New Pespective of Proprotein convertase subtilisin kexin 9 (PCSK 9) Inhibitor in CAD Patients

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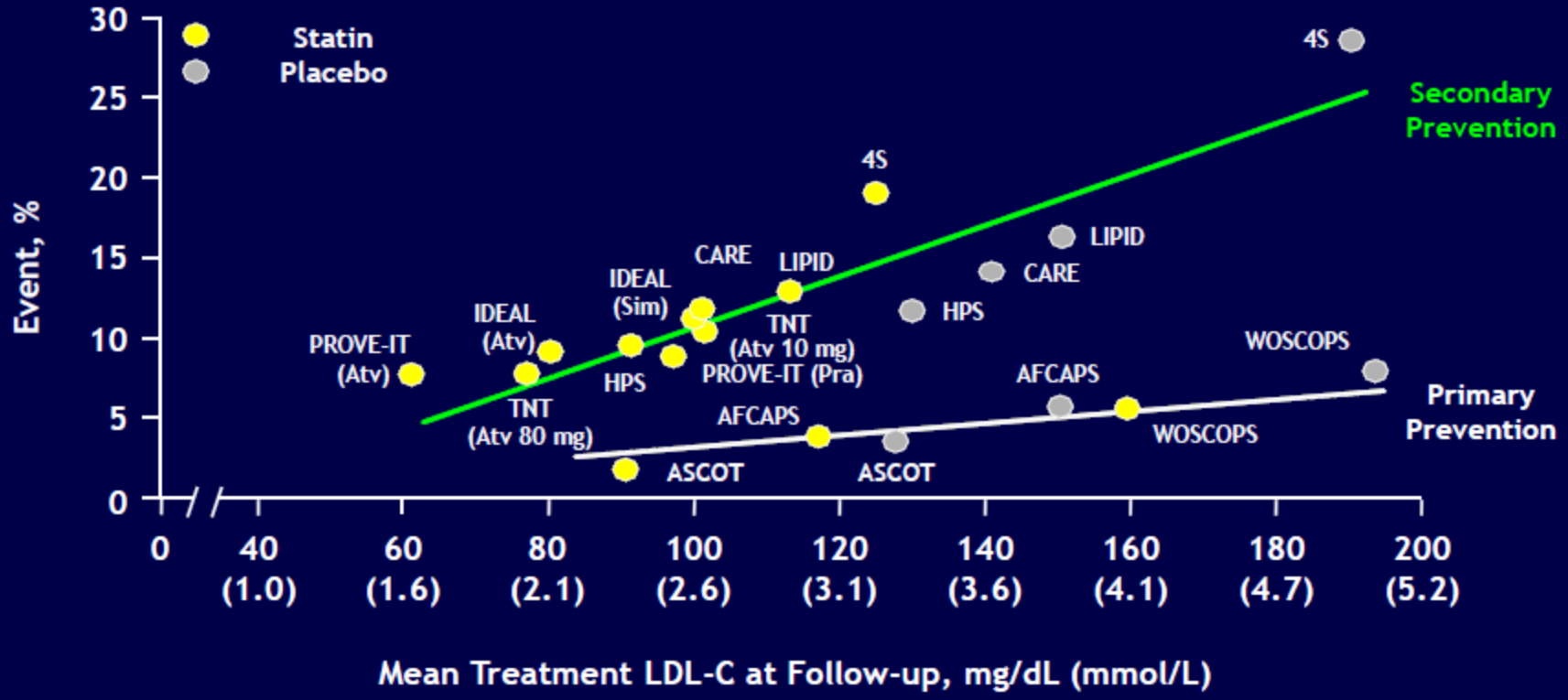
Relationship Between LDL-C and CV Incidence



Atv = atorvastatin; Pra = pravastatin; Sim = simvastatin; PROVE-IT = Pravastatin or AtorVastatin Evaluation and Infection Therapy; IDEAL = Incremental Decrease in Endpoints through Aggressive Lipid Lowering; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; AFCAPS = Air Force Coronary Atherosclerosis Prevention Study; WOSCOPS = West of Scotland Coronary Prevention Study

Adapted from Rosenson RS. *Expert Opin Emerg Drugs*. 2004;9:269-279; LaRosa JC, et al. *N Engl J Med*. 2005;352:1425-1435; Pedersen TR, et al. *JAMA*. 2005;294:2437-2445.

Statin Benefit

- Statins are the cornerstone of cholesterol-lowering theraphy for the prevention of CHD.
- Recent meta-analysis, in individuals with 5-year risk of major vascular events lower than 10%, each 1 mmol/L (39 mg/dl) reduction in LDL cholesterol with statin therapy produced an absolute reduction in major vascular events of about 11 per 1000 over 5 years.

Mihaylova B, et al. Lancet 2012;380:581-90.

Statins Issues

- Despite the widespread use of statins, patients continue to experience residual risk.

- 16-53% of patients worldwide fail to achieve goal lipid targets, with even higher rate (79%) in patients with familial forms of hypercholesterolemia.

- 10-20% patients are unable to tolerate statins due to statin-related adverse events, particularly higher doses.

Ford ES, et al. Int J Cardiol 2010; 140:226e35.
Waters DD, et al. Circulation 2009;120:28e34.
Kotseva K, et al. Eur J Cardiovasc Prev Rehabil 2009;16:121e37.
Pijlman AH, et al. Atherosclerosis 2010;209:189e94.
Zhang H, et al. Ann Intern Med 2013;158:526–34
Bruckert E, et al. Cardiovasc Drugs Ther 2005;19:403e14.

Statins & PCSK9

- Interestingly, statin treatment increases the expression of LDL-receptor gene, in addition upregulates convertase subtilisin kexin 9 (PCSK9) mRNA expression, increased the expression of PCSK9 may attenuate the LDL-lowering effect of statins.

- In other words, blocking PCSK9, PCSK9 inhibitors would enhance the LDL-lowering effects of statins.

Dubuc G, et al. Arteriosclerosis, thrombosis, and vascular biology 2004;24:1454-9.

Rashid S, et al. Proceedings of the National Academy of Sciences of the United States of America 2005;102:5374-9.

Discovery of PCSK9

- In 2003, Seidah et al. identified the ninth member of the proprotein convertase family-PCSK9.

- Gain-of fucntion (GOF) mutation in PSCK9 was associated with mild to severe hypercholesterolemia and an increased risk of CHD.

- In 2005, the first loss-of-function (LOF) described. (eg.Y142X and C679X) were associated with reduction in LDL-C and reduction in the risk of CHD.

Seidah NG, et al. Proceedings of the National Academy of Sciences of the United States of America 2003;100:928-33.
Tibolla G, et al. NMCD 2011;21:835-43.
Davignon J, et al. Current atherosclerosis reports 2010;12:308-15.
Cohen J, et al. Nature genetics 2005;37:161-5.
Cohen JC, et al .The New England journal of medicine 2006;354:1264-72.

PCSK9 gene mutation associated with a GOF on protein activity

Nucleotide position	Protein position	PCSK9 protein domain
c.−332C>A		5′ UTR
c.10G>A	p.Val4Ile	Signal peptide
c.94G>A	p.Glu32Lys	Pro-domain
c.161A>C	p.Glu54Ala	Pro-domain
c.381T>A	p.Ser127Arg	Pro-domain
c.385G>A	p.Asp129Asn	Pro-domain
c.386A>G	p.Asp129Gly	Pro-domain
c.644G>A	p.Arg215His	Catalytic
c.646T>C	p.Phe216Leu	Catalytic
c.654A>T	p.Arg218Ser	Catalytic
c.1070G>A	p.Arg357His	Catalytic
c.1120 G>T	p.Asp374Tyr	Catalytic
c.1120G>C	p.Asp374His	Catalytic
c.1274A>G	p.Asn425Ser	Catalytic
c.1405C>T	p.Arg469Trp	C-terminal domain
c.1486C>T	p.Arg496Trp	C-terminal domain
c.1540G>A	p.Ala514Thr	C-terminal domain
c.1564G>A	p.Ala522Thr	C-terminal domain
c.1658A>G	p.His553Arg	C-terminal domain
c.1863 + 6G>A		Intron 11
c.1870G>A	p.Val624Met	C-terminal domain

Tibolla G, et al. NMCD 2011;21:835-43.

PCSK9 gene mutation associated with a LOF on protein activity

Nucleotide position	Protein position	PCSK9 protein domain
c.202delG	A68fsL82X	Pro-domain
c.230C>T	p.Thr77Ile	Pro-domain
c.277C>T	p.Arg93Cys	Pro-domain
c.290_292delGCC	p.Arg97del	Pro-domain
c.316G>A	p.Gly106Arg	Pro-domain
c.341T>C	p.Val114Ala	Pro-domain
c.426C>G	p.Tyr142X	Pro-domain
c.655C>G	p.Gln219Glu	Catalytic
c.706G>A	p.Gly236Ser	Catalytic
c.716C>A	p.Ala239Asp	Catalytic
c.757C>T	p.Leu253Phe	Catalytic
c.1061A>T	p.Asn354Ile	Catalytic
c.1171C>A	p.His391Asn	Catalytic
c.1284G>A	p.Trp428X	Catalytic
c.1300C>T	p.Arg434Trp	C-terminal domain
c.1355G>A	p.Gly452Asp	C-terminal domain
c.1384T>C	p.Ser462Pro	C-terminal domain
c.1660C>G	p.Gln554Glu	C-terminal domain
c.1847C>T	p.Pro616Leu	C-terminal domain
c.2004C>A	p.Ser668Arg	C-terminal domain
c.2037C>A	p.Cys679X	C-terminal domain

Tibolla G, et al. NMCD 2011;21:835-43.

PCSK9-LOF (Y142X & C679X)

The NEW ENGLAND JOURNAL of MEDICINE

Cohen JC, et al .The New England journal of medicine 2006;354:1264-72

Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

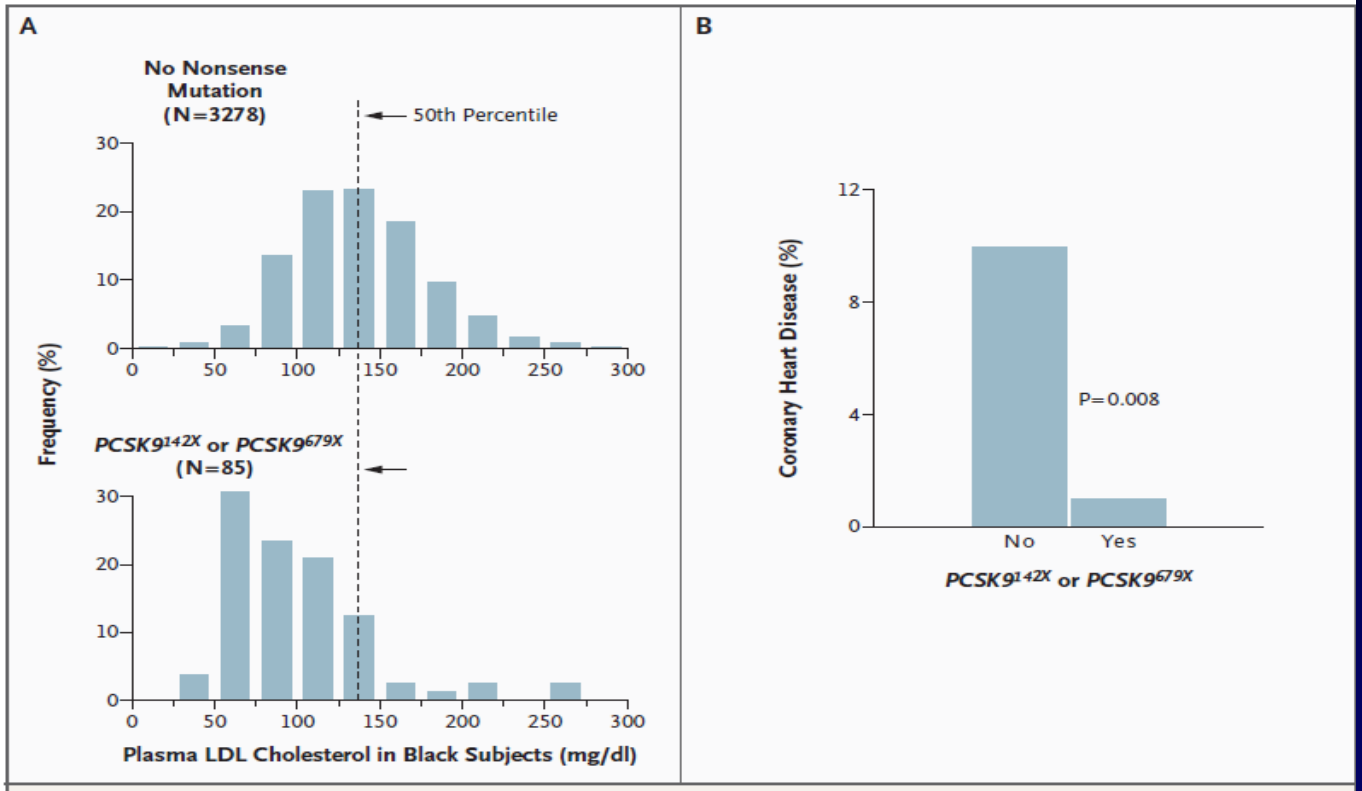


Figure 1. Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Heart Disease (Panel B) among Black Subjects, According to the Presence or Absence of a *PCSK9*^{142X} or *PCSK9*^{679X} Allele.

In Panel A, the distribution of plasma LDL cholesterol levels at baseline among 3278 black subjects who did not have a *PCSK9*^{142X} or *PCSK9*^{679X} allele (top) is compared with the distribution of levels among the 85 black subjects who had one of these two alleles (bottom). Panel B shows the percentage of participants from these two groups who had no evidence of coronary heart disease at baseline and in whom coronary heart disease developed during the 15-year follow-up period. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

Introduction PCSK9

- PCSK9, as a newly discovered serine protease, directly interacts with the LDLR both within the cell and at the surface of the plasma membrane, caused the degradation of hepatic LDLR and thereby controls the level of LDL in plasma.

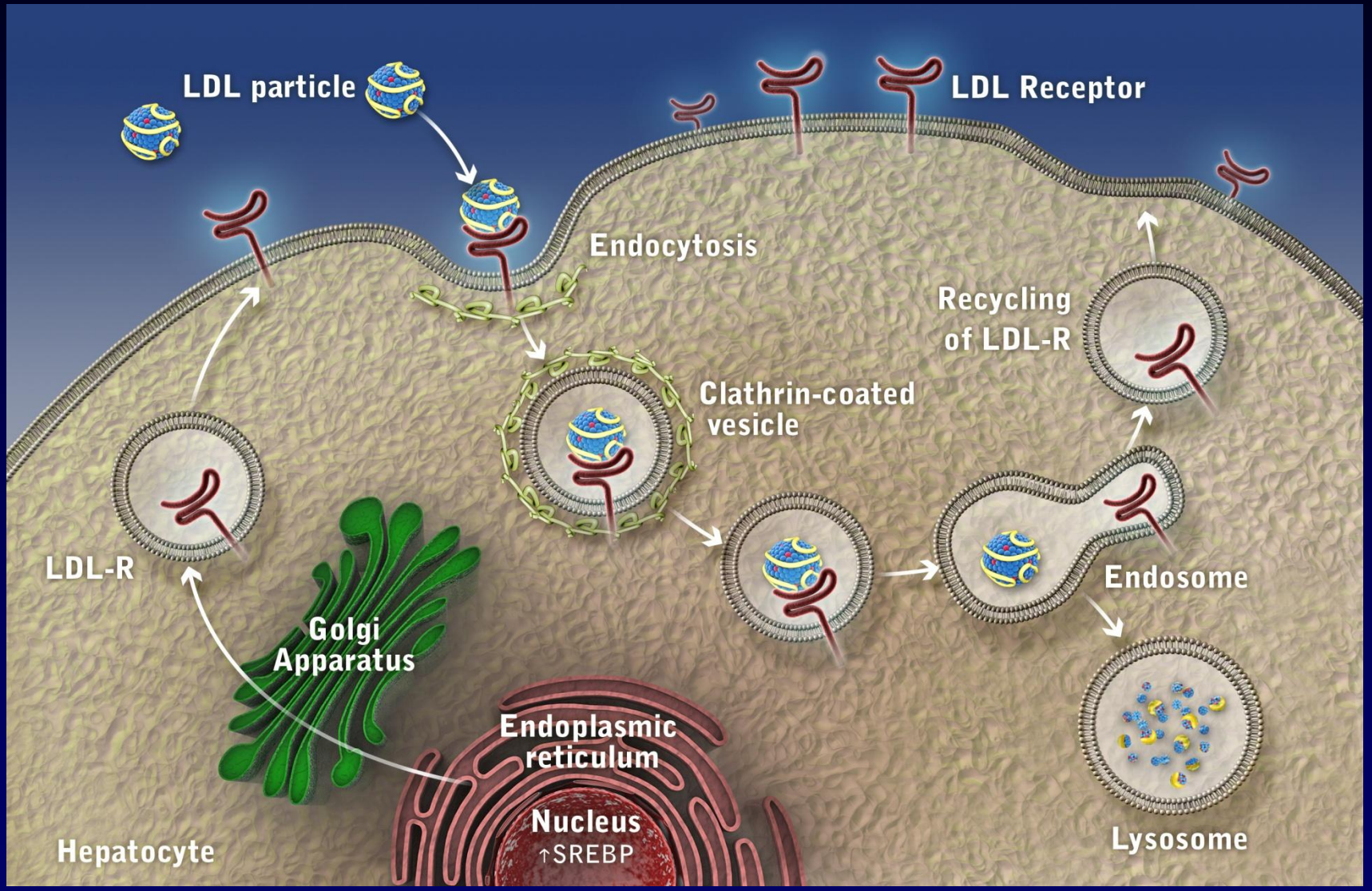
Seidah NG. Expert Opin Ther Targets 2009;13:19-28.

Seidah NG, et al. Nat Rev Drug Discov 2012;11:367-83.

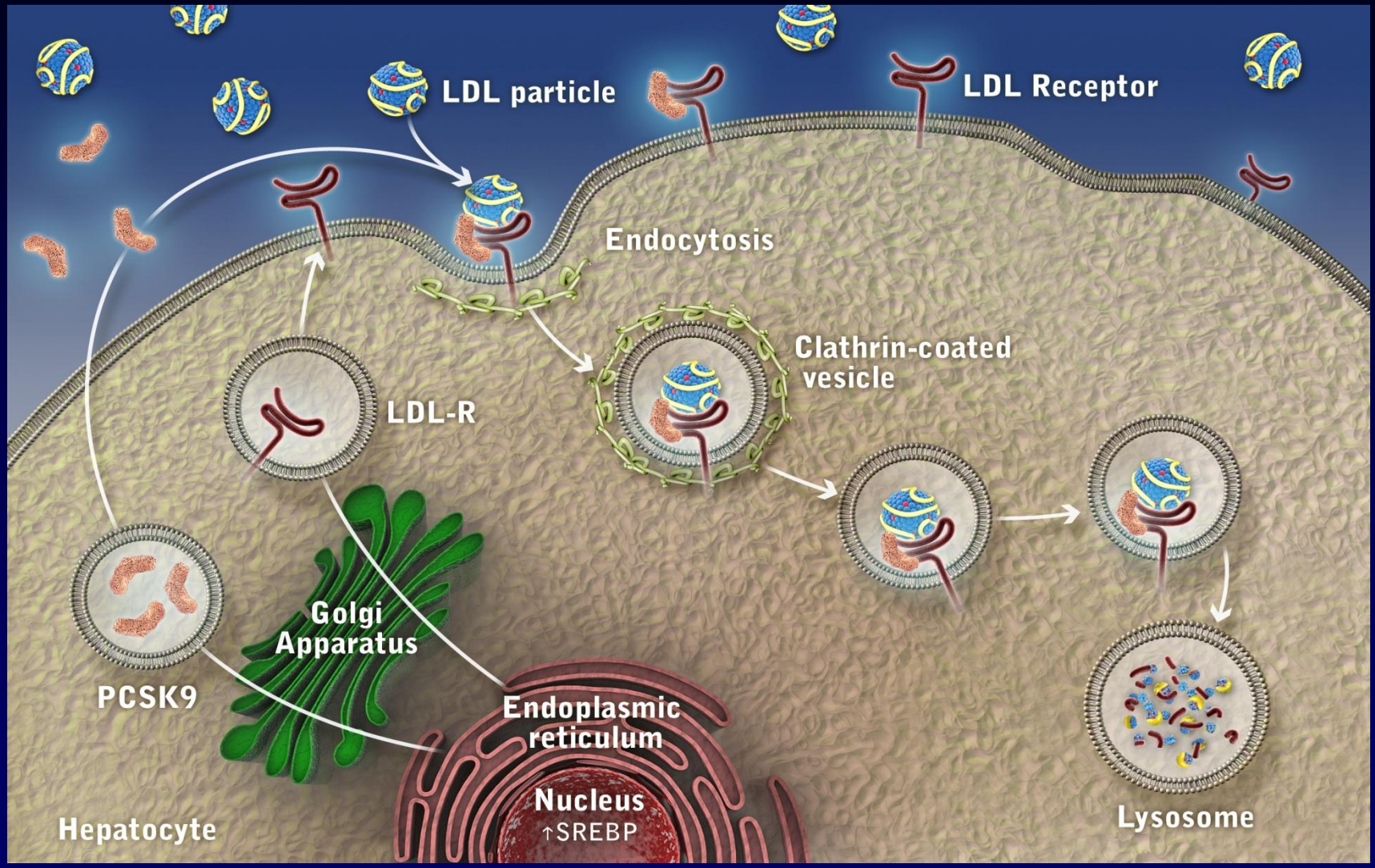
Tibolla G, et al. NMCD 2011;21:835-43.

Lambert G, et al. J Lipid Res 2012;53:2515-24.

LDL Receptor Function and Life Cycle



The Role of PCSK9 in the Regulation of LDL Receptor Expression



Introduction PCSK9 & Atherosclerosis

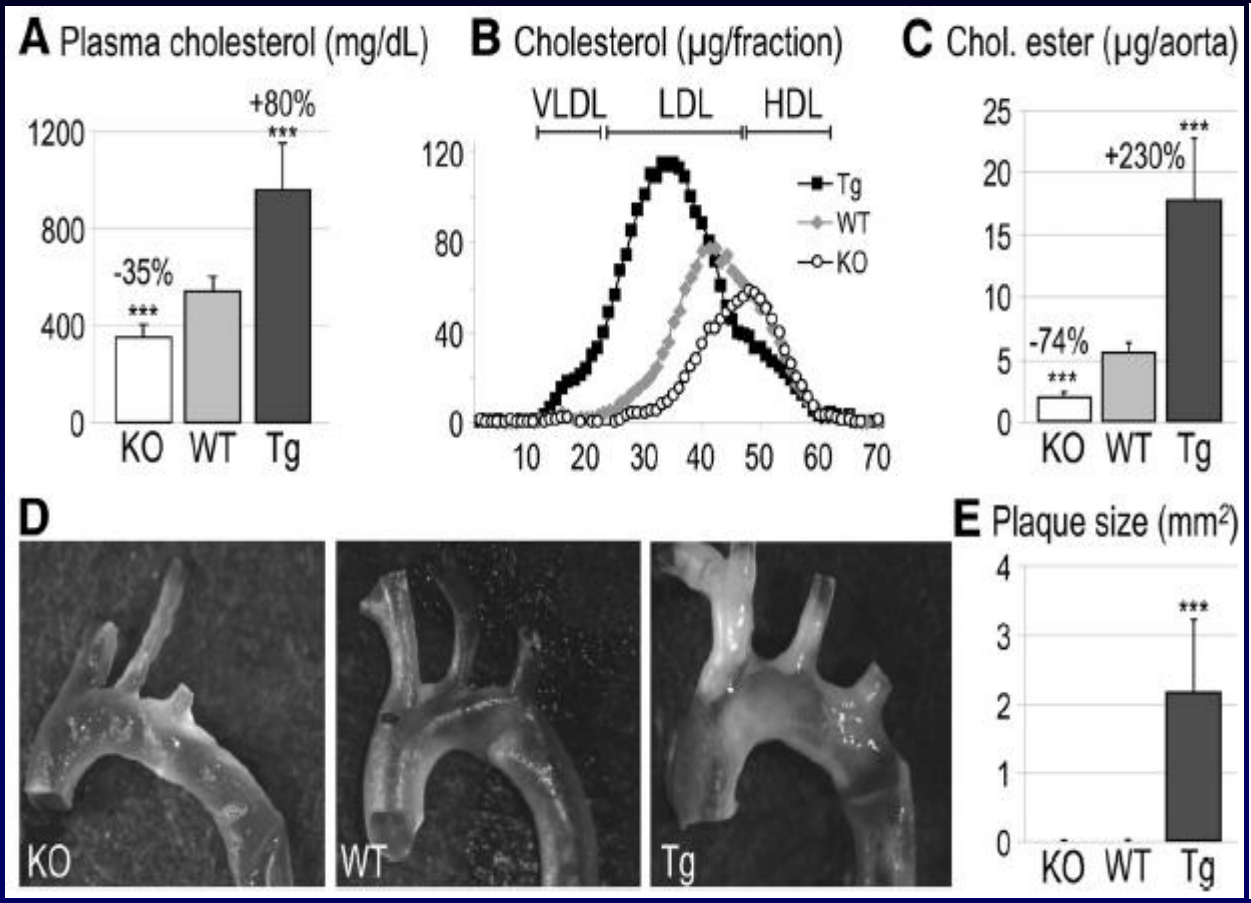


Figure 1. Direct relationship between atherosclerosis and proprotein convertase subtilisin/kexin type 9 (PCSK9) in mice. C57BL/6 male mice that express no PCSK9 (knockout [KO]), normal levels (wild-type [WT]), and high levels of murine PCSK9 (transgenic [Tg]) were fed a Western diet for 12 months (n=5–6 mice per genotype). **A**, Plasma cholesterol. **B**, Fast protein liquid chromatography cholesterol profiles (pooled plasma); very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) fractions are indicated. **C**, Cholesteryl (Chol.) ester accumulation in the whole aorta. **D**, Representative en face preparations of aortic arches. **E**, Cumulative plaque size at the level of aortic valves and root. Bars and error bars represent mean±SD; by comparison with WT values, *P* (***$P \leq 0.001$) was obtained with a 2-tailed Student *t* test.

Denis M, et al. Circulation 2012;125:894-901.

Introduction PCSK9 inhibition

Including:

- (1) inhibition of PCSK9 synthesis by gene silencing agents (antisense oligonucleotides or small interfering RNA_siRNA)
- (2) inhibition of PCSK9 binding to LDLDR by monoclonal antibodies (mAbs), small peptides or adnectins.
- (3) inhibition of PCSK9 autocatalytic processing by small molecule inhibitors

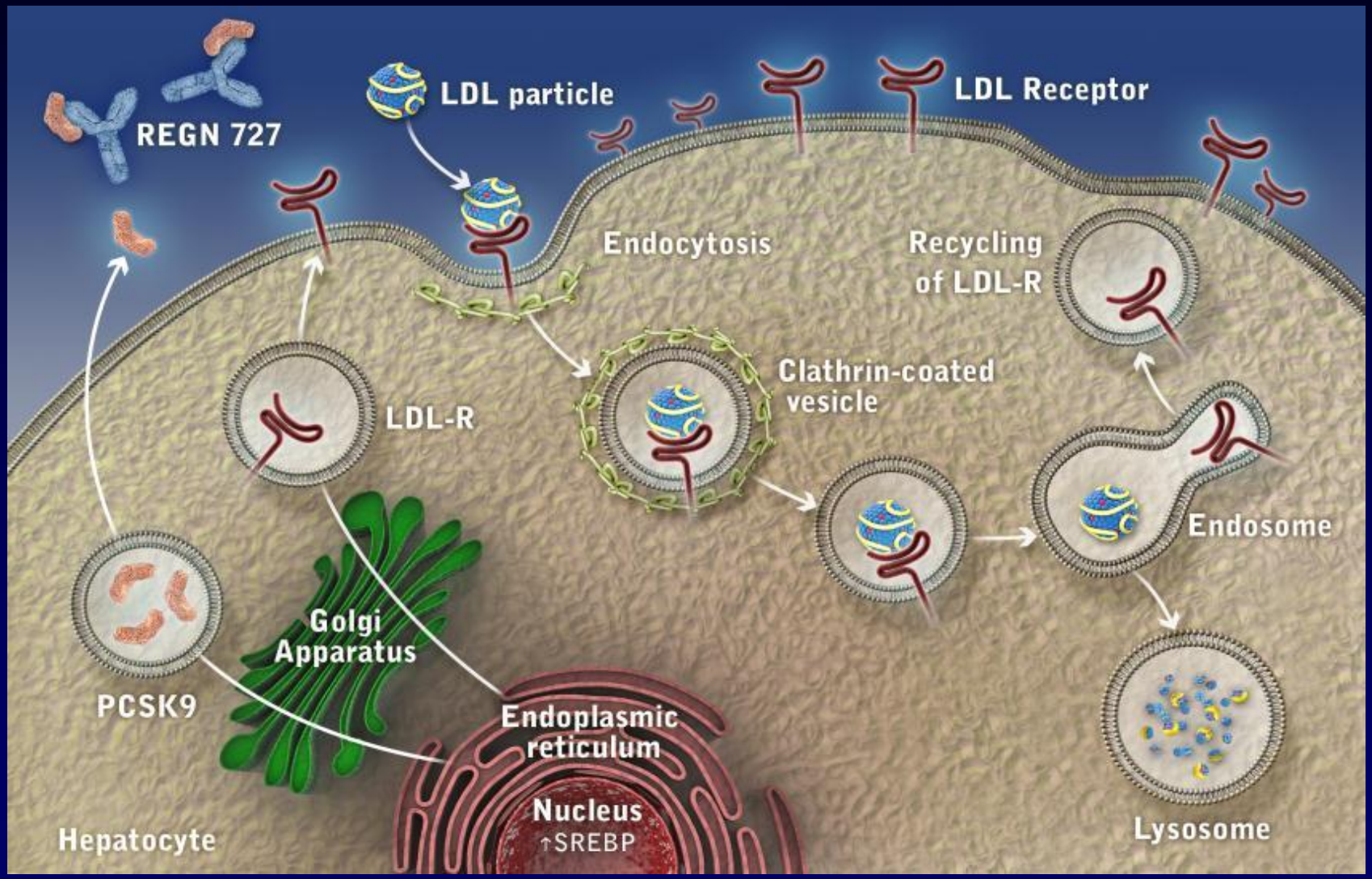
Hedrick JA. Curr Opin Investig Drugs 2009;10:938-46.
Rhainds D, et al. Clin Lipid 2012;7:621-40.
Seidah NG. Expert Opin Ther Targets 2009;13:19-28.
Seidah NG, et al. Nat Rev Drug Discov 2012;11:367-83.
Hooper AJ, et al. Expert Opin Biol Ther 2013;13:429-35.

Introduction PCSK9 inhibition- human monoclonal antibodies

- Several mAbs targeting PCSK9 have been tested in preclinical studies to assess their disruption of the PSCK9-LDLR interaction or inhibition of PCSK9 internalization.
- Targeting PCSK9 in FH patients with novel anti-PCSK9 therapies will be useful in reducing cardiovascular risk in affected subjects.

Rhainds D, et al. Clin Lipid 2012;7:621-40.
Saavedra YGL,et al. Arteriosclerosis, thrombosis, and vascular biology 2014;34:2700-2705.

Impact of PCSK9 inhibition on LDL Receptor Expression



PCSK9 Inhibition

Mechanism	Substances	Human data
Monoclonal antibody	SAR 236553 (Sanofi)	available
	AMG145 (Amgen)	available
	RN316/Rf04950615 (Pfizer)	available

- Heterozygous Familial Hypercholesterolemia
- Statin intolerance
- High-risk patients not at target levels

PCSK9-directed agents in development

Company	Drug name	Agent	Indication	Phase
Sanofi/Regeneron	REGN727/SAR236553	Monoclonal antibody	Hypercholesterolemia	III
Amgen	AMG 145	Monoclonal antibody	Hypercholesterolemia	III
Pfizer/Rinat	RN316 (PF-04950615)	Monoclonal antibody	Hypercholesterolemia	III
Novartis	LGT-209	Monoclonal antibody	Hypercholesterolemia	II
Roche	RG7652	Monoclonal antibody	Metabolic syndrome	II
Eli Lilly	LY3015014	Monoclonal antibody	Cardiovascular disease	II
Alnylam Pharmaceuticals	ALN-PCS02	siRNA oligonucleotide	Hypercholesterolemia	I
Adnexus Therapeutics/ Bristol-Myers Squibb	BMS-962476	Fusion protein using Adnectin technology	Cardiovascular disease	I
Santaris Pharma A/S	SPC5001	Antisense oligonucleotides	Familial hypercholesterolemia	Terminated
Isis pharmaceuticals/ Bristol-Myers Squibb	BMS-844421/ISIS-405879	Antisense oligonucleotide		Terminated

siRNA, small interfering RNA.

SAR236553/REN727 Phase III trial

Study name	The primary objective	ClinicalTrials.gov identifier
ODYSSEY FH I, FH II and HIGH FH	To demonstrate the efficacy and safety of SAR236553/REGN727 as an add-on therapy in patients with HeFH who are not adequately controlled with standard lipid-modifying therapy	NCT01623115, NCT01709500, NCT01617655
ODYSSEY COMBO I and COMBO II	To demonstrate the safety and efficacy of SAR236553/REGN727 as an add-on therapy in patients with primary hypercholesterolemia at high cardiovascular risk who are not adequately controlled with standard lipid-modifying therapy	NCT01644175, NCT01644188
ODYSSEY MONO	To demonstrate the safety and efficacy of SAR236553/REGN727 as monotherapy in comparison with ezetimibe in patients with primary hypercholesterolemia	NCT01644474
ODYSSEY ALTERNATIVE	To demonstrate the safety and efficacy of SAR236553/REGN727 in comparison with ezetimibe in patients with primary hypercholesterolemia (HeFH and nonfamilial hypercholesterolemia) who are unable to tolerate statins	NCT01709513
ODYSSEY OPTIONS I and OPTIONS II	To evaluate the safety and efficacy of SAR236553/REGN727 as an add-on therapy in patients with primary hypercholesterolemia at high cardiovascular risk or with HeFH who are not adequately controlled on statins, in comparison with several second-line lipid-lowering strategies	NCT01730053, NCT01730040
ODYSSEY LONG TERM	To evaluate the long-term safety and tolerability of SAR236553/REGN727 in patients with hypercholesterolemia at high cardiovascular risk or patients with HeFH inadequately controlled with their current lipid-modifying therapy	NCT01507831
ODYSSEY OUTCOMES	A cardiovascular outcomes trial which will enroll about 18,000 patients and evaluate the effect of SAR236553/REGN727 on the occurrence of cardiovascular events	NCT01663402
ODYSSEY CHOICE	To determine the efficacy and safety of alirocumab every 4 weeks compared with placebo in lowering cholesterol, if used alone or added to the participants' current cholesterol-lowering medication	NCT01926782
ODYSSEY OLE	To assess the long-term safety of alirocumab when added to lipid-lowering therapy in patients with heterozygous familial hypercholesterolemia (heFH)	NCT01954394

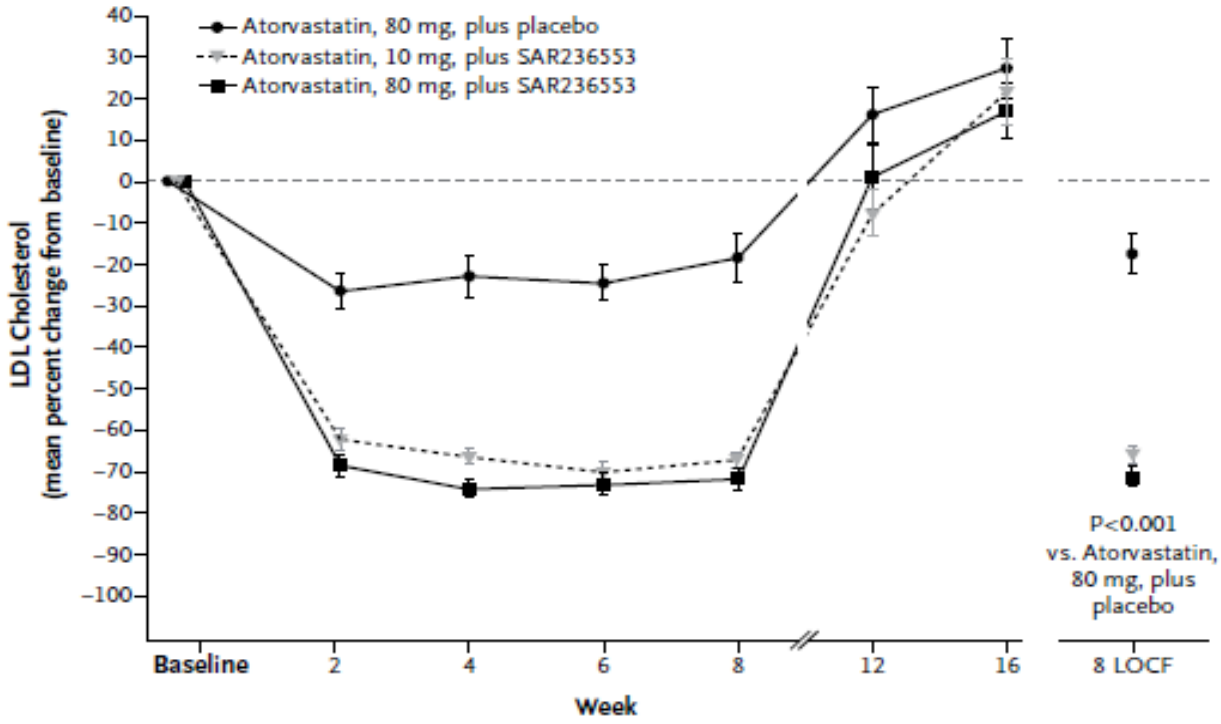
AMG145 Phase III trial

Study name	The primary objective	ClinicalTrials.gov identifier
FOURIER	To evaluate the safety and efficacy on cardiovascular events when used in addition to other treatments for dyslipidemia	NCT01764633
GAUSS-2	To evaluate the safety and efficacy of AMG 145 compared to ezetimibe in hypercholesterolemic subjects unable to tolerate an effective dose of statin	NCT01763905
MENDEL-2	To evaluate the safety and efficacy of lipid-lowering monotherapy with AMG 145 in subjects with a 10-year Framingham risk score of 10% or less	NCT01763827
LAPLACE-2	To evaluate the safety, tolerability, and efficacy of AMG 145 on LDL-C in combination with statin therapy in subjects with primary hypercholesterolemia and mixed dyslipidemia	NCT01763866
RUTHERFORD-2	To evaluate the safety, tolerability, and efficacy of AMG 145 on LDL-C in subjects with heterozygous familial hypercholesterolemia	NCT01763918
OSLER-2	To evaluate the long-term safety, tolerability, and efficacy of AMG 145 in subjects with hyperlipidemia and subjects with mixed dyslipidemia	NCT01854918
TESLA	To determine the safety, tolerability, and efficacy of AMG 145 in subjects with homozygous familial hypercholesterolemia	NCT01588496
GLAGOV	To evaluate whether low-density lipoprotein (LDL-C) lowering with AMG 145 results in greater change from baseline in percent atheroma volume (PAV) than placebo in subjects with coronary artery disease taking lipid-lowering therapy	NCT01813422
DESCARTES	To evaluate the efficacy, safety, and tolerability of 52 weeks of AMG 145 compared with placebo when added to assigned background lipid-lowering therapy	NCT01516879

RN316 (PF-04950615) Phase III trial

Study name	The primary objective	ClinicalTrials.gov identifier
SPIRE-1, SPIRE-2	To evaluate RN316 (PF-04950615), compared to placebo, in reducing the occurrence of major cardiovascular events in high-risk subjects	NCT01975376, NCT01975389
SPIRE-LDL	To assess the efficacy, safety, and tolerability of RN316 (PF-04950615) to lower LDL-C in subjects with high cholesterol receiving highly effective statins	NCT01968967
SPIRE-HR	To assess the efficacy, safety, and tolerability of RN316 (PF-04950615) to lower LDL-C in subjects with high cholesterol receiving highly effective statins	NCT01968954
SPIRE-HF	To assess the safety, efficacy, and tolerability of RN316 (PF-04950615) to lower LDL-C in subjects with heterozygous familial hypercholesterolemia receiving highly effective statins	NCT01968980

SAR236553/REN727 vs. Atorvastatin
Phase II Trial Randomized Clinical Trial



No. of Patients								
Atorvastatin, 80 mg, plus placebo	29	29	27	25	24	25	21	29
Atorvastatin, 10 mg, plus SAR236553	29	29	26	26	27	27	24	29
Atorvastatin, 80 mg, plus SAR236553	30	29	28	28	28	27	27	30

Figure 1. Mean Percent Change from Baseline in Low-Density Lipoprotein (LDL) Cholesterol Levels, According to Treatment Group.

Roth EM, et al. The New England journal of medicine 2012;367:1891-900.

SAR236553/REN727 vs. Atorvastatin
Phase II Trial Randomized Clinical Trial

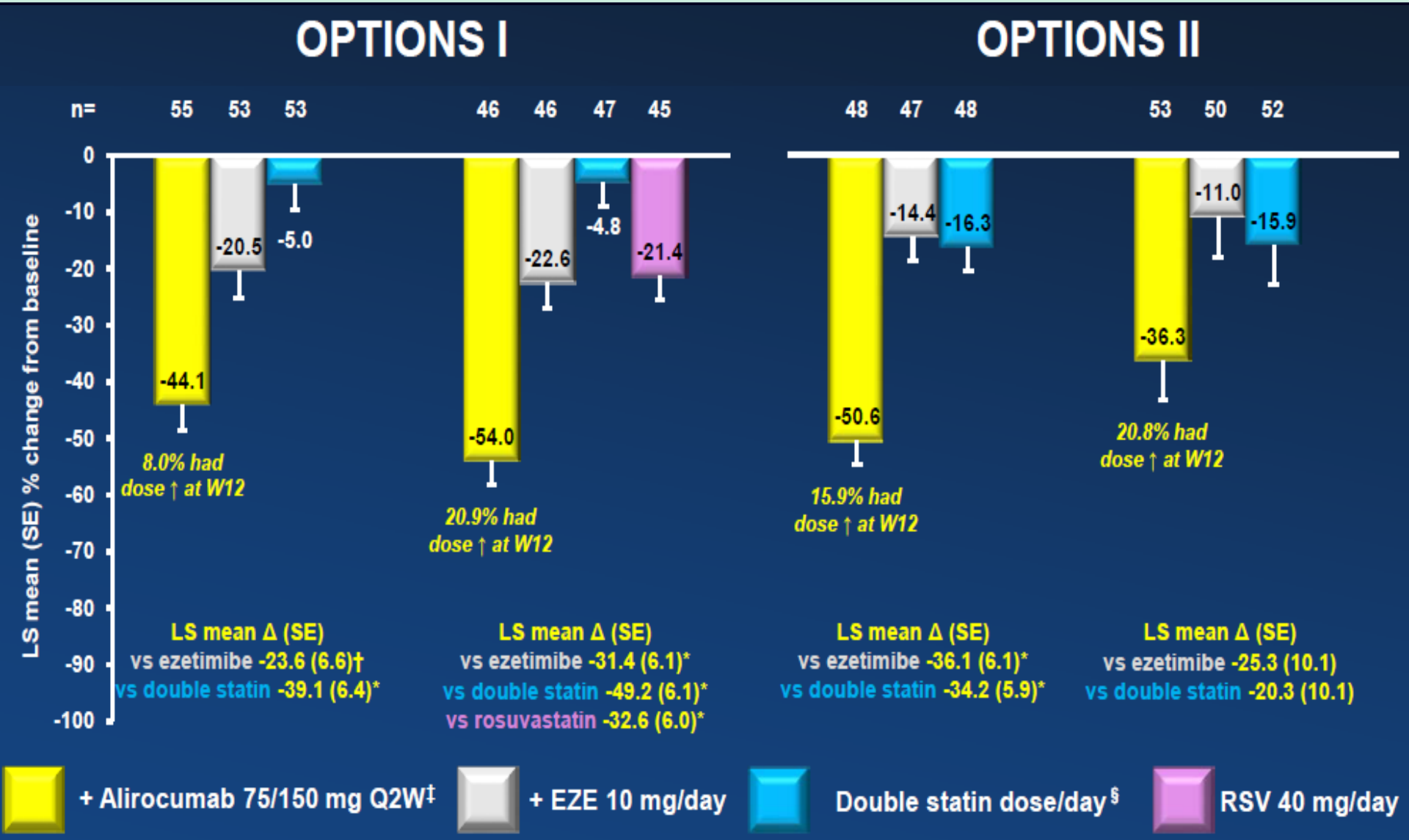
Adverse Events and Potentially Clinically Significant Abnormalities in the Safety Population ☆

Event or Abnormality	Atorvastatin, 80 mg, plus Placebo (N=31)	Atorvastatin, 10 mg, plus SAR236553 (N=31)	Atorvastatin, 80 mg, plus SAR236553 (N=30)
	number of patients (percent)		
Adverse events occurring during study treatment			
Any	19 (61)	14 (45)	18 (60)
Any serious	0	0	1 (3)
Resulting in death	0	0	0
Resulting in permanent discontinuation of treatment	4 (13)	0	1 (3)
Potentially clinically significant abnormalities			
Alanine aminotransferase >3× ULN	0	0	0
Aspartate aminotransferase >3× ULN	0	0	1 (3)
Total bilirubin >1.5× ULN	0	0	1 (3)
Creatine kinase >3× ULN	1 (3)	0	0

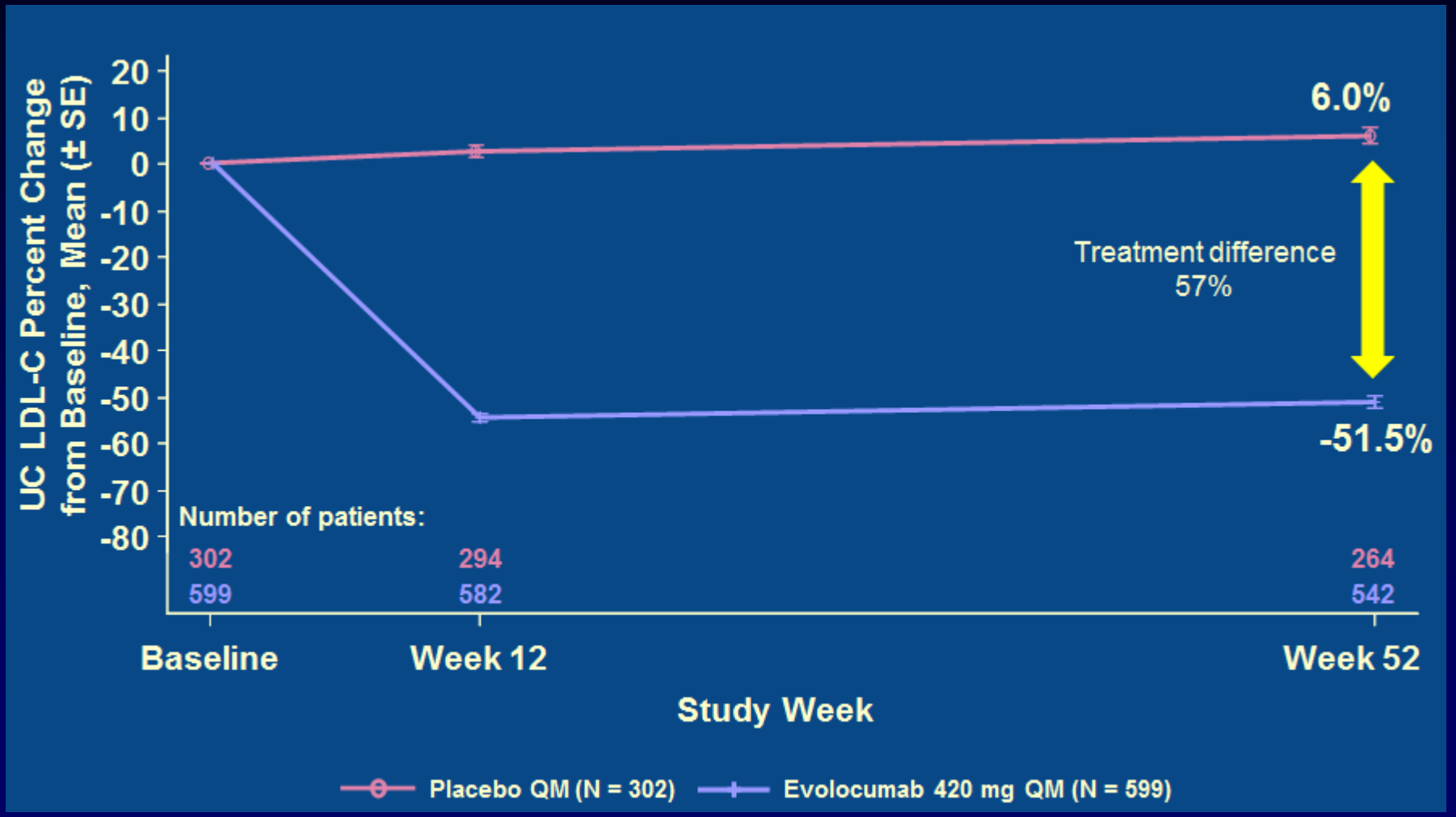
☆The safety population included all patients who underwent randomization and who received at least one dose or partialdose of SAR236553 or placebo

Roth EM, et al. The New England journal of medicine 2012;367:1891-900.

SAR236553/REN727 vs. Statin
The ODYSSEY OPTIONS I and II

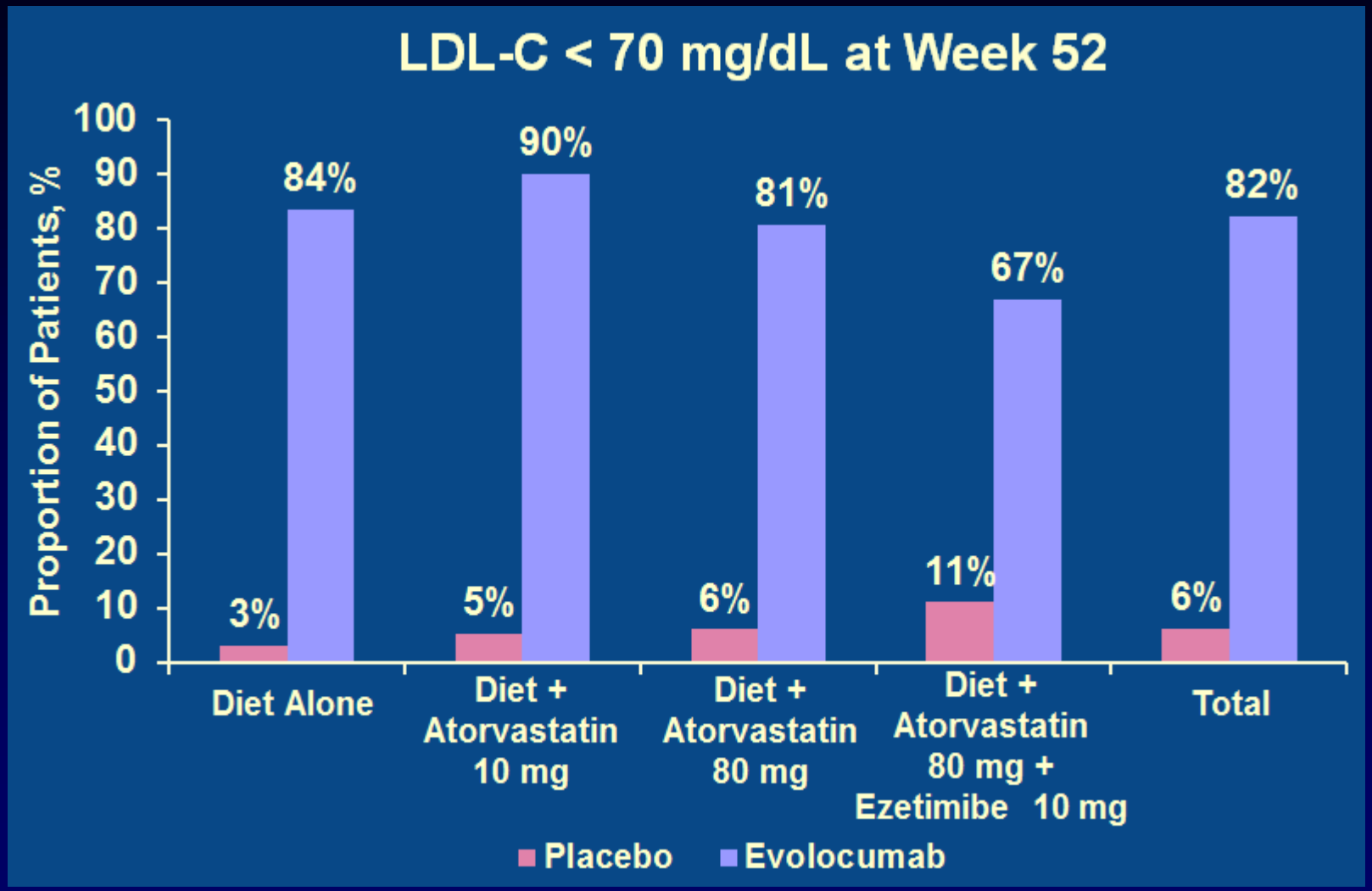


AMG145 (Evolocumab)
DESCARTES Randomized Placebo-controlled Study



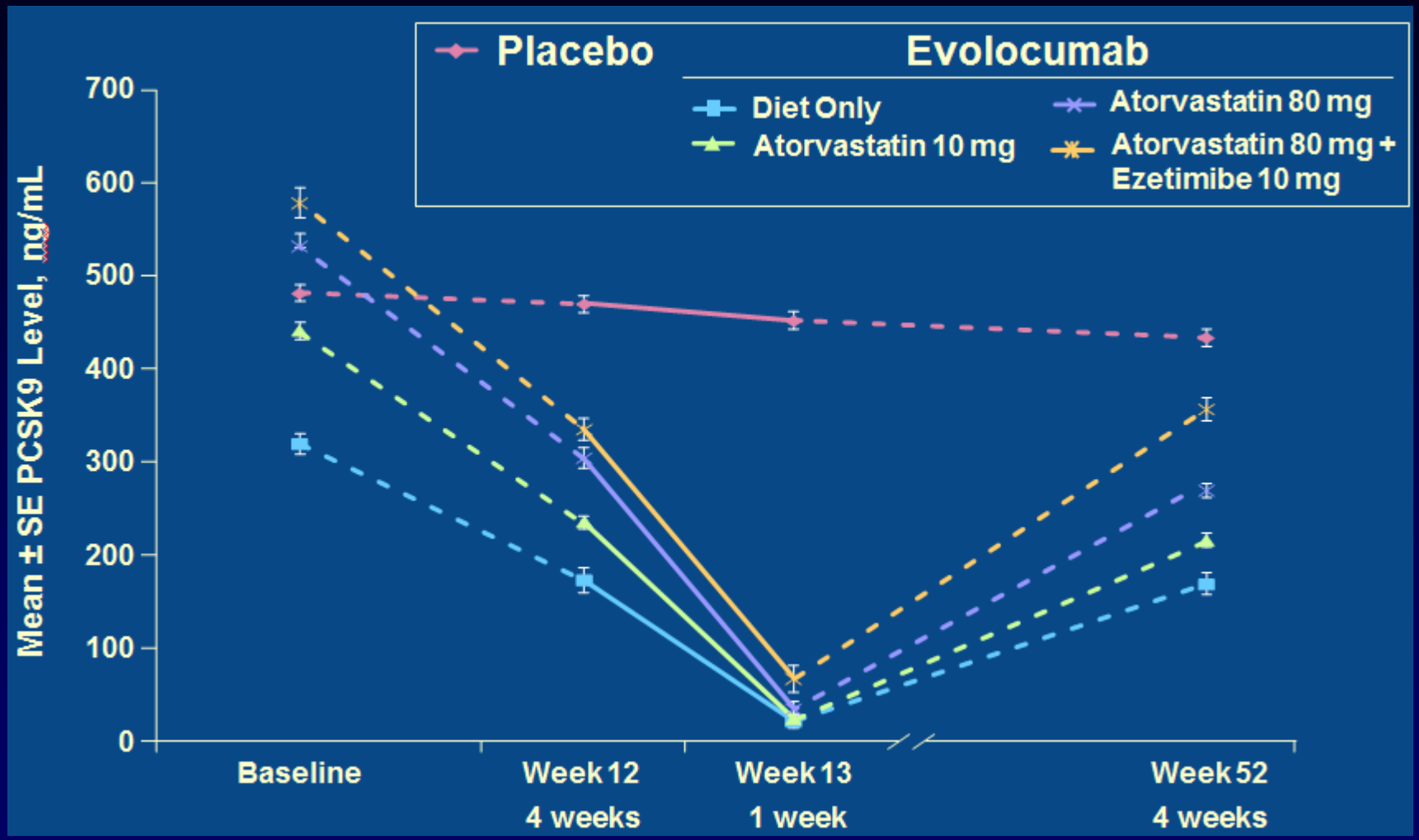
Blom DJ, et al. The New England journal of medicine 2014;370:1809-19.

DESCARTES: LDL-C Goal Achievement



Blom DJ, et al. The New England journal of medicine 2014;370:1809-19.

DESCARTES: Changes in Mean Levels of PCSK9



Blom DJ, et al. The New England journal of medicine 2014;370:1809-19.

DESCARTES: Treatment Emergent Adverse Events

n (%)	Placebo N=302	Evolocumab N=599
Any Treatment Emergent Adverse Event	224 (74.2)	448 (74.8)
Serious	13 (4.3)	33 (5.5)
Death	0 (0.0)	2 (0.3)
Adjudicated events	2 (0.7)	6 (1.0)
Leading to discontinuation of study drug	3 (1.0)	13 (2.2)

Blom DJ, et al. The New England journal of medicine 2014;370:1809-19.

DESCARTES: Treatment Emergent Adverse Events II

n (%)	Placebo N=302	Evolocumab N=599
Most Common Treatment Emergent AEs		
Nasopharyngitis	29 (9.6)	63 (10.5)
Upper respiratory tract infection	19 (6.3)	56 (9.3)
Influenza	19 (6.3)	45 (7.5)
Back pain	17 (5.6)	37 (6.2)
Neurocognitive AEs	2 (0.7)	1 (0.2)
Amnesia - Short-term memory loss	0 (0.0)	1 (0.2)
Dementia With Lewy Bodies	1 (0.3)	0 (0.0)
Encephalopathy	1 (0.3)	0 (0.0)

Blom DJ, et al. The New England journal of medicine 2014;370:1809-19.

DESCARTES: Hepatic and Muscle Safety

n (%)	Placebo N=302	Evolocumab N=599
Liver function tests		
ALT or AST > 3 × ULN*	3 (1.0)	5 (0.8)
ALT or AST > 5 × ULN*	1 (0.3)	3 (0.5)
Muscle TEAEs and Laboratory Results		
Myalgia	9 (3.0)	24 (4.0)
CK > 5 × ULN*	1 (0.3)	7 (1.2)
CK > 10 × ULN*	1 (0.3)	3 (0.5)

Blom DJ, et al. The New England journal of medicine 2014;370:1809-19.

SAR236553/REN727 Phase III trial

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RUTHERFORD-2	To evaluate the safety, tolerability, and efficacy of AMG 145 on LDL-C in subjects with heterozygous familial hypercholesterolemia	NCT01763918
OSLER-2	To evaluate the long-term safety, tolerability, and efficacy of AMG 145 in subjects with hyperlipidemia and subjects with mixed dyslipidemia	NCT01854918
TESLA	To determine the safety, tolerability, and efficacy of AMG 145 in subjects with homozygous familial hypercholesterolemia	NCT01588496
GLAGOV	To evaluate whether low-density lipoprotein (LDL-C) lowering with AMG 145 results in greater change from baseline in percent atheroma volume (PAV) than placebo in subjects with coronary artery disease taking lipid-lowering therapy	NCT01813422
DESCARTES	To evaluate the efficacy, safety, and tolerability of 52 weeks of AMG 145 compared with placebo when added to assigned background lipid-lowering therapy	NCT01516879

RN316 (PF-04950615) Phase III trial

Study name	The primary objective	ClinicalTrials.gov identifier
SPIRE-1, SPIRE-2	To evaluate RN316 (PF-04950615), compared to placebo, in reducing the occurrence of major cardiovascular events in high-risk subjects	NCT01975376, NCT01975389
SPIRE-LDL	To assess the efficacy, safety, and tolerability of RN316 (PF-04950615) to lower LDL-C in subjects with high cholesterol receiving highly effective statins	NCT01968967
SPIRE-HR	To assess the efficacy, safety, and tolerability of RN316 (PF-04950615) to lower LDL-C in subjects with high cholesterol receiving highly effective statins	NCT01968954
SPIRE-HF	To assess the safety, efficacy, and tolerability of RN316 (PF-04950615) to lower LDL-C in subjects with heterozygous familial hypercholesterolemia receiving highly effective statins	NCT01968980

Summary

- CSK9 inhibitors, REGN727/SAR236553 or AMG145, whether combination with other lipid-lowering agents or not, have significantly decreased LDL-C levels with well tolerance.
- Long-term clinical studies are required to define their roles in clinical practice.

Thank you for your attention.