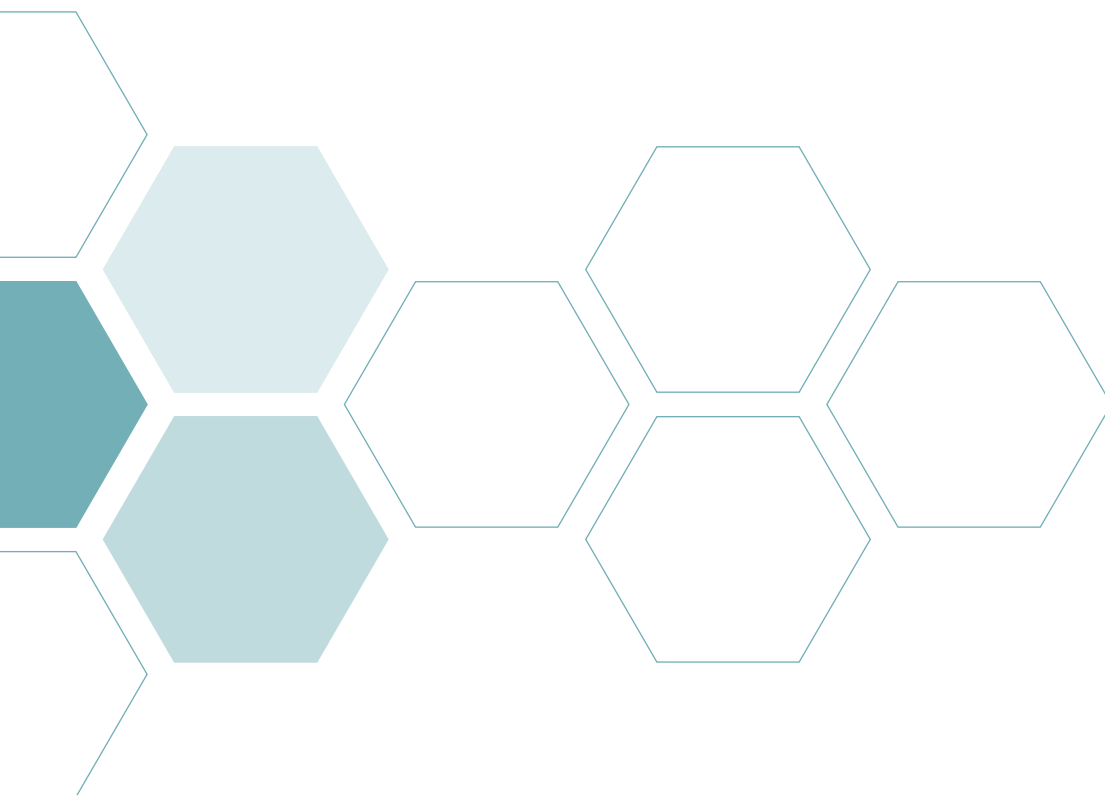


# The Role of PCSK9 Inhibitors in Lowering LDL-C in Patients with Dyslipidemia: What Managed Care Needs to Know

A CME/CNE Approved Activity



**JOURNAL** of **MANAGED CARE MEDICINE**



This activity is supported by educational grants from Amgen and Sanofi US and Regeneron Pharmaceuticals.

## The Role of PCSK9 Inhibitors in Lowering LDL-C in Patients with Dyslipidemia: What Managed Care Needs to Know

Instructions for CME/CNE: Activity is valid from September 1, 2018 to August 1, 2020.

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Dr. Owens, MD is the President of Gary Owens and Associates.

### Learning Objectives:

1. Analyze the latest clinical trial safety and efficacy data for PCSK9 inhibitors to lower LDL-C and cardiovascular events.
2. Examine current evidence for the optimal LDL-C goal for patients with dyslipidemia.
3. Discuss current guidelines for the treatment of dyslipidemia, including the updated ACC Expert Consensus Decision Pathway on the role of non-statin therapies.
4. Implement current evidence to identify patient populations that are expected to derive the greatest benefit from non-statin therapies.
5. Describe "statin intolerance" and "statin failure" and appropriate treatment options for patients with either of these conditions.
6. Address payer- and provider-related barriers to appropriate evidence-based use of PCSK9 inhibitors.

### Faculty Disclosure:

Dr. Cannon has disclosed the following relevant financial relationships having received grants for clinical research from Amgen, Arisaph, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Merck and Takeda, and serves as a consultant for, Alnylam, Amgen, Amarin, Arisaph, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Kowa, Lipimedix, Merck, Pfizer, Regeneron, Sanofi and Takeda.

Dr. Nissen has disclosed the following relevant financial relationships having received grants for clinical research from Amgen, AstraZeneca, Daiichi-Sankyo, Eli Lilly, Medical Research Institute, Novartis, Novo Nordisk, Omthera Pharmaceuticals, Orexigen, Pfizer, Resverlogix, Roche, Sanofi-Aventis, Southern Australian Health, and Vivus.

Dr. Owens has disclosed the following relevant financial relationships serving as a consultant for Lilly, Regeneron, and Sanofi.

All material has been peer reviewed for bias.

### Planning Committee Disclosure

Bill Williams, MD; Jacqueline Cole, RN,CPHQ, CMCN; Jeremy Williams have no relevant financial relationships to disclose.

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**This program is supported by educational grants from Amgen and Sanofi US and Regeneron Pharmaceuticals**

# The Role of PCSK9 Inhibitors in Lowering LDL-C in Patients with Dyslipidemia: What Managed Care Needs to Know

## Post-Test Questions

1. Cardiovascular disease accounts for about one of every \_\_\_\_\_ deaths in the United States (U.S.).  
a. 3                      b. 4                      c. 5                      d. 6
2. LDL-C levels below 70 mg/dL appear to be necessary for plaque regression in those who already have atherosclerosis.  
a. True                      b. False
3. According to the Cholesterol Treatment Trialists Collaboration meta-analysis, which of the following is NOT a benefit of LDL-C lowering with statins?  
a. Reduced risk of CHD death  
b. Reduced risk of non-fatal MI  
c. Reduced risk of hemorrhagic stroke  
d. Reduced risk of coronary revascularization procedure
4. Which of the following is the most common adverse effect of the PCSK9 inhibitors?  
a. Allergic hypersensitivity                      b. Injection site reactions  
c. Seizures                      d. Myopathy
5. Which of the following is an accurate statement about PCSK9 inhibitors?  
a. These agents produce a 90 percent reduction in LDL-C as monotherapy.  
b. They are contraindicated in combination with other lipid lowering agents and in those with renal failure.  
c. They significantly but modestly improve outcomes (CV death, MI, stroke, hospitalization for unstable angina or revascularization) over statins alone in adults with established CVD.  
d. Alirocumab is FDA approved for primary prevention in adults, 20 to 75 years of age, who have baseline LDL-C.
6. Based on the FOURIER trial results, which of the following is an additional benefit of PCSK9i in patients with peripheral arterial disease?  
a. Reduced risk of major limb events  
b. Reduced risk of pressure ulcers requiring hospitalization  
c. Reduced secondary infection rates  
d. Improved quality of life
7. Which of the following would be an alternative lipid lowering agent for a patient with statin intolerance who requires a 50 percent reduction in LDL-C?  
a. Cholestyramine                      b. Niacin  
c. Ezetimibe                      d. Evolocumab
8. Per the ACC/AHA guidelines, which of the following is NOT a group that would benefit from statin therapy?  
a. Patients with any form of clinical ASCVD  
b. Patients with primary LDL-C levels of 190 mg/dL or greater  
c. Patients with diabetes mellitus, 20 to 60 years of age, with LDL-C levels of 70 to 189 mg/dL  
d. Patients without diabetes, 40 to 75 years of age, with an estimated 10-year ASCVD risk greater than or equal to 7.5 percent.
9. According to the 2017 ACC/AHA non-statin therapy guidelines, which of the following is a clinical factor predicting benefit from ezetimibe addition to statin?  
a. Heart failure                      b. Age < 75 years  
c. Good renal function                      d. Moderate alcohol use
10. An appropriate and cost effective use of PCSK9i would be to limit use to patients with ASCVD who have not achieved 50 percent reduction of LDL-C on maximized statin and ezetimibe treatment (or intolerant to statin).  
a. True                      b. False

## Activity Evaluation and Improvement Process

*(Please rate this activity on the following scale:  
4 - Excellent    3 - Good    2 - Fair    1 - Poor)*

1. Based on the content presented, I am better able to:  
  
Analyze the latest clinical trial safety and efficacy data for PCSK9 inhibitors to lower LDL-C and cardiovascular events.  
  
4      3      2      1  
  
Examine current evidence for the optimal LDL-C goal for patients with dyslipidemia.  
  
4      3      2      1  
  
Discuss current guidelines for the treatment of dyslipidemia, including the updated ACC Expert Consensus Decision Pathway on the role of non-statin therapies.  
  
4      3      2      1  
  
Implement current evidence to identify patient populations that are expected to derive the greatest benefit from non-statin therapies.  
  
4      3      2      1  
  
Describe "statin intolerance" and "statin failure" and appropriate treatment options for patients with either of these conditions.  
  
4      3      2      1  
  
Address payer- and provider-related barriers to appropriate evidence-based use of PCSK9 inhibitors.  
  
4      3      2      1
2. The activity and presenters were free of bias.  
  
4      3      2      1
3. The activity was applicable to my position.  
  
4      3      2      1
4. How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)  
  
4      3      2      1
5. Do you plan to change management strategies or patient care in your organization or practice based on the content presented?  
  
 Yes                       No
6. If yes, what changes do you plan to implement in management strategies or patient care in your organization or practice?  
  
\_\_\_\_\_  
  
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7. Did the content of the activity help in meeting your above goal?  
  
 Yes                       No

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Douglas Murphy Communications, Inc.

### Custom Article Reprints

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are available in print and electronic formats.

Contact Jeremy Williams,  
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804-527-1905 for reprints.

ISSN: 1094-1525. The *Journal of Managed Care Medicine* is published by NAMCP Medical Directors Institute. Corporate and Circulation offices: 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060; Tel (804) 527-1905; Fax (804) 747-5316. Editorial and Production offices: P.O. Box 71895, Richmond, VA 23255-1895; Tel (804) 387-7580; Fax (703) 997-5842. Advertising offices: Sloane Reed, 4435 Waterfront Drive Ste 101, Glen Allen, VA 23060 Tel (804) 527-1905, Fax (804) 747-5316. All rights reserved. Copyright 2018. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage or retrieval system, without written consent from the publisher. The publisher does not guarantee, either expressly or by implication, the factual accuracy of the articles and descriptions herein, nor does the publisher guarantee the accuracy of any views or opinions offered by the authors of said articles or descriptions.

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# JOURNAL of MANAGED CARE MEDICINE

The Official Journal of the  
NATIONAL ASSOCIATION OF MANAGED CARE PHYSICIANS MEDICAL DIRECTORS INSTITUTE

A Peer-Reviewed Publication

Dyslipidemia Monograph 2018

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# The Role of PCSK9 Inhibitors in Lowering LDL-C in Patients with Dyslipidemia: What Managed Care Needs to Know

Christopher P. Cannon, MD, Steven Nissen, MD, Gary Owens, MD

## Introduction

CARDIOVASCULAR DISEASE (CVD) IS THE leading cause of death, disability, and medical costs in the United States (U.S.), and it affects one in three Americans. Cardiovascular disease, accounts for nearly 836,546 deaths in the U.S.; that is about one of every three deaths in the U.S.<sup>1</sup> Approximately 2,300 Americans die of cardiovascular disease each day, an average of one death every 38 seconds. Importantly, CVD claims more lives each year than all forms of cancer and chronic lung disease combined. By 2030, the American Heart Association estimates 40.5 percent of the U.S. population will have some form of CVD.<sup>2</sup> The annual direct and indirect costs for CVD have been estimated at \$400 billion and \$200 billion respectively.<sup>2,3</sup> Direct medical costs of CVD are projected to triple by 2030.

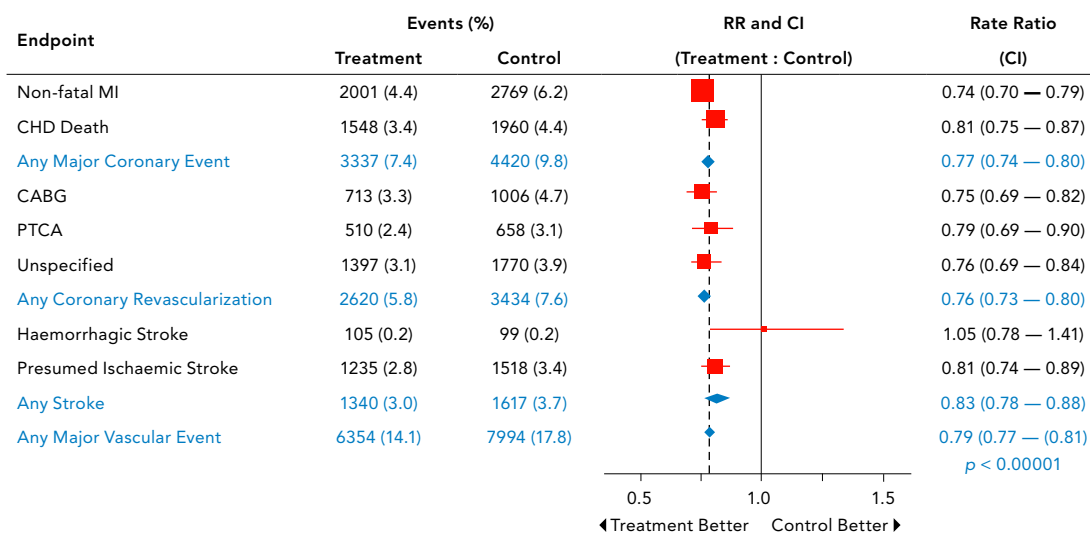
A major treatment for reducing risk of CVD (primary prevention) and reducing risk of cardiovascular (CV) events in those who already have atherosclerotic cardiovascular disease (ASCVD, secondary prevention) is lipid lowering. As more potent lipid-lowering therapies have reached the market, the management of dyslipidemia has changed significantly. There has been a steady march toward ever lower low-density lipoprotein cholesterol (LDL-C) targets. Trials, which started in the 1970s and were published in the 1980s, provided the first evidence that reducing LDL-C specifically provided CVD benefits. The seven-year LRC trial (cholestyramine vs placebo) reduced LDL-C from 215.6 mg/dL to 174.9 mg/dL (18.9% reduction), which reduced

coronary heart disease (CHD) death and non-fatal myocardial infarction (MI).<sup>4</sup> [Note: all LDL-C values presented for studies are median values achieved] This trial showed that even modest reductions in LDL-C reduced morbidity and mortality.

The use of intracoronary ultrasound to measure the cross-sectional area of plaque is a tool developed to provide evidence of benefits of significant LDL-C lowering in stabilizing and regressing coronary atherosclerotic plaques. It was used in the Reversal trial (atorvastatin 80 mg vs pravastatin 40 mg) which showed that high-dose, intensive statin therapy reduced LDL-C to 79 mg/dL versus 100 mg/dL with moderate-intensity dosing.<sup>5</sup> At an LDL-C of 110 mg/dL, there was unequivocal progression of coronary atherosclerosis (2.7%) compared with no change in the plaque with lower LDL-C. The ASTEROID trial, which achieved LDL-C of 60.8 mg/dL, actually showed regression of atherosclerosis.<sup>6</sup> Sixty-three percent of patients in this trial had regression in their coronary disease. LDL-C levels below 70 mg/dL appear to be necessary to regress plaque in those who already have atherosclerosis.

Providing additional evidence of the benefits of low LDL-C values, the Prove-IT trial (atorvastatin 80 mg, LDL-C 62 mg/dL vs pravastatin 40 mg, LDL-C 95 mg/dL) showed that intensive statin therapy reduced death and major CV events compared with moderate-intensity therapy.<sup>7</sup> A post-hoc analysis of the trial suggested that even lower LDL-C (<60 mg/dL) might be more beneficial.<sup>8</sup> The TNT trial (atorvastatin 80 mg, LDL-C 77 mg/dL vs atorvastatin 10

Exhibit 1: Effects on Major Vascular Events per 1 mmol/L (39mg/dL) LDL-C Reduction<sup>11</sup>



mg, LDL-C 110 mg/dL) showed a 22 percent reduction in major CV events.<sup>9</sup> More recently, even a weak LDL lowering agent, ezetimibe a cholesterol absorption inhibitor, has been shown to provide additional benefit when added to statin therapy in those with recent acute coronary syndrome (ACS) by reducing LDL-C further (69.5 mg/dL compared to 53.7 mg/dL).<sup>10</sup> The combination of ezetimibe and simvastatin provided a 2 percent absolute risk reduction (ARR) in CV death, MI, unstable angina, coronary revascularization, and stroke over seven years. Even small incremental reductions in LDL-C, regardless of how it is achieved, translate as a major benefit. The effect of LDL-C lowering on major vascular events from the Cholesterol Treatment Trialists Collaboration meta-analysis is shown in Exhibit 1.<sup>11</sup> Overall, it is well proven that getting LDL-C to low levels is beneficial in terms of morbidity and mortality and progression of atherosclerosis.

### PCSK9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme that regulates LDL receptor expression (LDL-R, Exhibit 2). Inhibition of PCSK9 prevents the degradation of the LDL-R on the surface of the hepatocyte and allows increased activity of the LDL-R to increase removal of LDL-C from circulation.<sup>12</sup> Carriers of a PCSK9 loss of function mutation naturally have less PCSK9 activity and thus have lower serum LDL-C than those without the mutation (~26%). African Americans with this mutation have a 28 percent lower LDL-C and 88 percent lower risk of CHD over their life-

time. Caucasians with the same mutation have a 15 percent lower LDL-C and 47 percent lower risk.<sup>13</sup> The benefit of this mutation occurs even in populations with a high prevalence of non-lipid-related cardiovascular risk factors.<sup>13</sup>

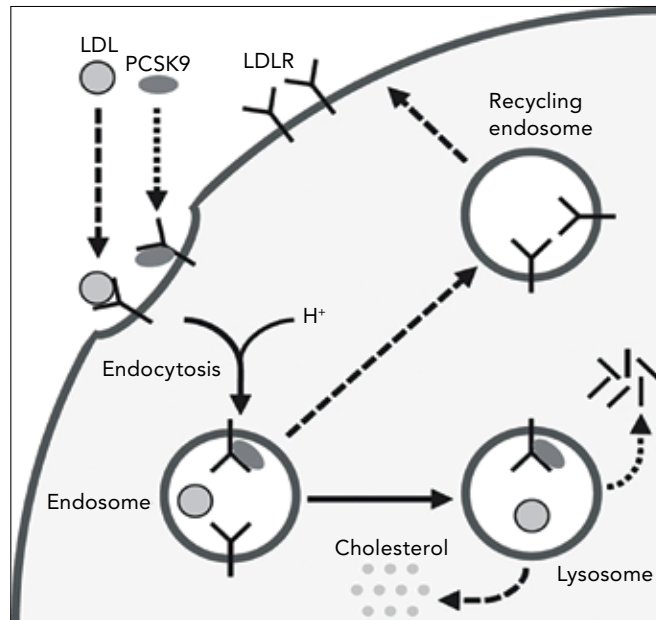
The first two PCSK9 inhibitors (PCSK9i) were approved by the FDA in 2015. Alirocumab (Praluent<sup>®</sup>) and evolocumab (Repatha<sup>®</sup>) are human monoclonal antibodies against PCSK9 which are given by subcutaneous injection. These are the most effective LDL-C lowering agents to date (50 – 70% as monotherapy or on a background of statin therapy).

Compared to placebo, evolocumab reduced LDL-C by 56 percent to 61 percent in subjects with heterozygous familial hyperlipidemia (HeFH).<sup>14</sup> Alirocumab reduced LDL-C 49 percent in a placebo controlled trial in a HeFH population.<sup>15</sup> Those with homozygous FH (HoFH) have much higher LDL-C values and develop CHD very early in life. In HoFH, evolocumab compared to placebo reduced LDL-C by 30.9 percent.<sup>16</sup>

Evolocumab in combination with a statin has also been shown to regress atherosclerosis by intracoronary ultrasound compared with statin therapy alone.<sup>17</sup> Sixty-four percent of the evolocumab/statin treated patients had regression. The LDL-C achieved with the combination of a statin and evolocumab was 36.6 mg/dL. In those subjects who at baseline had LDL-C less than 70 mg/dL, the LDL-C on the combination was 24.0 mg/dL and 81.2 percent had regression of atherosclerosis.

The initial FDA approval of the proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i)

Exhibit 2: PCSK9 and the LDL Receptor



was fairly narrow because the effect of this class on CV morbidity and mortality had not been determined. That changed with the publication of two outcomes trials which showed significant benefits. In a trial of evolocumab added to background statin compared to a statin alone (FOURIER), LDL-C of 30 mg/dL was achieved and a 15 percent relative risk reduction (RRR) and 2 percent ARR in CV death, MI, stroke, hospitalization for unstable angina or revascularization was shown for the combination.<sup>18</sup> There was a 20 percent RRR and 2 percent ARR in the secondary endpoint of CV death, MI, or stroke. The curves for primary and secondary endpoints began to separate after six months of therapy and continued to diverge during the 36-month study. There was a 16 percent RRR during the first year, which increased to 25 percent in years two and three. Thus, the longer people are treated to lower LDL-C levels the greater the incremental benefit. This has also been shown in the statin trials.<sup>11</sup> Persisting with aggressive LDL-C lowering is one of the keys to getting the best outcome with lipid lowering. Overall, there appears to be no lower threshold for benefit across a broad LDL-C range.<sup>11,18</sup> Even if someone starts out with LDL-C less than 70 mg/dL there are incremental benefits to further reduction. This tells us that only treating people with very high LDL-C is wrong.

The Odyssey Outcomes trial attempted to maxi-

mize the number of patients in a target range (LDL-C 25-50 mg/dL) and minimize the number below target by blindly titrating alirocumab (75 or 150 mg SC Q2W), or blindly switching to placebo (for LDL-C < 15 mg/dL) in a post-acute coronary syndrome (ACS) population.<sup>20</sup> Subjects in this trial had an episode of acute coronary syndrome within the prior 12 months and an LDL-C  $\geq 70$  mg/dL, non-high-density lipoprotein cholesterol  $\geq 100$  mg/dL, or apolipoprotein B  $\geq 80$  mg/dL on maximally tolerated statins. The majority of patients in this trial were on guideline-recommended post-ACS medications (aspirin, other antiplatelet agents, ACE-I/ARB, beta-blockers) in addition to the statin. Final data from this trial has not yet been published but was presented at a March 2018 American College of Cardiology (ACC) meeting. After a median follow-up of 2.8 years, LDL-C was 53.3 mg/dL in the alirocumab group and 101.4 mg/dL in the placebo group. The primary endpoint of major adverse cardiovascular events – the time to first occurrence of CHD death, nonfatal MI, unstable angina requiring hospitalization or ischemic stroke – was significantly lower in the alirocumab group versus the placebo group (9.5 vs. 11.1%, 24% RRR, 3.4% ARR).<sup>21</sup> There was not a statistically significant benefit on CHD death alone, but none was shown in the FOURIER trial either.

Statin intolerance has been a major barrier to



### Exhibit 3: FDA Approved and Emerging Indications for PCSK9 Inhibitors from Recent Trial Data<sup>17,18,20-23,35</sup>

#### Alirocumab

- Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD, who require additional lowering of LDL-C

#### Evolocumab

- Reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established CV disease.
- Adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C).
- Adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional lowering of LDL-C.

HeFH = heterozygous familial hyperlipidemia  
ASCVD = atherosclerotic cardiovascular disease  
LDL-C = low density lipoprotein cholesterol  
CV = cardiovascular  
HoFH = homozygous FH  
PAD = peripheral arterial disease  
ACS = acute coronary syndrome

#### Emerging Indications

- Statin intolerance
- Inadequate LDL lowering despite maximally tolerated statin dosing ± ezetimibe
- Progressive coronary disease despite aggressive lipid lowering
- High residual risk despite excellent background therapy with established treatments, including those with PAD
- Post-ACS on maximal statins with LDL-C higher than optimal

achieving adequate LDL-C reduction in many patients. Statin intolerance can be defined as adverse symptoms, signs and/or laboratory abnormalities attributed by the patient and/or provider to a statin and perceived by the patient to interfere with daily life activities. The PCSK9 inhibitors are an option for the statin intolerant patient. The tolerability of evolocumab was compared to ezetimibe in a trial where subjects had intolerable muscle symptoms or greater than 10 times the upper limit of normal creatinine kinase during a run in phase of atorvastatin. Evolocumab monotherapy reduced LDL-C by 53 percent (LDL-C 104 mg/dL) compared with 16.7 percent with ezetimibe monotherapy.<sup>22</sup> There was a very low discontinuation rate for muscle-related symptoms (1% with evolocumab, 6.8% with ezetimibe). A trial comparing alirocumab to ezetimibe found similar results.<sup>23</sup> Thus, patients, who are truly intolerant of statins because of muscle-related symptoms, can get effective LDL-C lowering safely with a PCSK9i.

Another group to target with PCSK9 inhibitors may be those with peripheral arterial disease (PAD). In the FOURIER trial, those with PAD, who have a very high risk of events, had a greater ARR in the primary endpoint with evolocumab compared with those who did not (3.5% vs 1.4%).<sup>21</sup> Additionally,

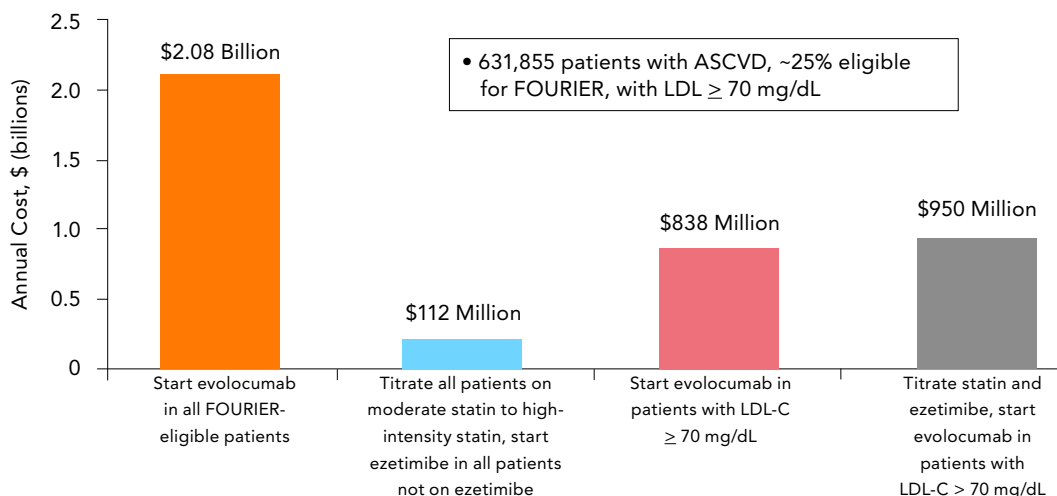
the rate of major limb events was also reduced (45% RRR). Major limb events include amputation, urgent revascularization, and acute limb ischemia. Exhibit 3 lists some emerging indications for PCSK9 inhibitors based on recent trials and the current FDA approved indications.

In general the PCSK9 inhibitors are well tolerated. In most trials, injection site reactions were the only adverse effect which were higher than the placebo group. The rate of new cases of diabetes does not appear to be increased nor are neurocognitive adverse effects an issue with the PCSK9i over the duration of the available trials.<sup>24,25</sup>

#### Cost Effectiveness

The big debate with the PCSK9 inhibitors is their price (~\$14,000/year before discounts and rebates) and whether they are cost effective. Early cost-effectiveness analyses of PCSK9 inhibitors were only based on benefits estimated from reductions in LDL-C that occurred in trials. An updated analysis using outcomes data from the FOURIER trial found that at current prices, the addition of a PCSK9i to statin therapy is estimated to provide an additional quality-adjusted life year of \$337,729 (2016 U.S. dollars).<sup>26</sup> The authors concluded that significant discounts would be necessary to meet conven-

**Exhibit 4: Modelled Costs with Different LDL-C Lowering Regimens in Veterans Affairs System<sup>29</sup>**



tional cost-effectiveness standards.

The Institute for Clinical and Economic Review (ICER) reported on PCSK9 inhibitors in 2015 and released an updated report in 2017 based on the FOURIER trial results. Extrapolating from the LDL-C level reductions, the 2015 cost-effectiveness analysis estimated a number needed to treat (NNT) of 28. Despite favorable assumptions, cost-effectiveness ratios for PCSK9i far exceed commonly accepted thresholds.<sup>27</sup> The updated ICER report in 2017 noted strong evidence of benefit for evolocumab in reducing heart attacks, strokes, and revascularization, but not unstable angina or CVD death in patients with clinical CVD on statin therapy.<sup>28</sup> This analysis gave evolocumab added to statin therapy an ICER rating of C+ (comparable or better) based on moderate certainty of a small net benefit compared to statin therapy alone.

A cost analysis from the Veterans Affairs medical system, applying the eligibility criteria of the FOURIER trial to their population, is shown in Exhibit 4.<sup>29</sup> This group found that 24.5 percent of their population with ASCVD would meet the criteria; only 49.9 percent of those eligible were on a high-intensity statin, 47.5 percent were on a moderate-intensity statin, and 2.6 percent were on statin/ezetimibe. The authors concluded that up-titration of standard therapy could lead to significant cost savings by decreasing eligibility for evolocumab by approximately 20 percent with high-intensity statins, by 50 percent with the addition of ezetimibe, or by approximately 60 percent with the combination of high-intensity statins and ezetimibe. Another analysis found that

68 percent of patients can get to an LDL of less than 70 with just a statin alone if the dose is appropriately intensified, about another 18 percent would reach goal with the addition of ezetimibe, and only 14 percent would need the addition of a PCSK9i.<sup>30</sup> Efforts to maximize statin and ezetimibe use would be augmented by concomitantly targeting improved adherence. Overall, this approach would limit PCSK9i use to those who do not achieve goal with a statin plus ezetimibe, if tolerated, and would minimize the overall cost impact.

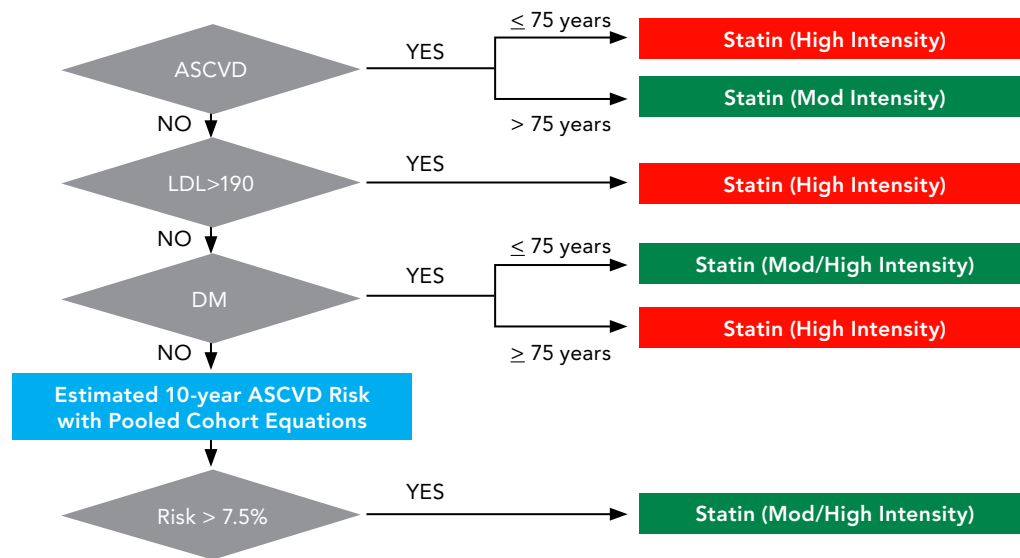
One group where treatment with PCSK9 inhibitors may be cost effective is those who have had a recent ACS event. Higher event rates in ACS patients drive potential for more favorable cost-effectiveness. In the IMPROVE-IT trial, there was a 21 percent event rate even at LDL-C values of 69 mg/dL at three years. Additionally, it is very expensive to treat patients who have an ACS episode; costs for post-ACS care are approximately twice the values used in the Arietta and colleagues' analysis.<sup>26</sup> Exhibit 5 shows the first year costs related to an ACS event.<sup>31,32</sup> Several years of PCSK9i therapy could be paid for by avoiding invasive cardiovascular procedures.

Another cost-effectiveness analysis found the value-based price range under a willingness-to-pay threshold of \$150,000/quality-adjusted life-year gained for evolocumab was \$11,990 (\$9,341 – \$14,833) to \$16,856 (\$12,903 – \$20,678) in ASCVD patients with baseline LDL-C levels greater than or equal to 70 mg/dL and 100 mg/dL, respectively.<sup>33</sup> This analysis showed that the expected value-based price for evolocumab is higher than its current an-

**Exhibit 5: First Year Financial Costs Related to ACS Events<sup>31,32</sup>**

	Direct Medical Costs	Short-Term Disability	Absenteeism	Total Costs
Medically Managed	\$34,087	\$6,048	\$9,826	\$49,961
PCI	\$52,673	\$9,221	\$9,460	\$71,354
CABG	\$86,914	\$17,355	\$14,960	\$119,209

**Exhibit 6: Recommendations for the Four Statin Benefit Groups<sup>34</sup>**



nual cost in this population, as long as the payer discount off the list price is greater than 20 percent.<sup>33</sup> This analysis did not specifically analyze data on only those patients who had a recent ACS event.

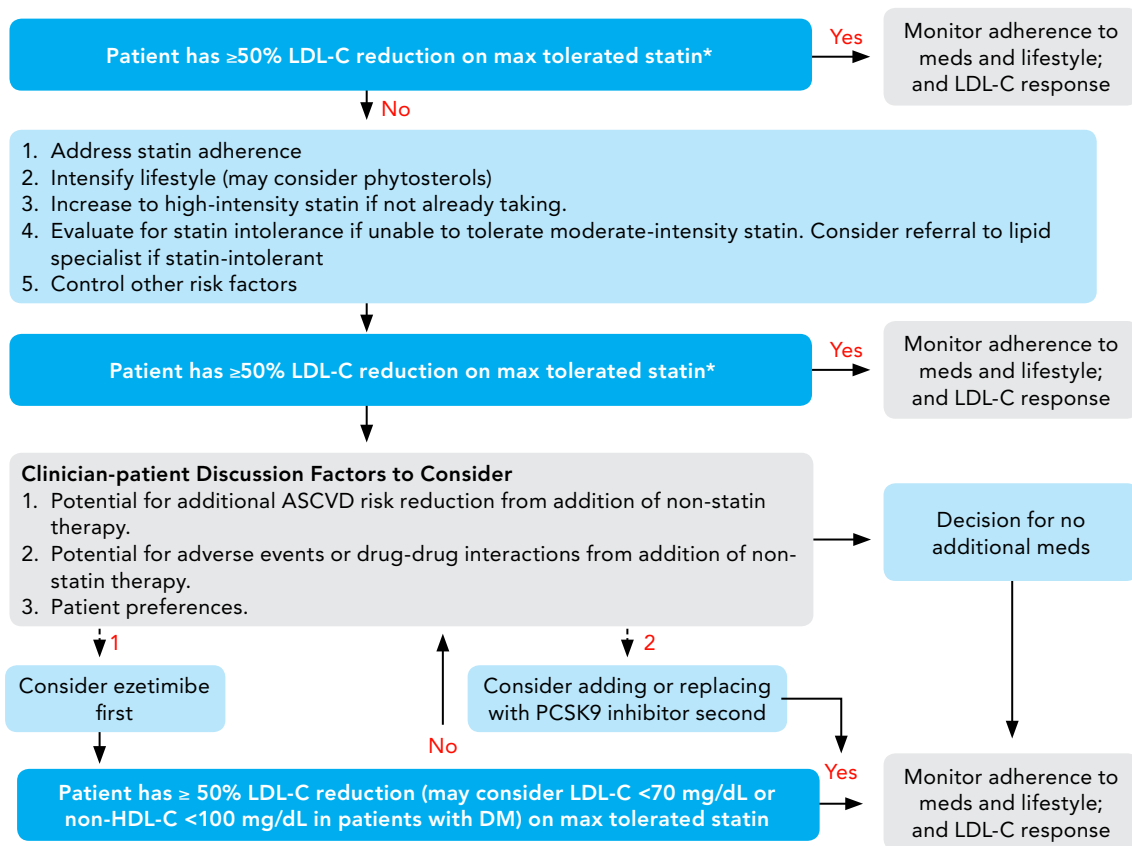
**Guideline-Directed Therapy**

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for lipid lowering were last fully updated in 2013, and they likely will be updated in 2018 – 2019. The 2013 guidelines emphasize that lifestyle modification remains a critical component of ASCVD reduction. The guidelines focused on four risk groups who are most likely to have benefit from statin therapy – patients with any form of clinical ASCVD; patients with primary LDL-C levels of 190 mg/dL or greater; patients with diabetes mellitus, 40 to 75 years of age, with LDL-C levels of 70 to 189 mg/dL; and patients

without diabetes, 40 to 75 years of age, with an estimated 10-year ASCVD risk greater than or equal to 7.5 percent (Exhibit 6).<sup>34</sup> Statins should be dosed at high and moderate intensity, if possible, with a goal of at least a 50 percent reduction in LDL-C. This iteration of the guidelines eliminated specific target LDL-C goals. The guidelines recommend specific non-statin therapies only in higher-risk patients who have inadequate response to statins or statin intolerance. High-dose statin therapy does require monitoring for adverse effects even more carefully than moderate dosing. One issue which has emerged with high-dose statin therapy is an increased incidence of the type 2 DM development.

In 2017, the ACC/AHA published a consensus document on the role of non-statin therapies for LDL-C lowering for patients who have less than 50 percent LDL-C reduction with statins.<sup>35</sup> The guide-

Exhibit 7: Patients with ASCVD with Comorbidities on Statin for 2° Prevention<sup>35</sup>



\*For patients with stable ASCVD without comorbidities, may consider LDL-C <100 mg/dL.  
For patients with ASCVD may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL in patients with DM

lines recommend that it is reasonable to consider the addition of either ezetimibe or a PCSK9i based on considerations of the additional percent LDL-C reduction desired, patient preferences, costs, route of administration, and other factors. Considerations that may favor the initial choice of ezetimibe include: patients who require < 25 percent additional lowering of LDL-C, patients with recent ACS < three months, cost considerations with recent availability of generic ezetimibe and future cost savings, ease of use as oral agent with low pill burden, patient preferences, and clinical variables that predict benefit from ezetimibe [heart failure, hypertension, age > 75 years, diabetes, stroke, CABG, PAD, eGFR < 60 ml/min/1.73 m<sup>2</sup>, and smoking]. If patients with clinical ASCVD and comorbidities require > 25 percent additional lowering of LDL-C, a PCSK9i may be preferred as the initial non-statin agent. The clinician/patient discussion should consider the extent of available scientific evidence for net ASCVD risk- reduction benefit, cost, administration by sub-

cutaneous injection, every 14-day or monthly dosing schedule, and storage requirements (refrigeration). Only the algorithm for secondary prevention is shown in Exhibit 7.<sup>35</sup>

### When to Treat

Some clinicians believe in treating lipids aggressively earlier in life when there is more to gain. In one analysis, long-term exposure to lower LDL-C was associated with a 54.5 percent (95% confidence interval: 48.8% to 59.5%) reduction in the risk of CHD for each mmol/L (38.7 mg/dL) lower LDL-C.<sup>36</sup> This represents a threefold greater reduction in the risk of CHD per unit lower LDL-C than that observed during treatment with a statin started later in life. The duration of current trials vastly underestimates the overall reduction in morbidity and mortality with treatment. The guidelines have not embraced the philosophy of early, aggressive treatment and recommend treatment only in those at higher risk.

### Safety of Very Low LDL-C Levels

There have been concerns over the years about the possibility of adverse effects, particularly neurocognitive, with very low LDL-C levels. At this point, no significant change in various adverse effects has been shown with lowering LDL-C to very low levels (< 30 mg/dL with statins, < 15 mg/dL with PCSK9i).<sup>37,38</sup> No difference in neurocognitive effects, gallbladder disease, or hemorrhagic stroke has been shown. It is important to note that physiological or “normal” LDL-C is likely 50 to 70 mg/dL, which is what is typically found in humans at birth and in primitive populations with low rates of CVD.<sup>39</sup> Yet, the average LDL-C level in the untreated Western population is approximately 130 mg/dL.<sup>39</sup> Extrapolation of data from meta-analyses of large-lipid lowering trials suggest that the incidence of cardiovascular events would approach zero if LDL-C were < 60 mg/dL in primary prevention and approximately 30 mg/dL in secondary prevention.<sup>39</sup>

### Managed Care

Managed care has clinical concerns about many aspects of managing CV risk in their populations. Specifically, with lipid-lowering therapy, these concerns include clinician lack of adherence with guideline-directed therapy, patient adherence with therapy, and the cost of the newer agents.

Unfortunately, patients with lipid disorders, even high-risk patients, are not always treated to guidelines. In one claims database study, 38.7 percent of patients with CHD, who had a CV event within the past year, were not prescribed a statin.<sup>40</sup> An analysis using data from the American College of Cardiology National Cardiovascular Data Registry-Practice Innovation and Clinical Excellence registry found significant practice variations in lipid-lowering prescribing. The proportion of patients with a starting LDL-C > 190 mg/dL receiving a statin, high-intensity statin, therapy associated with ≥50 percent LDL-C reduction, ezetimibe, or PCSK9i were 58.5 percent, 31.9 percent, 34.6 percent, 8.5 percent, and 1.5 percent, respectively.<sup>41</sup> Improving adherence with guideline-directed therapy should be one goal of managed care.

Patient adherence and persistence with lipid-lowering therapy is poor. Nonadherence with statin use has been reported to be 22 to 50 percent, depending on the population examined.<sup>42</sup> Only 26 percent of patients are considered adherent after five years of therapy. Being adherent and persistent makes a difference in outcomes. One trial found that patients who filled more than 90 percent of the prescribed doses began to achieve significant reductions in nonfatal CV events within one year.<sup>43</sup> Adherence

support and interventions are an important focus for managed care and providers to optimize outcomes from lipid-lowering therapy.

Given the cost of PCSK9 inhibitors and the lack of initial data on CV outcomes, most managed care plans instituted prior authorization requirements on prescribing when adding them to their formularies. Most payers implemented some or all of the following – step therapy through at least two statins, step therapy through a statin + ezetimibe, aggressive thresholds for LDL levels required to justify use, prescribing by a cardiologist, endocrinologist or lipidologist, and specialty tier placement.<sup>44</sup> Some large plans have also entered into value-based contracting with the PCSK9i manufacturers to minimize costs.<sup>45</sup>

Major barriers to prescribing the PCSK9 inhibitors include insurer processes, lack of provider documentation, and administrative burden. Patient barriers include high out-of-pocket copays. Though many lipid specialists, cardiovascular disease prevention experts, endocrinologists, and others prescribed the drugs on label, they were denied the majority of the time.<sup>46</sup> In one survey, only 30.9 percent of those prescribed a PCSK9i eventually received the agent.<sup>47</sup> The most common reasons for denial of a PCSK9i prescription from a recent survey by the National Lipid Association were not on insurance formulary, missing required medical documentation, and not on a maximum tolerated statin in patients with ASCVD.<sup>48</sup> The most common reasons for denial for a patient with FH were inadequate documentation of FH, not on a maximum tolerated statin, and not on formulary.<sup>48</sup> The high frequency of denials prompted the American Society for Preventive Cardiology (ASPC) to gather multiple stakeholder organizations, including the American College of Cardiology, National Lipid Association, American Association of Clinical Endocrinologists (AACE), and the FH Foundation, for two town hall meetings to identify access issues and implement viable solutions. They designed an easier method to provide this documentation to managed care through pre-printed documentation forms and appeal letters.<sup>46</sup>

### Conclusion

CVD continues to be a significant area of opportunity, as it affects one in three Americans and is a leading cause of death and a major cost driver. Mortality rates and costs are projected to keep increasing through 2030. The current ACC/AHA guidelines recommend statins for four benefit groups and adding non-statin agents such as ezetimibe and PCSK9 inhibitors if LDL-C is not sufficiently reduced. Achieving low LDL-C levels (< 50 mg/dL) has

been shown to be safe and significantly reduces the risk of cardiovascular events, particularly in high-risk ASCVD. Opportunities exist to optimize treatment and improve outcomes for patients by enhancing guideline adherence and medication adherence. Optimizing appropriate use of PCSK9 inhibitors continues to be a challenge for payers, and prescribing restrictions continue to be a challenge for providers. Clinicians and insurers need to integrate the new data on the PCSK9 inhibitors and offer them to patients at high CV risk. Being prudent and only using PCSK9 inhibitors after maximizing statins and ezetimibe in HeFH, HoFH, and clinical ASCVD is likely the most cost-effective way to utilize these agents.

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