

## REVIEW ARTICLE

# PCSK9 Inhibitors, The Most Significant Advance in Lipid Lowering Therapy Since Statins? A Literature Review

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## KEYWORDS:

Alirocumab  
Cardiology  
Evolocumab  
Lipid Lowering  
PCSK9 Inhibitor

**OBJECTIVE:** The purpose of this study was to evaluate efficacy, safety and cost of PCSK9 inhibitors.

**METHODS:** PubMed was used to search for literature regarding PCSK9 inhibitors up to May 1, 2018. Clinical trials, systematic reviews, meta-analyses and prescribing information were utilized for this review. Inclusion criteria was Phase II, III randomized control trials (RCT) and review articles comparing treatment of hypercholesterolemia in adults with and without PCSK9 inhibitors. All studies were completed from 2012-2017 and were conducted primarily in America.

**RESULTS:** Evolocumab and alirocumab are the only FDA approved PCSK9 inhibitors and have been shown to reduce baseline LDL-C by 50-60% in multiple clinical trials. Although there is no proven all-cause or cardiovascular mortality benefit associated with these drugs, there is a significant reduction in myocardial infarction (MI), stroke and coronary revascularization in treatment groups.

**DISCUSSION:** Low-density lipoprotein cholesterol (LDL-C) is a well characterized risk factor for cardiovascular disease (CVD). While hypercholesterolemia is often well controlled with statins, there remains a need for additional lipid lowering therapy in select patients. PCSK9 inhibitors represent a novel approach to lowering LDL-C in patients with familial hypercholesterolemia and clinical atherosclerotic cardiovascular disease (ASCVD) alone or in combination with other cholesterol lowering medications. PCSK9 inhibitors are well tolerated, with the most common side effects being local injection site reactions and flu-like symptoms. High cost remains the most significant obstacle for widespread use. PCSK9 inhibitors have a valuable role in the lipid lowering treatment algorithm with their full therapeutic potential yet to be realized.

## INTRODUCTION

Heart disease, with the most common type being coronary artery disease (CAD), remains the leading cause of death in the United States as of 2016 and has been so for the past 40 years, according to the CDC<sup>1</sup>. It is well known that elevated levels of low-density lipoprotein cholesterol (LDL-C) increase the risk of developing atherosclerotic cardiovascular disease (ASCVD). When atherosclerotic plaques occlude coronary vessels, it often results in ischemic heart disease and life-threatening myocardial infarctions. Primary care physicians are predominantly responsible for managing patients with elevated LDL-C and its comorbidities, making it essential for them to be aware of all advances in treatment of hypercholesterolemia. Statins have long been the mainstay of lipid lowering therapy and have been shown to decrease morbidity and mortality associated with cardiovascular

disease. Other adjunct agents such as fenofibrates, bile acid resins, omega 3 fatty acids and niacin are frequently used in combination with statins but have not shown consistent additional cardiac risk reduction in clinical trials<sup>2</sup>. The most recent lipid lowering guidelines from the *American College of Cardiology/American Heart Association (ACC/AHA)* in 2014 do not recommend initiating statin therapy based on absolute LDL-C levels, but rather calculating the 10-year risk of cardiac events defined as myocardial infarction (MI) or cerebrovascular accident (CVA). The 10-year risk is based on the following risk factors: sex, race, smoking status, presence of diabetes, high density lipoprotein cholesterol (HDL) level, total cholesterol level and systolic blood pressure. In general, statin therapy is indicated when the 10-year risk is > 7.5%<sup>3</sup>. Overall, the ACC recommends aggressively lowering LDL-C below 70 mg/dL in patients with high risk of developing adverse CV events<sup>4</sup>. Even with maximal statin therapy there is strong evidence to show that residual risk for cardiovascular disease (CVD) remains, especially in patients who are statin intolerant and do not have adequate reduction in LDL-C<sup>2</sup>. As early as 2007, inhibition of an enzyme called proprotein convertase subtilisin/kexin type 9 (PCSK9) was being proposed as a target for lipid lowering therapy<sup>5</sup>. Nearly a decade of research and clinical trials later resulted in the FDA approval

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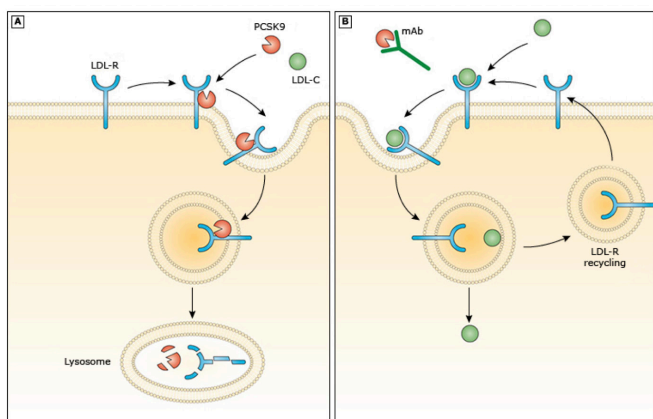
of the first PCSK9 inhibitors in 2015, Repatha (evolocumab) and Praluent (alirocumab) both indicated for the treatment of hypercholesterolemia<sup>6,7</sup>. This article aims to explore the role of PCSK9 inhibitors in lipid lowering therapy and investigate their efficacy, safety and cost effectiveness.

## MECHANISM OF ACTION AND PHARMACOLOGY

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease produced primarily in the liver. PCSK9 binds to the low-density lipoprotein receptor (LDL-R) on the hepatocyte cell surface causing degradation of the LDL-R and subsequent elevated plasma levels of LDL-cholesterol (LDL-C). PCSK9 inhibitors, including alirocumab and evolocumab, are fully humanized monoclonal antibodies against the PCSK9 enzyme. Once bound, degradation of the enzyme follows and results in decreased PCSK9 available to bind LDL-R. The outcome is more recycled LDL-R expressed on the surface of hepatocytes and less degradation of the receptor, allowing the liver to remove more LDL-C from circulation and lower its plasma levels (*Figure 1*). PCSK9 inhibitors bind quickly, inactivating the PCSK9 enzyme within 4-8 hours of the first subcutaneous injection. They prevent availability of PCSK9 for 2-3 weeks following administration. Regarding drug interactions, statins have been shown to increase PCSK9 levels making its inhibition an effective target for further lowering of LDL-C. Combination therapy with statin and PCSK9 inhibitor is considered safe and produces a synergistic reduction of serum LDL-C. Since monoclonal antibodies are eliminated through the reticuloendothelial system, dose adjustment in patients with renal or hepatic impairment is not necessary<sup>8</sup>.

### FIGURE 1:

Mechanism of action for PCSK9 inhibitors



[A] PCSK9 binds to LDL-R and promotes lysosomal degradation

[B] PCSK9 inhibitor is a monoclonal antibody (mAb) that blocks the action of PCSK9

## EFFICACY OF PCSK9 INHIBITORS

An initial study in 2009 targeting PCSK9 showed success in lowering LDL-C levels<sup>9</sup>. Phase I and II trials followed demonstrating adequate safety and up to 70% reduction in LDL-C at high dose

administration in addition to substantially increasing high density lipoprotein (HDL) and decreasing total cholesterol, triglycerides, apolipoprotein B and lipoprotein(a)<sup>10</sup>. Extensive phase III trials have since been conducted with promising results, consistently reducing baseline LDL-C 50-60% over a wide spectrum of pretreatment LDL-C levels, CVD risk, as monotherapy, adjunct to statin therapy and in patients with familial hypercholesterolemia (*Table 1*). Of note, it is estimated that 15-20% of patients being treated with statins suffer from intolerance secondary to muscle aches, pains, cramps or weakness<sup>33</sup>. In the GAUSS-2,3 clinical trials, PCSK9 inhibitors were shown to have superior LDL-C lowering efficacy (52.8% reduction LDL-C) in patients with clinically diagnosed statin intolerance compared to treatment with ezetimibe (16.7% reduction LDL-C). Furthermore, fewer patients had to discontinue evolocumab therapy due to associated adverse muscular events (0.7%) versus ezetimibe (6.8%)<sup>17,18</sup>. It is important to recognize that evolocumab has recently been FDA approved for secondary prevention of CV events in patients with established CVD, while this indication was denied for ezetimibe<sup>34,35</sup>. The FOURIER phase III RCT completed in 2016 recruited 27,564 patients 40-85 years old with known ASCVD, LDL-C > 70 mg/dL undergoing statin therapy and compared outcomes with evolocumab versus placebo. Those treated with evolocumab showed a 59% decrease in baseline LDL-C in addition to a 15% reduction in primary end points of cardiovascular death, MI, coronary revascularization, unstable angina and stroke. Despite this, there was no benefit in all-cause mortality (p=0.54) or cardiovascular mortality (p=0.62)<sup>11</sup>. One meta-analysis made up of 35 RCTs looking at all-cause and cardiovascular mortality benefits gained from treatment with PCSK9 inhibitor compared to no treatment with PCSK9 inhibitor showed similar results. Inhibition of PCSK9 was not associated with a statistically significant change in either outcome (all-cause mortality=0.3% reduction, p=0.12, cardiovascular mortality=0.2% reduction, p=0.95). However, multiple RCTs included in the meta-analysis showed a statistically significant reduction in myocardial infarction (MI) (1.3% reduction, p<0.001), stroke (0.4% reduction, p=0.02) and coronary revascularization (1.6% reduction, p<0.001) with PCSK9 inhibitor therapy<sup>36</sup>. The efficacy of PCSK9 inhibitors has been addressed by the American College of Cardiology in a 2016 expert consensus decision pathway for treatment of hypercholesterolemia with non-statin therapies. It stated PCSK9 inhibitors should be considered first or second line treatment for patients with clinical ASCVD or a baseline LDL-C > 190 mg/dL not due to secondary modifiable etiology who have not reached an ideal reduction in LDL-C on maximum tolerated statin (<50% or <70-100 mg/dL)<sup>37</sup>. According to Navarese et al, more intensive compared with less intensive LDL-C lowering therapy correlates with greater risk reduction of total and cardiovascular mortality (7.08% more intensive therapy vs 7.70% low intensive therapy) in patients with elevated baseline LDL-C levels > 100 mg/dL. The systematic review/meta-analysis defined more intensive therapy as statin in combination with PCSK9 inhibitor and less intensive therapy as statin monotherapy or combination of statin and ezetimibe. This substantiates a significant cardiovascular mortality benefit with use of PCSK9 inhibitors in patients with elevated baseline LDL-C > 100 mg/dL<sup>38</sup>.

**TABLE 1:**

Phase III clinical trials for Evolocumab and Alirocumab

STUDY	DRUG AND DOSE	DESCRIPTION	NUMBER OF PATIENTS	POPULATION	WEEKS	BASELINE E. LDL	MEAN % LDL LOWERING
FOURIER <sup>11</sup>	Evolocumab 420 mg q4w/140 mg q2w	Maximum statin vs placebo	27,564	HC	48	92	59
YUKAWA II <sup>12</sup>	Evolocumab 420 mg q4w/140 mg q2w	Statin therapy vs placebo	404	HC	12	128	67
MENDEL-2 <sup>13</sup>	Evolocumab 420 mg q4w/140 mg q2w	Monotherapy vs ezetimibe and placebo	614	HC	12	140-144	55-57
DESCARTES <sup>14</sup>	Evolocumab 420 mg q4w	Long term efficacy/ tolerability atorvastatin 10-80 + ezetimibe	901	HC	52	104 (95-120)	55-57
RUTHERFORD-2 <sup>15</sup>	Evolocumab 420 mg q4w/140 mg q2w	LDL-C goal reached in HeFH with statin	331	HeFH	12	151-161	59-61
LAPLACE-2 <sup>16</sup>	Evolocumab 420 mg q4w/140 mg q2w	Combination with different statins vs ezetimibe and placebo	2067	HC	12	108	55-76
GAUSS-2 <sup>17</sup>	Evolocumab 420 mg q4w/140 mg q2w	Statin intolerance vs ezetimibe	307	HC-statin intolerant	12	192-195	53-56
GAUSS-3 <sup>18</sup>	Evolocumab 420 mg q4w	Statin intolerance vs ezetimibe	511	HC-statin intolerant	24	212-219	53
TESLA PART B <sup>19</sup>	Evolocumab 420 mg q4w	HoFH on stable lipid lowering therapy vs placebo	49	HoFH	12	348	30.9
TAUSSIG <sup>20</sup>	Evolocumab 420 mg q4w/140 mg q2w	Homozygous FH statin + ezetimibe, open label	94	HoFH	12	321	20.9
ODYSSEY ALTERNATIVE <sup>21</sup>	Alirocumab 75 mg q2w/up-titration 150 mg q2w	Statin intolerance vs ezetimibe	361	HC-statin intolerant	24	191.3	45
ODYSSEY JAPAN <sup>22</sup>	Alirocumab 75 mg q2w/up-titration 150 mg q2w	Maximum statin therapy vs placebo	216	HC	52	141.2	62.5
ODYSSEY OPTIONS I <sup>23</sup>	Alirocumab 75 mg q2w/up-titration 150 mg q2w	High intensity statin vs ezetimibe	355	HC	24	105.1	44-54
ODYSSEY OPTIONS II <sup>24</sup>	Alirocumab 75 mg q2w/up-titration 150 mg q2w	High intensity statin vs ezetimibe	305	HC	24	111.3	36.3-50.6
ODYSSEY FH I <sup>25</sup>	Alirocumab 75 mg q2w/up-titration 150 mg q2w	HeFH vs ezetimibe	486	HeFH	24	145	58
ODYSSEY FH II <sup>25</sup>	Alirocumab 75 mg q2w/up-titration 150 mg q2w	HeFH vs ezetimibe	249	HeFH	24	135	51
ODYSSEY-High FH <sup>26</sup>	Alirocumab 150 mg q2w	HeFH on statin vs placebo	106	HeFH	24	196-201	46
ODYSSEY-COMBO I <sup>27</sup>	Alirocumab 75 mg q2w/up-titration 150 mg q2w	Hypercholesterolemia vs placebo	316	HC	24	95-100	48
ODYSSEY-COMBO II <sup>28</sup>	Alirocumab 75 mg q2w/up-titration 150 mg q2w	High CVD risk with ezetimibe vs placebo/ ezetimibe	707	HC	24	105-109	51
ODYSSEY CHOICE I <sup>29</sup>	Alirocumab 75 mg q2w/up-titration 150 mg q2w	Maximum statin or statin intolerant vs placebo	803	HC	24	112-148	52 (no statin) 59 (+ statin)
ODYSSEY CHOICE II <sup>30</sup>	Alirocumab 75 mg q2w/up-titration 150 mg q2w b	Combination with ezetimibe or fenofibrate or as monotherapy vs placebo	233	HC-statin intolerant	24	154-164	56
ODYSSEY LONG TERM <sup>31</sup>	Alirocumab 150 mg q2w	Maximum statin therapy vs placebo	2341	HC	78	122.4	62
ODYSSEY MONO <sup>32</sup>	Alirocumab 75 mg q2w/up titration 150mg q2w	Monotherapy vs ezetimibe	103	HC	24	139.7	47.2

CVD = cardiovascular disease; HC=Hypercholesterolemia; FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; YUKAWA II= Study of LDL-Cholesterol Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients with Advanced Cardiovascular Disease Risk; MENDEL-2=Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels-2; DESCARTES = Durable Effect of PCSK9 Antibody Compared With Placebo Study; Rutherford-2=Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder Study-2; Laplace-2=LDL-C Assessment w/ PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy-2; GAUSS-2 = Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-2; GAUSS-3 = Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-3; HeFH = heterozygous familial hypercholesterolemia; HoFH= homozygous familial hypercholesterolemia; TESLA PART B= Trial Evaluating PCSK9 Antibody in Subjects With LDL Receptor Abnormalities Part B; LDL-C = low-density lipoprotein cholesterol; TAUSSIG = Trial Assessing Long Term Use of PCSK9 Inhibition in Subjects With Genetic LDL Disorders ODYSSEY ALTERNATIVE= Efficacy and Safety of Alirocumab vs Ezetimibe in Statin-Intolerant patients, with a Statin Rechallenge Arm; ODYSSEY JAPAN= Efficacy and Safety of Alirocumab in Japanese Patients with Heterozygous Familial Hypercholesterolemia or at High Cardiovascular Risk With Hypercholesterolemia Not Adequately Controlled With Statins; ODYSSEY OPTIONS I, II=Alirocumab as Add-On to Atorvastatin Versus Other Lipid Treatment Strategies I and II; ODYSSEY FH I,II= Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia Not Adequately Controlled With Their Lipid-Modifying Therapy; ODYSSEY-High FH = Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia; ODYSSEY COMBO I = Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With High Cardiovascular Risk and Hypercholesterolemia; ODYSSEY COMBO II = Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe on Top of Statin in High Cardiovascular Risk Patients With Hypercholesterolemia; ODYSSEY CHOICE I = Study to Evaluate the Efficacy and Safety of an Every Four Weeks Treatment Regimen of Alirocumab (REGN727/ SAR236553) in Patients With Primary Hypercholesterolemia; ODYSSEY CHOICE II = Phase III Study To Evaluate Alirocumab in Patients With Hypercholesterolemia Not Treated With a Statin; ODYSSEY LONG TERM= Long-term Safety and Tolerability of Alirocumab SAR236553 (REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in High Cardiovascular Risk Patients With Hypercholesterolemia; ODYSSEY MONO= Efficacy and Safety of Alirocumab Versus Ezetimibe in Patients With Hypercholesterolemia

## PCSK9 INHIBITORS IN LIPID LOWERING THERAPY

Current indications from the FDA for the use of PCSK9 inhibitors evolocumab and alirocumab in lipid lowering therapy are as follows: an adjunct to diet, alone or in combination with maximum tolerated dose of statin for treatment of adult patients with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) who require additional reduction of LDL-C. Evolocumab is also used for the treatment of homozygous familial hypercholesterolemia (HoFH) for additional lowering of LDL-C. In adults with known cardiovascular disease, PCSK9 inhibitors are indicated as preventative therapy to reduce risk of MI, coronary revascularization and stroke. The only known contraindication for use of evolcumab and alirocumab is serious hypersensitivity reactions (urticaria, rash) occurring with administration that cannot be tolerated by patients<sup>6,7</sup>.

## SAFETY AND DOSING INFORMATION

Both FDA approved PCSK9 inhibitors are administered as subcutaneous injections with variable dosing. Repatha (evolocumab) is formulated into a single-use prefilled autoinjector 140 mg/mL dosed every 2 weeks or a single-use on-body infusor with a prefilled cartridge 420 mg/3.5 mL dosed once monthly [6]. Praluent (alirocumab) is also formulated as a single-dose prefilled pen autoinjector with 75 mg/ml or 150 mg/ml. Either dose can be administered every two weeks although the manufacturer recommends starting with the 75 mg/ml dose and titrating up as necessary. Alternatively, 300 mg/2mL can be dosed every 4 weeks as two consecutive injections at different sites on the body, recommended injection sites include thighs, stomach and upper arms<sup>7</sup>. The most common side effects of both drugs are nasopharyngitis, flu or flu-like symptoms, common cold symptoms and local injection site reactions including erythema/redness, itching, swelling, pain and tenderness. Transaminitis, hyperglycemia and neurocognitive events such as confusion and memory impairment are other adverse events associated

with these drugs<sup>6,7</sup>. A recent meta-analysis made up of 35 RCTs extensively characterized the safety profile of PCSK9 inhibitors. Neurocognitive adverse events defined as memory loss and confusion was analyzed over 21 RCTs comparing PCSK9 inhibitors with placebo. There was no statistically significant change in neurocognitive adverse events associated with PCSK9 inhibitors (1.2% incidence with and without PCSK9 inhibitor therapy,  $p=0.37$ ). In the context of diabetes mellitus (DM), there was no statistically significant change in newly manifested or worsening of preexisting DM (0.3% increased incidence with PCSK9 inhibitor therapy,  $p=0.32$ ). Other adverse events studied included increased creatine kinase, increased alanine or aspartate aminotransferase, myalgias or treatment-emergent serious adverse events. Compared to placebo, PCSK9 inhibitors were associated with fewer elevations of creatine kinase. There was no statistically significant increase in any of the other adverse events described above as well<sup>36</sup>.

## COST AND VALUE

The efficacy and benefits of PCSK9 inhibitors in CVD has been well established, but what about the cost and accessibility to patients? Priced at over \$14,000 in the US and \$5580 in the UK annually, affordability is a significant barrier to treatment. Initially, many patients in the US were provided financial assistance for PCSK9 inhibitor therapy from the Patient Access Network (PAN) foundation funded by pharmaceutical companies. Much of this financial aid has since decreased and patients are now responsible for significantly higher copays<sup>39</sup>. Compared to the cost of generic statin therapy at \$48-120 annually and newer brand name agents like Livalo (pitavastatin) priced at \$3840 yearly, these novel medications are quite a bit more expensive. Ezetimibe, a non-statin therapy often compared with PCSK9 inhibitors, has now become available in generic form. It ranges in cost from \$552 to \$2544 annually, also significantly cheaper than PCSK9 inhibitor therapy<sup>4</sup>. In addition, coverage by healthcare plans is often difficult to obtain, with payer rejections upwards of 80% for first time prescriptions and overall approvals of only 40%.

A potential solution to the high out of pocket costs PCSK9 inhibitors place on patients is utilization of specialty pharmacy programs. Specialty pharmacy programs are found primarily at large medical institutions that are sites for research on pharmaceutical usage and cost control. The data collected from these programs are relayed to the FDA who can expand access to specialty drugs by expediting approvals, making it less difficult for patients that will benefit most from these medications to be started on therapy<sup>39</sup>. Considering the high financial burden that major adverse cardiovascular events (MACE) place on the healthcare system, it can be argued that a medication that decreases these events is worth the cost. The widespread benefit of PCSK9 inhibitors will likely not be realized until they are more readily available to patients and more affordable for third-party payers. Responses from physicians and patients alike about the use of alirocumab has been positive as described in clinical trials by Roth et al. Physicians and patients stated devices were easy to operate, with the majority of patients willing to self-inject after an initial demonstration and counseling. The study was limited by patients injecting the device into a prosthetic pad rather than themselves in order to assess their willingness to use the device. A brief survey was filled out after the finishing the practice exercise bringing into question the validity of the feedback versus actual administration of the medication. Out of the 200 physicians selected for this study, 99 were primary care physicians further highlighting the importance of using PCSK9 inhibitors in a primary care setting, rather than referring to subspecialties for treatment<sup>40</sup>.

## CONCLUSION

The high morbidity and mortality associated with atherosclerotic cardiovascular disease (ASCVD) are being driven in large part by hyperlipidemia, specifically elevated LDL-C. Statin therapy remains the gold standard for treatment of hypercholesterolemia due to its LDL-C lowering capabilities and proven CVD risk reduction. However, there remains a significant patient population that does not reach adequate LDL-C treatment goals with statins alone or combination therapy or who are completely statin intolerant. PCSK9 inhibitors offer a new approach to lipid lowering therapy that have been shown to reduce LDL-C levels by 50-60% in multiple clinical trials. These drugs have also proven to significantly reduce MI, stroke and coronary revascularization in treatment groups. They are well tolerated according to current data and do not cause intolerance secondary to myalgias typical of statins. The definitive clinical role of PCSK9 inhibitors must be based on LDL-C reduction, CVD events reduction, long-term safety, tolerability versus their high annual cost of \$14,000 in the US, insurance coverage and overall benefit when added to conventional therapies. Current data are promising and suggests these drugs may be the greatest advance in lipid lowering therapy since statins. Advantages and disadvantages of PCSK9 inhibitors are summarized in *Table 2*.

**TABLE 2:**

Advantages and Disadvantages of PCSK9 inhibitors

ADVANTAGES
<ul style="list-style-type: none"> <li>Consistently lowers LDL-C by 50-60% in multiple phase III randomized control trials<sup>36</sup></li> <li>Increases HDL, decreases triglycerides and total cholesterol<sup>10</sup></li> <li>Significantly reduces MI, coronary revascularization and stroke in patients with clinical ASCVD and familial hypercholesterolemia<sup>36</sup></li> <li>Evolocumab is FDA approved for secondary prevention of MI, coronary revascularization and stroke in patients with established cardiovascular disease<sup>34</sup></li> <li>Few adverse effects associated, effective treatment option for patients with statin intolerance</li> <li>Can be used as monotherapy or in combination with other lipid lowering medications</li> </ul>
DISADVANTAGES
<ul style="list-style-type: none"> <li>High annual cost, \$14,000 US and \$5580 UK<sup>39</sup></li> <li>Most third-party payers will not provide coverage</li> <li>Only available as subcutaneous injection, may not be tolerated by some patients</li> <li>Has not been proven to reduce all cause or cardiovascular mortality<sup>36</sup></li> </ul>

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No relevant financial affiliations

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