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.
of the first PCSK9 inhibitors in 2015, Repatha (evolocumab) and Praluent (alirocumab) both indicated for the treatment of hypercholesterolemia. This article aims to explore the role of PCSK9 inhibitors in 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.

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.

FIGURE 1:
Mechanism of action for PCSK9 inhibitors

[Panel A] PCSK9 binds to LDL-R and promotes lysosomal degradation
[Panel 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. 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). 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. 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%)17,18. 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. 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)19. 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. 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)20. 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/dL21.
### TABLE 1:

Phase III clinical trials for Evolocumab and Alirocumab

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DRUG AND DOSE</th>
<th>DESCRIPTION</th>
<th>NUMBER OF PATIENTS</th>
<th>POPULATION</th>
<th>WEEKS</th>
<th>BASELINE E. LDL</th>
<th>MEAN % LDL LOWERING</th>
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<tbody>
<tr>
<td>FOURIER31</td>
<td>Evolocumab 420 mg q4w/140 mg q2w</td>
<td>Maximum statin vs placebo</td>
<td>27,564</td>
<td>HC</td>
<td>48</td>
<td>92</td>
<td>59</td>
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<tr>
<td>YUKAWA II32</td>
<td>Evolocumab 420 mg q4w/140 mg q2w</td>
<td>Statin therapy vs placebo</td>
<td>404</td>
<td>HC</td>
<td>12</td>
<td>128</td>
<td>67</td>
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<tr>
<td>MENDEL-233</td>
<td>Evolocumab 420 mg q4w/140 mg q2w</td>
<td>Monotherapy vs ezetimibe and placebo</td>
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<td>HC</td>
<td>12</td>
<td>140-144</td>
<td>55-57</td>
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<tr>
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<td>Long term efficacy/ tolerability atorvastatin 10-80 + ezetimibe</td>
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<td>52</td>
<td>104 (95-120)</td>
<td>55-57</td>
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<tr>
<td>RUTHERFORD-235</td>
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<td>LDL-C goal reached in HoFH with statin</td>
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<td>HeFH</td>
<td>12</td>
<td>151-161</td>
<td>59-61</td>
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<tr>
<td>LAPLACE-236</td>
<td>Evolocumab 420 mg q4w/140 mg q2w</td>
<td>Combination with different statins vs ezetimibe and placebo</td>
<td>2067</td>
<td>HC</td>
<td>12</td>
<td>108</td>
<td>55-76</td>
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<td>GAUSS-237</td>
<td>Evolocumab 420 mg q4w/140 mg q2w</td>
<td>Statin intolerance vs ezetimibe</td>
<td>307</td>
<td>HC-statin intolerant</td>
<td>12</td>
<td>192-195</td>
<td>53-56</td>
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<td>GAUSS-338</td>
<td>Evolocumab 420 mg q4w</td>
<td>Statin intolerance vs ezetimibe</td>
<td>511</td>
<td>HC-statin intolerant</td>
<td>24</td>
<td>212-219</td>
<td>53</td>
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<td>TESLA PART B39</td>
<td>Evolocumab 420 mg q4w</td>
<td>HoFH on stable lipid lowering therapy vs placebo</td>
<td>49</td>
<td>HoFH</td>
<td>12</td>
<td>348</td>
<td>30.9</td>
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<td>TAUSIG40</td>
<td>Evolocumab 420 mg q4w/140 mg q2w</td>
<td>Homozygous FH statin + ezetimibe, open label</td>
<td>94</td>
<td>HoFH</td>
<td>12</td>
<td>321</td>
<td>20.9</td>
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<tr>
<td>ODYSSEY ALTERNATIVE41</td>
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<td>Statin intolerance vs ezetimibe</td>
<td>361</td>
<td>HC-statin intolerant</td>
<td>24</td>
<td>191.3</td>
<td>45</td>
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<td>ODYSSEY JAPAN42</td>
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<td>Maximum statin therapy vs placebo</td>
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<td>HC</td>
<td>52</td>
<td>141.2</td>
<td>62.5</td>
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<td>ODYSSEY OPTIONS I43</td>
<td>Alirocumab 75 mg q2w/up-titration 150 mg q2w</td>
<td>High intensity statin vs ezetimibe</td>
<td>355</td>
<td>HC</td>
<td>24</td>
<td>105.1</td>
<td>44-54</td>
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<tr>
<td>ODYSSEY OPTIONS II44</td>
<td>Alirocumab 75 mg q2w/up-titration 150 mg q2w</td>
<td>High intensity statin vs ezetimibe</td>
<td>305</td>
<td>HC</td>
<td>24</td>
<td>111.3</td>
<td>36.3-50.6</td>
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<td>ODYSSEY FH I45</td>
<td>Alirocumab 75 mg q2w/up-titration 150 mg q2w</td>
<td>HeFH vs ezetimibe</td>
<td>486</td>
<td>HeFH</td>
<td>24</td>
<td>145</td>
<td>58</td>
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<td>ODYSSEY FH II46</td>
<td>Alirocumab 75 mg q2w/up-titration 150 mg q2w</td>
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<td>HeFH</td>
<td>24</td>
<td>135</td>
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<td>ODYSSEY High FH47</td>
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<td>HeFH on statin vs placebo</td>
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<td>HeFH</td>
<td>24</td>
<td>196-201</td>
<td>46</td>
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<tr>
<td>ODYSSEY-COMBO I48</td>
<td>Alirocumab 75 mg q2w/up-titration 150 mg q2w</td>
<td>Hypercholesterolemia vs placebo</td>
<td>316</td>
<td>HC</td>
<td>24</td>
<td>95-100</td>
<td>48</td>
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<tr>
<td>ODYSSEY-COMBO II49</td>
<td>Alirocumab 75 mg q2w/up-titration 150 mg q2w</td>
<td>High CVD risk with ezetimibe vs placebo/ ezetimibe</td>
<td>707</td>
<td>HC</td>
<td>24</td>
<td>105-109</td>
<td>51</td>
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<td>ODYSSEY CHOICE I50</td>
<td>Alirocumab 75 mg q2w/up-titration 150 mg q2w</td>
<td>Maximum statin or statin intolerant vs placebo</td>
<td>803</td>
<td>HC</td>
<td>24</td>
<td>112-148</td>
<td>52 (no statin)</td>
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<td>ODYSSEY CHOICE II51</td>
<td>Alirocumab 75 mg q2w/up-titration 150 mg q2w</td>
<td>Combination with ezetimibe or fenofibrate or as monotherapy vs placebo</td>
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<td>HC-statin intolerant</td>
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<td>154-164</td>
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<tr>
<td>ODYSSEY LONG TERM52</td>
<td>Alirocumab 150 mg q2w</td>
<td>Maximum statin therapy vs placebo</td>
<td>2341</td>
<td>HC</td>
<td>78</td>
<td>122.4</td>
<td>62</td>
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<td>ODYSSEY MONO53</td>
<td>Alirocumab 75 mg q2w/up-titration 150mg q2w</td>
<td>Monotherapy vs ezetimibe</td>
<td>103</td>
<td>HC</td>
<td>24</td>
<td>139.7</td>
<td>47.2</td>
</tr>
</tbody>
</table>
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; 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

PCS9 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 kinded contraindication for use of evolocumab and alirocumab is serious hypersensitivity reactions (urticaria, rash) occurring with administration that cannot be tolerated by patients6,7. 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 well8,9.

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 infusion 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 arms1. 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 drugs6,7. 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 well8,9.

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 copays8,9. 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. 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. 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.

**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 expand 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 US and $5580 UK. Most third-party payers will not provide coverage. Only available as subcutaneous injection, may not be tolerated by some patients.Has not been proven to reduce all cause or cardiovascular mortality. Also 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.

**TABLE 2:**

Advantages and Disadvantages of PCSK9 inhibitors

**ADVANTAGES**

- Consistently lowers LDL-C by 50-60% in multiple phase III randomized control trials.
- Increases HDL, decreases triglycerides and total cholesterol.
- Significantly reduces MI, coronary revascularization and stroke in patients with clinical ASCVD and familial hypercholesterolemia.
- Evolocumab is FDA approved for secondary prevention of MI, coronary revascularization and stroke in patients with established cardiovascular disease.
- Few adverse effects associated, effective treatment option for patients with statin intolerance.
- Can be used as monotherapy or in combination with other lipid lowering medications.

**DISADVANTAGES**

- High annual cost, $14,000 US and $5580 UK.
- Most third-party payers will not provide coverage.
- Only available as subcutaneous injection, may not be tolerated by some patients.
- Has not been proven to reduce all cause or cardiovascular mortality.

**REFERENCES:**

Wilson

PCSK9 Inhibitors


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