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CLINICAL UPDATES IN **LDL-C MANAGEMENT**

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FACULTY

PETER P. Toth, MD, PhD, FAAFP, FNLA, FAHA

Director of Preventative Cardiology
CGH Medical Center
Sterling, Illinois
Professor of Clinical Family and Community Medicine
University of Illinois College of Medicine
Peoria, Illinois
Professor of Clinical Medicine
Michigan State University College of Osteopathic Medicine
East Lansing, Michigan
Adjunct Associate Professor Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland

PATRICK M. Moriarty, MD, FACC, FACP

Professor, Department of Internal Medicine
Director, Division of Clinical Pharmacology and Atherosclerosis/ Lipid Apheresis Center
University of Kansas Medical Center
Kansas City, Kansas

JAMES A. Underberg, MD, MS, FACPM, FACP, FNLA

VIRTUAL PROFESSOR

Lipidology & Cardiovascular Disease Prevention
Clinical Assistant Professor of Medicine
New York University School of Medicine
Director, Bellevue Hospital Lipid Clinic
Treasurer, National Lipid Association
New York, New York

LEARNING OBJECTIVES

- Discuss key processes in cholesterol homeostasis with an emphasis on clinically relevant relationships among atherosclerotic cardiovascular disease, low-density lipoprotein cholesterol levels, and new targets for lipid-lowering therapies
- Individualize treatment goals for patients with dyslipidemia to reflect the latest clinical practice guidelines
- Describe the mechanism of action and clinical profiles of new PCSK9 inhibitors for hypercholesterolemia, including patient populations that may benefit from these therapies
- Tailor multimodal lipid-lowering regimens based on current lipid profiles, cardiovascular risks, treatment responses, and patient preferences
- Communicate with patients to promote treatment adherence and encourage shared decision making during ongoing preventative care

FACULTY FINANCIAL DISCLOSURE STATEMENTS

The presenting faculty reported the following:

Peter P. Toth, MD, PhD, FAAFP, FNLA, FAHA, is a member of the Speakers Bureau for Amarin Corp., Amgen Inc., Kowa Pharmaceuticals America, Inc., Merck & Co., Inc., Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC. He is also a member of the Medical Advisory Board for Amarin Corp., Amgen Inc., AstraZeneca, Kowa Pharmaceuticals America, Inc., Merck & Co., Inc., Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC.

Patrick M. Moriarty, MD, FACC, FACP, is a member of the Speakers Bureau for Aegerion Pharmaceuticals, Inc., Alexion Pharmaceuticals, Inc., Amgen Inc., Genzyme Corporation, Kowa Pharmaceticals America, Inc., Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC. He is also a member of the Medical Advisory Board for Aegerion Pharmaceuticals, Inc., Esperion Therapeutics, Inc., and Ionis Pharmaceuticals, Inc. He has recieved funds from Amgen Inc., Genzyme Corporation, Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC. He has participated in Contracted Research for Amgen Inc., Catabasis Pharmaceuticals, Inc., Genzyme Corporation, Ionis Pharmecuticals, Inc., Kaneka Corporation, Novartis Pharmaceuticals Corporation, Pfizer Inc., Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC. He has Ownership Interest in Eliaz Therapeutics, Inc.

James A. Underberg, MD, MS, FACPM, FACP, FNLA, is a member of the Speakers Bureau for Alexion Pharmaceuticals, Inc., Amgen Inc., Genzyme Corporation, Merck & Co., Inc., New Haven Pharmaceuticals, Inc., Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC. He is also a member of the Medical Advisory Board for Akcea Therapeutics, Alexion Pharmaceuticals, Inc., Amgen Inc., Invitae Corporation, Merck & Co., Inc., New Haven Pharmaceuticals, Inc., Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC. He has participated in Contracted Research for Aegerion Pharmaceuticals, Inc. and Pfizer Inc.

EDUCATION PARTNER FINANCIAL DISCLOSURE STATEMENTS

The content collaborators at Integritas Communications have reported the following:

Jim Kappler, PhD, has nothing to disclose.

Rose O'Connor, PhD, has nothing to disclose.

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www.**ExchangeCME**.com/**Lipids2016**

Drug List

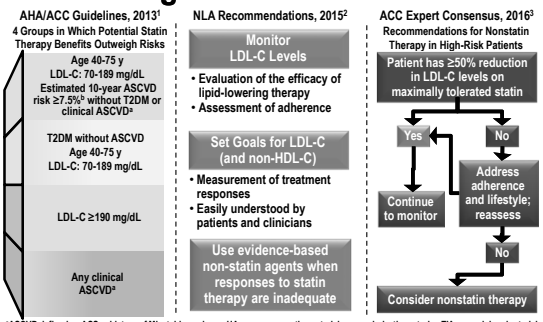
1.	Alirocumab	1.	Praluent
2.	Amiodarone	2.	Cordarone, Pacerone, Cordarone IV, Nexterone
3.	Atenolol	3.	Tenormin
4.	Atorvastatin	4.	Lipitor
5.	Bococizumab	5.	Investigational agent
6.	Colestipol	6.	Colestid
7.	Colesevelam	7.	Welchol
8.	Cholestyramine	8.	Prevalite, Questran
9.	Cyclosporine	9.	Neoral, Restasis, Sandimmune, Gengraf
10.	Evolocumab	10.	Repatha
11.	Ezetimibe	11.	Zetia
12.	Fenofibric acid	12.	Trilipix, Tricor, Lipofen, Triglide, Fenoglide, etc
13.	Fluvastatin	13.	Lescol, Lescol, XL
14.	Gemfibrozil	14.	Lopid, Jezil, Gen-Fibro
15.	Lisinopril	15.	Prinivil and Zestril
16.	Lomitapide	16.	Juxtapid
17.	Lovastatin	17.	Altoprev, Mevacor
18.	Mipomersen	18.	Kynamro
19.	Niacin	19.	NIASPAN, Niacor
20.	Pitavastatin	20.	Livalo
21.	Pravastatin	21.	Pravachol
22.	Rosuvastatin	22.	Crestor
23.	Simvastatin	23.	Zocor

Scientific Insights Into LDL-C, PCSK9, and CV Risks

- High circulating LDL-C levels are associated with increased risk for ASCVD[1,2]
- Statin drugs interfere with cholesterol production, lowering serum LDL-C levels and reducing the rate of CV events[3-5]
- Many patients do not tolerate or adhere to statin therapy[6]
- A new class of therapeutic antibodies, the PCSK9 inhibitors, can markedly reduce plasma LDL-C levels[7-9]
  - Alirocumab and evolocumab interfere with PCSK9 binding to LDL receptors
    - This increases recycling of the receptors back to the cell surface to clear circulating LDL[7-9]

1. Stamler J, et al. *JAMA*. 1986; 256(20):2823-2838; 2. Anderson KM, et al. *JAMA*. 1987;257(16):2176-2180;
3. Jacobson TA, et al. *J Clin Lipidol*. 2015;9(2):129-169. 4. Gill S, et al. *Cell Metab*. 2011;13(3):260-273;
5. Minhas R. *Br J Cardiol*. 2004;11(6); 6. Cohen JD, et al. *J Clin Lipidol*. 2012;6(3):208-215;
7. Duff CJ, et al. *Biochem J*. 2009;419(3):577-584; 8. Ni YG, et al. *J Biol Chem*. 2010;285(17):12882-12891;
9. Poirier S, Mayer G. *Drug Des Devel Ther*. 2013;7:1135-1148.

Translating Guidelines Into Practice



[a]ASCVD defined as ACS, a history of MI, stable angina or UA, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin; [b]From Pooled Cohort Equations.
ACC, American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; MI, myocardial infarction; NLA, National Lipid Association; TIA, transient ischemic attack; T2DM, type 2 diabetes mellitus; UA, unstable angina.

1. Stone NJ, et al. *Circulation*. 2014;129(25 suppl 2):S1-S45; 2. Jacobson TA, et al. *J Clin Lipidol*. 2015;9(2):129-169;
3. Lloyd-Jones DM, et al. *J Am Coll Cardiol*. 2016 Mar 28. [Epub ahead of print].

NLA Recommendations

Treatment Goals Stratified by Risk Assessment

Risk Category	Criteria	Treatment Goal Non-HDL-C, mg/dL LDL-C, mg/dL	Consider Drug Therapy Non-HDL-C, mg/dL LDL-C, mg/dL
Low	• 0-1 major ASCVD risk factors • Consider other risks, if known	<130 <100	≥190 ≥160
Moderate	• 2 major ASCVD risk factors • Consider quantitative risk scoring • Consider other risk indicators	<130 <100	≥160 ≥130
High	• ≥3 major ASCVD risk factors • Diabetes mellitus (type 1 or 2)[a] – 0-1 other major ASCVD risk factors – No evidence of end-organ damage • CKD stage 3B or 4[b] • LDL-C ≥190 mg/dL[c] • Risk score reaches high threshold[d]	<130 <100	≥130 ≥100
Very high	• ASCVD • Diabetes mellitus (type 1 or 2) – ≥2 other major ASCVD risk factors OR – Evidence of end-organ damage[e]	<100 <70	≥100 ≥70

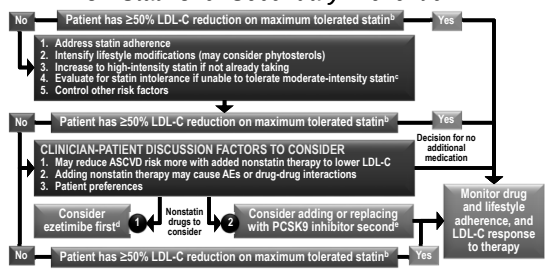
For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate or high-intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.

[a]Consider non-HDL-C goal of <100 mg/dL (LDL-C <70 mg/dL) for diabetes + 1 major ASCVD risk; [b]Calculators may underestimate risk in CKD Stage 3B or 4; [c]Consider severe phenotype (eg, FH); [d]High-risk: ≥10% with Adult Treatment Panel III Framingham Risk Score for hard CHD, ≥15% with 2013 Pooled Cohort Equations for hard ASCVD, or ≥45% with Framingham long-term CVD risk calculation; [e]Increased ACR, CKD, or retinopathy.
ACR, albumin-to-creatinine ratio; CHD, coronary heart disease; CKD, chronic kidney disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol.

Jacobson TA, et al. *J Clin Lipidol*. 2015;9(2):129-169.

Patients With Clinical ASCVD With Comorbidities[a]

On Statins for Secondary Prevention



[a]Comorbidities: T2DM, acute ASCVD event (within 3 months), ASCVD event on statin therapy, baseline LDL-C ≥190 mg/dL, poorly controlled major ASCVD risk factors, elevated lipoprotein(a), and CKD; [b]Consider if LDL-C <70 mg/dL or non-HDL-C <100 mg/dL in patients with diabetes; [c]Consider specialist referral if statin intolerant; [d]Consider bile acid sequestrant if ezetimibe-intolerant and triglycerides <300 mg/dL; [e]Consider only if on maximally tolerated statin. and ezetimibe or bile acid sequestrant with persistent <50% LDL-C reduction or LDL-C ≥70 mg/dL.
AE, adverse event.

Lloyd-Jones DM, et al. *J Am Coll Cardiol*. 2016 Mar 28. [Epub ahead of print].

Statin Therapy Reduces LDL-C Levels by 30% to ≥50% Depending on Treatment Intensity

Intensity of Therapy	High Intensity	Moderate Intensity	Low Intensity
Average Reduction in LDL-C With Daily Dose	≥50%	30% to <50%	<30%
Examples	• Atorvastatin 40-80 mg • Rosuvastatin 20-40 mg	• Atorvastatin 10-20 mg • Fluvastatin 40 mg twice daily • Fluvastatin XL 80 mg • Lovastatin 40 mg • Pitavastatin 2-4 mg • Pravastatin 40-80 mg • Rosuvastatin 5-10 mg • Simvastatin 20-40 mg	• Fluvastatin 20-40 mg • Lovastatin 20 mg • Pitavastatin 1 mg • Pravastatin 10-20 mg • Simvastatin 10 mg

Stone NJ, et al. *Circulation*. 2014;129(25 suppl 2):S1-S45; Lloyd-Jones DM, et al. *J Am Coll Cardiol*. 2016 Mar 28. [Epub ahead of print]. .

Patient Populations Who May Benefit From Further Reductions in LDL-C Despite Statin Therapy

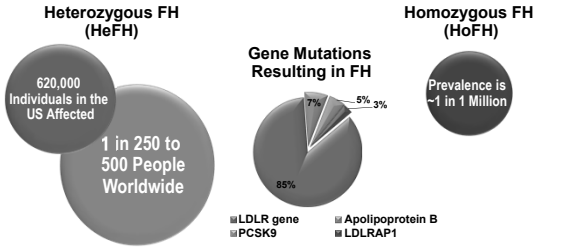
Patients with a diagnosis of familial hypercholesterolemia

Patients who are intolerant to statin therapy

Patients with suboptimal LDL-C levels and at high risk for ASCVD

Stone NJ, et al. *Circulation*. 2014;129(25 suppl 2):S1-S45.

Familial Hypercholesterolemia
High Risk for Premature CVD



99% of all cases of FH are undiagnosed in most countries.

Sjouke B, et al. *Eur Heart J*. 2015;36(6):560; Nordestgaard BG, et al. *Eur Heart J*. 2013;34(45):3478-3490; Goldstein JL, et al. in: Eds Scriver CR, Sly WS, Childs B, et al. *The Metabolic and Molecular Bases of Inherited Disease*, 8th ed. New York: McGraw-Hill Professional; 2000: 2863–22913; Goldstein JL, et al. *J Clin Invest*. 1973;52(7):1544-1568.

Familial Hypercholesterolemia
Clues to a Diagnosis

- Very elevated levels of LDL-C
  - LDL-C ≥190 mg/dL in adults aged ≥20 years
  - LDL-C ≥160 mg/dL in children aged <20 years
- Physical characteristics
  - Tendon xanthomas at any age (most common in Achilles tendon and finger extensor tendons but can also occur in patellar and triceps tendons)
  - Arcus corneae in patients <45 years of age
  - Tuberous xanthomas or xanthelasma in patients <20 years of age
- Family history of premature CHD

Cascade screening is recommended after an established FH index case is identified.

Goldberg AC, et al. *J Clin Lipidol*. 2011;5(suppl 3):S1-S8; Robinson JG. *J Manage Care Pharm*. 2013;19(2):139-149.

Familial Hypercholesterolemia
Goals of Therapy

- **Initial goal**
  - **50% reduction** in LDL-C from baseline
- **Optimal Goals**

Criteria	LDL-C
NO ASCVD or major CV risk factors	<100 mg/dL
ANY ASCVD or major CV risk factors	<70 mg/dL

Gidding SS, et al. *Circulation*. 2015;132(22):2167-2192.

Statin-Related Adverse Events Can Be Challenging

- In a large internet study of >10,000 current and former statin users[1]
  - **62%** of former users cited **side effects** as primary reason for discontinuation
    - **60%** of former and **25%** of current statin users reported **muscle-related** side effects
    - **One third** of those who stopped their statin due to muscle side effects did **not** inform their doctor
- Statin rechallenge can help confirm whether muscle symptoms are statin-associated[2]

Myalgia	Myositis
Muscle ache, weakness, cramps, stiffness	Muscle ache, weakness, cramps, stiffness
No elevation in CK levels	Elevated CK levels

CK, creatine kinase.
1. Cohen JD, et al. *J Clin Lipidol*. 2012;6(3):208-215; 2. Rosenson RS, et al. *J Clin Lipidol*. 2014;8(suppl 3):S58-S71.

Factors Increasing the Risk of Statin Intolerance

- History of:
  - Muscle symptoms with other lipid-lowering therapies
  - Unexplained muscle symptoms
  - Unexplained creatine kinase elevation
- Family history of muscle symptoms with other lipid-lowering therapies
- Strenuous exercise
- Hypothyroidism
- Statin dose
- Female sex
- Advanced age
- Low body mass index
- Alcohol abuse
- Vitamin D deficiency
- Drug interactions
  - Gemfibrozil
  - Macrolides
  - Azole antifungals
  - Verapamil
  - Amiodarone
  - Protease inhibitors
  - Cyclosporine

Stulc T, et al. *Curr Atheroscler Rep*. 2015;17(12):69.

Managing Statin Intolerance

- LDL-C lowering with statins remains the primary lipid target for most patients to reduce CHD risk
- Options for the patient with myalgia and normal CK
  - Trial of discontinuation for a few weeks and rechallenge
  - Try a lower dose
  - Try a different statin (perhaps with different metabolism or hydrophilicity)
  - Trial of alternate day or weekly dosing (off-label)
  - Check and correct hypothyroidism
  - Check and/or supplement vitamin D
  - Trial of Coenzyme Q10 (free ubiquinone)?
  - Consider nonstatin medication (either as monotherapy or combination therapy)

Rosenson RS, et al. *J Clin Lipidol*. 2014;8(suppl 3):S58-S71.

Suboptimal LDL-C Levels in High-Risk Patients Despite Statin Therapy

Patient Cohorts on Statin Therapy	Patients Achieving LDL-C <100 mg/dL, %	Patients Achieving LDL-C <70 mg/dL, %
Overall (N=4,154)	65.1%	18.7%
History of CHD	67.7%	19.9%
History of stroke/AAA but not CHD	63.5%	18.2%
Diabetes without history of CHD or stroke/AAA	62.7%	18.2%
FRS >20% without history of CHD, stroke/AAA, or diabetes	48.6%	5.6%

N=11,611 US patients in the REGARDS study cross-sectional analysis were ≥45 y of age with a history of CHD or risk equivalents.
AAA, abdominal aortic aneurysm; FRS, 10-year Framingham CHD risk score.
Gamboa CM, et al. *Am J Med Sci*. 2014;348(2):108-114.

Unmet Needs in Patients on Statin Therapy

- Despite well-documented efficacy of statins, many patients are still at risk for:[1,2]
  - Insufficient response to therapy
  - Statin intolerance
  - Poor treatment adherence
- Subgroups of patients have not been well studied[1]
  - Older patients
  - Patients <40 years with low estimated 10-yr ASCVD risk, but high lifetime ASCVD risk
  - Patients with comorbid conditions

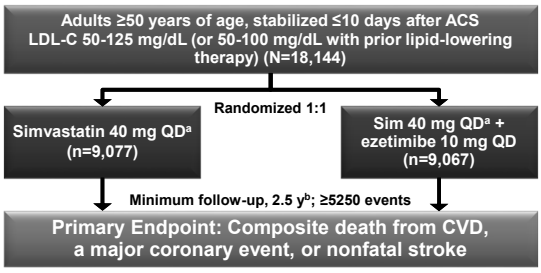
1. Stone NJ, et al. *Circulation*. 2014;129(25 suppl 2):S1-S45; 2. Cohen JD, et al. *J Clin Lipidol*. 2012;6(3):208-215.

Nonstatin Agents With Efficacy in Reducing LDL-C Levels

Drug Class	Examples of Agents
Bile acid sequestrants	Colestipol Colesevelam Cholestyramine
Cholesterol absorption inhibitors	Ezetimibe
Microsomal triglyceride transfer protein inhibitor	Lomitapide[a]
Nicotinic acid	Niacin[b]
Oligonucleotide inhibitor of apo B-100 synthesis	Mipomersen[a]
PCSK9 inhibitors	Alirocumab Evolocumab

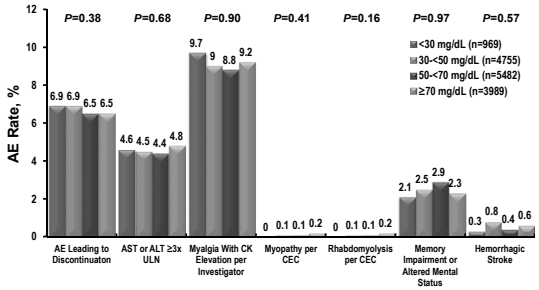
[a]FDA-approved as an adjunct to lipid-lowering treatments and diet for people with HoFH; [b]In April 2016, the FDA withdrew approval of niacin extended-release tablets in combination with statins due to lack of evidence that coadministration further reduced CV risk. https://www.federalregister.gov/articles/2016/04/18/2016-08887/abbvie-inc-et-al-withdrawal-of-approval-of-indications-related-to-the-coadministration-with-statins Accessed May 20, 2016.

IMPROVE-IT Trial
Study Design



IMPROVE-IT, IMproved Reduction of Outcomes Vytorin Efficacy International Trial.
[a]Dose increased to simvastatin 80 mg QD if LDL-C >79 mg/dL on 2 consecutive follow-up visits, until FDA guidance issued in June 2011 limited new prescriptions of simvastatin 80 mg; [b]Median follow-up, 6 y.
Sim, simvastatin; QD, once daily.
Cannon CP, et al. *N Engl J Med*. 2015;372(25):2387-2397.

IMPROVE-IT
Safety of Very Low LDL-C Levels



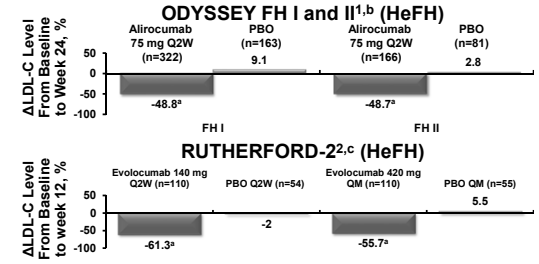
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CEC, clinical events committees.
Giugliano RP, et al. Poster presented at *European Society of Cardiology*. August 29-September 2, 2015; London, UK. Abstract 68.

Novel Therapy
PCSK9 Inhibitors

	Alirocumab[1]	Evolocumab[2]
FDA-Approved Indication	In people who require additional LDL-C lowering, adjunct to diet and maximally tolerated statin therapy for the treatment of adults with • HeFH • Clinical ASCVD	In people who require additional LDL-C lowering, adjunct to diet and • Maximally tolerated statin in adults with HeFH or clinical ASCVD • Other LDL-C lowering therapies in patients with HoFH
Approved Dosing	75 mg SQ Q2W; dose can be increased to 150 mg SQ Q2W if response is inadequate	• Clinical ASCVD or HeFH, 140 mg SQ Q2W or 420 mg SQ QM • HoFH, 420 mg QM
Clinical Topics	• LDL-C levels should be measured 4-8 weeks after initiating or titrating therapy • Current trials assessing effects on CV morbidity and mortality	• Current trials assessing effects on CV morbidity and mortality

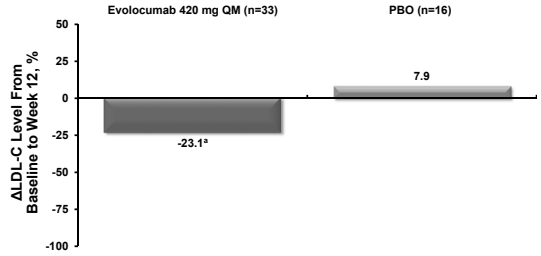
Q2W, every 2 weeks; QM, every month; SQ, subcutaneously.
1. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125559Orig1s000lbledt.pdf. Accessed May 31, 2016;
2. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125522s000lbl.pdf. Accessed May 31, 2016.

PCSK9 Inhibitors in Heterozygous Familial Hypercholesterolemia



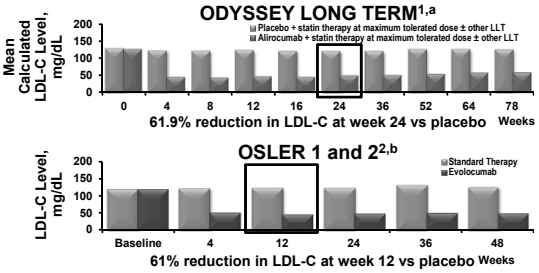
[a]P<0.0001 vs PBO; [b]Patients with HeFH (diagnosed clinically or with genetic testing) who had an LDL-C level ≥100 mg/dL or an LDL-C level ≥70 mg/dL and a history of CVD despite high-dose statin therapy (alirocumab dose increased to 150 mg Q2W at week 12 if LDL-C level at week 8 was ≥70 mg/dL). [c]Patients 18-80 y of age with HeFH diagnosed clinically and on a stable statin dose.
PBO, placebo.
1. Kastelein JJP, et al. *Euro Heart J*. 2015;36(43):2996-3003; 2. Raal FJ, et al. *Lancet*. 2015;385(9965):331-340.

PCSK9 Inhibitors in Homozygous Familial Hypercholesterolemia



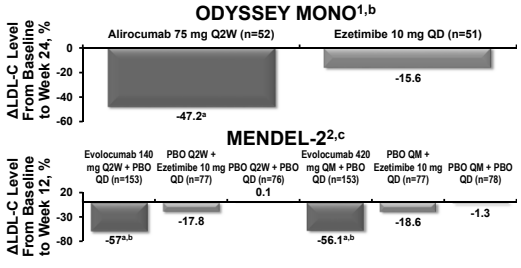
[a]P<0.0001 vs PBO; [b]Patients ≥12 y of age with HoFH (diagnosed clinically or with genetic testing) and an LDL-C level ≥130 mg/dL after at least 4 weeks of a stable, low-fat diet and baseline lipid-lowering therapies.
Raal FJ, et al. *Lancet*. 2015;385(9965):341-350.

PCSK9 Inhibitors in Patients With Suboptimal LDL-C Levels Despite Maximally Tolerated Statin Therapy



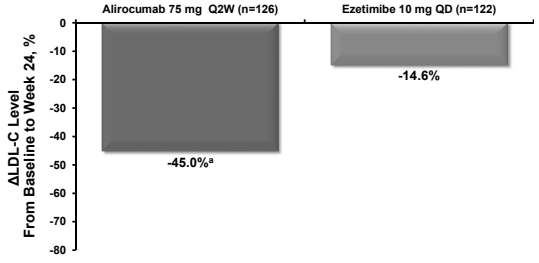
[a]Adults ≥18 y of age with HeFH, CHD, or CHD risk equivalent and LDL-C ≥70 mg/dL; [b]Study participants were eligible if they completed 1 of 12 phase 2 or 3 clinical trials with evolocumab.
LLT, lipid-lowering therapy.
1. Robinson JG, et al. *N Engl J Med*. 2015;372(16):1489-1499; 2. Sabatine MS, et al. *N Engl J Med*. 2015;372(16):1500-1509.

PCSK9 Inhibitors vs Ezetimibe as Monotherapy



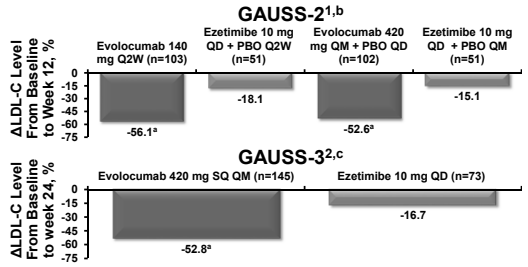
[a]P<0.0001 vs ezetimibe; [b]P<0.0001 vs placebo; [c]Patients with LDL-C levels 100-190 mg/dL and a 10-year risk of fatal CV events ≥1% and <5% (European Systematic Coronary Risk Estimation); no LLT was used in the 4 weeks prior to screening and alirocumab dose could be titrated up to 150 mg Q2W at week 12 if LDL-C levels were ≥70 mg/dL at Week 8; [d]Adults with LDL-C levels of 100-190 mg/dL, TG levels ≤400 mg/dL, and 10-year Framingham CHD risk scores ≤10; no LLT was used in the 3 months before study initiation.
1. Roth EM, et al. *Intern J Cardiol*. 2014;176(1):55-61; 2. Koren MJ, et al. *J Am Coll Cardiol*. 2014;63(23):2531-2540.

Alirocumab in Statin-Intolerant Patients
Odyssey Alternative



[a]P<0.0001.
Adults ≥18 y of age with primary hypercholesterolemia, moderate-high CV risk and an LDL-C ≥100 mg/dL, or very high risk and an LDL-C ≥70 mg/dL, who previously discontinued ≥2 statins due to intolerance.
Moriarty PM, et al. *J Clin Lipid*. 2015;9(6):758-769.

Evolocumab in Statin-Intolerant Patients



[a]P<0.001 vs ezetimibe; [b]Study population included adults 18-80 y of age on no to low-dose statins due to previous intolerance to ≥2 statins. [c]Study population included adults with history of intolerance to ≥2 statins. Phase A used a 24-wk crossover procedure with atorvastatin or placebo to identify patients having symptoms only with atorvastatin, but not placebo. Phase B, after a 2-wk washout patients were randomized to ezetimibe or evolocumab for 24 wk..

1. Stroes E, et al. *Am J Cardiol*. 2014;63(23):2541-2548. 2. Nissen SE, et al. *JAMA*. 2016;315(15):1580-1590.

PCSK9 Inhibitors Are Generally Safe

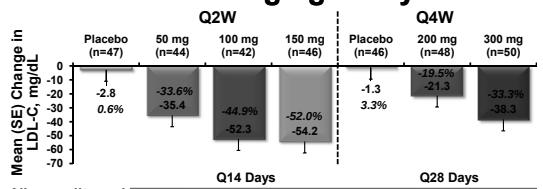
AE[a]	Placebo (n=1276)	Alirocumab (n=2476)[1,b]
Nasopharyngitis	11.1%	11.3%
Injection-site reactions[c]	5.1%	7.2%
Influenza	4.6%	5.7%
Urinary tract infection	4.6%	4.8%
Diarrhea	4.4%	4.7%
Bronchitis	3.8%	4.3%
Myalgia	3.4%	4.2%

AE[a]	Placebo (n=302)	Evolocumab (n=599)
Nasopharyngitis	9.6%	10.5%
Upper respiratory tract infection	6.3%	9.3%
Influenza	6.3%	7.5%
Back pain	5.6%	6.2%
Injection-site reactions[d]	5.0%	5.7%
Cough	3.6%	4.5%
Urinary tract infection	3.6%	4.5%
Sinusitis	3.0%	4.2%

[a]AEs occurring in >4% of drug-treated patients and more frequently than placebo arm. [b]75 mg Q2W and 150 mg Q2W combined; [c]Includes erythema/redness, itching, swelling, pain/tenderness; [d]Includes erythema, pain, bruising.

1. www.accessdata.fda.gov/drugsatfda_docs/label/2015/125559Orig1s000lbledt.pdf; Accessed May 31, 2016.
2. www.accessdata.fda.gov/drugsatfda_docs/label/2015/125522s000lbl.pdf; Accessed May 31, 2016.

Bococizumab[a] Dose-Ranging Study



All causality and (treatment-related) AEs	Q14 Days				Q28 Days		
	Placebo (n=49)	Bococizumab (mg) 50 (n=50)	100 (n=51)	150 (n=49)	Placebo (n=49)	Bococizumab (mg) 200 (n=51)	300 (n=51)
AEs	84% (29%)	74% (24%)	84% (31%)	82% (37%)	80% (16%)	90% (28%)	82% (33%)
Serious AEs	14% (0%)	8% (0%)	4% (0%)	8% (2%)	4% (0%)	10% (0%)	8% (0%)
Discontinuation of treatment due to AEs	2% (0%)	2% (2%)	4% (0%)	10% (8%)	0%	0%	10% (4%)

[a]Bococizumab is not currently FDA approved for the treatment of hypercholesterolemia.

Study population included adults ≥18 y of age with hypercholesterolemia, on stable statin therapy, and with an LDL-C level ≥80 mg/dL and triglycerides ≤400 mg/dL; n=number of treated patients; percent change from baseline in italics.

Ballantyne CM, et al. *Am J Cardiol*. 2015;115(9):1212-1221.

PCSK9 Inhibitors and CV Outcomes

Alirocumab: ODYSSEY LONG TERM[1,c]

CV AEs of Interest, N (%)	Alirocumab (n=1550)	PBO (n=788)
Nonfatal MI	14 (0.9)[a]	18 (2.3)
Adjudicated major adverse CV events in post hoc analysis[d]	27 (1.7)[b]	26 (3.3) HR, 0.52 (0.31-0.90)

Evolocumab: OSLER 1 and 2[2,e]

Endpoint, N (%)	Evolocumab + SOC (n=2976)	SOC (n=1489)
All CV events	29 (0.95)	31 (2.18) HR, 0.47 (0.28-0.78)
Post hoc analysis included death, major coronary events, and major cerebrovascular events	28 (0.95)	30 (2.11) HR, 0.47 (0.28-0.78)

[a]P=0.01 vs PBO; [b]P=0.02 vs PBO; [c]Adults ≥18 y of age with HeFH, CHD, CHD risk equivalent and LDL-C ≥70 mg/dL; [d]Post hoc analysis not specified in the study protocol (composite primary end point from ODYSSEY OUTCOMES: death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, or UA requiring hospitalization; [e]Participants were eligible if they completed 1 of 12 phase 2 or 3 trials.
SOC, standard of care.

1. Robinson JG, et al. *N Engl J Med*. 2015;372(16):1489-1499; 2. Sabatine MS, et al. *N Engl J Med*. 2015;372(16):1500-1509.

Effect of PCSK9 Inhibitor Therapy on CV Outcomes

Large, Prospective Trials Currently Underway

	Alirocumab[1,2]	Evolocumab[3,4]	Bococizumab[5,6]	
Trial	ODYSSEY OUTCOMES	FOURIER	SPIRE I	SPIRE II
Sample size	18,000	27,564	17,000	11,000
Inclusion criteria	4 to 52 weeks post-ACS	MI, stroke, or symptomatic PAD	High risk for CV event	
Statin therapy	Atorvastatin 40 mg or 80 mg or rosuvastatin 20 mg or 40 mg daily	Atorvastatin ≥20 mg daily or equivalent	Any lipid-lowering therapy	
Baseline LDL-C (mg/dL)	≥70	≥70	≥70	≥100
Pcsk9i dosing	75 mg SQ Q2W or 150 mg SQ Q2W	140 mg SQ Q2W or 420 mg SQ Q4W	150 mg SQ Q2W	
Endpoint	CHD death, MI, ischemic stroke, or hospitalization for UA	CV death, MI, stroke, hospitalization for UA, or coronary revascularization	CV death, MI, stroke, or urgent revascularization	
Estimated completion	12/2017	10/2017	4/2018	1/2018

PAD, peripheral artery disease; PCSK9i, PCSK9 inhibitor.

1. Schwartz GG, et al. *Am Heart J*. 2014;168(5):682-689.
2. https://clinicaltrials.gov/ct2/show/NCT01663402?term=odyssey+outcomes&rank=1 Accessed May 31, 2016;
3. Sabatine MS, et al. *Am Heart J*. 2016;173:94-101. 4. https://clinicaltrials.gov/ct2/show/NCT01764633 Accessed May 31, 2016
5. https://clinicaltrials.gov/ct2/show/NCT01975376?term=SPIRE-1&rank=1, Accessed May 31, 2016.
6. https://clinicaltrials.gov/ct2/show/NCT01975389?term=SPIRE-2&rank=1, Accessed May 31, 2016.

Importance of Shared Decision Making

- Communicate ASCVD risk in language patients can understand
  - Explain benefits of lower LDL-C levels
- When discussing treatment options, communicate
  - Efficacy and safety of statin and nonstatin therapy options
    - Set expectations for percent LDL-C reduction with chosen treatment
  - Potential for adverse events
    - Outline strategies to mitigate risk and address emergence of side effects
- Engage patients in health care decisions to improve treatment adherence
  - Integrate patient preferences on dosing frequency, mode of administration, cost, and potential for adverse events into treatment decisions

1. Martin SS, et al. *J Am Coll Cardiol*. 2015;65(13):1361-1368; 2. Barrett B, et al. *BMC Fam Pract*. 2016;17:41; 3. Turin A, et al. *J Cardiovasc Pharmacol*. 2015;20(5):447-456; 4. Lloyd-Jones DM, et al. *J Am Coll Cardiol*. 2016 Mar 28. [Epub ahead of print].