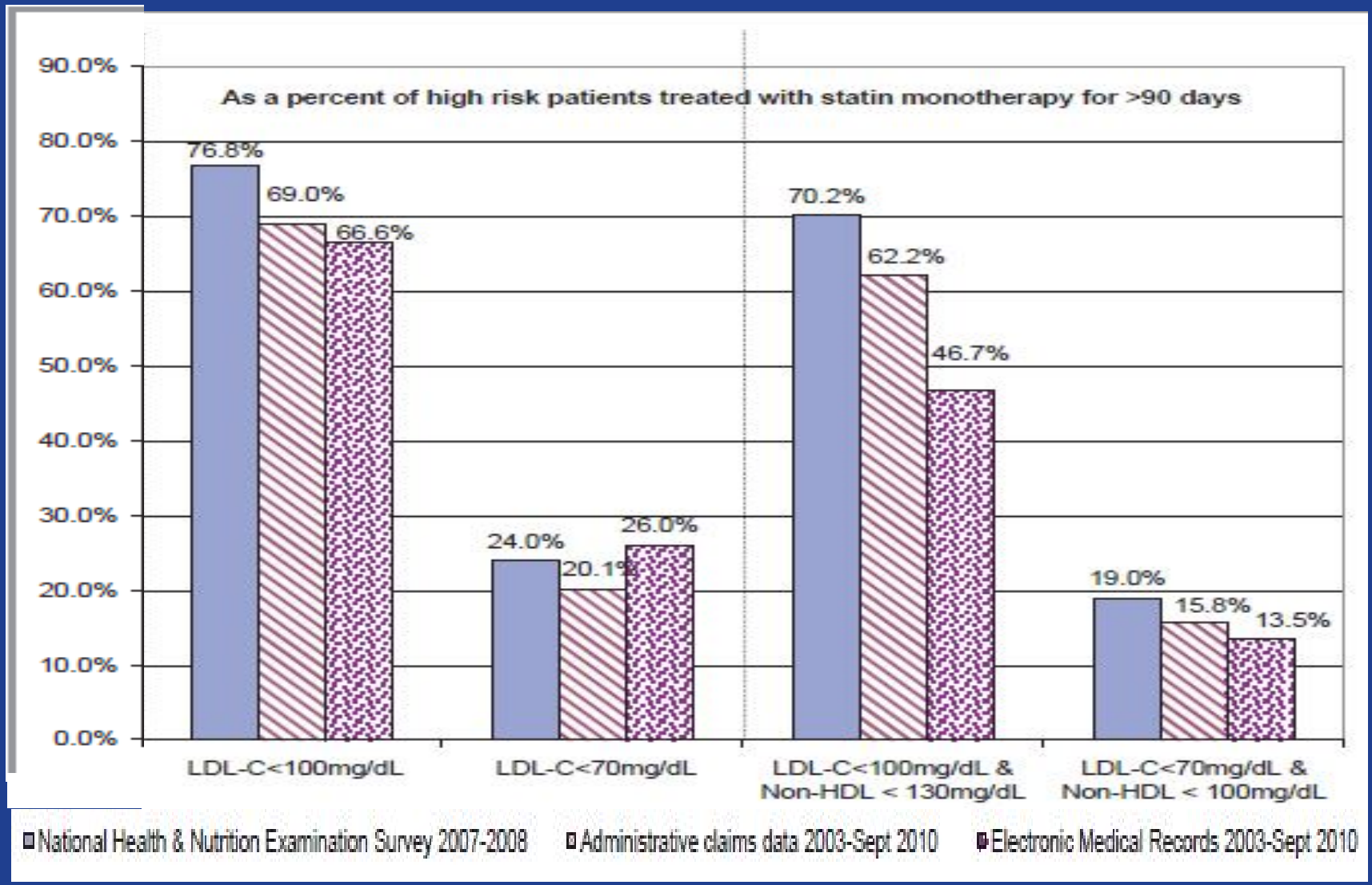
טיפולים חדשים בדיסליפידמיה

ד"ר רפי ביצור

מרכז שטרסבורגר לליפידים

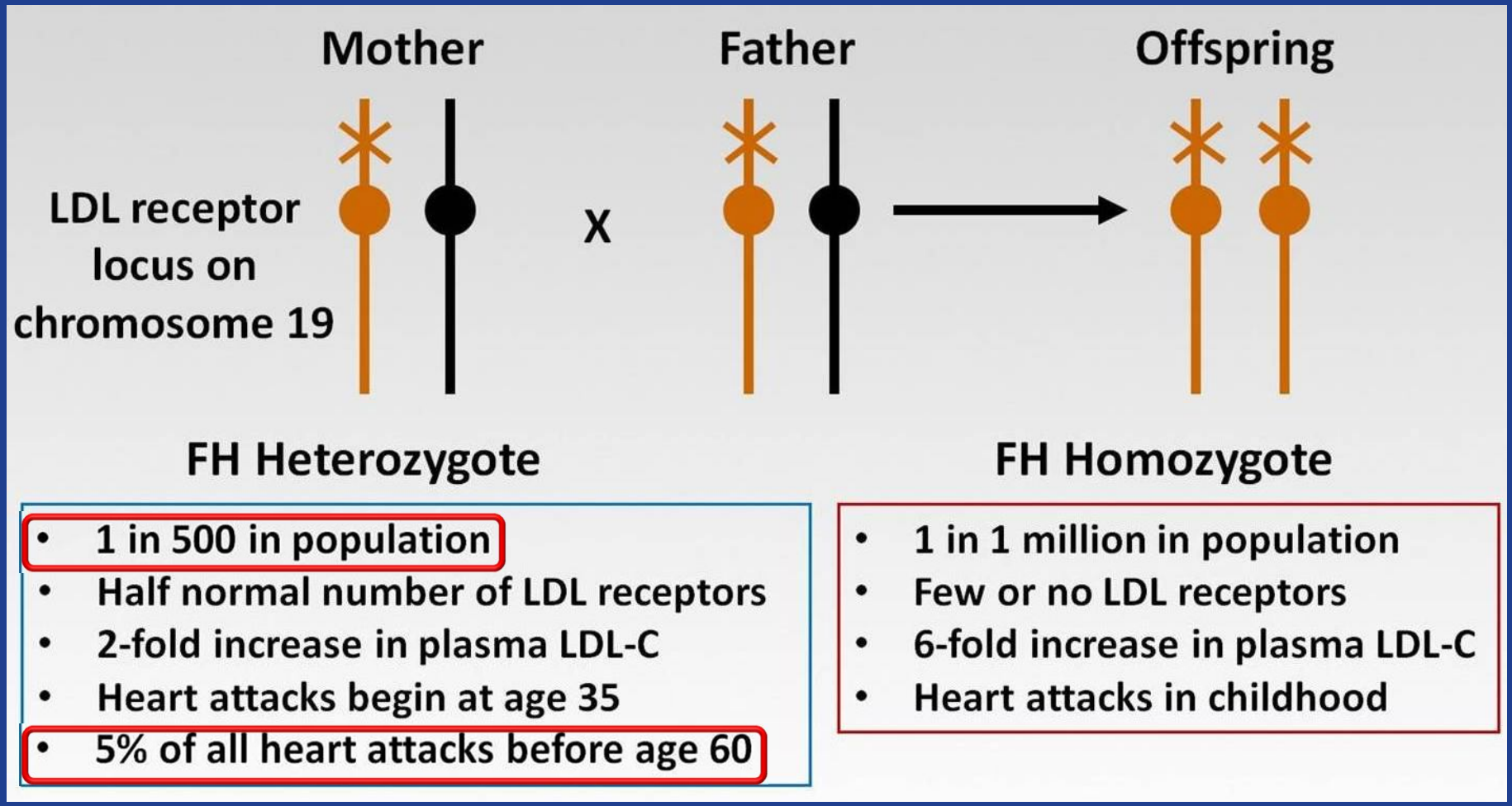
המרכז הרפואי ע"ש שיבא, תל-השומר

LDL-C Goal Attainment of High-Risk Patients Treated with Statins



J Am Heart Assoc. 2012

Familial Hypercholesterolemia



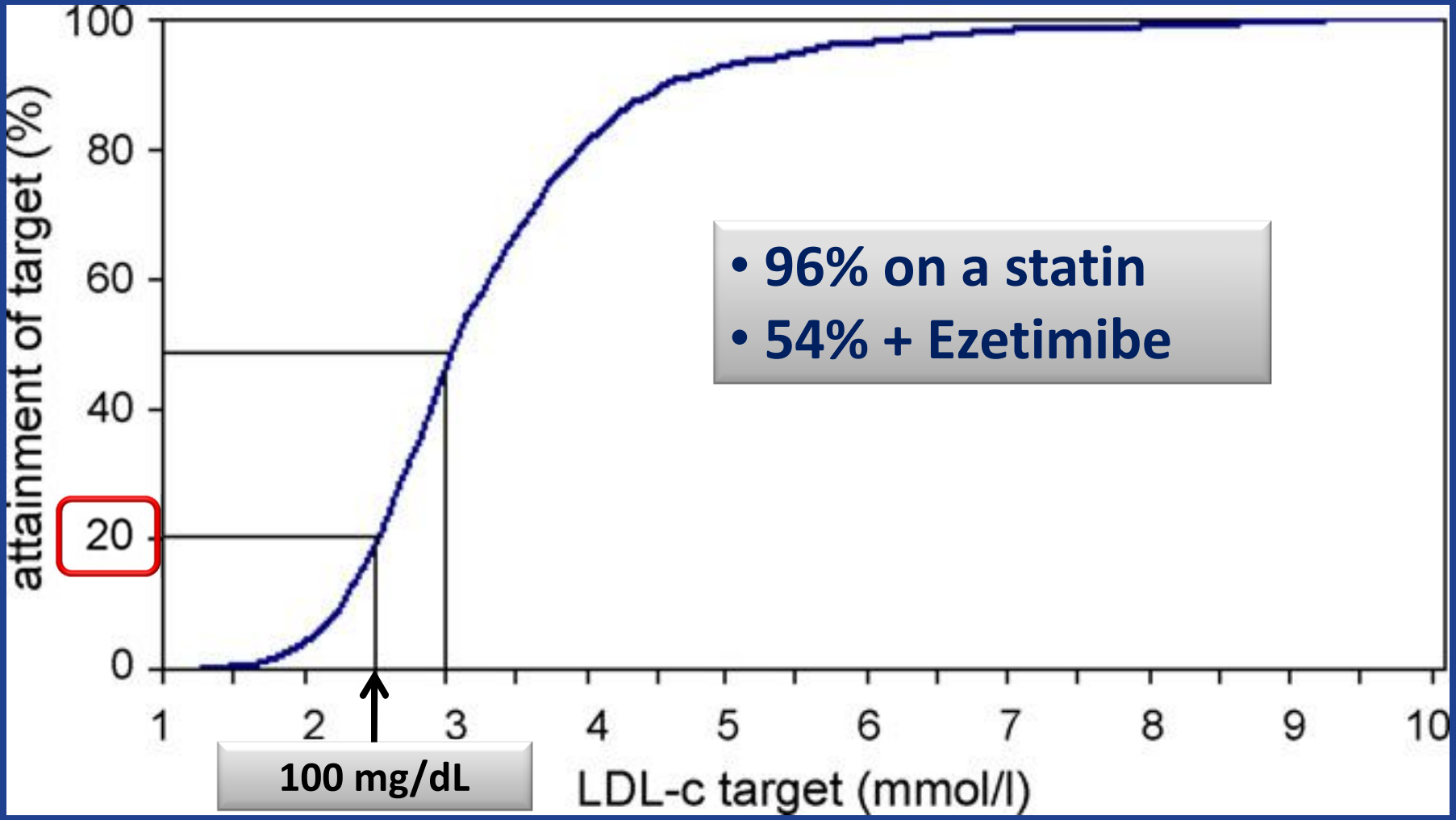
FH Heterozygote

- 1 in 500 in population
- Half normal number of LDL receptors
- 2-fold increase in plasma LDL-C
- Heart attacks begin at age 35
- 5% of all heart attacks before age 60

FH Homozygote

- 1 in 1 million in population
- Few or no LDL receptors
- 6-fold increase in plasma LDL-C
- Heart attacks in childhood

LDL-C Goal Attainment in 1249 Patients with HeFH in the Netherlands



Atherosclerosis. 2010;209:189–94

Mortality in Statin-Treated FH Patients

Mortality from CVD/CHD and all causes in statin-treated patients with HeFH compared with the general population

	Relative Risk (95% CI)
Total mortality	1.5 (1.0, 2.3) men 1.0 (0.5, 1.9) women
CVD mortality*	1.4 (0.6, 3.3)
CHD mortality*	2.6 (1.1, 6.3)

- Statin therapy started at a mean age of 42 years
- Mean TC upon treatment: > 7 mmol/L

*No history of CVD (patients in primary prevention). For total mortality: 345 statin-treated patients; for CVD and CHD mortality: 214 statin-treated patients.

Atherosclerosis 2004;172:329-35

Statin-Induced Myopathy

Population	Muscular Adverse Effect	Citation
Managed care population	Myositis from 33* to 6400*	McClure DL, et al. *J Clin Epidemiol.* 2007;60:812-818.
Cohort of historical pharmacy and medical data (215,191 patients)	Myopathy with mild elevation of CK: 640/100,000 patients	Chan J. *Ann Pharmacother.* 2005;39:1611-1616.
FDA reporting system	Rhabdomyolysis: 0.7/100,000 patients	Kashani A, et al. *Circulation.* 2006; 114:2788-2797.
Observational study with high dosage (7924 patients)	Myopathy: 10.5%	Bruckert E, et al. *Cardiovasc Drug Ther.* 2005;19:403-414.
Market survey interview (10,000)	Myopathy: 10%	Rosenbaum D, et al. *Nutr Metab Cardiovasc Dis.* 2012. [Epub ahead of print]
Observational cohort in England N = 2,004,692 (30-84 y)	Moderate /serious myopathy incidence: women, 10.8*and men, 19.6*	Hippisley-Cox J, Coupland C. *BMJ.* 2010;340:c2197.

*Per 100,000 person-years.

The NEW ENGLAND JOURNAL of MEDICINE

"…this population's needs are not being met…"

Perspective

Needed: Pragmatic Clinical Trials for Statin-Intolerant Patients

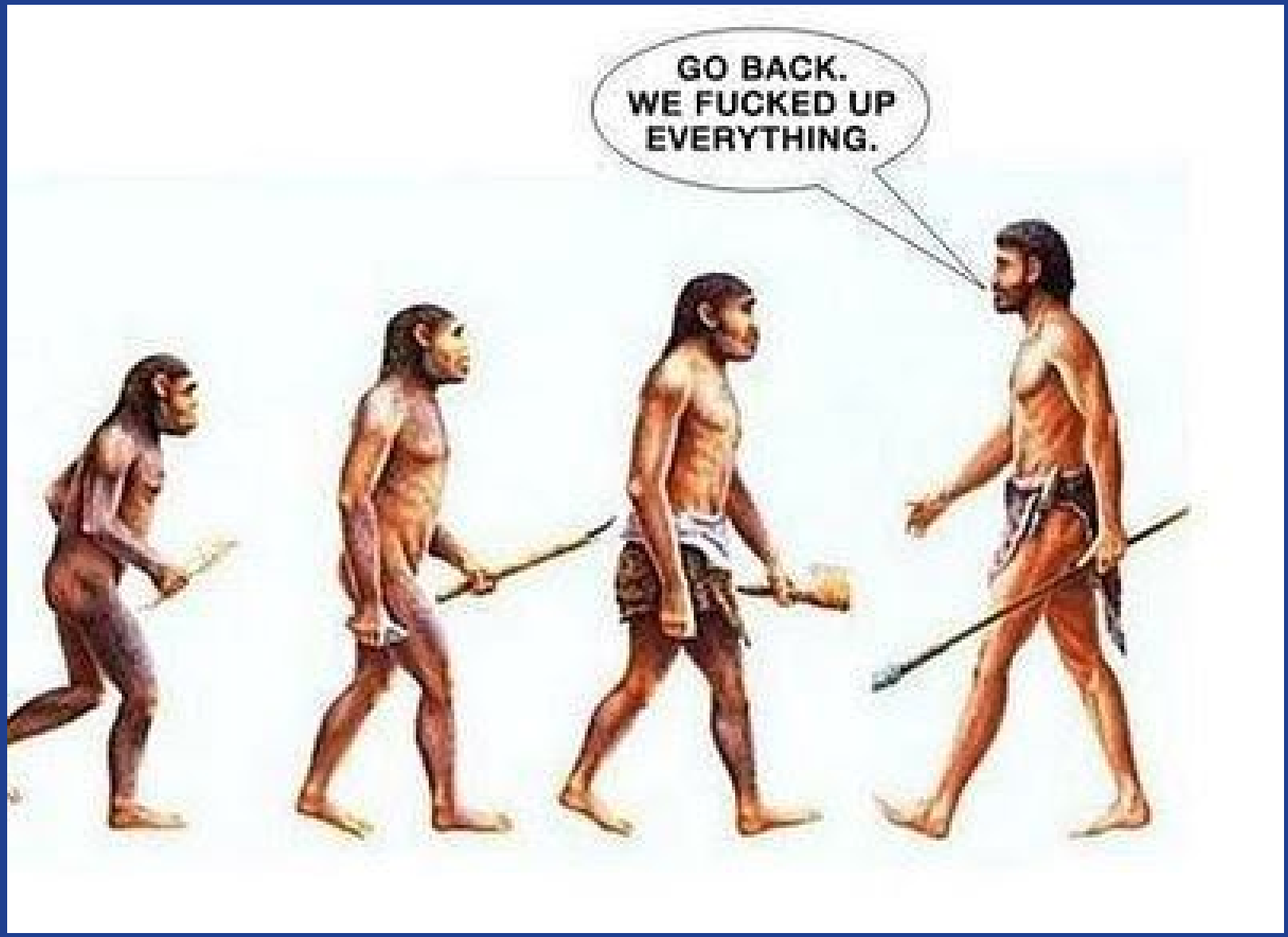
Patricia Maningat, M.D., and Jan L. Breslow, M.D.

N Engl J Med. 2011;365:2250-1

Drugs That Failed

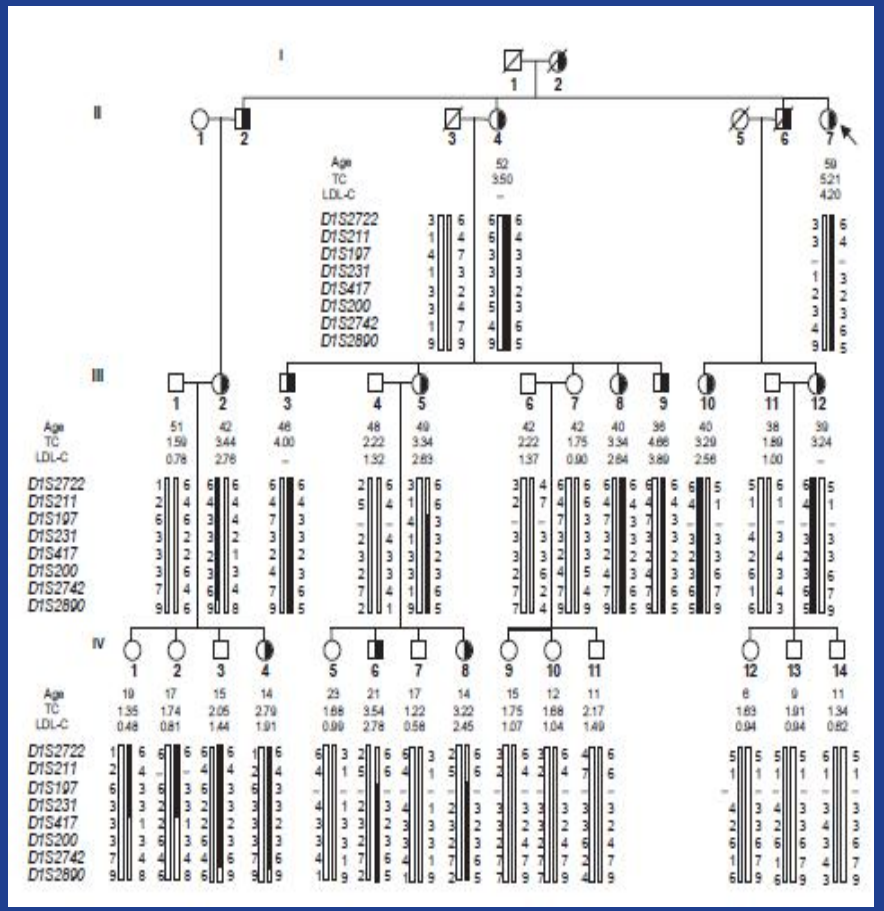
- Fibrates (ACCORD)
- Niacin (AIM-HIGH, HPS2-THRIVE)
- Eprotirome (AKKA)
- Omega 3 (Alpha-Omega)
- HRT (WHI)
- CETP inhibitors? (ILLUMINATE, dal-OUTCOMES)
- Ezetimibe? (IMPROVE-IT)

So, is it Hopeless?



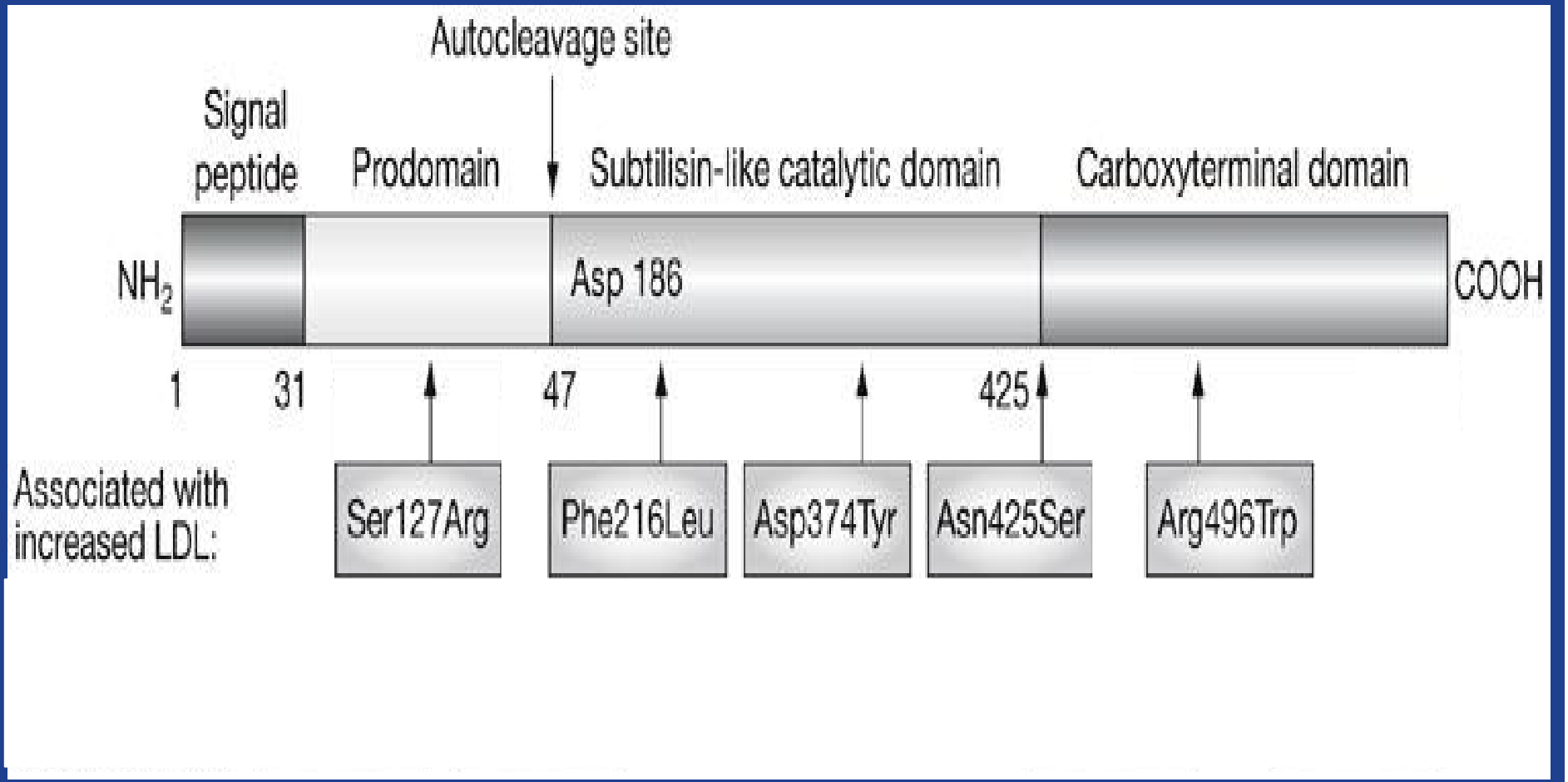
A New Gene Mutated in a Family with FH Phenotype

- Tendon xanthomas
- Early MI and stroke
- LDL-C > 250 mg/dL
- Autosomal dominant
- No mutations in LDL-R or ApoB genes



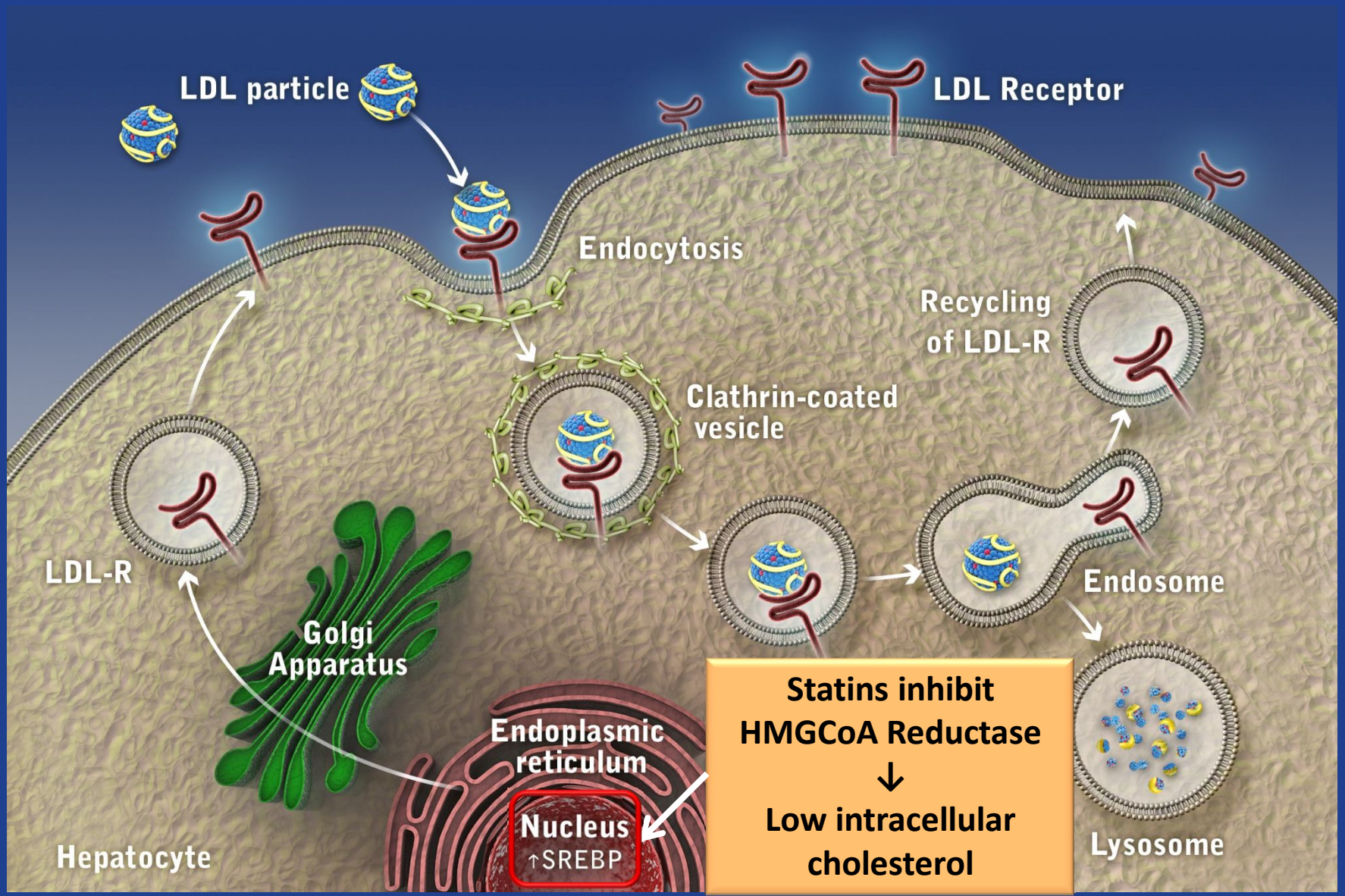
Nat Genet 2003;34:154-6

PCSK9 Gene
proprotein convertase subtilisin-like/kexin type 9

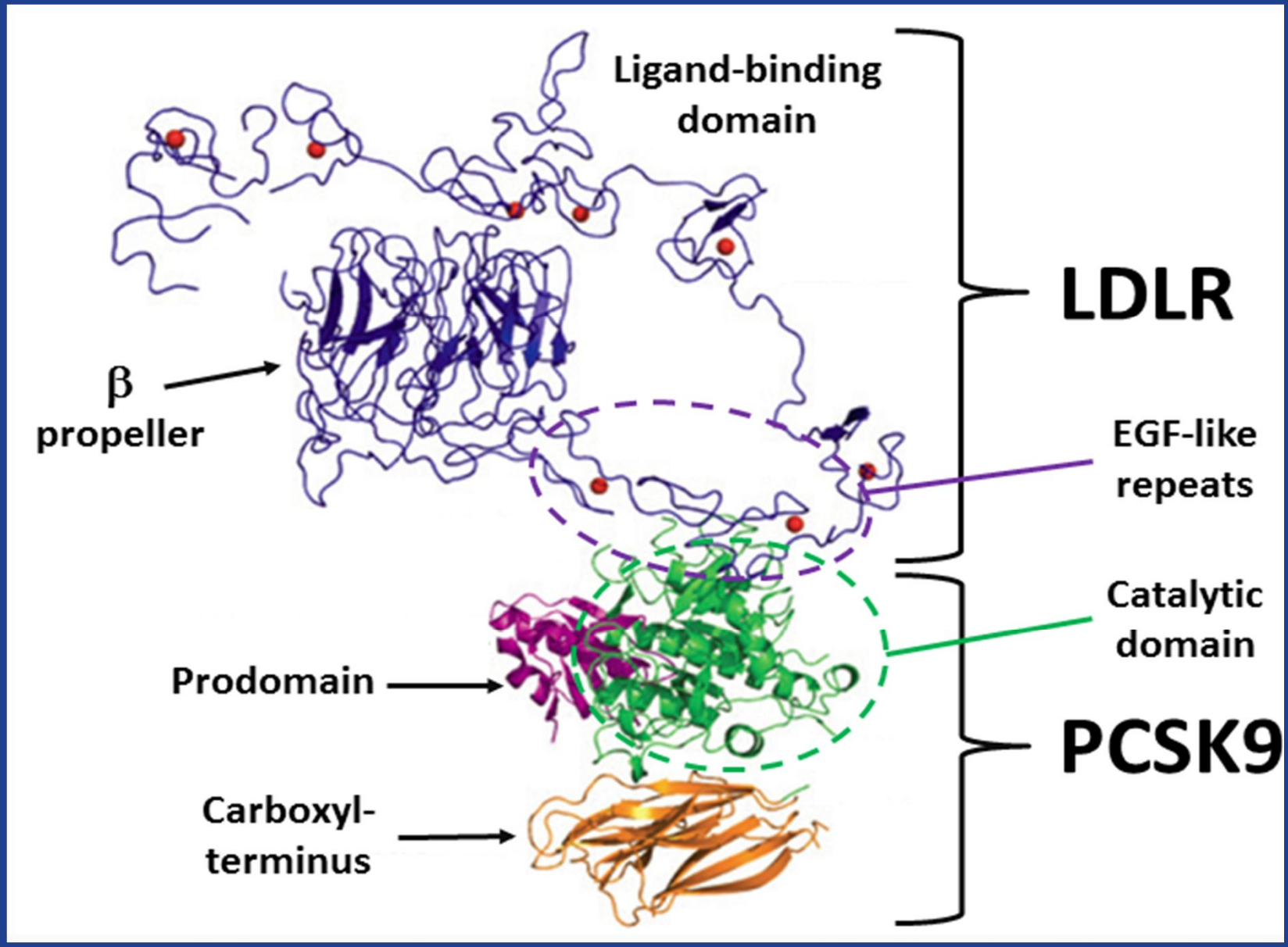


Nat Clin Pract Cardiovasc Med 2007;4: 214–225

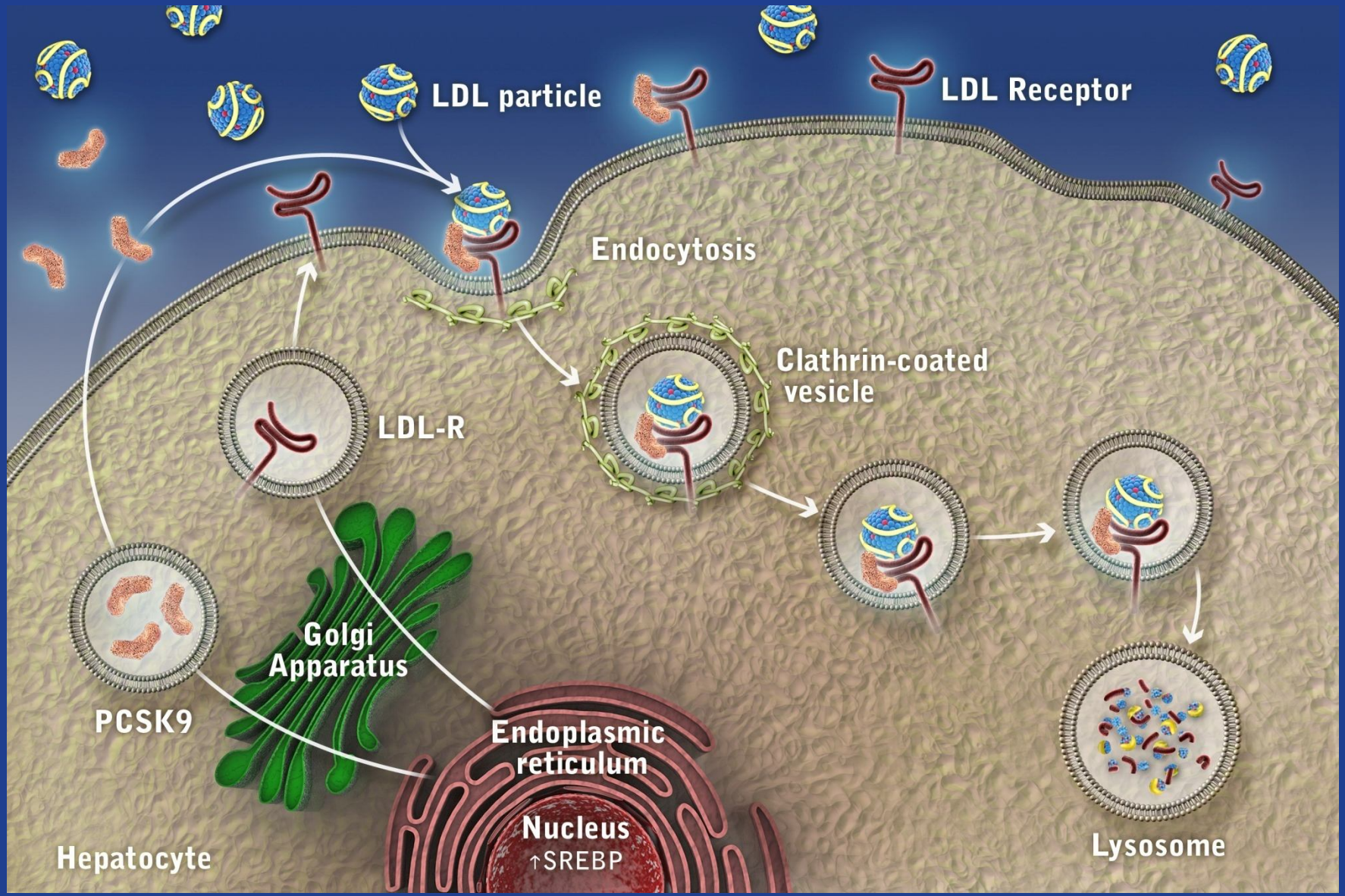
LDL Receptor Function and Life Cycle



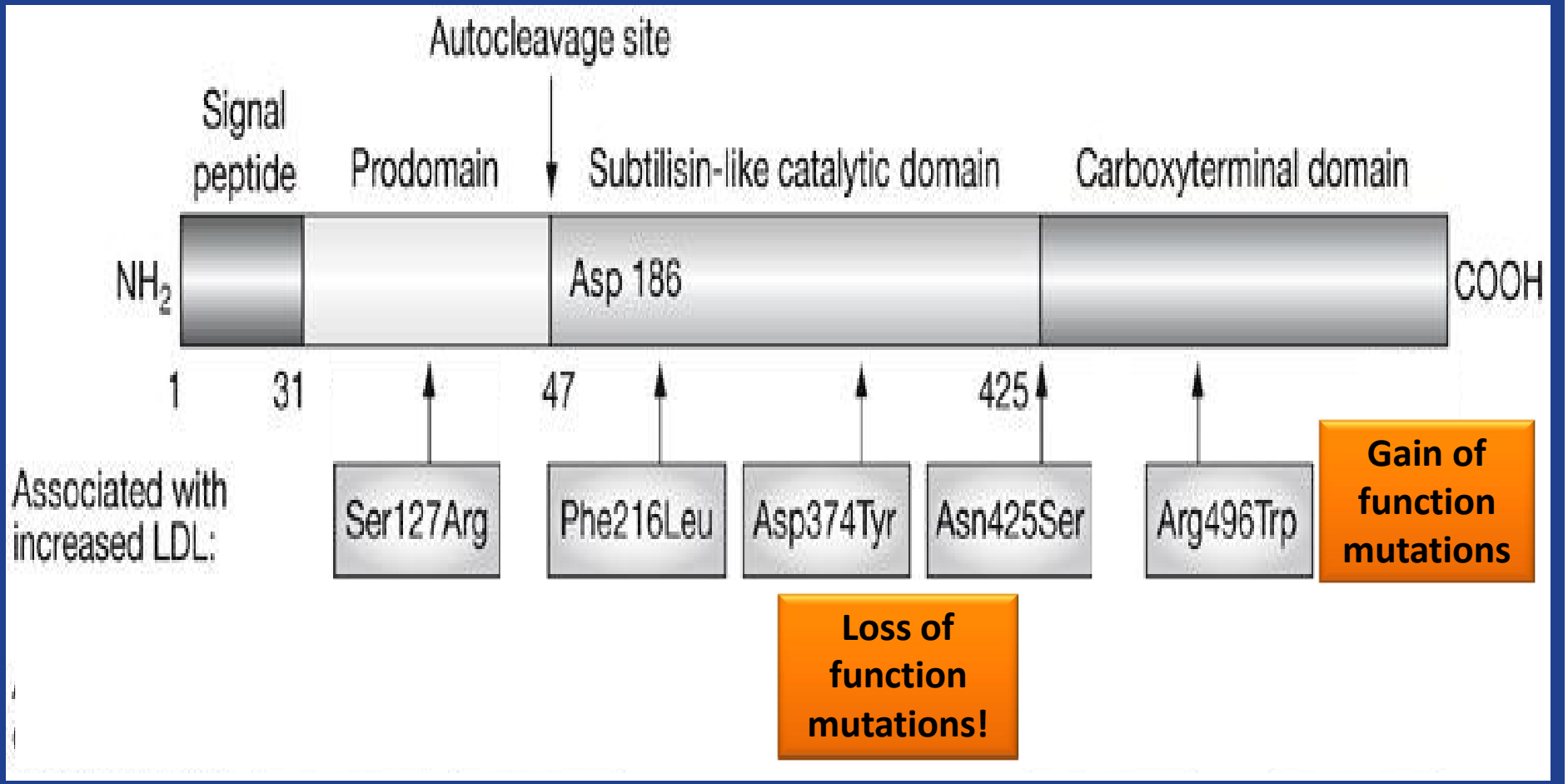
PCSK9 and the LDL Receptor



The Role of PCSK9 in the Regulation of LDL Receptor Expression



PCSK9 Gene



Nat Clin Pract Cardiovasc Med 2007;4: 214–225

Population studies of PCSK9 Loss of Function Mutations

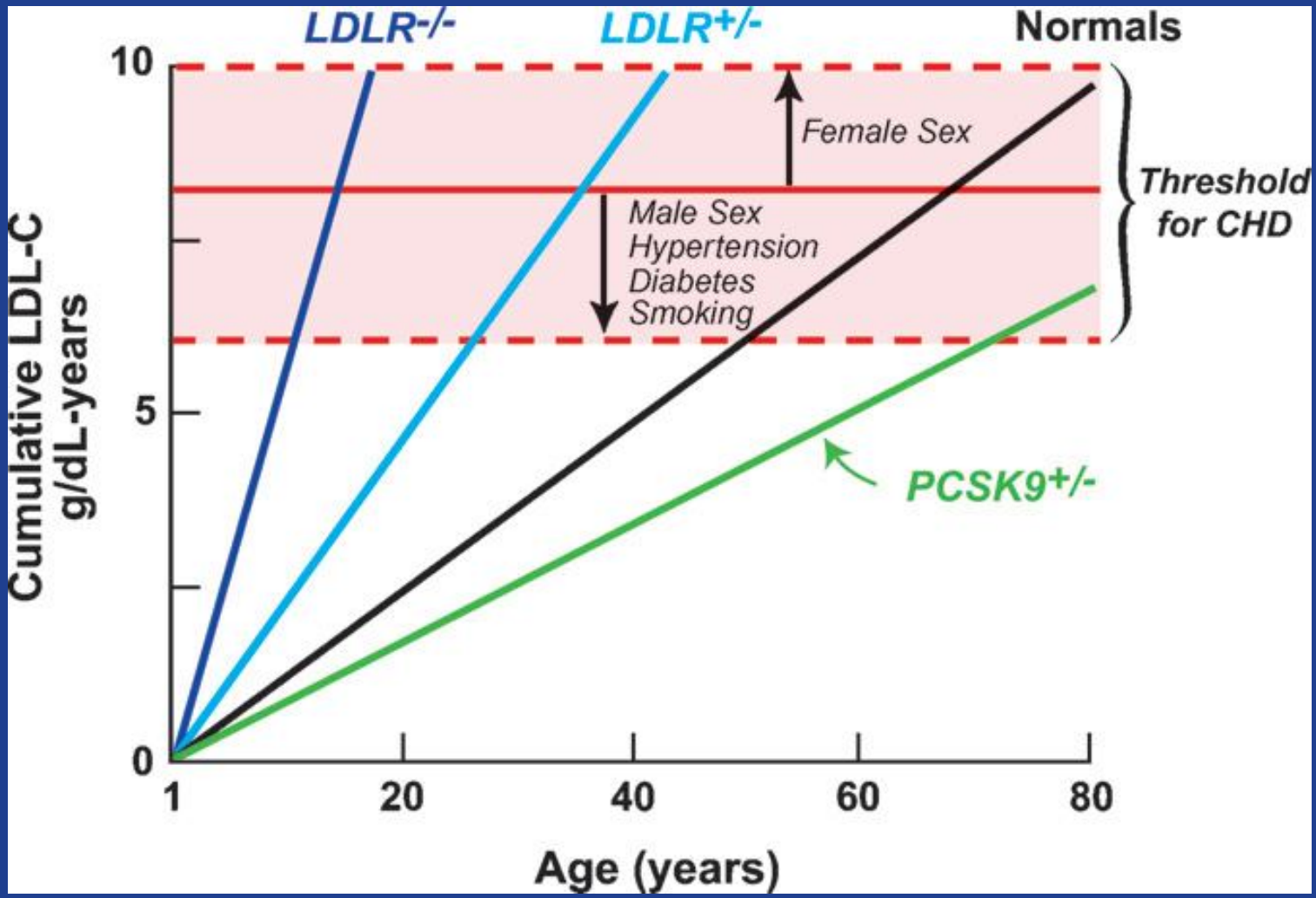
Patients with loss-of-function mutations in *PCSK9* or total lack of PCSK9

- Have naturally low levels of LDL-C and reduced coronary heart disease (→ efficacy)
- Are not associated with other detectable abnormalities (→ safety)

	PCSK9 Mutation	LDL-C Reduction	CHD Reduction	Population
Benn M, et al [1]	R46L	12%	46%	Copenhagen City Heart Study Copenhagen General Population Study Copenhagen Ischemic Heart Disease Study
Cohen JC, et al [2]	R46L	15%	47%	Atherosclerosis Risk in Community Study (US)
	Y142X or C679X	28%	88%	

[1]JACC 2010;55:2833-42
[2]NEJM 2006;354:1264-72

Relationship Between Cumulative LDL-C Exposure and Age

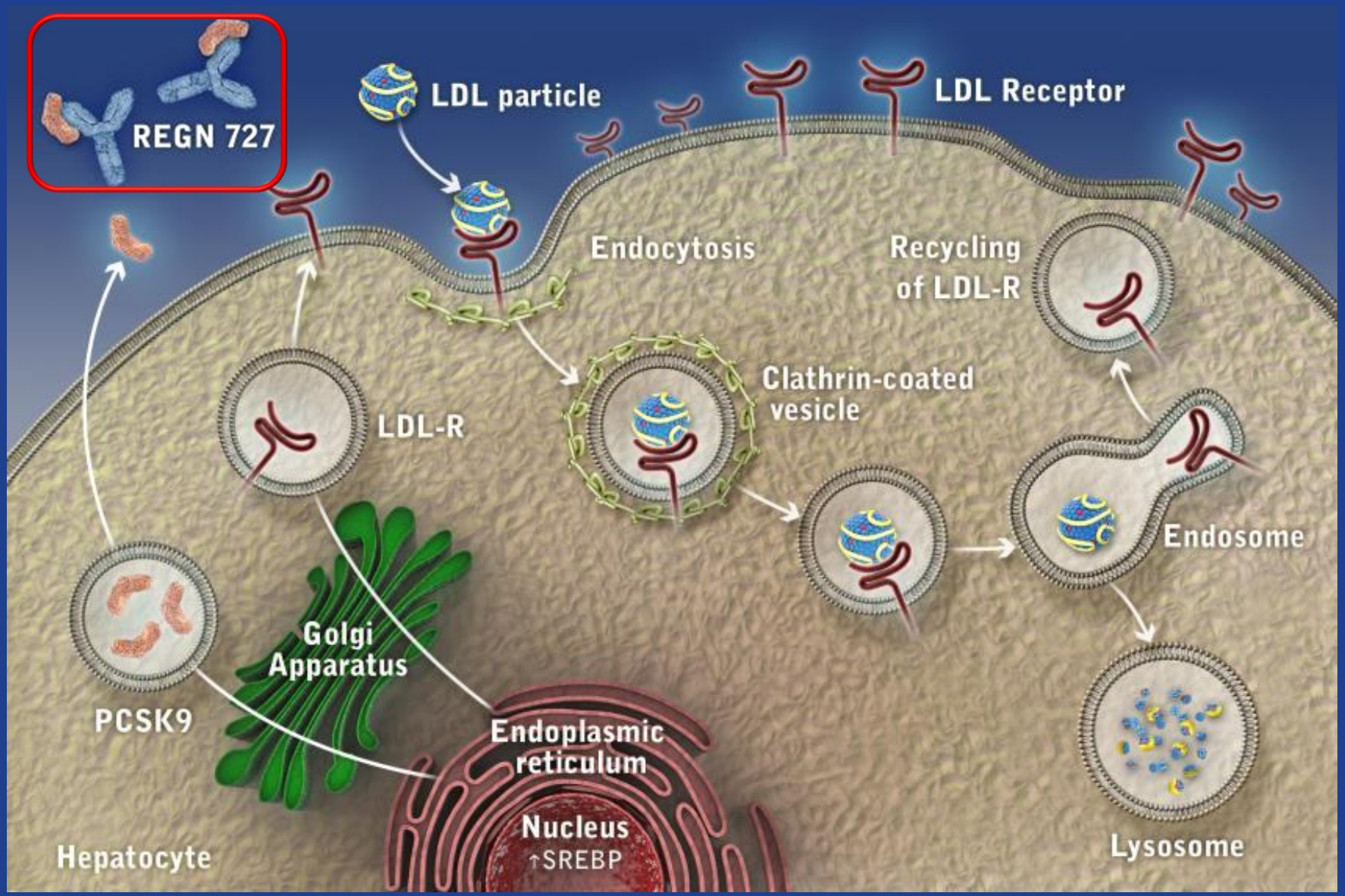


J. Lipid Res. 2009;50:S172-S177

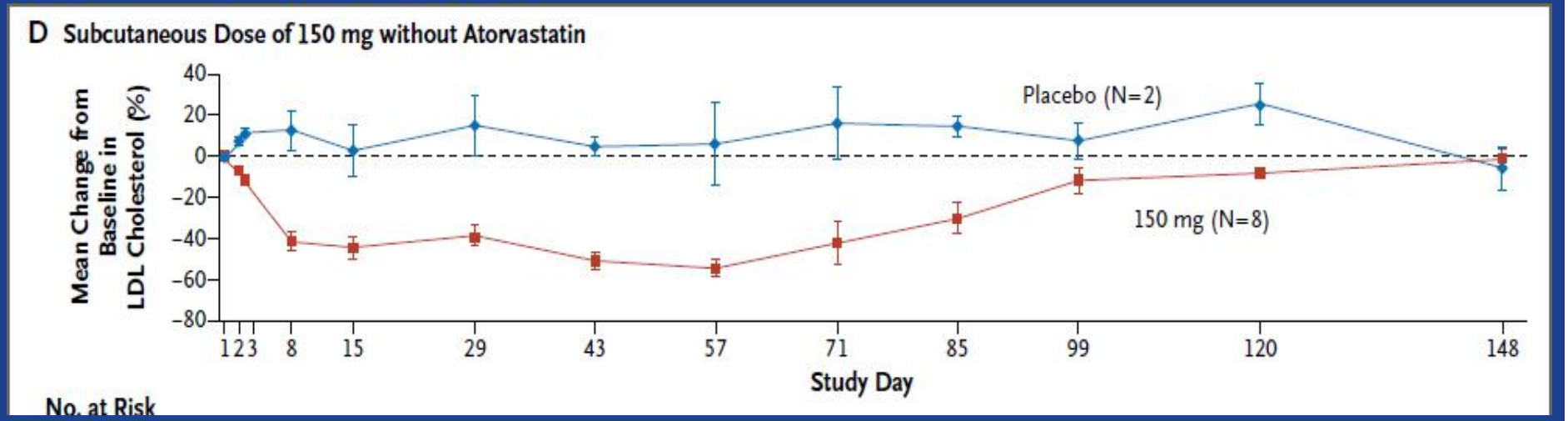
PCSK9 Directed Therapies in Development

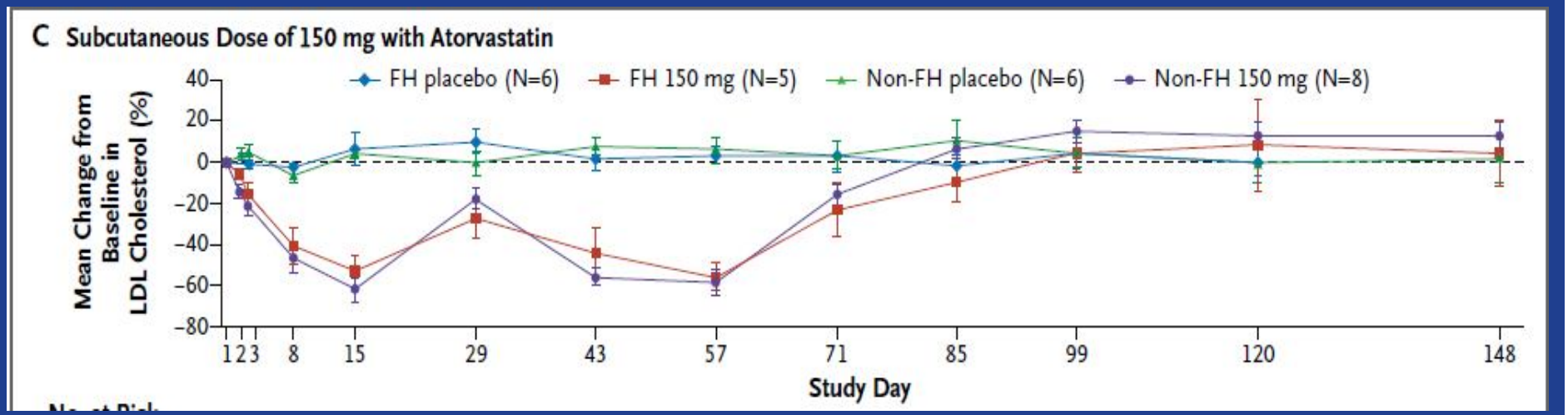
Company	Drug (Alternate Name)	Agent	Indication	Phase
Sanofi/Regeneron	SAR236553/REGN727	Human monoclonal antibody	Hypercholesterolemia	2
Amgen	AMG-145	Human monoclonal antibody	Hypercholesterolemia	2
Novartis	LGT-209	Monoclonal antibody	Hypercholesterolemia	2
Pfizer/Rinat	RN316 (PF-04950615)	Monoclonal antibody	Hypercholesterolemia	2
Genentech	MPSK3169A, RG7652	Monoclonal antibody	Hypercholesterolemia	2
Alnylam Pharmaceuticals	ALN-PCS02	siRNA oligonucleotide	Hypercholesterolemia	1
Adnexus Therapeutics/Bristol-Myers Squibb	BMS-962476	Fusion protein using Adnectin technology	Cardiovascular disease	Preclinical
Idera Pharmaceuticals	TBD	Antisense oligonucleotide	Hypercholesterolemia	Preclinical
Serometrix	SX-PCK9	Small peptide mimetic; LDLR antagonist	Hypercholesterolemia	Preclinical
Shifa Biomedical Corp.	TBD	Small molecule PCSK9 modulator	Metabolic disorders	Preclinical

Impact of an PCSK9 mAb on LDL Receptor Expression



Efficacy of SAR236553 in Patients With Hypercholesterolemia

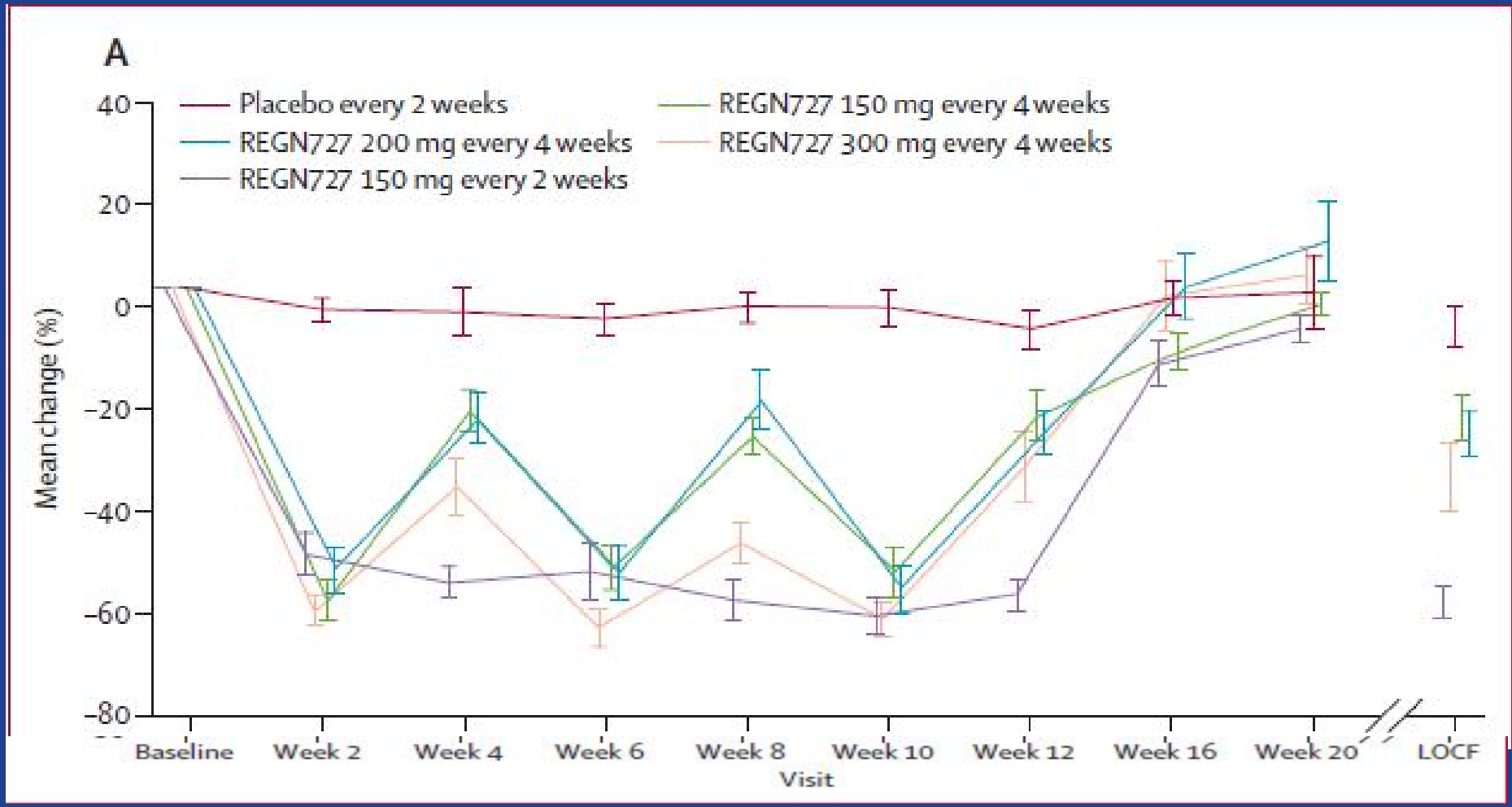




N Engl J Med 2012;366:1108-18

Efficacy of SAR236553 in Patients With HeFH

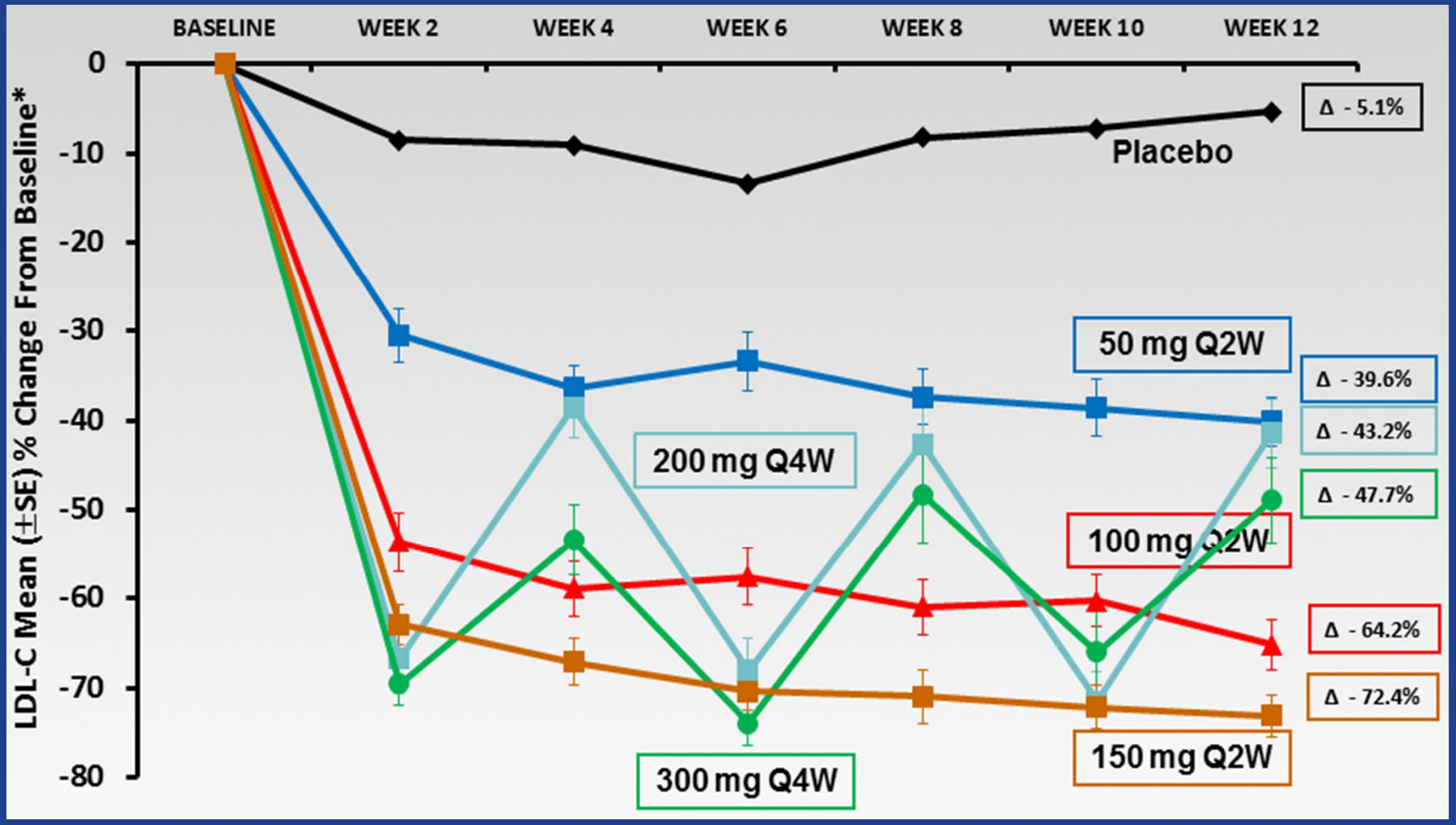
Patients with LDL-C >100 mg/dL on stable-dose statin ± ezetimibe



Lancet. 2012 ;380:29-36

Efficacy of SAR236553 in Patients With Primary Hypercholesterolemia

Patients with LDL-C >100 mg/dL on stable-dose atorvastatin 10, 20, or 40 mg



J Am Coll Cardiol 2012;59:2344–53

Efficacy of SAR236553 in Patients With Primary Hypercholesterolemia

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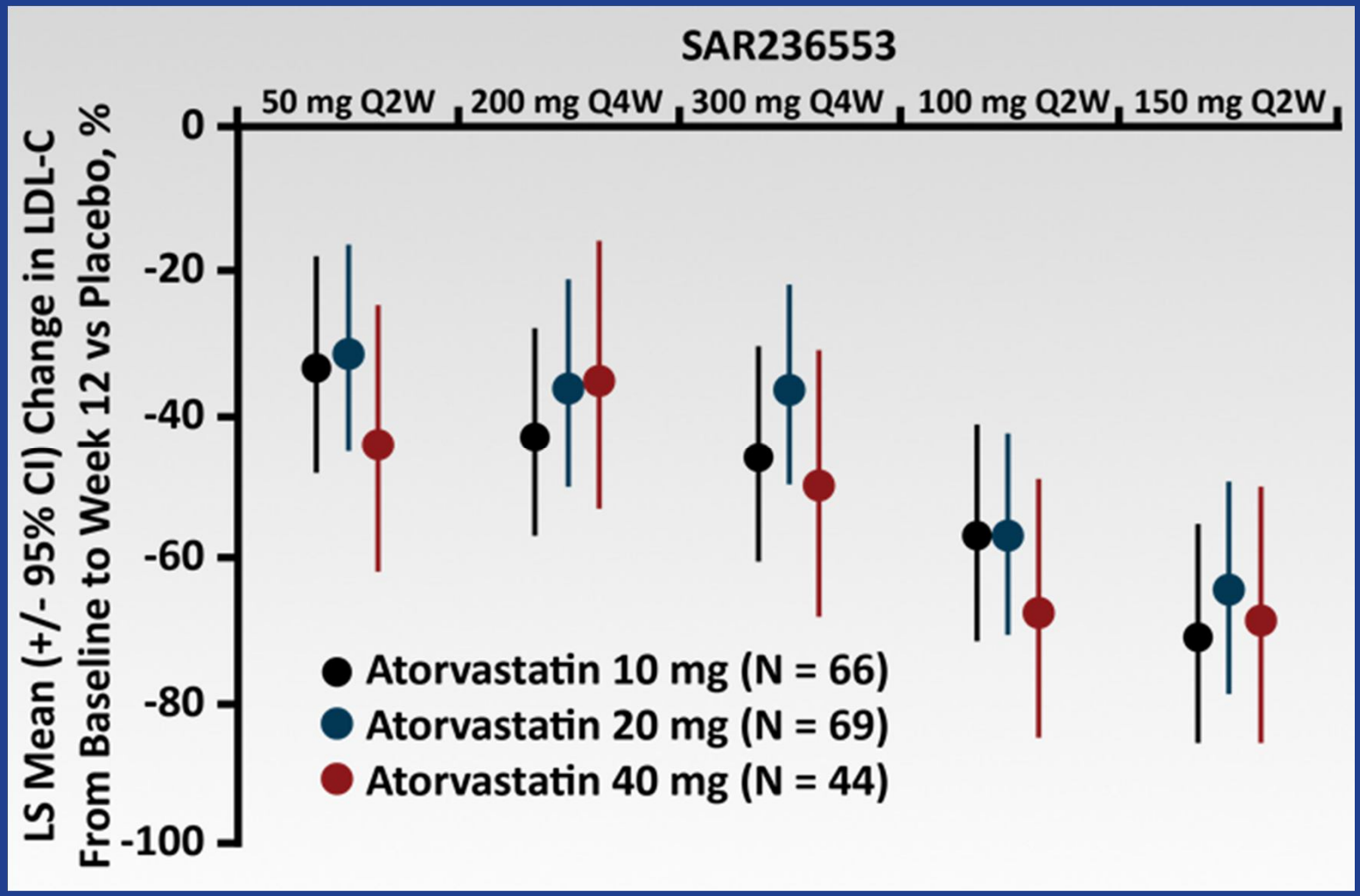
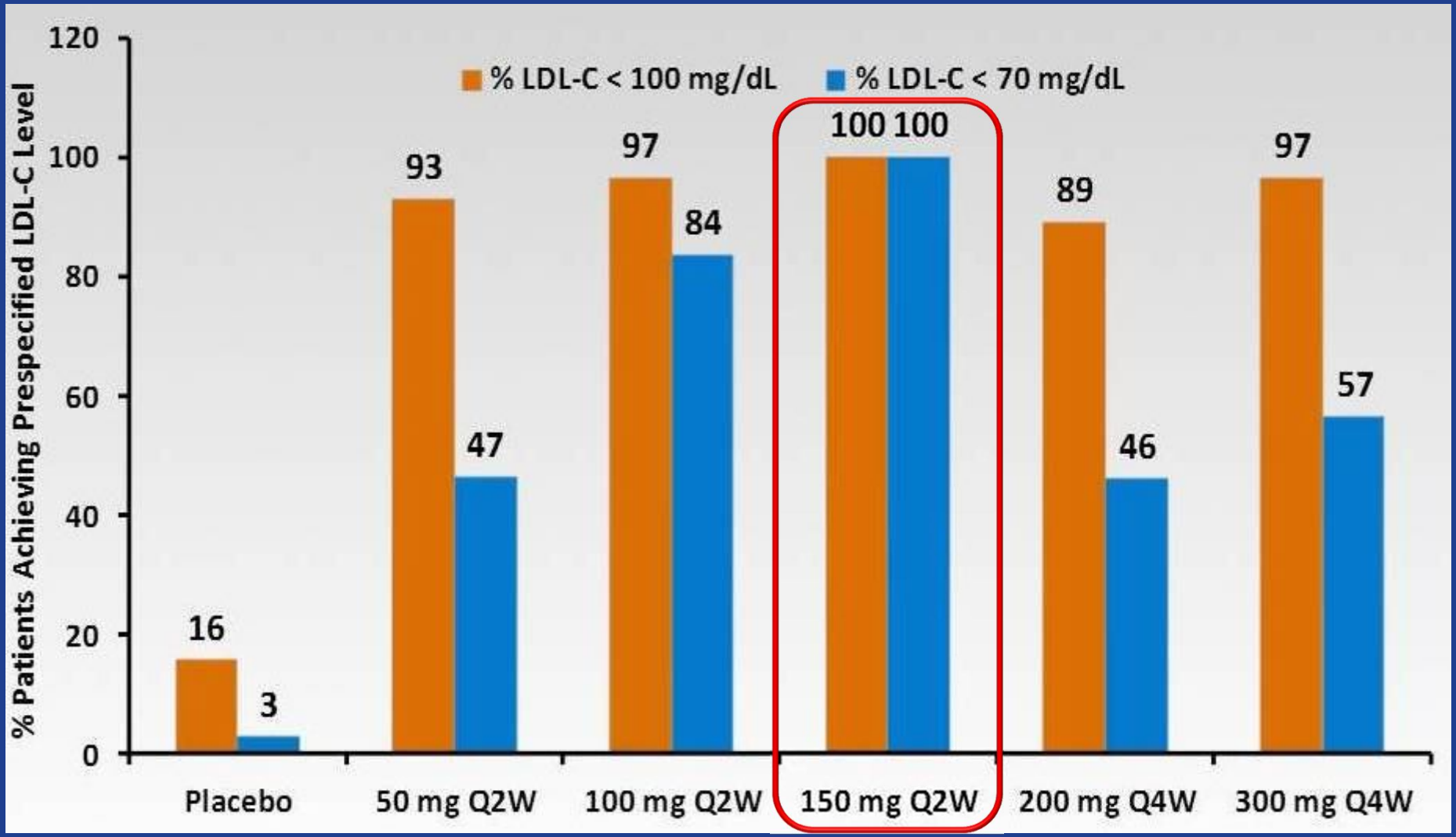


J Am Coll Cardiol 2012;59:2344–53

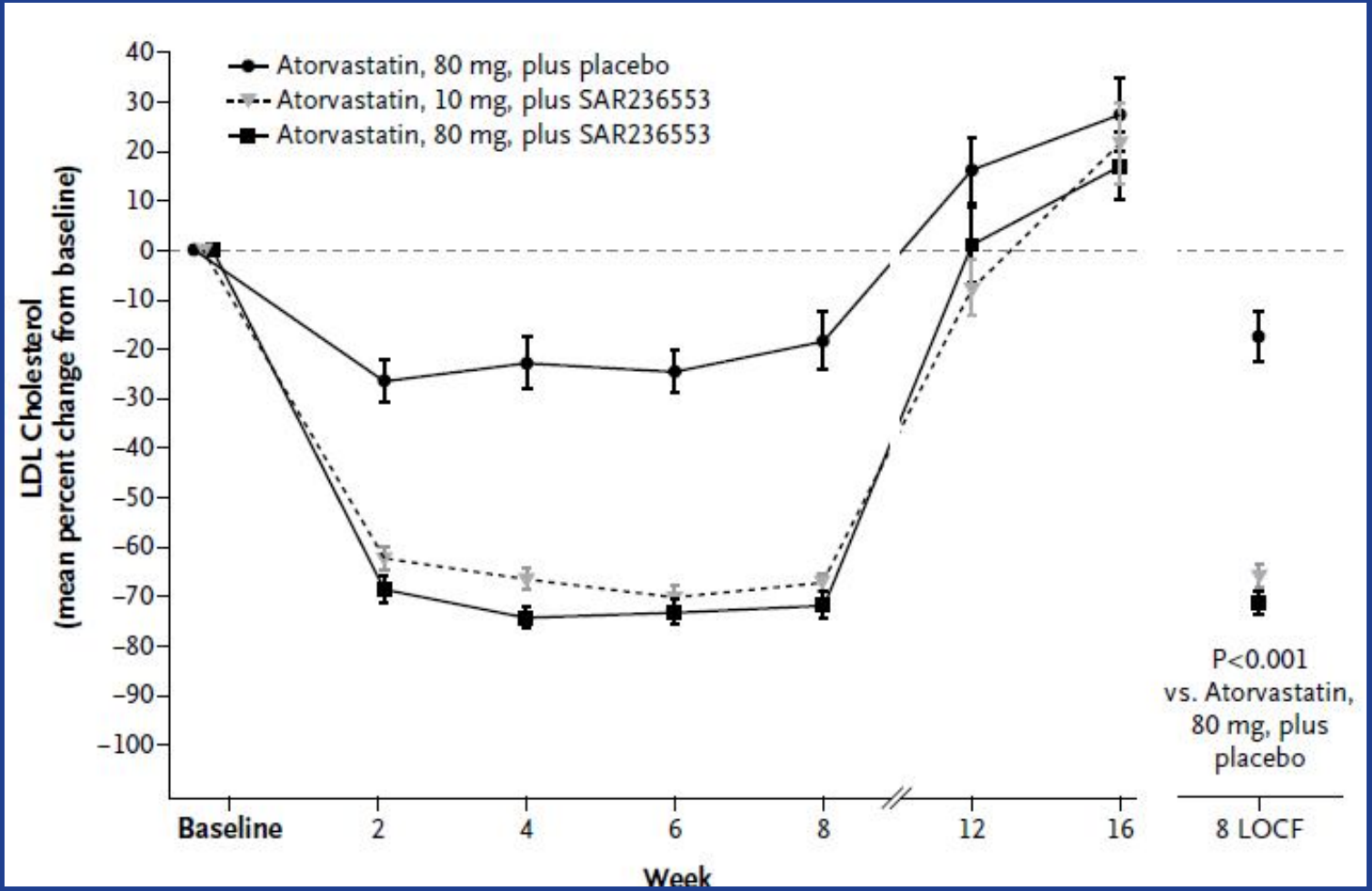
SAR236553: Attainment of LDL-C Goals



J Am Coll Cardiol 2012;59:2344–53

Efficacy of SAR236553 in Patients With Primary Hypercholesterolemia

Patients with LDL-C >100 mg/dL on stable-dose atorvastatin 80 mg



NEJM 2012;367:1891-900

SAR236553: Treatment-Emergent Adverse Events (TEAEs)

		Every-2-week Dosing			Every-4-week Dosing	
	Placebo (N=31)	50 mg (N=30)	100 mg (N=31)	150 mg (N=31)	200 mg (N=30)	300 mg (N=30)
Overview of all Treatment-emergent Adverse Events, no.						
Any treatment-emergent adverse event	14	18	20	19	20	14
Any treatment-emergent severe adverse event	1	0	1	0	1	1
Any treatment-emergent adverse event leading to permanent treatment discontinuation	0	0	1	1	3	1
Adverse Events of Special Interest, no.						
Alanine aminotransferase or aspartate aminotransferase > 3X upper limit of normal	0	0	0	0	0	0
Muscle (including pain, weakness)	1	1	2	1	1	2
Creatine kinase > 10X upper limit of normal	1	0	0	0	0	0

- Injection-site reactions occurred in the SAR236553 groups only and were generally mild and non-progressive.
- No anti-SAR236553 Antibodies

J Am Coll Cardiol 2012;59:2344–53

ODYSSEY: Phase 3 Trial of SAR236553

18,000 Pts, Age > 40 y, 4-16 weeks post-ACS

- On evidence-based medical therapy
- LDL-C > 70 mg/dL
- 2-4 month run-in phase
- Up to 64 months Rx + 2 month f/u post Rx

Estimated completion: March 2018

Randomization (N = 18,000) 1:1

SAR236553 SQ (n = 9000)

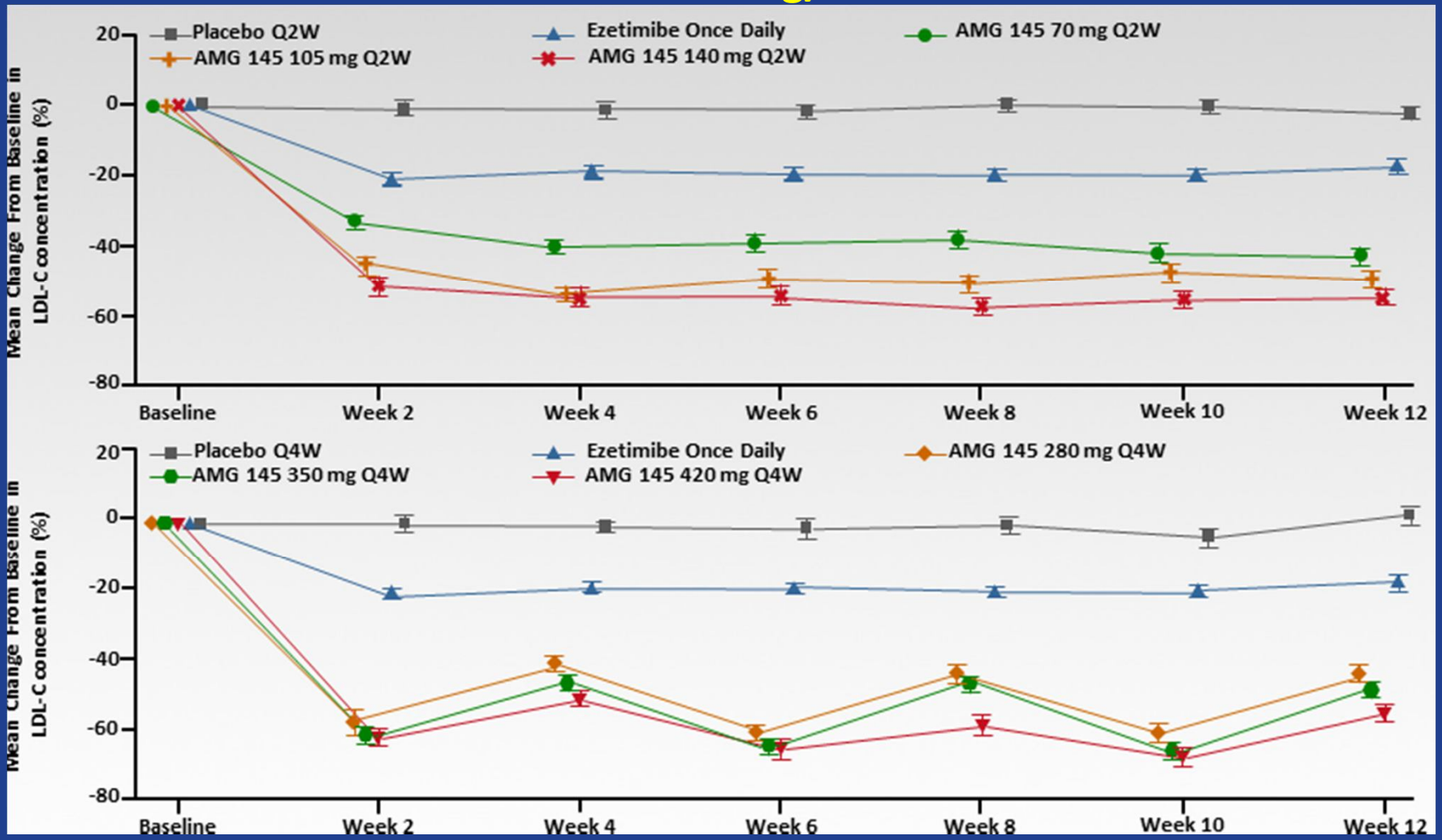
Placebo SQ (n = 9000)

Primary end point: CHD death, nonfatal MI or stroke, or UA requiring hospitalization

Secondary end point: Any CHD event, major CHD event, any CV event; composite of all-cause mortality, nonfatal MI or stroke; all-cause mortality

MENDEL: Efficacy of AMG145 Monotherapy in Patients With Hypercholesterolemia

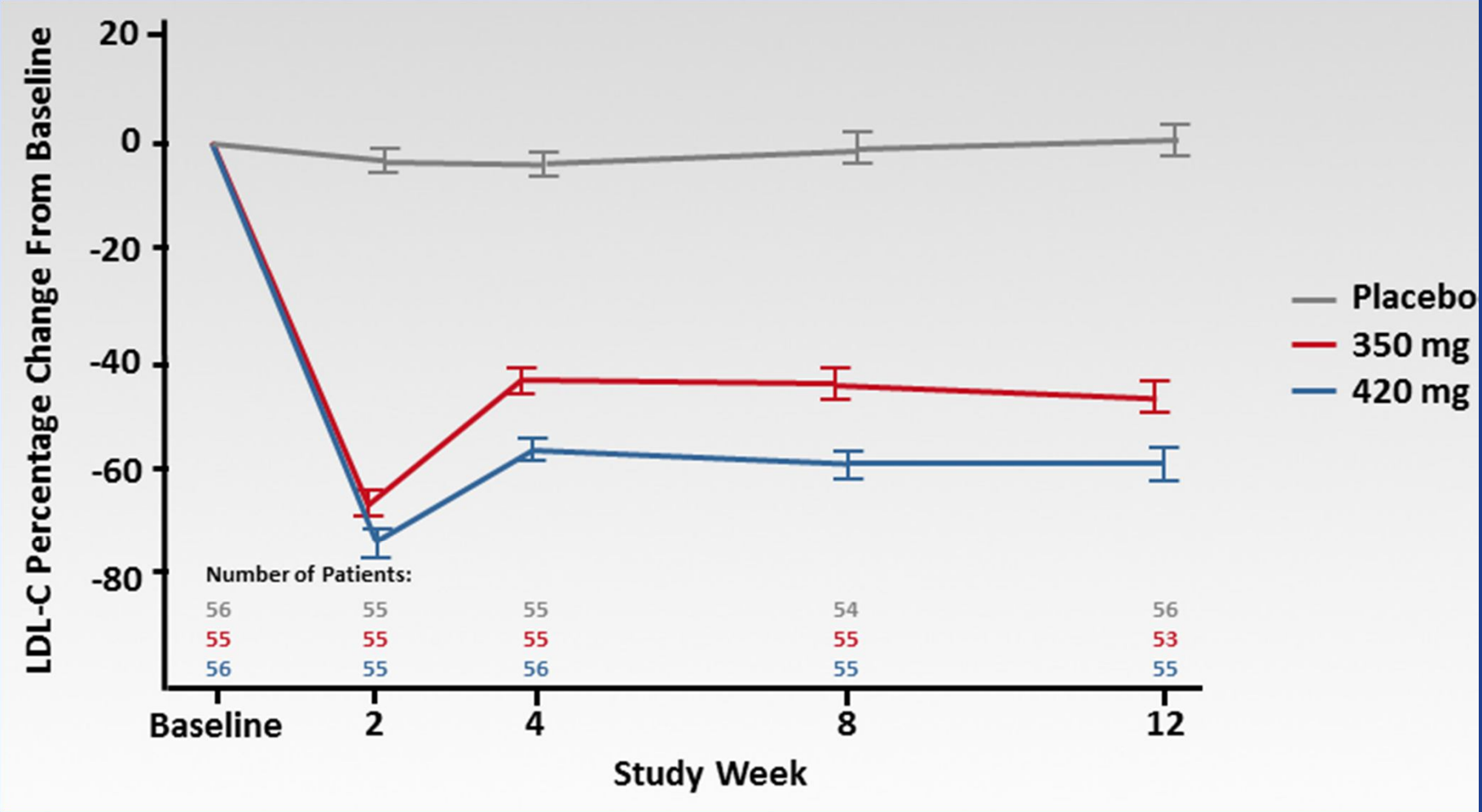
Patients with LDL-C >100 mg/dL without statin



Lancet 2012;380:1995-2006

RUTHERFORD: Efficacy of AMG145 in Patients With HeFH

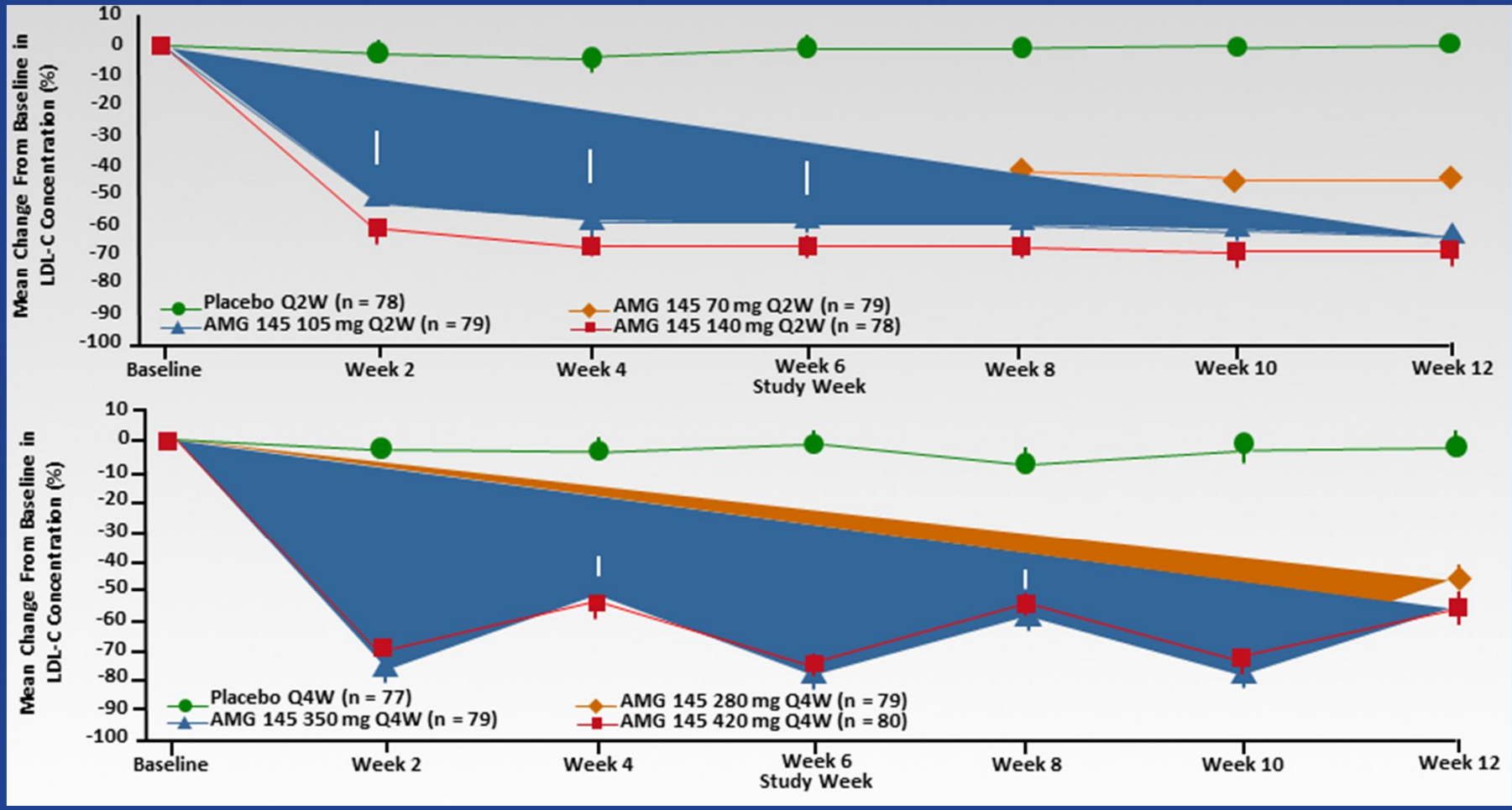
Patients with LDL-C >100 mg/dL on stable-dose statin ± ezetimibe



Circulation. 2012;126:2408-17

LAPLACE-TIMI 57: Efficacy of AMG145 in Patients With Hypercholesterolemia

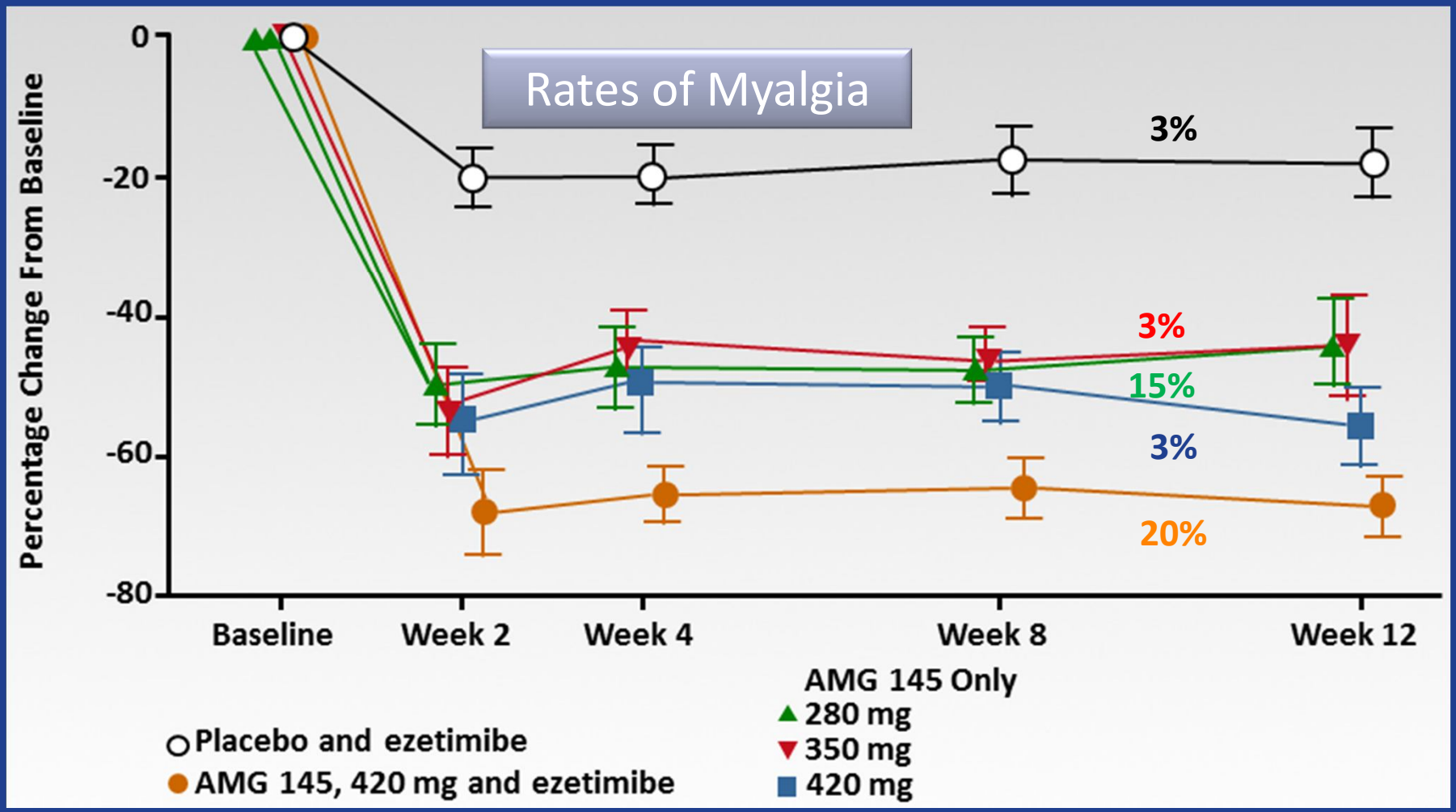
Patients with LDL-C >100 mg/dL on stable-dose statin ± ezetimibe



Lancet 2012; 380: 2007–17

GAUSS: Efficacy of AMG145 in Statin Intolerant Patients With Hypercholesterolemia

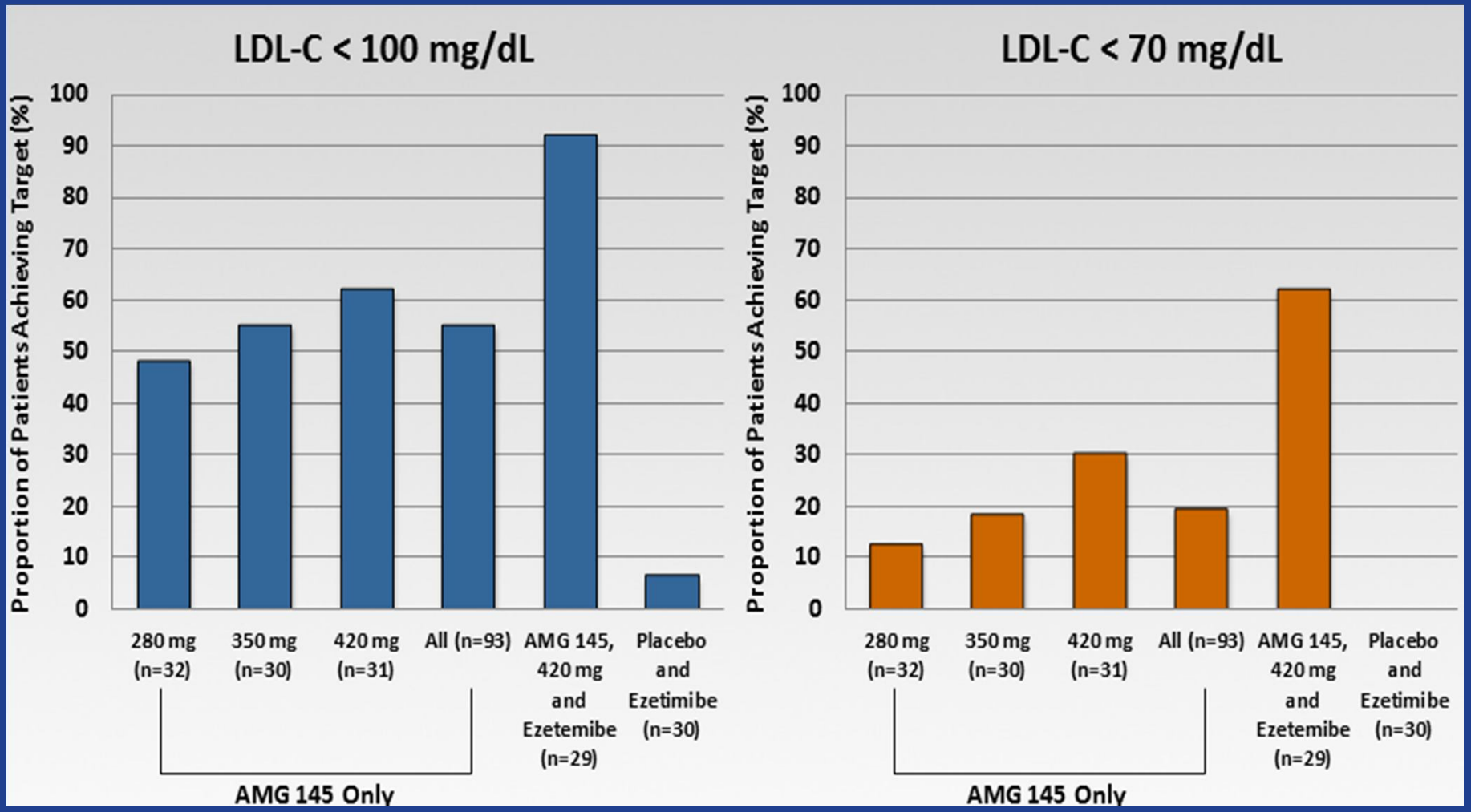
Patients with LDL-C above goal without statin



JAMA 2012; [Epub ahead of print]

GAUSS: Attainment of LDL-C Goals in Statin Intolerant Patients With Hypercholesterolemia

Patients with LDL-C above goal without statin



JAMA 2012; [Epub ahead of print]

AMG145: Adverse Events in LAPLACE

	Placebo Q2W (n = 78)	AMG 145 70 mg Q2W (n = 79)	AMG 145 105 mg Q2W (n = 79)	AMG 145 140 mg Q2W (n = 78)	Placebo Q4W (n = 77)	AMG 145 280 mg Q4W (n = 79)	AMG 145 350 mg Q4W (n = 79)	AMG 145 420 mg Q4W (n = 80)
All Adverse Events	33 (42%)	41 (52%)	52 (66%)	43 (55%)	38 (49%)	45 (57%)	48 (61%)	48 (60%)
Serious Adverse Events	4 (5%)	0	1 (1%)	4 (5%)	0	2 (3%)	2 (3%)	2 (3%)
Leading to Drug Discontinuation	0	0	0	2 (3%)	0	0	0	0
Treatment-related Events*	7 (9%)	4 (5%)	9 (11%)	4 (5%)	4 (5%)	6 (8%)	7 (9%)	9 (11%)
Leading to Drug Discontinuation	0	0	0	0	0	0	0	0
Injection-site Reactions	2 (3%)	1 (1%)	1 (1%)	0	1 (1%)	2 (3%)	3 (4%)	1 (1%)
AST or ALT >3 Times ULN	1 (1%)	0	0	0	0	0	0	0
Creatine Phosphokinase >3 Times ULN†	0	1 (1%)	1 (1%)	1 (1%)	0	0	0	1 (1%)
Positively Adjudicated Clinical Cardiovascular Events‡	1 (1%)	1 (1%)	0	4 (5%)	0	1 (1%)	1 (1%)	0
All-cause Mortality	0	0	0	1 (1%)	0	0	0	0

*All 50 treatment-related adverse events were reported as non-serious by the investigator and none led to discontinuation of drug. †All were asymptomatic.
‡Acute coronary syndrome, coronary revascularization, transient ischemic attack, congestive heart failure requiring hospital admission, or death.

- No anti-AMG145 Antibodies

Lancet 2012; 380: 2007–17

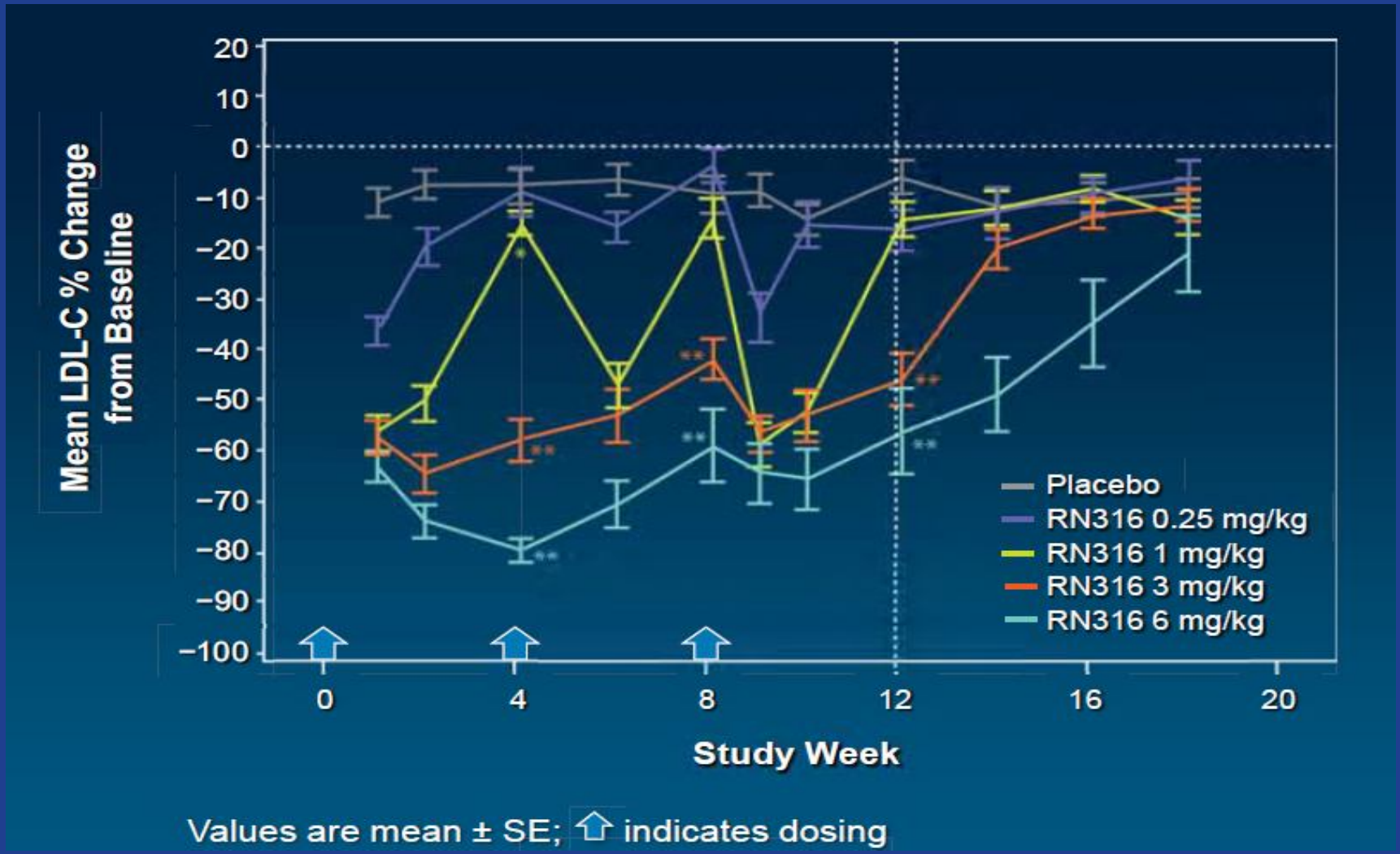
Ongoing Trials with AMG145

- On a background of lipid-lowering therapy in hypercholesterolemia (DESCARTES; NCT01516879)[17]
- In homozygous familial hypercholesterolemia (TESLA; NCT01588496)[18]

Long-term Extension of the Above Studies

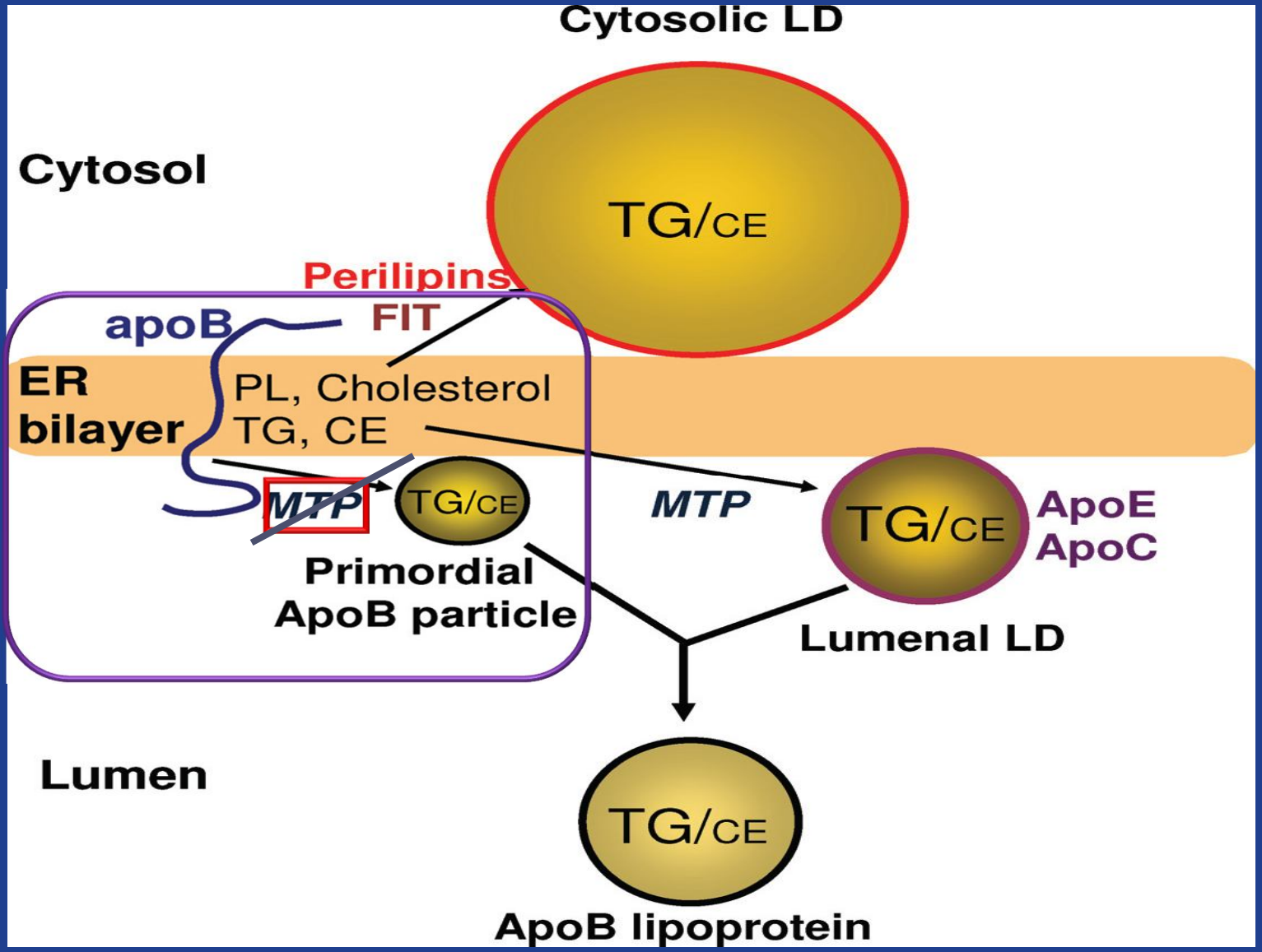
- As a long-term open-label extension safety and tolerability study of AMG145 (OSLER; NCT01439880)[19]

Intravenous RN316 in Hypercholesterolemic Patients on High-Dose Statin



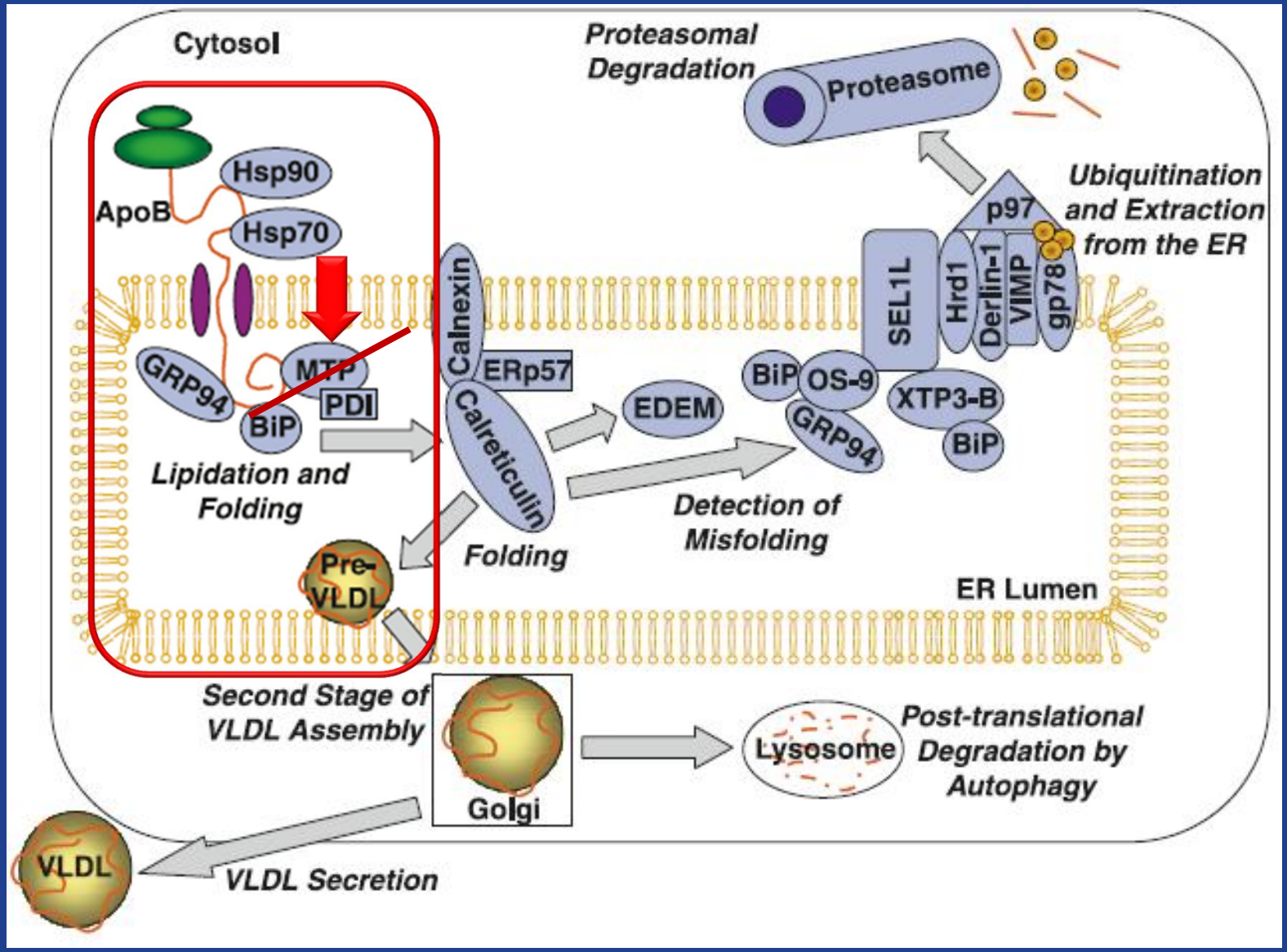
Presented at AHA Scientific Sessions, Los Angeles 2012

Microsomal Transfer Protein (MTP)



Arterioscler Thromb Vasc Biol.2012;32:1087-1093

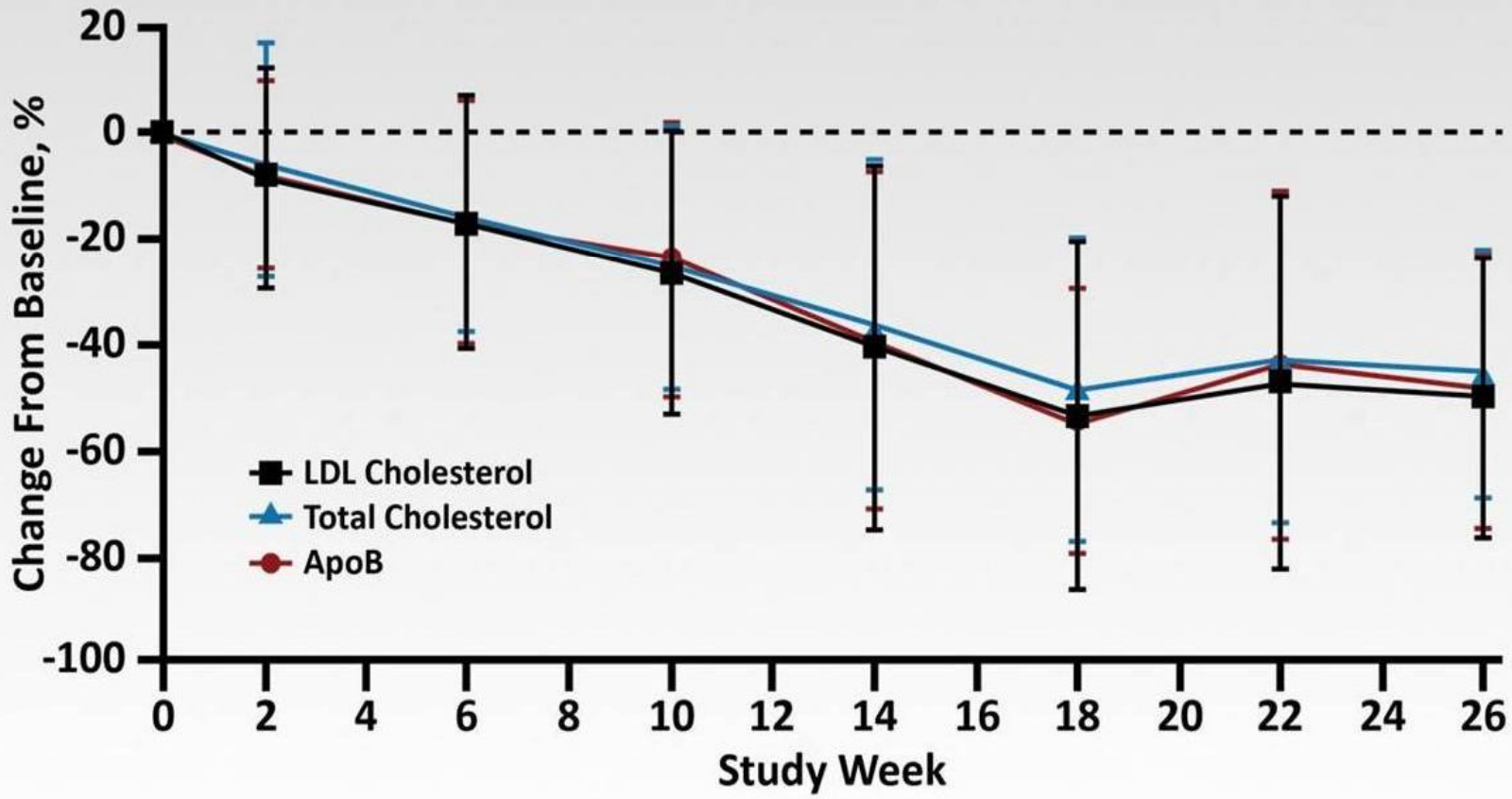
Microsomal Transfer Protein (MTP)



Biochem Cell Biol. 2010;88:251-67

Lomitapide: Phase 3 Results in Homozygous FH

Microsomal triglyceride transfer protein inhibitor, interferes in the assembly of plasma lipoproteins in the liver by mediating the transfer of triglycerides onto VLDL and chylomicron



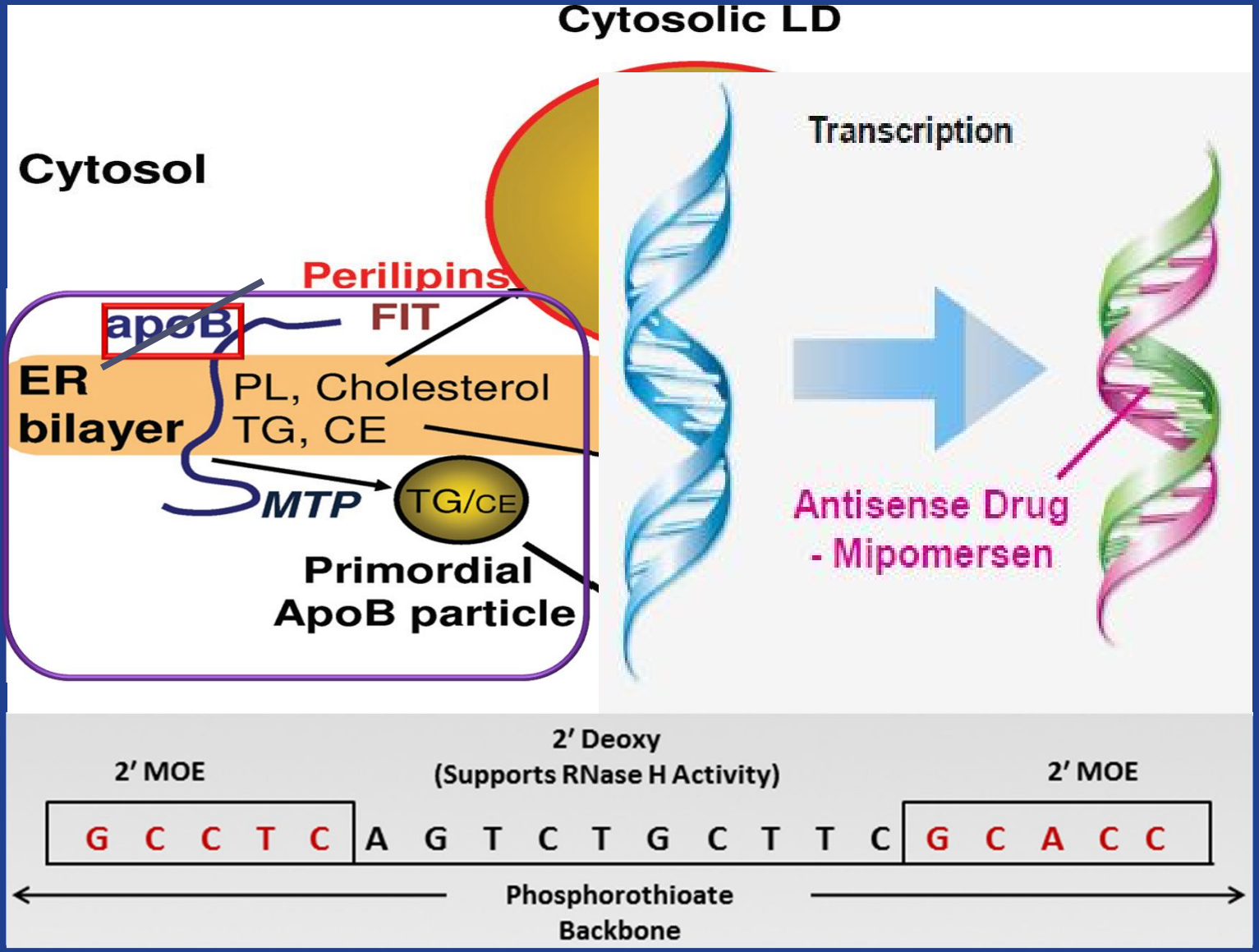
Lancet Published Online November 2, 2012

December 24, 2012

FDA Approves Aegerion Pharmaceuticals' JUXTAPID(TM) (lomitapide) Capsules for Homozygous Familial Hypercholesterolemia (HoFH)

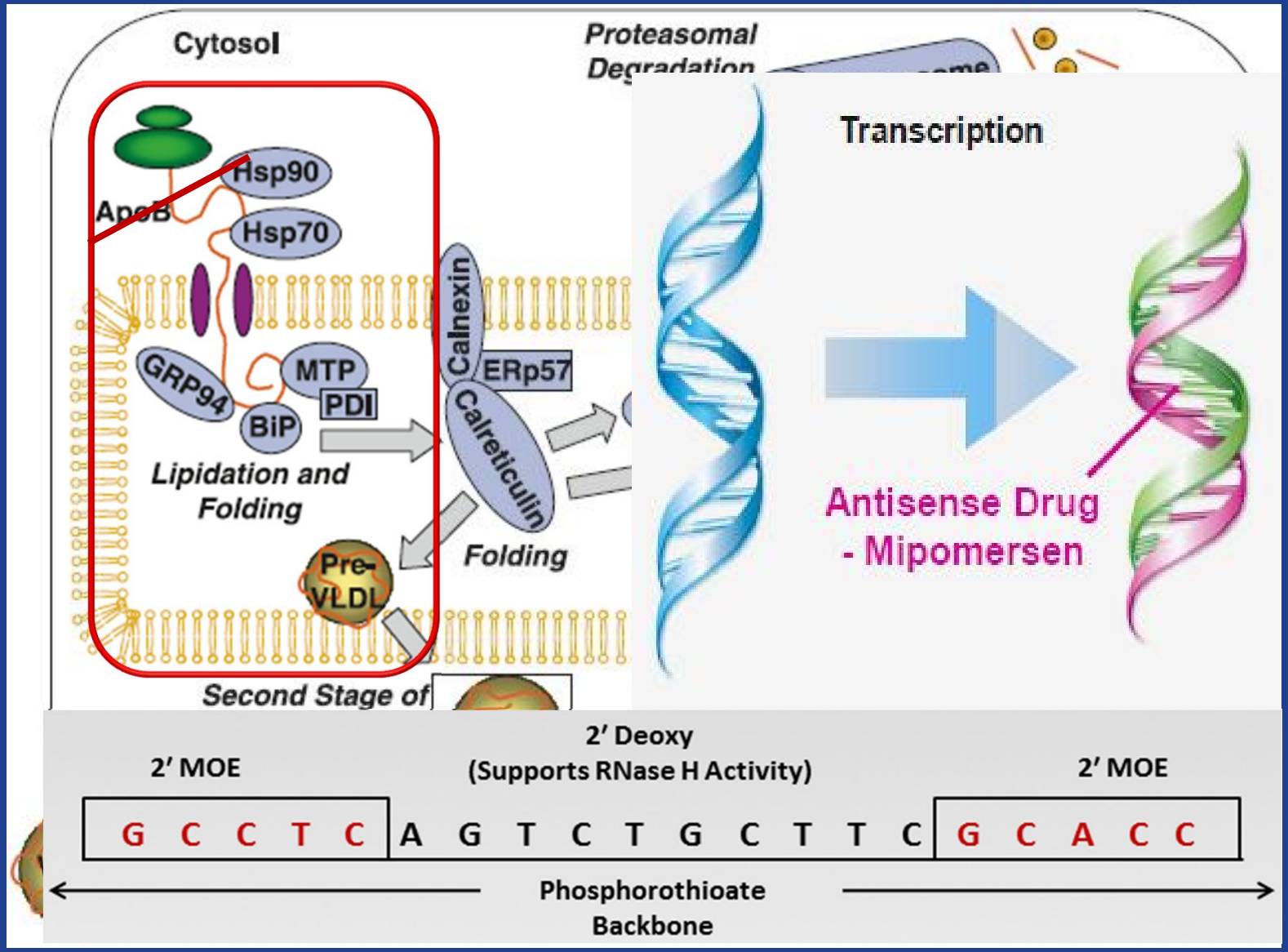
- The product will carry a boxed warning stating the risk of hepatotoxicity
- Lomitapide will be available only through a Risk Evaluation and Mitigation Strategy (REMS). Aegerion will certify all healthcare providers who prescribe Juxtapid and all pharmacies that dispense the medicine

Microsomal Transfer Protein (MTP)



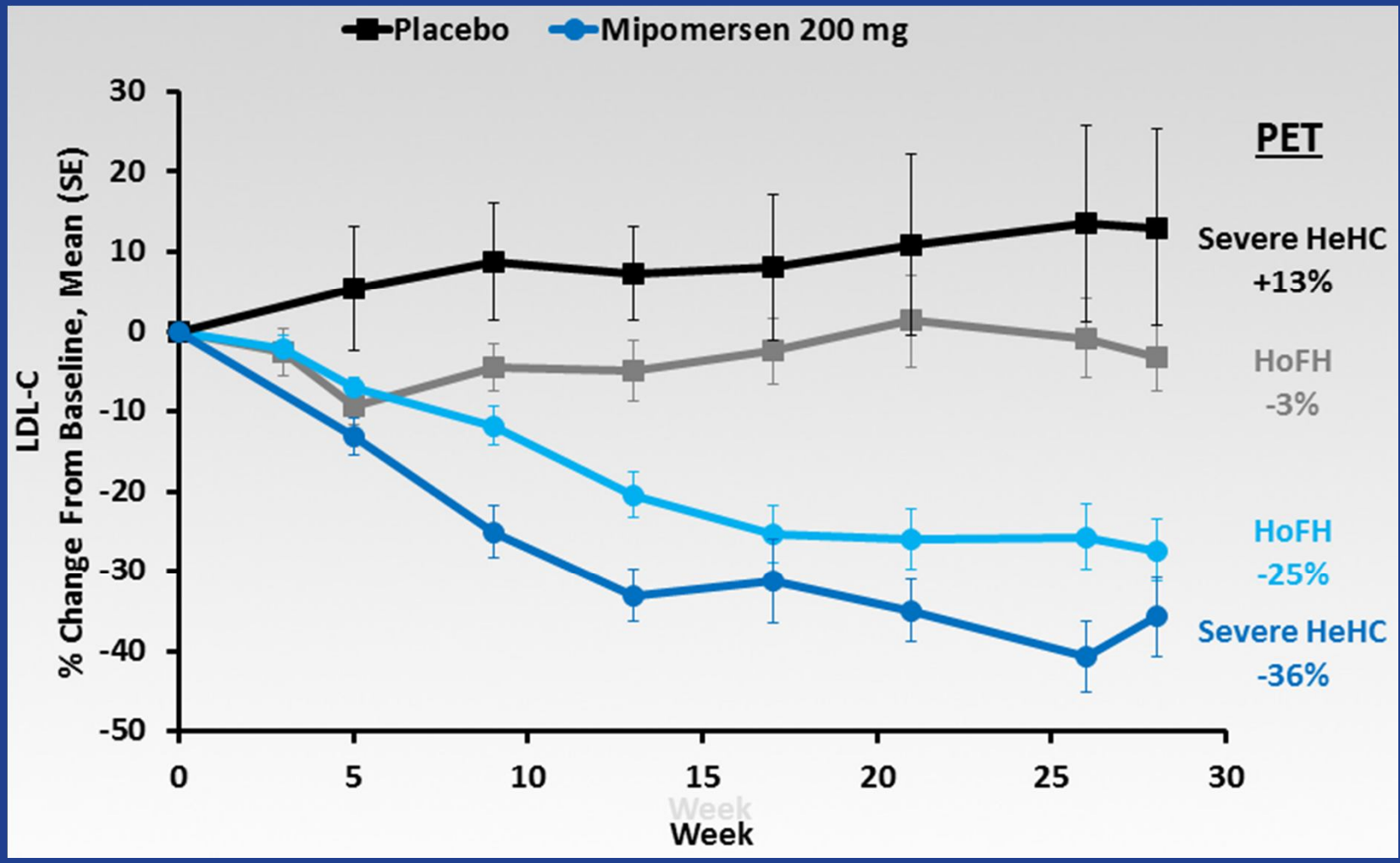
Arterioscler Thromb Vasc Biol.2012;32:1087-1093

Microsomal Transfer Protein (MTP)



Biochem Cell Biol. 2010;88:251-67

Mipomersen: Phase 3 Results in Homozygous and Severe Heterozygous FH



Lancet 2010;375:998-1006
JACC 2011;57:E492

Mipomersn: Regulatory Status

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2012
EMA/792736/2012
EMEA/H/C/002429

Questions and answers

Refusal of the marketing authorisation for Kynamro (mipomersen)

- Flu-like symptoms
- Injections site reactions
- Liver toxicity: fatty liver and ↑LFT's
- Serious cardiovascular events

FDA advisors vote 9 to 6 to approve mipomersen for homozygous FH

October 18, 2012

FDA

Anti-Inflammatory Therapies in Phase 3 Studies

Darapladib[a]

- Selective inhibitor of lipoprotein-associated phospholipase A_2
- Trial to evaluate efficacy in preventing cardiovascular death, nonfatal MI, and nonfatal stroke in patients following acute coronary syndrome[1]

Canakinumab[b]

- Anti-IL-1β monoclonal antibody
- Trial to evaluate efficacy in preventing recurrent cardiovascular events in patients with MI prior to study entry and elevated hsCRP

Future Prospects

Summing up, it is clear the future holds great opportunities. It also holds pitfalls. The trick will be to avoid the pitfalls, seize the opportunities, and get back home by six o'clock .

Woody Allen