New Targets and Treatments for LDL Lowering: Role of PCSK9 Inhibitors

Supported by an educational grant from Amgen

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Announcements

- The session is being videotaped. Please turn off all cell phones and pagers.
- ARS keypads are provided on the table for use during the symposium.
- During the panel discussion, please use the Question Cards located on each table.
- Complete and return a CME Evaluation Form at the conclusion of the symposium.

Introduction and Opening Remarks

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Case 1

53-year-old white male with a family history of premature CHD, father died of MI at age 50. He has a history of hypertension which has been treated for 6 years and also a history of high cholesterol for as long as he can remember. He is a nonsmoker who walks 30 min 3 times a week.

PE: BMI 28.6 kg/m^2, waist 40", BP 136/88 mm Hg

Current meds: lisinopril 20 mg/HCTZ 12.5 mg, ASA 81 mg, atorvastatin 80 mg

ARS QUESTION 1

According to the new ACC/AHA guidelines, should you check his lipid profile?

a. Yes
b. No
c. Unsure

ARS QUESTION 2

Would you get any specialized lipid tests for this patient at this time?

a. Yes
b. No
c. Unsure

Lab Results

- Glucose 110 mg/dL
- TC 199 mg/dL
- HDL-C 35 mg/dL
- non-HDL-C 164 mg/dL
- TG 180 mg/dL
- LDL-C 128 mg/dL
- Lp(a) 310 nmol/L (ULN <75 nmol/L)
- ALT 48 IU/L (ULN 44 IU/L)
- AST 30 IU/L (ULN 40 IU/L)

ARS QUESTION 3

Which of the following statements is not true regarding lipid profiles in the new ACC/AHA guidelines?

a. Not necessary after maximal statin therapy is initiated
b. Should be checked within a few months to assess compliance and response to therapy
c. Values may be used to consider intensifying therapy with lifestyle and drugs
d. In individuals with LDL-C over 190 mg/dL, after ruling out secondary causes should consider FH and screen family members

Case 1, cont.

He says he is compliant and does not miss his medications. He has 4 children and does not know their cholesterol values.

How does this information influence your care of the patient?

What do you do now?

Case 1: Follow-up

After being instructed by you that he should exercise more and lose weight and that there is no evidence for a target LDL-C level anymore or evidence for adding a second drug, he was seen by his family practitioner who ordered some other tests that he is concerned about.

LDL-P	1880 nmol/L
Small LDL-P	1020 nmol/L
Apo B	105 mg/dL
Coronary calcium score	677

ARS QUESTION 4

What is your response to his question as to whether he may benefit from additional therapy?

a. There is evidence that additional therapy may be of benefit
b. There is no evidence to support additional therapy at this time
c. I'm unsure
d. What is LDL-P???????

ARS

ARS QUESTION 5

Do you believe that his lipids are optimally treated?

a. Yes
b. No
c. I am unsure

LDL-C Focused Cardioprotection: What Do Recent Trials and Global Lipid Guidelines Tell Us?

James A. Underberg, MS, MD, FACPM, FACP, FASH, FNLA

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NYU School of Medicine &

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Director, Bellevue Hospital Lipid Clinic,

New York, New York

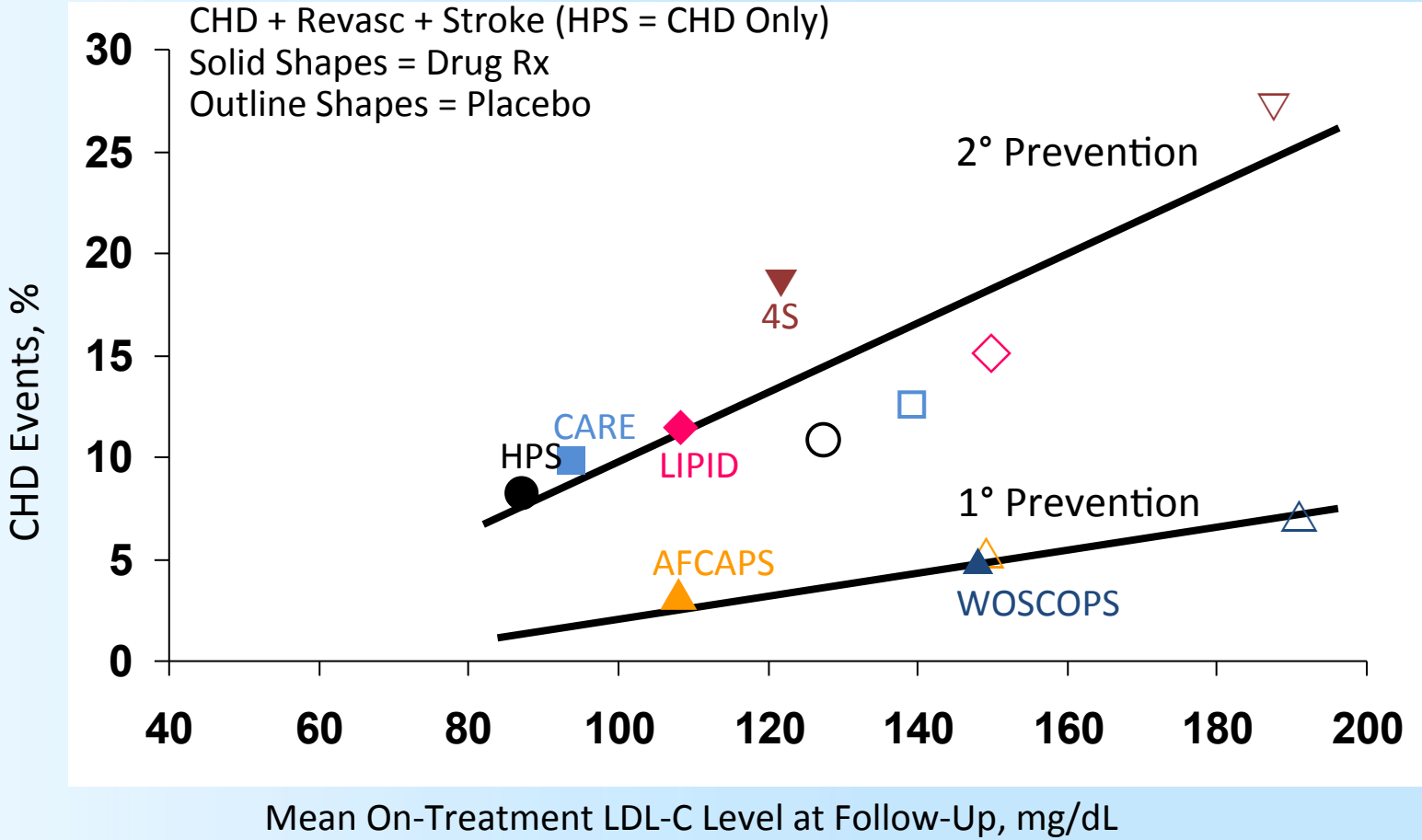
Objectives

- LDL-C and CHD risk
- Guidelines
- Low LDL attainment
- Unmet need

Support for LDL Causality in ASCVD

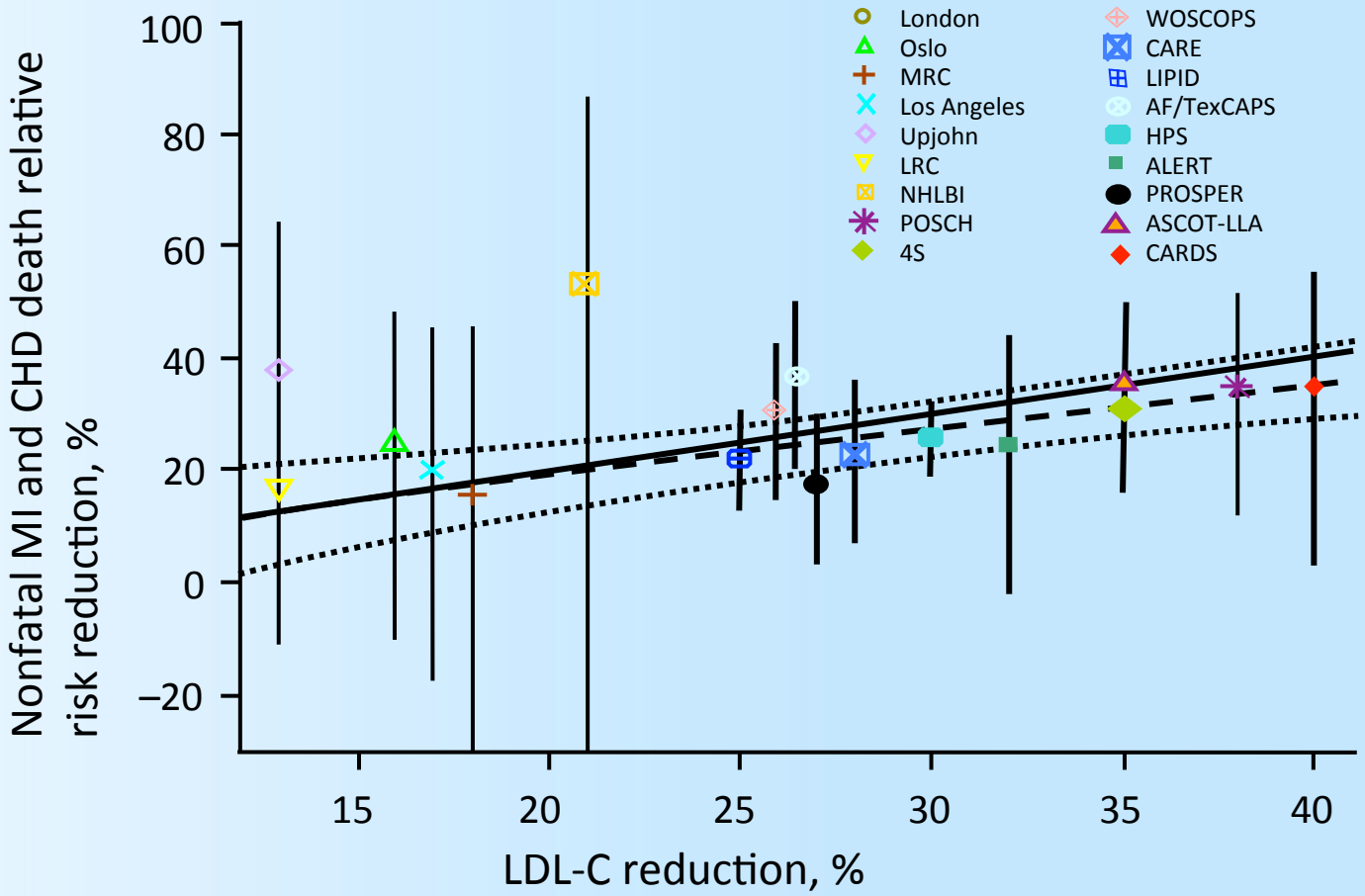
- Observational data
- Interventional data
- Genetic studies
- Conflicting data analysis

LDL-C Levels and CHD Risk



Adapted from Ballantyne. Am J Cardiol, 1998; 82:3Q-12Q
Heart Protection Study Collaborative Group. Lancet. 2002;360:7–22.

Multiple Studies Showed a Relationship Between LDL-C Reduction and CHD Relative Risk

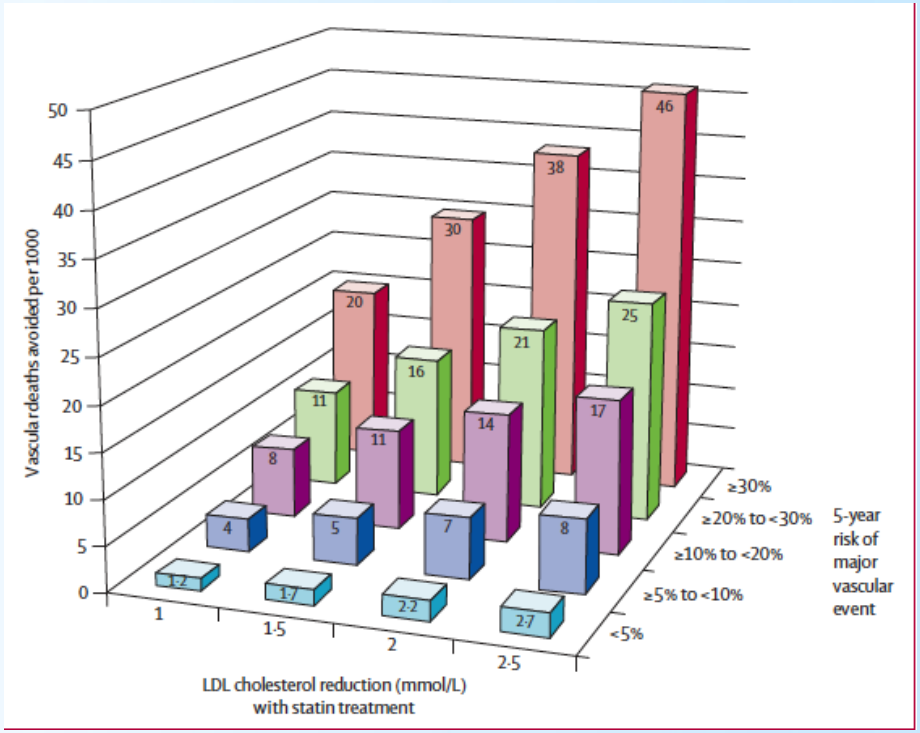


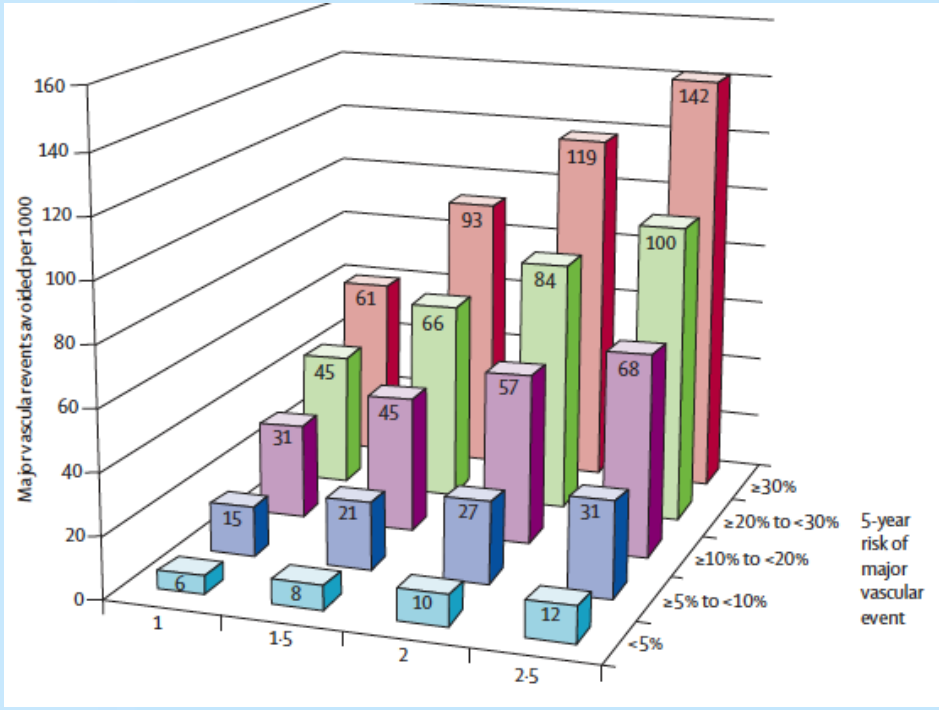
MI = myocardial infarction.

Adapted with permission from Robinson et al. J Am Coll Cardiol. 2005;46:1855–62.

Effects of Lowering LDL-C with Statin Therapy in People at Low Risk of Vascular Disease

Meta-analysis of individual data from 27 randomised trials





Cholesterol Treatment Trialists' (CTT) Collaborators. Lancet 2012;380:581–90.

	Observed MCE event rate (% per annum)*	Observed vascular death rate (% per annum)*	Broad eligibility under current guidelines		
			ATP-III†	ESC task force‡	NICE§
CTT risk category					
<5%	0·2	0·1	×	×	×
≥5% to <10%	0·8	0·3	×	×	×
≥10% to <20%	1·6	1·0	✓	✓	✓
≥20% to <30%	3·2	2·3	✓	✓	✓
≥30%	5·6	5·8	✓	✓	✓

Cholesterol Treatment Trialists' (CTT) Collaborators. Lancet 2012;380:581–90.

Estimate of the Association of Genetically Raised LDL-C or HDL-C and Risk of MI Using Multiple Genetic Variants as Instruments

	Odds ratio (95% CI) per SD increase in plasma lipid based on observational epidemiology*	Odds ratio (95% CI) per SD increase in plasma lipid conferred by genetic score†
LDL cholesterol	1·54 (1·45–1·63)	2·13 (1·69–2·69), $p=2\times10^{-10}$
HDL cholesterol	0·62 (0·58–0·66)	0·93 (0·68–1·26), p=0·63

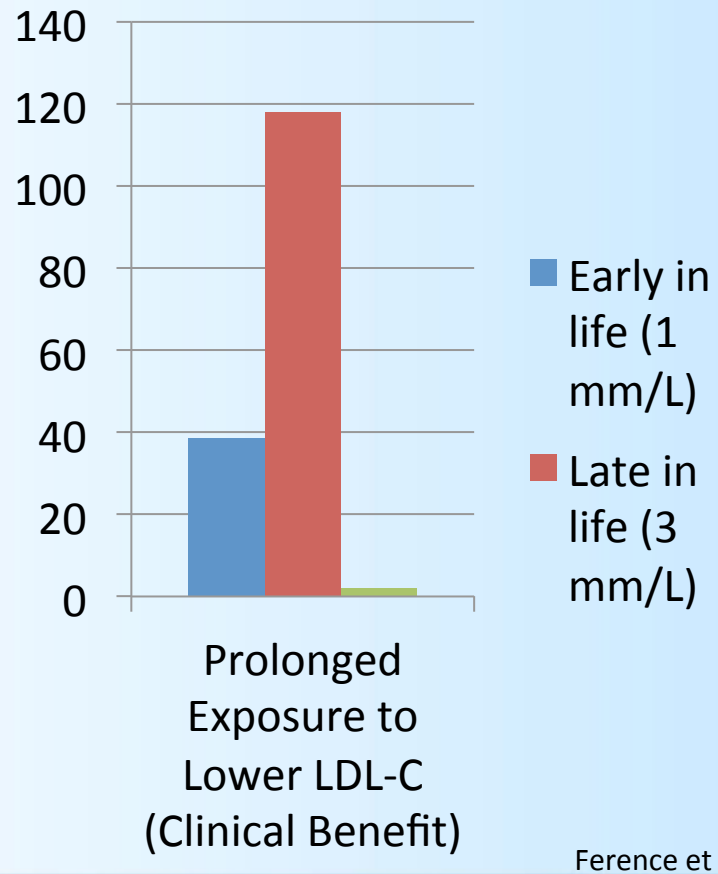
*Observational epidemiology estimates derived from more than 25 000 individuals from prospective cohort studies as shown in the appendix p 22. †LDL genetic score consisting of 13 single nucleotide polymorphisms (SNPs) as shown in the appendix p 27; HDL genetic score consisting of 14 SNPs as shown in the appendix p 28.

Lancet. May 17, 2012 DOI:10.1016/S0140- 6736(12)60312-2

Long-Term Reduction in LDL-C Early in Life

Background: RCTS demonstrate that lowering LDL-C with a statin started in middle and later life reduces the risk of major coronary events, but residual risk persists.

Purpose: To make casual inferences about the association between a biomarker and a disease, to determine if lowering LDL-C earlier (n=326,443) in life, versus later (n+169,183), before the development of atherosclerosis, prevents or delays the progression of coronary atherosclerosis , improving the clinical benefit of therapies that lower LDL-C.



Methods: Mendelian randomized controlled trial (mRCT) to study effects of 9 single-nucleotide polymorphisms (SNPs), or single-letter changes in DNA sequence, that are each associated with lower LDL-C. SNP allocation is determined randomly at conception, inheriting one of them is equal to randomly assigned treatment that lowers LDL-C at birth.

Primary Endpoint: Coronary Heart Disease (CHD): cardiovascular death, MI, coronary revascularization.

Results: All 9 SNPs were associated with a 50-60% reduction in CHD risk for each 1 mmol/L (38.67 mg/dL) lower lifetime exposure to LDL-C.

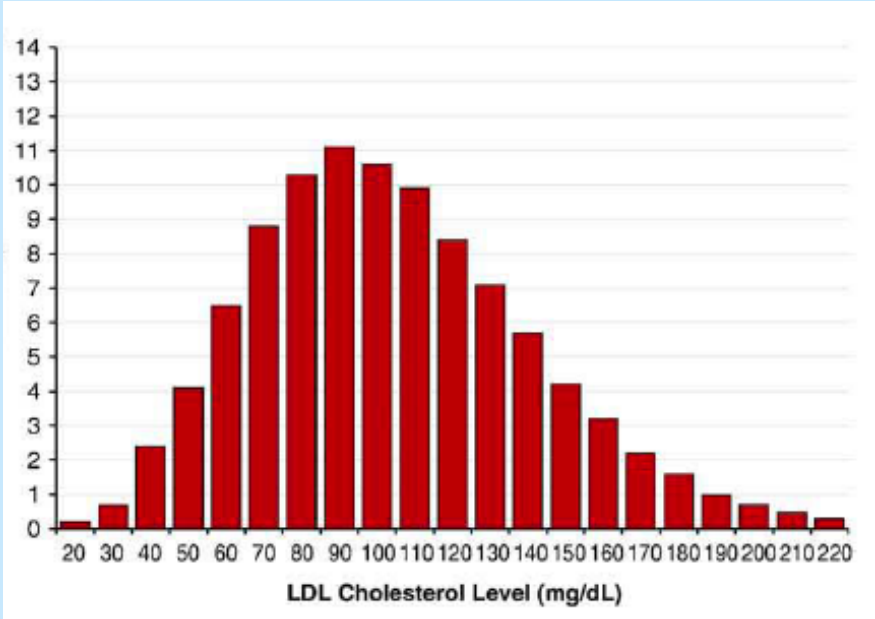
Conclusion: An 80% reduction in CHD risk could occur by lowering LDL by 2 mmol/L (77.34 mg/dL). Focusing on reductions in LDL-C beginning early in life has the potential to substantially reduce CHD burden globally.

Ference et al. J Am Coll Cardiol. 2012;60:2631-9.

Lipid levels in patients hospitalized with coronary artery disease: An analysis of 136,905 hospitalizations in Get With The Guidelines

Amit Sachdeva, MD,[a] Christopher P. Cannon, MD,[b] Prakash C. Deedwania, MD,[c] Kenneth A. LaBresh, MD,[d] Sidney C. Smith, Jr, MD,[e] David Dai, MS,[f] Adrian Hernandez, MD,[f] and Gregg C. Fonarow, MD[a] on behalf of the GWTG Steering Committee and Hospitals *Los Angeles and San Francisco, CA; Boston and Waltham, MA; and Chapel Hill and Durham, NC*

Body mass index (kg/m^2)	28.9
Admission systolic blood pressure (mm Hg)	124.0 ± 20.9
Total cholesterol (mg/dL)	174.4 ± 47.7
LDL cholesterol (mg/dL)	104.9 ± 39.8
HDL cholesterol (mg/dL)	39.7 ± 13.2
Triglycerides (mg/dL)	161 ± 128



Alonso et al. Am Heart J 2009;157:111-7.

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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Review of Clinical Practice Guidelines for the Management of LDL-Related Risk

Pamela B. Morris, MD,* Christie M. Ballantyne, MD,† Kim K. Birtcher, MS, PharmD, CDE, BCPS,‡
Steven P. Dunn, PharmD, BCPS,§ Elaine M. Urbina, MD, MS‖

Morris et al. J Am Coll Cardiol 2014;64:196–206.

SOURCE	Recommended Lipoprotein Measurements for Risk Assessment	Recommended Lipoprotein Targets of Therapy	Recommended Risk Assessment Algorithm
National Cholesterol Education Program Adult Treatment Panel III[7,8]	Fasting lipid panel Calculation of non-HDL-C when TG >200 mg/dl	Primary target: LDL-C Secondary target: non-HDL-C	Identify number of CHD risk factors Framingham 10-year absolute CHD risk
International Atherosclerosis Society[16]	Fasting lipid panel with calculation of non-HDL-C	Non-HDL-C LDL-C is considered alternative target of therapy	Lifetime risk of total ASCVD morbidity/mortality (by Framingham, CV Lifetime Risk Pooling Project, or QRISK)
European Society of Cardiology/European Atherosclerosis Society[22]	Fasting lipid panel with calculation of non-HDL-C and TC/HDL-C ratio apoB or apoB/apoA1 ratio are considered alternative risk markers	Primary target: LDL-C Secondary targets: non-HDL-C or apoB in patients with cardiometabolic risk	10-year total fatal ASCVD risk by the Systematic Coronary Risk Evaluation (SCORE) system
Canadian Cardiovascular Society[27]	Fasting lipid panel with calculation of non-HDL-C apoB considered alternative marker of risk	Primary target: LDL-C Secondary targets: non-HDL-C and apoB	10-year risk of total ASCVD events by the Framingham Risk Score
American Association of Clinical Endocrinologists[31]	Fasting lipid panel Calculation of non-HDL-C more accurate risk assessment if TG in between 200–500 mg/dl, diabetes, insulin resistance, or established CAD	Primary target: LDL-C Secondary targets: non-HDL- in patients with cardiometabolic risk or established CAD apoB recommended to assess success of LDL-C-lowering therapy	Men: Framingham Risk Score 10-year risk of coronary event Women: Reynolds Risk Score (10-year risk of coronary event, stroke, or other major heart disease)
American Diabetes Association/ American Heart Association Statement on Cardiometabolic Risk[34]	Stronger risk discrimination provided by non-HDL-C, apoB, LDL-P	Strong recommendation for apoB and non-HDL-C as secondary targets	30-year/lifetime global ASCVD risk
American Diabetes Association: Standards of Medical Care in Diabetes[39]	Fasting lipid panel	LDL-C	Not applicable in setting of diabetes (CHD risk equivalent)

Morris et al. J Am Coll Cardiol 2014;64:196–206.

SOURCE	Recommended Lipoprotein Measurements for Risk Assessment	Recommended Lipoprotein Targets of Therapy	Recommended Risk Assessment Algorithm
Kidney Disease: Improving Global Outcomes: Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease[41]	Fasting lipid panel to screen for more severe forms of dyslipidemia and secondary causes of dyslipidemia	None: therapy guided by absolute risk of coronary event based on age, Stage of CKD or eGFR	CKD considered CHD risk equivalent Treatment with evidence-based statins/statin doses based on age, Stage of CKD or eGFR
Secondary Prevention of Atherosclerotic Cardiovascular Disease in Older Adults: A Scientific Statement from the American Heart Association[36]	Fasting lipid panel Calculation of non-HDL-C when TG >200 mg/dl	Primary target: LDL-C Secondary target: non-HDL-C	N/A
National Lipid Association: Familial Hypercholesterolemia[40]	Fasting lipid panel	LDL-C	Not applicable due to extremely high lifetime risk
Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents[34,35]	Fasting lipid panel with calculation of non-HDL-C	Primary target: LDL-C Secondary target: non-HDL-C	No risk algorithm, treatment based on number of ASCVD risk factors
AHA Women's Cardiovascular Disease Prevention Guidelines[37]	Fasting lipid panel Consider hs-CRP in women >60 years and CHD risk >10%	LDL-C	Updated Framingham risk profile (coronary, cerebrovascular, and peripheral arterial disease and heart failure events) Reynolds Risk Score (10-year risk of coronary event, stroke, or other major heart disease)
2013 American College of Cardiology/American Heart Association: Blood Cholesterol Guidelines for ASCVD Prevention[50]	Fasting lipid panel to screen for more severe forms of dyslipidemia and secondary causes of dyslipidemia	LDL-C measured for assessment of therapeutic response and compliance Therapy guided by identification of 4 categories of patients who benefit from high or moderate-dose statin therapy	CV Risk Calculator based on Pooled Risk Equations (10-year risk of total ASCVD events) Lifetime risk provided for individuals 20–59 years of age

Morris et al. J Am Coll Cardiol 2014;64:196–206.

REVIEW

CLINICIAN'S CORNER

Association of LDL Cholesterol, Non–HDL Cholesterol, and Apolipoprotein B Levels With Risk of Cardiovascular Events Among Patients Treated With Statins

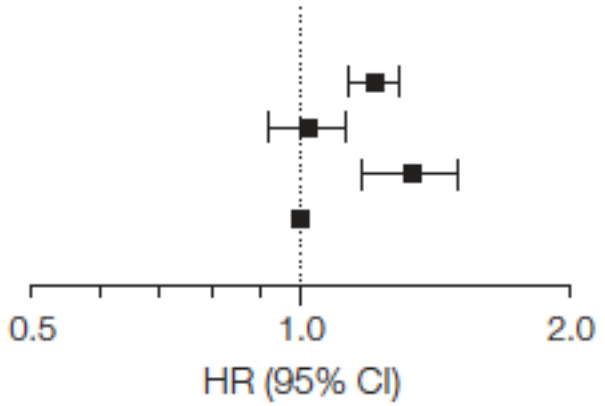
A Meta-analysis

Conclusion Among statin-treated patients, on-treatment levels of LDL-C, non–HDL-C, and apoB were each associated with risk of future major cardiovascular events, but the strength of this association was greater for non–HDL-C than for LDL-C and apoB.

Boekholdt et al. JAMA. 2012;307:1302-09.

Non-HDL-C vs LDL-C

Target Level		No. of Major Cardiovascular Events	Total No. of Participants	HR (95% CI)
LDL-C	Non–HDL-C			
≥100 mg/dL	≥130 mg/dL	1877	10419	1.21 (1.13-1.29)
≥100 mg/dL	<130 mg/dL	467	2873	1.02 (0.92-1.12)
<100 mg/dL	≥130 mg/dL	283	1435	1.32 (1.17-1.50)
<100 mg/dL	<130 mg/dL	2760	23426	1.00 [Reference]



Boekholdt et al. JAMA. 2012;307:1302-09.

Journal of Clinical Lipidology (2014) 8, 473–488

Journal of Clinical Lipidology

Original Articles

National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1 – executive summary☆

Terry A. Jacobson, MD*, Matthew K. Ito, PharmD, Kevin C. Maki, PhD, Carl E. Orringer, MD, Harold E. Bays, MD, Peter H. Jones, MD, James M. McKenney, PharmD, Scott M. Grundy, MD, PhD, Edward A. Gill, MD, Robert A. Wild, MD, PhD, Don P. Wilson, MD, W. Virgil Brown, MD

Jacobson et al. J Clin Lipidol 2014;8:473-88.

Criteria for ASCVD Risk Assessment, Treatment Goals, Levels at Which to Consider Drug Therapy

Risk Category	Criteria	Treatment Goal	Consider Drug Therapy
		Non-HDL-C mg/dL LDL-C mg/dL	
Low	▪ 0-1 major ASCVD risk factors ▪ Consider other risk indicators, if known	<130 <100	≥190 ≥160
Moderate	▪ 2 major ASCVD risk factors ▪ Consider quantitative risk scoring ▪ Consider other risk indicators	<130 <100	≥160 ≥130

High	▪ ≥3 major ASCVD risk factors
	▪ Diabetes mellitus* (Type 1 or 2)
	  ▪ 0-1 other major ASCVD risk factors, and
	  ▪ No evidence of end organ damage
	▪ Chronic kidney disease Stage 3B or 4
	▪ LDL-C ≥190 mg/dL (severe hypercholesterolemia)
	▪ Quantitative risk score reaching the high risk threshold
		<130
		<100
			≥130
			≥100

Very High	▪ ASCVD*
	▪ Diabetes mellitus* (Type 1 or 2)
	  ▪ ≥2 other major ASCVD risk factors or
	  ▪ Evidence of end organ damage
		<100
		<70
			≥100
			≥70

****For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate or high intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.***

Jacobson et al. J Clin Lipidol 2014;8:473-88.

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Very Low Levels of Atherogenic Lipoproteins and the Risk for Cardiovascular Events

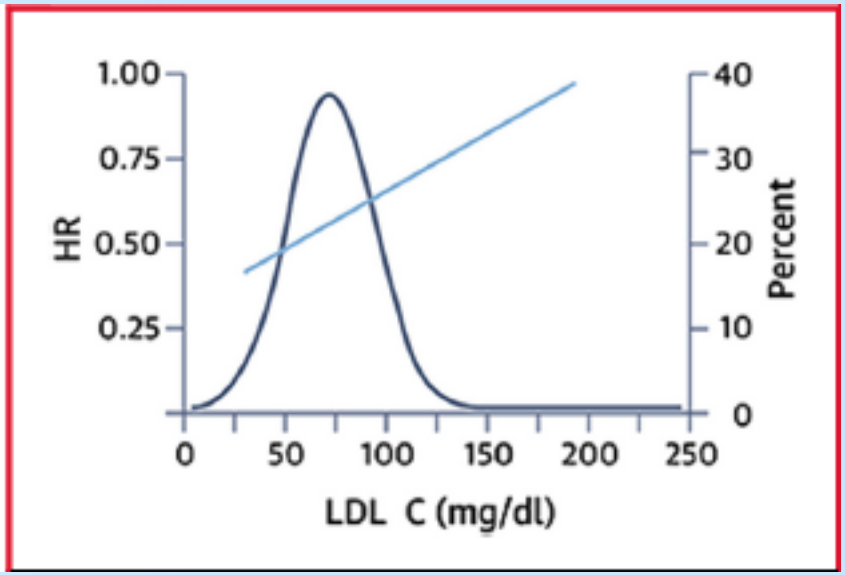
A Meta-Analysis of Statin Trials

S. Matthijs Boekholdt, MD, PhD,* G. Kees Hovingh, MD, PhD,† Samia Mora, MD, MHS,‡ Benoit J. Arsenault, PhD,† Pierre Amarenco, MD,§ Terje R. Pedersen, MD, PhD,‖ John C. LaRosa, MD,¶ David D. Waters, MD,# David A. DeMicco, DPharm,** R. John Simes, MD,†† Antony C. Keech, MBBS, MSc,†† David Colquhoun, MD,‡‡ Graham A. Hitman, MD,§§ D. John Betteridge, MD,‖‖ Michael B. Clearfield, DO,¶¶ John R. Downs, MD,##*** Helen M. Colhoun, MD,††† Antonio M. Gotto, Jr, MD, DPhil,‡‡‡ Paul M. Ridker, MD, MPH,‡ Scott M. Grundy, MD, PhD,§§§ John J.P. Kastelein, MD, PhD†

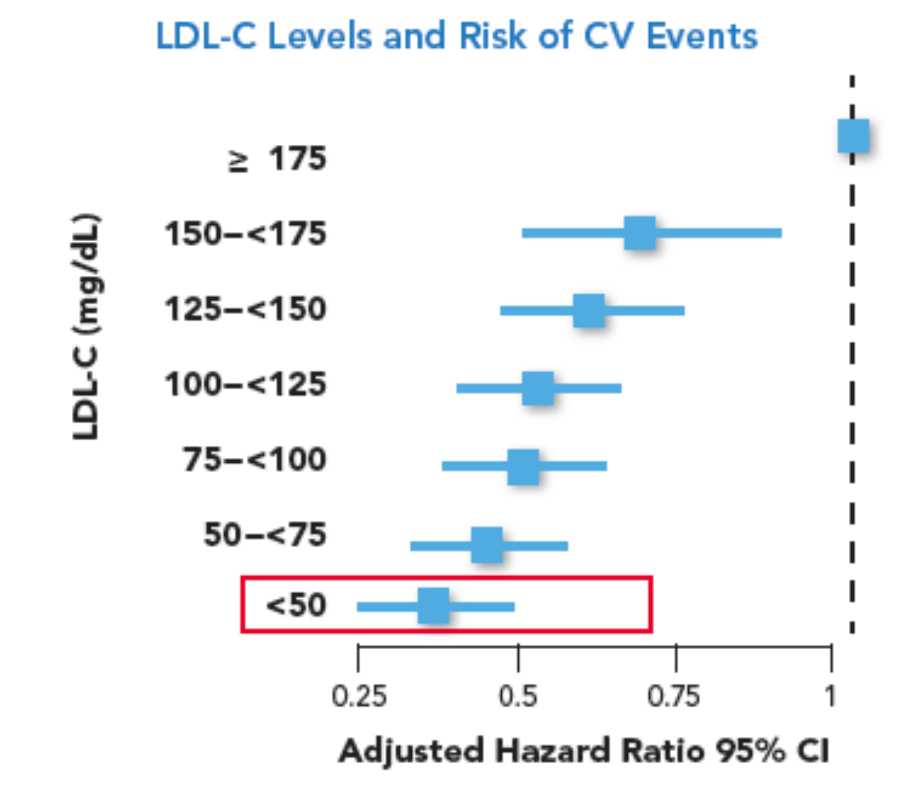
Boekholdt et al. J Am Coll Cardiol 2014;64:485–94.

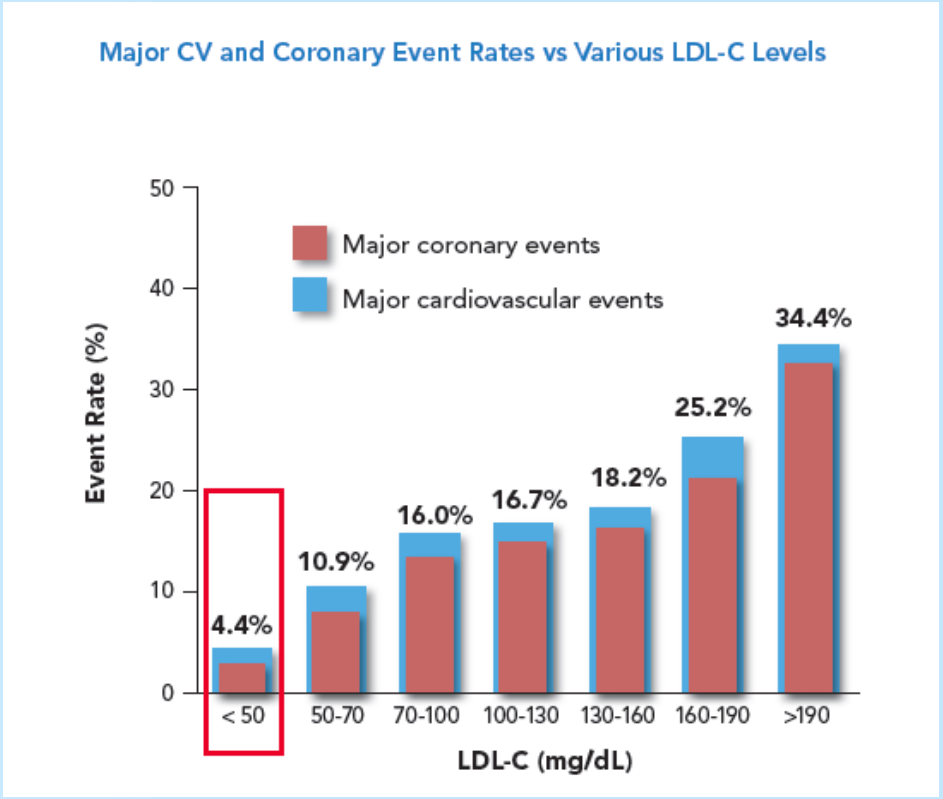
CONCLUSIONS The reductions of LDL-C, non-HDL-C, and apoB levels achieved with statin therapy displayed large interindividual variation. Among trial participants treated with high-dose statin therapy, >40% did not reach an LDL-C target <70 mg/dl. Patients who achieve very low LDL-C levels have a lower 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 et al. J Am Coll Cardiol 2014;64:485–94.





Boekholdt et al. J Am Coll Cardiol 2014;64:485–94.

Non-HDL Cholesterol

TABLE 2 Risk for Major Cardiovascular Events, by Achieved Non-HDL-C Concentration

	Achieved On-Trial Non-HDL-C Concentration, mg/dl (mmol/l)						
	<75 (<1.94) (n = 6,341)	75–<100 (1.94–<2.58) (n = 8,318)	100–<125 (2.58–<3.23) (n = 9,764)	125–<150 (3.23–<3.88) (n = 7,956)	150–<175 (3.88–<4.52) (n = 3,992)	175–<200 (4.52–<5.17) (n = 1,178)	≥200 (≥5.17) (n = 604)
Major cardiovascular events	390 (6.2)	970 (11.7)	1,555 (15.9)	1,349 (17.0)	697 (17.5)	259 (22.0)	167 (27.6)
Unadjusted HR (95% CI)	0.31 (0.26–0.38)	0.48 (0.41–0.57)	0.59 (0.50–0.69)	0.60 (0.51–0.71)	0.61 (0.52–0.72)	0.80 (0.66–0.97)	1.00 (ref)
Adjusted HR (95% CI)*	0.57 (0.47–0.69)	0.60 (0.51–0.71)	0.64 (0.54–0.75)	0.69 (0.59–0.81)	0.75 (0.63–0.89)	0.89 (0.73–1.08)	1.00 (ref)
Major coronary events	260 (4.1)	760 (9.1)	1,338 (13.7)	1,220 (15.3)	627 (15.7)	232 (19.7)	146 (24.2)
Unadjusted HR (95% CI)	0.24 (0.20–0.29)	0.44 (0.37–0.52)	0.59 (0.49–0.69)	0.63 (0.53–0.75)	0.64 (0.53–0.76)	0.82 (0.67–1.01)	1.00 (ref)
Adjusted HR (95% CI)*	0.58 (0.47–0.72)	0.61 (0.51–0.73)	0.66 (0.56–0.79)	0.73 (0.62–0.87)	0.79 (0.66–0.94)	0.94 (0.76–1.15)	1.00 (ref)
Major cerebrovascular events	145 (2.3)	246 (3.0)	278 (2.8)	191 (2.4)	100 (2.5)	38 (3.2)	31 (5.1)
Unadjusted HR (95% CI)	0.72 (0.49–1.06)	0.71 (0.49–1.03)	0.59 (0.41–0.86)	0.47 (0.33–0.69)	0.49 (0.33–0.73)	0.64 (0.40–1.02)	1.00 (ref)
Adjusted HR (95% CI)*	0.49 (0.33–0.73)	0.55 (0.37–0.80)	0.54 (0.37–0.79)	0.54 (0.37–0.79)	0.59 (0.40–0.89)	0.68 (0.42–1.10)	1.00 (ref)

Values are n (%) unless otherwise indicated. *Adjusted for sex, age, smoking status, presence of diabetes mellitus, systolic blood pressure, high-density lipoprotein cholesterol (HDL-C) concentration, and trial. The highest non-HDL-C category was used as the reference category.

Abbreviations as in Table 1.

Boekholdt et al. J Am Coll Cardiol 2014;64:485–94.

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

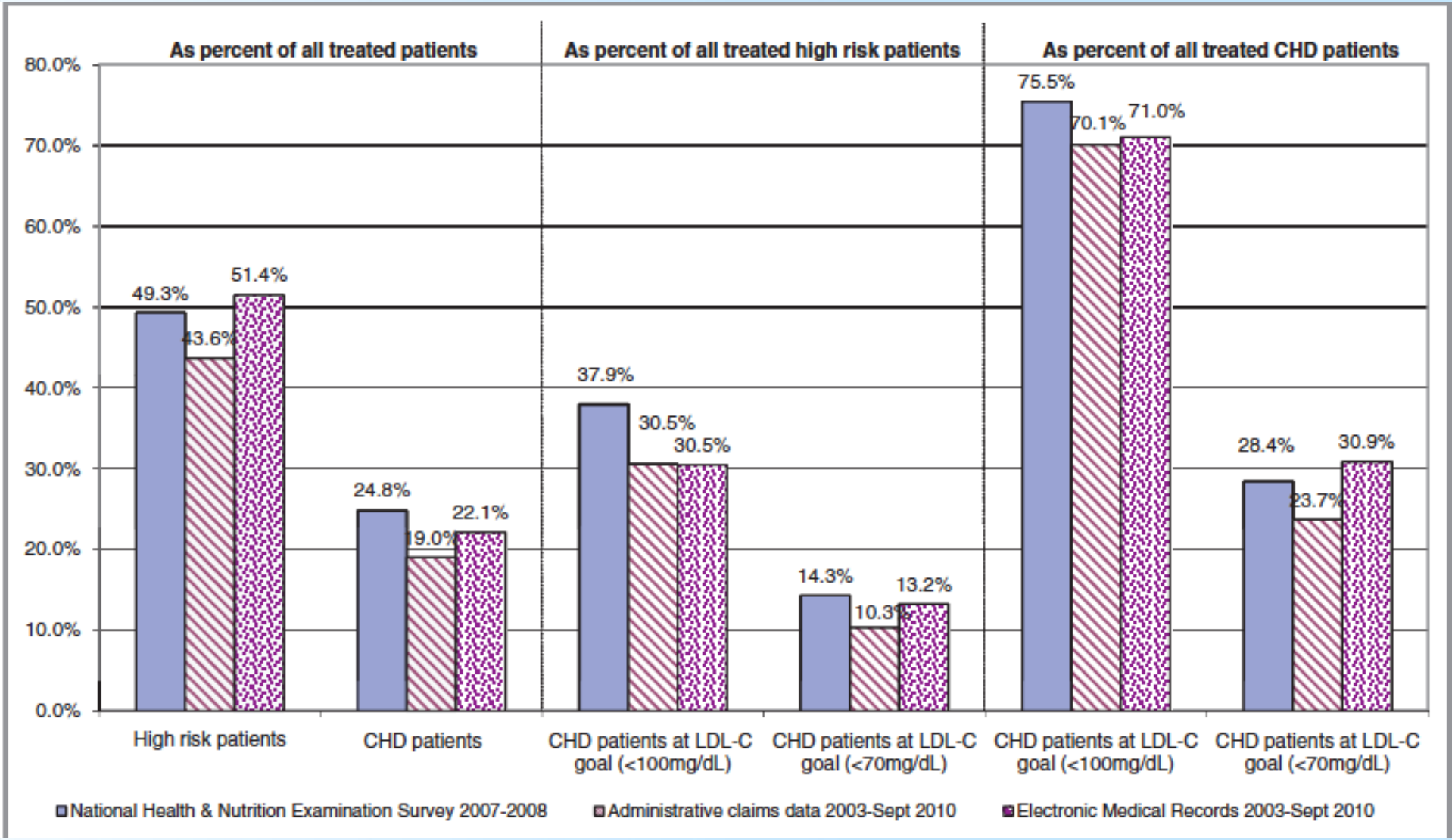
Prevalence of Dyslipidemia and Lipid Goal Attainment in Statin-Treated Subjects From 3 Data Sources: A Retrospective Analysis

Peter H. Jones, MD; Radhika Nair, PhD; Kamlesh M. Thakker, PhD, MBA

Conclusions—Across the 3 data sources, there was consistency in the proportion of high-risk patients treated with statin monotherapy who were at LDL-C goal. A significant number of these statin-treated patients had additional dyslipidemias.

Jones et al. J Am Heart Assoc. 2012; doi: 10.1161/JAHA.112.001800

Treated CHD Patients Achieving LDL-C <100 mg/dL and <70 mg/dL in 3 Data Sources



Jones et al. J Am Heart Assoc. 2012; doi: 10.1161/JAHA.112.001800.

USAGE Survey Respondents
Statin Use and Cholesterol Levels

- Average age of statin initiation: 50 years
- All survey participants had received ≥1 statin prescription
- Current (persisting) statin users—88%
- Discontinued statins altogether (non-persistent)—12%
- Generic statin use
  - 63% of current users
  - 45% of those who discontinued
- Adherence: 82% reported missing ≤1dose/month
- Total cholesterol levels (latest, by self-report):
  - Current users—173 mg/dL
  - Former users—223 mg/dL

statinUSAGE™
Understanding Statin use in America and Opportunities for Education

Cohen et al. J Clin Lipidol. 2012;6:208-15.

Key Finding: Side Effects were Common and the Leading Reason for Statin Discontinuation

Among the 12% who **discontinued**

- Reasons for discontinuing:
  - **Side-effects—62%**
  - Cost—17%
  - Lack of cholesterol lowering—12%
- When/how they stopped:
  - 57% stopped after a side effect (no further Rx fill)
  - One-third stopped **without** asking or telling their healthcare provider, however
  - 32% reported being told they had high risk of CHD w/o a statin
- Statin switches (for side effects): average two statins tried before stopping

statinUSAGE™

Cohen et al. J Clin Lipidol. 2012;6:208-15.

Annals of Internal Medicine | Review

Effectiveness of Combination Therapy With Statin and Another Lipid-Modifying Agent Compared With Intensified Statin Monotherapy

A Systematic Review

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Conclusion : "Clinicians could consider using lower-intensity statin combined with bile acid sequestrant or ezetimibe among high-risk patients intolerant of or unresponsive to statins; however, this strategy should be used with caution given the lack of evidence on long-term clinical benefits and harms."

Gudzune et al. Ann Intern Med. 2014;160:468-76.

NLA Recommendations on Combination Rx

- Combination therapy with a statin plus a second (or third) agent may be considered for patients who have not reached their treatment goals for atherogenic cholesterol levels, particularly in those at high and very high risk. Generally, the maximally tolerated statin dose should be used before add-on therapy is considered.
- For patients with statin intolerance, reducing the dose of statin, switching to a different statin, and alternate regimens such as every other day statin dosing may be considered.
- For patients who cannot tolerate a statin using the above strategies, alternate agents alone or in combination may be considered.

Jacobson. J Clin Lipidol. 2014;8:473-88.

Conclusions

- LDL-C remains a central factor in ASCVD
- Patients with lifetime low LDL-C are at low risk for ASCVD
- Low LDL-C can associate with metabolic syndrome and increased ASCVD risk
- Additional markers of LDL-related risk such as non-HDLC and Apolipoprotein B may better represent ASCVD risk in some populations
- High-risk patients remain untreated to LDL goals for many reasons including statin intolerance
- Alternative LDL-lowering therapies may represent an additional option to ASCVD risk reduction

Translating Genetic Discoveries into Novel Targets for Lipid Management

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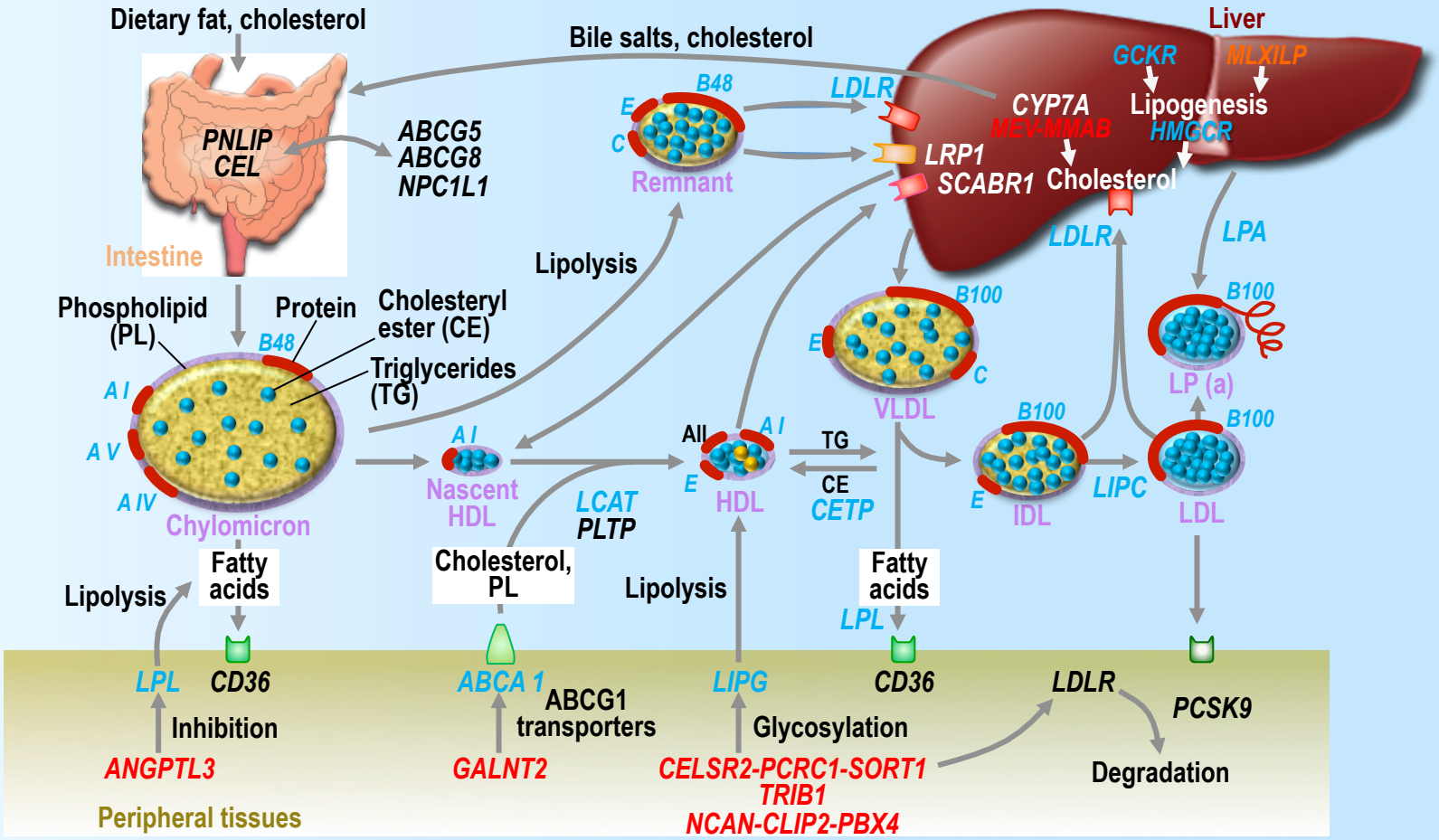
A Treasure Trove of Information for Lipoprotein Biology



Adapted from Lusis et al. Nat Genet. 2008;40:129-30.

Genome Wide Association Study (GWAS) in >100,000 Individuals of European Ancestry

- In 2010, 95 loci across the human genome were reported to harbor common variants associated with plasma lipid traits

LDL-C (newly identified loci in red)			HDL-C			Triglycerides	
ABCG5/8	HFE	SORT1	ABCA1	HNF4A	PDE3A		
ABO	HMGCR	ST3GAL4	ABCA8	IRS1	PGS1		GCKR
ANGPTL3	HNF1A	TIMD4		KLF14	PLTP	ANGPTL3	IRS1
APOA	HPR	TOP1	ANGPTL4	LACTB	PPP1R3B	ANKRD55	JMJD1C
APOB		TRIB1	APOA	LCAT	SBNO1	APOA	LIPC
APOE	IRF2BP2		APOB	LILRA/B	SCARB1	APOB	LPL
BRAP	LDLR		APOE	LIPC	SLC39A8	APOE	LRP1
	LDLRAP1		ARL15	LIPG	STARD3		MLXIPL
	LPA		C6orf106	LPA	TRIB1	CAPN3	MSL2L1
CETP	MAFB		CETP	LPL	TRPS1	CETP	NAT2
CILP2	MOSC1		CITED2	LRP1	TTC39B	CILP2	PINX1
CYP7A1	NPC1L1		CMIP	LRP4	UBASH3B	COBLL1	PLA2G6
DNAH11	OSBPL7		COBLL1		UBE2L3	CTF1	PLTP
FADS	PCSK9			MC4R	ZNF648	CYP26A1	TIMD4
FRK	PLEC1		FADS	MLXIPL	ZNF664	FADS	TRIB1
GPAM	PPP1R3B		GALNT2	MMAB			TYW1B
							ZNF664

Total Cholesterol				
ERGIC3	EVI5	RAB3GAP1	RAF1	SPTY2D1

Teslovich et al. Nature. 2010;466:707-13.

Note, the loci shown may have different traits associated with them, and therefore may appear in more than one category for LDL-C, HDL-C, Triglycerides, and Total Cholesterol.

GWAS Lipid Loci: Known Lipid Genes

- These 95 loci include all of the 36 loci previously reported by GWAS at genome-wide significance

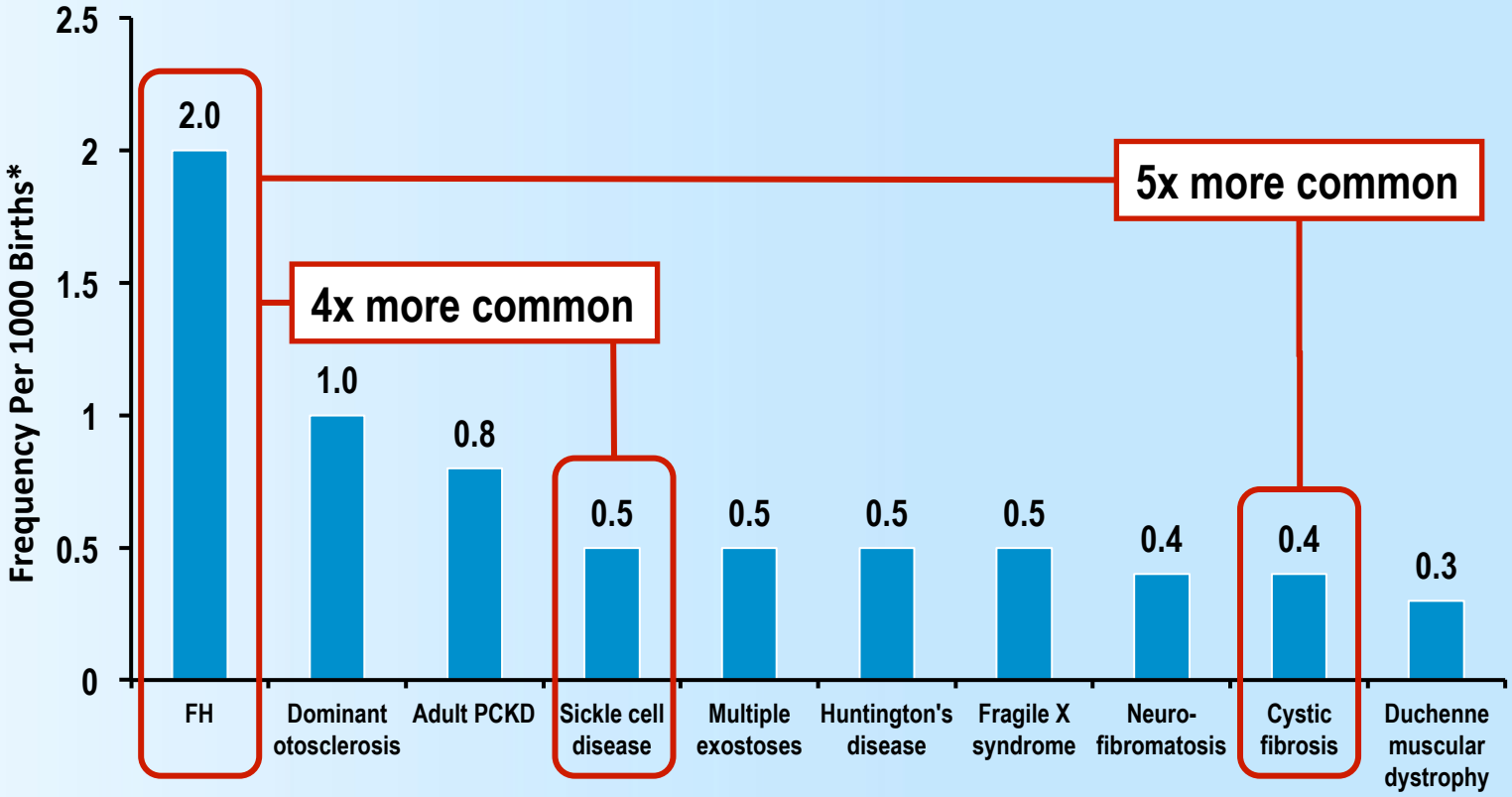
LDL-C (newly identified loci in red)			HDL-C			Triglycerides	
ABCG5/8	HFE	SORT1	ABCA1	HNF4A	PDE3A		
ABO	HMGCR	ST3GAL4	ABCA8	IRS1	PGS1		GCKR
ANGPTL3	HNF1A	TIMD4		KLF14	PLTP	ANGPTL3	IRS1
APOA	HPR	TOP1	ANGPTL4	LACTB	PPP1R3B	ANKRD55	JMJD1C
APOB		TRIB1	APOA	LCAT	SBNO1	APOA	LIPC
APOE	IRF2BP2		APOB	LILRA/B	SCARB1	APOB	LPL
BRAP	LDLR		APOE	LIPC	SLC39A8	APOE	LRP1
	LDLRAP1		ARL15	LIPG	STARD3		MLXIPL
	LPA		C6orf106	LPA	TRIB1	CAPN3	MSL2L1
CETP	MAFB		CETP	LPL	TRPS1	CETP	NAT2
CILP2	MOSC1		CITED2	LRP1	TTC39B	CILP2	PINX1
CYP7A1	NPC1L1		CMIP	LRP4	UBASH3B	COBLL1	PLA2G6
DNAH11	OSBPL7		COBLL1		UBE2L3	CTF1	PLTP
FADS	PCSK9			MC4R	ZNF648	CYP26A1	TIMD4
FRK	PLEC1		FADS	MLXIPL	ZNF664	FADS	TRIB1
GPAM	PPP1R3B		GALNT2	MMAB			TYW1B
							ZNF664

Total Cholesterol				
ERGIC3	EVI5	RAB3GAP1	RAF1	SPTY2D1

Note, the loci shown may have different traits associated with them, and therefore may appear in more than one category for LDL-C, HDL-C, Triglycerides, and Total Cholesterol.

Teslovich et al. Nature. 2010;466:707-13.

Familial Hypercholesterolemia (FH): Most Common of Inherited Disorders



*UK population

Familial combined hyperlipidemia has a frequency of 1:200 births.

Sickle cell disease varies greatly by ethnicity. PCKD = polycystic kidney disease.

Genetic Alliance UK. Available at: http://www.geneticalliance.org.uk/education3.htm; Streetly et al. *J Clin Pathol*. 2010;63:626-29.

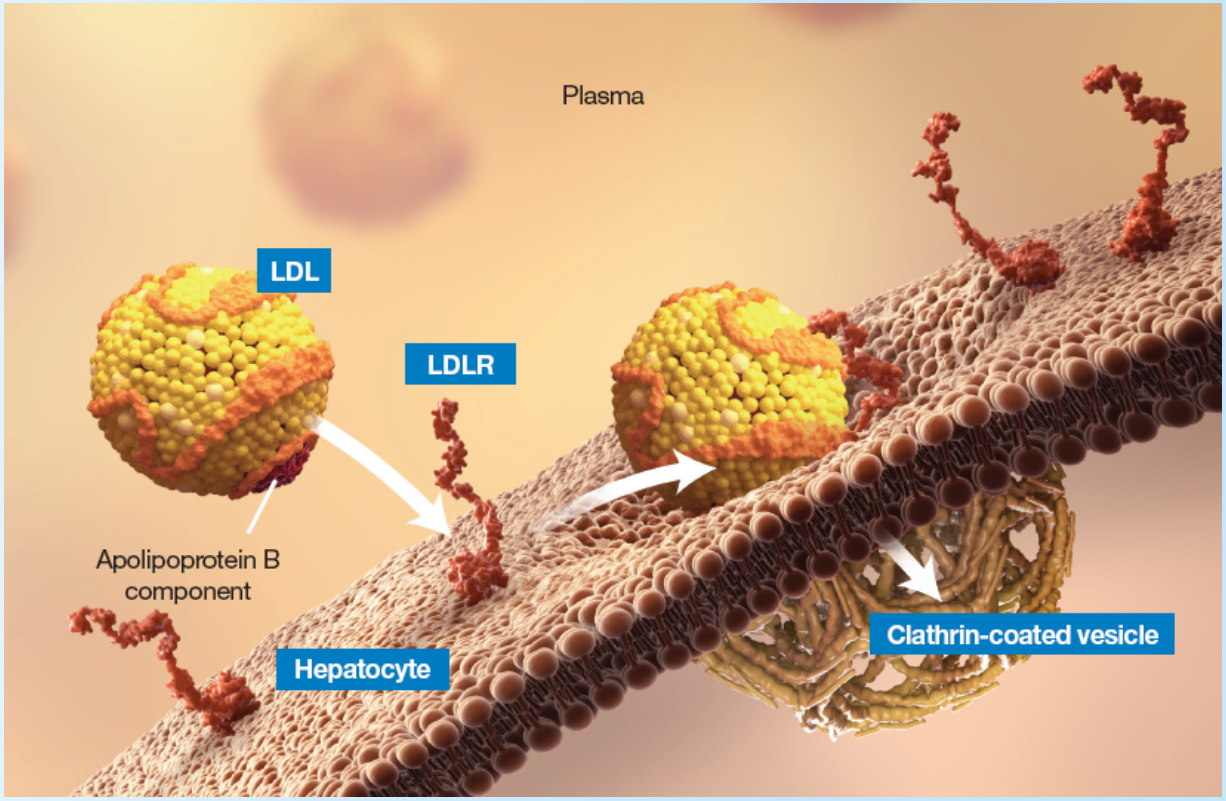
Introduction: Autosomal Dominant Hypercholesterolemia (ADH)

- Familial hypercholesterolemia (FH) is the most common form of ADH[1]
- Characterized by[2]
  - Severely elevated LDL-C levels
  - Enhanced atherosclerosis progression
  - Premature CV events
- Prior to 2003, mutations in 2 genes were identified as being associated with ADH[3]
  - Low-density lipoprotein receptor (*LDL-R*)
  - Apolipoprotein B (*apoB*)
- Mutations in proprotein convertase subtilisin/kexin type 9 (*PCSK9*) were also identified as being associated with ADH[3]

LDL = low-density lipoprotein.

1. Abifadel et al. In: Toth PP. The Year in Lipid Disorders. Vol. 2. Oxford, UK: Atlas Medical Publishing Ltd. 2010:3-23. 2. van der Graaf et al. Circulation. 2011;123:1167-73. 3. Abifadel et al. Nat Genet. 2003;34:154-56.

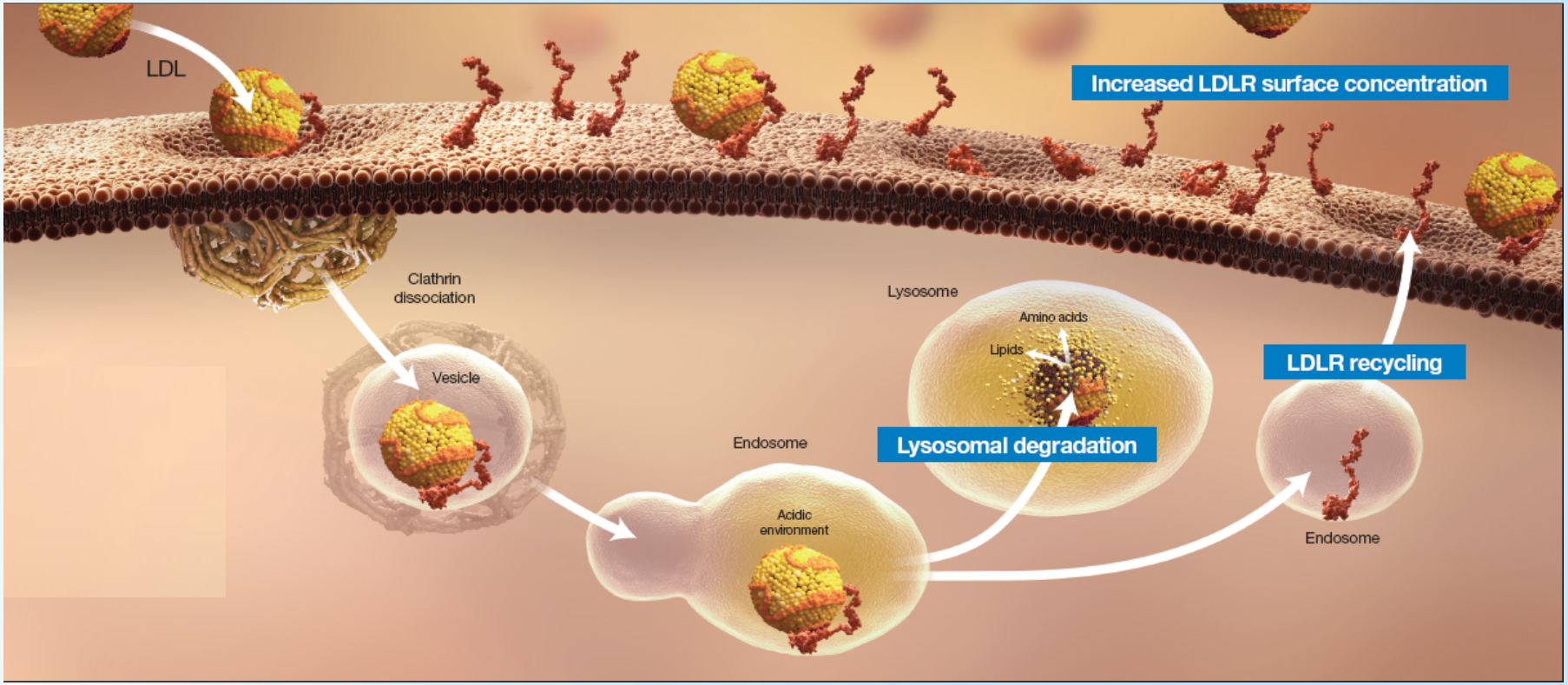
Hepatic LDL-Rs Play a Central Role in Cholesterol Homeostasis



- 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 et al. Proc Natl Acad Sci USA. 1979;76:3330-37. **2.** Goldstein et al. Arterioscler Thromb Vasc Biol. 2009;29:431-38. **3.** Brown et al. J Lipid Res. 2009;50:S15-S27. **4.** Brown et al. Science. 1986;232:34-47. **5.** Steinberg et al. Proc Natl Acad Sci USA. 2009;106:9546-47.

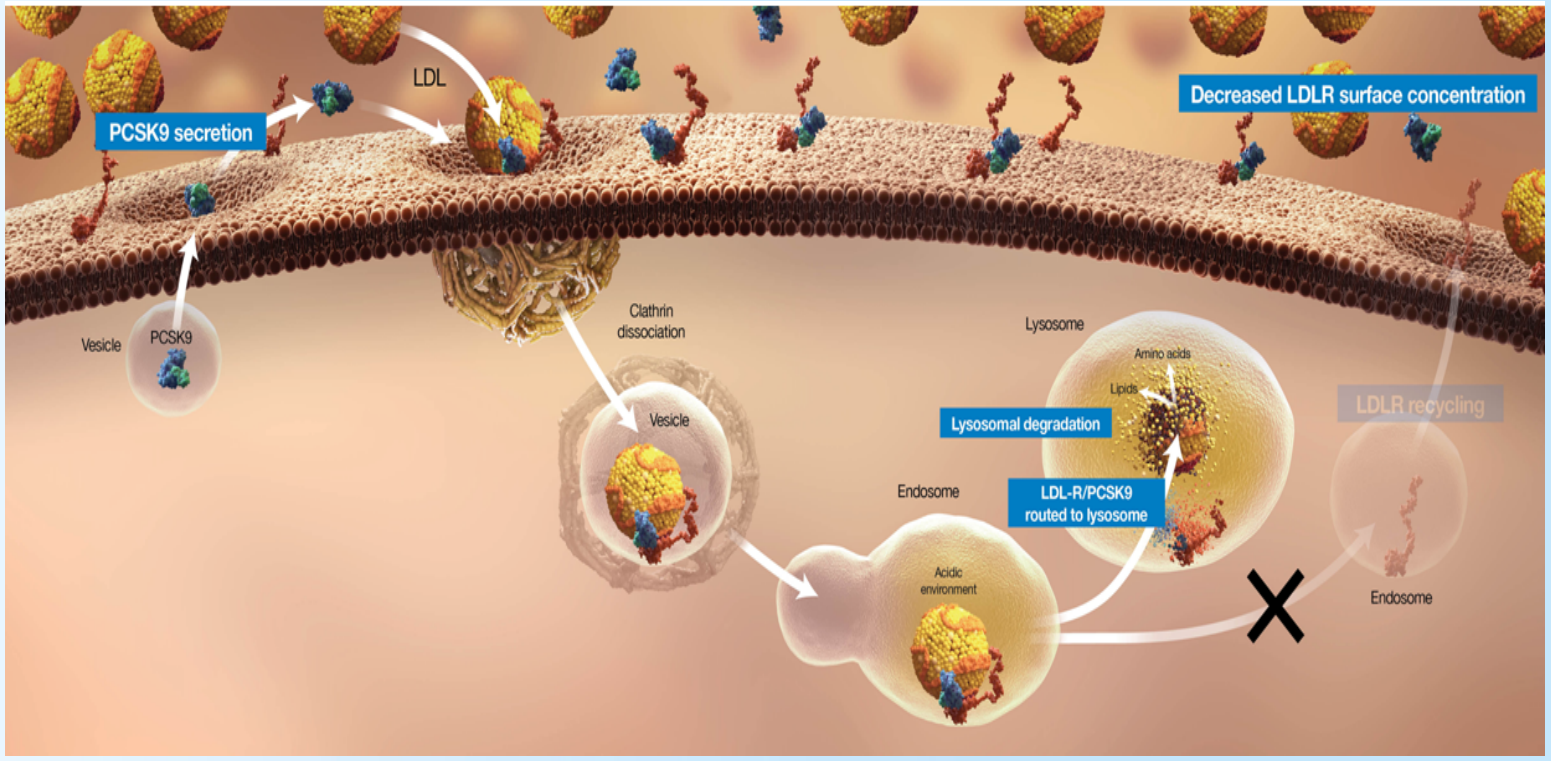
Recycling of LDL-Rs Enables Efficient Clearance of LDL Particles



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

Goldstein et al. Arterioscler Thromb Vasc Biol. 2009;29:431-38. Brown et al. Science. 1986;232:34-47. Steinberg et al. Proc Natl Acad Sci USA. 2009;106:9546-47. Brown et al. Proc Natl Acad Sci USA. 1979;76:3330-37.

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Is a Key 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 et al. J Lipid Res. 2009;50:S172-S177. Qian et al. J Lipid Res. 2007;48:1488-1498. Zhang et al. J Biol Chem. 2007;282:18602-12. **4.** Lopez. Biochim Biophys Acta. 2008;1781:184-91.

Plasma PCSK9 Highly Correlates With Demographic and Metabolic Parameters in a Large Multiethnic Population

Correlation Among Clinical Parameters and Plasma PCSK9 Levels

Parameter	All	*P* Value	Women	*P* Value	Men	*P* Value
Age (y)	0.18	< 0.0001	0.2	< 0.0001	0.008	0.75
BMI (kg/m^2)	0.12	< 0.0001	0.13	< 0.0001	0.05	0.1
Systolic BP (mm Hg)	0.07	0.0001	0.15	< 0.0001	0.02	0.44
Diastolic BP (mm Hg)	0.08	< 0.0001	0.16	< 0.0001	0.04	0.1
LDL-C (mg/dL)	**0.24**	**< 0.0001**	**0.31**	**< 0.0001**	**0.20**	**< 0.0001**
HDL-C (mg/dL)	0.08	0.003	0.06	0.01	0.02	0.50
TGs (mg/dL)	**0.25**	**< 0.0001**	**0.29**	**< 0.0001**	**0.26**	**< 0.0001**
Glucose (mg/dL)	0.17	< 0.0001	0.20	< 0.0001	0.17	< 0.0001
Insulin (U)	0.19	< 0.0001	0.13	< 0.0001	0.18	< 0.0001
HOMA-IR	0.21	< 0.0001	0.20	< 0.0001	0.20	< 0.0001
CRP	0.11	< 0.0001	0.14	< 0.0001	0.003	0.90
CAC (Agatson U)	0.07	< 0.0001	0.14	< 0.0001	0.05	0.11
Lipoprotein(a)	0.02	0.33	0.020	0.50	–0.01	0.84
Hepatic TG content	**0.13**	**< 0.0001**	**0.14**	**< 0.0001**	**0.12**	**< 0.0001**

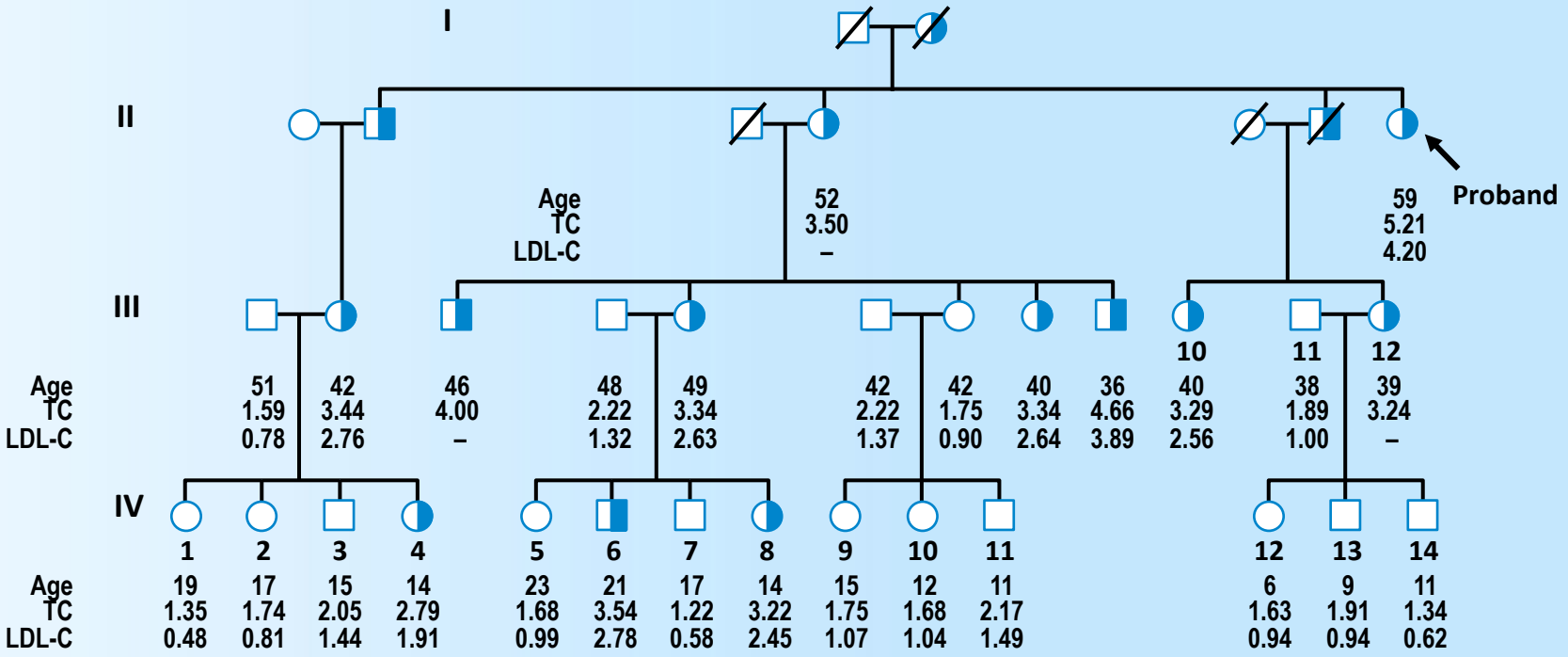
Values are in Spearman correlation coefficients between plasma concentrations of PCSK9 and clinical parameters and associated *P* values.
n = 3,138

Higher PCSK9 levels were significantly associated with increased blood LDL-C, blood TGs, and hepatic TGs and measures of glucose metabolism (glucose, insulin, HOMA-IR)

BMI = body mass index; BP = blood pressure; CAC = coronary artery calcium; CRP = C-reactive protein; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostasis model assessment-insulin resistance; TG = triglyceride.

Adapted from Lakoski et al. J Clin Endocrinol Metab. 2009;94:2537-43.

PCSK9 Mutation Causing ADH Was Identified in a French Family



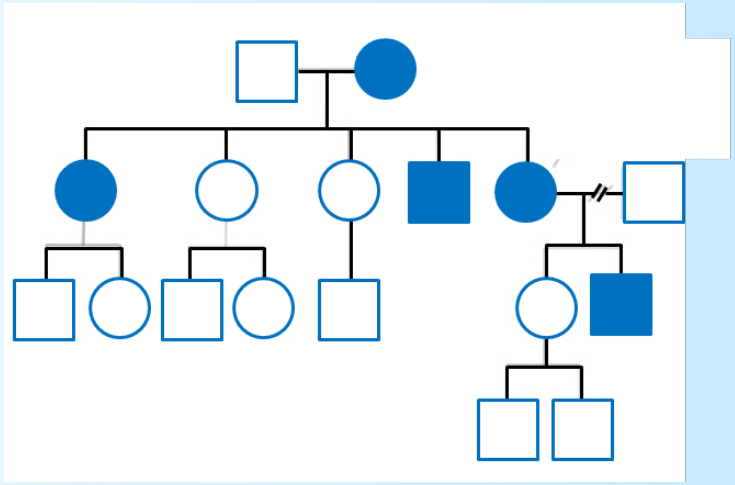
- **PCSK9 mutations (625T→A resulting in amino-acid substitution S127R) was found in the 12 affected family members and in individual HC92-IV-3[1]**
- **Prevalence of PCSK9 mutations is very low compared with the prevalence of mutations in LDL-R and apoB[2]**

*Filled bars indicate the mutated allele. Age (in years) at lipid measurement, total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C; in g per liter; untreated values for affected individuals) are given.

1. Abifadel et al. Nat Genet. 2003;34:154-56. 2. Humphries et al. J Med Genet. 2006;43:943-49.

ADH Is a Heterogeneous Genetic Disorder

- **Autosomal dominant inheritance pattern[1]**
  - **ADH individuals are typically heterozygous**



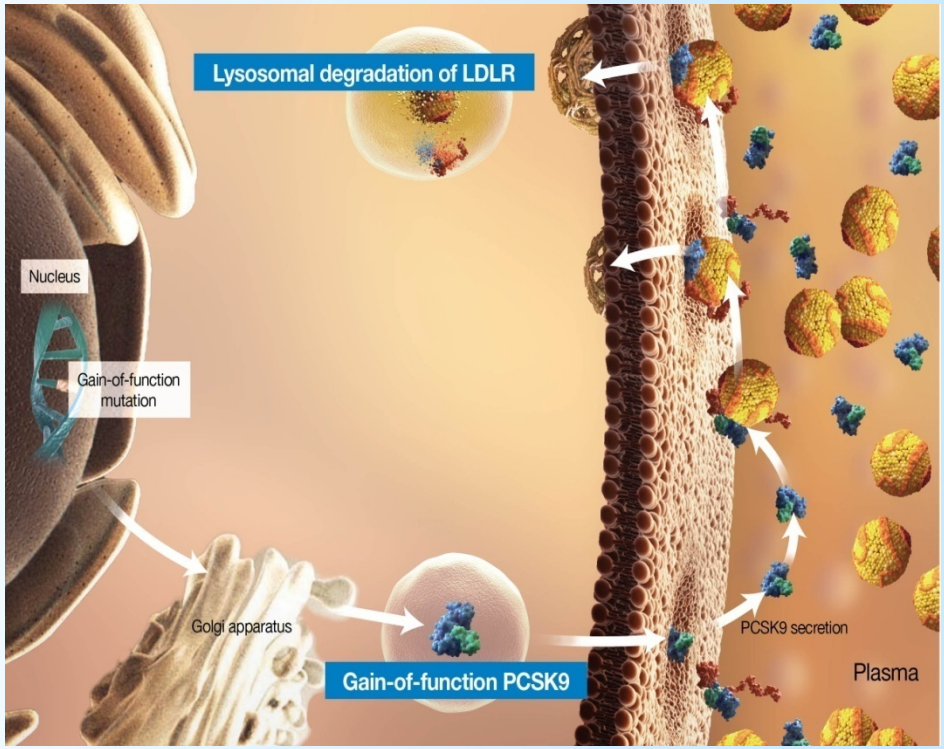
Female mutant for LDL-R, apoB, or PCSK9[2]

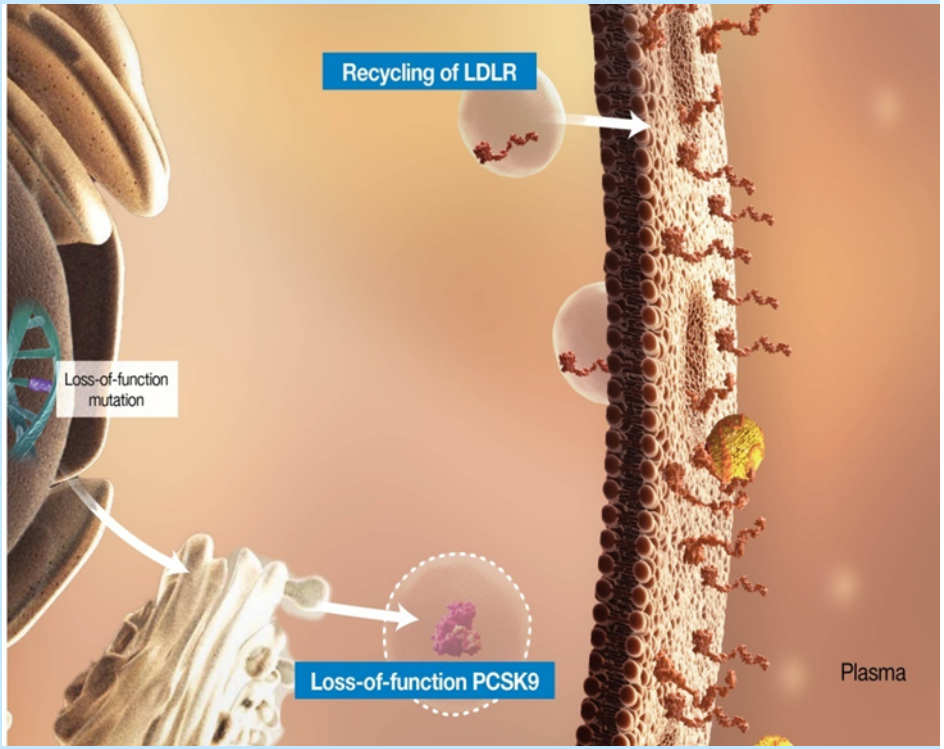
Male mutant for LDL-R, apoB, or PCSK9[2]

- **Locus heterogeneity: same disorder (eg, FH) is caused by mutations in different genes[1]**
- **Allelic heterogeneity: disorder is caused by a variety of different mutations within a gene[1]**
  - **Different protein defects result in different levels of disease severity[1]**
  - **Penetrance differs depending on the specific mutation**

1. US National Library of Medicine. Genetics Home Reference. http://ghr.nlm.nih.gov/glossary. 2. Abifadel et al. In: Toth PP. The Year in Lipid Disorders. Vol. 2. Oxford, UK: Atlas Medical Publishing Ltd. 2010:3-23.

Genetic Variants of PCSK9 Demonstrate Its Importance in Regulating LDL Levels





PCSK9 Gain of Function (GOF) = <u>Less</u> LDL-Rs[1,3,5]

PCSK9 Loss of Function (LOF) = <u>More</u> LDL-Rs[2,4,5]

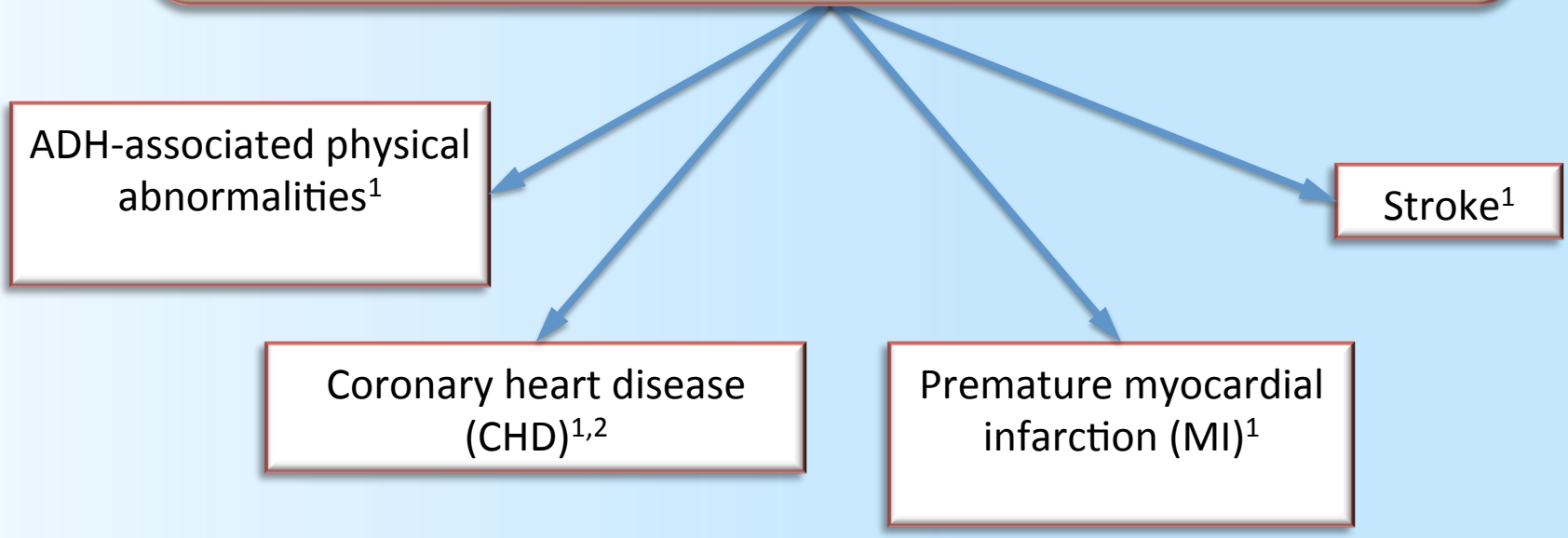
1-3% of population[6,7]

1. Horton et al. J Lipid Res. 2009;50:S172-S177. **2.** Lakoski et al. J Clin Endocrinol Metab. 2009;94:2537-43. **3.** Abifadel et al. Hum Mutat 2009;30:520-29. **4.** Cohen et al. Nat Genet. 2005;37:161-65. **5.** Steinberg et al. PNAS. 2009;106:9546-7. **6.** Cohen et al. N Engl J Med. 2006;354:1264-72. **7.** Benn et al. J Am Coll Cardiol. 2010;55:2833-42.

PCSK9 Gain of Function (GOF) Mutations

Clinical Outcomes Associated With PCSK9 GOF Mutations

ADH caused by rare PCSK9 GOF mutations have a clinical phenotype resembling FH caused by LDL-R or apoB gene mutations[1,2]



1. Abifadel et al. In: Toth PP. The Year in Lipid Disorders. Vol. 2. Oxford, UK: Atlas Medical Publishing Ltd. 2010:3-23. 2. Benn et al. J Am College Cardiol. 2010;55:2833-42.

Clinical Outcomes Associated With PCSK9 GOF Mutations: Tendinous Xanthoma

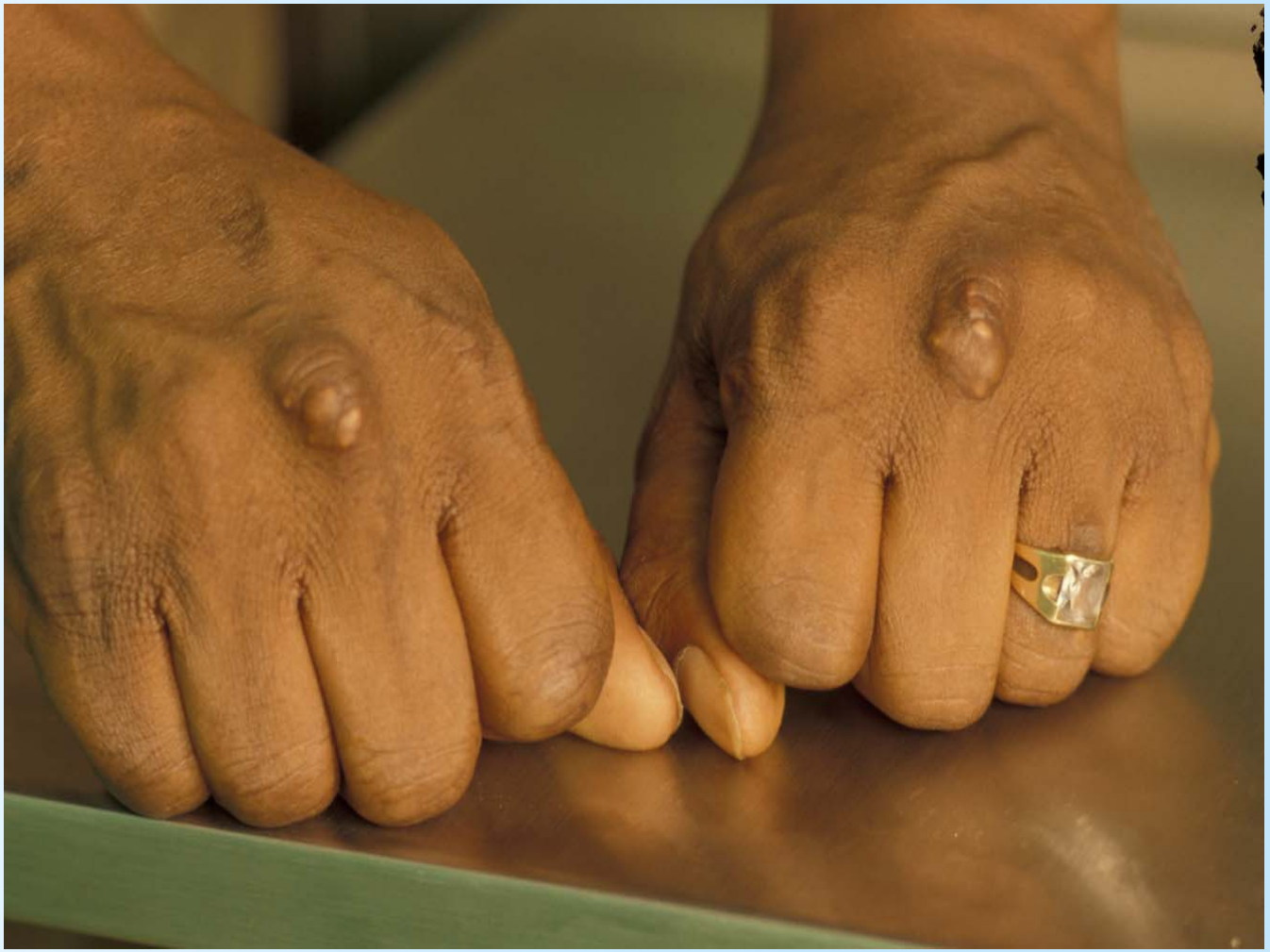


Image courtesy of Michael H. Davidson, MD.

Case Reports Highlight Hypercholesterolemia Associated With PCSK9 GOF Mutations

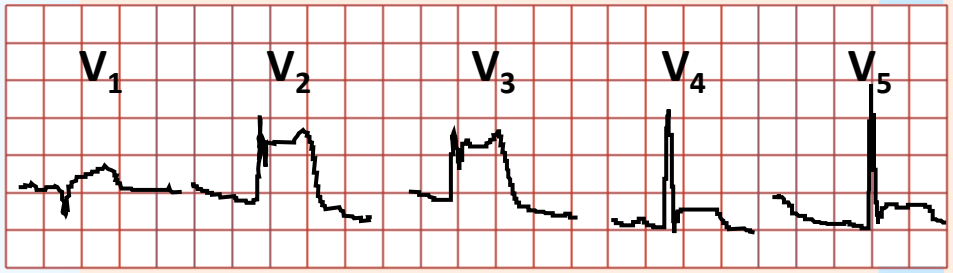
F216L mutation[1]

French proband died from MI

Age: 49 years

TC: 441 mg/dL

LDL-C: 356 mg/dL



Acute Myocardial Infarction[4]

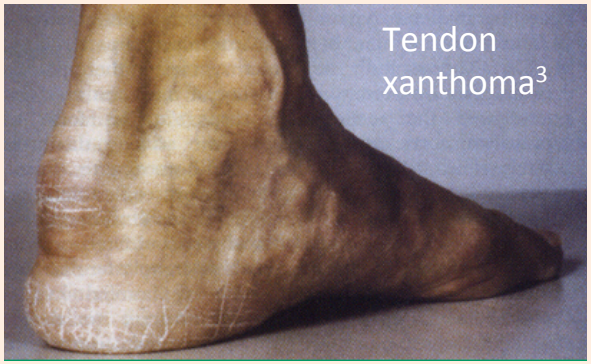
R218S mutation[2]

French proband presented with tendinous xanthoma and arcus corneae

Age: 45 years

TC: 402 mg/dL

LDL-C: 293 mg/dL



TC = total cholesterol.

1. Abifadel et al. Nat Genet. 2003;34:154-56. 2. Abifadel et al. Hum Mutat. 2009;30:520-29. 3. Durrington. Lancet. 2003;362:717-31. 4. Podrid. UpToDate; March 1, 2012.

PCSK9 GOF Mutations Associated With ADH

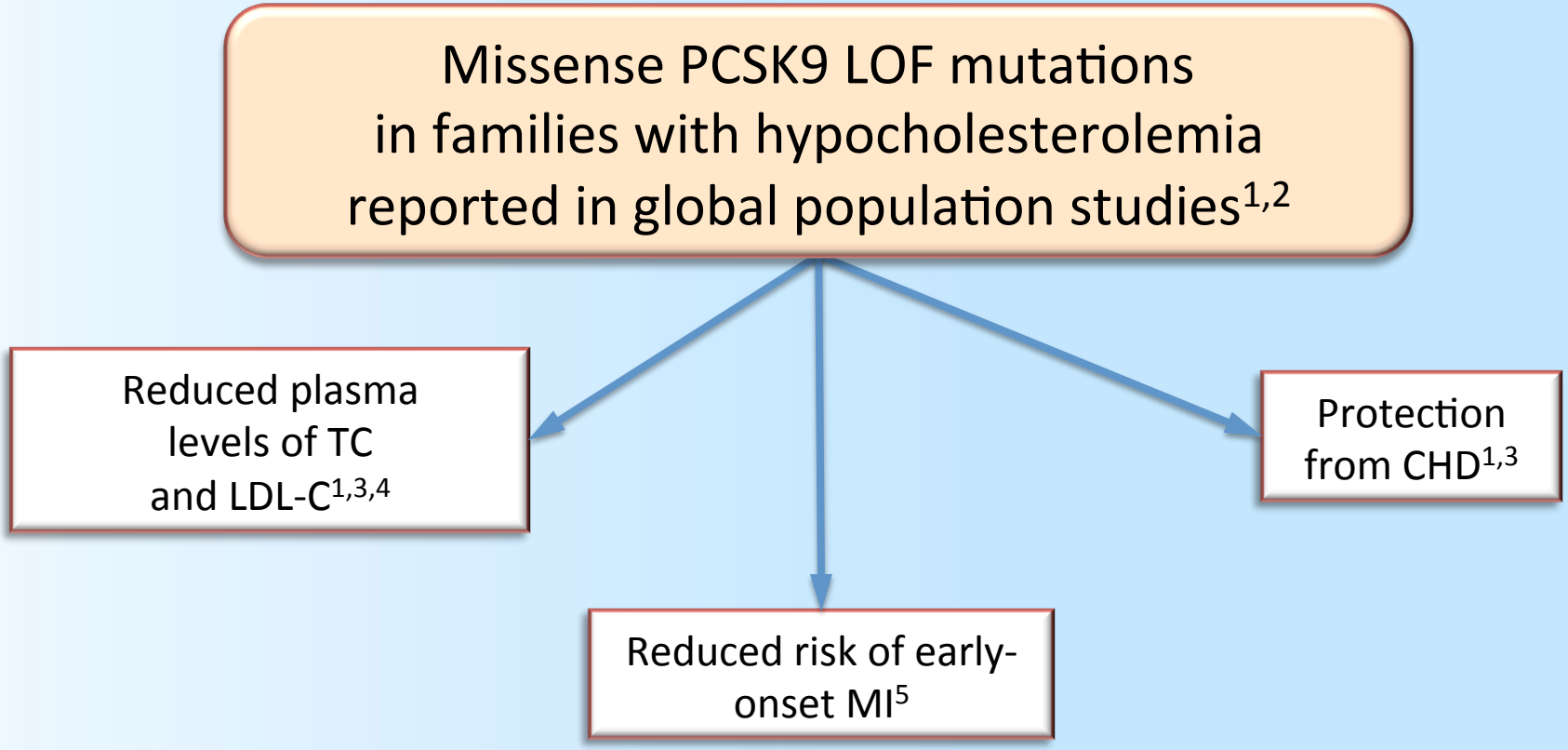
PCSK9 Genotype	Mutation	Biochemical Phenotype	Clinical Phenotype
S127R	Missense	5x higher LDL-R affinity; decreased LDL-R expression/activity; may interfere with trafficking of LDL-R[1,2]	Cholesterol levels in 90th percentile; tendon xanthomas, CHD, early MI, stroke[3]
D129G	Missense	Decreased LDL-R expression and activity[1]	Elevated LDL-C; strong family history of CV disease[2]
F216L	Missense	Loss of PCSK9 activation; increased LDL-R degradation; higher circulating PCSK9 (prolonged half-life)[2,3]	Premature CHD; Early MI[3]
R218S	Missense	Normal processing/secretion but no PCSK9 enzymatic activity[1]	Tendon xanthomas, arcus corneae[4]
D374Y	Missense	10–25x higher LDL-R affinity; decreased LDL-R recycling; increased degradation[1,5]	Tendon xanthomas; premature atherosclerosis[4]

Please refer to Lopez et al. (2008) and Abifadel et al. (2009) for comprehensive lists of PCSK9 mutations and variants.

1. Lopez. Biochem Biophys Acta. 2008;1781:184-191. **2.** Horton et al. J Lipid Res. 2009;50:S172-7. **3.** Abifadel et al. Nat Genet. 2003;34:154-56. **4.** Abifadel et al. Hum Mutat. 2009;30:520-29. **5.** Cunningham et al. Nat Struct Mol Biol. 2007;14:413-19.

PCSK9 Loss of Function (LOF) Mutations

Clinical Outcomes Associated With PCSK9 LOF Mutations



1. Abifadel et al. Hum Mutat. 2009;30:520-29. 2. Abifadel et al. Hum Mutat. 2009;30: supplementary information. 3. Abifadel et al. In: Toth. The Year in Lipid Disorders. Vol. 2. Oxford, UK: Atlas Medical Publishing Ltd. 2010:3-23. 4. Benn et al. J Am Coll Cardiol. 2010;55:2833:2842. 5. Kathiresan. N Engl J Med. 2008;358:2299-2300.

Epidemiologic Genetic Data Support a Role for PCSK9 in CHD

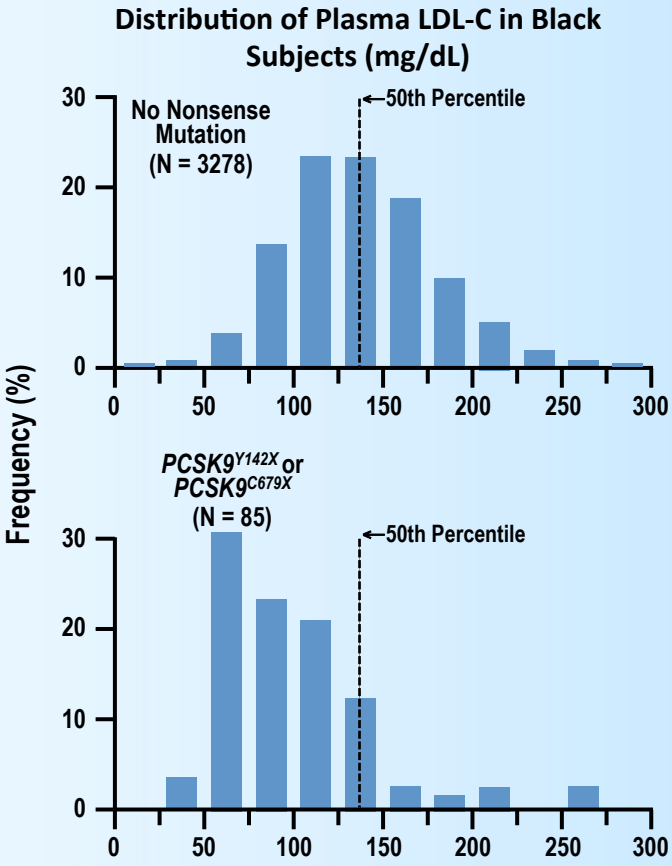
- Lifelong reduction in plasma LDL-C is associated with a CV risk reduction benefit, even in populations with a moderate LDL-C reduction or a high prevalence of nonlipid-related CV risk factors
- Over a 15-year period in the Atherosclerosis Risk in Communities (ARIC) study:
  - 2.6% of African Americans were heterozygous for $PCSK9^{Y142X}$ or $PCSK9^{C679X}$ nonsense mutation
    - 28% reduction in plasma LDL-C; 88% reduction in CHD ($P = 0.008$)*
  - 3.2% of white subjects had the $PCSK9^{G137T}$ sequence variant
    - 15% reduction in mean LDL-C and a 47% reduction in CHD ($P = 0.003$)

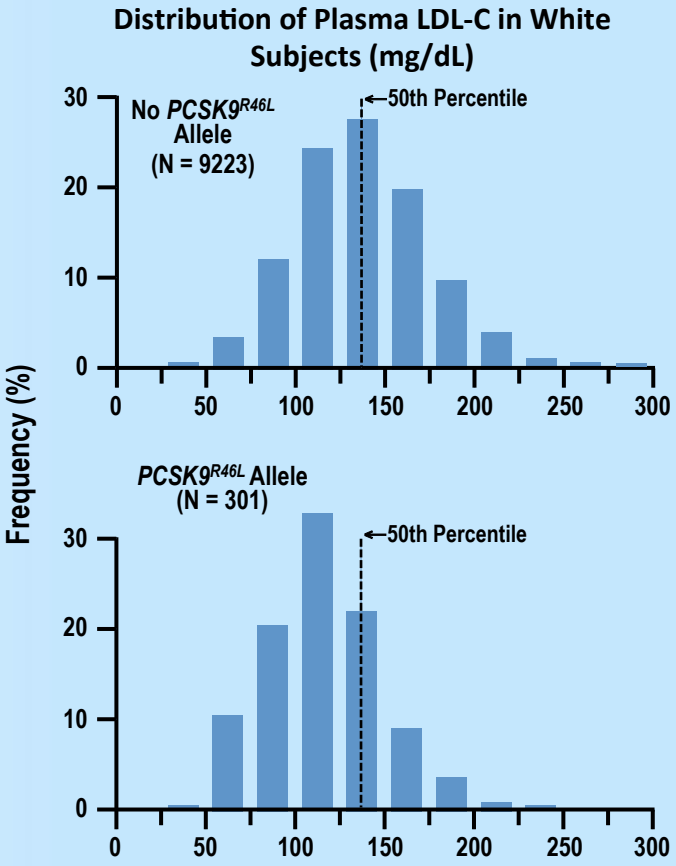
Sequence variations in *PCSK9* associated with lower plasma levels of LDL cholesterol conferred protection against CHD

* Prevalence of nonlipid-related risk factors was similar in Y142X or C679X carriers and noncarriers, with the exception of hypertension, which was more common in noncarriers ($P = 0.001$).

Cohen et al. New Engl J Med. 2006;354:1264-72.

PCSK9 LOF Mutations Are Associated With Decreased Plasma LDL-C Concentrations





81% of PCSK9^{Y142X} and PCSK9^{C679X} subjects had mean plasma LDL-C below 50th percentile

Moderate mean plasma LDL-C lowering effect in PCSK9^{R46L} allele carriers

Adapted from Cohen et al. New Engl J Med. 2006;354:1264-72.

$PCSK9^{R46L}$ Minor Allele Genotype Carriers Have Reduced LDL-C

	N (R46L carriers)	LDL-C Difference (mg/dL ± SEM)	LDL-C Reduction (%)	*P* Value*
CCHS	10,032 (243)	–21.2 ± 3.1	15%	< 0.0001
CGPS	26,013 (730)	–13.5 ± 1.5	11%	< 0.0001
CIHDS	9,654 (231)	–19.3 ± 3.1	16%	< 0.0001
All	**45,699 (1,204)**	**–16.6 ± 1.2**	**13%**	**< 0.0001**

- R46L allele carriers versus noncarriers:
  - Significantly reduced LDL-C
  - Lower TC (6% vs 9%), non-HDL-C (9% vs 13%), and apoB (8% vs 13%)
    - » *P* <0.001 for all

Loss of function in PCSK9 is associated with decreased LDL-C levels

CCHS = Copenhagen City Heart Study; CGPS = Copenhagen General Population Study;
CIHDS = Copenhagen Ischemic Heart Disease Study

Noncarriers = RR homozygotes; R46L allele carriers = RL heterozygotes and LL homozygotes.
*R46L allele carriers versus noncarriers.

Adapted from Benn et al. J Am Coll Cardiol. 2010;55:2833-42.

$PCSK9^{R46L}$ Missense LOF Variant Associated With Reduced Risk of Early-Onset MI*

- The minor $PCSK9^{R46L}$ allele was associated with a reduced risk of early-onset MI*
- In a study of 1,454 cases of early-onset MI and 1,617 age- and sex-matched controls:
  - Odds ratio (OR) for early MI was 0.40 (95% confidence interval [CI], 0.26–0.61), *P* = 0.00002
  - 2.4% frequency of R46L minor L allele in controls (n = 1,617)

Loss of function in PCSK9 may provide protection against MI, in addition to its effect of decreasing LDL-C levels

*Early onset defined as MI in men ≤ age 50 years or women ≤ age 60 years.

Kathiresan. N Engl J Med. 2008;258:2299-2300.

Association of PCSK9^{R46L} and Risk for MI

- Study of 1,880 Italian patients (1,670 men) with premature MI and 1,880 age- and sex-matched controls
  - R46L allele frequency: controls 1.42% and cases 1.04%
- L46 carriers have significantly lower LDL-C (P = 0.00022) and TC (P = 0.00019) than noncarriers
- Significantly reduced MI risk with PCSK9^{R46L} observed when an additional 1,056 older (mean, 15 years) controls were included in the dataset
  - OR, 0.67; 95% CI, 0.46–0.97; P = 0.036

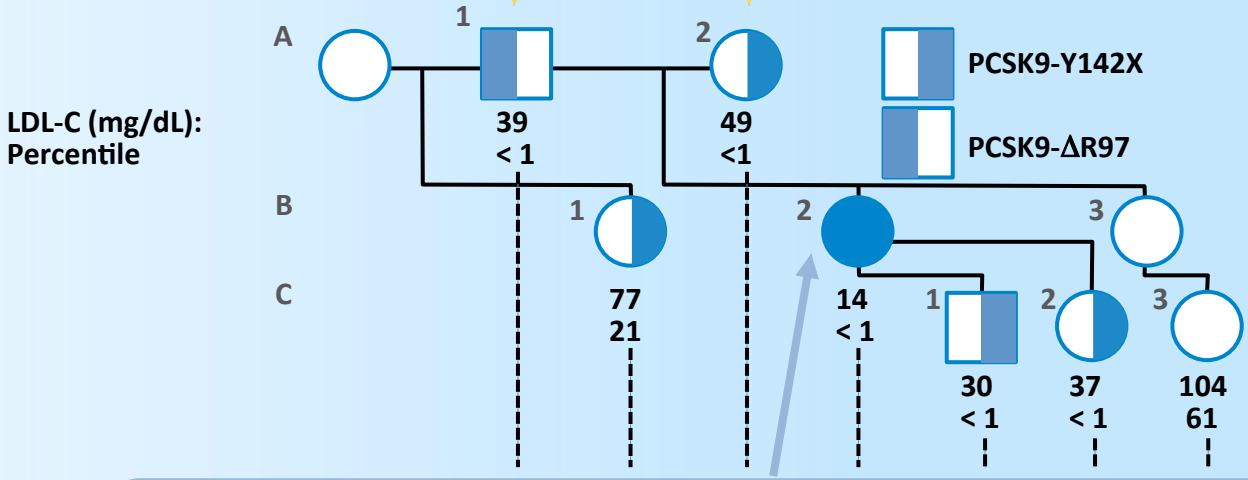
L46 allele has been shown not only to decrease LDL cholesterol but also to protect against MI.

Guella et al. J Lipid Res. 2010;51:3342-49.

PCSK9 LOF Compound Heterozygote With No Detectable Circulating PCSK9

Paternal allele: PCSK9$^{\Delta R97}$
(disrupted processing/secretion)
LDL-C: 39 mg/dL

Maternal allele: PCSK9^{Y142X}
(disrupted synthesis)
LDL-C: 49 mg/dL



Compound heterozygote

Mutation prevented autocatalytic cleavage and secretion of PCSK9
LDL-C: 14 mg/dL

Apparently healthy, fertile, normotensive, college-educated woman with normal liver and renal function who worked as an aerobics instructor

Adapted from Zhao et al. Am J Hum Genet. 2006;79:514-23.

$PCSK9^{C679X}$-Associated Cholesterol Lowering in a Population With Low LDL-C

- 653 young black women from Zimbabwe with low basal LDL-C
- ***One homozygous $PCSK9^{C679X/C679X}$ subject identified***
- Heterozygote $PCSK9^{C679X}$ genotype associated with 27% reduction in LDL-C versus normal genotype

	Normal C679C/C679C (CC) ***mean (SD)***	**Homozygous C679X/C679X (XX)**	**Heterozygous C679C/C679X (CX)** ***mean (SD)***
n	629	1	23
Age (y)	24 (5)	21	25 (5)
Cholesterol (mg/dL)	139 (27)	84.9	**119.7 (27.0)***
Triglyceride (mg/dL)	61.9 (26.5)	70.8	53.1 (17.7)
LDL-C (mg/dL)	84.9 (27)	15.4	61.8 (11.6)†
HDL-C (mg/dL)	46.3 (15.4)	54.1	46.3 (15.4)

No adverse clinical sequelae were reported in the homozygous *$PCSK9^{C679X/C679X}$* subject who exhibited a total deficiency of PCSK9

*$P < 0.005$. †$P < 0.001$.

Adapted from Hooper et al. Atherosclerosis. 2007;193:445-48.

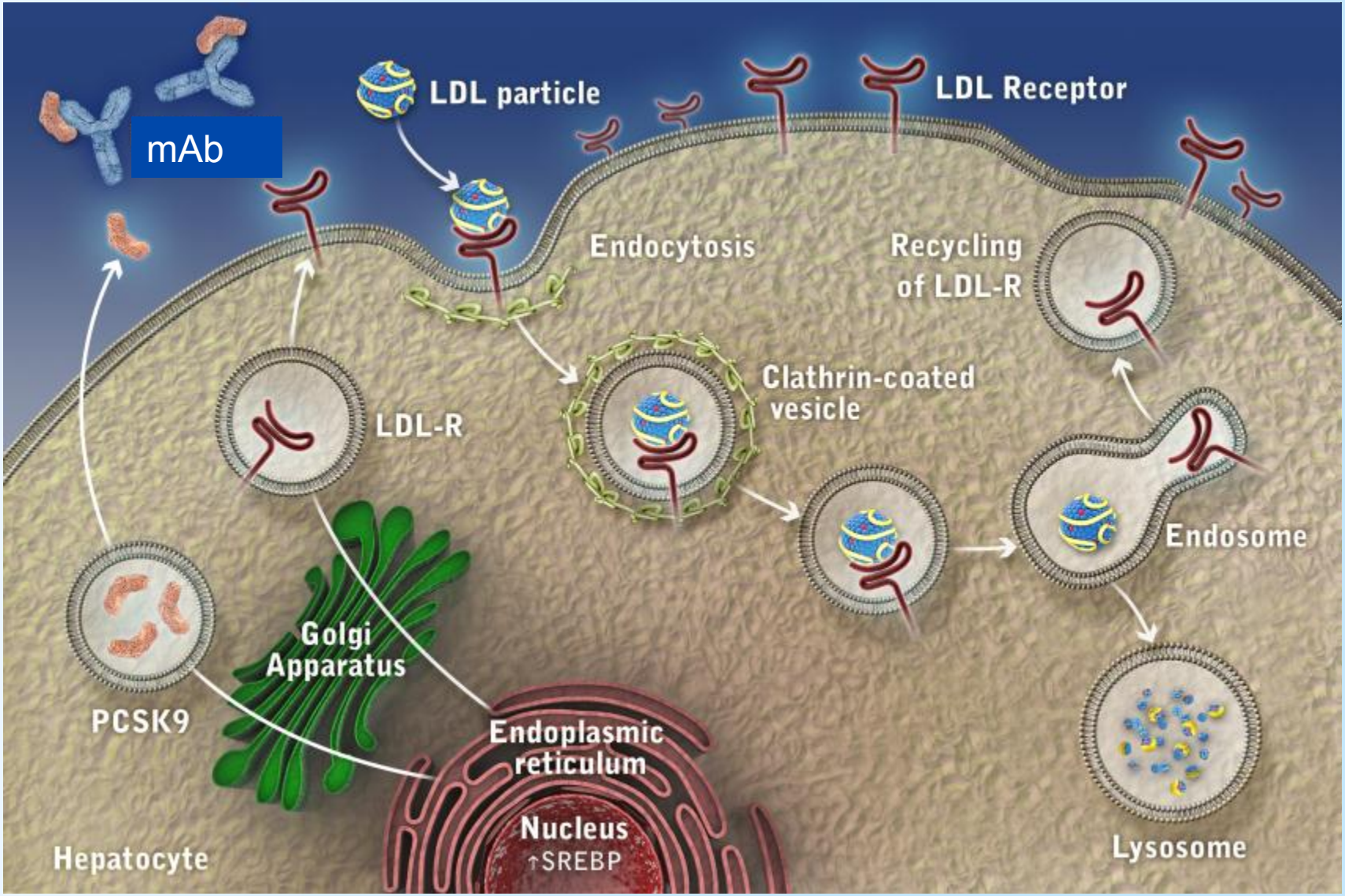
PCSK9 LOF Mutations and Variants Associated With Hypocholesterolemia

PCSK9 Genotype	Mutation Type	Biochemical Phenotype	Clinical Phenotype
R46L	Missense Polymorphism	No effect on processing or secretion[1]	11%–16% reduction in LDL-C[5]; 30% reduction in IHD[5]; reduced risk of early onset MI[6]; 47% reduction of CHD[1]
G106R	Missense	Defective protein not secreted[1]	Reduced LDL-C[1]
Y142X	Nonsense	Disrupted protein synthesis resulting in no detectable protein[3]	40% reduction in LDL-C; 88% reduction in CHD[1,2]
Q152H	Missense	Defective autocatalytic cleavage and secretion[4]	48% decrease in LDL-C; 79% decrease in plasma PCSK9[4]
L253F	Missense	Poorly cleaved and secreted[1]	30% reduction in LDL-C[2,3]; Reduced risk of CHD[3]
A443T	Missense Polymorphism	Normally cleaved and secreted; higher susceptibility to cleavage[1]	Modest (2%) reduction in LDL-C[7]
Q554E	Missense	Poorly cleaved and secreted[1]	Reduced LDL-C[8]
C679X	Nonsense	Disrupted protein folding; impaired protein secretion[1,2]	40% reduction in LDL-C; 88% reduction in CHD[1,2]

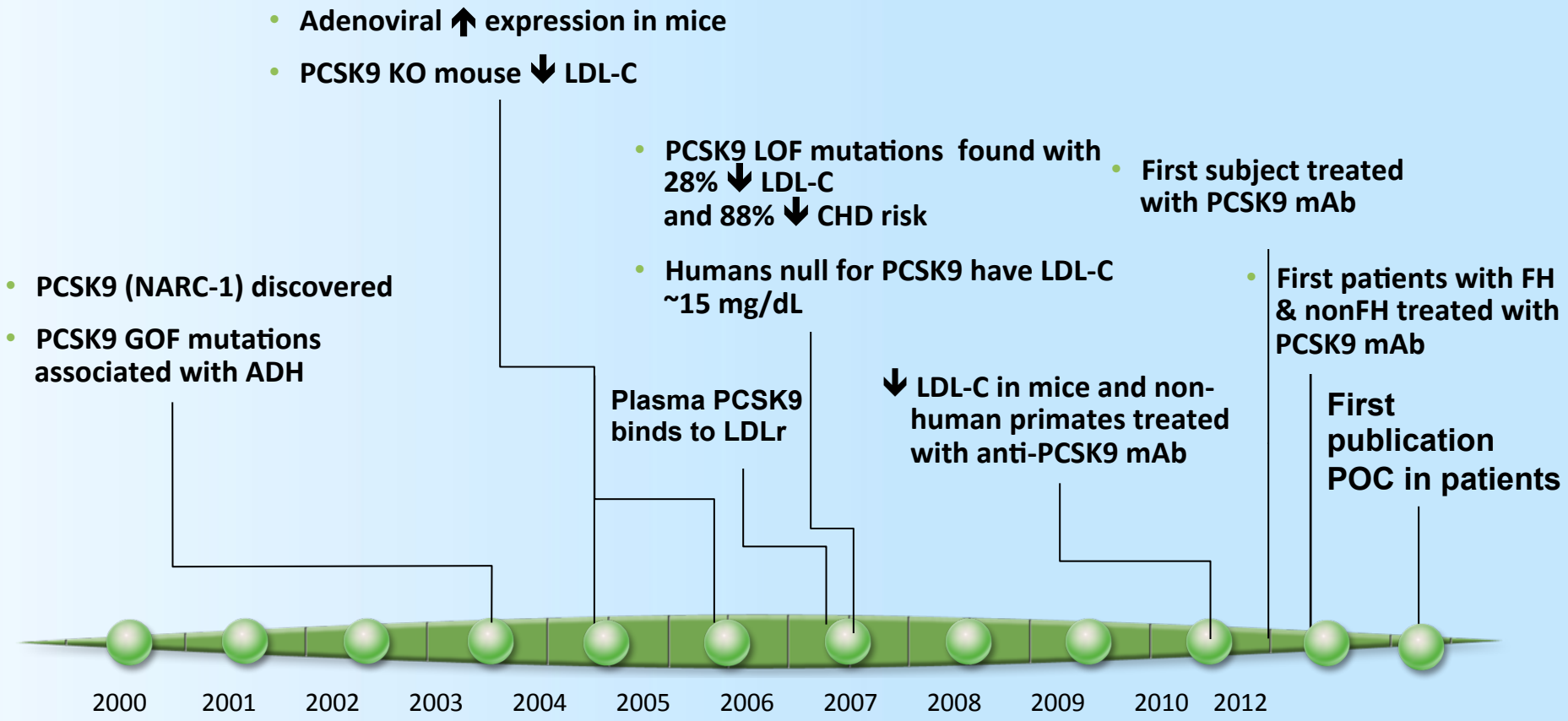
Please refer to Lopez et al. (2008) and Abifadel et al. (2009) for comprehensive lists of PCSK9 mutations and variants.

1. Lopez. Biochem Biophys Acta. 2008;1781:184-91. 2. Abifadel et al. Hum Mutat. 2009;30:520-29. 3. Cunningham et al. Nat Struct Mol Biol. 2007;14:413-19. 4. Mayne et al. Clin Chem. 2011;57:1415-23. 5. Benn et al. J Am Coll Cardiol. 2010;55:2833-42. 6. Kathiresan. N Engl J Med. 2008;358:2299-3200. 7. Zhao et al. Am J Hum Genet. 2006;79:S14-S23. 8. Abifadel et al. In: Toth PP. The Year in Lipid Disorders. Vol. 2. Oxford, UK: Atlas Medical Publishing Ltd. 2010:3-23.

Impact of PCSK9 mAb on LDL Receptor Expression



PCSK9:
Rapid Progress From Discovery to Clinic



Seidah. Proc Natl Acad Sci USA 2003;100:928-33, Abifadel. Nat Genet 2003;34:154-6, Maxwell KN. Proc Natl Acad Sci USA 2004;101:7100-5, Rashid. Proc Natl Acad Sci USA 2005;102:5374-79, Lagace et al. JCI 2006;116:2995-3005 Cohen. N Engl J Med 2006;354:1264-72, Zhao. Am J Hum Genet 2006;79:514-23, Hooper. Atherosclerosis 2007;193:445-8, Chan. Proc Natl Acad Sci USA 2009;106:9820-5; Stein et al N Engl J Med 2012;366:1108-18

Summary

- Genetic variants of PCSK9 have improved understanding of the role of PCSK9 in regulating LDL levels[1]
- GOF has been associated with hypercholesterolemia and enhanced atherosclerosis progression leading to premature CV events
- LOF has been associated with hypocholesterolemia and protection against CVD
- PCSK9 regulates the surface expression of hepatic LDL-Rs[2] by targeting LDL-Rs for degradation

1. Abifadel et al. In: Toth PP. The Year in Lipid Disorders. Vol. 2. Oxford, UK: Atlas Medical Publishing Ltd. 2010:3-23. 2. Cameron et al. Hum Mol Genet. 2006;15:1551-8.

PCSK9 Inhibitors: Clinical Evidence for a New Therapeutic Approach to LDL-C Lowering

Marc S. Sabatine, MD, MPH

Chairman, TIMI Study Group

Senior Physician, Division of Cardiovascular Medicine, BWH

Professor of Medicine, Harvard Medical School

Boston, Massachusetts

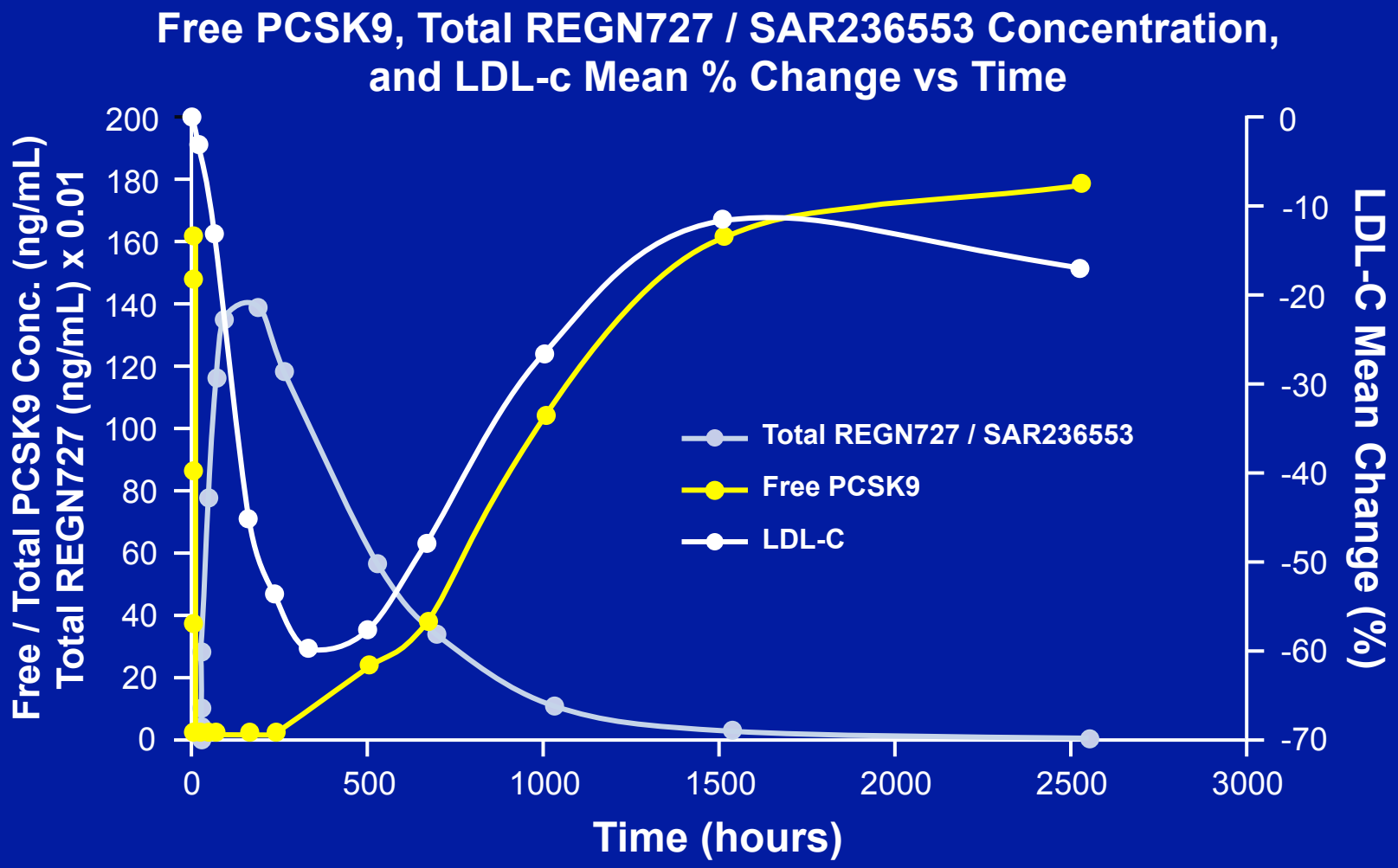
Approaches to PCSK9 Inhibition

Mode of Action	Drug	Company	Phase
PCSK9 binding: Monoclonal antibodies	Alirocumab (REGN727/SAR236553) Evolocumab (AMG 145) Bococizumab (RN316) LY3015014 RG7652 LGT209	Sanofi/Regeneron Amgen Pfizer Eli Lilly Roche/Genentech Novartis	3 3 3 2 2 (terminated) 2 (terminated)
Modified binding protein (adnectin)	BMS-962476	Bristol-Myers Squibb/Adnexus	1
PCSK9 synthesis: RNA interference	ALN-PCS02	Alnylam	1
LNA antisense oligonucleotide	SPC-5001	Santaris	1 (terminated)
RNA antisense	BMS-844421	Isis/Bristol-Myers Squibb	1 (terminated)

Adapted from Stein, Swergold. Curr Atheroscler Rep. 2013;15:310.

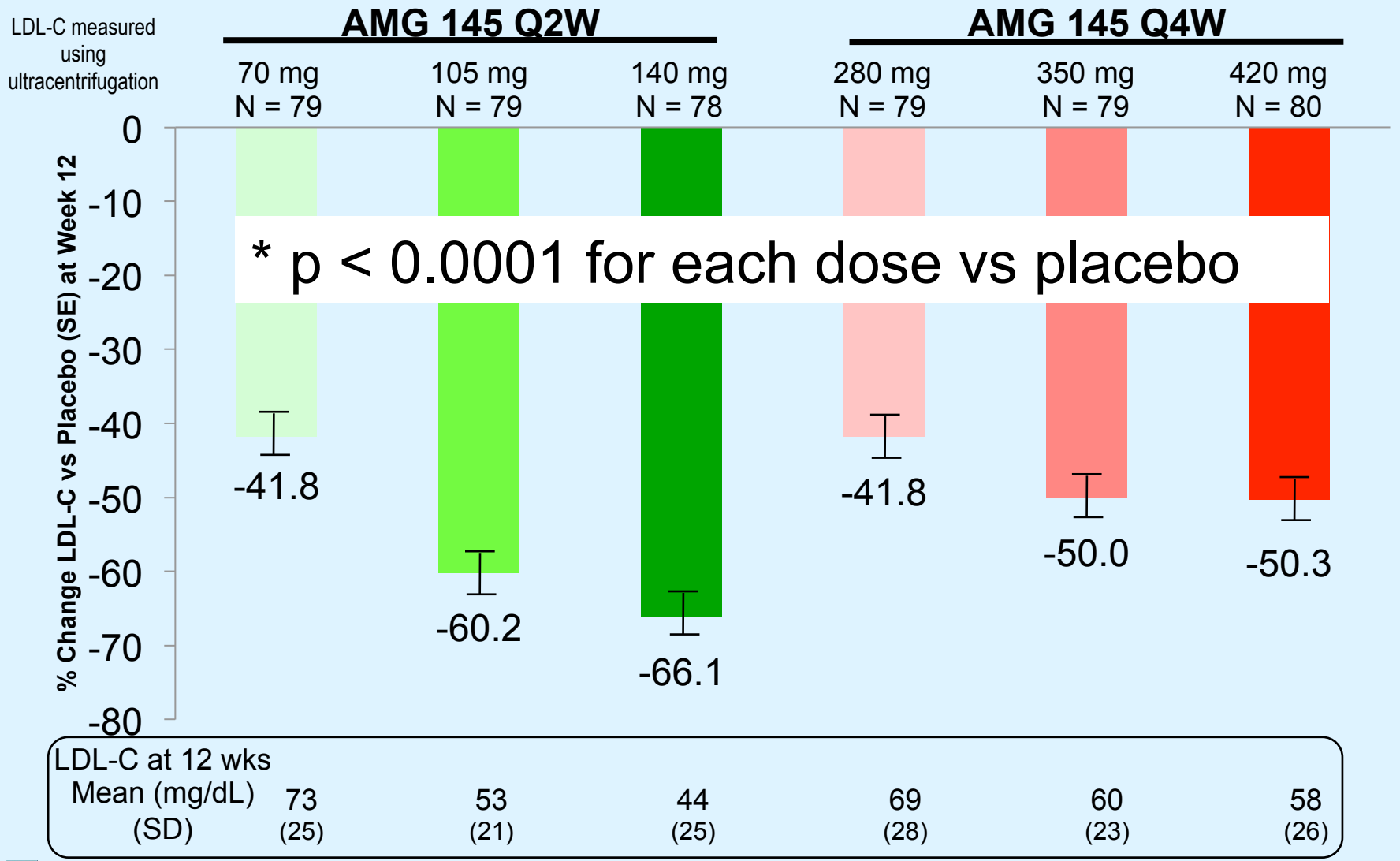
LNA = locked nucleic acid

Dynamic Relationship Between Monoclonal Antibody Levels, Free PCSK9, and LDL-C



Stein et al. N Engl J Med. 2012;366:1108-18.

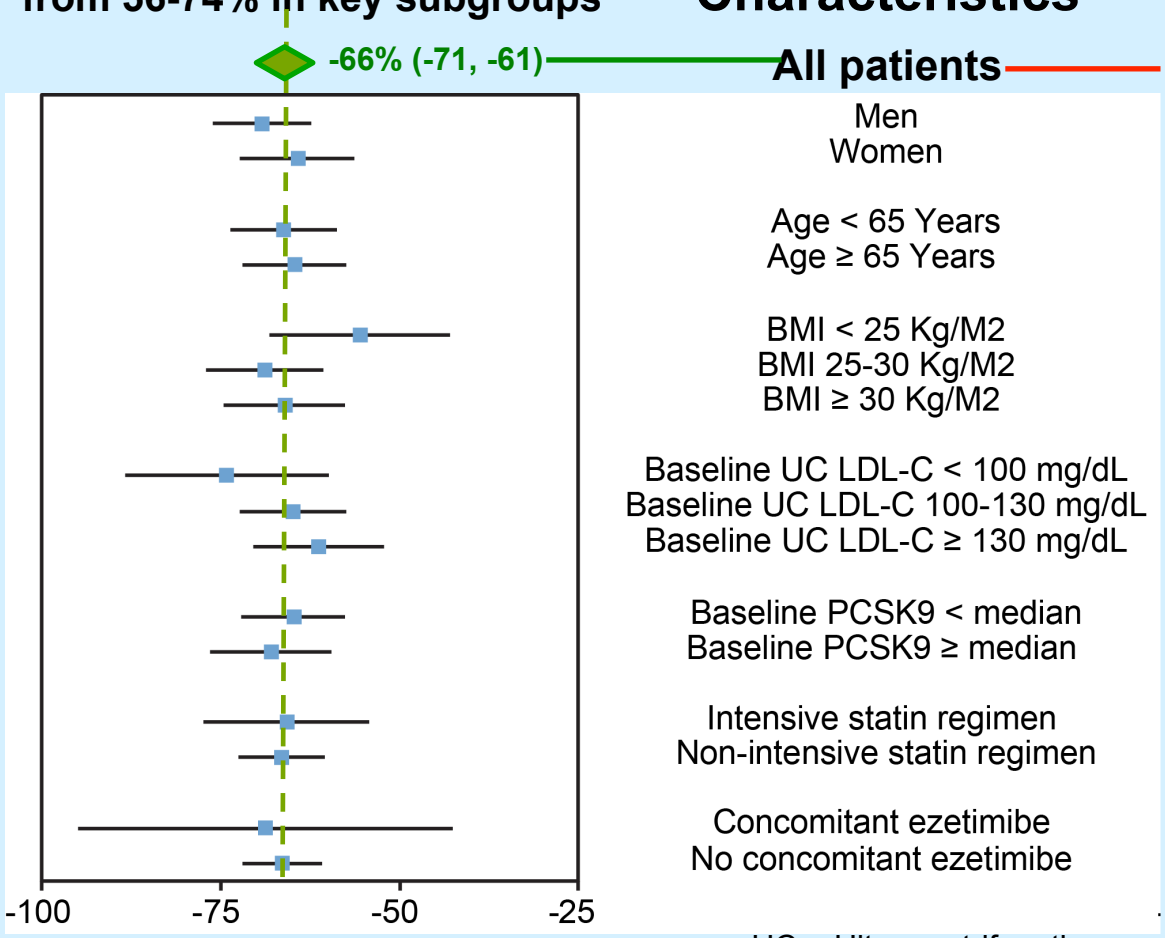
LDL-C Reduction with Evolocumab



Giugliano et al. Lancet 2012;380:2007-17.

% Reduction in LDL with Top 2 AMG 145 Doses: Major Subgroups

140 mg Q2W dose of AMG 145 reduced LDL at 12 weeks ranging from 56-74% in key subgroups

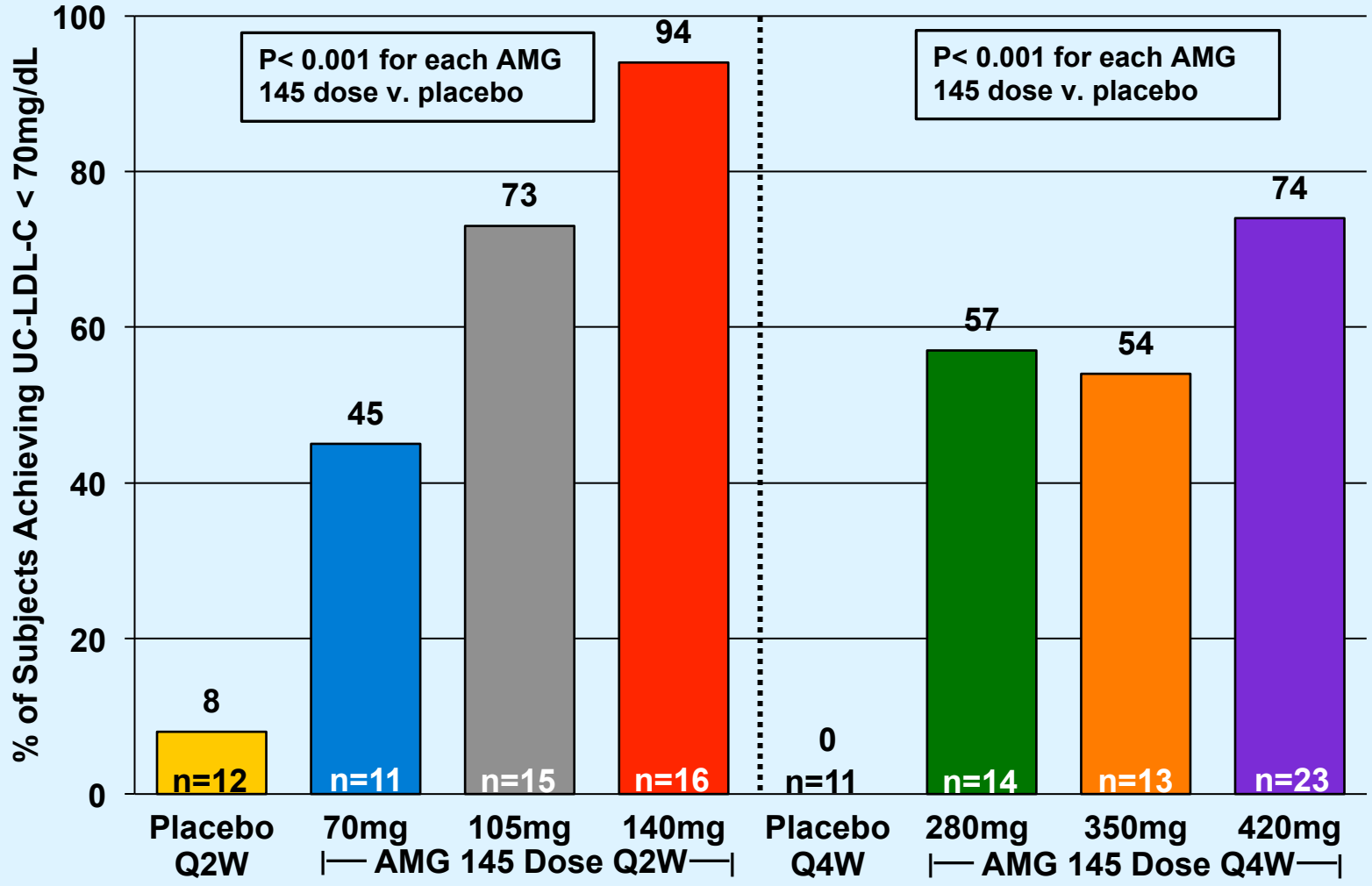


Baseline Characteristics
All patients
Men
Women
Age < 65 Years
Age ≥ 65 Years
BMI < 25 Kg/M2
BMI 25-30 Kg/M2
BMI ≥ 30 Kg/M2
Baseline UC LDL-C < 100 mg/dL
Baseline UC LDL-C 100-130 mg/dL
Baseline UC LDL-C ≥ 130 mg/dL
Baseline PCSK9 < median
Baseline PCSK9 ≥ median
Intensive statin regimen
Non-intensive statin regimen
Concomitant ezetimibe
No concomitant ezetimibe

UC = Ultra centrifugation

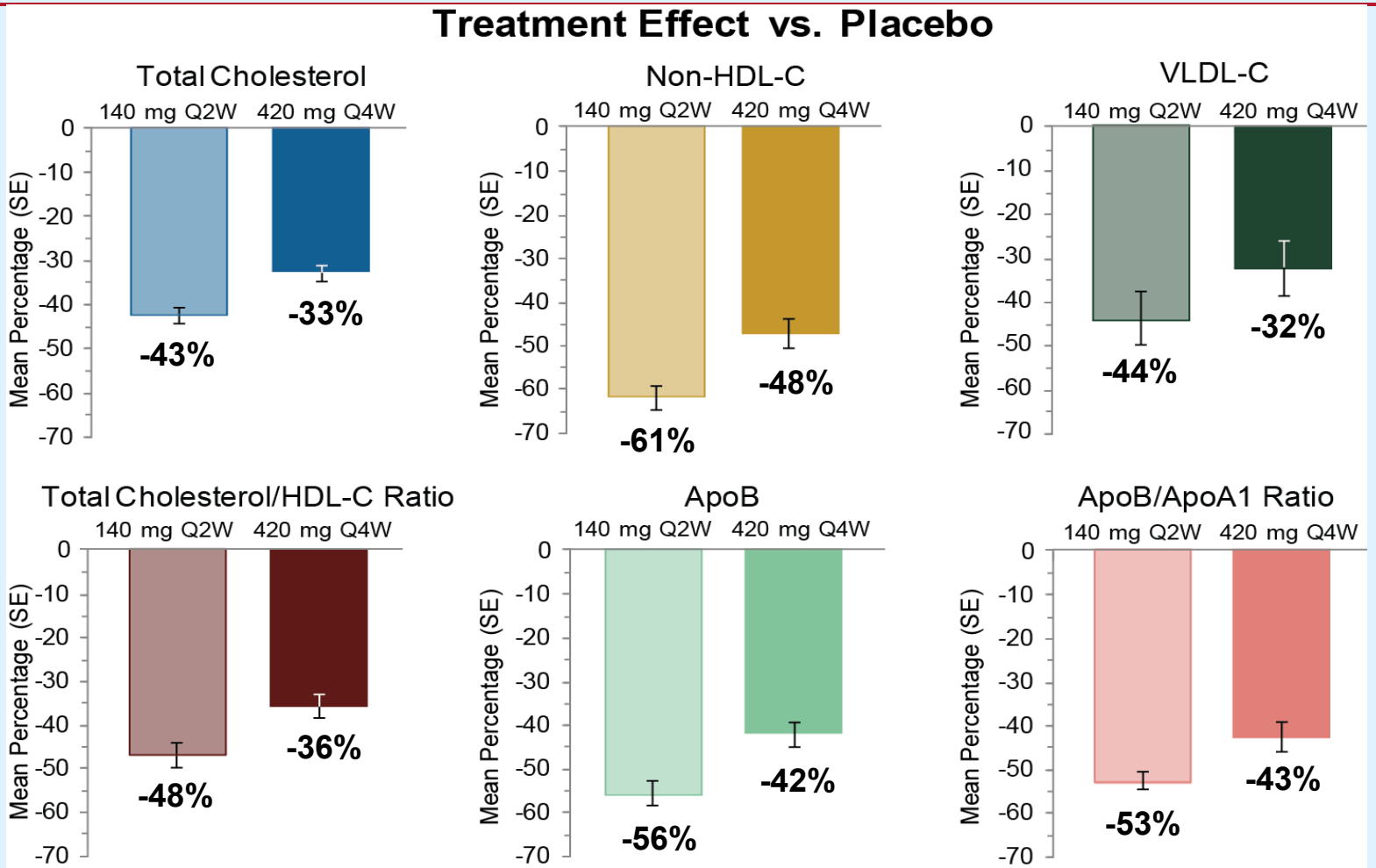
% Subjects Reaching LDL-C < 70mg/dL

Among High-Risk Subjects on Intensive Lipid-Lowering Therapy (N=115)



Desai et al. JACC 2014 63:430-3.

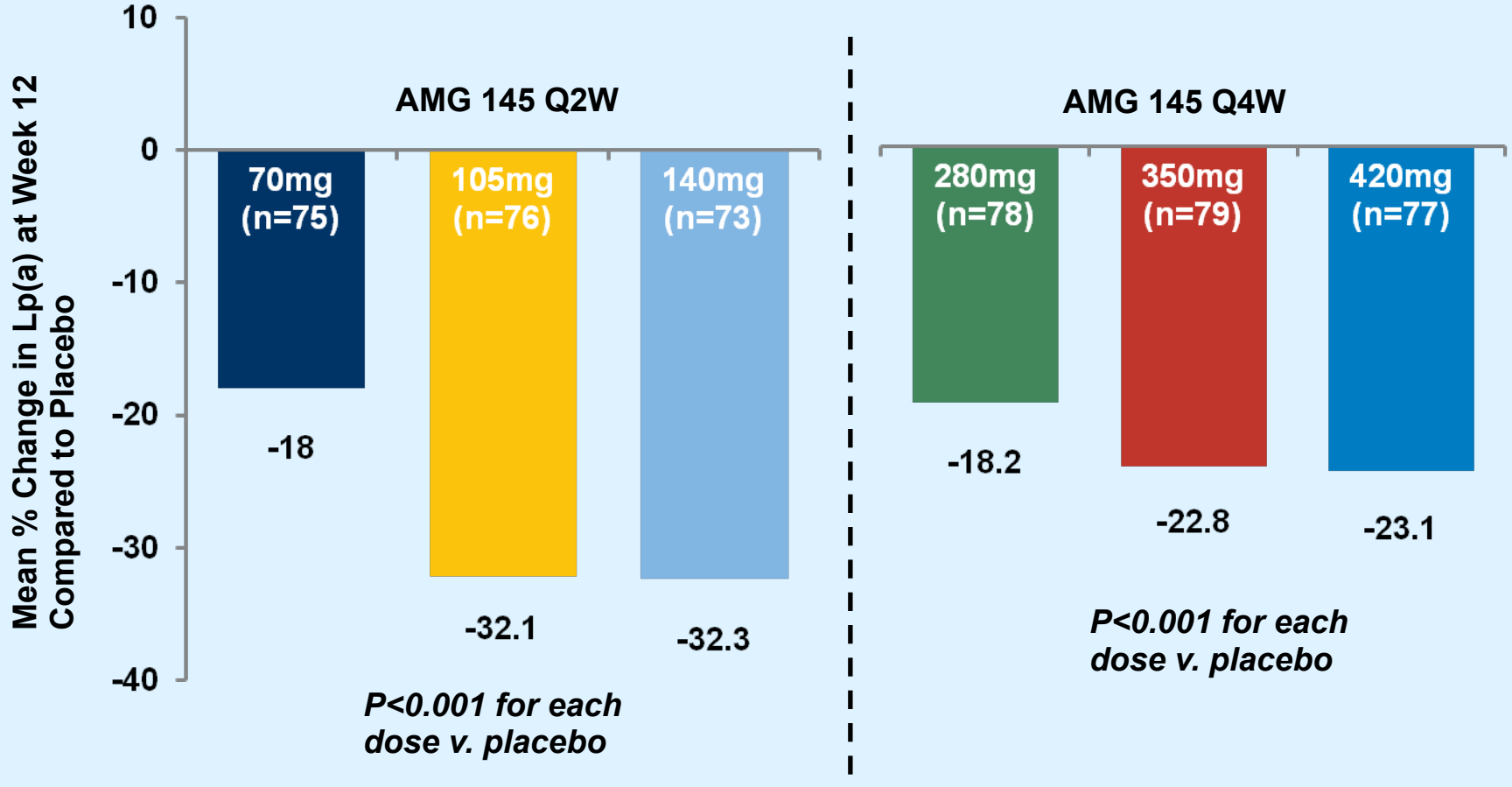
Secondary Results at 12 Wks with Top 2 AMG 145 Doses



***P* < 0.0001 versus placebo for all parameters**
Q2W, every 2 weeks; Q4W, every 4 weeks; SE, standard error

Giugliano et al. Lancet 2012;380:2007-17.

Results: Mean % Change in Lp(a) at Week 12 with AMG 145 vs. Placebo

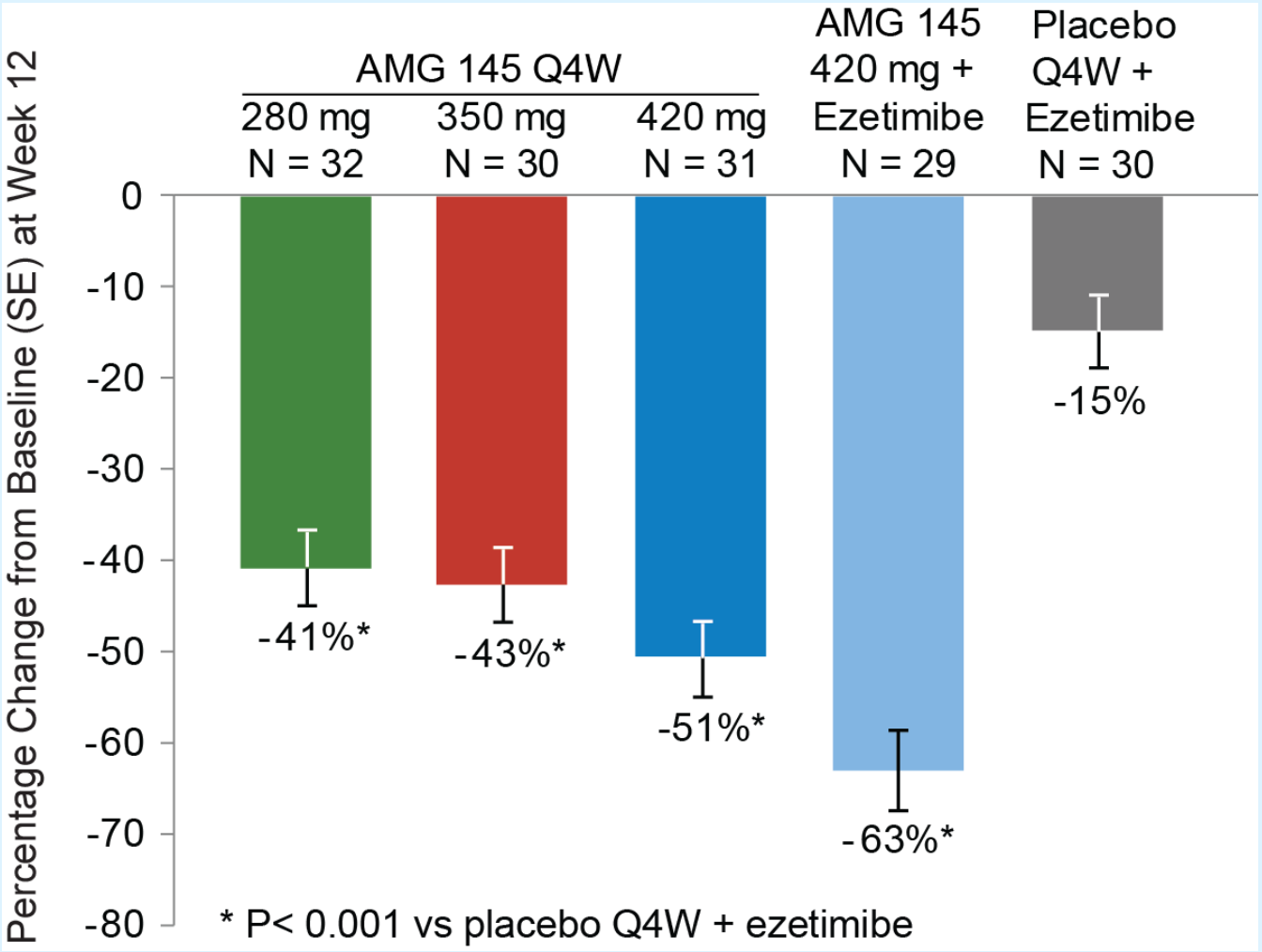


Achieved Lp(a) at week 12, nmol/L, median (IQR)	30.0 (9-116)	27.0 (7-148)	29.0 (7-97)	21.5 (7-125)	17.0 (7-155)	40.0 (9-167)

Desai et al. Circulation 2013;128:962-9.

GAUSS: Statin-Intolerant Patients (Intolerable Myalgias)

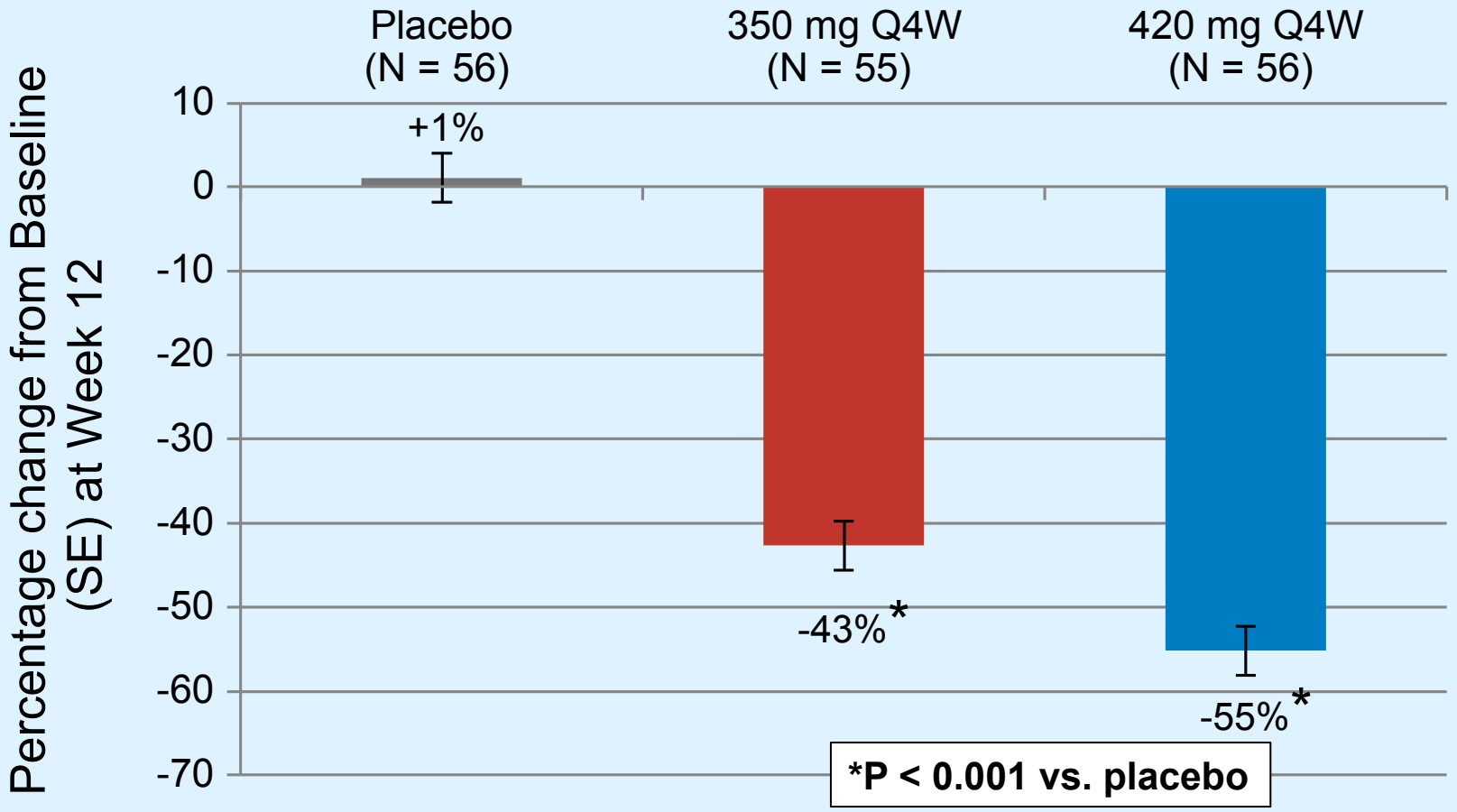
Elevated LDL-C: ≥100 mg/dL if coronary heart disease (CHD) or risk equivalent; ≥ 130 mg/dL w/o CHD but w/ ≥2 risk factors; or ≥160 mg/dL w/ ≤1 risk factor



Sullivan et al. JAMA 2012:308:2497-506.

RUTHERFORD: Heterozygous Familial Hypercholesterolemia

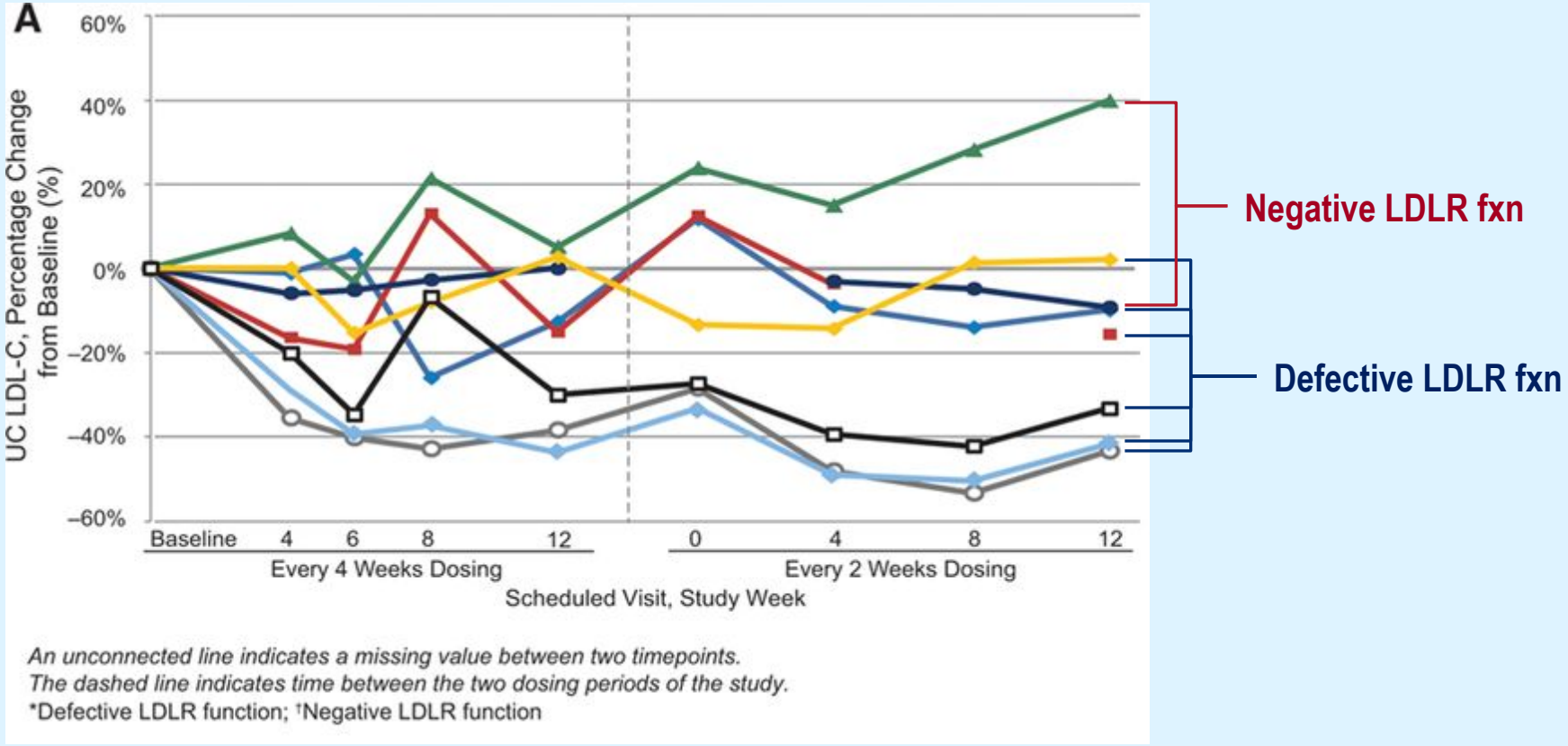
- ***LDL-C ≥ 100 mg/dL and triglycerides ≤ 400 mg/dL***
- ***At least 4 weeks of stable lipid-lowering therapy***



Raal et al. Circulation 2012:126:2408-17.

TESLA: Homozygous Familial Hypercholesterolemia

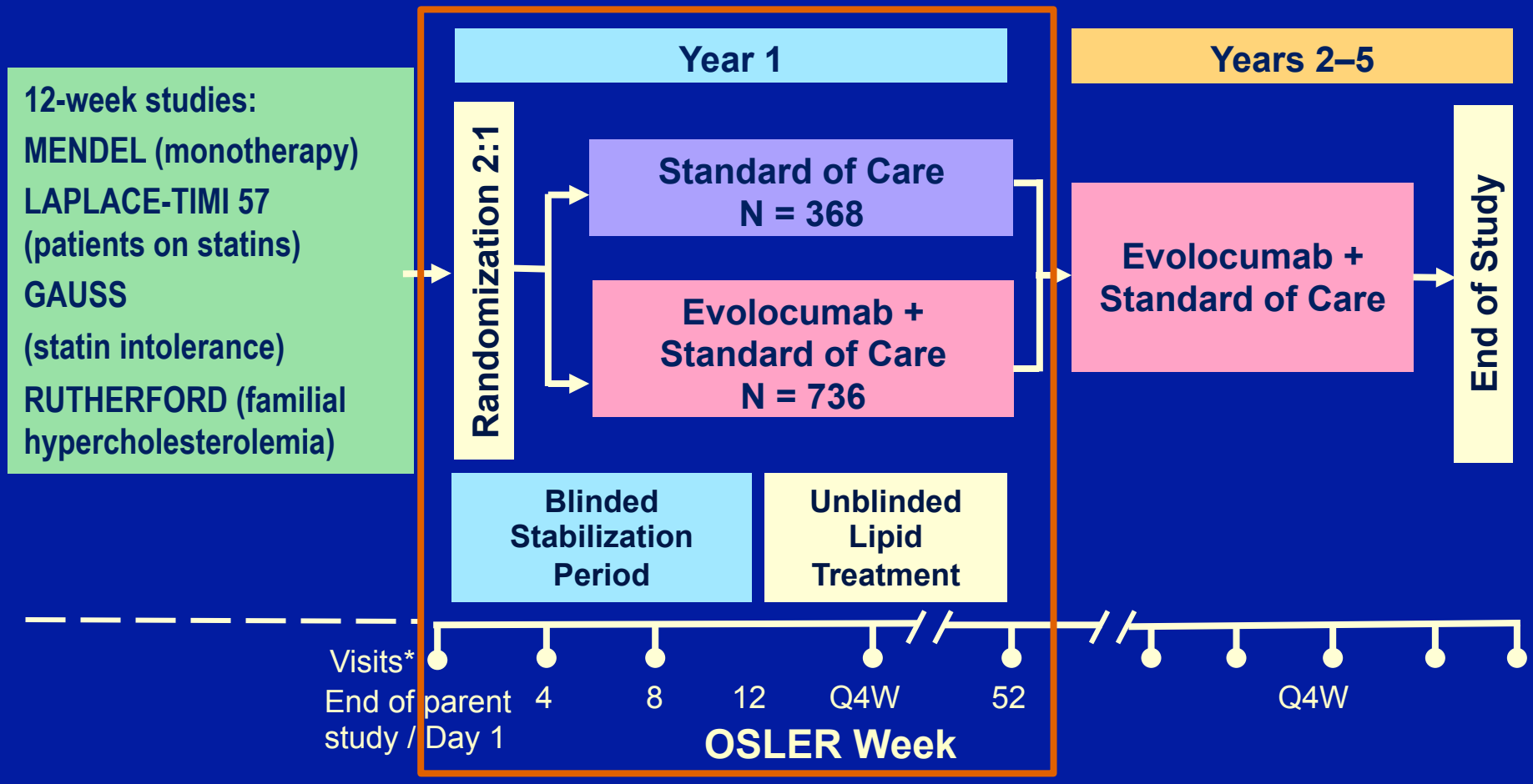
- ***LDL-C ≥ 100 mg/dL and triglycerides ≤ 400 mg/dL***
- ***At least 4 weeks of stable lipid-lowering therapy***



An unconnected line indicates a missing value between two timepoints.
The dashed line indicates time between the two dosing periods of the study.
*Defective LDLR function; †Negative LDLR function

Stein et al. Circulation 2013:128:2113-20.

OSLER Study Design

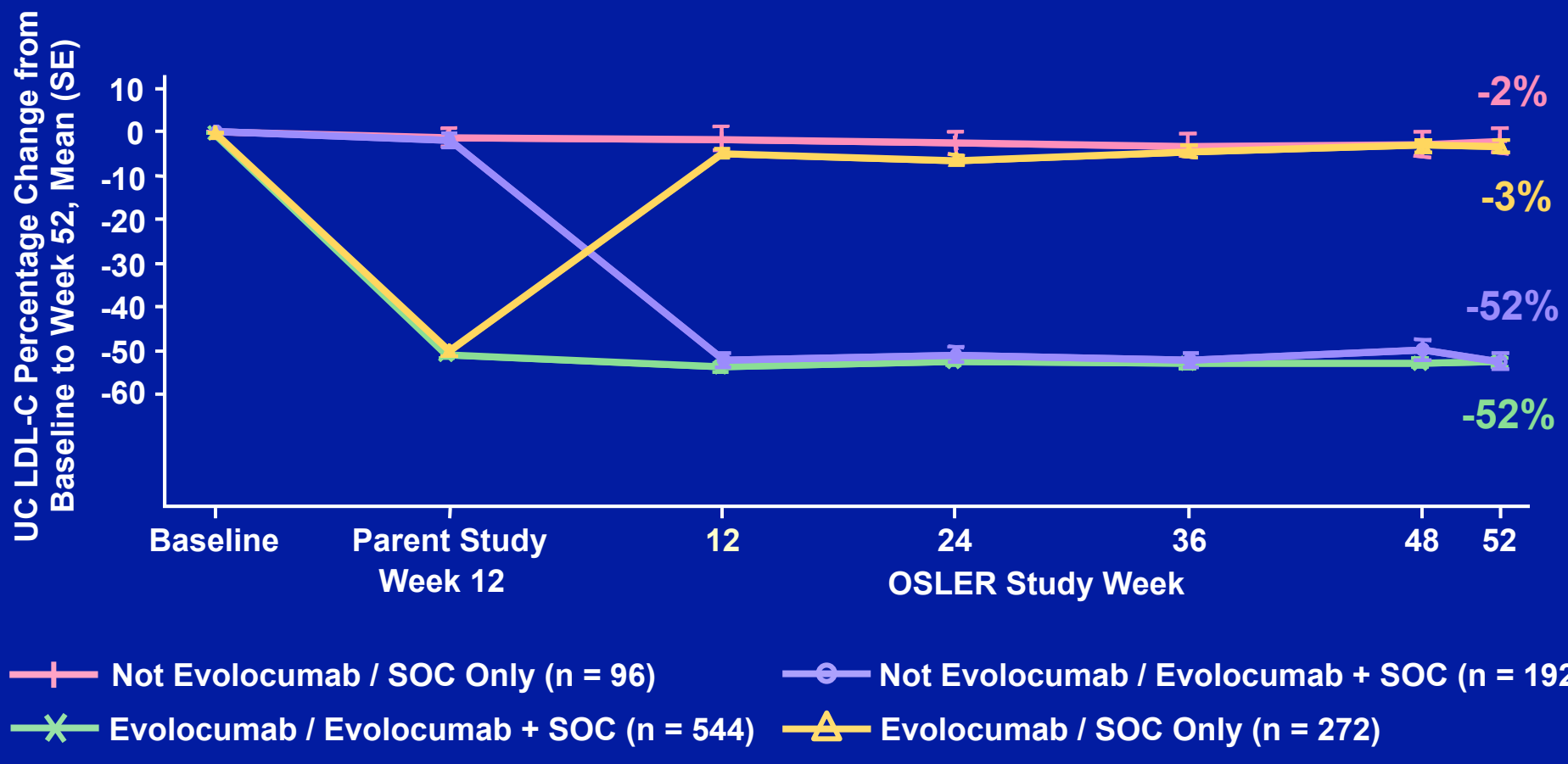


Primary Objectives:

- Effects on LDL-C over 1 year
- Safety and Tolerability

Q4W, every 4 weeks. * Patients in the evolocumab + SOC group had in-person visits every 4 weeks. Patients in the SOC group had in-person visits at week 4, then every 3 months, with telephone visits every 4 weeks.

OSLER: Percentage Change in LDL-C, by UC, from Baseline to 1 Year



SOC, standard of care; UC, ultracentrifugation

Koren et al. Circulation 2014;129:234-43.

OSLER: Safety and Tolerability

Adverse events, %	SOC N = 368	Evolocumab + SOC N = 736
Any adverse event	73.1	81.4
Serious	6.3	7.1
Possibly treatment-related (none serious)	NA	5.6
Leading to discontinuation of evolocumab	NA	3.7
Injection-site reactions	NA	5.2
ALT or AST >3× ULN	1.6	1.8
Creatine kinase >5× ULN	1.9	1.0

SOC, standard of care.

Koren et al. Circulation 2014;129:234-43.

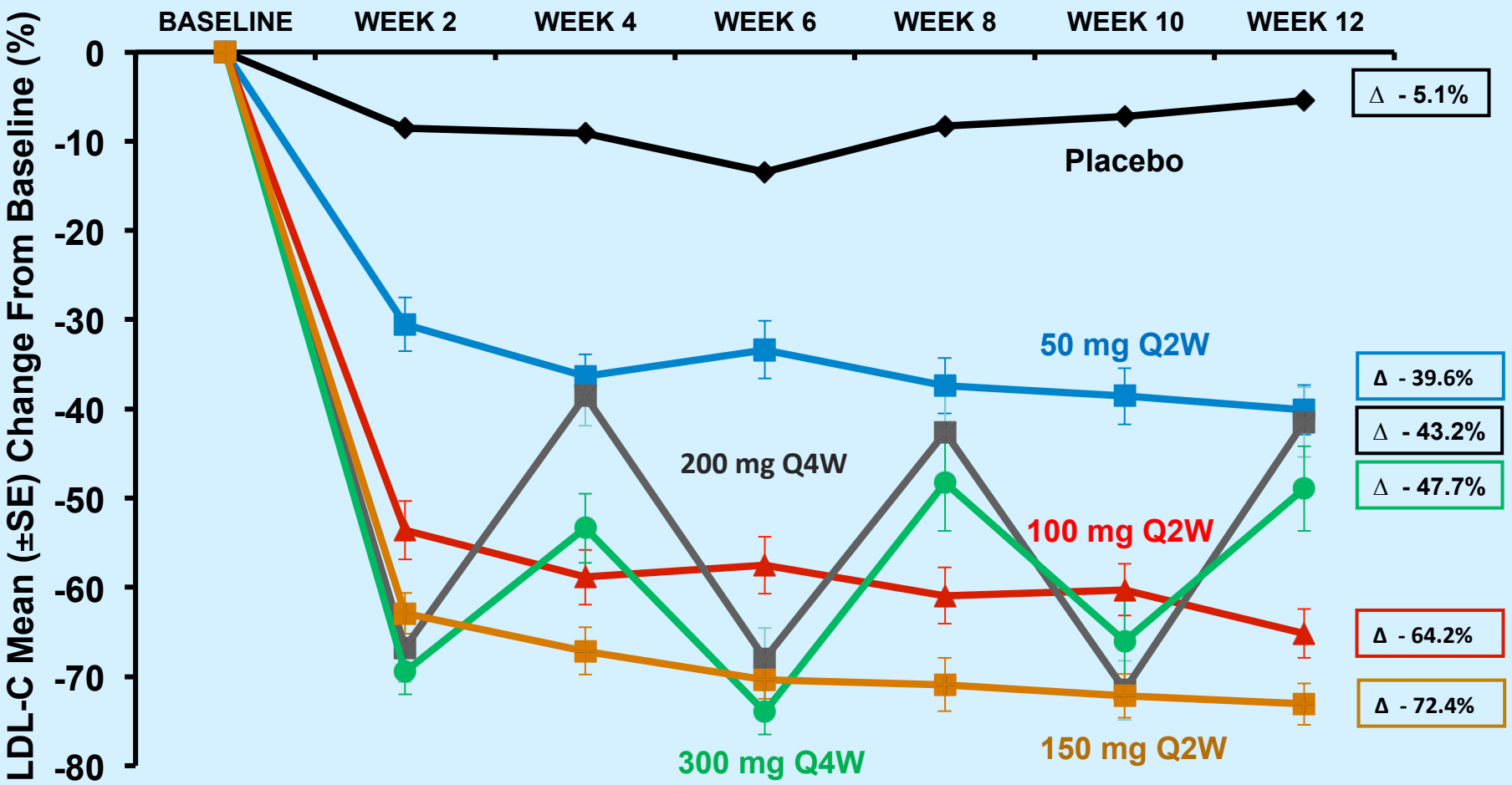
OSLER: Adverse Events by Lowest Post-Baseline LDL-C Value

	LDL-C < 25 mg/dL*	LDL-C < 50 mg/dL*	LDL-C ≥ 50 mg/dL	
Adverse events, %	**Evolocumab + SOC N = 98**	**Evolocumab + SOC N = 409**	**Evolocumab + SOC N = 323**	**SOC N = 359**
Any AE	81.6	82.2	81.1	74.7
Serious AEs	5.1	6.6	7.7	6.1
Musculoskeletal AEs	34.7	33.0	26.0	24.8
Back pain	12.2	7.6	5.3	5.6
Nervous System AEs	19.4	15.6	13.6	10.3
Headache	9.2	6.1	6.5	2.8
Memory impairment	0.0	1.0	0.3	0.0
Psychiatric AEs	5.1	4.9	4.6	3.3

SOC, stnd of care. *In SOC group, no Pts had LDL-C <25 mg/dL, and 2 had LDL-C <50 mg/dL.

Koren et al. Circulation 2014;129:234-43.

Alirocumab Ph2 Data



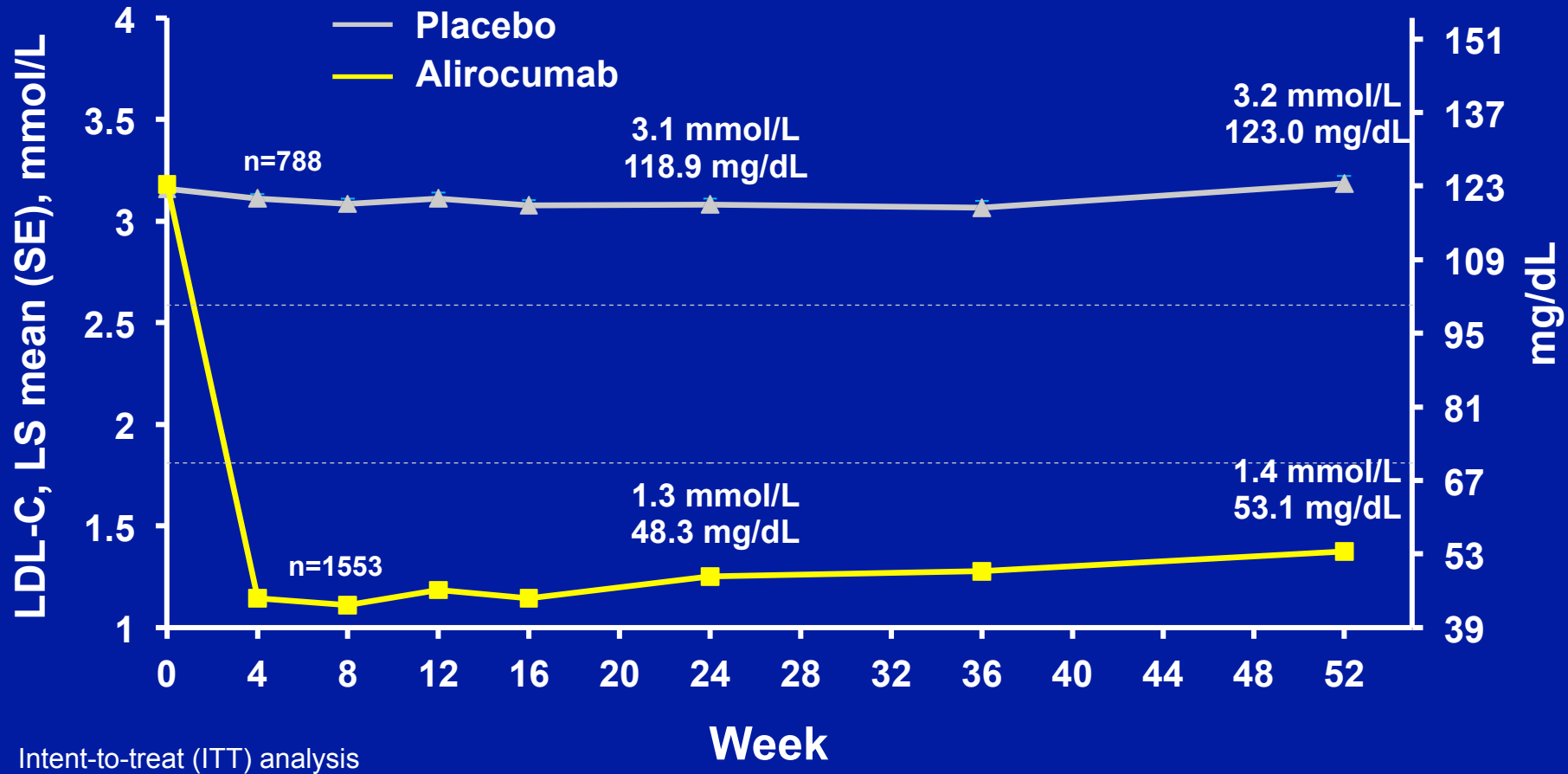
***On stable-dose atorvastatin 10 mg, 20 mg, or 40 mg; 80-mg dose not studied.**

McKenney et al. J Am Coll Cardiol. 2012;59:2344-53.

ODYSSEY Outcomes: Long-term LDL-C Reduction with Alirocumab 150 mg Q2W

Achieved LDL-C Over Time

All patients on background of maximally tolerated statin ±other lipid-lowering therapy



Intent-to-treat (ITT) analysis

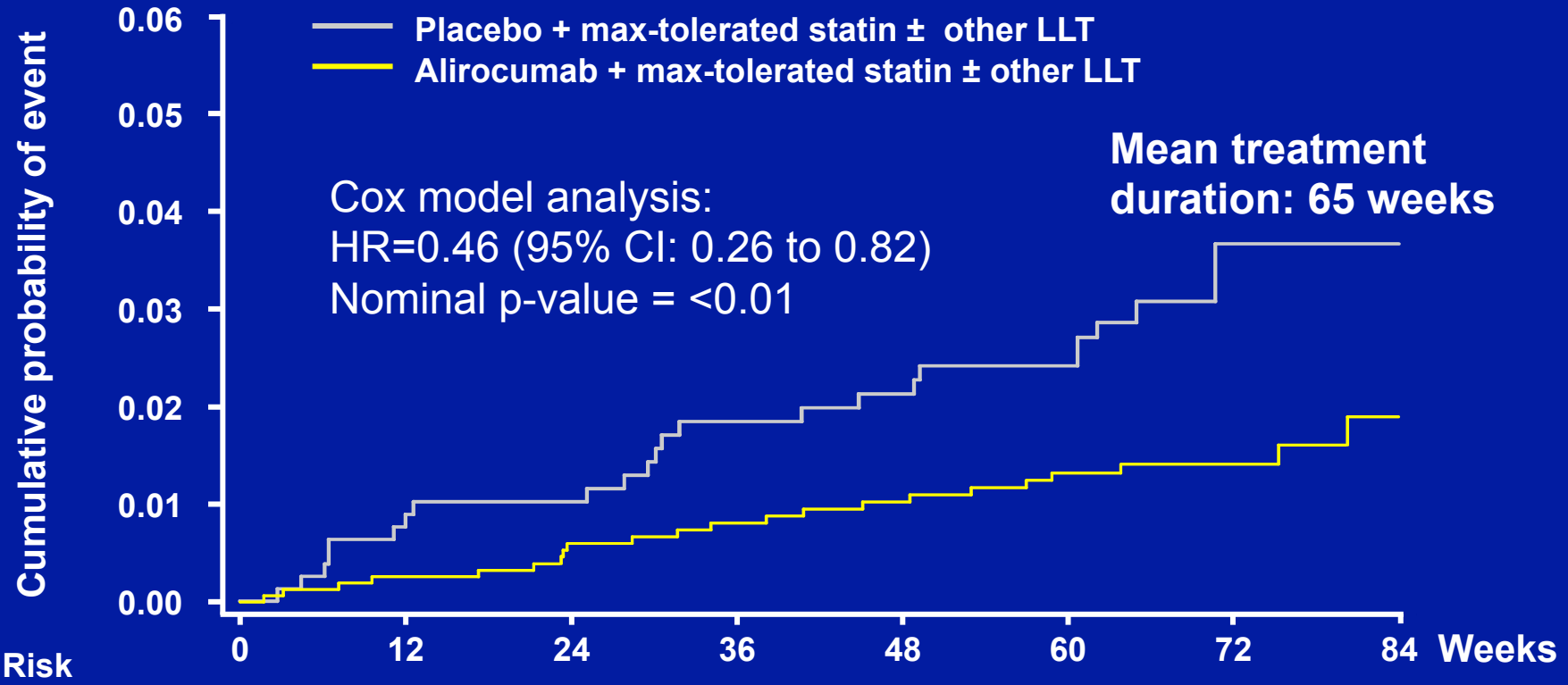
Robinson et al ESC hotline session; Barcelona Aug 31, 2014

Post-hoc Adjudicated Cardiovascular TEAEs†

Safety Analysis (at least 52 weeks for all patients in ongoing study)

Kaplan-Meier Estimates for Time to First Adjudicated Major CV Event

Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)



No. at Risk								
Placebo	788	776	731	703	682	667	321	127
Alirocumab	1550	1534	1446	1393	1352	1335	642	252

†Primary endpoint for the ODYSSEY OUTCOMES trial: CHD death, Non-fatal MI, Fatal and non-fatal ischemic stroke, Unstable angina requiring hospitalisation. LLT, lipid-lowering therapy

Robinson et al . Presented at ESC hotline session; Barcelona, Aug 31, 2014

Bococizumab: Phase II Trial

(Multicenter, randomized, double-blind, placebo-controlled)

- Statin-treated patients w/ hypercholesterolemia; LDL-C ≥80 mg/dL
- Subjects randomized to Q14d SC placebo; bococizumab 50, 100, or 150 mg; or Q28d placebo, bococizumab 200 or 300 mg
- **Results:** Bococizumab significantly reduced LDL-C across all doses

	BOCO 50 mg Q14d	BOCO 150 mg Q14d	BOCO 200 mg Q28d	BOCO 300 mg Q28d
Change from baseline in LDL-C at week 12 vs placebo, mg/dL	**-34.3**	**-53.4**	**-27.6**	**-44.9**

Ballantyne et al. Poster presented at ACC 2014.

Cardiovascular Outcomes Trials of PCSK9 Inhibitors

	Alirocumab (SAR236553 /REGN727)	Evolocumab (AMG 145)	Bococizumab (RN 316)	
Sponsor	Sanofi / Regeneron	Amgen	Pfizer	
Trial	**ODYSSEY Outcomes**	**FOURIER**	**SPIRE I**	**SPIRE II**
Sample size	18,000	22,500	12,000	6,300
Patients	4-52 wks post-ACS	MI, stroke or PAD	High risk of CV event	
Statin	Evid-based med Rx	Atorva ≥20 mg or equiv	Lipid-lowering Rx	
LDL-C (mg/dL)	≥70	≥70	70-99	≥100
PCSK9i Dosing	Q2W	Q2W or Q4W	Q2W	
Endpoint	CHD death, MI, ischemic stroke, or hosp for UA	1°: CV death, MI, stroke, hosp for UA, or cor revasc Key 2°: CV death, MI, or stroke	CV death, MI, stroke, or urgent revasc	
Completion	1/2018	12/2017	8/2017	

Conclusions

PCSK9 inhibitors:

- Robustly lower LDL-C
- Consistent effect among clinical subgroups
- Also lower TG and Lp(a); raise HDL & ApoA1 modestly
- Effective as monoRx, in conjunction w/ statins, in statin-intolerant, and in HeFH
- Appear to be safe and well-tolerated over 52 weeks
- Dedicated CV outcomes trials underway

The Roadmap of PCSK9 Inhibitors to the Clinic: Panel Discussion and Q&A

Moderator: Christie M. Ballantyne, MD

Presenters & Discussants:

Michael H. Davidson, MD

Marc S. Sabatine, MD, MPH

James A. Underberg, MD

Case 2

62-year-old black female with history of hypertension and diabetes who had PCI and stent 6 weeks ago is seen in follow-up. She has been walking on a regular basis after discharge and now complains of sore muscles in her legs and back.

PE: BMI 32 kg/m^2, waist 39"

Current meds: metformin 1000 mg BID, amlodipine 10 mg, losartan 100 mg/HCTZ 12.5 mg, ASA 81 mg, clopidogrel 75 mg, atorvastatin 80 mg

Lab Results

- TC 155 mg/dL
- HDL-C 50 mg/dL
- non-HDL-C 105 mg/dL
- TG 150 mg/dL
- LDL-C 75 mg/dL
- CK 650 U/L (ULN 200 U/L)

Case 2: Follow-up

Her atorvastatin is reduced to 10 mg. She continues to walk and complain of sore muscles but there may be some improvement. Follow-up lipids at 8 weeks:

LDL-C	100 mg/dL
TG	200 mg/dL
HDL-C	50 mg/dL
CK	440 IU

ARS QUESTION 6

What percentage of your patients on maximal dose of high efficacy statin have muscle complaints?

a. Less than 10%
b. 10 – 20%
c. 20 – 30 %
d. Over 30%
e. I don’t believe in statins or lipids

ARS

ARS QUESTION 7

Do you feel that her lipids are optimally treated?

a. Yes
b. No
c. Unsure
d. What do you mean by optimally?
e. Lipids are not important, it's all about inflammation

ARS QUESTION 8

Would of the following would you consider the best option?

a. Increase atorvastatin to 40 mg
b. Change to rosuvastatin 10 mg
c. Change to pravastatin 10 mg
d. Add ER niacin and titrate to 2000 mg
e. Add ezetimibe 10 mg
f. Add colesevalam 625 mg 3 po bid
g. Chelation therapy

Question

How would you discuss this with the patient?