SPECIAL FEATURE

How Do PCSK9 Inhibitors Stack Up to Statins for Low-Density Lipoprotein Cholesterol Control?

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Despite advances in the approach toward treating hypercholesterolemia and widespread access to statin medications, not all people are able to reach target low-density lipoprotein cholesterol (LDL-C) levels to reduce their cardiovascular risk. Some of the reasons include the inability to tolerate statin therapy, LDL-C levels that remain high even in the presence of statin therapy, and a familial disorder that is characterized by extremely high levels of LDL-C. A new therapeutic class, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, represents a novel and promising approach to reducing LDL-C levels using a mechanism at the LDL receptor level. The recent approval of the first 2 PCSK9 inhibitors and the anticipated approval of the third agent in this class within approximately 1 year may provide clinicians powerful new weapons to lower LDL-C levels in patients who are not satisfactorily managed with statins. However, the results of long-term studies of the ability of these new medications to influence cardiovascular outcomes will not be known for several years.

KEY WORDS: familial hypercholesterolemia, low-density lipoprotein cholesterol, statin treatment, statin adverse effects, PCSK9 inhibitors, alirocumab, evolocumab, bococizumab

Drugs for hypercholesterolemia represent 1 of the 10 most widely prescribed pharmaceutical classes in the United States.[1] Rosuvastatin ranks second among the most widely prescribed drugs, with 21.4 million total prescriptions monthly as of March 2015.[2] This is not surprising considering that more than 73 million (31.7%) adults in the United States have high levels of low-density lipoprotein cholesterol (LDL-C)[3]; however, less than 50% of US adults with elevated LDL-C levels are receiving treatment to lower their cholesterol.[3] Using the currently available treatments, less than 33% of patients have reached their target LDL-C levels.[3]

Some of the reasons for not achieving target LDL-C levels include adherence to prescribed drug regimens, intolerance of drugs because of adverse events, and a familial hypercholesterolemia (FH) disorder. Even though many statin treatments are available as generic medications today, interest has been high for alternatives to conventional treatments, especially in certain patient populations.

The first agent of a new drug class was approved by the US Food and Drug Administration (FDA) for use in patients with FH in July 2015, and the second agent in this class approved in August 2015. Their new mechanism of action offers considerable promise as highly effective LDL-C–lowering medications. However, these proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors concern payers for several reasons, most of which relate to their potential cost. They are injectable agents that are likely to be priced as specialty pharmaceuticals, and their use may spread to not only the limited population of patients with a particular type of genetic hypercholesterolemia abnormality, but also to the much wider population of people who currently receive oral statin treatment.

The goal of this article is to explore the target population for the PCSK9 inhibitors and to review the clinical trial results that support their use.

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Patients with Familial Hypercholesterolemia

Genetic mutations are responsible for FH. The most frequently involved genes include apolipoprotein B (*APOB*), the LDL receptor (*LDLR*), and the *PCSK9* (**Table 1**).[4] Most patients with FH have a mutation in the *LDLR* gene, which leads to "receptor-defective" activity, whereas some patients have minimal receptor activity ("receptor-negative").[5] These 2 types of FH affect a relatively small proportion of the US population.

The heterozygous form of FH—when 1 parent contributes a mutation that causes it—is seen in 1 of 200 to 1 of 500 people worldwide.[6] The homozygous genotype—when both parents contribute a mutated gene—has a much lower prevalence of approximately 1 in 160,000 to 1 in 1 million people worldwide.[6] It is estimated that approximately 620,000 to 650,000 people

have FH in the United States.[4,7] Patients with FH have a 20-fold higher risk for heart disease than those without the disease.[6] Many young and middle-aged Americans may have heterozygous FH and may not be aware they have it until they have a cardiovascular (CV) event.[6]

If there is a family history of FH, early CV disease, or early elevated cholesterol levels, children should be considered for cholesterol screening at age 2 years; everyone should be screened by the age of 20 years.[4] If LDL-C levels are elevated (≥250 mg/dL in patients aged >30 years; ≥220 mg/dL in patients aged 20 to 29 years; or ≥190 mg/dL in patients aged <20 years) in the absence of cholesterol-lowering therapy, there is an 80% chance that the patient has FH.[4]

Many individuals with FH exhibit tendon xanthomas, tuberous xanthomas or xanthelasma (deposits of cholesterol-rich material), or arcus corneae (a white or grey ring in the area of the cornea). Several validated criteria exist for diagnosing FH (US Make Early Diagnosis to Prevent Early Death [MEDPED], Dutch Lipid Clinic Network, Simon-Broome Registry), and genetic screening is usually not needed.[4] Genetic testing is not completely accurate; up to 20% of patients will have FH despite having a genetic test result indicating that they do not have a genetic mutation indicative of this disease.[4]

Adults with heterozygous FH should receive statin therapy.[8] Statin therapy reduces LDL-C levels by lowering cholesterol synthesis as well as by upregulating the number of LDL receptors. Other drugs typically added include ezetimibe, a bile-acid sequestrant, or niacin.[8] If a patient cannot tolerate the starting statin therapy, another statin can be tried. If a patient does not have an adequate response after 6 months, LDL-C apheresis should be considered (apheresis removes *APOB*-containing lipoproteins that, in turn, reduce LDL-C levels). The procedure is routinely repeated every 1 to 2 weeks.[8] Most patients with homozygous FH will be candidates for apheresis; approximately 15,000 patients with heterozygous FH are eligible for apheresis, although <5% of those with FH will receive it.[7]

The 2 therapies that are available to specifically treat the homozygous form of FH include mipomersen and lomitapide.[9,10] Mipomersen is administered subcutaneously once weekly, and lomitapide is an oral capsule administered once daily. Both drugs have mechanisms of action that reduce *APOB* and are only indicated for homozygous FH.[9,10]

The *PCSK9* Gene as a Target for Familial Hypercholesterolemia

The *PCSK9* gene impacts the body's ability to make functional LDL receptors, which leads to the inability to effectively remove LDL-C from the blood.[4] Inhibiting the *PCSK9* gene increases the number of LDL receptors, thus decreasing LDL-C levels.[4] Genetic mutations can be either loss of function, which decreases *LDLR* degradation, and protects people from CV disease, or gain of function, in which the acceleration of the *LDLR* degradation leads to an increased risk for CV disease.[5]

The 3 injectable drugs are being developed to inhibit the activity of the *PCSK9* gene (**Table 2**). Alirocumab (Praluent) was approved by the FDA on July 24, 2015,[11] and evolocumab (Repatha) was approved in August 2015.

Alirocumab

In the randomized, placebo-controlled study ODYSSEY COMBO I, alirocumab was compared with placebo in patients receiving a maximally tolerated dose of a statin (atorvastatin 40-80 mg, rosuvastatin 20-40 mg, or sim-

KEY POINTS

- The first PCSK9 inhibitor was approved by the US Food and Drug Administration in July 2015, and the second was approved in August 2015.
- These novel agents present a concern for payers, mostly because of the anticipated cost of therapy.
- The PCSK9 inhibitors are likely to be priced as specialty pharmaceuticals, and be used by patients with familial hypercholesterolemia (FH) and by the large population of people who use oral statins.
- Oral statins may be insufficient in many patients with or without FH because of adverse effects, nonadherence, or inadequate cholesterol levels.
- Clinical data demonstrate significant reductions in low-density lipoprotein cholesterol with PCSK9 inhibitors versus placebo or versus standard of care, with a good safety profile.
- Information on whether PCSK9 inhibitor therapy affects cardiovascular events or mortality is not yet available, but long-term studies are ongoing.

Table 1 The Prevalence of Familial Hypercholesterolemia Gene Mutations

Gene mutations causing FH	Proportion of FH cases with the mutation, %
LDLR	85-90
APOB	5-10
PCSK9	<5

FH indicates familial hypercholesterolemia.
Source: Hopkins PN, et al. *J Clin Lipidol*. 2011;5(3 suppl): S9-S17.

Table 2 PCSK9 Inhibitors in Late-Stage Development

Generic (trade) name/manufacturer	Clinical trials	Phase 3 clinical trial data available	FDA approval date	MAb type	Route	Dose
Alirocumab (Praluent) Sanofi-Aventis/ Regeneron	ODYSSEY series	Yes	Approved July 24, 2015	Fully human MAb	SC	75 mg every 2 weeks or 150 mg every 4 weeks
Bococizumab (not available) Pfizer	SPIRE series	No, phase 3, scheduled to be completed in 2015, 2016, and 2017	Expected approval in 2017	Humanized MAb	SC	150 mg every 2 weeks or 300 mg every 28 days
Evolocumab (Repatha) Amgen	OSLER PROFICIO; DESCARTES; MENDEL; GAUSS; RUTHERFORD; TESLA; FOURIER; LAPLACE, TAUSSIG, GLAGOV	Yes	Approved August 27, 2015	Fully human MAb	SC	140 mg every 2 weeks or 420 mg monthly

FDA indicates US Food and Drug Administration; MAb, monoclonal antibody; SC, subcutaneous.

vastatin 80 mg) with or without other lipid-lowering therapy.[12] The patients in the alirocumab arm of the study received 75 mg subcutaneously every 2 weeks via a self-administered prefilled pen. If at week 8 the LDL-C level was at least 70 mg/dL, the alirocumab dose was increased to 150 mg subcutaneously every 2 weeks. The researchers found that by week 24, the LDL-C was lowered a mean 48.2% (51 mg/dL) and 2.3% (98 mg/dL) in the alirocumab and placebo groups, respectively (P <.001). The majority (83.2%) of patients were receiving the 75-mg dose at week 12.[12]

The patients in the alirocumab group had more injection-site reactions than those in the placebo group (5.3% vs 2.8%, respectively), as well as more potential general allergic reactions (8.7% vs 6.5%, respectively). A positive response for the antialirocumab antibody assay was seen in 13 patients; however, 3 patients had preexisting immunoreactivity. Of the treatment-emergent adverse events that were observed in >5% of patients, upper respiratory tract infections, nasopharyngitis urinary tract infections, dizziness, and sinusitis occurred in a larger percentage in the alirocumab group, whereas arthralgia and noncardiac chest pain were observed more often in the placebo group.[12]

Alirocumab was compared with ezetimibe in a 24-week, double-blind, randomized (1:1 ratio), phase 3 clinical trial in 100 patients with a 10-year risk for fatal CV events, based on the European Systematic Coronary Risk Evaluation.[13] The participants (FH status unknown) received alirocumab 75 mg subcutaneously every 2 weeks or ezetimibe 10 mg daily. The alirocumab dose could be increased to 150 mg subcutaneously every 2 weeks at week 12 if their week 8 LDL-C level was ≥70 mg/dL (14 patients had their dose increased).[13] The LDL-C levels were reduced approximately 47 mg/dL in the alirocumab group and by approximately 16 mg/dL in the ezetimibe group from baseline (95% confidence interval [CI], –40.2 to –23.0; P <.001). Of the treatment-emergent adverse events, patients in the alirocumab group had more nasopharyngitis, diarrhea, influenza, arthralgia, and headaches, whereas patients in the ezetimibe group had more upper respiratory tract infections, back pain, dizziness, and urinary tract infections. Each group experienced the same number of cases of nausea, and, overall, the number of treatment-emergent adverse events was similar in both groups.[13]

A study comparing alirocumab 75 mg every 2 weeks to ezetimibe 10 mg daily in patients already receiving maximally dosed statins (atorvastatin 40/80 mg; rosuvastatin 20/40 mg; or simvastatin 80 mg, if using the dose for >1 year) was conducted in 720 patients for 52 weeks.[14] The dose of alirocumab could be increased to 150 mg every 2 weeks if the patient's LDL-C level at week 12 was >70 mg/dL, which occurred in 82 (18.4%) patients. The efficacy results were reported at 24 weeks and at 52 weeks. The investigators found a reduction in LDL-C levels of 29.8 ± 2.3 mg/dL (95% CI, –34.4 to –25.3; P <.001) between the alirocumab and ezetimibe groups at 24 weeks. The differences in LDL-C levels remained constant over 52 weeks.[14] More patients in the alirocumab group discontinued treatment as a result of treatment-emergent adverse events (7.5% vs 5.4%, respectively); however, no pattern could be detected in the type of adverse event. The percentage of patients experiencing a treatment-emergent adverse event was similar in each group (18.8%

vs 17.8%, respectively). The patients in the alirocumab group had more upper respiratory tract infections and injection-site reactions, whereas those in the ezetimibe group had more dizziness, myalgia, and neurocognitive disorders. The FH status of these patients was not disclosed by the investigators.[14]

In a phase 3 randomized trial, patients who were intolerant of statins (ie, the inability to take at least 2 different statins because of muscle-related adverse events) were assigned to receive alirocumab 75 mg every 2 weeks or ezetimibe 10 mg daily or atorvastatin 20 mg daily for 24 weeks.[15] The alirocumab group exhibited a 45% reduction in LDL-C levels, whereas the patients in the ezetimibe group demonstrated 15% lower levels from baseline (P <.001 for both groups).[16] The adverse events observed included myalgia, nasopharyngitis, arthralgia, upper respiratory tract infection, headache, and fatigue.[15,16]

The patients who were diagnosed with heterozygous FH received alirocumab 75 mg every 2 weeks, or 150 mg of alirocumab beginning at week 12 if their week 8 LDL-C level was ≥70 mg/dL, for a total of 24 weeks.[15] A 46% reduction of LDL-C was observed in the 72 patients receiving alirocumab compared with a 7% LDL-C lowering in the 35 patients receiving standard-of-care lipid-lowering therapy (P <.001 for both groups).[16] Adverse events reported included nasopharyngitis, injection-site reaction, diarrhea, sinusitis, bronchitis, headache, and fatigue.[16] Similar results were seen after 24 weeks of therapy in the ODYSSEY FHI and ODYSSEY FHII 78-week trials in patients with heterozygous FH who had LDL-C levels that were not controlled with a statin or with another lipid-lowering therapy.[17] The patients received alirocumab 75 mg or 150 mg every 2 weeks. The reductions in LDL-C in the 2 trials were 48.8% and 48.7%, respectively (P <.001). The 735 patients will remain in these trials for a total of 78 weeks.[17]

A study of 2341 patients at high risk for CV events who were receiving the maximum tolerated doses of statins were enrolled in a 2:1 ratio to receive alirocumab 150 mg every 2 weeks or placebo, for 78 weeks.[18] The results were reported at 24 weeks, at which time the mean change from baseline in LDL-C levels was 62% lower in the alirocumab group versus placebo (P <.001). The subgroup analysis of patients with heterozygous FH had a 56% reduction in LDL-C levels, whereas the non-heterozygous FH group had a 62% reduction in LDL-C levels.[18] The least squares mean differences versus placebo were reductions of 57% to 69% and 59% to 64%, respectively.[16] The alirocumab group experienced more injection-site reactions (5.9% vs 4.2%, respectively), myalgia (5.4% vs 2.9%, respectively), neurocognitive disorders (1.2% vs 0.5%, respectively), and ophthalmologic events (2.9% vs 1.9%, respectively).[18] A post hoc analysis of the rate of major CV events showed a lower percentage of participants experiencing these adverse events in the alirocumab group than in the placebo group (1.7% vs 3.3%; hazard ratio, 0.52; 95% CI, 0.31-0.90; P = .02).[18]

The 18,000-patient ODYSSEY OUTCOMES trial to assess the CV benefits and outcomes with alirocumab was announced in July 2014.[19] The patients in the trial will be followed for 2 years, and the trial is expected to be completed in 2016.

Evolocumab

A phase 3 study of 614 patients (FH status not revealed) evaluated the use of evolocumab 140 mg every 2 weeks; evolocumab 420 mg and a placebo, monthly; and a regimen of placebo and ezetimibe 10 mg daily, for 12 weeks.[20,21] Both doses of evolocumab administered at the different dosing intervals decreased LDL-C levels more than the comparator groups (ie, those receiving placebo or ezetimibe). The differences in LDL-C versus ezetimibe were reductions of 33.6% (95% CI, –37.2 to –30.0) in the group receiving evolocumab 140 mg every 2 weeks, and of 34.6% (95% CI, –38.0 to –31.3) in those taking evolocumab 420 mg monthly (P <.001 for both groups). The treatment-emergent adverse events were similar in all of the treatment groups (40%-48%). No evolocumab antibodies were detected during the study.[20]

Another 12-week phase 3 clinical trial was conducted in 307 patients who were intolerant of statins (ie, the inability to tolerate any dose or an increase in dose above the smallest tablet strength because of intolerable muscle-related side effects).[22] Less than 50% of the study participants continued to take lipid-lowering therapy (33%) or a low-dose statin (18%). The participants received placebo, ezetimibe 10 mg daily, and evolocumab 140 mg every 2 weeks, or evolocumab 420 mg once every month. The group receiving evolocumab 140 mg every 2 weeks had a 38.1% greater LDL-C reduction than the ezetimibe group (–56.1% vs –18.1%, respectively), whereas the difference in the evolocumab 420-mg group was 37.6% greater than the ezetimibe group (52.6% vs 15.1%, respectively; P <.001 for both groups). No antibodies to evolocumab were detected. There were more treatment-emergent adverse events in the combined evolocumab groups than in the ezetimibe groups, with a greater number leading to study discontinuation in the ezetimibe groups. There was more myalgia in the ezetimibe groups than in the evolocumab groups.[22] The FH status of these patients was also not revealed by the investigators.

In a phase 3 study, 901 patients (FH status unknown) were classified into 1 of 4 lipid-lowering regimens, including diet alone, diet plus 10 mg of atorvastatin daily, diet plus 80 mg of atorvastatin daily, or diet plus 80 mg of

atorvastatin and 10 mg of ezetimibe daily, for up to 12 weeks. The patients were then assigned in a 2:1 ratio into 2 groups to receive either evolocumab 420 mg or placebo subcutaneously every 4 weeks, for 48 weeks. Patients receiving evolocumab had a greater reduction in LDL-C than any of the comparator groups after 52 weeks. The mean reductions in LDL-C from baseline were 55.7%, 61.6%, 56.8%, and 48.5%, for the groups receiving diet alone, diet plus 10-mg atorvastatin, diet plus 80-mg atorvastatin, or diet plus 80-mg atorvastatin and 10-mg ezetimibe (P <.001), respectively. The most frequently observed adverse events in the evolocumab group were nasopharyngitis, upper respiratory tract infection, influenza, and back pain. Injection-site reactions were seen in 34 (5.7%) patients receiving evolocumab and in 15 (5.0%) patients receiving placebo. No patients were found to have produced any antievolocumab-neutralizing antibodies.[23]

Evolocumab was evaluated in a trial of 415 patients with a clinical diagnosis of heterozygous FH who were receiving a stable dose of a lipid-lowering therapy.[24] The patients were randomized in a 2:2:1:1 ratio to receive evolocumab 140 mg every 2 weeks, evolocumab 420 mg monthly, or placebo every 2 weeks or monthly, for 12 weeks. Compared with placebo, evolocumab 140 mg every 2 weeks resulted in a reduction in LDL-C levels of 59.2% (95% CI, –65.1 to –53.4); evolocumab 420 mg monthly resulted in a reduction in LDL-C levels of 61.3% versus placebo (95% CI, –69.0 to –53.6; P <.001 for both groups). Nasopharyngitis (7% and 10% vs 4% and 5%, respectively) and muscle-related adverse events (7% and 0% vs 9% and 2%, respectively) were seen more frequently in the evolocumab than in the placebo groups. There was no development of antievolocumab antibodies during the study.[24]

A phase 2 trial of patients with homozygous FH and confirmed homozygous mutations found that patients with defective *LDLR* activity had a reduction in LDL-C levels with evolocumab, whereas patients who were *LDLR* negative showed no response to treatment with evolocumab.[25] A placebo-controlled, phase 3 clinical trial of 49 patients with confirmed homozygous FH who were taking stable lipid-regulating therapy, compared the use of evolocumab 420 mg or placebo every 4 weeks, for 12 weeks.[26] The researchers found that LDL-C levels were 30.9% lower in the evolocumab group than in the placebo group (95% CI, –43 to –18.0; P <.001). There were no serious adverse events. No anti-evolocumab antibodies were detected during the study.[26]

The question of whether the lowering of LDL-C levels with the use of PCSK9 inhibitors translates into a reduction in CV events has yet to be answered conclusively. Two open-label trials of 4465 patients who had completed 1 of 12 phase 2 or phase 3 studies were randomized to receive evolocumab 140 mg every 2 weeks or 420 mg monthly in addition to standard lipid-lowering therapy, or to standard therapy alone, for an average of 11.1 months.[27] The patients receiving evolocumab had a reduction in LDL-C levels of 61% (P <.001). The investigators found a reduction in CV events in both groups; however, the rate of CV events was lower in the evolocumab group than in the placebo group (0.95% vs 2.18%, respectively; hazard ratio, 0.47; 95% CI, 0.28-0.78; P = .003).[27]

The 27,500-patient outcomes trial FOURIER is assessing whether evolocumab reduces the risk for recurrent CV events in patients with hypercholesterolemia and clinical evidence of CV disease is expected to be completed in 2017.[28]

Bococizumab

Bococizumab, the third PCSK9 inhibitor, is a humanized monoclonal antibody, whereas alirocumab and evolocumab are fully human monoclonal antibodies. Clinical trials will identify whether there are differences in antibody production and sensitivity reactions, as well as clinically significant differences, with the humanized monoclonal antibody drug versus the human monoclonal antibody drug. The developers of bococizumab have announced a robust phase 3 clinical trial plan, with initial completion dates for the clinical trials starting in December 2015 and continuing through August 2017.[29]

Phase 2 trial data have demonstrated impressive reductions in LDL-C levels with bococizumab, similar to those seen with alirocumab and evolocumab. In a phase 2 dose-ranging clinical trial of patients receiving stable statin therapy (FH status not revealed) bococizumab was administered in various doses every 14 days or every 28 days, for 12 weeks.[30]

Therapy was continued for a total of 24 weeks to assess the safety of the doses. The greatest reductions of LDL-C were seen in patients receiving bococizumab 150 mg every 14 days and bococizumab 300 mg every 28 days, which were given with statins and were compared with patients who were only receiving a statin. The mean placebo-adjusted changes in LDL-C at week 12 were –53.4 mg/dL in the group receiving bococizumab 150 mg every 14 days and –44.9 mg/dL in the group receiving 300 mg of the drug every 28 days (both P <.001).[30]

The treatment-emergent adverse events were similar in the 14-day and 28-day regimens. The most frequently reported treatment-emergent adverse events were an injection-site reaction and injection-site erythema. The most frequent adverse events in the bococizumab and in the placebo groups observed in ≥10% of the patients included nasopharyngitis, upper respiratory tract infection, diarrhea, urinary tract infection, bronchitis, arthralgia,

gastroesophageal reflux disease, cough, anemia, and injection-site reactions.[30]

Considerations for Initiating PCSK9 Inhibitor Therapy

Based on the clinical trials evidence, a consensus has been reached that the new mechanism of action of PCSK9 inhibitors results in powerful reductions in LDL-C levels in several patient populations.[31,32] However, the safety profile of these drugs (including alirocumab and evolocumab) raises some concerns, specifically regarding new-onset diabetes, liver-related safety (eg, pancreatitis, elevated liver enzymes), neurocognitive events, hypersensitivity, renal issues, musculoskeletal issues, and potential deleterious effects of very low LDL-C levels.[31,32] Both alirocumab and evolocumab are administered via subcutaneous injection, which may deter some patients from wanting to use them, even though the drugs are only dosed every 2 weeks or as an every month regimen.

These drugs have shown efficacy in patients with the heterozygous and homozygous subtypes of FH, as well as in patients with other types of hypercholesterolemia.

Conclusion: Identifying Patients Who May Benefit from PCSK9 Inhibitor Therapy

Alirocumab, evolocumab, and, so far to a lesser extent, bococizumab have demonstrated effective reductions in LDL-C levels. These drugs have shown efficacy in patients with the heterozygous and homozygous subtypes of FH, as well as in patients with other types of hypercholesterolemia. For this patient population, the drugs demonstrated efficacy in patients who cannot tolerate statins, when used in combination with statins, in patients taking a statin and ezetimibe, and in patients receiving ezetimibe as monotherapy.

The US patient population with FH is relatively small (approximately 600,000), which translates to a relatively low number of patients who are candidates to receive PCSK9 inhibitors.[6] However, the number of patients who may benefit from these drugs is much larger, because the number of patients who are intolerant of statin treatment may be as high as 3 million (or up to 15% of patients taking statins).[33] The number of any patient taking statins but not reaching target LDL-C levels raises the potential population who may benefit from PCSK9 inhibitors far higher.[33]

The cost per dose of a PCSK9 inhibitor therapy has not been established, but it is anticipated that the annual cost will be in the range of $7000 to $12,000.[34] The drugmakers of alirocumab (Sanofi-Aventis and Regeneron Pharmaceuticals) have indicated that the average wholesale price for the drug for both doses would be $1120 for a 4-week (28-day) course of therapy, or approximately $14,000 annually ($40 daily).[35] Because these medications are intended for the treatment of a chronic condition, the per-member per-month costs could significantly impact the pharmacy drug budget.

Large, long-term outcome studies will not be available for approximately 2 years. These trials should provide data regarding the drugs' impact on CV morbidity and mortality, as well as important information about other safety aspects of the drugs. ■

Author Disclosure Statement

Ms Zimmerman has no conflicts of interest to report.

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