Inhibition of PCSK9: The Birth of a New Therapy

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Novel Approaches to Modify Lipids and Lipoproteins

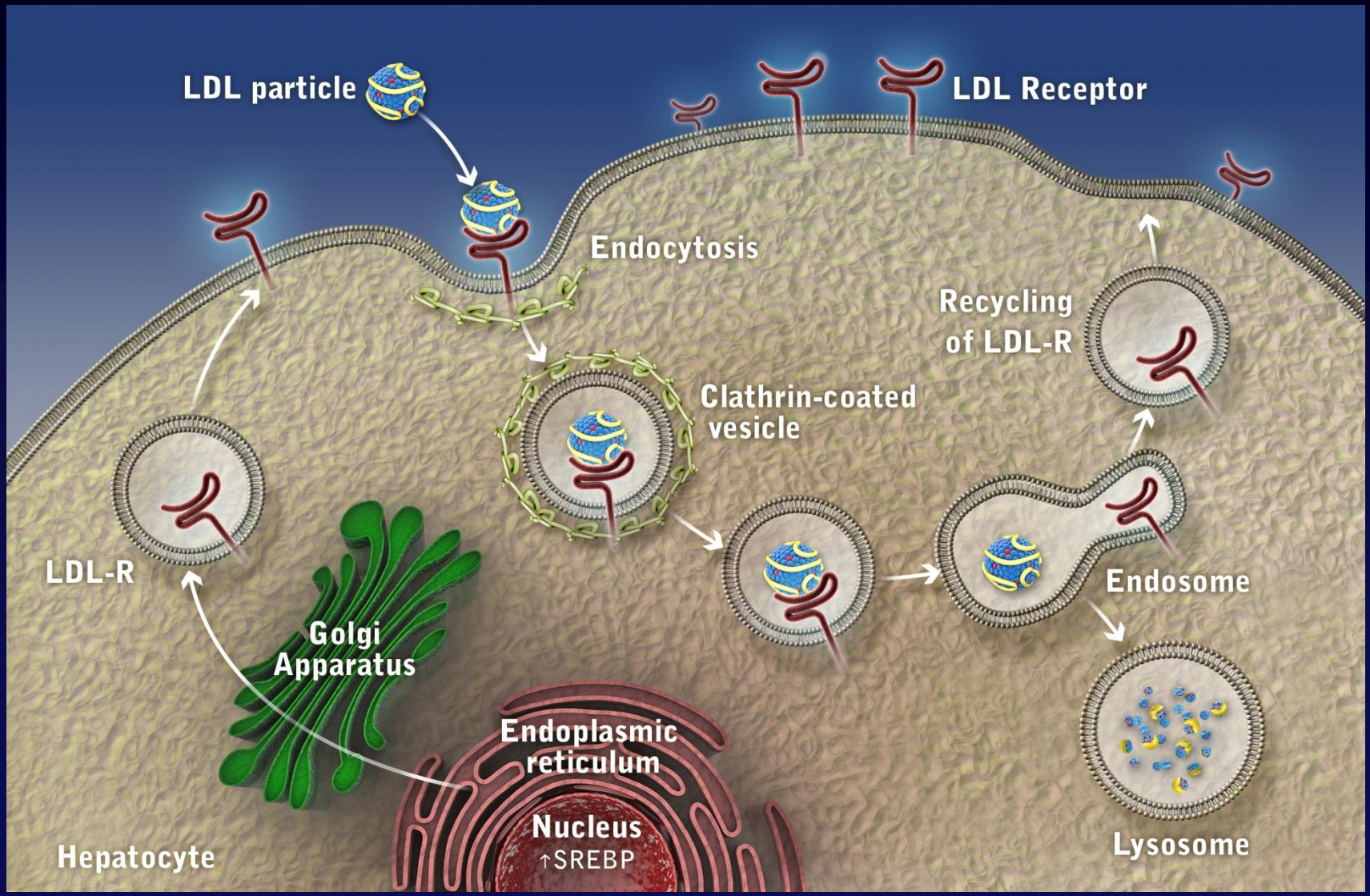
- Low Density Lipoprotein
- High Density Lipoprotein
- Triglyceride Rich Lipoproteins
- Inflammation
- Lipoprotein a

New Approaches to LDL Reduction

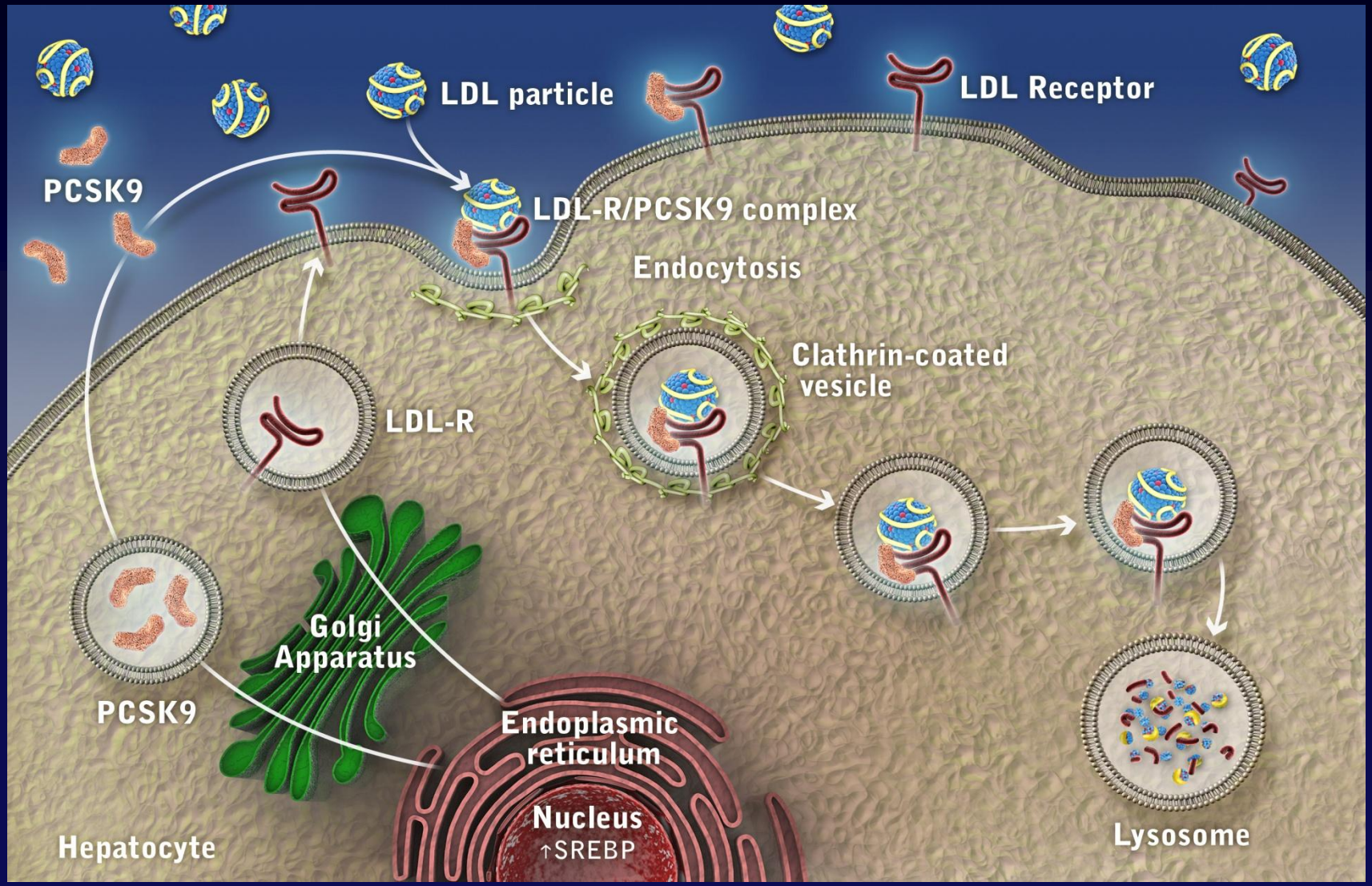
What is in development?

- Cholesterol Absorption Inhibitors
- Squalene Synthase (SSI) inhibitors
- Apo B mRNA antisense drugs
- Microsomal Triglyceride Transfer Protein (MTP) inhibitors
- Thyroxin Receptor Agonists
- PCSK9 Inhibitors

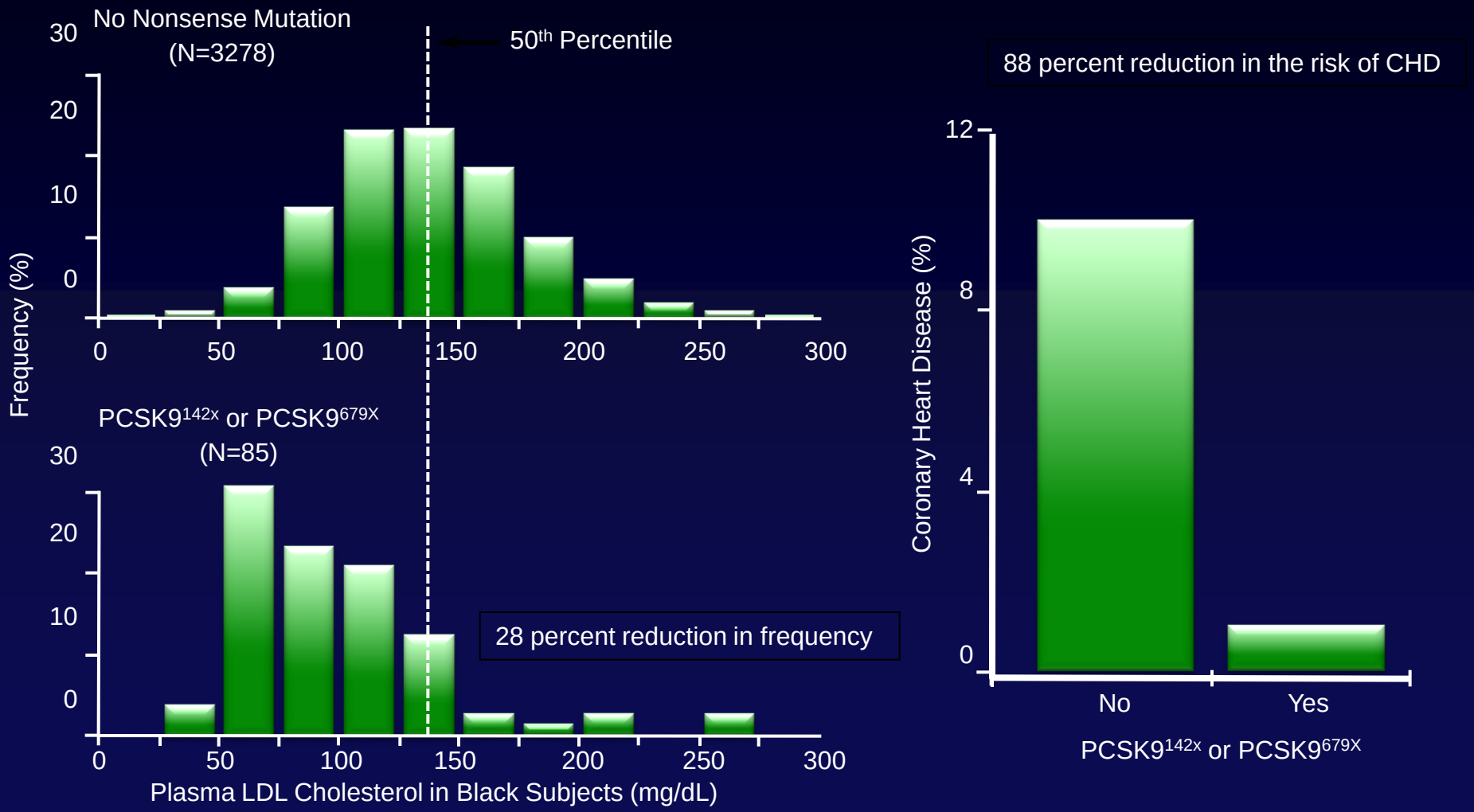
LDL-Receptor Function and Life Cycle



The Role of PCSK9 in the Regulation of LDL Receptor Expression



PCSK9 LOF Mutations

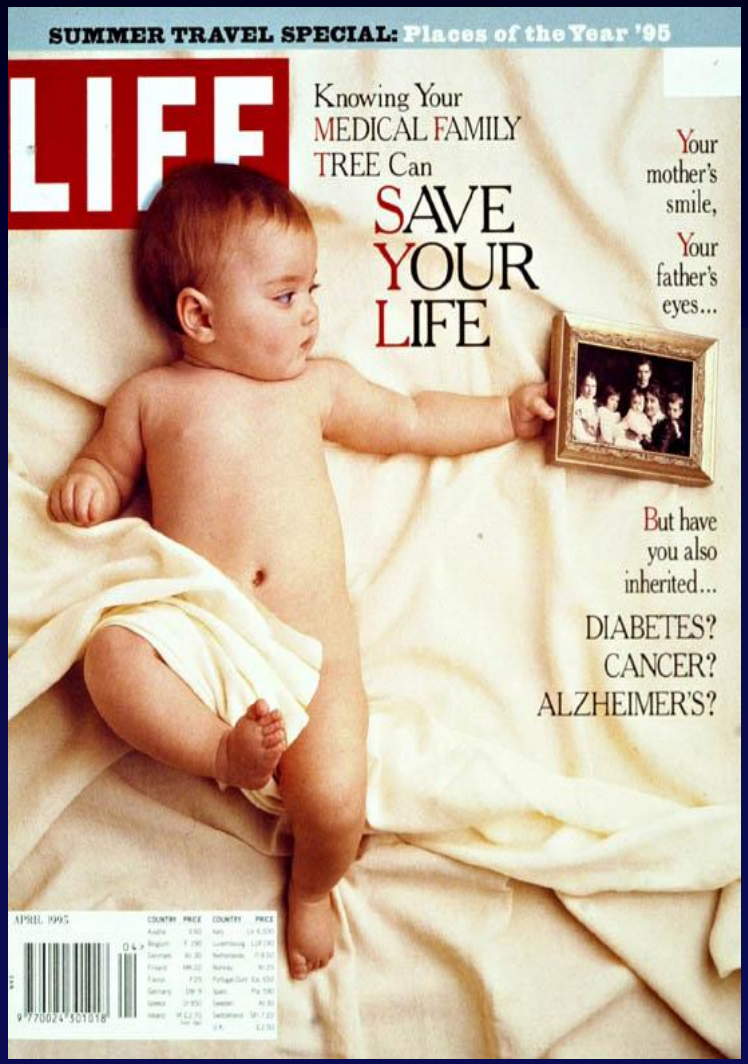


Adapted from Cohen JC. N Engl J Med 2006;354:1264-72; ARIC=Atherosclerosis Risk in the Community

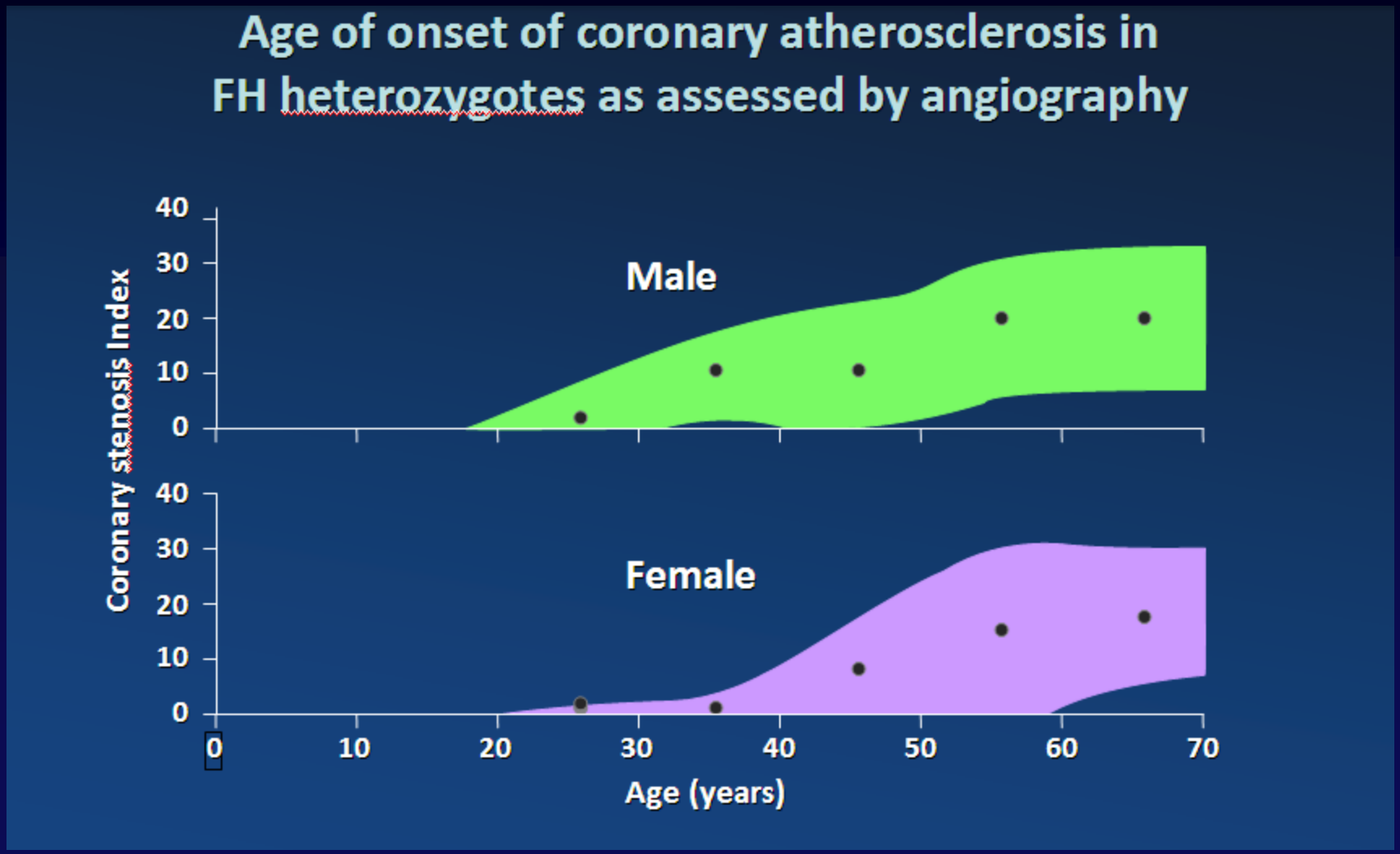
Loss of Function PCSK9 Mutations

- Only a small number of patients who are homozygous (or compound heterozygotes) for PCSK9 have been discovered and studied.
- These patients appear to have:
  - Very low LDL-C levels (~10-20 mg/dL)
  - Relatively low TG levels
  - Normal HDL-C levels
- These patients have no other health problems

Familial Hypercholesterolemia

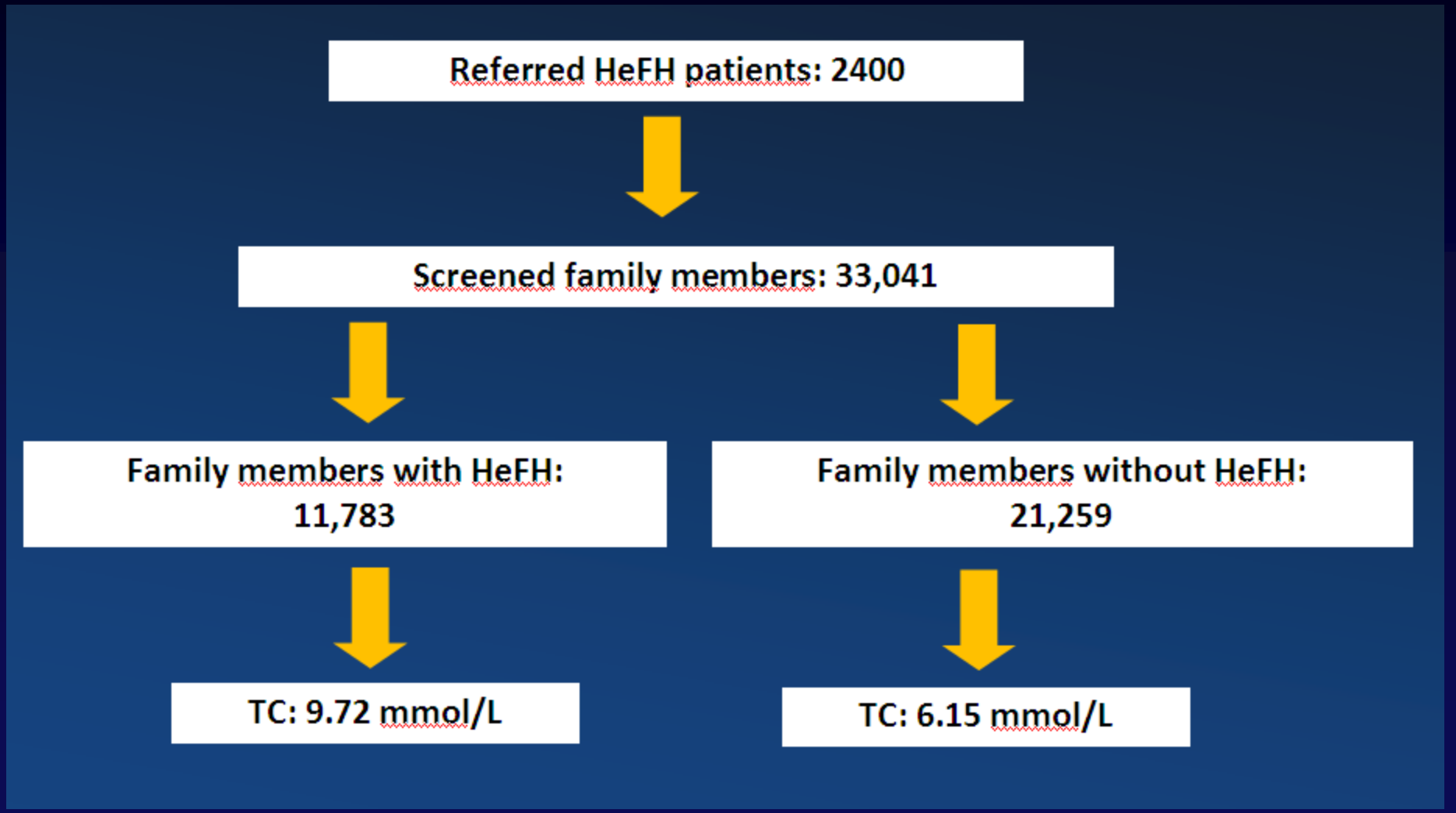


Familial Hypercholesterolemia



Mabuchi H et al. *Circulation* 1989;79:225–232.

FH in the Netherlands: Screening between January 1994 and December 2010



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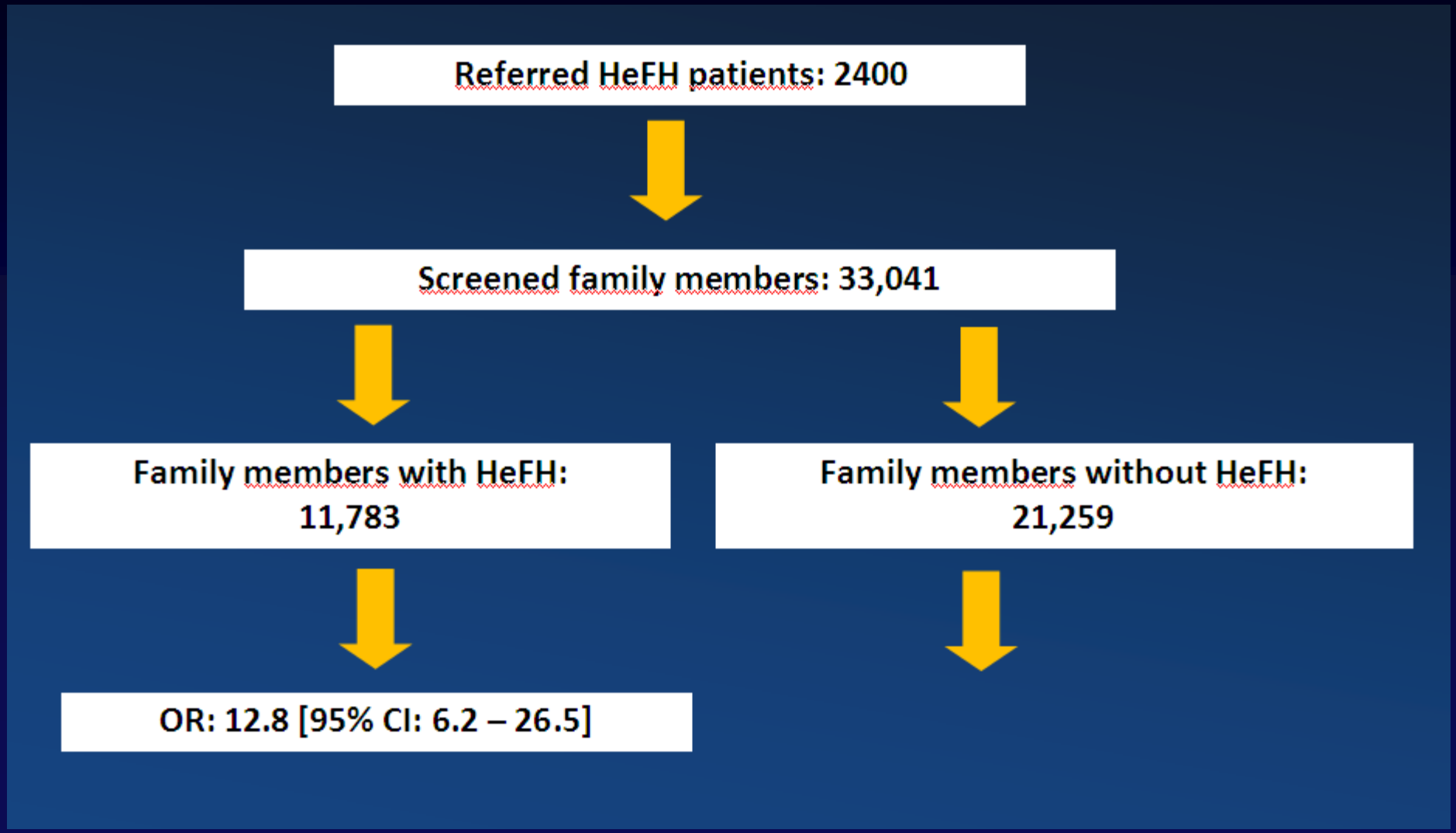
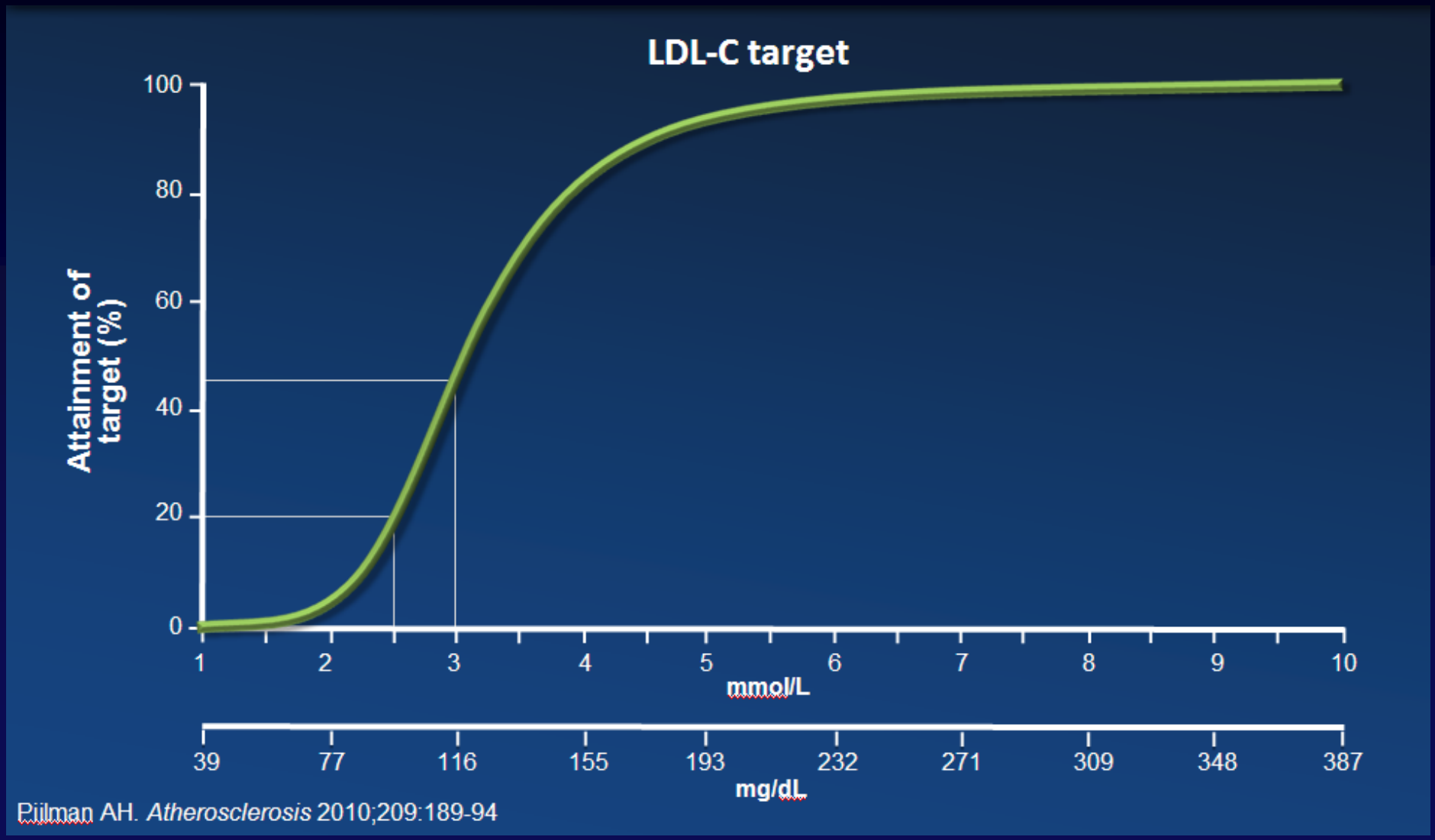
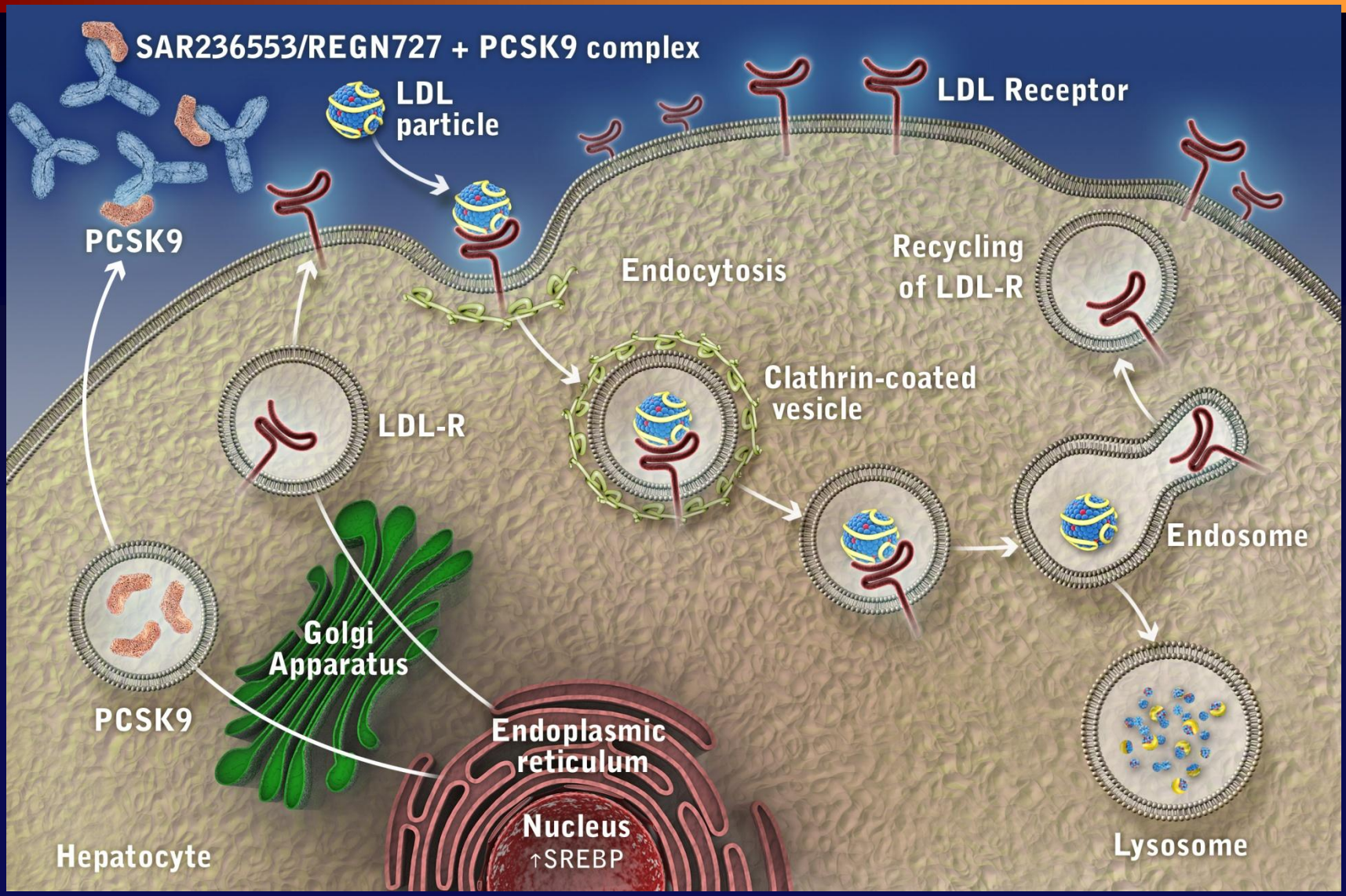


FH Patients at LDL Goal



Piilman AH. *Atherosclerosis* 2010;209:189-94

Impact of a SAR236553/REGN727 on LDL Receptor Expression



The Use of a PCSK9 Monoclonal AB in heFH Patients

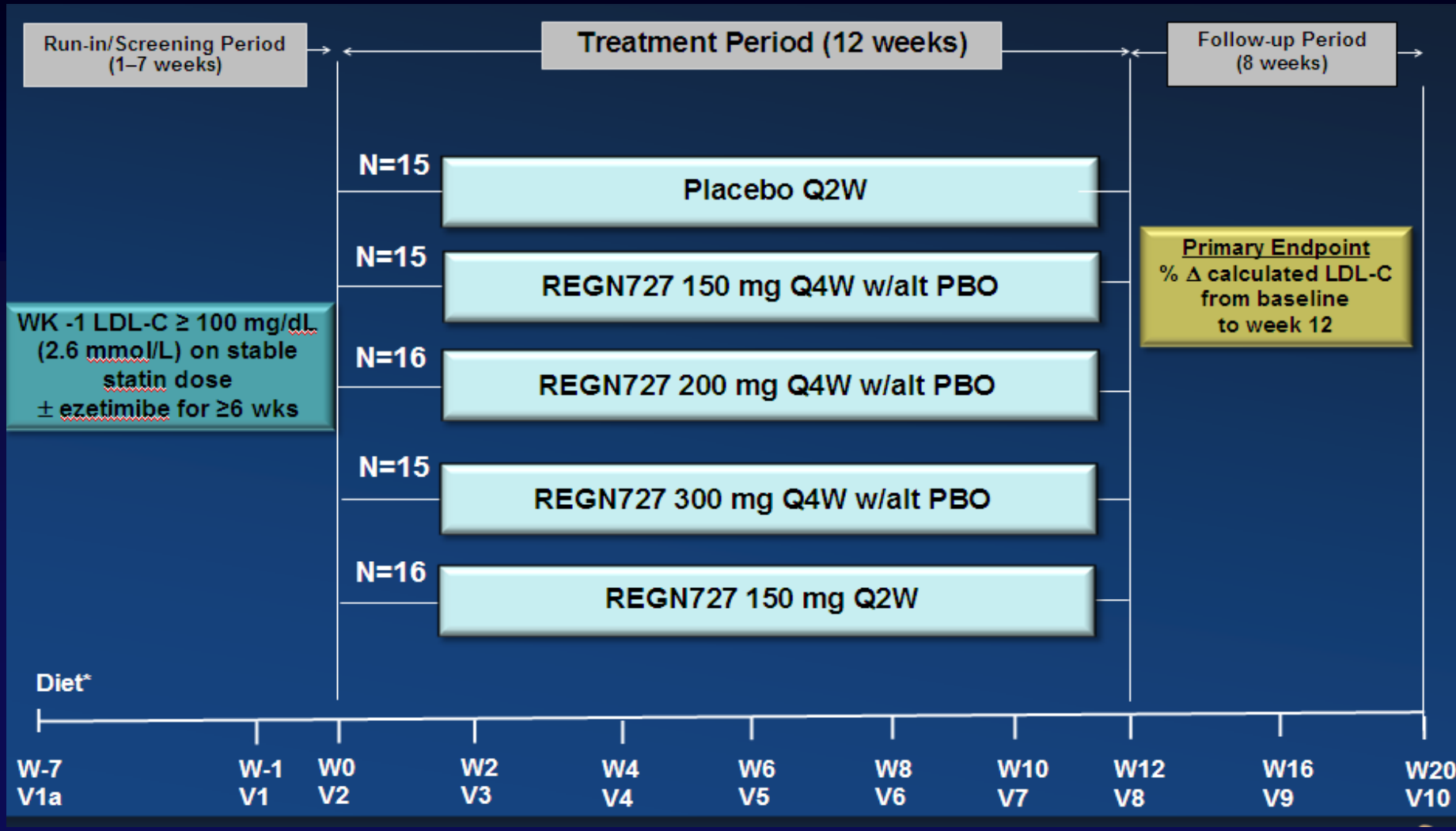
A Randomized, Double-Blind, Placebo-Controlled Trial of the Safety and Efficacy of a Monoclonal Antibody to PCSK9, REGN727/SAR236553, in Patients with Heterozygous Familial Hypercholesterolemia on Stable Statin Dose With or Without Ezetimibe Therapy

Evan A. Stein, Dan Gipe, Jean Bergeron, Daniel Gaudet, Robert Weiss, Robert Dufour, Richard Wu, Robert Pordy. Lancet, May 2012

The Use of a PCSK9 Monoclonal AB in heFH Patients

- The goal of this Phase II trial was to evaluate the LDL-C efficacy and safety of REGN727/SAR236553 in:
  - A larger population
  - More diverse HeFH population in terms of LDLr defects
  - More severely affected and aggressively treated group of HeFH patients, including those with CAD
  - Assess multiple and higher doses combined with different dosing regimens of REGN727/SAR236553

The Use of a PCSK9 Monoclonal AB in heFH Patients



The Use of a PCSK9 Monoclonal AB in heFH Patients

Number of randomized patients	77
Age, mean	53.4 years
Female	39.0%
White race	94.8%
BMI, kg/m^2	29.1
Coronary artery disease	41.6%
Type 2 diabetes	3.9%
'High-dose' statin treatment*	76.6%
Ezetimibe treatment	71.4%

*atorvastatin 40 mg/80 mg; rosuvastatin 20 mg/40 mg; simvastatin 80 mg.

The Use of a PCSK9 Monoclonal AB in heFH Patients: Results

Intervention	Baseline LDL-C mg/dL [mmol/L]	% Change LDL-C[1]
Placebo	150.8 [3.9]	–10.7 (5.0)
REGN727 150 mg Q4W	166.7 [4.3]	–28.9 (5.1)*
REGN727 200 mg Q4W	169.8 [4.4]	–31.5 (4.9)*
REGN727 300 mg Q4W	139.6 [3.6]	–42.5 (5.1)*
REGN727 150 mg Q2W	147.2 [3.8]	–67.9 (4.9)*

*$P<0.0001$ for % change REGN727 vs. Placebo.

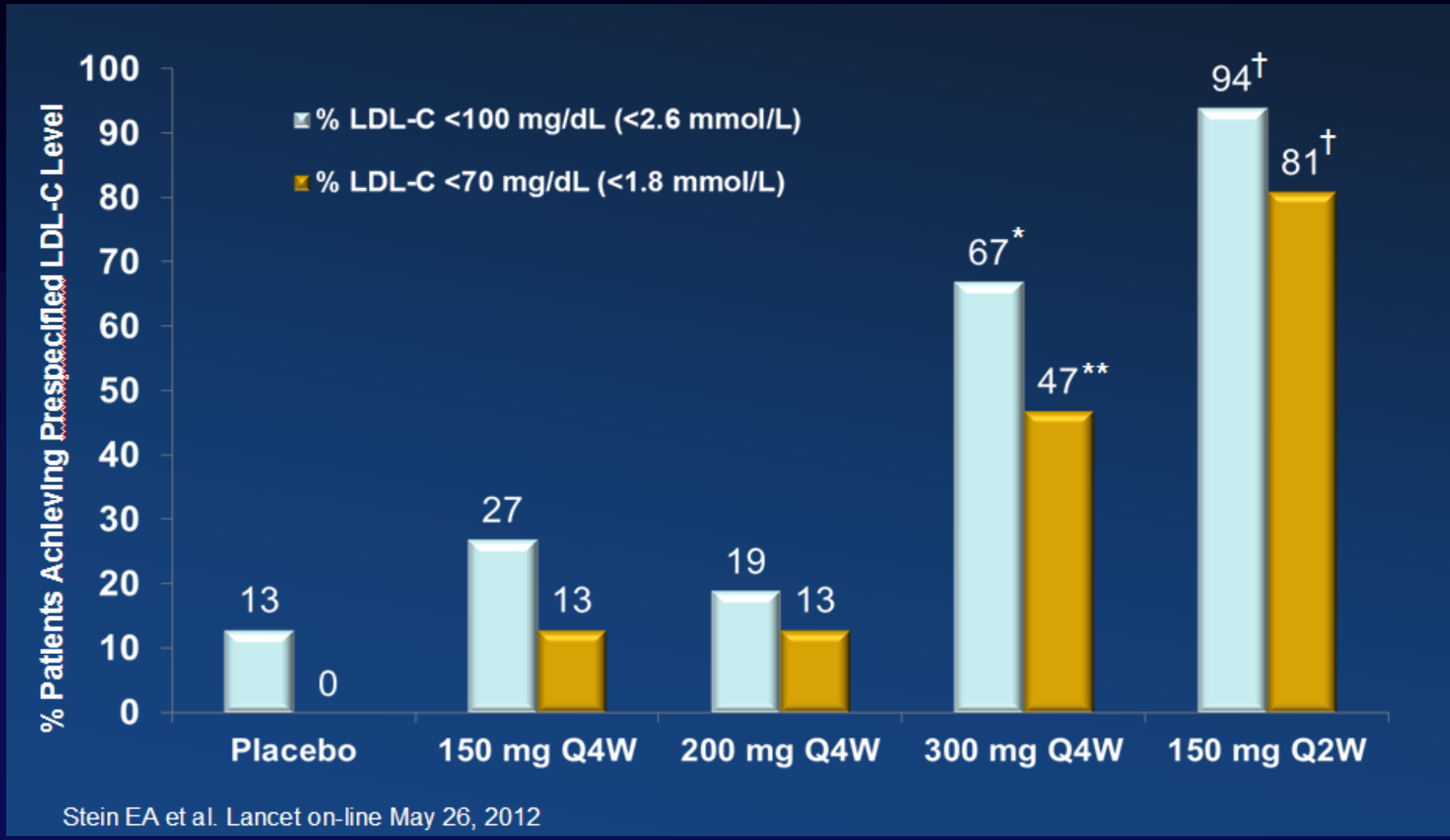
[1]LS mean (SE), using LOCF method.

Stein EA et al. Lancet on-line May 26, 2012

The Use of a PCSK9 Monoclonal AB in heFH Patients: Results

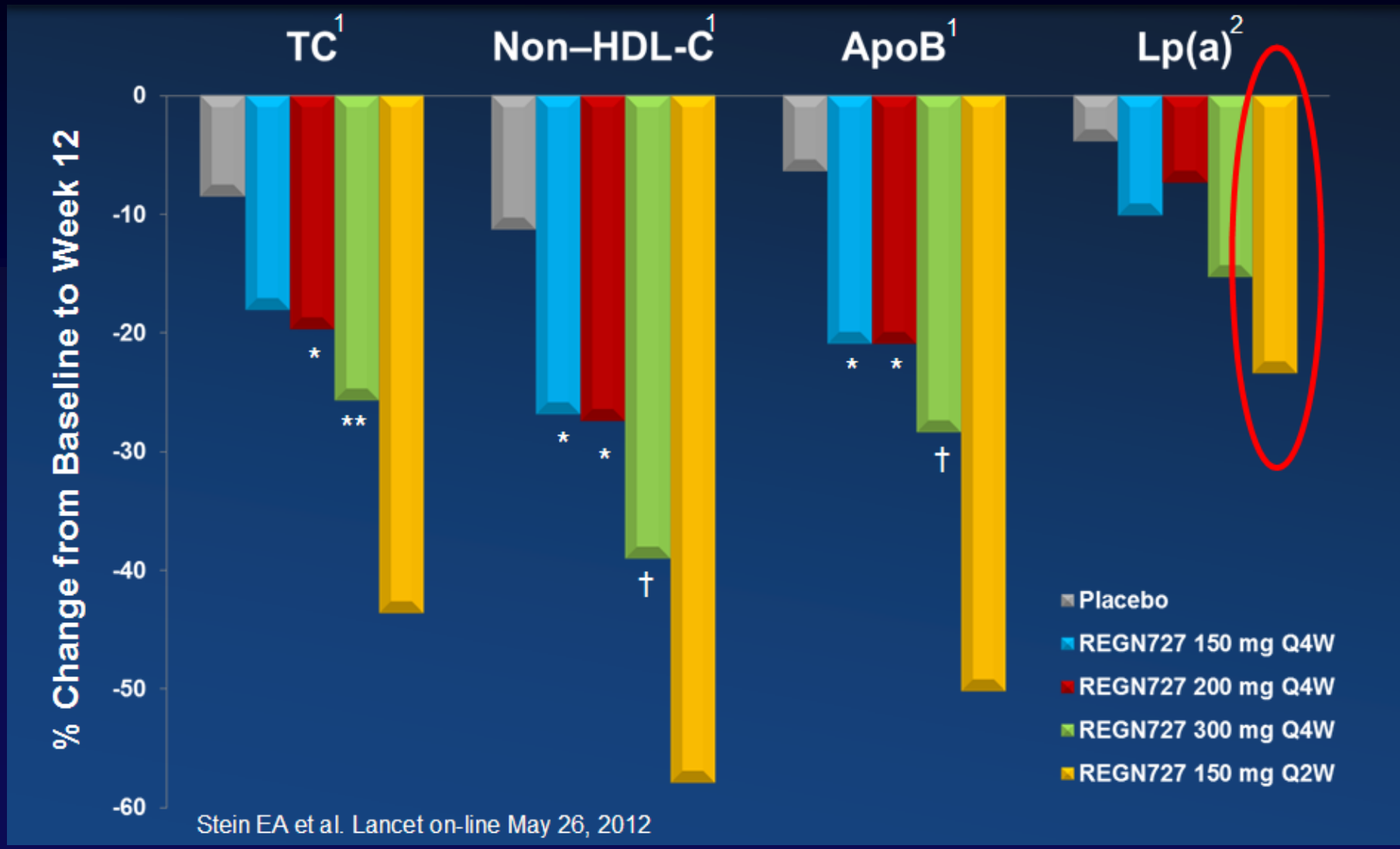
Stein EA et al. Lancet on-line May 26, 2012

The Use of a PCSK9 Monoclonal AB in heFH Patients: Goal Attainment



Stein EA et al. Lancet on-line May 26, 2012

The Use of a PCSK9 Monoclonal AB in heFH Patients: Secondary Results



The Use of a PCSK9 Monoclonal AB in heFH Patients: Safety

	PBO (n=15)	150 mg Q4W (n=15)	200 mg Q4W (n=16)	300 mg Q4W (n=15)	150 mg Q2W (n=16)
Creatinine, mg/dL (Mean [SD])					
Baseline	0.7 (0.1)	0.9 (0.1)	0.8 (0.2)	0.8 (0.2)	1.0 (0.2)
Week 12	0.7 (0.1)	0.8 (0.1)	0.8 (0.2)	0.8 (0.2)	0.9 (0.2)
Glucose, mg/dL (Mean [SD])					
Baseline	98.7 (10.7)	98.5 (8.5)	102.6 (18.2)	95.1 (6.9)	104.1 (15.1)
Week 12	98.7 (7.7)	95.6 (9.2)	98.4 (18.9)	95.9 (11.8)	101.8 (11.7)
ALT, IU/L >3x ULN, n	0	0	0	0	0
AST, IU/L >3x ULN, n	0	0	0	0	0
Creatinine kinase, IU/L >3x ULN, n	0	0	0	0	0
hsCRP mg/L, (Median [Q1;Q3])					
Baseline	0.9 (0.4; 1.6)	0.6 (0.3; 1.4)	0.7 (0.5; 2.5)	0.7 (0.5; 1.3)	1.4 (0.6; 3.4)
Week 12	0.7 (0.4; 1.2)	0.4 (0.3; 1.4)	0.7 (0.5; 1.3)	0.6 (0.4; 1.7)	1.0 (0.7; 3.7)

hsCRP=high sensitivity C-reactive protein; PBO=Placebo.

Stein EA et al. Lancet on-line May 26, 2012

The Use of a PCSK9 Monoclonal AB in Hypercholesterolemic Patients

LAPLACE-TIMI 57 Primary Results

A Double-blind, Randomized, Placebo-controlled, Dose-ranging Study to Evaluate the Efficacy, Safety, and Tolerability of a Monoclonal Antibody to PCSK9 in Combination with a Statin in Patients with Hypercholesterolemia

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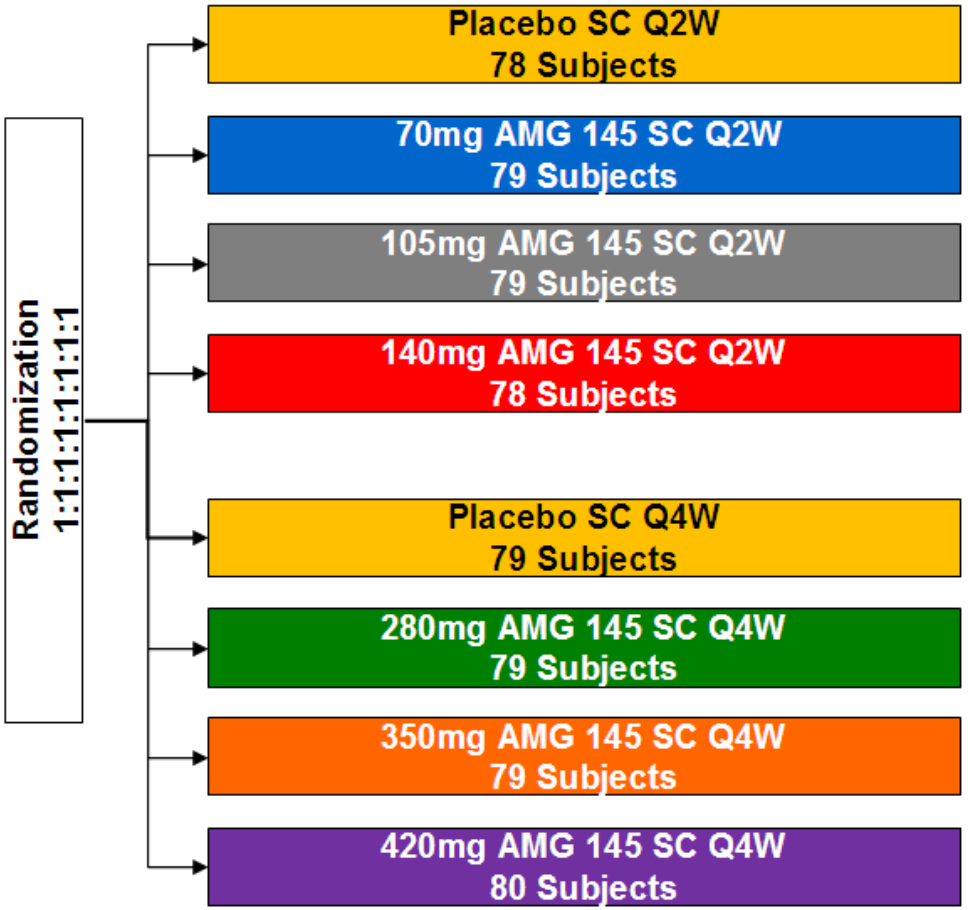
Supported by research grant from Amgen, Inc.

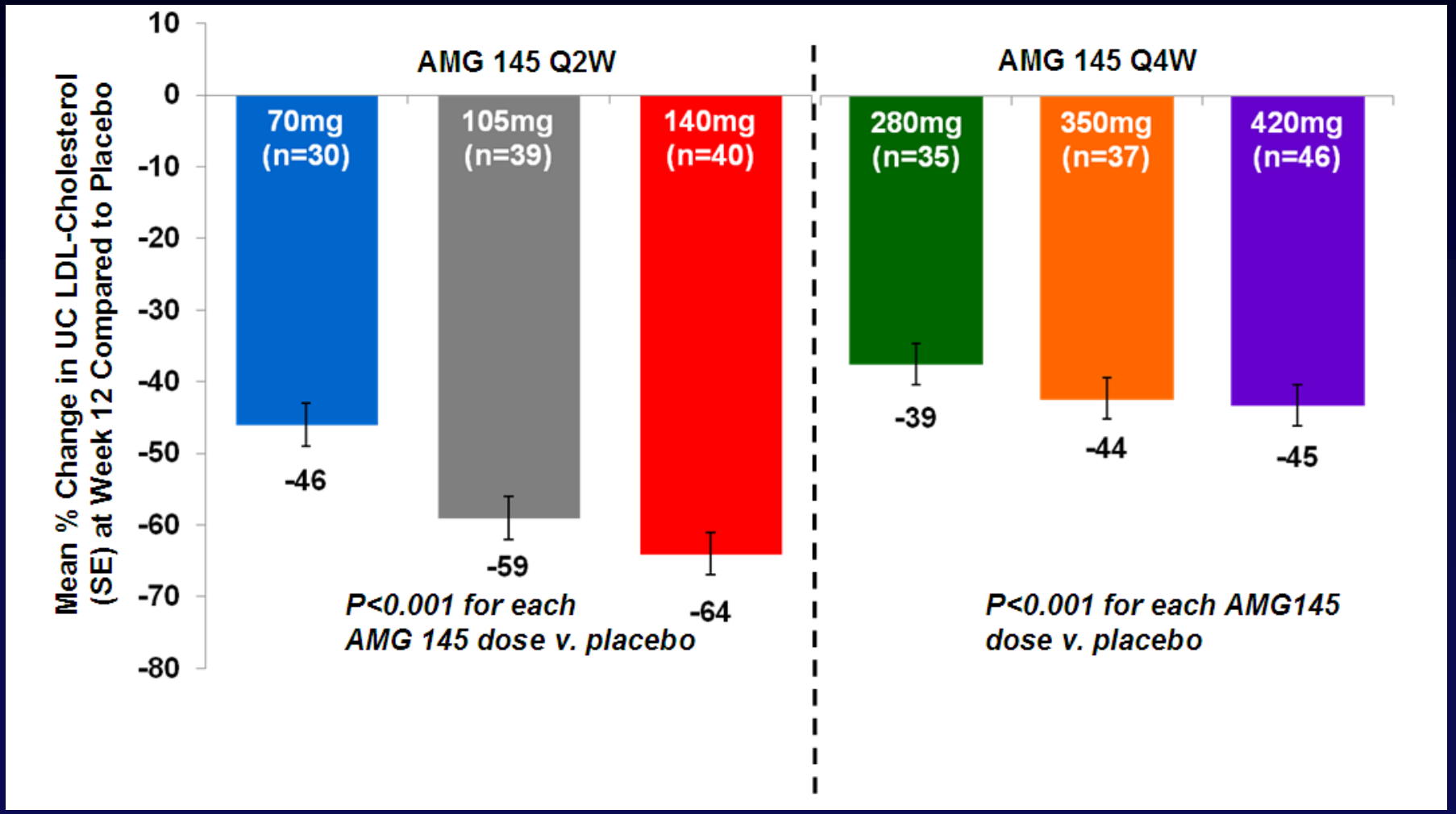
The Use of a PCSK9 Monoclonal AB in Hypercholesterolemic Patients

- A global, randomized, double-blind, phase 2 trial
- Patients
  - 18–80 years
  - On stable dose of statin ± ezetimibe
  - LDL-C ≥ 85 mg/dL



Kohli P, et al. *Clin Cardiol*. 2012;35:385-391.

The Use of a PCSK9 Monoclonal AB in Hypercholesterolemic Patients: Results



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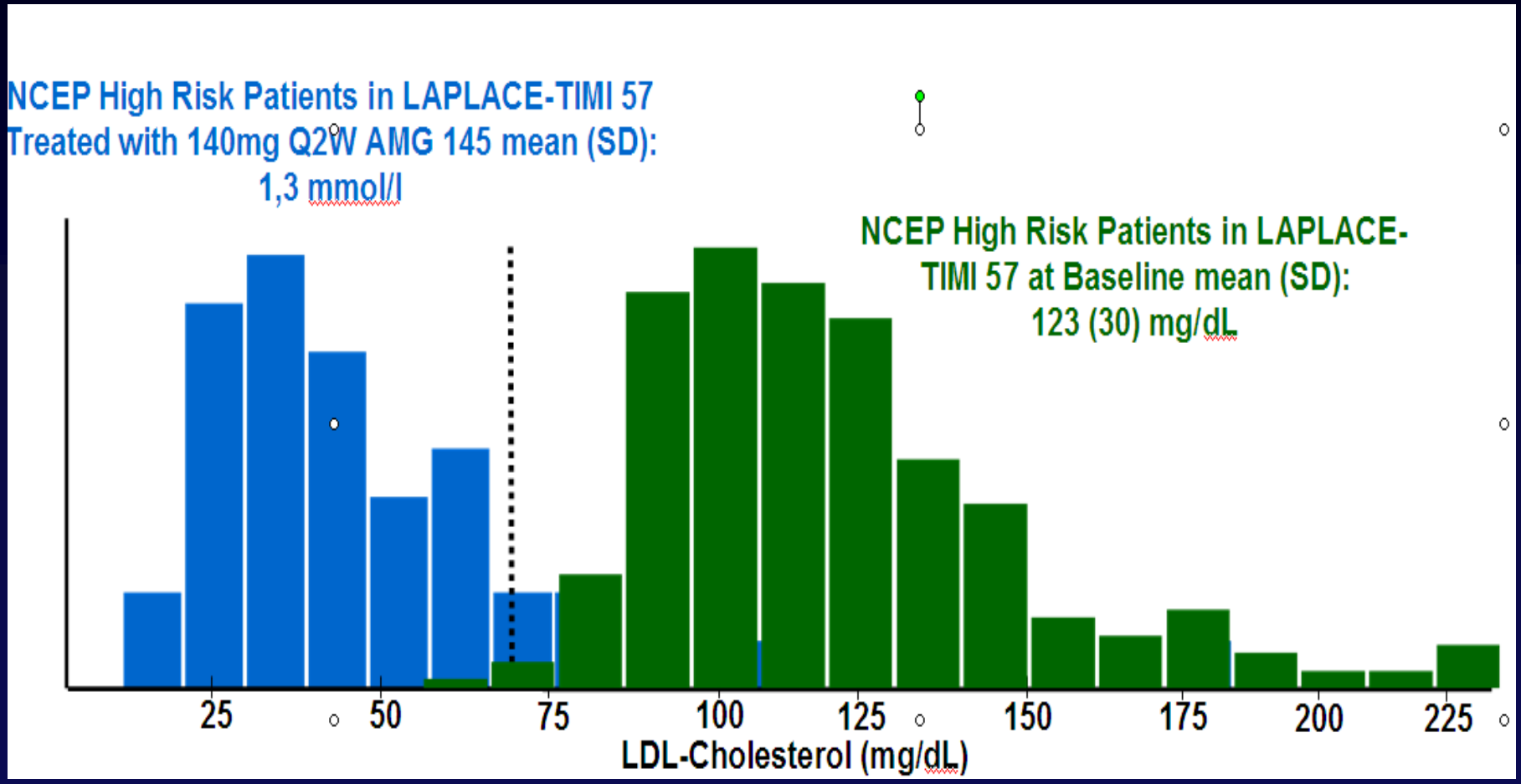

Conclusion

In the next five years, we will prove or disprove that additional LDL lowering with other agents than statins is effective

and

we will show or not show that the HDL hypothesis is true.