Evolving Strategies for LDL-Lowering: Novel Targets and Treatments for CVD Risk Reduction

Supported by an educational grant from Sanofi US and Regeneron Pharmaceuticals

Opening Remarks

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CME Information & Faculty Disclosures

- This activity is jointly provided by HealthScience Media, Inc. (HSM) and Medical Education Resources (MER).
- This CME/CE activity is supported by an educational grant from Sanofi US and Regeneron Pharmaceuticals.
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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.

Pretest ARS Question 1

Which of the following is TRUE of <u>both</u> the ACC/AHA and the NCEP III guidelines for the management of dyslipidemia?

a. The recommendations are based almost exclusively on what has been demonstrated to reduce ASCVD risk in randomized controlled trials.

b. The recommendations are conceptually grounded in the view that lowering "atherogenic cholesterol" (LDL-C and non-HDL-C) will reduce risk.

c. Target LDL-C levels are <100 and <70 mg/dL for primary and secondary prevention, respectively.

d. The recommendations emphasize statins as first-line drug therapy.

e. The recommendations do not emphasize lifestyle interventions.

Pretest ARS Question 2

Which of the following patients would most likely benefit from a high-intensity statin therapy according to the 2013 ACC/AHA Blood Cholesterol Guideline?

a. A 33-year old male with an estimated 10-year ASCVD risk of 7%
b. A 50-year old woman with an LDL-C of 195 mg/dL
c. An 80-year old with an LDL-C of 189 mg/dL
d. 25-year old woman with diabetes and a LDL-C of 92 mg/dL

Pretest ARS Question 3

Which of the following statements regarding the potential consequences of untreated FH is TRUE?

a. If left untreated, men with FH have a 50% risk of CVD by age 50
b. FH causes 20% of all myocardial infarctions in patients $\leq$ 45 years old
c. Risk of premature coronary heart disease in patients with FH who are untreated is 20 times greater than the general population
d. All of the above are TRUE
e. A & B are TRUE

Pretest ARS Question 4

How do PCSK9 monoclonal antibodies affect LDL-C levels?

a. They increase LDL-R recycling
b. They increase the expression of LDL-R
c. They increase PCSK9 production
d. They inhibit ApoB production

Evolution of lipid management guidelines

ATP I 1988	ATP II 1993	ATP III 2001	ATP III Update 2004
Exclusive focus on LDL-C	Risk assessment guides therapy	Lower LDL-C threshold for therapy initiation in high-risk patients	Lower LDL-C threshold for therapy initiation in very-high-risk patients
Strong support for resins, niacin	Goal LDL-C reduced for CHD (≤100 mg/dL)	LDL-C goal <100 mg/dL for CHD equivalent	Optional LDL-C goal <70 mg/dL for CVD + multiple/severe risk or ACS
Statins, fibrates not first line	Statins included in "major drugs," fibrates for mixed HPL	Non-HDL-C and metabolic syndrome as secondary targets	Optional LDL-C goal <100 mg/dL for moderately high-risk primary prevention

Low- to moderate-dose monotherapy

Moderate- to high-dose statin

High-dose statin, increased combination therapy

2013 AHA/ACC Cholesterol Guidelines: Statin Benefit Groups

- Clinical ASCVD*
- LDL-C ≥190 mg/dL, Age ≥21 years
- Diabetes: Age 40-75 years, LDL-C 70-189 mg/dL
- Primary prevention - No Diabetes†: ≥7.5%‡ 10-year ASCVD risk, Age 40-75 years, LDL-C 70-189 mg/dL

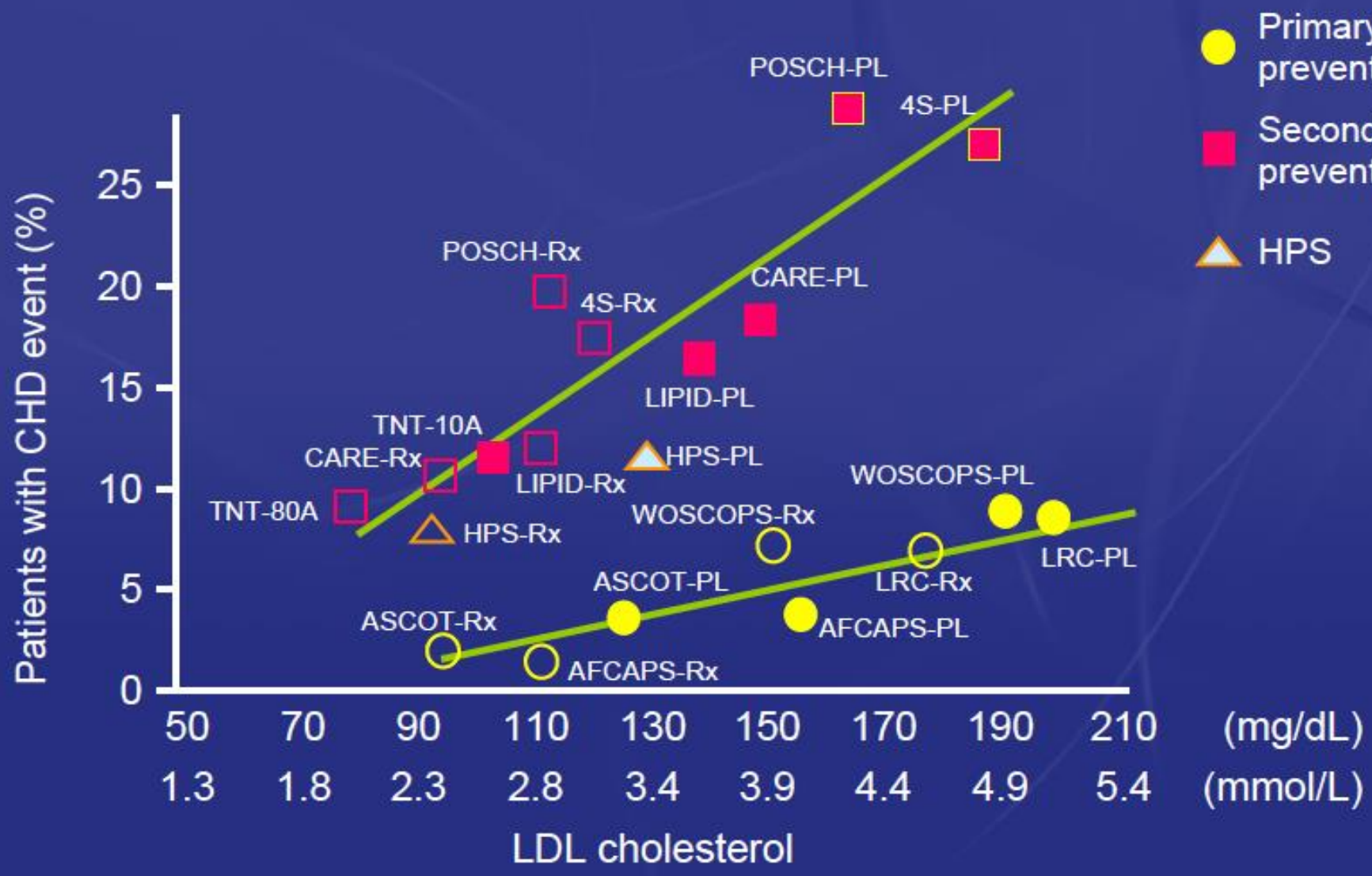
*Atherosclerotic cardiovascular disease

†Requires risk discussion between clinician and patient before statin initiation

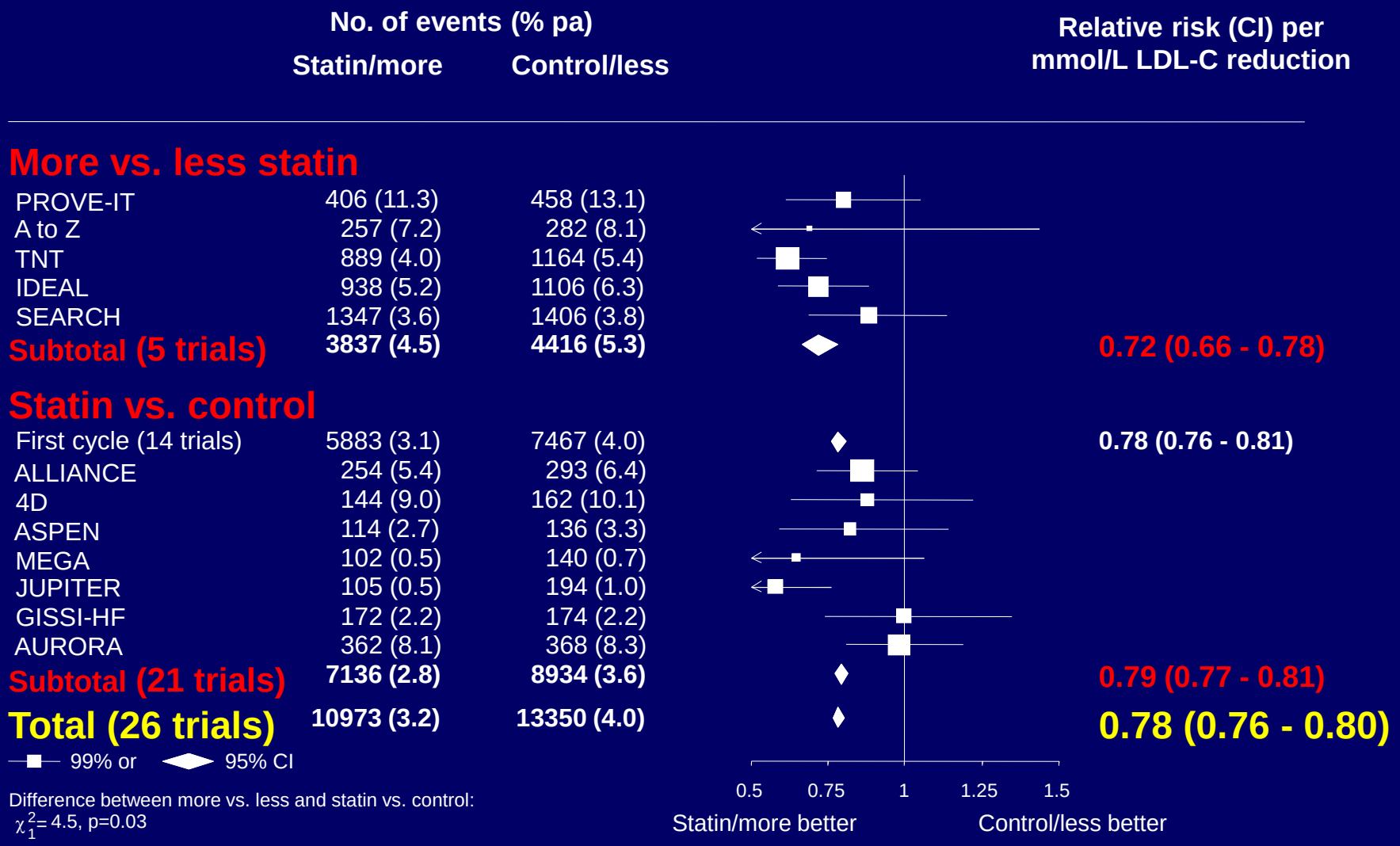
‡Statin therapy may be considered if risk decision is uncertain after use of ASCVD risk calculator

Stone et al. 2014 J Am Coll Cardiol. 2014;63:2889–934

Clear Cardiovascular Benefits of Intensive Lipid-Lowering Therapy

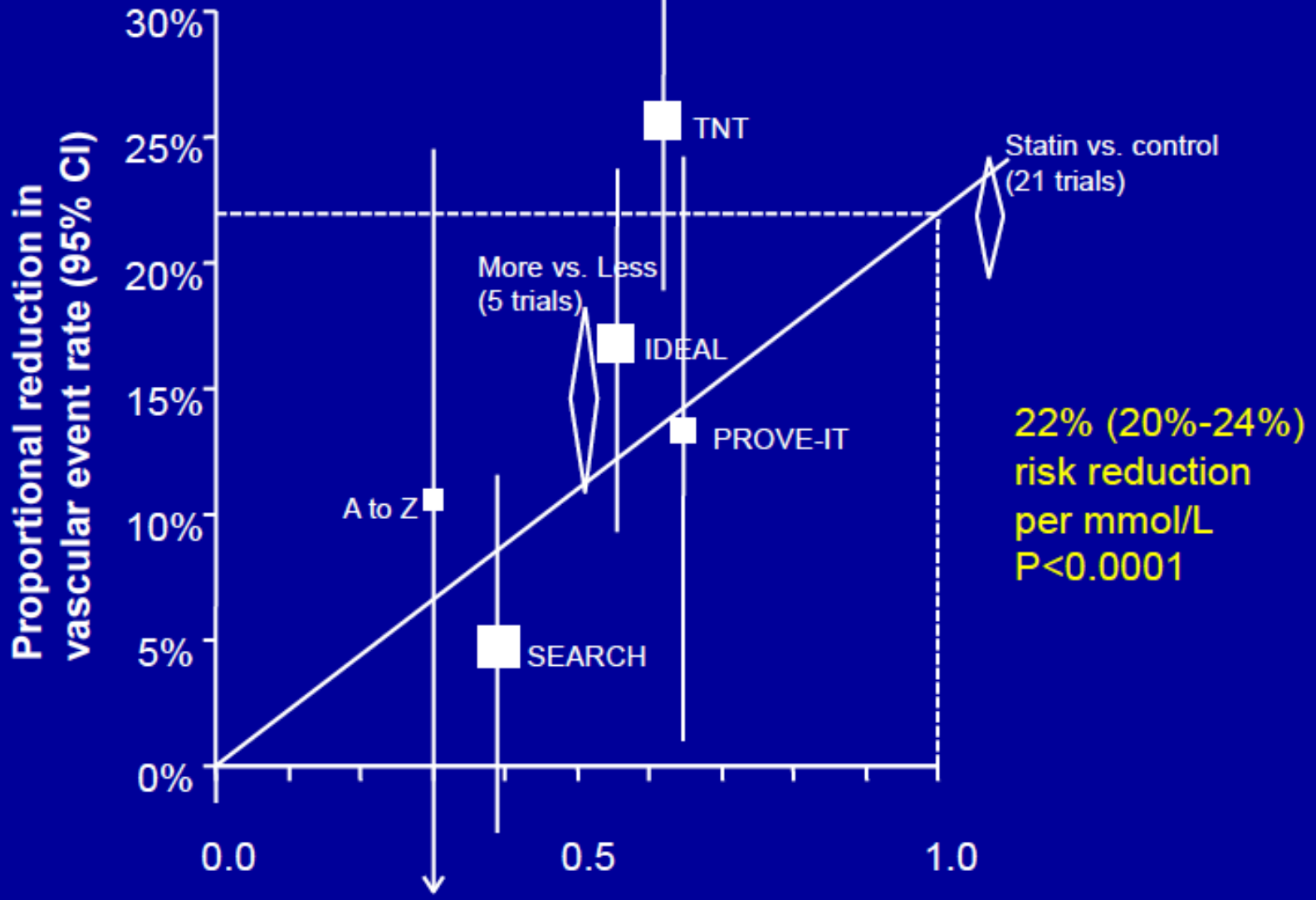


CTT Analysis: Proportional effects on MAJOR VASCULAR EVENTS per mmol/L (~39 mg/dl) LDL-C reduction



Cholesterol Treatment Trialists' (CTT) Collaboration. Lancet 2010; 376: 1670–81

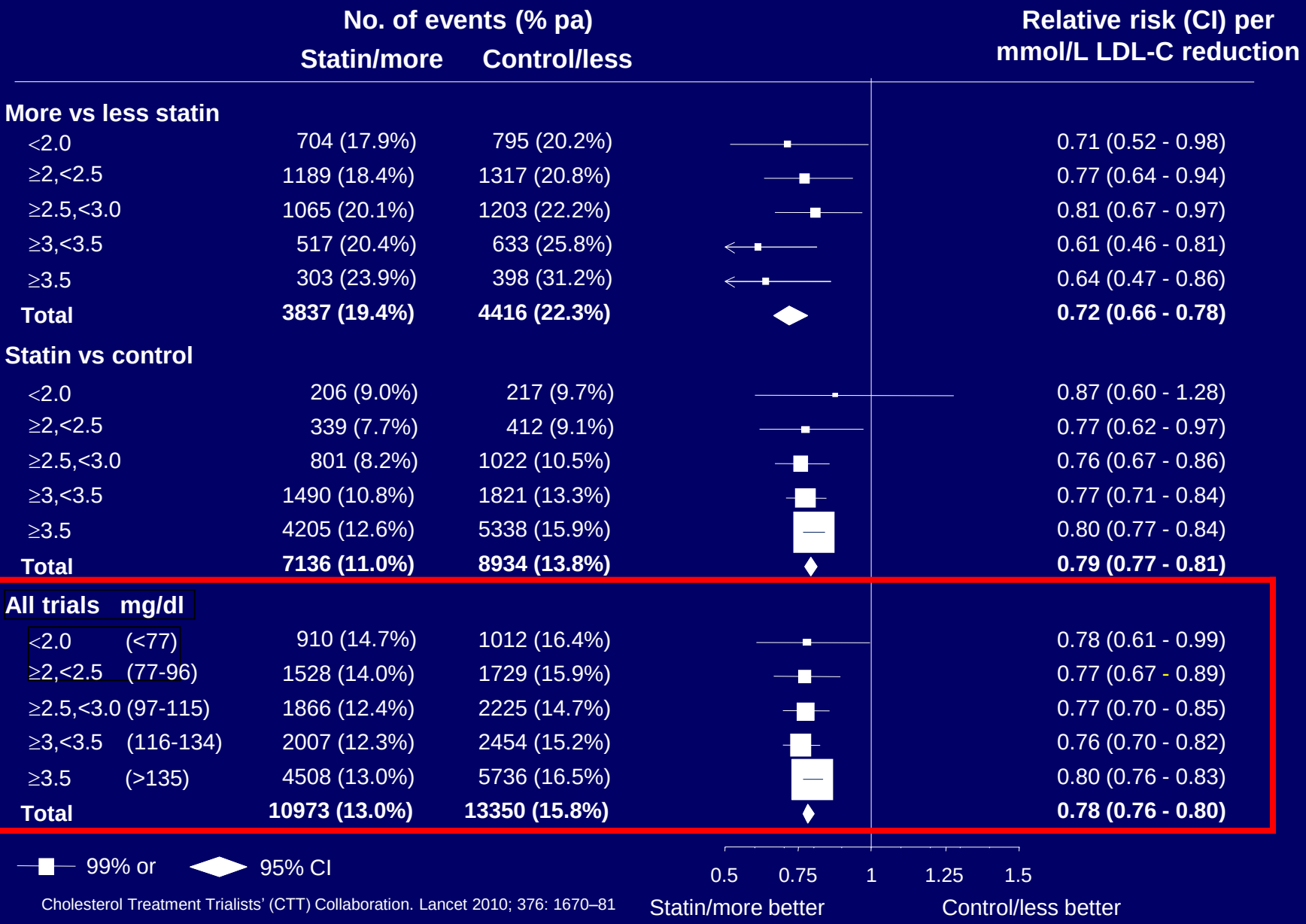
CTT meta analysis: Proportional reduction in MAJOR VASCULAR EVENTS versus absolute LDL-C reduction



22% (20%-24%)
risk reduction
per mmol/L
P<0.0001

CTT Collaboration, Lancet 2010

Proportional effects on MAJOR VASCULAR EVENTS per mmol/L (~39 mg/dl) LDL-C reduction, by baseline LDL-C



Cholesterol Treatment Trialists' (CTT) Collaboration. Lancet 2010; 376: 1670–81

Is there evidence for a benefit of statin therapy in people at low risk of vascular disease?

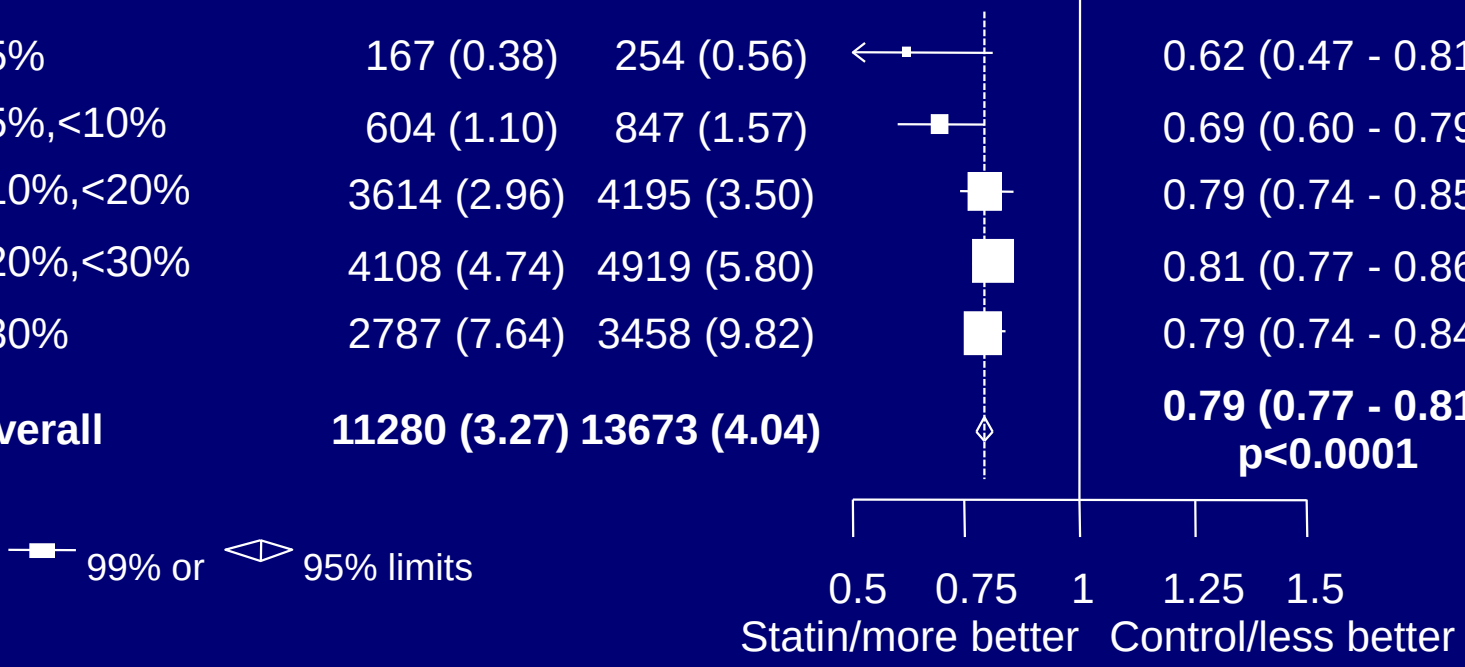
The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials

*Cholesterol Treatment Trialists' (CTT) Collaborators**

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

Effects on MAJOR VASCULAR EVENTS per mmol/L (~39mg/dl) LDL-C reduction

5-year MVE risk at baseline	Events (% per annum) Statin/more	Control/less	RR (CI) per mmol/L LDL-C reduction	Trend test
<5%	167 (0.38)	254 (0.56)	0.62 (0.47 - 0.81)	
≥5%,<10%	604 (1.10)	847 (1.57)	0.69 (0.60 - 0.79)	
≥10%,<20%	3614 (2.96)	4195 (3.50)	0.79 (0.74 - 0.85)	χ^2_1=4.29
≥20%,<30%	4108 (4.74)	4919 (5.80)	0.81 (0.77 - 0.86)	(p=0.04)
≥30%	2787 (7.64)	3458 (9.82)	0.79 (0.74 - 0.84)	
Overall	**11280 (3.27)**	**13673 (4.04)**	**0.79 (0.77 - 0.81) p<0.0001**	



Conclusions for lipid-modifying therapy

- Each 1 mmol/L LDL-C reduction reduces the annual rate of major vascular events by about one-fifth
- Larger LDL-C reductions safely produce definite larger reductions in the incidence of heart attacks, revascularisations and ischaemic strokes
- Similar proportional reductions in all of the subgroups studied (including renal disease and 1° prevention)
- No threshold within the cholesterol range studied, which implies that reducing LDL-C by 2-3 mmol/L would reduce vascular event risk by about 40-50%

Addressing the Unmet Need for LDL-Targeted Atheroprotection in High-Risk Populations

Eliot A. Brinton, MD, FAHA, FNLA
President, American Board of Clinical Lipidology
Director, Atherometabolic Research
Utah Foundation for Biomedical Research
President, Utah Lipid Center
Salt Lake City, Utah

Learning Objectives

- Discuss the rationale for the deletion of LDL-C and non-HDL-C goals by the writing panel for the 2013 ACC/AHA Cholesterol guidelines
- Discuss the rationale for the unanimous re-affirmation of LDL-C and non-HDL-C goals by all other expert panels (NLA, AACE, European, Canadian, etc.)
- Discuss the evidence base for use of statin adjuncts and how to use them appropriately to achieve LDL-C and non-HDL-C goals
- Appreciate practical definitions of statin intolerance and best methods for diagnosing and treating underlying causes
- Discuss the evidence base for currently available statin alternatives and implement best care in their use

2013 ACC/AHA Cholesterol Guidelines

Evidence Levels for Guidelines

Evidence Level*		2013 ACC/AHA Cholest. Guidelines	All other Lipid Guidelines
A	Multiple HQ RCTs	Yes	Yes
	Meta-analyses of RCTs	Yes	Yes
B	Single HQ RCT	No	Yes
C	Lower-quality (& earlier) RCTs	No	Yes
	Observational Data	No	Yes
	Biological MoA (animals, cells, etc)	No	Yes
	Expert Opinion	No	Yes

**Certainty of Evidence (descending order): Level A, Level B, Level C.*

Stone et al. JACC 2014;63:2889-2934.

Why Not *Continue* to Treat to Goal?

"Given the absence of data on titration of drug therapy to specific goals, no recommendations were made for or against specific LDL-C or non-HDL-C goals for primary or secondary prevention of ASCVD."

Stone et al. JACC 2014;63:2889-2934.

Why Not *Continue* to Treat to Goal?

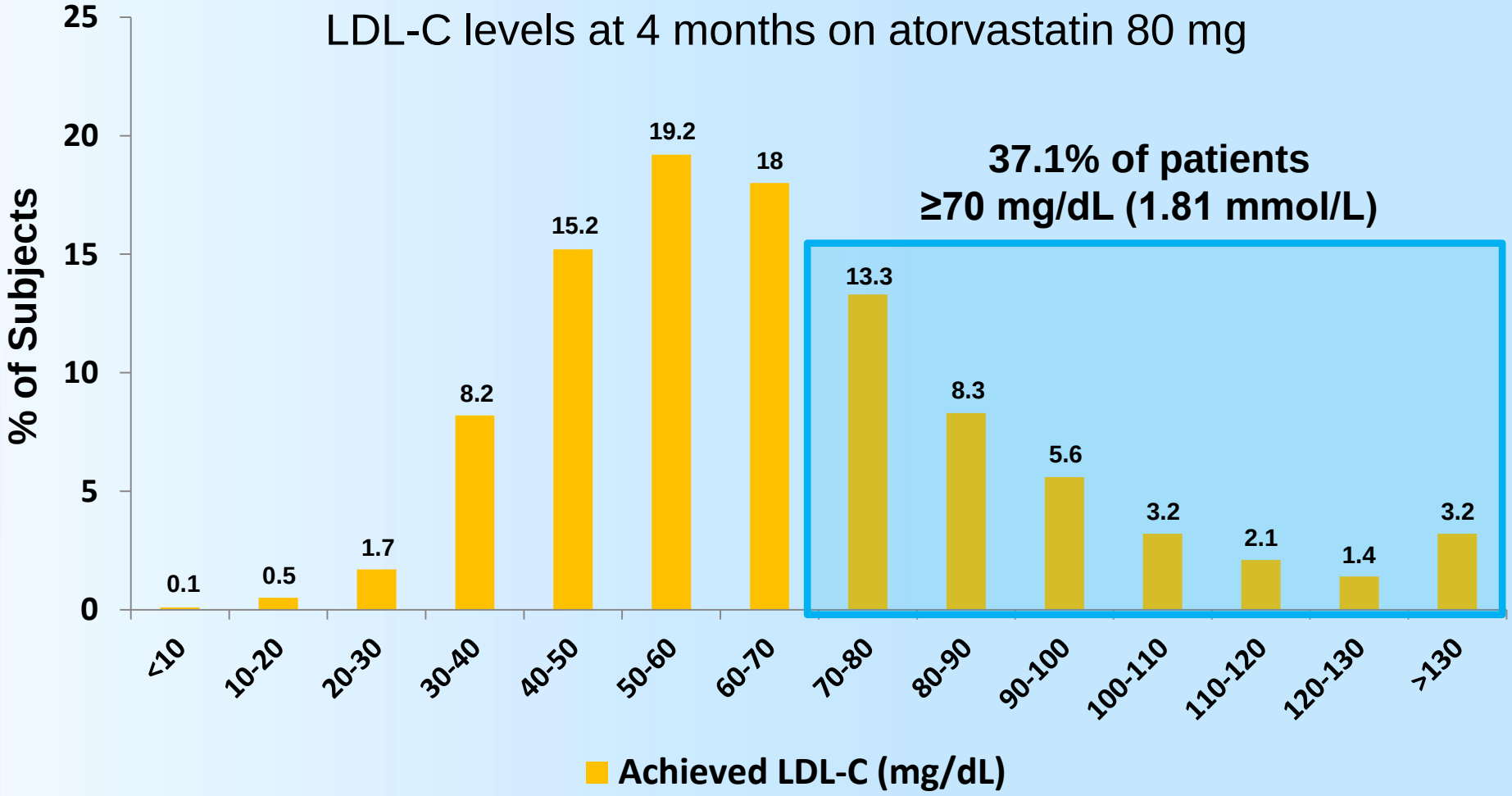
"Given the absence of data on titration of drug therapy to specific goals, no recommendations were made for or against specific LDL-C or non-HDL-C goals for primary or secondary prevention of ASCVD."

- **Excluding most evidence (B+C) → "absence of data"**
- **"Absence of data"**
  → "no recommendations for or against…goals"
- **Agnosticism re: goals**
  → "goals are <u>bad"</u> → goals are <u>eliminated</u>

Commentary by Eliot Brinton, MD

Stone et al. JACC 2014;63:2889-2934.

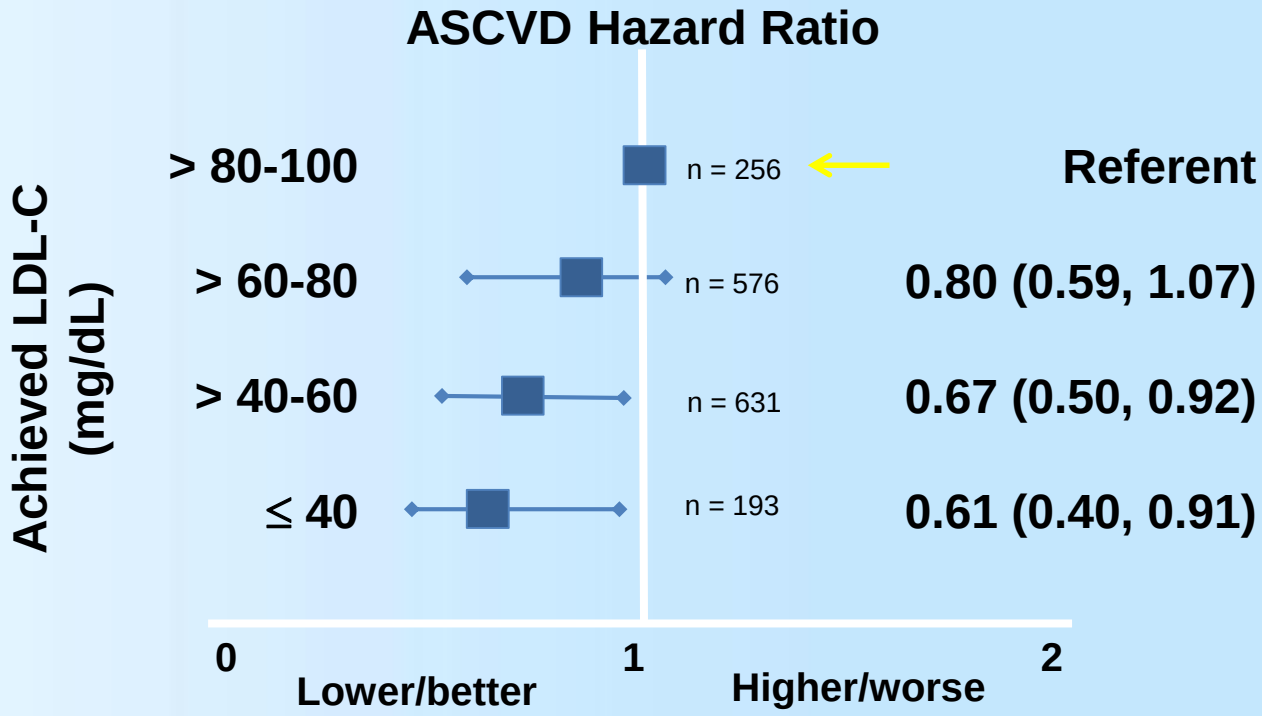
LDL-C Varies *Greatly* on High-Intensity Statin



Wiviott et al. for the PROVE-IT TIMI-22 Investigators. Am J Cardiol. 2005;46:1411-16.

Lower On-Treatment LDL-C *IS* Better!

Atorvastatin 80 mg or pravastatin 40 mg in 2099 ACS patients for 24 months



Endpoint: CHD death, nonfatal MI, CVA, recurrent ischemia, revascularization

*Adjusted for age, gender, baseline LDL-C, diabetes mellitus, and prior MI

PROVE-IT/TIMI 22 Substudy.
Wiviott SD et al. JACC. 2005;46:1411-16.

Canadian Expert Statement About ACC/AHA Cholesterol Guidelines

"The ACC/AHA guidelines advocated a novel yet controversial approach of treatment …not recommending LDL-C targets…"

"[We] had certainly considered this option but in the end elected to continue to support the concept of lipid targets for several reasons…"

"We continue to recommend LDL-C (or alternative) targets as a useful concept for physicians and patients, as it is utilized for example with blood pressure management."

Anderson et al. Can J Cardiol. 2014;30:377-80. Emphasis added.

European Expert Statement About ACC/AHA Cholesterol Guidelines

"In summary, the new ACC/AHA guidelines differ quite considerably from their predecessor and the ESC/EAS guidelines as well as those in other geographical regions by discarding targets. This approach appears unhelpful for family physicians. Furthermore, considering only RCT data seems too narrow an approach as it provides no clear guidance in many grey areas of prevention."

Ray et al. Eur Heart J. 2014;35:960-68. Emphasis added.

European Expert Statement About ACC/AHA Cholesterol Guidelines

"In summary, the new ACC/AHA guidelines differ quite considerably from their predecessor and the ESC/EAS guidelines as well as those in other geographical regions by discarding targets. This approach appears unhelpful for family physicians. Furthermore, considering only RCT data seems too narrow an approach as it provides no clear guidance in many grey areas of prevention."

NLA, AACE, and IAS also agree with the European and Canadian expert panels*

*Jacobson et al. J Clin Lipidol. 2014 epub September 15.
Jellinger et al. Endocrine Practice, 2013;18(Suppl 1) March/April:1-78.
Grundy et al. J Clin Lipidol. 2014;8:1-8.

Proposed Guideline Compromise

2013 ACC/AHA

- Use 4 pt categories for statin Rx (sl. modif.)
  - Prior ASCVD (or bad subclinical athero.)
  - DM1 >40 y/o and DM2 all ages
  - Severe hypercholesterolemia (LDL-C > 190)
  - 10 y risk >7.5% (or higher; alt: lifelong >40%?)

ATP-III/NLA/IAS/AACE…

- More aggressive statin use, but also retain low-dose statin option
- Reinstate goals (simplified):
  - Non-HDL-C (<130/<100)
  - LDL-C (<70/<100)
- Add/return RFs: FHx, MetSynd, HTG, CRF…?
- Consider non-statin adjuncts for:
  - Residual dyslipidemia
  - Residual CVD risk

Brinton. 2014; unpublished.

Proposed Inclusive US Expert Consensus Statement on Lipid Management

What should be included?

- All evidence: no more "unprecedented" exclusion of valid evidence
- All doses of statins
- All non-statins
- All lipid disorders
- All good elements of all lipid guidelines (don't reinvent the wheel!)

Who should be included?

- Lipidologists: NLA
- Endocrinologists: Endo Society, AACE, ADA
- Cardiologists: AHA, ACC, ASPC, ABC, etc.
- Other specialists & generalists: ACP, AAFP, AAP, ASH, etc.

ALL interested professional societies as expert partners (attempt to return to collaborative NCEP paradigm)

Brinton. 2014; unpublished.

What About Non-Statin Lipid Drugs?

- "Nonstatin therapies do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD."

Stone et al. *Circulation.* 2013; doi: 10.1161/01.cir.0000437738.63853.7a.

- "The ACC/AHA guidelines demonstrate that even in a topic area with extensive amounts of data and published clinical trials, crucial evidence is still missing."

Ioannidis. *JAMA*. December 2, 2013. doi:10.1001/jama.2013.284657.

- "…we find there to be an absence of discussion regarding other therapeutic options for patients on high-dose statins but which still exhibit high residual risk and/or significantly elevated LDL-C levels."

National Lipid Association. https://www.lipid.org/nla/2013-accaha-guideline-treatment-blood-cholesterol-reduce-atherosclerotic-cardiovascular-risk

Emphasis added.

Evidence Base for Non-Statins as Statin Adjuncts (or Alternatives)

Ezetimibe

SHARP

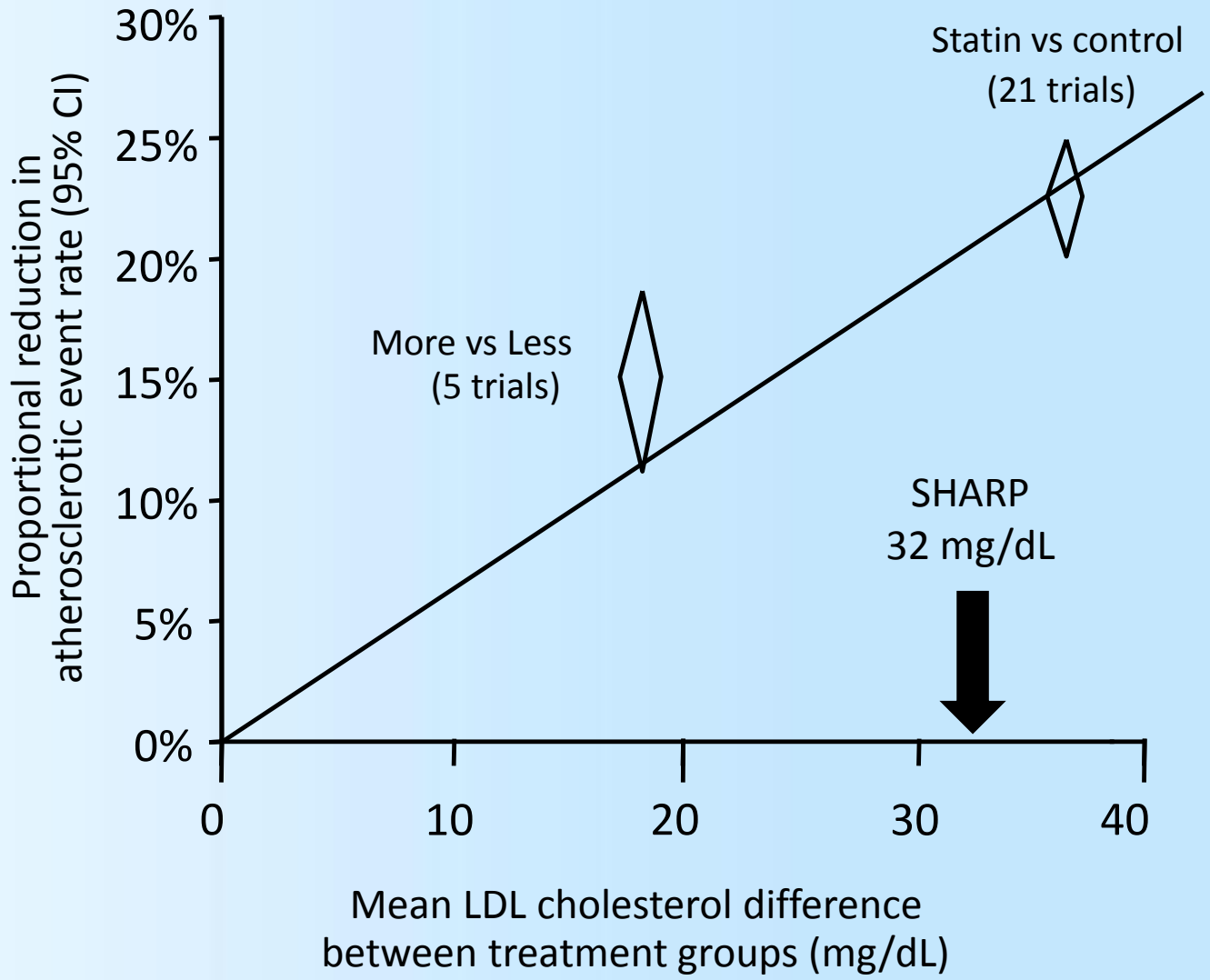
IMPROVE-IT

SHARP

- N=9438, all w/ CKD (creat > 1.5/1.7)
- Randomized 4:1:4 to Ezet/simva:simva:pbo x 1 y
- Simva-only pts re-randomized 1:1 Ezet/simva: pbo thereafter
- 4.9 y median total f/u
- 33% ↓LDL-C
- 17% ↓major athero events (incl isch stroke)
- Minimal safety issues (↑myalgia→Rx d/c—NNH 200; ↓pancreatitis—NNT 333)

Baigent et al. Lancet. 2011;377:2181-92.

CTT: Effects on Major Atherosclerotic Events



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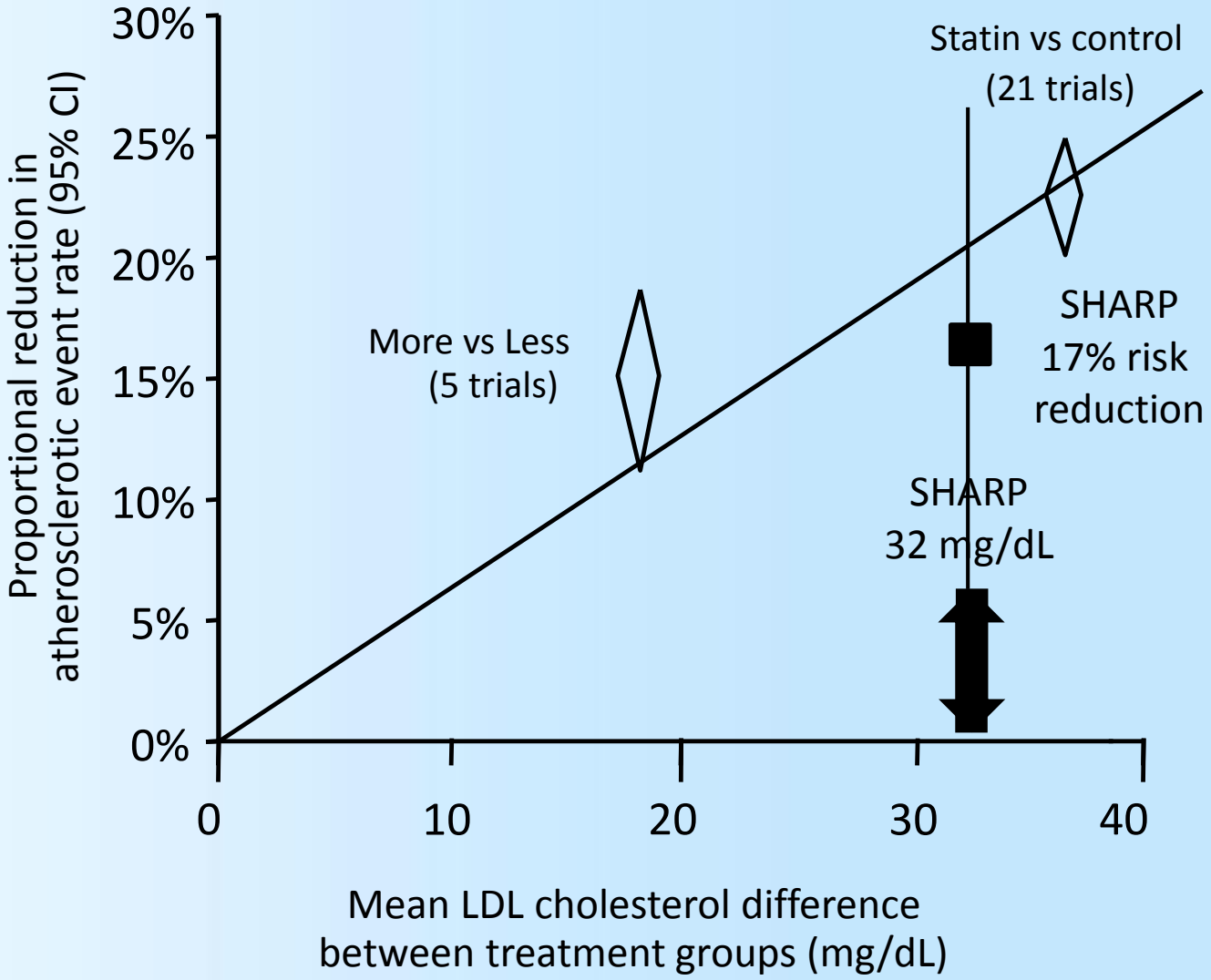

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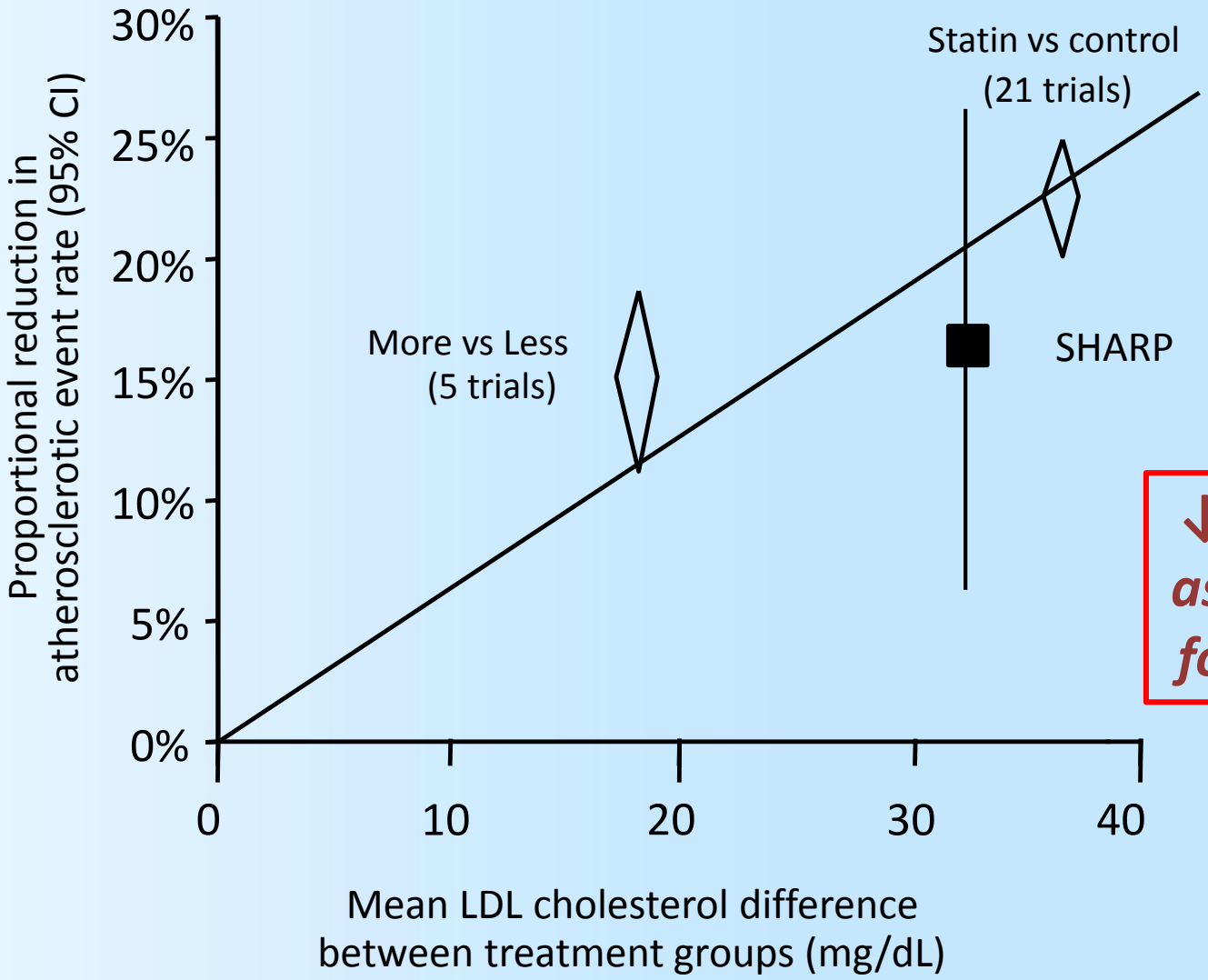

↓ASCVD is as expected for ↓LDL-C

Trial of ↓CVD with Ezetimibe: IMPROVE-IT

- First *real* test of ezetimibe (statin + ezet vs pbo)
- N=18,141 subjects post ACS
- Start September 2005, end September 2014
- Goal of 5250 pts w/ 1^{o} endpoint (MACE)
- Estimated on-Rx LDL-C ~66 vs 52 mg/dL
- Will ~14 mg/dL lower LDL-C provide
  - *Statistically* significant ↓ASCVD?
  - *Clinically* meaningful ↓ASCVD?

http://clinicaltrials.gov/ct2/show/NCT00202878?term=improve-it&rank=1 Accessed 10/4/14.

Ezetimibe Clinical Uses vs IMPROVE-IT Design

- **Best** uses of ezetimibe:
  - LDL-C/Non-HDL-C > goal w/ statin monotherapy
  - Statin intolerance
  - Statin phobia
- **Marginal** use of ezetimibe:
  - Patients with **very well controlled** LDL-C/Non-HDL-C on statin monotherapy=IMPROVE-IT

Califf. Am Heart J. 2010;159:705-9.

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IMPROVE-IT study population

Not sure we need to know if LDL-C of ~52 mg/dL is better than ~66!

Califf. Am Heart J. 2010;159:705-9.

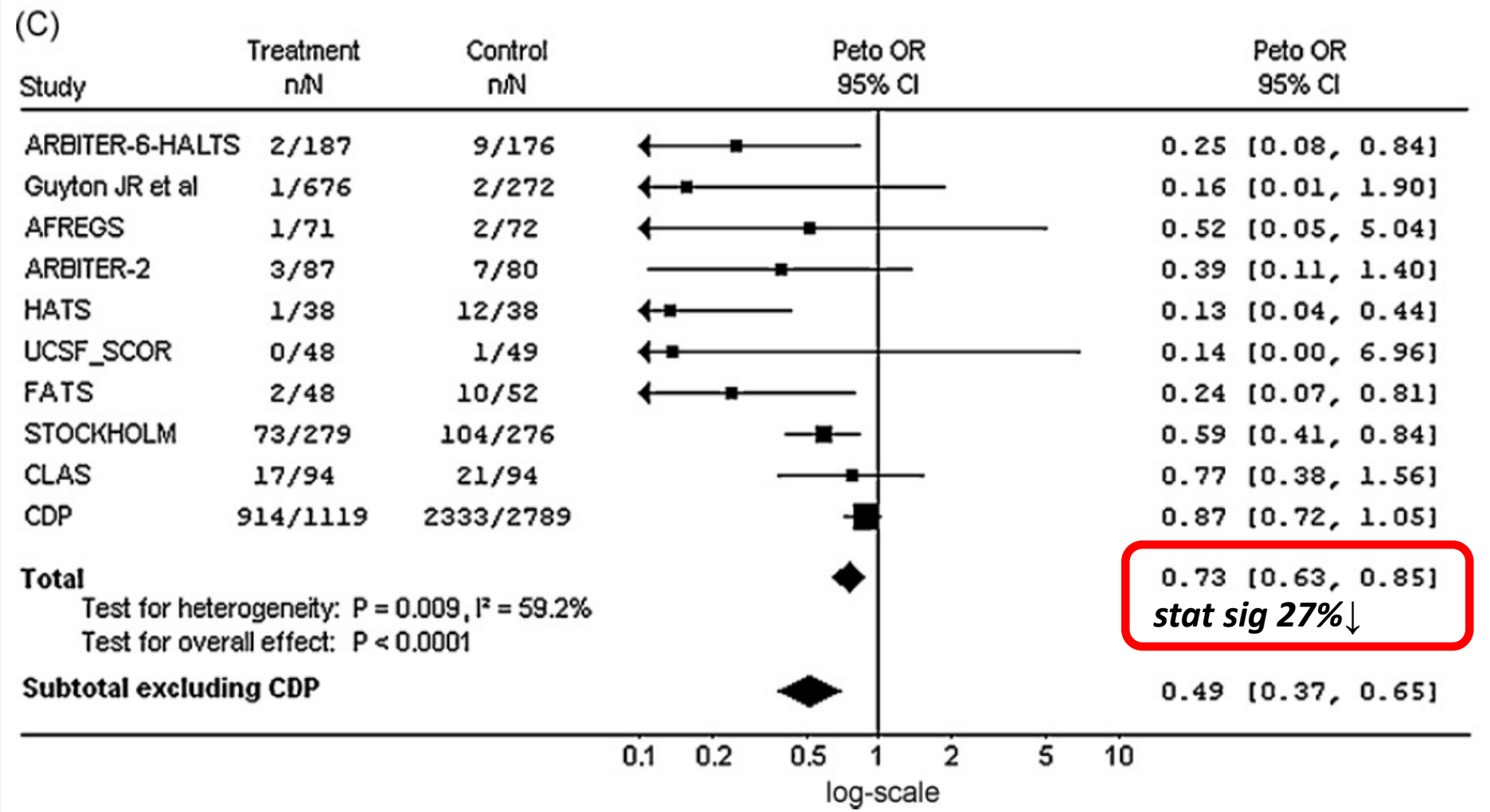
Niacin

Older Clinical Trials

AIM-HIGH

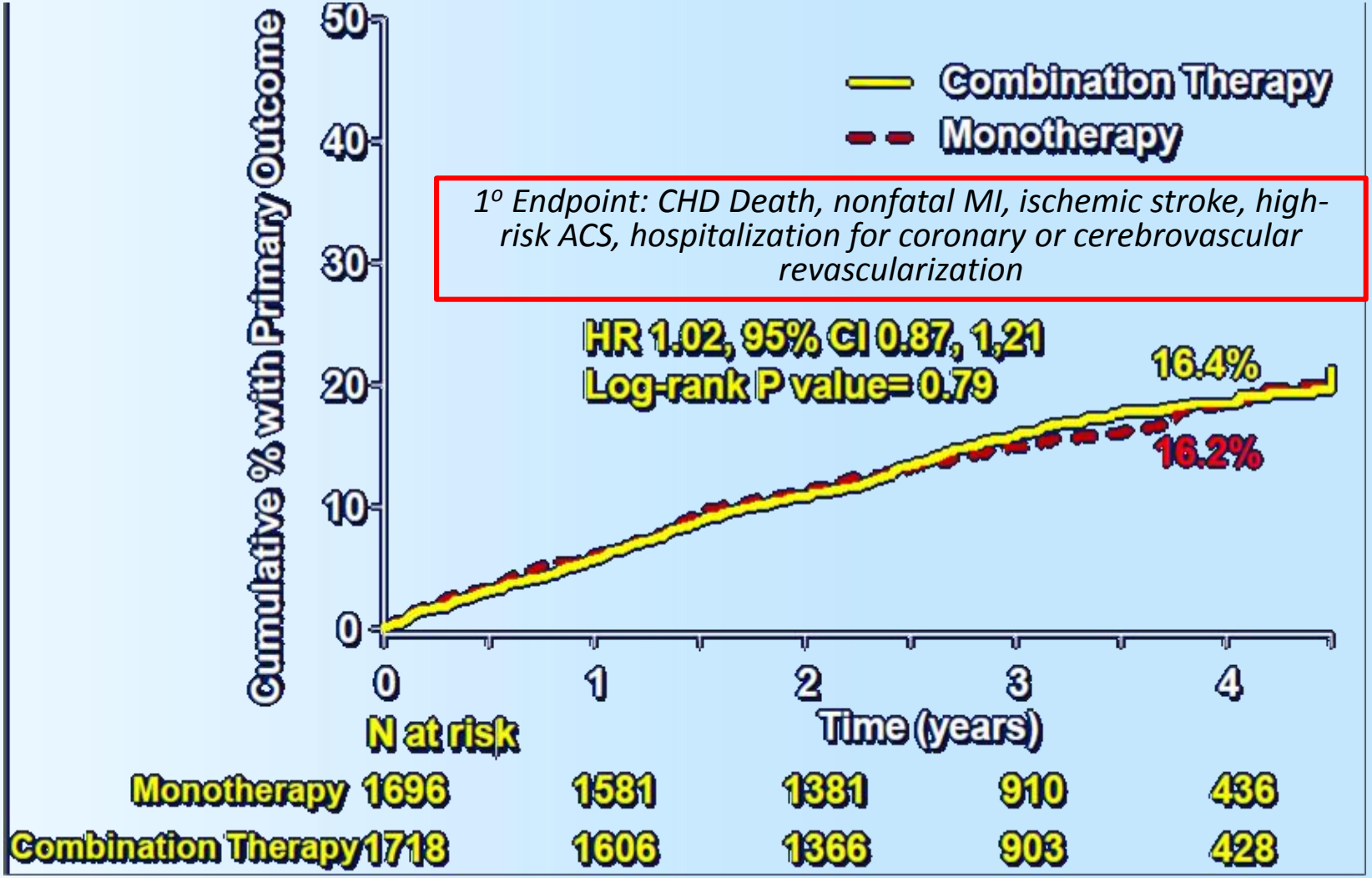
HPS2/THRIVE

Niacin Reduces CVD: *Pre*-AIM-HIGH & HPS2



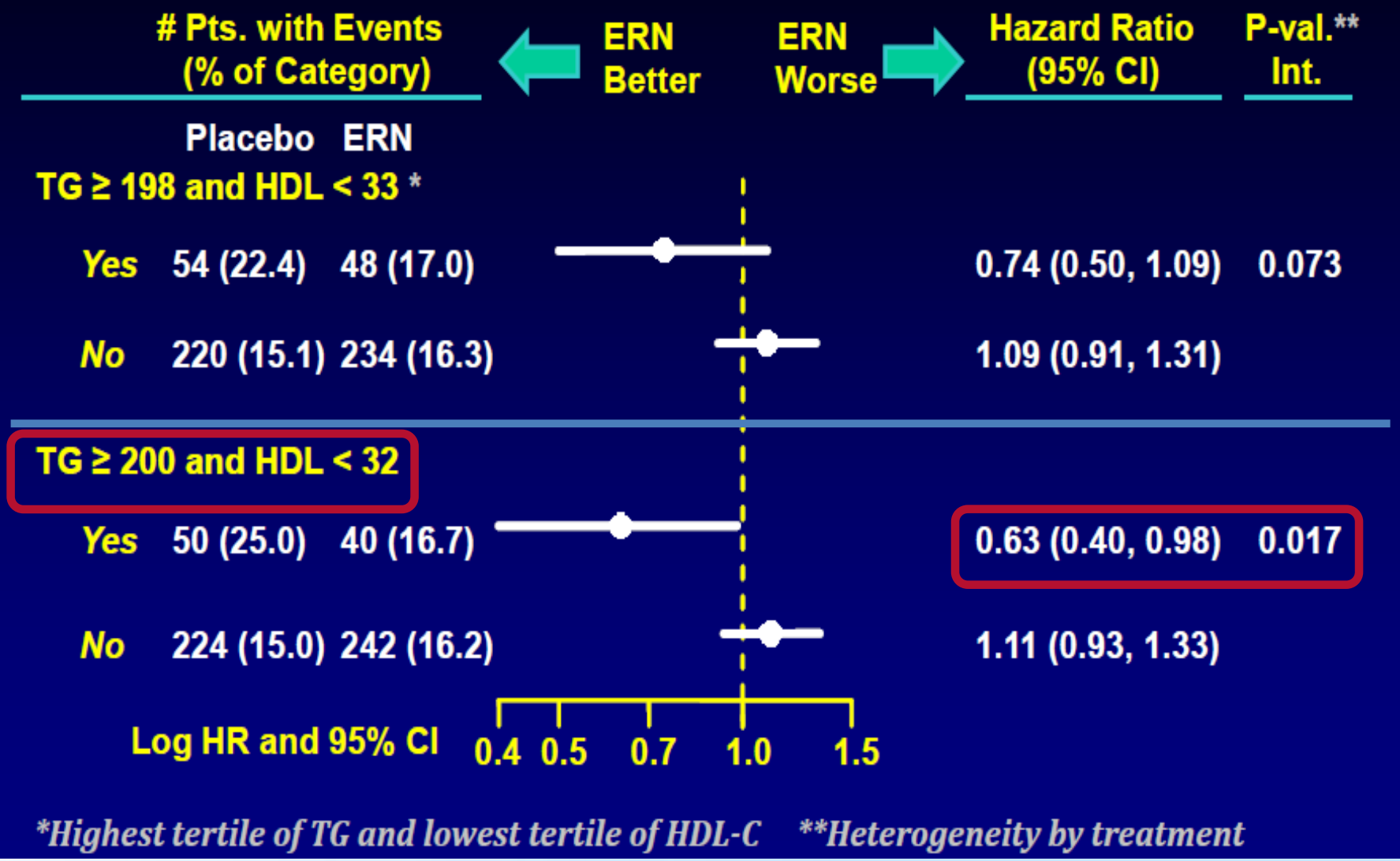
Bruckert. Atherosclerosis 2010;210:353-61.

AIM-HIGH — *Primary Outcome*



Boden. N Engl J Med. 2011;365:2255-67.

AIM-HIGH: ERN ↓CVD in HTG / Low HDL-C Patients



All lipid measurements in mg/dL. ERN=extended release niacin.

Guyton et al. J Am Coll Cardiol. 2013;62:1580-4. Guyton et al. Paper presented at: AHA SS; Nov. 6, 2012; Los Angeles, CA.

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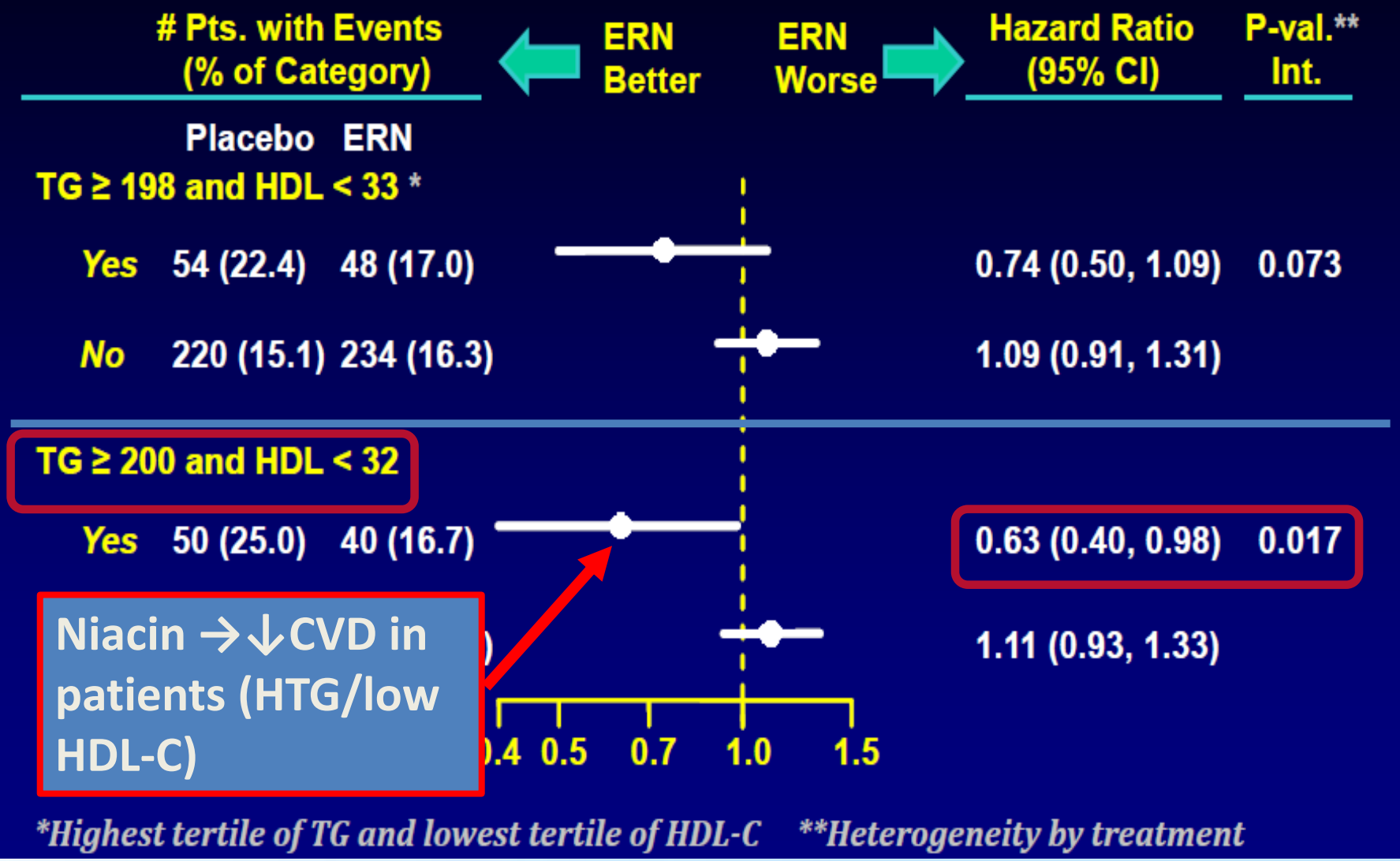

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Guyton et al. J Am Coll Cardiol. 2013;62:1580-4. Guyton et al. Paper presented at: AHA SS; Nov. 6, 2012; Los Angeles, CA.

AIM-HIGH Summary

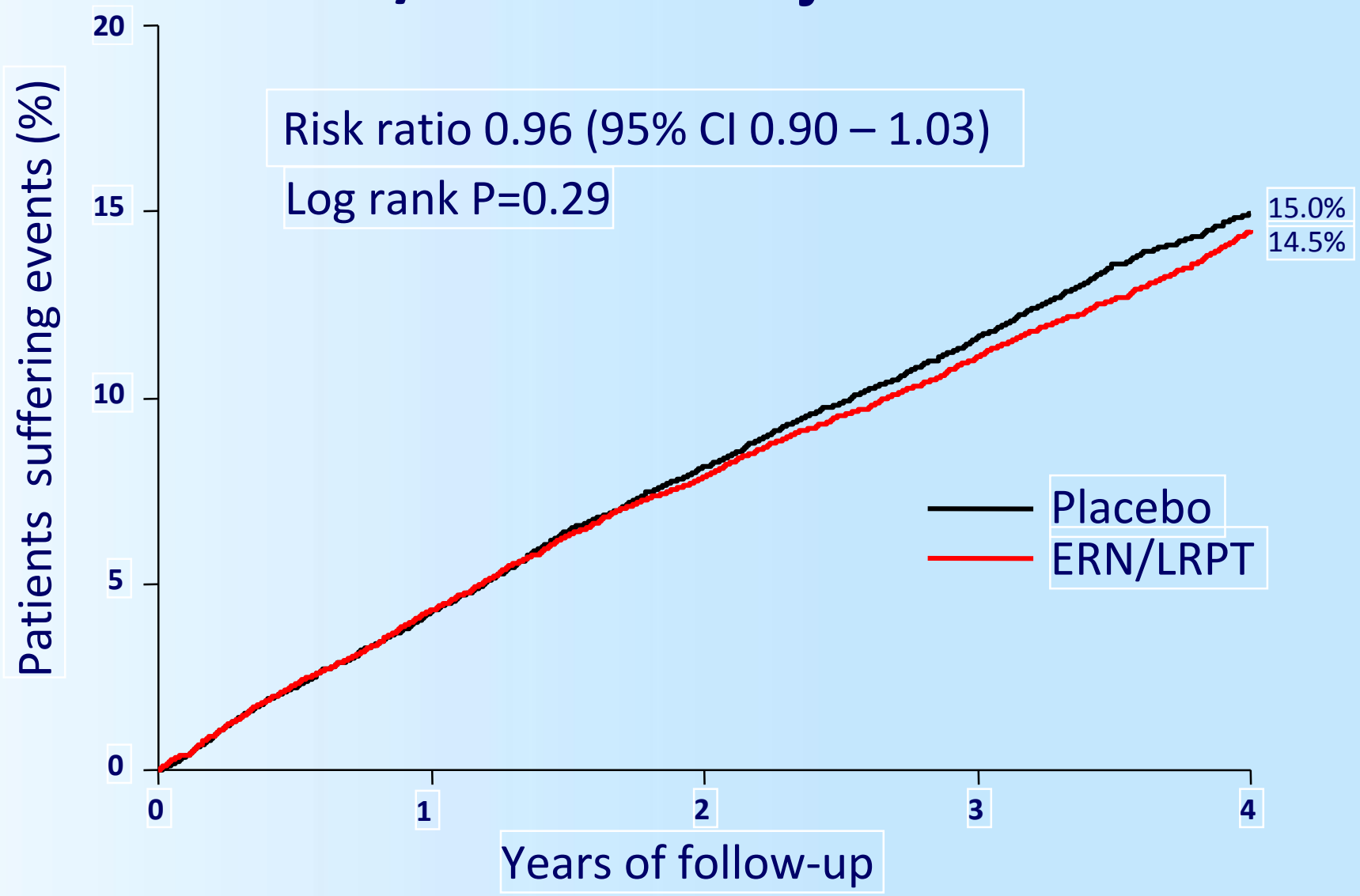
AIM-HIGH did NOT prove that niacin doesn't work

- ***NOT*** intended/designed to test CVD effects of ERNA (+/- test of HDL-raising hypothesis)
- *NOT* true placebo-controlled
  - High-dose ERNA vs
  - Low-dose IRNA + ↑simva & ↑ezet
- Stopped at 3 y—*too early* for benefit in some trials
- Benefit in HTG/low HDL-C subset*
- Dose and formulation issues not resolved

Boden. N Engl J Med. 2011;365:2255-67.

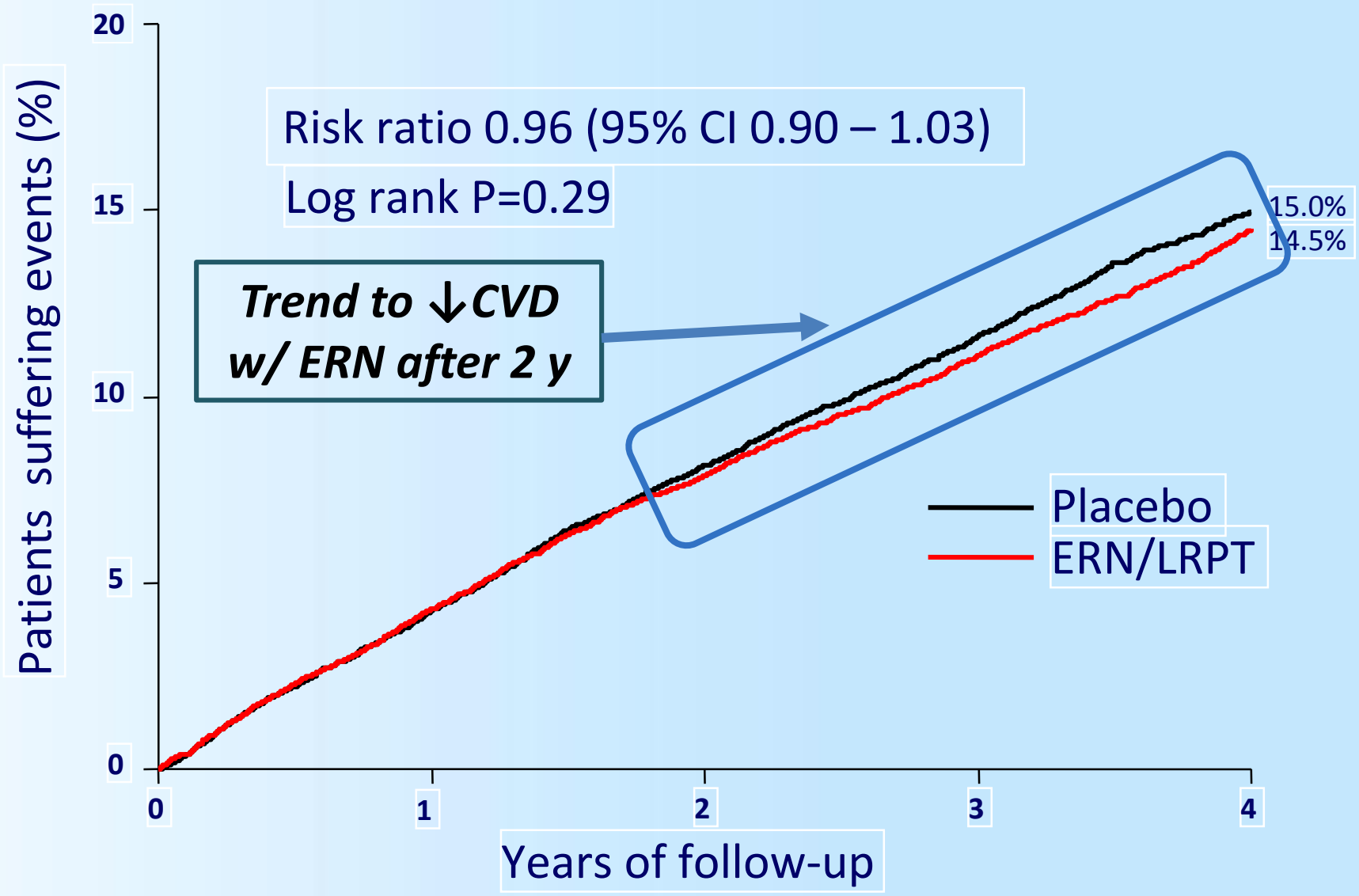
*Guyton. JACC 2013;62:1580

Effect of ERN/LRPT on Major Vascular Events



Armitage J; Presented at AHA Scientific Sessions. Nov 2012.

Effect of ERN/LRPT on Major Vascular Events



Armitage J; Presented at AHA Scientific Sessions. Nov 2012.

HPS2/THRIVE: Baseline Lipids

- LDL-C 63 mg/dL on statin
- HDL-C 44 mg/dL (no selection)
- TG 125 mg/dL (no selection)

*No need for or **benefit** from niacin!*

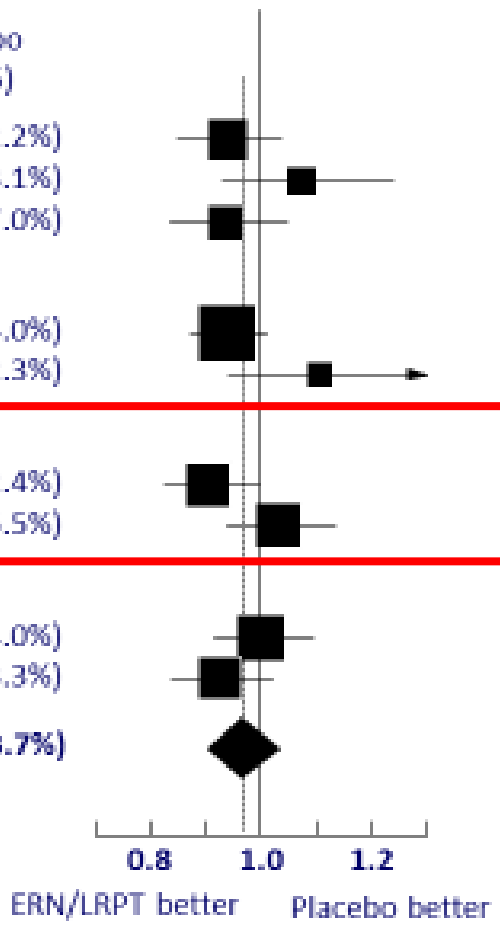
Additional Observations

- Niacin tended to reduce ASCVD:
  - In Caucasians (tended to harm Chinese!)
  - If LDL-C was above 57 mg/dL on a statin
  - After about 4 years? (curves diverging at end)
- Some harms may be specific for laropiprant (hemor. stroke and infection)

Unpublished commentary by Brinton EA on Landray et al. 2014 N.Engl.J Med. 371:203.

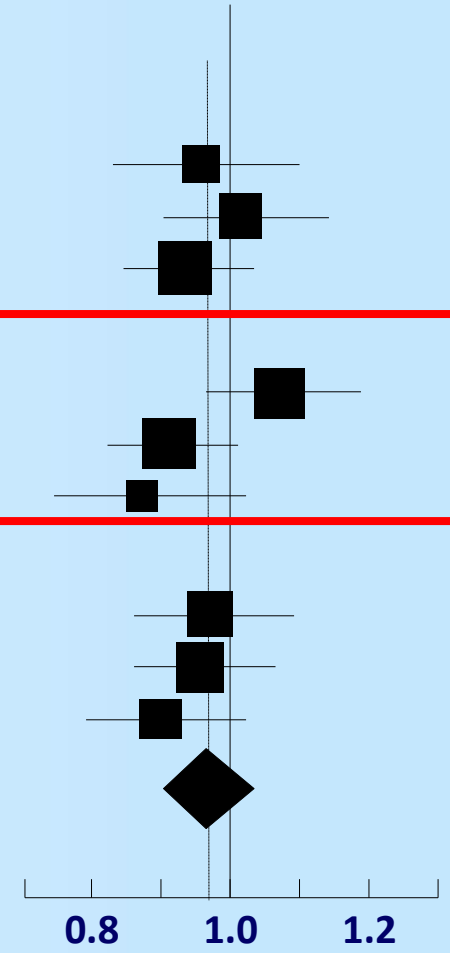
MVE by age, sex, region and statin-based therapy

	Randomized allocation ERN/LRPT (12,838)	Placebo (12,835)	Het or trend χ^2 (uncorrected p value)
Age (years)			
< 65	740 (11.4%)	786 (12.2%)	0.00 (p=0.98)
≥ 65 <70	392 (13.9%)	367 (13.1%)	
≥ 70	564 (15.9%)	605 (17.0%)	
Sex			
Male	1397 (13.2%)	1485 (14.0%)	3.21 (p=0.07)
Female	299 (13.4%)	273 (12.3%)	
Region			
Europe	832 (11.3%)	913 (12.4%)	3.61 (p=0.06)
China	864 (15.8%)	845 (15.5%)	
Statin-based therapy			
Simvastatin 40mg	945 (14.0%)	949 (14.0%)	1.28 (p=0.26)
Ezetimibe/simvastatin	751 (12.4%)	809 (13.3%)	
All	**1696 (13.2%)**	**1758 (13.7%)**	**3.5% SE 3.3 reduction**



Major Vascular Events by Baseline Lipids

mg/dL (mmol/L)	Randomized allocation ERN/LRPT (12838)	Placebo (12835)	Risk ratio & 95% CI	Het or trend X^2 (uncorrected p value)
HDL cholesterol				
<35 (0.9)	388 (15.8%)	399 (16.3%)		0.20 (p=0.66)
≥35 <43	560 (13.7%)	546 (13.5%)		
≥43 (1.1)	748 (11.9%)	813 (12.8%)		
LDL cholesterol				
<58 (1.5)	724 (14.7%)	679 (13.8%)		5.91 (p=0.02)
≥58 <77	685 (12.4%)	761 (13.7%)		
≥77 (2.0)	287 (12.0%)	318 (13.5%)		
Triglycerides				
<89 (1.0)	541 (13.2%)	563 (13.4%)		0.66 (p=0.42)
≥89 <151	694 (12.8%)	712 (13.2%)		
≥151 (1.7)	461 (13.9%)	483 (14.8%)		
All	**1696 (13.2%)**	**1758 (13.7%)**		**3.5% SE 3.3 reduction**



Statin Intolerance

The USAGE Survey

Understanding Statin Use in America and Gaps in Education

Subjects: N=10,138 (66.1%) eligible (physician Dx increased total cholesterol, any prior statin use, ≥18 years old)—**internet survey**

Key findings: Side effects are common and the leading reason for statin discontinuation (12% discontinued)

- Reasons for discontinuation
  - Side effects – 62% (**muscle symptoms in ~50% who discontinued**)
    - Average of 2 statins tried before stopping
  - Cost - 17%
  - Lack of efficacy - 12%
- When/how they stopped
  - Promptly after a side effect (no further Rx) – 57%
  - Stopped without asking or telling their HCP – 33%
- Among the 88% current statin users
  - **Muscle pain or weakness reported by 25%**, but they continued anyway (with or without switching)

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

(HCP = healthcare provider; Rx = prescription)

The PRIMO Study

Muscle Symptoms on High-Dose Statin Therapy

N=7900

Statin	% Patients with muscle complaints (N=832)
Pravastatin 40 mg	10.9
Atorvastatin 40–80 mg	14.9
Simvastatin 40–80 mg	18.2
Fluvastatin XL 80 mg	5.1

Bruckert et al. Cardiovasc Drugs Ther. 2005:19:403-14.

Statin Intolerance: Summary

Working definition:

- Failure to tolerate at least two statins (one at lowest marketed dose)

Manifestations:

- Muscle: myalgia, weakness, cramps, stiffness, rhabdo.
- Cognitive or mood disturbance
- Arthralgia
- Other (GI Sx, rash, peripheral neuropathy, ↑transaminase levels?)

Workup:

- W/U for primary myopathy if not resolved ~2 mos after statin D/C'd
- Test for and treat treatable causes
  - Hypothyroidism
  - Drug-drug interaction (change either drug)
  - Vitamin D deficiency?
  - CoQ 10 deficiency?
- Trial of less-than-daily statin treatment
- Trial of extended-release fluvastatin
- Treat with non-statins (Ezetimibe, BAS, NA, EPA om-3)

Arca, Pigna. Diabetes Metab Syndr Obes. 2011;4:155-66.

Statin Phobia

- Definition: irrational fear of statins, unwilling to try
- Causes:
  - Negative information on internet
  - Distrust of big corporations/big pharma
  - Distrust of Western medicine
  - Adverse experiences of family and friends
- Suggested approaches
  - Red yeast rice? “natural”= good (unaware of variable potency, potential harm from non-statin content)
  - Other dietary supplements?
    - Niacin (avoid multi-dose sustained release, flush-free)
    - Omega-3 oil (avoid non-marine, check potency)

Brinton. 2014; unpublished.

Unmet Needs in Treating LDL-C/Non-HDL-C: Summary

- 2013 ACC/AHA guidelines are good in many ways but not helpful with regard to:
  - Abandoning LDL-C/Non-HDL-C goals
  - Abandoning endorsement of statin adjuncts
- Statin adjuncts appear to have favorable risk/benefit ratio:
  - Rx LDL-C/Non-HDL-C to goal—Ezet, BAS, EPA, NA
  - Rx residual HTG/low HDL-C—Fibrates, Om-3, NA
- Statin intolerance or phobia are poorly understood and difficult to manage
- Emerging non-statins promise to be very useful

Genetic Insights into Mechanisms Underlying Regulation of LDL Cholesterol

Sekar Kathiresan, MD
Associate Professor of Medicine, Harvard Medical School
Associate Member, Broad Institute
Director, Preventive Cardiology, MGH

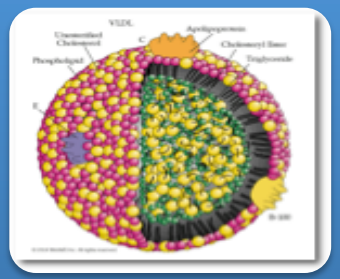
October 23, 2014

Massachusetts General Hospital

Harvard Medical School

BROAD INSTITUTE

Two questions:

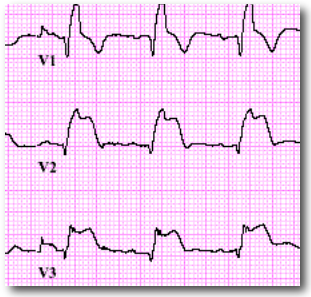


Which lipid risk factors are key drivers for CAD?

Can we identify protective mutations and use these to develop new treatments?

Human genetics can be a tool to identify ‘root causes’ of disease

DNA Sequence Variant



Myocardial Infarction

There are ~3.2 billion bases of DNA sequence

Which ones confer risk for CAD?

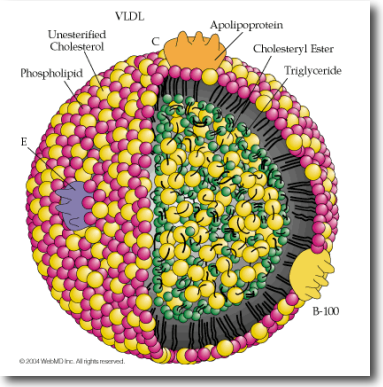
Genetic studies for CAD

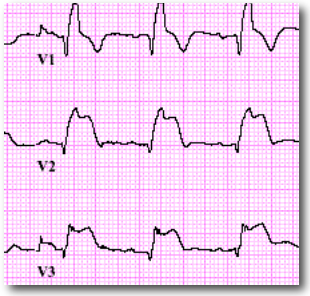
50 gene regions identified for CAD

19p13 LDLR	8p21 LPL	6q26 LPA	21q22 MRPS6	17p13 SMG6
1p32 PCSK9	11q23 APOA5	6p21 KCNK5	1p32 PPAP2B	17q21 GIP
2p24 APOB	8q24 TRIB1	6q26 PLG	6p21 ANKS1A	6q23 TCF21
2p21 ABCG5/G8	ANGPTL4	13q12 FLT1	7q32 ZC3HC1	14q32 HHIPL1
12q24 HNF1A	APOC3	4q31 EDNRA	2q33 NBEAL1	15q25 ADAMTS7
9q34 ABO	10q11 CXCL12	7p21 HDAC9	9p21 CDKN2BAS	17p11 RASD1
1p13 SORT1	12q24 SH2B3	7q22	1q41 MIA3	3q22 MRAS
APOE	4q32 GUCY1A3	10q23 LIPA	13q34 COL4A1	6p24 PHACTR1
LDLRAP1	10q24 CYP17A1	2p11 GGCX	2q22 ZEB2	11q22 PDGFD
LRP6	10p11 KIAA1462	15q26 FURIN	1q21 IL6R	5q31 SLC22A4

Which plasma risk factors
do these genes relate to?

DNA Sequence Variant





Risk factor
(e.g., LDL)

Myocardial Infarction

10 relate to LDL cholesterol

19p13 LDLR	8p21 LPL	6q26 LPA	21q22 MRPS6	17p13 SMG6
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9q34 ABO	10q11 CXCL12	7p21 HDAC9	9p21 CDKN2BAS	17p11 RASD1
1p13 SORT1	12q24 SH2B3	7q22	1q41 MIA3	3q22 MRAS
APOE	4q32 GUCY1A3	10q23 LIPA	13q34 COL4A1	6p24 PHACTR1
LDLRAP1	10q24 CYP17A1	2p11 GGCX	2q22 ZEB2	11q22 PDGFD
LRP6	10p11 KIAA1462	15q26 FURIN	1q21 IL6R	5q31 SLC22A4

Lp(a) gene confers risk for CAD

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5 relate to TG-rich lipoproteins

19p13 LDLR	8p21 LPL	6q26 LPA	21q22 MRPS6	17p13 SMG6
1p32 PCSK9	11q23 APOA5	6p21 KCNK5	1p32 PPAP2B	17q21 GIP
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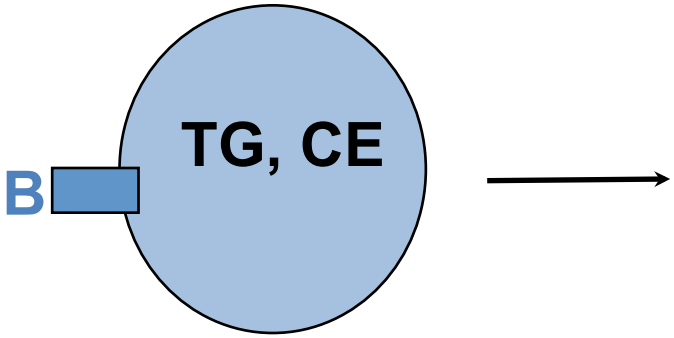
LDLRAP1	10q24 CYP17A1	2p11 GGCX	2q22 ZEB2	11q22 PDGFD
LRP6	10p11 KIAA1462	15q26 FURIN	1q21 IL6R	5q31 SLC22A4

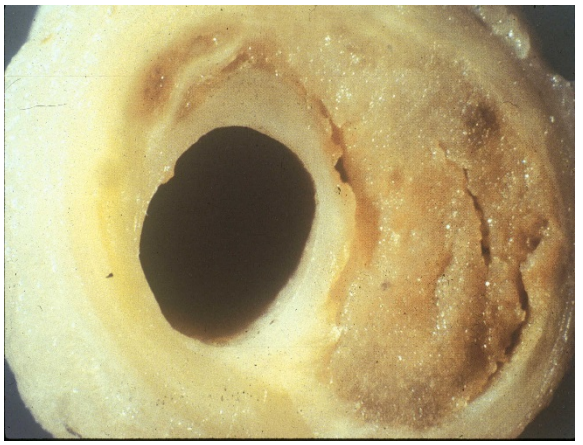
Human genetics: apoB-containing lipoproteins are main drivers of atherosclerosis



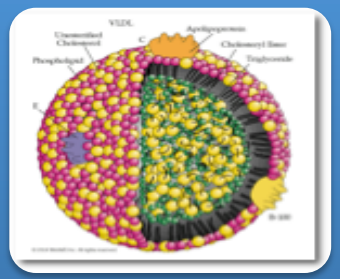
LDL

TG-rich lipoproteins

Lp(a)



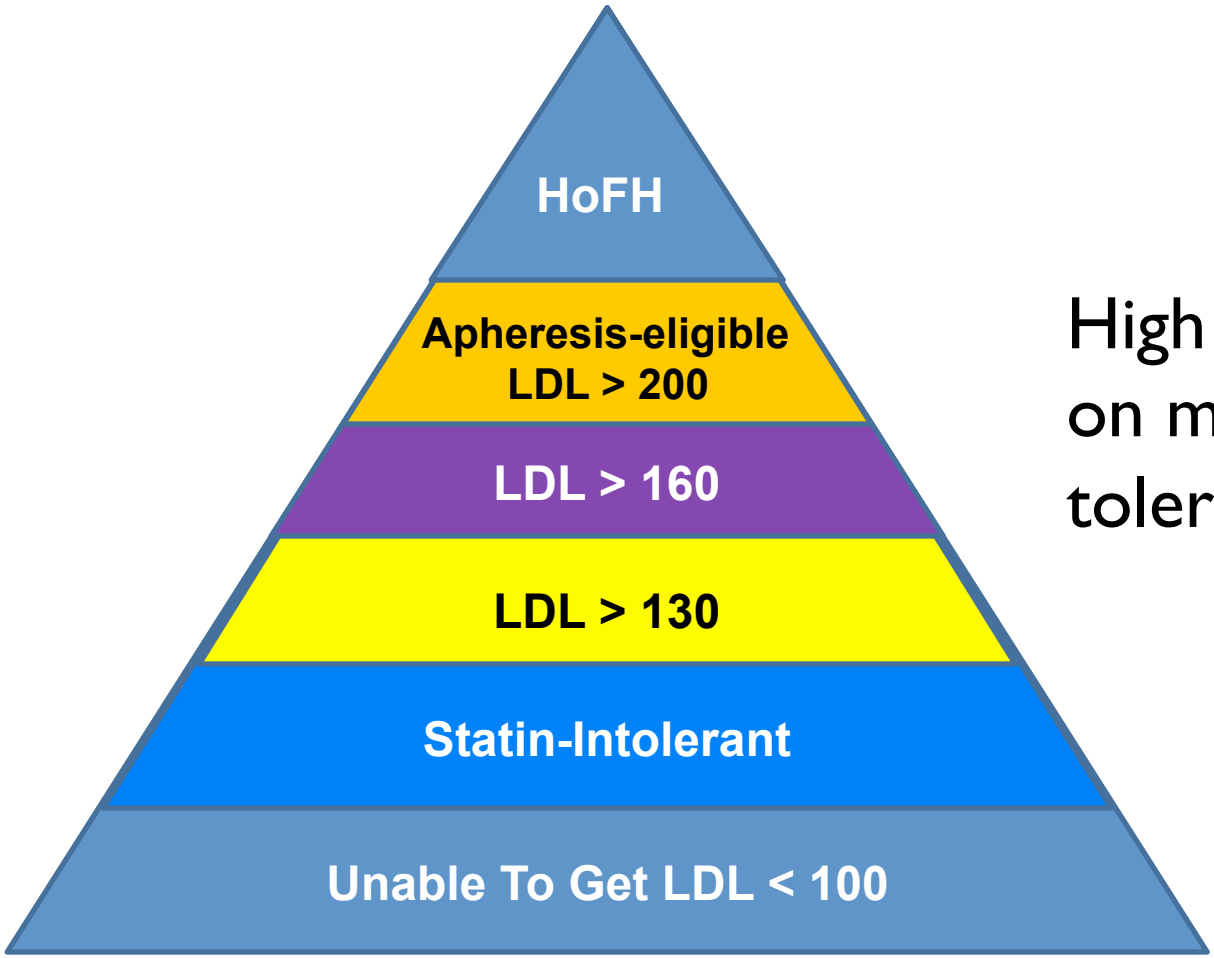
Two questions:



Which lipid risk factors are key drivers for CAD?

Can we identify protective mutations and use these to develop new treatments?

Large unmet medical need in the treatment of elevated LDL-C



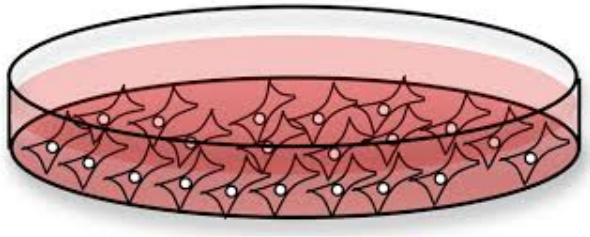
High risk and on maximal tolerated statin

Problem:

Only about 5% of medicines in development succeed into clinic

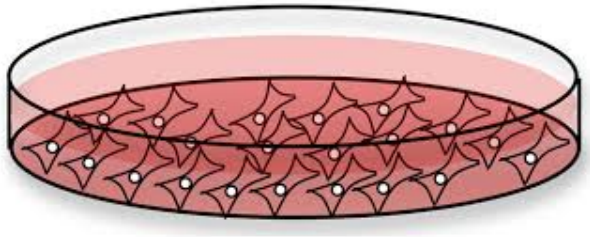
Two reasons:

Poorly predictive models



Two reasons:

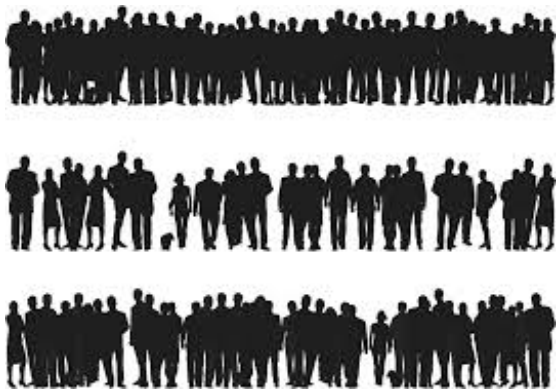
Poorly predictive models

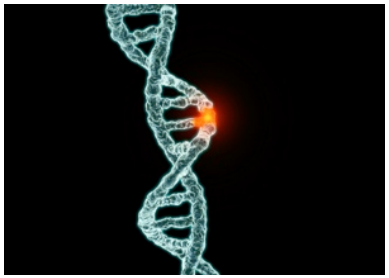


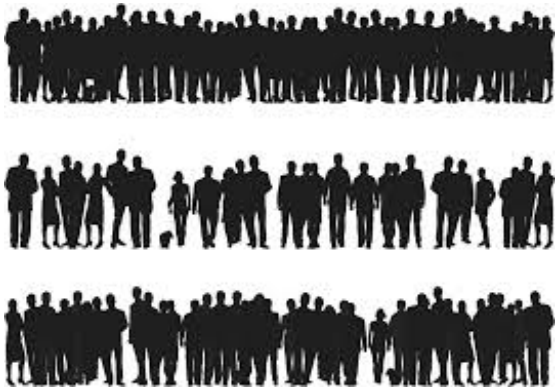
Don't know impact of blocking a gene over many years

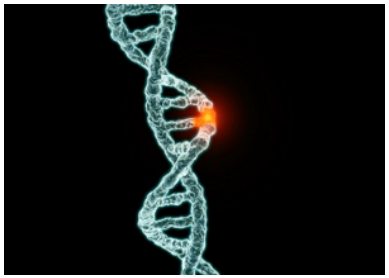
Idea:

Find protective mutations in people
and develop medicines that
mimic these natural successes



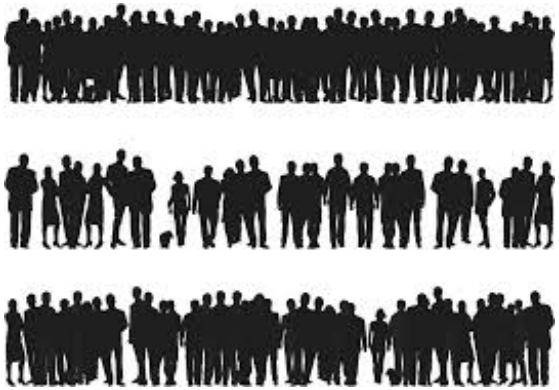


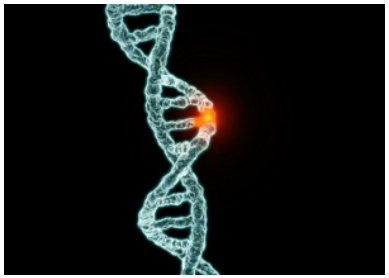




LDL-C

Develop medicines against genes where mutations reduce risk for disease



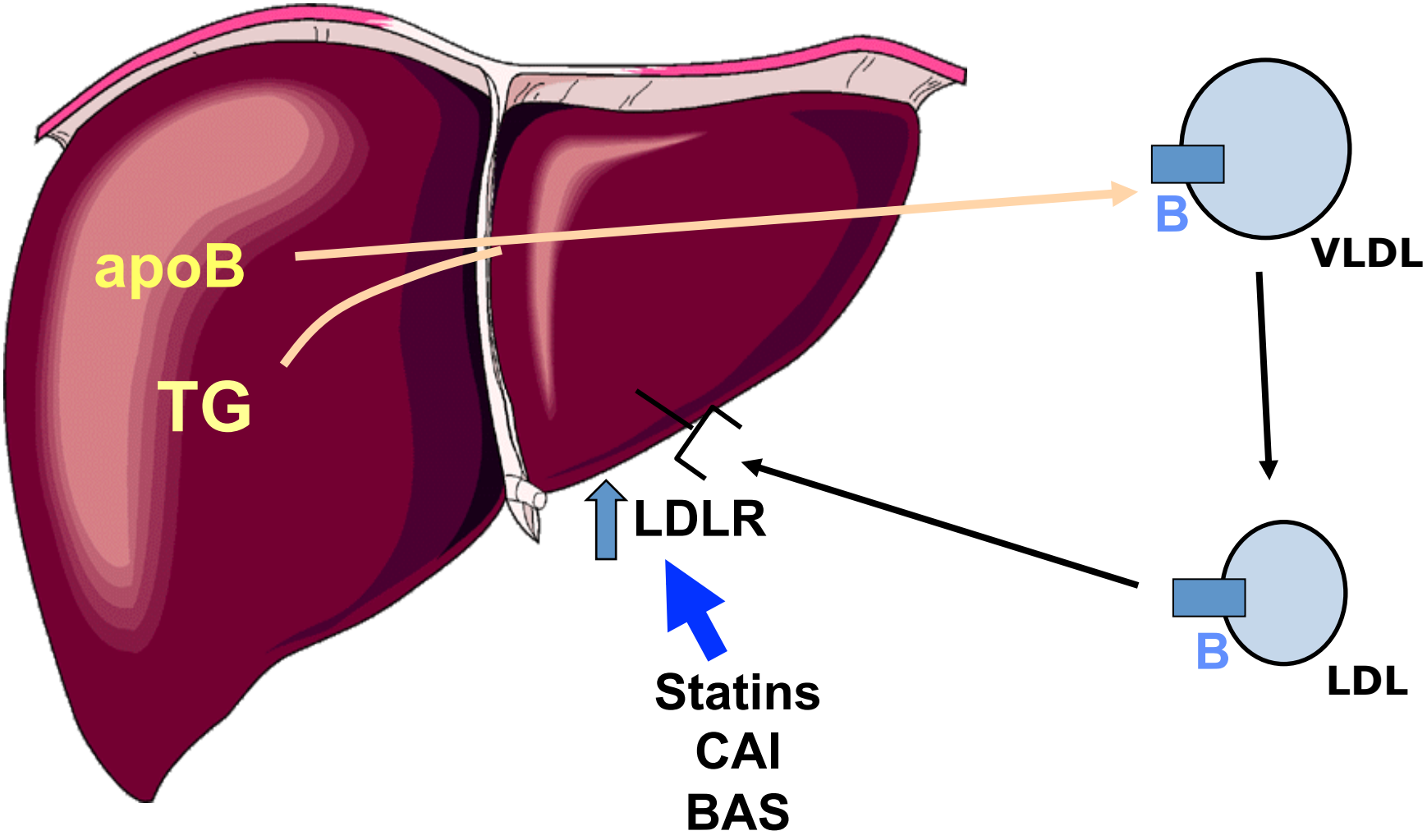


LDL-C

Medicines that mimic the genome

Genetics	Pharmacology

Current LDL-lowering therapies converge on upregulation of the hepatic LDL Receptor



Genome-wide association experiment

100, 000 people

Measure LDL-C in each person

Measure ~2 million SNPs in each person

Vol 466|5 August 2010|doi:10.1038/nature09270 nature

ARTICLES

Biological, clinical and population relevance of 95 loci for blood lipids

Tanya Teslovich

Kiran Musunuru

Results: 95 SNPs associated with lipids

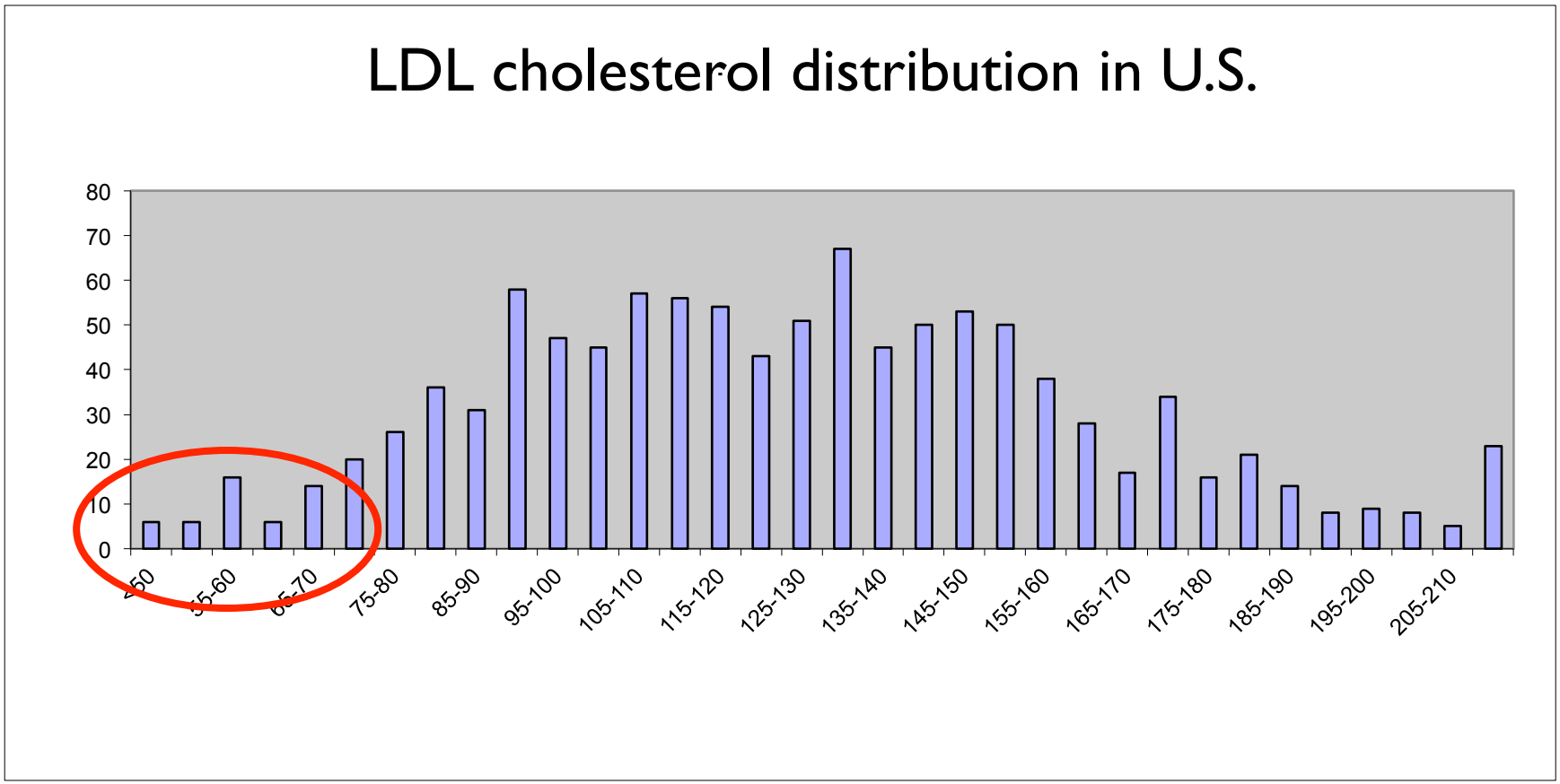
LDL-C			HDL-C			Triglycerides	
ABCG5/8	[illegible]	SORT1	ABCA1	HNF4A	PDE3A	ACSS2	GALNT2
ABO	HMGCR	ST3GAL4	ABCA8	IRS1	PGS1	AFF1	GCKR
ANGPTL3	HNF1A	TIMD4	ADM	KLF14	PLTP	ANGPTL3	IRS1
APOA	HPR	TOP1	ANGPTL4	LACTB	PPP1R3B	ANKRD55	JMJD1C
APOB	IDOL	TRIB1	APOA	LCAT	SBNO1	APOA	LIPC
APOE	IRF2BP2		APOB	LILRA/B	SCARB1	APOB	LPL
BRAP	LDLR		APOE	LIPC	SLC39A8	APOE	LRP1
BTNL2	LDLRAP1		ARL15	LIPG	STARD3	BTNL2	MLXIPL
CBLN3	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	[illegible]		COBLL1	MACF1	UBE2L3	CTF1	PLTP
FADS	PCSK9		DOCK6	MC4R	ZNF648	CYP26A1	TIMD4
FRK	PLEC1		FADS	MLXIPL	ZNF664	FADS	TRIB1
GPAM	PPP1R3B		GALNT2	MMAB		FRMD5	TYW1B
							ZNF664

Teslovich*, Musunuru*, *Nature* 2014

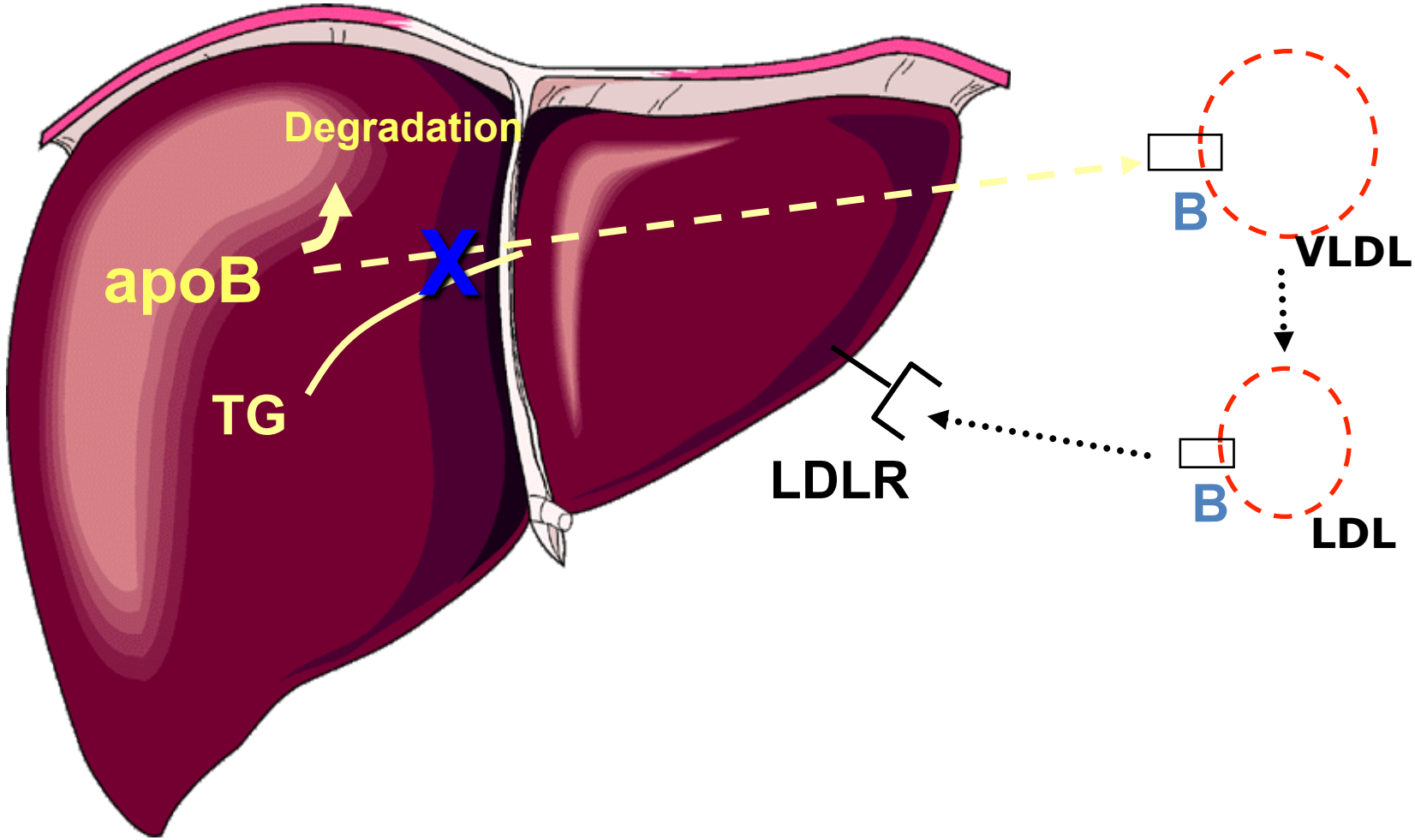
LDL-C and CAD

Target Gene (Drug)	**Genetics**		**Pharmacology**	
	LDL cholesterol	CAD	LDL cholesterol	CAD
HMCGR (statins)	✓	✓	✓	✓
NPC1L1 (ezetimibe)	✓		✓	Phase III trial ongoing

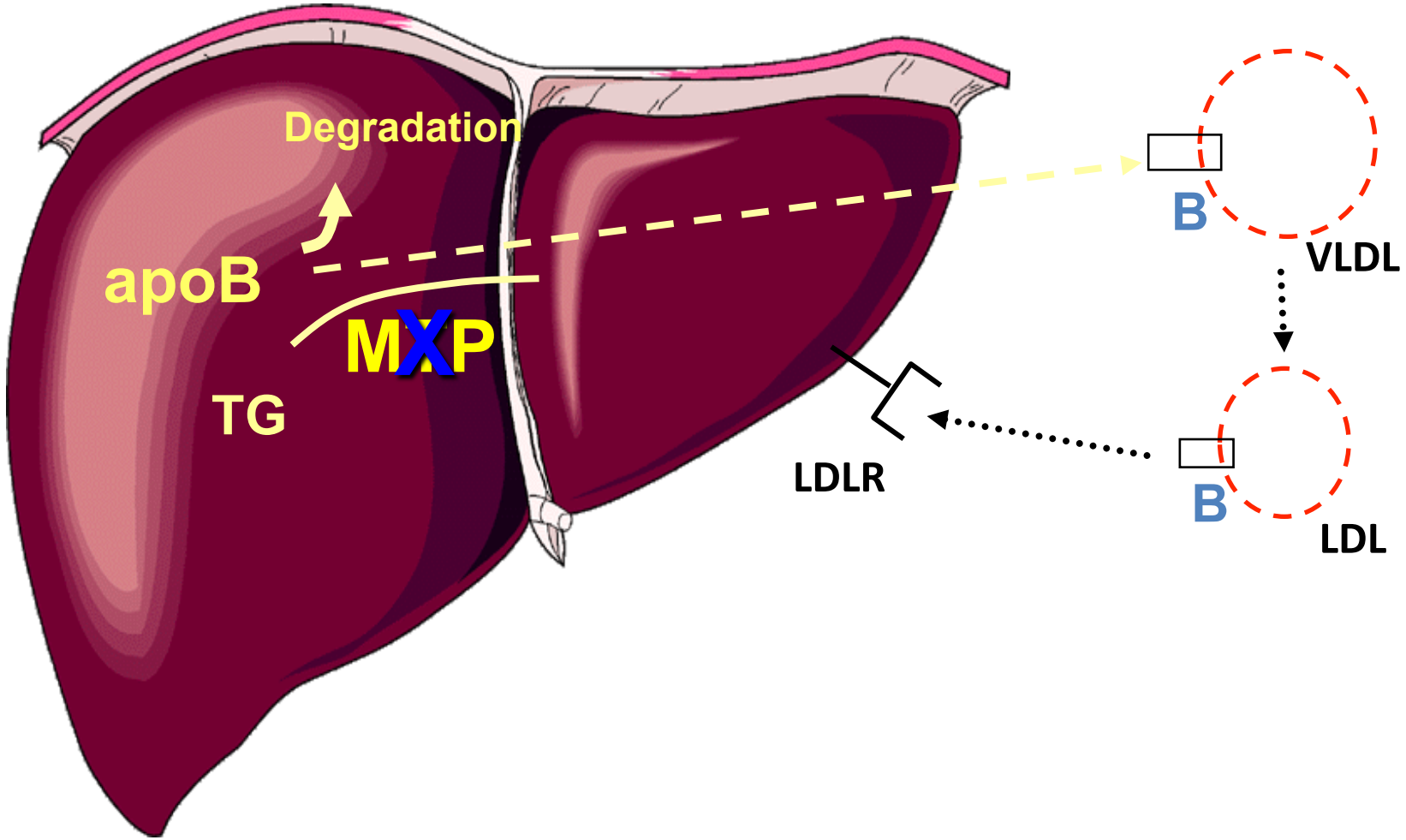
Inherited syndromes of low LDL Provide new targets for reducing LDL



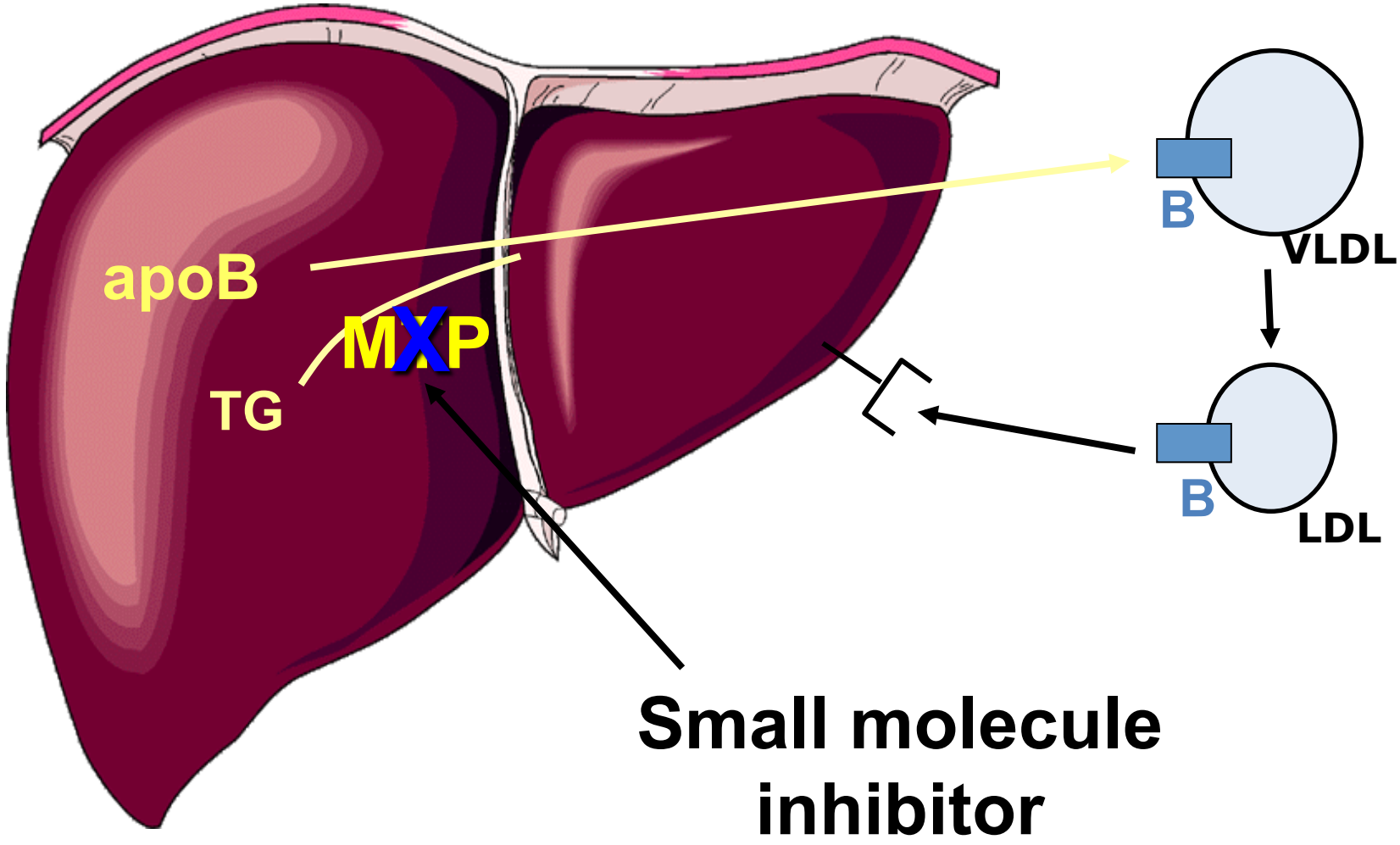
Abetalipoproteinemia



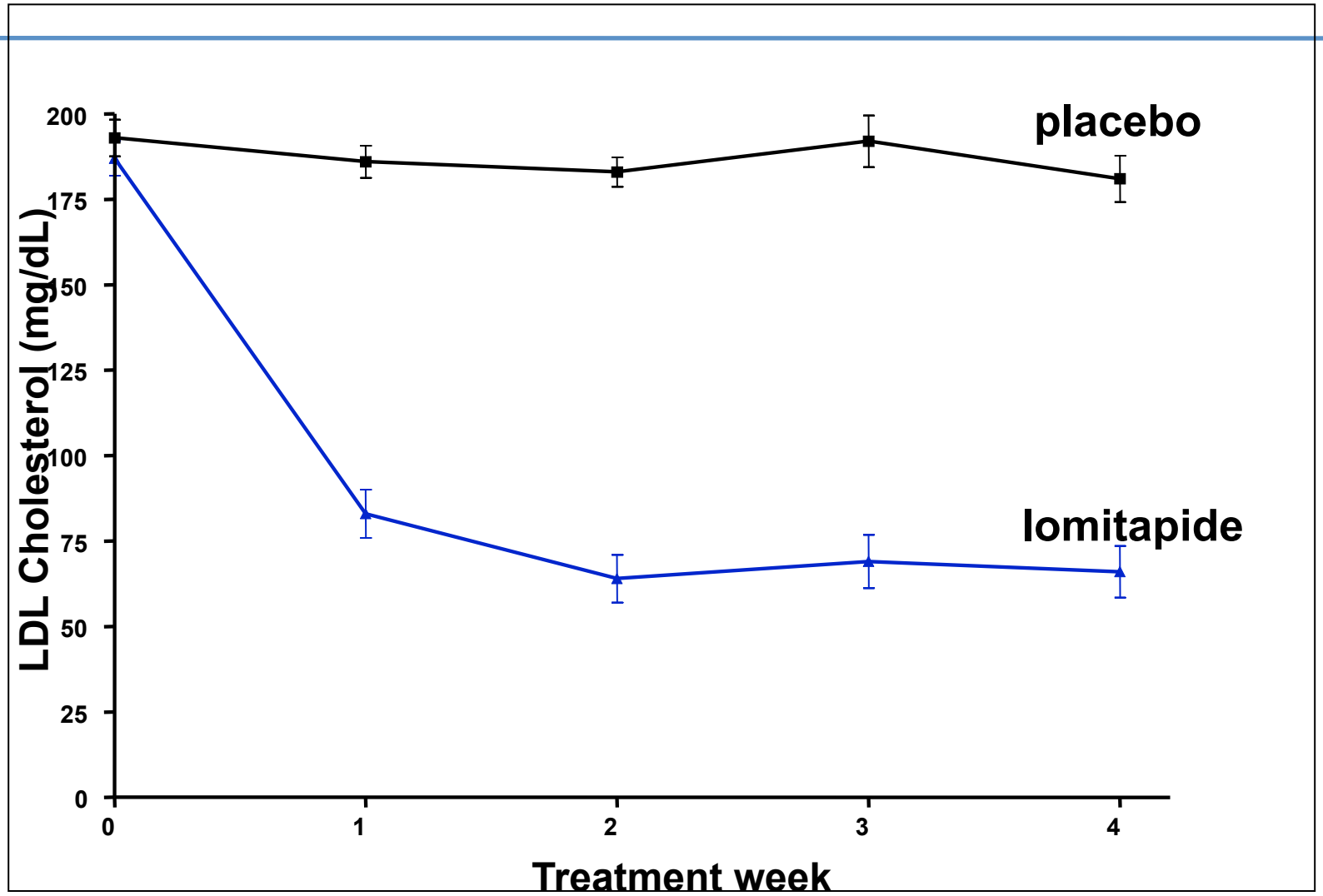
Genetic deficiency of MTP eliminates VLDL and LDL production and causes abetalipoproteinemia



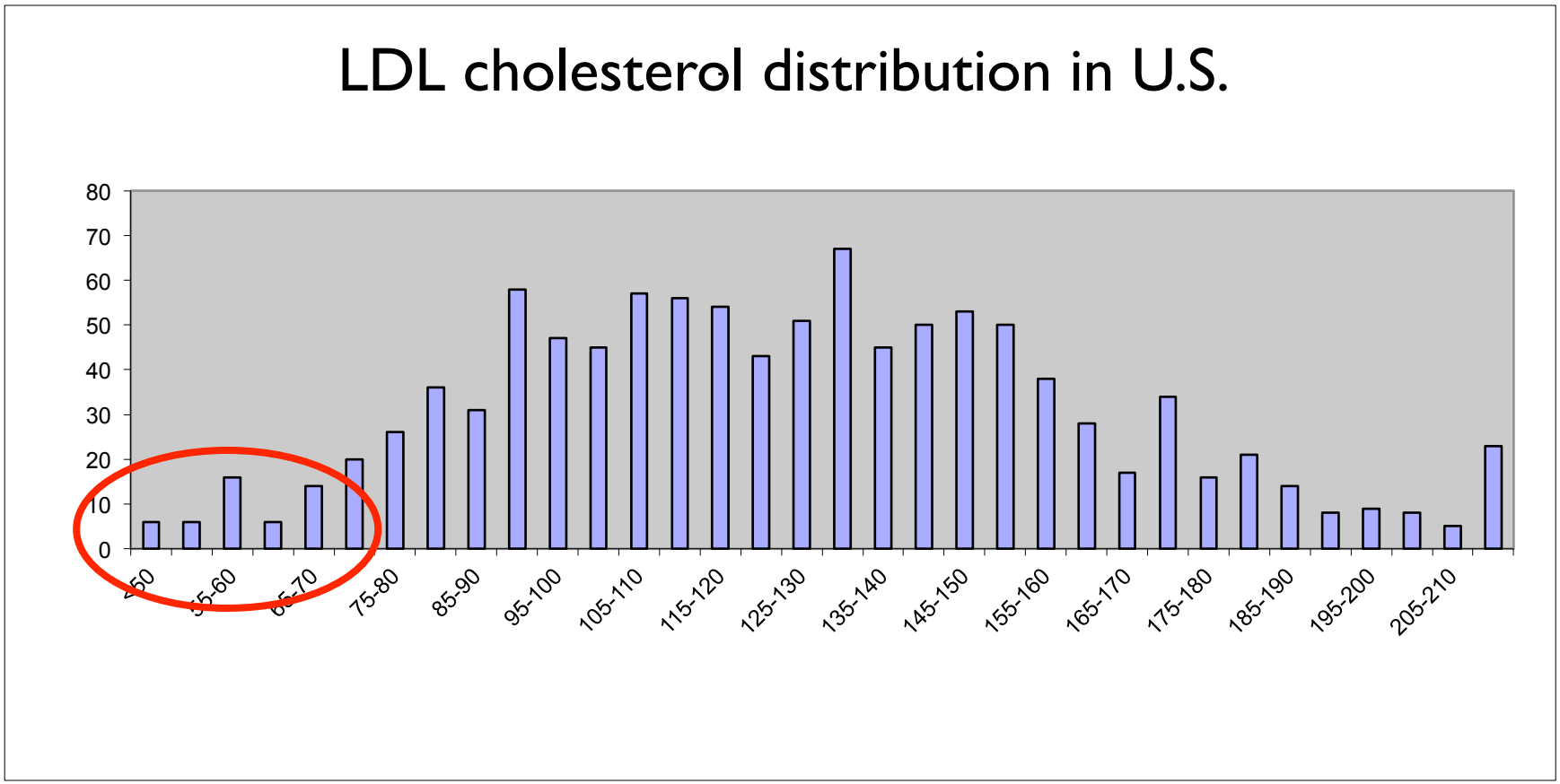
MTP Inhibition: a new strategy for reducing hepatic VLDL secretion



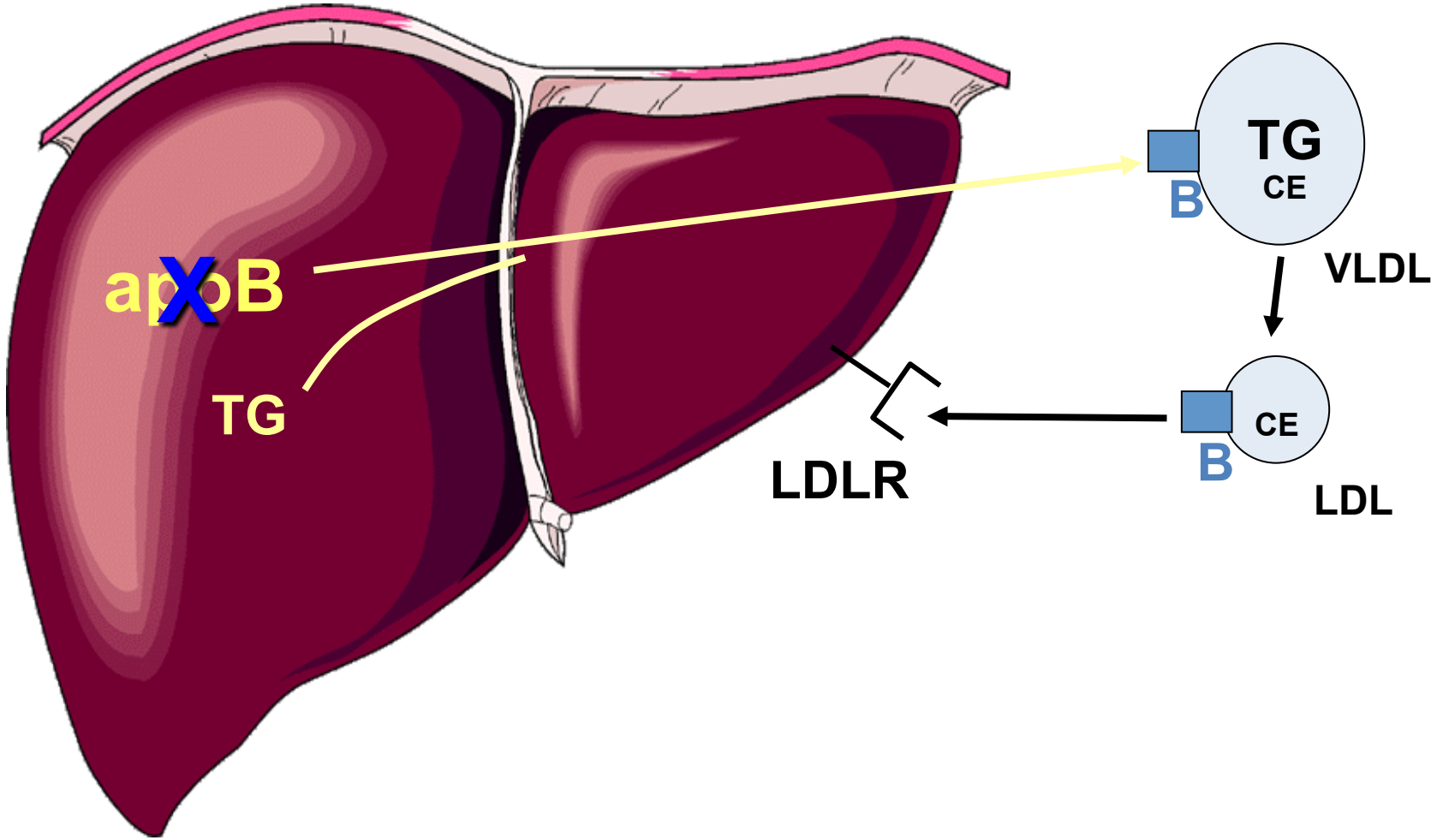
MTP inhibitor lomitapide markedly reduced LDL-C in hypercholesterolemic subjects



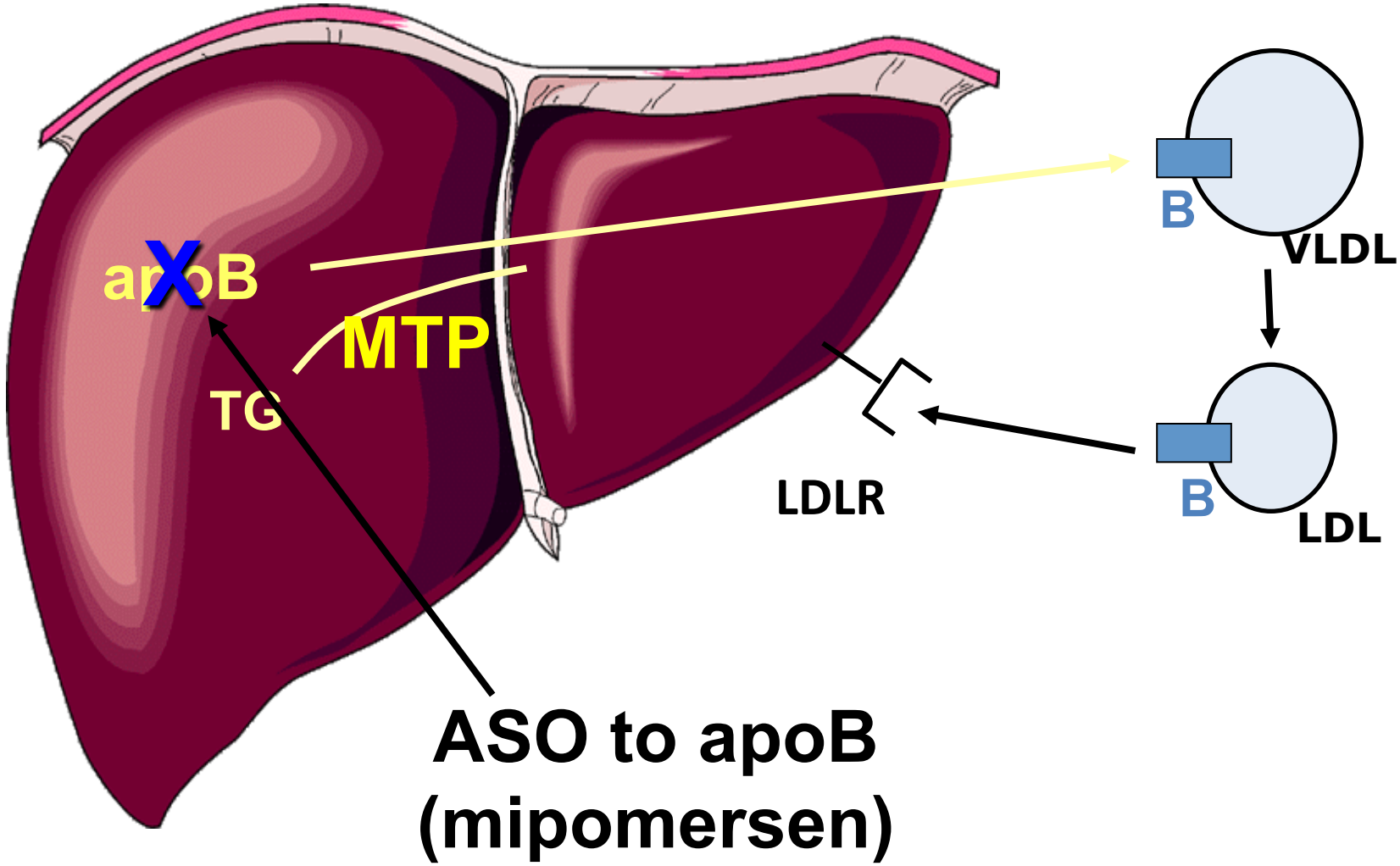
Inherited syndromes of low LDL provide new targets for reducing LDL



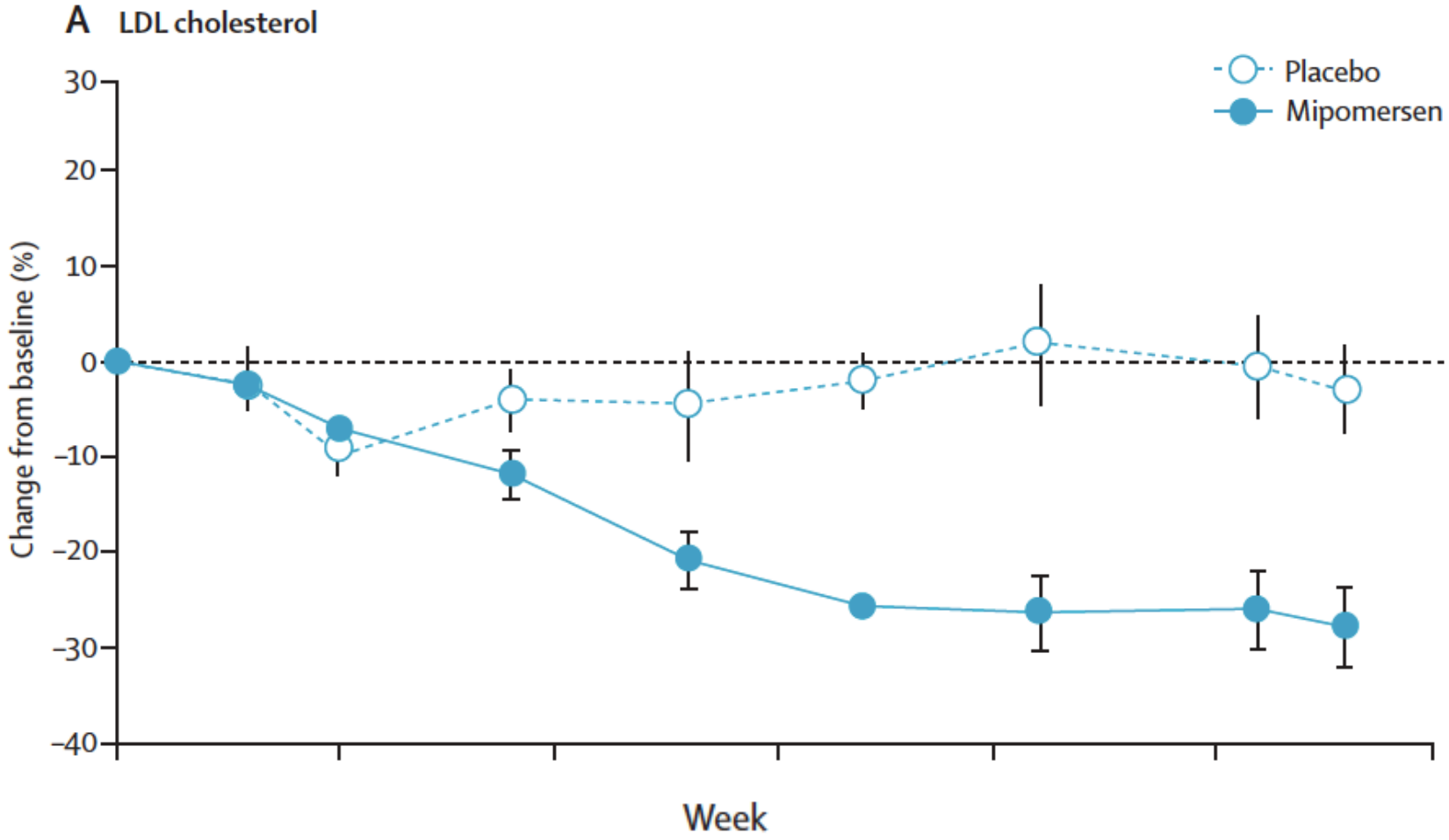
Truncation mutations in ApoB cause familial hypobetalipoproteinemia (Low LDL-C)



Antisense oligonucleotide to ApoB: A strategy for reducing hepatic VLDL secretion and LDL

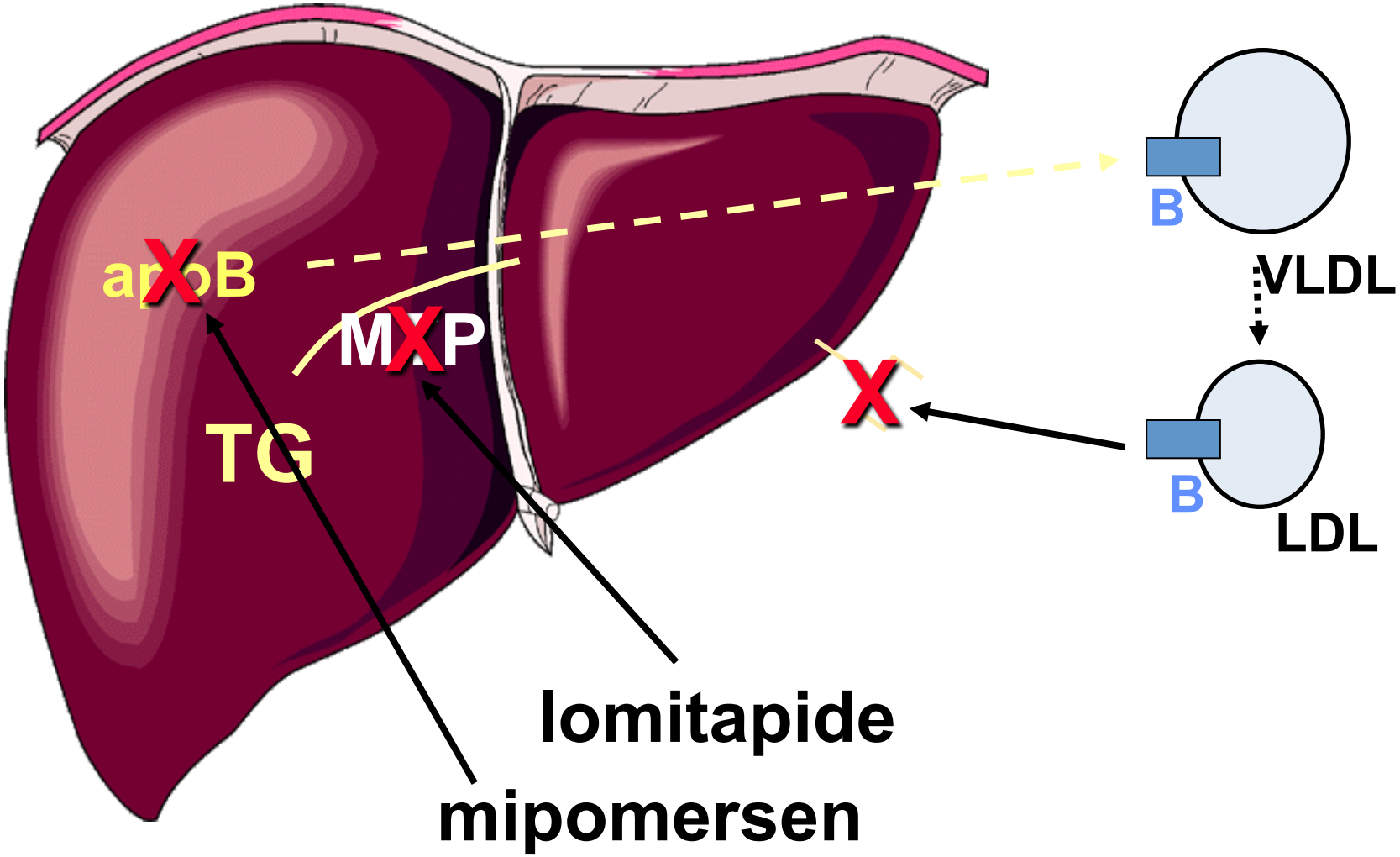


Mipomersen significantly reduced LDL-C in homozygous familial hypercholesteromia



Raal, *Lancet* 2010

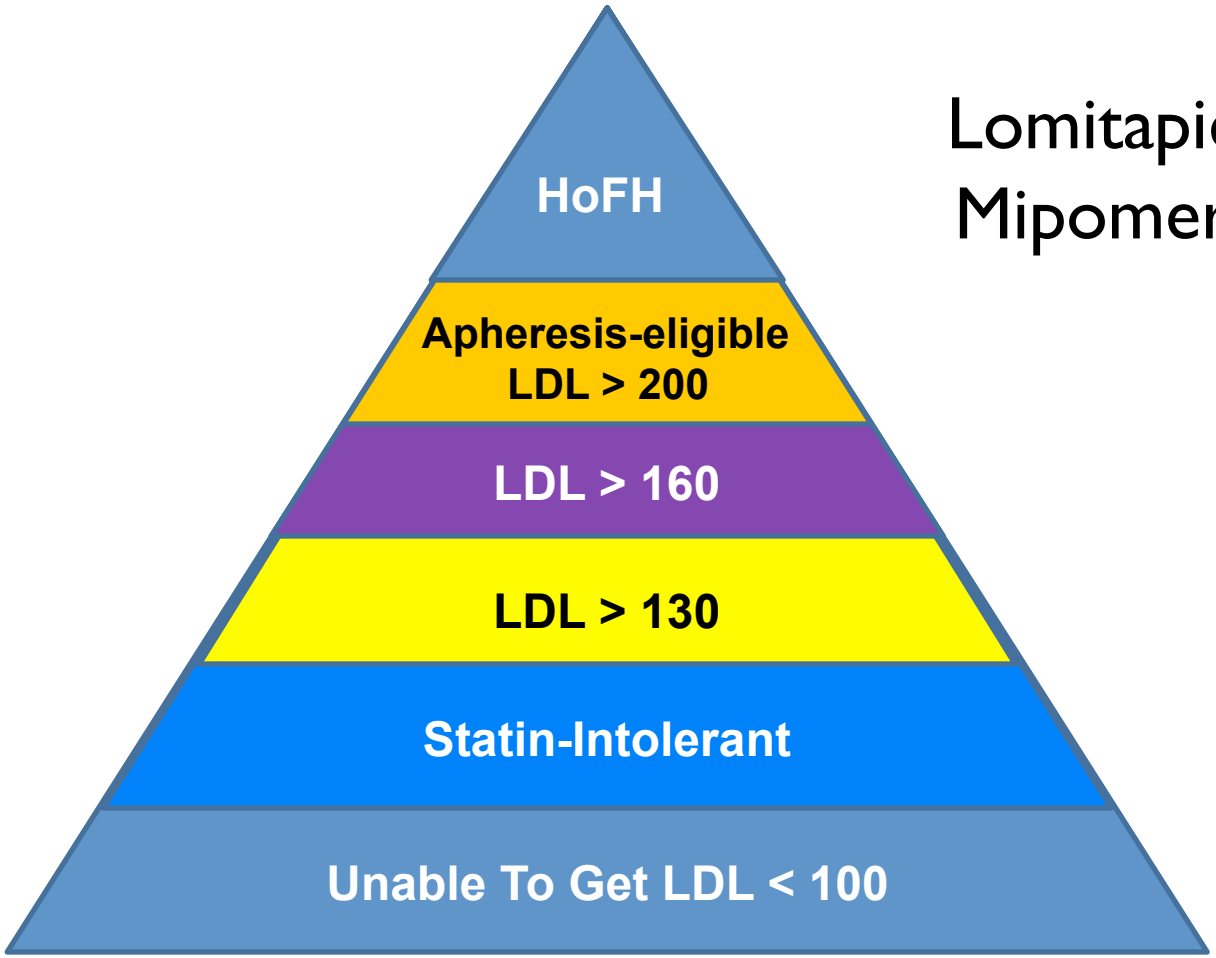
New approved therapies for homozygous FH that reduce LDL-C by targeting VLDL production



LDL-C and CAD

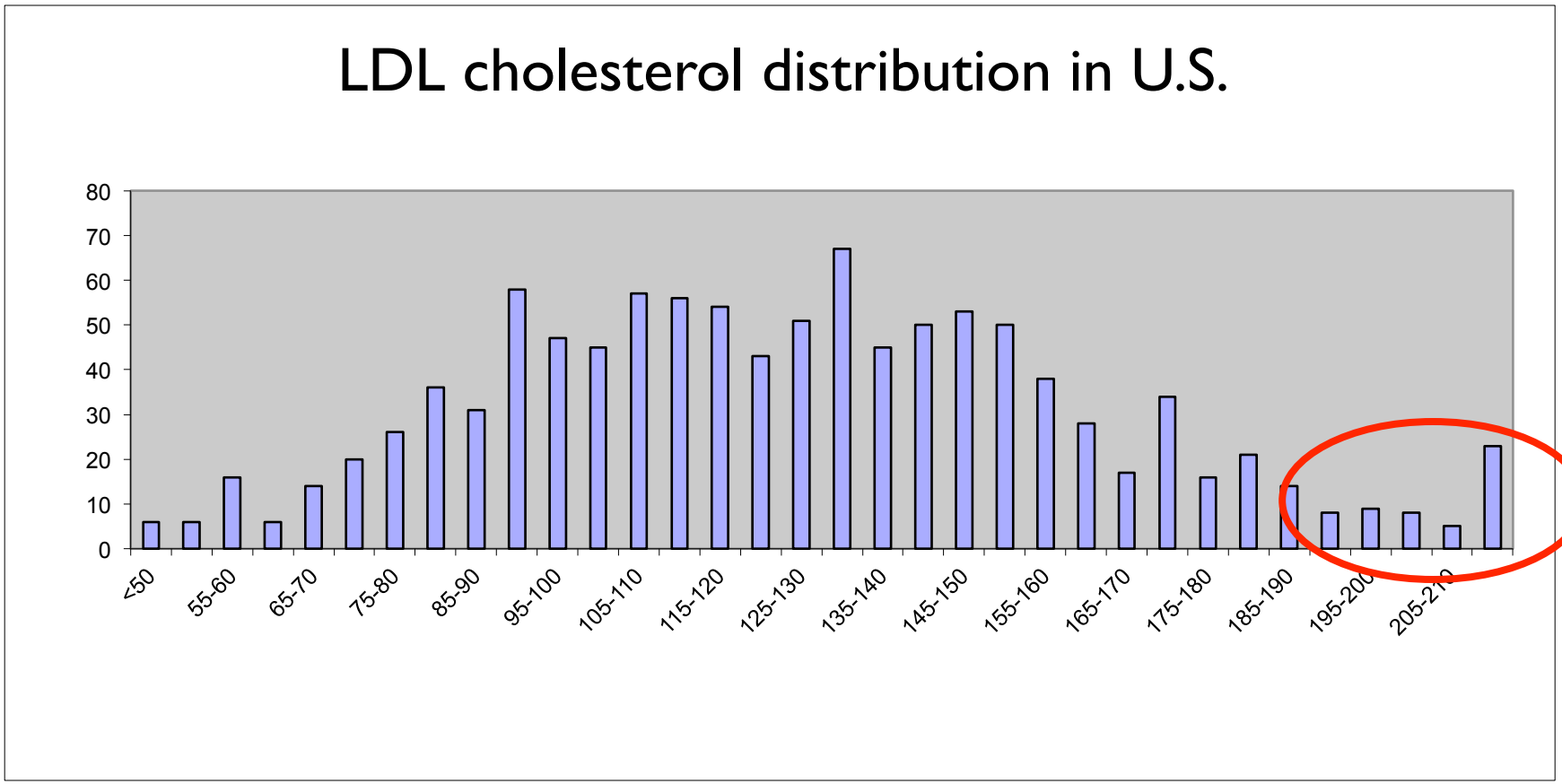
Target Gene (Drug)	**Genetics**		**Pharmacology**	
	LDL cholesterol	CAD	LDL cholesterol	CAD
HMCGR (statins)	✓	✓	✓	✓
NPC1L1 (ezetimibe)	✓		✓	Phase III trial ongoing
MTTP (lomitapide)	✓		✓	
APOB (mipomersen)	✓	✓	✓	

Addressing unmet medical needs in the treatment of elevated LDL-C

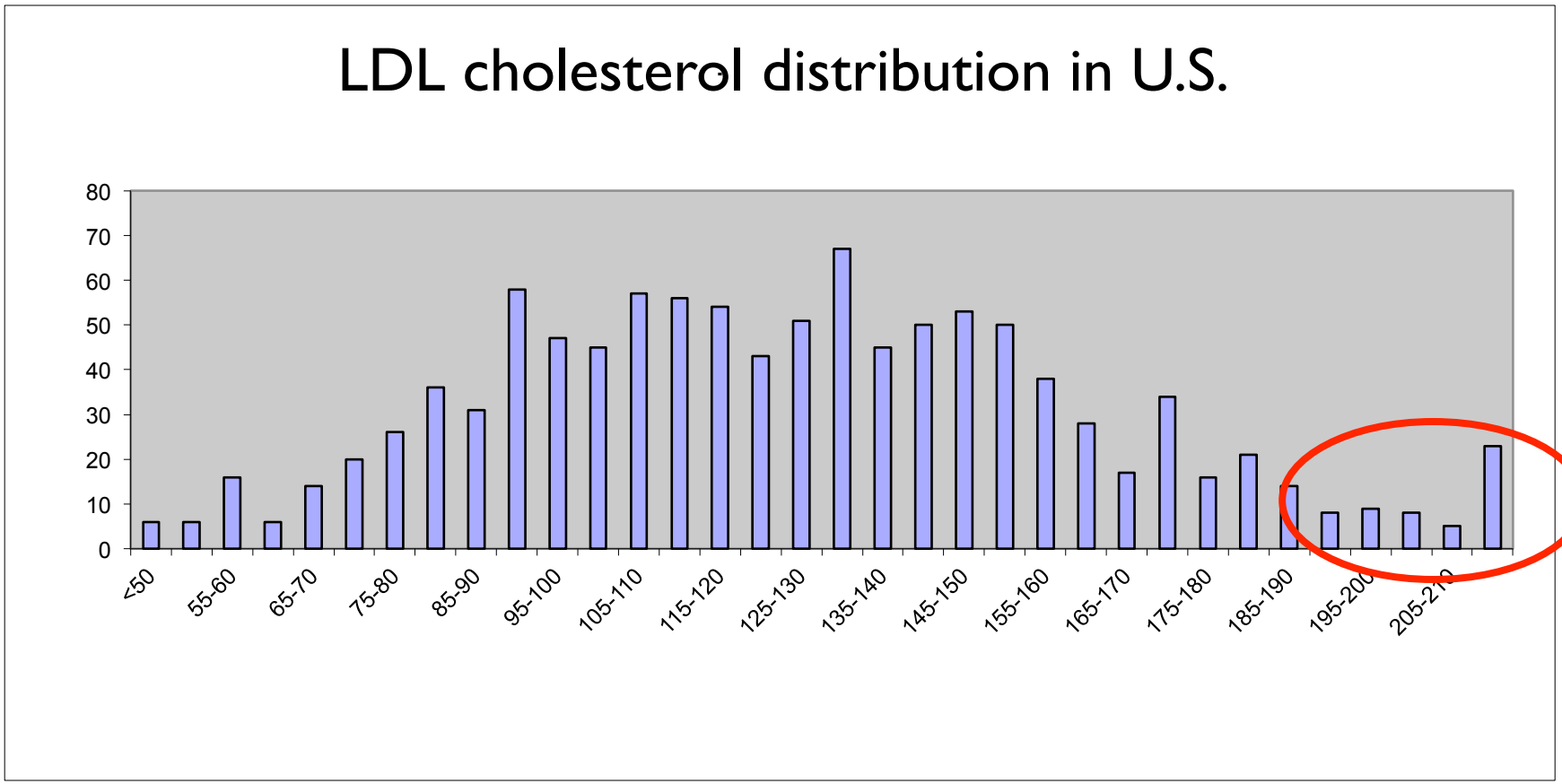


Lomitapide
Mipomersen

Inherited Syndromes of Extremes of LDL-C: Story of PCSK9



Autosomal dominant hypercholesterolemia: PCSK9 identified as a causal gene

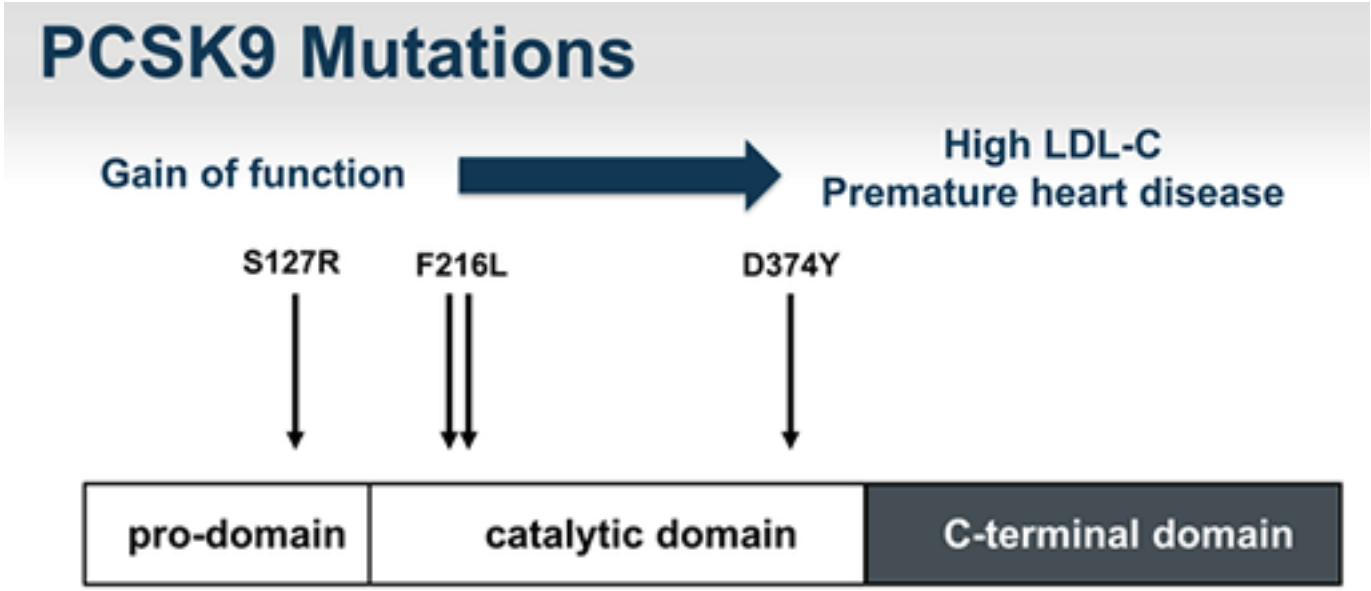


Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

Marianne Abifadel[1,2], Mathilde Varret[1], Jean-Pierre Rabès[1,3], Delphine Allard[1], Khadija Ouguerram[4], Martine Devillers[1], Corinne Cruaud[5], Suzanne Benjannet[6], Louise Wickham[6], Danièle Erlich[1], Aurélie Derré[1], Ludovic Villéger[1], Michel Farnier[7], Isabel Beucler[8], Eric Bruckert[9], Jean Chambaz[10], Bernard Chanu[11], Jean-Michel Lecerf[12], Gerald Luc[12], Philippe Moulin[13], Jean Weissenbach[5], Annick Prat[6], Michel Krempf[4], Claudine Junien[1,3], Nabil G Seidah[6] & Catherine Boileau[1,3]

Nature Genetics 2003

Gain-of-function PCSK9 mutations increase LDL and risk for CAD

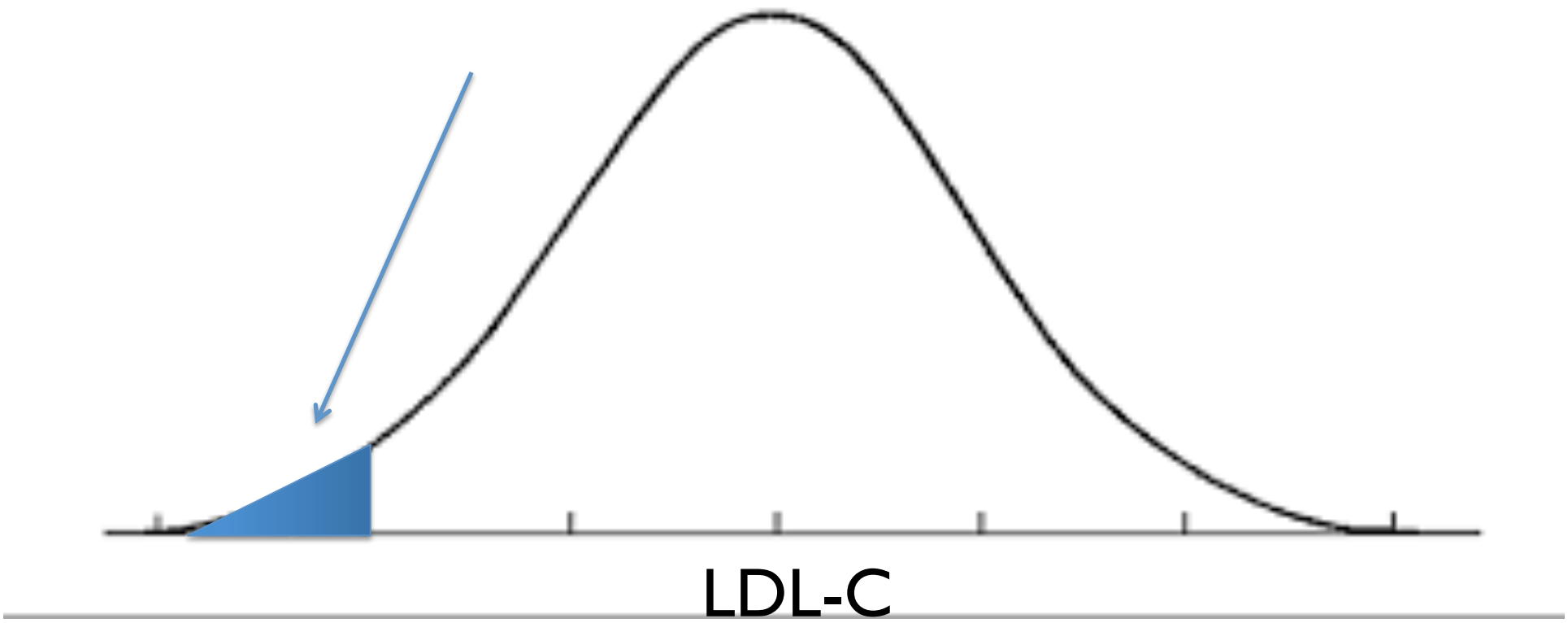


Lambert, *Curr Opin Lipidol* 2007

Hypothesis

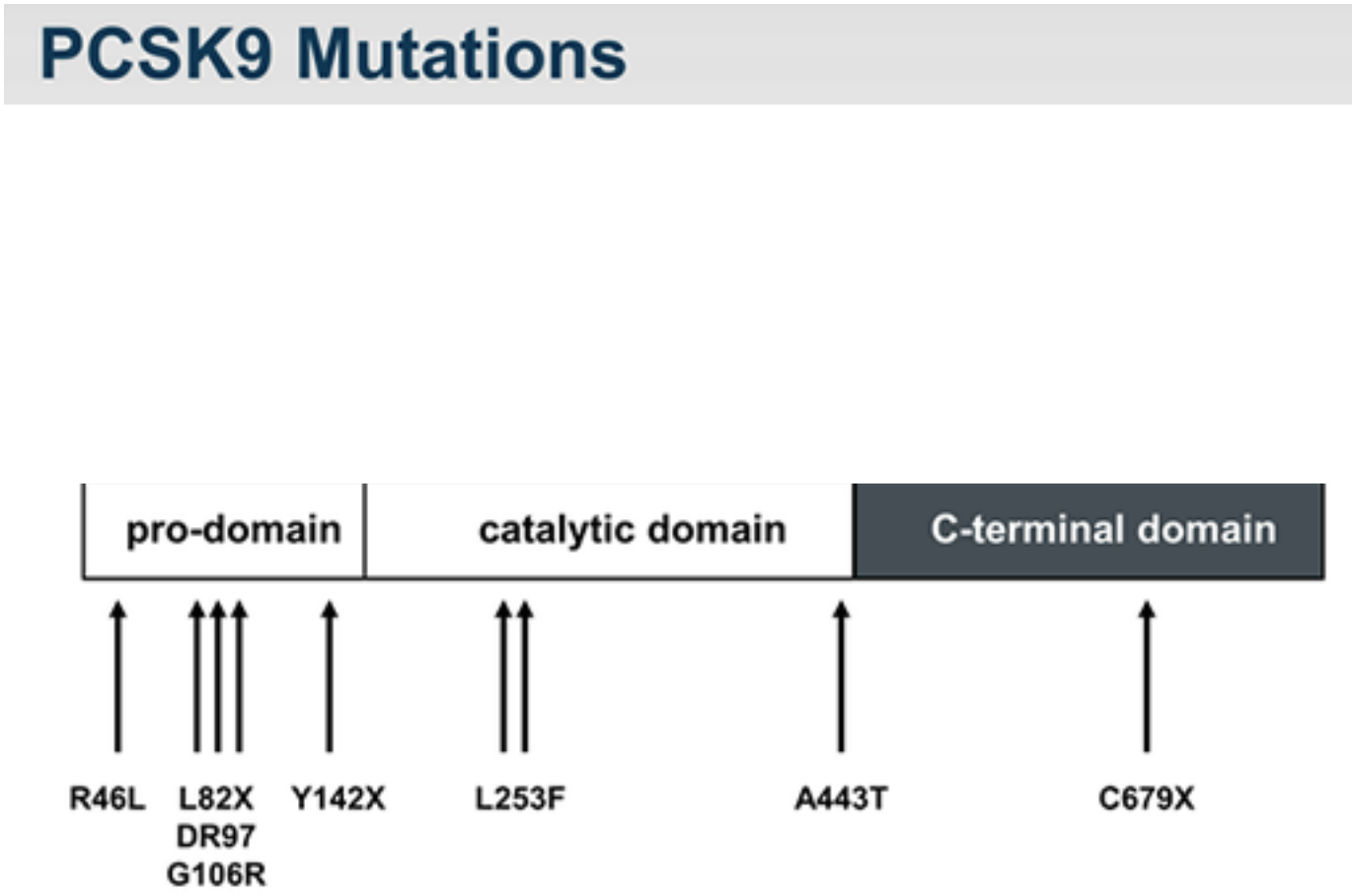
Loss of PCSK9 function should
lead to low LDL cholesterol and
protect against CAD

Sequencing of PCSK9 in individuals with extremely low LDL cholesterol



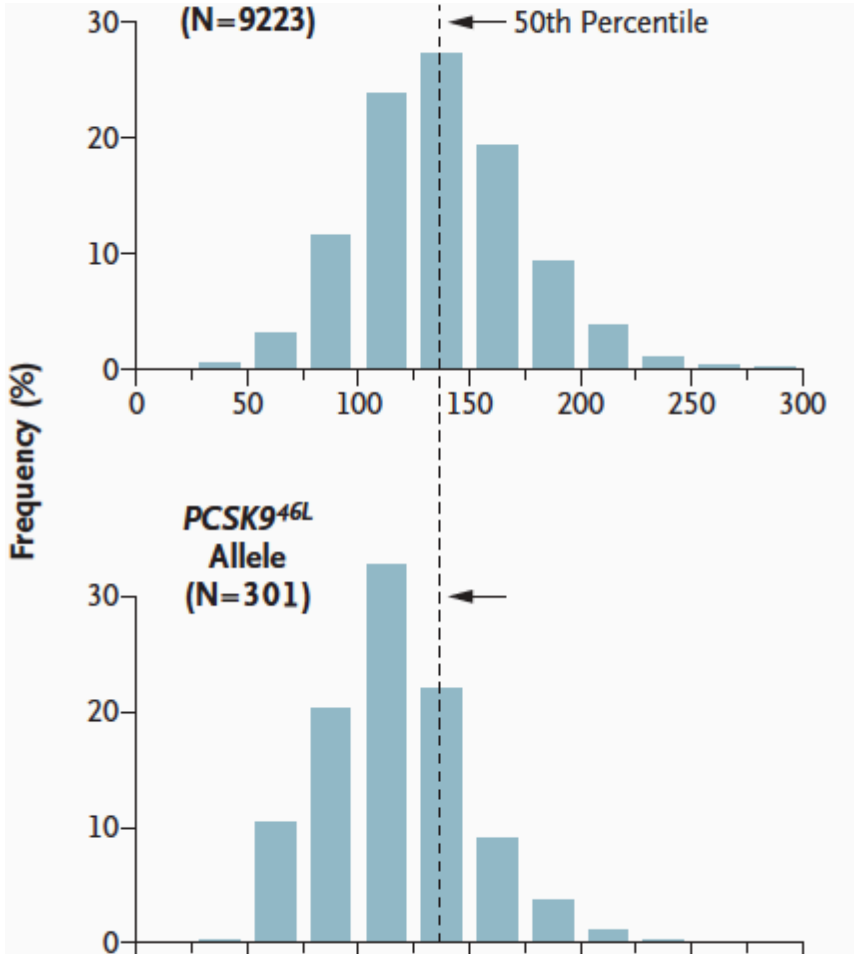
Cohen, *Nature Genetics* 2005

Several loss of function mutations discovered



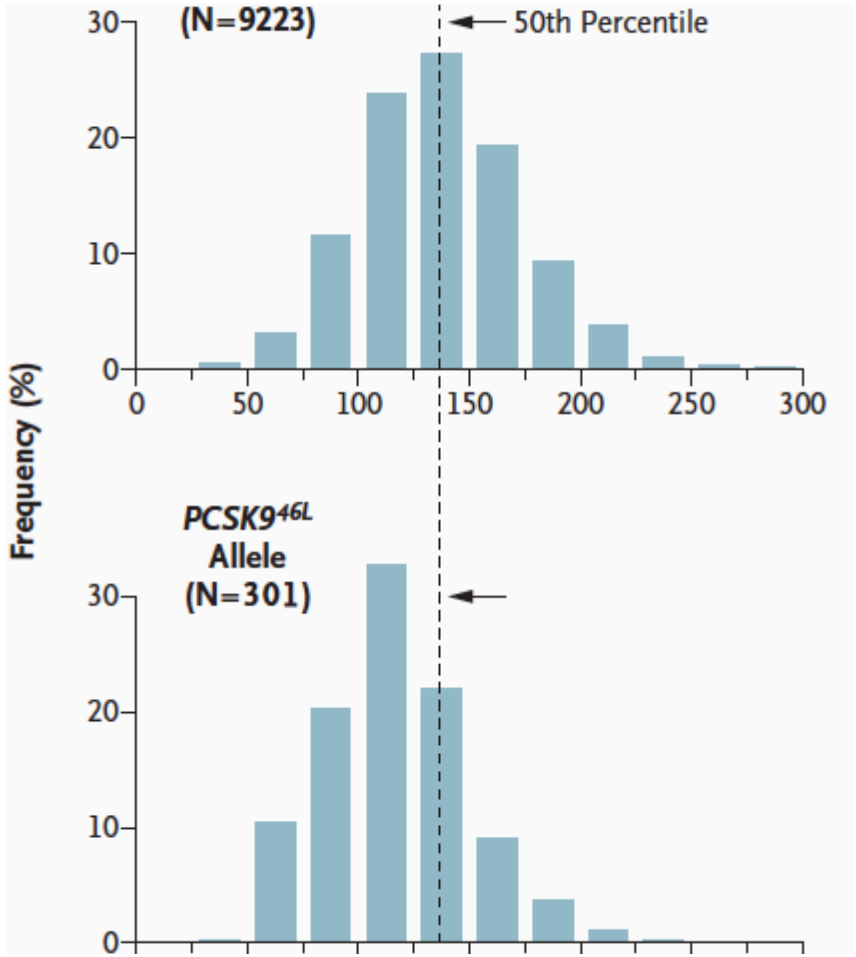
Lambert, *Curr Opin Lipidol* 2007

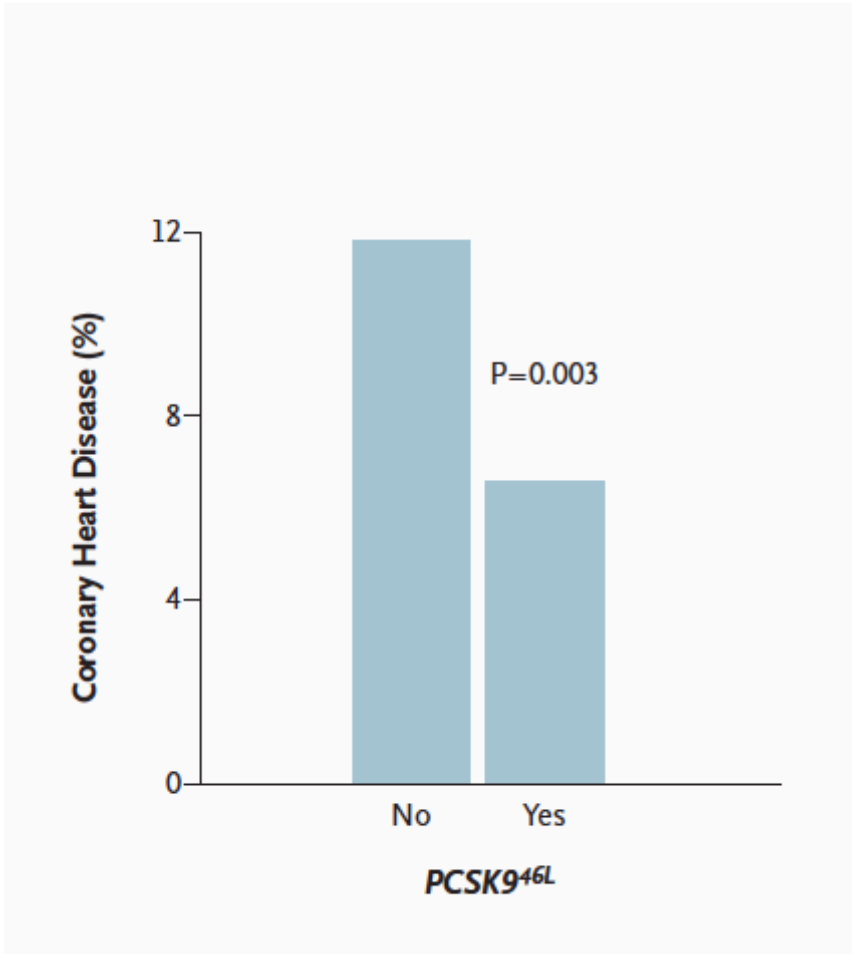
PCSK9 R46L – carried by 3% whites; 21 mg/dl lower LDL



Cohen, *N Engl J Med* 2006

PCSK9 R46L – 21 mg/dl lower LDL; 47% reduction in CAD risk

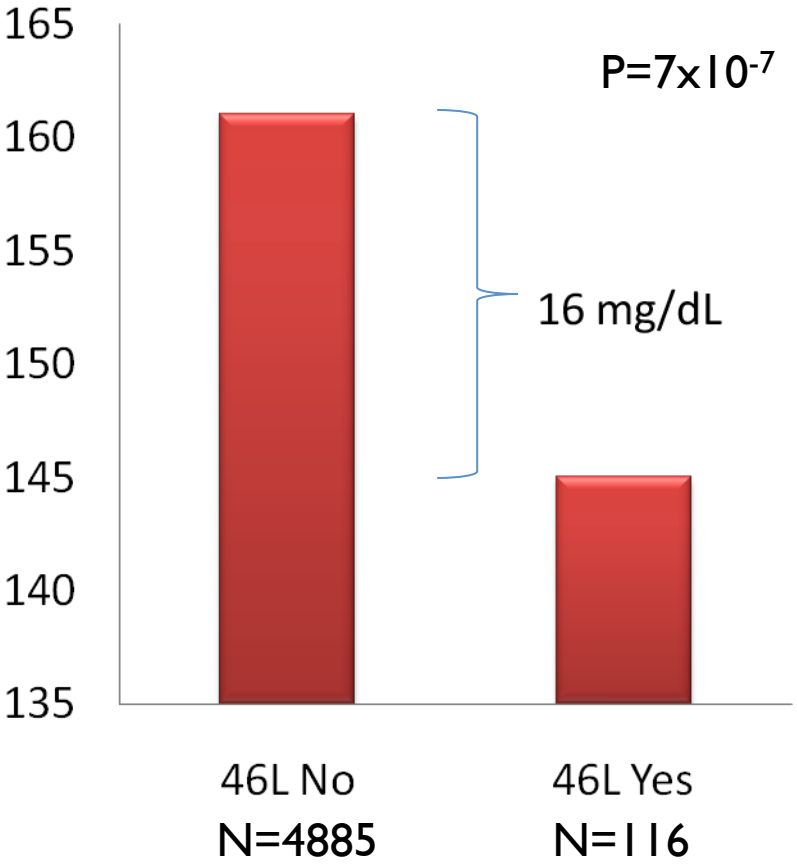




Cohen, *N Engl J Med* 2006

Replication PCSK9 R46L for LDL-C, early MI

Malmo Prospective Cohort



Kathiresan, *N Engl J Med* 2008a

MIGen Cases/Controls

Odds Ratio for MI:

0.54 (0.40 – 0.72)

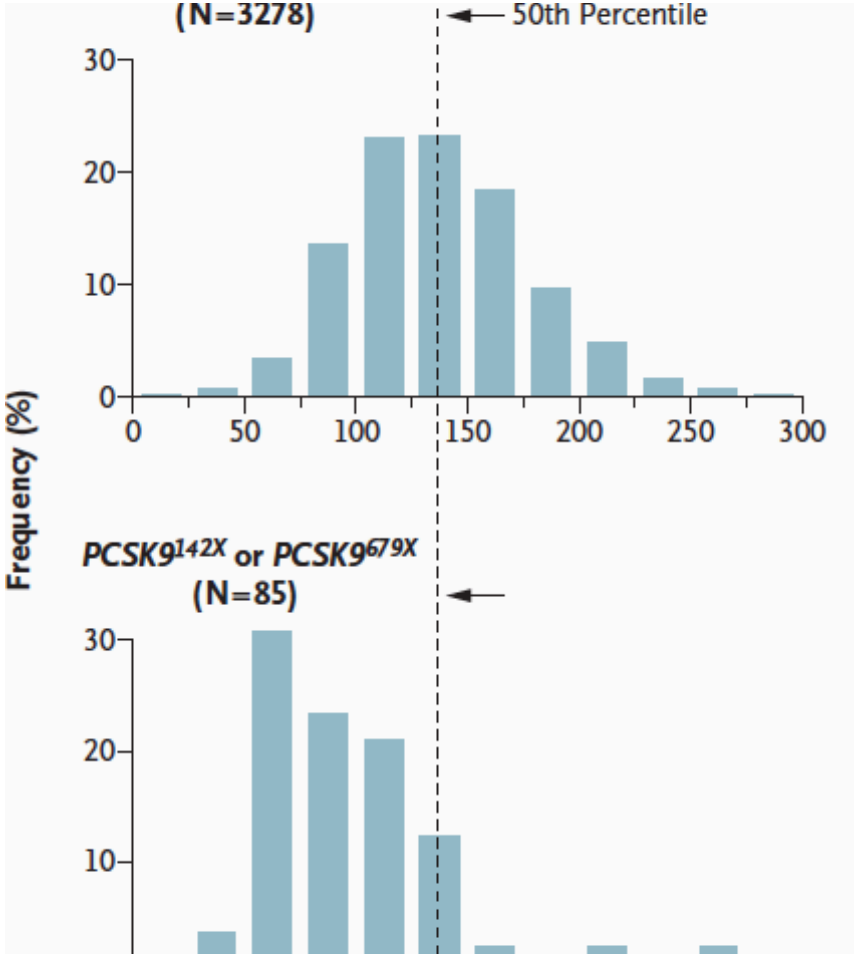
$P=2x10^{-5}$

N=3490 cases,

3497 controls

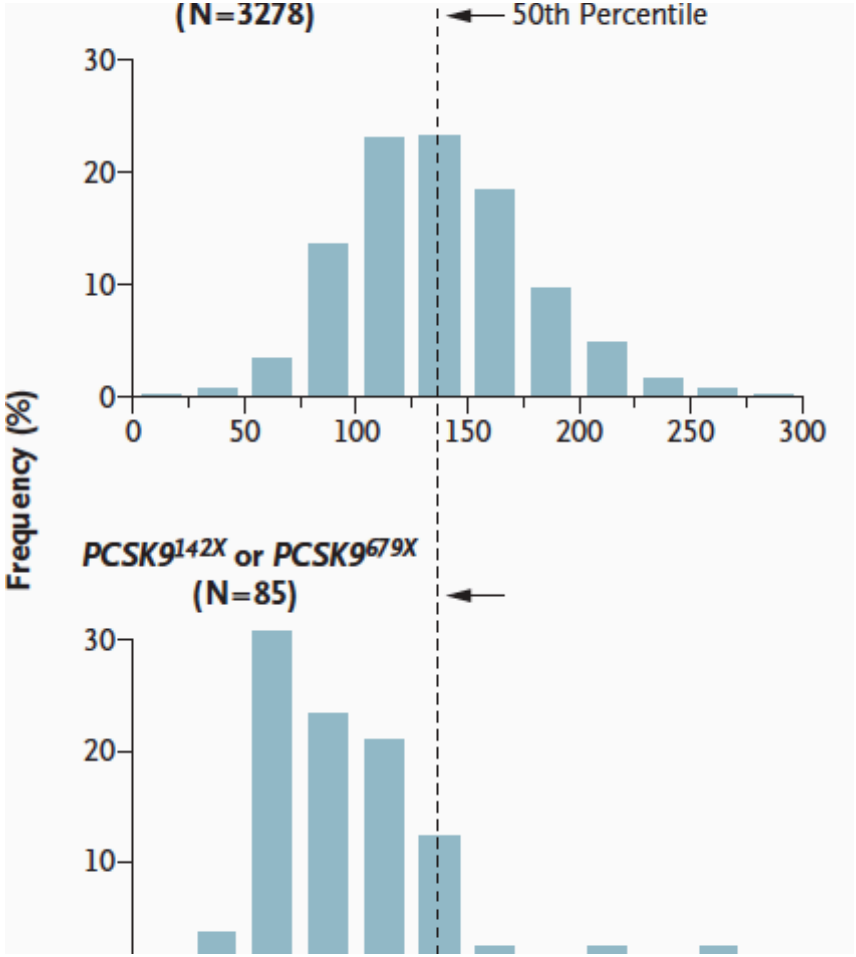
Kathiresan, *N Engl J Med* 2008b

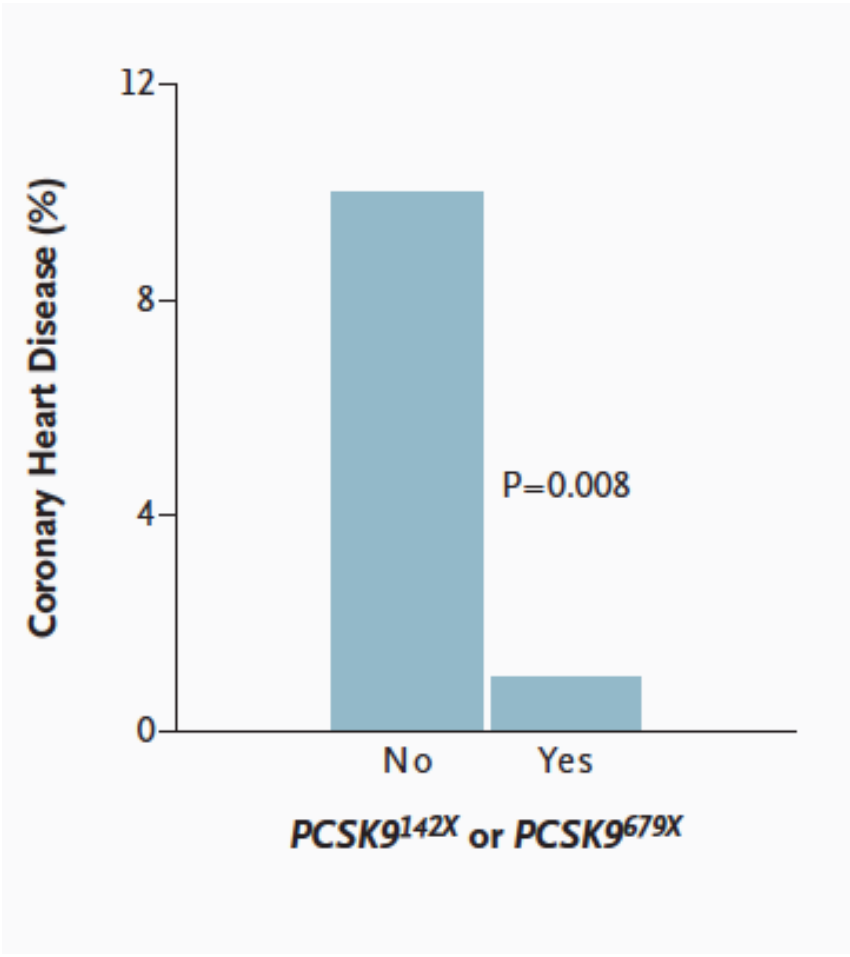
2% of blacks carry either of two null mutations; 38 mg/dl lower LDL-C



Cohen, *N Engl J Med* 2006

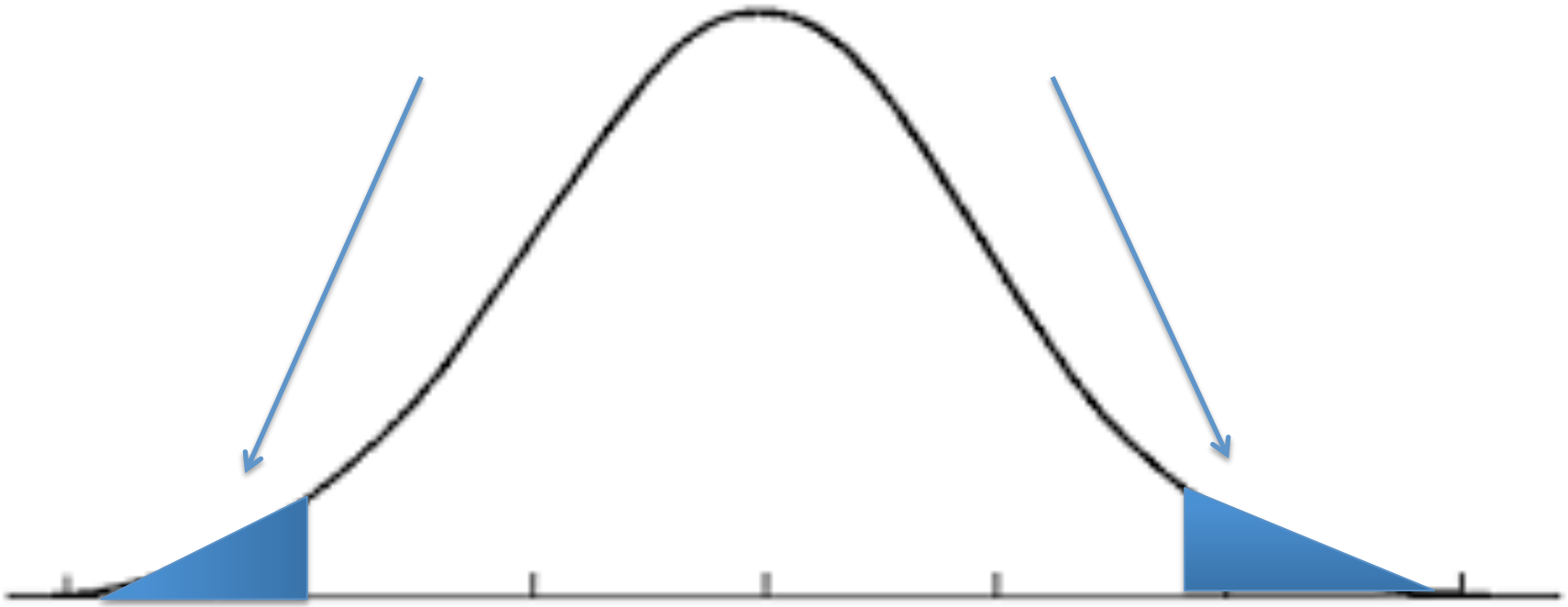
Null mutations - 38 mg/dl lower LDL-C; 88% reduction in CAD risk





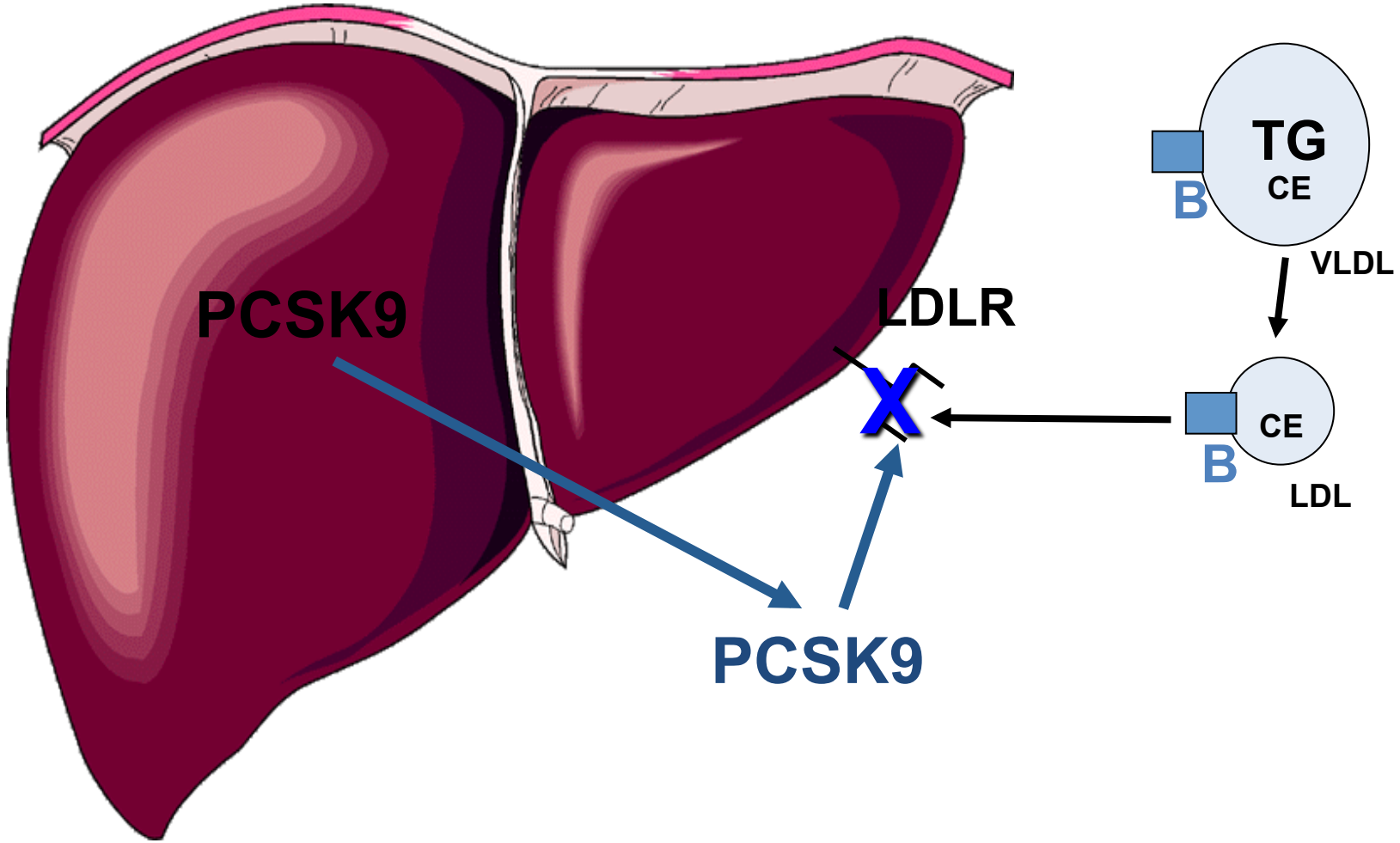
Cohen, *N Engl J Med* 2006

Inherited syndromes of extremes of LDL-C: story of PCSK9

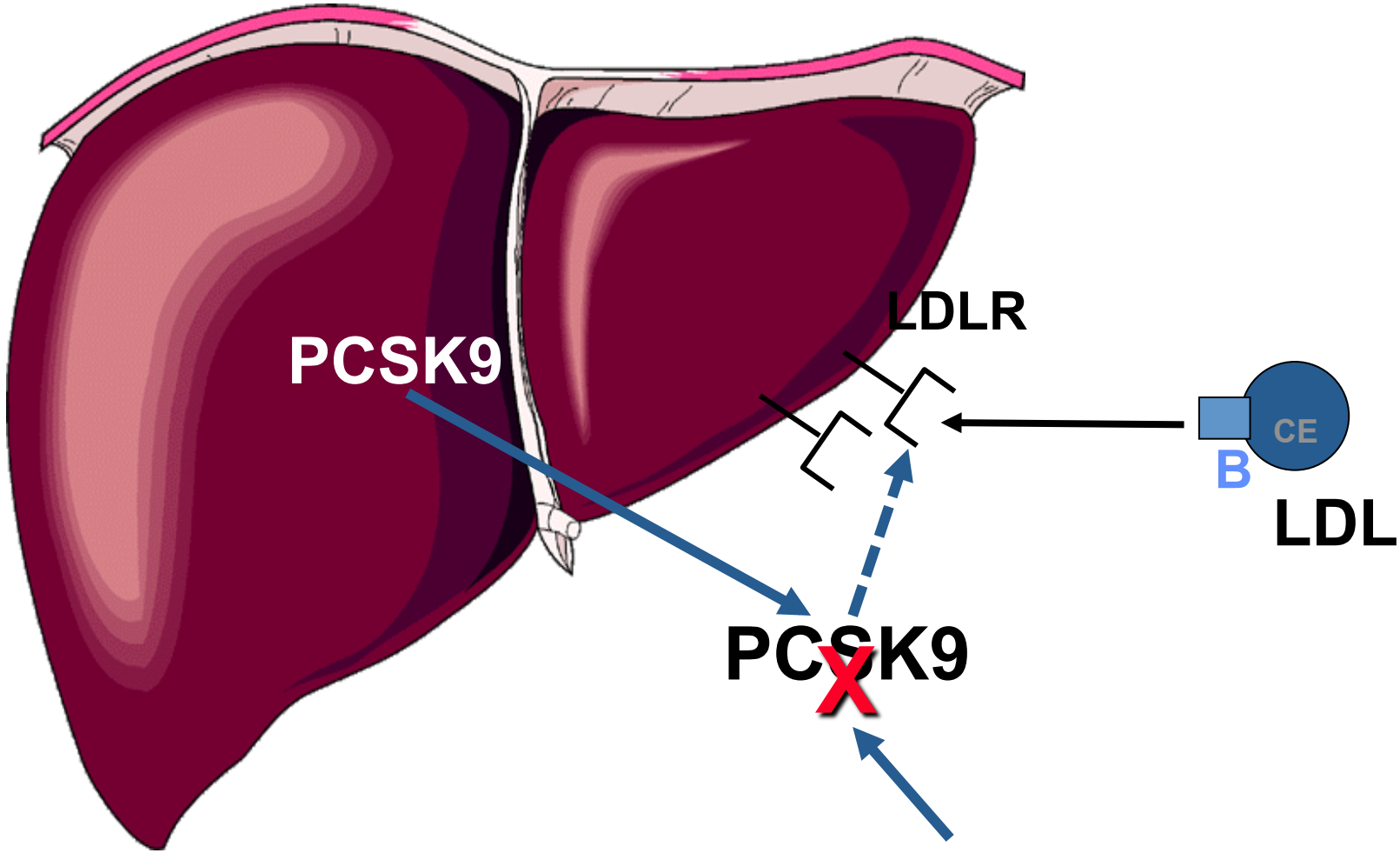


Abifadel, *Nature Genetics* 2003
Cohen, *N Engl J Med* 2006

Negative Post-Transcriptional Regulation of LDL Receptor by PCSK9



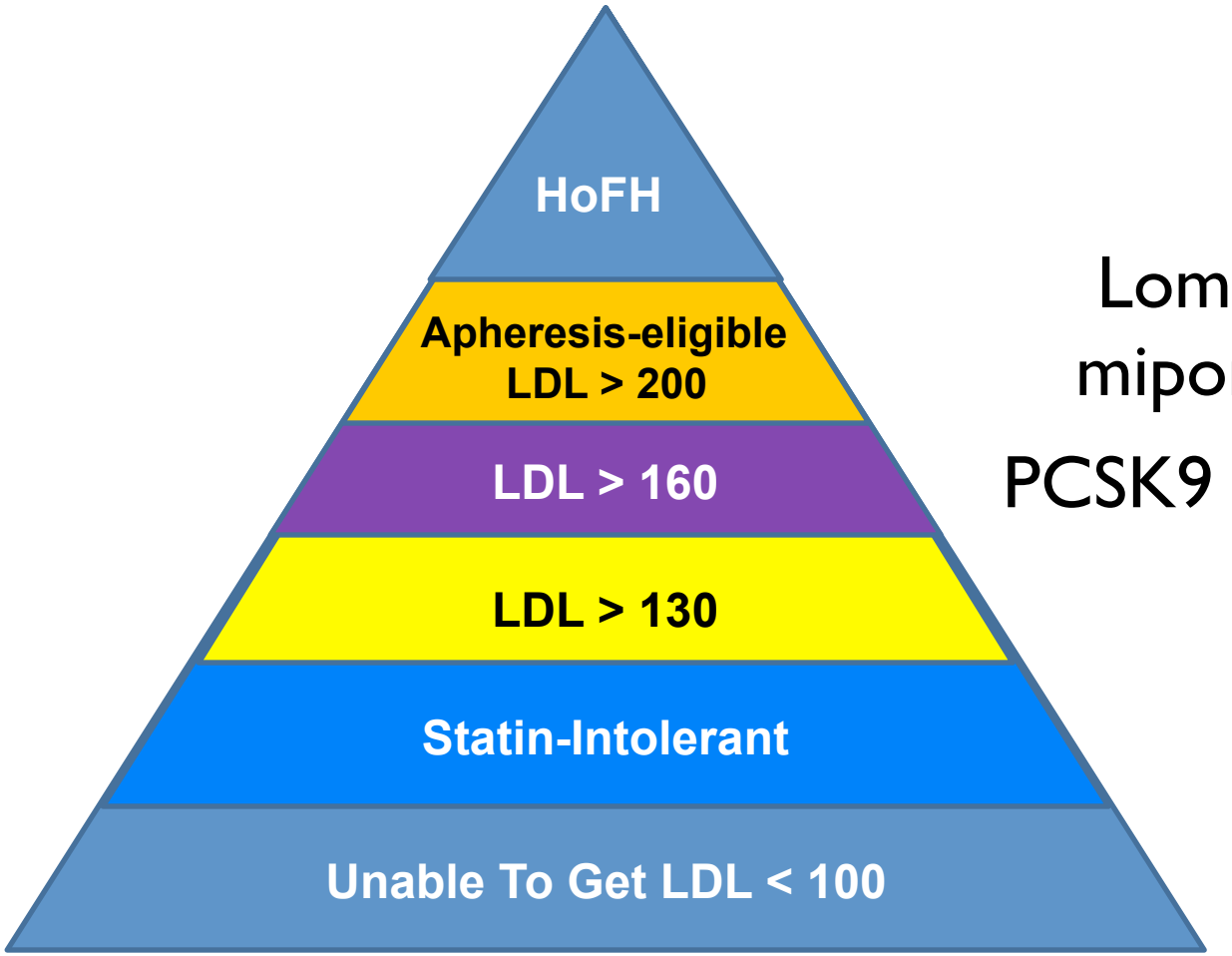
PCSK9 as a Novel Therapeutic Target



LDL-C and CAD

Target Gene (Drug)	**Genetics**		**Pharmacology**	
	LDL cholesterol	CAD	LDL cholesterol	CAD
HMCGR (statins)	✓	✓	✓	✓
NPC1L1 (ezetimibe)	✓		✓	Phase III trial ongoing
MTTP (lomitapide)	✓		✓	
APOB (mipomersen)	✓	✓	✓	
PCSK9 (Mabs and RNAi)	✓	✓	✓	Phase III trials ongoing

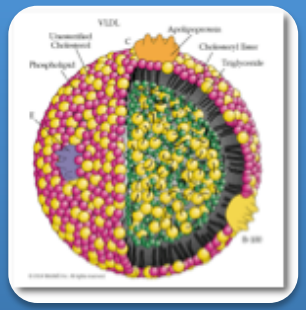
Addressing the unmet medical needs in the treatment of elevated LDL-C



Lomitapide
mipomersen

PCSK9 inhibitors

Conclusions



Human genetics reveals apoB-containing lipoproteins as key drivers of CAD

Mutations that lower LDL-C and reduce risk for CAD can point to new targets

Clinical Evidence for New Therapeutic Approaches to LDL-C Lowering

Evan A. Stein, MD, PhD
Director Emeritus
Metabolic & Atherosclerosis Research Center
Cincinnati, Ohio

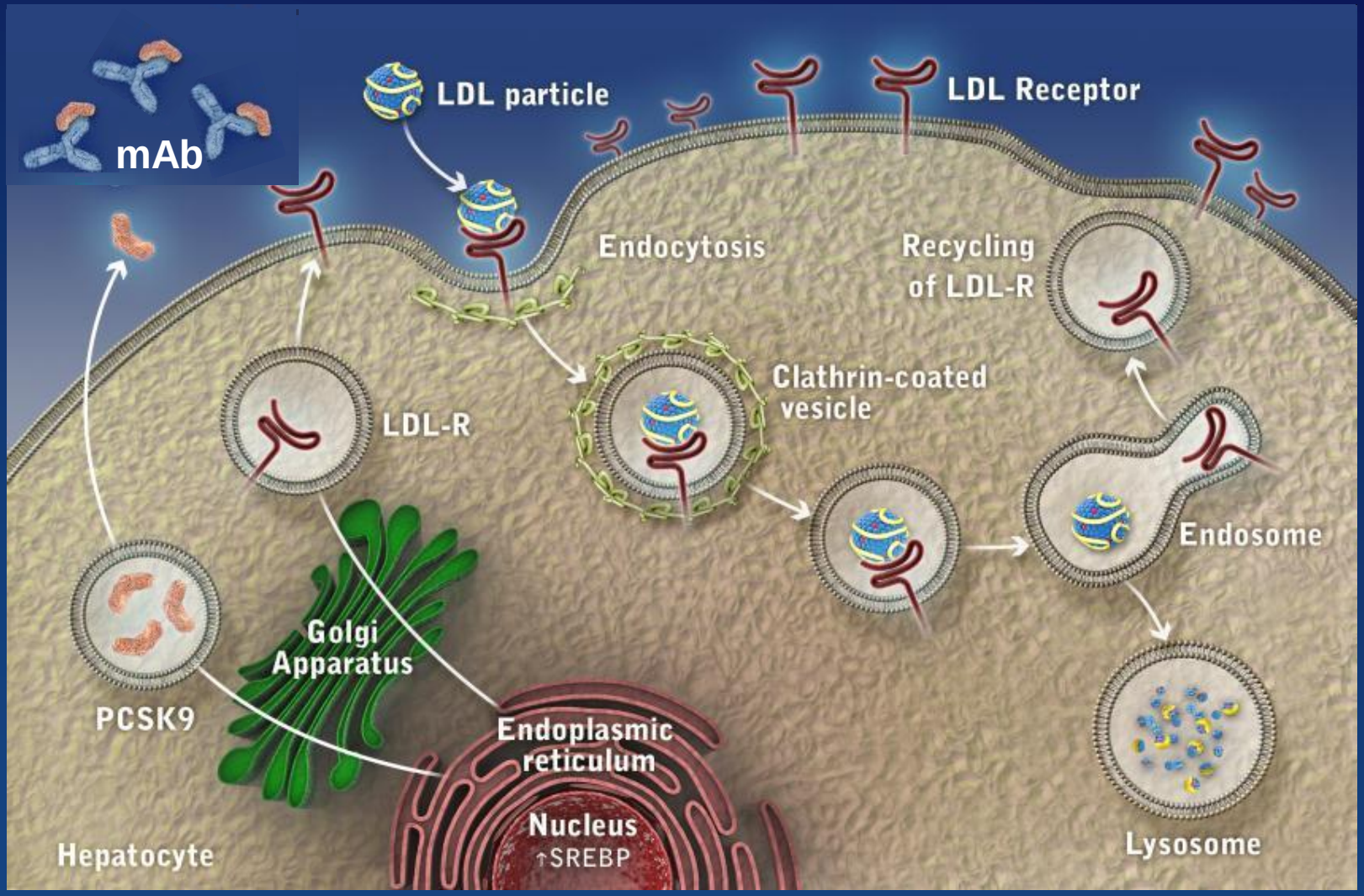
PCSK9 Inhibition: New Therapeutic Approaches to LDL-C Lowering

- PCSK9 inhibition efficacy in various pheno- and geno-types
  - Nonfamilial hypercholesterolemia
    - Monotherapy
    - Added to statins
    - Statin averse patients
  - Familial hypercholesterolemia
    - Heterozygous FH
    - Homozygous FH
- Effect on Lp(a)
- Safety and tolerability
- Outcomes trials

Approaches to Reducing PCSK9 Interaction with LDL Receptor

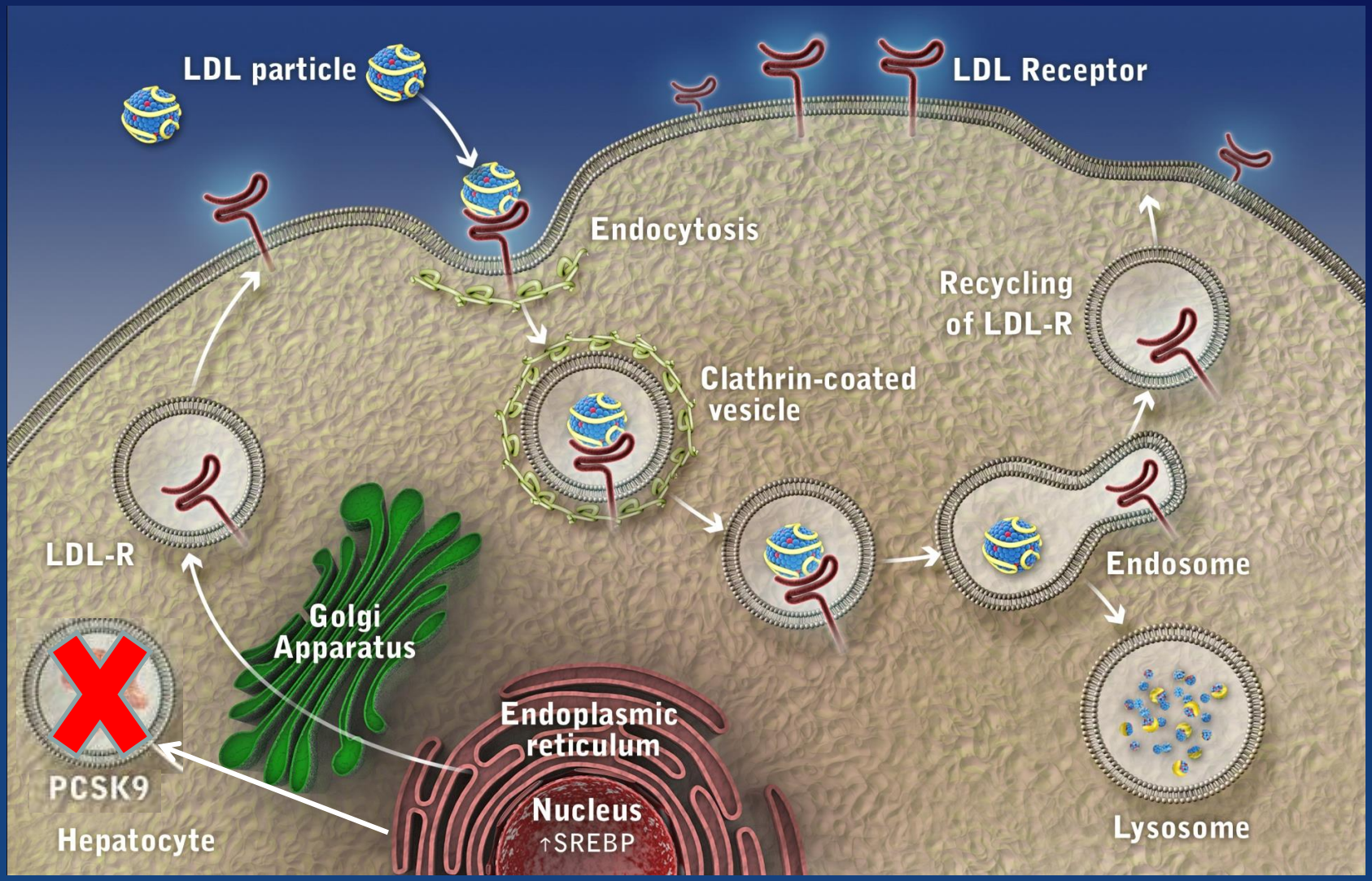
- **Bind plasma PCSK9**
  - **Monoclonal antibodies**
  - **Adnectins**
- **Reduce PCSK9 synthesis**
  - **siRNA**

Impact of a PCSK9 mAb on LDL Receptor Expression



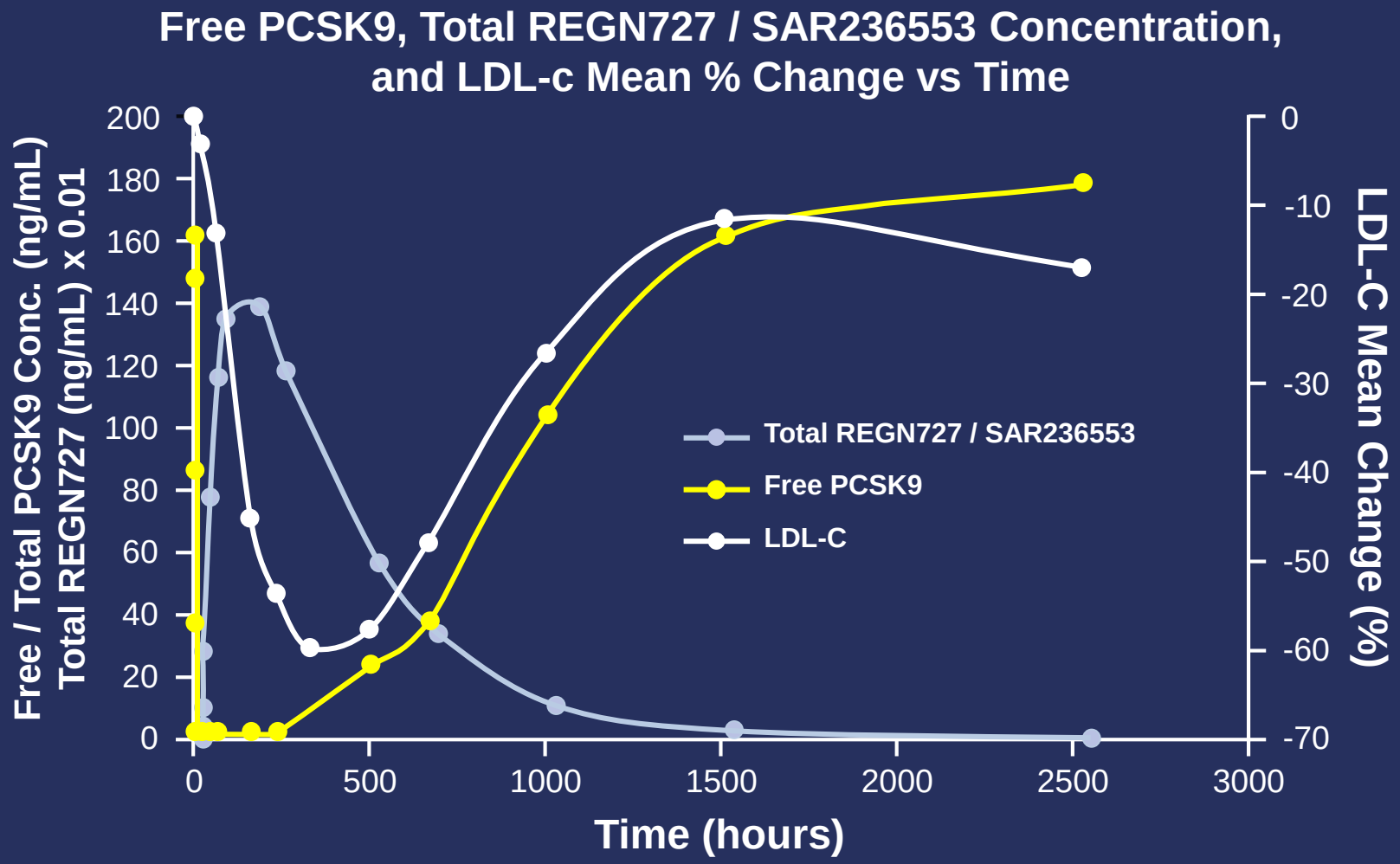
Adapted from Lambert et al. J Lipid Res. 2012;53(12):2515-24.

Impact of PCSK9 Synthesis Inhibition on LDL Receptor Expression



Adapted from Lambert et al. J Lipid Res. 2012;53:2515-24.

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



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

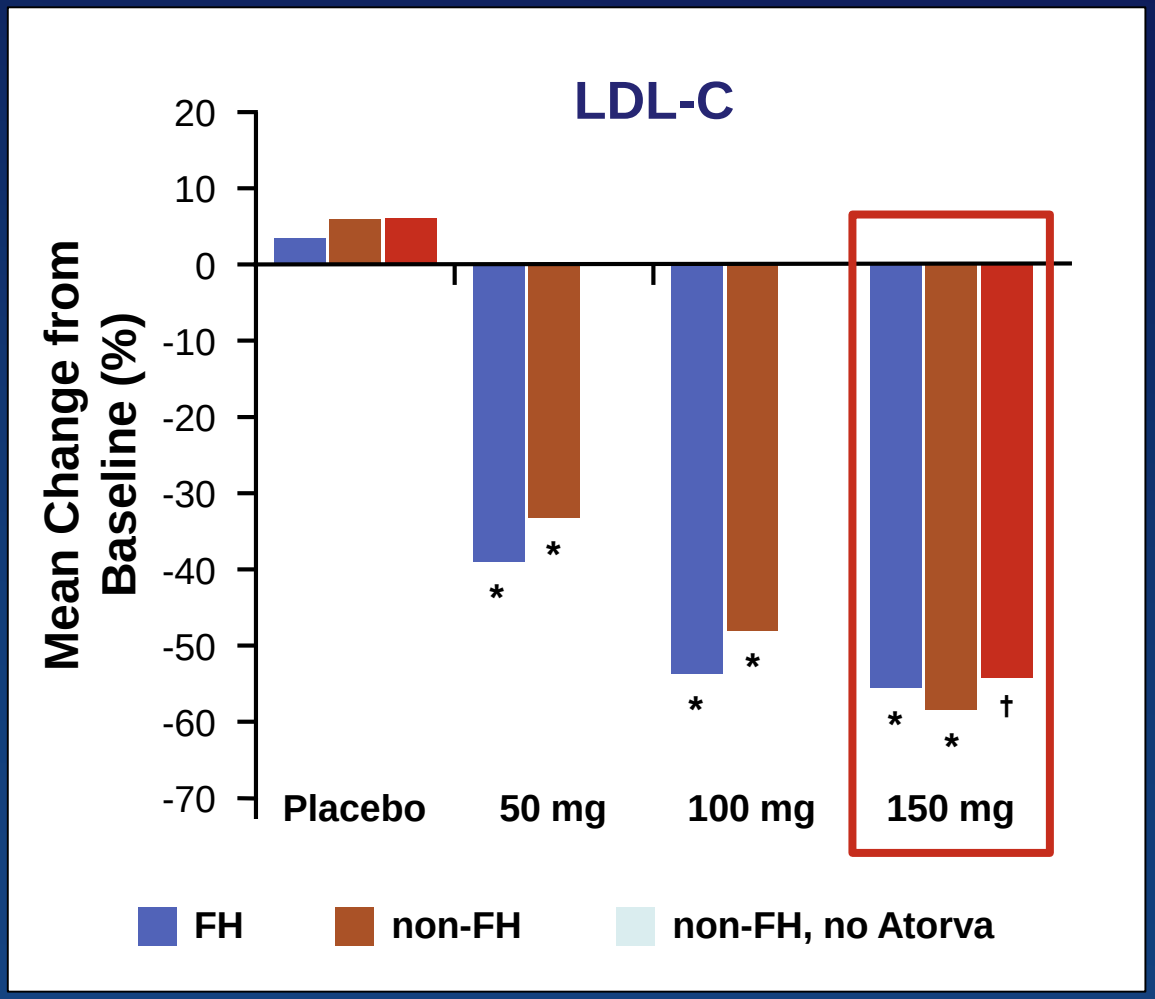
REGN727/SAR236553* Dose Groups

REGN727/SAR236553 Dose	Patient Group	Total # Pts (R727:Pbo)	HeFH Status	Screening LDL-C (mg/dL)	Atorvastatin Dose
50mg	1	7 (5:2)	HeFH	>100	10-40 mg QD
	2	10 (8:2)	Non-FH	>100	10-40 mg QD
100mg	3	7 (5:2)	HeFH	>100	10-40 mg QD
	4	10 (8:2)	Non-FH	>100	10-40 mg QD
150mg	5	7 (5:2)	HeFH	>100	10-40 mg QD
	6	10 (8:2)	Non-FH	>100	10-40 mg QD
	7	10 (8:2)	Non-FH	>130	None (Diet alone)

***REGN727/SAR236553 is same as alirocumab.**

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

LDL-C Response: Mean % Change from Baseline with Alirocumab



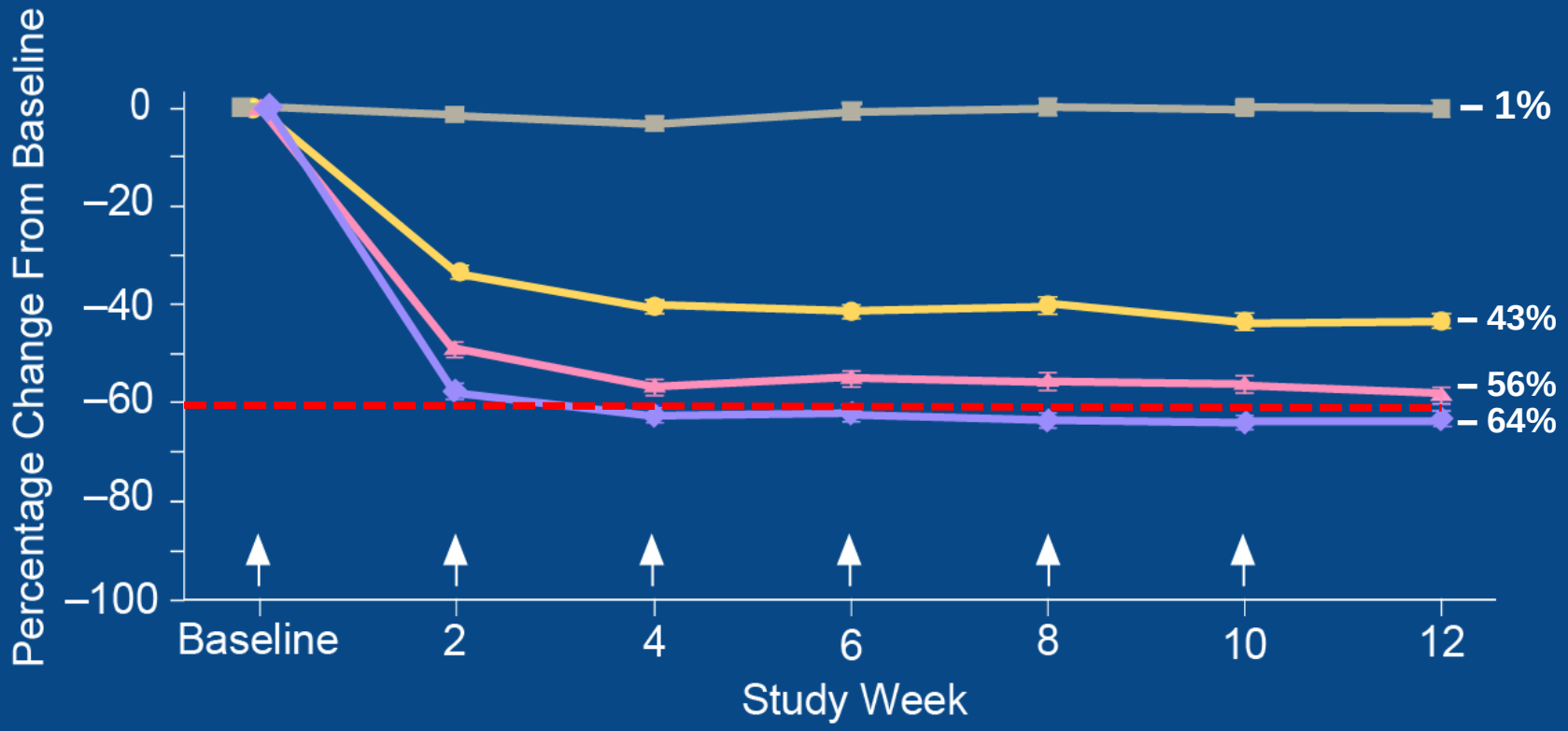
* P < 0.0001 vs. Placebo
† P < 0.01 vs. Placebo

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

Monoclonal Antibody (mAb) Inhibition of PCSK9

- Is there a limit to LDL-C reduction with a mAb?
- How long will effect last?

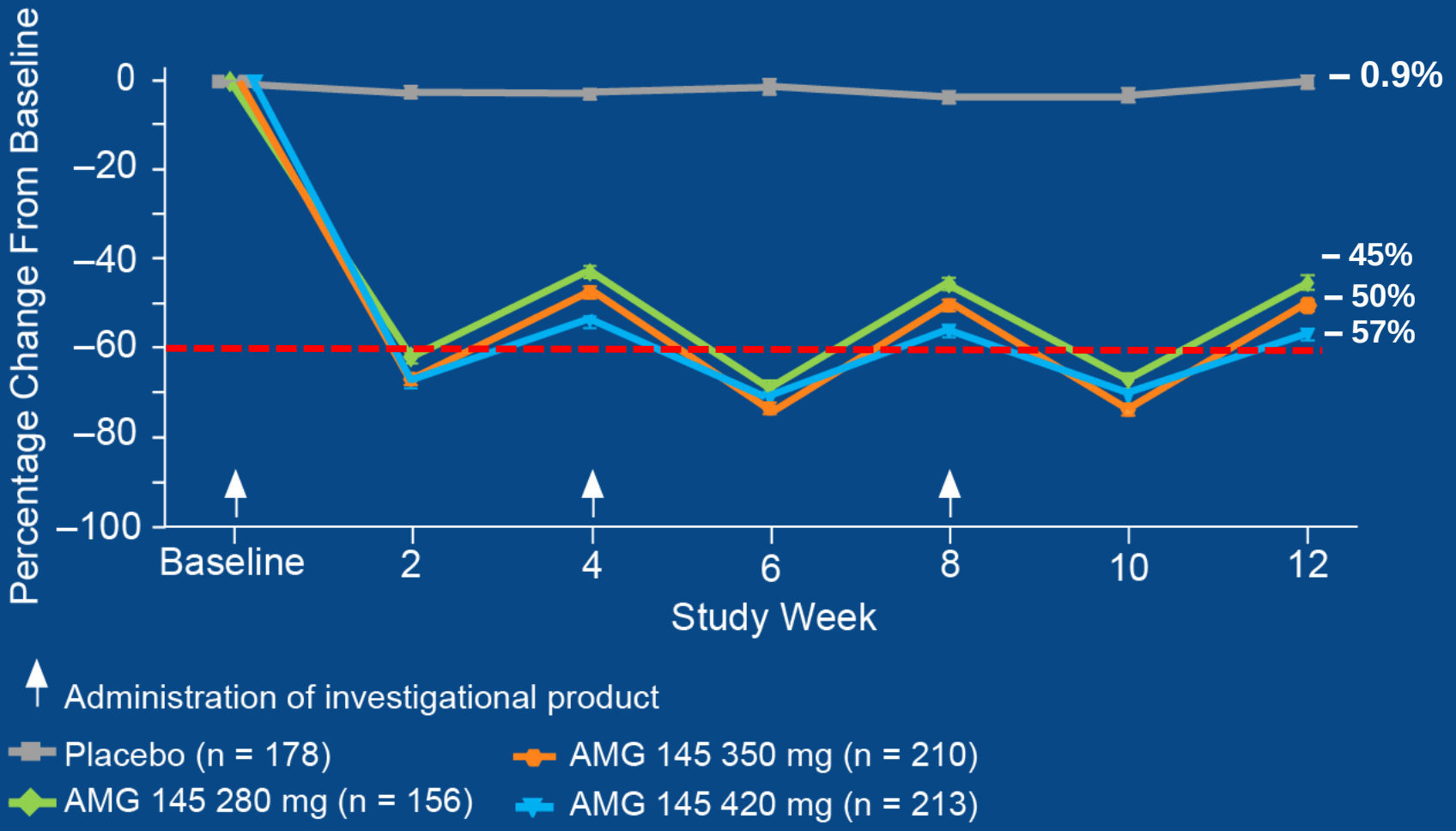
Evolocumab (AMG 145) Every 2 Weeks: LDL-C Percentage Change from Baseline



Mean percentage change from baseline in calculated LDL-C.

Stein et al Euro Heart J 2014 doi:10.1093/eurheartj/ehu085

Evolocumab (AMG 145) Every 4 Weeks: LDL-C Percentage Change from Baseline



Mean percentage change from baseline in calculated LDL-C.

Stein et al Euro Heart J 2014 doi:10.1093/eurheartj/ehu085

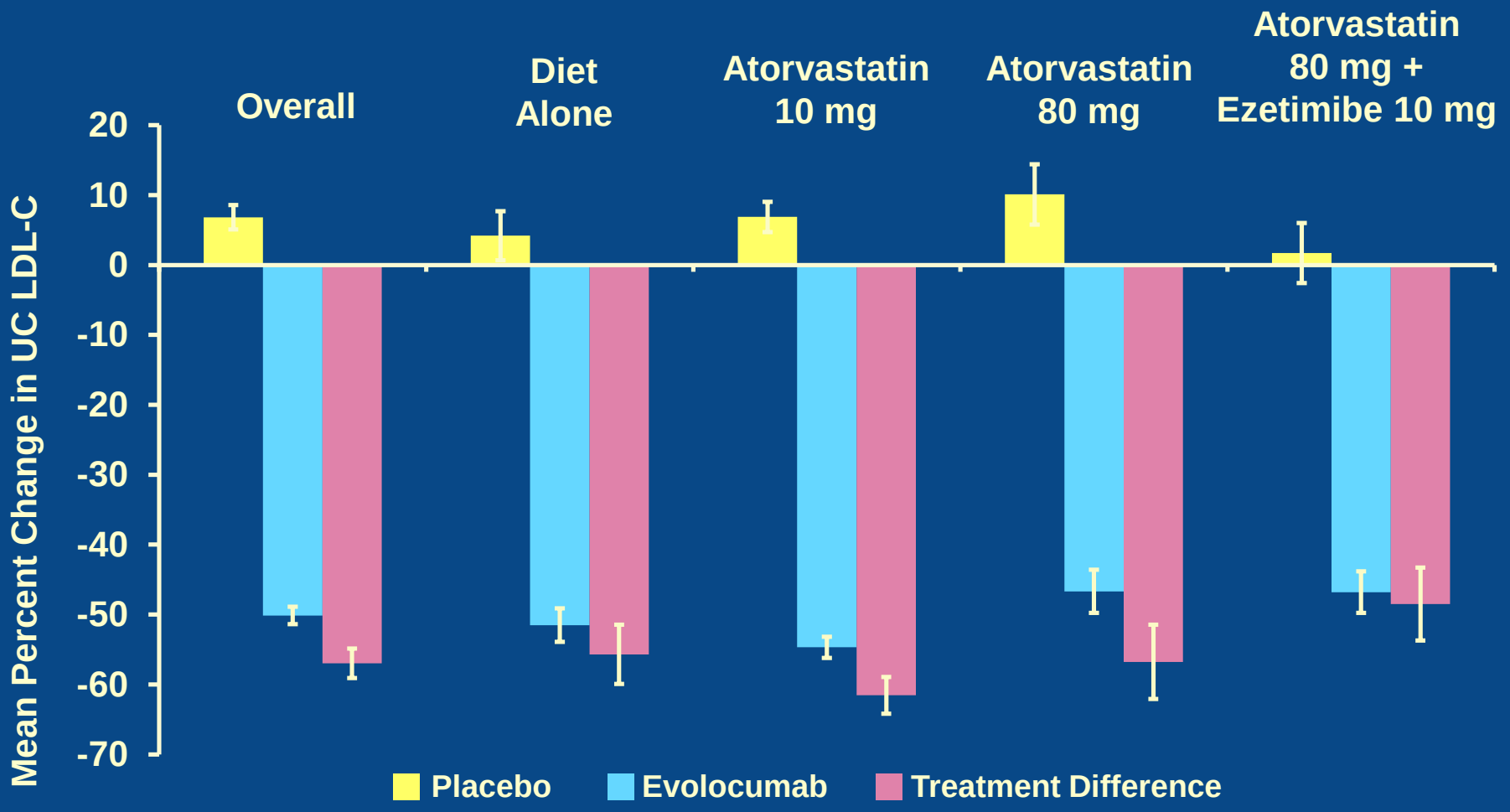
Inhibition of PCSK9 with mAb

- **Is there a limit to LDL-C reduction with a mAb?**
  - **Yes – once all free PCSK9 is bound, no additional LDL-C reductions occurs**
- **How long will effect last?**
  - **The larger the dose, the longer the duration of the effect**
  - **‘Rule of thumb’ is it requires 3 times higher dose to achieve same reduction in LDL-C when dosed every 4 weeks than is required for every 2 week dosing (e.g. 140 Q2W = 420 mg Q4W)**
  - **The physical limitation on the amount of mAb in 1 mL is ~150 mg, thus larger doses require larger injection volumes**

PCSK9 Inhibition: New Therapeutic Approaches to LDL-C Lowering

- PCSK9 inhibition efficacy in various pheno- and geno-types
  - Nonfamilial hypercholesterolemia
    - Monotherapy
    - Added to statins
    - Statin averse patients
  - Familial hypercholesterolemia
    - Heterozygous FH
    - Homozygous FH
- Effect on Lp(a)
- Safety and tolerability
- Outcomes trials

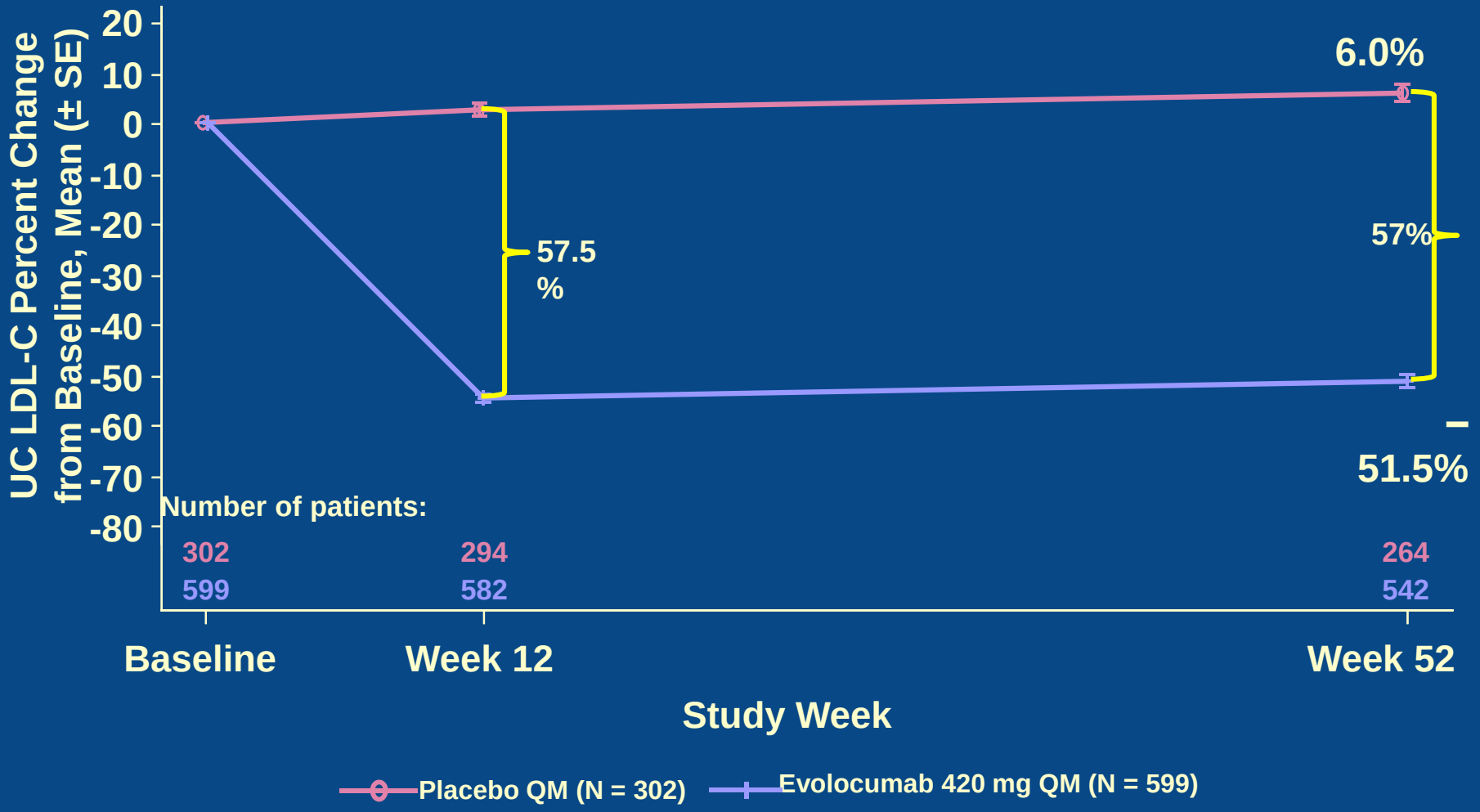
DESCARTES: % Change in LDL-C from Baseline in Patients on Various Background Treatments



Error bars represent standard error for treatment difference
Treatment difference are least squares mean derived from a repeated measures model
UC LDL-C at week 52

Blom et al NEJM 2014:370:1809-19

DESCARTES: Long-term Stability of LDL-C Reduction



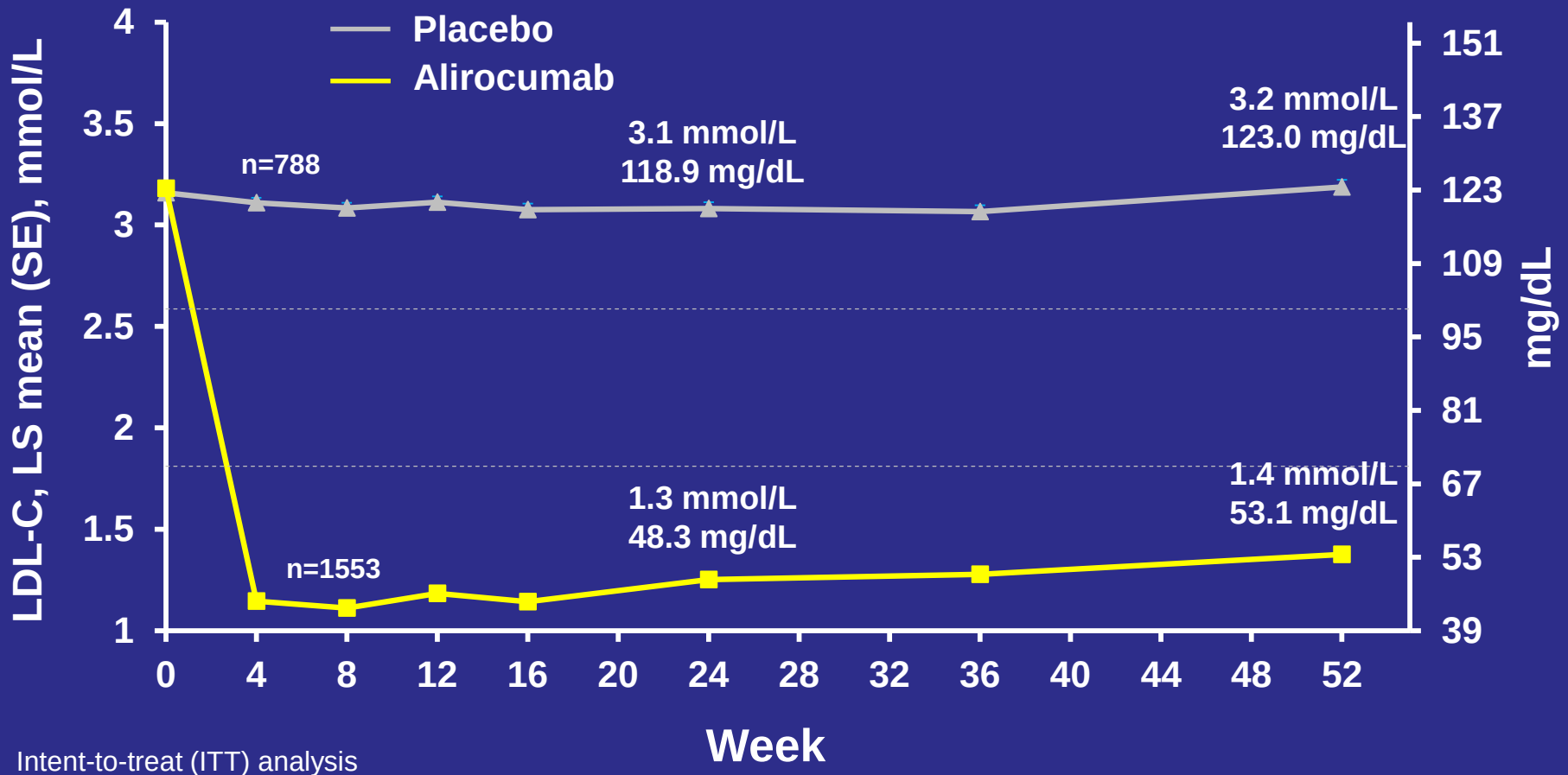
FAS = Full analysis set, UC = Ultracentrifugation

Blom et al NEJM 2014:370:1809-19

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

Achieved LDL-C Over Time

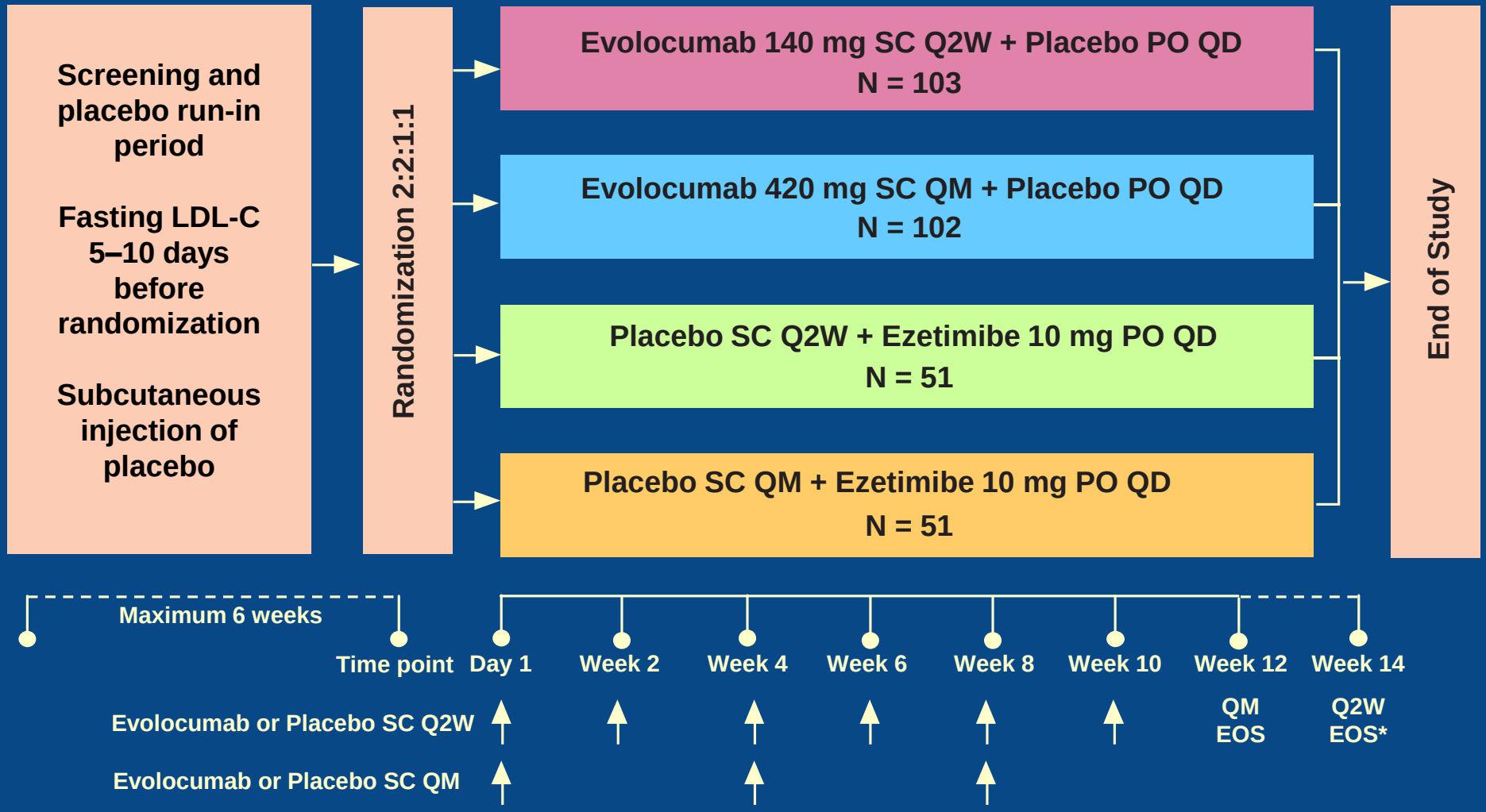
All patients on background of maximally tolerated statin ±other lipid-lowering therapy



Intent-to-treat (ITT) analysis

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

GAUSS-2 Study Design



- Prior intolerance to ≥2 statins: LDL-C above NCEP ATP III risk category goal : Weekly dose 7 times the smallest available tablet strength or less

Stroes et al J Am Coll Cardiol. 2014;63:2541-48

GAUSS-2: Statin Intolerance History

	Biweekly		Monthly	
	PBO Q2W + EZE QD (N = 51)	Evolocumab 140 mg Q2W + PBO QD (N = 103)	PBO QM + EZE QD (N = 51)	Evolocumab 420 mg QM + PBO QD (N = 102)
Number of intolerable statins, %				
2	**100**	**100**	**100**	**100**
3	74	81	76	80
≥4	26	19	24	20
Worst muscle-related side effect*, %				
Myalgia	78	78	88	79
Myositis	22	19	8	19
Rhabdomyolysis	0	2	4	2
Any lipid-lowering therapy at baseline, %	29	33	31	36
Any statin at baseline	18	18	20	17

*Data missing for one patient in the evolocumab Q2W arm. EZE, ezetimibe; PBO, placebo; Q2W, biweekly; QM, monthly; QD, daily.

Stroes et al J Am Coll Cardiol. 2014;63:2541-48

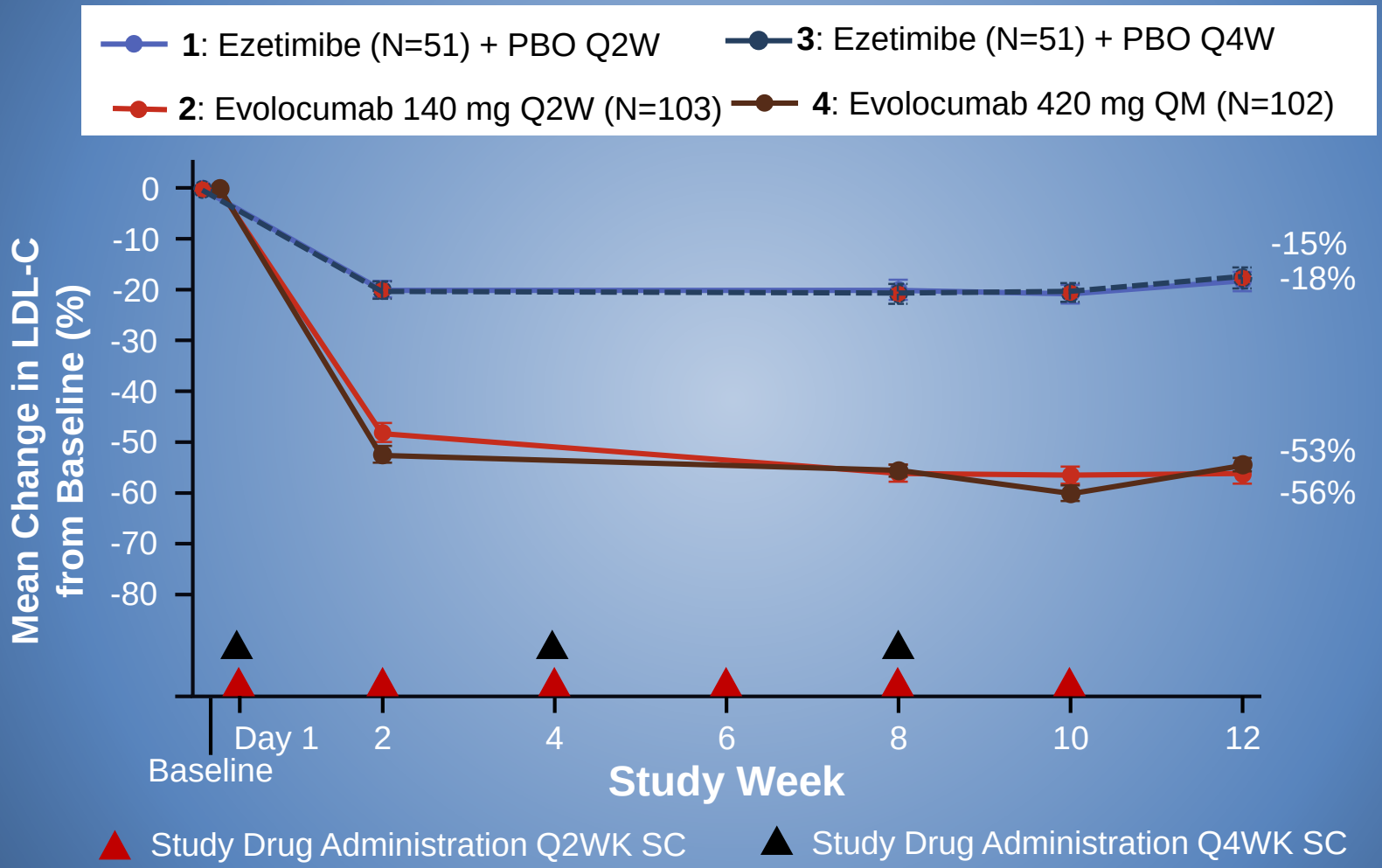
GAUSS-2: Key Baseline Lipids

	Biweekly		Monthly	
	PBO Q2W EZE QD (N = 51)	Evolocumab 140 mg Q2W + PBO QD (N = 103)	PBO QM + EZE QD (N = 51)	Evolocumab 420 mg QM + PBO QD (N = 102)
LDL-C*, mg/dL, mean (SD)	**195 (64)**	**192 (57)**	**195 (52)**	**192 (61)**
ApoB, md/dL, mean (SD)	140 (37)	140 (32)	140 (31)	133 (32)
Lp(a), nmol/L, median (Q1,Q3)	57 (22, 205)	39 (10, 101)	26 (7, 181)	31 (9, 80)
TG, mg/dL, median (Q1,Q3)	170 (120, 243)	165 (123, 224)	168 (124, 240)	139 (103, 190)
PCSK9, ng/mL, mean (SD)	317 (125)	285 (80)	295 (98)	266 (95)

*Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation when calculated LDL-C was <40 mg/dL (1.0 mmol/L) or triglyceride levels were >400 mg/dL (3.9 mmol/L).
EZE, ezetimibe; PBO, placebo; Q2W, biweekly; QM, monthly; QD, daily; TG, triglycerides.

Stroes et al J Am Coll Cardiol. 2014;63:2541-48

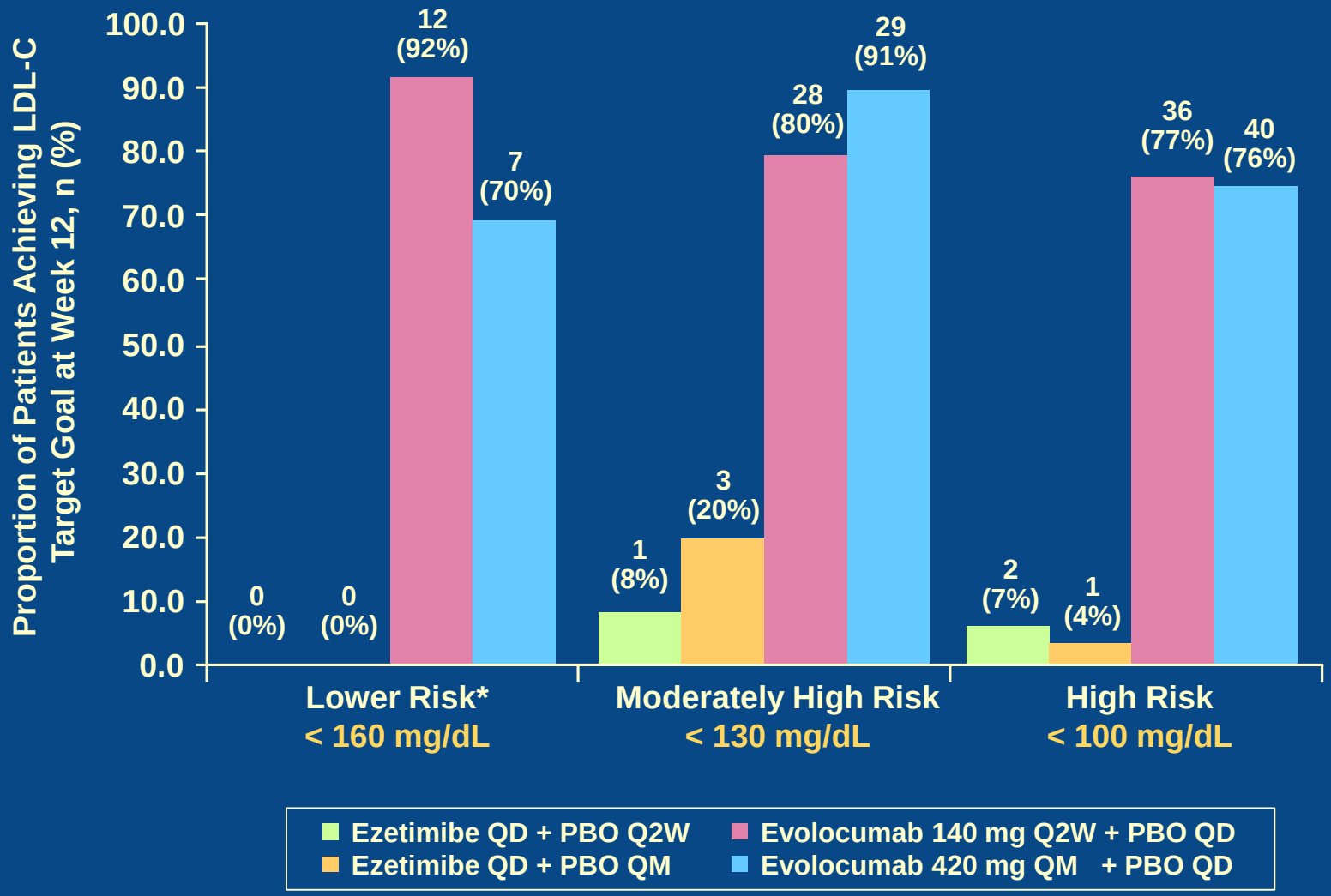
GAUSS-2: LDL-C Response to Evolocumab Q2WK and Q4WK



Vertical lines represent the standard error around the mean. Plot is based on observed data with no imputation for missing values.

Stroes et al J Am Coll Cardiol. 2014;63:2541-48

GAUSS-2: LDL-C Goal Achievement at Week 12



*Combination of NCEP ATP IIII moderate and low risk categories.
Rate based on subjects with observed values at Week 12 and LDL-C above target goal at baseline

Stroes et al J Am Coll Cardiol. 2014;63:2541-48

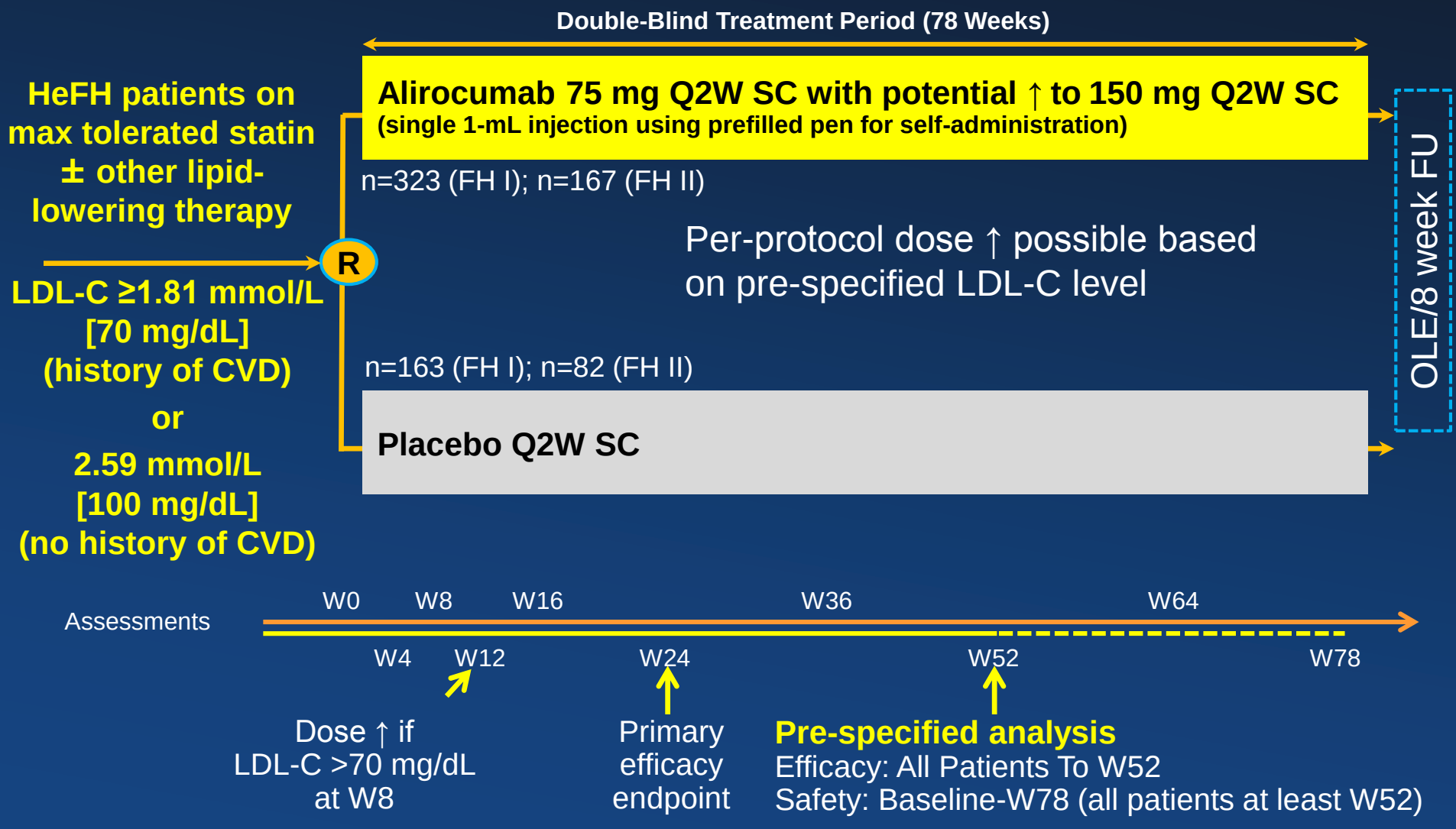
PCSK9 Inhibition: New Therapeutic Approaches to LDL-C Lowering

- PCSK9 inhibition efficacy in various pheno- and geno-types
  - Nonfamilial hypercholesterolemia
    - Monotherapy
    - Added to statins
    - Statin averse patients
  - Familial hypercholesterolemia
    - Heterozygous FH
    - Homozygous FH
- Effect on Lp(a)
- Safety and tolerability
- Outcomes trials

PCSK9 Monoclonal Antibodies in FH

- Will initial phase 1 results seen in small group of HeFH from one center be maintained in larger and more diverse HeFH populations with additional LDLr defects?
- Will PCSK9 monoclonal antibodies be effective in homozygous FH ?

ODYSSEY FH I and FH II Study Design

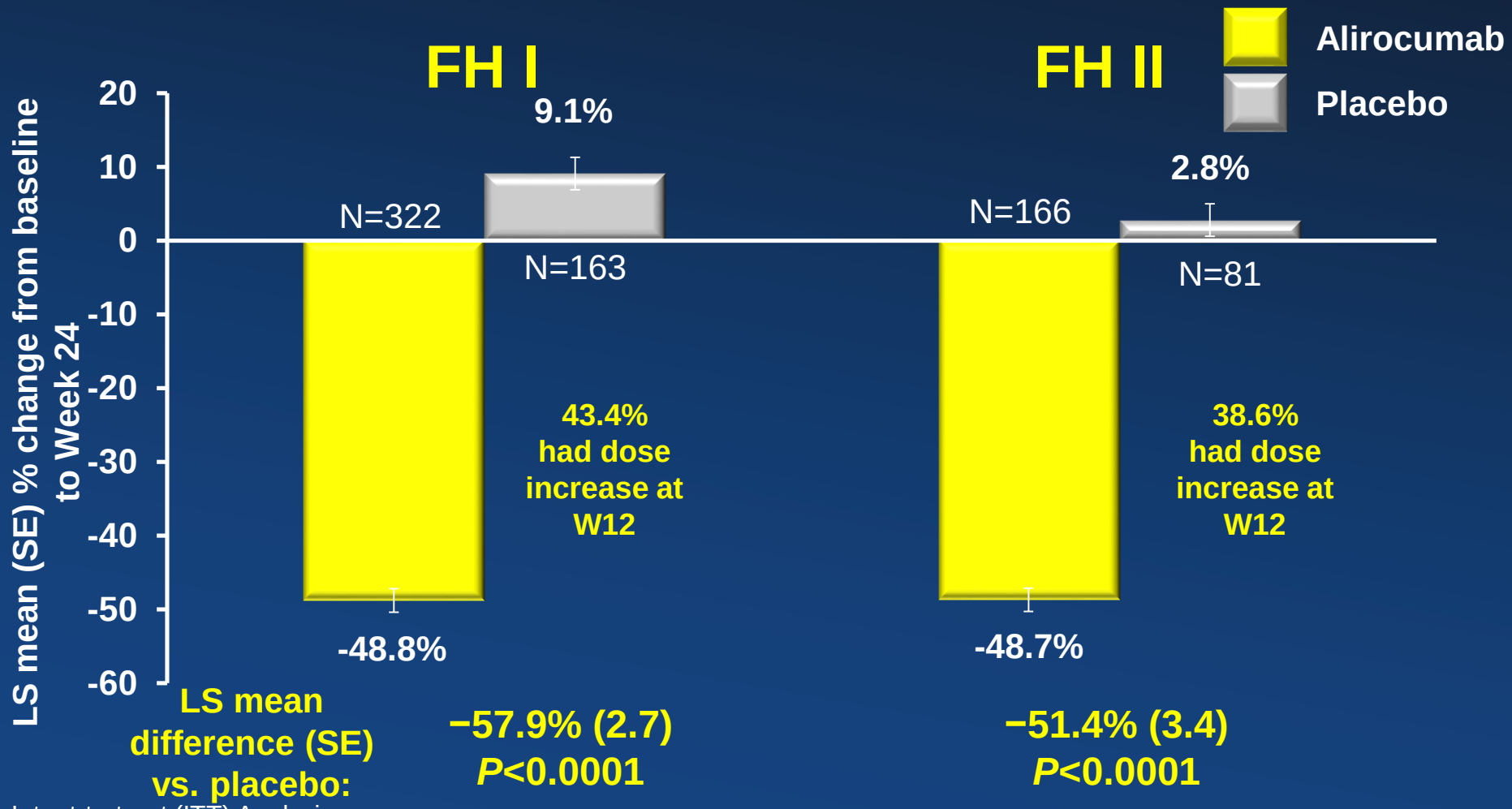


Clinicaltrials.gov identifiers: ODYSSEY FH I: NCT01623115; ODYSSEY FH II: NCT01709500.

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

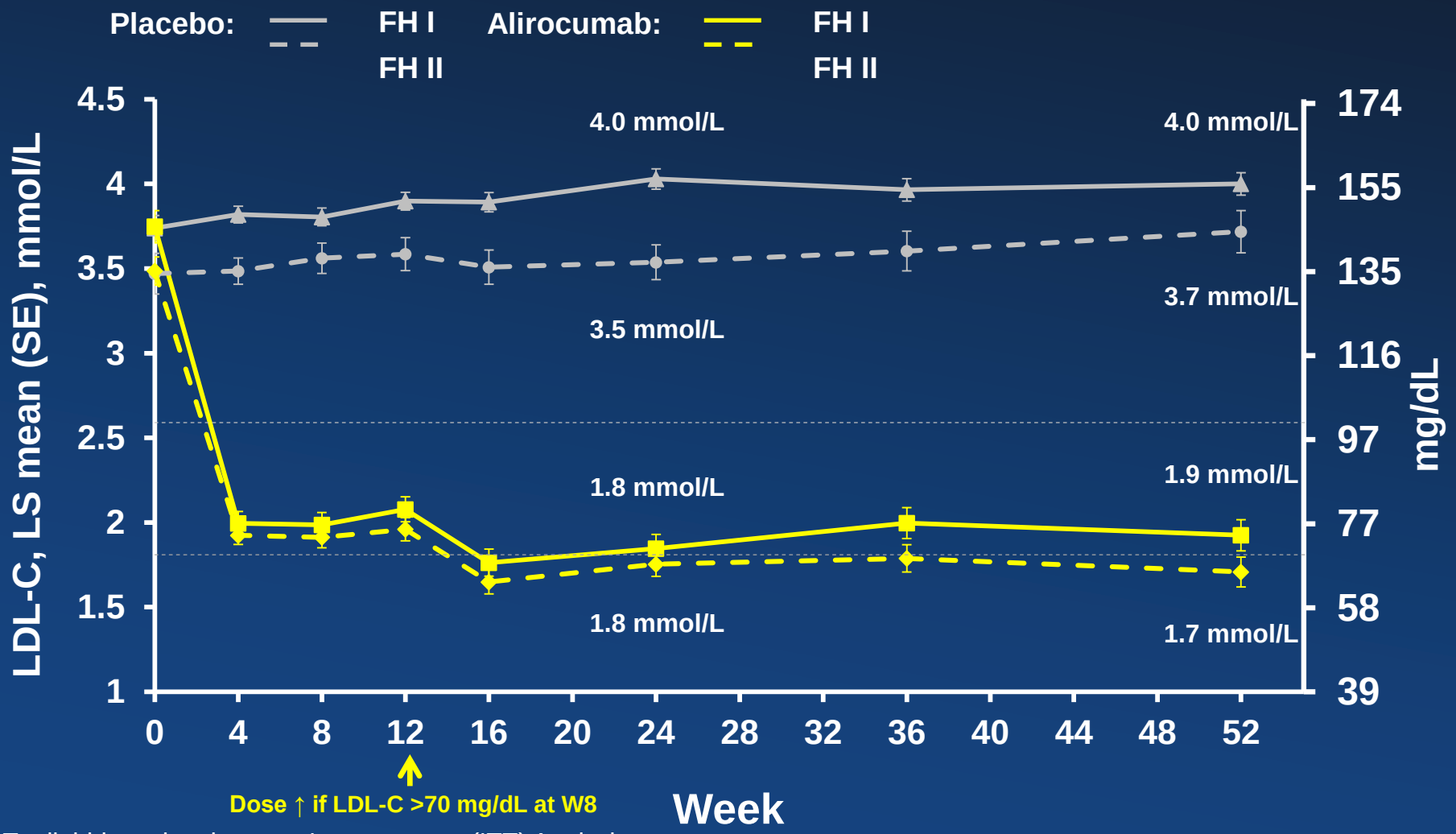


Intent-to-treat (ITT) Analysis.

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

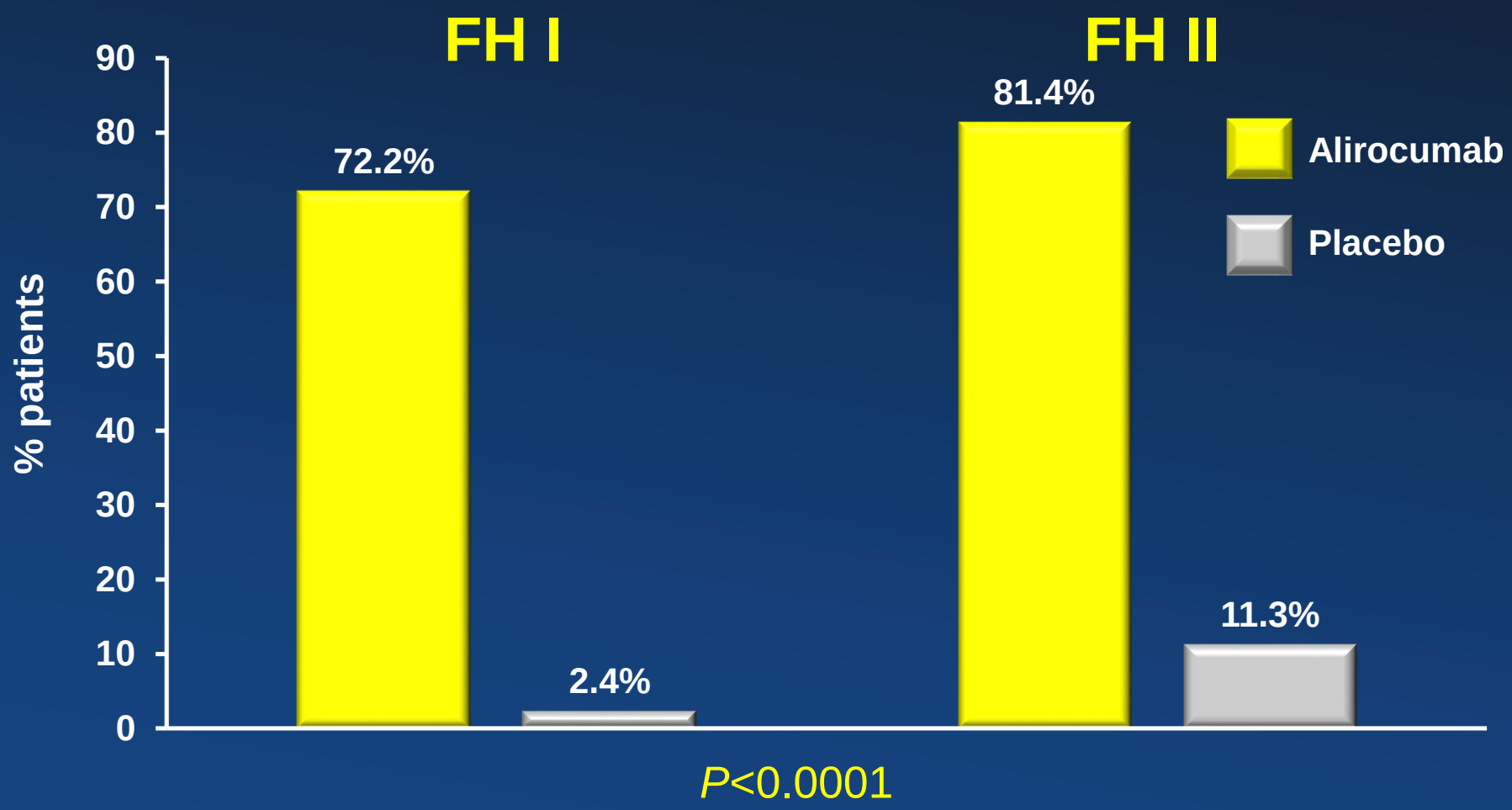


LLT = lipid-lowering therapy. Intent-to-treat (ITT) Analysis.

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

ODYSSEY FH I and FH II Study: LDL-C Goal Attainment

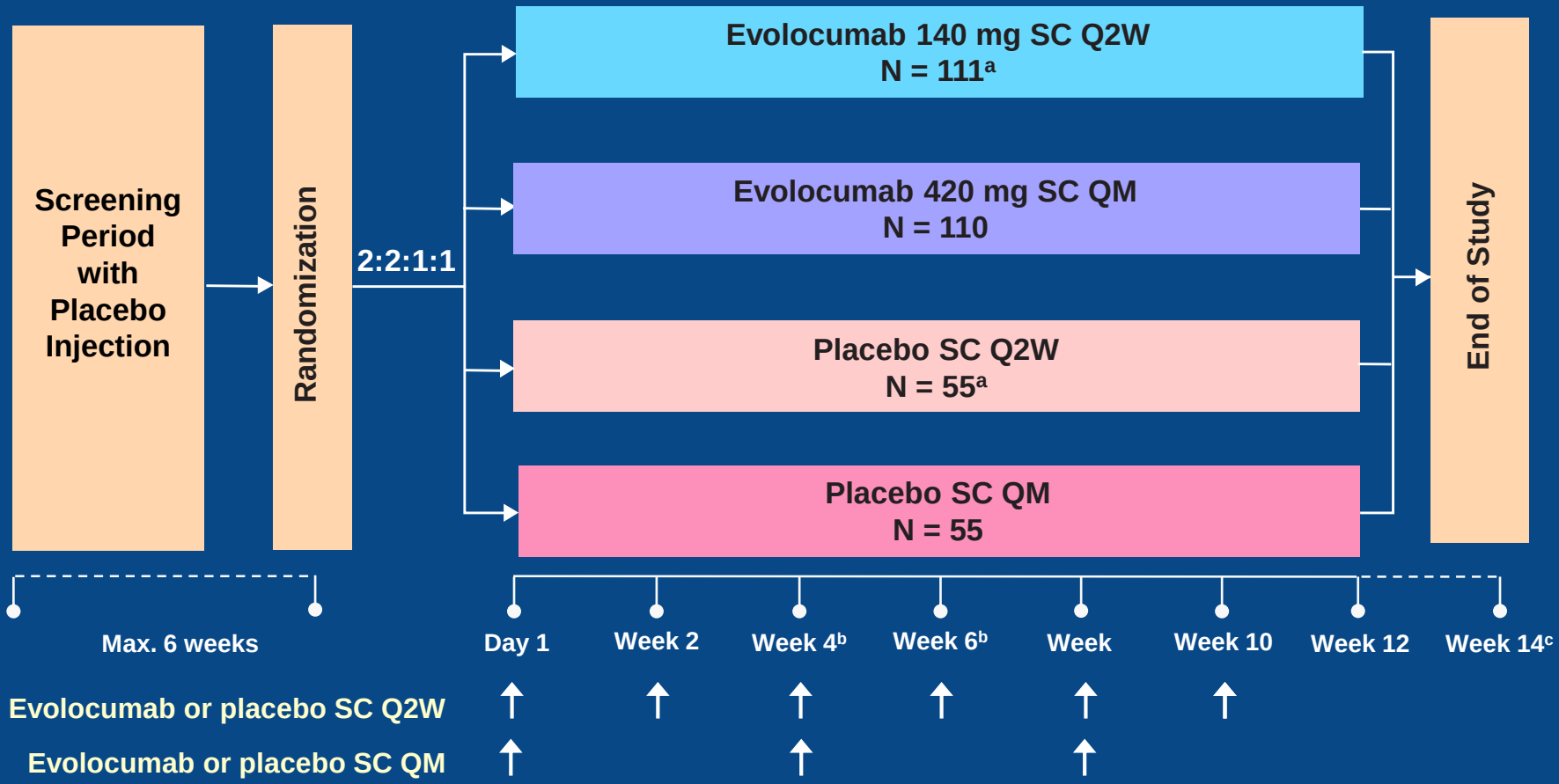
Proportion of patients reaching LDL-C goal† at Week 24



†Very high-risk: <1.81 mmol/L (70 mg/dL); high-risk: <2.59 mmol/L (100 mg/dL). LLT = lipid-lowering therapy.

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

RUTHERFORD-2 Study: Evolocumab in HeFH



[a] N's are number of patients randomized. One patient in each of the placebo Q2W and evolocumab Q2W groups did not receive any doses of the study drug and were not included in the analyses

[b] Injections at weeks 4 and 6 were done at home

[c] Week 14 was a follow-up call for Q2W patients to capture adverse events and concomitant medications

Q2W, biweekly; QM, monthly; SC, subcutaneous

Raal et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399-4

RUTHERFORD-2: Baseline Lipids

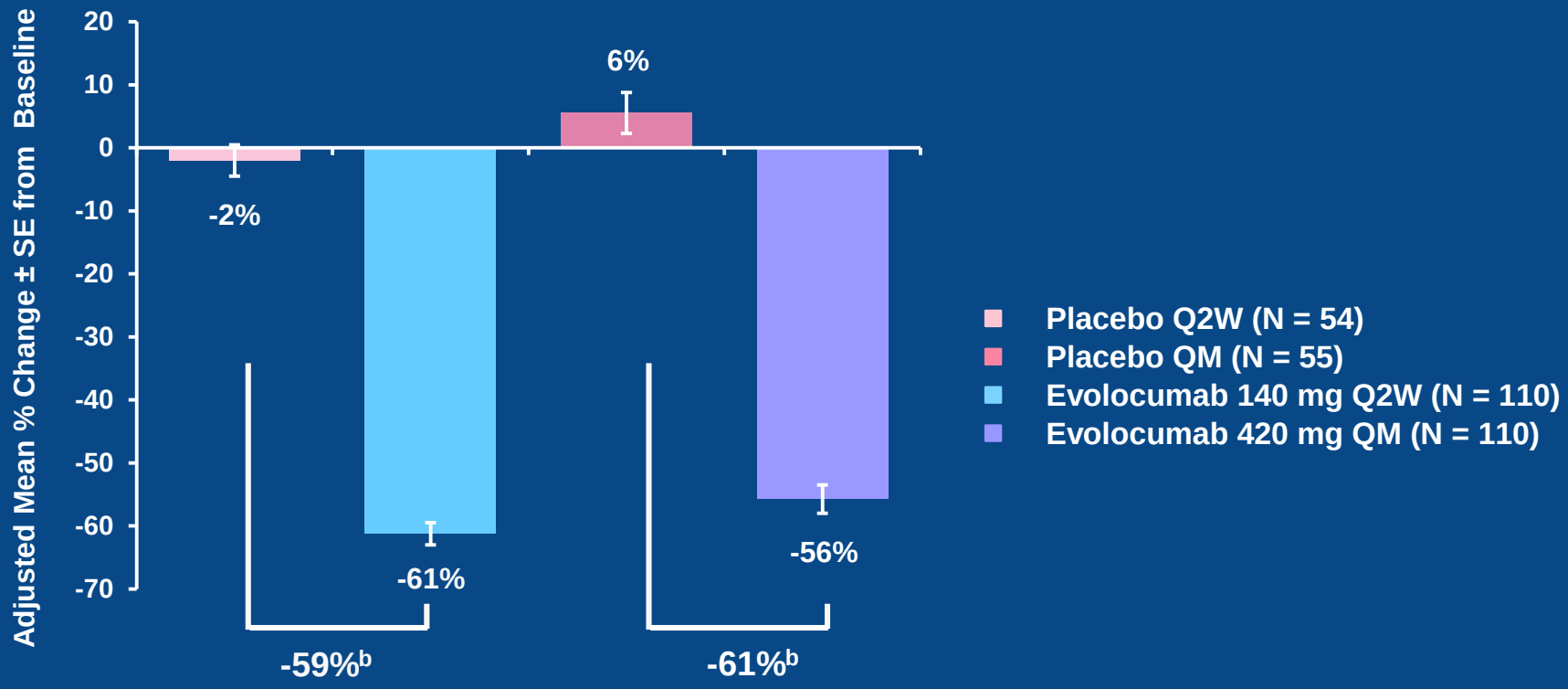
Characteristic	Placebo Q2W (N = 54)	Evolocumab 140 mg Q2W (N = 110)	Placebo QM (N = 55)	Evolocumab 420 mg QM (N = 110)
LDL-C[a] (mg/dL), mean (SD)	151 (37)	161 (51)	152 (43)	154 (43)
ApoB (mg/dL), mean (SD)	114 (30)	119 (31)	110 (22)	115 (26)
HDL-C (mg/dL), mean (SD)	53 (17)	50 (16)	49 (13)	52 (16)
ApoA1 (mg/dL), mean (SD)	145 (28)	142 (34)	135 (24)	143 (29)
Triglycerides (mg/dL), median (Q1, Q3)	96 (75, 143)	119 (87, 161)	102 (79, 151)	113 (85, 157)
Lp(a) (nmol/L), median (Q1, Q3)	44 (24, 105)	78 (29, 206)	87 (36, 219)	61 (17, 194)

[a] Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation; when calculated LDL-C was < 40 mg/dL or triglyceride levels were > 400 mg/dL

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); Q2W, biweekly; QM, monthly; SD, standard deviation

Raal et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399-4

RUTHERFORD-2: Mean % Change in LDL-C[a] from Baseline to Week 12



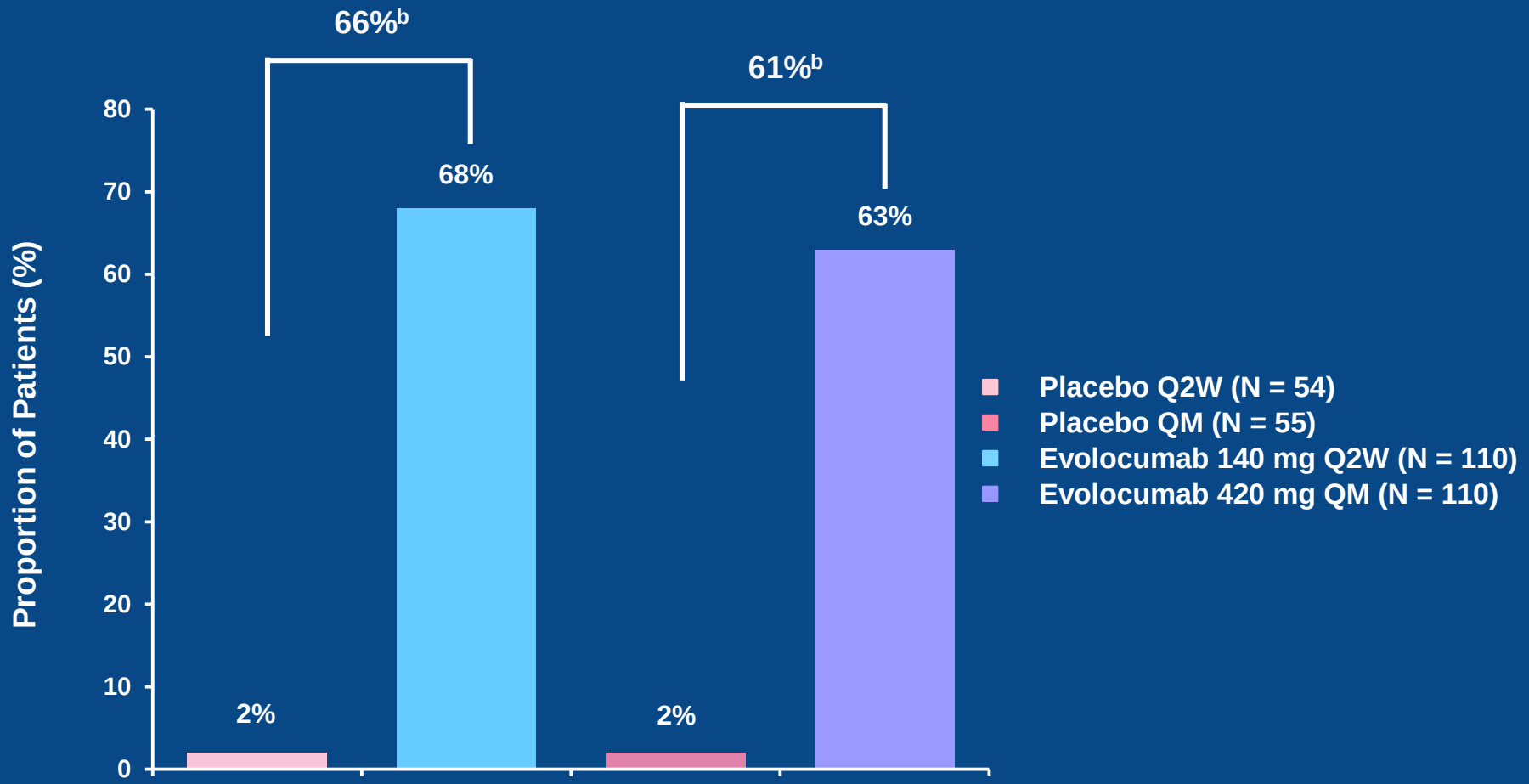
[a] Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation; when calculated LDL-C was < 40 mg/dL or triglyceride levels were > 400 mg/dL

[b] P < 0.001; placebo-adjusted treatment difference analyzed using repeated measures model which included treatment group, stratification factors (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates

LDL-C, low-density lipoprotein cholesterol; Q2W, biweekly; QM, monthly; SE, standard error

Raal et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399-4

RUTHERFORD-2: LDL-C[a] Goal Achievement < 70 mg/dL at Week 12



[a] Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation when calculated LDL-C was < 40 mg/dL or triglyceride levels were > 400 mg/dL

[b] P < 0.001; analyzed using CMH test, stratified by the stratification factors

LDL-C, low-density lipoprotein cholesterol; Q2W, biweekly; QM, monthly

Raal et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399-4

RUTHERFORD-2: Demographics and Lipid Parameters in Patients in the Genetic Sub-analysis

Mutations causative of familial hypercholesterolaemia were found in 80% (211/264) of patients who consented to the genetic analysis

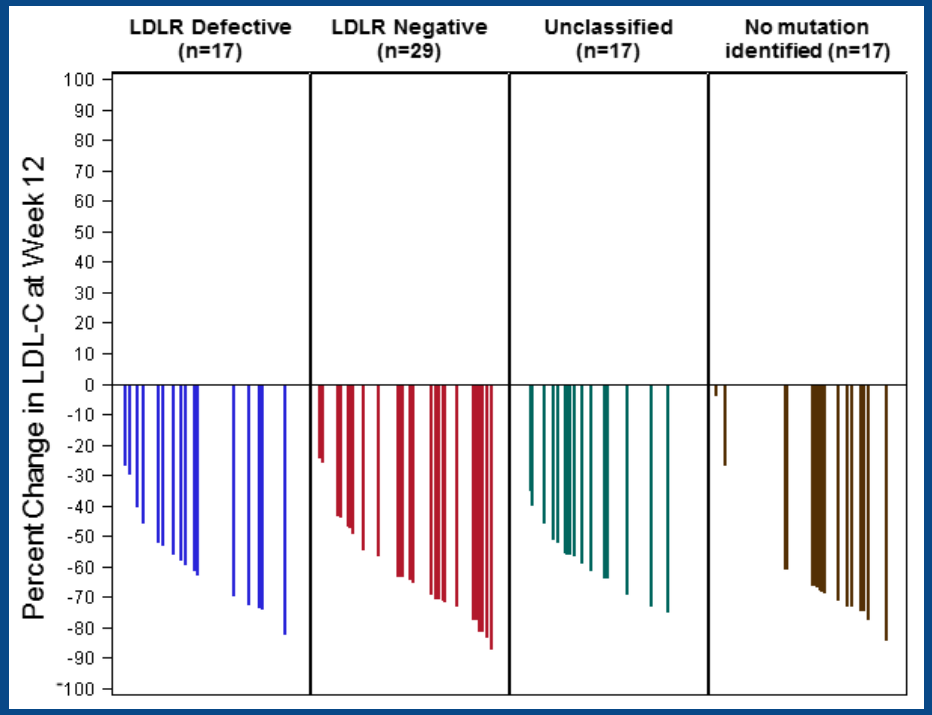
	LDLR Mutation (n=195)				
	Negative (n=66)	Defective (n=75)	Unclassified (n=54)	Apo B Mutation (n=9)	HoFH/Compound HeFH (n=7)
Age (years), mean (SD)	48·1 (13·0)	49·5 (12·3)	51·0 (12·8)	57·1 (11·2)	53 (10·3)
Coronary artery disease, n (%)	23 (34·8)	15 (20·0)	23 (42·6)	2 (22·2)	4 (57·1)
LDL-C (mg/dL), mean (SD)	170 (50)	153 (39)	154 (46)	143 (39)	205 (108)
Apo B (mg/dL), mean (SD)	120 (30)	110 (20)	120 (30)	100 (20)	150 (60)
LDL-C reduction* at wk 12 (mean %)	61%	62%	64%	51%	68%

*evolocumab 140 mg every 2 weeks

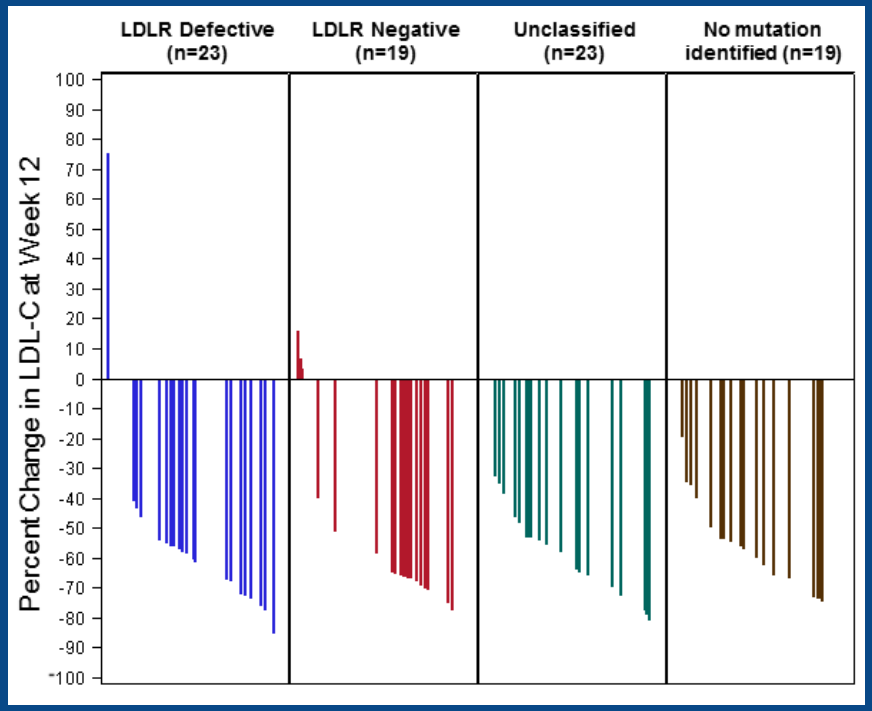
Raal et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399-4

Individual Patient % Change from Baseline to Week 12 in LDL-C in Heterozygous FH by Genetic Subgroup Treated with Evolocumab

140 mg every 2 weeks



420 mg every 4 weeks



Raal et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399-4

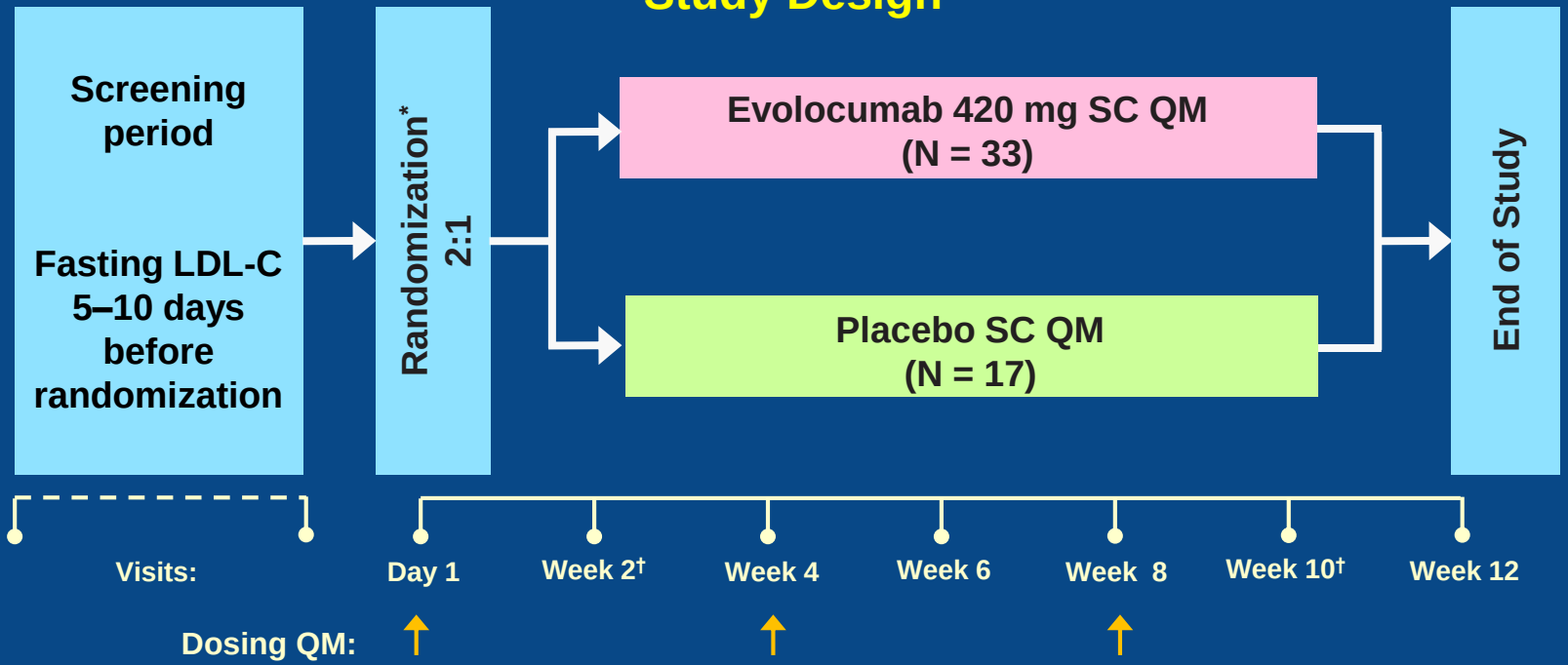
Phase 2/3 Trials with PCSK9 mAb in FH

- Will initial phase 1 results in small a group of HeFH patients from one center be maintained in a larger and more diverse HeFH populations with additional LDL-R defects? **YES**
- **Response is NOT related to underlying genetic defect**
- Will PCSK9 mAb be effective in homozygous FH?

Trial Evaluating Evolocumab, a PCSK9 Antibody, in Patients with Homozygous FH (TESLA Part B)

A Global, Phase 3, Randomized, Double-blind, Placebo-controlled Trial

Study Design



↑ Study drug administration

*Randomization stratified by screening LDL-C (<10.9 mmol/L or ≥10.9 mmol/L).
†Week 2 and week 10 study visits were optional.
SC = subcutaneous; QM = every 4 weeks; LDL-C = low-density lipoprotein cholesterol

Primary endpoint: % change from baseline in ultracentrifugation LDL-C at week 12

Raal et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399-4

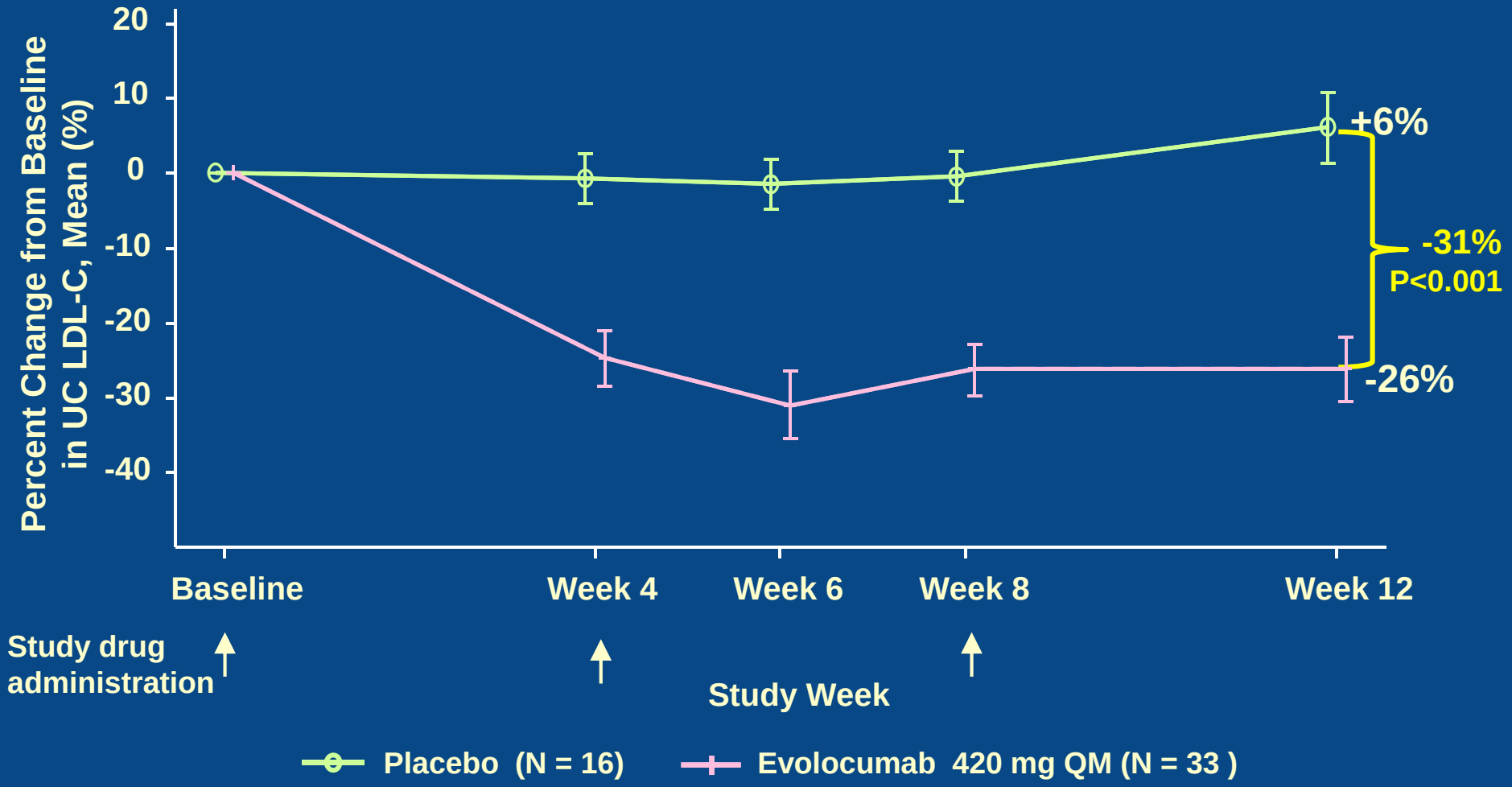
TESLA Part B: Patient Genotype and Receptor Function

	Placebo QM N = 16	Evolocumab 420 mg QM N = 33	Total N = 49
Genotype, n (%)			
LDLR	14 (88)	31 (94)	45 (92)
Homozygous	7 (43)	15 (45)	22 (45)
Compound heterozygous	7 (43)	16 (49)	23 (47)
Heterozygous*	0	1(3)	1 (2)
Apolipoprotein B	2 (13)	0	2 (4)
ARH	0	1(3)	1 (2)
LDLR functional status, n (%)	14 (88)	31 (94)	45 (92)
Defective/any†	8 (50)	20 (61)	28 (57)
Defective/defective	5 (31)	8 (24)	13 (27)
Negative/defective	3 (25)	6 (18)	9 (20)
Unclassified‡	6 (31)	16 (48)	22 (43)
Negative/negative	0	1 (3)	1 (2)

*Patient met clinical diagnostic criteria for HoFH based on history of untreated LDL-C concentration >13 mmol/L plus either xanthoma before 10 yr or evidence of heterozygous FH in both parents. †Receptor defective in at least one allele. ‡Function of one or both LDLR mutations is unknown (includes 6 patients from the defective/any group). ARH, autosomal recessive hypercholesterolemia; LDLR, LDL receptor

Raal et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399-4

TESLA Part B: Percent Change in UC LDL-C from Baseline to Week 12



Vertical lines represent the standard error around the mean. Plot is based on observed data with no imputation for missing values.

Raal et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399-4

TESLA Part B: LDL-C Lowering by Type of Mutation

Percent Change from Baseline in UC LDL-C at Week 12, Mean (SE)

Mutation Status	N	Placebo	Evolocumab 420 mg QM	Treatment Difference
All	49	7.9 (5.3)	-23.1 (3.8)	-30.9 (6.4)*
LDLR				
Defective/any†	28	11.2 (5.1)	-29.6 (3.4)	**-40.8 (6.1)‡**
Defective/defective	13	15.1 (7.3)	-31.8 (5.8)	**-46.9 (9.4)‡**
Negative/defective	9	3.5 (5.8)	-21.0 (4.0)	**-24.5 (7.0)§**
Unclassified‖	22	3.8 (11.7)	-17.9 (8.8)	**-21.7 (13.9)**
Median (Q1, Q3)		7.2 (0.0, 9.9)	-39.2 (-48.8, -14.6)	-
Negative/negative	1	-	10.3	-
LDLR Heterozygous	1	-	-55.7	-
Apolipoprotein B	2	-10.8, 13.1	-	-
ARH	1	-	3.5	-

Data are least squares (LS) mean for groups with sufficient data; otherwise actual value at week 12. LS mean is from the repeated measures model, which includes treatment group, screening LDL, scheduled visit and the interaction of treatment with scheduled visit as covariates. *Adjusted P-value < 0.001; †Receptor defective in at least one of two affected alleles. ‡ Nominal P-value < 0.001; §Nominal P-value = 0.013; ‖Function of one or both LDLR mutations is unknown (includes 6 patients from the defective/any group).

Raal et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399-4

Phase 2/3 Trials with PCSK9 mAb in FH

- Will initial phase 1 results in small a group of HeFH patients from one center be maintained in a larger and more diverse HeFH populations with additional LDL-R defects? **YES**
- **Response is NOT related to underlying genetic defect**

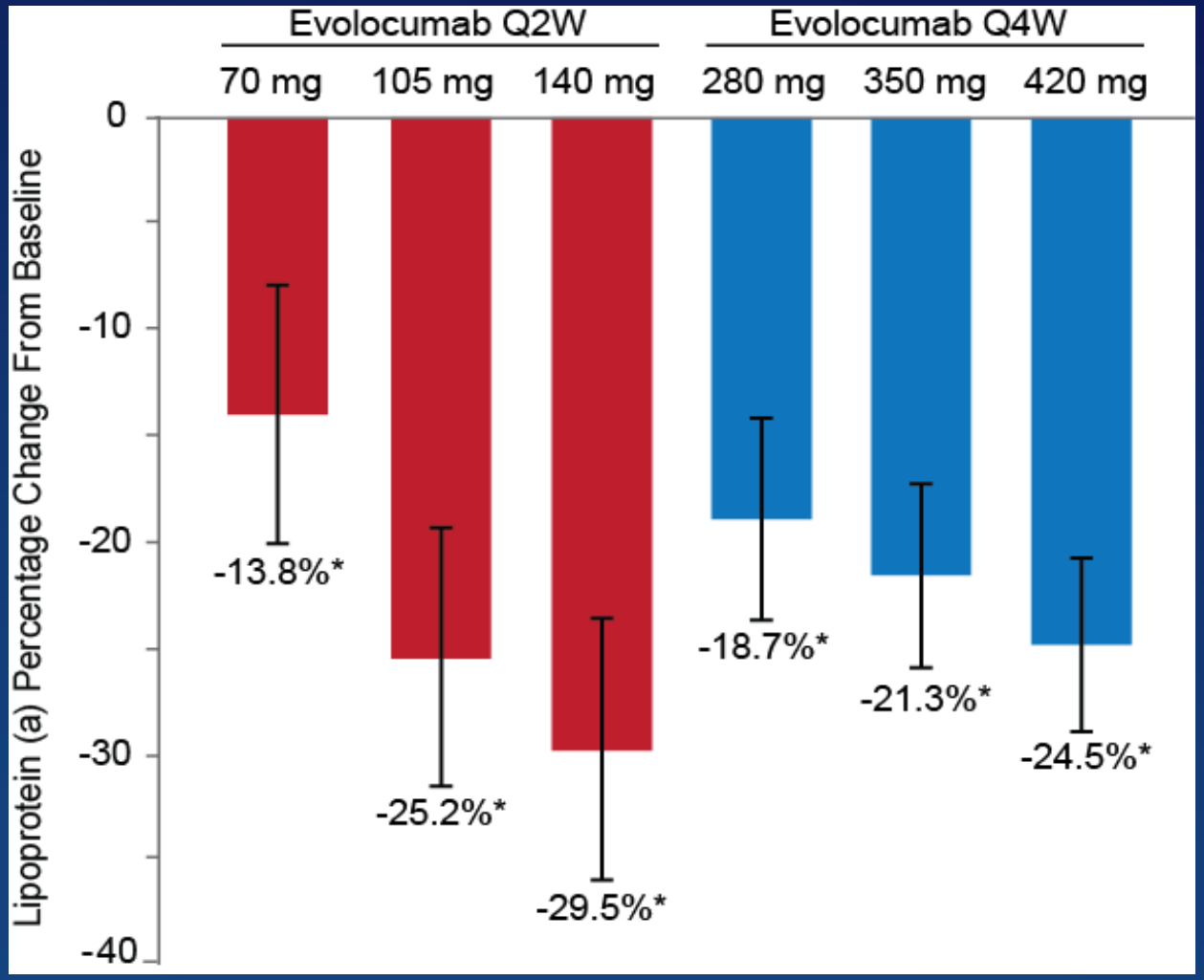
- Will PCSK9 mAb be effective in homozygous FH? **YES**
- **Response IS related to underlying genetic defect(s)**

PCSK9 Inhibition: New Therapeutic Approaches to LDL-C Lowering

- PCSK9 inhibition efficacy in various pheno- and geno-types
  - Nonfamilial hypercholesterolemia
    - Monotherapy
    - Added to statins
    - Statin averse patients
  - Familial hypercholesterolemia
    - Heterozygous FH
    - Homozygous FH
- Effect on Lp(a)
- Safety and tolerability
- Outcomes trials

Reduction in Lipoprotein(a) with PCSK9 Monoclonal Antibody Evolocumab (AMG 145)

A Pooled Analysis of More than 1,300 Patients in 4 Phase II Trials

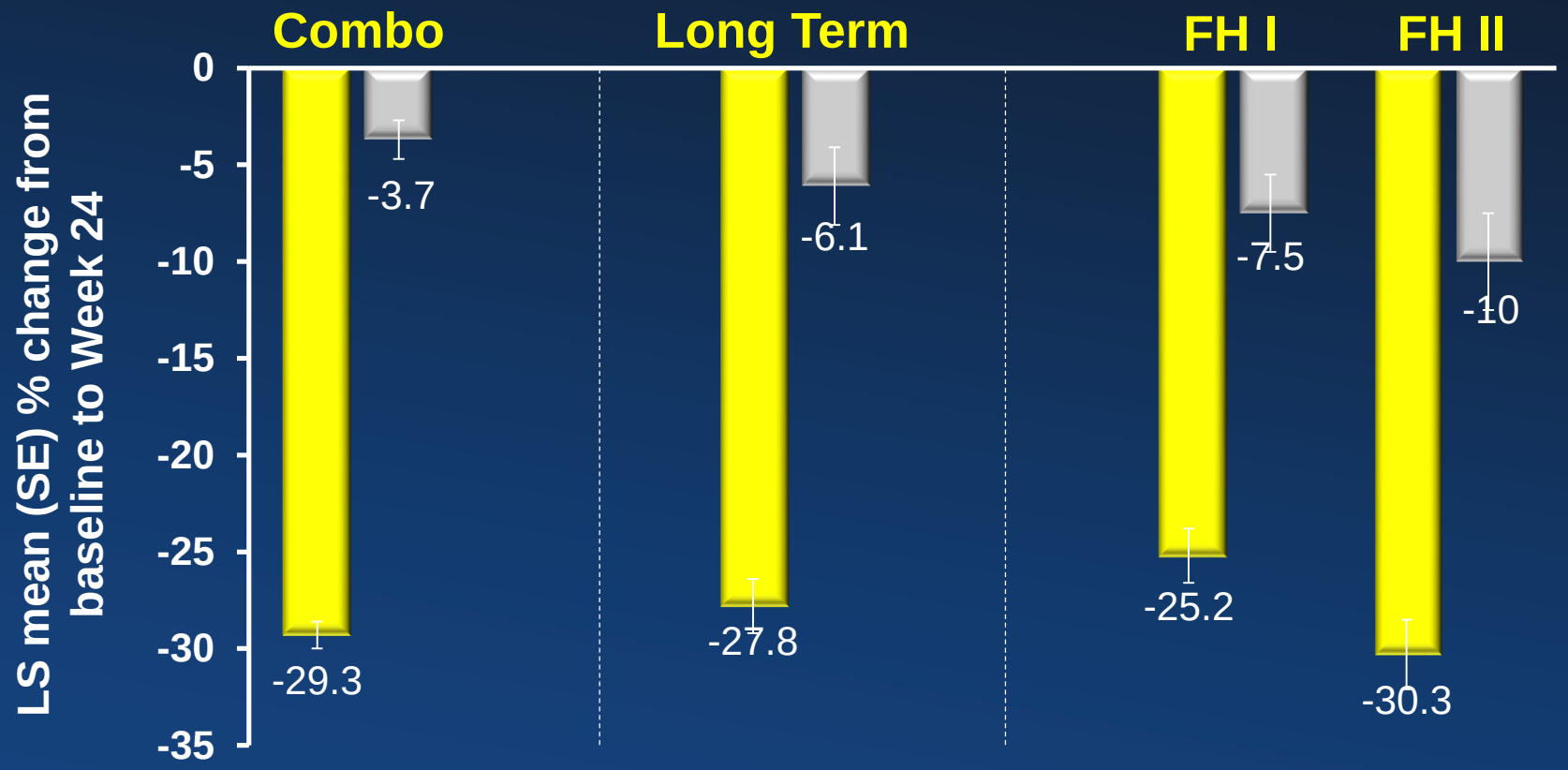


Error bars represent standard error.

*** P < 0.001**

Raal et al JACC 2014;63:1278-88.

Alirocumab: Lp(a) Reductions in ODYSSEY Combo II, Long Term, FH I and FH II Studies



All comparisons vs. placebo are *P*<0.0001

Alirocumab + max-tolerated statin ±other LLT

Placebo + max-tolerated statin ±other LLT

Adjusted mean (SE) shown for Lp(a). LLT = lipid-lowering therapy.

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

PCSK9 Inhibition: New Therapeutic Approaches to LDL-C Lowering

- PCSK9 inhibition efficacy in various pheno- and geno-types
  - Nonfamilial hypercholesterolemia
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    - Heterozygous FH
    - Homozygous FH
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AMG 145 Pooled Analysis >1300 Patients: Clinical Adverse Effects

	AMG 145 – by dose and dose frequency						Placebo	All AMG 145
	70 mg Q2W (n=124)	105 mg Q2W (n=125)	140 mg Q2W (n=123)	280 mg Q4W (n=156)	350 mg Q4W (n=210)	420 mg Q4W (n=213)	(n=333)	(n=981)
AEs[a]	65 (52.4)	74 (59.2)	69 (56.1)	89 (57.1)	118 (56.2)	122 (57.3)	164 (49.2)	557 (56.8)
Nasopharyngitis	11 (8.9)	10 (8.0)	8 (6.5)	11 (7.1)	20 (9.5)	18 (8.5)	25 (7.5)	81 (8.3)
Headache	4 (3.2)	3 (2.4)	6 (4.9)	1 (0.6)	6 (2.9)	6 (2.8)	11 (3.3)	32 (3.3)
Diarrhoea	3 (2.4)	4 (3.2)	4 (3.3)	2 (1.3)	6 (2.9)	8 (3.8)	11 (3.3)	28 (2.9)
Myalgia	4 (3.2)	2 (1.6)	3 (2.4)	7 (4.5)	7 (3.3)	3 (1.4)	4 (1.2)	32 (3.3)
Nausea	0 (0.0)	1 (0.8)	6 (4.9)	7 (4.5)	5 (2.4)	7 (3.3)	6 (1.8)	26 (2.7)
Fatigue	0 (0.0)	2 (1.6)	4 (3.3)	4 (2.6)	4 (1.9)	8 (3.8)	7 (2.1)	22 (2.2)
Treatment-related AEs	8 (6.5)	16 (12.8)	13 (10.6)	19 (12.2)	27 (12.9)	25 (11.7)	32 (9.6)	113 (11.5)
AEs leading to discont	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)	2 (1.0)	2 (0.9)	5 (1.5)	7(0.7)
SAEs	0 (0.0)	2 (1.6)	5 (4.1)	4 (2.6)	4 (1.9)	5 (2.3)	4 (1.2)	20 (2.0)
Treatment-related SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Stein et al Euro Heart J 2014 doi:10.1093/eurheartj/ehu085 [a]Reported in at least 2% of evolocumab recipients, all values represent no. (%).

AMG 145 Pooled Analysis >1300 Patients: Lab of Interest

	AMG 145 – by dose and dose frequency						Placebo	All AMG 145
	70 mg Q2W (n=124)	105 mg Q2W (n=125)	140 mg Q2W (n=123)	280 mg Q4W (n=156)	350 mg Q4W (n=210)	420 mg Q4W (n=213)	(n=333)	(n=981)
AEs and labs of interest								
Injection-site reaction	2 (1.6)	7 (5.6)	2 (1.6)	9 (5.8)	13 (6.2)	5 (2.3)	11 (3.3)	40 (4.1)
Muscle-related AEs	7 (5.6)	5 (4.0)	4 (3.3)	13 (8.3)	11 (5.2)	13 (6.1)	13 (3.9)	59 (6.0)
CK > 5 x ULN[b]	3 (2.4)	2 (1.6)	1 (0.8)	0 (0.0)	3 (1.4)	5 (2.3)	3 (0.9)	14 (1.4)
ALT or AST >3 x ULN	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	1 (0.5)	2 (0.6)	4 (0.4)
Binding antibodies	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Neutralizing antibodies	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[b]5 patients in the AMG 145 treatment group had creatine kinase >10 x ULN, all of which were resolved at follow-up blood test

Stein et al Euro Heart J 2014 doi:10.1093/eurheartj/ehu085

ODYSSEY LONG TERM Study: TEAEs

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

% (n) **of patients** All patients on background of max-tolerated statin ± other lipid-lowering therapy	**Alirocumab (n=1550)**	**Placebo (n=788)**
TEAEs	**78.6%** (1218)	**80.6%** (635)
Treatment-emergent SAEs	**16.5%** (255)	**17.6%** (139)
TEAE leading to death	**0.5%** (7)	**1.0%** (8)
TEAEs leading to treatment discontinuation	**6.2%** (96)	**5.5%** (43)

- **Mean treatment duration: 65 weeks (both treatment arms)**
- **26.1% (405/1553 alirocumab) and 25.6% (202/788 placebo) completed 78 weeks**
- **Statistical analyses have not been performed.**

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

ODYSSEY LONG TERM Study: TEAEs ≥5%

% (n) of patients	Alirocumab (n=1550)	Placebo (n=788)
Infections and infestations	**45.5%** (705)	**46.1%** (363)
Musculoskeletal and connective tissue disorders	**27.2%** (422)	**28.6%** (225)
Gastrointestinal disorders	**18.6%** (288)	**18.8%** (148)
Nervous system disorders	**17.0%** (264)	**17.8%** (140)
General disorders and administration site conditions	**15.4%** (238)	**17.0%** (134)
Injury, poisoning, and procedural complications	**13.4%** (207)	**14.2%** (112)
Respiratory, thoracic, and mediastinal disorders	**11.0%** (171)	**10.9%** (86)
Cardiac disorders	**9.1%** (141)	**11.8%** (93)
Skin and subcutaneous tissue disorders	**9.1%** (141)	**8.5%** (67)
Metabolism and nutrition disorders	**9.1%** (141)	**8.4%** (66)
Vascular disorders	**7.9%** (122)	**8.9%** (70)
Eye disorders	**6.5%** (100)	**6.1%** (48)
Investigations (lab parameters)	**6.1%** (95)	**5.2%** (41)
Psychiatric disorders	**5.9%** (91)	**8.0%** (63)

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

PCSK9 Inhibition: New Therapeutic Approaches to LDL-C Lowering

- PCSK9 inhibition efficacy in various pheno- and geno-types
  - Nonfamilial hypercholesterolemia
    - Monotherapy
    - Added to statins
    - Statin averse patients
  - Familial hypercholesterolemia
    - Heterozygous FH
    - Homozygous FH
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Adjudicated CVD End Points in Published and Presented Evolocumab Phase 2 & 3 Trials

End Point	Placebo or Control (N=2080)	Evolocumab (N=3633)
	no. of patients (%)	
Death, myocardial infarction, or stroke	9 (0.43)	15 (0.41)
Coronary revascularization, hospitalization for unstable angina, hospitalization for heart failure, or transient ischemic attack	8 (0.38)	19 (0.52)

* Data were pooled from all phase 2 and 3 trials of evolocumab.[1-3]

Blom et al NEJM 2014;371:377-8

Post-hoc Adjudicated Cardiovascular TEAEs

(Same as primary endpoint of ongoing ODYSSEY OUTCOMES trial†)

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

% (n) of patients All patients on background of max tolerated statin ± other lipid-lowering therapy	**Alirocumab (n=1550)**	**Placebo (n=788)**
CV events confirmed by adjudication	**1.4%** (22)	**3.0%** (24)
CHD death	**0.2%** (3)	**0.8%** (6)
Non-fatal MI	**0.7%** (11)	**2.2%** (17)
Fatal + non-fatal ischaemic stroke	**0.5%** (8)	**0.3%** (2)
Unstable angina requiring hospitalisation	0	**0.1%** (1)

Patients are censored at the end of TEAE period (last injection of study treatment + 70 days).

†Primary endpoint for the ODYSSEY OUTCOMES trial: CHD death, Non-fatal MI, Fatal and non-fatal ischemic stroke, Unstable angina requiring hospitalisation. “Unstable angina requiring hospitalisation” is limited to the UA events with definite evidence of progression of the ischemic condition (strict criteria).

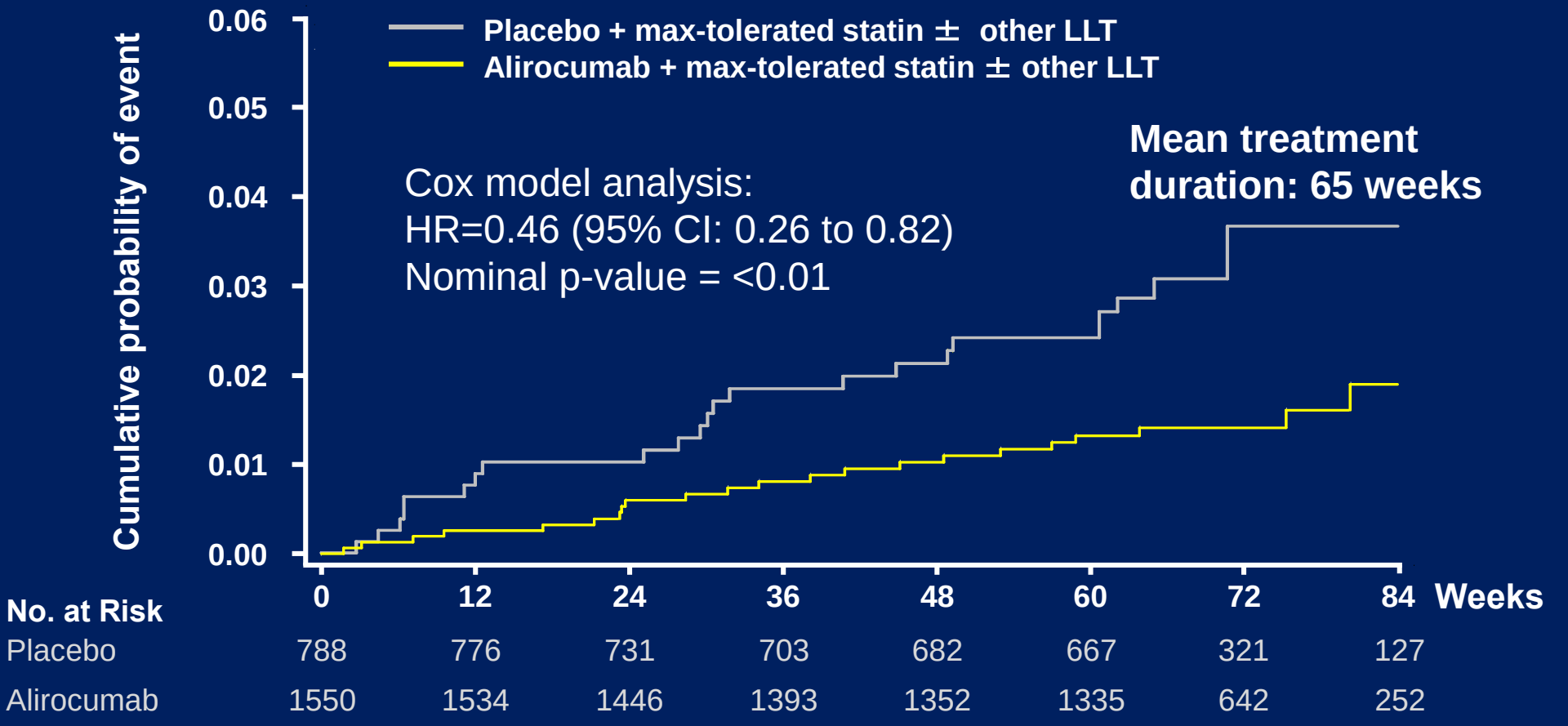
Robinson et al . Presented at ESC hotline session; Barcelona, Aug 31, 2014

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

PCSK9 Inhibitor Cardiovascular Outcomes Trials

	Evolocumab (AMG 145)	Alirocumab (SAR236553 /REGN727)	Bococizumab (RN 316)	
Sponsor	Amgen	Sanofi / Regeneron	Pfizer	
Trial	**FOURIER**	**ODYSSEY Outcomes**	**SPIRE I**	**SPIRE II**
Sample size	22,500	18,000	12,000	6,300
Patients	MI, stroke or PAD	4-52 wks post-ACS	High risk of CV event	
Statin	Atorva ≥20 mg or equiv	Evid-based med Rx	Lipid-lowering Rx	
LDL-C mg/dL(mmol/L)	≥70 (≥1.8)	≥70 (≥1.8)	70-99 (1.8-2.6)	≥100 (≥2.6)
PCSK9i Dosing	Q2W or Q4W	Q2W	Q2W	
Endpoint	1°: CV death, MI, stroke, revasc or hosp for UA, Key 2°: CV death, MI, or stroke	CHD death, MI, ischemic stroke, or hosp for UA	CV death, MI, stroke, or urgent revasc	
Completion	12/2017	1/2018	8/2017	

www.clinicaltrials.gov

PCSK9 Inhibition: Conclusions

- Inhibition of PCSK9 with monoclonal antibodies is a very promising, and potentially the most effective, approach to reducing LDL-C including patients:
  - With nonFH, HeFH and LDLr defective HoFH
  - On statins or diet alone
  - When added to all existing therapy
  - Unable to tolerate statins, or effective doses of statins
  - SC delivery every 2 or 4 weeks
- PCSK 9 inhibitors have also been shown to significantly reduce Lp(a)
- In large phase 2 and 3 program of 2 agents of over 6,000 patients no significant adverse effects have emerged so far
- Early data on CVD is encouraging and in the right direction
- Four large CVD outcomes trials are already underway with evolocumab, alirocumab, and bococizumab monoclonal antibodies

A Look Ahead:
Clinical Implications of New LDL-C Lowering Therapies to the Clinic

Panel Discussion and Q&A

Moderator:

Terry A. Jacobson, MD

Discussants:

Eliot A. Brinton, MD

Sekar Kathiresan, MD

Evan A. Stein, MD, PhD

Post-test ARS Question 1

Which of the following is TRUE of <u>both</u> the ACC/AHA and the NCEP III guidelines for the management of dyslipidemia?

a. The recommendations are based almost exclusively on what has been demonstrated to reduce ASCVD risk in randomized controlled trials.

b. The recommendations are conceptually grounded in the view that lowering “atherogenic cholesterol” (LDL-C and non-HDL-C) will reduce risk.

c. Target LDL-C levels are <100 and <70 mg/dL for primary and secondary prevention, respectively.

d. The recommendations emphasize statins as first-line drug therapy.

e. The recommendations do not emphasize lifestyle interventions.

Post-test ARS Question 2

Which of the following patients would most likely benefit from a high-intensity statin therapy according to the 2013 ACC/AHA Blood Cholesterol Guideline?

a. A 33-year old male with an estimated 10-year ASCVD risk of 7%
b. A 50-year old woman with an LDL-C of 195 mg/dL
c. An 80-year old with an LDL-C of 189 mg/dL
d. 25-year old woman with diabetes and a LDL-C of 92 mg/dL

Post-test ARS Question 3

Which of the following statements regarding the potential consequences of untreated FH is TRUE?

a. If left untreated, men with FH have a 50% risk of CVD by age 50
b. FH causes 20% of all myocardial infarctions in patients $\leq$ 45 years old
c. Risk of premature coronary heart disease in patients with FH who are untreated is 20 times greater than the general population
d. All of the above are TRUE
e. A & B are TRUE

Post-test ARS Question 4

How do PCSK9 monoclonal antibodies affect LDL-C levels?

a. They increase LDL-R recycling
b. They increase the expression of LDL-R
c. They increase PCSK9 production
d. They inhibit ApoB production