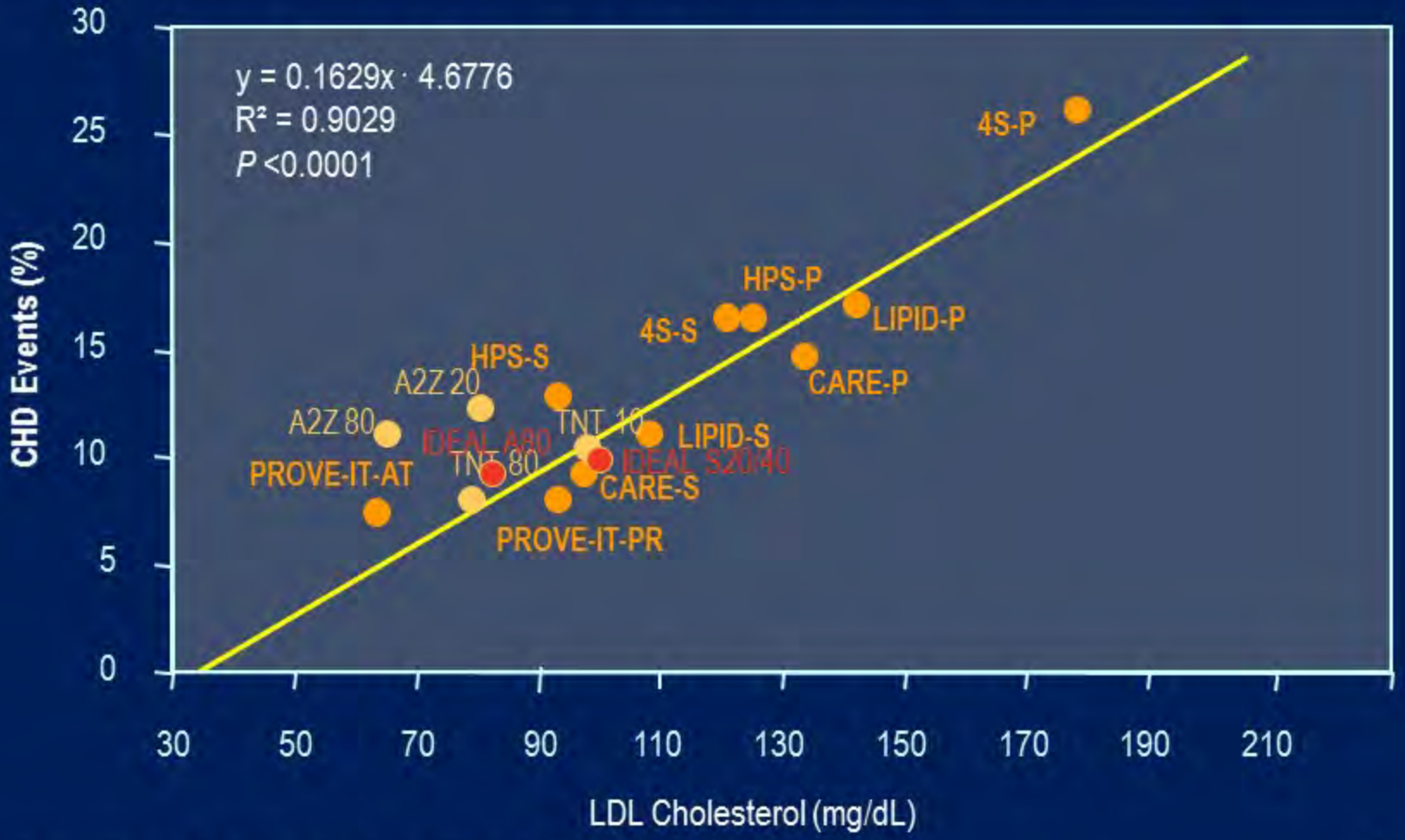
ROCKPOINTE

Statins

The Gold Standard for LDL-C Reduction

CHD Events Are Reduced Proportional to LDL-C Lowering with Statins

ACS and Other Secondary Prevention Trials



Updated from O'Keefe J et al. *J Am Coll Cardiol.* 2004;43:2142-2146.

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High, Moderate, and Low-intensity Statin Therapy Used in Clinical Trials

High-intensity Statin Therapy	Moderate-intensity Statin Therapy	Low-intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately ≥50%	Daily dose lowers LDL-C, on average, by approximately 30% to <50%	Daily dose lowers LDL-C, on average, by approximately <30%
Atorvastatin 40*-80* mg Rosuvastatin 20*-40** mg	Atorvastatin 10* (20**) mg Rosuvastatin (5**) 10* mg Simvastatin 20*-40* mg Pravastatin 40* (80**) mg Lovastatin 40* mg Fluvastatin XL 80** mg Fluvastatin 40 mg BID* Pitavastatin 2-4** mg	Simvastatin 10** mg Pravastatin 10*-20* mg Lovastatin 20* mg Fluvastatin 20**-40** mg Pitavastatin 1** mg

*Statins demonstrated reduction in major CVD events

***FDA-approved doses not tested in clinical trials*

FDA = Food and Drug Administration

Stone NJ et al. *Circulation.* 2014;129(25 Suppl 2):S1-45.
Goff DC et al. *Circulation.* 2014;129(25 Suppl 2):S49-73.

2013: ACC/AHA Guideline

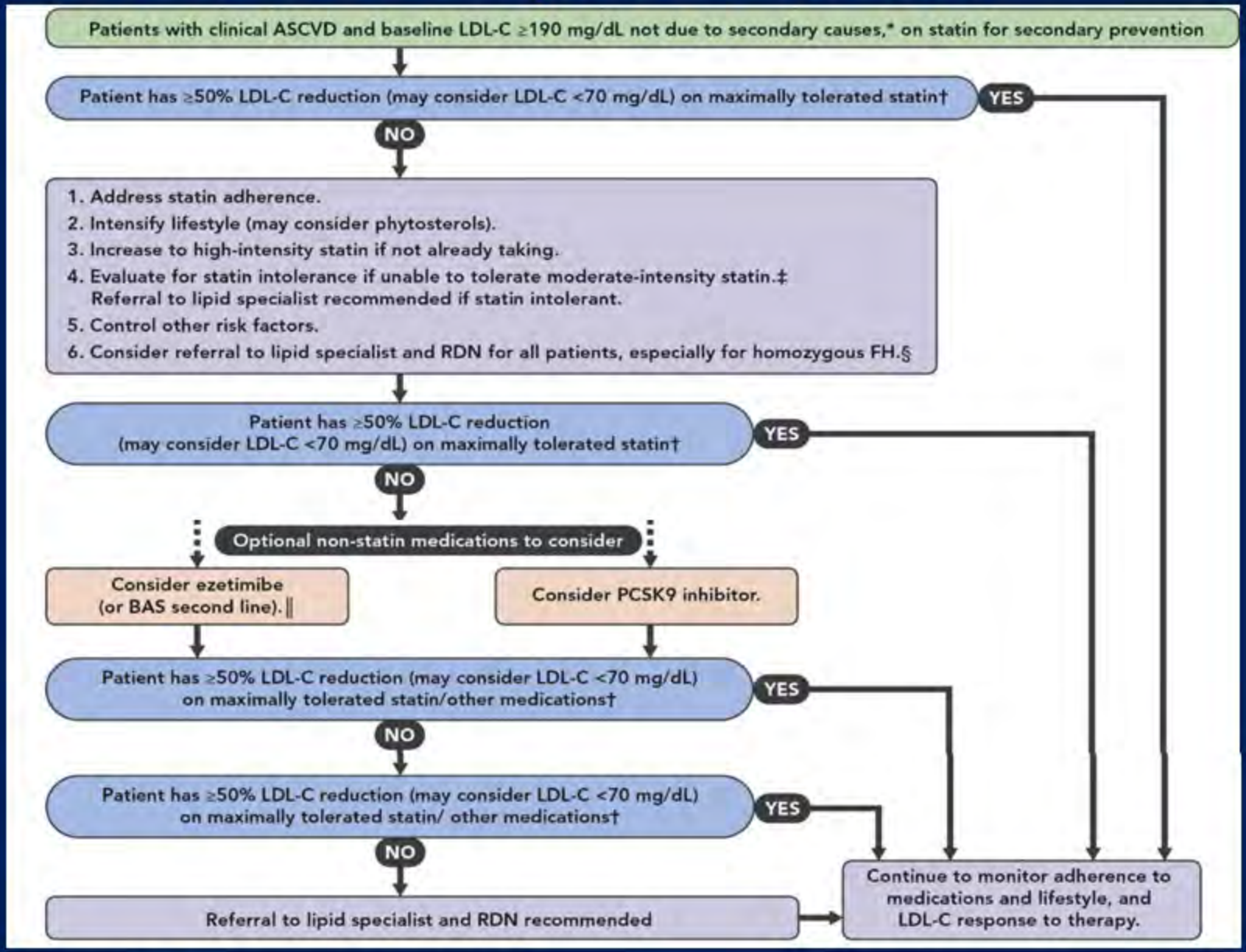
Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

- Low-intensity statins are recommended only in patients with history of or at risk for adverse drug effects
- Moderate-to-high-intensity statins recommended for patients with clinical ASCVD and those with diabetes
- High-intensity statins recommended for patients with LDL-C >190 mg/dL
- Did not find evidence to support LDL-C thresholds or targets of therapy. No evidence was found that titration or combination drug therapy to achieve specific LDL-C or non-HDL-C levels or percent reduction improved ASCVD outcomes. No dose titration recommended.
- Monitor LDL-C to assess compliance and response to therapy

HDL-C = high-density lipoprotein cholesterol

Stone NJ et al. *Circulation.* 2014;129(25 Suppl 2):S1-45.
Goff DC et al. *Circulation.* 2014;129(25 Suppl 2):S49-73

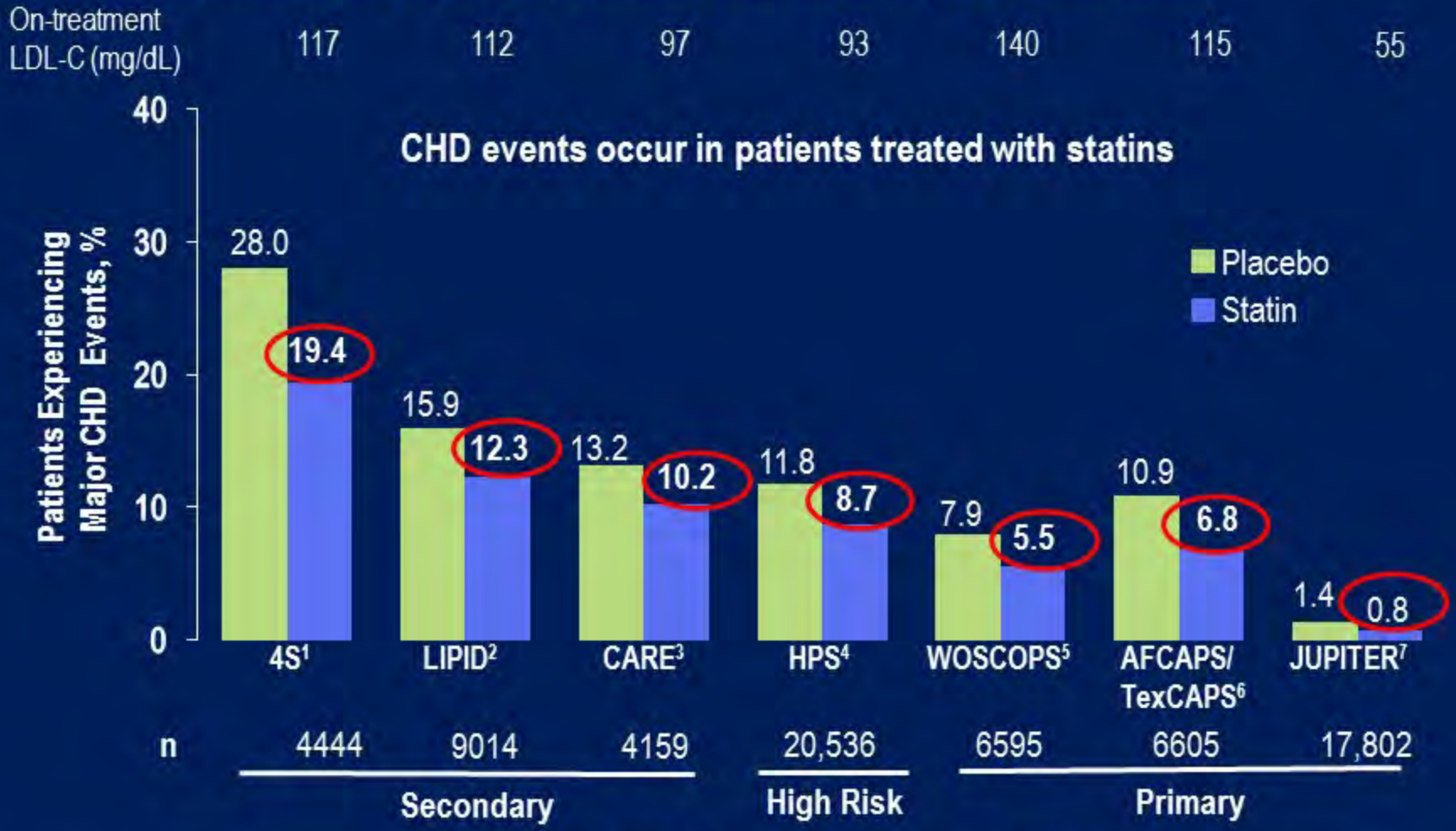
2016 ACC/AHA Expert Consensus



Lloyd-Jones D et al. *J Am Coll Cardiol.* 2016;68:92-125.

Residual CHD Risk Despite Statin Therapy

Major Statin Trials: Despite Benefit, Substantial Residual CV Risk Remains



[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.

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Ezetimibe

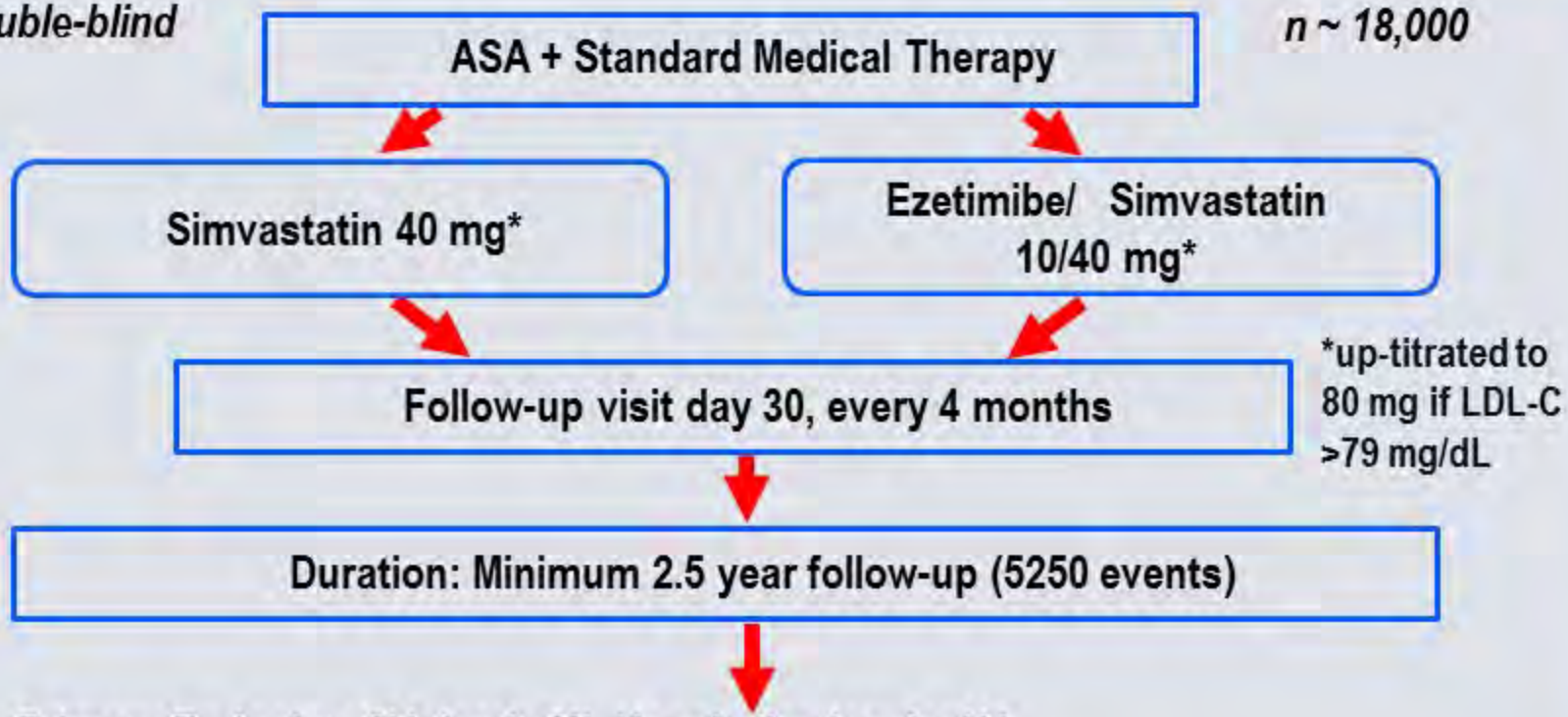
Ezetimibe

IMPROVE IT Trial Design

Patients stabilized post-ACS ≤10 days
LDL-C ≤125 mg/dL (or ≤100 mg/dL if prior statin)

Double-blind

n ~ 18,000



Primary Endpoint: CV death, MI, Hospitalization for UA, Revascularization (>30 days after randomization), or Stroke

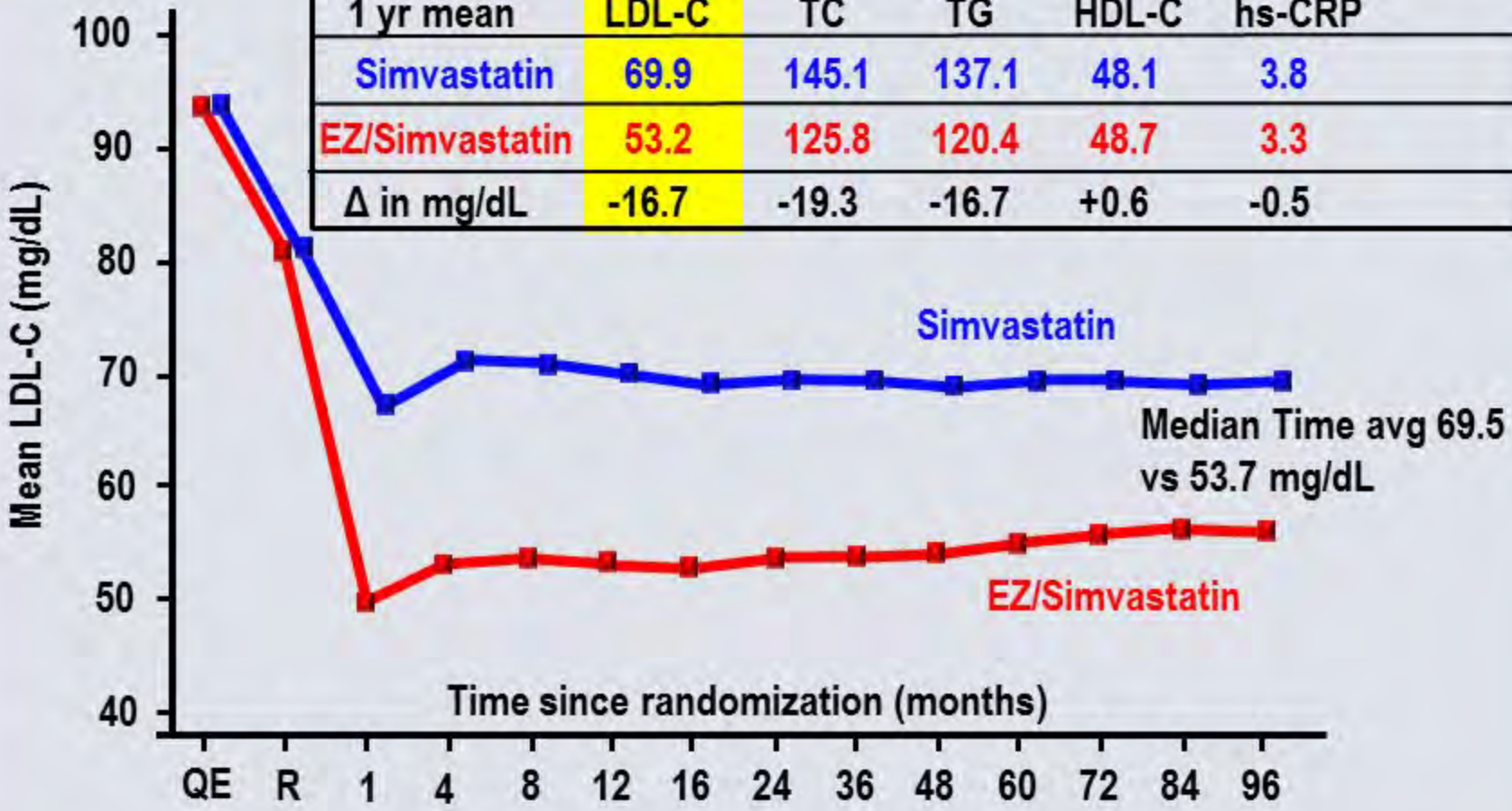
Cannon CP et al. *Am Heart J.* 2008;156:826-832.

Study drug is administered once daily in the evening.

IMPROVE IT Trial: Effect on LDL-C

Ezetimibe (EZ) + Simvastatin vs Simvastatin Alone

1 yr mean	LDL-C	TC	TG	HDL-C	hs-CRP
Simvastatin	69.9	145.1	137.1	48.1	3.8
EZ/Simvastatin	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5



Cannon CP et al. *Am Heart J.* 2008;156:826-832.

Study drug is administered once daily in the evening.

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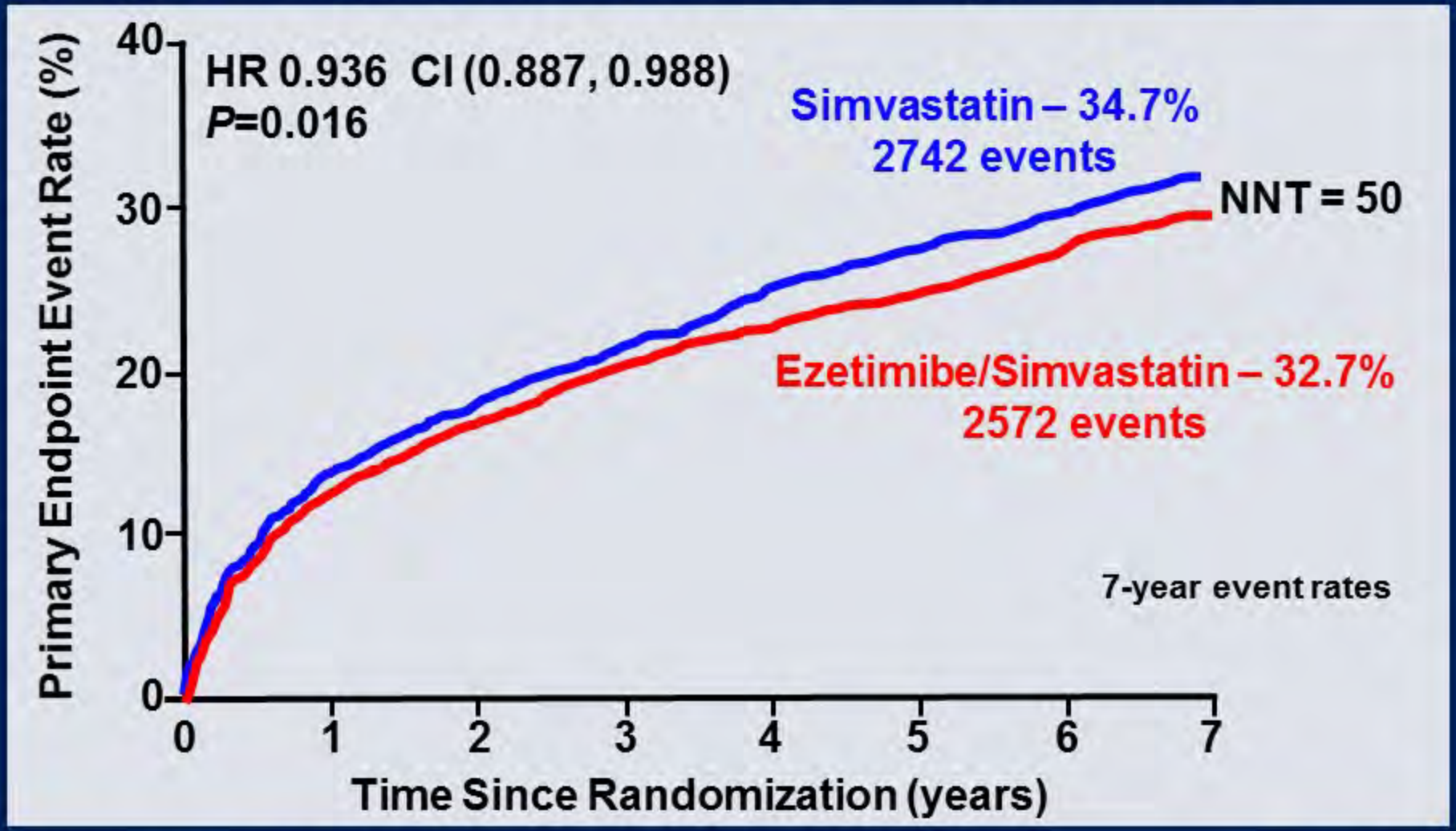
IMPROVE IT Trial

Ezetimibe + Simvastatin vs Simvastatin Alone

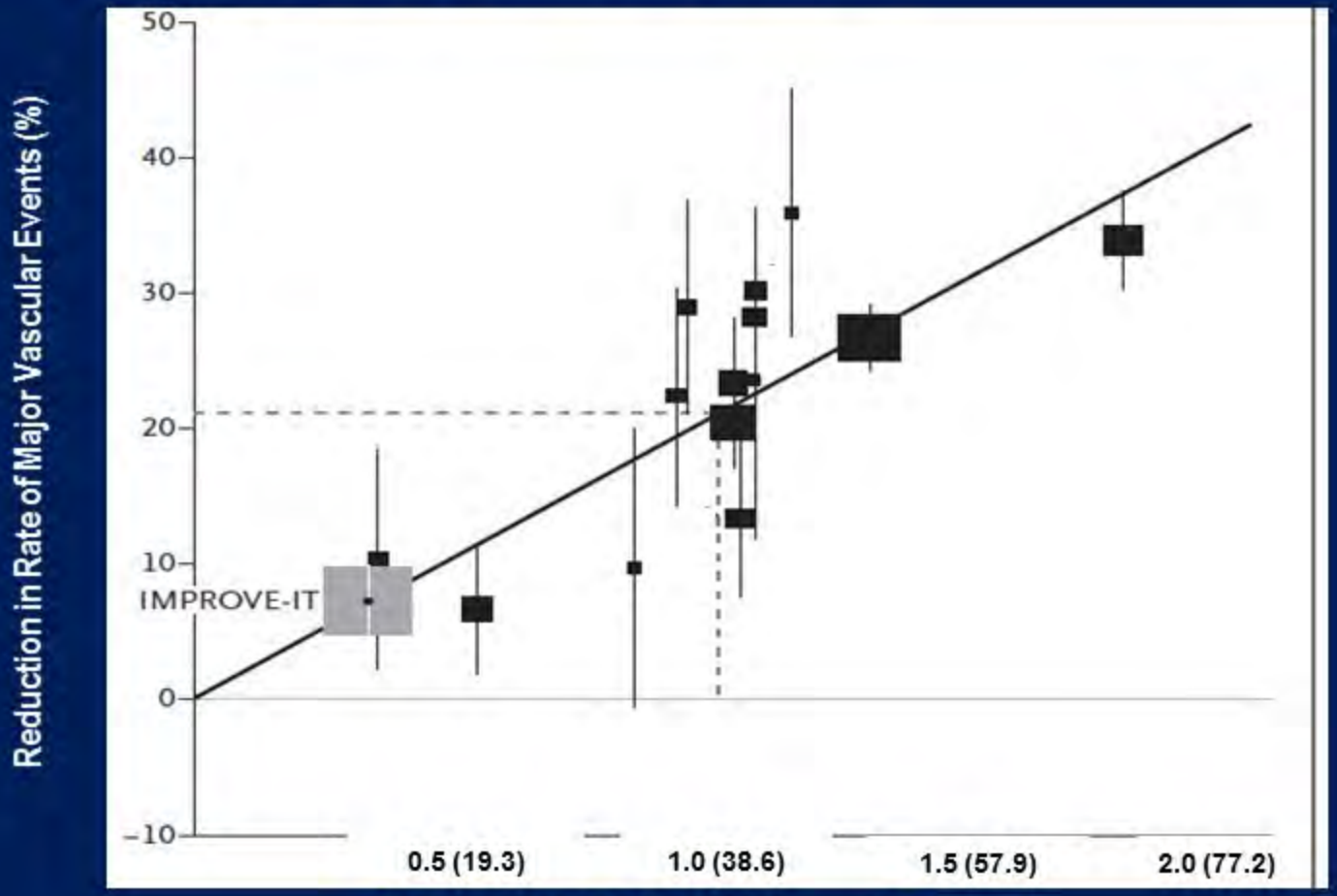
Primary Endpoint: death from cardiovascular disease, a major coronary event, or nonfatal stroke



Cannon CP et al. *N Engl J Med.* 2015;371:2387-2397.

IMPROVE-IT: Ezetimibe vs Statin Benefit

Change in LDL-C vs Clinical Benefit



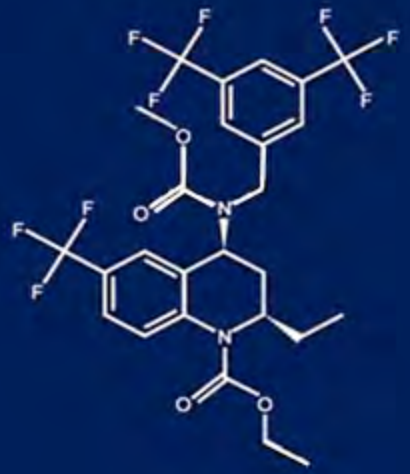
Cannon CP et al. CTT Collaboration. *Lancet.* 2005;366:1267-1278.
CCT Collaboration. *Lancet.* 2010;376:1670-1681.
Cannon CP et al. *N Engl J Med.* 2015;372:2387-2397.

CETP Inhibition

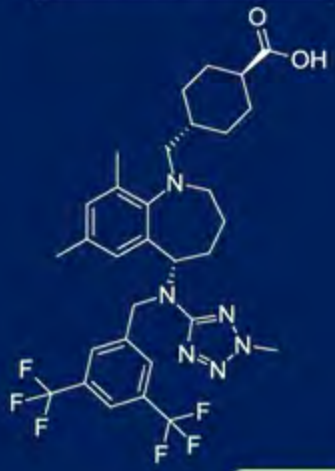
CETP = Cholesteryl ester transfer protein

CETP Inhibitors and Modulators

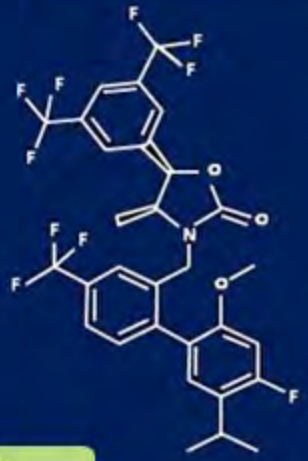
Torcetrapib (discontinued)



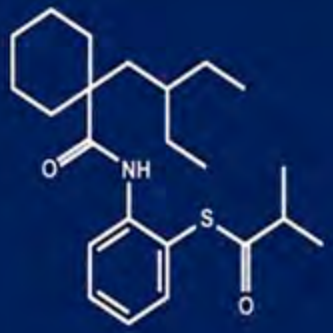
Evacetrapib (discontinued)



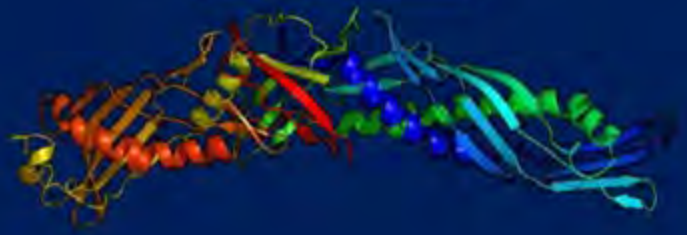
Anacetrapib (investigational)



Dalcetrapib (discontinued)



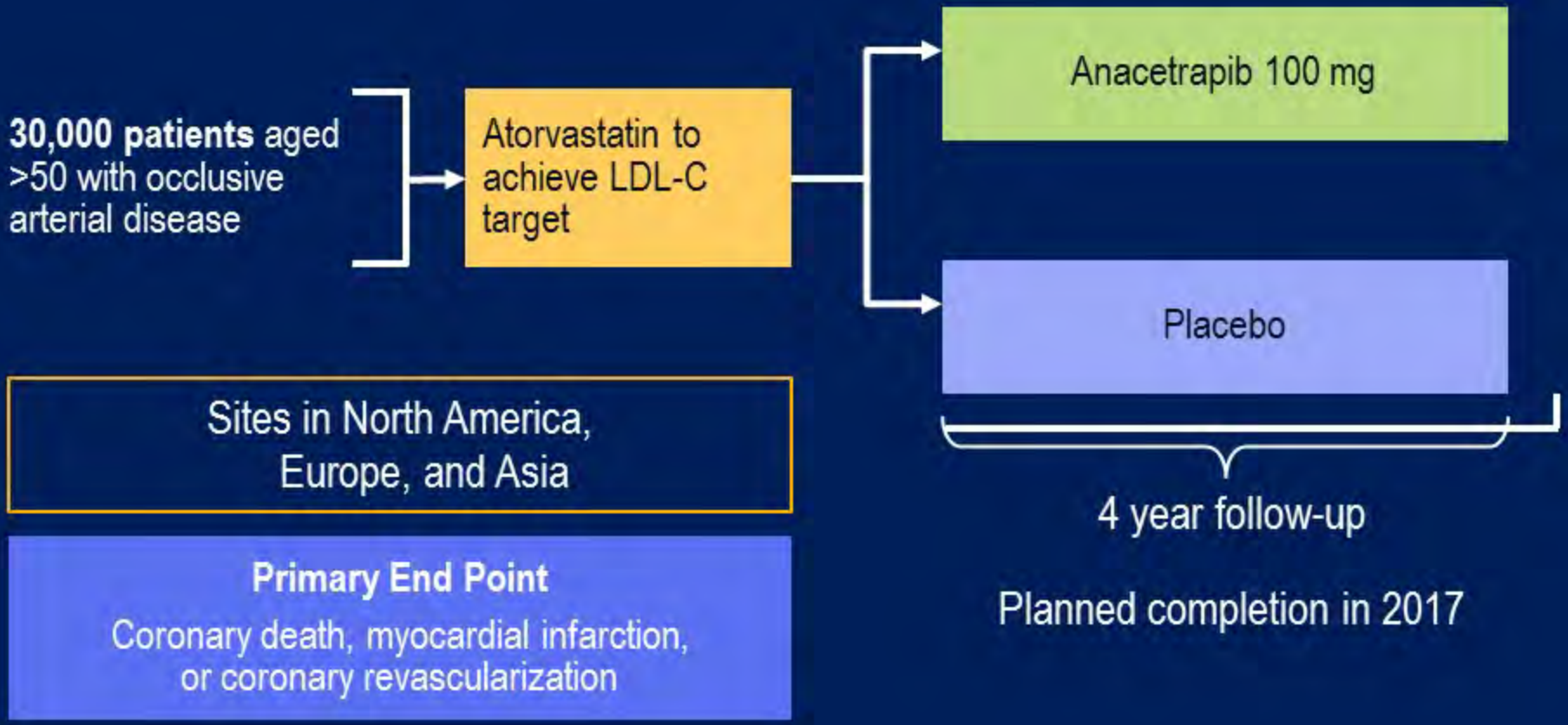
CETP



Barter PJ et al. *N Engl J Med.* 2007;357:2109-2122.
Qiu X et al. *Nat Struct Mol Biol.* 2007;14:106-112.

REVEAL

Trial Design for Efficacy of Anacetrapib



Sites in North America, Europe, and Asia

Primary End Point

Coronary death, myocardial infarction, or coronary revascularization

Planned completion in 2017

Available at: www.revealtrial.org.

ROCKPOINTE

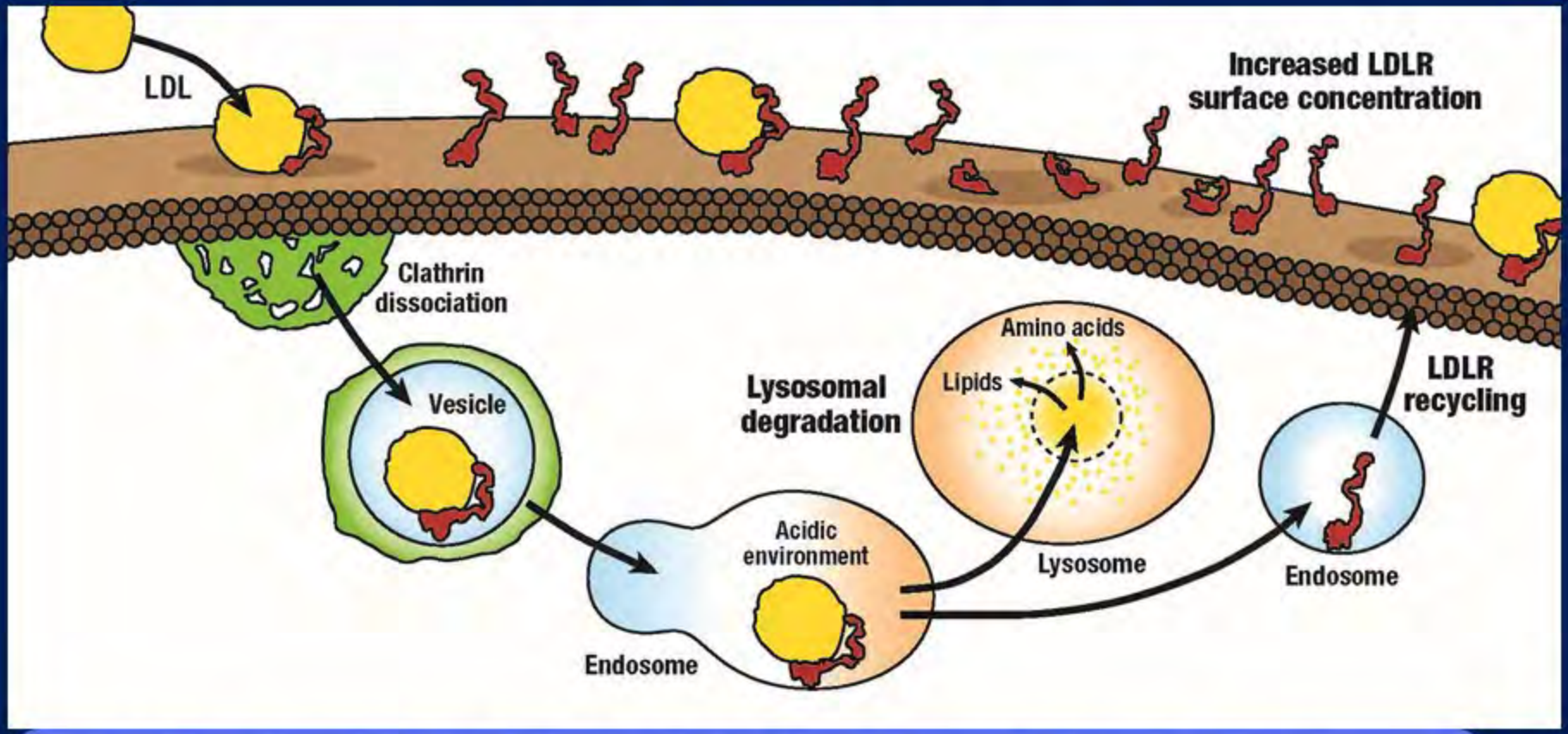
Modulation of Hepatic LDL Receptors

Modulation of Hepatic LDL Receptors

PCSK9 Inhibitors

PCSK9 = proprotein convertase subtilisin/kexin type 9

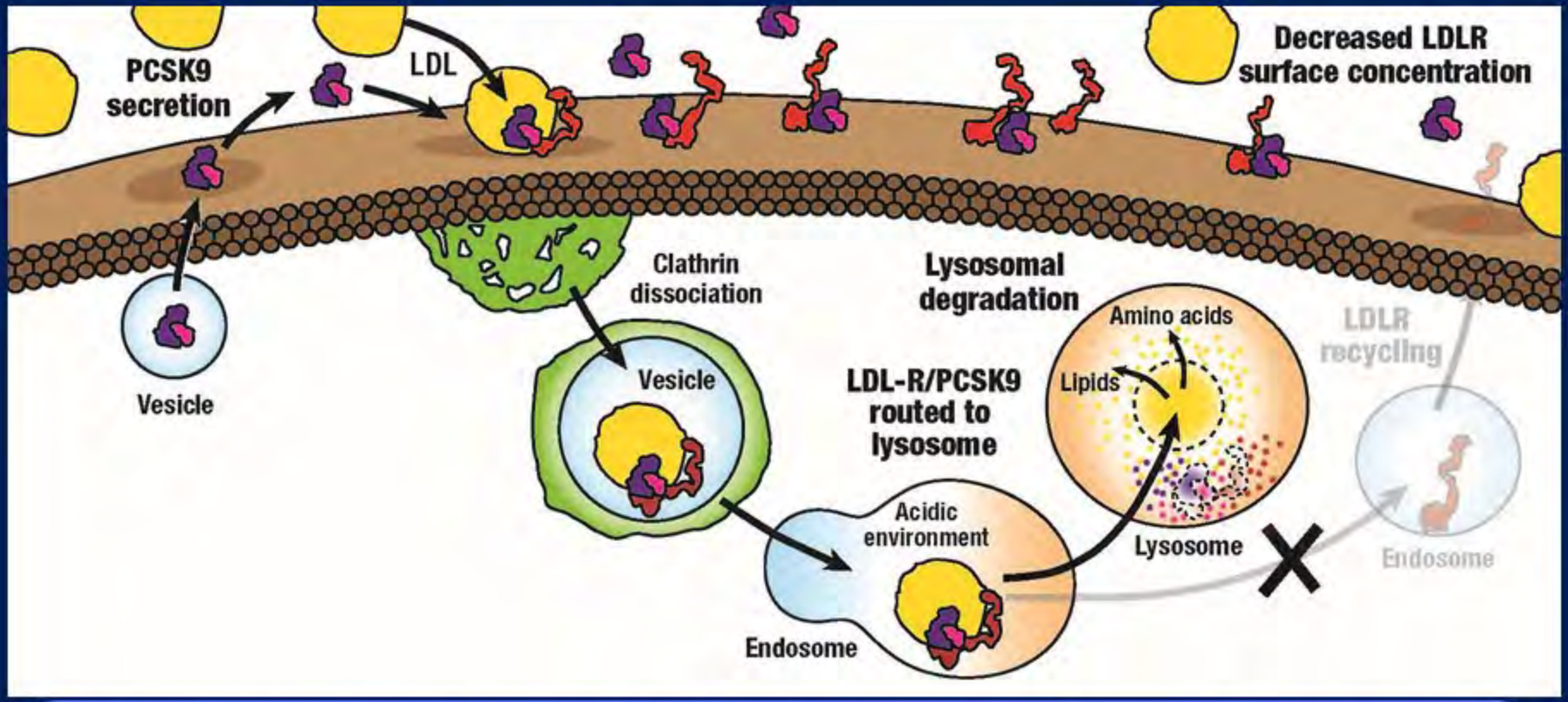
Recycling of LDL-Receptors Enables Efficient Clearance of LDL Particles



- The ability of hepatic LDLRs to be recycled is a key determinant of hepatic efficacy in lowering plasma LDL levels

Goldstein JL, Brown MS. *Arterioscler Thromb Vasc Biol.* 2009;29:431-438.
Brown MS, Goldstein JL. *Science.* 1986;232:34-47.
Steinberg D, Witztum JL. *Proc Natl Acad Sci USA.* 2009;106:9546-9547.
Brown MS, Goldstein JL. *Proc Natl Acad Sci USA.* 1979;76:3330-3337.

PCSK9 Is a Regulator of LDL-R Recycling



- PCSK9 mediates degradation of the LDL-R by interacting with the extracellular domain and targeting the receptor for degradation
- PCSK9 is highly expressed in the liver, small intestine, and kidney

Horton JD et al. *J Lipid Res.* 2009;50:S172-S177.
Qian YW et al. *J Lipid Res.* 2007;48:1488-1498.
Zhang DW et al. *J Biol Chem.* 2007;282:18602-18612.
Lopez D. *Biochim Biophys Acta.* 2008;1781:184-191.

Genetic Variants of PCSK9 Demonstrate Its Importance in Regulating LDL Levels

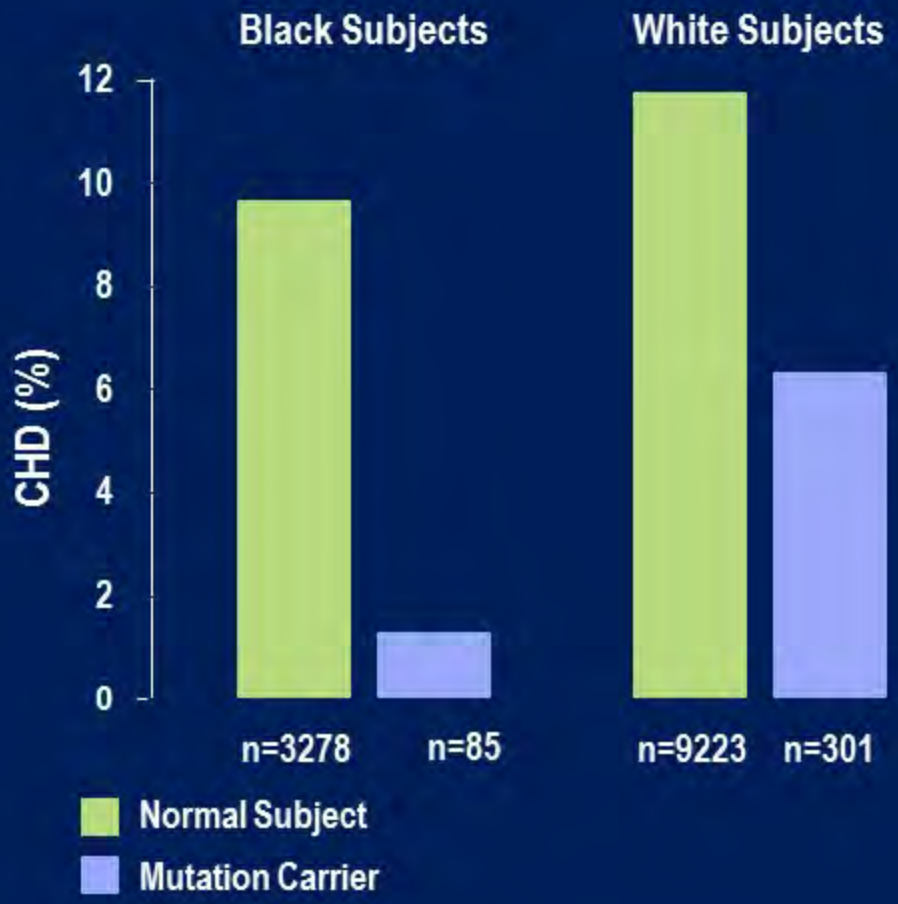
PCSK9 Gain of Function	Fewer LDL-Receptors[1,3,5]
PCSK9 Loss of Function	More LDL-Receptors[2,4]
1% - 3% of population have Loss of Function PCSK9[6,7]	

1. Horton JD et al. *J Lipid Res.* 2009;50:S172-S177.
2. Lakoski SG et al. *J Clin Endocrinol Metab.* 2009;94:2537-2543.
3. Abifadel M et al. *Hum Mutat.* 2009;30:520-529.
4. Cohen J et al. *Nat Genet.* 2005;37:161-165.
5. Steinberg D et al. *Proc Natl Acad Sci U S A.* 2009;106:9546-9547.
6. Cohen JC et al. *N Engl J Med.* 2006;354:1264-1272.
7. Benn M et al. *J Am Coll Cardiol.* 2010;55:2833-2842.

PCSK9 Loss-of-Function Mutations

Resulted in Lower LDL-C Levels and Reduced CHD Rates

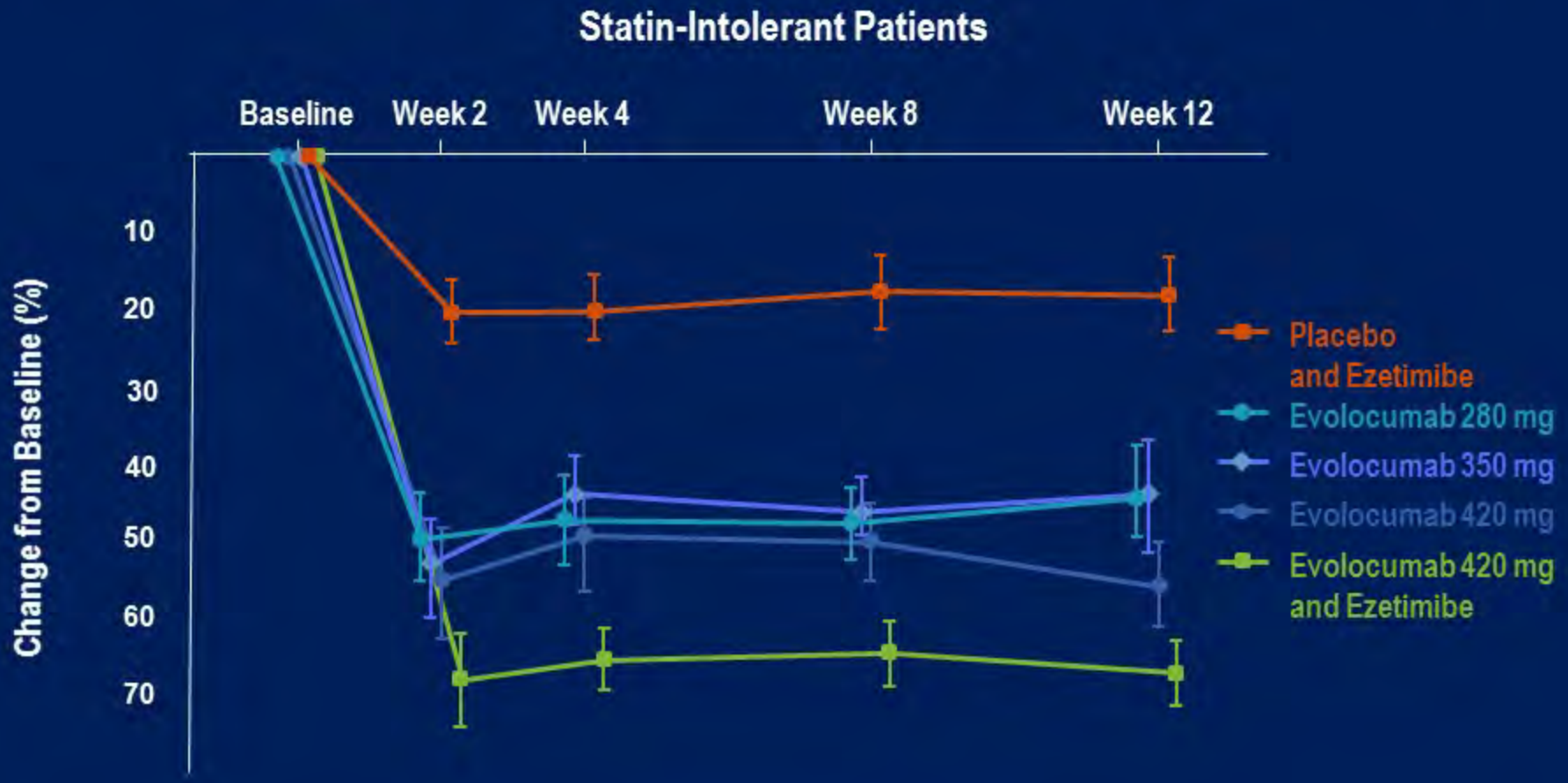
- Wild-type PCSK9 degrades LDL receptors.[1,2]
- Loss-of-function (LOF) mutations increase hepatic LDL receptor expression, reducing LDL-C levels by 15%-40%.[2,3]
- CHD incidence was reduced 47%-88% in PCSK9 loss-of-function mutation carriers compared with normal individuals.[3]



1. Peterson AS et al. *J Lipid Res.* 2008;49:1595-1599.
2. Cohen J et al. *Nature Genetics.* 2005;37:161-165.
3. Cohen JC et al. *N Engl J Med.* 2006;354:1264-1272.

ROCKPOINTE

GAUSS: Effect of Evolocumab on Percentage Change in LDL-C from Baseline



GAUSS = Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects

Sullivan D et al. *JAMA.* 2012;308:2497-2506.

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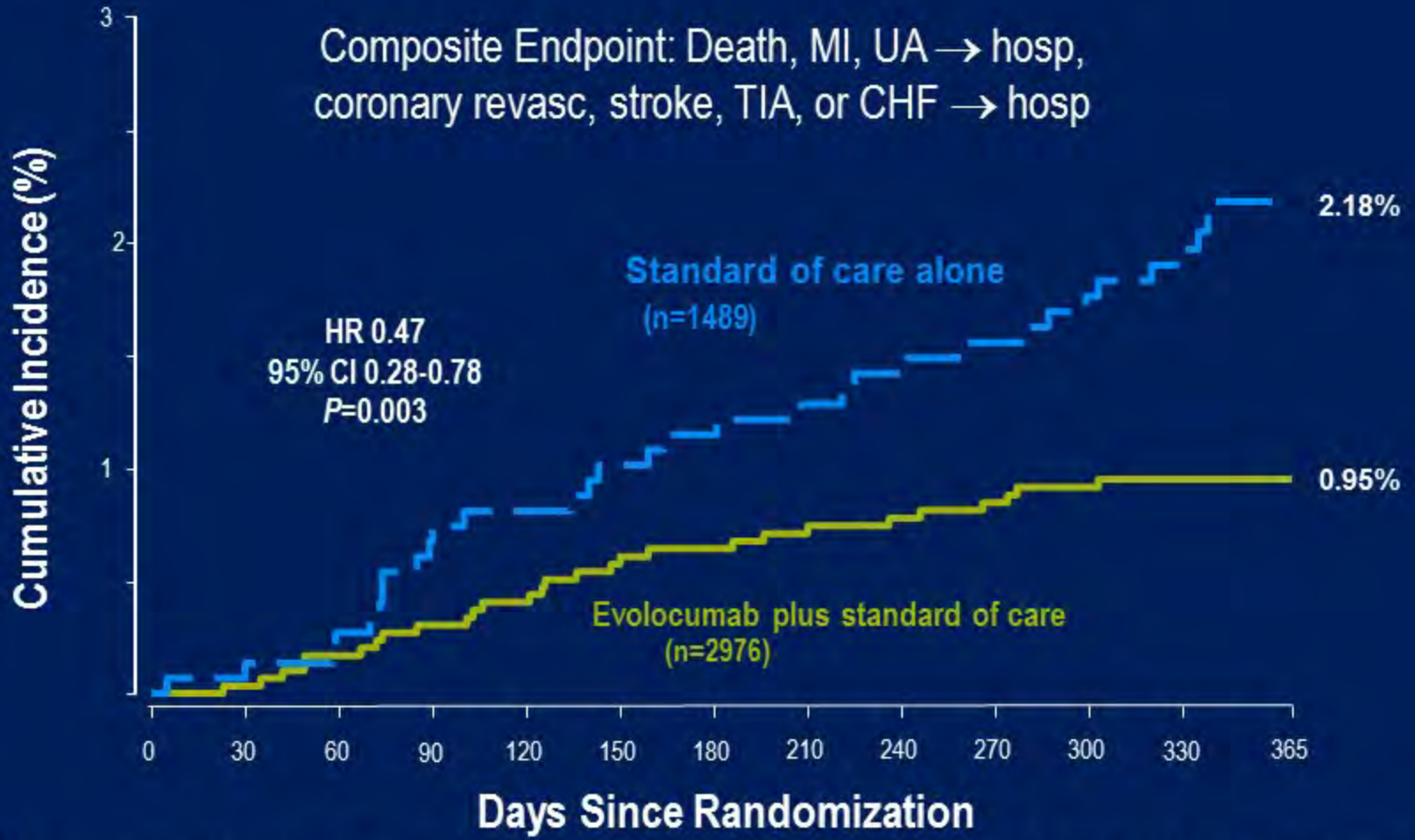
OSLER Trial

Evolocumab on Cardiovascular Outcomes



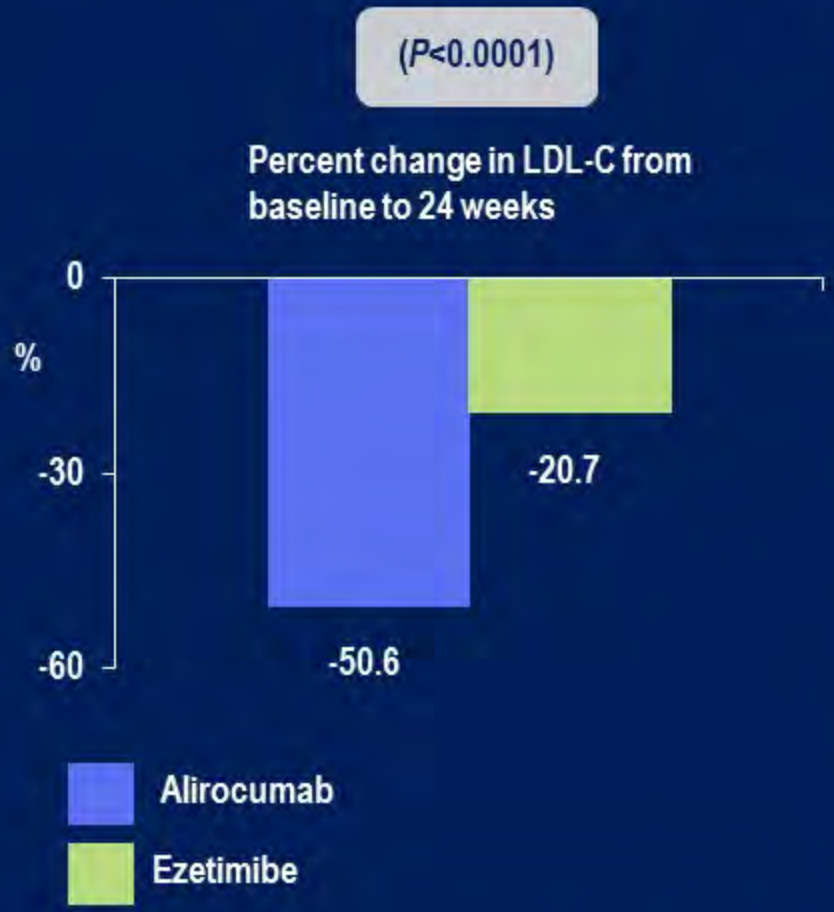
TIA = transient ischemic attack; CHF = congestive heart failure; MI = myocardial infarction; UA = unstable angina

Sabatine MS et al. *N Engl J Med.* 2015;372:1500-1509.

ROCKPOINTE

Alirocumab: ODYSSEY COMBO II

Patients with High CV Risk and Max Statin Therapy



Results

- From baseline to 24 weeks, the change in LDL-C: -50.6% for alirocumab vs -20.7% for ezetimibe (*P*<0.0001)
- LDL-C was maintained at 52 weeks: 53 mg/dL with alirocumab vs 85 mg/dL with ezetimibe
- Treatment-emergent adverse events leading to drug discontinuation: 7.5% of the alirocumab group vs 5.4% of the placebo group

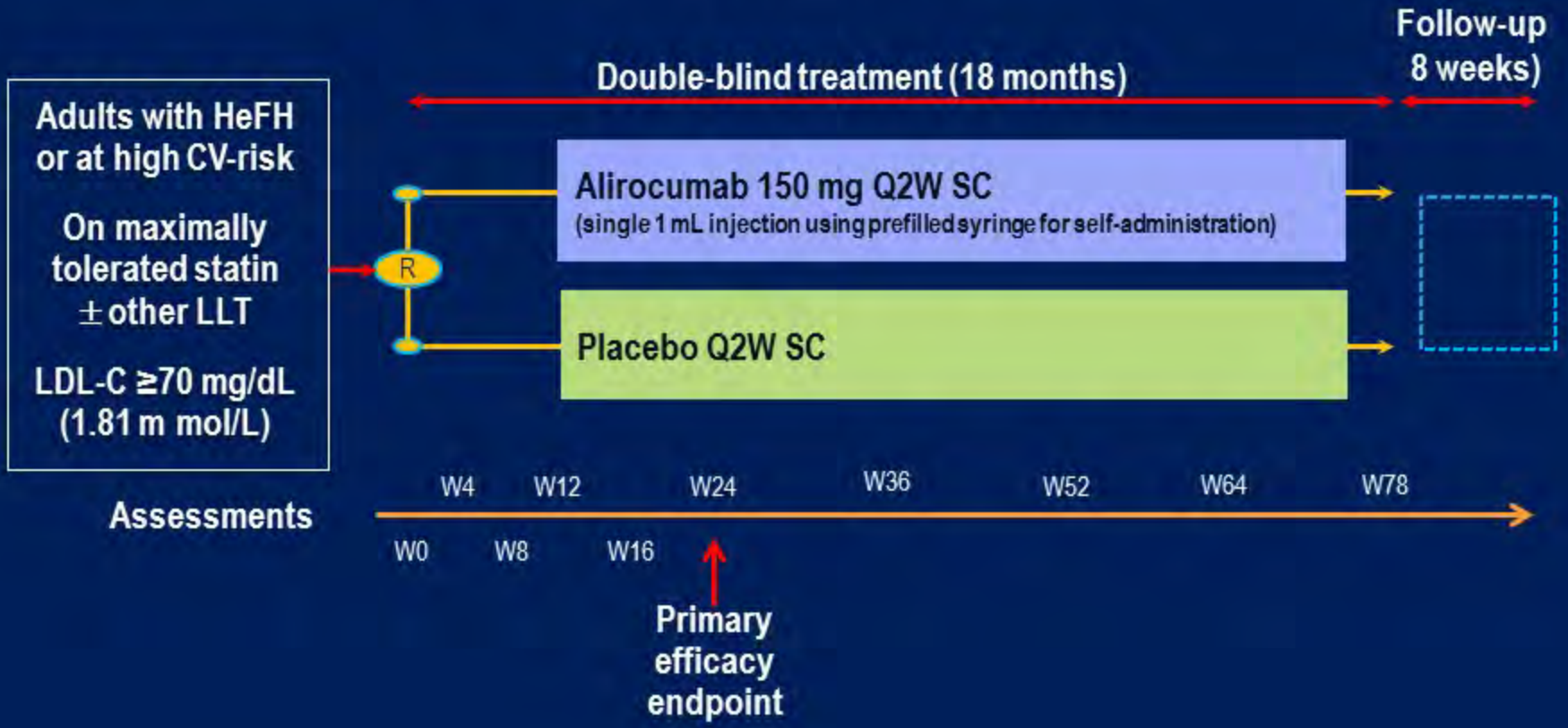
Conclusions

- Among patients with high CV risk, alirocumab resulted in large reduction in LDL-C compared with ezetimibe, which was maintained to 52 weeks

Presented by Cannon CP at European Society of Cardiology; 2014.

Alirocumab

ODYSSEY Long Term: Study Design



SC = subcutaneous; W = week

Robinson JG et al. *N Eng J Med.* 2015;372:1489-1499.

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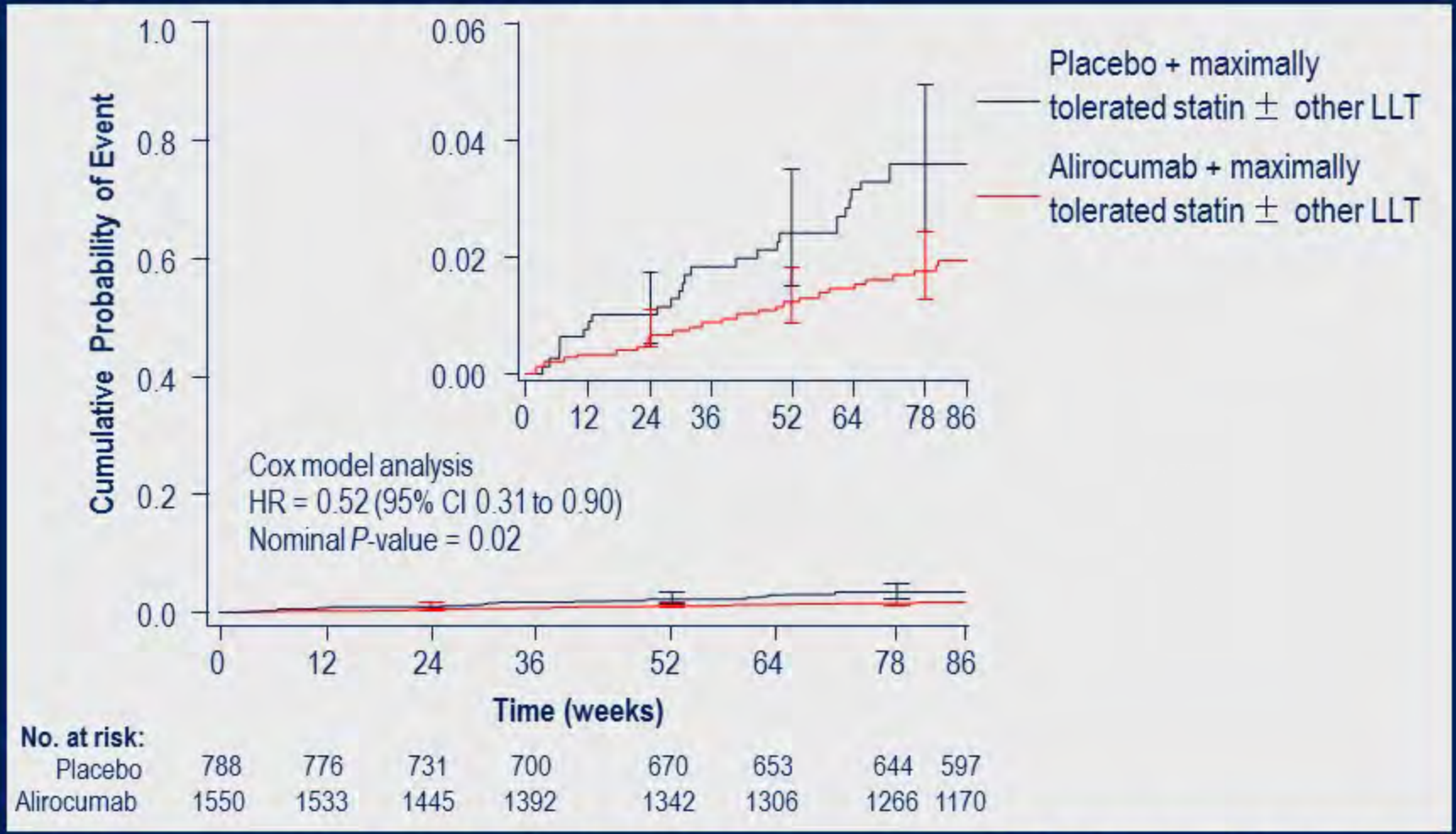
Alirocumab: Post hoc Analysis

*Major Adverse Cardiovascular Events**



*Based on primary endpoint for the ODYSSEY OUTCOMES trial, including CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, and unstable angina requiring hospitalization. Unstable angina requiring hospitalization was considered based on strict criteria/clear progression of ischemia.

Robinson JG et al. *N Eng J Med.* 2015;372:1489-1499.

ROCKPOINTE

Indications for Use of Alirocumab

- Indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C
- The effect of alirocumab on cardiovascular morbidity and mortality has not been determined

Alirocumab package insert. Available at: www.regeneron.com/Praluent/Praluent-fpi.pdf.

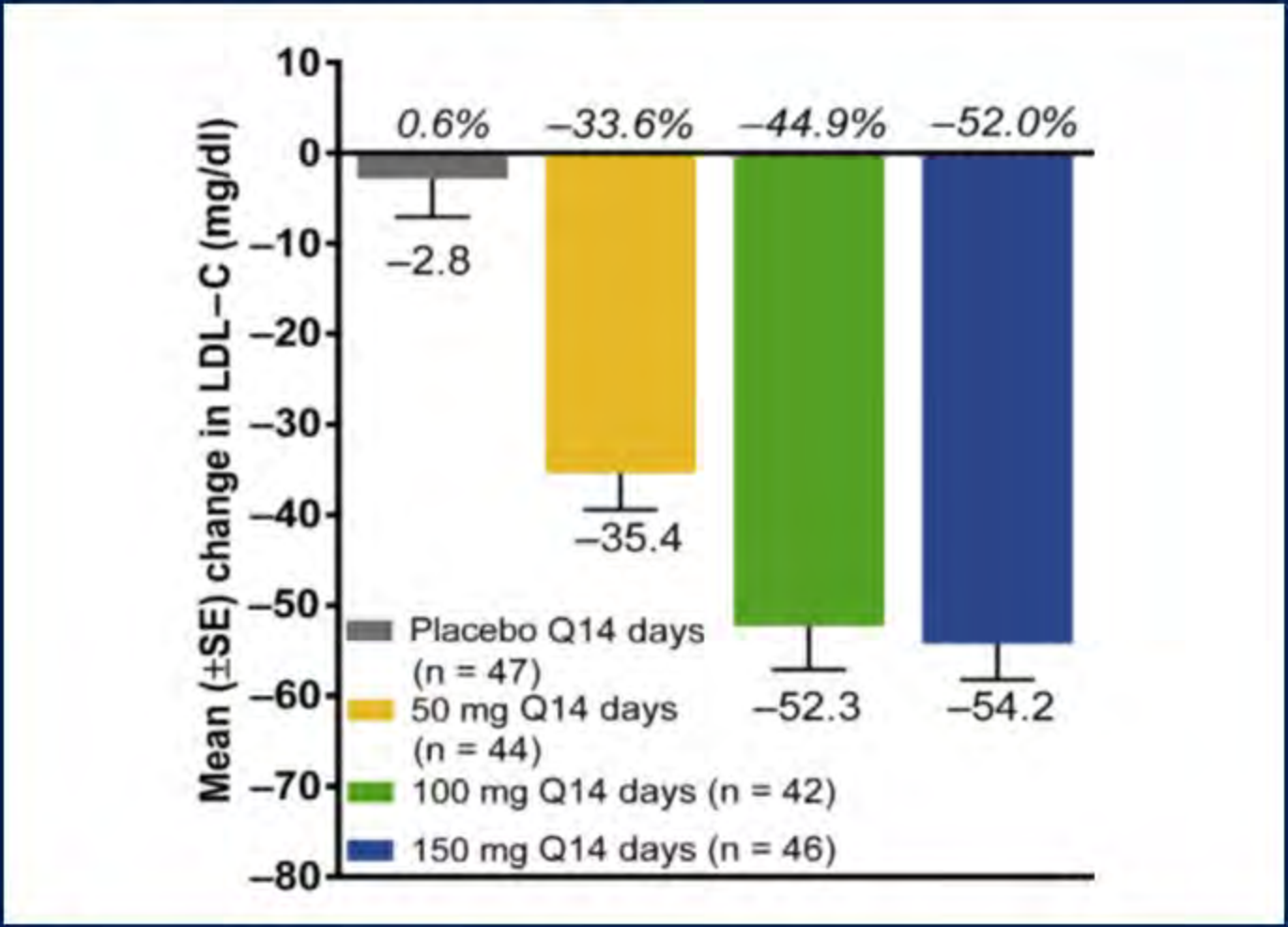
Indications for Use of Evolocumab

- Primary Hyperlipidemia
  - Indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic CVD, who require additional lowering of LDL-C
- Homozygous Familial Hypercholesterolemia
  - Indicated as an adjunct to diet and other LDL-lowering therapies (e.g. statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C

Evolocumab package insert: pi.amgen.com/united_states/repatha/repatha_pi_hcp_english.pdf.

Bococizumab

Effect of 12 Weeks of SQ Dosing on LDL-C in Patients Receiving Stable Statin Therapy



Ballantyne CM et al. *Am J Cardiol.* 2015;115:1212-1221.

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PCSK9 Inhibitors

Cardiovascular Outcomes Trials

	Alirocumab	Evolocumab	Bococizumab
Sponsor	Sanofi/Regeneron	Amgen	Pfizer
Trial	ODYSSEY Outcomes	FOURIER	SPIRE I
Sample Size	18,000	28,000	17,000
Patients	4-16 weeks post-ACS	MI, stroke, or PAD	High risk of CV event
Statin	Evidence-based Rx	Atorvastatin ≥20 mg or equivalent	Lipid-lowering Rx
LDL-C	≥70 mg/dL	≥70 mg/dL	70-99 mg/dL
Dosing (sc)	Every 2 weeks	Every 2 or Every 4 weeks	Every 2 weeks
Endpoint	CHD death, MI, ischemic stroke, or UA hospitalization	Primary: CV death, MI, stroke, UA hospitalization or coronary revascularization Key Secondary: CV death, MI, or stroke	CV death, MI, stroke, or urgent revascularization
Completion	February 2018	November 2016	June 2018

Available at: Clinicaltrials.gov.

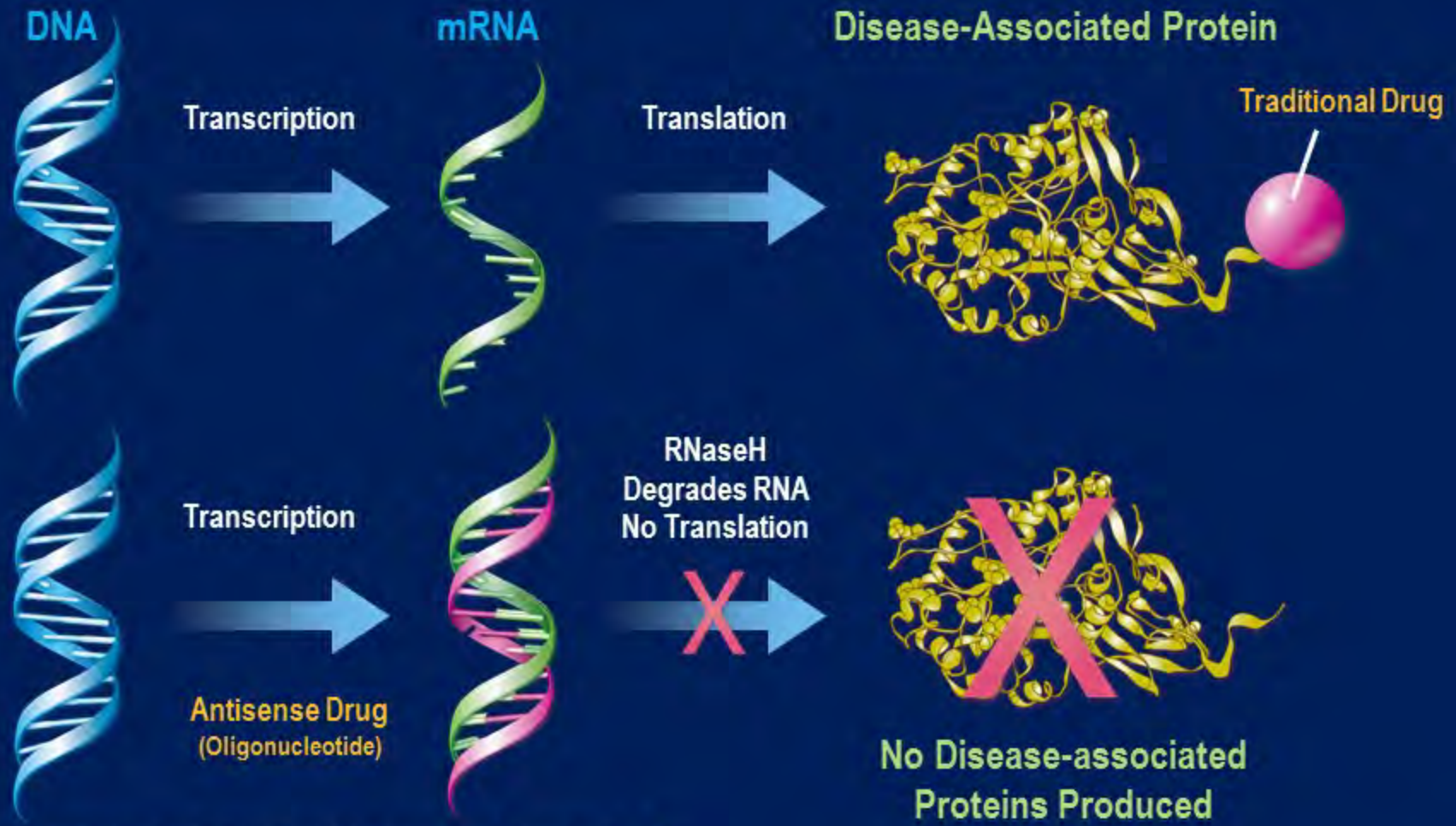
Modulation of VLDL Production

Mipomersen

Antisense Direct Inhibitor of Apo-B

A New Mechanism of Action

Antisense Oligonucleotide

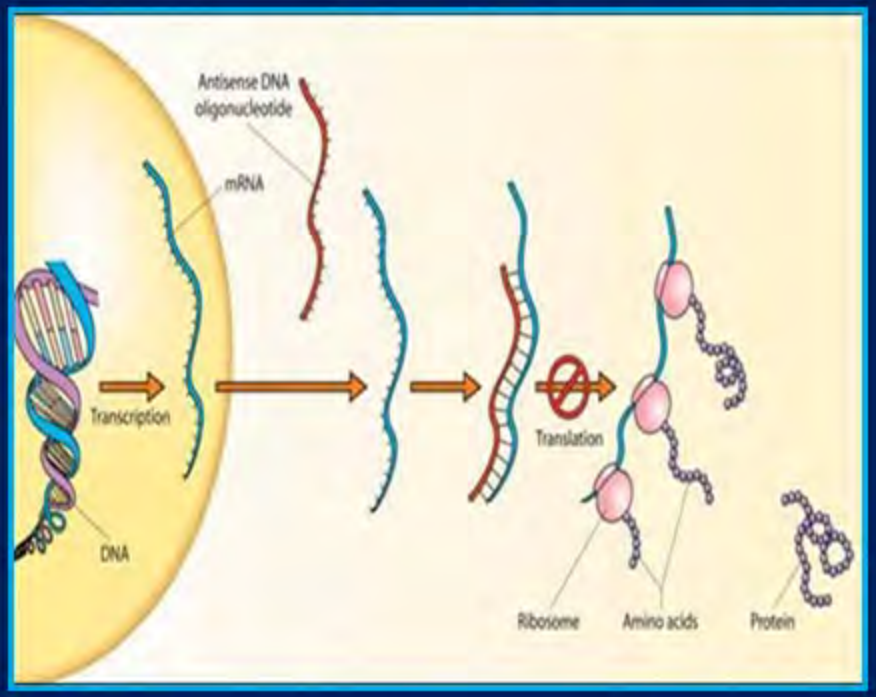


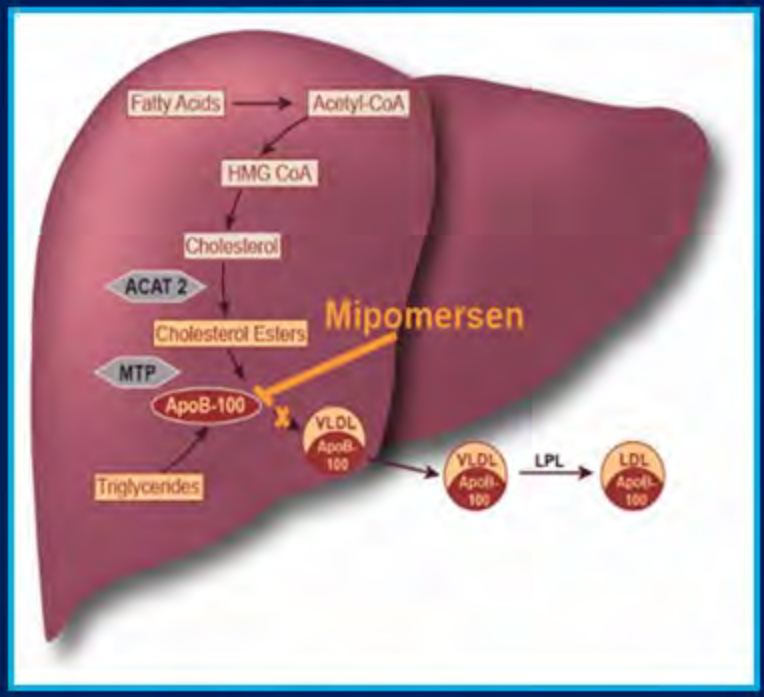
DNA = deoxyribonucleic acid; mRNA = messenger ribonucleic acid

Goldberg AC. *J Clin Lipidol*. 2010;4:350-356.

Mipomersen

ASO (Antisense Oligonucleotide)





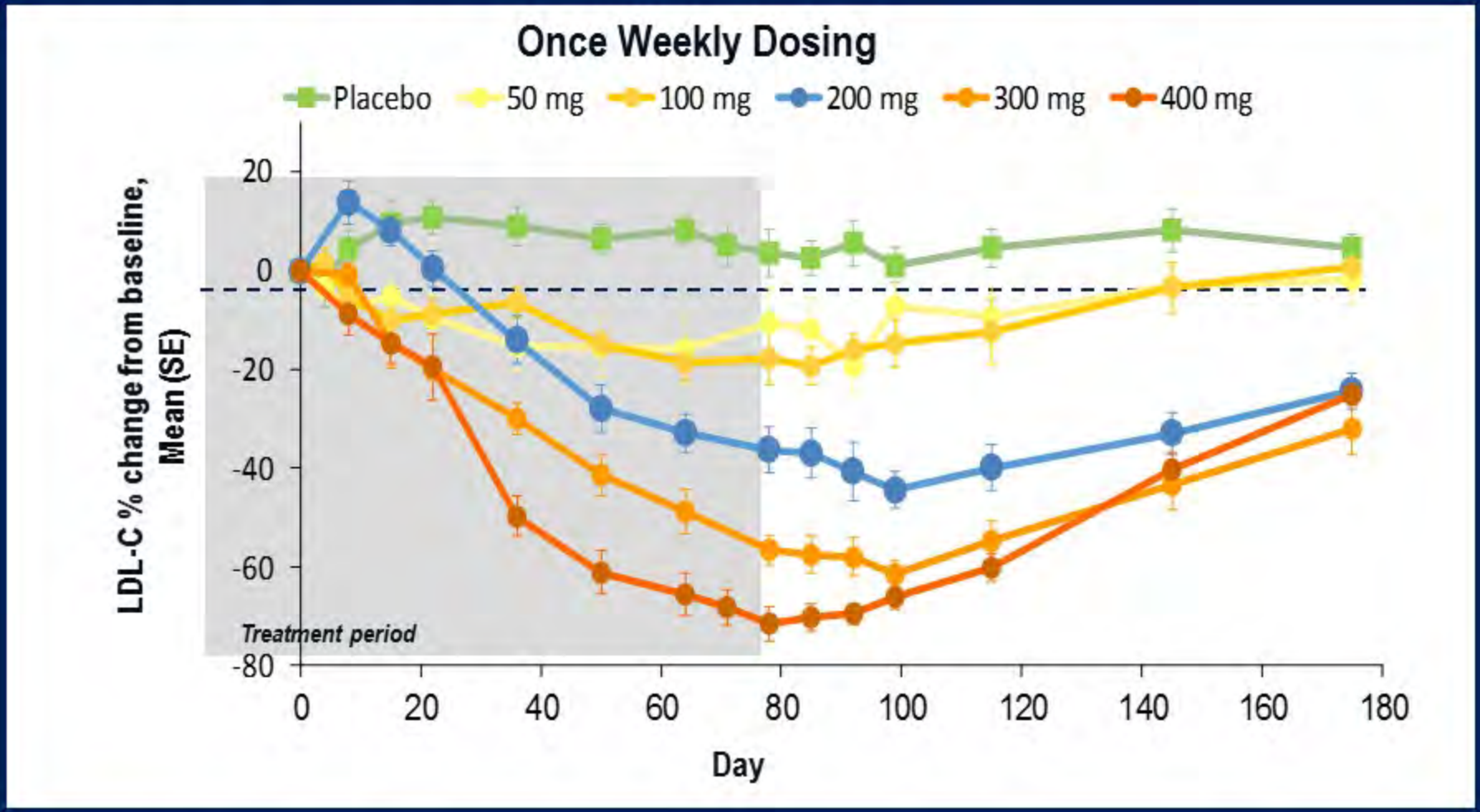
- An apoB antisense mRNA blocking protein synthesis[1]

- ApoB-100 as target[2]
- Essential for the synthesis and transport of VLDL and LDL-C[2]
- Plays a critical role in lipid management[2]

1. Castanotto D, Rossi JJ. *Nature.* 2009;457:426-433.
2. Sjouke B et al. *Curr Cardiol Rep.* 2011;13:527-536.

Phase II: Hypercholesterolemia, Monotherapy

Dose-dependent Reduction of LDL-C



SE = standard error

Akdim F et al. *Eur Heart J.* 2011;32:2650-2659.

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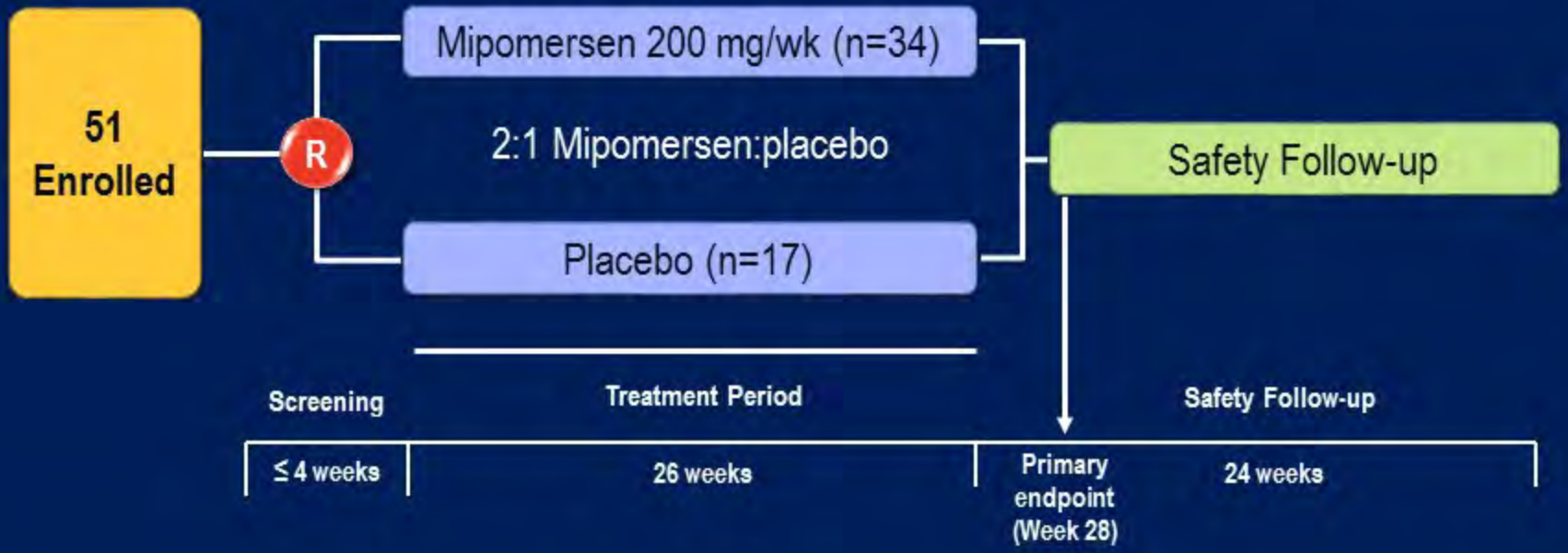
Mipomersen

Phase III Study Design in HoFH Patients

- Multi-national, randomized, placebo-controlled, double-blind trial
- Mipomersen as an adjunct to lipid-lowering medications
- Weekly subcutaneous injections for 26 weeks
- Primary efficacy endpoint: % change in LDL-C from baseline at week 28



Raal FJ et al. *Lancet.* 2010;375:998-1006.

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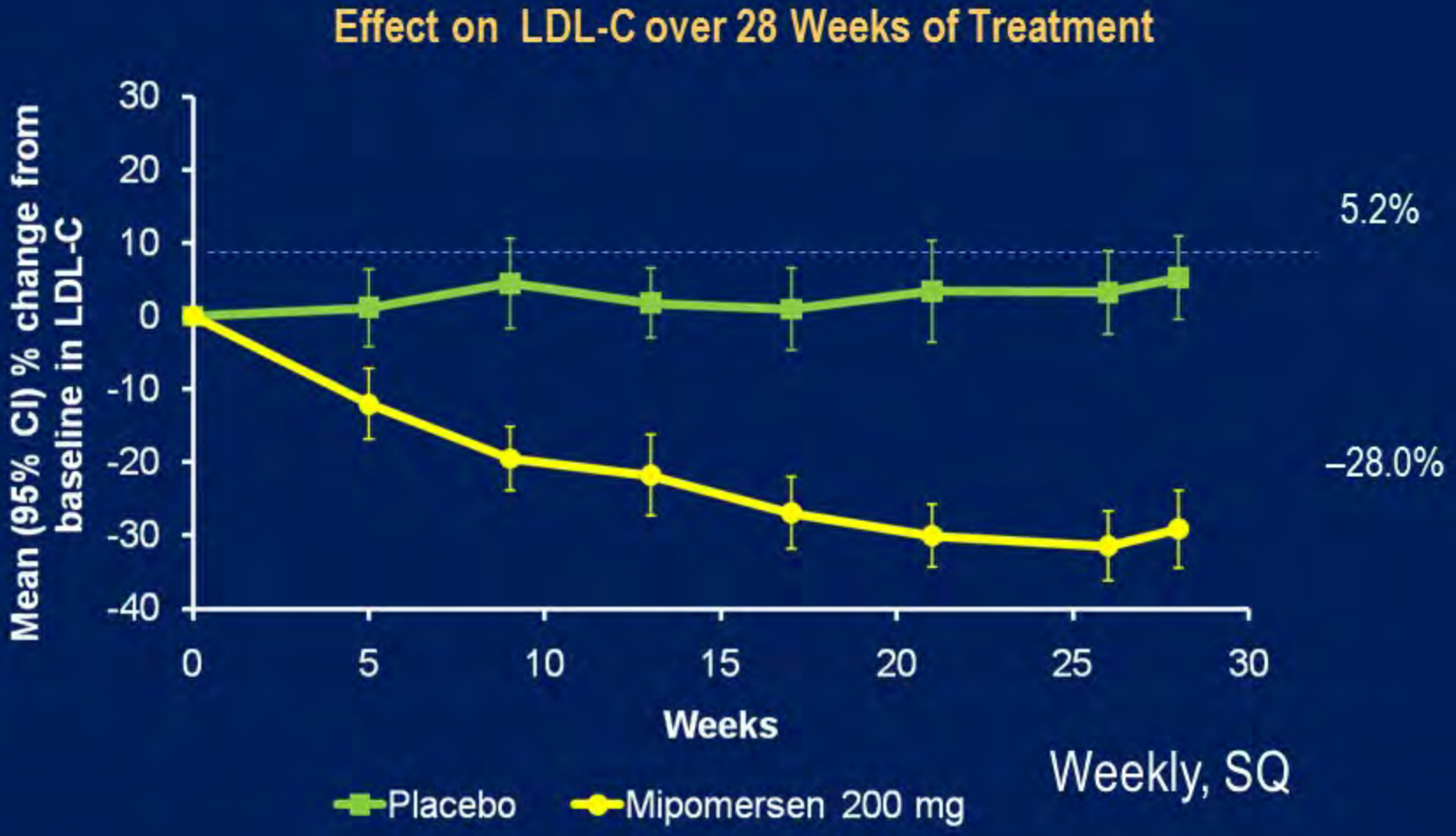
Mipomersen

Antisense Oligonucleotide for apoB-1000



Thomas GS et al. *J Am Coll Cardiol.* 2013;62:2178-2184.

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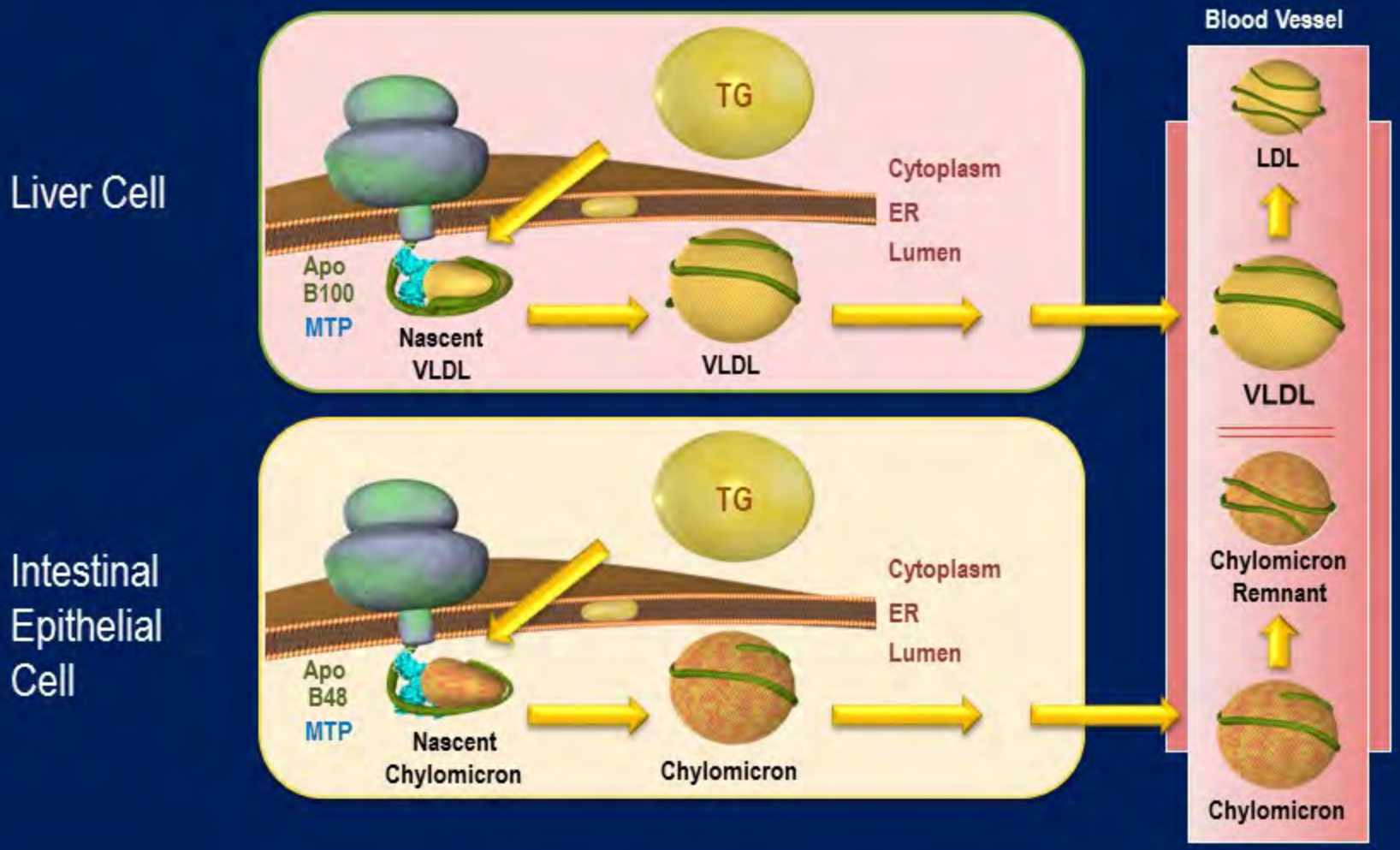
Modulation of VLDL Production

Lomitapide

Inhibitor of MTP (microsomal triglyceride transfer protein)

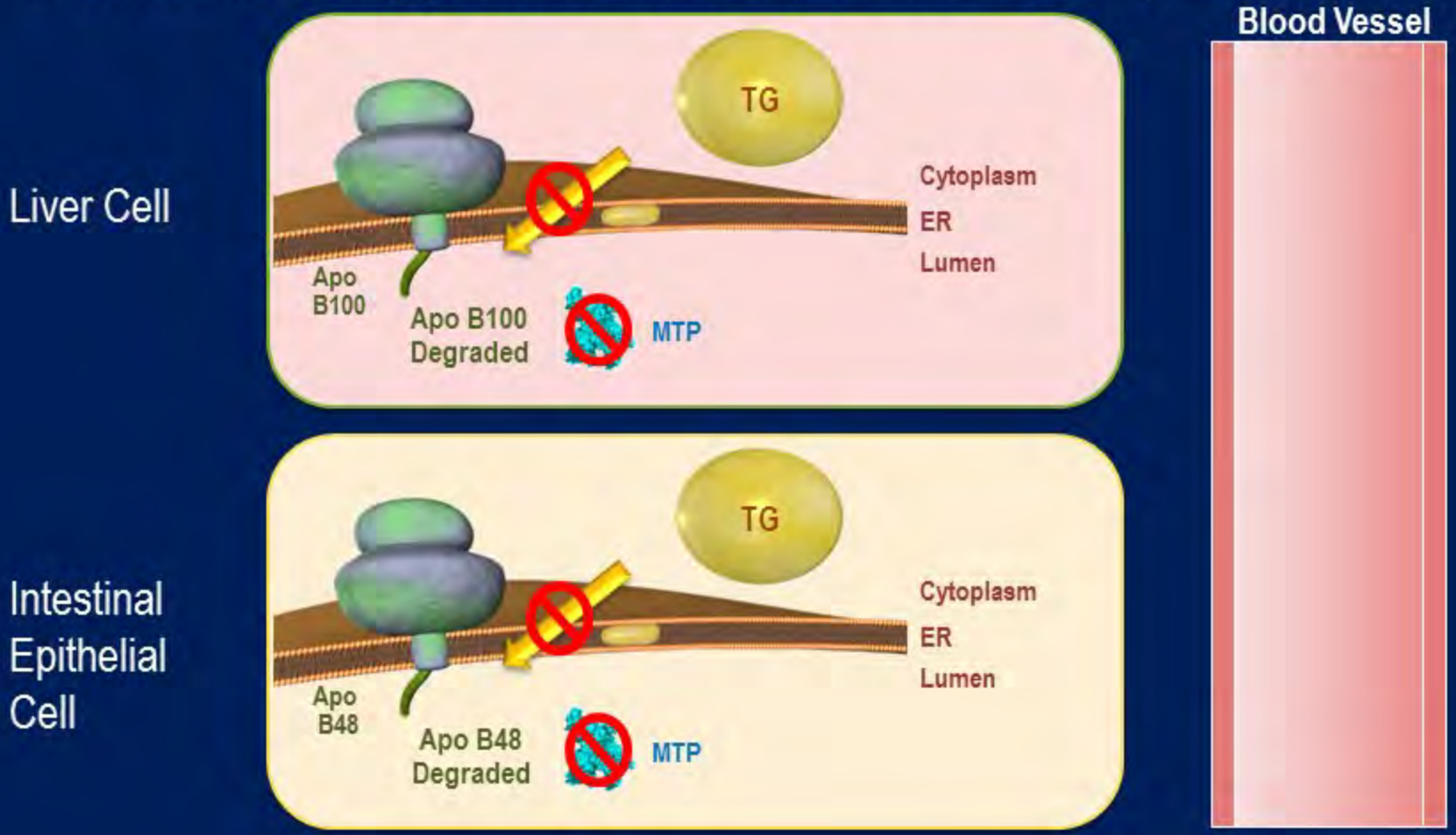
VLDL and Chylomicron Synthesis



Hussain MM et al. *J Lipid Res.* 2003:44;22-32.

Lomitapide Inhibits MTP

Microsomal Triglyceride Transfer Protein (MTP) Inhibitor



Hussain MM et al. *J Lipid Res.* 2003:44;22-32.

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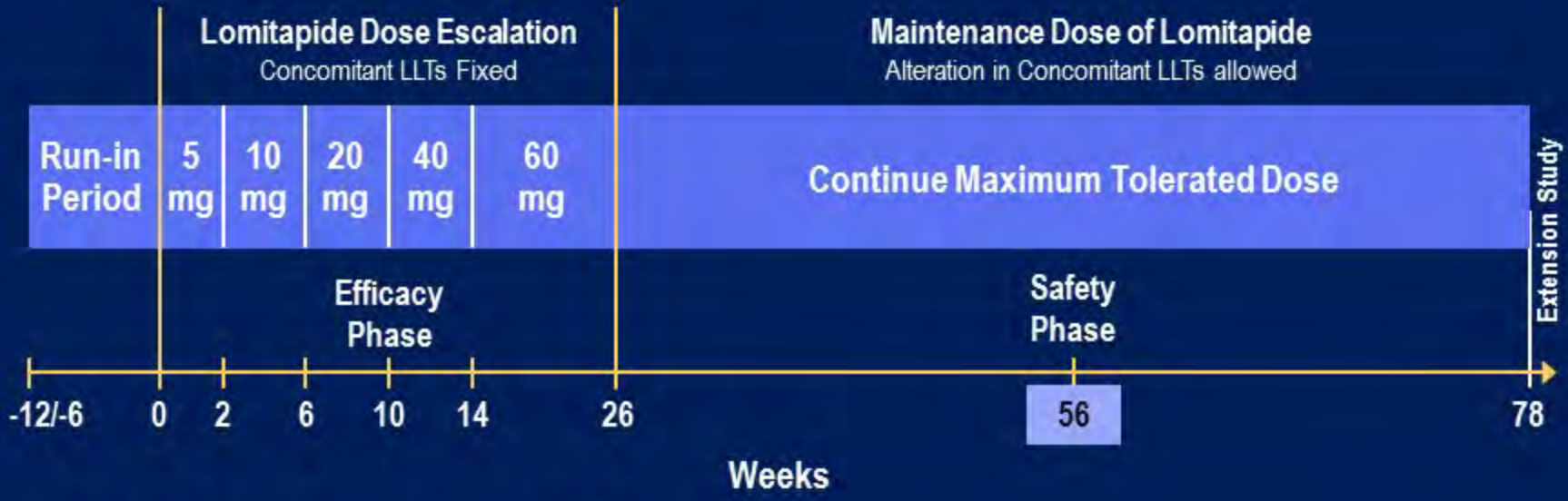
Lomitapide: Phase III Study Design



- Safety Phase: From Week 26-78
  - Continued maximum tolerated dose
  - Changes in concomitant LLTs allowed
  - Week 56 data submitted in NDA
- Extension study for patients who successfully completed the Phase III study
- 4-month safety report through week 78 and the extension study

Cuchel M et al. *Lancet.* 2013;381:40-46.

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Lomitapide

Microsomal Triglyceride Transfer Protein Inhibitor

Change in Lipid; No Background Therapy

Cuchel M et al. *N Engl J Med.* 2007;356:148-156.

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Lomitapide

Long-term Effects in Patients with HoFH

Data are mean, 95%CI (n=23)

Cuchel M et al. *Lancet.* 2013;381:40-46.

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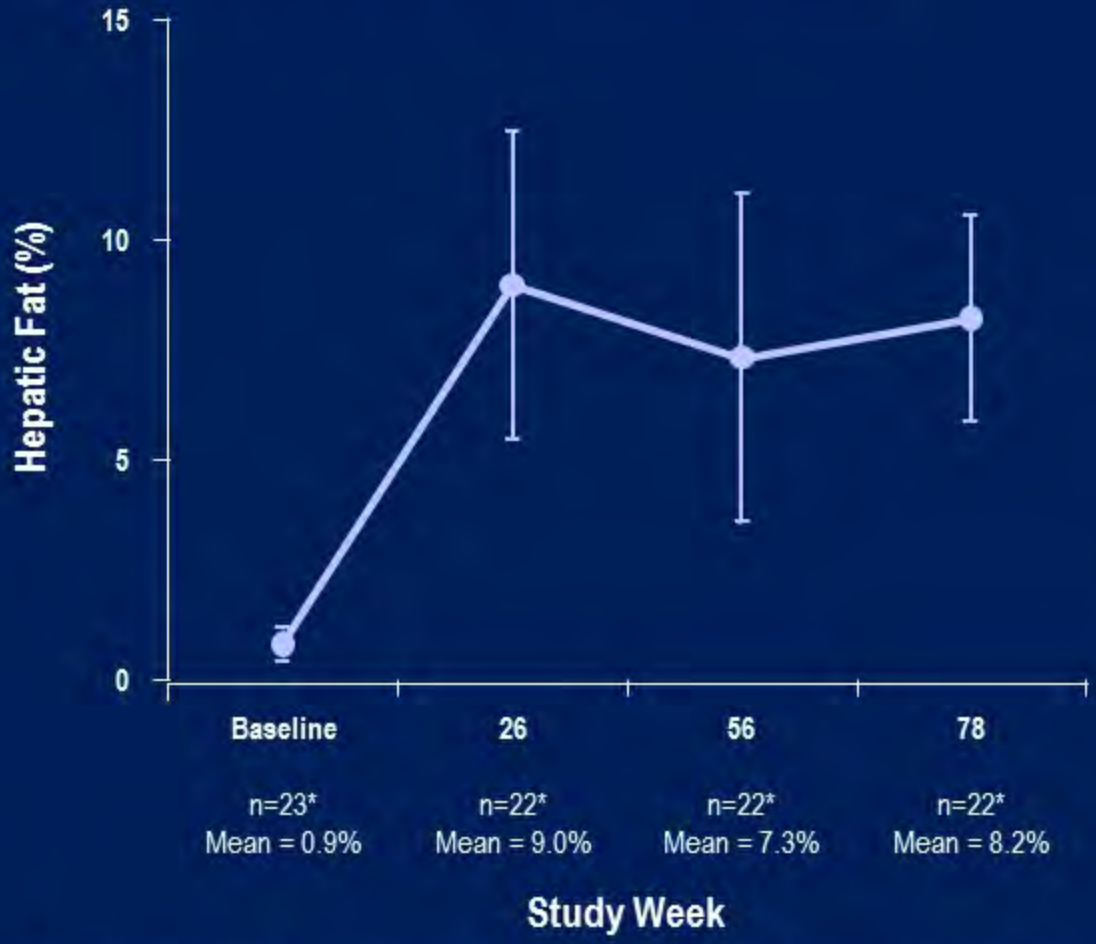
Lomitapide HoFH Phase III Study

Safety: Effects on Hepatic Fat Content



*Fewer number of nuclear magnetic resonance spectroscopy reads due to patients with contraindication for MRI

Cuchel M et al. *Lancet.* 2013;381:40-46.

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Conclusions

Conclusions

- Despite significant reduction in LDL-C and CVD risk associated with statin use, considerable residual risk persists.
- The addition of ezetimibe to statins yields incremental but modest improvements in CVD risk.
- The addition of CETP inhibitors to statins have not demonstrated improvements in CVD risk to date.
- PCSK9 inhibitors represent the most promising new class of LDL-C lowering therapy and ongoing outcomes trials will help to determine the clinical utility of these agents.
- Direct and indirect inhibitors of apoB are FDA approved for adjunctive treatment of HoFH.

Managing Severe or Resistant Hypercholesterolemia

The Next Generation of LDL-C Lowering Agents

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EVALUATION FORM.

Your participation will help shape future
CME activities.