Learning Objectives

- Assess the safety and efficacy of PCSK9 inhibitors in reducing cardiovascular events in patients with acute coronary syndrome and hypercholesterolemia
- Appropriately integrate PCSK9 inhibitors in clinical practice to reduce the risk of cardiovascular events in high-risk patients
- Review current evidence and set optimal LDL-cholesterol targets for patients with documented ASCVD
- Identify common reasons for PCSK9 inhibitor denial and implement a team-based approach to improve patient access

Drug List

Generic Drug Name	US Trade Name
alirocumab	Praluent
amlodipine	Norvasc
aspirin	—
atorvastatin	Lipitor
cholestyramine	Prevalite
empagliflozin	Jardiance
evolocumab	Repatha
extended release niacin	Niaspan
ezetimibe	Zetia
fenofibrate	Tricor

Drug List

Generic Drug Name	US Trade Name
fluvastatin	Lescol
losartan	Cozaar
lovastatin	Mevacor
metformin	Glucophage
metoprolol succinate	Toprol XL
pitavastatin	Livalo
pravastatin	Pravachol
rosuvastatin	Crestor
simvastatin	Zocor

Case 1

Case 1 – History

- **HPI:** GP is a 67-year-old woman who presents at her local emergency department with 3½ hours of stuttering pain in her upper chest radiating to her bilateral jaw. She reports that she has never experienced these symptoms previously.
- She has mild associated shortness of breath and nausea. She denies diaphoresis, vomiting, lightheadedness or dizziness.
- **PMH:** Hypertension, "borderline diet-controlled high cholesterol", emphysema, GERD and osteoarthritis
- **Meds (prior):** Aspirin 81 mg/day, lisinopril/hydrochlorothiazide 40 mg/12.5 mg daily, omeprazole 20 mg/day, and ibuprofen 400 mg as needed

Case 1 – History and Physical Exam

- **SH:** 36-pack/year history of tobacco abuse; she quit in 2011. Social alcohol use. No illicit drug use.
- **FH:** Her father experienced a myocardial infarction at age 48
- **PE:**
  - **Vitals:** 5' 5", 164 lb, BMI 27.3 kg/m2, 88 bpm, 144/86 mm Hg
  - **No other significant findings**

Case 1 – Diagnostic Testing and Hospital Course

- **ECG:** Normal sinus rhythm at 82 bpm. Displays 2 mm of horizontal-to-downsloping ST segment depression in the inferolateral leads. No Q waves. The ST segment changes are new.
- **Labs (pertinent):** Serum creatinine of 1.2 mg/dL, troponin I of 1.34 mg/dL, total cholesterol of 252 mg/dL, LDL-cholesterol (LDL-C) of 167 mg/dL, HDL-cholesterol of 46 mg/dL, and triglyceride of 193 mg/dL
- **Hospital course:** She is diagnosed with a type 1 non-ST-elevation myocardial infarction (NSTE-MI) and is initiated on IV unfractionated heparin, aspirin 81 mg x 4, atorvastatin 80 mg, and metoprolol succinate 25 mg in the emergency department. Four hours later, she is taken to the cath lab and is found to have 80% mid right coronary artery and 60% proximal LAD stenoses, of which the former is treated with a drug-eluting stent.

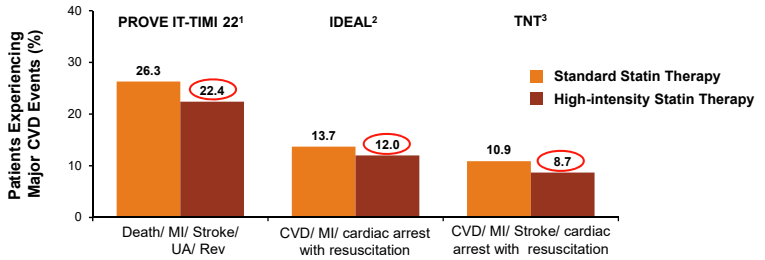
Case 1 – Continued

- GP was continued on atorvastatin 80 mg/day and discharged. She is instructed to follow-up with her primary care physician and cardiologist within 1-2 weeks.
- Approximately 2 weeks after discharge, she notes mild mylagias that improves with a decrease in the atorvastatin dose to 40 mg/day. A repeat lipid panel six weeks later demonstrates a total cholesterol of 187 mg/dL, LDL-cholesterol of 104 mg/dL, HDL-cholesterol of 49 mg/dL, and triglycerides of 169 mg/dL.

Case 1 – Discussion Points

1. **No additional treatment is needed, she is on a high intensity statin**
   - In spite of treatment with a high-intensity statin, her LDL-C remains elevated, putting her at increased CV risk. Because of this result, intensification of LDL-C lowering is warranted.

Substantial Residual Risk Still Exists



N	4162		8888		10,001	
LDL-C mg/dL	95	62	104	81	101	77

1. Cannon CP, et al. *N Engl J Med*. 2004;350(15):1495-1504. 2. Pedersen TR, et al. *JAMA*. 2005;294(19):2437-2445. 3. LaRosa JC, et al. *N Engl J Med*. 2005;352(14):1425-1435.

High-Risk Patients Are Not Receiving Guideline Recommended Care

Cross-sectional analysis of 1,295 patients with heterozygous familial hypercholesterolemia (FH) enrolled in the CASCADE FH registry

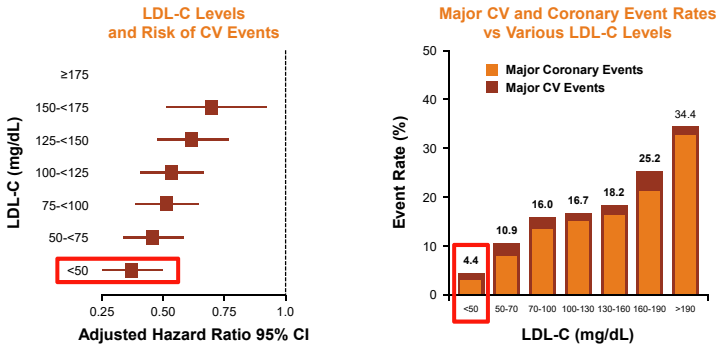
Medications Used	No Coronary Heart Disease	Coronary Heart Disease
High-intensity statin	39.3%	46.9%
Low- or moderate-intensity statin	35.9%	27.3%
No statin	24.8%	25.8%

Medications Used	On Statin Therapy	Not on Statin Therapy
Ezetimibe	45.2%	25.2%
Bile acid sequestrant	15.0%	15.0%
Nicotinic acid	14.4%	9.4%

deGoma EM, et al. *Circ Cardiovasc Genet*. 2016;9:240-249.

Rationale for Pushing LDL-C Levels Even Lower

Meta-analysis of 38,153 patients from eight randomized statin trials



CI = confidence interval.

Boekholdt SM, et al. *JACC*. 2014;64(5):485-494.

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Case 1 – Discussion Points (Continued)

2. Change to rosuvastatin 40 mg/day

- This is a **reasonable treatment option**; however, it may only achieve an additional 5-7% reduction in LDL-C.

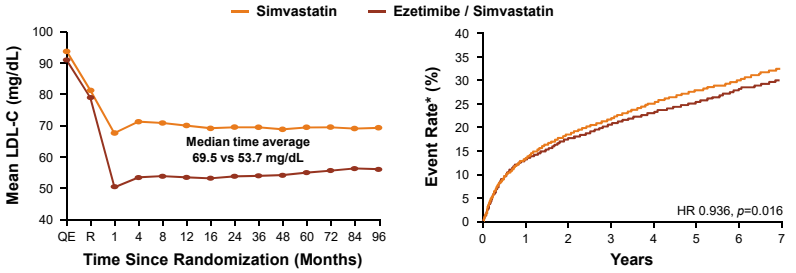
3. Add ezetimibe 10 mg/day

- This option is likely the preferred **and best next step.** Although she was unable to tolerate atorvastatin at the highest dose, she still remains on high-intensity statin therapy. Unfortunately, however, her LDL-C level remains elevated. This option will provide an approximate 20% reduction in LDL-C.

Impact of Ezetimibe in ASCVD

IMPROVE-IT Study

18,144 ACS patients randomized to simvastatin (40 mg QHS) or simvastatin/ezetimibe (40 mg/10 mg QHS) for seven years



*Composite of CV death, MI, unstable angina, coronary revascularization, or stroke.
ACS = acute coronary syndrome; HR = hazard ratio.

Cannon CP, et al. *New Engl J Med* . 2015;372(25):2387-2397.

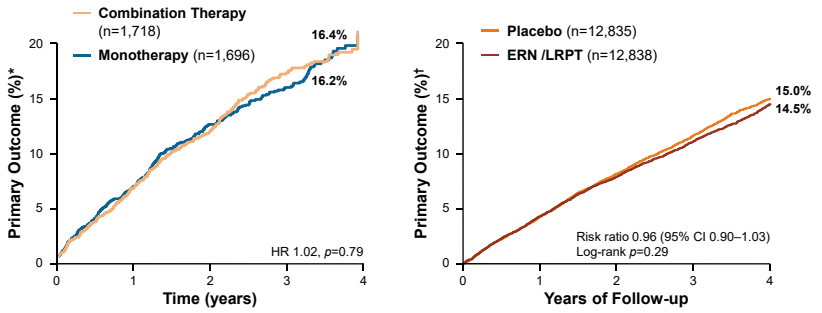
Case 1 – Discussion Points (Continued)

4. Add extended release niacin 500 mg/day, increasing as tolerated

- **Not a good option.** Extended release niacin can significantly lower LDL-C, especially when used at the highest doses. However, its addition to statin therapy in the AIM-HIGH and HPS2-THRIVE trials did not reduce the risk of cardiovascular events but in fact, resulted in a higher risk of adverse side effects.

Impact of Nicotinic Acid in ASCVD

AIM-HIGH Trial | **HPS2-THRIVE Trial**



*CHD death, nonfatal MI, ischemic stroke, hospitalization for ACS, or symptom-driven coronary/cerebral revascularization;
†Patients with CV death, MI, stroke, or revascularization; ERN/LRPT = extended-release niacin/laropiprant.

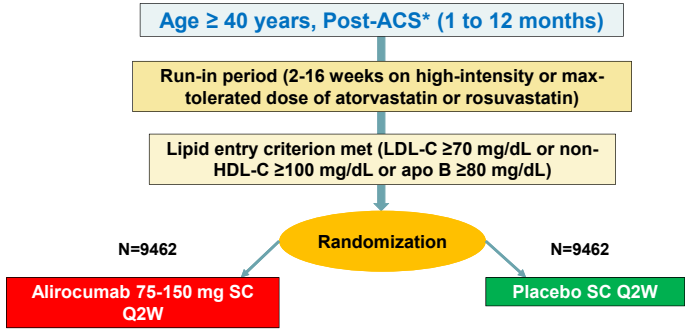
AIM-HIGH Investigators. *N Engl J Med.* 2011;365(24):2255-2267. HPS2-THRIVE Collaborative Group, Landray MJ, et al. *N Engl J Med.* 2014;371(3):203-12.

Case 1 – Discussion Points (Continued)

5. Add a PCSK9 inhibitor

- This is a **reasonable treatment option.** She is in need of additional LDL-cholesterol lowering, which can certainly be achieved with this treatment regimen. Additionally, she represents a patient that could have been enrolled in the ODYSSEY Outcomes trial, which demonstrated a 15% relative risk reduction in major adverse cardiovascular events (MACE) and a nominal 15% relative risk reduction in all-cause mortality among ACS patients treated with alirocumab. However, given their high cost, PCSK9 inhibitors usually are much more difficult to get approved.

ODYSSEY OUTCOMES Trial: Design



Primary endpoint: CHD, MI, fatal or not-fatal stroke, or UA requiring hospitalization

ACS is defined as acute MI or unstable angina; CHD = Coronary heart disease death; UA = unstable angina.
Schwartz GG, et al. Am Heart J. 2014;168(5):682-9.

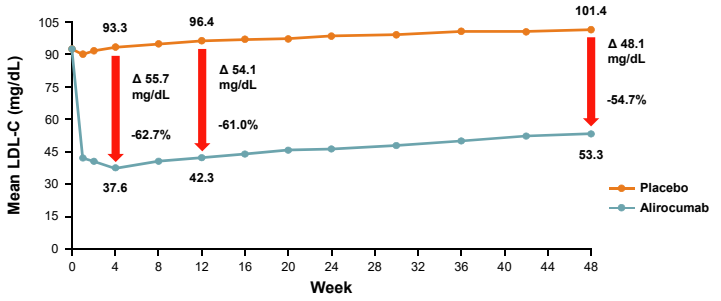
ODYESSEY OUTCOMES: Baseline Characteristics

Characteristic	Alirocumab (N=9462)	Placebo (N=9462)
Median age (years)	58	58
Female (%)	25.3	25.1
Medical History (%)		
Diabetes	**28.5**	**29.1**
Prior MI	18.9	19.5
Time from index ACS to randomization (months)	**2.6**	**2.6**
ACS type (%)		
NSTEMI	48.4	48.7
STEMI	35.0	34.2
Unstable angina	16.6	17.1
Cholesterol (mg/dL)		
LDL-C	**87**	**87**
Non-HDL-C	115	115
Apo B	79	80
HDL-C	43	42
Baseline LLT (%)		
High-dose atorva-/rosuvastatin	**88.6**	**89.1**
Low-/moderate-dose atorva-/rosuvastatin	8.8	8.2

Steg PG, et al. Presented at: ACC.18 Scientific Sessions; March 10, 2018; Orlando, FL.

ODYSSEY Outcomes Trial: LDL-C Reduction with Alirocumab in ACS

18,924 high-risk patients with an ACS within the preceding 1-12 months and an LDL-C ≥70 mg/dL on background high-intensity statin therapy randomized to alirocumab or placebo for a median of 2.8 years



Steg PG, et al. Presented at: ACC.18 Scientific Sessions; March 10, 2018; Orlando, FL.

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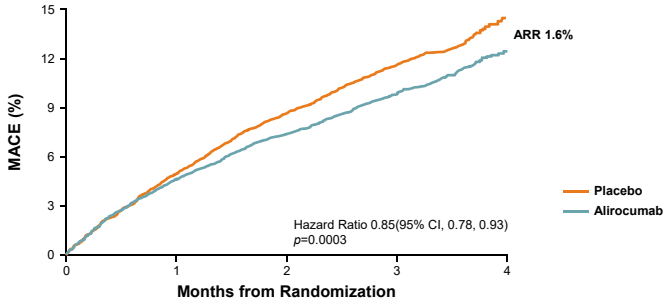
ODYSSEY Outcomes Trial: Primary Endpoint Results

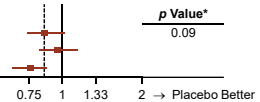


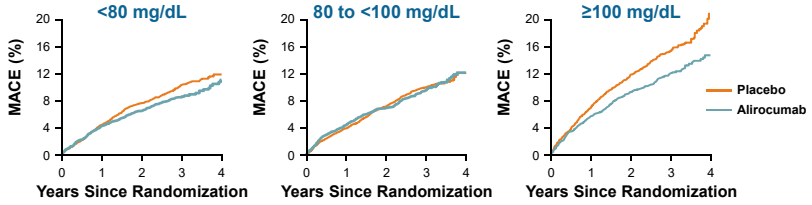
ARR = absolute risk reduction.

Steg PG, et al. Presented at: ACC.18 Scientific Sessions; March 10, 2018; Orlando, FL.

ODYSSEY Outcomes Trial: Primary Endpoint in Prespecified Subgroups

Subgroup	Incidence (%) Patients	Alirocumab	Placebo	HR (95% CI)	*p* Value*
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	0.09
80 to <100	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)	





***p*-values for interaction.**

Steg PG, et al. Presented at: ACC.18 Scientific Sessions; March 10, 2018; Orlando, FL.

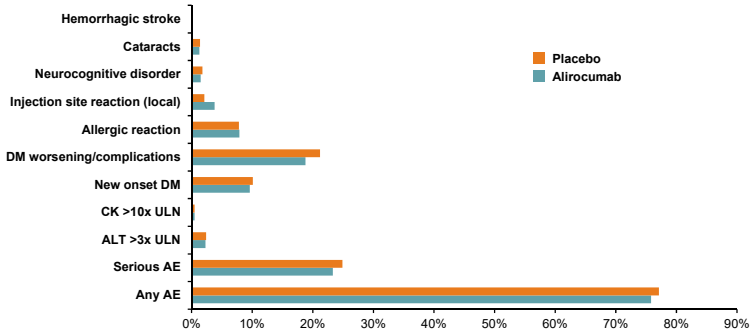
ODYSSEY Outcomes Trial: Primary and Secondary Outcomes

Endpoint	Alirocumab	Placebo	HR (95% CI)	*p* Value
MACE	903 (9.5%)	1052 (11.1%)	0.85 (0.78-0.93)	0.0003
CHD death	205 (2.2%)	222 (2.3%)	0.92 (0.76-1.11)	0.38
Nonfatal MI	626 (6.6%)	722 (7.6%)	0.86 (0.77-0.96)	0.006
Ischemic stroke	111 (1.2%)	152 (1.6%)	0.73 (0.57-0.93)	0.01
Unstable angina	37 (0.4%)	60 (0.6%)	0.61 (0.41-0.92)	0.02
Death, MI, ischemic stroke	973 (10.3%)	1126 (11.9%)	0.86 (0.79-0.93)	0.0003
Coronary heart disease death	205 (2.2%)	222 (2.3%)	0.92 (0.76-1.11)	0.38
Cardiovascular death	240 (2.5%)	271 (2.9%)	0.88 (0.71-1.05)	0.15
All-cause death	334 (3.5%)	392 (4.1%)	0.85 (0.73-0.98)	0.026*

***Nominal *p* value.**
CHD = coronary heart disease; MACE = major adverse cardiac events.

Steg PG, et al. Presented at: ACC.18 Scientific Sessions; March 10, 2018; Orlando, FL.

ODYSSEY Outcomes Trial: Safety Results



Steg PG, et al. Presented at: ACC.18 Scientific Sessions; March 10, 2018; Orlando, FL.

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FOURIER vs ODYSSEY OUTCOMES

	Alirocumab (*N* = 9,462)[1]	Evolocumab (*N* = 13,784)[2]
Patient type	ACS patients (within 1–12 months of event)	ASCVD patients with history of MI, stroke, or symptomatic PAD
Time from index event to randomization	2.6 months	~3.3 years (MI or stroke)
High-intensity statin	88.6%	69.5%
Baseline LDL-C	87 mg/dL	92 mg/dL
Median follow up	2.8 years	2.2 years
Outcomes		
Primary endpoint[a,b]	0.85 HR *P* = 0.0003	0.85 HR *P* <0.001
Nonfatal MI	0.86 HR *P* = 0.006	0.73 HR *P* <0.001
Stroke	0.73 HR *P* = 0.01	0.79 HR *P* = 0.01
CVD	0.92 HR *P* = 0.38	1.05 HR *P* = 0.62
All-causes death	0.85 HR *P* = 0.026	1.04 HR *P* = 0.54

[a] Alirocumab = CVD, non-fatal MI, ischemic stroke, or UA requiring hospitalization; [b] Evolocumab = CVD, MI, stroke, hospitalization for UA, or coronary revascularization.

1. Steg PG. ACC 2018, Orlando, FL. 2. Sabatine MS, et al. *New Engl J Med.* 2017;376:1713–1722.

Approved PCSK9 Inhibitors

	Alirocumab	Evolocumab
Indication	Adjunct to diet and maximum-tolerated statin for adults with HeFH or clinical ASCVD who require additional lowering of LDL-C	Adjunct to diet, alone or in combination with other LLT for treatment of hypercholesterolemia including HeFH; HoFH patients on other LLT who require additional lowering of LDL-C; reduce the risk of MI, stroke, and coronary revascularization in adults with established cardiovascular disease
Dosing	75-150 mg SQ Q2W; 300 mg SQ monthly	140 mg SC Q2W; 420 mg SC monthly
How supplied	Single-dose prefilled pens and prefilled glass syringes that deliver 75-mg/mL or 150-mg/mL solution	Single-use prefilled syringe or autoinjector that delivers 1 mL of 140-mg/mL solution or 420 mg/3.5 mL on-body infusion pump
Side effects	Nasopharyngitis, injection-site reactions; hypersensitivity reactions	Nasopharyngitis, injection-site reactions; hypersensitivity reactions

http://www.pdr.net/drug-summary/Praluent-alirocumab-3765. Accessed May 8, 2018. http://www.pdr.net/drug-summary/Repatha-evolocumab-3781. Accessed May 2018.

Case 1 – 'What If' Questions

In this case, the patient's LDL-C on atorvastatin 40 mg/day was 104 mg/dL. Ezetimibe at 10 mg/day was added subsequently.

- Would your approach have been any different if the LDL-C on maximally tolerated statin therapy was:
  - Much higher (e.g., 135 mg/dL)
  - Lower (e.g., 76 mg/dL)
  - Much lower (e.g., 38 mg/dL)
- What if the patient was diabetic or had additional markers of increased cardiovascular risk?

Case 2

Case 2 – History

- **HPI:** RS is a 73 year old man who presents to your office to establish care after recently relocating to the area.
- He notes exercising regularly on most days of the week without limitation. He denies complaints of chest pain, pressure, or heaviness. He acknowledges, however, the opportunity to improve his diet.
- **PMH:** Hypertension, hypercholesterolemia, type 2 diabetes, and coronary artery disease (CAD) manifesting as stable angina three years ago that required percutaneous coronary intervention (PCI) of the LAD
- **Meds (prior):** Amlodipine 5 mg/day, aspirin 81 mg/day, empagliflozin 25 mg/day, ezetimibe 10 mg/day, losartan 100 mg/day, metformin 1000 BID, metoprolol succinate 50 mg/day, rosuvastatin 5 mg QD

Case 2 – History and Physical Exam

- **SH:** No prior tobacco use. Social alcohol use. No illicit drug use.
- **FH:** Mother – stroke at 64 years old
- **PE:**
  - **Vitals:** 5'10", 214 lb, BMI 30.7 kg/m2, 58 bpm, 124/72 mm Hg
  - **No other significant findings**

Case 2 – Diagnostic Testing and Treatment History

- **ECG:** Normal sinus rhythm at 82 bpm. Abnormal findings include left anterior fascicular block and nonspecific T-wave changes.
- **Labs (pertinent):** Serum creatinine of 0.9 mg/dL, total cholesterol of 177 mg/dL, LDL-C of 97 mg/dL, HDL-C of 36 mg/dL, and triglycerides of 221 mg/dL
- **Treatment history:** Myalgias even at the lowest dose of atorvastatin and all but the lowest dose of rosuvastatin. Tolerate ezetimibe.

Case 2 – Discussion Points

1. **A ≥50% reduction in LDL-C**
   - **This appropriate goal** is recommended by the 2017 ACC Non-statin Expert Consensus Decision Pathway. However, we do not know his baseline LDL-C and his current on-treatment LDL-C remains >70 mg/dL.
2. **An LDL- C <100 mg/dL**
   - **This option is not correct.** He has ASCVD and diabetes. As such, he is at even higher cardiovascular risk. The 2017 recommendations by the ACC and the National Lipid Association (NLA) support LDL-C and non-HDL-C targets of <70 mg/dL and <100 mg/dL, respectively.

Case 2 – Discussion Points (Continued)

3. An LDL-cholesterol <70 mg/dL

– **This option is correct.** In the presence of ASCVD and diabetes, both the ACC and NLA support a LDL-C target of <70 mg/dL as secondary goals. However, in light of data from IMPROVE-IT, FOURIER, REVEAL, and most recently ODYSSEY OUTCOMES, a more aggressive target may be warranted for this patient.

Guidance on Use of Nonstatin Therapy


EXPERT CONSENSUS DECISION PATHWAY

2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways

Endorsed by the National Lipid Association

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4 statin benefit groups

- Adherence and lifestyle

All patients with ASCVD

Primary:
≥50% reduction in LDL-C

***Secondary* (may consider):**
LDL-C <70 mg/dL
Non-HDL-C <100 mg/dL

- Bile acid sequestrant
- PCSK9 inhibitor
- Other therapies (LDL apheresis, lomitapide, mipomersen)

PCSK9 = proprotein convertase subtilisin/kexin type 9 serine protease.

Lloyd-Jones DM, et al. *JACC*. 2017;70(14):1785-1822.

2017 NLA Treatment Recommendations

Disorder	Threshold for Treatment LDL-C / Non-HDL (mg/dL)	Strength / Quality of Evidence
ASCVD + risk factors	≥70 / ≥100	A / High
Progressive ASCVD	≥70 / ≥100	B / Moderate
LDL-C ≥190 mg/dL, age 40-79 no uncontrolled RF or key risk markers	≥100 / ≥130	B / Moderate
LDL-C ≥190 mg/dL, age 40-79 uncontrolled RF or key risk markers	≥70 / ≥100	B / Moderate
LDL-C ≥190 mg/dL, age 18-39 uncontrolled RF or key risk markers or FH causing mutation	≥100 / ≥130	E / Low
Homozygous FH	≥70 / ≥100	B / Moderate
ASCVD + statin intolerance	Clinical judgement	C / Low

RF = risk factor.

Orringer CE, Underberg JA, et al. *J Clin Lipidol*. 2017;11(4):880-890.

Case 2 – Discussion Points (Continued)

4. An LDL-cholesterol <55 mg/dL

– **This option is also appropriate,** particularly in light of data from IMPROVE-IT, FOURIER, REVEAL, and most recently ODYSSEY OUTCOMES. Each of these trials demonstrated that an on-treatment LDL-C <70 mg/dL achieved by adding a non-statin to patients with documented CVD or ACS lowered the risk of CV events. Additionally, the American Association of Clinical Endocrinologists (AACE) guidelines recommend a LDL-C <55 mg/dL for extremely high-risk patients with diabetes such as RS.

Impact of Lower LDL on Outcomes

Trial	Comparison	LDL Achieved (mean, mg/dL)	Outcomes	*p* Value
IMPROVE-IT[a]	Simvastatin vs. EZ / Simvastatin	70 vs. 54	34.7% vs. 32.7%	0.016
FOURIER[a]	Placebo vs. Evolocumab	92 vs. 30	11.3% vs. 9.8%	<0.001
ODYSSEY OUTCOMES[b]	Placebo vs. Alirocumab	93 vs. 38	11.1% vs. 9.5%	0.0003

***Median values; [a]CV death, MI, coronary revascularization, UA, or stroke; [b]CV death, MI, stroke, or UA requiring hospitalization.**

Cannon CP, et al. *N Engl J Med*. 2015;372(25):2387-97. Sabatine MS, et al. *N Engl J Med*. 2017;376(18):1713-1722. Steg PG, et al. Presented at: ACC.18 Scientific Sessions; March 10, 2018; Orlando, FL.

2017 AACE Dyslipidemia Guidelines

Risk Category	Risk Factors[a,b]	LDL-C Goal
Low risk	0 risk factors	**<130 mg/dL**
Moderate risk	≤2 risk factors and 10-year risk <10%	**<100 mg/dL**
High risk	≥2 risk factors and 10-year risk 10-20%; DM/CKD 3/4 with no other risk factors	**<100 mg/dL**
Very high risk	Established or recent hospitalization for ACS; ASCVD; 10-year risk >20%; DM/CKD 3/4 with ≥1 risk factor(s); HeFH	**<70 mg/dL**
Extreme risk	Progressive ASCVD including unstable angina in patients with an LDL-C <70 mg/dL; ASCVD in patients with DM, CKD 3/4, or HeFH; premature ASCVD (<55 male, <65 female)	**<55 mg/dL**

[a]High LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension, low HDL-C (<40 mg/dL), family history of CAD, chronic renal disease (CKD) stage 3/4, evidence of coronary artery calcification and age (men ≥45; women ≥55 years). Subtract 1 risk factor if the person has high HDL-C. [b]Framingham risk scoring is applied to determine 10-year risk.

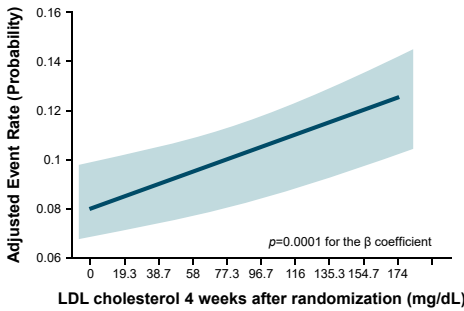
Jellinger PS, et al. *Endocr Pract*. 2017;23(Suppl 2):1-87.

Case 2 – Discussion Points (Continued)

5. An LDL-cholesterol 25-50 mg/dL

– **This option may be appropriate** for very high risk patients such as RS. We have learned from trials using PCSK9 inhibitors that patients achieving very low levels of LDL-C have reduced rates of CV events without an increased risk of serious side effects.

FOURIER – Lower CV Event Rates with Lower LDL-C Levels*, Even Down to 20 mg/dL

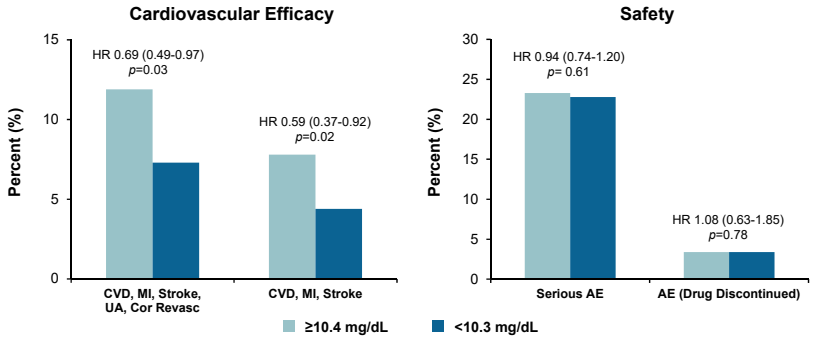


There were no safety concerns with very low LDL-cholesterol concentrations over a median of 2.2 years.

***Relationship between the achieved LDL-C concentration at 4 weeks and the risk of CVD, MI, or stroke.**

Giugliano RP, et al. *Lancet*. 2017 Aug 25. [Ahead of print]

FOURIER Trial – Efficacy and Safety in Patients with an LDL-C <10 mg/dL



Cor revasc = coronary revascularization; UA = unstable angina.

Giugliano RP, et al. *Lancet*. 2017;390(10106):1962-1971.

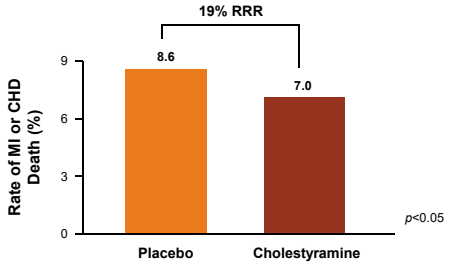
Case 2 – Discussion Points

1. **Add cholestyramine 4 g 2x/day**
   - **This is not the best option.** The ACC Non-statin Pathway considers a bile acid sequestrant (BAS) an optional alternative in patients intolerant of ezetimibe with triglycerides <300 mg/dL. This consideration is partly due to the absence of cardiovascular outcomes data evaluating the incremental effect of a BAS on a background of statin therapy. A BAS, however, has been shown to improve cardiovascular outcomes when used as monotherapy.

Impact of a Bile Acid Sequestrant

Lipid Research Clinics-Coronary Primary Prevention Trial (LRC-CPPT)

3,806 men with primary hypercholesterolemia randomized to cholestyramine (24 g) or placebo for 7.4 years



The LRC-CPPT Investigators. *JAMA*. 1984;251:351-364.

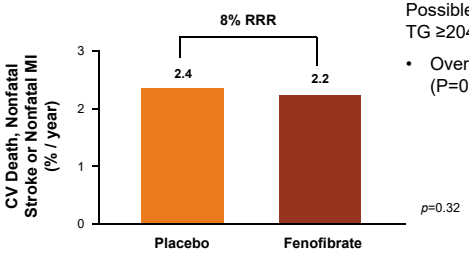
Case 2 – Discussion Points (Continued)

2. **Add fenofibrate 160 mg/day**
   - This is **not an appropriate option.** Fibrates have a rather modest LDL-cholesterol lowering effect. Further, the addition of fenofibrate to background statin therapy was associated with no improvement in cardiovascular events in the ACCORD Lipid Trial. However, prespecified subgroup analysis in ACCORD suggest a possible heterogeneity in treatment effect with a possible benefit in patients with both a high baseline triglyceride level and low HDL-C (P=0.057 for interaction)

Impact of a Fibrate

Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial

5,518 diabetic patients on statin therapy randomized to fenofibrate (160 mg) or placebo for 4.7 years



Possible benefit in subgroup patients with both TG ≥204 mg/dL and HDL-C ≤34 mg/dL:

- Overall event rate of 12.4% vs 17.3% (P=0.057 for interaction)

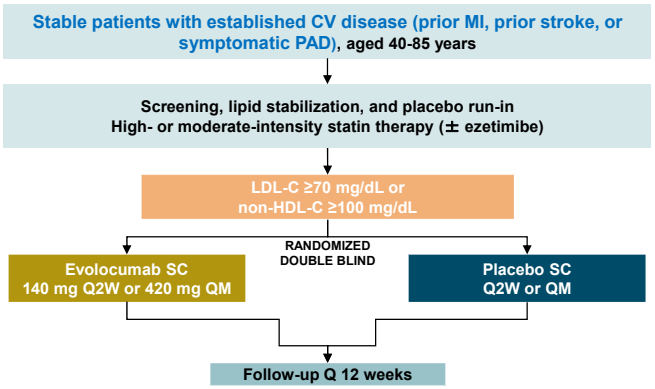
ACCORD study group. *NEJM*. 2010;362:1563-1574.

Case 2 – Discussion Points (Continued)

3. Add a PCSK9 inhibitor

– **Correct option.** Our patient has been unable to tolerate two different high-intensity statin regimens, but appears to be doing well on a moderate-intensity statin. With the addition of ezetimibe, the patient persists in having an elevated LDL-cholesterol that places him at increased CV risk. In the FOURIER trial, addition of a PCSK9 inhibitor to patients with stable ASCVD and a LDL-C >70 mg/dL was associated with significant cardiovascular benefit.

FOURIER Trial: Design



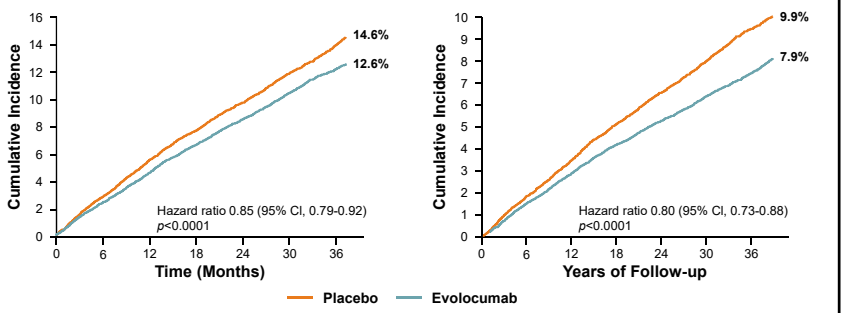
Sabatine MS, et al. *Am Heart J.* 2016;173:94-101.

FOURIER Trial: Baseline Characteristics

Characteristic	Evolocumab (N=13,784)	Placebo (N=13,780)
Median age (years)	62.5	62.5
Female (%)	24.6	24.5
Medical History (%)		
Diabetes	**36.7**	**36.5**
Type of atherosclerosis (%)		
MI	**80.9**	**81.3**
Median time from most recent MI (year)	3.4	3.3
Ischemic stroke	**19.5**	**19.2**
Median time from most recent stroke (year)	3.2	3.3
PAD	**13.5**	**12.9**
Cholesterol (mg/dL)		
LDL-C	**92**	**92**
Non-HDL-C	168	168
HDL-C	44	44
Baseline LLT (%)		
High intensity statin	**69.5**	**89.1**
Moderate intensity statin	30.2	30.7
Low intensity statin	0.3	0.2

Sabatine MS, et al. *N Engl J Meda.* 2017;376(18):1713-1722.

FOURIER: Results

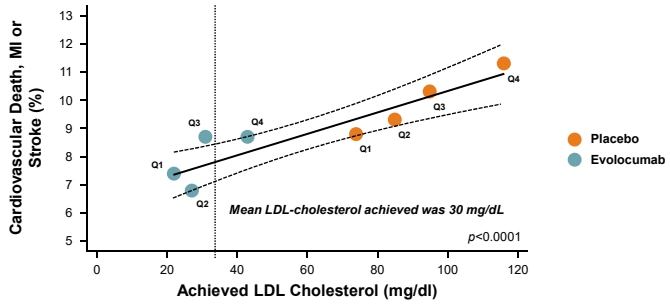


*Cardiovascular death, MI, stroke, hospitalization for unstable angina or coronary revascularization;
†Cardiovascular death, MI, or stroke.

Sabatine MS, et al. *N Engl J Med*. 2017;376(18):1713-1722.

FOURIER Trial—Relationship Between LDL-C and Event Rate

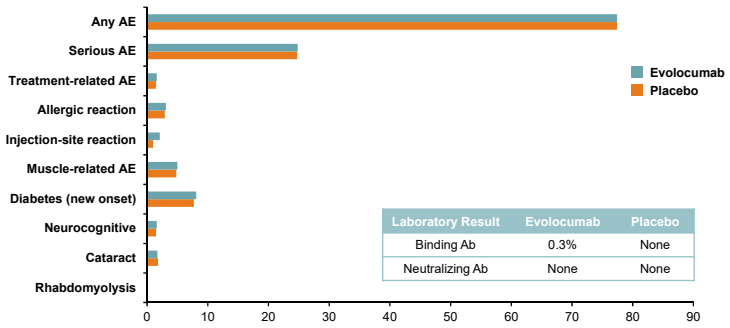
Patients divided by quartile of baseline LDL-C and by treatment arm



Sabatine MS, et al. *N Engl J Med*. 2017;376(18):1713-1722.

Impact of PCSK9 Inhibition in ASCVD (Continued)

FOURIER Trial—Key safety endpoints



Laboratory Result	Evolocumab	Placebo
Binding Ab	0.3%	None
Neutralizing Ab	None	None

Ab = antibody; AE = adverse event.

Sabatine MS, et al. *N Engl J Med*. 2017;376(18):1713-1722.

Case 2 – Discussion Points (Continued)

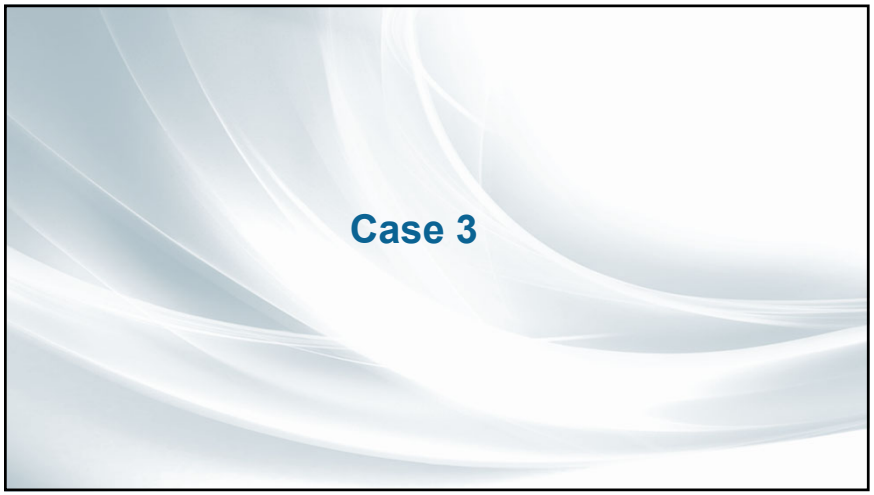
4. Change rosuvastatin 5 mg/day to pravastatin 40 mg QHS

- This is **not the best option**. Because both are moderate-intensity statins, little difference can be anticipated in the LDL-C levels achieved by a therapeutic interchange.

Case 2 – 'What If' Questions

In this case, myalgias precluded the use of atorvastatin and limited the use of rosuvastatin to 5 mg/day.

- What if the patient had limiting myalgia with rosuvastatin at 5 mg/day?
  - What would be your next steps?
  - Would any laboratory testing be warranted?
  - What's the role for Co-enzyme Q-10 or vitamin D?
- What if the patient was unable to afford a PCSK9 inhibitor?
  - What's the role for combining ezetimibe with a bile acid sequestrant (or other non-statin)?



Case 3 – History

- **HPI:** SC is a 43-year-old woman who is referred for initial consultation because of "high cholesterol levels".
- She reports no prior medical problems and largely feels well. She has noticed "for years," however, intermittent aching in her Achilles tendons with prolonged exercise.
- **PMH:** "High cholesterol"
- **Meds (prior):** None
- **SH:** No prior tobacco use. Rare alcohol use. No illicit drug use.

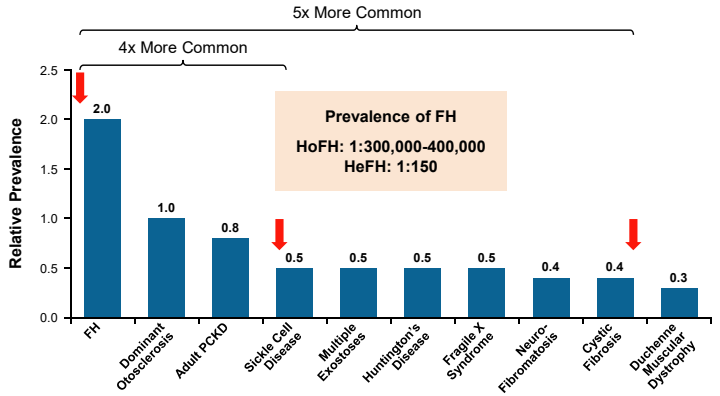
Case 3 – History, Physical Exam and Diagnostic Testing

- **FH:** Her father experienced a heart attack at age 52. He was a smoker, however.
- **PE:**
  - **Vitals:** 5'7", 134 lb, BMI 20.99 kg/m2, 58 bpm, 118/66 mm Hg
  - **Both eyes demonstrate arcus cornealis and small xanthomas extend along the Achilles tendons. No other significant findings.**
- **Labs (pertinent):** Total cholesterol of 395 mg/dL, LDL-C of 319 mg/dL, HDL-C of 56 mg/dL, and triglyceride of 101 mg/dL

Case 3 – Continued

- She is diagnosed with FH based on the Dutch Lipid Clinic Network Criteria. She is started on rosuvastatin at 40 mg/day which she tolerates well. A repeat lipid panel 8 weeks later demonstrates a total cholesterol of 269 mg/dL, LDL- C of 191 mg/dL, HDL-C of 61 mg/dL, and triglycerides of 84 mg/dL.

Prevalence of FH Relative to Other Conditions



Sjouke B, et al. *Eur Heart J*. 2015:560-565; de Ferranti SD, et al. *Circulation*. 2016;133:1067-1072.

Case 3 – Discussion Points

1. **Add omega-3-acid ethyl esters 4 gm daily**
   - This is **not a good option** because omega-3 fatty acids do not appreciably lower LDL-C and some actually increase LDL-C. They are used to treat high triglycerides. Her triglycerides do not require treatment.

Lipid Effects of Omega-3-Acid Ethyl Esters

Dose	LDL	HDL	TG
4 g daily	↑ 44.5%	↑ 9.1%	↓ 45%
4 g daily in combination with statins	↑ 0.7%	Further ↑ 3.4%	Further ↓ 29.5%

PL Detail-Document, Non-Statin Lipid-Lowering Agents. Pharmacist's Letter/Prescriber's Letter. January 2013. Koski RR. P T. 2008;33(5): 271-303.

Case 3 – Discussion Points

2. Add colesevelam 625 mg tabs, 3 tabs BID

– This option **could be considered**, but it will lower her LDL-C by only an additional 10-16%. It is unlikely this change would help her reach her LDL-C goal.

3. Add ezetimibe 10 mg/day

– This choice is **an option, but not preferred** in this case. She is very unlikely to achieve her LDL-C goal of <100 mg/dL with ezetimibe.

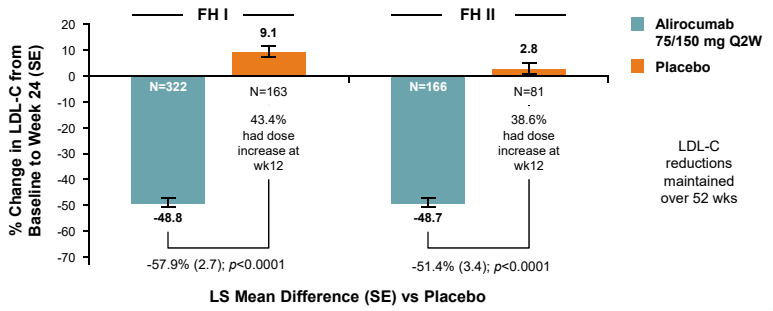
Case 3 – Discussion Points (Continued)

4. Add a PCSK9 inhibitor

– **This is likely the best option.** Although she is on high-intensity statin therapy, she persists in having a significantly elevated LDL-C level (48% above her desired goal). The ACC Non-statin Pathway considers a LDL-C <100 mg/dL or non-HDL-C <130 mg/dL as secondary targets for patients with FH. Given the much greater LDL-C lowering effect of PCSK9 inhibitors, this option is the preferred form of non-statin therapy for this patient.

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

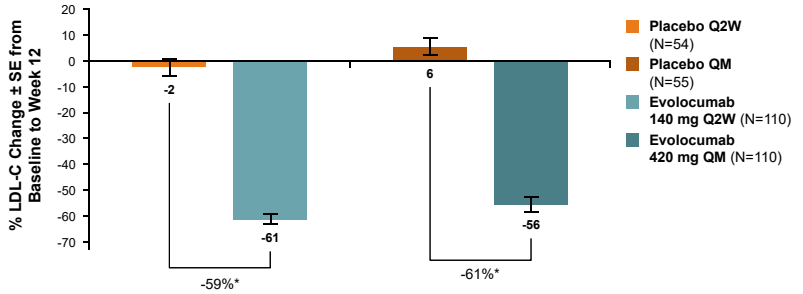
All patients on background maximally-tolerated statin ± another LLT



Kastelein JJ, et al. *Eur Heart J*. 2015;36(43):2996-3003.

RUTHERFORD-2: Evolocumab in Patients with FH

All patients on background maximally-tolerated statin ± another LLT



*$p<0.001$; SE = standard error.

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

Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.

Case 3 – Continued

- You realize SC likely will need a PCSK9 inhibitor to get her LDL-C to goal but decide to add ezetimibe 10 mg/day to her current regimen of rosuvastatin 40 mg/day first because many insurance plans require a trial of both before they approve a PCSK9 inhibitor.
- After 8 weeks of treatment with rosuvastatin 40 mg/day and ezetimibe 10 mg/day, her LDL-C is 161 mg/dL and you decide to prescribe a PCSK9 inhibitor. Her insurance company, however, denies it.

Case 3 – Discussion Points

1. **35%**
   - **Not correct.** This number represents the percentage of PCSK9 inhibitor prescriptions that are filled, but not picked up by patients at the pharmacies.
2. **57%**
   - **Also incorrect.** Approximately 53-57% of PCSK9 inhibitor prescriptions ultimately are denied by payors.
3. **65%**
   - **Incorrect.**

Case 3 – Discussion Points (Continued)

4. **79%**
   - **Correct.** Approximately 79-83% of PCSK9 inhibitor prescriptions are denied by insurance companies within 24 hours of submission.

Access to PCSK9 Inhibitors Restricted

- Baum et al. (44,234 prescriptions)[1]
  - 83% of PCSK9 inhibitor prescription rejected initially; 57% rejected ultimately
  - Patients with **approved** PCSK9 prescriptions were more likely to be on high-intensity statin and ezetimibe
- Navar et al. (prescriptions for 45,029 patients)[2]
  - 79% rejected within 24 hours; 53% rejected ultimately
  - Rejection rates: 33-78% for commercial payers; 38-84% for government insurance programs; 33-75% across PBMs
  - 35% of filled prescriptions were abandoned at the pharmacy
  - **Coupon program use increased the likelihood of receiving PCSK9 inhibitor therapy 17-fold**

1. Baum SJ, et al. Presented at the 66th Scientific Session of the ACC, Washington, DC, March 17-19, 2017. Abstract 1258-435.
2. Navar AM, et al. Presented at the 66th Scientific Session of the ACC, Washington, DC. March 17-19, 2017. Abstract 415-08.

PCSK9 Inhibitor Support and Copay Programs

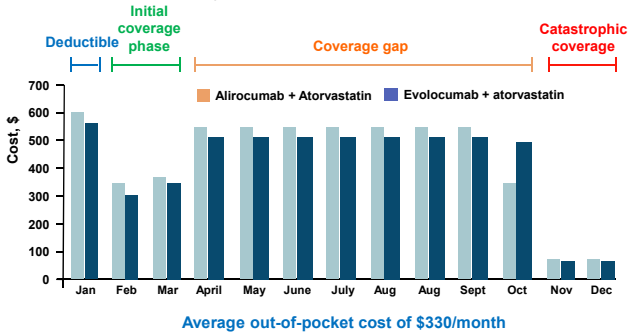
- **Alirocumab programs**[1]
  - Commercial insurance: Copay card for $0 per month with annual cap of $5,500 for eligible patients
  - Government insurance: Low income subsidy program for Medicare patients
  - No insurance or lack pharmacy benefits: Patient assistance program to provide free medication to eligible patients for as many as 12 months, which can be renewed
  - Insurance specialist available to assist with prior authorization
- **Evolocumab programs**[2]
  - Commercial insurance: Copay card ≤$5 for eligible patients
  - Insurance specialist available to offer assistance with coverage issues

These programs change over time so can only be counted on short-term.

1. https://www.praluenthcp.com/support. Accessed September 18, 2017. 2. https://www.repatha.com/repathaready-services/. Accessed May 18, 2018.

Medicare Part D Cost-Sharing With PCSK9 Inhibitors

Analysis of 2575 Part D Medicare Plans Across 50 States



Average out-of-pocket cost of $330/month

Coverage sequence

- **$360 deductible**
- **Coverage phase**
- **Coverage gap (donut hole) when total drug costs reach $3,310 with cost-sharing to 45% for brand-name drug**
- **Catastrophic coverage when total costs reach $4,850 with cost-sharing reduced to 5% for the remainder of the year**

Kazi DS, et al. *JAMA Cardiol.* 2017;(10):1164-1166.

Common Reasons Cited for PCSK9 Inhibitor Denial

- **Patient has not tried ezetimibe**
- **Re-challenge with statin not documented in statin-intolerant patient**
- **Patient has not tried a bile acid sequestrant**
- **LDL <100 mg/dL with ASCVD or <130 mg/dL without ASCVD**
- **Requires 80% compliance in fill history from pharmacy for statin and ezetimibe during a 12-month period**
- **Nutrition intervention not documented (specifically reduced intake of saturated fats and cholesterol; increased fruits and vegetables)**
- **Triglycerides >400 mg/dL**
- **Exercise and weight management regimen not documented**
- **Requires confirmation of FH with genetic testing**
- **Criteria for "definite" FH undocumented (requires DLCN Score >8)**
- **Indication for PCSK9 inhibitor not clearly documented**
- **Failure to submit office notes or labs with prior authorization request**
- **Missing statement that patient will continue to receive a maximally tolerated statin (or ezetimibe) while on PCSK9 inhibitor**
- **ASCVD criteria not met**

Kaufman TM, Duell PB, et al. *Circ Res.* 2017;121(5):499-501.

DLCN = Dutch Lipid Clinic Network

Required Documentation for PCSK9 Inhibitor PA

- **Detailed medical history including prior and current medications, doses, dates of administration, and reasons for discontinuation**
- **Family history of hypercholesterolemia and/or coronary artery disease**
- **Physical exam for xanthomas and DLCN score (for patients with FH)**
- **American Heart Association criteria for diagnosis of FH**
- **Most recent lab results (≤30 days) - including lipid panel and lipoprotein (a)**
- **Highest documented LDL-C concentration (ideally off treatment)**
- **Evidence of subclinical atherosclerosis (coronary artery calcium, carotid intima media thickness, ankle brachial index) or clinical ASCVD (MI, stroke, angina, angiographic evidence, ischemia testing, arterial revascularization)**
- **Clear specification of diagnosis for which PCSK9 inhibitor therapy is being prescribed**

PA = prior authorization; DLCN = Dutch Lipid Clinic Network.

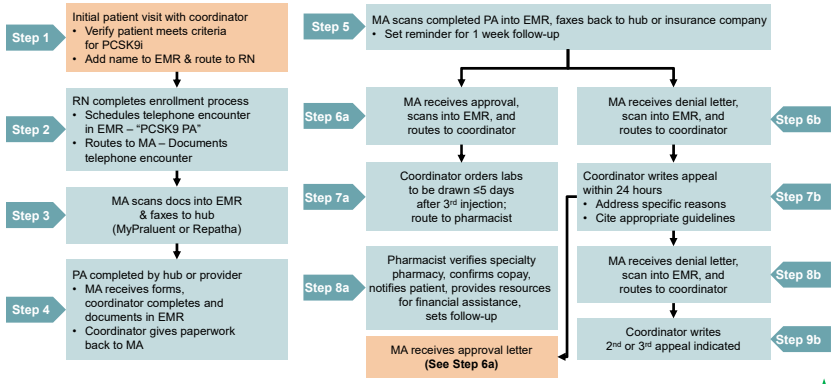
Kaufman TM, Duell PB, et al. Circ Res. 2017;121(5):499-501.

Tactics to Improve PCSK9 Inhibitor Access Using a Team-Based Approach

- Establish a dedicated team to deal with prior authorizations, appeals, reappeals, and peer-to-peer reviews
- This multi-disciplinary team should include physicians, a nurse, a medical assistant, a clinical pharmacist, and a physician assistant (the "PCSK9 inhibitor Clinic")
  - PCSK9 inhibitor eligible patients are referred to the "PCSK9 inhibitor Clinic"
  - Coordinator oversees the approval process, provides injection training, and arranges longitudinal management and surveillance
  - 92% success rate (n=142/153)
- Key to successful PCSK9 inhibitor PA approval
  - Meticulous documentation of all data required for PA submission

Kaufman TM, Duell PB, et al. *Circ Res*. 2017;121(5):499-501.

PCSK9 Inhibitor PA Process with Team-Based Approach



EMR= electronic medical record; MA = medical assistant.

Kaufman TM, Duell PB, et al. *Circ Res*. 2017;121(5):499-501.

Populations in Whom to Consider a PCSK9 Inhibitor

Patient Type	LDL-C Reduction on Maximally Tolerated Statin and/or Other LLT	Consideration for PCSK9 Inhibitor
Established ASCVD with or without comorbidities	<50% LDL-C reduction or LDL-C >70 mg/dL	Yes
ACS with or without comorbidities	<50% LDL-C reduction or LDL-C >70 mg/dL	Yes
HeFH or HoFH	<50% LDL-C reduction or LDL-C >70 mg/dL	Yes

http://www.pdr.net/drug-summary/Praluent-alirocumab-3765. Accessed May 8, 2018. http://www.pdr.net/drug-summary/Repatha-evolocumab-3781. Accessed May 2018. Sabatine MS, et al. *Am Heart J*. 2016;173:94-101. Steg PG, et al. Presented at: ACC.18 Scientific Sessions; March 10, 2018; Orlando, FL.

Case 3 – 'What If' Questions

In this case, the presence of FH had a significant impact on the treatment approach.

- What if the patient had FH and ASCVD?
  - Would that have changed the treatment approach?
- What if the patient had homozygous FH (HoFH)?
  - Would any other pharmacologic or non-pharmacologic options need to be considered if the patient was not at her desired LDL-C goal?

Key Takeaways

- While statins remain the standard for treatment of patients with ASCVD and hypercholesterolemia, non-statin therapies such as ezetimibe, alirocumab, and evolocumab offer additional options for reducing the risk of adverse CV events.
- FOURIER and ODYSSEY OUTCOMES have shown PCSK9 inhibitors alirocumab and evolocumab to be effective in lowering LDL-C and CV events in patients with ACS and stable ASCVD, respectively
- Achieving lower LDL levels (< 50 mg/dL) has been shown to be safe and significantly reduces the risk of cardiovascular events

Key Takeaways

- PCSK9 inhibitor access continues to be restricted, but is appropriate in patients who are at increased CV risk despite optimal statin therapy:
  - Statin therapy is suboptimal or statin intolerance – defined as unacceptable adverse effects that resolve with discontinuation of therapy and recur with rechallenge of 2 to 3 statins
  - Stable ASCVD or ACS
  - HeFH or HoFH
- A team-based approach to managing the PA process, along with additional resources can increase PCSK9 inhibitor approval rate and improve patient access
- Support and copay programs can help to significantly lower the out-of-pocket cost, particularly among those on commercial insurance