12:30 – 1:45 pm

Dyslipidemia in Primary Care: New Guideline Recommendations and Treatment Options

SPEAKERS

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Presenter Disclosure Information

The following relationships exist related to this presentation:

- Carl E. Orringer, MD, FACC, FNLA: No financial relationships to disclose.
- James A. Underberg, MD, MS, FACPM, FACP, FASH, FNLA: Speakers Bureau for AstraZeneca, Merck & Co., Inc; Amgen, Inc.; Aegerion Pharmaceuticals Inc.; sanofi-aventis U.S.; Genzyme; and Alexion Pharmaceuticals, Inc. Research for Pfizer, Inc. and Aegerion Pharmaceuticals Inc. Consultant for Amgen, Inc. and Amarin Pharma Inc.

Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Objectives

- Outline the key differences between the 2013 AHA/ACC guideline recommendations and those from other hypercholesterolemia guidelines
- Implement optimal medical therapy for patients with hypercholesterolemia based on the latest guideline recommendations and clinical data
- Discuss the role of PCSK9 in LDL-C metabolism and its potential as a therapeutic target for the treatment of hypercholesterolemia
- Evaluate recent clinical trial data and the potential role of PCSK9 inhibitors in reducing cardiovascular risk among various patient groups with hypercholesterolemia

Hypercholesterolemia and Coronary Heart Disease

Hypercholesterolemia Is a Global Public Health Epidemic

In U.S.
Nearly 71 Million
adults have high
LDL cholesterol (LDL-C)

<50%
of people with dyslipidemia are receiving treatment

~2/3
of the people with high LDL-C on treatment are not able to control their cholesterol

Mozaffarian D, et al. *Circulation*. 2015;131(4):e29-322.

LDL Cholesterol

- Remains the cornerstone of the relationship between lipids and CHD and is now accepted as causative in the atherosclerotic pathway
- Epidemiological studies supported that the increase in LDL is associated with an increase in CHD
- 10 mg/dL increase in LDL-C results in 12% increase in CVD risk
- Studies showed that it is the most abundant & clearly evident atherogenic lipoprotein
- The ultimate proof in the LDL hypothesis is the compendium of evidence from both observational and clinical trials demonstrating its reduction resulted in CHD reduction

NCEP, Adult Treatment Panel III. JAMA. 2001;285:2486-2497. Wood D, et al. *Atherosclerosis*. 1998;140:199-270. Howard BV, et al. *Arterioscler Thromb Vasc Biol*. 2000;20:830-835.

Risk for Hard CVD Events for LDL-C at Various Intervals According to Global CVD Risk*

Risk of Non-Fatal Myocardial Infarction, CHD Death and Stroke (%) over ~5 Years Rx

LDL-C mg/dL	CVD + DM	CVD + MS/IFG	CVD w/o DM/MS	DM w/o CVD	No CVD No DM
190	62%	36%	27%	16%	9%
160	43%	27%	21%	12%	7%
130	30%	20%	16%	9%	5%
100	21%	15%	13%	7%	4%
70	14%	11%	10%	5%	3%
40	10%	8%	8%	4%	2%

CVD = cardiovascular disease; DM = diabetes mellitus; MS = metabolic syndrome; IFG = impaired fasting glucose.

*Adapted from Robinson JG, Stone NJ. *Am J Cardiol*. 2006;98:1405-1408.

Guideline Recommendations for the Treatment of Dyslipidemia

ATP III Updated Treatment Recommendations

Risk Category	LDL-C Goal (mg/dL)	Non-HDL Goal	Recommended Therapy
High risk: **CHD or CHD risk equivalents (10-year risk >20%)**	**<100 mg/dL (Optional: <70 mg/dL)**	**<130 mg/dL (Optional: <100 mg/dL)**	Statins Bile acid sequestrants Nicotinic acid Fibric acids
Moderately high risk: **≥2 risk factors (10-year risk 10%-20%)**	**<130 mg/dL (Optional: <100 mg/dL)**	**<160 mg/dL (Optional: <130 mg/dL)**	
Moderate risk: **≥2 risk factors (10-year risk <10%)**	**<130 mg/dL**	**<160 mg/dL**	
Lower risk: **0-1 risk factor**	**<160 mg/dL**	**<190 mg/dL**	

NCEP, Adult Treatment Panel III. *JAMA*. 2001;285:2486-2497. Grundy SM et al. *Circulation*. 2004;110:227-239.

2014 NLA Treatment Recommendations

Risk Category	LDL-C Goal (mg/dL)	Non-HDL Goal (mg/dL)	Recommended Therapy
Low Risk	<100	<130	**First line:** Moderate to high intensity statin
Moderate Risk	<100	<130	
High Risk	<100	<130	**Second line:** Bile acid sequestrants Cholesterol absorption inhibitors Nicotinic acid Fibric acids
Very High Risk	<70	<100	

Treatment recommendations in the Canadian and European guidelines are consistent with those of the 2014 NLA.

Jacobson TA, et al. *J Clin Lipidol*. 2014;8:473-488. European Association for Cardiovascular Prevention & Rehabilitation, et al. *Eur Heart J*. 2011;32(14):1769-818. Anderson TJ, et al. *Can J Cardiol*. 2013;29(2):151-67.

2013 ACC/AHA Guidelines

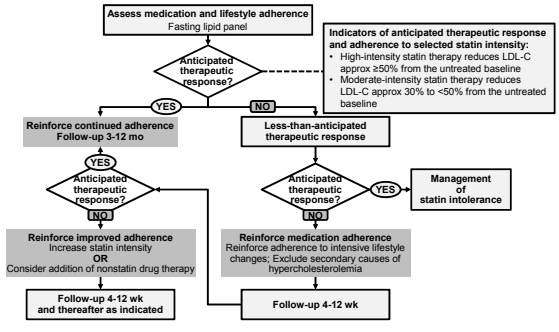
Treatment Recommendations

Statin Benefit Group	LDL-C Reduction	Recommended Therapy
Clinical atherosclerotic cardiovascular disease (ASCVD)	≥50% 30% to <50%	Age ≤75 y: High-intensity statin Age >75 y: Mod-intensity statin
LDL-C ≥190 mg/dL	≥50%	High-intensity statin
40-70 years of age with DM + LDL-C 70-189 mg/dL	30% to <50% or ≥50%	Mod-intensity statin ASCVD risk ≥7.5%: High-intensity statin
40-70 years of age with LDL-C 70-189 mg/dL + 10-year ASCVD risk ≥7.5%	30% to <50% or ≥50%	Moderate-to-high intensity statin

Non-statin therapy should only be considered in patients unable to tolerate less-than-recommended intensity of a statin, or who are completely statin intolerant.

Stone NJ, et al. *Circ* 2014;129(suppl 25):S1-45.

Monitoring Statin Adherence and Therapeutic Response



Stone NJ, et al. Circulation. 2014;129(25 Suppl 2):S1-45. Goff DC, et al. Circulation. 2014;129(25 Suppl 2):S49-73.

2013 ACC/AHA Guidelines

Individuals Not in a Statin Benefit Group

- For patients not in 1 of the 4 statin benefit groups, additional factors may inform treatment decision-making:
  - Family history of premature ASCVD
  - Elevated lifetime risk of ASCVD
  - LDL-C ≥160 mg/dL
  - hs-CRP ≥2.0 mg/L
  - Subclinical atherosclerosis: Coronary calcium score ≥300 or ankle brachial index <0.9
- Discussion of the benefit, risks, and patient preferences

Stone NJ, et al. *Ann Intern Med*. 2014;160(5):339-43.

2013 ACC/AHA Guidelines

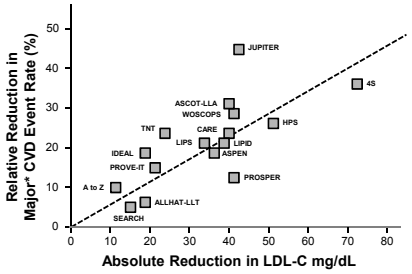
A New Perspective on LDL-C and/or Non-HDL-C Treatment Goals

- The Expert Panel was unable to find RCT evidence to support continued use of specific LDL-C and/or non-HDL-C treatment targets.
  - Statin therapy reduces ASCVD events across the spectrum of baseline LDL-C levels >70 mg/dL
  - Decreasing statin dose may be considered when LDL-C <40 mg/dL
- The appropriate intensity of statin therapy should be used to reduce CVD risk in those most likely to benefit.
- Nonstatin therapies do not provide acceptable CVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of CVD.

Stone NJ, et al. *Ann Intern Med*. 2014;160(5):339-43.

Is Lower LDL-C Better ?

CVD Event Reduction from Randomized Outcome Trials



***Defined as coronary death, confirmed nonfatal acute MI, or cardiac arrest with resuscitation or stroke. 1 mmol/L = ~40 mg/dL.**

Stein EA, Raal FJ. *Best Pract Res Clin Endocrinol Metab*. 2014;28(3):309-24.

IMPROVE-IT: Study Design

Patients stabilized post ACS ≤10 days:

LDL-C 50-125*mg/dL (or 50-100**mg/dL if prior lipid-lowering Rx)

N=18,144 — Standard Medical & Interventional Therapy

- **Simvastatin 40 mg**
- Uptitrated to Simva 80 mg if LDL-C >79 (adapted per FDA label 2011)
- **Ezetimibe / Simvastatin 10 / 40 mg**

Follow-up Visit Day 30, every 4 months

90% power to detect ~9% difference

Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

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

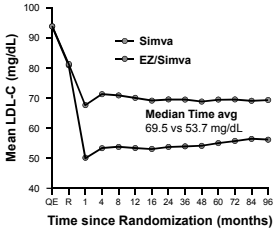
***3.2 mM; **2.6 mM.**

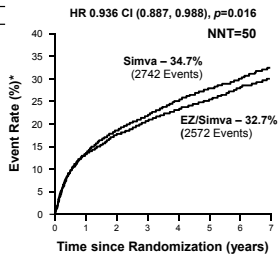
Cannon CP, et al. *Am Heart J*. 2008;156:826-32. Blazing MA, et al. *Am Heart J*. 2014;168:205-12.

IMPROVE-IT: Results

18,144 ACS patients randomized to simva alone or EZ/simva, mean follow-up 5.68 years

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5





***Primary end point (Cardiovascular death, MI, unstable angina, coronary revascularization, or stroke).**

Cannon CP, et al. *N Engl J Med*. 2015;372(25):2387-97.

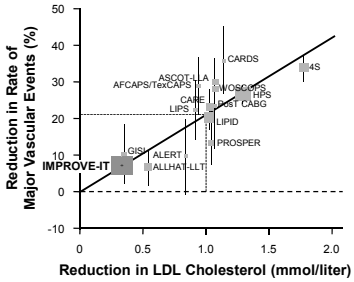
IMPROVE-IT: Safety

	Simva (n=9077)	EZ/ Simva (n=9067)	*p*
ALT and/or AST ≥3x ULN	2.3%	2.5%	0.43
Cholecystectomy	1.5%	1.5%	0.96
Gallbladder-related AEs	3.5%	3.1%	0.10
Rhabdomyolysis*	0.2%	0.1%	0.37
Myopathy*	0.1%	0.2%	0.32
Rhabdo, myopathy, myalgia with CK elevation*	0.6%	0.6%	0.64
Cancer* (7-yr KM %)	10.2%	10.2%	0.57

***Adjudicated by Clinical Events Committee.**

Cannon CP, et al. *N Engl J Med*. 2015;372(25):2387-97.

IMPROVE-IT vs CTT: Ezetimibe vs Statin Benefit



***Using CTT methods: LDL difference between groups using baseline LDL for Pts without blood samples. Endpoint of CV Death, MI, stroke or revasc >30days post Rand. Cox HR reported.**

Cannon CP, et al. *N Engl J Med*. 2015;372(25):2387-97. Baigent C, et al. *Lancet*. 2005;366(9493):1267-78. Baigent C, et al. *Lancet*. 2010;376(9753):1670-81.

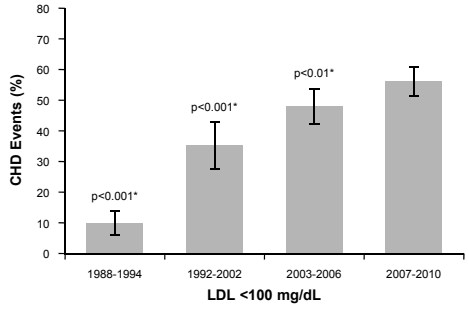
IMPROVE-IT: Conclusions

- First trial to show incremental CVD benefit when adding non-statin agent (ezetimibe) to statin therapy
- Reaffirms the LDL hypothesis
- Demonstrates even lower LDL-C is even better (achieved LDL-C 54 vs 70 mg/dL at year 1)
- Confirms ezetimibe safety profile
- Results further support LDL targets
- Results could be considered for future guidelines

Cannon CP, et al. *N Engl J Med*. 2015;372(25):2387-97.

Achieving LDL-C Goals Is a Challenge

Poor LDL-C Control in Diabetes Patients: NHANES 1988-2010

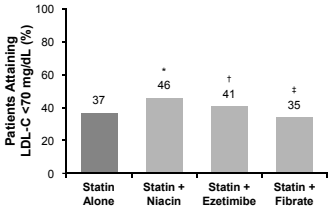


***Compared to 2007-2010.**

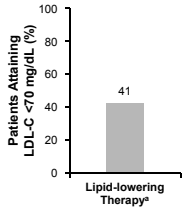
Casgrande SS, et al. *Diabetes Care*. 2013;36(8):2271-9.

Achieving LDL-C Goals Remains a Challenge

Real world retrospective analysis of 9,950 CAD patients from a large cardiology practice[1]



Real world retrospective analysis of 21,801 CHD patients from a VA Hospital Network[2]



More patients achieved an LDL-C <70 mg/dL with statin plus niacin (P*<0.001) and with statin plus ezetimibe (†*P*=0.01) as compared with statin alone. Statin plus fibrate did not improve LDL-cholesterol goal attainment as compared to statin alone (‡*P*=0.23); [a]80.4% of patients used statins.**

1. Karalis DG, et al. *Cholesterol*. 2012;2012:861924. 2. Virani SS, et al. *Am Heart J*. 2011;161:1140-6.

LDL-C <70 mg/dL Difficulty to Achieve Even with High-Dose Statin

But low event rates occur if you can

- Meta-analysis of 8 randomized statin trials with 38,153 patients
  - LDL-C <70 mg/dL: >40% on high-dose statin did not reach goal
- Major cardiovascular events based on achieved LDL-C
  - 75 to <100 mg/dL: HR 0.56 (95% CI, 0.46-0.67)
  - 50 to <75 mg/dL: HR 0.51 (95% CI, 0.42-0.62)
  - <50 mg/dL: HR 0.44 (95% CI. 0.35-0.55)

Boekholdt SM, et al. *J Am Coll Cardiol*. 2014;64(5):485-94.

FH: A Clinically Recognizable Genetic Disorder

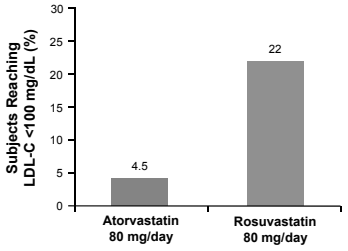
- The most common inheritable, autosomal dominant disorder associated with morbidity and mortality in man – present in 1 in 250 people[1,2]
- Usually due to mutations in LDL receptor gene[3-5] of which over 1600 have been described, and result in decreased clearance of LDL[1]
  - Other mutations include those in the ApoB and PCSK9 genes
- Results in severe hypercholesterolemia and lifelong accumulation of LDL in tissues and arteries
- Evidence of CVD early in life
  - MI at an average age of 42 years and coronary death at an average age of 45 years[6]
  - Carotid arterial wall atherosclerosis progression noted from age 12 onwards[7]

FH = familial hypercholesterolemia; CVD = cardiovascular disease.

1. Marais AD. *Clin Biochem Rev*. 2004;25:49-68. 2. Nordestgaard BG, et al. *Eur Heart J*. 2013;34:3478-90. 3. Mahley RW, et al. In: *Kronenberg: Williams Textbook of Endocrinology*. 2008. 4. Rader DJ, et al. *J Clin Invest*. 2003;111:1795-1803. 5. Hopkins PN, et al. *J Clin Lipidol*. 2011;5(3 Suppl):S9-175. 6. Williams RR, et al. *JAMA*. 1986;255(2):219-224. 7. Weigman A. *Lancet*. 2004;363(9406):369-70.

Patients with Familial Hypercholesterolemia (FH)

623 patients with heterozygous FH (HeFH) were randomized to either atorvastatin 80 mg/day or rosuvastatin with forced titration at 6-wk intervals to 80 mg/day



Stein EA, et al. *Am J Cardiol*. 2003;92(11):1287-93.

Novel Approaches to LDL-C Reduction

Hypercholesterolemia Associated with PCSK9 GOF Mutations

F216L mutation[1]

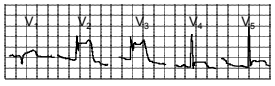
French proband died from MI
Age: 49 years

TC: 441 mg/dL
LDL-C: 356 mg/dL

R218S mutation[2]

French proband presented with tendinous xanthoma and arcus corneae
Age: 45 years

TC: 402 mg/dL
LDL-C: 293 mg/dL

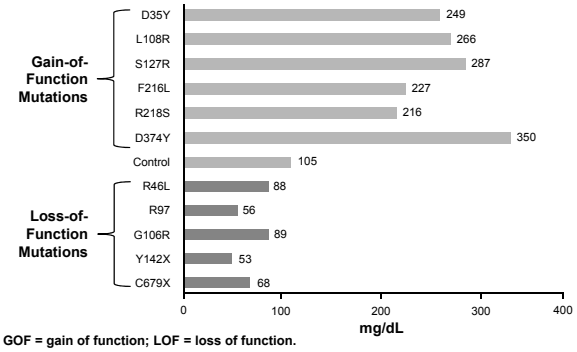


Acute Myocardial Infarction[4]

TC = total cholesterol; GOF = gain of function.

1. Abifadel M, et al. *Nat Genet*. 2003;34:154-156. 2. Abifadel M, et al. *Hum Mutat*. 2009;30:520-529. 3. Durrington P. *Lancet*. 2003;362:717-731. 4. Podrid PJ. UpToDate; March 1, 2012.
Reprinted from The Lancet, Vol. 362, Durrington P, Copyright 2003, with permission from Elsevier.

Mean LDL-C Levels in Patients with GOF and LOF PCSK9 Mutations



GOF = gain of function; LOF = loss of function.

Modified from Poirier S, Mayer G. *Drug Des Devel Ther*. 2013;7:1135-48.

PCSK9 Missense/LOF Variant R46L Associated with Lower Risk of Early-Onset MI

Site	Study	Patients	Controls	Frequency of Minor L Allele (%)		OR for Early-Onset MI (95% CI)*	*p*-value
				Patients	Controls		
Finland	FINRISK	209	210	1.3	4.1	0.30 (0.11-0.84)	0.02
Sweden	Malmö Diet and Cancer Study – cardiovascular cohort	150	149	0.7	2.0	0.32 (0.07-1.61)	0.17
Spain	Registre Gironi del Cor (REGICOR)	361	361	1.0	2.8	0.35 (0.15-0.82)	0.02
Seattle	Heart Attack Risk in Puget Sound	542	631	0.9	1.9	0.45 (0.21-0.98)	0.049
Boston	Massachusetts General Hospital Premature Coronary Artery Disease Study	192	266	1.4	2.3	0.59 (0.21-1.69)	0.46
Combined Analysis		1454	1617	0.99	2.4	0.40 (0.26-0.61)	0.00002

OR = odds ratio; CI = confidence interval.

Kathiresan S and the Myocardial Infarction Genetics Consortium. *N Engl J Med*. 2008;358:2299-2300.

Approaches to Reducing PCSK9 Interaction with LDL Receptor

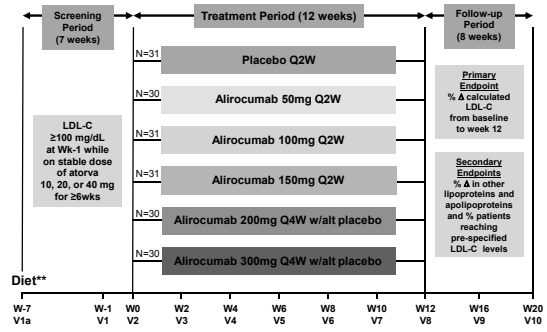
- Bind plasma PCSK9 with
  - Monoclonal antibodies
    - Alirocumab – Regeneron/Sanofi
    - Evolocumab – Amgen
    - Bococizumab* – Pfizer
    - LY3015014* – Eli Lilly
  - Small binding protein
    - BMS-962476 (Adnexis)* – Bristol-Myers Squibb
- Reduce PCSK9 synthesis
  - siRNA (Alnylam)*

***Not FDA approved.**

http://www.medscape.com/viewarticle/822814. Accessed Oct. 3, 2014. http://www.pharmatimes.com/article/13-09-02/Antibody_lipid_treatments_enter_final_furlong.aspx. Accessed Oct. 3, 2014. Mitchell T, et al. *J Pharmacol Exp Ther*. 2014;350(2):412-24. Tang Z, et al. *Int J Mol Med*. 2012;30(4):931-8.

Safety and Efficacy of PCSK9 Inhibitors

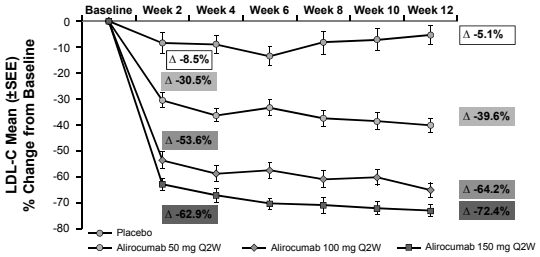
Phase II 12-Week RCT of Alirocumab



****NCEP ATP-III TLC or equivalent diet.**
Alirocumab = SAR236553/REGN727.

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

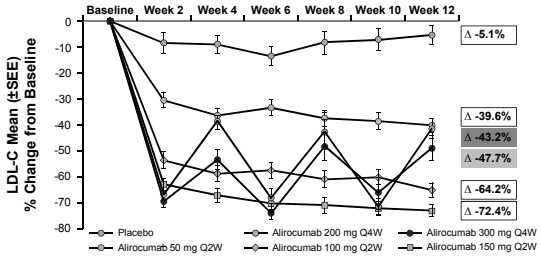
LDL-C Dose Response to Alirocumab Every 2 Weeks



Mean percentage change in calculated LDL-C from baseline in the modified intent-to-treat (mITT) population by treatment group.
Alirocumab = SAR236553/REGN727.

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

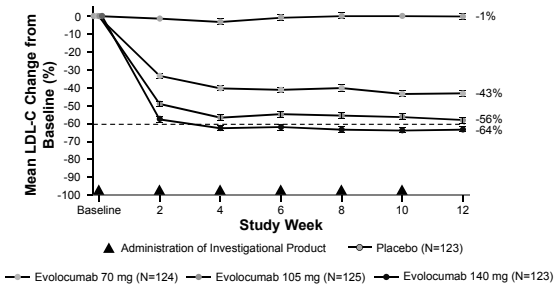
LDL-C Dose Response to Alirocumab Every 4 Weeks



Mean percentage change in calculated LDL-C from baseline in the modified intent-to-treat (mITT) population by treatment group.
Alirocumab = SAR236553/REGN727.

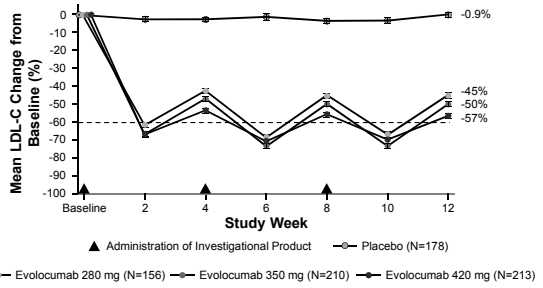
McKenney JM, et al. *J Am Coll Cardiol*. 2012;59:2344-2353.

LDL-C Dose Response to Evolocumab Every 2 Weeks



Stein EA, et al. *Euro Heart J*. 2014;35:2249-2259.

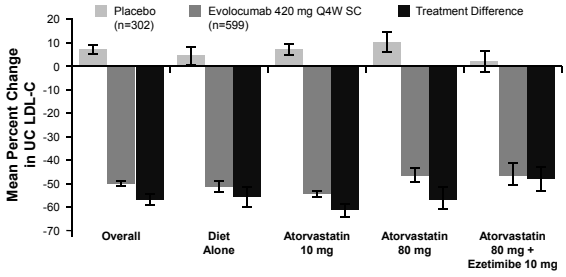
LDL-C Dose Response to Evolocumab Every 4 Weeks



Stein EA, et al. *Euro Heart J*. 2014;35:2249–2259.

DESCARTES: Change in LDL-C at Week 52 with Evolocumab

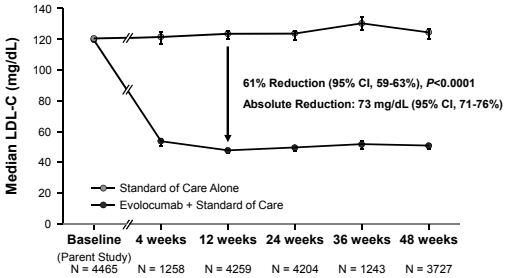
905 patients with LDL-C ≥75 mg/dL were randomized to the treatment below



Blom DJ, et al. *NEJM*. 2014:370:1809-19.

OSLER Program: LDL-C Reduction

OSLER 1 and 2 are open-label extension studies of phase 2 and 3 evolocumab trials



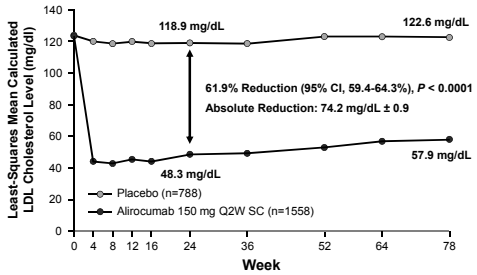
OSLER = Open-Label Study of Long-Term Evaluation Against LDL-C.

Sabatine MS, et al. N *Engl J Med*. 2015;372:1500-1509.

ODYSSEY LONG TERM: Alirocumab in High CV Risk Patients

Achieved LDL-C Over Time

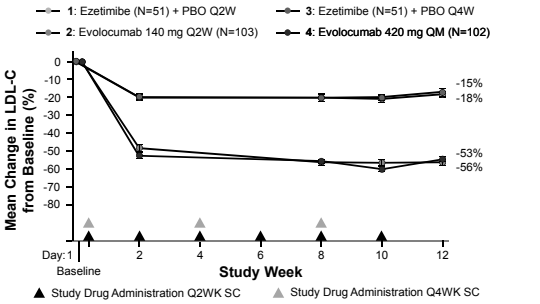
All patients on background of maximally-tolerated statin ± other lipid-lowering therapy



Intent-to-treat (ITT) analysis.

Robinson JG, et al. *N Engl J Med*. 2015;372:1489-99.

GAUSS-2 Study: Evolocumab in Statin Intolerant Patients



Stroes, et al. *J Am Coll Cardiol*. 2014;63(23):2541-2548.

GAUSS-2 Study: Skeletal Muscle Adverse Events

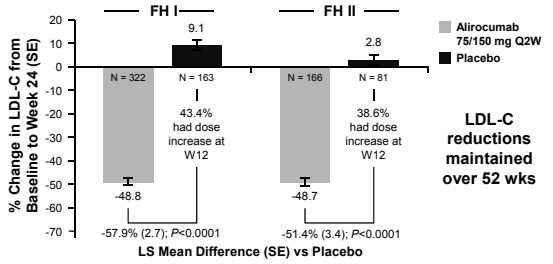
Adverse Event	Biweekly		Monthly	
	PBO Q2W + EZE QD (N=51)	Evolocumab 140 mg Q2W + PBO QD (N=103)	Placebo every month + EZE QD (N=51)	Evolocumab 420 mg every month + PBO QD (N=102)
CK > 5x ULN	6%	0%	0%	2%
Myalgia	14%	22%	7%	9%
Muscle-related SMQ*	16%	29%	13%	12%

***Includes myositis, myalgia, musculoskeletal pain, muscular weakness, increased plasma creatine, and blood CK increase.**
EZE = ezetimibe; CK = creatine kinase; ULN = upper limit of normal; SMQ = Standard MedDRA Queries.

Stroes, et al. *J Am Coll Cardiol*. 2014;63(23):2541-2548.

ODYSSEY FH I and FH II: Alirocumab in Patients with FH

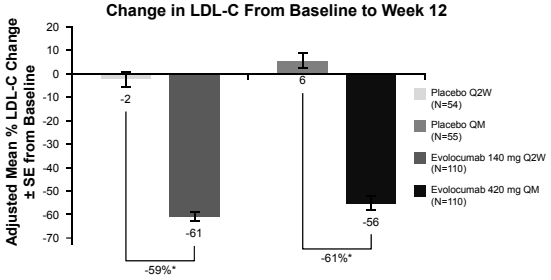
% Change from Baseline to Week 24 in LDL-C
All patients on background max-tolerated statin ± other lipid-lowering therapy



Kastelein JJ, et al. *Eur Heart J*. 2015 Sep 1. pii: ehv370. [Epub ahead of print]

RUTHERFORD-2: Evolocumab in Patients with FH

Change in LDL-C From Baseline to Week 12

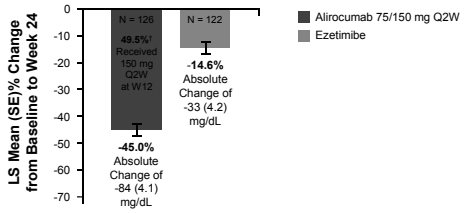


***P<0.001.**
SE = standard error.

Raal FJ, et al. *Lancet*. 2015;385(9965):331-40.

ODYSSEY ALTERNATIVE: Alirocumab in Statin Intolerant Patients

Percent Change from Baseline to Week 24 in LDL-C
(ITT, Primary Endpoint)



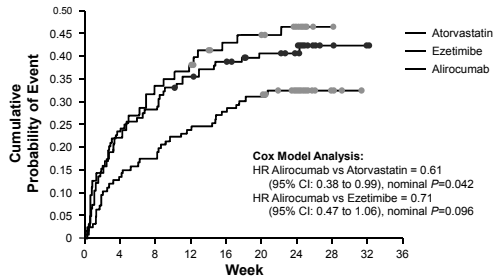
LS Mean Difference (SE) vs Ezetimibe: -30.4 (3.1); P<0.0001

†49.5% of 109 patients who received at least one injection after Week 12 had dose increase.

Moriarty PM, et al. ODYSSEY ALTERNATIVE. American Heart Association 2014 Scientific Sessions; November 17, 2014; Chicago, IL. Abstract.

ODYSSEY ALTERNATIVE: Skeletal Muscle Adverse Events

Kaplan-Meier Estimates for Time to First Skeletal Muscle Event†



†Pre-defined category including myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, muscle fatigue. HR = hazard ratio.

Moriarty PM, et al. ODYSSEY ALTERNATIVE. American Heart Association 2014 Scientific Sessions; November 17, 2014; Chicago, IL. Abstract.

Alirocumab: Significant LDL-C Reduction Across All Phase 3 Trials*

Study	Population	Duration (Weeks)	% LDL-C Reduction	
			Alirocumab	Comparator
MONO	Hypercholesterolemia and moderate ASCVD risk	24	47%	16% (ezetimibe)
FH I	HeFH	24	49%	9% (placebo)
FH II	HeFH	24	49%	3% (placebo)
HIGH FH	HeFH	24	46%	7% (placebo)
LONG TERM	High ASCVD risk/HeFH	78	52%	+4% increase (placebo)
ALTERNATIVE	High ASCVD risk and history of intolerance to at least two statins	24	45%	15% (ezetimibe)
OPTIONS I	High ASCVD risk	24	44-54%	21-23% (ezetimibe) 5% (double dose statin) 21% (statin switch)
OPTIONS II	High ASCVD risk	24	36-51%	11-14% (ezetimibe) 16% (double statin dose)
COMBO I	High ASCVD risk	24	48%	2% (placebo)
COMBO II	High ASCVD risk	24	51%	21% (ezetimibe)

***P value <0.0001 for all trials except OPTIONS I (p=0.01) and OPTIONS II (p=0.0125).**

Shapiro MD, et al. Shapiro et al. *Curr Atheroscler Rep*. 2015;17(4):499. Robinson JG, et al. *N Engl J Med*. 2015;372:1489-99.

Evolocumab: Significant LDL-C Reduction Across All Phase 3 Trials*

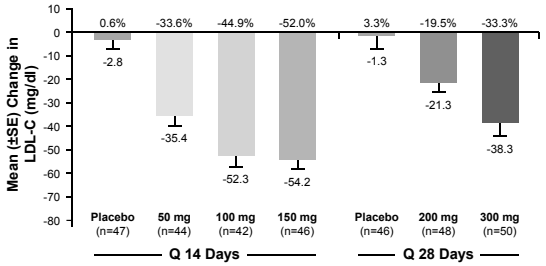
Study	Population	Duration (Weeks)	% LDL-C Reduction	
			Evolocumab	Comparator
MENDEL-2	Hypercholesterolemia and low ASCVD risk	12	56-57%	18-19% (ezetimibe) 0.1-1% (placebo)
DESCARTES	Hypercholesterolemia with varying levels of ASCVD risk	52	47-55%	2-10% (placebo)
LAPLACE-2	Hypercholesterolemia and mixed dyslipidemia	12 but mean of 10	63-75%	19-32% (ezetimibe)
GAUSS-2	Hypercholesterolemia and history of intolerance to at least two statins	12 but mean of 10	55-56%	37-39% (ezetimibe)
RUTHERFORD-2	HeFH	12	56-61%	1% reduction to +5% increase (ezetimibe)
TESLA Part B	HoFH	12	23%	+8% increase (placebo)

***P* value <0.001 for all trials except MENDEL-2 (*p*=0.01) and TESLA Part B (*p*=0.0001).**

Shapiro MD, et al. Shapiro et al. *Curr Atheroscler Rep*. 2015;17(4):499.

Bococizumab*: LCL-C Reduction at Week 12

Patients with LDL-C ≥80 mg/dL on stable statin were randomized to Q14 days SC placebo or bococizumab 50, 100, or 150 mg or Q28 days SC placebo or bococizumab 200 or 300 mg



***Not FDA approved.**

Ballantyne CM, et al. *Am J Cardiol*. 2015;115:1212-1221.

Alirocumab: Adverse Events in ODYSSEY LONG TERM

Event	Alirocumab (N=1550)	Placebo (N=788)	*P*-Value
Summary of adverse events – no. of patients (%)			
Any adverse event	1255 (81.0)	650 (82.5)	.40
Serious adverse event	290 (18.7)	154 (19.5)	.66
Adverse event leading to study-drug discontinuation	111 (7.2)	46 (5.8)	.26
Adverse event leading to death	8 (0.5)	10 (1.3)	.08
Cardiovascular adverse events of interest – no. of patients (%)			
Adjudicated major adverse cardiovascular events in post hoc analysis	27 (1.7)	**26** (3.3)	.02
Other adverse events of interest			
General allergic reaction – no. of patients (%)	156 (10.1)	75 (9.5)	.71
Local injection-site reaction – no. of patients (%)	91 (5.9)	33 (4.2)	.10
Myalgia – no. of patients (%)	84 (5.4)	23 (2.9)	.006
Neurologic event – no. of patients (%)	65 (4.2)	35 (4.4)	.83
Neurocognitive disorder – no. of patients (%)	18 (1.2)	4 (0.5)	.17
Laboratory values of interest – no. of patients (%)			
Alanine aminotransferase >3x ULN	28/1533 (1.8)	16/779 (2.1)	.75
Aspartate aminotransferase >3x ULN	22/1533 (1.4)	18/779 (2.3)	.13
Creatine kinase >3x ULN	56/1507 (3.7)	38/771 (4.9)	.18

Robinson JG, et al. *N Engl J Med*. 2015;372:1489-99.

Evolocumab: Adverse Events in OSLER Program

Variable	Evolocumab Group (N=2976) No. (%)	Standard Therapy Group (N=1489) No. (%)
Adverse events		
Any	**2060** (69.2)	**965** (64.8)
Serious	**222** (7.5)	**111** (7.5)
Leading to discontinuation of evolocumab	**71** (2.4)	NA
Muscle-related	**190** (6.4)	**90** (6.0)
Injection-site reaction	**129** (4.3)	NA
Neurocognitive event	**27** (0.9)	**4** (0.3)
Other		
Arthralgia	**137** (4.6)	**48** (3.2)
Headache	**106** (3.6)	**32** (2.1)
Limb pain	**99** (3.3)	**32** (2.1)
Fatigue	**83** (2.8)	**15** (1.0)
Laboratory results		
Alanine or aspartate aminotransferase >3 x ULN at any visit after baseline	**31** (1.0)	**18** (1.2)
Creatine kinase >5 x ULN at any visit after baseline	**17** (0.6)	**17** (1.1)

OSLER = Open-Label Study of Long-Term Evaluation Against LDL-C.

Sabatine MS, et al. *N Engl J Med*. 2015;372:1500-1509.

Bococizumab[a]: Adverse Events

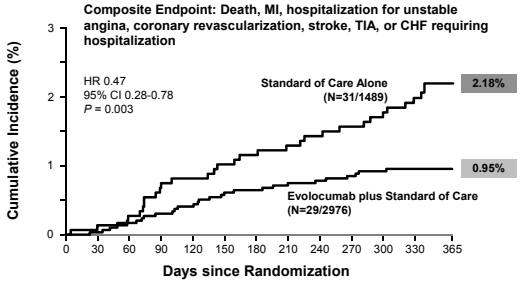
Variable	Placebo (n=49)	Bococizumab (mg) 50 (n=47)	100 (n=30)	150 (n=24)	Placebo (n=51)	Bococizumab (mg) 200 (n=16)	300 (n=13)
AEs	41 (84%)	36 (77%)	25 (83%)	20 (83%)	41 (80%)	15 (94%)	11 (85%)
Most frequent AEs (≥~10%)†							
Nasopharyngitis	6 (12%)	8 (17%)	4 (13%)	3 (13%)	7 (14%)	1 (6%)	3 (23%)
Upper respiratory tract infection	7 (14%)	4 (9%)	2 (7%)	3 (13%)	9 (18%)	0	1 (8%)
Diarrhea	4 (8%)	3 (6%)	2 (7%)	3 (13%)	2 (4%)	0	0
Injection site pain	4 (8%)	4 (9%)	41 (84%)	0	0	2 (4%)	0
Arthralgia	2 (4%)	0	3 (10%)	1 (4%)	3 (6%)	0	2 (15%)
Headache	2 (4%)	2 (4%)	0	1 (4%)	1 (2%)	3 (19%)	2 (15%)
Injection site reaction	1 (2%)	3 (6%)	0	4 (17%)	1 (2%)	0	2 (15%)
Creatine kinase (>2 x ULN)	15%*	0%*	10%	6%	12%*	14%*	6%
Alanine aminotransferase (>3 x ULN)	0%*	0%*	0%	0%	0%*	0%*	0%
Aspartate aminotransferase (>3 x ULN)	0%*	0%*	0%	0%	0%*	0%*	0%

†AEs among subjects without an LDL-C ≤25 mg/dL; *Data missing from 1 patient; [a]Not FDA approved.

Ballantyne CM, et al. *Am J Cardiol*. 2015;115:1212-1221.

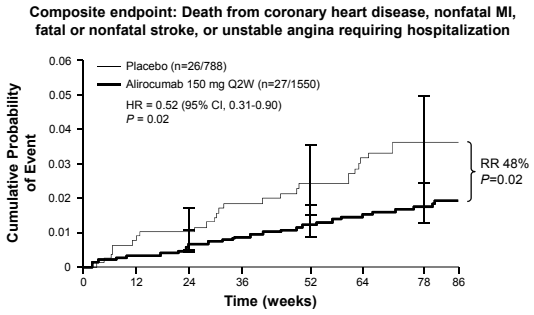
Do we have any data related to CVD events with PCSK9 inhibitors?

OSLER Program: Cardiovascular Outcomes with Evolocumab



Sabatine MS, et al. *N Engl J Med*. 2015;372:1500-1509.

ODDYSSY LONG TERM: Major Adverse Cardiovascular Events



Robinson JG, et al. *N Engl J Med*. 2015;372:1489-1499.

PCSK9 Inhibitor Cardiovascular Outcomes Trials

	Evolocumab (AMG 145)	Alirocumab (SAR236553 /REGN727)	Bococizumab* (RN 316)	
Sponsor	Amgen	Sanofi / Regeneron	Pfizer	
Trial	**FOURIER**	**ODYSSEY Outcomes**	**SPIRE I**	**SPIRE II**
Sample size	22,500	18,000	12,000	6,300
Patients	MI, stroke or PAD	4-52 wks post-ACS	High risk of CV event	
Statin	Atorva ≥20 mg or equiv	Evid-based med Rx	Lipid-lowering Rx	
LDL-C mg/dL(mmol/L)	≥70 (≥1.8)	≥70 (≥1.8)	70-99 (1.8-2.6)	≥100 (≥2.6)
PCSK9i Dosing	Q2W or Q4W	Q2W	Q2W	
Endpoint	1°: CV death, MI, stroke, revasc or hosp for UA, Key 2°: CV death, MI, or stroke	CHD death, MI, ischemic stroke, or hosp for UA	CV death, MI, stroke, or urgent revasc	
Completion	2/2018	12/2017	6/2018; 3/2018	

***Not FDA approved.**

www.clinicaltrials.gov.

PCSK9 Inhibitors – Where do they fit?

Currently Available PCSK9 Inhibitors

	Alirocumab	Evolocumab
FDA approval	July 2015	August 2015
Indication	Adjunct to diet and max tolerated statin for adults with HeFH, or clinical ASCVD, who require additional lowering of LDL-C	Adjunct to diet and max tolerated statin for adults with HeFH, or clinical ASCVD, who require additional lowering of LDL-C, HoFH pts on other LTT
Dosing	75 – 150 mg SC Q2W	140 mg SC Q2W or 420 mg SC monthly for HoFH
How supplied	Single-dose pre-filled pens and pre-filled glass syringes that deliver – 75 mg/mL or 150 mg/mL solution	Single-use pre-filled syringe or SureClick® autoinjector that deliver – 1mL of 140 mg/mL solution
Side effects	Nasopharyngitis, injection site reactions; hypersensitivity reactions	Nasopharyngitis, injection site reactions; hypersensitivity reactions

HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous FH. LLT = lipid lowering therapy.

Evolocumab - Repatha. *Drugs@FDA FDA Approved Drug Products*. August 2015. http://www.accessdata.fda.gov/
Alirocumab - Praluent. *Drugs@FDA FDA Approved Drug Products*. July 2015. http://www.accessdata.fda.gov/
Accessed September 8, 2015.

When to consider a PCSK9 inhibitor?

- FH patients not achieving LDL-C goal on max tolerated statins?
- Patients who are intolerant to statins needing additional LDL-C lowering?
- High CV risk patient not achieving LDL-C goal on max tolerated statin therapy?

Summary

- Increased LDL-C levels are associated with a linear increase in CVD risk and every 1 mmol/L (39mg/dL) reduction in LDL-C is associated with a significant 22% reduction in ischemic events
- Multiple guidelines are available on the treatment of dyslipidemia and differences exist regarding LDL-C goals and therapeutic options to use
- PCSK9 plays a significant role in the regulation and synthesis of cholesterol, and inhibition has been shown to be an effective approach to reducing LDL-C
- Emerging data with PCSK9 inhibitors show these agents to be well tolerated, safe within the duration of follow up, and highly efficacious in reducing LDL-C in FH patients and patients at high CV risk treated with statins ± other LLT; cardiovascular outcome trials are needed and ongoing

Case Study

Case Study

- A 53 year old male has been treated with primary PCI for a STEMI. He is discharged on the following meds:
  - Aspirin 81 mg daily
  - Ticagrelor 90 mg twice daily
  - Enalapril 20 mg daily
  - Metoprolol 150mg daily
  - Atorvastatin 80 mg daily
- When you see him at follow-up at one month, he is doing well. He is on a diet that is low in saturated fats. He is biking daily. He is tolerating all his medications and states he is adherent.
- His LDL cholesterol is 128 mg/dl.

Case Study Cont'd

- He is started on ezetimibe 10 mg daily.
- At 1 month check up his LDL cholesterol was at 95 mg/dL