Defining the role of PCSK9 inhibitor alirocumab in the treatment of hyperlipidemia

SATELLITE LECTURE

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Disclosures

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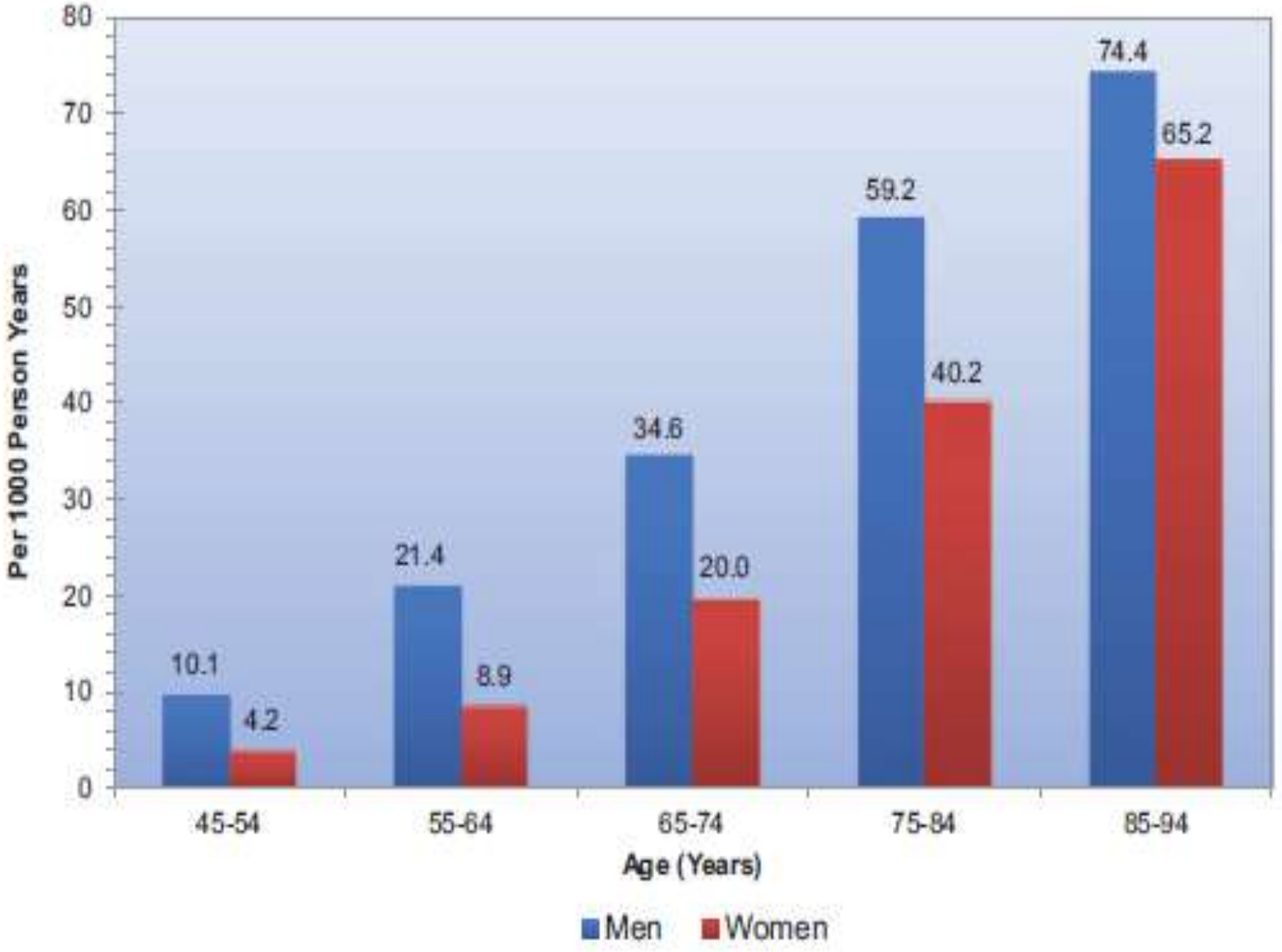
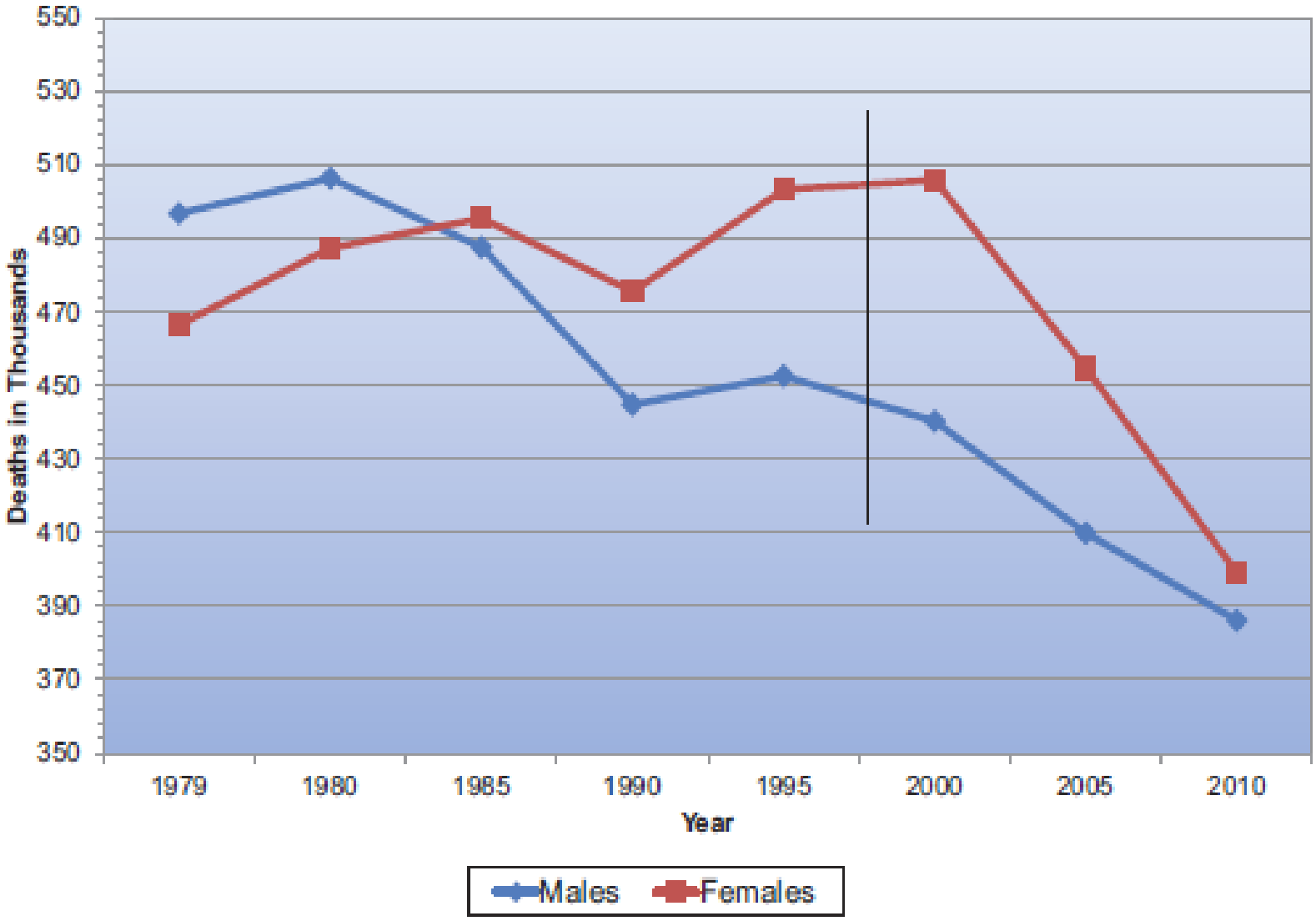
Introduction

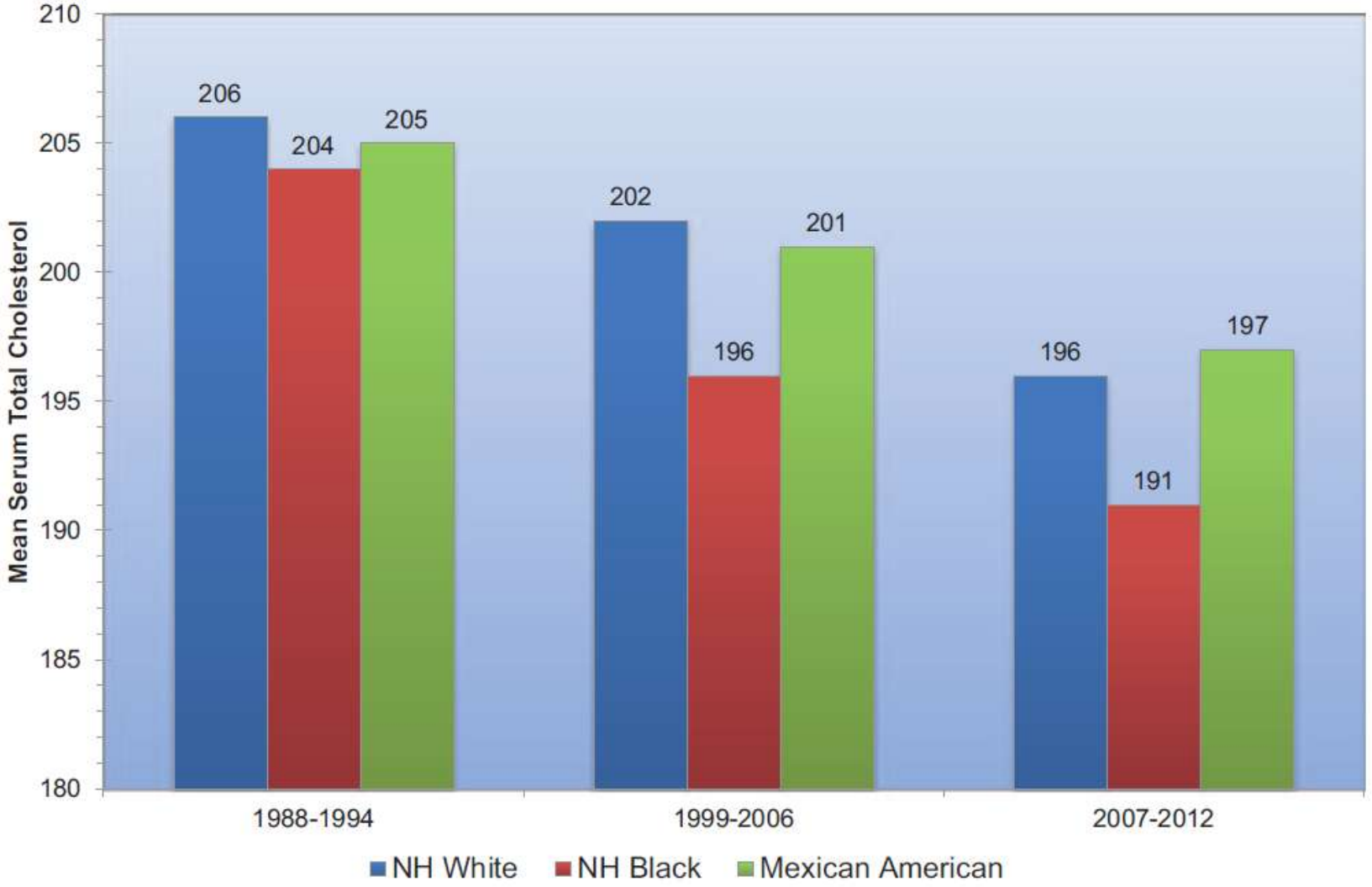
Incidence of cardiovascular disease (doesn't include hypertension alone) by age & sex **(Framingham Heart Study, 1980–2003).**



Cardiovascular disease mortality trends for males and females (United States: 1979–2010).

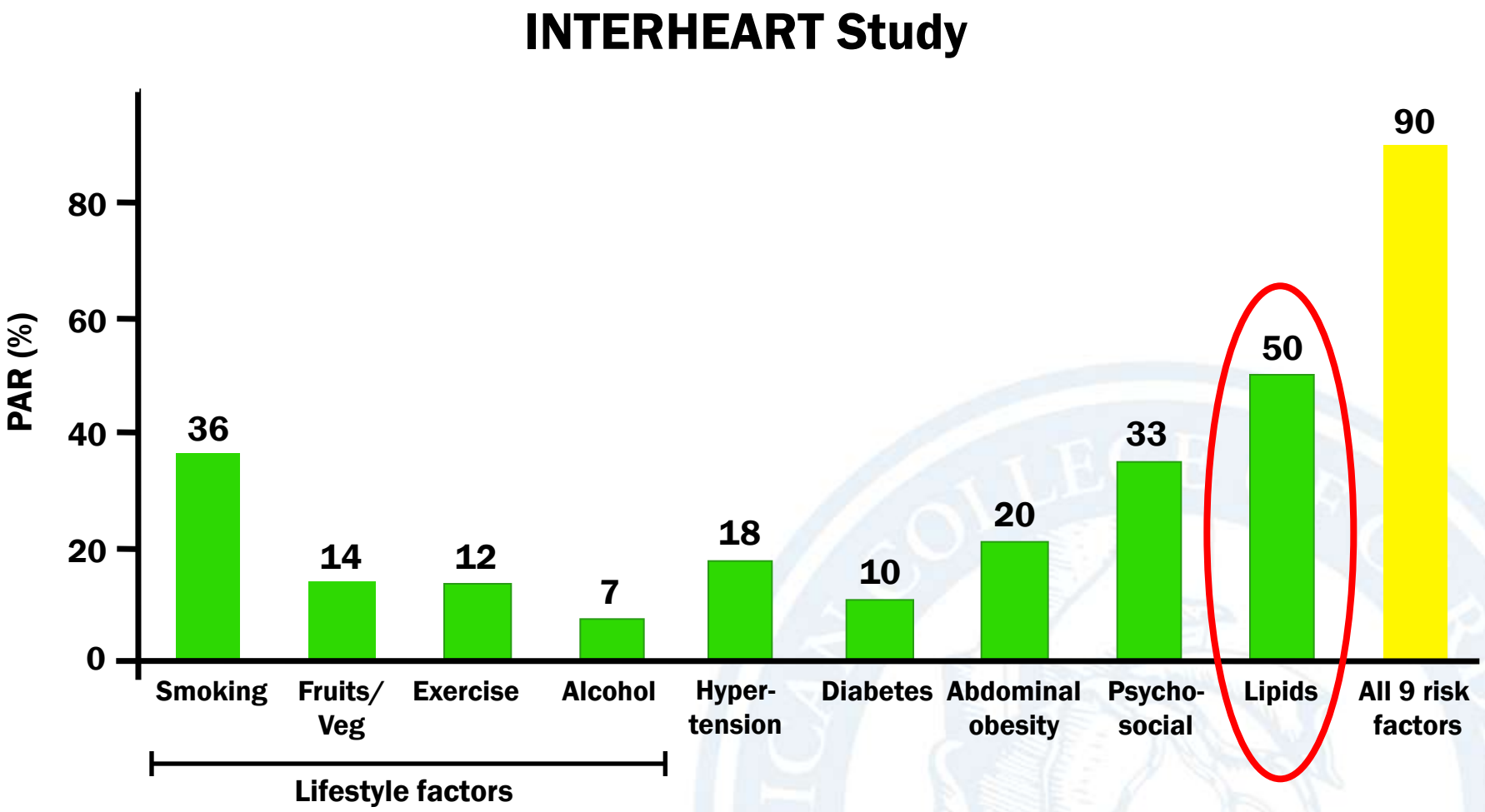


Trends in mean serum total cholesterol among adults aged ≥20 years by race and survey year



Mozaffarian D et al. Circulation. 2015;131:e29-e322
Heart Disease and Stroke Statistics—2015 Update

Attributable Risk Factors for a First Myocardial Infarction



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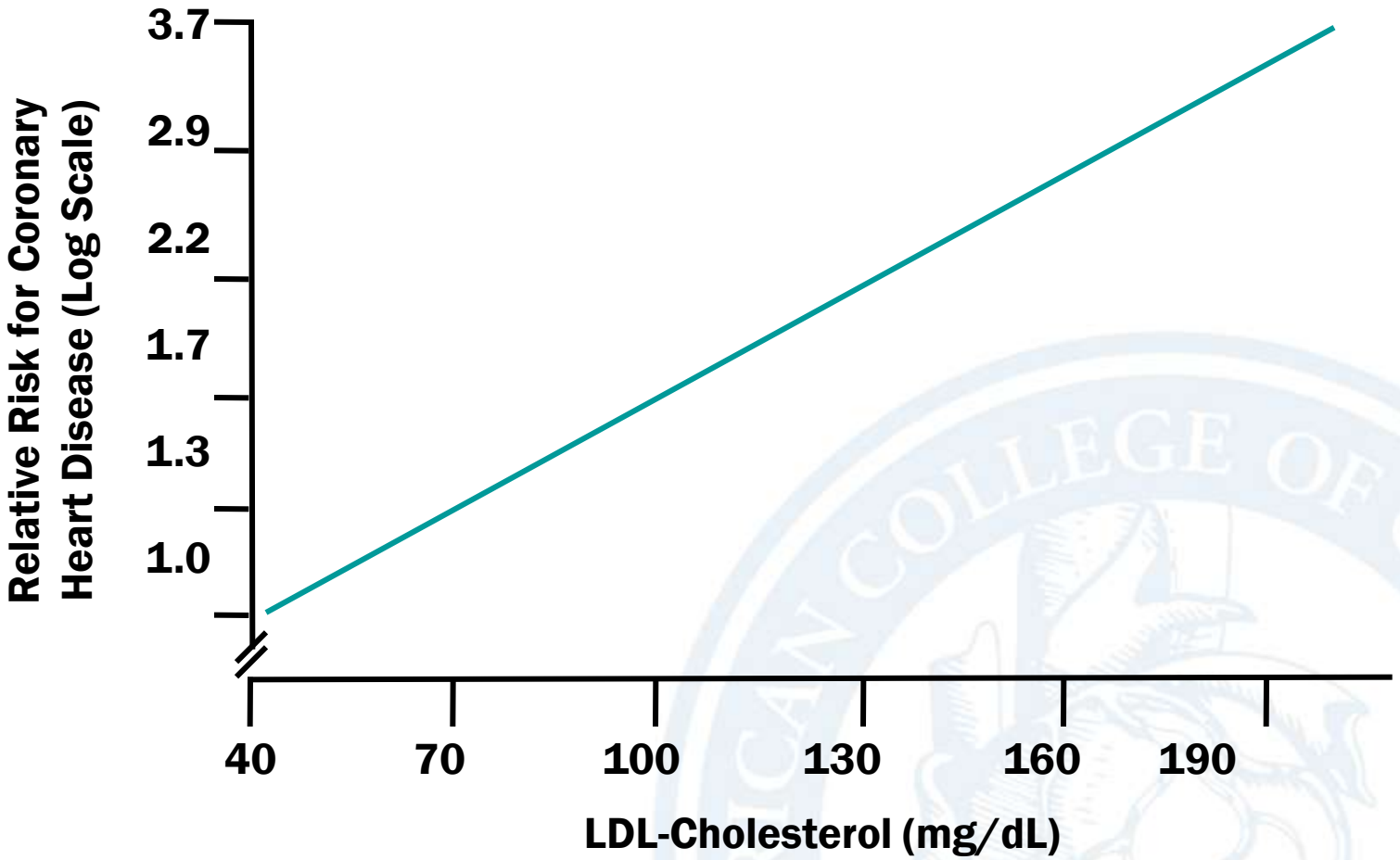
n=15,152 patients and 14,820 controls in 52 countries

MI=Myocardial infarction, PAR=Population attributable risk (adjusted for all risk factors)

Yusuf S et al. Lancet. 2004;364:937-952

Coronary Heart Disease Risk According to LDL-C Level



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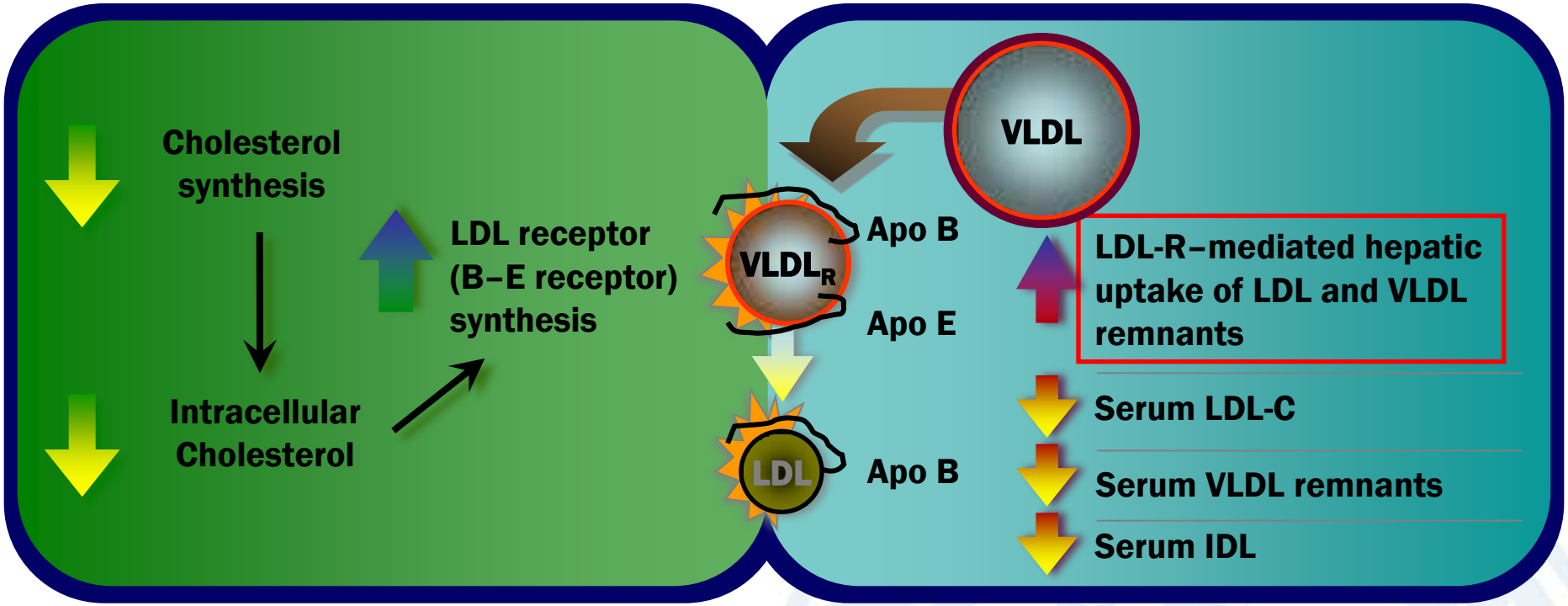
CHD=Coronary heart disease, LDL-C=Low-density lipoprotein cholesterol

Grundy S et al. Circulation 2004;110:227-239

Therapies to Lower Levels of LDL-C

Class	Drug(s)
3-Hydroxy-3-Methylglutaryl Coenzyme A (HMG-CoA) reductase inhibitors [Statins]	Atorvastatin (Lipitor) Fluvastatin (Lescol XL) Lovastatin (Mevacor) Pitavastatin (Livalo) Pravastatin (Pravachol) Rosuvastatin (Crestor) Simvastatin (Zocor)
Bile acid sequestrants	Cholestyramine (Questran) Colesevelam (Welchol) Colestipol (Colestid)
Cholesterol absorption inhibitor	Ezetimibe (Zetia)
Nicotinic acid	Niacin
Dietary Adjuncts	Soluble fiber Soy protein Stanol esters
PCSK9 inhibitors (Monoclonal antibodies)	Alirocumab Evolocumab Bococizumab

HMG-CoA Reductase Inhibitor: Mechanism of Action

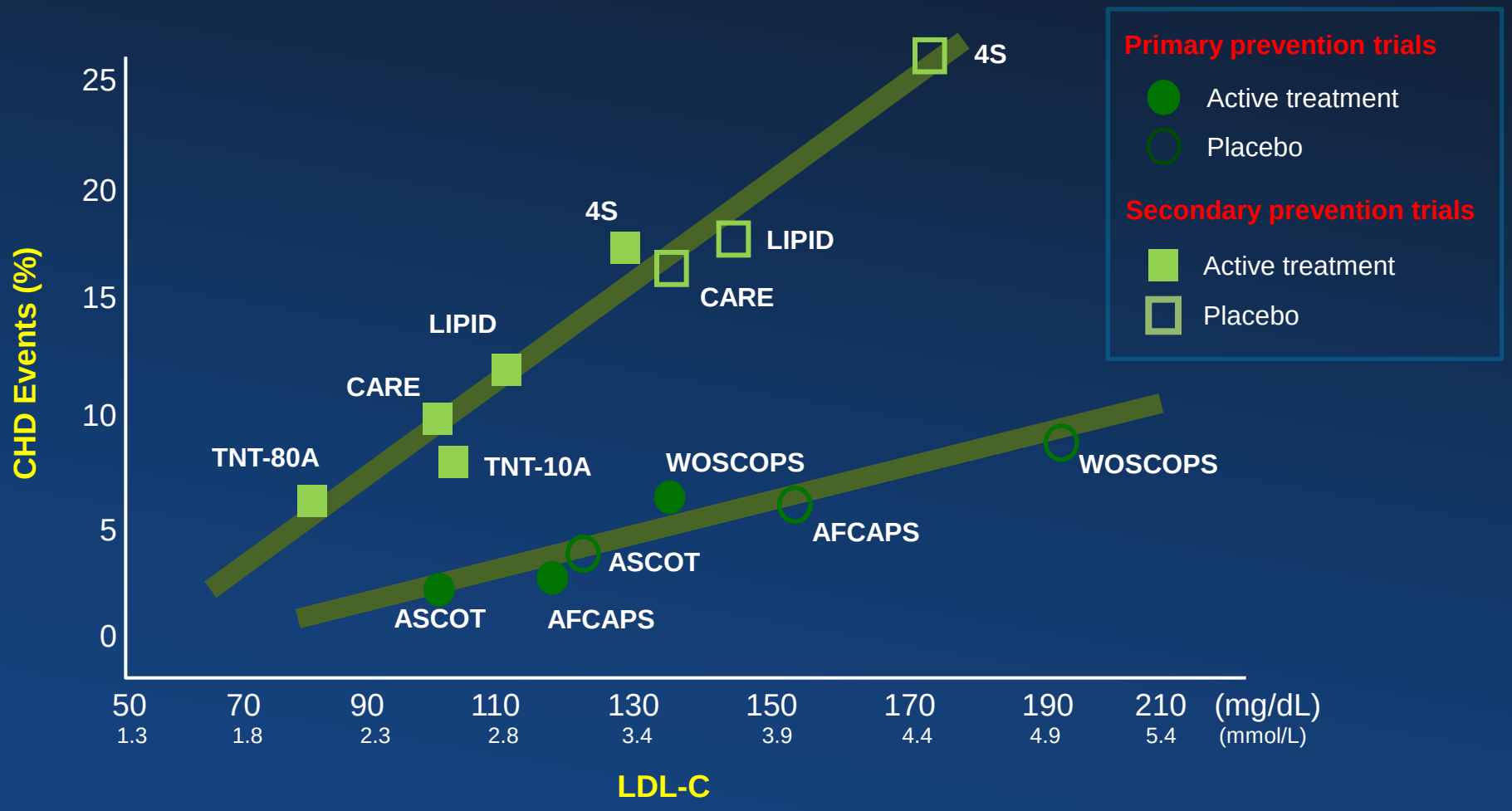


The reduction in hepatic cholesterol synthesis lowers intracellular cholesterol, which stimulates upregulation of the LDL receptor and increases uptake of non-HDL particles from the systemic circulation

HDL=High density lipoprotein, LDL=Low density lipoprotein

Source: McKenney JM. *Selecting Successful Lipid-lowering Treatment* presentation, 2002. Available at http://www.lipidsonline.org/slides/slide01.cfm?tk=23&dpg=4.

Lowering LDL-C With Statins Reduces CV Risk in Both Primary and Secondary Prevention



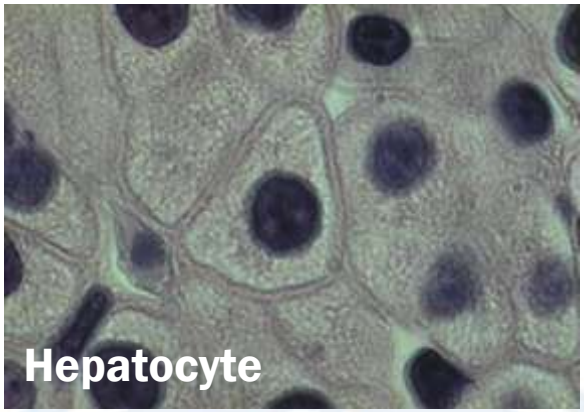
Adapted from O'Keefe et al. *J Am Coll Cardiol* 2004;43:2142-6;
LaRosa JC et al. *N Engl J Med* 2005;352:1425-35.

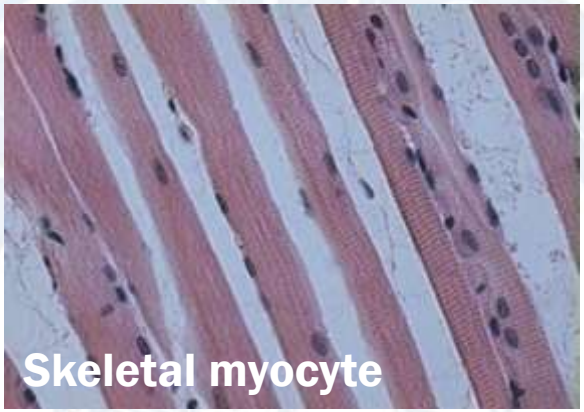
HMG-CoA Reductase Inhibitor: Adverse Effects

74,102 subjects in 35 randomized clinical trials with statins

- **1.4% incidence of elevated hepatic transaminases (1.1% incidence in control arm)**
- **Dose-dependent phenomenon that is usually reversible**

- **15.4% incidence of myalgias* (18.7% incidence in control arm)**
- **0.9% incidence of myositis (0.4% incidence in control arm)**
- **0.2% incidence of rhabdomyolysis (0.1% incidence in control arm)**


Hepatocyte


Skeletal myocyte

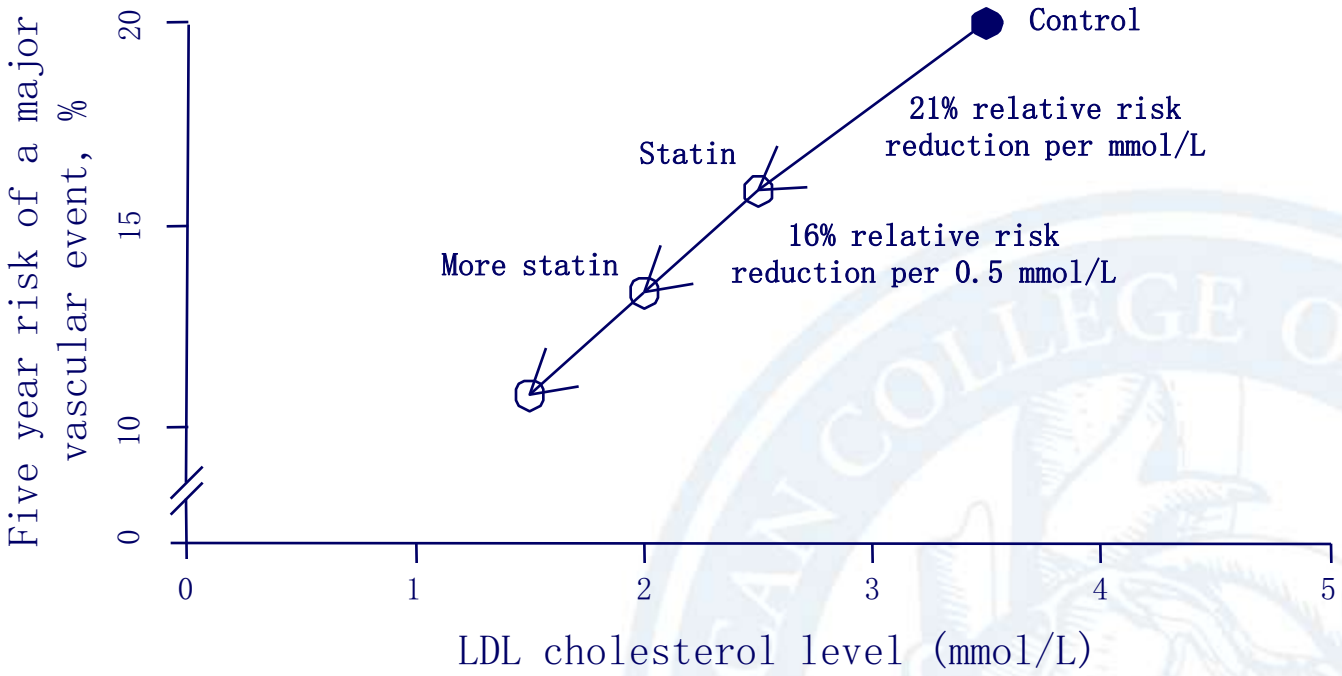
*The rate of myalgias leading to discontinuation of atorvastatin in the TNT trial was 4.8% and 4.7% in the 80 mg and 10 mg arms, respectively

Source: Kashani A et al. *Circulation 2006;114:2788-2797*

HMG-CoA Reductase Inhibitor Evidence: Effect of Intensive Therapy

Cholesterol Treatment Trialists' (CTT) Collaboration

Meta-analysis of 169,138 patients randomized to at least 2 years of statin therapy



There is a proportionate reduction in CV events with greater LDL-cholesterol reduction

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CV=Cardiovascular, LDL=Low density lipoprotein

Source: Cholesterol Treatment Trialists' Collaboration. *Lancet 2010;376:1670-1681*

Recommendations for treatment targets for LDL Cholesterol (LDL-C)

ESC/EAS Guidelines for the management of dyslipidaemias

Recommendations	Class[a]	Level[b]	
In patients at VERY HIGH CV risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE level ≥10%) the LDL-C goal is <1.8 mmol/L (less than ~70 mg/dL) and/or ≥50% LDL-C reduction when target level cannot be reached.	I	A	LDL-C ≤ 70 mg/dL
In patients at HIGH CV risk (markedly elevated single risk factors, a SCORE level ≥5 to <10%) an LDL-C goal <2.5 mmol/L (less than ~100 mg/dL) should be considered.	IIa	A	LDL-C ≤ 100 mg/dL
In subjects at MODERATE risk (SCORE level >1 to ≤5%) an LDL-C goal <3.0 mmol/L (less than ~115 mg/dL) should be considered.	IIa	C	LDL-C ≤ 115 mg/dL

European Heart Journal (2011) 32, 1769–1818

- European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines suggest reducing LDL cholesterol levels to lower than 70 mg/dL for very high risk patients.
- However, up to 80% of these patients fail to reach this target.
- Many patients have familial hypercholesterolemia (FH) and therefore very high baseline LDL cholesterol levels and inability to achieve lipid targets with statin alone or even in combination with ezetimibe.
- Of note, patients receiving statins have a significant residual cardiovascular risk that underlines the need for more effective decrease of LDL cholesterol.
- Moreover, 5–10% of patients cannot tolerate an effective or any dose of statins because of myopathy.

Eur Heart J 2011, 32:1769–1818.
Lancet 2010, 376:1670–1681.

Overview of PCSK9 Physiology

LDL metabolism and the discovery of PCSK9

- Genetic mutations lowering LDL receptor activity or mutations in apolipoprotein B (ApoB) lead to Familial Hypercholesterolemia (FH).
- In 1999, Varret et al reported for the first time a 3rd genetic locus, mutations of which result in FH. Further study showed in 2003 an association of a protein with the LDL receptor and LDL cholesterol levels.
- This protein was named proprotein convertase subtilisin/kexin type 9 (PCSK9) and is the product of PCSK9 gene in chromosome 1p32.3.
- Two mutations of that gene were described, both resulting in autosomal dominant FH. The genetic sequence analysis though, revealed mutations in PCSK9 gene that enhanced the protein's activity (gain-of-function mutations) and decreased LDL receptor function.

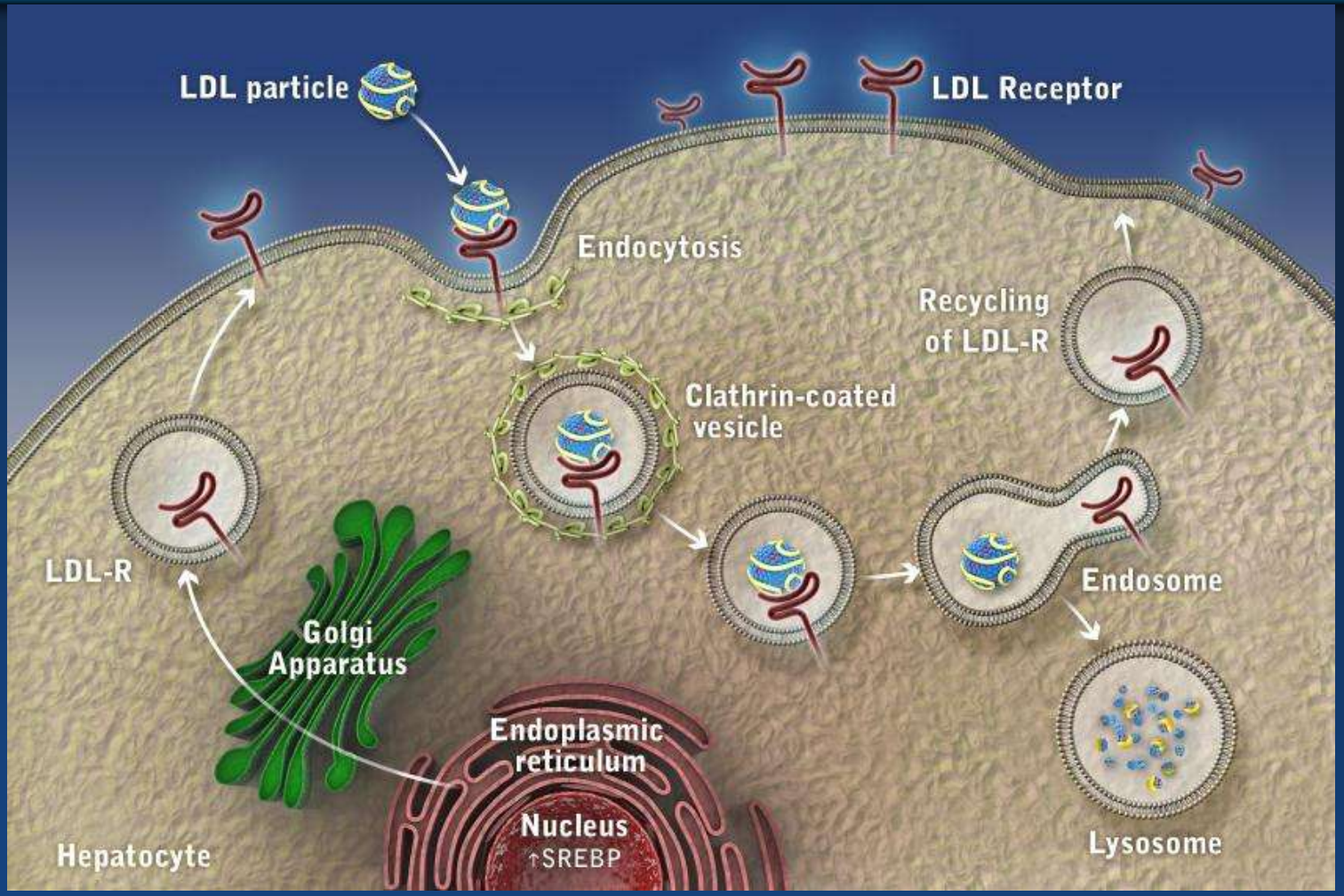
European Heart Journal 2015;36:2415–2424

LDL metabolism and the discovery of PCSK9

- Overexpression of PCSK9 protein leads to increased LDL cholesterol and a phenotype similar to complete LDL receptor absence.
- In addition, administering the PCSK9 protein to mice decreased LDL receptors on hepatic cell surface, without decreasing their mRNA.
- In contrast, deleting the PCSK9 gene from mice genome increased LDL receptors and reduced LDL cholesterol by increasing its hepatic clearance.
- In humans, it was found that PCSK9 mutations resulting in decreased activity of PCSK9 (loss-of-function mutations) are associated with decreased LDL cholesterol levels.
- Two mutations of the PCSK9 gene, present in 2% of the blacks, decrease LDL cholesterol up to 40%, while another mutation, present in 3.2% of the whites, decreases LDL cholesterol up to 21%.

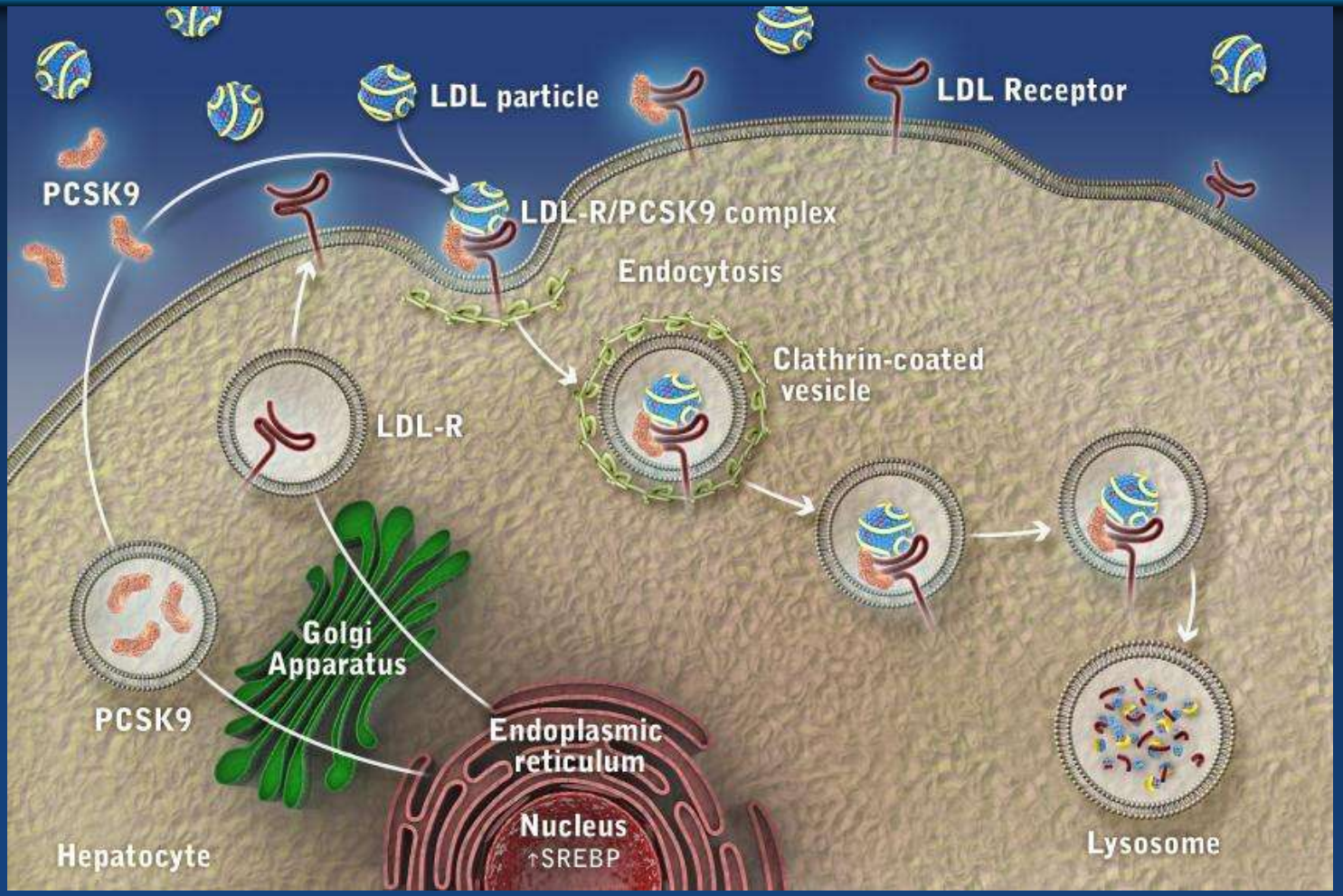
European Heart Journal 2015;36:2415–2424

LDL Receptor Function and Life Cycle



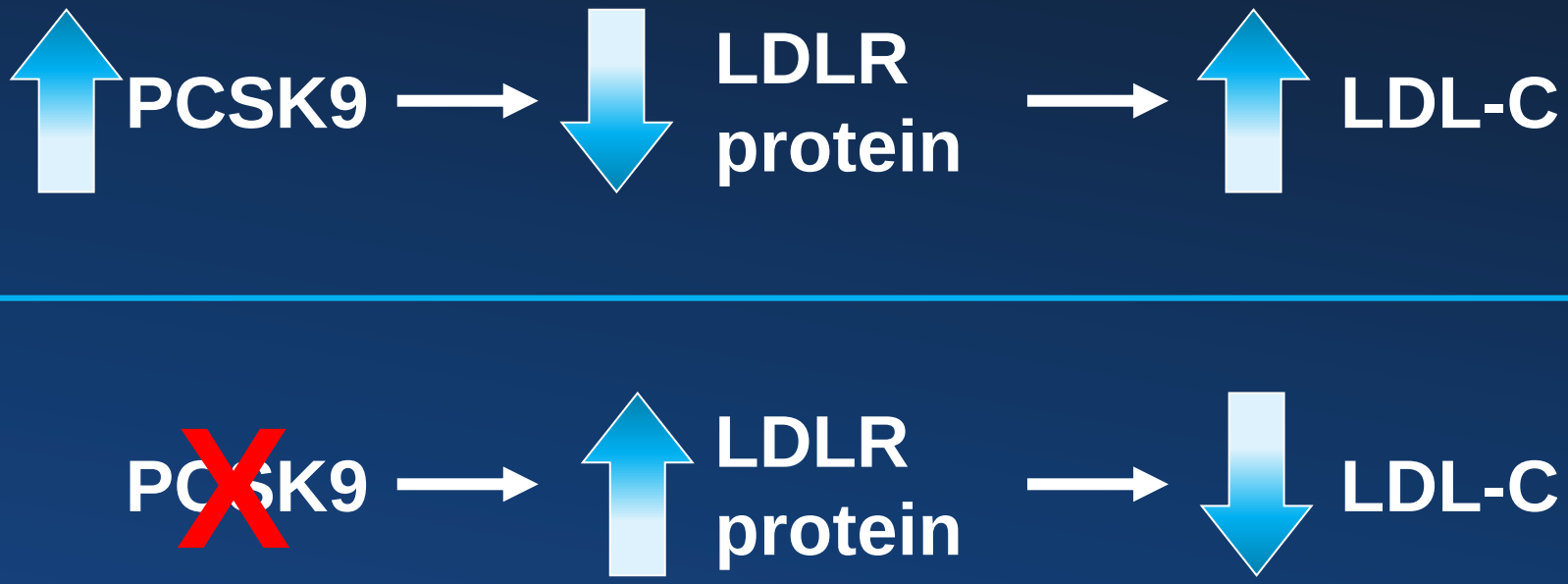
LDL=low-density lipoprotein; LDLR=LDL receptor; SREBP2=sterol regulatory element-binding protein-2.
Source: Semenkovich CF et al. In: *Williams Textbook of Endocrinology*. 12th ed. Philadelphia, PA: Elsevier Saunders; 2011:1633-1674.

The Role of PCSK9 in the Regulation of LDL Receptor Expression



LDL=low-density lipoprotein; LDLR=LDL receptor; PCSK9=proprotein convertase subtilisin/kexin type 9; SREBP2=sterol regulatory element-binding protein-2.
Source: Lambert G et al. *J Lipid Res.* 2012;53:2515–2524.

PCSK9 Promotes Degradation of LDLRs

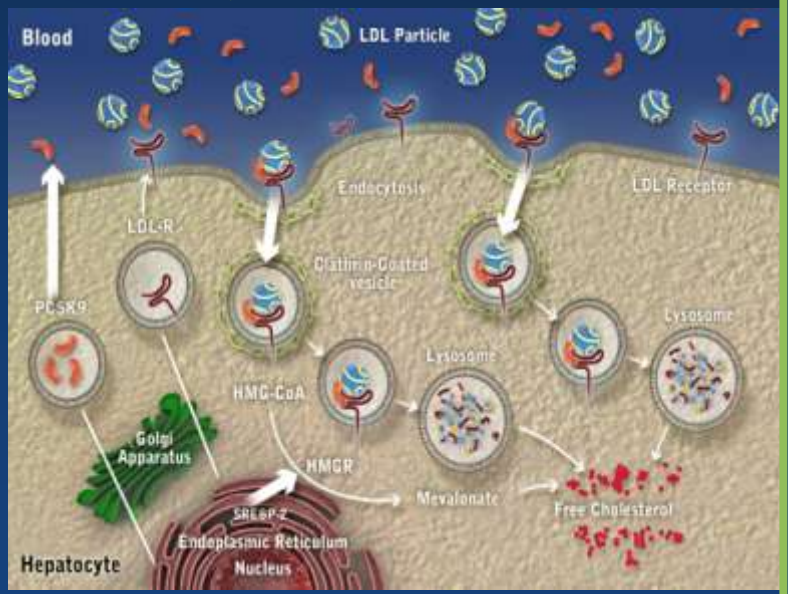


LDL-C=low-density lipoprotein cholesterol; LDLR=low-density lipoprotein receptor.

PCSK9 Mutations: Gain of Function (GoF)

Gain of Function

↓LDLR levels
↓LDL clearance



↑LDL
High risk for atherosclerosis and CHD

- **PCSK9 GoF mutations are a rare cause of FH and high LDL-C levels, and more than 20 such mutations have already been found[1]**
  - PCSK9 GoF mutations first found in 2003 in French families with hypercholesterolemia and high LDL-C[2]

Adapted from: Catapano AL and Papadopoulos N. *Atherosclerosis*. 2013;228:18-28; Soufi M et al. *Gene*. 2013;521:200-203.

1. Tibolla G, et al. *Nutr Metab Cardiovasc Dis*. 2011;21:835-843.
2. Abifadel M, et al. *Nat Genet*. 2003;34:154-156.

PCSK9 Mutations: Loss of Function (LoF)

Loss of Function

↑LDL-R levels
↑LDL clearance

↓LDL

Protection from atherosclerosis and CHD

- **PCSK9 LoF mutations are a rare cause of hypocholesterolemia and low LDL-C levels[1]**
  - PCSK9 LoF mutations first found in 2005, with one variant (Cys679X) occurring at a frequency of 1.4% in African Americans but only rarely in European Americans[2]

1. Tibolla G, et al. *Nutr Metab Cardiovasc Dis*. 2011;21:835-843.
2. Cohen J, et al. *Nat Genet*. 2005;37:161-165.

Adapted from: Catapano AL and Papadopoulos N. *Atherosclerosis*. 2013;228:18-28; Soufi M et al. *Gene*. 2013;521:200-203.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

The ARIC study

Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

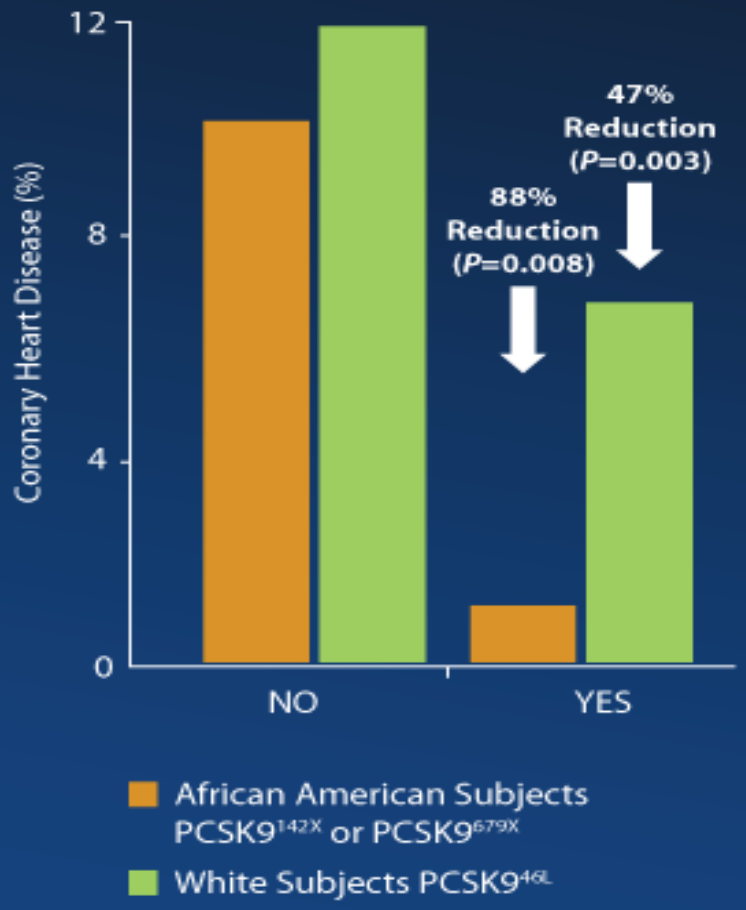
Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.

RESULTS

Of the 3363 black subjects examined, 2.6 percent had nonsense mutations in *PCSK9*; these mutations were associated with a 28 percent reduction in mean LDL cholesterol and an 88 percent reduction in the risk of CHD ($P=0.008$ for the reduction; hazard ratio, 0.11; 95 percent confidence interval, 0.02 to 0.81; $P=0.03$). Of the 9524 white subjects examined, 3.2 percent had a sequence variation in *PCSK9* that was associated with a 15 percent reduction in LDL cholesterol and a 47 percent reduction in the risk of CHD (hazard ratio, 0.50; 95 percent confidence interval, 0.32 to 0.79; $P=0.003$).

N Engl J Med 2006;354:1264-72.

PCSK9 Loss of Function (LoF) Mutations Are Associated With Low LDL-C and Low Prevalence of CAD Events



N Engl J Med 2006;354:1264-72.

PCSK9 LoF Mutations Provide Genetic Validation for the Potential Role of PCSK9 Inhibition in LDL-C Metabolism

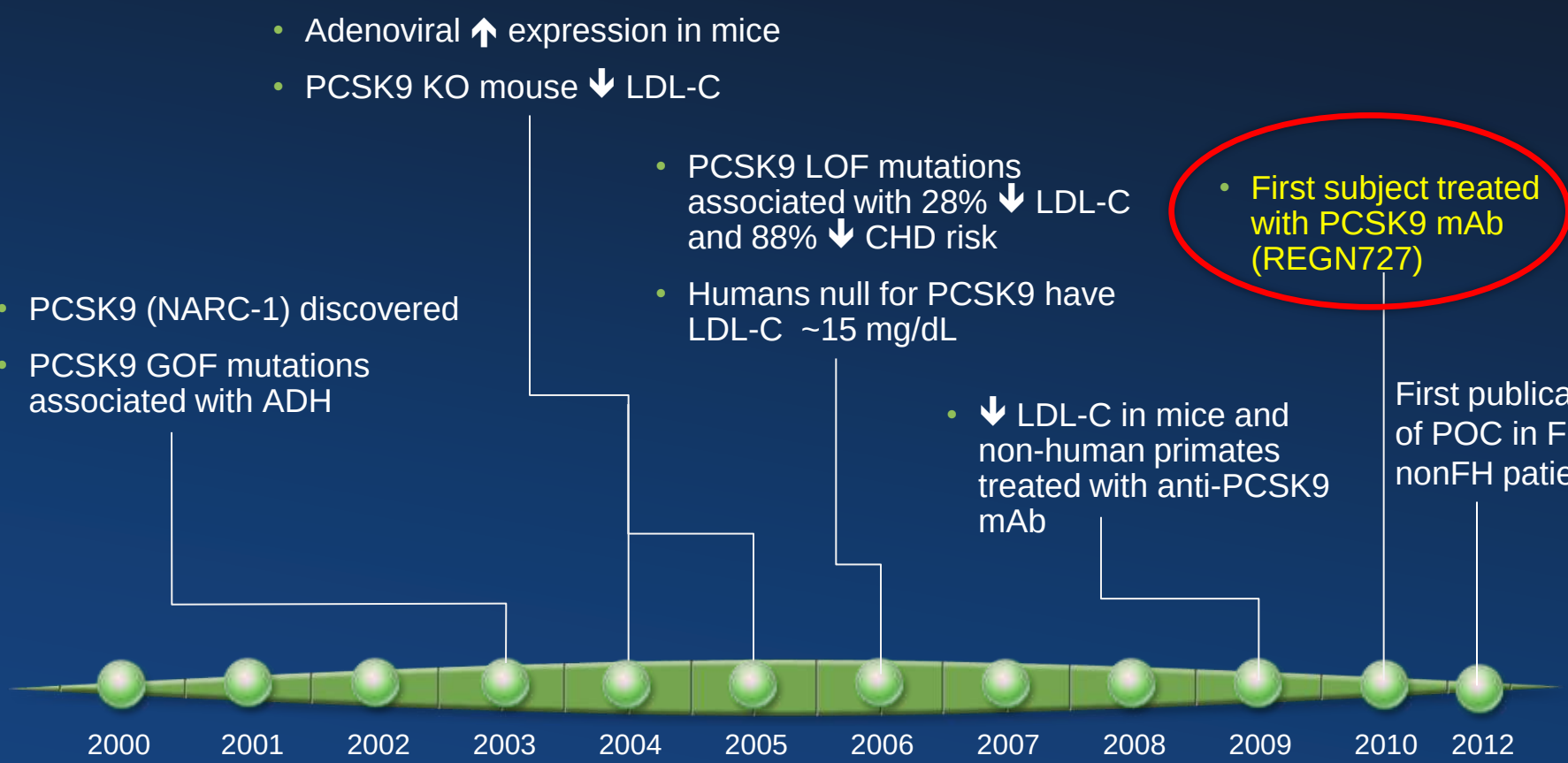
- Subjects with loss-of-function mutations in PCSK9:
  - Have naturally low levels of LDL-C and reduced CVD relative to the general population[1,2]
  - These mutations are not associated with other detectable abnormalities[1,2]

	PCSK9 Mutation	LDL-C Reduction	CAD Reduction
Benn et al. *JACC* 2010[1]	R46L	13%	30%
Cohen et al. *NEJM* 2006[2]	R46L	15%	47%
	Y142X or C679X	28%	88%

- Two healthy women completely deficient in PCSK9 have been described without sequelae[3]

1. Benn M, et al. *J Am Coll Cardiol.* 2010; 55:2833-2842.
2. Cohen JC, et al. *N Engl J Med.* 2006;354:1264-1272.
3. Tibolla G, et al. *Nutr Metab Cardiovasc Dis*. 2011;21:835-843.

PCSK9:
Progress From Discovery to Clinic



Sources: Seidah NG. *Proc Natl Acad Sci USA* 2003;100(3):928-33, Abifadel M. *Nat Genet* 2003;34(2):154-6, Maxwell KN. *Proc Natl Acad Sci USA* 2004;101(18):7100-5, Rashid S. *Proc Natl Acad* Sci *USA* 2005;102(15):5374-79, Cohen JC. *N Engl J Med* 2006;354(12):1264-72, Zhao Z. *Am J Hum Genet* 2006;79(3):514-23, Hooper AJ. *Atherosclerosis* 2007;193(2):445-8, Chan JC. *Proc Natl Acad Sci USA* 2009;106(24):9820-5; Stein et al *N Engl J Med* 2012;366:1108-18.

Modified from Gary Swergold, Regeneron.

PCSK9 as a treating target

- PCSK9 can be inhibited in various ways using monoclonal antibodies (mAbs), oligonucleotides (antisense oligonucleotides), small sectors of silence RNA (siRNA) or small molecule inhibitors.

- Current research has mainly focused on monoclonal antibodies as PCSK9 inhibitors. Human monoclonal antibodies against PCSK9 protein have been developed and tested in animals first.

- **Intravenous infusion of these antibodies resulted in a decrease of LDL cholesterol by 50%.**

- In humans, 3 monoclonal antibodies have been developed and tested, namely alirocumab (SANOFI-REGENERON) evolocumab (AMGEN), and bococizumab (PFIZER).

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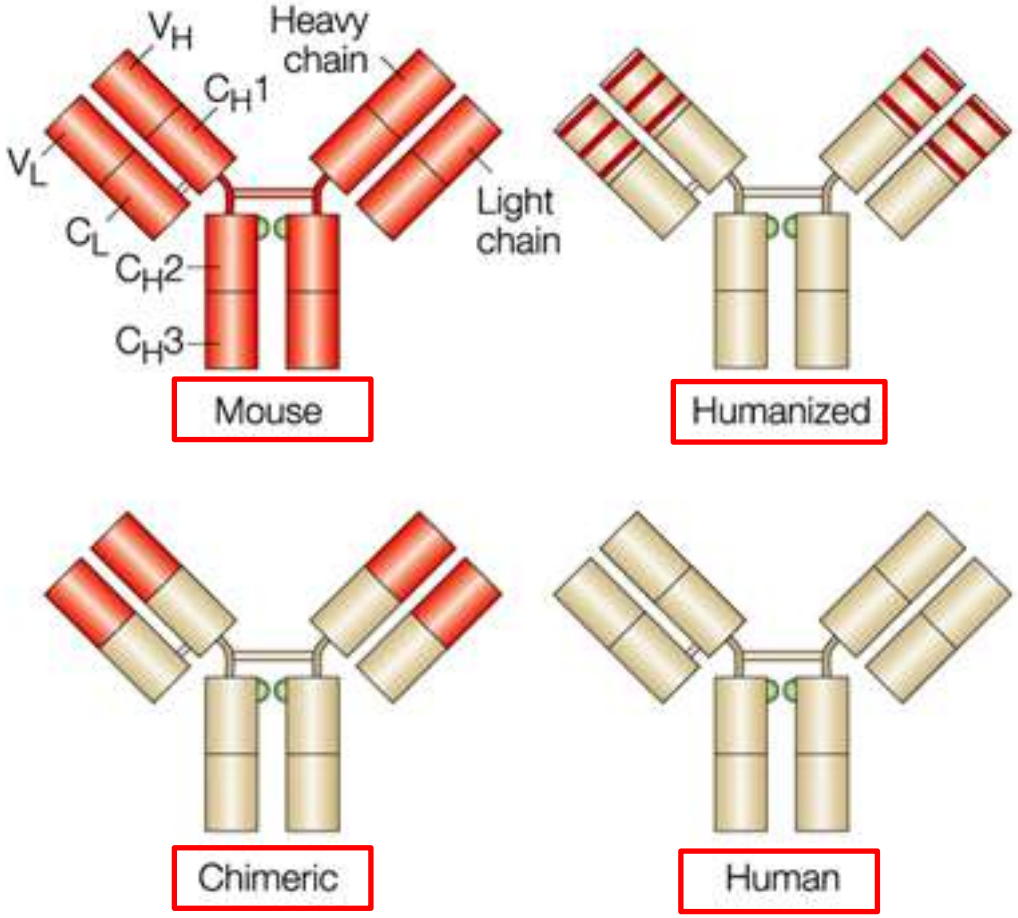
V_H
Heavy chain
C_H1
V_L
Light chain
C_L
C_H2
C_H3
Mouse
Humanized
Chimeric
Human
Mouse sequences
Human sequences
Glycosylation
Complementarity determining regions

PCSK9 as a treating target

Table I Selected proprotein convertase subtilisin/kexin type 9-directed therapies in development

Company	Drug	Agent	Indication	Phase
Sanofi/Regeneron	Alirocumab	Human monoclonal antibody	Hypercholesterolaemia	3 (published)
Amgen	Evolocumab	Human monoclonal antibody	Hypercholesterolaemia	3 (published)
Pfizer/Rinat	Bococizumab	Monoclonal antibody	Hypercholesterolaemia	3 (ongoing)
Novartis	LGT-209	Monoclonal antibody	Hypercholesterolaemia	2
Genentech	MPSK3169A, RG7652	Monoclonal antibody	Hypercholesterolaemia	2
Alnylam Pharmaceuticals/The Medicines Company	ALN-PCS02	siRNA oligonucleotide	Hypercholesterolaemia	1
Idera Pharmaceuticals	TBD	Antisense oligonucleotide	Hypercholesterolaemia	Preclinical

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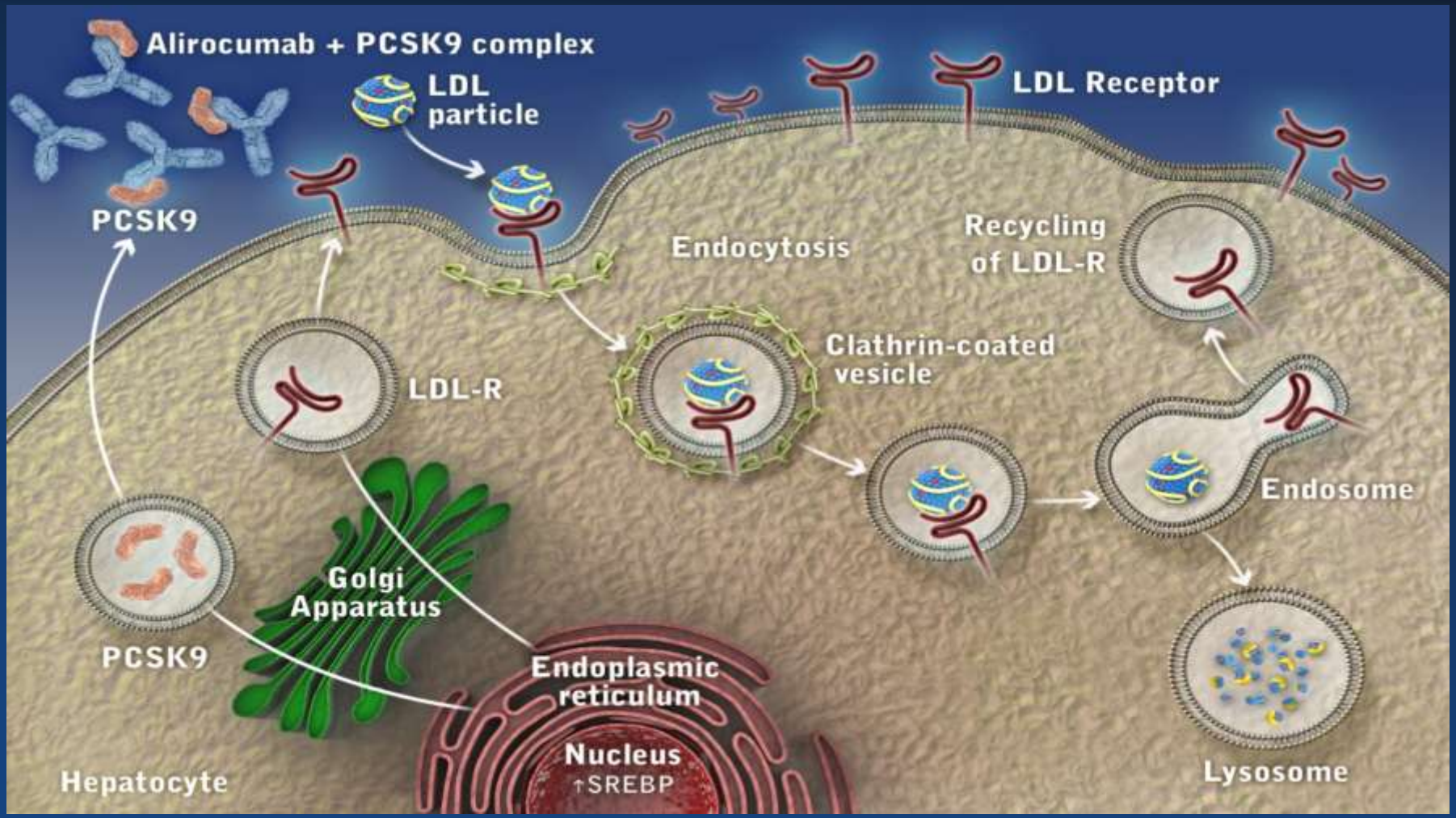
Impact of Alirocumab on LDL Receptor Expression



LDL=low-density lipoprotein; LDLR=LDL receptor; PCSK9=proprotein convertase subtilisin/kexin type 9; SREBP2=sterol regulatory element-binding protein-2.

Source: Catapano AL and Papadopoulos N. *Atherosclerosis*. 2013;228(1):18-28.

Clinical Studies

Trial name	PCSK9 inhibitor	Population and study design
ODYSSEY Mono	Alirocumab	Patients with hypercholesterolaemia on no statins, compared with ezetimibe
ODYSSEY COMBO I	Alirocumab	Hypercholesterolaemia not adequately controlled (with maximum dose of a statin with or without other lipid-modifying therapy), and high CVD risk
ODYSSEY COMBO II	Alirocumab	Hypercholesterolaemia not adequately controlled (maximum dose of a statin with or without other lipid-modifying therapy), and high CVD risk
ODYSSEY LONG TERM	Alirocumab	Hypercholesterolaemia not adequately controlled with current lipid-modifying therapy, and high CVD risk
ODYSSEY ALTERNATIVE	Alirocumab	Statin intolerance; primary hypercholesterolaemia (heterozygous FH or non-FH); and moderate, high, or very high CVD risk (no statin therapy)
ODYSSEY OPTIONS I	Alirocumab	Hypercholesterolaemia (heterozygous FH or non-FH) not adequately controlled (atorvastatin with or without other lipid-modifying therapy), and high CVD risk
ODYSSEY OPTIONS II	Alirocumab	Hypercholesterolaemia not adequately controlled (rosuvastatin with or without other lipid-modifying therapy), and high CVD risk
ODYSSEY FH I	Alirocumab	Heterozygous FH not adequately controlled with current lipid-modifying therapy (no specification regarding statin therapy)
ODYSSEY FH II	Alirocumab	Heterozygous FH not adequately controlled (with maximally tolerated statin with or without other lipid-modifying therapy)
ODYSSEY OUTCOMES	Alirocumab	Recent (in the past 4–16 weeks) acute coronary syndrome event requiring hospitalization	To compare the effect of alirocumab vs. placebo on CVD events (cardiovascular death, nonfatal myocardial infarction, fatal and non-fatal ischaemic stroke, and unstable angina requiring hospitalization), for up to 64 months

Ongoing Phase 3 Trial

European Heart Journal 2015;36:2415–2424

PublishedTrials

Trial name	PCSK9 inhibitor	Population and study design
DESCARTES	Evolocumab	Patients with hyperlipidaemia 420 mg Q4W added to diet alone or to diet plus atorvastatin or to diet plus atorvastatin plus ezetimibe
LAPLACE-2	Evolocumab	Patients with hypercholesterolaemia, 140 mg Q2W or 420 mg Q4W added to moderate- or high-intensity statin therapy, compared with ezetimibe or placebo
GAUSS-2	Evolocumab	Patients with statin intolerance, 140 mg Q2W or 420 mg Q4W compared with ezetimibe
MENDEL-2	Evolocumab	Patients with hypercholesterolaemia on no statins, 140 mg Q2W or 420 mg Q4W compared with ezetimibe
RUTHERFORD-2	Evolocumab	Patients with heFH, 140 mg Q2W or 420 mg Q4W
OSLER-2	Evolocumab	Hypercholesterolaemia or mixed dyslipidaemia; completion of previous evolocumab study (no specification regarding statin therapy)
TESLA Part B	Evolocumab	Patients with hoFH, not on apheresis, 420 mg Q4W

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Ongoing Phase 3 Trials

Name of study	Monoclonal antibody	Patient population
(A)		
GLAGOV	Evolocumab	Coronary heart disease; clinical indication for coronary catheterization; and LDL-C level ≥80 mg/dL or, with additional risk factors, ≥60 and <80 mg/dL (no specification regarding statin therapy)
FOURIER	Evolocumab	Clinical CVD, high risk of recurrent CVD event, and LDL-C level ≥70 mg/dL or non-HDL-C ≥100 mg/dL (no specification regarding statin therapy)
TAUSSIG	Evolocumab	Homozygous FH or PCSK9 mutations; LDL-C level above ATP III target or receiving apheresis; and completion of previous evolocumab study (no specification regarding statin therapy)
SPIRE-HF	Bococizumab	Heterozygous FH; high or very high CVD risk; LDL-C level >70 mg/dL and Tg level ≤400 mg/dL (with statin therapy)
SPIRE-HR	Bococizumab	High or very high CVD risk; LDL-C level >70 mg/dL and Tg level ≤400 mg/dL (with statin therapy)
SPIRE-LDL	Bococizumab	High or very high CVD risk; LDL-C level >70 mg/dL and Tg level ≤400 mg/dL (with statin therapy)
SPIRE-1	Bococizumab	High CVD risk; LDL-C level ≥70 mg/dL and <100 mg/dL, or non-HDL-C level ≥100 mg/dL and <130 mg/dL, with lipid-lowering therapy (no specification regarding statin therapy)
SPIRE-2	Bococizumab	High CVD risk; LDL-C level ≥100 mg/dL or non-HDL-C level ≥130 mg/dL, with lipid-lowering therapy (no specification regarding statin therapy)

European Heart Journal 2015;36:2415–2424

Phase 3 Program to Support LDL-C Reduction in Targeted Populations

- **High CV Risk Patients**
  - Patients not at LDL-C goal with currently available LLT (even high doses of potent statins) = >persistent risk
- **Familial Hypercholesterolemia**
  - LDL-C levels often far from goal, even with potent statins and combination Tx
  - Life-long exposure to high LDL-C; considered high risk even w/o additional risk factors
- **Statin Intolerant Patients**
  - LDL-C levels often far from goal, due to intolerance
  - Definition: unable to tolerate at least 2 statins, including one at the lowest dose

Summary of ODYSSEY by Study

Study	N	Population	Background Rx	Dosing	Comparator	Trial Length
LONG TERM	2341	High Risk + HeFH	Statin MTD +/-	150	PBO	18 mo
COMBO I	316	High risk	Statin MTD +/-	75 → 150	PBO	12 mo
COMBO II	720	High Risk	Statin MTD only	75 → 150	+ EZE	24 mo
FH I	486	HeFH	Statin MTD +/-	75 → 150	PBO	18 mo
FH II	249	HeFH	Statin MTD +/-	75 → 150	PBO	18 mo
HIGH FH	107	HeFH	Statin MTD +/-	150	PBO	18 mo
ALTERNATIVE	314	Statin Intolerance	No LMT or non-statin LMT	75 → 150	EZE	6 mo
MONO	103	Monotherapy	No LMT	75 → 150	EZE	6 mo
OPTIONS I	355	High Risk	Submax. statin +/-	75 → 150	+EZE, Statin	6 mo
OPTIONS II	305	High Risk	Submax. statin +/-	75 → 150	+EZE, Statin	6 mo

MTD: maximal tolerated dose of statin;
MTD +/-: maximal tolerated dose of statin +/- other LMT [lipid-modifying therapy(ies)].

Alirocumab Dose Selection Based on Patient Needs

A flexible model to address:

- Different baseline LDL-C
- Different background LLT
- Treat to target approach

75 mg Q2W
1 ml

LDL-C
-50%

Additional offer Q4W:

- **300 mg (+ statins)**
- **150 mg (- statins)**

150 mg Q2W
1 ml

LDL-C
-70%

Alirocumab: ODYSSEY Program (Phase 3 Data)

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Cardiometabolic Disorders

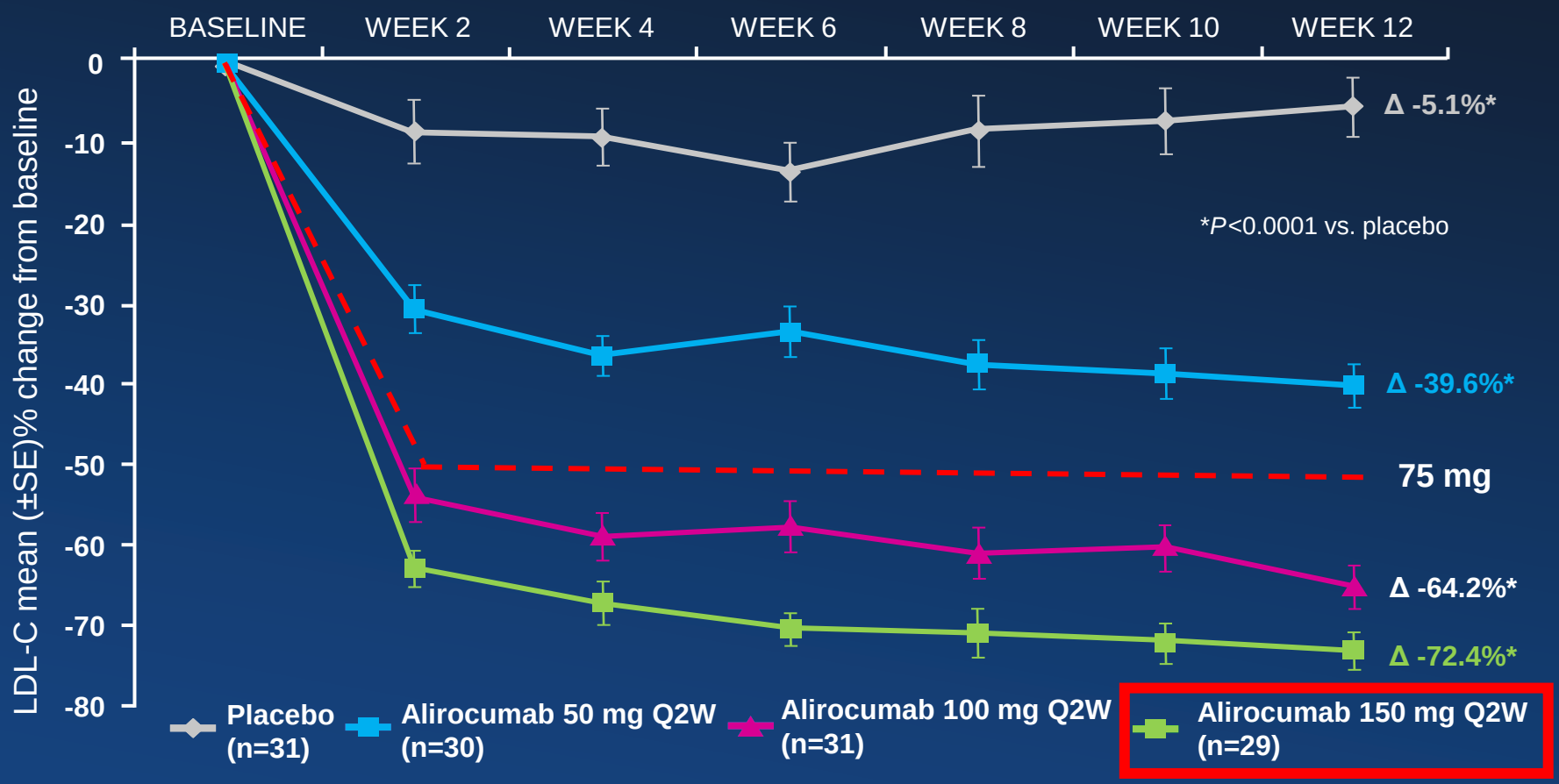
Safety and Efficacy of a Monoclonal Antibody to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease, SAR236553/REGN727, in Patients With Primary Hypercholesterolemia Receiving Ongoing Stable Atorvastatin Therapy

James M. McKenney, PharmD,* Michael J. Koren, MD, CPI,† Dean J. Kereiakes, MD,‡
Corinne Hanotin, MD,§ Anne-Catherine Ferrand, MSc,§ Evan A. Stein, MD, PhD‖
Richmond, Virginia; Jacksonville, Florida; Cincinnati, Ohio; and Paris, France

- The primary objective of this study was to evaluate the LDL-C lowering efficacy of (SAR236553-alirocumab) dosing regimens versus placebo at week 12 in patients with LDL-C ≥100 mg/dl on stable atorvastatin therapy.
- Secondary objectives included evaluation of effects on other lipid parameters and the attainment of LDL-C treatment goals of <100 mg/dl and <70 mg/dl.
- This double-blind, parallel-group, placebo-controlled trial randomized 183 patients with LDL-C ≥100 mg/dl on stable-dose atorvastatin 10, 20, or 40 mg for 6 weeks to: subcutaneous placebo every 2 weeks (Q2W); alirocumab 50, 100, or 150 mg Q2W; or alirocumab 200 or 300 mg every 4 weeks (Q4W), alternating with placebo for a total treatment period of 12 weeks.

J Am Coll Cardiol. 2012;59:2344-2353.

Effects on LDL-C of Adding Alirocumab Q2W to Atorvastatin



Patients with LDL-C ≥100 mg/dL on stable atorvastatin dose (10 mg, 20 mg, or 40 mg) for at least 6 weeks.
Primary efficacy endpoint: % change in LDL-C from baseline to week 12; *P<0.0001 vs. placebo.

McKenney JM et al. *J Am Coll Cardiol.* 2012;59:2344-2353.

Studies in Patients at High CV Risk and Not at LDL-C Goal

ODYSSEY COMBO I
ODYSSEY COMBO II

Kereiakes DJ et al. *Am Heart J.* 2015; In press. DOI: http://dx.doi.org/10.1016/j.ahj.2015.03.004
Cannon CP et al. *Eur Heart J* 2015 [epub ahead of print].

ODYSSEY

ODYSSEY COMBO I & II studies

ODYSSEY COMBO I study

A randomized (2:1 alirocumab vs placebo), double-blind, 52-week trial enrolled 316 patients with established coronary heart disease or coronary heart disease risk equivalents and hypercholesterolemia.

Alirocumab (75 mg every 2 weeks [Q2W]) or placebo Q2W was self-administered subcutaneously via 1 mL prefilled pen. The alirocumab dose was increased to 150 mgQ2W (also 1 mL) at week 12 if week 8 low-density lipoprotein cholesterol (LDL-C) was ≥70 mg/dL.

The primary efficacy end point was percent change in LDL-C from baseline to week 24 (intention-to-treat analysis).

ODYSSEY COMBO II study

COMBOII is a double-blind, double-dummy, active-controlled, parallel-group, 104-week study of alirocumab vs. ezetimibe.

Patients (n=720) with high cardiovascular risk and elevated LDL-C despite maximal doses of statins were enrolled. This pre-specified analysis was conducted after the last patient completed 52 weeks.

Patients were randomized to subcutaneous alirocumab 75 mg every 2weeks (plus oral placebo) or oral ezetimibe 10 mg daily (plus subcutaneous placebo) on a background of statin therapy.

Am Heart J 2015;169:906-915.e13.
European Heart Journal 2015;36:1186–1194.

Baseline Characteristics: COMBO I and II

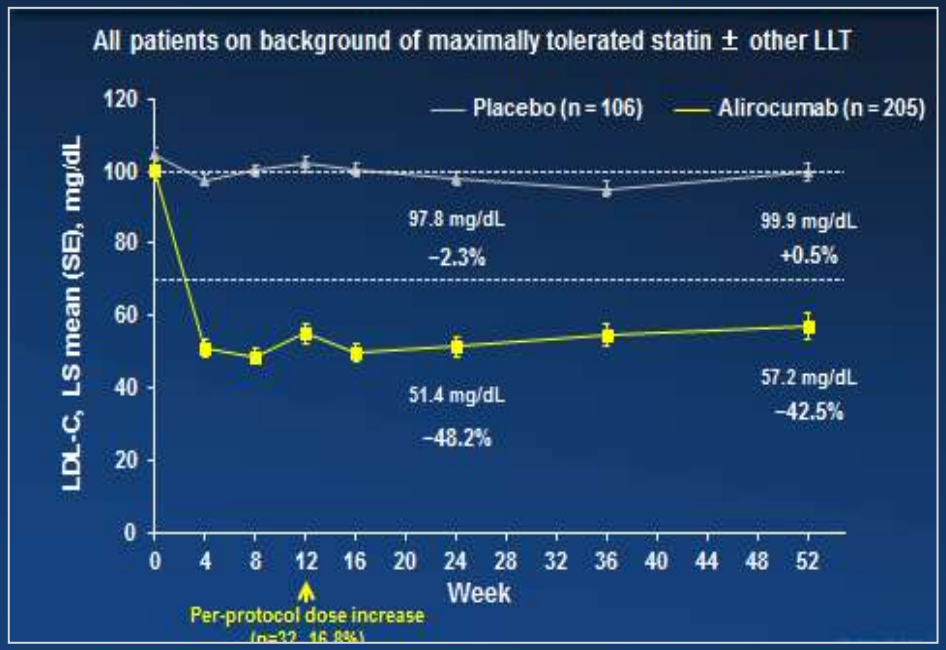
All patients on background maximally tolerated statin ±other LLT	COMBO I		COMBO II	
	Alirocumab (N=209)	**Placebo** (N=107)	**Alirocumab** (n=479)	**Ezetimibe** (n=241)
Age, years, mean (SD)	**63.0** (9.5)	**63.0** (8.8)	**61.7** (*9.4*)	**61.3** (*9.2*)
Male, % (n)	**62.7%** (131)	**72.0%** (77)	**75.2%** (360)	**70.5%** (170)
Race, white, % (n)	**81.3%** (170)	**82.2%** (88)	**84.3%** (404)	**85.5%** (206)
BMI, kg/m^2, mean (SD)	**32.6** (6.3)	**32.0** (7.1)	**30.0** (*5.4*)	**30.3** (*5.1*)
CHD history, % (n)	**78.5%** (164)	**77.6%** (83)	**91.2%** (437)	**88.0%** (212)
Hypertension, % (n)	**88.5%** (185)	**88.8%** (95)	**79.7%** (382)	**82.2%** (198)
Type 2 diabetes, % (n)	**45.0%** (94)	**39.3%** (42)	**30.3%** (145)	**31.5%** (76)
Any statin*, % (n)	**99.5%** (208)	**100%** (107)	**99.8%** (478)	**100%** (241)
High-intensity statin†, % (n)	**61.7%** (129)	**64.5%** (69)	**66.8%** (320)	**66.4%** (160)
LDL-C, calculated mean (*SD*)**, mg/dL**	**100.2** (29.5)	**106.0** (35.3)	**109** (*37*)	**105** (*34*)

*Patients should receive either rosuvastatin 20-40 mg, atorvastatin 40-80 mg daily, or simvastatin 80 mg daily unless not tolerated and/or appropriate other dose given according to the judgement of the investigator.
†High-intensity statin: atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily.

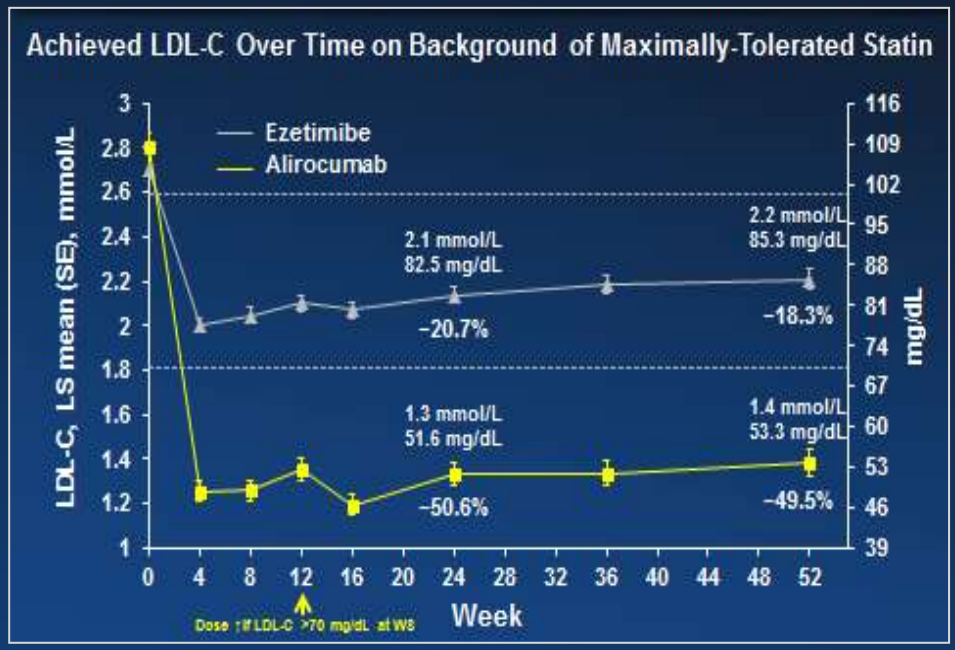
Kereiakes DJ et al. *Am Heart J.* 2015; In press. DOI: http://dx.doi.org/10.1016/j.ahj.2015.03.004
Cannon CP et al. *Eur Heart J* 2015 [epub ahead of print].

Consistent LDL-C Reductions Over 52 Weeks

COMBO I



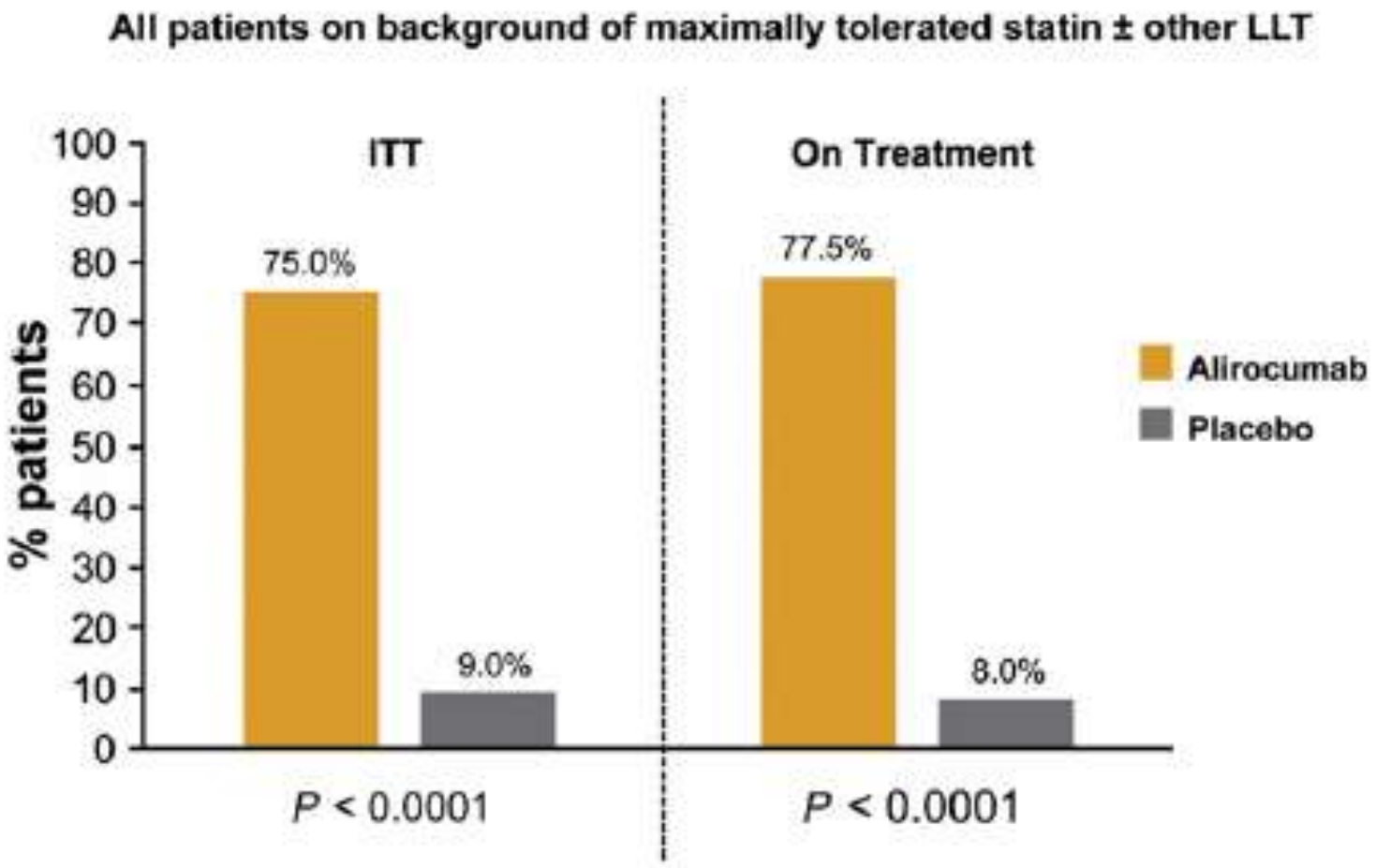
COMBO II



- LDL-C ↓ from baseline maintained over 52 weeks with alirocumab
- Mean achieved LDL-C levels of 57.2 mg/dL in COMBO I and 53.3 mg/dL in COMBO II at week 52 with alirocumab
- Consistent effects of alirocumab vs comparator through 52 weeks

Kereiakes DJ et al. *Am Heart J.* 2015;169:906-915.e13. DOI: http://dx.doi.org/10.1016/j.ahj.2015.03.004
Cannon CP et al. *Eur Heart J* 2015;36:1186–1194.

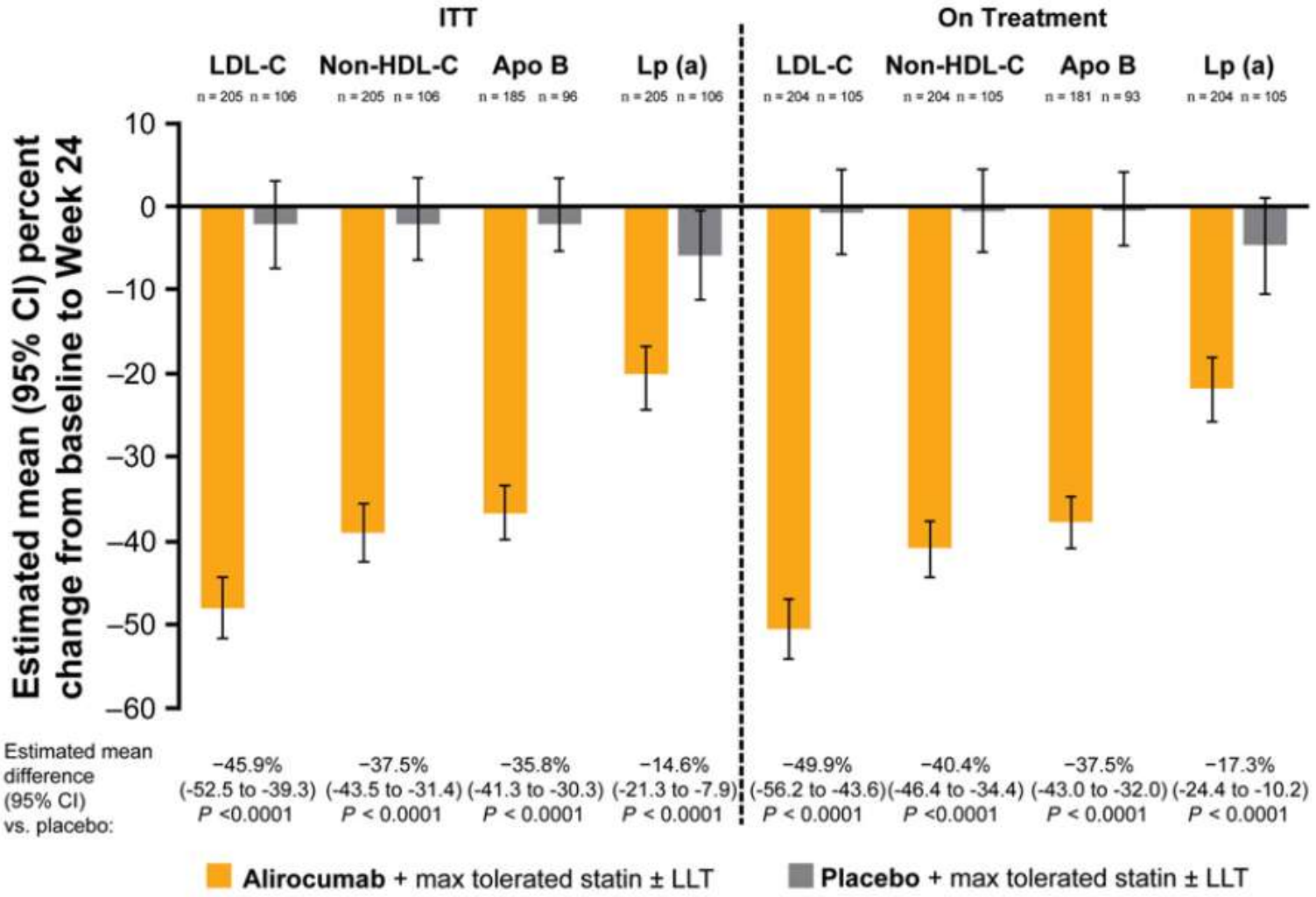
ODYSSEY COMBO I study



Proportion of patients reaching LDL-C <70 mg/dL at week 24.

Am Heart J 2015;169:906-915.e13.

ODYSSEY COMBO I study



End point analysis: percent reduction in LDL-C and other lipid parameters from baseline to week 24.

Am Heart J 2015;169:906-915.e13.

ODYSSEY COMBO II study

Table 2 Percent change from baseline to week 24 in LDL-C (ITT and on-treatment) and in secondary lipid parameters (ITT)

All patients on maximally tolerated statin therapy[a]	Alirocumab[b]	Ezetimibe[c]	Alirocumab vs. ezetimibe		
			LS mean difference ± SE (%)	95% CI	*P*-value
Primary endpoint: LDL-C					
ITT	$n = 467$	$n = 240$			
LS mean ± SE change from baseline (%)	−50.6 ± 1.4	−20.7 ± 1.9	−29.8 ± 2.3	−34.4 to −25.3	<0.0001
On-treatment	$n = 464$	$n = 235$			
Baseline LDL-C, mean ± SD (mmol/L)	2.8 ± 0.9	2.7 ± 0.9	–	–	–
Range	0.6–7.9	1.0–6.3			
LS mean ± SE change from baseline (%)	−52.4 ± 1.3	−21.8 ± 1.8	−30.6 ± 2.2	−34.9 to −26.2	<0.0001
Secondary lipid parameters (ITT), LS mean ± SE change from baseline (%)	$n = 467$	$n = 240$			
LDL-C (beta-quantification method)[d]	−47.7 ± 1.6	−18.0 ± 2.2	−29.7 ± 2.7	−35.0 to −24.4	<0.0001
LDL-C (baseline to Week 12)	−51.2 ± 1.3	−21.8 ± 1.8	−29.4 ± 2.2	−33.7 to −25.1	<0.0001
Apolipoprotein B	−40.7 ± 1.1	−18.3 ± 1.5	−22.4 ± 1.8	−26.0 to −18.8	<0.0001
Non-HDL-C	−42.1 ± 1.2	−19.2 ± 1.7	−22.9 ± 2.0	−26.9 to −18.9	<0.0001
Total cholesterol	−29.3 ± 0.9	−14.6 ± 1.2	−14.7 ± 1.5	−17.7 to −11.7	<0.0001
Lipoprotein a[e]	−27.8 ± 1.4	−6.1 ± 2.0	−21.7 ± 2.4	−26.4 to −17.0	<0.0001
HDL-C	8.6 ± 0.8	0.5 ± 1.1	8.1 ± 1.3	5.4 to 10.7	<0.0001
Triglycerides (fasted)[e]	−13.0 ± 1.5	−12.8 ± 2.0	−0.3 ± 2.5	−5.1 to 4.6	0.91
Apolipoprotein A-1	5.0 ± 0.6	−1.3 ± 0.8	6.3 ± 1.0	4.3 to 8.3	<0.0001[f]

European Heart Journal 2015;36:1186–1194.

Safety Analysis

Including All Data Collected Until Last Patient Visit at Week 52

% (n) of patients All patients on background maximally tolerated statin ± other LLT	COMBO I		COMBO II	
	Alirocumab (N=207)	**Placebo** (N=107)	**Alirocumab** (n=479)	**Ezetimibe** (n=241)
TEAEs	**75.8%** (157)	**75.7%** (81)	**71.2%** (341)	**67.2%** (162)
Treatment-emergent SAEs	**12.6%** (26)	**13.1%** (14)	**18.8%** (90)	**17.8%** (43)
TEAE leading to death*	**1.0%** (2)	**2.8%** (3)	**0.4%** (2)	**1.7%** (4)
TEAEs leading to discontinuation	**6.3%** (13)	**7.5%** (8)	**7.5%** (36)	**5.4%** (13)
Adverse events of interest				
Injection-site reactions	**5.3%** (11)	**2.8%** (3)	**2.5%** (12)	**0.8%** (2)
Adjudicated CV events†	**2.9%** (6)	**2.8%** (3)	**4.8%** (23)	**3.7%** (9)
Neurocognitive disorders	**0**	**0.9%** (1)	**0.8%** (4)	**1.2%** (3)
ALT >3 x ULN	**1.5%** (3/206)	**0.9%** (1/106)	**1.7%** (8/470)	**0.4%** (1/240)
Creatine kinase >3 x ULN	**2.0%** (4/205)	**4.9%** (5/103)	**2.8%** (13/467)	**2.5%** (6/236)

*The two deaths occurring during treatment with alirocumab (COMBO I) were due to myocardial infarction and pulmonary embolism. Three deaths in the placebo group were due to sudden cardiac death, esophageal adenocarcinoma and dementia - Both deaths in the alirocumab arm (COMBO II) were due to CV events (cardiac arrest and sudden cardiac death). Of the four deaths in the ezetimibe arm, two were due to CV events (malignant lung neoplasm, suicide, defect conduction intraventricular, sudden cardiac death and sudden death – one patient was counted in two categories).

† Adjudicated CV events include all CV AEs positively adjudicated. The adjudication categories are the following: CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, ischemia driven coronary revascularization procedure (PCI, CABG).

Am Heart J 2015;169:906-915.e13.
European Heart Journal 2015;36:1186–1194.

COMBO I: Safety Analysis

TEAEs Occurring in ≥5% of Either Alirocumab or Placebo Patients

% (n) of patients All patients on background maximally tolerated statin ± other LLT	**Alirocumab** (N=207)	**Placebo** (N=107)
Upper respiratory tract infection	**7.7%** (16)	**10.3%** (11)
Nasopharyngitis	**7.2%** (15)	**4.7%** (5)
Urinary tract infection	**6.3%** (13)	**3.7%** (4)
Dizziness	**5.3%** (11)	**5.6%** (6)
Sinusitis	**5.3%** (11)	**3.7%** (4)
Injection-site reaction	**5.3%** (11)	**2.8%** (3)
Arthralgia	**3.9%** (8)	**7.5%** (8)
Non-cardiac chest pain	**1.0%** (2)	**6.5%** (7)

Preferred terms, MedDRA version 17.0; statistical analyses have not been performed.

Am Heart J 2015;169:906-915.e13.

COMBO II: Safety Analysis

TEAEs Occurring in ≥5% of Either Alirocumab or Ezetimibe Patients

% (n) of patients All patients on background max tolerated statin	**Alirocumab** (n=479)	**Ezetimibe** (n=241)
Upper respiratory tract infection	**6.5%** (31)	**5.8%** (14)
Accidental overdose*	**6.3%** (30)	**6.6%** (16)
Dizziness	**4.8%** (23)	**5.4%** (13)
Myalgia	**4.4%** (21)	**5.0%** (12)

*Accidental overdose is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic injection/capsule counts) and defined as at least twice the intended dose within the intended therapeutic interval (ie, ≥2 injections from the double-blind treatment kit administered in <7 calendar days or ≥2 capsules from the double-blind treatment kit are administered within 1 calendar day).

Statistical analyses have not been performed.

European Heart Journal 2015;36:1186–1194.

Studies in Familial Hypercholesterolemia

ODYSSEY FH I
ODYSSEY FH II
ODYSSEY HIGH FH

Kastelein et al., ESC 2014 oral presentation, Efficacy and safety of alirocumab in patients with heFH not adequately controlled with current lipid-lowering therapy: Results of ODYSSEY FH I and FH II studies

Ginsberg et al. AHA 2014 oral presentation, ODYSSEY HIGH FH: Efficacy and Safety of Alirocumab in Patients with Severe Heterozygous Familial Hypercholesterolemia

ODYSSEY

Lipid Medication and LDL-C at Baseline

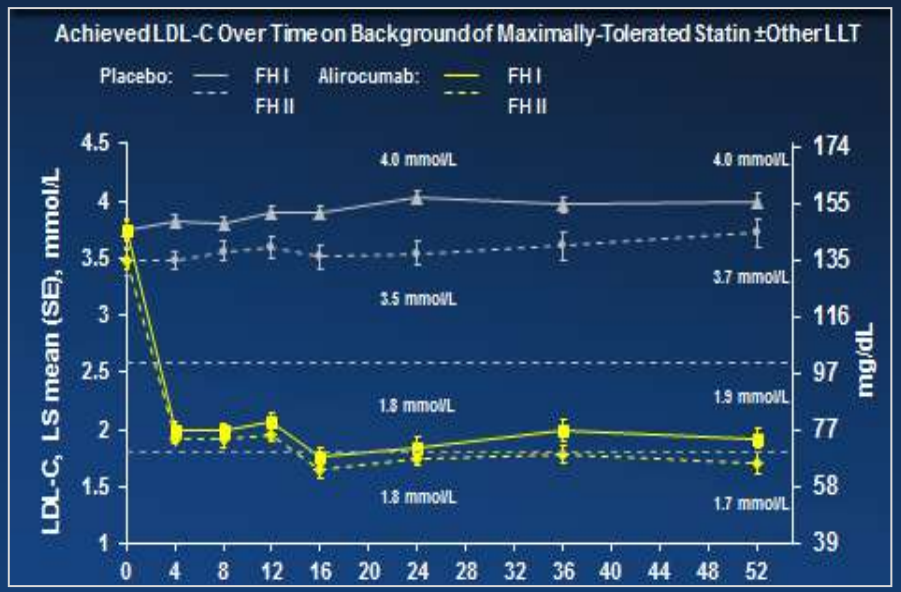
All patients on background of max-tolerated statin ± other lipid-lowering therapy	FH I		FH II		HIGH FH	
	Alirocumab (N=323)	**Placebo** (N=163)	**Alirocumab** (N=167)	**Placebo** (N=82)	**Alirocumab** (N=72)	**Placebo** (N=35)
Any statin*, % (n)	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**
High-intensity statin†, % (n)	**80.8%** (261)	**82.8%** (135)	**86.2%** (144)	**87.8%** (72)	**79.2%** (57)	**80.0%** (28)
Ezetimibe, % (n)	**55.7%** (180)	**59.5%** (97)	**67.1%** (112)	**64.6%** (53)	**19.4%** (14)	**34.3%** (12)
LDL-C, mean (SD), **mg/dL**	**144.7** (51.2)	**144.4** (46.8)	**134.6** (41.3)	**134.0** (41.6)	**196.3** (57.9)	**201.0** (43.4)

*Patients should receive either rosuvastatin 20-40 mg, atorvastatin 40-80 mg daily, or simvastatin 80 mg daily unless not tolerated and/or appropriate other dose given according to the judgement of the investigator.

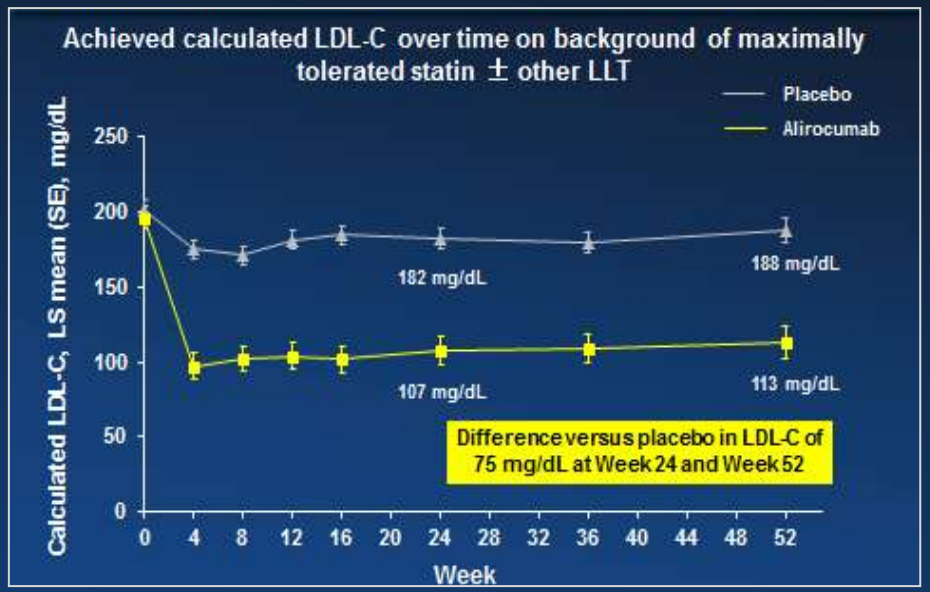
† High-intensity statin: atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily.

Consistent LDL-C Reductions Over 52 Weeks

FH I and FH II



HIGH FH



- Significantly greater LDL-C ↓ vs placebo at week 24 in FH I, FH II, and HIGH FH (*P*<0.001 for all studies)
- Mean achieved LDL-C levels with alirocumab of 65.9-74.3 mg/dL at week 52 in FH I and II and 107 mg/dL at week 24 in HIGH FH
- In HIGH FH, percentage decrease from baseline informed by high baseline LDL-C (196.3 mg/dL):
  - The absolute mean decrease from baseline in LDL-C was –90.8 mg/dL at Week 24 with alirocumab versus 182 mg/dL with placebo

Safety Analysis (Pooled FH I/FH II and HIGH FH)

All Data Collected Until Last Patient Visit at Week 52

% (n) of patients All patients on background of max tolerated statin ± other lipid-lowering therapy	**Pooled FH I and FH II**		**HIGH FH**	
	Alirocumab (N=489)	**Placebo** (N=244)	**Alirocumab** (N=72)	**Placebo** (N=35)
TEAEs	**74.8%** (366)	**75.4%** (184)	**61.1%** (44)	**71.4%** (25)
Treatment-emergent SAEs	**10.0%** (49)	**9.0%** (22)	**11.1%** (8)	**11.4%** (4)
TEAEs leading to death	**0.8%** (4)	**0**	**0**	**0**
TEAEs leading to discontinuation	**3.1%** (15)	**3.7%** (9)	**4.2%** (3)	**2.9%** (1)
Adverse Events of Interest				
Adjudicated CV events*	**1.6%** (8)	**1.2%** (3)	**8.3%** (6)	**0**
Injection-site reactions	**11.5%** (56)	**9.0%** (22)	**8.3%** (6)	**2.9%** (1)
Neurocognitive disorders	**0.2%** (1)	**1.2%** (3)	**1.4%** (1)	**2.9%** (1)
ALT >3 x ULN	**2.1%** (10/488)	**1.2%** (3/244)	**4.2%** (3)	**2.9%** (1)
Creatine kinase >3 x ULN	**3.5%** (17/483)	**6.2%** (15/243)	**2.8%** (2/71)	**0**

- **4 TEAE-related deaths were all in alirocumab arm, 2 due to metastatic cancer (non-small cell lung and pancreatic), 2 due to MI (1 acute, 1 sudden cardiac death)**

*Adjudicated CV events include all CV AEs positively adjudicated. The adjudication categories are the following: CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, ischemia-driven revascularization procedure (PCI, CABG).
Statistical analyses have not been performed.

Studies in Statin Intolerance

ODYSSEY ALTERNATIVE

Moriarty et al. AHA 2014 oral presentation, ODYSSEY ALTERNATIVE:
Efficacy and safety of alirocumab versus ezetimibe, in patients with statin intolerance defined by placebo run-in and statin rechallenge arm

Journal of Clinical Lipidology 2015;9:758–769

Journal of Clinical Lipidology (2015) 9, 758–769

Journal of Clinical Lipidology

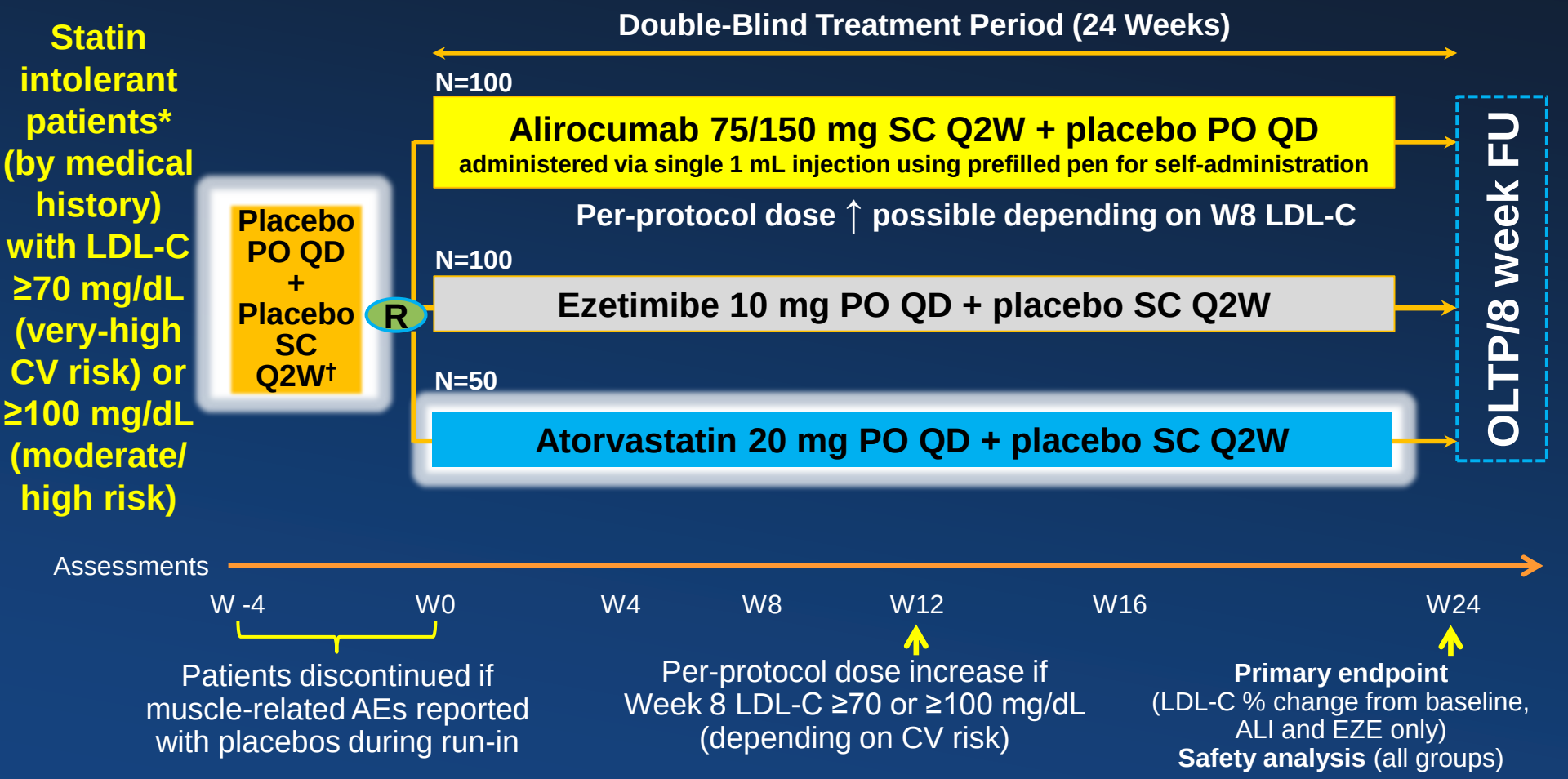
Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial

ODYSSEY ALTERNATIVE compared alirocumab with ezetimibe in patients at moderate to high cardiovascular risk with statin intolerance (unable to tolerate ≥2 statins, including one at the lowest approved starting dose) due to muscle symptoms. A placebo run-in and statin rechallenge arm were included in an attempt to confirm intolerance.

Patients (n=361) received single-blind subcutaneous (SC) and oral placebo for 4 weeks during placebo run-in. Patients reporting muscle-related symptoms during the run-in were to be withdrawn. Continuing patients were randomized (2:2:1) to double-blind alirocumab 75 mg SC every 2 weeks (Q2W; plus oral placebo), ezetimibe 10 mg/d (plus SC placebo Q2W), or atorvastatin 20 mg/d (rechallenge; plus SC placebo Q2W) for 24 weeks. Alirocumab dose was increased to 150 mg Q2W at week 12 depending on week 8 LDL-C values.

Primary end point was percent change in LDL-C from baseline to week 24 (intent-to-treat) for alirocumab vs ezetimibe.

ODYSSEY ALTERNATIVE Study Design



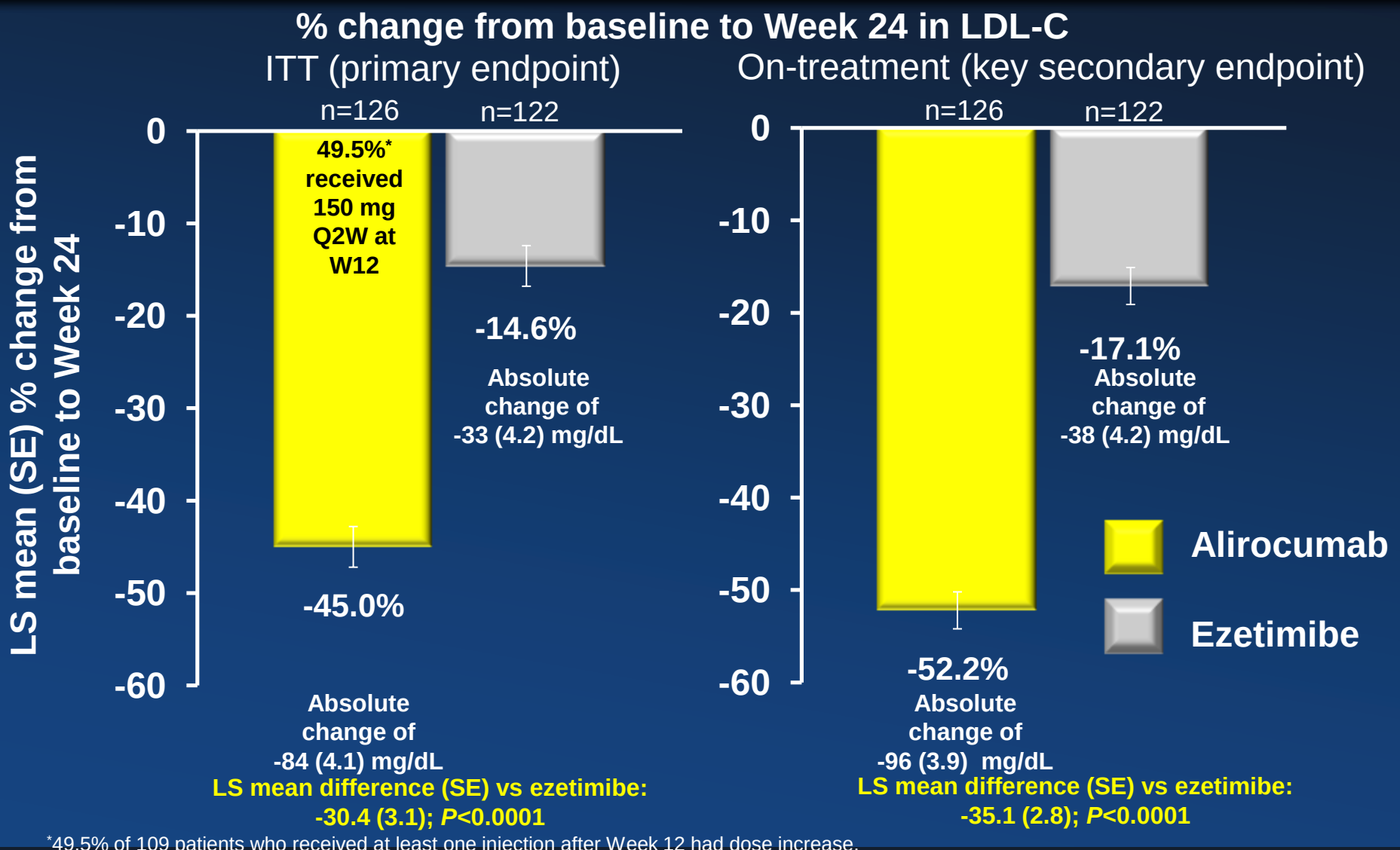
*Unable to tolerate at least two different statins, including one at the lowest dose, due to muscle-related symptoms

†4-week single-blind placebo run-in follows 2-week washout of statins, ezetimibe and red yeast rice.

OLTP: Alirocumab open-label treatment period; W, Week.

Journal of Clinical Lipidology 2015;9:758–769

Alirocumab Significantly Reduced LDL-C From Baseline to Week 24 vs Ezetimibe



*49.5% of 109 patients who received at least one injection after Week 12 had dose increase.

Journal of Clinical Lipidology 2015;9:758–769

Safety Analysis

Safety analysis from double-blind treatment period

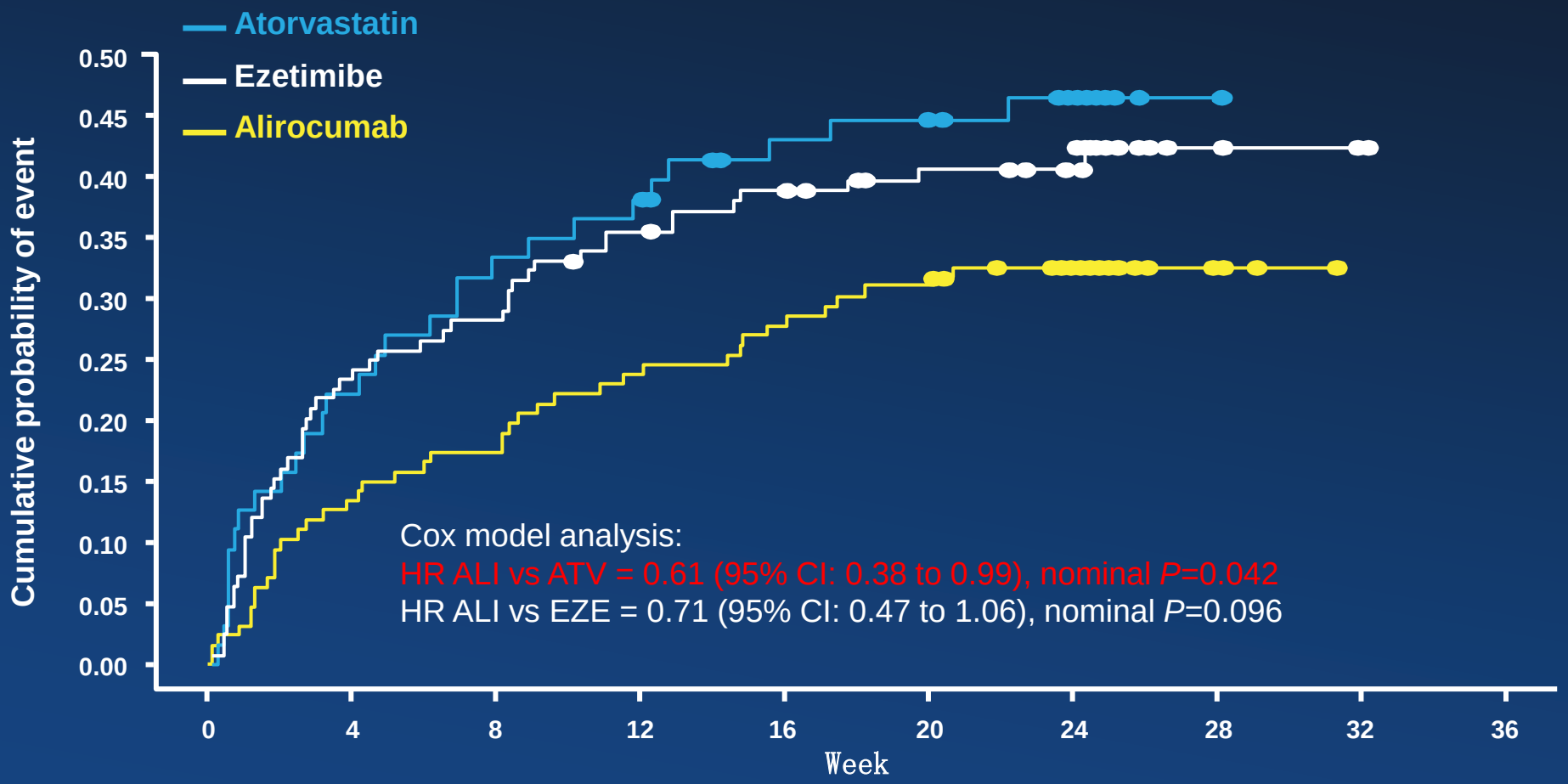
% of patients	Alirocumab (N=126)	Ezetimibe (N=124)	Atorvastatin (N=63)
TEAEs*	82.5%	80.6%	85.7%
Treatment-emergent SAEs	9.5%	8.1%	11.1%
TEAEs leading to death	0	0	0
TEAEs leading to discontinuation	18.3%	25.0%	25.4%
Any skeletal-muscle related TEAE†	32.5%	41.1%	46.0%
HR (95% CI) alirocumab vs comparator	-	0.71 (95% CI: 0.47 to 1.06)	0.61 (95% CI: 0.38 to 0.99)
P-value vs alirocumab‡	-	0.096	0.042
Skeletal-muscle related TEAE leading to discontinuation	15.9%	20.2%	22.2%
HR (95% CI) alirocumab vs comparator	-	0.78 (95% CI: 0.43 to 1.41)	0.67 (95% CI: 0.34 to 1.32)
P-value vs alirocumab‡	-	0.409	0.240

*TEAE (treatment emergent adverse event) period = time from first to last injection of study treatment + 70 days.
SAE=serious adverse event.
† Pre-defined category including myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, muscle fatigue.
‡ Although not pre-planned analysis, the *P*-value is shown for descriptive purposes.

Journal of Clinical Lipidology 2015;9:758–769

Fewer Skeletal Muscle AEs With Alirocumab Than With Atorvastatin

Kaplan-Meier estimates for time to first skeletal muscle event*



*Pre-defined category including myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, muscle fatigue.

ALI=alirocumab; ATV= atorvastatin, EZE=ezetimibe.

Journal of Clinical Lipidology 2015;9:758–769

Trial Designs

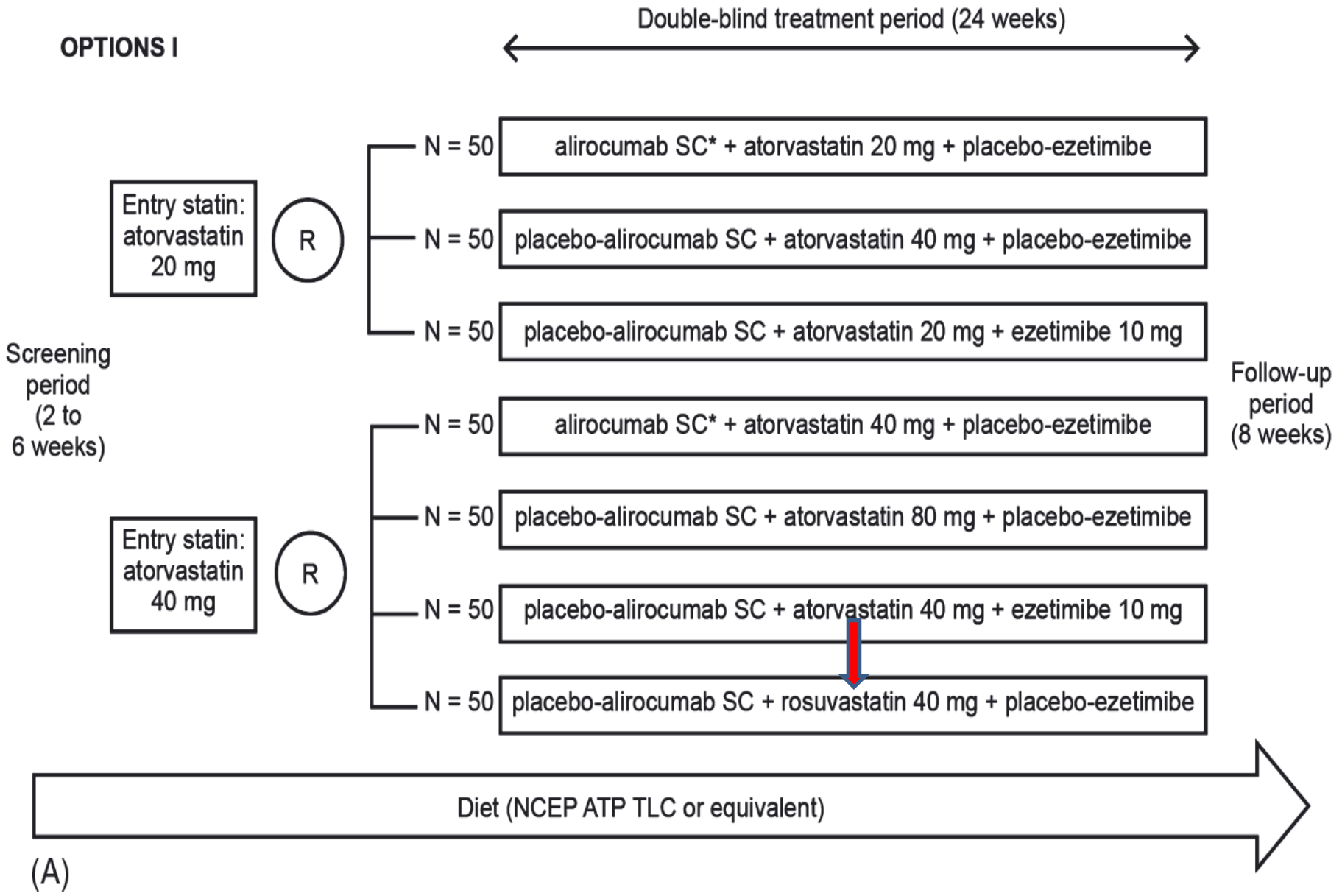
PREVENTION

Efficacy and Safety of Alirocumab as Add-on Therapy in High–Cardiovascular-Risk Patients With Hypercholesterolemia Not Adequately Controlled With Atorvastatin (20 or 40 mg) or Rosuvastatin (10 or 20 mg): Design and Rationale of the ODYSSEY OPTIONS Studies

ODYSSEY OPTIONS I & II studies

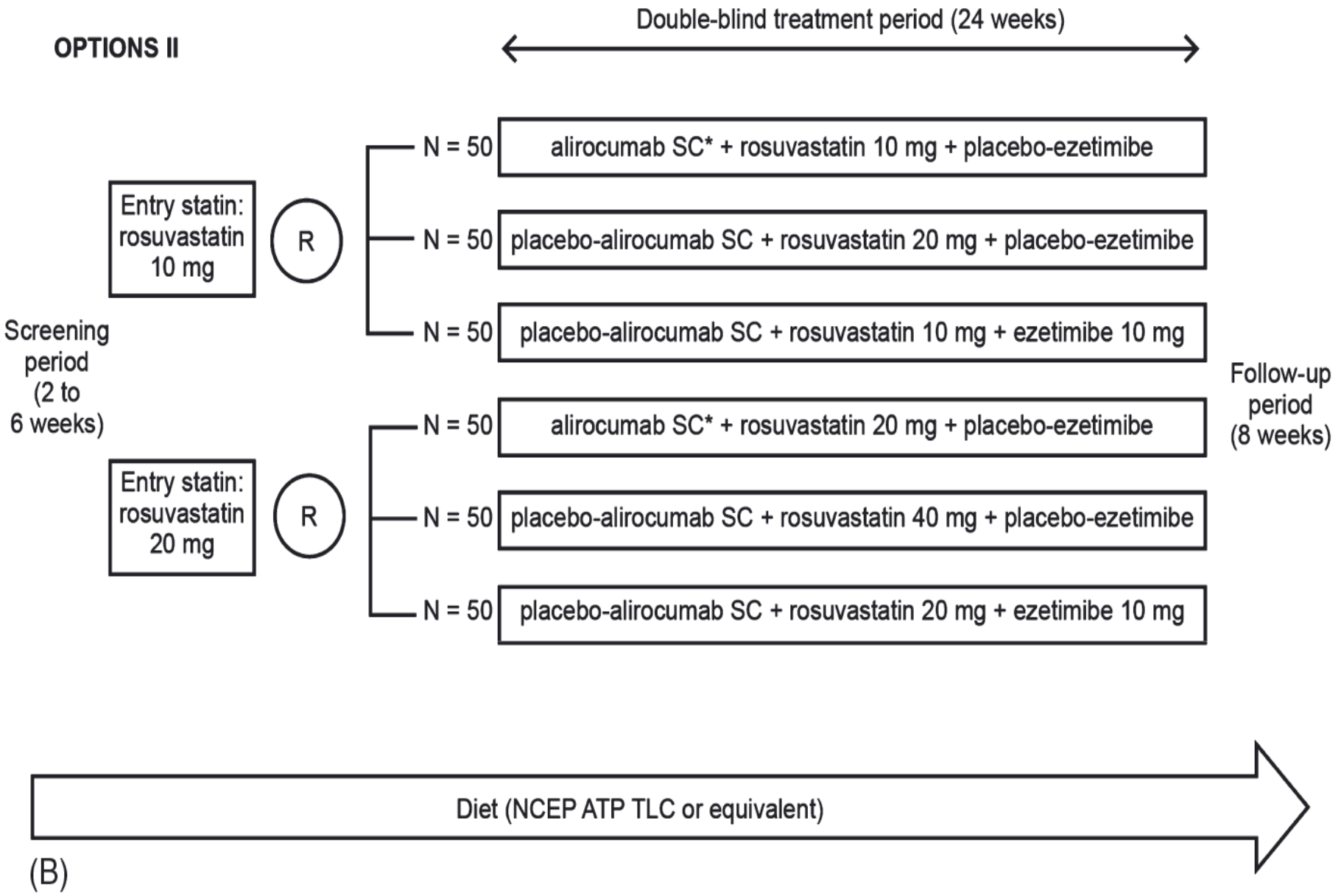
Clin. Cardiol. 37, 10, 597–604 (2014)

ODYSSEY OPTIONS I Study (Atorvastatin)



Clin. Cardiol. 37, 10, 597–604 (2014)

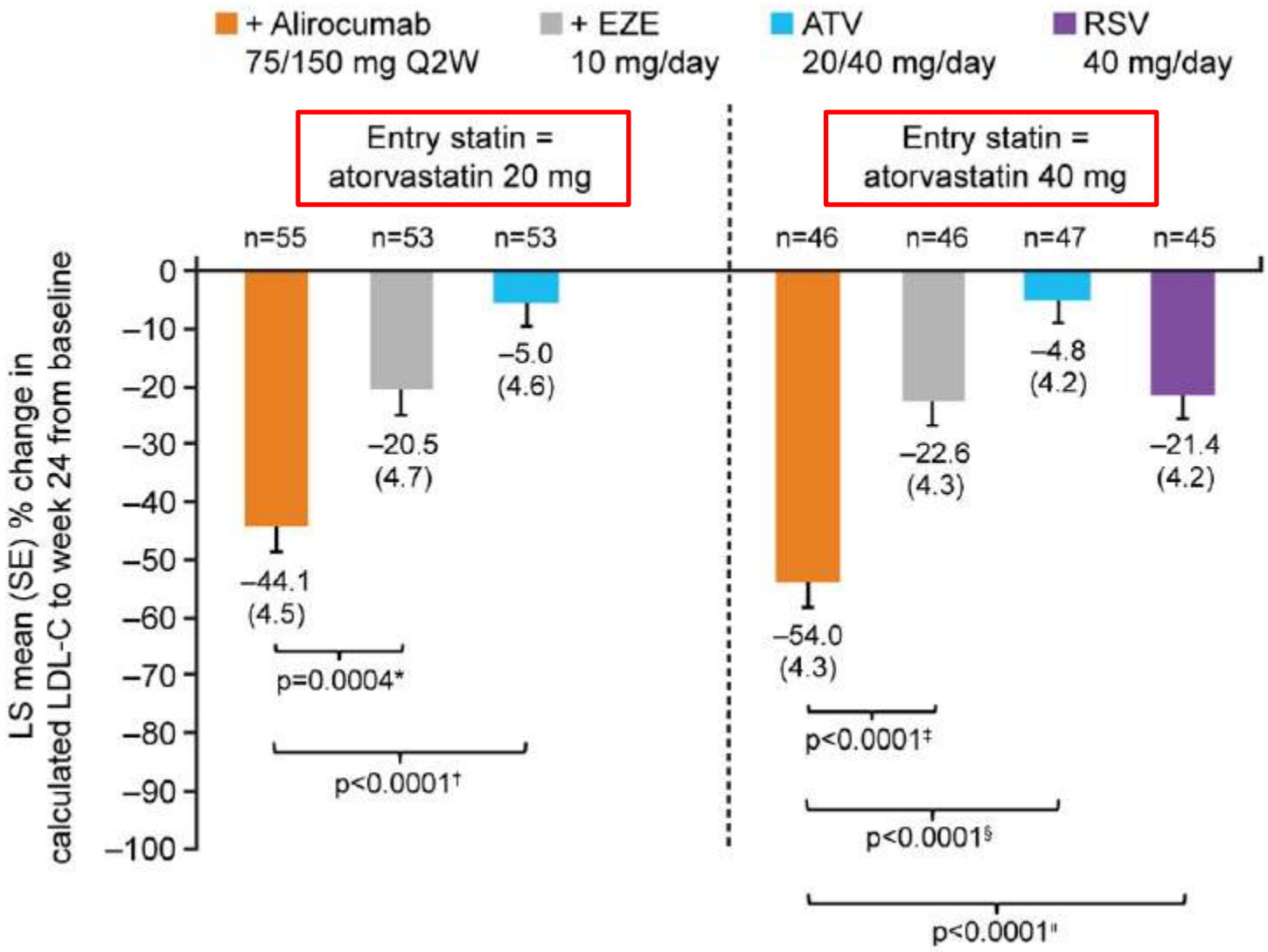
ODYSSEY OPTIONS II Study (Rosuvastatin)



Clin. Cardiol. 37, 10, 597–604 (2014)

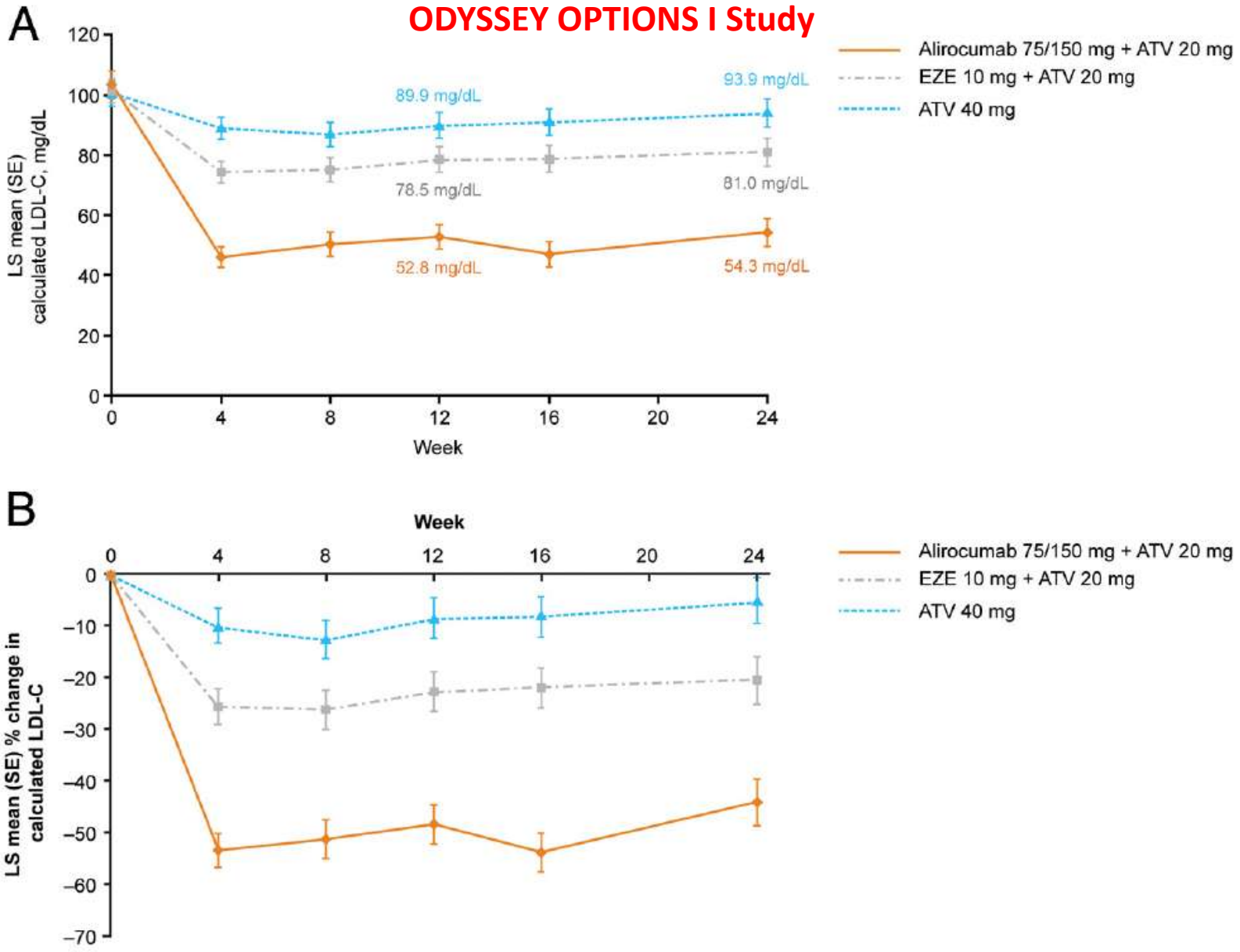
Primary end point. LS mean (SE) percentage change from baseline in calculated LDL-C to week 24 (ITT analysis).

ODYSSEY OPTIONS I Study (Atorvastatin)



J Clin Endocrinol Metab 2015;100: 3140–3148

Absolute levels and percentage change from baseline in calculated LDL-C over time for patients entering on **atorvastatin 20 mg (A and B)**

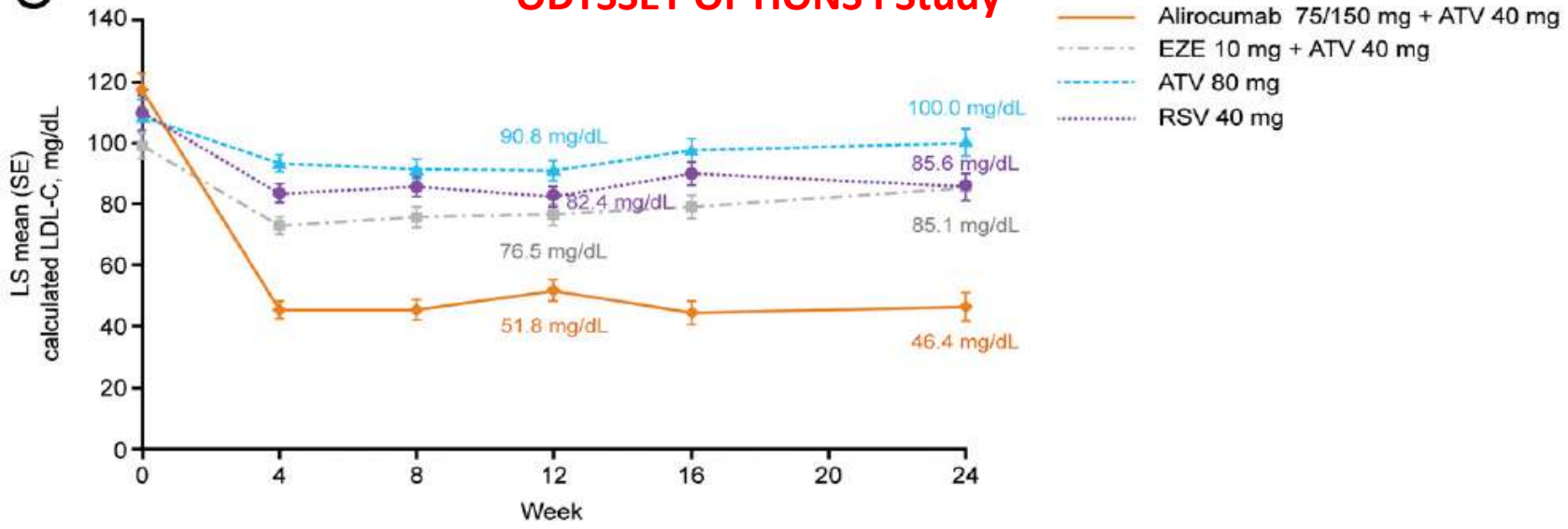


J Clin Endocrinol Metab 2015;100: 3140–3148

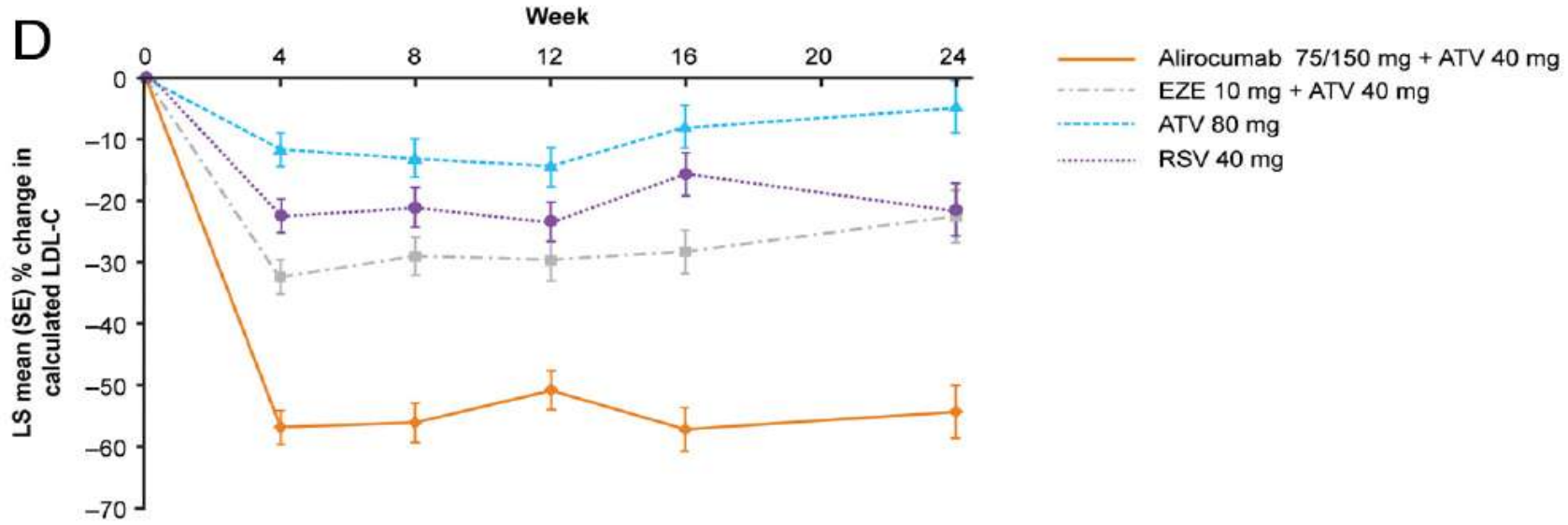
Absolute levels and percentage change from baseline in calculated LDL-C over time for patients entering on **atorvastatin 40 mg (C and D)**

C

ODYSSEY OPTIONS I Study



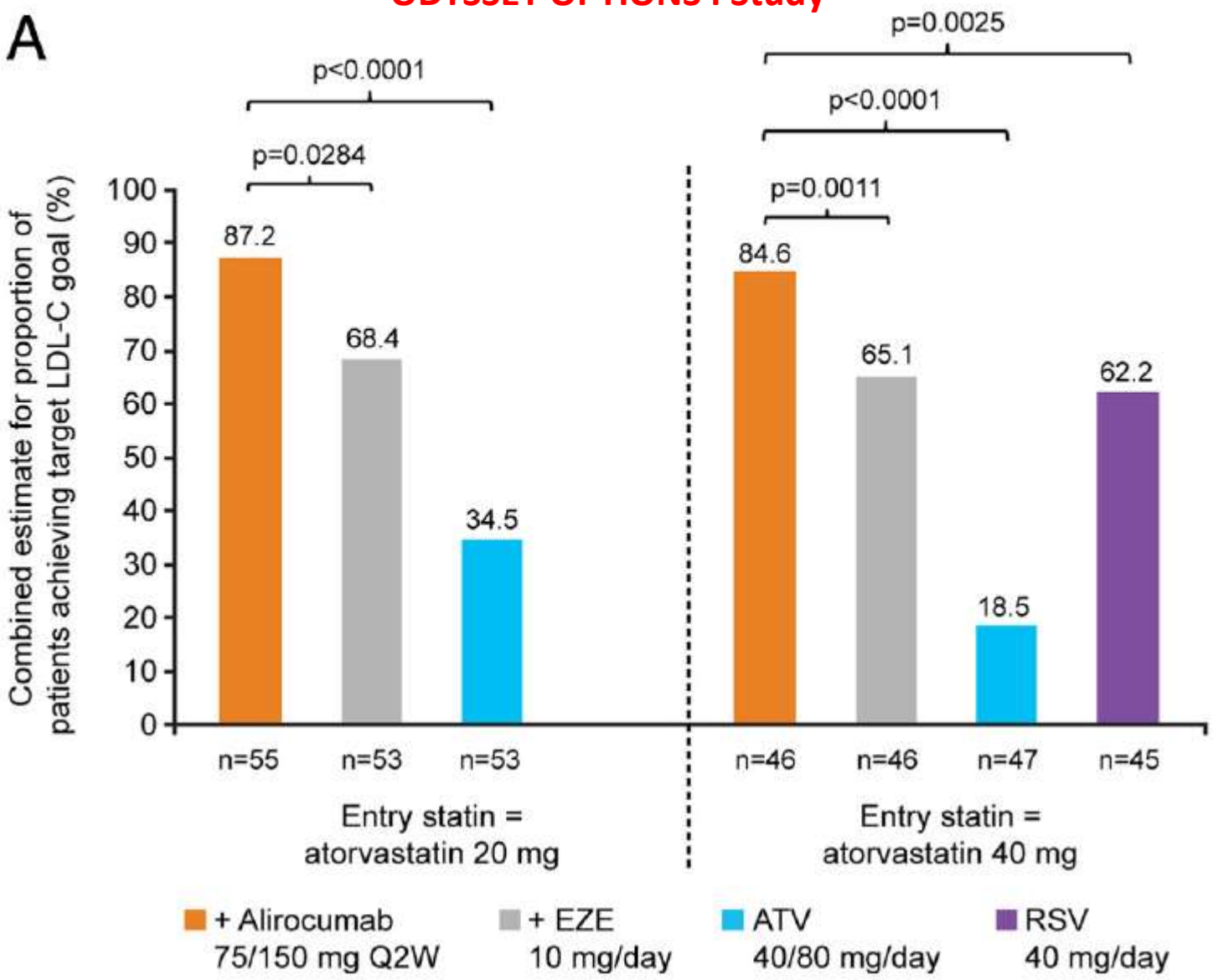
D



J Clin Endocrinol Metab 2015;100: 3140–3148

Proportion of patients achieving LDL-C goals at week 24: LDL-C less than 70 mg/dL (very high CVD risk) or less than 100 mg/dL (high CVD risk) (A) or less than 70 mg/dL (regardless of risk)

ODYSSEY OPTIONS I Study



J Clin Endocrinol Metab 2015;100: 3140–3148

Safety Analysis (Pooled Data Across Atorvastatin 20 mg and 40 mg Entry Regimens)

ODYSSEY OPTIONS I Study

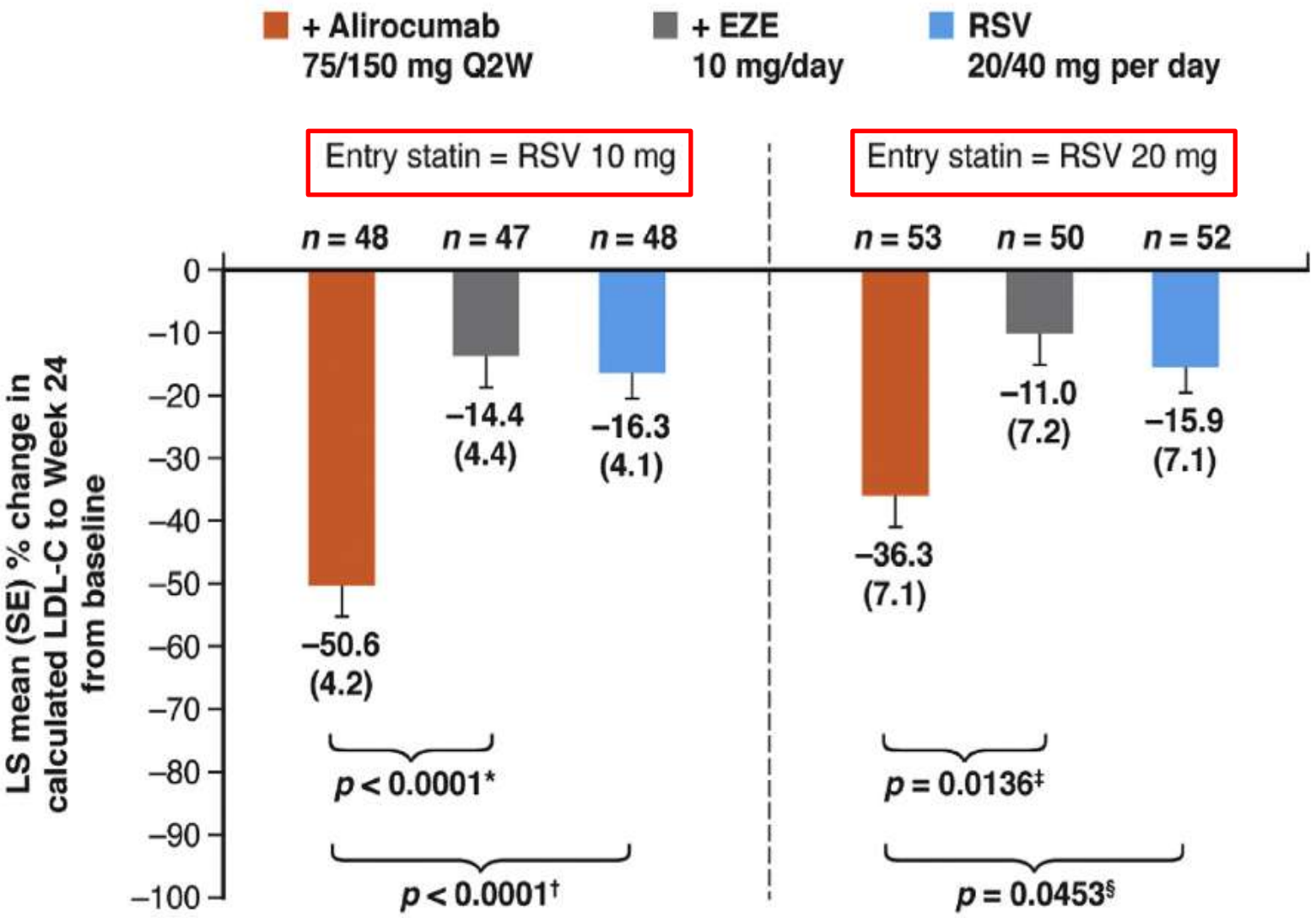
Table 3. Safety Analysis (Pooled Data Across Atorvastatin 20 mg and 40 mg Entry Regimens)

Patients, %, n	Pooled Alirocumab (n = 104)	Pooled EZE (n = 101)	Pooled Double ATV or RSV Switch (n = 149)	*P* Value
TEAEs[a]	65.4 (68)	64.4 (65)	63.8 (95)	.9796
Treatment-emergent SAEs	3.8 (4)	6.9 (7)	5.4 (8)	.6036
TEAE leading to death	0	2.0 (2)	0	.0808
TEAEs leading to discontinuation	6.7 (7)	4.0 (4)	5.4 (8)	.6950
TEAEs in 5% or more of patients in any group				
Back pain	6.7 (7)	3.0 (3)	4.0 (6)	.4409
Nasopharyngitis	4.8 (5)	3.0 (3)	5.4 (8)	.7254
Upper respiratory tract infection	4.8 (5)	8.9 (9)	4.7 (7)	.3479
Hypertension	4.8 (5)	5.9 (6)	0.7 (1)	.315
Urinary tract infection	2.9 (3)	7.9 (8)	5.4 (8)	.2690
Diarrhea	1.9 (2)	3.0 (3)	5.4 (8)	.3726
Nausea	1.0 (1)	4.0 (4)	7.4 (11)	.0390
AEs of interest				
Potential allergic event[b]	1.9 (2)	5.0 (5)	4.0 (6)	.4858
Injection-site reactions	2.9 (3)	3.0 (3)	2.0 (3)	.8354
Neurological events[c]	2.9 (3)	1.0 (1)	2.0 (3)	.6485
Adjudicated CV events	1.0 (1)	1.0 (1)	0	.3347
ALT greater than 3 × ULN, %, n/N	0 (0/101)	0 (0/99)	0.7 (1/147)[d]	1.000
Creatine kinase greater than 3 × ULN, %, n/N[e]	3.0 (3/100)	1.0 (1/98)	5.4 (8/147)	.1859

J Clin Endocrinol Metab 2015;100: 3140–3148

Percent change in calculated LDL-C from baseline to Week 24 (ITT analysis).

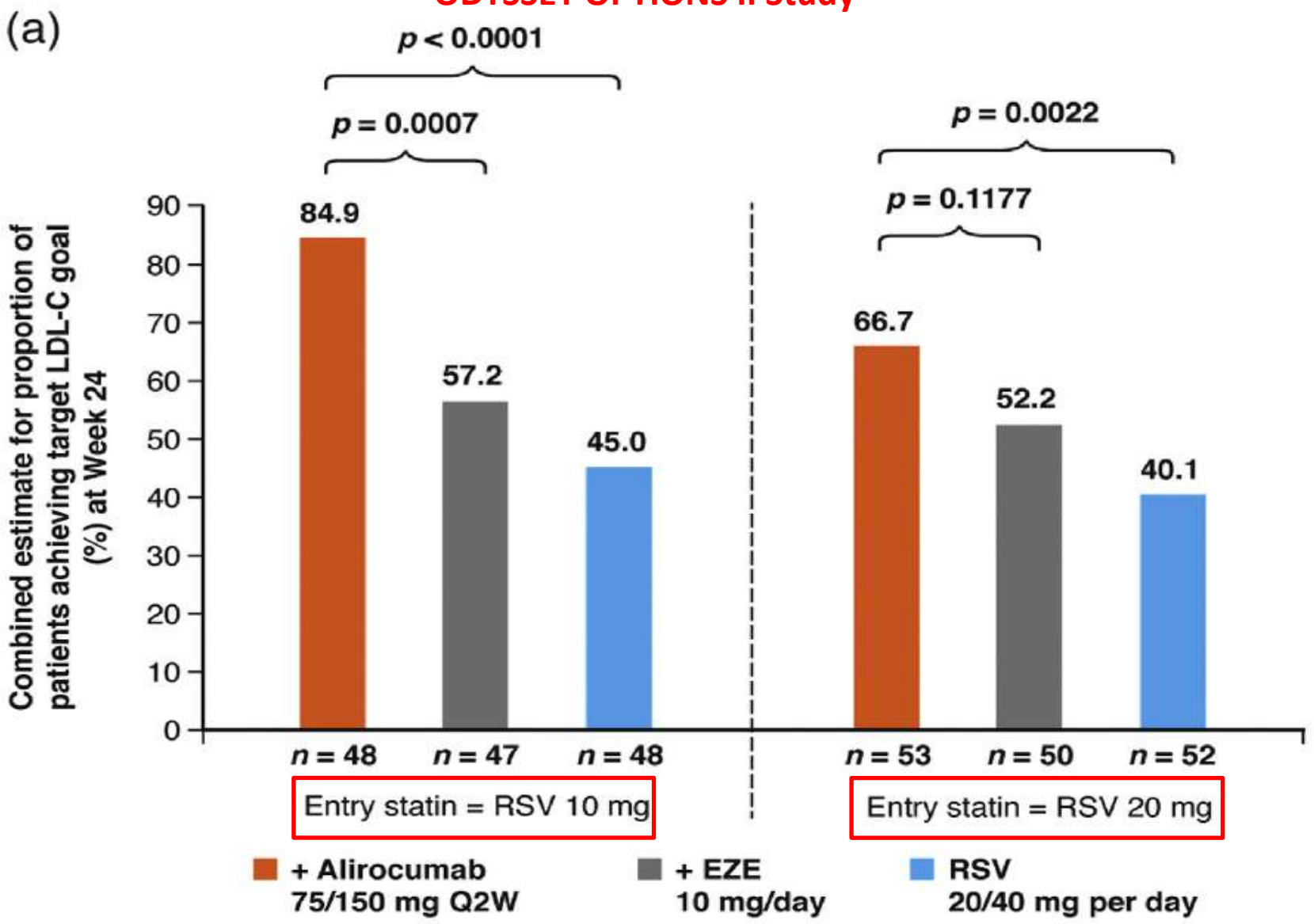
ODYSSEY OPTIONS II Study - Rosuvastatin



Atherosclerosis 2016;244:138-146

Proportion of patients achieving LDL-C goals at Week 24
(a) LDL-C <70 mg/dL (very-high CV risk) or <100 mg/dL (high CV risk).

ODYSSEY OPTIONS II Study



Atherosclerosis 2016;244:138-146

Safety analysis (safety population pooled across statin entry regimens)

ODYSSEY OPTIONS II Study

Safety analysis (safety population pooled across statin entry regimens).

% (n) of patients	Pooled ALI 75/150 (*n* = 103)	Pooled EZE (*n* = 101)	Pooled double RSV (*n* = 101)
Any TEAEs	56.3 (58)	53.5 (54)	67.3 (68)
Treatment-emergent SAEs	5.8 (6)	7.9 (8)	7.9 (8)
TEAE leading to death	0	1.0 (1)	0
TEAEs leading to discontinuation	4.9 (5)	7.9 (8)	5.0 (5)
Most frequently reported TEAEs by preferred term (≥5% of patients in any group)			
Nasopharyngitis	3.9 (4)	5.0 (5)	6.9 (7)
Upper respiratory tract infections	5.8 (6)	4.0 (4)	8.9 (9)
Dizziness	2.9 (3)	2.0 (2)	5.0 (5)
Pain in extremity	1.9 (2)	3.0 (3)	7.9 (8)
Safety events of special interest			
Allergic events[a]	8.7 (9)	2.0 (2)	6.9 (7)
Injection-site reactions	3.9 (4)	0	2.0 (2)
Adjudicated CV events[b]	0	1.0 (1)	1.0 (1)
Hemolytic anemia	0	0	0
Neurocognitive disorders[c]	1.0 (1)	1.0 (1)	1.0 (1)
Neurologic disorders[d]	1.9 (2)	3.0 (3)	2.0 (2)
Ophthalmologic events[e]	0	0	0
Laboratory values			
ALT >3 × ULN, % (n/N)	1.0 (1/101)	0/99	0/100
Creatine kinase >3 × ULN, % (n/N)	0/98	3.1 (3/97)	2 (2/100)

Atherosclerosis 2016;244:138-146

ODYSSEY MONO study

International Journal of Cardiology 176 (2014) 55–61

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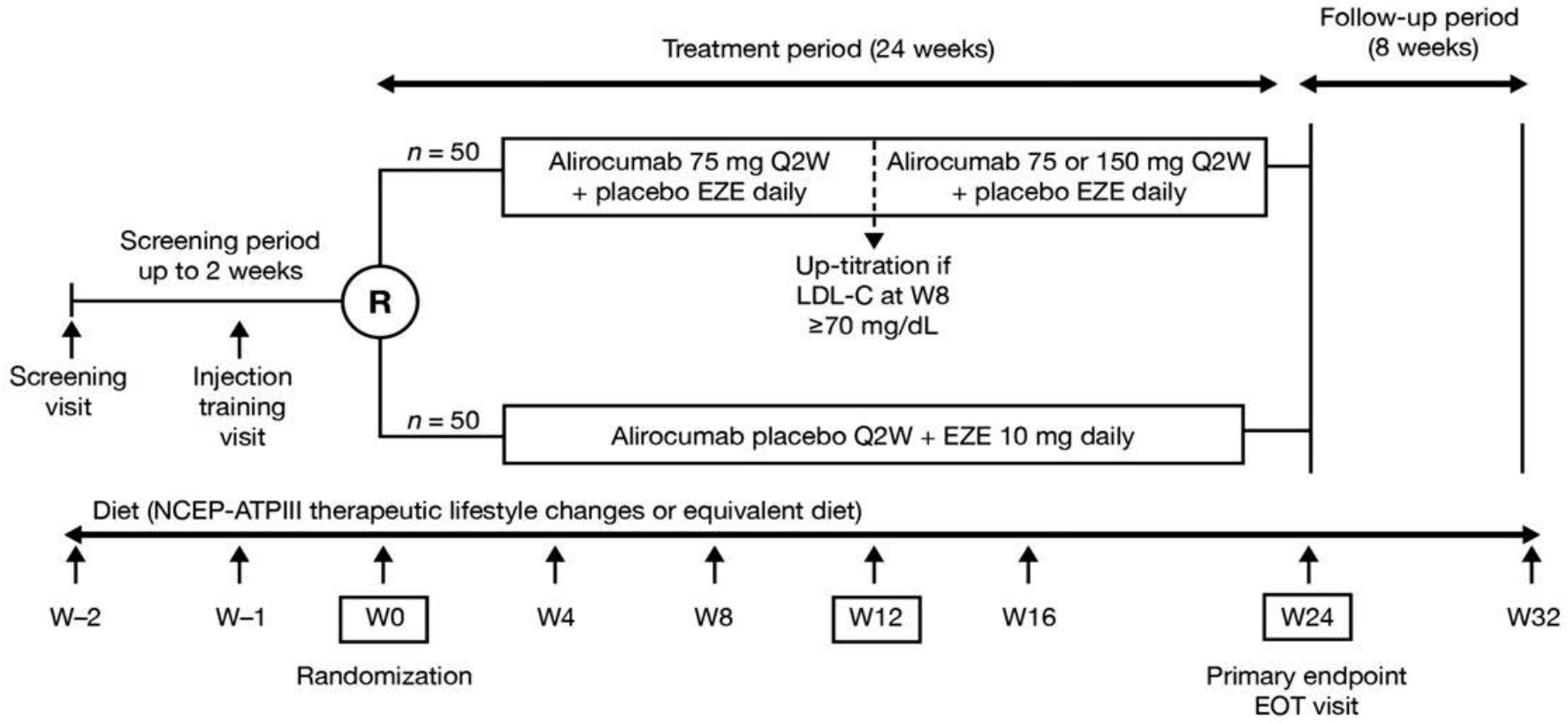
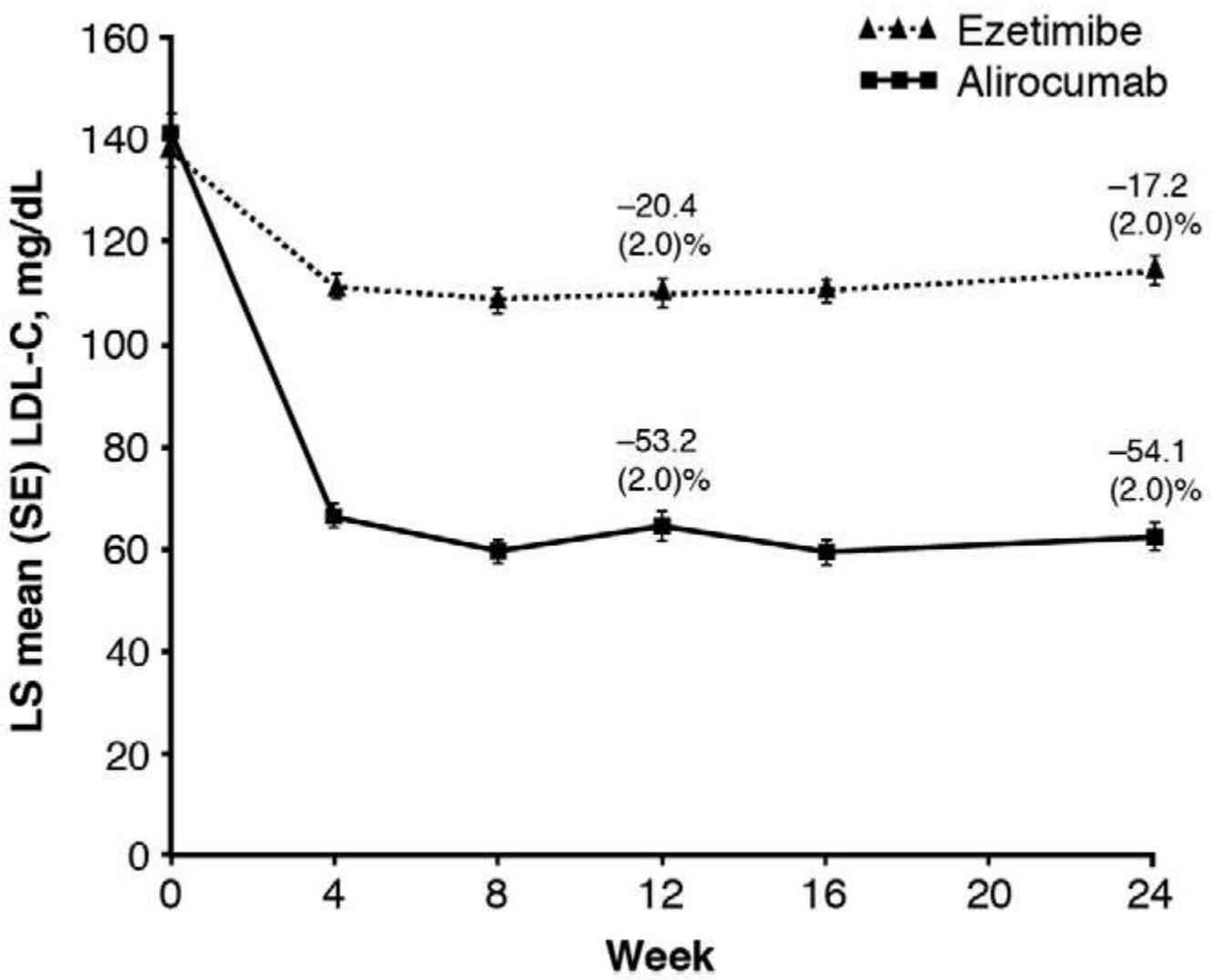
ODYSSEY MONO study

Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: Results of a 24 week, double-blind, randomized Phase 3 trial



LDL-C levels (mg/dl) versus study time point (on-treatment analysis).

ODYSSEY MONO study



International Journal of Cardiology 176 (2014) 55–61

Percent change from baseline in secondary lipid parameters

ODYSSEY MONO study

Table 3

Percent change from baseline in secondary lipid parameters (ITT and on-treatment analysis).

LS mean (SE) % change from baseline to week 24	Alirocumab 75 mg Q2W	Ezetimibe 10 mg	Alirocumab versus ezetimibe		
			LS mean difference (SE) %	95% CI	*p*-Value
ITT	*N* = 52	*N* = 51			
Apo B	−36.7 (2.3)	−11.0 (2.4)	−25.8 (3.3)	−32.3 to −19.2	<0.0001[a]
Non-HDL-C	−40.6 (2.8)	−15.1 (2.9)	−25.5 (4.1)	−33.5 to −17.4	<0.0001[a]
Total cholesterol	−29.6 (2.1)	−10.9 (2.2)	−18.7 (3.0)	−24.7 to −12.7	<0.0001[a]
Lp(a)[b]	−16.7 (3.7)	−12.3 (3.8)	−4.4 (5.3)	−14.8 to 5.9	0.4013
TGs[b]	−11.9 (4.2)	−10.8 (4.3)	−1.2 (5.9)	−12.7 to 10.3	0.8433[c]
HDL-C	6.0 (1.9)	1.6 (1.9)	4.4 (2.7)	−1.0 to 9.8	0.1116[c]
Apo A-1	4.7 (1.6)	−0.6 (1.6)	5.3 (2.2)	0.9 to 9.8	0.0196[c]
On-treatment	*N* = 51	*N* = 50			
Apo B	−40.8 (1.9)	−11.5 (1.9)	−29.2 (2.6)	−34.4 to −24.0	<0.0001[d]
Non-HDL-C	−47.1 (1.9)	−16.6 (1.9)	−30.5 (2.7)	−35.9 to −25.1	<0.0001[d]
Total cholesterol	−34.2 (1.6)	−12.0 (1.6)	−22.2 (2.3)	−26.7 to −17.7	<0.0001[d]
Lp(a)[b]	−17.7 (4.1)	−12.3 (4.0)	−5.4 (5.7)	−16.6 to 5.9	0.3506[d]
TGs[b]	−14.7 (4.4)	−12.7 (4.2)	−1.9 (6.0)	−13.7 to 9.8	0.7452[d]
HDL-C	8.0 (1.9)	1.7 (1.9)	6.2 (2.7)	0.8 to 11.6	0.0241[d]
Apo A-1	5.3 (1.6)	−0.7 (1.6)	6.1 (2.3)	1.6 to 10.6	0.0084[d]

International Journal of Cardiology 176 (2014) 55–61

Studies Exploring Long-Term Efficacy and Safety

ODYSSEY LONG-TERM

Studies Exploring Long-Term Efficacy and Safety

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 16, 2015 VOL. 372 NO. 16

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

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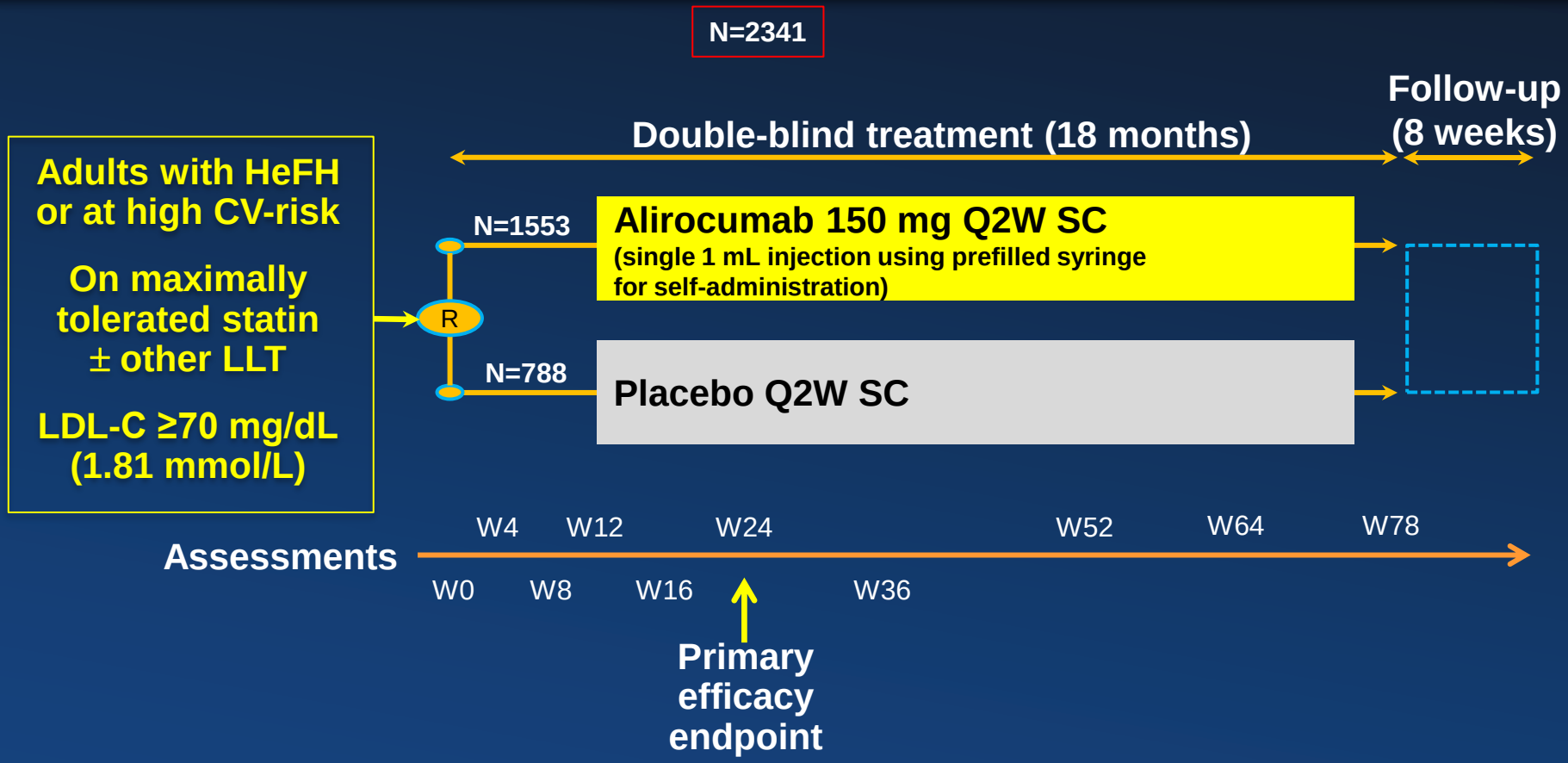
The ODYSSEY LONG TERM trial

ODYSSEY LONG TERM

Study Design



CV, cardiovascular; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Q2W, every 2 weeks; SC, subcutaneous; W, week.
ClinicalTrials.gov identifier: NCT01507831.

Robinson JG et al. *NEJM* 2015; 372:1489-99.

ODYSSEY LONG TERM
Endpoints

Primary efficacy endpoint

- % change in calculated LDL-C level from baseline to week 24 using an ITT approach

Secondary efficacy endpoints

- % change in LDL-C level while the study drug was being taken
- Other lipoprotein variables at Week 12 and 24

Safety endpoints

- Adverse events, including adjudicated cardiovascular events, occurring between first and up to 10 weeks after last injection
- Laboratory, vital sign and electrocardiogram abnormalities
- Safety in patients with LDL-C level <25 mg/dL (0.6 mmol/L) at two consecutive measurements

ITT, intention-to-treat

Robinson JG et al. *NEJM* 2015; 372:1489-99.

Baseline Characteristics

Lipid and lipoprotein profile and LLTs

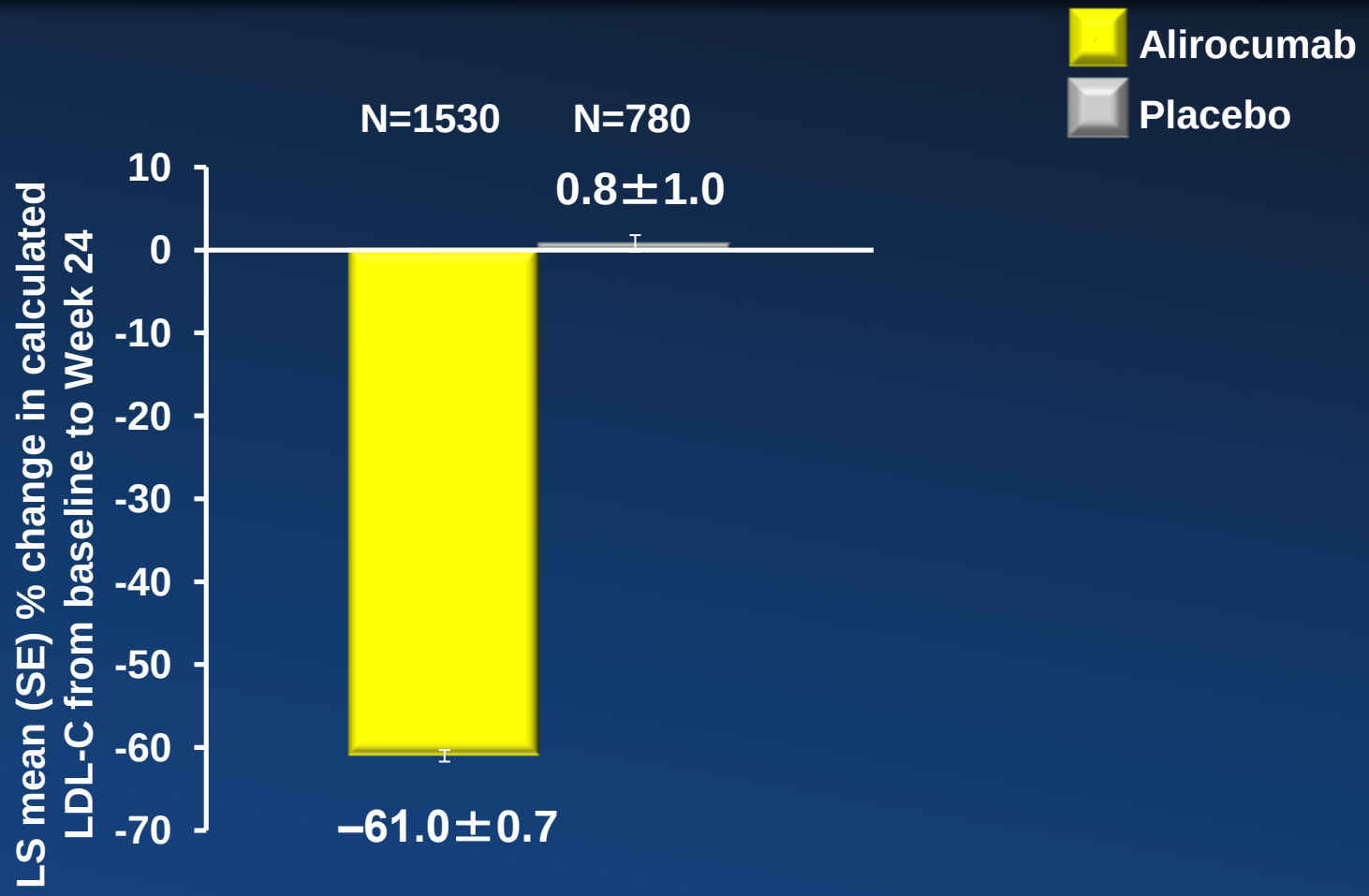
All randomized patients	Alirocumab (N=1553)	Placebo (N=788)
LLTs, n (%)		
Any statin	1552 (>99.9)	787 (99.9)
High-dose statin*	727 (46.8)	368 (46.7)
Other LLT	437 (28.1)	220 (27.9)
Ezetimibe	216 (13.9)	118 (15.0)
Lipid/lipoprotein profile, mg/dL, mean±SD		
Calculated LDL-C*	122.7±42.6	121.9±41.4
Non-HDL-C	152.6±46.6	152.0±45.8
Apolipoprotein B	101.9±27.7	101.4±27.3
Lipoprotein(a), median (IQR)	22.2 (7.6–66.5)	20.9 (6.5–66.8)
Fasting triglycerides, median (IQR)	132.0 (93.8–183.0)	135.0 (94.7–188.5)
HDL-C	49.8±12.2	50.0±12.4
Apolipoprotein A1	146.5±25.1	147.3±27.3

*Daily dose of 40 to 80 mg of atorvastatin, 20 to 40 mg of rosuvastatin, or 80 mg of simvastatin; †Calculated with the use of the Friedewald formula; IQR, interquartile range.

Robinson JG et al. *NEJM* 2015; 372:1489-99.

Change in LDL-C from Baseline to Week 24

ITT Analysis (primary efficacy endpoint)

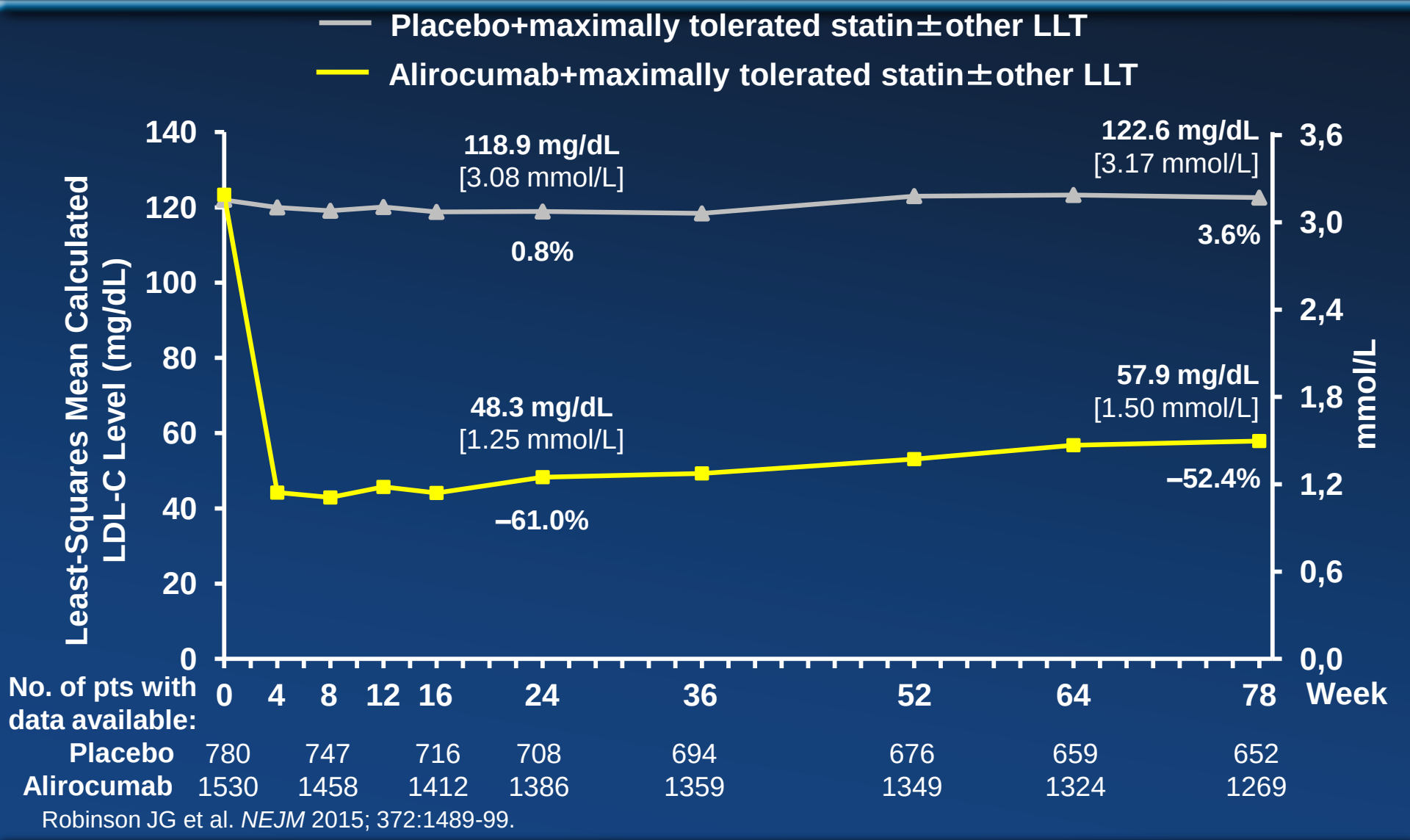


LS mean difference (SE) versus placebo: −61.9% (1.3); 95% CI (–64.3 to –59.4); *P*<0.001

Robinson JG et al. *NEJM* 2015; 372:1489-99.

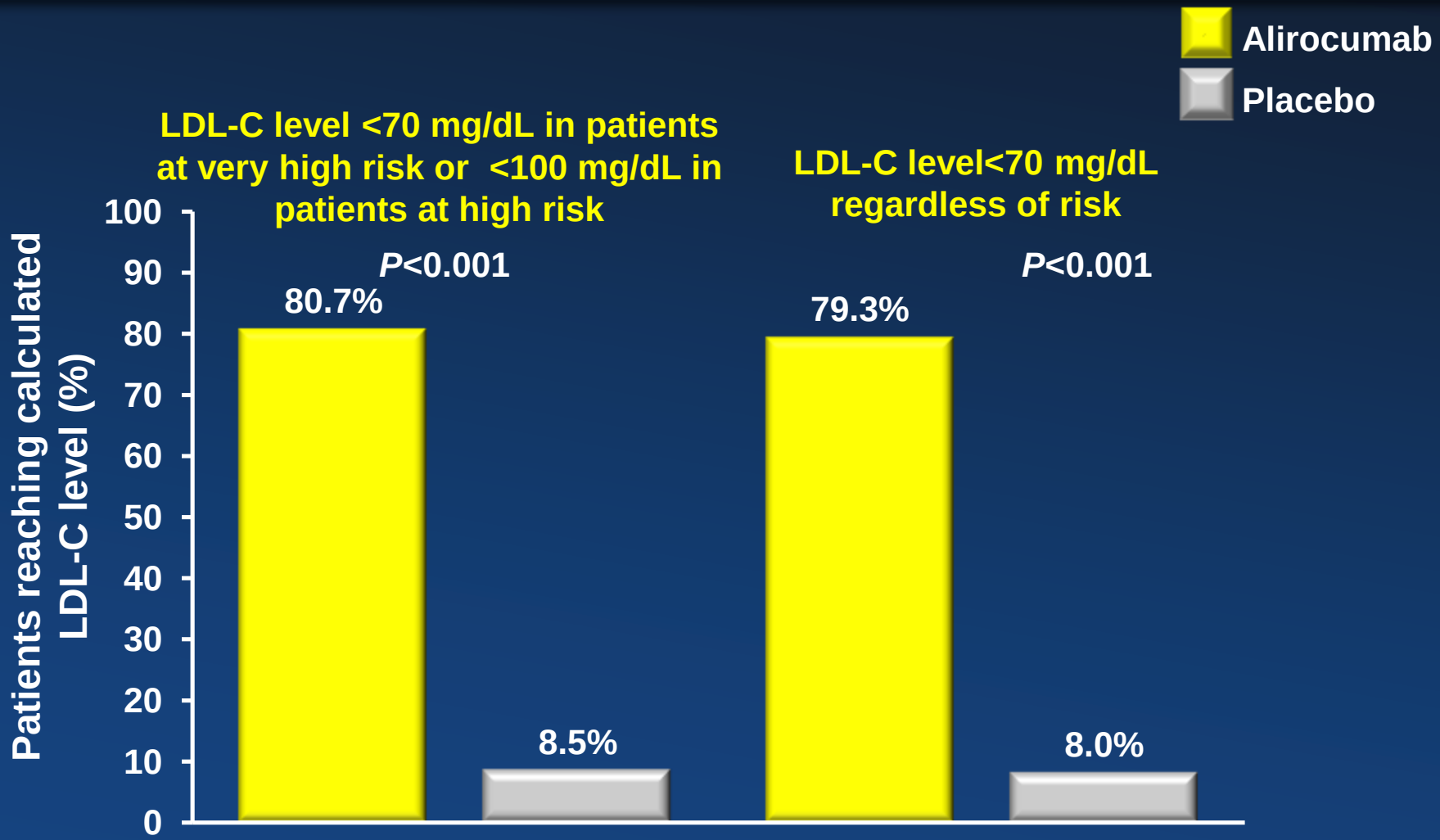
Calculated LDL-C Levels over Time

ITT Analysis



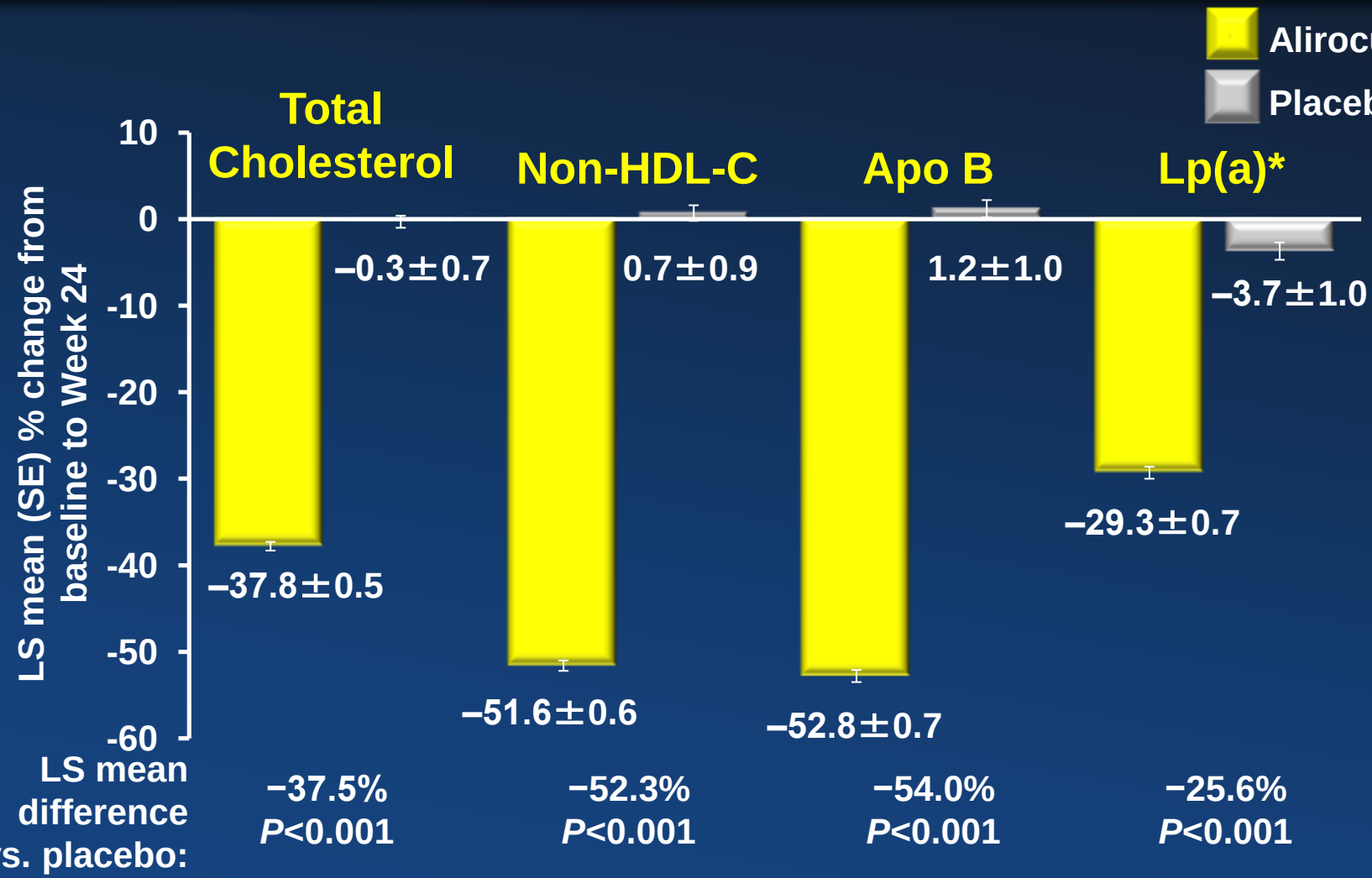
Robinson JG et al. *NEJM* 2015; 372:1489-99.

% Patients Reaching Target LDL-C Levels:
<70 or <100 mg/dL by Week 24 (ITT)



ITT=Intention-to-treat. Analysis of this secondary endpoint was performed with multiple imputation, followed by logistic regression
Robinson JG et al. *NEJM* 2015; 372:1489-99.

Change from Baseline to Week 24:
Total Cholesterol, Non-HDL-C, Apo B and Lp(a) (ITT)

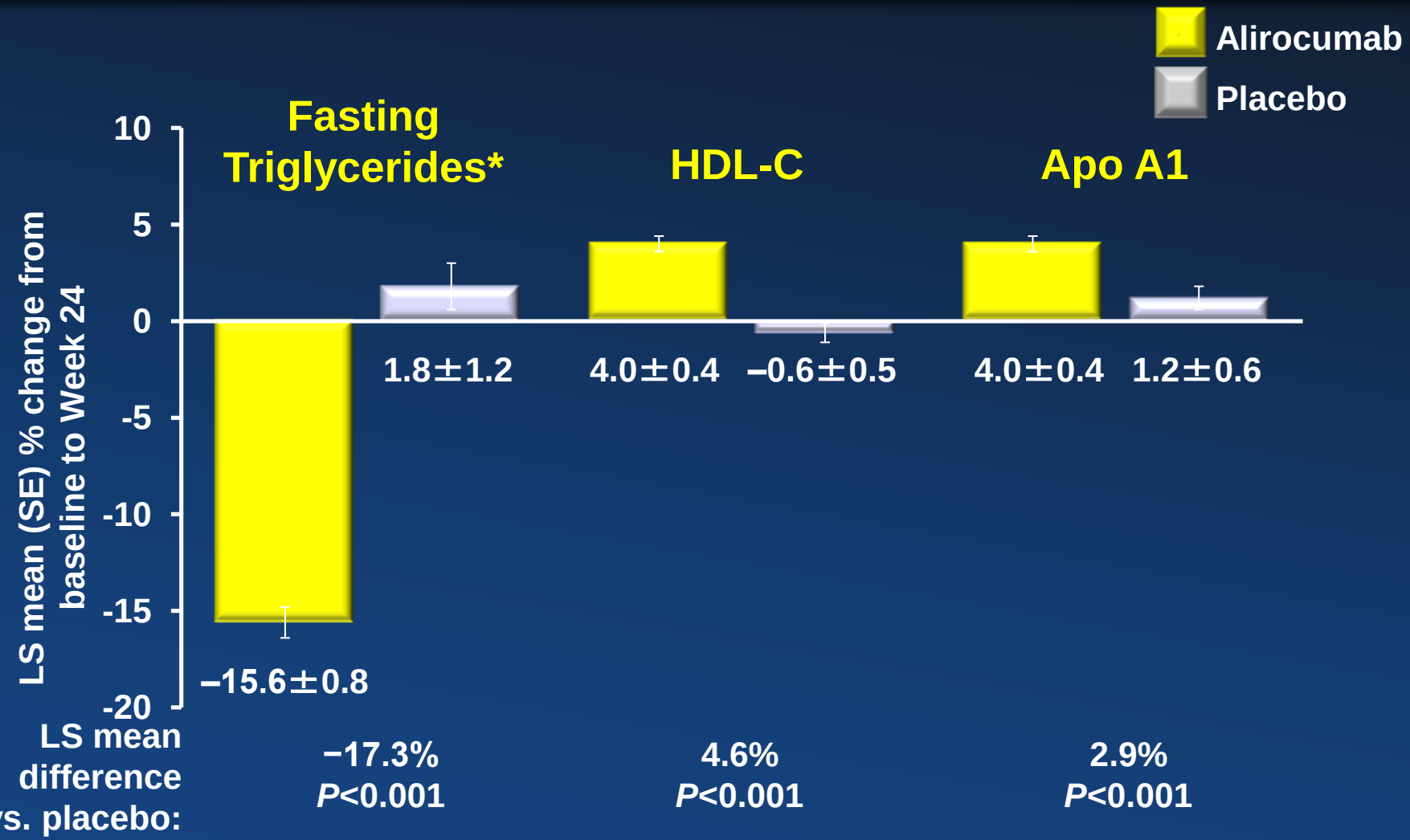


These are secondary endpoints in ITT analysis population. *Analyzed with the use of multiple imputation, followed by robust regression. A combined estimate for adjusted mean (±SE) is shown.

Robinson JG et al. *NEJM* 2015; 372:1489-99.

Change from Baseline to Week 24

Fasting Triglycerides, HDL-C and Apo A1 (ITT)

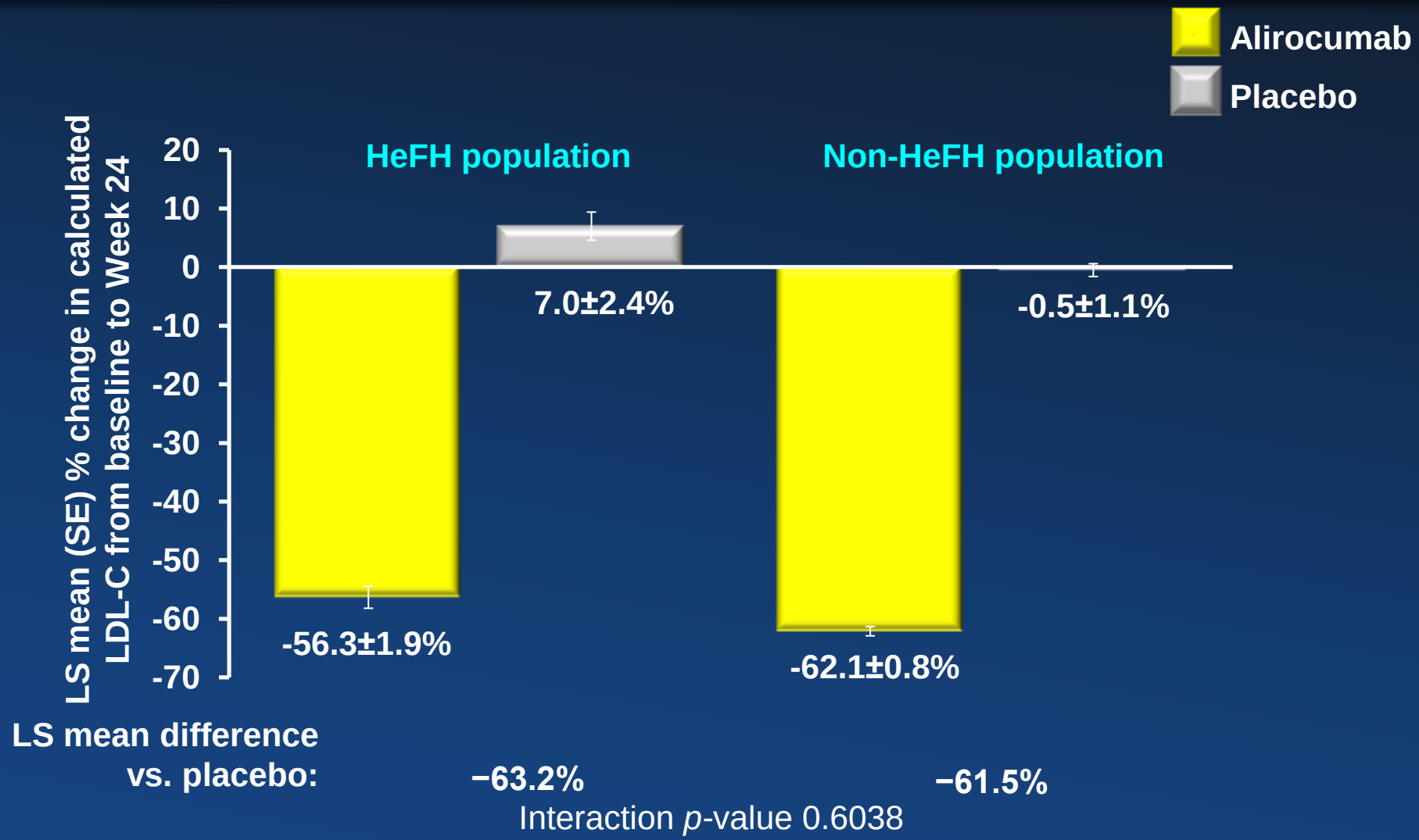


These are secondary endpoints in ITT analysis population. *Analyzed with the use of multiple imputation, followed by robust regression. A combined estimate for adjusted mean (±SE) is shown.

Robinson JG et al. *NEJM* 2015; 372:1489-99.

Change in LDL-C from Baseline to Week 24

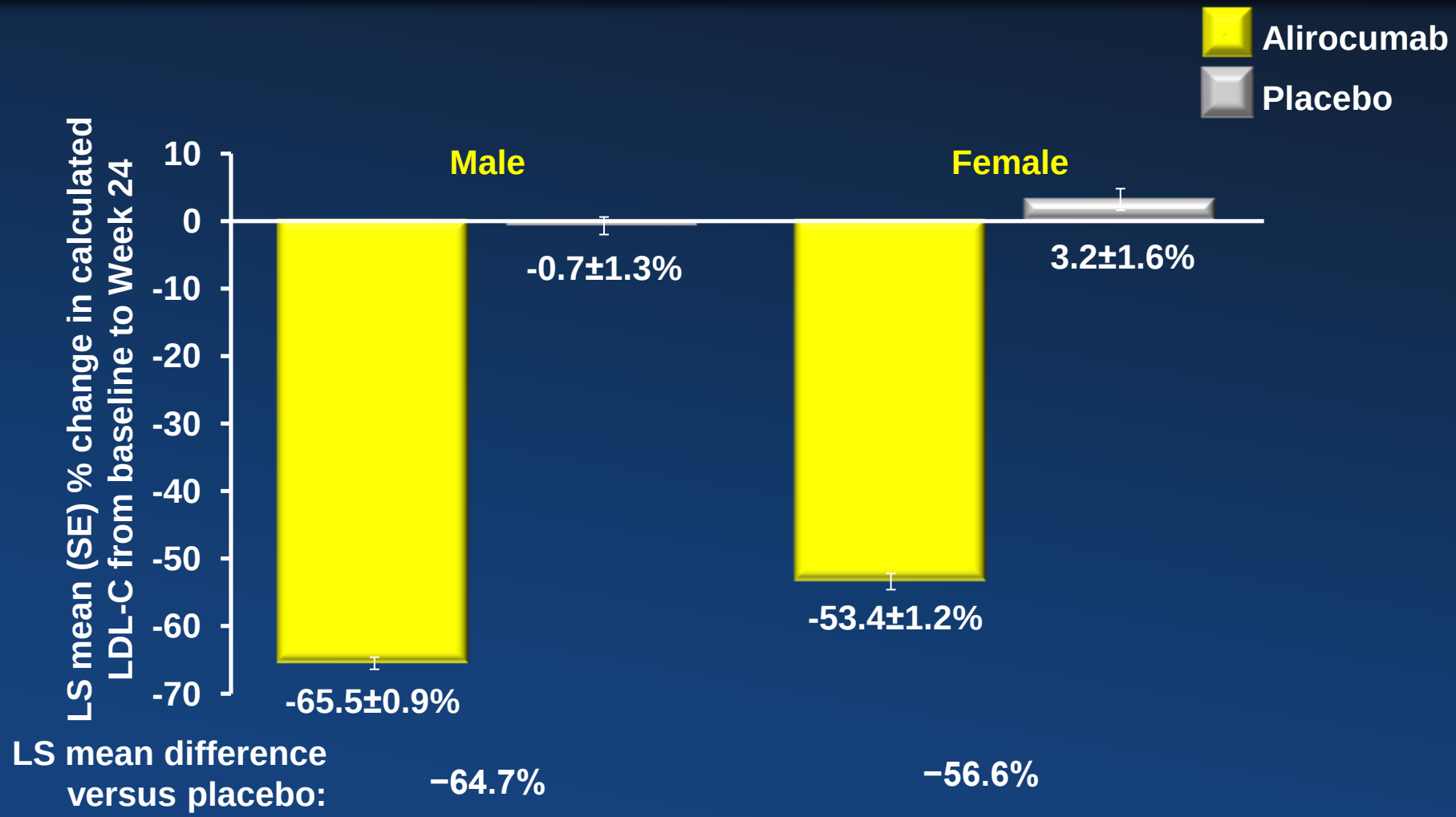
According to HeFH status (ITT)



Robinson JG et al. *NEJM* 2015; 372:1489-99.

Change in LDL-C from Baseline to Week 24

According to Sex



Robinson JG et al. *NEJM* 2015; 372:1489-99.

Adverse Events
Summary

Number of patients (%)	Alirocumab (N=1550)	Placebo (N=788)	*p*-value
Any adverse event	1255 (81.0)	650 (82.5)	0.40
Serious adverse event	290 (18.7)	154 (19.5)	0.66
Adverse event leading to study-drug discontinuation	111 (7.2)	46 (5.8)	0.26
Adverse event leading to death	8 (0.5)	10 (1.3)	0.08

- Mean study-drug exposure in the 1550 alirocumab-treated patients and 788 placebo patients:
  - 70 weeks
  - 2061 patient-years of exposure to alirocumab 150 mg Q2W

Robinson JG et al. *NEJM* 2015; 372:1489-99.

Adverse Events of Interest and Laboratory Values

Number of patients (%)	Alirocumab (n=1550)	Placebo (n=788)	*p*-value
Positively adjudicated cardiovascular events†	72 (4.6)	40 (5.1)	0.68
General allergic reaction	156 (10.1)	75 (9.5)	0.71
Local injection-site reaction	91 (5.9)	33 (4.2)	0.10
Myalgia	84 (5.4)	23 (2.9)	0.006
Neurologic event	65 (4.2)	35 (4.4)	0.83
Neurocognitive disorder	18 (1.2)	4 (0.5)	0.17
Amnesia	5 (0.3)	0	0.17
Memory impairment	4 (0.3)	1 (0.1)	0.67
Confusional state	4 (0.3)	1 (0.1)	0.67
Ophthalmologic event	45 (2.9)	15 (1.9)	0.65
Hemolytic anemia	0	0	–
Diabetes in patients with no history of diabetes, n/N (%)	18/994 (1.8)	10/509 (2.0)	0.84
Worsening diabetes in patients with diabetes, n/N (%)	72/556 (12.9)	38/279 (13.6)	0.83
Laboratory values of interest, n/N (%)			
Alanine aminotransferase >3× ULN	28/1533 (1.8)	16/779 (2.1)	0.75
Aspartate aminotransferase >3× ULN	22/1533 (1.4)	18/779 (2.3)	0.13
Creatine kinase >3× ULN	56/1507 (3.7)	38/771 (4.9)	0.18

†Includes death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, unstable angina or congestive heart failure requiring hospitalization and ischemia-driven coronary revascularization

Robinson JG et al. *NEJM* 2015; 372:1489-99.

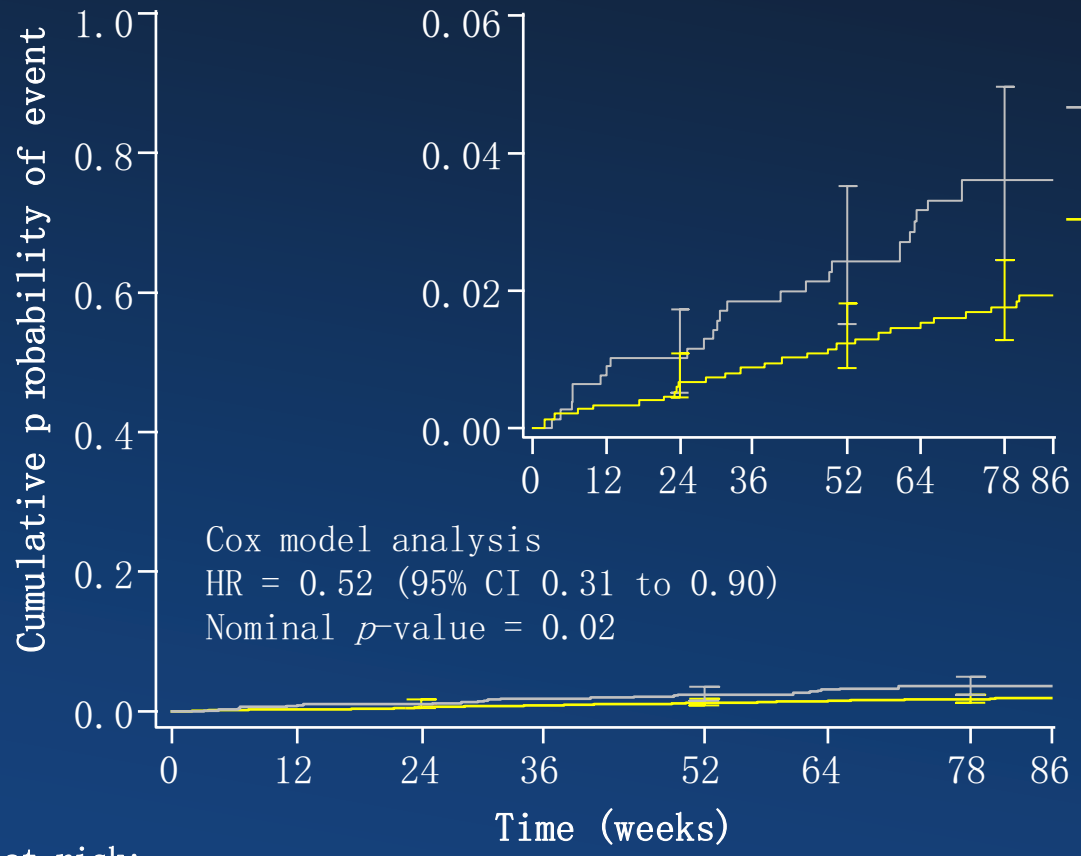
Cardiovascular Adverse Events of Interest

Number of patients (%)	Alirocumab (n=1550)	Placebo (n=788)	*p*-value
Death from coronary heart disease, including death from unknown cause	4 (0.3)	7 (0.9)	0.26
Nonfatal myocardial infarction	14 (0.9)	18 (2.3)	0.01
Fatal or nonfatal ischemic stroke	9 (0.6)	2 (0.3)	0.35
Unstable angina requiring hospitalization	0	1 (0.1)	0.34
Congestive heart failure requiring hospitalization	9 (0.6)	3 (0.4)	0.76
Ischemia-driven coronary revascularization procedure	48 (3.1)	24 (3.0)	1
Positively adjudicated cardiovascular events, including all cardiovascular adverse events listed above	72 (4.6)	40 (5.1)	0.68
Adjudicated major adverse cardiovascular events in post-hoc analysis*	27 (1.7)	26 (3.3)	0.02

*The post-hoc analysis was not specified in the study protocol. It included the following cardiovascular event categories, which also comprise the endpoint in the Study to Evaluate the Effect of Alirocumab on the Occurrence of Cardiovascular Events in Patients Who Have Experienced an Acute Coronary Syndrome (ODYSSEY OUTCOMES).

Robinson JG et al. *NEJM* 2015; 372:1489-99.

Post hoc Analysis of Adjudicated Major Adverse Cardiovascular Events*



Placebo + maximally tolerated statin ± other LLT

Alirocumab + maximally tolerated statin ± other LLT

Congestive heart failure requiring hospitalization and ischemia - driven coronary revascularization procedure were not included in the post hoc analysis.

*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. *NEJM* 2015; 372:1489-99.

Conclusions:
The ODYSSEY LONG TERM trial

- This trial of 2341 high-risk patients provides data on the long-term efficacy and safety of alirocumab treatment over a 78-week period when added to a maximally tolerated dose of statin with or without other LLT.
- Overall, alirocumab reduced LDL-C levels by 62% versus placebo at 24 weeks. LDL-C reduction in the alirocumab group was consistent over the 78-week treatment period.
- Based on post-hoc analysis, there was evidence of a reduced rate of cardiovascular events with alirocumab treatment.
- The duration of follow-up is still relatively short for a treatment for a chronic disease, and longer-term studies will be needed. (ODYSSEY OUTCOMES 18,000 patients over a period of 5 years)

Robinson JG et al. *NEJM* 2015; 372:1489-99.

Recommendations

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ΕΛΛΗΝΙΚΗ ΕΠΙΘΕΩΡΗΣΗ ΑΘΗΡΟΣΚΛΗΡΩΣΗΣ

Συμφωνία (Consensus) ειδικών για την ορθολογική χορήγηση των αναστολέων της PCSK9

Επίσημη Έκδοση της Ελληνικής Εταιρείας Αθηροσκλήρωσης

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Τόμος 6 • ΣΥΜΠΛΗΡΩΜΑ 2015

Ελληνική Επιθεώρηση Αθηροσκλήρωσης 6(Συμπλήρωμα):3–8

Συμφωνία (Consensus) ειδικών για την ορθολογική χορήγηση των αναστολέων της PCSK9

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Πίνακας 1. Ομάδες υποψήφιων ασθενών για χορήγηση των μονοκλωνικών αντισωμάτων κατά της PCSK9 μέχρι την ολοκλήρωση των μεγάλων τυχαιοποιημένων κλινικών δοκιμών με καρδιαγγειακές εκβάσεις.

Ομάδα ατόμων υψηλού-πολύ υψηλού κινδύνου		Τελικός στόχος αγωγής
1α. Ενήλικες ασθενείς με εγκατεστημένη αθηρωματική καρδιαγγειακή νόσο (στεφανιαίων αγγείων, καρωτίδων ή περιφερικών αγγείων) και LDL χοληστερόλη ≥100 mg/dL 1β. Διαβητικοί ασθενείς με: γνωστή καρδιαγγειακή νόσο ή χρόνια νεφρική νόσο ή άλλη βλάβη οργάνου-στόχου και LDL χοληστερόλη ≥100 mg/dL	Υπό κατάλληλη υγιεινοδιαιτητική αγωγή και φαρμακευτική αγωγή με τη μέγιστη ανεκτή δόση αποτελεσματικής στατίνης (ατορβαστατίνη 40/80 mg ή ροσουβαστατίνη 20/40 mg)+ezetimibe 10 mg	LDL χοληστερόλη <70 mg/dL
2. Ενήλικες ασθενείς με οικογενή υπερχοληστερολαιμία χωρίς γνωστή αθηρωματική καρδιαγγειακή νόσο και LDL χοληστερόλη ≥130 mg/dL*	Υπό αγωγή με τη μέγιστη ανεκτή δόση αποτελεσματικής στατίνης (ατορβαστατίνη 40/80 mg ή ροσουβαστατίνη 20/40 mg) + εζετιμίμπη 10 mg	LDL χοληστερόλη <100 mg/dL
3. Ασθενείς υψηλού ή πολύ υψηλού κινδύνου (HELLENIC SCORE >5% ή >10%, αντίστοιχα) που εμφανίζουν δυσανεξία στις στατίνες και έχουν LDL χοληστερόλη ≥130 ή >100 mg/dL, αντίστοιχα	Υπό οποιαδήποτε ανεκτή υπολιπιδαιμική αγωγή	LDL χοληστερόλη <70 mg/dL σε ασθενείς πολύ υψηλού κινδύνου LDL χοληστερόλη <100 mg/dL σε ασθενείς υψηλού κινδύνου

*Το evolocumab έχει λάβει επιπλέον ένδειξη σε εφήβους άνω των 12 ετών με ομόζυγη οικογενή υπερχοληστερολαιμία σε συνδυασμό με άλλες υπολιπιδαιμικές θεραπείες

Conclusions

- Statins are an essential element of lipid lowering treatment for decades with undisputable benefits.
- However, there are patients who cannot tolerate statins or cannot achieve the goal of lipid lowering treatment only by statins.
- The important contribution of the PCSK9 to the catabolism of the low density lipoprotein (LDL) receptor renders it as the main regulator in cholesterol metabolism.
- Inhibiting the PCSK9 protein by using monoclonal antibodies is the most advanced approach, given that it achieves an additional reduction of LDL cholesterol by 50–60%, while having an excellent safety profile.
- While awaiting for robust evidence of a reduction in cardiovascular events, it seems prudent to use these cautiously.

Questions

1. **All of the following statements are true EXCEPT:**

   a. In pts at Very High CV Risk (Score≥10), LDL-C target should be ≤ 70 mg/dL

   b. In pts at High CV Risk (Score <10 & ≥5), LDL-C target should be ≤ 100 mg/dL

   c. The incidence of rhabdomyolysis in pts on statin treatment is approx. 0.2-0.5%

   d. 50–60% of patients cannot tolerate statins because of myopathy.

1. **All of the following statements are true EXCEPT:**

   a. In pts at Very High CV Risk (Score≥10), LDL-C target should be ≤ 70 mg/dL

   b. In pts at High CV Risk (Score <10 & ≥5), LDL-C target should be ≤ 100 mg/dL

   c. The incidence of rhabdomyolysis in pts on statin treatment is approx. 0.2-0.5%

   d. 50–60% of patients cannot tolerate statins because of myopathy. (5-10%)

2. **Gain-of-function mutations of PCSK9 gene:**

a. Decrease LDL-cholesterol levels

b. Increase LDL-cholesterol clearance

c. Decrease LDL-cholesterol receptor levels

d. Decrease cardiovascular events

2. Gain-of-function mutations of PCSK9 gene:

a. Decrease LDL-cholesterol levels

b. Increase LDL-cholesterol clearance

c. Decrease LDL-cholesterol receptor levels

d. Decrease cardiovascular events

3. All of the following statements regarding alirocumab are true EXCEPT:

a. Decreases LDL-cholesterol by an additional 50-60%

b. It is a chimeric anti-PCSK9 monoclonal antibody

c. Increases LDL-cholesterol receptor levels

d. Decreases ApoB and Lp(a) levels

3. All of the following statements regarding alirocumab are true EXCEPT:

a. Decreases LDL-cholesterol by an additional 50-60%

b. It is a chimeric anti-PCSK9 monoclonal antibody

c. Increases LDL-cholesterol receptor levels

d. Decreases ApoB and Lp(a) levels

Thank You

The Ancient Theatre of Larissa, Greece

3rd Century B.C.

Alirocumab and Evolocumab

Alirocumab and Evolocumab: Basic Characteristics

	Evolocumab (AMG-145)	Alirocumab (REGN727)
Dosing	• **Q2wk (140 mg)** • **Q4wk/ QM (420 mg)** Both doses being tested in PhIII	• **Q2wk (75 mg, 150 mg)** • **Q4wk* (150 mg; 300 mg)** Q2wk being used in 11 out of 13 studies
Administ-ration	• Patient-administered SC injections using **autoinjector OR automated patch-pump injector device** used in trials† – Single injection for q2wk dosing **(1ml volume)** – 3 simultaneous injections for q4wk dosing if using autoinjector **(1 ml each)** – 9 min. administration with patch-pump injector for q4wk dosing **(3.5 ml volume) – N/A at launch**	• Patient-administered SC injection using **autoinjector** used in trials – Single injection for q2wk dosing **(1 ml volume)** – Single injection for q4wk 150 mg dosing **(1 ml volume)** – 2 simultaneous injections for q4wk 300 mg dosing **(1 ml each)**

* Dosing at 150 mg for monotherapy; 300 mg for combination therapy (data on Q4W pending).
† Autoinjector likely used for majority of patients in trials so far.

Potential for q4WK dosing with single 1 ml injection

Overview of Clinical Trial Programs (ODYSSEY and PROFICIO)

Trial Type	Alirocumab Trials	N	Duration (Mos)	Patient Exposure (Yrs)	Pop at High Risk*	Evolocumab Trials	N	Duration (Mos)	Patient Exposure (Yrs)	Pop at High Risk*
Long Term	*LONG TERM*	2341	18	2340	Some	*DESCARTES*	905	12	602	Some
Combo Therapy	*COMBO I*	316	12	210	All	*LAPLACE-2*	1700	3	231	Some
	COMBO II	720	24	960	All					
	OPTIONS I	355	6	50	All					
	OPTIONS II	305	6	50	All					
HeFH	*FH I*	486	18	496	Some	*RUTHERFORD-2*	300	3	36	Some
	FH II	249	18	250.5	Some					
	HIGH FH	107	18	106.5	Some					
Statin Intolerance	*ALTERNATIVE*	314	6	63	Some	*GAUSS-2*	300	3	92	Some
Monotherapy	*Mono*	103	6	25	None	*MENDEL-2*	614	3.5	~175	None

- **ODYSSEY : ~4500 patient-years of double-blind exposure (≈5,300 pts)**
- **PROFICIO: ~1200 patient-years of double-blind exposure**

* In PCSK9 inhibitor arm only - defined as CAD or CAD risk equivalents based on NCEP definition (peripheral arterial disease, abdominal aortic aneurysm, carotid artery disease (transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery), diabetes, 2 risk factors with 10-year risk for hard CHD >20%).

Percentages include only pre-existing CHD since NCEP risk score not available.

Summary of Evolocumab Efficacy

Study	Population	420 mg Q4W (wk 12)	420 mg Q4W (wk 10/12) †	140 mg Q2W
DESCARTES	Range of risk profiles	**-54%**	N/A	N/A
LAPLACE-2	Range of risk profiles	**-58.2%** to **-58.7%**	**-62.4%** to **-63.8%**	**-61.6%** to **-61.8%**
RUTHERFORD-2	HeFH*	**-56%**	**-64%**	**-61%**
GAUSS-2	Statin Intolerance	**-52.6%**	**-55.3%**	**-56.1%**
MENDEL-2	Monotherapy	**–56.1%**	**–58.8%**	**-57%**

Note: All efficacy figured here represented as *on treatment* values.

* HeFH=heterozygous familial hypercholesterolemia.
† Taken as the average of percentage decrease at week 10 and week 12. Was a co-primary endpoint in these trials.

Outcomes Trials for Alirocumab and Evolocumab

	ODYSSEY OUTCOMES	Evolocumab CVOT
Inclusion criteria	ACS within the last 4 to 52 weeks; LDL-C ≥70 (on atorvastatin 40-80 mg or rosuvastatin 20-40 mg)	MI, stroke, or symptomatic PAD + at least 1 major RF or at least 2 minor RFs; LDL-C ≥70 (or non-HDL ≥100) (on atorvastatin 20 to 80 mg or equivalent)
Number of patients	18,000	27,500
Primary endpoint	CV death, MI, stroke, and hospitalization for UA	CV death, MI, stroke, coronary revascularization and hospitalization for UA
Background Therapy	Max tolerated doses of atorvastatin and rosuvastatin	Atorvastatin: 20 (at least), 40 (recommended where locally approved), 80 mg (or equivalent)
Dosing regimen	75 mg → 150 mg Q2W (based on w8 LDL-C level)	140 Q2W (1 ml pen) or 420 QM (3 x 1 ml pen or 3.5 ml via personal injector (9' injection time)