The Wide Spectrum of Familial Hypercholesterolemia: Discovering Your Highest Risk Patients and Optimizing Treatment

Supported by educational grants from Aegerion Pharmaceuticals, Inc. and Genzyme, A SANOFI COMPANY

Endorsed by The FH Foundation

Opening Remarks

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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.

Familial Hypercholesterolemia: A Genetic Disease in Transition

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Cardiometabolic Health Congress
October 22 - 25, 2014 • Boston, MA

Origin of Familial Hypercholesterolemia (FH)

- Goldstein and Brown: 1972 defective HMG Coenzyme A Reductase. 1973 correction - defect in the LDL receptor was the basis of FH
- Original presumption: Mutation in LDLR gene causing defective function
- Single mutation with Heterozygous FH (HeFH) prevalence 1/500 and Homozygous FH (HoFH) prevalence 1/1,000,000. Estimates based upon Hardy Weinberg Equilibrium

Goldstein, Brown. Proc Nat Acad Sci. 1973;70:2804-08.

Evolution of FH

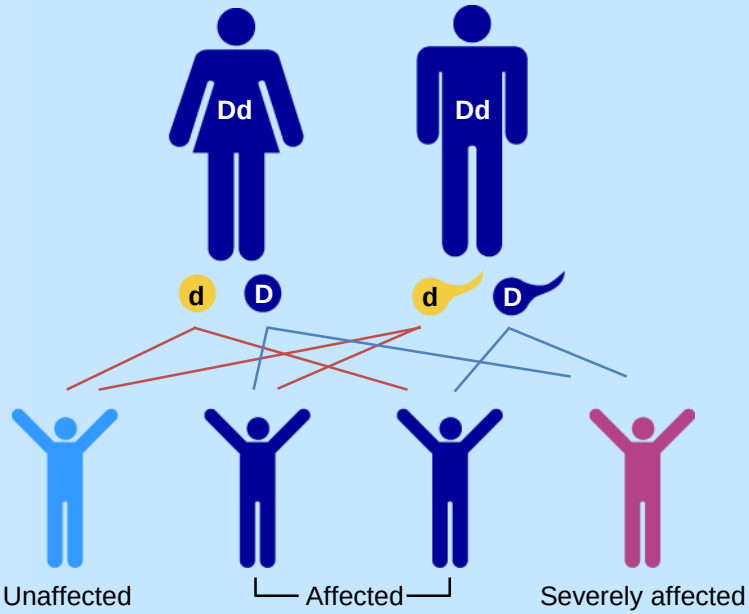
- Three genes responsible for Autosomal Dominant FH: LDLR, PCSK9, apoB
- Over 1,700 mutations in LDLR alone, many of them being pathogenic. Varying degrees of receptor activity
- Homozygous FH redefined:
  - True HoFH
  - Compound Heterozygous HoFH
  - Double Heterozygous HoFH

Soutar, Naoumova . Nat Clin Pract Cardiovasc Med. 2007;4:214-25.
Goldberg et al. J Clin Lipidol. 2011;5:133-40.

FH Is Almost Always Autosomal Dominant

- ≈70% identified FH-causing mutations are in the LDL receptor gene (*LDLR*). Less common defects include mutations in *APOB* or *PCSK9* genes[1] Unknown mutations account for 25%.
- Heterozygotes inherit a single abnormal gene from one parent. Given the dominant mode of inheritance, these individuals manifest the disorder.[2]
- Heterozygotes have approximately 2- to 3-fold higher serum LDL-cholesterol levels than normal.[2]
- Homozygotes inherit an abnormal gene from both parents. They typically have an LDL-cholesterol level 3- to 6-fold higher than normal.[2]

Autosomal Dominant
LDLR, ApoB, and PCSK9 mutations



A small spectrum of affected heterozygotes may have unusually severe phenotypes[3,4]

1. Marais. Clin Biochem Rev. 2004;25:49-68.
2. Vella et al. Mayo Clin Proc. 2001;76:1039-46.
3. Pisciotta et al. Atherosclerosis. 2006;186:433-40.
4. Tai et al. Clin Chem. 2001;47:438-43.

FH Starts Before Birth!

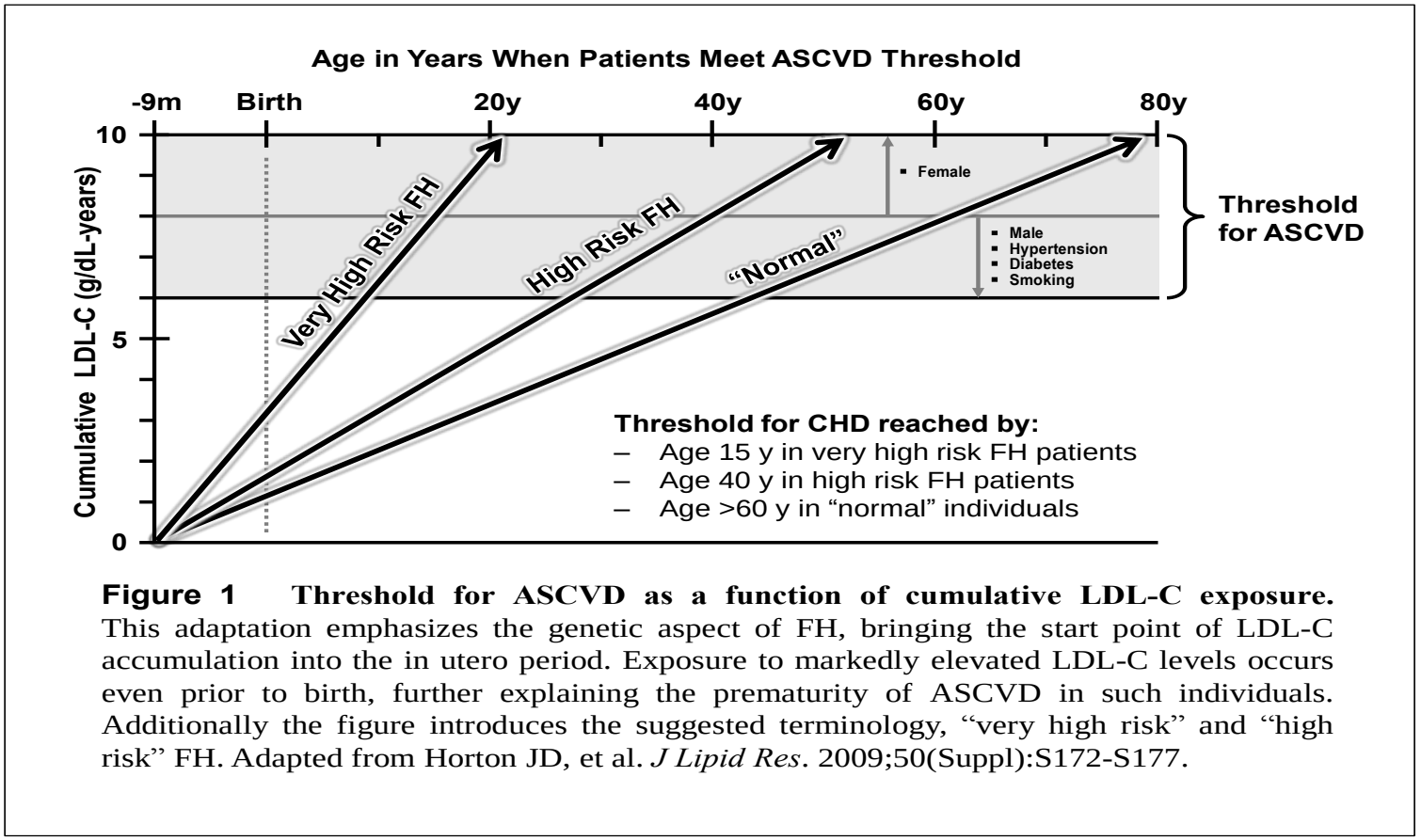


Figure 1 Threshold for ASCVD as a function of cumulative LDL-C exposure. This adaptation emphasizes the genetic aspect of FH, bringing the start point of LDL-C accumulation into the in utero period. Exposure to markedly elevated LDL-C levels occurs even prior to birth, further explaining the prematurity of ASCVD in such individuals. Additionally the figure introduces the suggested terminology, "very high risk" and "high risk" FH. Adapted from Horton JD, et al. *J Lipid Res*. 2009;50(Suppl):S172-S177.

Baum et al. J Clin Lipidol. 2014; doi. 10.1016/j.jacl.2014.09.005.

Improved Understanding of FH has Yielded New Prevalence Estimates

- HeFH approximately 1/200
- HoFH approximately 1/160,000
- Higher prevalence in Founder populations such as French Canadians, Ashkenazi Jews, South African Afrikaners, Christian Lebanese
- Huge LDL-C overlap between HeFH, HoFH, and even polygenic LDL disorders

Sjouke et al. Eur Heart J. 2014:ehu058

LDL-C Range in HoFH: Bigger than Believed!

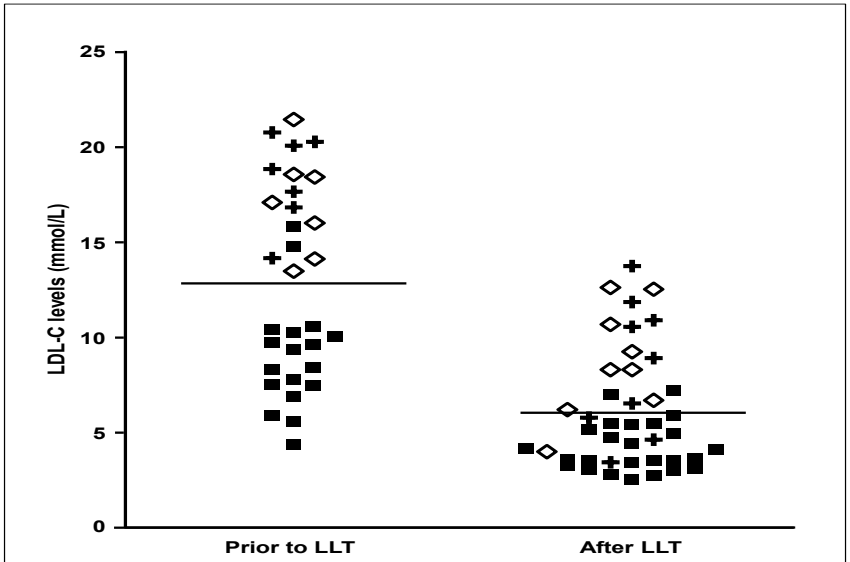


Figure 2 Low-density lipoprotein-cholesterol levels in homozygous autosomal dominant hypercholesterolaemia patients prior and after LLT. Plus indicates patients with two null alleles. Open diamond indicates patients with one null allele and one defective allele. Closed square indicates patients with two defective alleles. Horizontal lines indicate mean LDL-C levels. Statin naïve LDL-C levels were available for 32 homozygous autosomal dominant hypercholesterolaemia patients. Treated LDL-C levels were avail-able for 43 homozygous autosomal dominant hypercholesterol-aemia patients. LLT, lipid-lowering therapy. Reprinted with permission from the European Heart Journal. Sjouke B, Kusters DM, Kindt I, et al. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype–phenotype relationship, and clinical outcome. *Eur. Heart J.* 2014:ehu058.

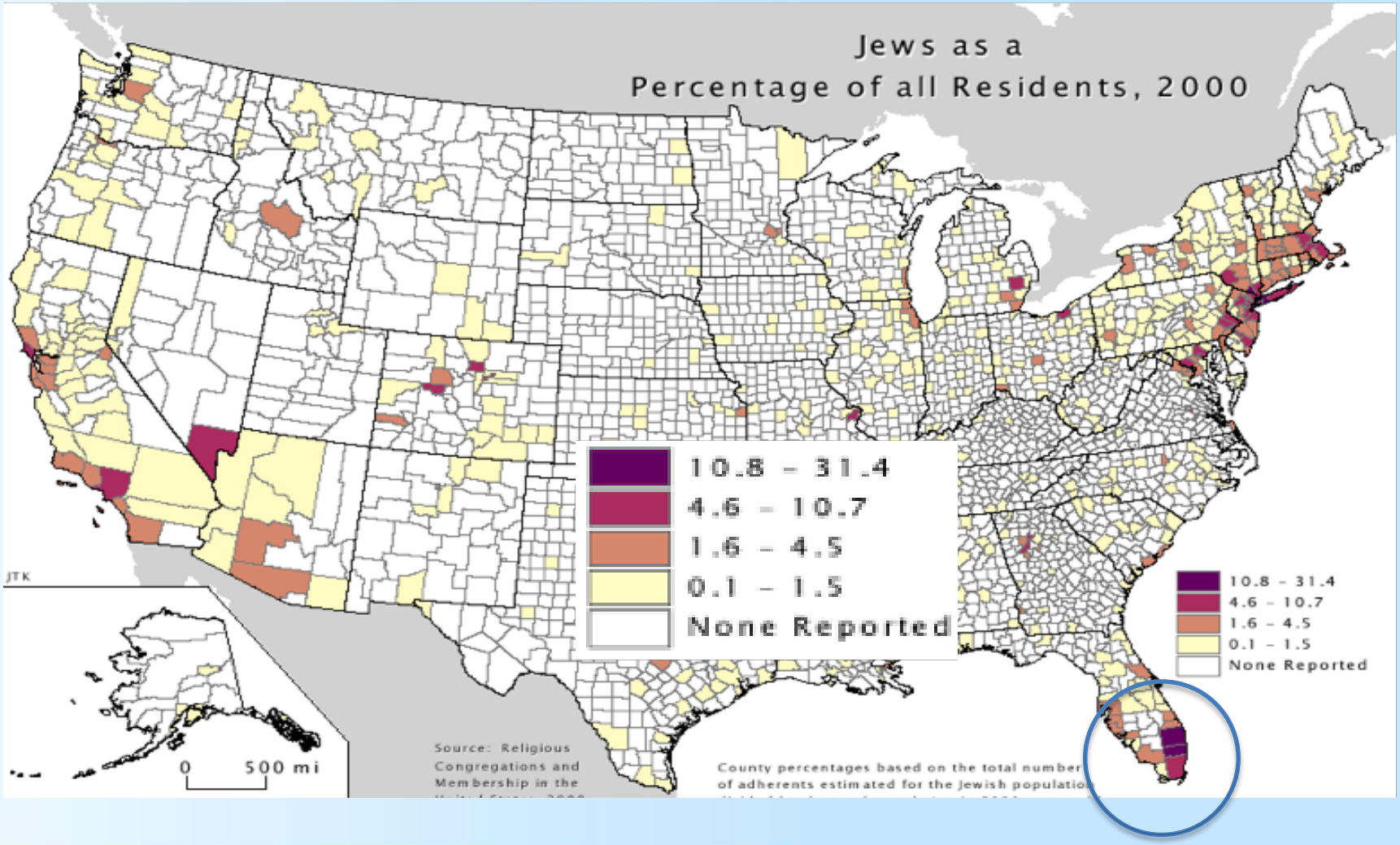
Sjouke et al. Eur Heart J. 2014:ehu058

Continued Undiagnosed and Concomitant Undertreated FH

- Fewer than 10% of FH patients diagnosed in many nations, including the US
- Healthcare practitioners continue to see FH as rare
- Diagnosis is complex: Relies upon FHx, Patient's history, PE, LDL-C level, Response to LLT
- Non-paternity and possible de novo mutations make diagnosis even more difficult
- Although FH is predominantly an LDL disorder, other lipid abnormalities can occur

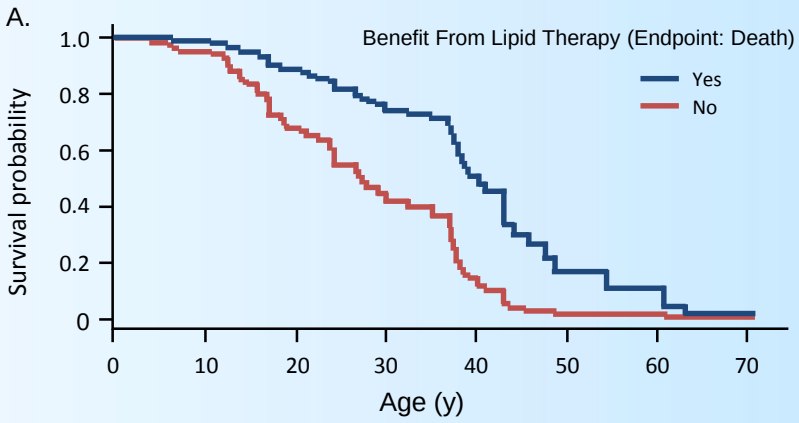
Nordestgaard et al. Eur Heart J. 2013; 34:3478-90.

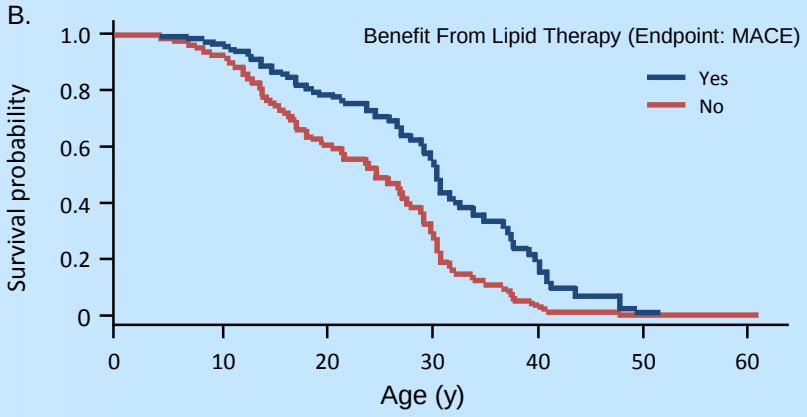
We Must Know Our Audience



Consequence of Under-Recognition and Under-treatment

- FH carries a 20x increased risk of ASCVD
- ASCVD events are usually premature
- FH causes 20% of All MIs in patients ≤ 45 years old
- Inadequate Cascade Screening
- Even in HoFH, treatment improves outcomes





Adapted from Raal et al. Circulation. 2011;124:2202-07.

A Modern Motto to Guide our Management of the FH Patient

- In the early days of thrombolysis we proclaimed:
  "Time is Muscle"
- Today, for those with FH our dictum must be:
  "Time is Plaque"

Baum et al. J Clin Lipidol. 2014;
doi. 10.1016/j.jacl.2014.09.005.

A Consideration

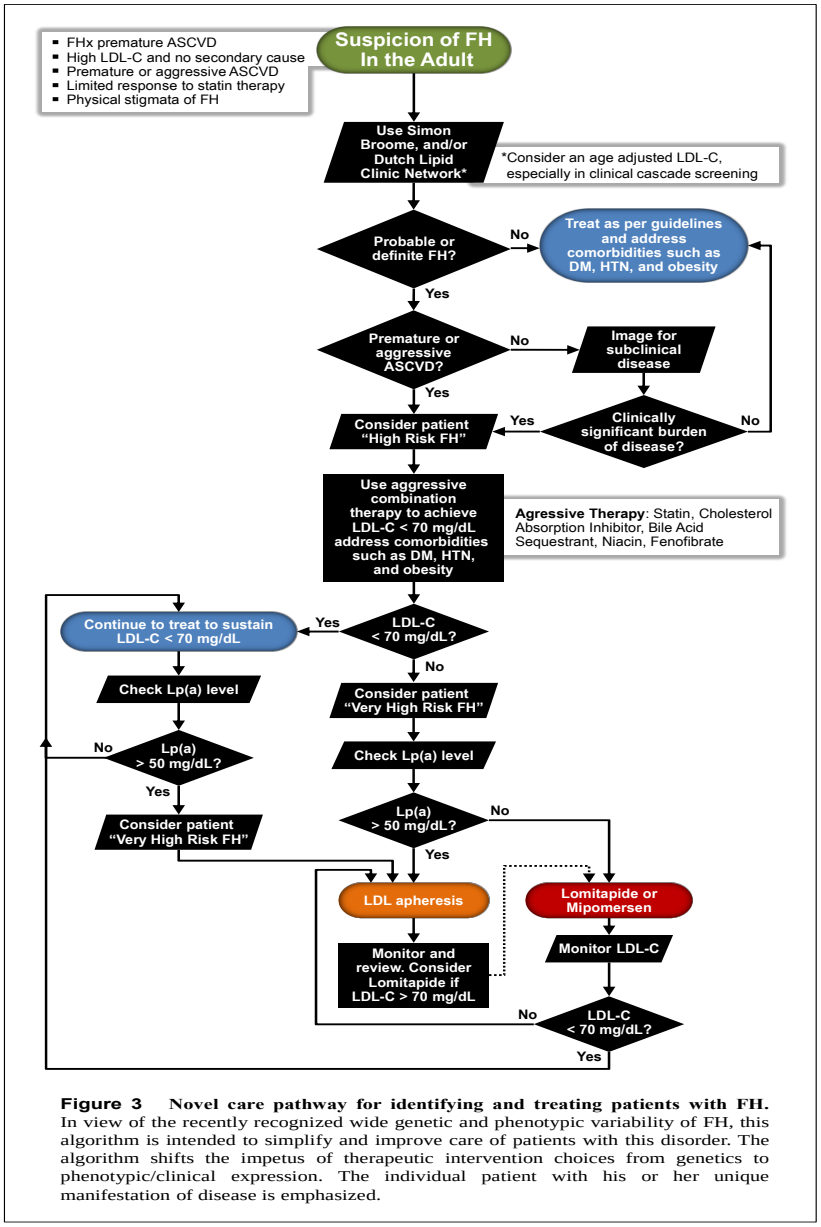


Figure 3 **Novel care pathway for identifying and treating patients with FH.** In view of the recently recognized wide genetic and phenotypic variability of FH, this algorithm is intended to simplify and improve care of patients with this disorder. The algorithm shifts the impetus of therapeutic intervention choices from genetics to phenotypic/clinical expression. The individual patient with his or her unique manifestation of disease is emphasized.

Baum et al. J Clin Lipidol. 2014;
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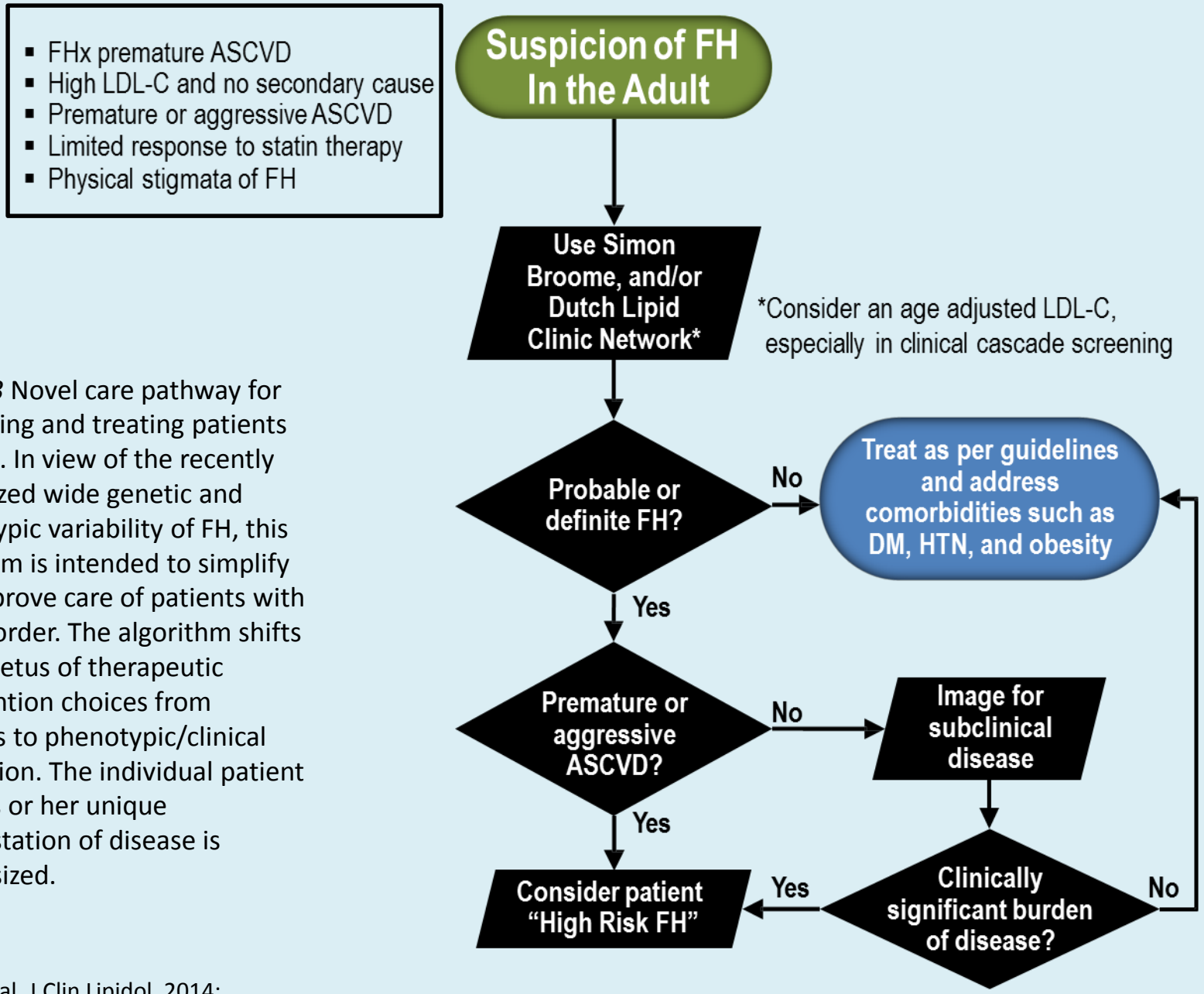

Figure 3 Novel care pathway for identifying and treating patients with FH. In view of the recently recognized wide genetic and phenotypic variability of FH, this algorithm is intended to simplify and improve care of patients with this disorder. The algorithm shifts the impetus of therapeutic intervention choices from genetics to phenotypic/clinical expression. The individual patient with his or her unique manifestation of disease is emphasized.

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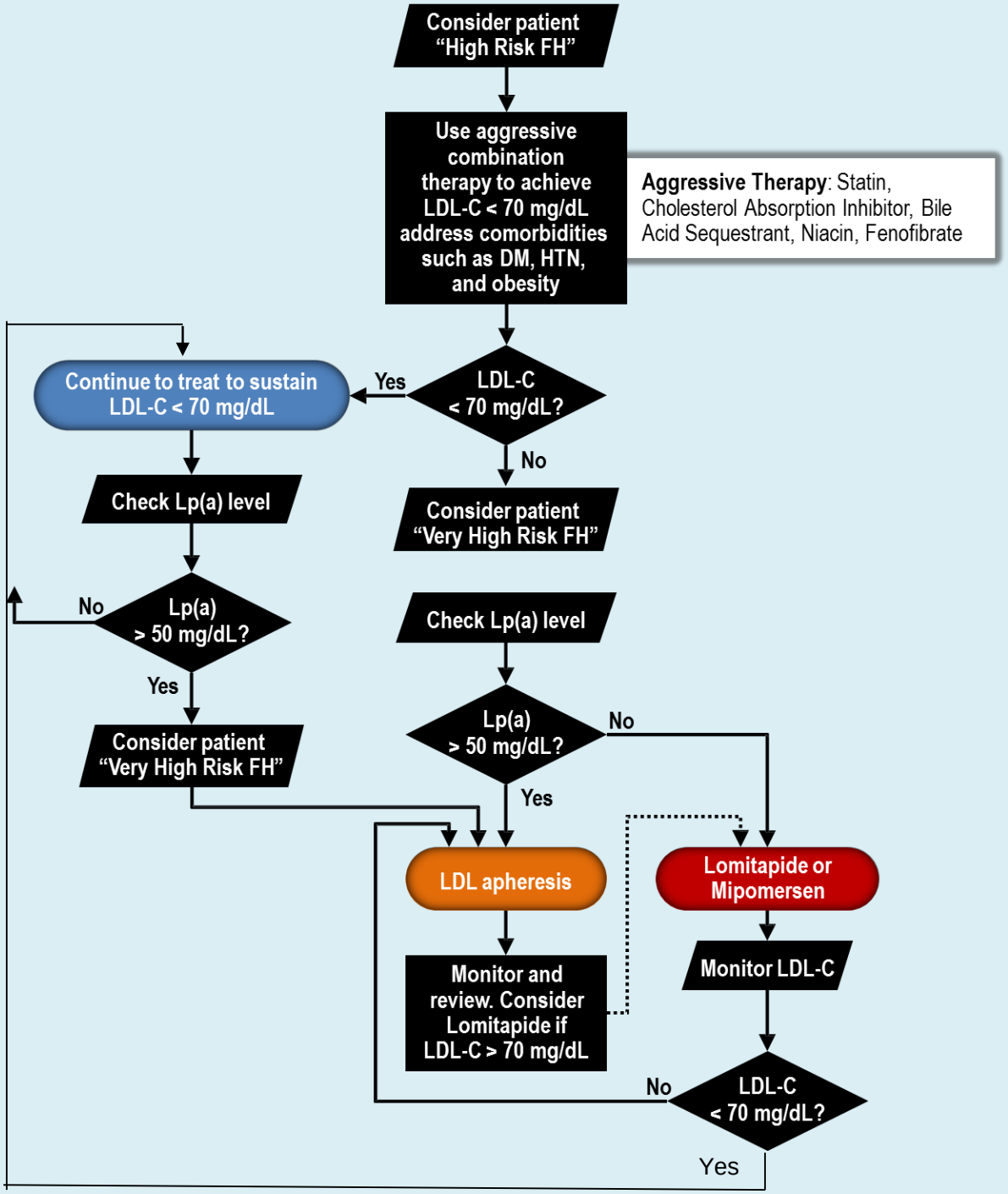


Baum et al. J Clin Lipidol. 2014;
doi. 10.1016/j.jacl.2014.09.005.

Strategies for Early Identification, Diagnosis, and Cascade Screening

Sarah de Ferranti, MD, MPH
Director, Preventive Cardiology Program
Assistant Professor of Pediatrics
Harvard Medical School
Boston, Massachusetts

Topics

- Screening
  - Strategies: selective, universal, cascade, genetic
- Diagnosing Familial Hyperlipidemia in childhood
  - Research diagnostic criteria
  - Clinical diagnosis
- Future avenues for refining treatment of pediatric lipid disorders
  - Genetic testing
  - Non-invasive imaging
- Transitioning from pediatric to adult provider

PEDIATRIC LIPID SCREENING

Pediatric Lipid Screening in the US

- Selective screening based on family history and/or personal risk factors (AAP)

Measure fasting lipid profile twice,[a] average results if:

Parent, grandparent, aunt/uncle, or sibling with MI, angina, stroke, CABG/stent/angioplasty at <55 y in males, <65 y in females

Parent with TC ≥ 240 mg/dL or known dyslipidemia

Parent with TC ≥ 240 mg/dL or known dyslipidemia

Child has diabetes, hypertension, BMI ≥ 95th percentile or smokes cigarettes

Child has a moderate- or high-risk medical condition (Table 5-2)

Daniels, Greer. Pediatrics. 2008;122:198-208; Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics. 2011;128 Suppl 5:S213-S256

Pediatric Lipid Screening in the US

- Selective screening based on family history and/or personal risk factors (AAP)
- Universal lipid screening all children once between the ages 9-11 years, and again between 17-21 years (NHLBI)

Non-FLP: **Calculate non–HDL cholesterol:**

Non–HDL cholesterol = TC − HDL cholesterol

If non-HDL ≥ 145 mg/dL ± HDL < 40 mg/dL[b]:

Obtain FLP twice,[a] average results

Daniels, Greer. Pediatrics. 2008;122:198-208; Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics. 2011;128 Suppl 5:S213-S256

Pediatric Lipid Screening in the US

- Selective screening based on family history and/or personal risk factors (AAP)
- Universal lipid screening all children once between the ages 9-11 years, and again between 17-21 years (NHLBI)
- USPSTF: “I” Not able to make any recommendation about cholesterol screening during childhood (USPSTF)

A Vigorous Discussion

NHLBI Integrated Guidelines on Cardiovascular Disease Risk Reduction: Can We Clarify the Controversy about Cholesterol Screening and Treatment in Childhood?

Moderator: Sarah D. de Ferranti[1,2,3*]
Experts: Stephen R. Daniels,[4,5] Matthew Gillman,[6] Louis Vernacchio,[7,8] Jorge Plutzky,[9,10] and Annette L. Baker[11]

ONLINE FIRST

Universal Scre of Dyslipidem

Bruce M. Psaty, MD, PhD
Frederick P. Rivara, MD, MPH

the use of statins and their indications have expanded. By 2005, an estimated 30 million Americans were taking statins, and in 2009, both simvastatin and atorvastatin were

Is Universal Pediatric Lipid Screening Justified?

Matthew W. Gillman, MD, SM
Stephen R. Daniels, MD, PhD

IN LATE 2011, AN EXPERT PANEL CONVENED BY THE NA- [illegible] (NHLBI), of which [illegible] guidelines

Fourth, relying on family history to drive the screening process, advocated by the American Academy of Pediatrics in 2008 and a previous NHLBI-sponsored panel in 1992, will miss many children with elevated LDL-C levels.[3,4]

However, even together these factors do not necessarily amount to a solid rationale for universal screening. Most ran-

New Studies Fuel Controversy Over Universal Cholesterol Screening During Childhood

Psaty et al. JAMA 2012;307:257-8; Gillman et al. JAMA 2012;307:259-60; de Ferranti et al. Clin Chem 2012;58:1626-30; Merz. JAMA 1989;261:861.

Cascade Screening for FH

- Screening relatives of index cases
  - Includes “reverse” cascade screening, e.g., the child identifies the higher-risk adult relative
- Can use lipid profiles or genetic testing
  - LDL > 130 mg/dL (3.5 mmol/L) in a child suggests FH in a relative of a confirmed FH index case
  - Can use MedPed criteria
    - Lipid cutpoints vary based on proximity of the relative
- Implemented in Wales and the Netherlands, not formally recommended in the US
  - Requires robust pool of index cases in order to efficiently identify new cases

PEDIATRIC SCREENING IN PRACTICE: Are Clinicians Screening for Lipid Disorders During Childhood?

Surveying Pediatric Providers About Lipid Screening – 1988, 1998

- Telephone surveys
  - Asked 1036 family practitioners, pediatricians, and general practitioners about their knowledge and practices related to cholesterol screening and treatment children*
- 75-80% reported screening for lipid disorders
  - Survey did not collect data on patient population or rates of testing or screening

*Kimm et al. Am J Dis Child. 1990;144:967-72; Kimm et al. Pediatrics 1998;102:E50.

Surveying Minnesota Providers About Cholesterol Screening – 2013

548 clinicians – pediatricians, NPs, family practice, general practice providers

- 74% supported lipid screening to reduce CVD
- Yet 34% did not screen for lipid disorders at all
- Of those who did screen:
  - 50% screened selectively
  - 16% screened universally
- Most (84%) were uncomfortable managing pediatric lipid disorders themselves

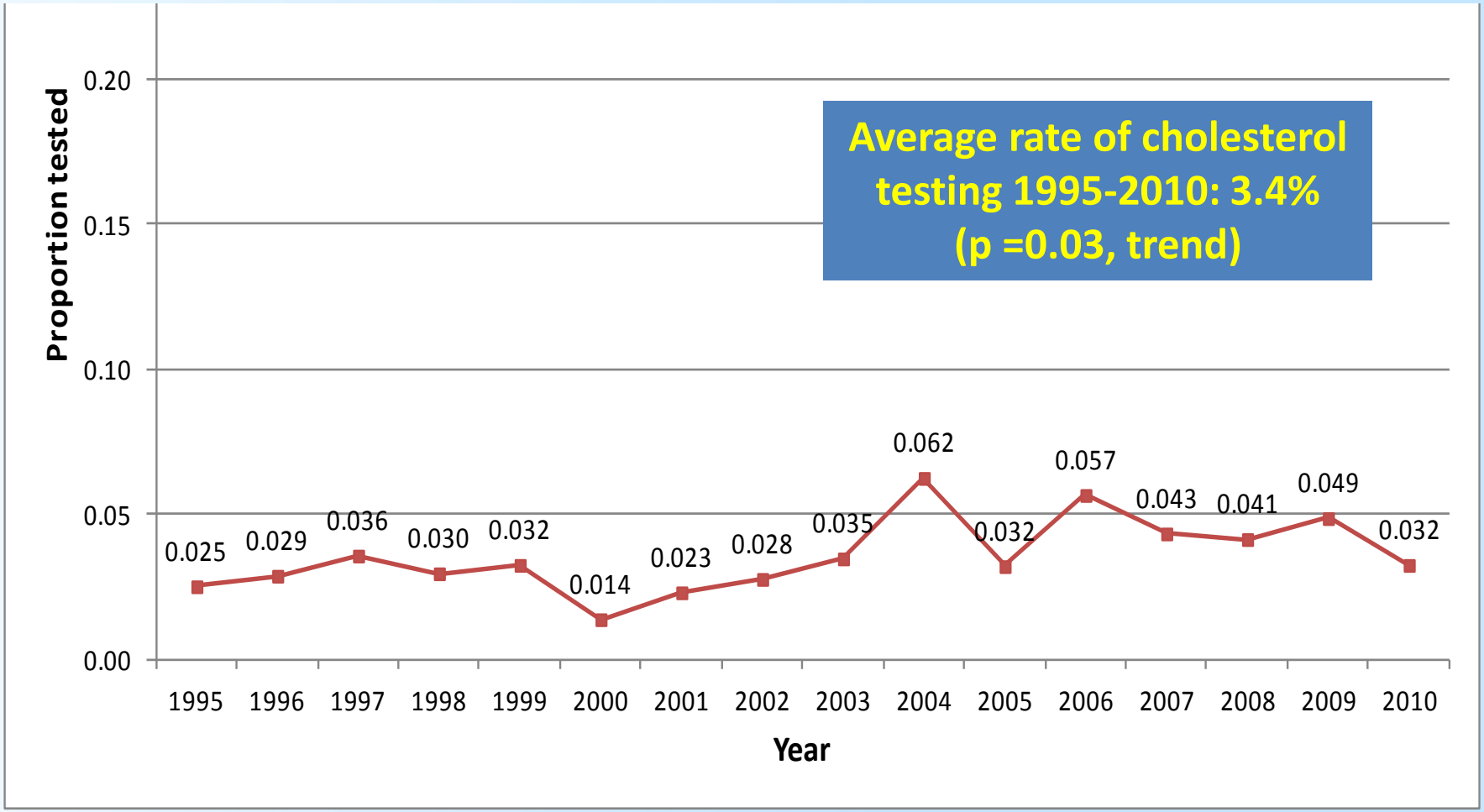
Dixon et al. J Pediatr 2014;164(3):572-576.

Measuring Cholesterol Testing Rates in US Pediatric Outpatient Visits

- US National Ambulatory Medical Care Survey
  - Repeated cross-sectional surveys, weighted to be nationally representative
- What is the rate of cholesterol testing at health maintenance visits
  - Recorded during 10,159 outpatient visits
  - Children aged 2 to 21 years
  - 1995 through 2010

Vinci et al. JAMA 2014;311:1804-7.

Pediatric Cholesterol in Ambulatory Visits – 1995-2010



Vinci et al. JAMA 2014;311:1804-7.

Predictors of Cholesterol Testing

- Adolescence
- Non-white race/ethnicity
- BMI ≥ 95th%tile
- Private insurance
- Living in the South or Northeast

<u>Study Limitations</u>:

Could not assess

- indications for testing (e.g., presence of family history)
- intention of testing (screening vs. f/up)

Vinci SR, et al. JAMA 2014

Rates of Cholesterol Testing in HMOs

- Electronic record review of 301,080 children ages 3-19 cared for 2007-2010
- 9.8% were tested
- Testing was more frequent in children with
  - Obesity (vs normal weight)
  - Adolescence (vs childhood)
- Abnormal results were as expected
  - TC 8.6%, HDL 22.5%, non-HDL 12.0%
  - LDL 8.0%, TG 21%

DIAGNOSING FH IN CHILDHOOD

Diagnostic Criteria for HeFH

- Simon Broome (UK, 1991)
  - Definite or probable
  - Includes genetic criteria

Pediatric: TC>260 mg/dL, LDL >155 mg/dL Definite: + xanthoma OR gene positive Probable: + family history

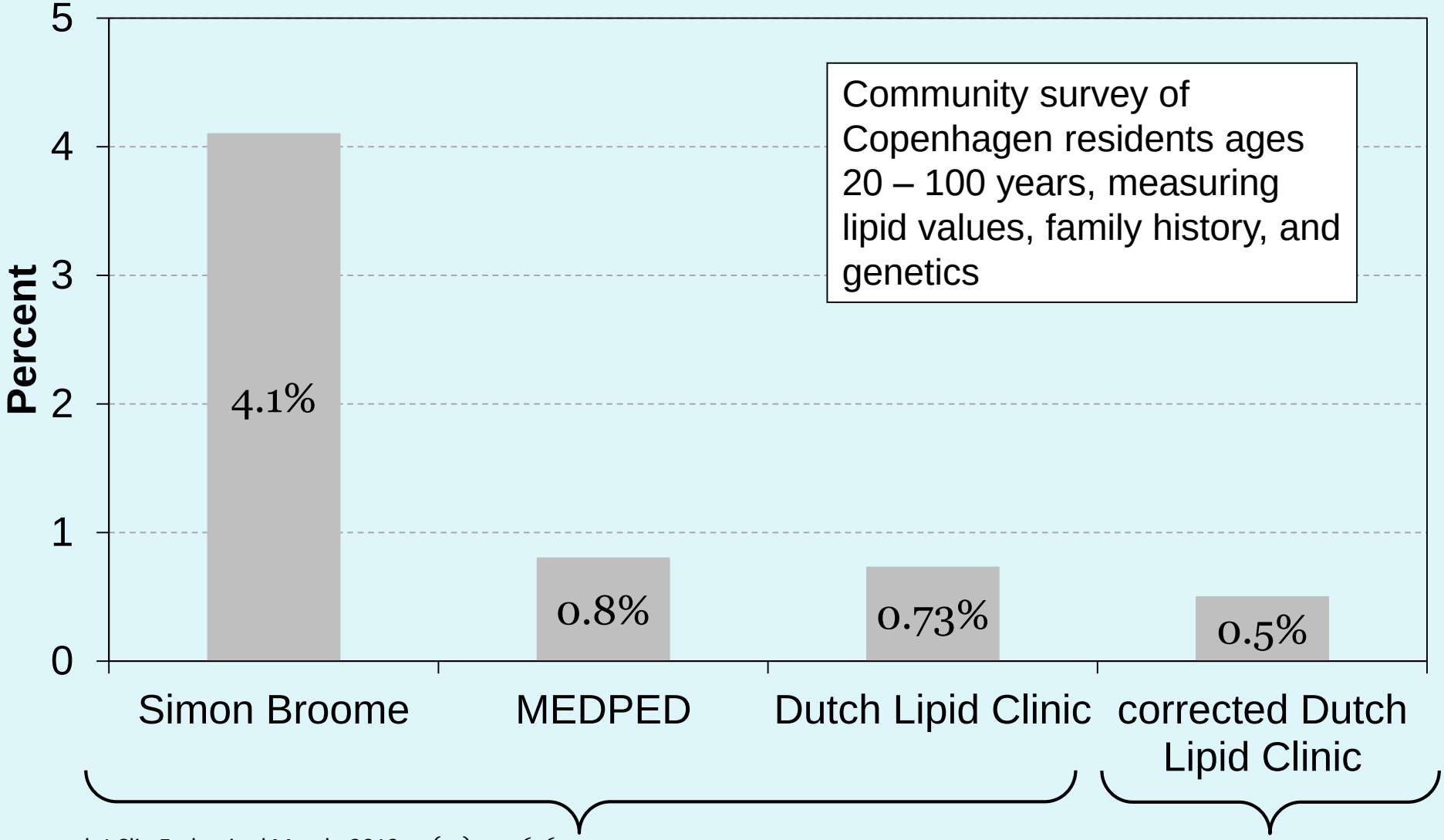
- MEDPED (US, 1993)
  a.k.a Make Early Diagnosis to Prevent Early Death
  - Definite or probable

Relative with FH TC or LDL criteria based on degree of relatedness (↑ lipid cutpoint if more distant)

- Dutch Lipid Clinic Network (NED, 1999)
  - Definite, probable or possible

Point-based system Includes: TC or LDL, xanthoma, gene testing, personal history of cardiovascular events Definite: >8, probable 6-8, possible 3-5

Prevalence of Probable + Definite FH in a Community Sample

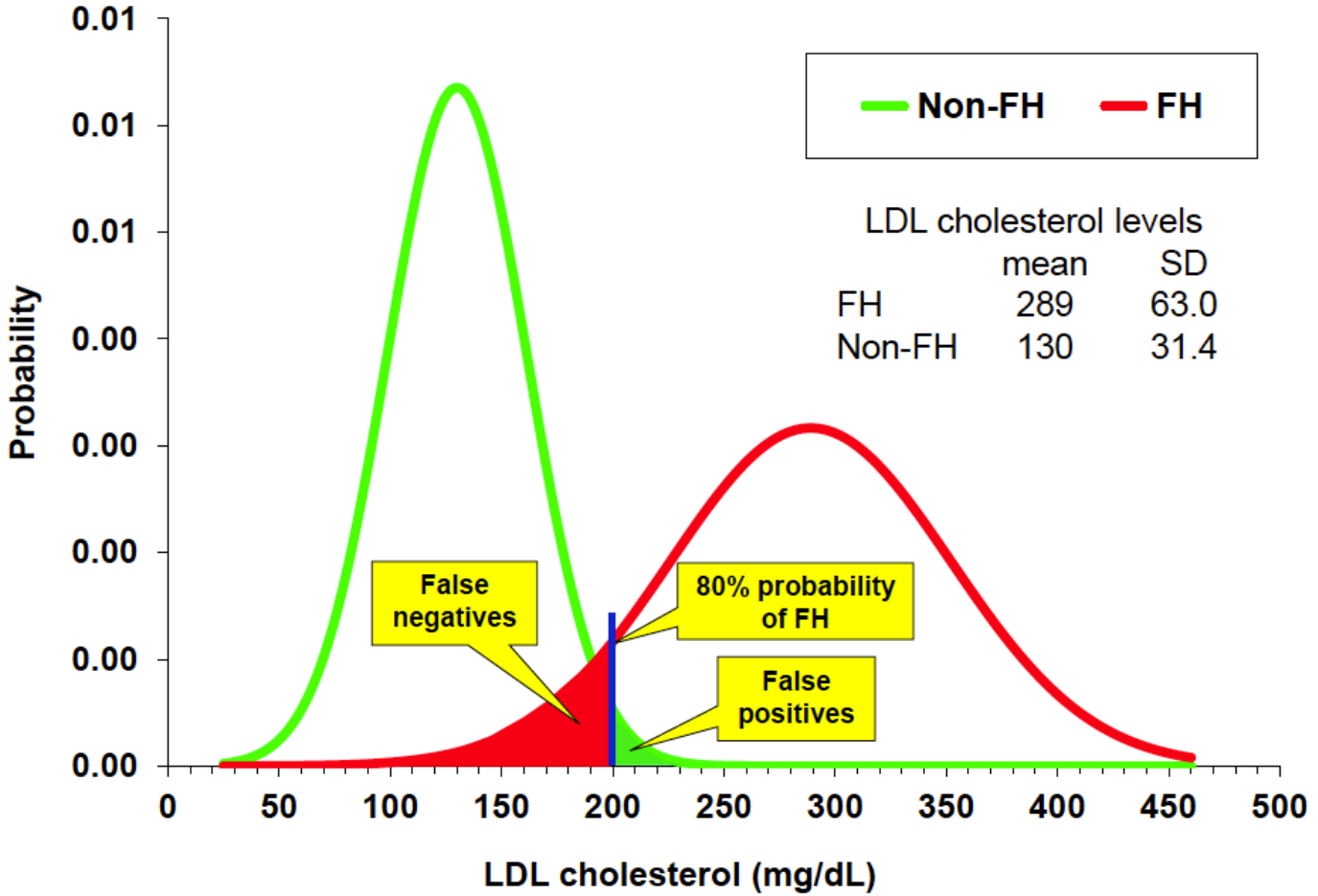


Benn et al. J Clin Endocrinol Metab. 2012 97(11):3956-64
Nordestgaard, et al. Eur Heart J. 2013

Clinical Diagnosis of Heterozygous FH in Childhood

- Untreated LDL-C ≥190 mg/dL
  - Some might use LDL-C ≥160 mg/dL
- Untreated LDL-C ≥160 mg/dL with family history of early atherosclerosis or high cholesterol in 1st and 2nd degree relatives

Lipid Values with and without FH



Hopkins PN. Clin Lipidol 2010

Clinical Diagnosis of Homozygous FH

- Cutaneous xanthomas before the age of 10, typically in the 1st year of life
- Untreated LDL-C ≥500 mg/dL (>13 mmol/L)
  - Some use LDL-C ≥400 mg/dL
  - Most patients have much higher levels

GENETIC TESTING FOR FH

Genetic Testing

- Yield depends on the patient population tested
  - Patients with xanthomas and high LDL ~70%
  - Patients with pre-clinical athero and high LDL 50-60%
- Not commonly used in the US due to provider/patient concerns
  - Cost
  - Future insurability
- Included as part of a comprehensive cascade screening program in the Netherlands
- Potential applications
  - The Gray Area

ROLE OF NON-INVASIVE IMAGING IN CHILDREN WITH FH

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
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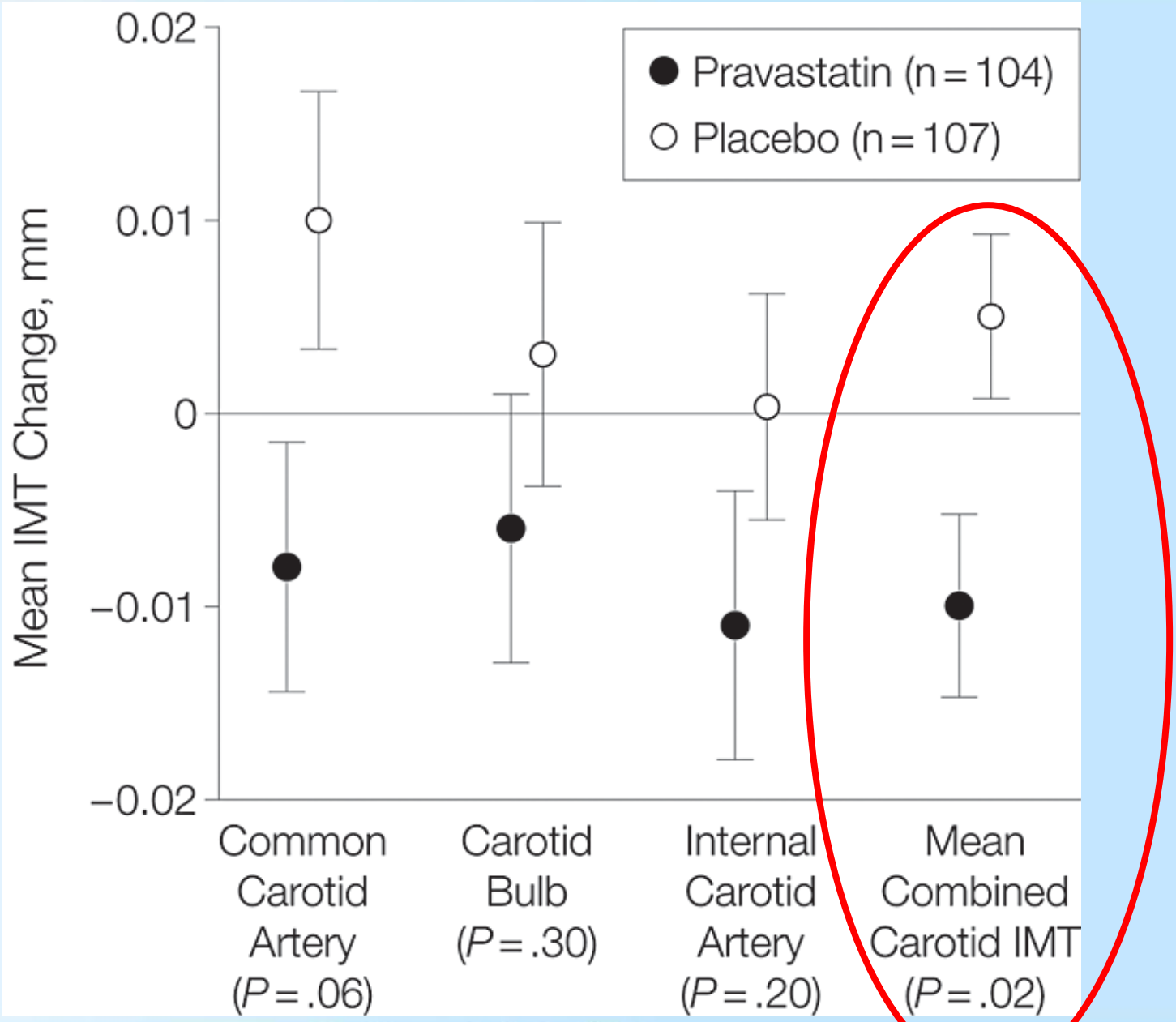
Pediatric Cardiology

Statin Treatment in Children With Familial Hypercholesterolemia

The Younger, the Better

Jessica Rodenburg, MD, PhD; Maud N. Vissers, PhD; Albert Wiegman, MD, PhD; A.S. Paul van Trotsenburg, MD, PhD; Anouk van der Graaf, MD; Eric de Groot, MD, PhD; Frits A. Wijburg, MD, PhD; John J.P. Kastelein, MD, PhD; Barbara A. Hutten, PhD

Background—We previously demonstrated in a randomized placebo-controlled trial that 2-year pravastatin treatme induced a significant regression of carotid intima-media thickness (IMT) in 8- to 18-year-old children with famili hypercholesterolemia. Subsequently, we continued to follow up these children to explore the relation between the a of statin initiation and carotid IMT after follow-up on statin treatment. We also examined safety aspects of statin thera during this long-term follow-up.

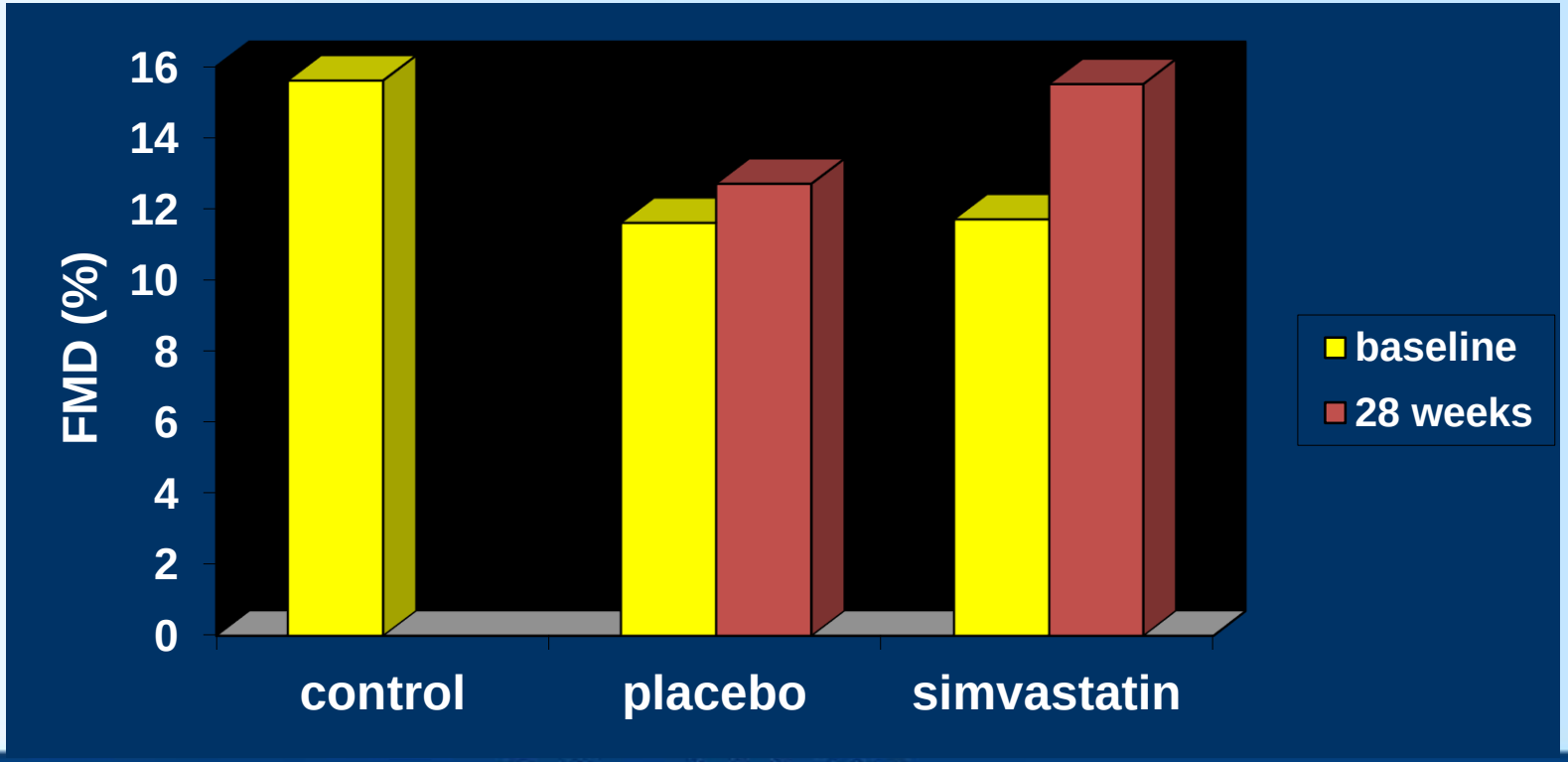


Lohia et al JAMA. 2004;292:331-37.

Statin Therapy Restores Endothelial Function in Children with FH

n=50 children with FH, age 9-18 yrs; 19 controls

Double-blind randomized clinical trial 40 mg simvastatin for 28 weeks; assessed FMD at baseline and 28 weeks



de Jongh et al, JACC 2002;40:2117-21

Pediatric Cases – The Gray Area

- 12-year-old with LDL 165-180 mg/dL
  - optimal lifestyle modification
  - many family members treated for high cholesterol but no family history of early CVD
- 14-year-old with LDL 150 mg/dL
  - family history of early CVD and high cholesterol
- 17-year-old LDL 145 mg/dL, HDL 32
  - obesity despite lifestyle counseling
  - family history of early CVD

2011 Guidelines say no pharmacotherapy

TRANSITIONING CARE AND THE YOUNG ADULT WITH FH

Adolescents Becoming Young Adults

Pediatric

- Guidelines
  - Universal screening poorly accepted
  - Treatment focused on LDL level
- Patient population
  - Parent plays a large role in treatment decisions
  - Patient feels invincible
  - Patient regularly seeks medical care (required for school)

Adult

- Guidelines
  - Universal screening well accepted
  - Treatment based on future (30-year) risk of CVD events
- Patient population
  - Parent not involved in treatment decisions
  - Patient may have other (competing) medical conditions
  - Patient rarely seeks medical care, may have no/marginal health insurance

Summary

- Pediatric lipid screening recommendations have broadened, but still uptake is low
- Clinical definitions for FH in childhood are primarily derived from adult definitions
- Genetic testing and non-invasive testing for pre-clinical atherosclerosis may have a role in the future diagnosis and care of FH patients
- Guideline gap in the transition from pedi to adult care may leave FH patients vulnerable

Advanced Approaches for Optimizing Outcomes in the Severe FH Patient

Patrick M. Moriarty, MD
Professor of Medicine
Director of Clinical Pharmacology and
the Atherosclerosis/Lipoprotein-apheresis Center
University of Kansas Medical Center
Kansas City, Missouri

Overview

- Present therapy for FH patient population
- Lipoprotein-apheresis (LA): techniques, guidelines and efficacy
- Lp(a): Its association with FH and present therapies

Mechanism of Action of Current Therapies for FH

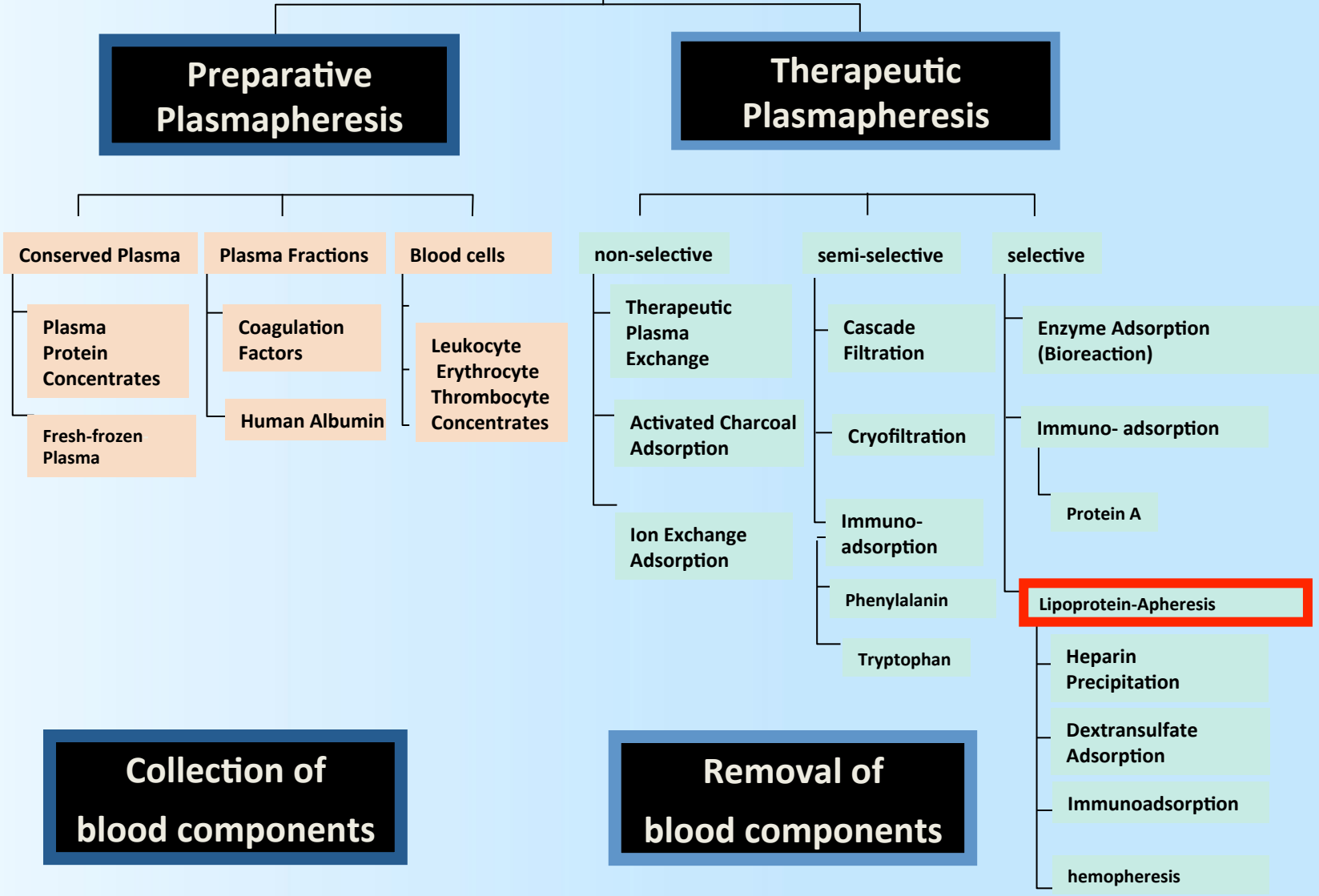
Class	Primary and secondary mechanism of action	LDL-lowering response	
		HeFH	HoFH
Statins	↑ LDLR activity (1^O)	>35%[1]	Up to 28%[2]
Resins	↓ Bile acid re-absorption (1^O), ↑ LDLR activity (2^O)	15%	<10%
Ezetimibe	↓ Cholesterol absorption (1^O), ↑ LDLR activity (2^O)	15%	<10%
Stanol esters	↓ Cholesterol absorption (1^O), ↑ LDLR activity (2^O)	10%	<10%
Nicotinic acid	↓ VLDL synthesis (1^O)	20%	<10%
Lomitapide	Inhibits microsomal triglyceride transfer protein	NA	50%
Mipomersen	Antisense oligonucleotide against apoB-100	NA	28%
Lipoprotein-apheresis	Removes LDL-c and Lp(a)	20-40% (up to 76% acutely)[6,7]	

Table adapted from Radar et al. J Clin Invest. 2003;111:1796-1803.

NA= not approved

1. Kastelein et al. N Engl J Med. 2008;358:1431-1443.
2. Raal et al. Atherosclerosis. 2000;150:421-428.
3. Konrad et al. Lipids Health Dis. 2011;10:38.
4. Vohl et al. Atherosclerosis.2002;160: 361–8
5. Chaves et al. Endocrinol Metab 2001; 86: 4926–32.
6. Gordon et al. Am J of Card. 1998;81:407-411.
7. Ito et al. J Clin Lipidol. 2011;5(3 Suppl):S38-S45.

Plasmapheresis



Mean Percentage Reduction of Plasma Proteins with Different Methods of Lipoprotein-Apheresis

mg/dL	MDF	Lipid Filtration	HELP	DALI	DSA	IA
LDL-C	56-62%	61%	55-61%	53-76%	49-75%	62-69%
HDL-C	25-42%	6%	5-17%	5-29%	4-17%	9-27%
Lp(a)	53-59%	61%	55-68%	28-74%	19-70%	51-71%
Triglycerides	37-49%	56%	20-53%	29-40%	26-60%	34-49%
Fibrinogen	52-59%	42%	51-58%	13-16%	17-40%	15-21%

High variation of values are partially due to differences in treated plasma and blood volumes.

MDF, membrane differential filtration;
HELP, heparin-induced extracorporeal LDL precipitation;
DALI, direct adsorption of lipoproteins;
DSA, dextran sulfate adsorption;
IA, immunoadsorption.

Moriarty. Clinical Lipidology. Ballantyne: A Companion to Braunwald's Heart Disease.2009;363-74.

Lipoprotein-Apheresis (LA) for FH Patients with CHD

(Hokuriku Study)

Patients: Heterozygous FH with CHD

Treatment: LA and Medication (n = 43)

(Average LA Interval = 14 days)

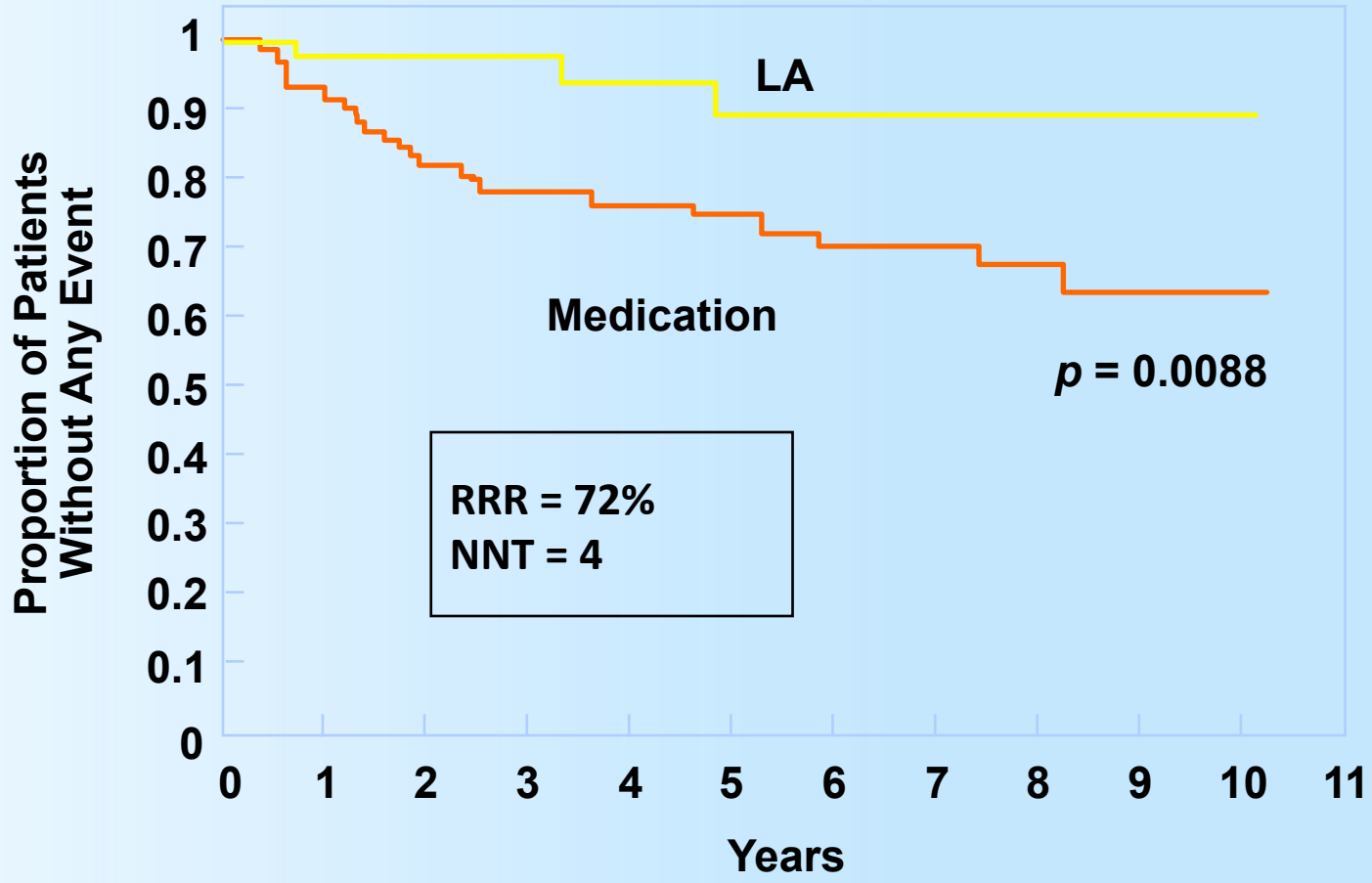
Medication Only (n = 87)

Follow-Up: 6 Year Observation of Coronary Events

(Non-Fatal MI, PTCA, CABG, CHD Death)

Mabuchi et al. Am J Cardiol 1998;82:1489-95

Lipoprotein-Apheresis (LA) and the Reduction of CV Events



Kroon et al. Ann Int Med 1996;125:945; Kroon et al. Circulation 1996; 93:1826;
Aengevaeren et al. JACC 1996; 28:1696

Lipoprotein-Apheresis (LA)

Lipids (mg/dL)	Pre-apheresis	Post-apheresis	% Change
Total Cholesterol	611	216	65
Triglycerides	128	49	62
HDL	78	72	8
LDL	507	134	65

International Guidelines for Initiating Lipoprotein-apheresis

North America

- LDL-C ≥ 200 mg/dL (with CHD)

-or -

- LDL-C ≥ 300 mg/dL (without CHD)

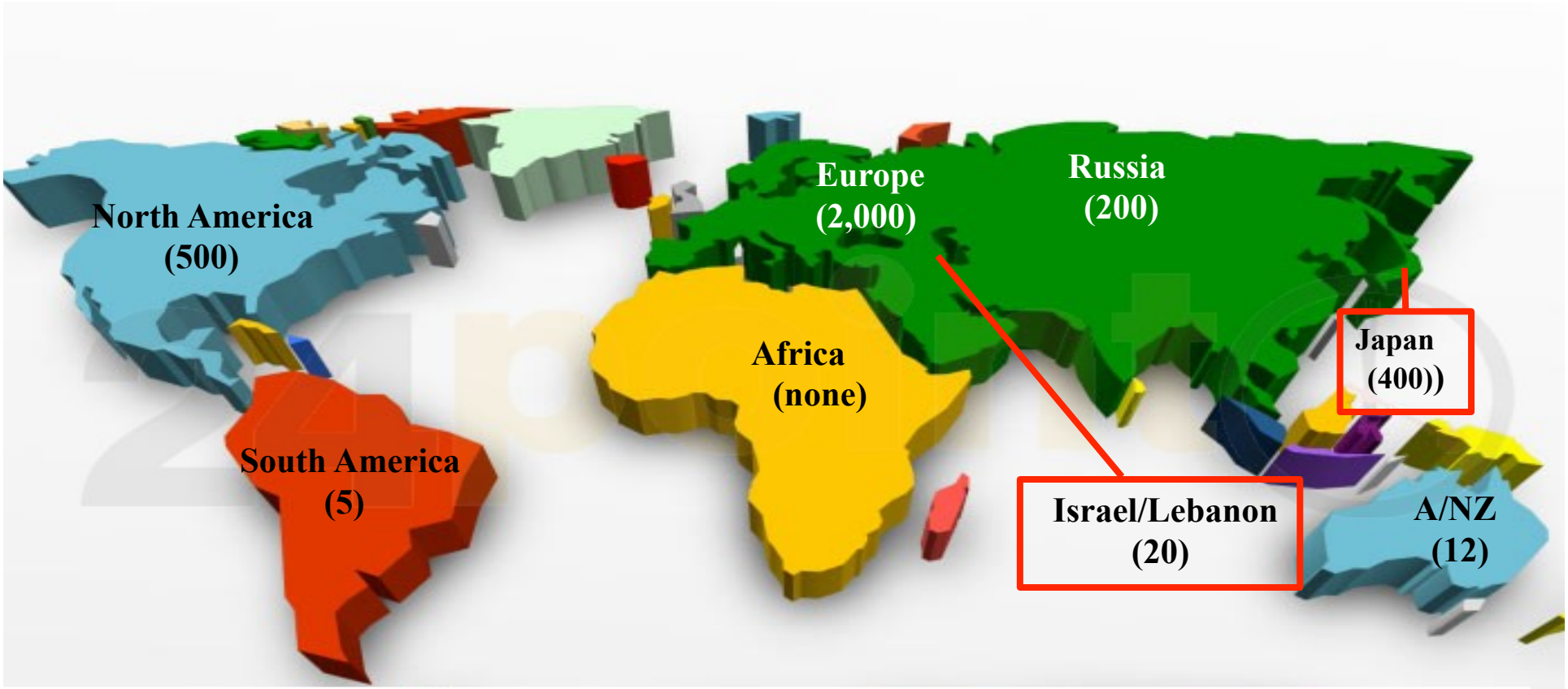
Japan

- TC ≥ 250 mg/dL (with CHD)

Germany

- LDL-C ≥ 130 mg/dL (with CHD)
- Lp(a) ≥ 60mg/dL (with progressive CHD)

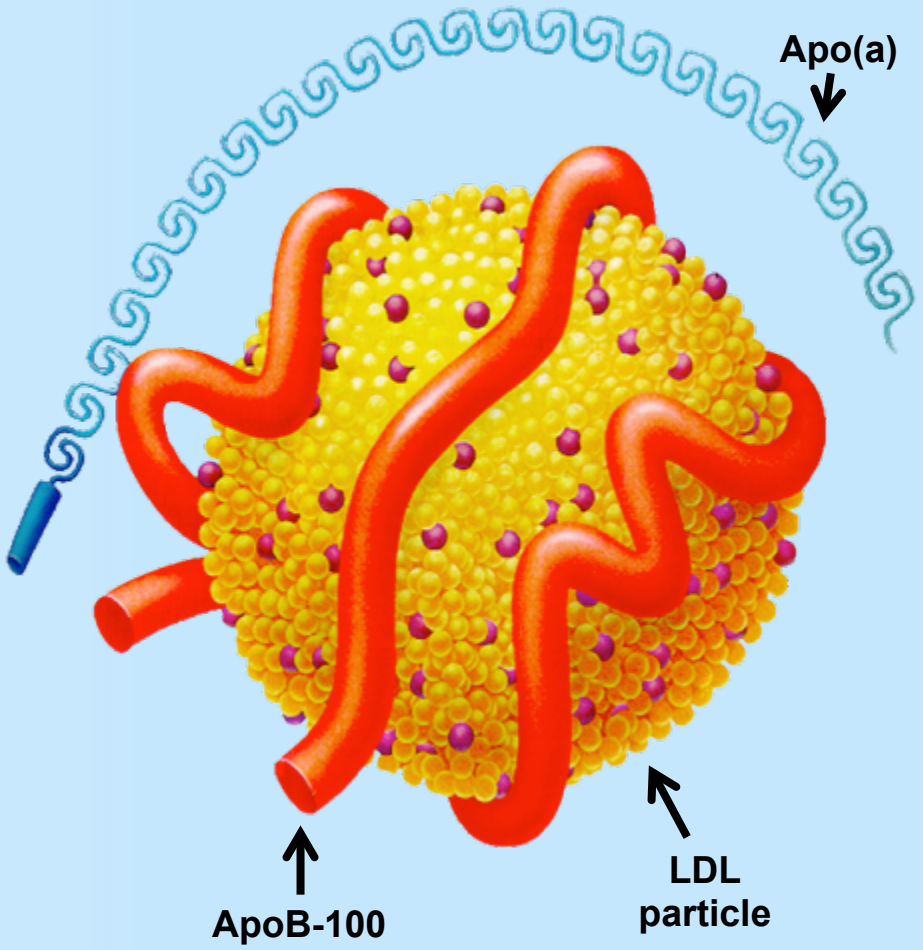
World-Wide Distribution of Lipoprotein-apheresis Therapy for FH Patients



- Less than 3,500 FH patients, from a potential world population of 12-30 million, receive regular weekly/ biweekly treatments

Lp(a): An independent and Causal Risk Factor

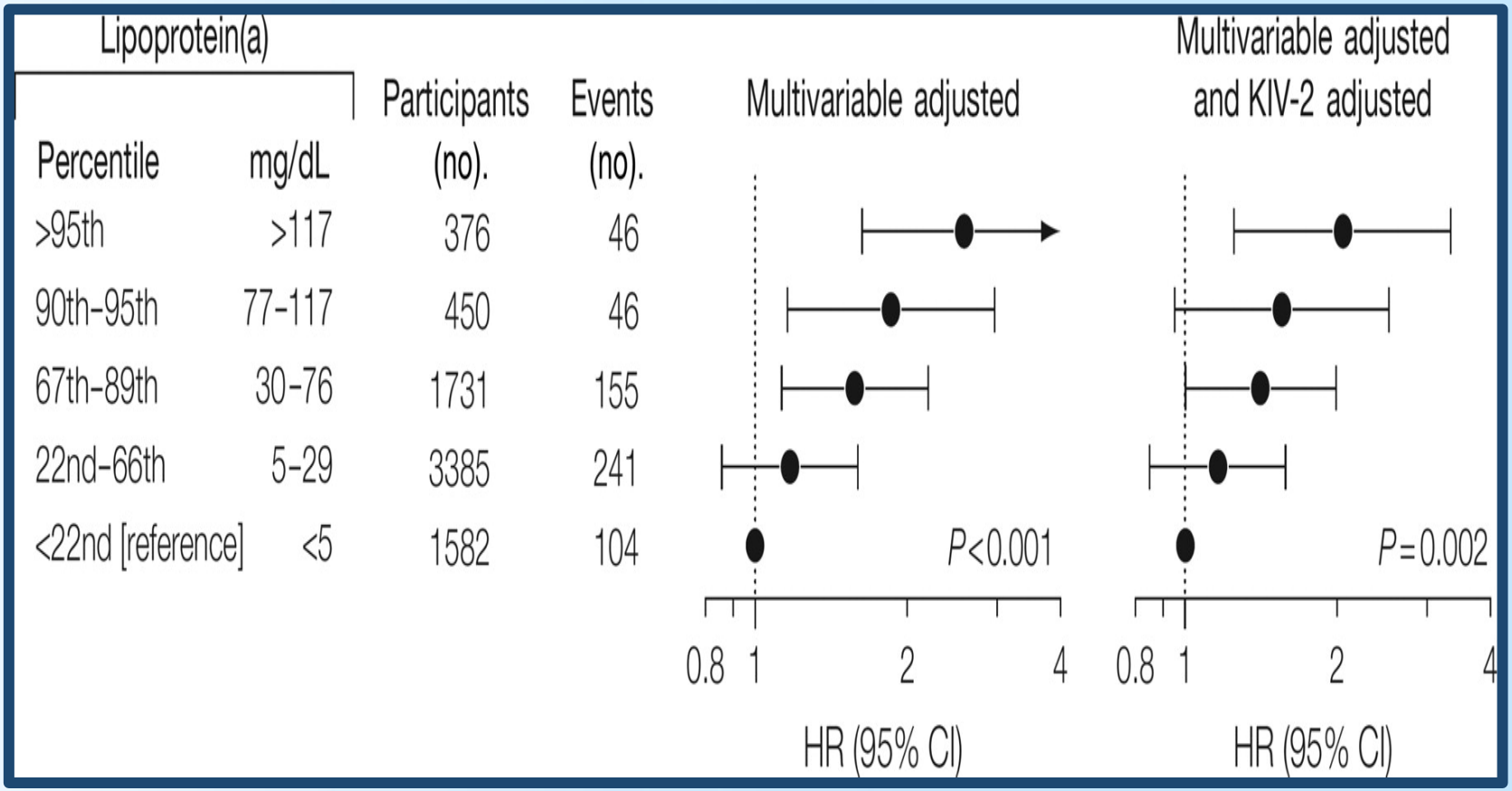
- Lp(a) consists of an LDL-like particle and the specific Apo(a), which is covalently bound to the ApoB of the LDL-like particle[1,3]
- Apo(a) is structurally homologous to plasminogen, and Lp(a)[1,3]
  - Competitively inhibits plasmin generation – antifibrinolytic[1,3]
  - Deposits oxidized phospholipids, increasing plaque inflammation leading to atherosclerosis[1,3]
- Lp(a) has a causal relationship to increased CV risk[2] and is recognized to predict atherosclerosis, MI[1]
- 2011 NLA Expert Panel cited Lp(a) as an independent driver of very high risk in FH[4]



1. Kiechl, Willeit. J Am Coll Cardiol. 2010;55(:2168-70; 2. Clarke et al. N Engl J Med. 2009;361:2518-28; 3. Kathiresan. N Engl J Med.2009;361:2573-74; 4. Goldberg et al. J Clin Lipidol. 2011;5(3 Suppl):S1-S8.

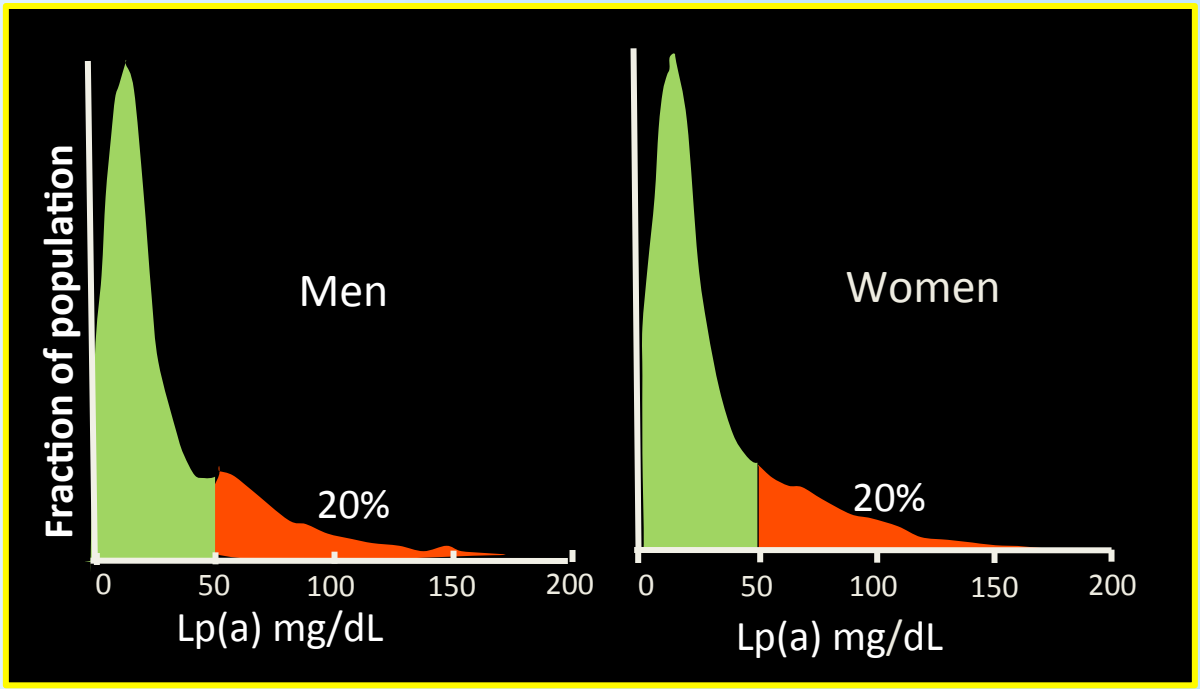
Figure adapted from Brown WV, et al. *J Clin Lipidol*. 2010;4(4):240-247.

Risk of Myocardial Infarction by Levels of Lp(a) in the General Population



Nordestgaard et al. Eur Heart J 2010;31:2844-53

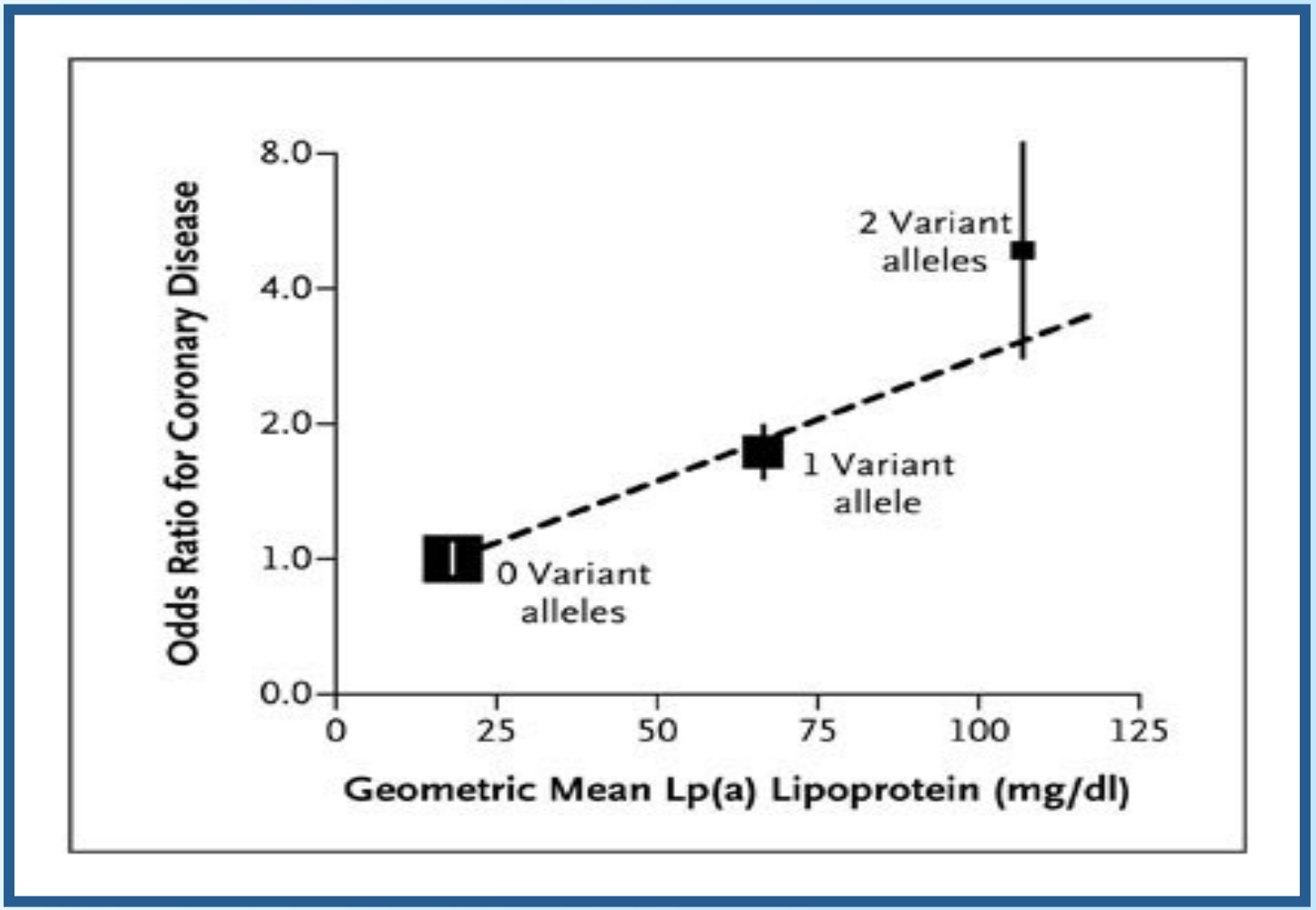
Distribution of Lp (a) Levels in the General Population



Typical distributions of lipoprotein(a) levels in the general population. These graphs are based on non-fasting fresh serum samples from 3000 men and 3000 women from the Copenhagen General Population Study collected from 2003 through 2004. GREEN COLOR indicates levels below the 80th percentile, whereas RED COLOR indicates levels above the 80th percentile.

Nordesgaard et al. Eur Heart J. 2010:2844-53

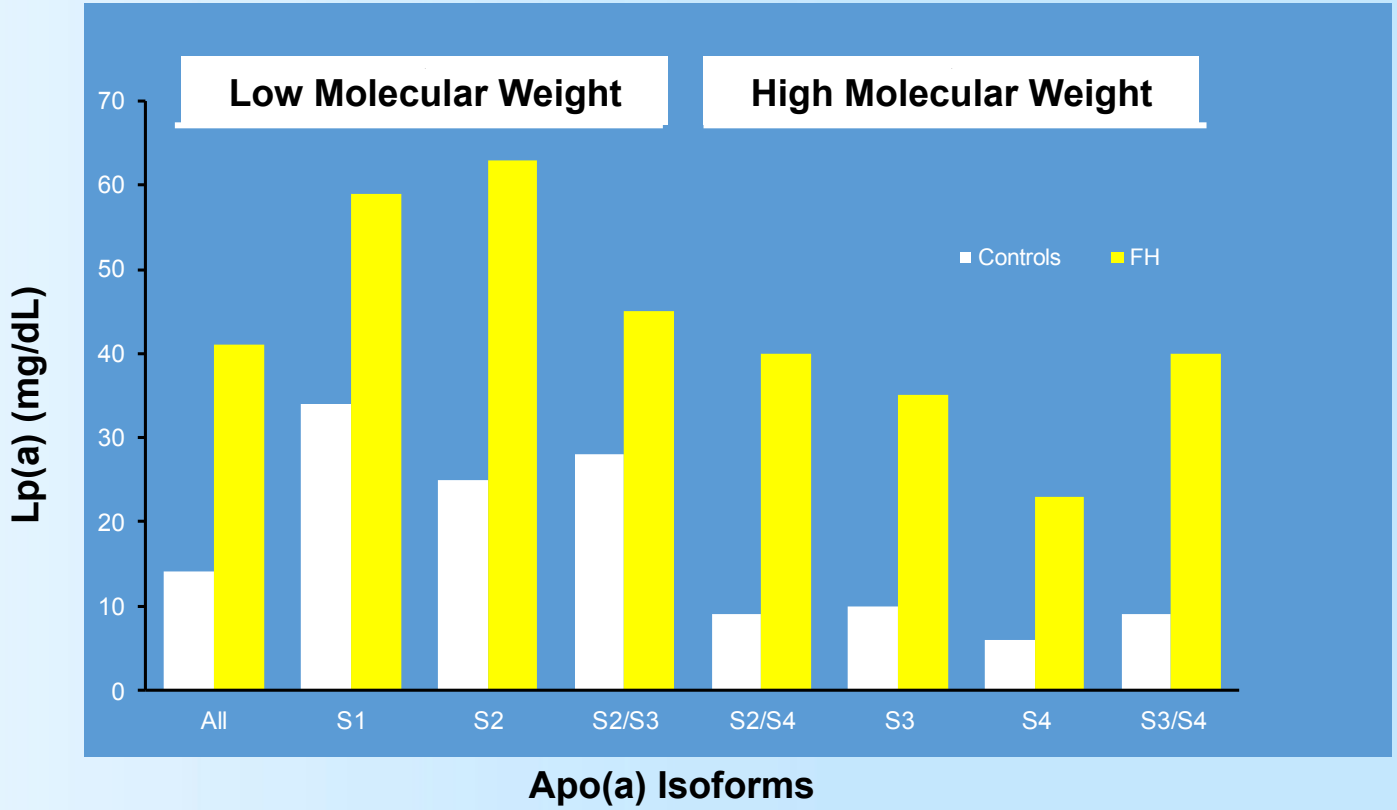
Association of the LPA Genotype Score with Lp(a) Levels and the Risk of CHD in the PROCARDIS Cohort



Clarke et al. N Engl J Med 2009;361:2518-28

Lp(a) Elevations More Frequent in FH

- In FH, Lp(a) levels increased 3-fold vs controls
- Across Lp(a) LMW range, levels are higher in FH versus controls



Utermann et al. *Proc Natl Acad Sci U S A.* 1989;86:4171-74.

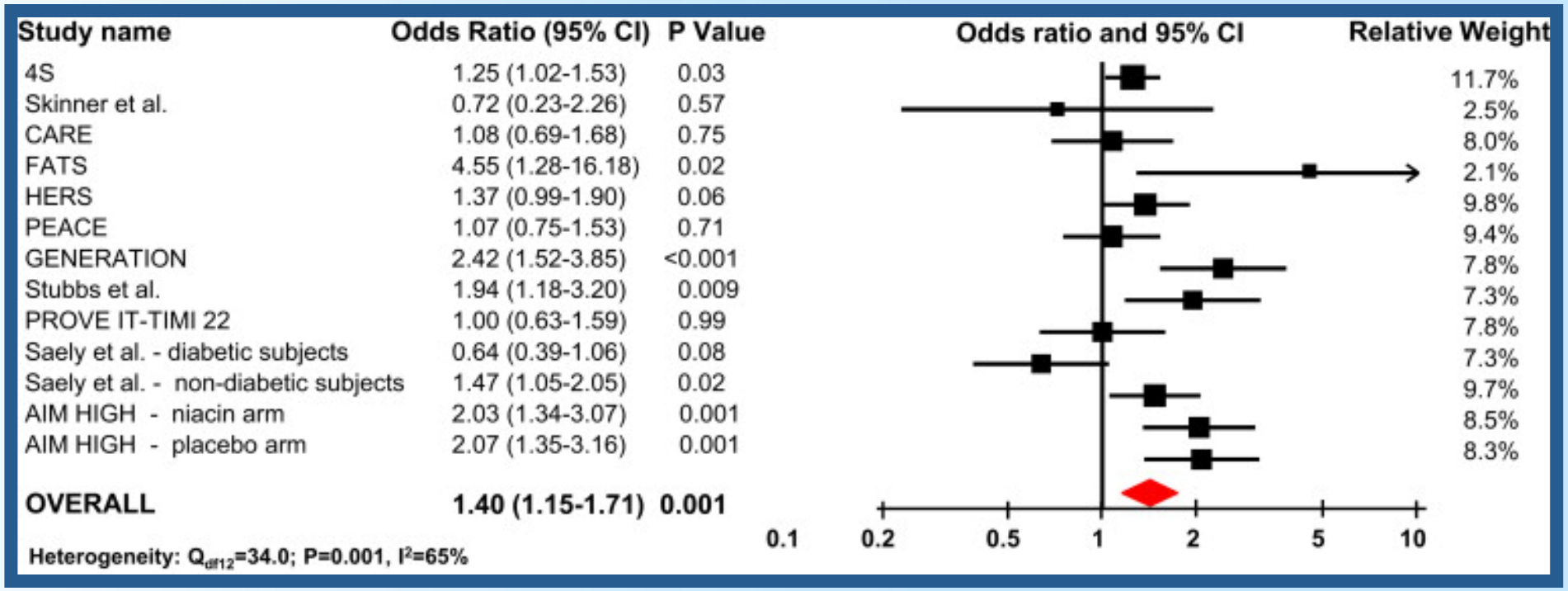
Lp(a) and CVD in the FH Population*

	RR	95% CI	P-value
Male	2.82	2.37-3.36	<0.0001
Smoking	1.67	1.40-1.99	<0.0001
Hypertension	1.36	1.06-1.75	0.02
Diabetes	2.19	1.36-3.54	0.001
Low HDL (m: <0.9, f: <1.1)	1.37	1.15-1.63	0.0004
Lp(a) >30 mg/dL	1.50	1.20-1.79	0.0001

*2,400 FH patients (782 with CVD and 1618 without CVD)
Multivariate analysis in 1956 patients

Jansen et al. *J Internal Medicine*. 2004;256:482-90.

The Odds of MACE for those Subjects* with the Highest Levels of Lp(a)

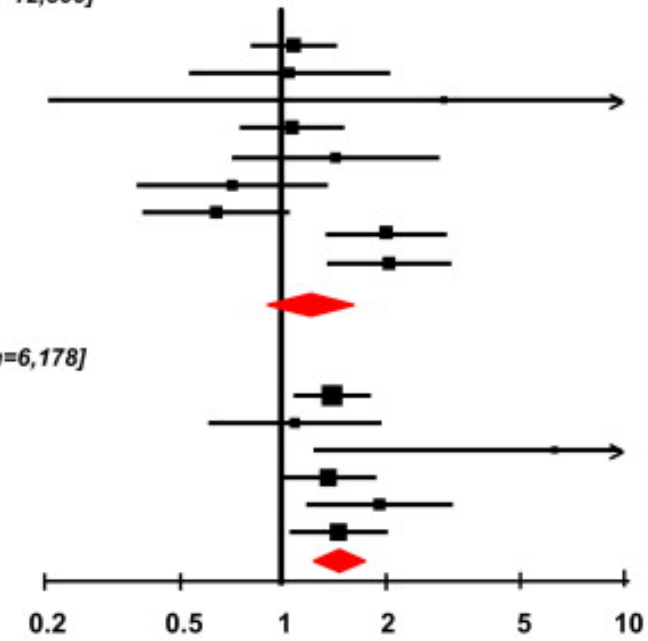


*Meta-Analysis of Published Studies in Secondary Prevention

O'Donoghue et al. JACC. 2014;63:520-27.

The Odds of MACE for those Subjects* with the Highest Levels of Lp(a) Stratified by LDL-C Concentration

Study Name	Subgroup	Odds Ratio (95% CI)	P Value	Relative Weight
Cohorts with average LDL<130mg/dl (or TC <240mg/dl if LDL unavailable) [n=12,800]				
4S	Simvastatin arm	1.09 (0.81-1.46)	0.59	16.1%
CARE	Pravastatin arm	1.05 (0.53-2.09)	0.88	9.3%
FATS	"Substantial" response	3.00 (0.20-44.1)	0.42	1.1%
PEACE	Overall	1.07 (0.75-1.53)	0.71	15.0%
PROVE IT-TIMI 22	Atorvastatin arm	1.44 (0.71-2.92)	0.31	9.0%
PROVE IT-TIMI 22	Pravastatin arm	0.72 (0.37-1.37)	0.31	9.8%
Saely et al.	Diabetic subjects	0.64 (0.39-1.06)	0.08	12.3%
AIM HIGH	Niacin arm	2.03 (1.34-3.07	0.001	13.9%
AIM HIGH	Placebo arm	2.07 (1.35-3.16)	0.001	13.7%
OVERALL		**1.20 (0.90-1.60)**	**0.21**	
Cohorts with average LDL≥130mg/dl (or TC ≥ 240mg/dl if LDL unavailable) [n=6,178]				
4S	Placebo arm	1.41 (1.08-1.84)	0.01	33.6%
CARE	Placebo arm	1.09 (0.61-1.97)	0.77	8.1%
FATS	"Minimal" response	6.36 (1.24-32.7)	0.03	1.1%
HERS	Overall	1.37 (0.99-1.90)	0.06	23.5%
Stubbs et al.	Overall	1.94 (1.18-3.20)	0.009	11.0%
Saely et al.	Non-diabetic subjects	1.47 (1.05-2.05)	0.02	22.8%
OVERALL		**1.46 (1.23-1.73)**	**<0.001**	



* **Meta-Analysis of Published Studies in Secondary Prevention**

O'Donoghue et al. JACC. 2014;63:520-27.

A Randomized Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among 17,802 Apparently Healthy Men and Women With Elevated Levels of C-Reactive Protein (hsCRP): The JUPITER Trial*

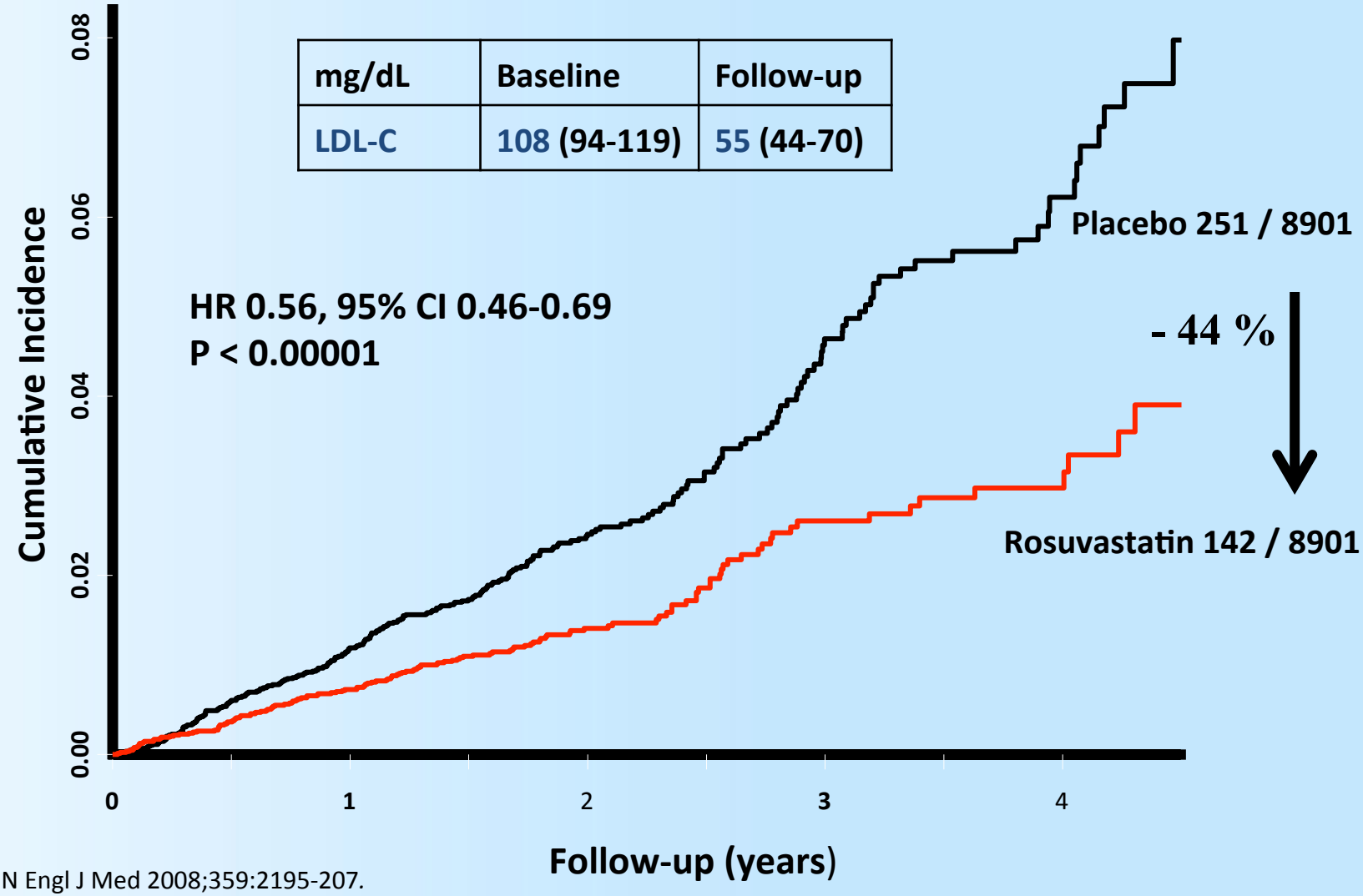
Paul M. Ridker, Eleanor Danielson, Francisco Fonseca*, Jacques Genest*,
Antonio Gotto*, John Kastelein*, Wolfgang Koenig*, Peter Libby*,
Alberto Lorenzatti*, Jean MacFadyen, Borge Nordestgaard*,
James Shepherd*, James Willerson, and Robert Glynn*
on behalf of the JUPITER Trial Study Group

*Primary Trial Endpoint : MI, Stroke, UA/Revascularization, CV Death

Ridker et al. N Engl J Med 2008;359:2195-207.

JUPITER Trial

mg/dL	Baseline	Follow-up
LDL-C	108 (94-119)	55 (44-70)



Ridker et al. N Engl J Med 2008;359:2195-207.

Lipoprotein(a) Concentrations, Rosuvastatin Therapy, and Residual Vascular Risk

JUPITER Trial

by Amit V. Khera, Brendan M. Everett, Michael P. Caulfield, Feras M. Hantash, Jay Wohlgemuth, Paul M Ridker, and Samia Mora

Circulation
Volume 129(6):635-642
February 11, 2014

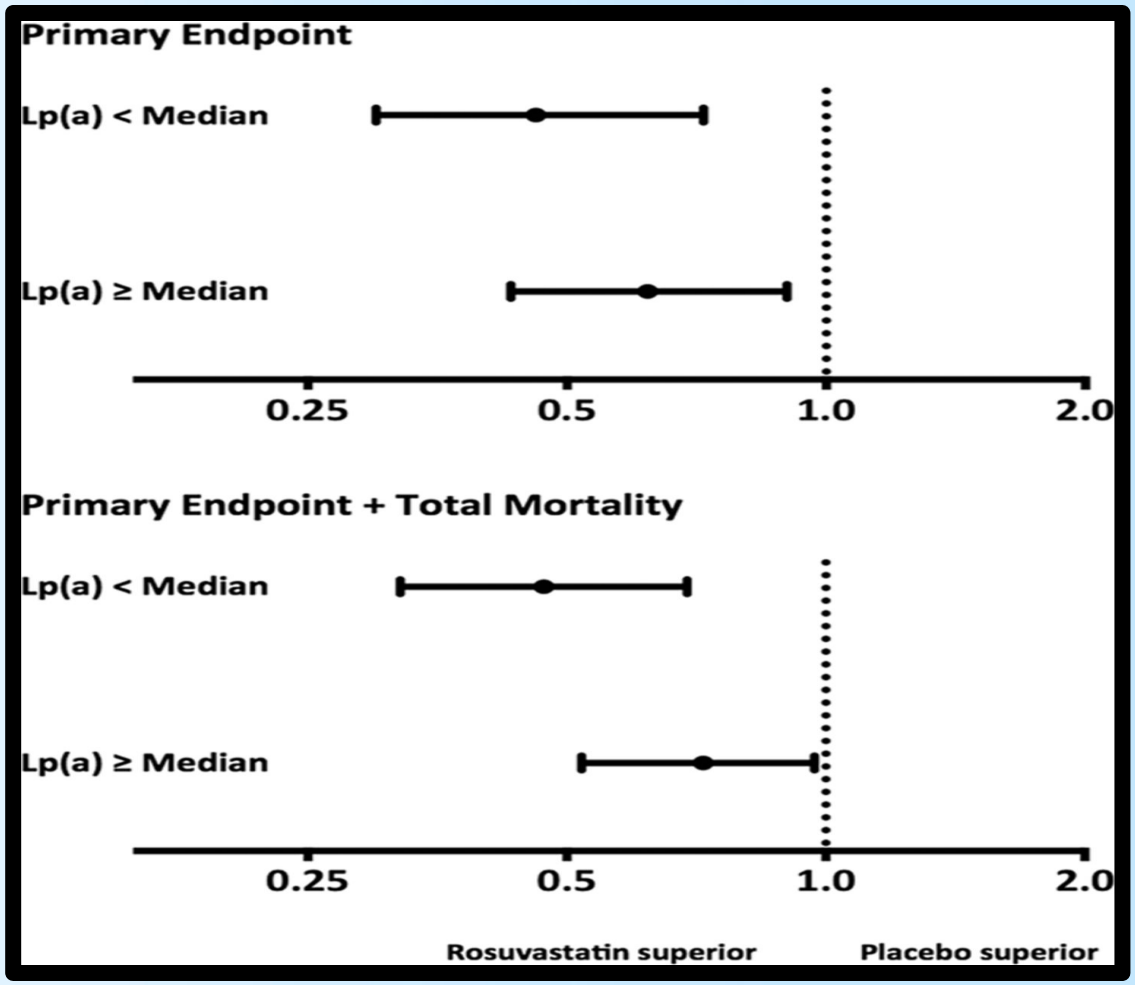
Association Between Baseline Lipoprotein(a) and Incident CVD Among White Participants in JUPITER

	Quartile One (≤10 nmol/L)	Quartile Two (11–23 nmol/L)	Quartile Three (24–49 nmol/L)	Quartile Four (≥50 nmol/L)	P for Trend	HR per SD Increment	P Value
Primary end point							
No. of events/N	44/1991	50/1884	45/1957	71/1898		210/7730	
Incidence rate, per 100 person-years	0.99	1.17	1.02	1.62	0.02	1.20	
Model One	1.00	1.18 *P*=0.44	1.04 *P*=0.87	1.70 *P*=0.006	0.01	1.19	0.008
Model Two	1.00	1.19 *P*=0.40	1.02 *P*=0.93	1.64 *P*=0.01	0.02	1.18	0.02
Primary end point plus total mortality							
No. of events/N	59/1991	63/1884	67/1957	94/1898		283/7730	
Incidence rate, per 100 person-years	1.32	1.47	1.53	2.14	0.004	1.62	
Model One	1.00	1.11 *P*=0.56	1.15 *P*=0.44	1.66 *P*=0.002	0.002	1.22	0.0005
Model Two	1.00	1.12 *P*=0.54	1.14 *P*=0.47	1.61 *P*=0.005	0.005	1.21	0.001

- Model One: Adjusted for age, sex, and treatment group.
- Model Two: Adjusted for age, sex, treatment group, Tob, FH, BMI, SBP, FG, HDL-c, LDL-c, Trigs, and hsCRP

Khera A et al. Circulation. 2014;129:635-42

Efficacy of Rosuvastatin* According to Baseline Lp(a)



***On-statin Lp(a) concentrations were associated with residual risk of CVD (adjusted hazard ratio, 1.27; 95% CI, 1.01-1.59; P=0.04), which was independent of LDL-c and other factors.**

Khera A et al. Circulation. 2014;129:635-42

Therapeutic Agents for Decreasing Lp(a)

Agent	Mechanism
Estrogen	Acts on LPA promoter
Anabolic Steroids	May act on gene expression
Tocilizumab	IL-6 receptor antagonist
FXR	Acts on hepatic LPA gene expression
Aspirin	Reduces LPA expression
ApoB peptides	Inhibit Lp(a) assembly
Niacin	Inhibits DGAT2 with apoB degradation
Anacetrapib	CETEP inhibitor and lowers LDL
Eprotirome	Thyroid mimetic. Increases LDLR and LDL clearence
PCSK9 inhibitors	Increase LDLR and decrease Lp(a)
Mipomersen	Antisense nucleotide, decreases LDL synthesis
ASO 144367	Antisense nucleotide, decreases Lp(a)
Lipoprotein-apheresis	Removes apoB containing lipoproteins (LDL, Lp(a),…)

Hoover-Plow et al. Metabolism. 2013;62:479-91.

Mean Percentage Reduction of Plasma Proteins with Different Methods of Lipoprotein-Apheresis

mg/dL	MDF	Lipid Filtration	HELP	DALI	DSA	IA*
Lp(a)	53-59%	61%	55-68%	28-74%	19-70%	51-71%

High variation of values are partially due to differences in treated plasma and blood volumes. MDF, membrane differential filtration; HELP, heparin-induced extracorporeal LDL precipitation; DALI, direct adsorption of lipoproteins; DSA, dextran sulfate adsorption; IA*, immunoadsorption.

*A type of immunoadsorption system uses antibodies to Lp(a) to remove only Lp(a). Lipopak (POCARD Ltd., Russia) = 80-85% reduction of Lp(a)

Moriarty. Clinical Lipidology. Ballantyne: A Companion to Braunwald's Heart Disease; 2009;363-74.

LA Reduction of Lp(a) and CVD

	JAEGER[1]		ROSADA[2]		LEEBMANN[3]	
Apheresis Treatment	**Pre-**	**Post-**	**Pre-**	**Post-**	**Pre-**	**Post-**
Patients	**120**	**120**	**170**	**166**	**37**	**37**
Duration (years)	**5.5**	**5.0**	**5.2**	**6.8**	**2**	**2**
LDL-C (mg/dL)	**125**	**45 (-65%)**	**84**	**34 (-60%)**	**99**	**29 (66%)**
Lp(a) (mg/dL)	**118**	**33 (-72%)**	**112**	**36 (-68%)**	**89**	**42 (-60%)**
MACE (total events)	**297**	**57 (-81%)**	**67**	**20 (-71%)**	**142**	**31 (78%)**
MACE (events per year)	**0.42**	**0.09 (-79%)**	**0.35**	**0.08 (-77%)**	**0.42**	**0.09 (79%)**

MACE=Major Coronary Event
Percentages are mean percent change

1. Jaeger et al. Nat Clin Pract Cardiovasc Med. 2009;6:229-39.
2. Rosada et al. Artif Organs. 2014;38:135-41.
3. Leebmann et al. Circulation. 2013;128:2567-76.

Specific Lp(a) Apheresis for Coronary Atherosclerosis Regression

Aim: To determine if Lp(a)-apheresis for patients with CHD and elevated Lp(a) can alter coronary plaque volume and composition.

Methods: 32 patients (54+/-8 years, 20 males) with CHD and Lp(a)= 50 mg/dL. Medical therapy included atorvastatin with LDL-C< 77mg/dL. Active group (15) treated with Lp(a) Lipopak (POCARD Ltd., Russia). Total atheroma volume (TAV), minimal lumen area (MLA), volume of necrotic core (NC) and dense calcium (DC) were measured by intravascular ultrasound at baseline and 18 months later to compare active and control (atorvastatin) groups.

Results: Mean Lp(a) (92+/-33mg/dL) decreased by 73%.

	TAV	NC size	NC/DC	MLA
Lp(a)-apheresis	-22%*	-45%*	-64%*	NC
Control	NC	NC	NC	-11%*

*p<0.05

Conclusion: Lp(a)-apheresis in CHD patients with elevated Lp(a) levels can stabilize plaque phenotype and regress atherosclerotic lesions in coronary arteries.

Safarova et al. EAS meeting Milano 5-2012

"In patients with evidence of progressive coronary disease and markedly elevated plasma Lp(a), serious consideration should be given to instituting Lipoprotein-apheresis."

- 2010 European Atherosclerosis Society Consensus Panel on Lp(a)

Nordesgaard BG et al. Eur Heart J. 2010 (23):2844-53

Conclusion

- Present lipid-lowering medications are unable to achieve LDL-C goals for FH patients
- LA therapy can successfully lower LDL levels and CVD in FH patients
- Lp(a) is an independent risk factor for CVD and should be measured in high-risk populations
- LA lowers levels of Lp(a) by 70% and has demonstrated clinical benefit for patients with CVD
- LA should be considered for patients with progressive CVD and elevated Lp(a)

Advanced Approaches for Optimizing Outcomes in the Severe FH Patient

Pamela B. Morris, MD, FACC, FACP, FACPM, FAHA, FNLA

Medical University of South Carolina

Director, Seinsheimer Cardiovascular Health Program

Co-director, Women's Heart Care

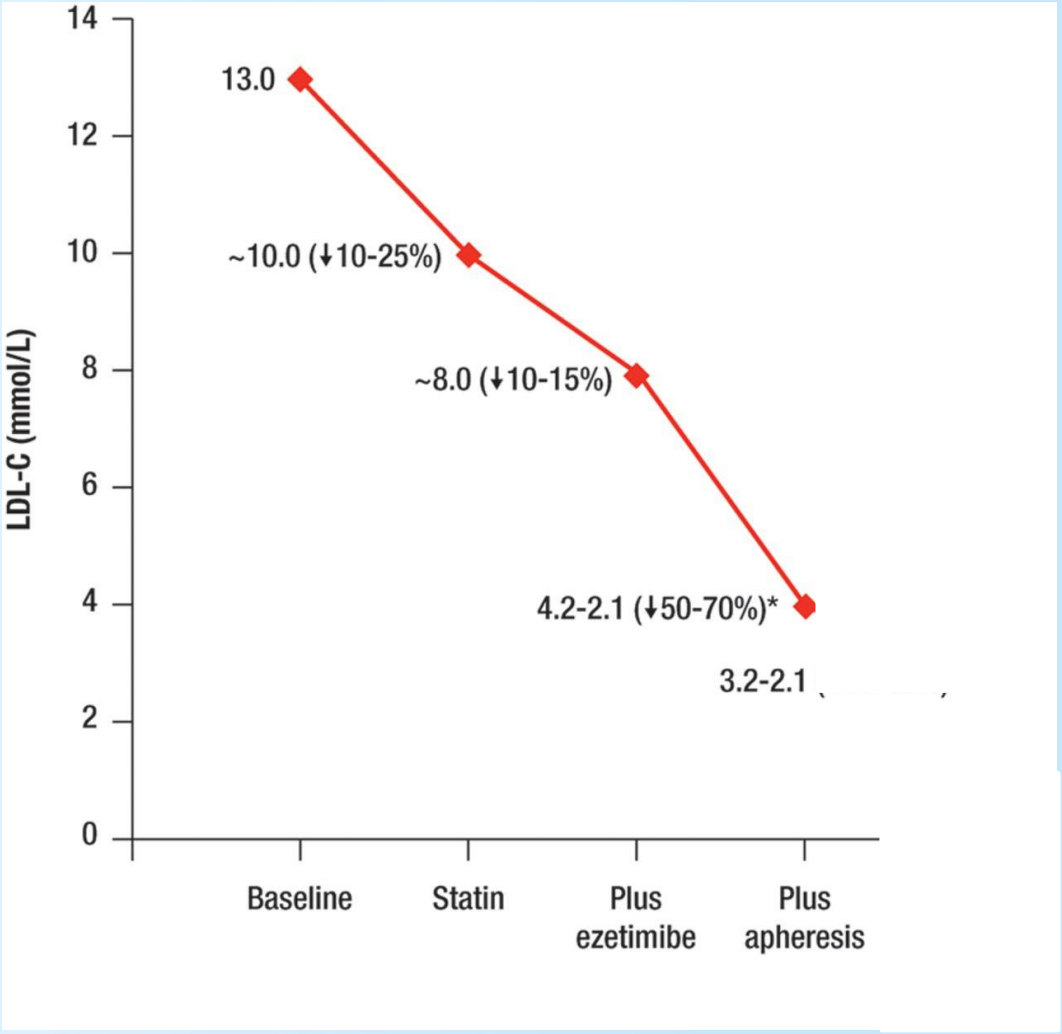
Charleston, South Carolina

Why Do We Need More LDL-Lowering Therapies for FH Patients?

- Homozygous patients cannot approach target levels on usual therapy
- Heterozygous patients may still need further lowering even if they achieve 70% reduction with multiple drug combinations
- Not all FH patients can tolerate current multi-drug combinations
- LDL-apheresis is not available everywhere and has drawbacks

Cumulative Low-Density Lipoprotein Cholesterol-Lowering Effects:

Statin, ezetimibe, adjunctive mipomersen, lomitapide or evolocumab, and lipoprotein apheresis in homozygous FH

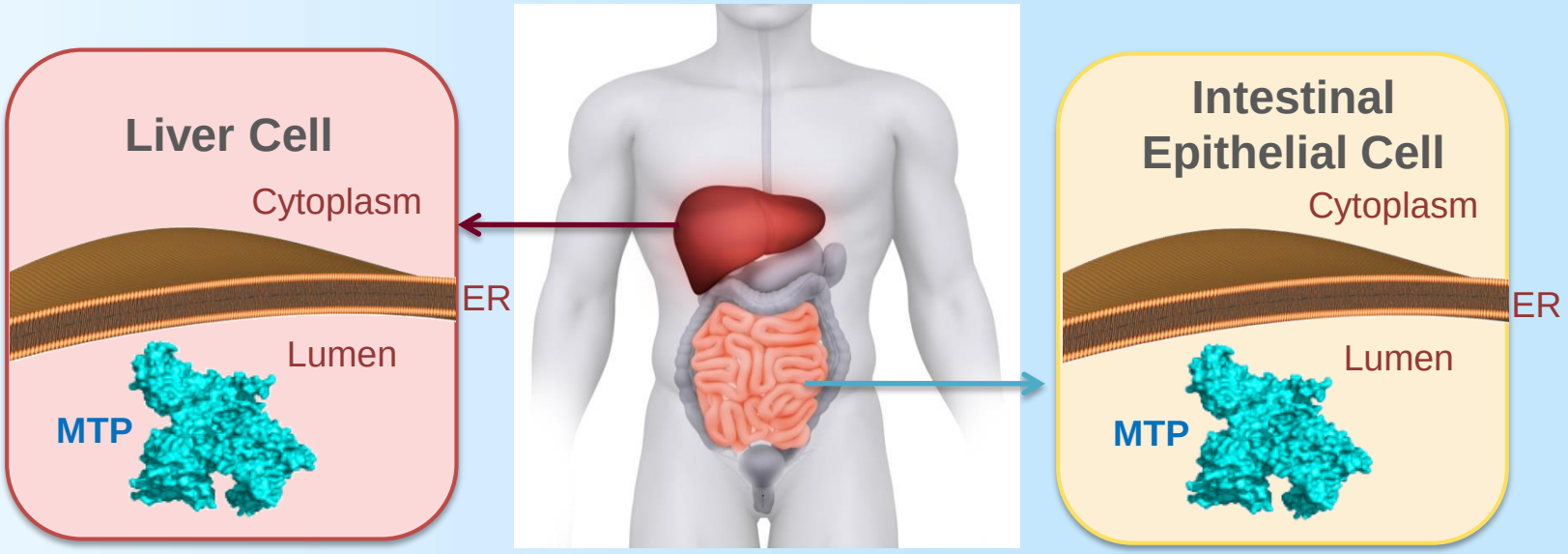


Cuchel et al. Eur Heart J 2014;35:2146-57.

MTP Inhibition: Lomitapide

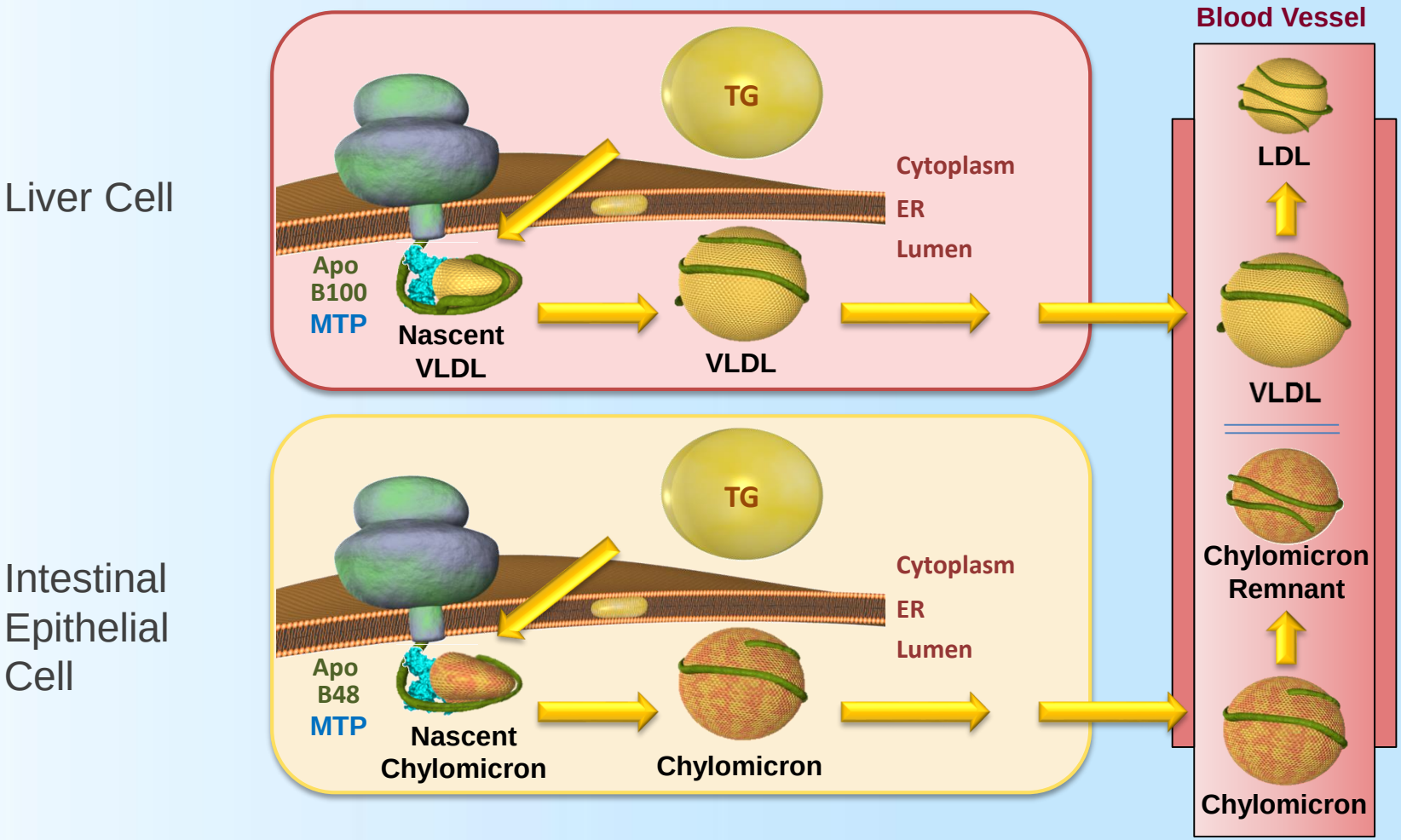
Microsomal Triglyceride Transfer Protein (MTP)

- MTP is an intracellular lipid-transfer protein found in the lumen of the endoplasmic reticulum (ER) responsible for binding and shuttling individual lipid molecules between membranes[1]
- Normal concentrations and function of MTP are necessary for the proper assembly and secretion of apo B-containing lipoproteins in the liver and intestines[2]



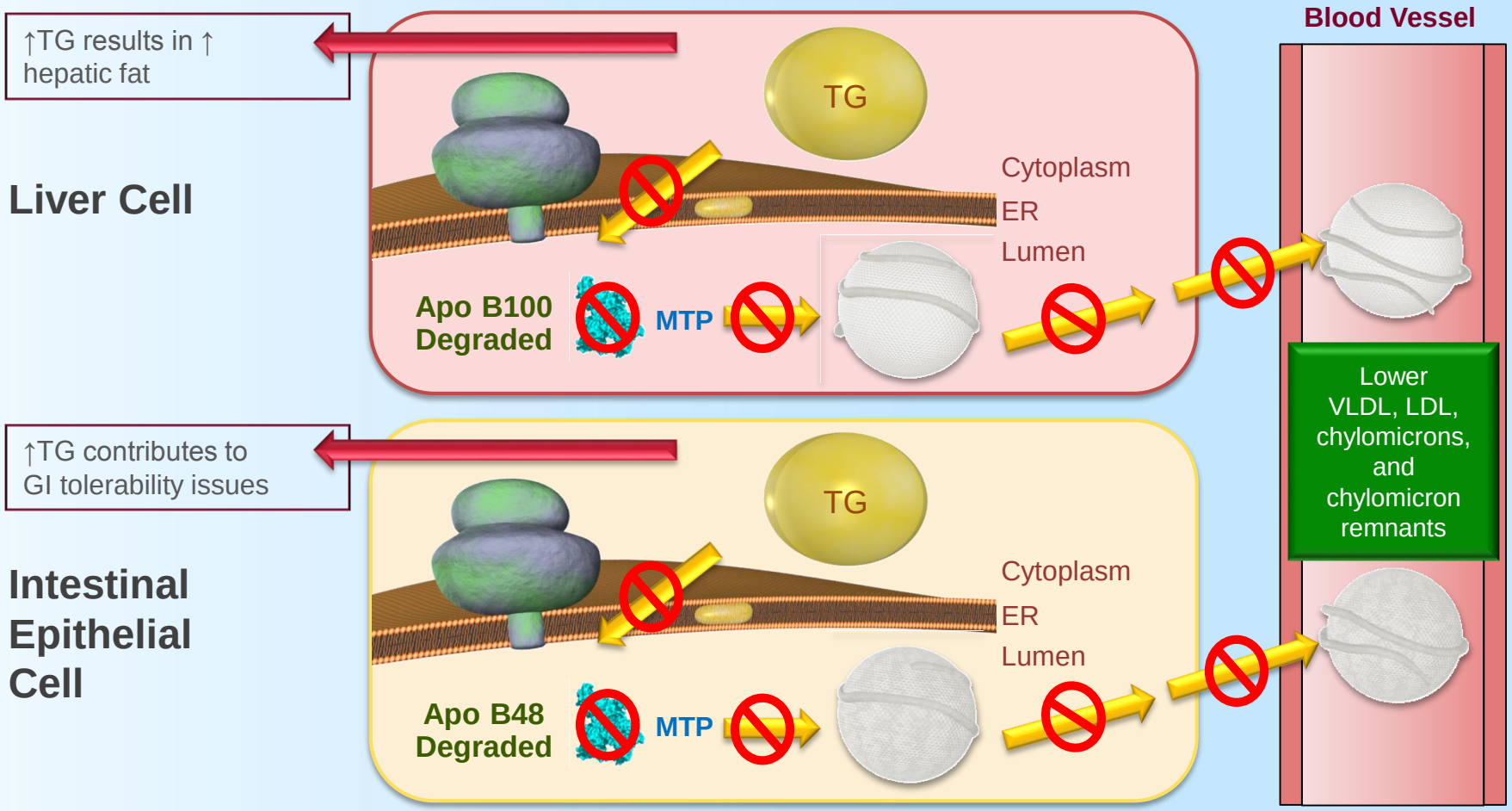
1. Hussain et al. J Lipid Res. 2003:44;22-32.
2. Liao et al. J Lipid Res. 2003:44;978-85.

VLDL and Chylomicron Synthesis



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

Predicted Effects of MTP Inhibition



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

Single-Arm, Open-Label, Multicenter Pivotal Phase 3 Study of Lomitapide in HoFH

- Multicenter study of 29 patients with HoFH (11 centers in US, Canada, South Africa, Italy)
  - Primary endpoint: % change in LDL-C
  - N=23 (mean age 30.7) completed efficacy phase (26 weeks) and full study (78 weeks)
  - Mean LDL-C 336, TC 430, apo B 259, HDL-C 44, TG 92
  - Statins 93%, ezetimibe 76%, LDL apheresis 62%
  - Median dose of lomitapide 40 mg
  - Mean age 30.7 (18-55) yrs
  - 25 Caucasian, 2 Asian, 1 AA, 1 other
  - Men: 16, Women: 13
  - Cardiovascular disease: 27 (21 valvular disease, 21 CAD)

Cuchel et al. Lancet 2013;381:40-6.

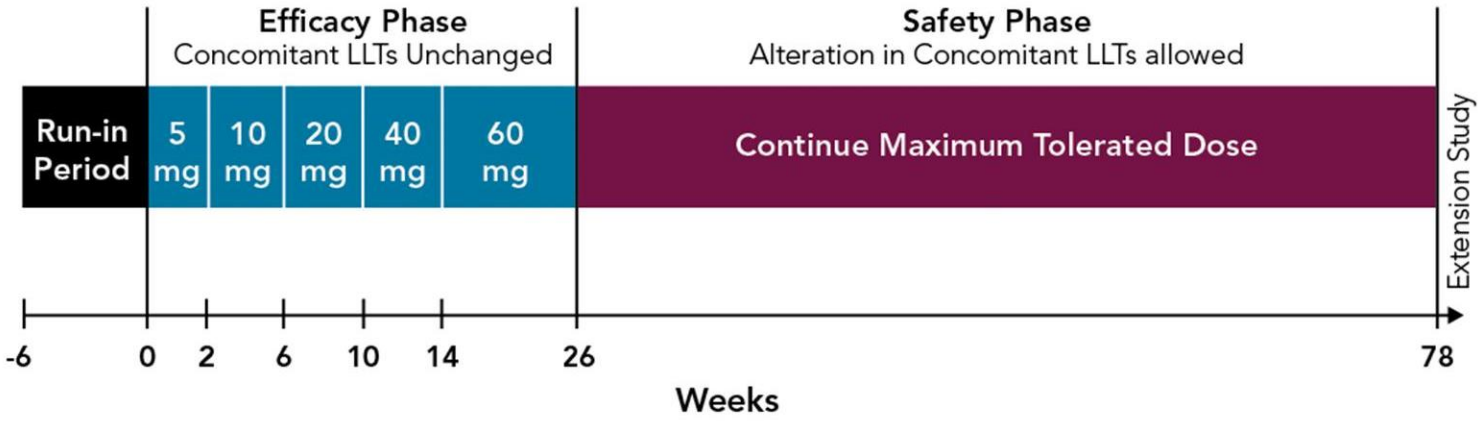
Single-Arm, Open-Label, Multicenter Phase 3 Study of Lomitapide in HoFH

- All confirmed HoFH by genotype:
  - 28 homozygotes or compound heterozygotes for mutations in LDL-R gene
  - One homozygous for ARH (LDLRAP1) gene mutation
- Median dose of lomitapide 40 mg
- Hepatic MRI at baseline and 6 month intervals (3 patients had contraindications—CT or US if indicated)

Cuchel et al. Lancet 2013;381:40-6.

Single-Arm, Open-Label, Multicenter Phase 3 Study of Lomitapide in HoFH

- **The 78 week study had three time periods (cont.):**



From Week 26 to Week 78 (Safety Phase):

- **Patients continued on maximum tolerated dose of lomitapide established during the efficacy phase.**
- **Changes in concomitant LLTs were allowed unless dose alteration rules were met.**

Cuchel, M. *et al.* Lancet 2013; 381: 40-46. (published online: 02 Nov 2012)
Juxtapid™ (lomitapide) capsules [US prescribing information: Aegerion Pharmaceuticals; 2012.Cambridge, MA

Single-Arm, Open-Label, Multicenter Phase 3 Study of Lomitapide in HoFH

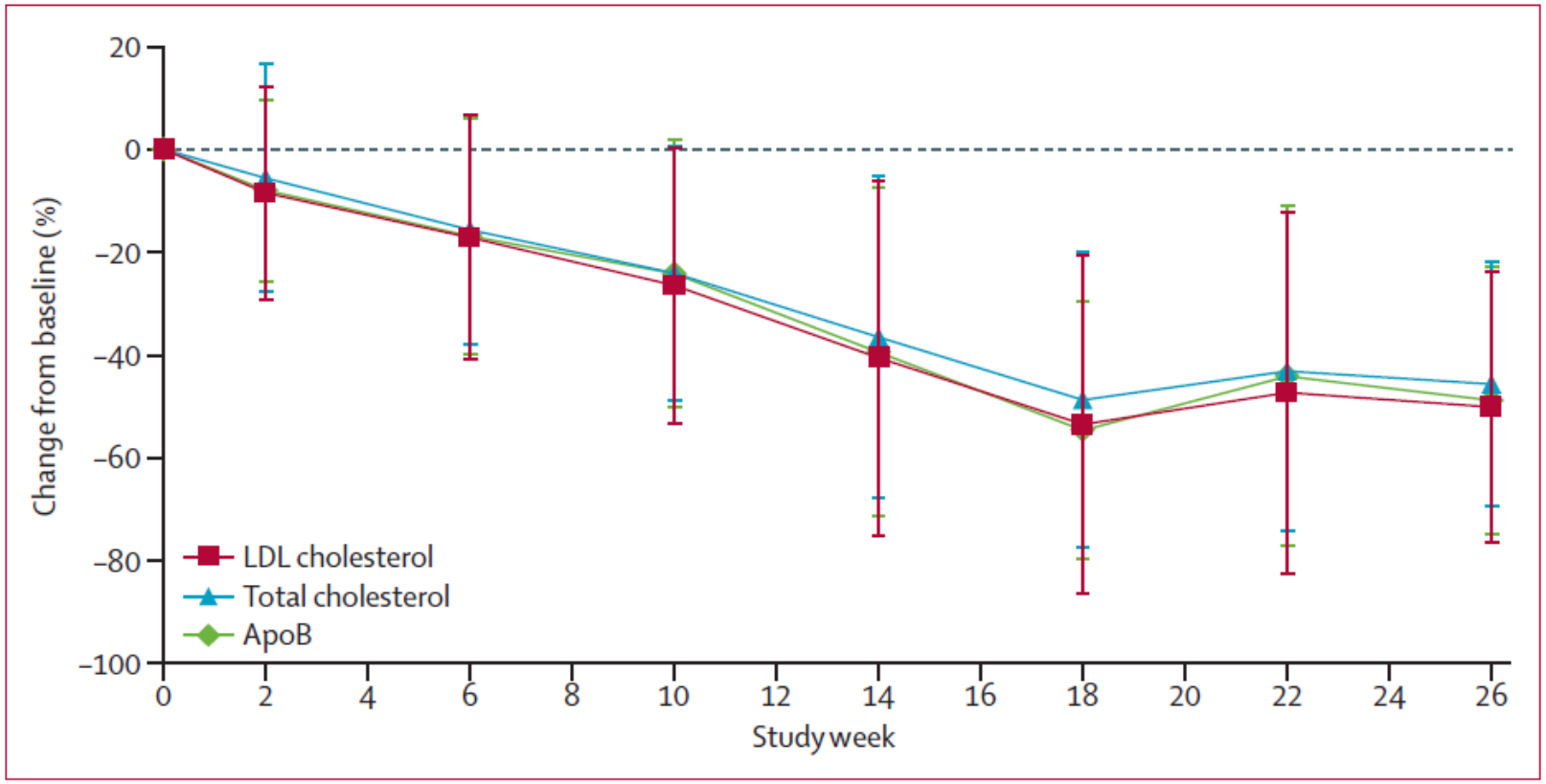


Figure 1: **Mean percent changes in LDL cholesterol, total cholesterol, and ApoB levels from baseline to week 26 (end of efficacy phase)**

Data available at each time point are expressed as mean (SD).

Cuchel et al. Lancet 2013;381:40-6.

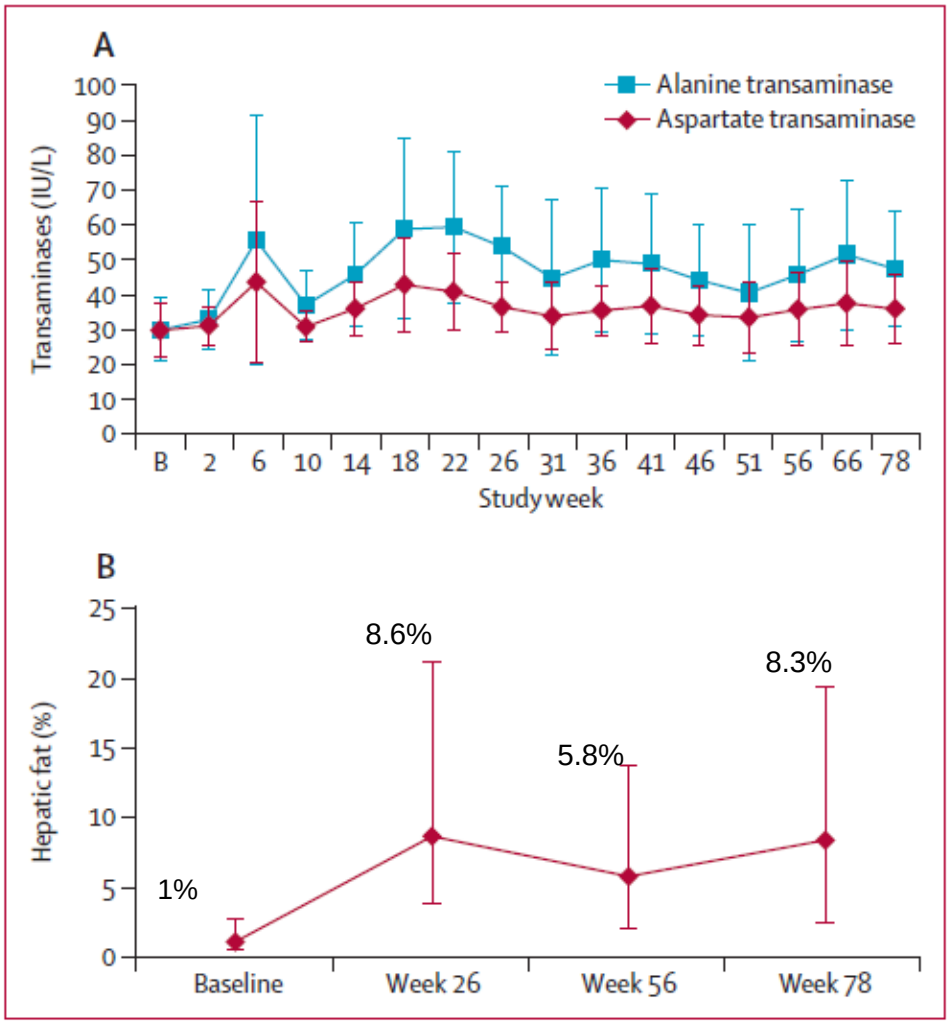


Figure 2: **Alanine transaminase and aspartate transaminase levels and percentage of hepatic fat in the liver**

Data are mean, 95% CI. Laboratory reference ranges for alanine transaminase levels were 10–40 U/L in men and 10–33 U/L in women; reference ranges for aspartate transaminase levels were 10–43 U/L in men and 10–36 U/L in women (A). Percentage of fat in the liver, as measured by nuclear magnetic resonance spectroscopy at baseline and 26, 56, and 78 weeks of lomitapide treatment (n=20; B).

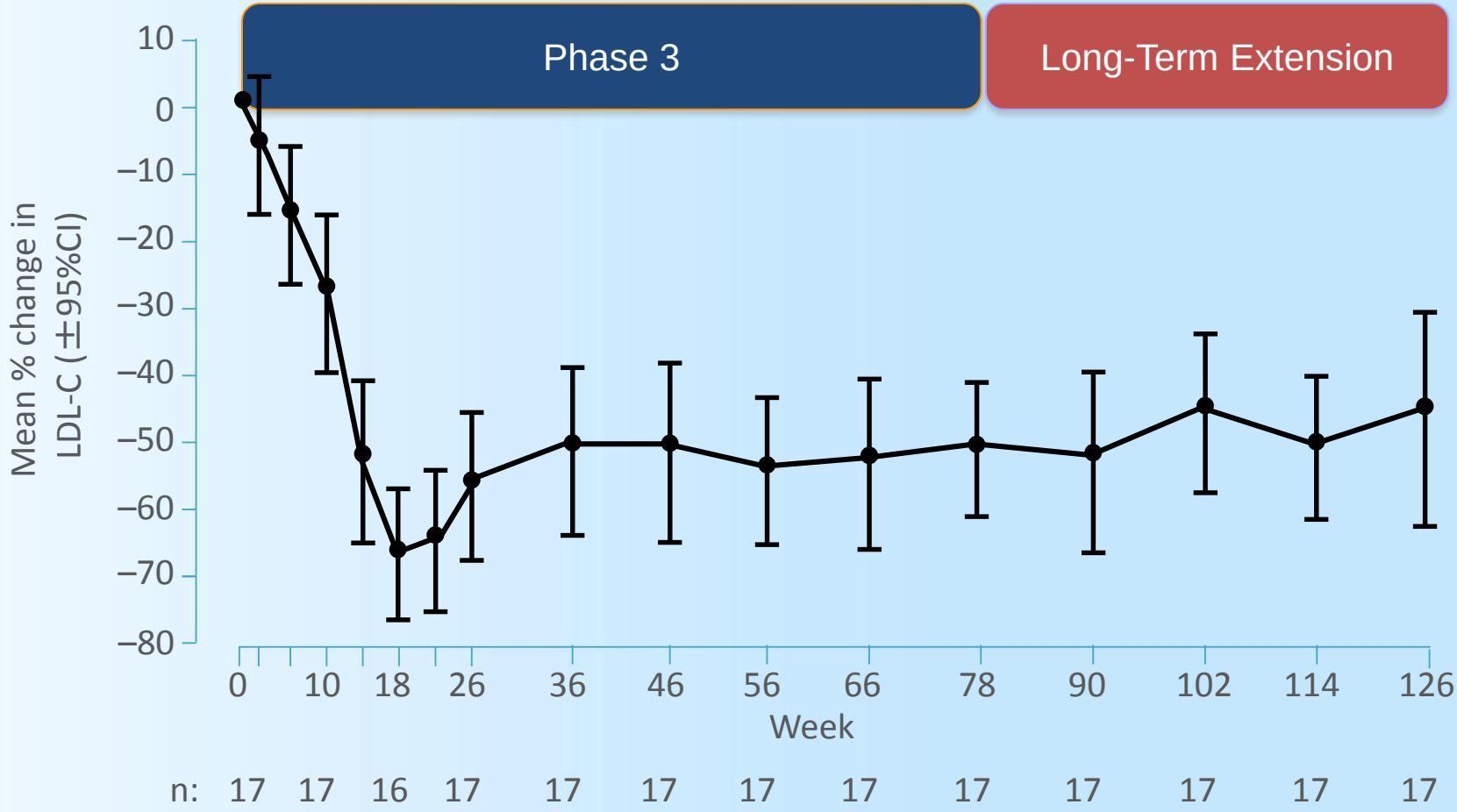
Cuchel et al.
Lancet 2013;381:40-6.

Single-Arm, Open-Label, Multicenter Phase 3 Study of Lomitapide in HoFH

- Most patients had at least one AE
  - 27 of 29 in efficacy phase, 21 of 23 in safety phase (most mild to moderate)
- No patient permanently discontinued therapy due to LFTs
- 6 patients discontinued therapy
  - 2 @ 5 mg, 2 @ 10 mg, 1 @ 20 mg, 1 @ 40 mg
  - 5 patients (17%) discontinued due to adverse events
- GI symptoms were most common side effect (93%)
  - 3 discontinuations due to GI side effects occurred during titration phase

Lancet 2013;381:40-46

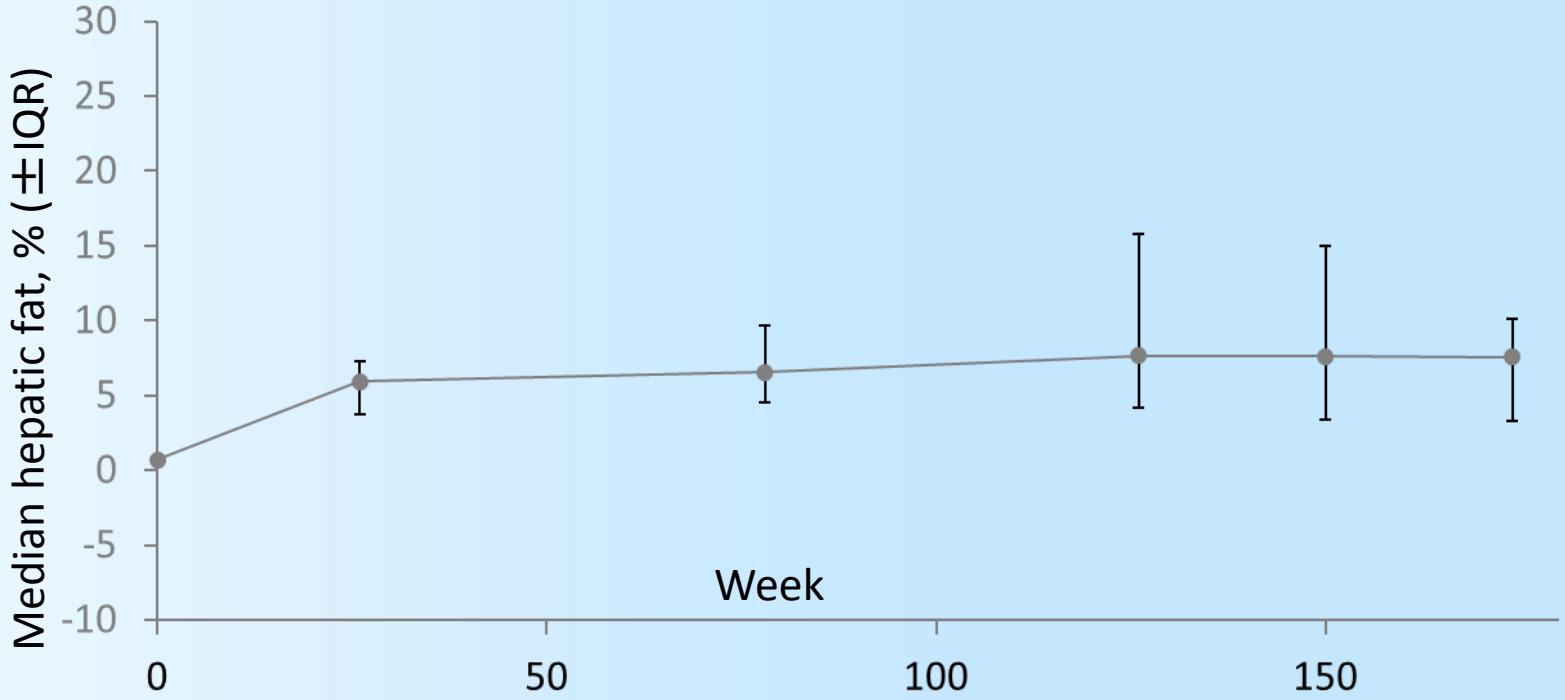
Phase 3 Long-Term Extension Trial:
Mean percent change from baseline in LDL-C by study visit (week 126 completers population)



Cuchel et al. Circulation. 2013; 128: A16516. Presented at 2013 AHA Scientific Sessions, Dallas, TX, Nov.16–20, 2013.

Hepatic Safety: Hepatic Fat

(N=19 safety population)*



Week	Baseline	26	78	126	150	174
N	17	17	17	13	12	7
Median, %	0.7	5.9	6.5	7.7	7.6	7.6
Mean, %	0.8	6.5	7.9	10.2	11.1	7.3
Range, %	0, 2.4	1.1–16.3	0.6–19.0	1.6–24.7	0.7–35.2	0.6–15.6

*NMRS was not performed in two patients due to contraindications Values represent median ± interquartile range (IQR)

Cuchel et al. Circulation. 2013; 128: A16516. Presented at 2013 AHA Scientific Sessions,Dallas, TX, Nov.16–20, 2013.

Lomitapide

- Dose titration schedule can limit GI side effects
- Due to its mechanism of action it may reduce absorption of fat-soluble vitamins
  - Patients are provided with supplements of vit E 400 IU, linoleic acid 200 mg, ALA 210 mg, EPA 110 mg, DHA 80 mg
- Patients must adhere to low-fat (<20%) diet to minimize GI side effects
- Limit alcohol to one serving daily
- Inhibitors of CYP3A4 may increase exposure to lomitapide
  - Do not exceed 30 mg in patients on weak CYP3A4 inhibitors
- Use only low-dose simvastatin and lovastatin
- Lomitapide increases plasma concentrations of warfarin

Lomitapide

- Orphan Drug: available for patients with rare genetic diseases
- Available through a REMS (Risk Evaluation and Mitigation Strategy) program
  - To educate providers about risk of hepatic toxicity and need for careful monitoring
  - To restrict access to patients with homozygous familial hypercholesterolemia
- Prescriber training and certification
- Controlled distribution through certified pharmacies
- Prescription authorization forms

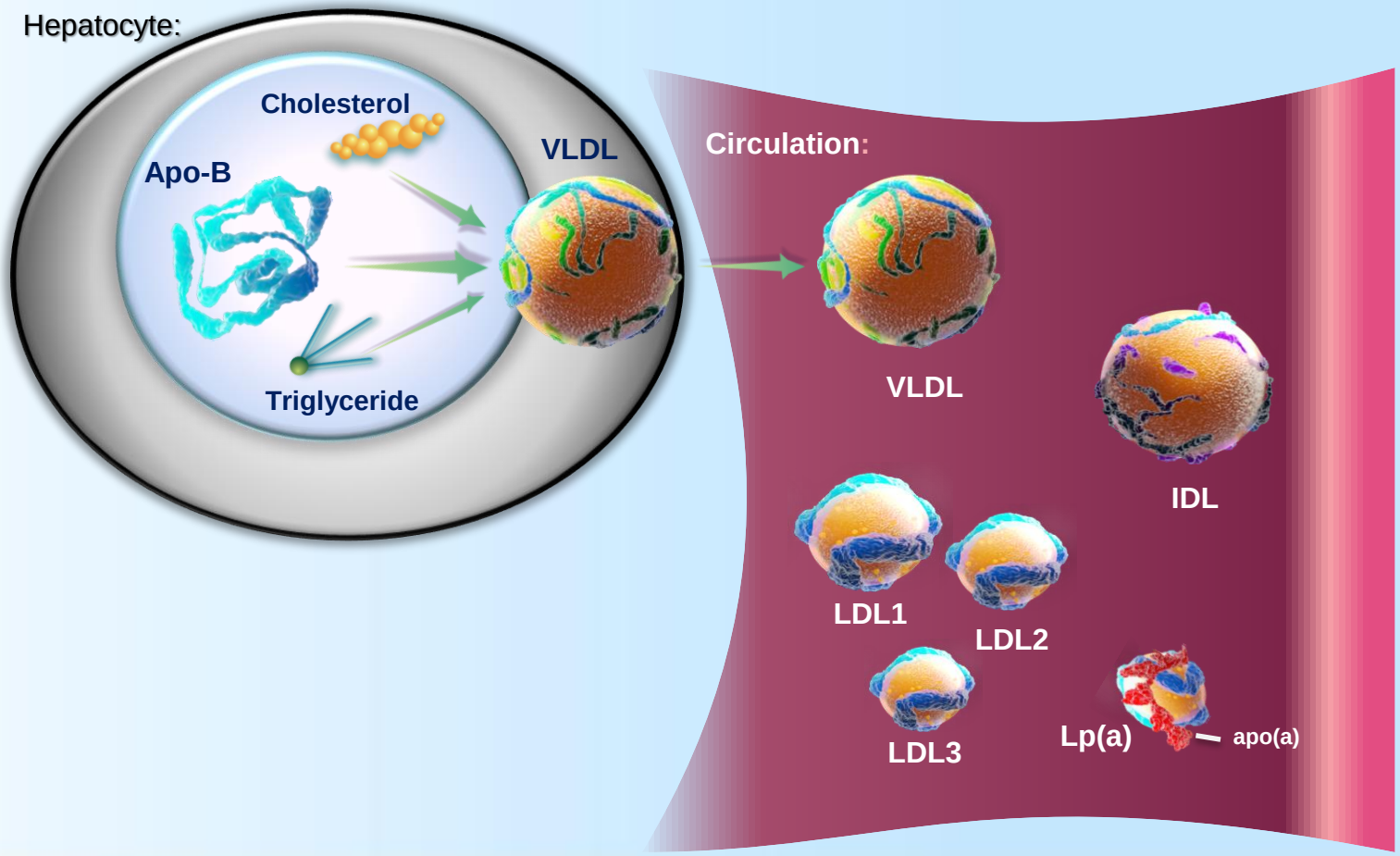
Antisense Oligonucleotides: Mipomersen

Antisense Oligonucleotides: ApoB-100 (mipomersen)

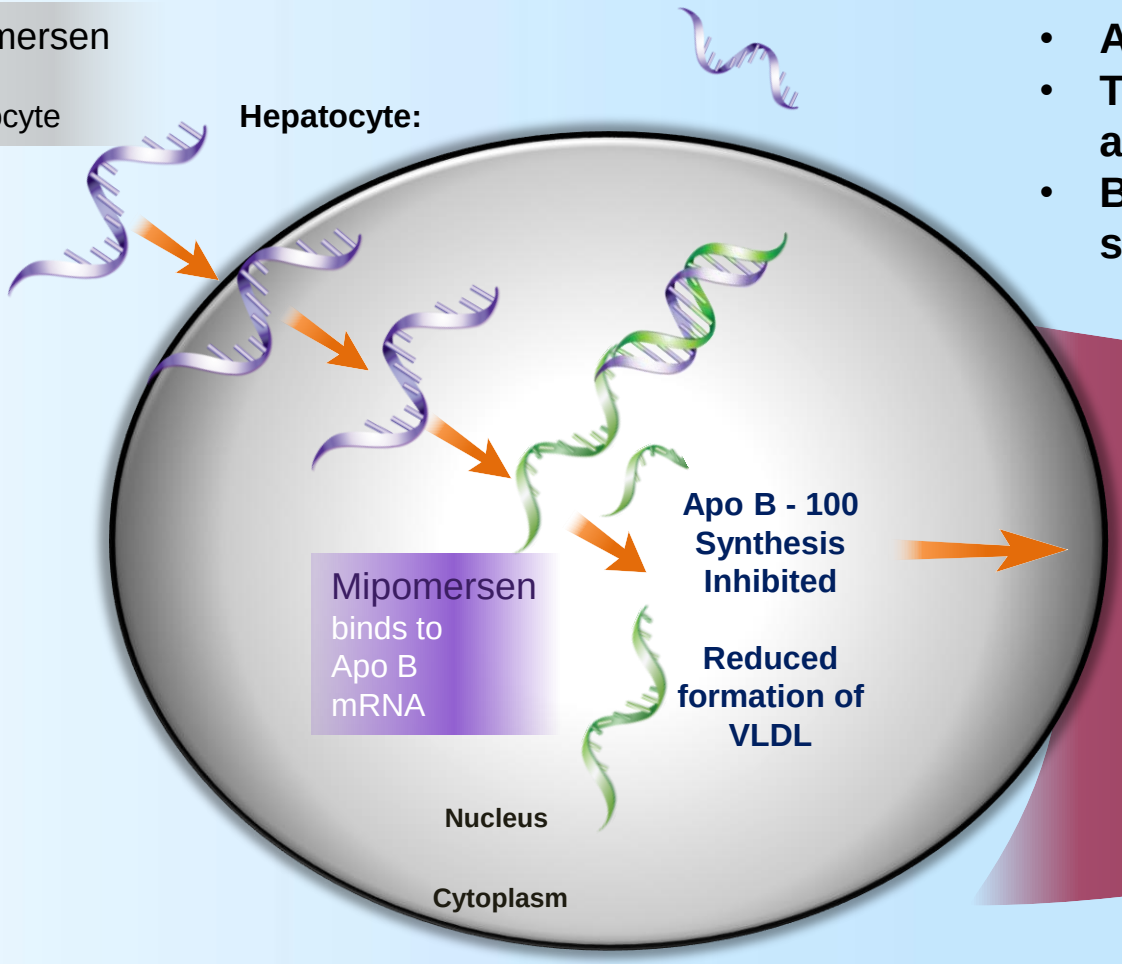
- Second-generation antisense oligonucleotide
  - Greater potency
  - Longer half-life
  - Reduced potential for side effects than earlier chemistries
  - No CYP450 interactions, few drug interactions (can be used in combination with other lipid-lowering agents)
  - Half-life 30 days, steady state at approximately 6 months
- Apo B 100 production inhibited
- Decreased secretion of apo B-containing lipoproteins from the liver
- Lowers apo B, LDL-cholesterol and lipoprotein (a) in humans

Stein. Endocrinol Metab Clin North Am 2009;38:99-119.

HoFH Is Associated With Increased Plasma Levels of Apo B–Containing Lipoproteins



Mipomersen: Mechanism of Action



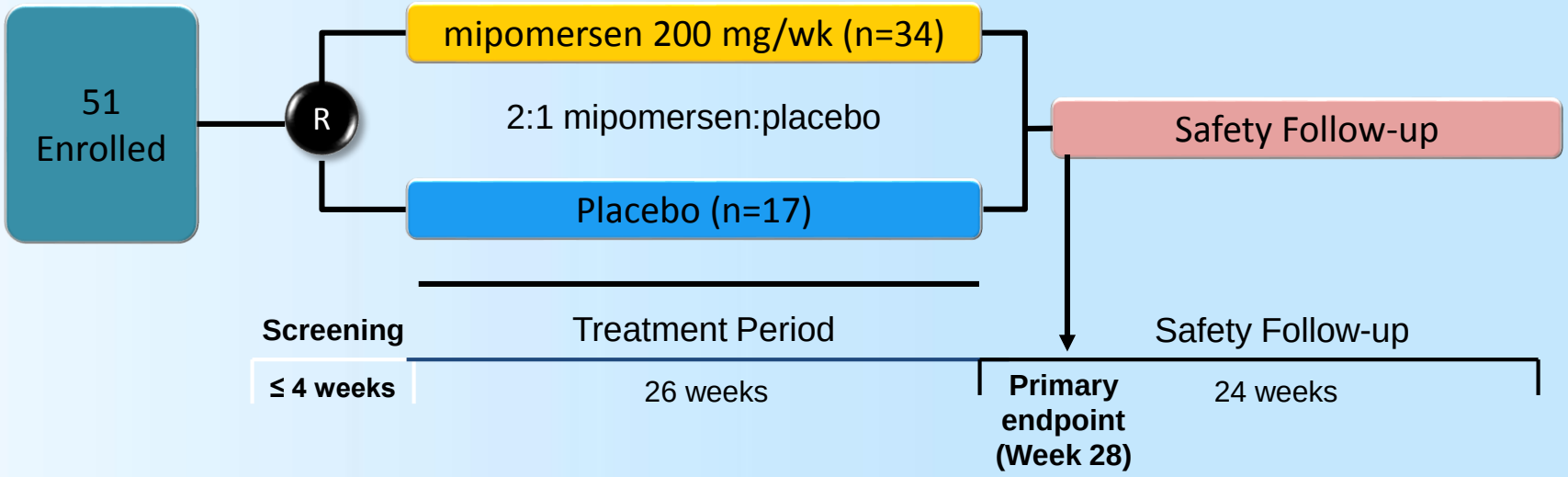
- **Antisense oligonucleotide**
- **Targets messenger RNA for apo B-100**
- **Binds to a unique 20-base sequence**

Circulation:

- Reduced secretion of VLDL, and
- Reduced formation of downstream, atherogenic lipoproteins

HoFH Phase 3 Study Design

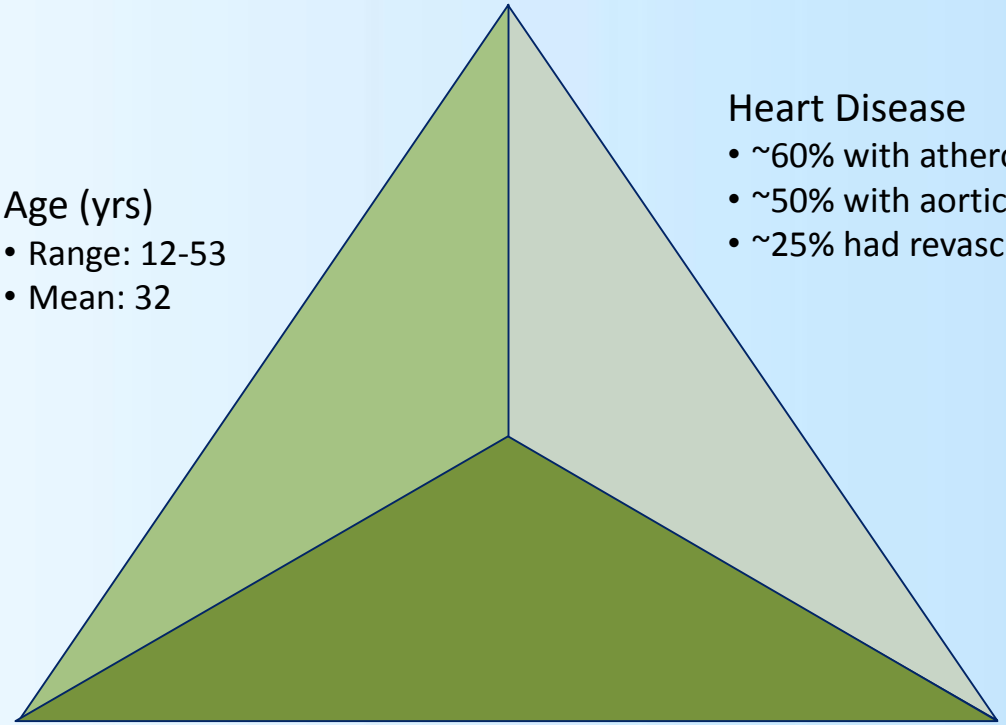
- Multi-national, randomized, placebo-controlled, double-blind trial
- Mipomersen as an adjunct to lipid-lowering medications
- Weekly subcutaneous injections for 26 weeks
- Primary efficacy endpoint: % change in LDL-C from baseline at week 28



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

Baseline Characteristics from Phase 3 Study of Mipomersen in HoFH

Premature Heart Disease, With Very High LDL-C Levels



Age (yrs)
- Range: 12-53
- Mean: 32

Heart Disease
- ~60% with atherosclerotic disease
- ~50% with aortic valve stenosis
- ~25% had revascularization

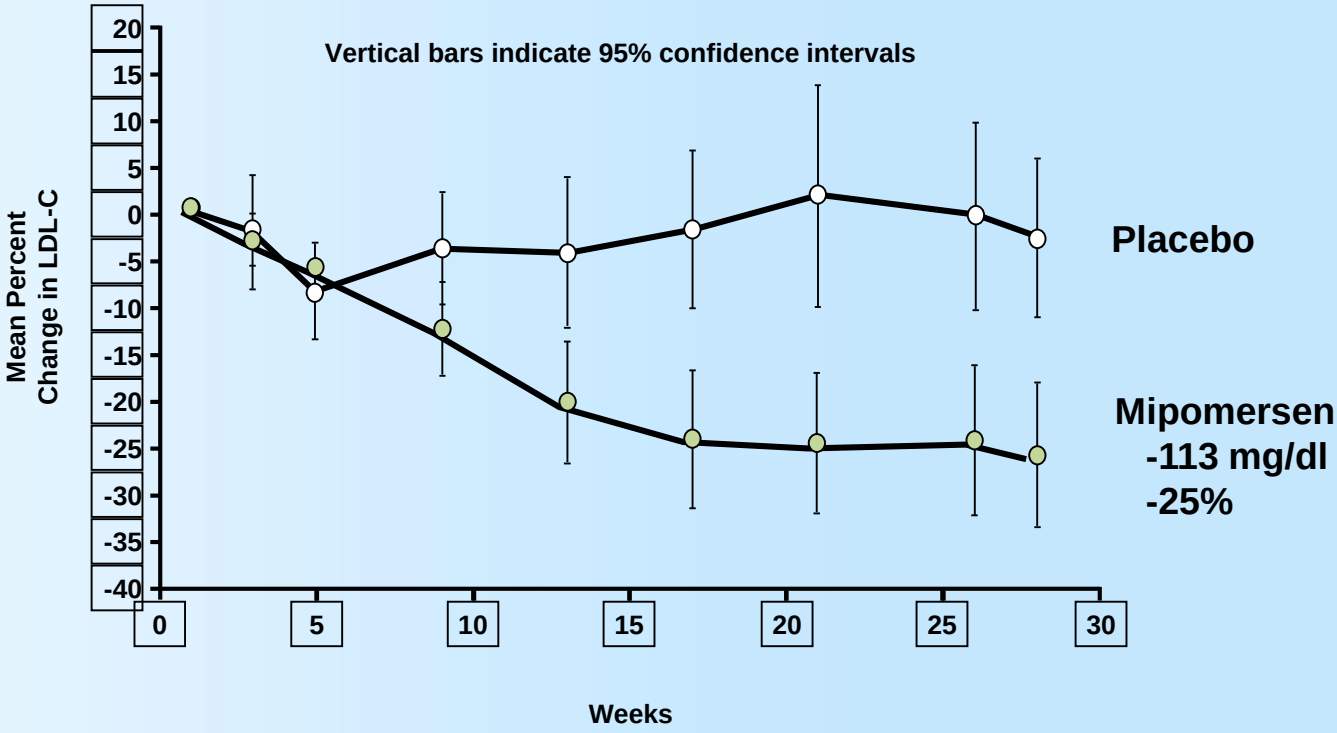
- In 98% (50 of 51) of patients, background therapy included statins
- 88% (44 of 50) were on maximum-dose statin therapy
- 76% (38 of 50) were also taking at least one other lipid-lowering medication
- 82-88% genetically confirmed HoFH

Very High LDL-C, after standard therapies[1]
- Range: 172-704 mg/dL
- Mean: 439 mg/dL*

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

Mipomersen Significantly Reduced LDL-C

- Mean % change in LDL-C was -25% for mipomersen compared with (-3% for placebo)
- This represents a mean reduction of 113 mg/dL and 12 mg/dL for mipomersen and placebo, from baselines of 439 mg/dL and 400 mg/dL, respectively
- LDL-C % change ranged from 2% to -82% for mipomersen



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

Response to Addition of Mipomersen in HoFH Patients

Mean Baseline LDL-C (mg/dL) (range)	Mipomersen n=34 439 (190, 704)	Placebo n=17 400 (172, 639)	
Parameter (mg/dL)	Mean or Median Percent Change from Baseline to End of Treatment*		Mean (95% CI) or Median Treatment Difference from Placebo (%)
LDL-C†	-25%	-3%	-21% (-33, -10)
Apo-B†	-27%	-3%	-24% (-34, -15)
TC†	-21%	-2%	-19% (-29, -9)
Non-HDL-C	-25%	-3%	-22% (-33, -11)
TG£	-18%	1%	-18%
HDL-C‡£	15%	4%	11%

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

Transaminase Elevations

Parameter	Statistic	Mipomersen (N=261)	Placebo (N=129)
ALT maximum	**Incidence rate, %**		
	≥3 × ULN and <5 × ULN	12%	1%
	≥5 × ULN and <10 × ULN	3%	0%
	≥10 × ULN	1%	0%
ALT	**≥3 × ULN, two consecutive results (at least 7 days apart)**	**8%**	**0%**
AST maximum	**Incidence rate, %**		
	≥3 × ULN and <5 × ULN	7%	1%
	≥5 × ULN and <10 × ULN	3%	0%
	≥10 × ULN	0%	0%
AST	**≥3 × ULN, two consecutive results (at least 7 days apart)**	**4%**	**0%**

Adults: ALT ULN = 41 U/L; AST ULN = 34 U/L. ULN = upper limit of normal

- ALT elevations were not associated with increased total bilirubin, changes in INR or PTT, or decreased albumin
- Elevations trended toward baseline over weeks to months after stopping therapy

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

Hepatic Steatosis

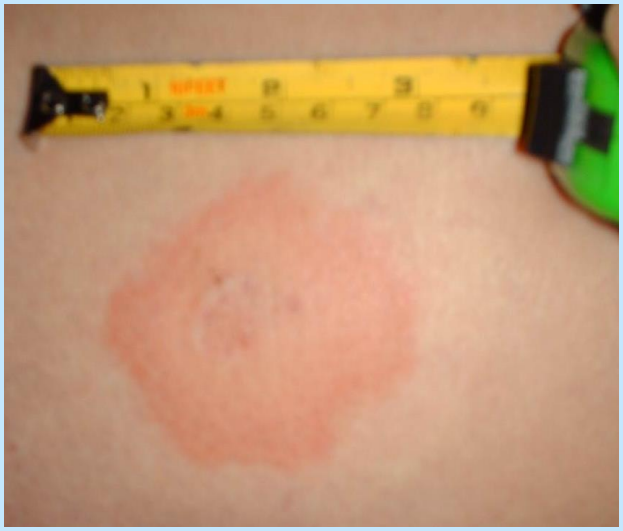
- Mipomersen increases hepatic fat (steatosis) with or without concomitant increases in transaminases
  - Long-term consequences of hepatic steatosis associated with mipomersen are unknown
- Median nominal increase in fat fraction (relative to baseline) as assessed by MRI:
  - 9.6% mipomersen-treated patients
  - 0.02% in the placebo group
- In general, elevations in fat fraction decreased when assessed 24 weeks after cessation of mipomersen

†Upper limit of normal hepatic triglyceride content as determined by MRI in general population is 5.56%, (corresponding to a hepatic triglyceride level of 55.6 mg/g)

Szczepaniak et al. Am J Physiol Endocrinol Metab 2005. 228: E462-8.

Injection Site Reactions

- Reported in 84% of patients receiving mipomersen therapy vs 33% of placebo-treated patients
  - Typically consist of one or more of the following: erythema, pain, tenderness, pruritus and local swelling
- Did not occur with all injections
- Resulted in discontinuation of therapy in 5% of patients



DOF: Phase III Clinical Studies

To minimize the potential for injection site reactions, proper technique for subcutaneous administration should be followed

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

Flu-like Symptoms

- Reported in 29.9% of patients receiving mipomersen therapy compared with 16.3% of placebo-treated patients
  - Include one or more of the following: influenza-like illness, pyrexia, chills, myalgia, arthralgia, malaise or fatigue
  - Typically occurred within 2 days after an injection
- These did not occur with all injections
- Resulted in discontinuation of therapy in 3% of patients

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

Drug Interactions

- Mipomersen is not a substrate for CYP450 metabolism and is metabolized in tissues by nucleases
- Co-administration of mipomersen with warfarin did not result in a pharmacodynamic interaction as determined by INR, aPTT and PT
- No clinically relevant pharmacokinetic interactions were reported between mipomersen and simvastatin or ezetimibe
- No dose adjustments recommended based on drug-drug interactions

Li et al. J Cardiovasc Pharmacol. 2014 Aug;64:164-71.
Yu et al. Clin Pharmacokinet. 2009;48:39-50.

Dosing

- Mipomersen is self-administered once weekly as 200 mg subcutaneous injection
  - The injection should be given on the same day every week
  - If a dose is missed, the injection should be given at least 3 days from the next weekly dose

Mipomersen is supplied as:
Single-use pre-filled syringe
Containing 1-mL solution (200 mg/mL)
With 0.5-cm, 30-gauge needle

Genzyme, Mipomersen (Kynamro) Prescribing Information

Mipomersen

- Orphan Drug: available for patients with rare genetic diseases
- Available through a REMS (Risk Evaluation and Mitigation Strategy) program
  - To educate providers about risk of hepatic toxicity and need for careful monitoring
  - To restrict access to patients with homozygous familial hypercholesterolemia
- Prescriber training and certification
- Controlled distribution through certified pharmacies
- Prescription authorization forms

Differences Between apoB Antisense and MTP Inhibitor Drugs

- Mipomersen
  - Reduces *hepatic* apoB containing lipoproteins
  - Administered SQ weekly, requires refrigeration
  - Large reductions in Lp(a)
  - Injection site reactions, flu-like syndrome
- Lomitapide
  - Lomitapide reduces both *hepatic* apoB100 and *intestinal* apoB48 containing lipoproteins
  - Administered orally on a daily basis
  - Loose stools, GI side effects
- Both require careful monitoring of LFTs
- Both Orphan Drugs require REMS certification to prescribe

Effects of Lomitapide and Mipomersen in hoFH (Phase 3 Studies)

	Lomitapide* (n=29)	Mipomersen† (n=34)
LDL-C		
Baseline, mg/dL	336	440
End point, mg/dL	190	324
Mean change, %	–40	–25
Non–HDL-C		
Baseline, mg/dL	386	463
Mean change, %	–40	–25
Total cholesterol		
Baseline, mg/dL	428	502
Mean change, %	–36	–21
apoB		
Baseline, mg/dL	260	280
Mean change, %	–39	–27
Lp(a)‡		
Baseline, mg/dL	66	60
Change, %	–13	–32

Rader, Kastelein. Circulation. 2014;129:1022-32.

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)

- Member of the family of proteases involved in degradation of LDL-C receptor
- Mutations leading to loss-of-function are associated with lifelong low LDL-C levels and decreased risk of cardiovascular disease
- Inhibitors of PCSK9 are in development
  - Fully monoclonal antibodies

Stein. Endocrinol Metab Clin North Am 2009;38:99-119.

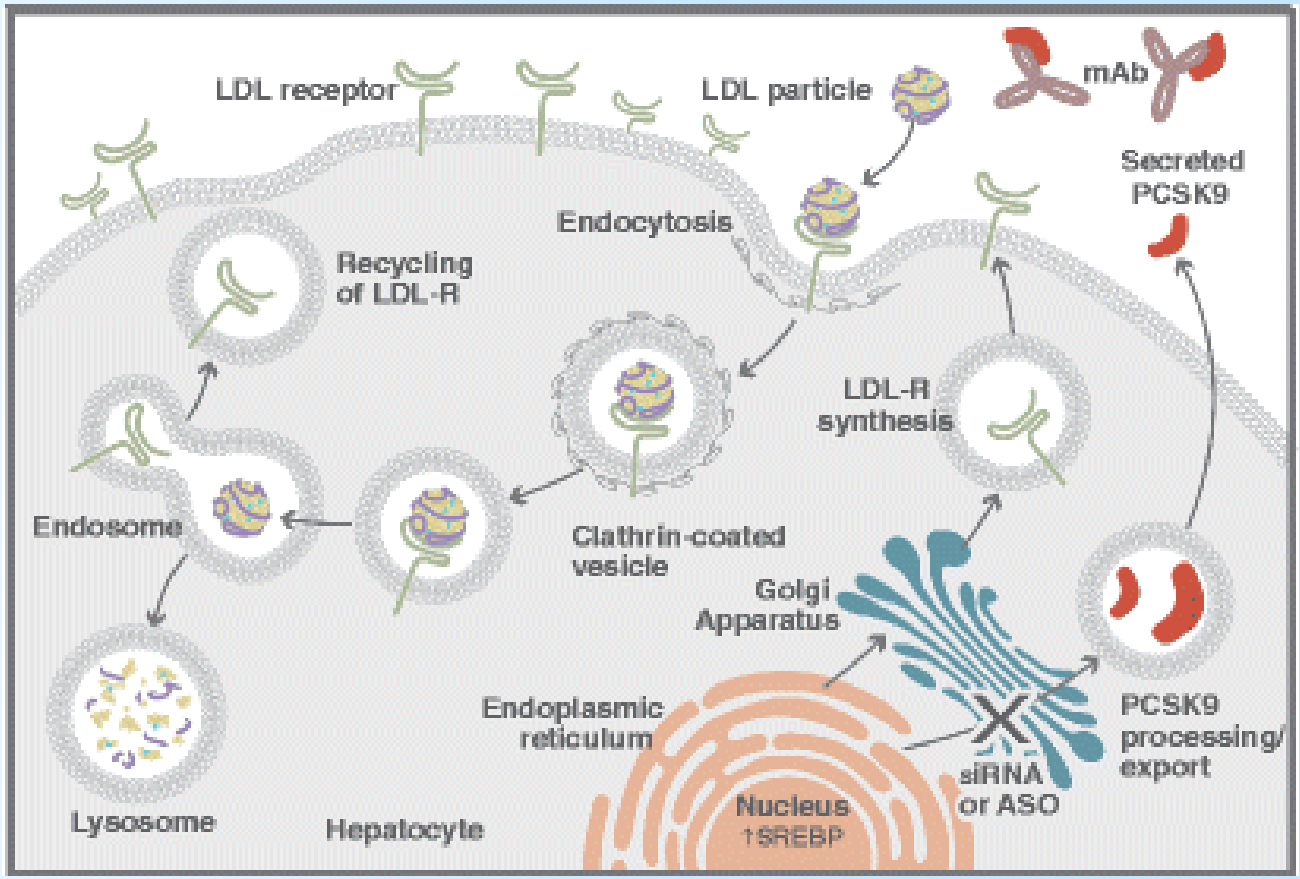
Approaches to PCSK9 Inhibition

Mode of Action	Drug	Company	Phase
PCSK9 binding: Monoclonal antibodies	**Alirocumab (REGN727/SAR236553)**	Sanofi/Regeneron	3
	Evolocumab (AMG 145)	Amgen	3
	Bococizumab (RN316)	Pfizer	3
	LY3015014	Eli Lilly	2
	RG7652	Roche/Genentech	2 (terminated)
	LGT209	Novartis	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)

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

LNA = locked nucleic acid

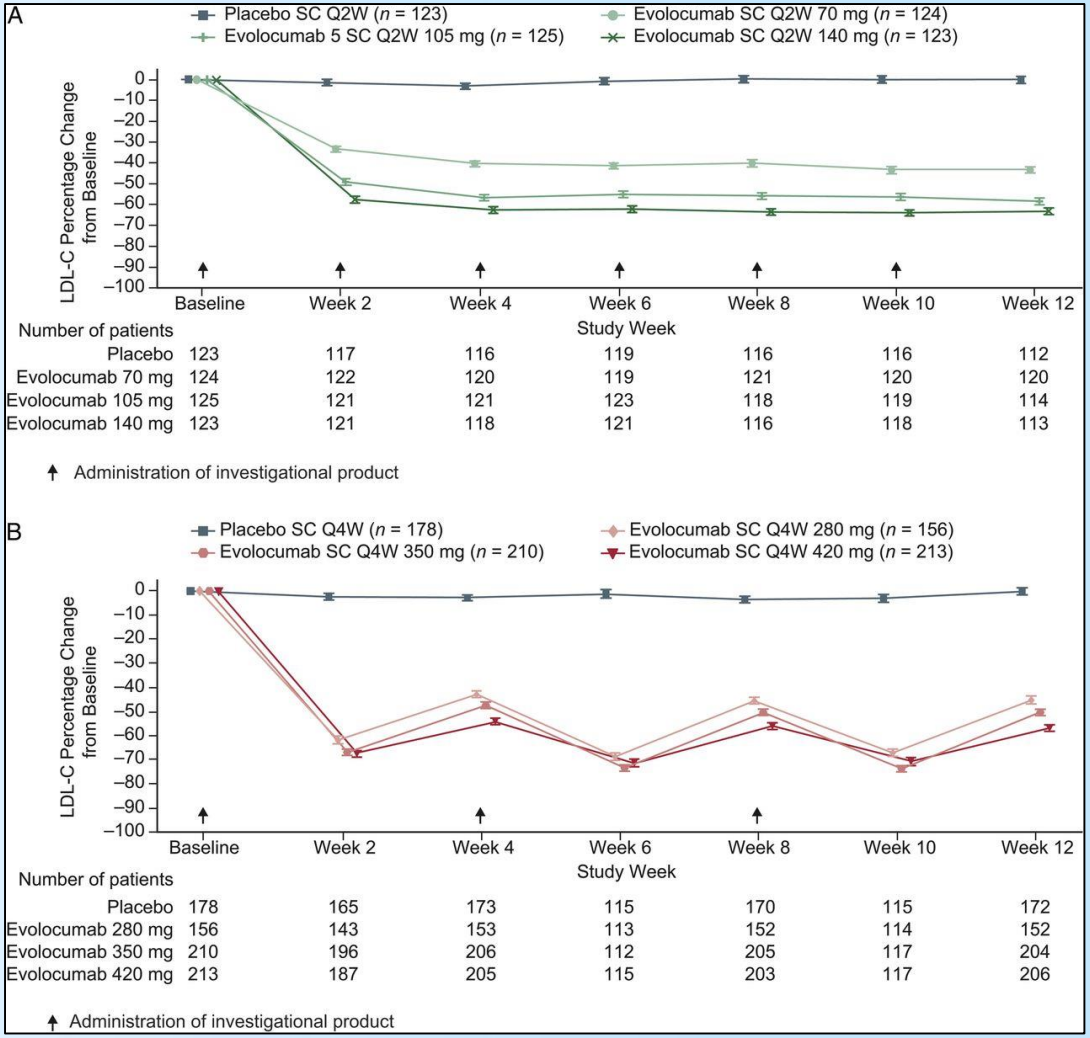
Interaction of PCSK9 and LDL Receptor



- Interaction of PCSK9 and LDL-R is through circulating PCSK9
- PCSK9 binds to receptor, is internalized with receptor, then diverts the receptor from recycling, toward acidic vesicles for destruction
- Binding of PCSK9 in plasma reduces its availability to bind to the LDL-R and leads to increased recycling, increased LDL-R density

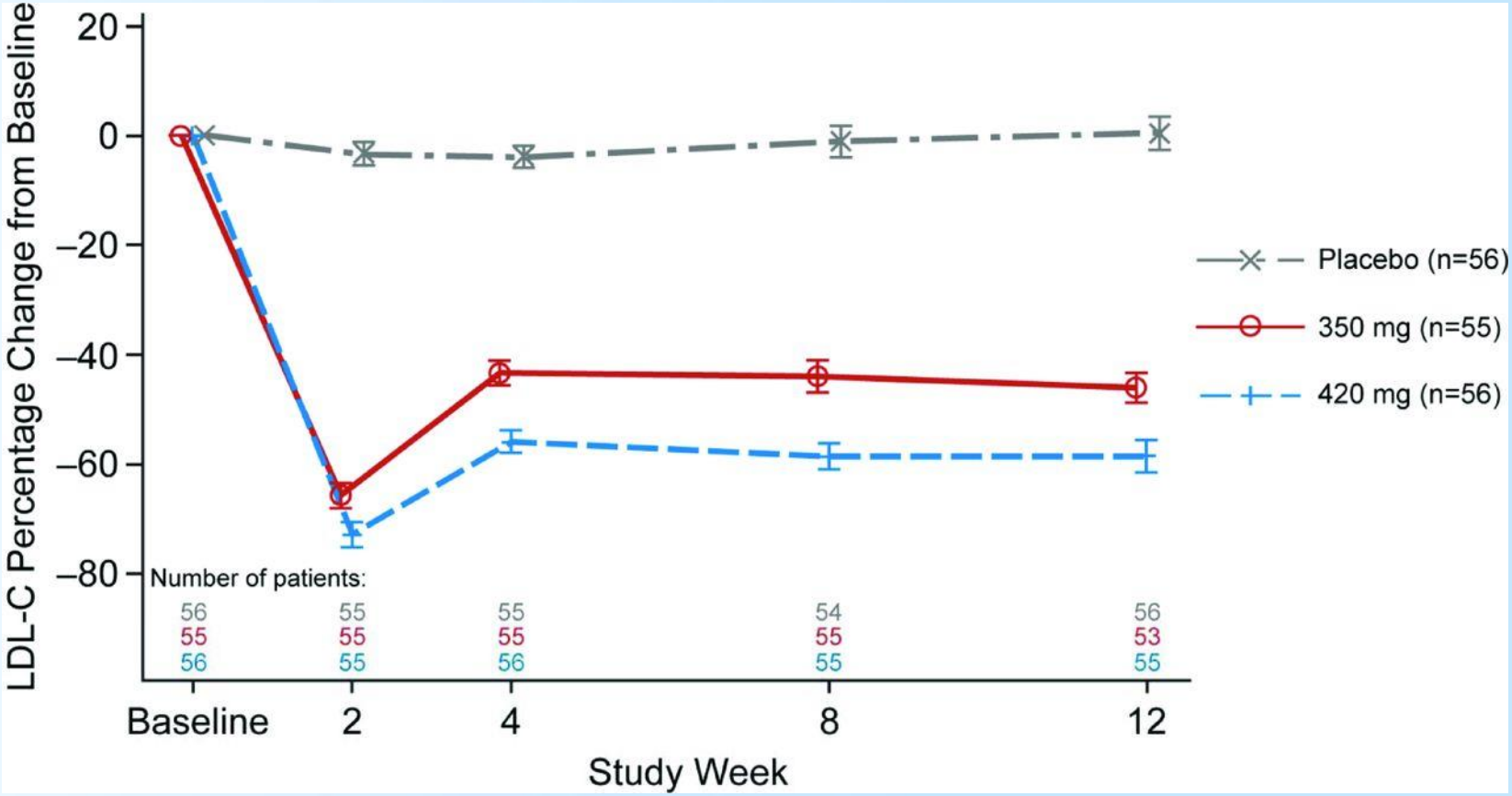
Stein, Swergold. Curr Atheroscler Rep. 2013;15:310.

(A) Percentage Changes from Baseline in Levels of LDL-C (calculated) for Patients Treated Every 2 Weeks (Q2W), (B) Treated Every 4 Weeks



Stein et al. Eur Heart J 2014;35:2249-59.

HeFH: Percentage Change from Baseline in Calculated LDL-C to Week 12



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

Effect of the PCSK9 Monoclonal Antibody, AMG 145, in Homozygous FH

Patient	Mutation Allele 1 (Estimated LDLR Function)	Mutation Allele 2 (Estimated LDLR Function)	Overall LDLR Function
1	Asp266Glu (15%–30%)	Asp266Glu (15%–30%)	Receptor defective
2	1187-10 G>A* (not determined)	Asp266Glu (15%–30%)	Receptor defective
3	Asp224Asn (<2%)	Cys296Tyr (not determined)	Negative†
4	Deletion exons 4–18 (not determined)	Cys197Gly (not determined)	Negative†
5	Asp221Gly (<2%)	Asp227Glu (5%–15%)	Receptor defective
6‡§	Asp227Glu (5%–15%)	Asp227Glu (5%–15%)	Receptor defective
7‡§	Asp227Glu (5%–15%)	Asp227Glu (5%–15%)	Receptor defective
8	Asp175Asn (not determined)	Asp227Glu (5%–15%)	Receptor defective

LDLR indicates low-density lipoprotein receptor.
*Mutation at splice acceptor site 10 nucleotides upstream of the first nucleotide of exon 9, 1187.
†Confirmed by fibroblast culture.
‡True homozygous patient.
§Patients share the same genotype.

Patient Genotypes

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

Effect of the PCSK9 Monoclonal Antibody, AMG 145, in Homozygous FH

A, Percentage change from baseline in low-density lipoprotein cholesterol (LDL-C) by ultracentrifugation at weeks 4, 6, 8, and 12 of the 4-week dosing period and weeks 4, 8, and 12 of the 2-week dosing period (n=8). As shown, data for patient 2 were missing at week 8 of the 2-week dosing p
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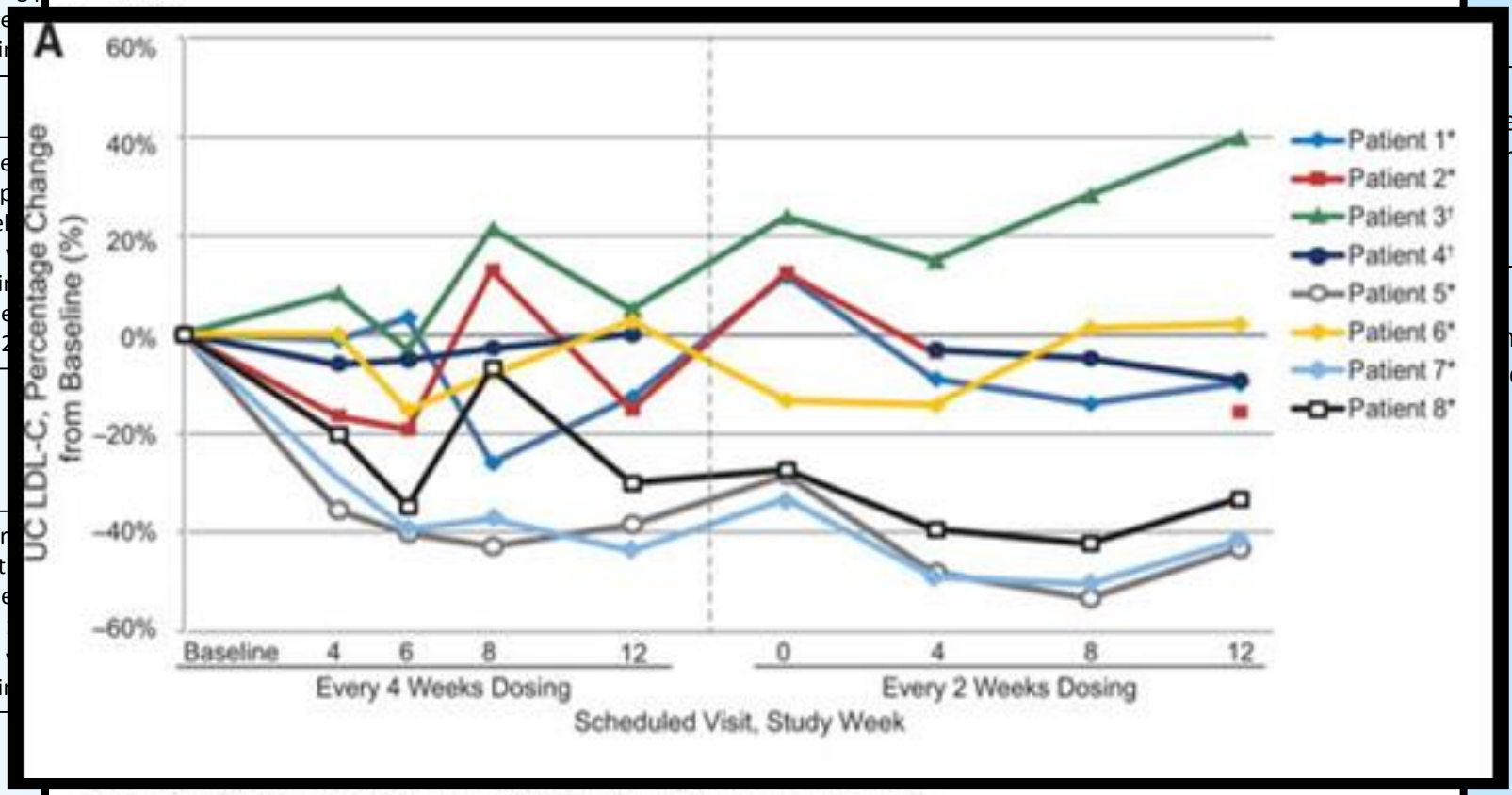

*Defective LDLR function; †Negative LDLR function

Every 4 Weeks Dosing
Every 2 Weeks Dosing
Scheduled Visit, Study Week

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

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

Effect of the PCSK9 Monoclonal Antibody, AMG 145, in Homozygous FH

Efficacy Outcomes Based on Mutation Status

Table 3. Efficacy Outcomes Based on Mutation Status

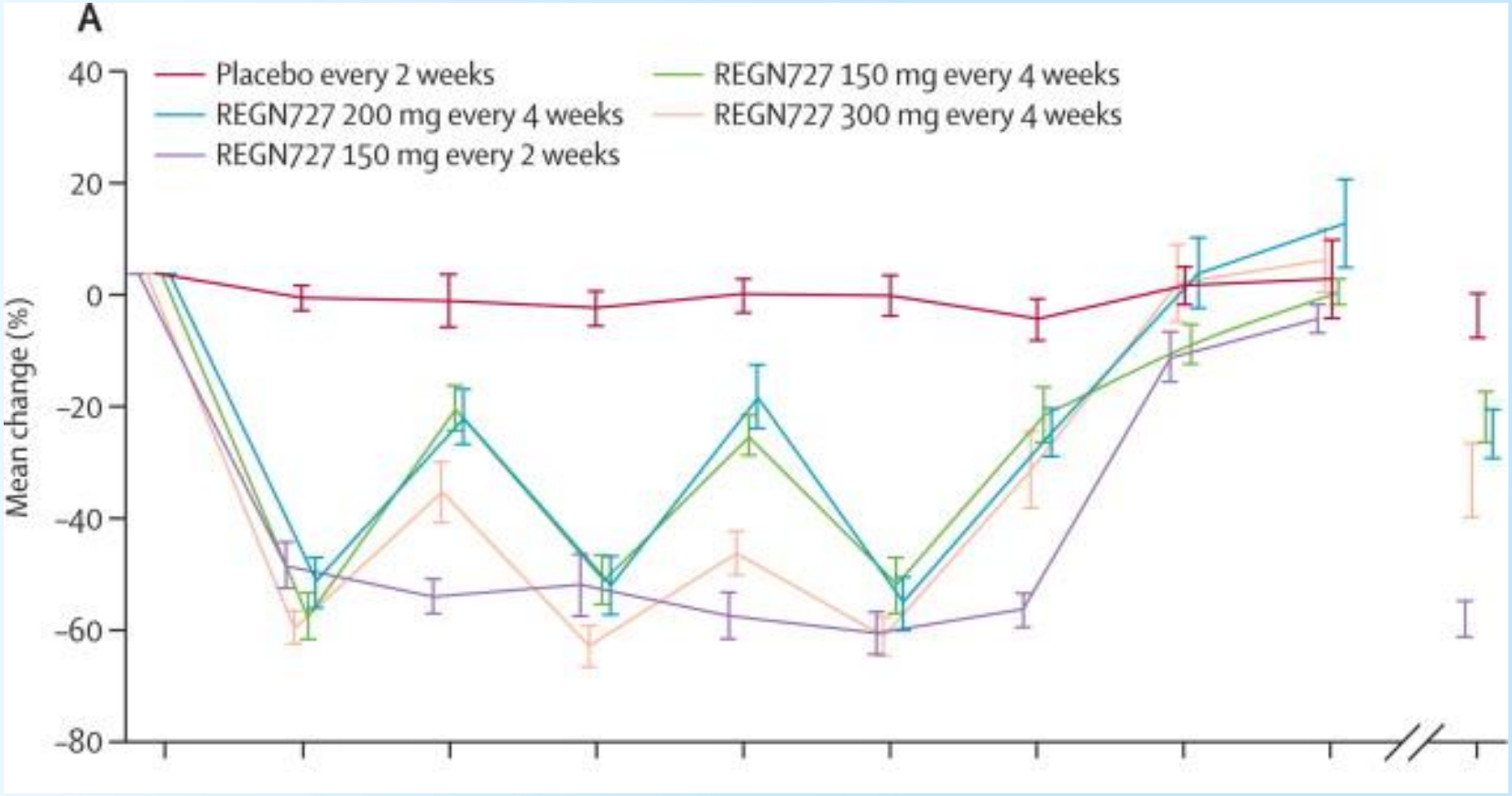
	Percentage Change From Baseline, Mean (SD), %					
	Week 12, Every-4-Week Dosing			Week 12, Every-2-Week Dosing		
Mutation Status	UC LDL-C	Apolipoprotein B	Lipoprotein(a)*	UC LDL-C	Apolipoprotein B	Lipoprotein(a)
Defective LDL receptor (n=6)	−22.9 (17.5)	−18.3 (14.9)	−10.0 (11.5)	−23.6 (18.5)	−17.9 (18.0)	−18.7 (14.1)
Negative LDL receptor (n=2)	2.6 (3.7)	−4.5 (3.5)	−16.8 (8.0)	15.3 (34.7)	3.4 (14.0)	−18.5 (5.3)
	Average of Week 4, 8, and 12, Every-4-Week Dosing			Average of Week 4, 8, and 12, Every-2-Week Dosing		
Defective LDL receptor (n=6)	−19.3 (15.5) *P*=0.0313†	−18.0 (13.1)	−10.0 (11.5)	−26.3 (20.4) (*P*=0.0313)†	−22.1 (18.7)	−20.0 (12.1)
Negative LDL receptor (n=2)	4.4 (10.3)	1.4 (5.6)	−16.8 (8.0)	11.0 (23.6)	2.1 (7.9)	−22.7 (11.2)

LDL indicates low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; and UC, ultracentrifugation.
*Lipoprotein(a) was collected only at week 12 for every-4-week dosing.
†Signed-rank test.

Although the study included only 2 patients who were receptor negative, neither experienced LDL cholesterol reduction even with dosing every 2 weeks and nearly 90% reduction in plasma PCSK9.

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

Effect of Alirocumab to Reduce LDL-C in 77 patients with HeFH on Stable Statin Dose with or without Ezetimibe Therapy
A Phase 2 Randomised Controlled Trial



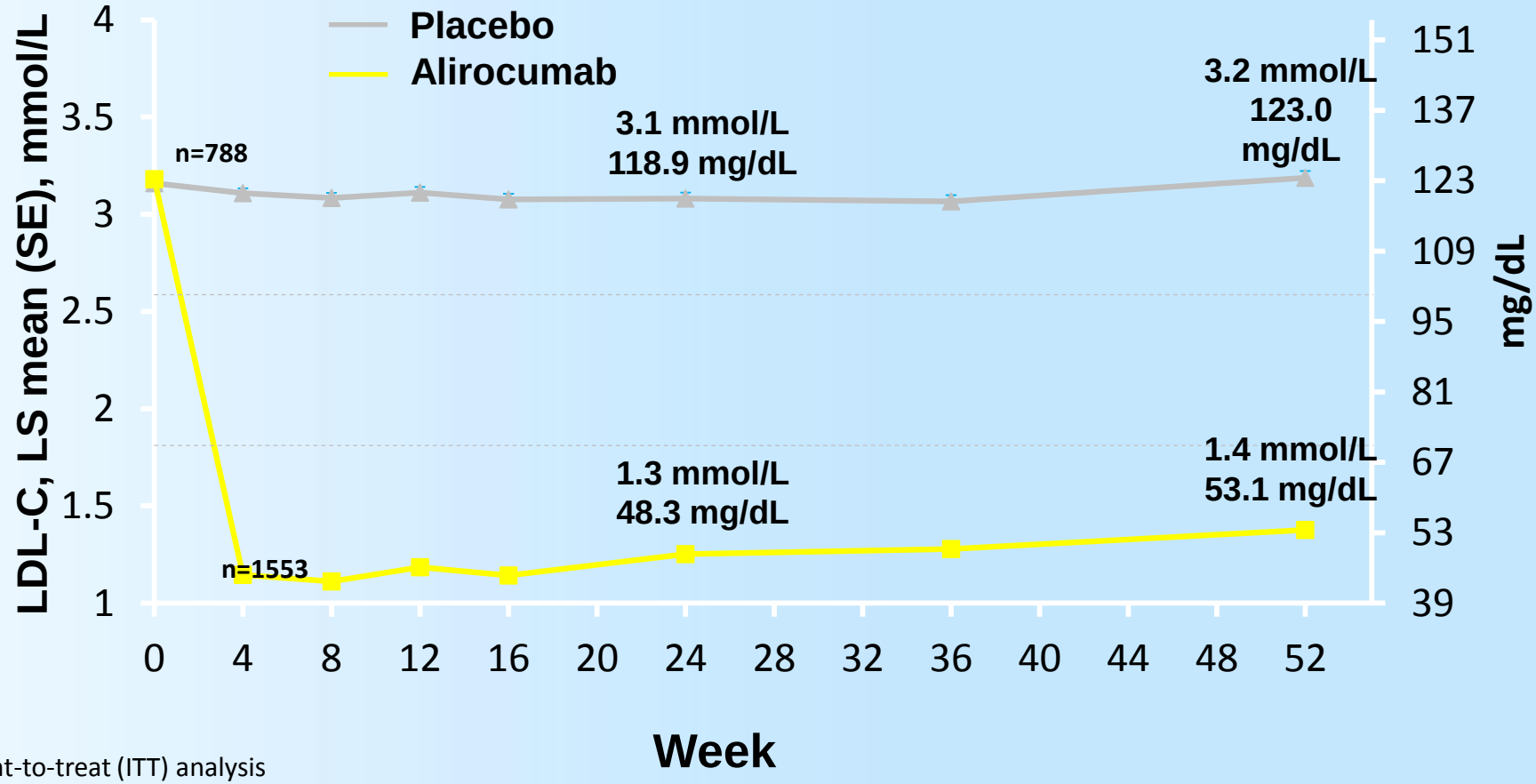
Mean percent change in baseline LDL-C (A) versus week during treatment and follow-up period for the mITT population Data are mean percent change (SE). LDL-C=low-density lipoprotein cholesterol. ApoB=apolipoprotein B. LOCF=last observ...

Stein et al. Lancet. 2012;380:29-36.

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



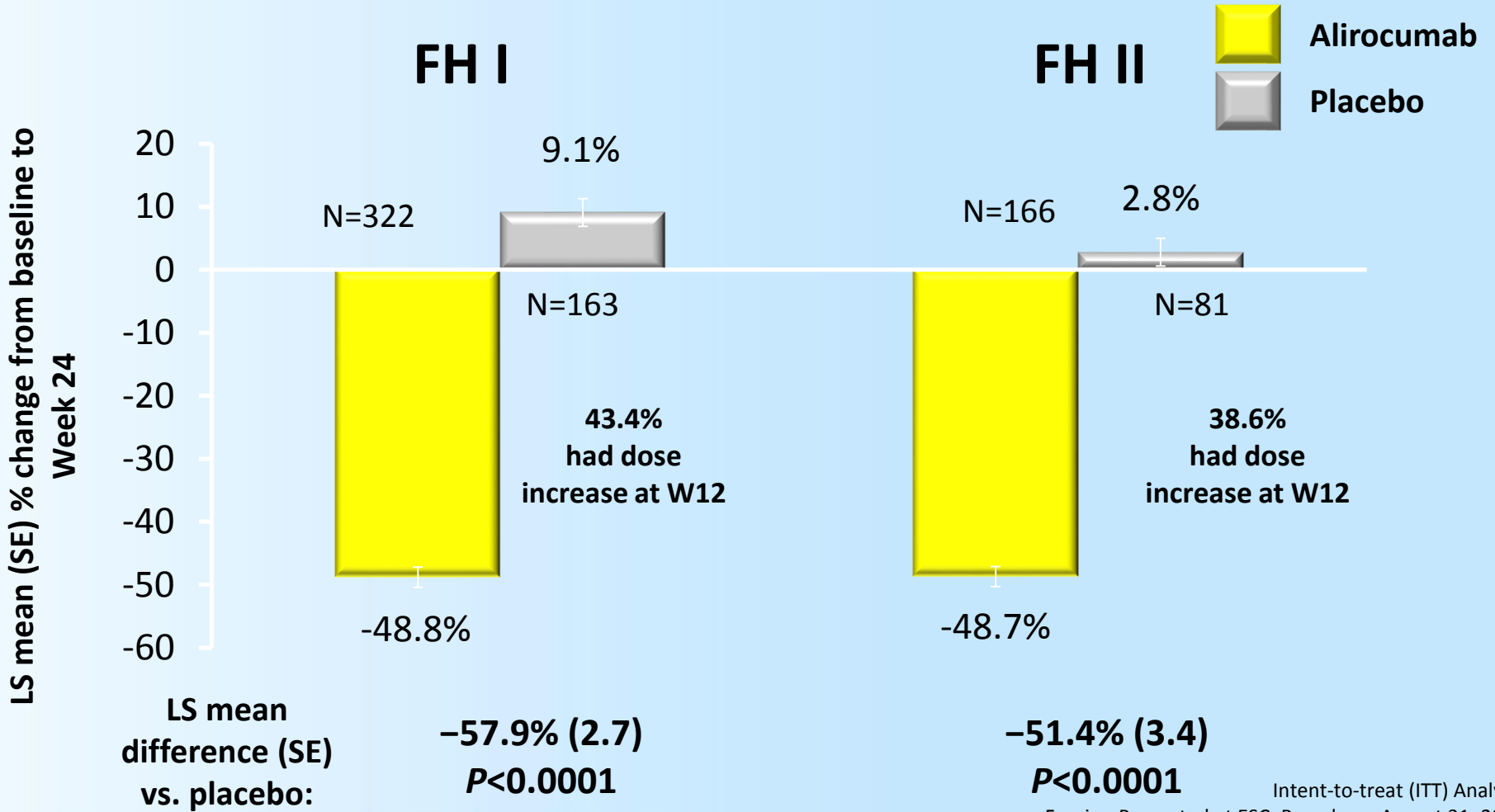
Intent-to-treat (ITT) analysis

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

ODYSSEY FH I and FH II Study: Primary Efficacy Results

Primary Endpoint: Percent Change from Baseline to Week 24 in LDL-C

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

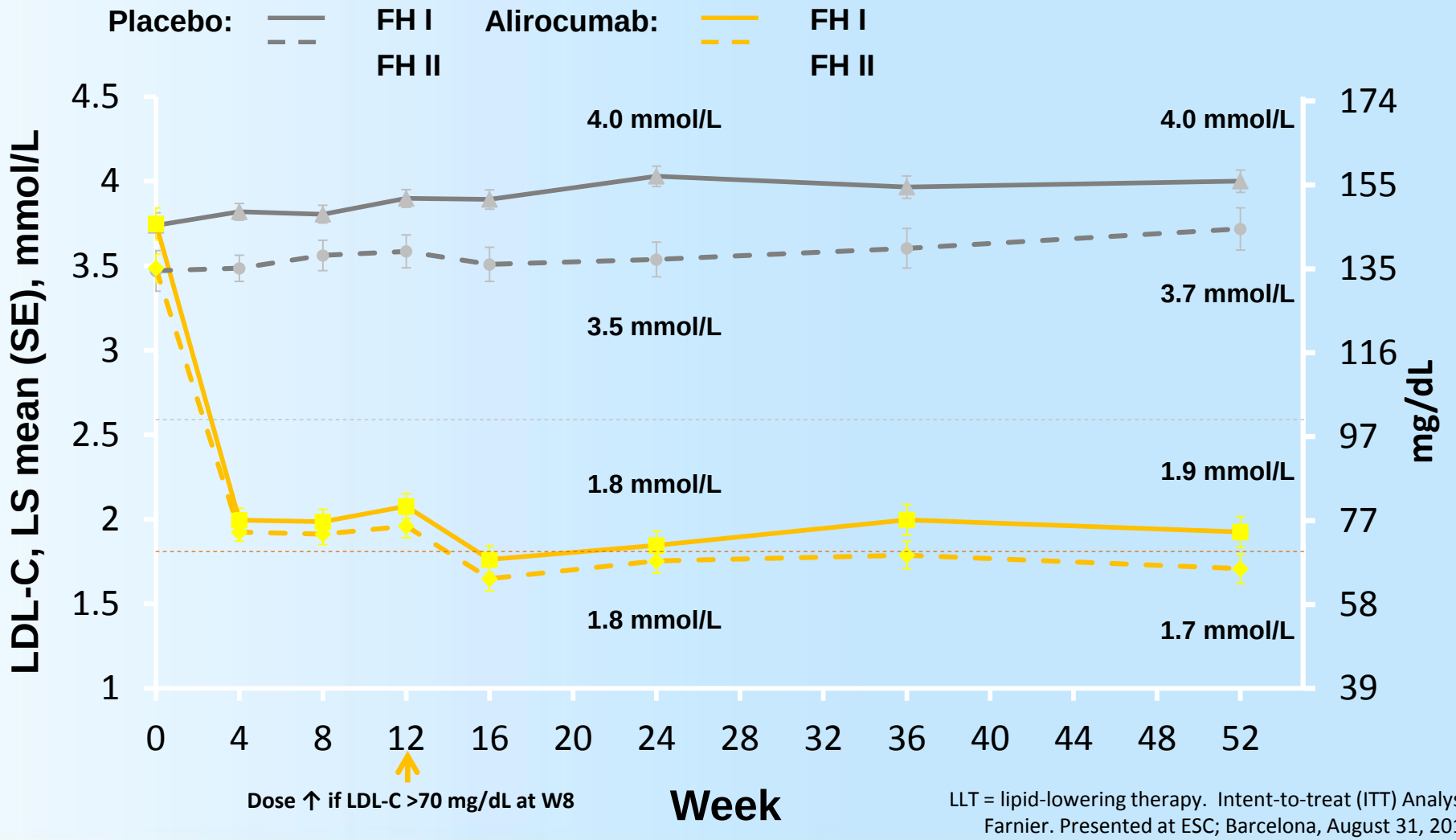


Intent-to-treat (ITT) Analysis.

Farnier. Presented at ESC; Barcelona, August 31, 2014.

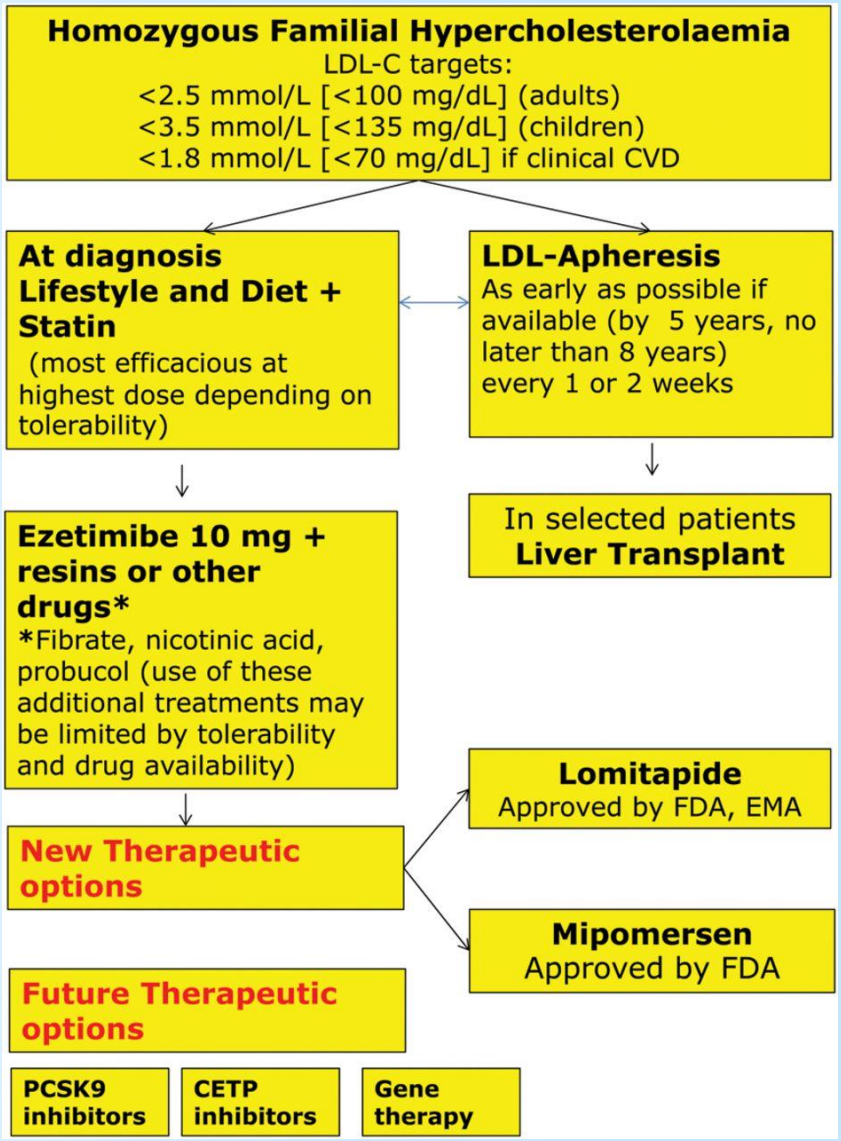
ODYSSEY FH I and FH II Study: LDL-C Reductions Maintained Over 52 Weeks

Achieved LDL-C Over Time on Background of Maximally-Tolerated Statin ±Other LLT



LLT = lipid-lowering therapy. Intent-to-treat (ITT) Analysis.
Farnier. Presented at ESC; Barcelona, August 31, 2014.

Suggested Algorithm for Management of Homozygous FH



Cuchel et al. Eur Heart J 2014;35:2146-57.

The Faces of Familial Hypercholesterolemia: A Call to Action from the FH Community

Scott Radabaugh
Patient Advocate

Catherine Davis Ahmed
Director of Outreach
The FH Foundation

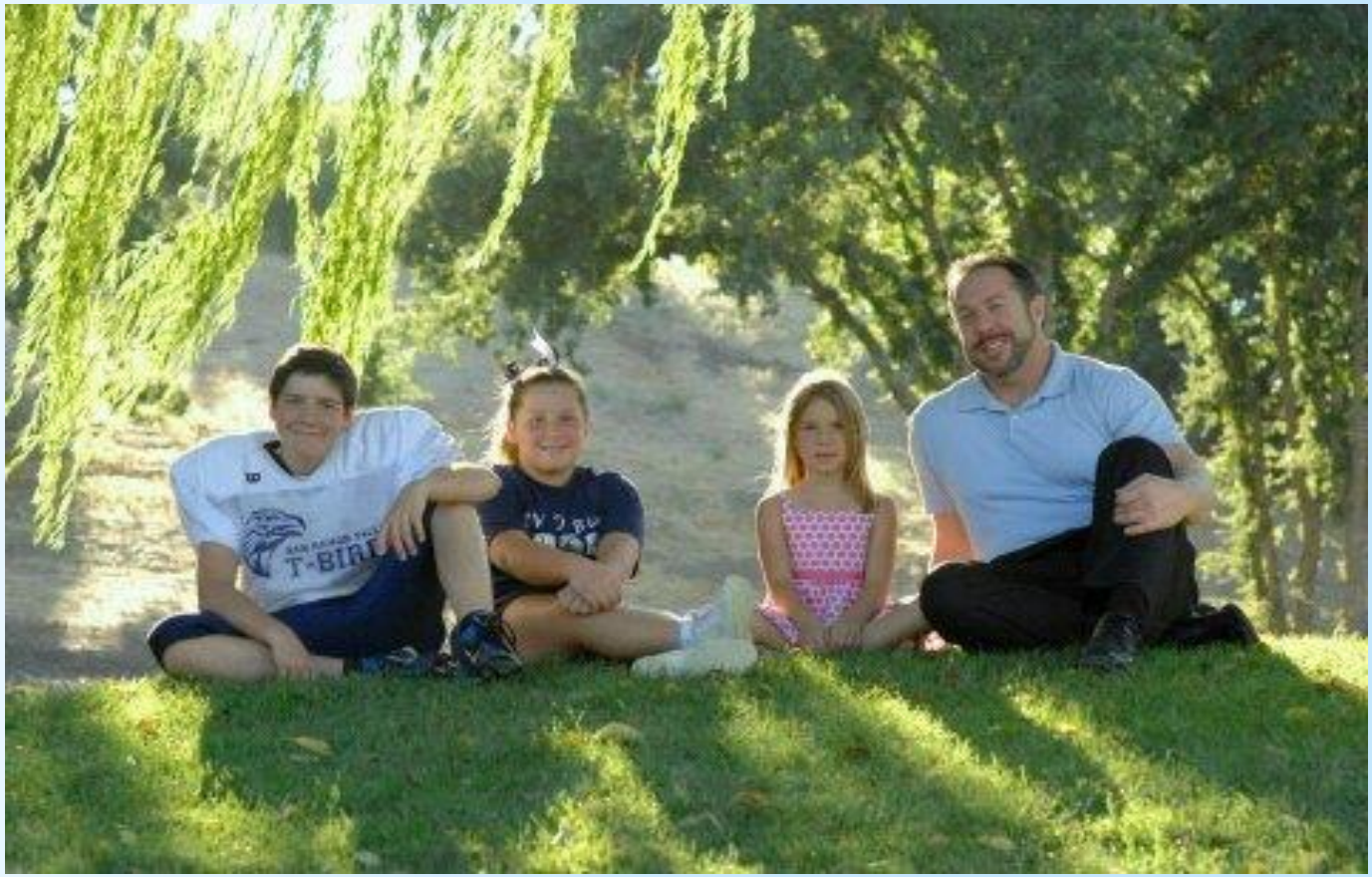
www.theFHFoundation.org

Agenda

- A Patient's Perspective
- The FH Foundation
- Call to Action

Living with FH

A Patient's Perspective: Scott Radabaugh



What Convinced Me

FH is High Risk: This is different. FH puts you at much higher risk for early heart attack or stroke.

FH is Genetic: You did not cause your high cholesterol, you were born with the disorder…"it's not your fault."

It's extremely important that your children and other first-degree relatives be screened for FH.

FH is Treatable: Don't waste time – time is plaque. You can reduce your risk starting today. You have to do your part with diet and exercise, but you also need medication. Together we can find the right treatment for you.

The FH Foundation

A patient-centered, nonprofit organization, dedicated to **education**, **advocacy,** and **research** of Familial Hypercholesterolemia (FH).

Our Mission: Raise awareness of FH and **save lives** by increasing the rate of early diagnosis and encouraging proactive treatment.

Our Vision: Find every individual and family with FH. Optimize FH management.

Our Values: Put patients first. Lead with integrity. Collaborate for impact.

2014 Programs

1. CASCADE FH REGISTRY™
- Hybrid Design
  - → Patient Portal
  - → Clinical Portal
- Enhance Cascade Screening
- Advance FH Research
- Raise awareness of FH
- Gathering data for improved health outcomes

2. GLOBAL FH SUMMIT
- FH As a Public Health Concern
- Learning From Other Countries' Success
- Bringing Together All Stakeholders

3. FH ADVOCATES FOR AWARENESS
- Public Speaking Training
- Digital and Print Resources
- Grand Rounds
- Community Outreach

4. FH AWARENESS DAY CAMPAIGN
- Tweet-A-Thon
- "Faces of FH" Video
- Community Advertising (billboards)

5. PATIENT and PROVIDER OUTREACH
- FH Tool Kits for Physicians
- Educational Materials for Patients

6. GLOBAL FH FOUNDATION NETWORK
- Foreign-language Materials
- Website Translation
- Global of FH Specialist Referral Network on website
- Global FH Registry (patient portal)

7. FH FAMILY FORUMS
- Educational Physician-Patient Gatherings
- CASCADE FH Registry enrollment

8. FIND FH
- Flag. Identify. Network. Deliver.

Will You Help?

90% of people with FH are undiagnosed.

We need your help to find FH.

- Join the FH Specialist Referral Network.
- Share our educational materials with your patients.
- Ask your patients to join the CASCADE FH Registry.
- Invite a Patient Advocate to speak.
- Tweet and Post to raise awareness #KnowFH.

Thank You!

www.theFHFoundation.org