Moving Beyond Statins for the Management of Hypercholesterolemia

Evaluating Novel Therapies that Target Lipoprotein Synthesis, Transport, and Regulation

CVLN®
CARDIOVASCULAR LEARNING NETWORK

Learning Objectives

- Identify and overcome low-density lipoprotein cholesterol (LDL-C) treatment shortfalls of statin therapy
- Outline the mechanisms of action of emerging hypercholesterolemia agents targeting lipoprotein synthesis, transport, and regulation
- Summarize clinical trial data on the benefits and limitations of novel agents for hypercholesterolemia management

Key Lesson from Statin Trials

>160,000 patients	No. of events (% per annum) Statin/more statin	Control/less statin	RR (CI) per 1 mmol LDL-C
Nonfatal MI	3485 (1.0)	4593 (1.3)	0.73 (0.69 - 0.78)
CHD death	1887 (0.5)	2281 (0.6)	0.80 (0.74 - 0.87)
Any major coronary event	**5105 (1.4)**	**6512 (1.9)**	**0.76 (0.73 - 0.78)**
CABG	1453 (0.4)	1857 (0.5)	0.75 (0.69 - 0.82)
PTCA	1767 (0.5)	2283 (0.7)	0.72 (0.65 - 0.80)
Unspecified	2133 (0.6)	2667 (0.8)	0.76 (0.70 - 0.82)
Any coronary revasc	**5353 (1.5)**	**6807 (2.0)**	**0.75 (0.72 - 0.78)**
Ischemic stroke	1427 (0.4)	1751 (0.5)	0.79 (0.72 - 0.87)
Hamorrhagic stroke	257 (0.1)	220 (0.1)	1.12 (0.88 - 1.43)

LOWERING LDL-C REDUCES CV EVENTS

Any major vascular event	**10,973 (3.2)**	**13,350 (4.0)**	**0.78 (0.76 - 0.80)**

99% or 95% CI

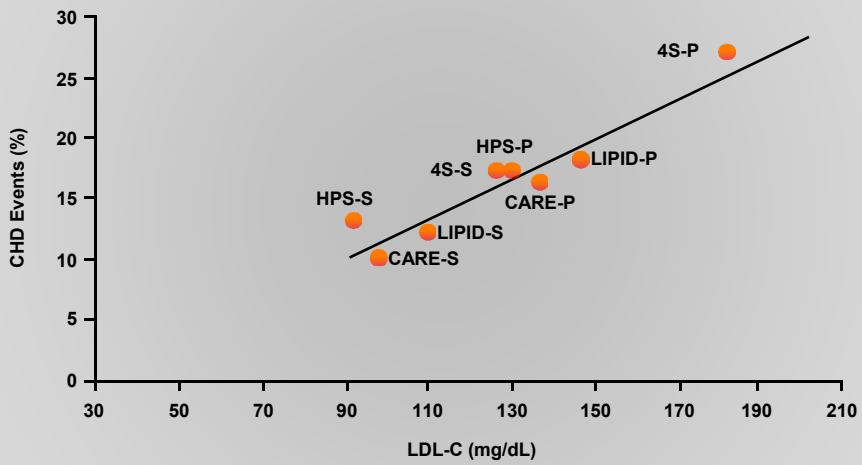
0.4 0.6 0.8 1 1.2 1.4

Statin/more statin better Control/less statin better

RR = relative risk; CI = confidence interval; MI = myocardial infarction; CHD = coronary heart disease; CABG = coronary artery bypass graft; PTCA = percutaneous trasluminal coronary angioplasty; CV = cardiovascular.

Cholesterol Treatment Trialists' (CTT) Collaboration. *Lancet.* 2010;376(9753):1670-1681.

How Low Should We Go in Secondary Prevention?

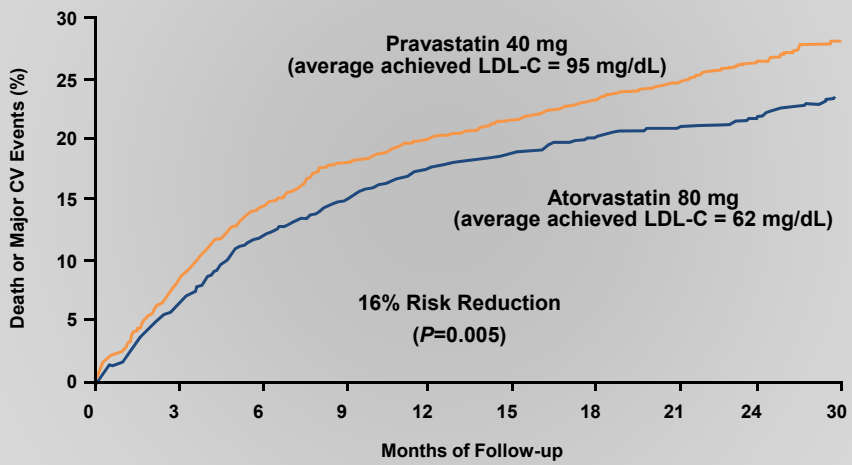


HPS = Heart Protection Study; 4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol and Recurrent Events; LIPID = Long-Term Intervention with Pravastatin in Ischemic Disease; P = placebo; S = statin; PR = pravastatin; AT = atorvastatin

O'Keefe JH Jr, et al. *J Am Coll Cardiol.* 2004;43(11):2142-2146.

PROVE IT–TIMI 22

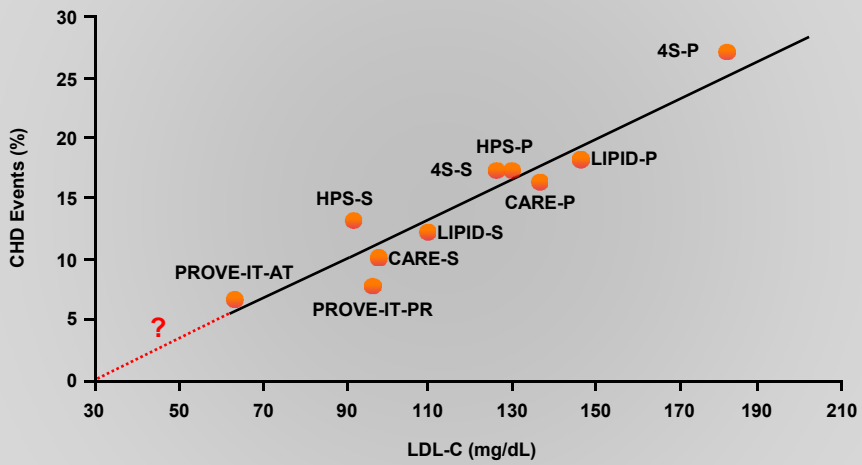
4162 patients hospitalized within prior 10 days for ACS



PROVE IT = Pravastatin or Atorvastatin in Evaluation and Infection Therapy; TIMI = Thrombolysis in Myocardial Infarction; ACS = acute coronary syndrome.

Cannon CP et al. *N Engl J Med.* 2004;350(15):1495-1504.

How Low Should We Go in Secondary Prevention?



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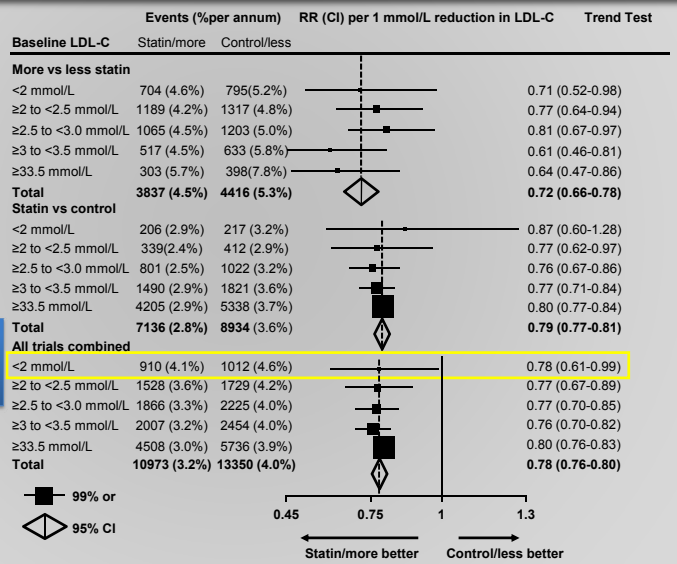
O'Keefe JH Jr, et al. *J Am Coll Cardiol.* 2004;43(11):2142-2146.

Meta-Analysis Supporting Benefit of Lowering LDL-C, Even When Starting "Low"

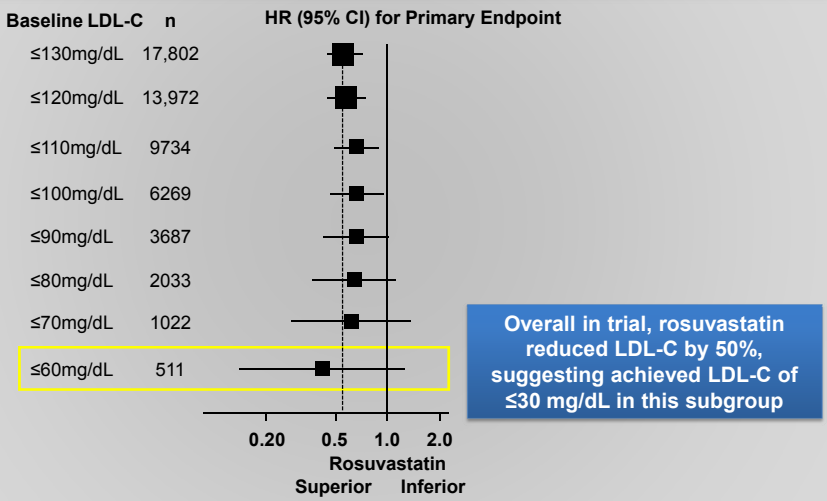
CTT Cycle #2



Benefit similar even if starting with LDL-C <77 mg/dL

CTT Collaboration. *Lancet.* 2010;376(9753):1670-1681.

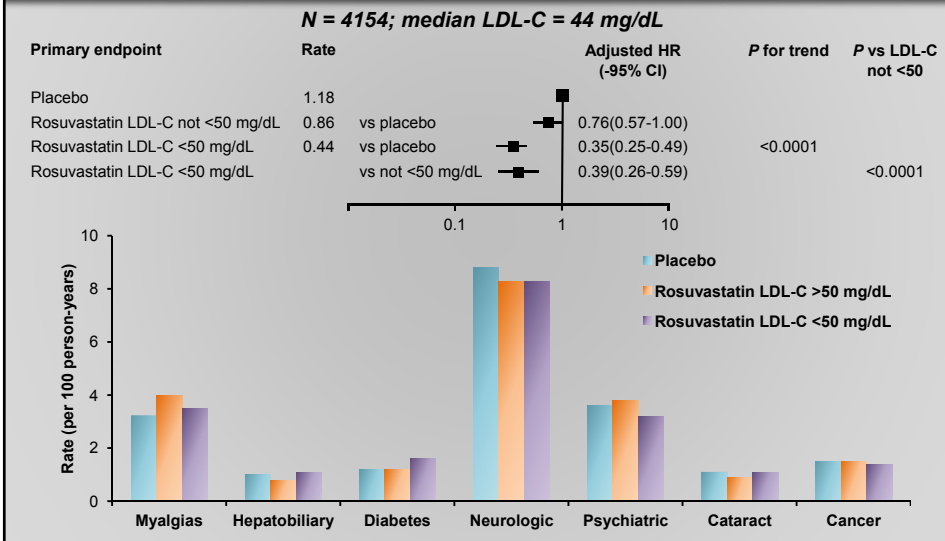
Risk Reduction in JUPITER by Baseline LDL-C



Overall in trial, rosuvastatin reduced LDL-C by 50%, suggesting achieved LDL-C of ≤30 mg/dL in this subgroup

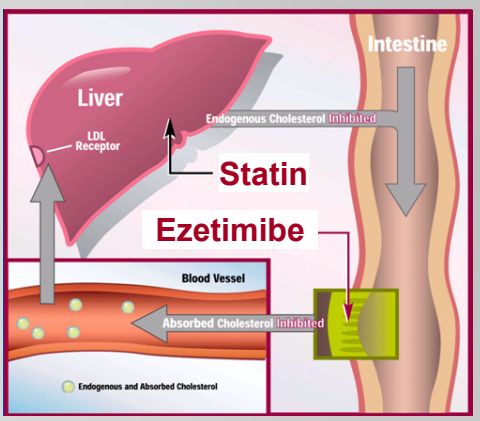
JUPITER = Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; HR = hazard ratio.
Hsia J et al. *J Am Coll Cardiol.* 2011;57(16):1666-1675.

Achieved LDL-C <50 mg/dL Subgroup From JUPITER



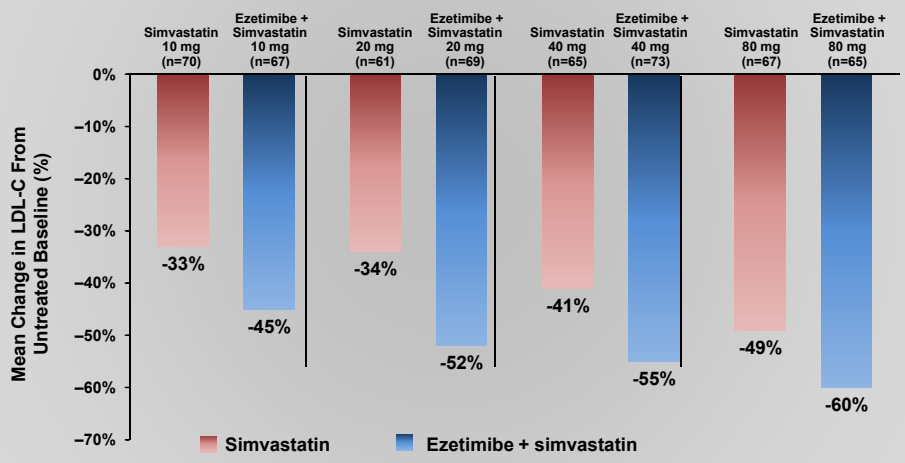
Hsia J, et al. *J Am Coll Cardiol.* 2011;57(16):1666-1675.

Dual Inhibition Approach: Attacking Cholesterol Production (statin) and Absorption (ezetimibe)



- Inhibit cholesterol *production* with a statin
  - Reduce cholesterol synthesis
  - Increase clearance of LDL-C from the blood via upregulation of LDL receptors
- Inhibit intestinal cholesterol *absorption* with ezetimibe
  - Ezetimibe localizes and appears to act at the brush border of the small intestine
  - 54% less cholesterol was absorbed compared with placebo in a clinical study
  - This action led to a reduction in hepatic cholesterol stores, increasing clearance of cholesterol from the blood

Ezetimibe + Simvastatin
Greater LDL-C Reduction at Each Dose



P≤0.01 for ezetimibe/simvastatin vs simvastatin for each comparison.
Vytorin [package insert]. Whitehouse Station, NJ: Merck & Co, Inc.

IMPROVE-IT: Study Design

18,057 patients stabilized post ACS ≤10 days
LDL-C ≤125 mg/dL* (or ≤100 mg/dL† if prior lipid-lowering therapy)

Double-blind

ASA + standard medical therapy

Simvastatin 40 mg

Ezetimibe/simvastatin 10 mg/40 mg

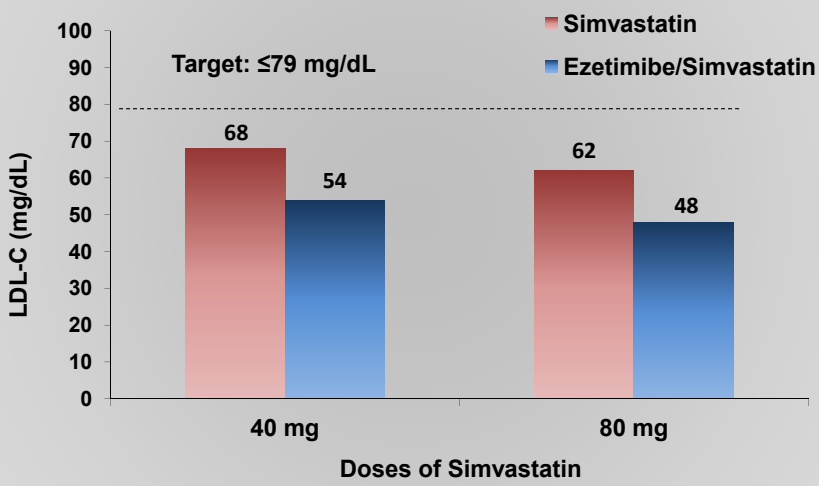
Follow-up visit day 30, every 4 months

Duration: minimum 2.5-year follow-up (5250 events)

Primary endpoint: CV death, MI, hospital admission for UA, revascularization (≥30 days after randomization), or stroke

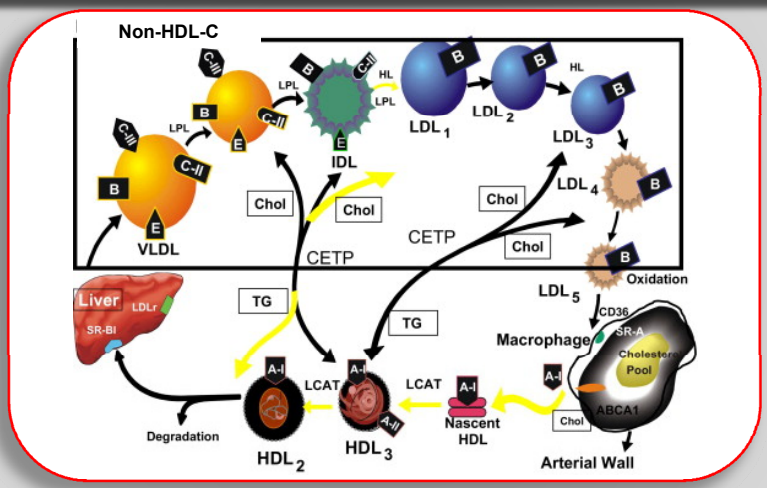
*3.2 mM. †2.6 mM
ASA = acetylsalicylic acid; UA = unstable angina.
Cannon CP, et al. *Am Heart J.* 2008;156(5):826-832.

Anticipated Achieved LDL-C in IMPROVE-IT



IMPROVE-IT = Improved Reduction of Outcomes: Vytorin Efficacy International Trial.
Cannon CP, et al. *Am Heart J.* 2008;156(5):826-832.

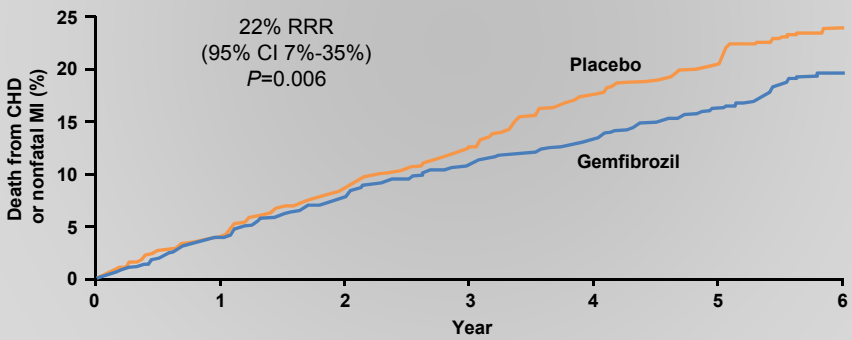
Lipoprotein Classes



HDL-C = high-density lipoprotein cholesterol; LPL = lipoprotein lipase; IDL = intermediate-density lipoprotein; HL = hepatic lipase; VLDL = very low-density lipoprotein; CETP = cholestryl ester transfer protein; LDLr = low-density lipoprotein receptor; SR-B1 = scavenger receptor class B, type 1; TG = triglycerides; CD36 = cluster of differentiation 36; SR-A = scavenger receptor class A; LCAT = lecithin-cholesterol acyltransferase; ABCA1 = ATP-binding cassette transporter 1.

VA-HIT Trial

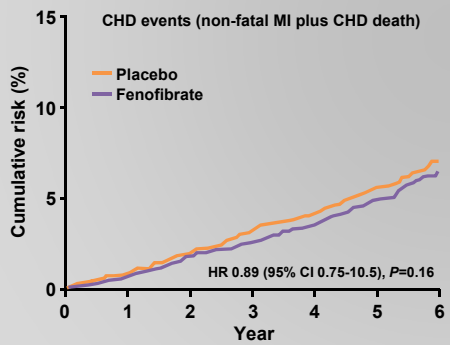
- 2531 men with CHD
- HDL-C ≤40 mg/dL, LDL-C ≤140 mg/dL, TG ≤300 mg/dL
- Gemfibrozil 1200 mg/day vs placebo
- Results: TG 115 mg/dL vs 166 mg/dL; HDL 34 mg/dL vs 32 mg/dL; LDL 113 mg/dL in both



VA-HIT = Veterans Affairs High-Density Lipoprotein Intervention Trial; RRR = relative risk reduction.
Rubins HB, et al. *N Engl J Med.* 1999;341(6):410-418.

FIELD Trial

- 9795 patients with diabetes mellitus not on a statin
- TC 3 mmol/L-6.5 mmol/L (116 mg/dL-251 mg/dL) + *either* TC/HDL ratio ≥4 *or* triglycerides 1 mmol/L-5 mmol/L (89 mg/dL-443 mg/dL)
- Fenofibrate 200 mg/day vs placebo
- Lipids effects at 4 months: TG ↓ 28.6%, HDL-C ↑ 5.1%, LDL-C ↓ 12%

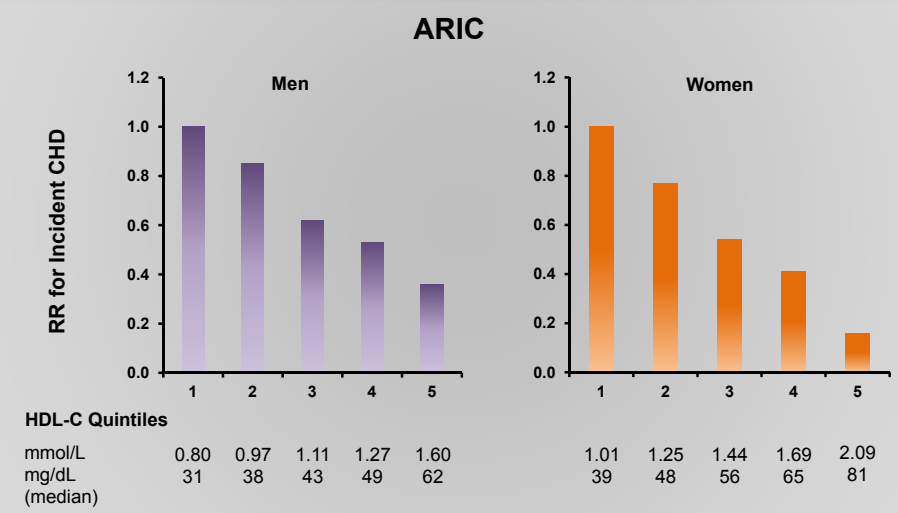


- More "drop in" of statin therapy in placebo arm (17% vs 8%)
- 11% ↓ in total coronary events (ie, including stroke and revascularization)

FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; TC = total cholesterol.
Keech A, et al. *Lancet.* 2005;366(9500):1849-1861.

Elevated HDL-C Levels and CHD Incidence

Adjusted for Age and Race, 12-Year Follow-Up; N=12,339



ARIC = Atherosclerosis Risk in Communities.

Sharrett AR, et al. *Circulation.* 2001;104(10):1108-1113.

Is HDL-C Simply a Marker of Increased CV Risk?

Low HDL-C levels are commonly found in patients who:

- Smoke
- Are sedentary
- Are obese
- Are insulin resistant or diabetic
- Have hypertriglyceridemia
- Have chronic inflammatory disorders

HDL-C Mendelian Randomization Studies

- Identify a genetic variant purely associated with HDL-C levels
  - SNP in endothelial lipase gene (*LIPG Asn396Ser)* in 2.6% of population
  - Associated with a 5.4-mg/dL increase in HDL-C
- From observational cohorts, estimate what association of genetic variant and MI should be if HDL-C is a true risk factor
  - In observational studies, 1 mg/dL ↑ HDL-C along with ~2% ↓ in odds of MI
  - ∴ Expect carriers of SNP to have 13% ↓ in odds of MI
- Determine association of genetic variant with outcomes
  - No association between SNP and MI (OR 0.99, 95% CI 0.88-1.11)
- Repeat using multi-SNP genetic risk score

	OR (95% CI) per 1-SD increase in plasma lipid	
	Observational Epidemiology	Genetic Score
LDL-C	1.54 (1.45-1.63)	2.13 (1.69-2.69), $P=2x10^{-10}$
HDL-C	0.62 (0.58-0.66)	0.93 (0.68-1.26), $P=0.63$

SNP = single neucleotide polymorphism; OR = odds ratio; SD = standard deviation.
Voight BF, et al. *Lancet.* 2011;380(9841):572-580.

Coronary Drug Project

- 1966-1969: randomized 3908 patients with prior MI to immediate-release niacin (3 g/day) or placebo
- 5 year follow-up
- Efficacy: ↓ nonfatal MI by **26%**, ↓ stroke/TIA by **24%**
- Caveats:
  - No effect on mortality (primary endpoint), although 11% ↓ seen ~9 years after termination of trial
  - No statins
  - Baseline TC ~250 mg/dL
  - Niacin known to ↓ LDL-C (↓ TC by 9.9% in trial)

TIA = transient ischemic attack.
***JAMA.* 1975;231(4):360-381. Canner PL, et al. *J Am Coll Cardiol.* 1986;8(6):1245-1255.**

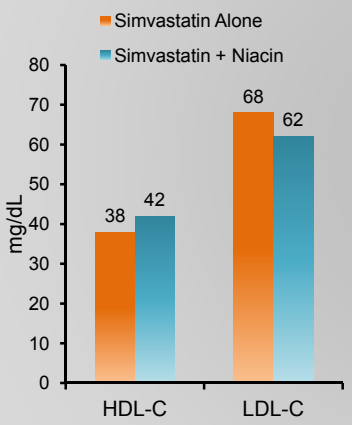
AIM-HIGH Trial: Design and Baseline

- 3414 patients with established CV disease, HDL-C <40 mg/dL (men) or <50 mg/dL (women)
- Extended-release niacin with open-label, run-in titration from 0.5 g/day to 2 g/day
- Simvastatin in all patients titrated to LDL-C 40 mg/dL-80 mg/dL
- Baseline lipids (median)
  - HDL-C: 35 mg/dL
  - LDL-C: 71 mg/dL
- Planned mean follow-up of 4.6 years
- Stopped early for futility

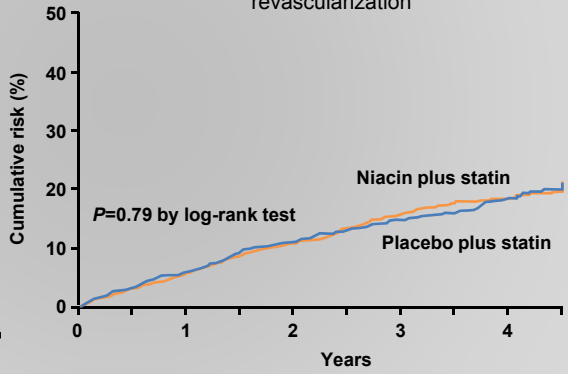
AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes.
AIM-HIGH Investigators. *N Engl J Med.* 2011;365(24):2255-2267.

AIM-HIGH Trial: Results

Achieved Lipid Levels at 2 Years



Primary endpoint:
CHD death, MI, stroke, hospitalization for ACS, symptom-driven coronary/cerebrovascular revascularization



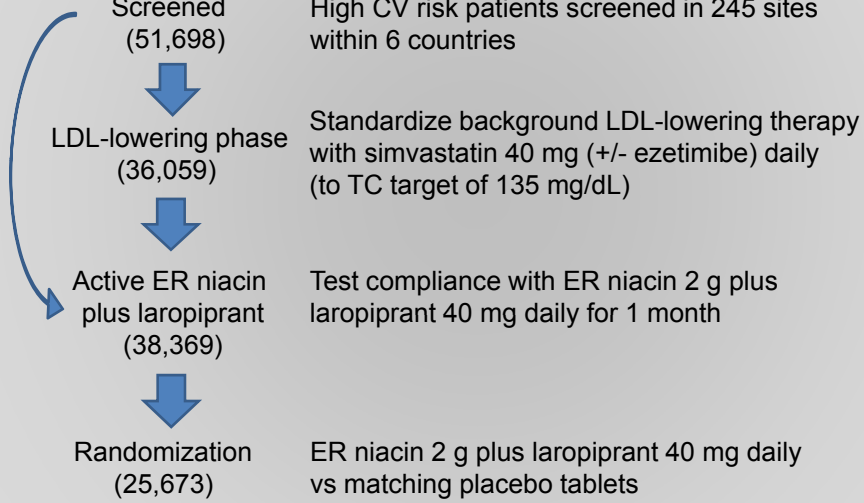
AIM-HIGH Investigators. *N Engl J Med.* 2011;365(24):2255-2267.

HPS2-THRIVE: Eligibility

- Men and women
- Aged 50-80 years
- Prior history of:
  - MI
  - Ischemic stroke or TIA
  - Peripheral arterial disease
  - Diabetes with other CHD
- No contraindication to study treatments
- No significant liver, kidney, or muscle disease

HPS2-THRIVE = Heart Protection Study 2 – Treatment of HDL to Reduce the Incidence of Vascular Events.
HPS2-THRIVE Collaborative Group. *Eur Heart J.* 2013;34:1279-1291.

HPS2-THRIVE: Active Prerandomization Run-In



ER = extended release.
HPS2-THRIVE Collaborative Group. *Eur Heart J.* 2013;34(17):1279-1291.

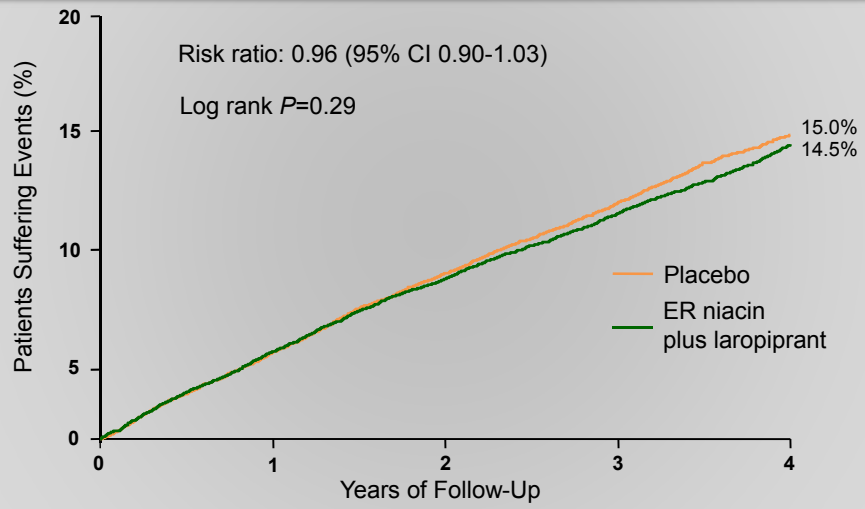
Effects of ER Niacin/Laropiprant on Lipids

Year of Follow-Up	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)
1	-12	6	-35
4	-7	6	-31
Study average	-10	6	-33
(mmol/L)	(-0.25)	(0.16)	(-0.37)

"Based on previous observational studies and randomized trials, it was anticipated such lipid differences might translate into a 10-15% reduction in vascular events."
***—European Heart Journal*, 2013**

HPS2-THRIVE Collaborative Group. *Eur Heart J.* 2013;34(17):1279-1291. Armitage J, et al. Presented at: The American College of Cardiology 2013; March 9, 2013; San Francisco, California. http://www.hps2-thrive.org/docs_prof.htm. Accessed May 29, 2013.

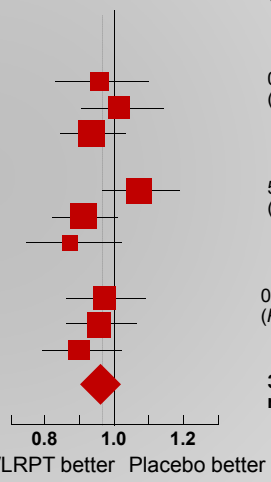
Effect of ER Niacin Plus Laropiprant on Major Vascular Events



HPS2-THRIVE Collaborative Group. *Eur Heart J.* 2013;34:1279-1291. Armitage J, et al. Presented at: The American College of Cardiology 2013; March 9, 2013; San Francisco, California. http://www.hps2-thrive.org/docs_prof.htm. Accessed May 29, 2013.

Major Vascular Events by Baseline Lipids

mg/dL (mmol/L)	Randomized allocation: ER niacin + laropiprant (12,838)	Randomized allocation: Placebo (12,835)	Het or trend X^2 (uncorrected *P* value)
HDL-C			
<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-C			
<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%)	
TG			
<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**

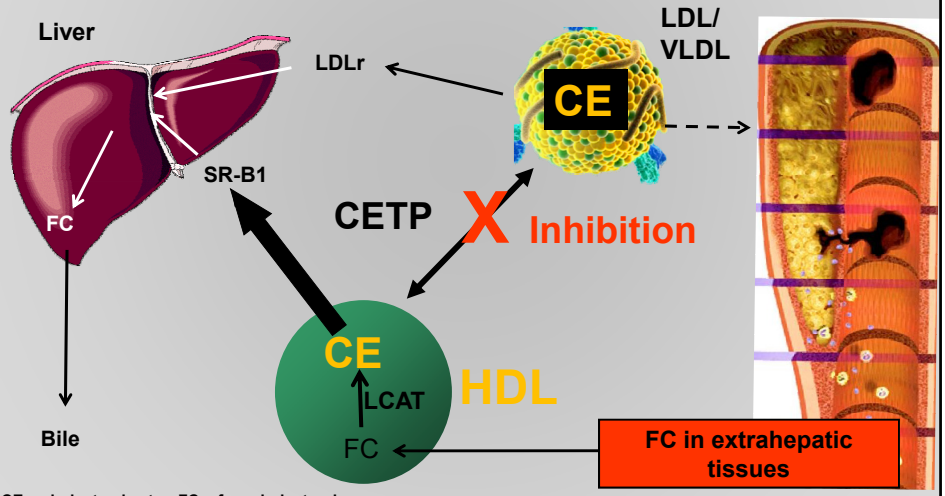


SE = standard error.

Armitage J, et al. Presented at: The American College of Cardiology 2013; March 9, 2013; San Francisco, California. http://www.hps2-thrive.org/docs_prof.htm. Accessed May 29, 2013.

CETP Inhibition

CETP is a plasma protein that catalyzes transfer of CE from HDL to apoB-containing lipoproteins (VLDL and LDL-C) in exchange for triglycerides.



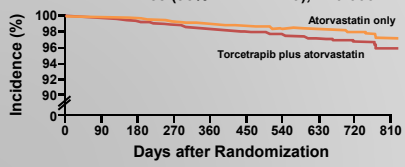
CE = cholesteryl ester; FC = free cholesterol.

ILLUMINATE: Torcetrapib

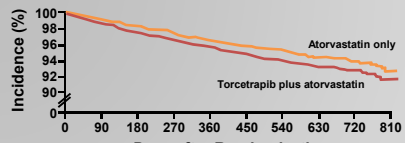
- 15,067 patients with vascular disease
- Atorvastatin titrated to achieve LDL-C <100 mg/dL
- Intervention: torcetrapib 60 mg once daily vs placebo

	Placebo	Torcetrapib
HDL-C		
Change (%)	2%↑	72%↑
Achieved (mg/dL)	49	83
LDL-C		
Change (%)	3%↑	25%↓
Achieved (mg/dL)	81	58

All-cause mortality:
HR 1.58 (95% CI 1.14-2.19), *P*=0.006



Major CV events:
HR 1.25 (95% CI 1.09-1.44), *P*=0.001

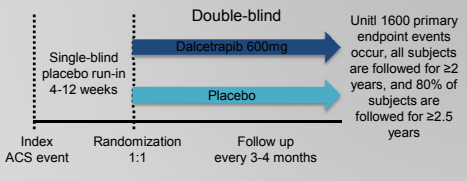


	Placebo	Torcetrapib	*P*
D SBP (mmHg)	+0.9	+5.4	<.001
D DBP (mmHg)	-0.1	+2.0	<.001

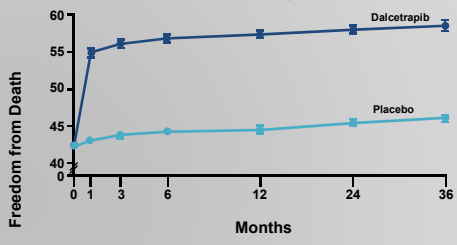
ILLUMINATE = Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events; SBP = systolic blood pressure; DBP = diastolic blood pressure.
Barter PJ, et al. *N Engl J Med.* 2007;357(21):2109-2122.

dal-OUTCOMES: Dalcetrapib

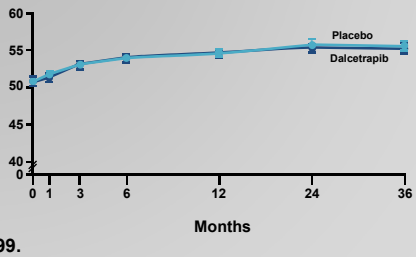
- 15,871 patients with ACS
- Target LDL-C <100 mg/dL and preferably <70 mg/dL, but not mandated or managed
- >97% on statins



HDL-C (mg/dl)

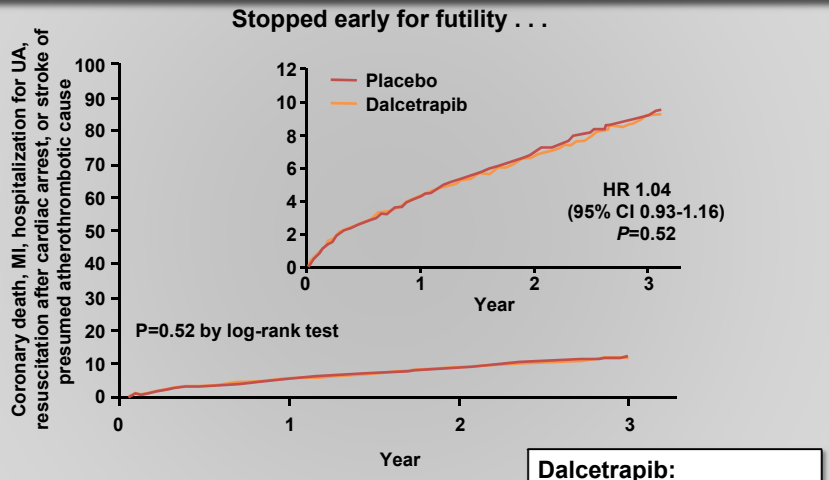


LDL-C (mg/dl)



Schwartz GG et al. *N Engl J Med.* 2012;367(22):2089-2099.

dal-OUTCOMES: Primary Endpoint



Dalcetrapib:
- ↑ SBP 0.6 mm Hg
- ↑ CRP 0.2 mg/L

CRP = C-reactive protein.

Schwartz GG et al. *N Engl J Med.* 2012;367(22):2089-2099.

CETP Inhibitors: Lipid Effects

	Torcetrapib (60 mg daily)	Dalcetrapib (600 mg daily)	Anacetrapib (100 mg daily)	Evacetrapib (130 mg daily)
Total cholesterol	+4%	N/A	+16%	N/A
LDL-C	-24%	-4%	~ -30%	? -30%
Apolipoprotein B	-12%	N/A	-21%	N/A
HDL-C	+61%	+25%	+140%	? +130%
Apolipoprotein A1	+25%	+10%	+45%	N/A

N/A = not available.

Adjudicated CV Events and Death

	Anacetrapib N=808 n (%)	Placebo N=804 n (%)	HR (95% CI)	*P* Value
Prespecified adjudicated CV safety endpoint	**16 (2.0)**	**21 (2.6)**	**0.76 (0.39, 1.45)**	**0.40**
CV death	4 (0.5)	1 (0.1)		
Nonfatal MI	6 (0.7)	9 (1.1)		
UA	1 (0.1)	6 (0.7)		
Nonfatal stroke	5 (0.6)	5 (0.6)		
Death from any cause	**11 (1.4)**	**8 (1.0)**		
Revascularization	**8 (1.0)**	**28 (3.5)**	**0.29 (0.13, 0.64)**	**0.001**
Death or major CV event (Death/MI/UA/Stroke/Revascularization)*	**27 (3.3)**	**43 (5.3)**	**0.62 (0.38, 1.01)**	**0.048**

***Post hoc analysis.**

Cannon CP, et al. *New Engl J Med.* 2010;363(25):2406-2415.

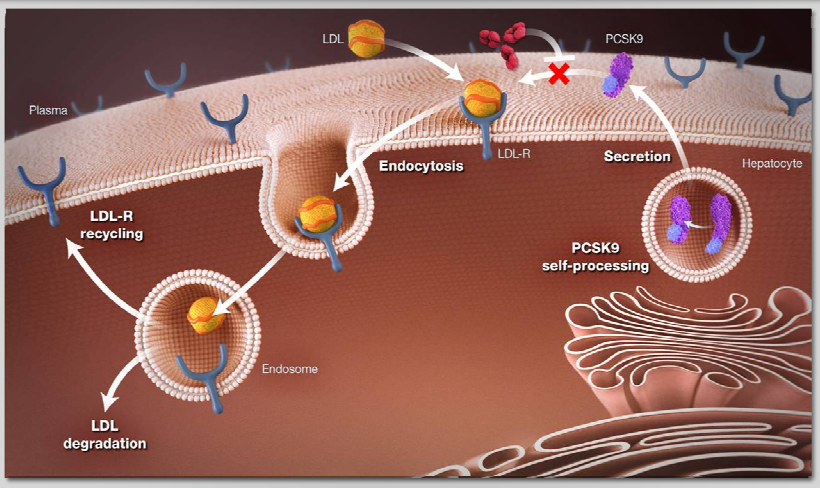
HPS3-TIMI55 REVEAL

- 30,000 patients with occlusive arterial disease in North America, Europe, and Asia
- Background LDL lowering with atorvastatin
- Randomized to anacetrapib 100 mg vs placebo
- Scheduled follow-up: 4 years
- Primary outcome: coronary death, MI, or coronary revascularization

REVEAL = Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification.

REVEAL study Web site. www.revealtrial.org. Accessed May 22, 2013.

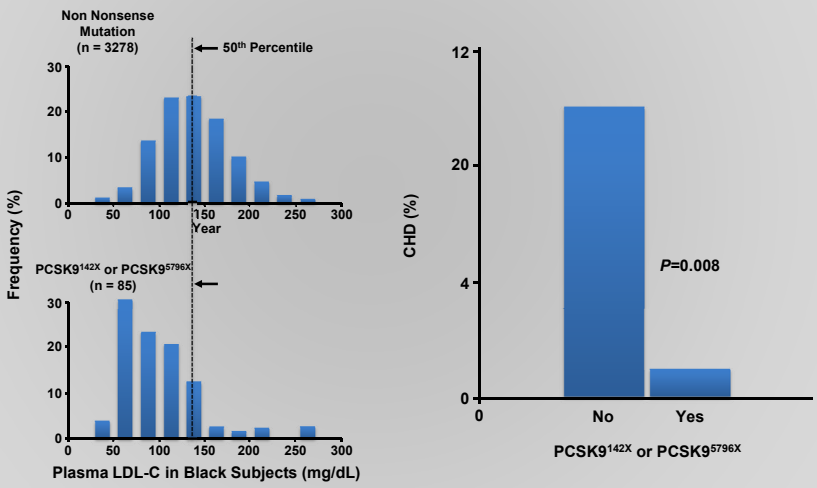
PCSK9 Inhibition with a Monoclonal Antibody



PCSK9 = proprotein convertase subtilisin-like/kexin type 9.

Qian YW, et al. *J Lipid Res.* 2007;48(7):1488-1498. Horton JD, et al. *J Lipid Res.* 2009;50(suppl):S172-S177. Rashid S, et al. *Proc Natl Acad Sci U S A.* 2005;102(15):5374-5379. Chan JC et al. *Proc Natl Acad Sci U S A.* 2009;106(24):9820-9825.

PCSK9 Loss-of-Function Mutations: Effect of Lifelong Low LDL-C on CHD

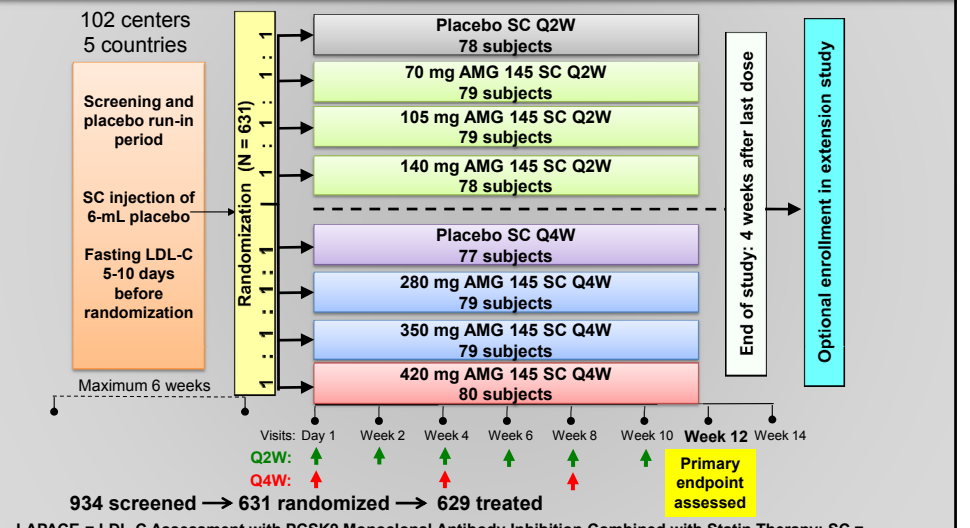


Cohen JC, et al. *N Engl J Med.* 2006;354(12):1264-1272.

PCSK9 Directed Therapy in Development

Company	Drug (Alternate Name)	Agent	Phase
Sanofi/Regeneron	SAR236553/REGN727 (SAR236553)	Human monoclonal antibody	3
Amgen	AMG-145	Human monoclonal antibody	3
Novartis	LGT-209	Monoclonal antibody	2
Pfizer/Rinat	RN316 (PF-04950615)	Monoclonal antibody	2
Genentech	MPSK3169A, RG7652	Monoclonal antibody	2
Alnylam Pharmaceuticals	ALN-PCS02	siRNA oligonucleotide	1
Adnexus Therapeutics/BMS	BMS-962476	Fusion protein using Adnectin technology	Preclinical
Idera Pharmaceuticals	TBD	Antisense oligonucleotide	Preclinical
Serometrix	SX-PCK9	Small peptide mimetic; LDLR antagonist	Preclinical
Shifa Biomedical Corp	TBD	Small molecule PCSK9 modulator	Preclinical

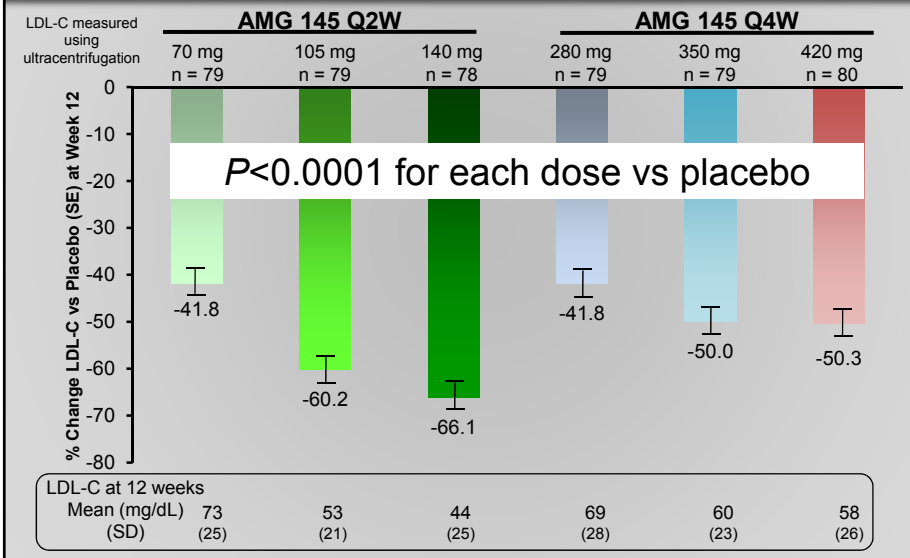
LAPLACE-TIMI 57



LAPACE = LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined with Statin Therapy; SC = subcutaneous; Q2W = every other week; Q4W = every 4 weeks.

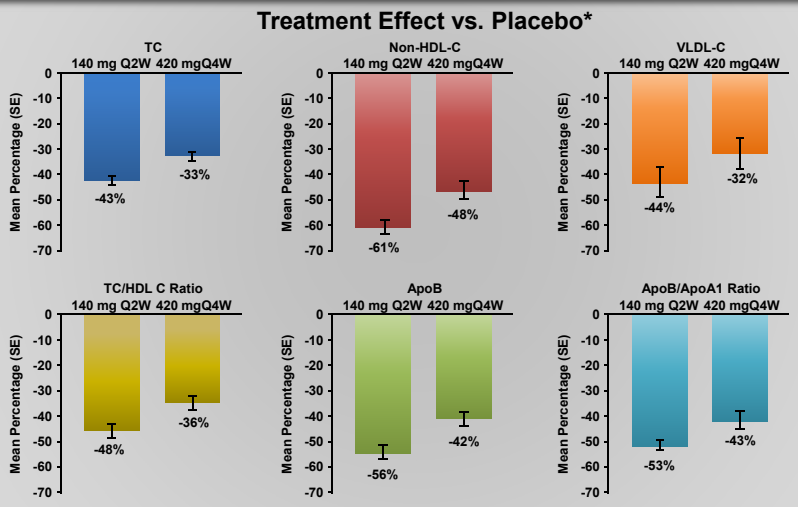
Kohli P, et al. *Clin Cardiol*. 2012;35(7):385-391.

Primary Endpoint:
AMG 145 Reduced LDL-C at 12 Weeks



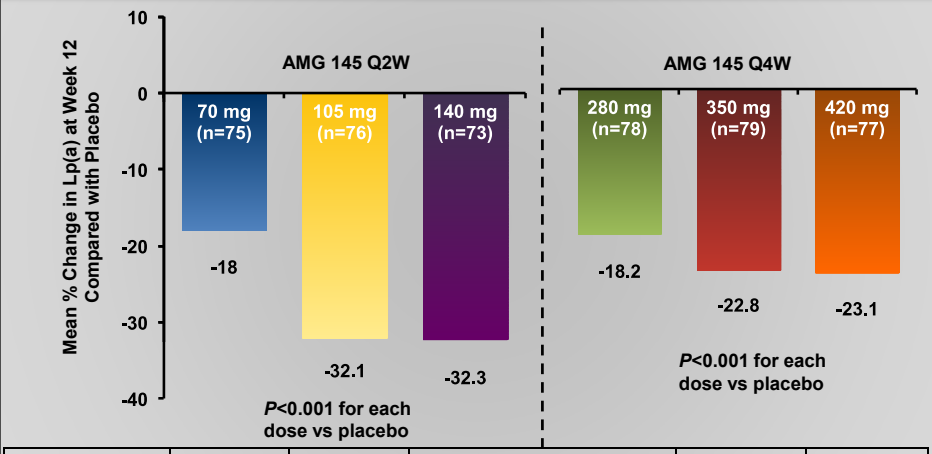
Giugliano RP, et al. *Lancet*. 2012;380(9858):2007-2017. Kohli P, et al. *Clin Cardiol*. 2012;35(7):385-391.

Secondary Results at 12 Weeks with Top 2 AMG 145 Doses



**P*<0.0001 versus placebo for all parameters.
Giugliano RP, et al. *Lancet* . 2012;380(9858):2007-2017.

Results: Mean % Change in Lp(a) at Week 12 with AMG 145 vs Placebo



Achieved Lp(a) at week 12, nmol/L, median (IQR)	30.0 (9-116)	27.0 (7-148)	29.0 (7-97)	21.5 (7-125)	17.0 (7-155)	40.0 (9-167)

Lp(a) = lipoprotein (a); IQR = interquartile range.
Giugliano RP, et al. *Lancet* . 2012;380(9858):2007-2017.

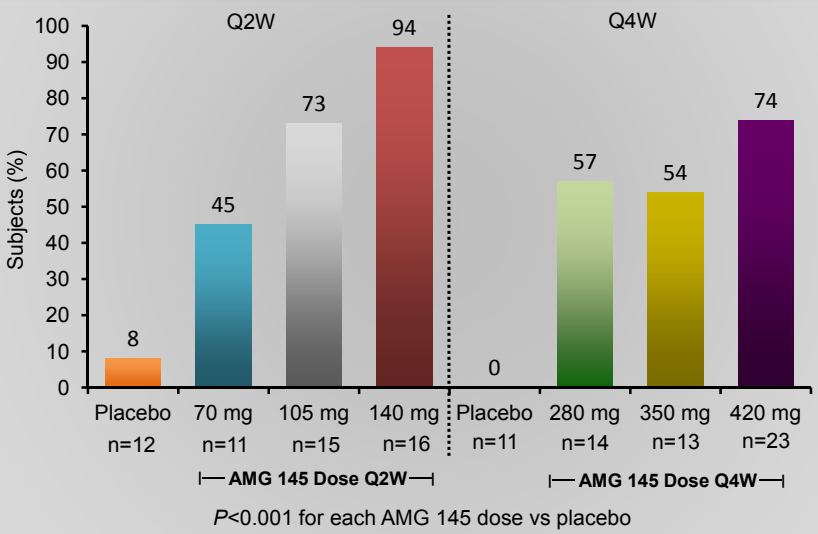
Safety

	Q2W Dose Groups				Q4W Dose Groups				
		AMG 145				AMG 145			
AE	Placebo n = 78	70 mg n = 79	105 mg n = 79	140 mg n = 78	Placebo n = 77	280 mg n = 79	350 mg n = 79	420 mg n = 80	Total N = 629
Any adverse event	33	41	52	43	38	45	48	48	348
Serious AE	4	0	1	4	0	2	2	2	15
Lead to drug DC	0	0	0	2*	0	0	0	0	2
Drug related AEs	7	4	9	4	4	6	7	9	50†
Lead to drug DC	0	0	0	0	0	0	0	0	0
Injection site reaction	2	1	1	0	1	2	3	1	11
AST or ALT >3 x ULN	1	0	0	0	0	0	0	0	1
CPK >5 x ULN	0	1	1	1	0	0	0	1	4‡
CV events§	1	1	0	4	0	1	1	0	8
Death	0	0	0	1	0	0	0	0	1

*Both events were reported as non-serious by the investigators. †All 50 were reported as non-serious by the investigator and none led to discontinuation of drug. ‡All were asymptomatic. §ACS, coronary revascularization, TIA, congestive heart failure requiring hospitalization, or death.
AE = adverse event; DC = discontinuation; AST = aspartate transaminase; ALT = alanine aminotransferase; ULN = upper limit of normal; CPK = creatinine phosphokinase.
Giugliano RP, et al. *Lancet.* 2012;380(9858):2007-2017.

Subjects Reaching LDL-C <70 mg/dL

Among High-Risk Subjects on Intensive Lipid-Lowering Therapy (N=115)

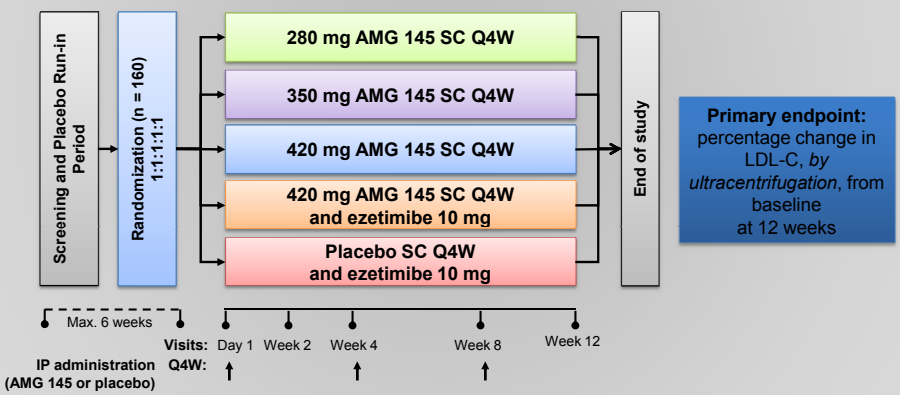


P<0.001 for each AMG 145 dose vs placebo

Giugliano RP, et al. *Lancet*. 2012;380(9858):2007-2017.

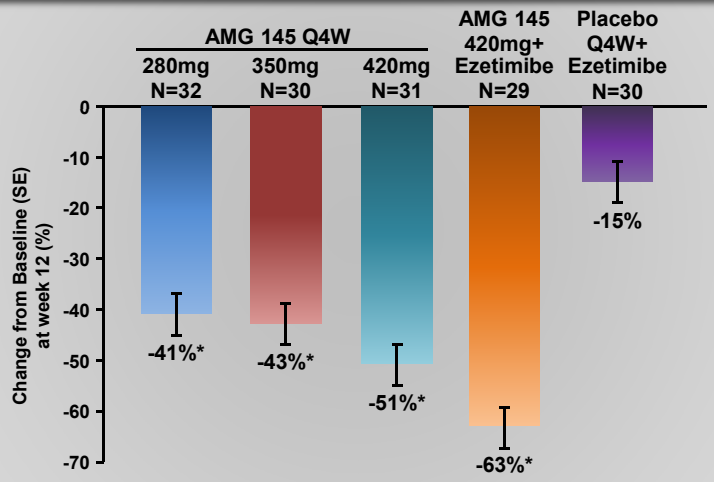
GAUSS: Study Design and Entry Criteria

- Statin intolerant because of intolerable myalgias
- Elevated LDL-C: ≥100 mg/dL if CHD or risk equivalent; ≥130 mg/dL without CHD but with ≥2 risk factors; or ≥160 mg/dL with ≤1 risk factor



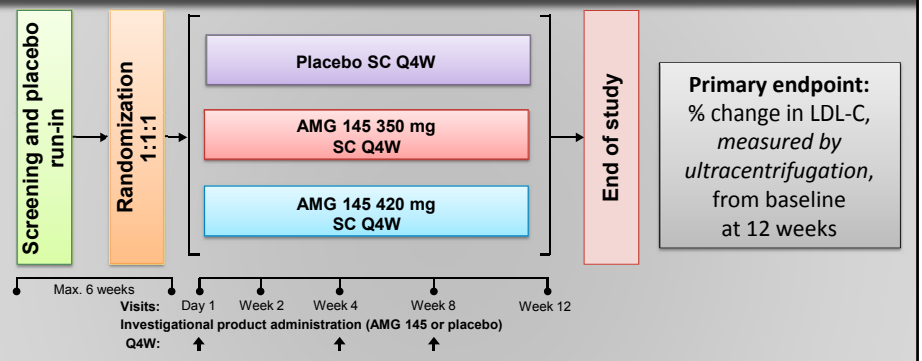
GAUSS = Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin-Intolerant Subjects; IP = intraperitoneal.
Sullivan D, et al. *JAMA*. 2012;308(23):2497-2506.

GAUSS: % Change in LDL-C by Ultracentrifugation, from Baseline at Week 12



*P<0.001 vs placebo Q4W + ezetimibe
LDL-C values at baseline and week 12 were measured using preparative ultracentrifugation.
Sullivan D, et al. *JAMA.* 2012;308(23):2497-2506.

RUTHERFORD: Study Design

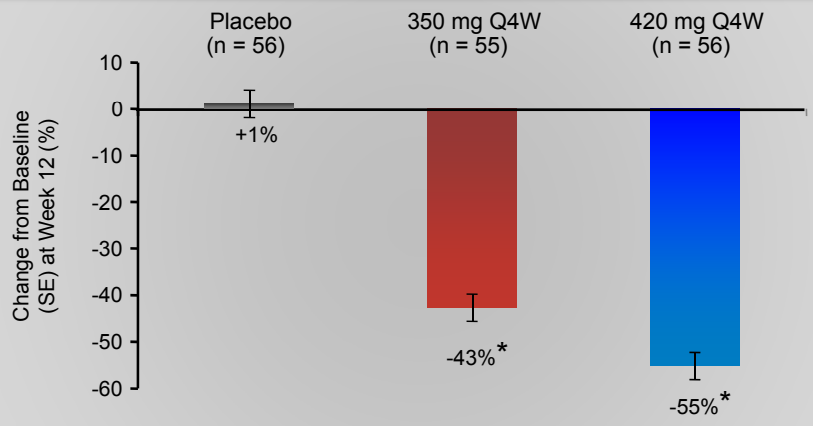


Population

- 18−75 years of age, with a diagnosis of HeFH by Simon Broome criteria
- LDL-C ≥100 mg/dL and TG ≤400 mg/dL
- At least 4 weeks of stable lipid-lowering therapy (eg, statin, ezetimibe, bile-acid sequestants, niacin)

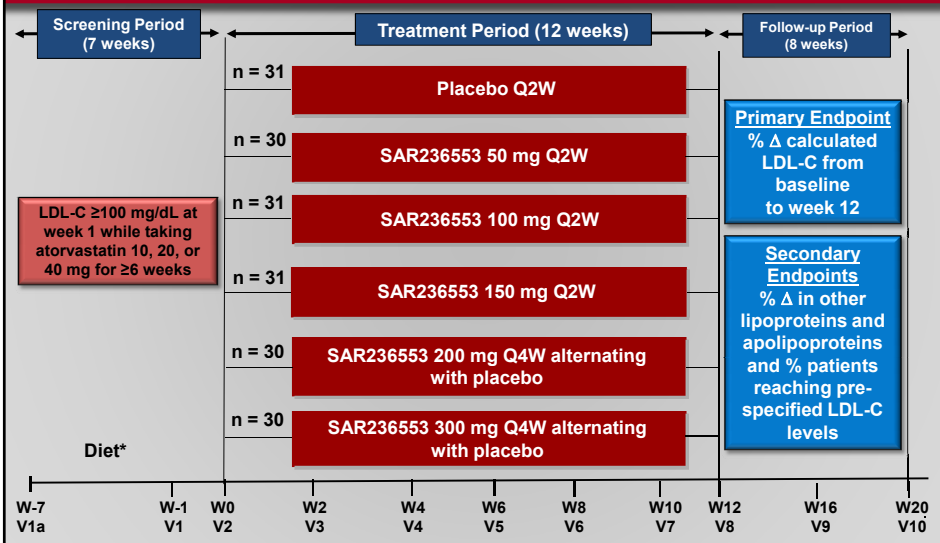
RUTHERFORD = Reduction of LDL-C with PCSK9 Inhibition in Heterzygous Familial Hypercholesterolemia Disorder Study; HeFH = heterzygous familial hypercholesterolemia.
Raal F, et al. *Circulation.* 2012;126(20);2408-2417.

RUTHERFORD: % Change in LDL-C, by UC, from Baseline to Week 12



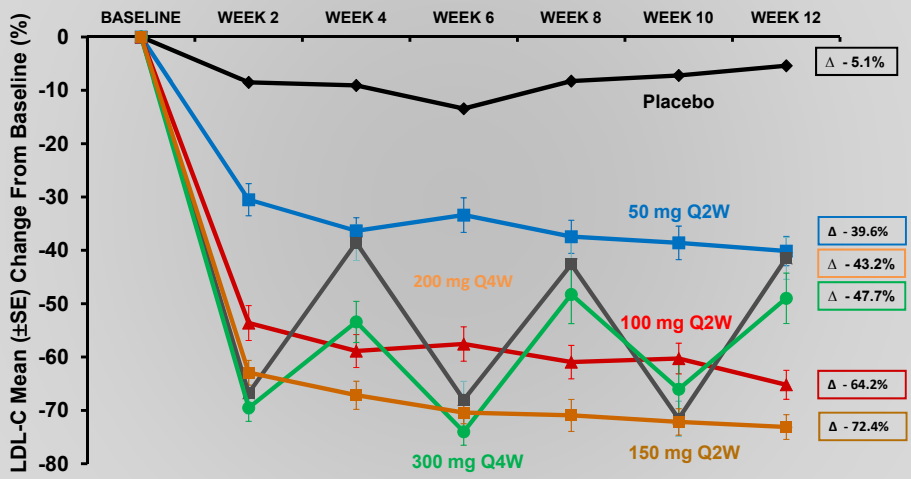
***P<0.001 vs. placebo**
LDL-C values at baseline and week 12 were measured using preparative UC. Least square means are presented from the ANCOVA model including treatment and stratification factors as covariates. Missing UC LDL-C values at week 12 were imputed using last observation carried forward and calculated LDL-C. A Hochberg adjustment was used to control the family wise error rate at ≤0.05.
ANCOVA = analysis of covariance.
Raal F, et al. *Circulation.* 2012;126(20);2408-2417.

SAR236553 Add-on to Atorvastatin



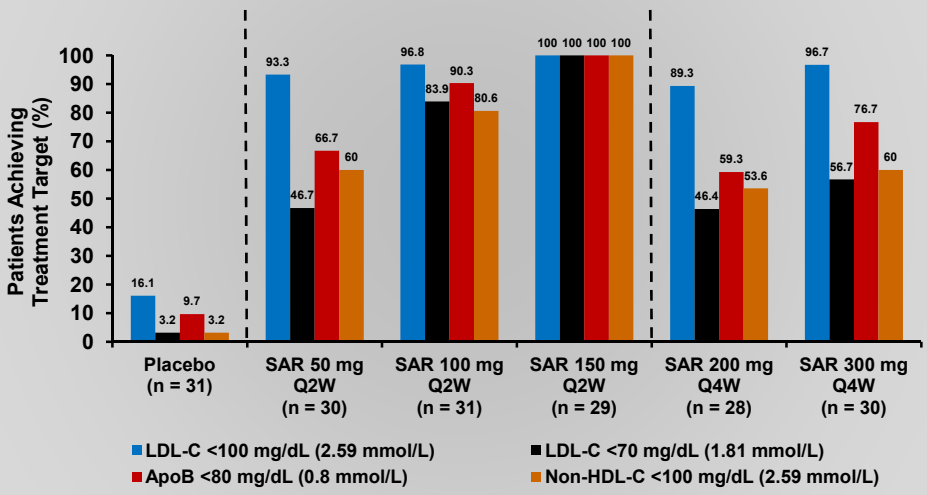
***National Cholesterol Education Program Adult Treatment Panel-III Therapeutic Lifestyle Changes or equivalent diet.**
McKenney JM, et al. *J Am Coll Cardiol.* 2012;59(25):2344-2353.

SAR236553 Phase 2: Change in LDL-C at 4-Week Dosing Intervals on Atorvastatin*



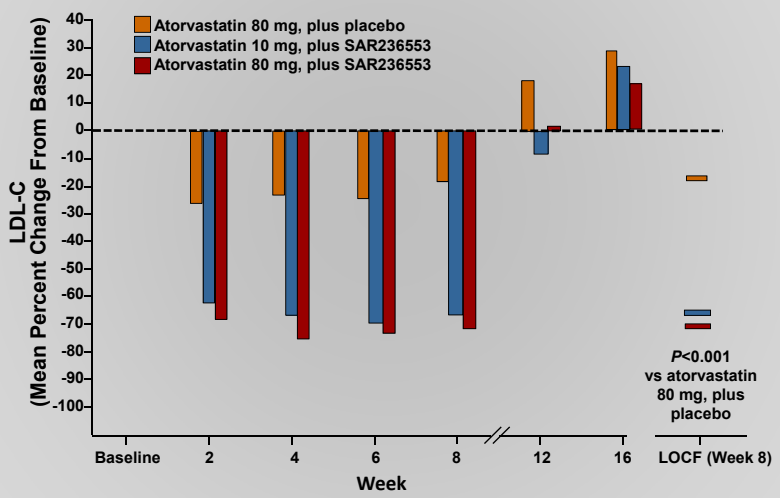
*On stable-dose atorvastatin 10 mg, 20 mg, or 40 mg; 80-mg dose not studied.
McKenney JM, et al. *J Am Coll Cardiol.* 2012;59(25):2344-2353.

Attainment of Treatment Targets for LDL-C, Non-HDL-C, and ApoB With SAR236553



McKenney JM, et al. *J Am Coll Cardiol.* 2012;59(25):2344-2353.

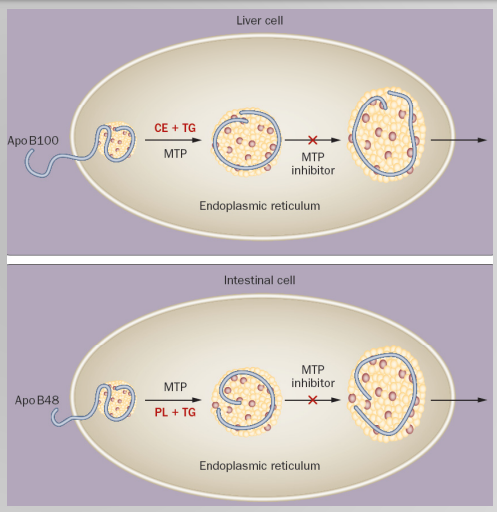
SAR236553 on Top of Atorvastatin in Primary Hypercholesterolemia: Phase 2



Roth EM, et al. *N Engl J Med*. 2012;367:1891-1900.

MTP Inhibition

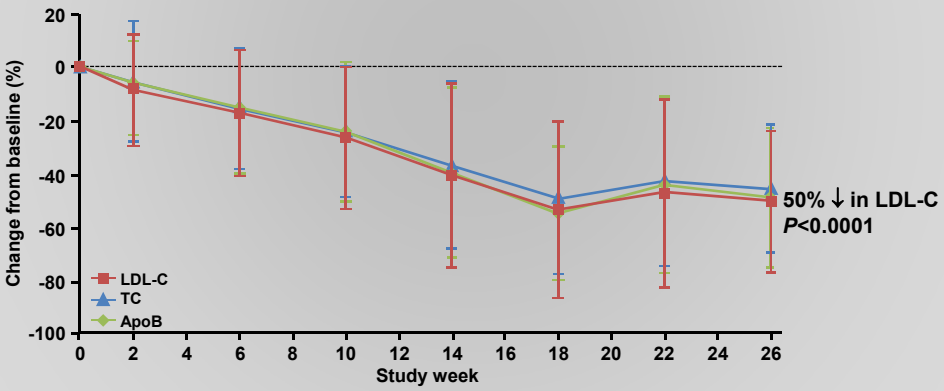
- MTP involved in assembly and secretion of apoB
- Inhibition ↓ production of apoB-containing lipoproteins
- Result is to ↓ LDL-C synthesis



MTP = microsomal triglyceride transfer protein; PL = phospholipids.
Brautbar A, et al. *Nat Rev Cardiol*. 2011;8(5):253-265.

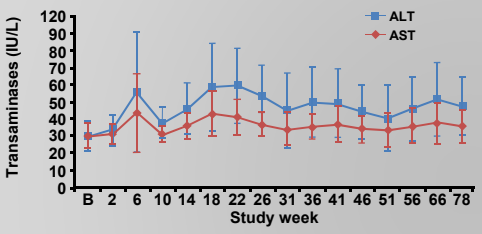
Lomitapide Efficacy Results

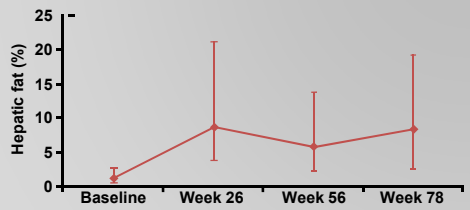
- Single-arm, open-label study
- 23 patients with HoFH
- Mean age 31 years; 93% on statin therapy; 62% had undergone apheresis
- LDL-C at enrollment 336±114 mg/dL
- Lomitapide escalated Q4W up to 60 mg or maximum tolerated dose (median 40 mg/day)



HoHF = homozygous familial hypercholesterolemia.
Cuchel M, et al. *Lancet.* 2013;381(9860):40-46.

Lomitapide Safety Results





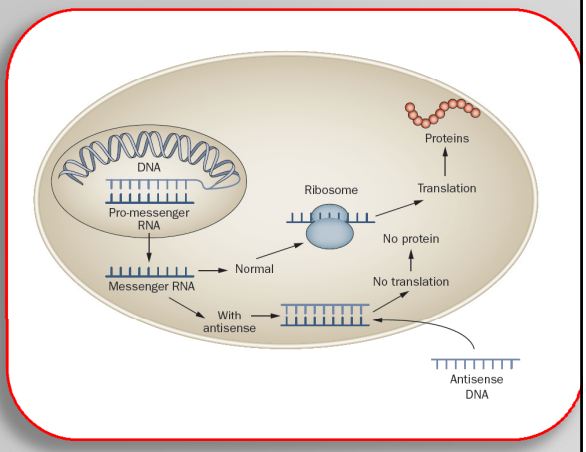
LFTs	n (%)
≥3 × ULN	10 (34)
≥5 × ULN	4 (14)

AE	n (%)
Any GI	27 (93)
Diarrhea	23 (79)
Nausea	19 (66)

LFT = liver function test; GI = gastrointestinal.
Cuchel M, et al. *Lancet.* 2013;381(9860):40-46.

ApoB Antisense Oligonucleotide

- Mipomersen is an antisense oligonucleotide that is complementary to coding region of mRNA for apo B-100
- Binding of mipomersen results in RNase H1-mediated degradation of mRNA leading to ↓ synthesis of apo B
- Apo B required for production of VLDL by the liver



mRNA = messenger riboneucleic acid; RNase = ribonuclease; DNA = deoxyribonucleic acid.
Brautbar A, et al. *Nat Rev Cardiol.* 2011;8(5):253-265. Genzyme Corporation. Mipomersen sodium NDA 203568. 2012. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM323931.pdf. Accessed May 22, 2013.

Mipomersen Efficacy Results

Mipomersen 200 mg SC QW

			Change from Baseline (%)			
Patient Population	**n**	**Baseline LDL-C**	**LDL-C**	**Lp(a)**	**TG**	**HDL-C**
HoFH	51	439	-25%	-32%	N/A	+15%
Severe HeFH	58	276	-36%	-39%	N/A	+6%
HeFH with CAD	124	153	-28%	-21%	-14%	+3%
HC, high CAD risk	157	123	-37%	-24%	-26%	+2%

All changes statistically significant

QW = every week; CAD = coronary artery disease; HC = hypercholesterolemia.
Crooke ST, et al. *Br J Clin Pharmacol.* 2012 [Epub ahead of print]. Genzyme Corporation. Mipomersen sodium NDA 203568. 2012. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM323931.pdf. Accessed May 22, 2013.

Mipomersen Safety Results

AE	Placebo (n = 129)	Mipomersen (n = 261)
GI disorder	28.7%	29.9%
Injection site pain	16.3%	56.3%
Injection site erythema	6.2%	58.6%
Injection site swelling	0%	17.6%
Influenza-like illness	3.1%	13.0%
ALT ≥2 x and 3 x ULN	4.7%	23.4%
ALT ≥3 x and <5 x ULN	0.8%	11.9%
ALT ≥5 x ULN	0%	2.3%
Hepatic steatosis	1.6%	7.3%

Genzyme Corporation. Mipomersen sodium NDA 203568. 2012. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM323931.pdf. Accessed May 22, 2013.

REMS Restrictions

- Lomitapide and mipomersen are restricted under REMS due to the risk of hepatoxicity
  - Available through a restricted program
  - Only certified healthcare providers and pharmacies may prescribe and distribute lomitapide

REMS = Risk Evaluation and Mitigation Strategies.

Juxtapid [package insert]. Cambridge, MA: Aegerion Pharmaceuticals; 2012. Kynamro [package insert]. Cambridge, MA: Genzyme Corporation; 2013.

Summary

- Statins remain the cornerstone of lipid-lowering therapy
- For high-risk patients, optional goal of <70 mg/dL and perhaps should target even lower
- Ezetimibe under study
- No clinical benefit to raising HDL with niacin or certain CETP inhibitors; other CETP inhibitors (that also lower LDL-C) under study
- PCSK9 inhibitors robustly lower LDL; outcomes trials underway
- New treatments for familial hypercholesterolemia: MTP inhibitors and antisense oligonucleotide

CVLN®

Moving Beyond Statins for the Management of Hypercholesterolemia:
Evaluating Novel Therapies that Target Lipoprotein Synthesis, Transport, and Regulation

Post-Activity Evaluation

NACCME would appreciate your feedback on the quality and impact of this activity.
Please answer the following questions, some of which are rated on a 5-point Likert scale
(1 = strongly disagree/poor; 5 = strongly agree/excellent).

1. Did this activity

Meet your educational needs?	□ Yes	□ No
Increase your knowledge?	□ Yes	□ No
Increase your competence?	□ Yes	□ No
Increase your confidence?	□ Yes	□ No

2. How much did you learn as a result of this CE program (1 = very little; 5 = great deal)?

1 2 3 4 5

3. To what extent were you able to achieve each of the following learning objectives?

Identify and overcome low-density-lipoprotein (LDL) treatment shortfalls of statin therapy

1 2 3 4 5

Outline the mechanisms-of-action of emerging hypercholesterolemia agents targeting lipoprotein synthesis, transport, and regulation

1 2 3 4 5

Summarize clinical trial data on the benefits and limitations of novel agents for hypercholesterolemia management

1 2 3 4 5

4. Please rate the faculty on the following:

SERGIO FAZIO, MD, PHD

Knowledge and Expertise

1 2 3 4 5

Teaching Ability

1 2 3 4 5

5. **Please rate the following components relating to this activity:**

Content

1 2 3 4 5

Relevance to your practice

1 2 3 4 5

Educational format

1 2 3 4 5

Audience-participation portions (eg, Q&A, pre/post-testing)

1 2 3 4 5

Handouts and/or other materials supporting the activity?

1 2 3 4 5

Overall

1 2 3 4 5

6. **The therapeutic recommendations presented in this activity did not encourage inappropriate or excessive use of products/devices.**

□ Agree □ Disagree

7. **The information presented in this activity did not serve to advance a proprietary interest of any commercial entity.**

□ Agree □ Disagree

8. **Of the patients you see on a weekly basis, how many will benefit from the information you learned today?**

□ 10 or fewer □ 20 □ 30 □ 40 □ 50 or more

9. **Naturally occurring mutations that lead to a loss of function of the PCSK9 gene are associated with:**
   a. An increase in LDL-C and coronary heart disease
   b. A decrease in LDL-C and coronary heart disease
   c. An increase in HDL-C and increase in coronary heart disease
   d. A decrease in HDL-C and increase in coronary heart disease

10. **How confident are you in your understanding of the LDL treatment shortfalls of statin therapy?**
    a. Very confident
    b. Confident
    c. Somewhat confident
    d. Not confident

11. **How would you rate your understanding of the mechanisms-of-action of emerging hypercholesterolemia agents designed to target lipoprotein synthesis, transport, and regulation?**
    a. Excellent
    b. Good
    c. Fair
    d. Poor

12. **How frequently do you intend to recommend alternate or add-on therapy in patients on statin therapy with an LDL > 100 mg/dL?**
    a. Always
    b. Often
    c. Rarely
    d. Never

13. **What factors do you intend to consider when developing treatment strategies for LDL management (select all that apply)?**
    a. Adherence
    b. Cost
    c. Efficacy
    d. Tolerance

14. **Do you intend to make any changes to your practice?**

    □ Yes, please specify: _____

    □ No

15. **What barriers outside of your control prevent you from changing your practice and/or optimizing patient outcomes (check all that apply)?**

    □ Lack of available guidelines for LDL-C management
    □ Formulary placement
    □ Affordability concerns on the part of the patient
    □ Patient adherence
    □ Lack of patient education regarding disease/treatment
    □ Adverse effects of LDL-lowering therapies
    □ Lack of influence over treatment selection
    □ Other: _____

16. **How might future activities help you address those barriers?**

    _____

    _____

    _____

17. **Would you be interested in additional educational activities within this therapeutic area?**

    □ Yes □ No

    If yes, what topics would you like to learn more about?_____

18. In which of the following other therapeutic or practice areas do you have educational needs?
(check all that apply)

- □ Acute Coronary Syndromes
- □ Alzheimer's Disease
- □ Anemia
- □ Anesthesia
- □ Bacterial Infections
- □ Breast Cancer
- □ Deep Vein Thrombosis
- □ Diabetes
- □ Fibromyalgia
- □ Fungal Infections
- □ Gastroenterology
- □ Glaucoma
- □ Hemostasis
- □ Hepatitis B or C
- □ HIV
- □ Hyperlipidemia
- □ Hypertension
- □ Hyponatremia
- □ Law
- □ Lung Cancer
- □ Lupus
- □ Medication Errors/Safety
- □ Multiple Myeloma
- □ Multiple Sclerosis
- □ Oncology Supportive Care
- □ Osteoporosis
- □ Overactive Bladder
- □ Pain
- □ Parkinson's Disease
- □ Prostate Cancer
- □ Psoriasis
- □ Psychiatry
- □ Pulmonary Medicine
- □ Rheumatoid Arthritis
- □ Sleep
- □ Stroke
- □ Transition of Care
- □ Transplant Medicine

Other_____

19. In which of the following formats do you prefer to receive education? (check all that apply)

- □ Live symposium
- □ Small-group meeting
- □ Phone teleconference
- □ Live web meeting
- □ On-demand web
- □ Handheld/mobile device
- □ Enduring print
- □ Other

20. How much time did you spend participating in this activity? _____

REQUEST FOR CREDIT
Please complete all sections to be eligible for credit and return to course registrar at the meeting site.

E-mail [REQUIRED] _____

Grand Rounds Location _____

Name _____ **Degree** _____

Title/Specialty _____ **Affiliation** _____

Address _____

City _____ **State** _____ **Zip** _____ **Phone**_____

REQUIRED FOR PHARMACISTS: Date of Birth (MM/DD) _____ **NABP ID** _____

NACCME: 300 Rike Drive, Suite A, Millstone Township, NJ 08535; Phone: 609-371-1137; Fax: 609-371-2733