**What are the current outcomes data for PCSK9 inhibitors in the treatment of hyperlipidemia?**

*Background*

Approximately 73.5 million adults have elevated levels of low-density lipoprotein cholesterol (LDL-C).[1] Per the National Lipid Association (NLA), elevated LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C) are the root causes of atherosclerosis, leading to clinical atherosclerotic cardiovascular disease (ASCVD).[2] Examples of ASCVD include coronary heart disease (CHD), stroke, and peripheral arterial disease.[3]

Dyslipidemia may occur secondary to multiple factors, including diet (e.g., high amount of saturated fats), medications (e.g., glucocorticoids), and diseases/conditions leading to altered metabolism (e.g., hypothyroidism).[3] With regard to primary dyslipidemia, familial hypercholesterolemia (FH) is a genetic condition notable for its high levels of LDL-C (range: 190 to 400 mg/dL or higher), in the absence of other (non-genetic) risk factors, and early ASCVD. FH may be further classified as homozygous (HoFH) or heterozygous (HeFH), depending on the number of mutated LDL-C receptors.[4] Both types are associated with markedly accelerated atherogenesis; however, they differ in magnitude of LDL-C elevation and in prevalence. HeFH has been characterized by LDL-C levels that are 2-fold higher than normal (approximately 190 to 350 mg/dL) and a prevalence in the United States (US) of approximately 1 in 500, while HoFH has been characterized by LDL-C levels that are 4-fold higher than normal (approximately 400 to 1,000 mg/dL) and a prevalence in the US of approximately 1 in 1,000,000.

Management of cholesterol includes therapeutic lifestyle changes and pharmacologic agents or lipid-lowering therapy (LLT).[2,5] Available LLT includes: bile acid sequestrants, cholesterol absorption inhibitors, fibric acids, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (i.e., statins), lomitapide, mipomersen, nicotinic acid, omega-3-fatty acids, and proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors. PCSK9 inhibitors represent the most novel class of LLT. Interest in PCSK9 as a drug target developed following observations of increased LDL-C receptors and decreased circulating LDL-C in patients with PCSK9 loss-of-function mutations.[6] At this time, there are 2 available agents: alirocumab (Praluent®) and evolocumab (Repatha®).[5] The available dosage forms, indications, and manufacturer-recommended dosage and administration may be seen in Table 1. A third agent, bococizumab, was under investigation, but Pfizer discontinued its development in 2016 based on findings of unanticipated attenuation of LDL-C lowering over time, as well as a higher level of immunogenicity and higher rate of injection-site reactions compared to other PCSK9 inhibitors.[7]

Table 1. Available dosage forms and recommended dosage and administration of PCSK9 inhibitors.[8,9]

| Agent | FDA-approval | Indications | Dosage forms | Dosage and administration |
|---|---|---|---|---|
| Alirocumab (Praluent®) | Jul 24, 2015 | • Adjunct to diet and maximally tolerated statin therapy for treatment of **HeFH or clinical ASCVD**, in adult patients who require further reductions in LDL-C | 75 or 150 mg/mL solution; single-use prefilled pen or syringe | Initial: 75 mg SC every 2 weeks or 300 mg SC every 4 weeks<br>Maximum: 150 mg SC every 2 weeks |
| Evolocumab (Repatha™) | Aug 27, 2015 | • Adjunct to diet and maximally tolerated statin therapy for treatment of **HeFH or clinical ASCVD**, in adult patients who require further reductions in LDL-C | 140 mg/mL solution; single-use prefilled syringe or SureClick® autoinjector<br>420 mg/3.5 mL solution; single-use Pushtronex® system | **HeFH or established CVD**: 140 mg SC every 2 weeks or 420 mg SC once monthly<br>**HoFH**: 420 mg SC once monthly |

| Agent | FDA-approval | Indications | Dosage forms | Dosage and administration |
|---|---|---|---|---|
| | | • Adjunct to diet and other LLT (e.g., statins, ezetimibe, LDL-C apheresis) in patients *aged ≥12 years* with **HoFH** who require further reductions in LDL-C<br>• Reduction in risk of MI, stroke, and coronary revascularization in adults with established CVD[a] | | |

[a]This indication was approved in December 2017[10]
ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; FDA=Food and Drug Administration; HeFH=heterozygous familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; LLT=lipid-lowering therapy; MI=myocardial infarction; SC=subcutaneous

*Phase 3 trials - alirocumab*

Alirocumab was investigated in a global clinical trial series known as the ODYSSEY program, which consisted of 16 phase 3 trials.[11] Published data are summarized in Table 2.[12-22] There were 7 placebo-controlled trials (CHOICE I and II, COMBO I, FH I and II, HIGH FH, LONG TERM);[12,13,18-21] with the exception of CHOICE I and II, the placebo-controlled trials were ≥52 weeks in duration. Most studies evaluated alirocumab in combination with a maximally tolerated statin, with or without other LLT.[14,18-22] Three trials investigated alirocumab as monotherapy (i.e., without other LLT; the trials were CHOICE II, ALTERNATIVE, and MONO).[13,16,17] One of these studies exclusively involved patients with statin intolerance (ALTERNATIVE).[16] In this study, statin intolerance was defined as the inability to tolerate at least 2 statins, with at least 1 at the lowest daily dose, due to muscle symptoms that began or intensified during statin therapy and resolved when the statin(s) was/were discontinued. Patients were re-challenged during the run-in period with atorvastatin 20 mg/day. Three of the trials exclusively involved patients with HeFH (FH I and II, HIGH FH).[19,20] Patients without FH and with established CHD or CHD risk equivalent(s) were also investigated (COMBO I, CHOICE I and II, OPTIONS I and II, COMBO II, ALTERNATIVE, MONO).[12-18,22]

The primary endpoint for all of the trials was mean percent change in LDL-C from baseline at week 24.[12-22] In all of the studies, alirocumab was superior to the comparator (placebo or ezetimibe) in LDL-C reduction from baseline. When used in combination with statins, mean percent changes in LDL-C reductions from baseline to week 24 ranged from -42.7% to -58.8%; over the same period, alirocumab monotherapy was associated with mean LDL-C reductions of -45.0% to -52.7%. Among the studies of longer duration, the reductions in LDL-C were reportedly sustained during the study periods and remained significantly different between alirocumab and comparators at study completion (exception: statistical analyses not reported for COMBO II at week 104).[18-23]

Table 2. Selected phase 3 trials evaluating alirocumab.

| Study | Population | Interventions | LS mean % change in LDL-C at 24 weeks | |
|---|---|---|---|---|
| | | | vs. placebo[a] | vs. ezetimibe[a] |
| 24-week trials | | | | |
| CHOICE I[12] | n=803<br>Moderate to high CV risk, with or without statin and other LLT | • Ali 300 mg q4w or 75 mg q2w<br>• Placebo<br>*Background statin or no statin therapy | On statin:<br>• Ali q4w: -58.8% vs. -0.1%<br>• Ali q2w: -51.6% vs. -0.1%<br>No statin:<br>• Ali q4w: -52.7% vs. -0.3%<br>• Ali q2w: -50.2% vs. -0.3% | Not applicable |
| CHOICE II[13] | n=233<br>Moderate/high/very high CV risk on ezetimibe, fenofibrate, or diet only, with or without statin intolerance | • Ali 150 mg q4w or 75 mg q2w<br>• Placebo<br>*No statin therapy | • Ali q4w: -51.7% vs. +4.7%<br>• Ali q2w: -53.5% vs. +4.7% | Not applicable |
| OPTIONS I[14] | n=355<br>High CV risk with LDL-C ≥100 mg/dL or very high CV risk with LDL-C ≥70 mg/dL, not at goal on atorvastatin | Atorvastatin 20 mg/d +<br>• Ali 75 or 150 mg q2w,<br>• Ezetimibe 10 mg/d, or<br>• Doubling of statin dose (i.e., 40 mg/d)<br>-or-<br>Atorvastatin 40 mg/d +<br>• Ali 75 or 150 mg q2w,<br>• Ezetimibe 10 mg/d,<br>• Doubling of statin dose (i.e., 80 mg/d), or<br>• Switch to rosuvastatin 40 mg/d | On atorvastatin 20 mg/d:<br>• Ali q2w: -44.1%<br>• Doubling statin: -5.0%<br><br>On atorvastatin 40 mg/d:<br>• Ali q2w: -54.0%<br>• Doubling statin: -4.8%<br>• Rosuvastatin: -21.4% | On atorvastatin 20 mg/d:<br>• Ali q2w: -44.1%<br>• Ezetimibe: -20.5%, p=0.0004<br><br>On atorvastatin 40 mg/d:<br>• Ali q2w: -54.0%<br>• Ezetimibe: -22.6% |
| OPTIONS II[15] | n=305<br>High CV risk with LDL-C ≥100 mg/dL or very high CV risk with LDL-C ≥70 mg/dL, not at goal on rosuvastatin | Rosuvastatin 10 or 20 mg/d +<br>• Ali 75 or 150 mg q2w<br>• Ezetimibe 10 mg/d<br>• Doubling of statin dose to 20 or 40 mg/d | On rosuvastatin 10 mg/d:<br>• Ali q2w: -50.6%<br>• Doubling statin: -16.3%<br><br>On rosuvastatin 20 mg/d:<br>• Ali q2w: -36.3%<br>• Doubling statin: -15.9%, p=0.0453 | On rosuvastatin 10 mg/d:<br>• Ali q2w: -50.6%<br>• Ezetimibe: -14.4%<br><br>On rosuvastatin 20 mg/d:<br>• Ali q2w: -36.3%<br>• Ezetimibe: -11.0%, p=0.0136 |
| ALTERNATIVE[16] | n=314<br>Statin-intolerant and moderate/high/very high CV risk | • Ali 75 or 150 mg q2w<br>• Ezetimibe 10 mg/d<br>• Atorvastatin 20 mg/d | Not applicable | • Ali q2w: -45.0%<br>• Ezetimibe: -14.6%<br>Results not available for atorvastatin |

| Study | Population | Interventions | LS mean % change in LDL-C at 24 weeks | |
|---|---|---|---|---|
| | | | vs. placebo[a] | vs. ezetimibe[a] |
| MONO[17] | n=103<br>Moderate CV risk (10-year risk of fatal CV events of 1 to 5% according to European Systemic Coronary Risk Estimation and LDL-C 100 to 190 mg/dL) | • Ali 75 or 150 mg q2w<br>• Ezetimibe 10 mg/d<br>*No background LLT | Not applicable | • Ali q2w: -47.2%<br>• Ezetimibe: -15.6% |
| 52-week trial | | | | |
| COMBO I[18] | n=316<br>Very high CV risk (CHD or CHD risk equivalent on statin with or without other LLT) | • Ali 75 or 150 mg q2w<br>• Placebo<br>*Background statin with or without other LLT | • Ali q2w: -48.2%<br>• Placebo: -2.3% | Not applicable |
| 78-week trials | | | | |
| FH I[19] | n=486<br>HeFH with LDL-C ≥100 mg/dL for primary prevention or ≥70 mg/dL for secondary prevention on statin with or without other LLT | • Ali 75 or 150 mg q2w<br>• Placebo<br>*Background statin therapy | • Ali q2w: -48.8%<br>• Placebo: +9.1% | Not applicable |
| FH II[19] | n=249<br>HeFH with LDL-C ≥100 mg/dL for primary prevention or ≥70 mg/dL for secondary prevention on statin with or without other LLT | • Ali 75 or 150 mg q2w<br>• Placebo<br>*Background statin therapy | • Ali q2w: -48.7%<br>• Placebo: +2.8% | Not applicable |
| HIGH FH[20] | n=107<br>HeFH with LDL-C ≥160 mg/dL on statin with or without other LLT | • Ali 150 mg q2w<br>• Placebo<br>*Background statin therapy | • Ali q2w: -45.7%<br>• Placebo: -6.6% | Not applicable |
| LONG TERM[21] | n=2,341<br>HeFH, very high CV risk (CHD or CHD risk equivalent with LDL-C ≥70 mg/dL on statin) | • Ali 150 mg q2w<br>• Placebo<br>*Background statin therapy | • Ali q2w: -61.0%<br>• Placebo: +0.8%, p<0.001 | Not applicable |
| 104-week trial | | | | |
| COMBO II[22] | n=720<br>Very high CV risk (CHD or CHD risk equivalent on statin) | • Ali 75 or 150 mg q2w<br>• Ezetimibe 10 mg/d<br>*Background statin therapy | Not applicable | • Ali q2w: -50.6%<br>• Ezetimibe: -20.7% |

[a]p<0.0001 for all listed comparisons to placebo or ezetimibe unless otherwise specified
Ali=alirocumab; CHD=coronary heart disease; CV=cardiovascular; d=day; HeFH=heterozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; LLT=lipid-lowering therapy; LS=least squares; q2w=every 2 weeks; q4w=every 4 weeks

*Phase 3 trials – evolocumab*

The efficacy and safety of evolocumab were investigated in the phase 3 PROFICIO clinical trial program, which included 14 studies.[11] Results from published studies are outlined in Table 3.[24-30] This includes one 6-week trial, six 12-week trials, and one 52-week study. THOMAS-1 and its 12-week version (THOMAS-2) were open-label, randomized trials.[24] Unlike the other studies, the primary endpoint of THOMAS-1 and THOMAS-2 was the patient-reported successful outcome of self-administered evolocumab in the home-use setting. TESLA part B was also a unique trial in that it evaluated the efficacy and safety of evolocumab in patients with HoFH.[29] TESLA part B was open-label and included adolescent patients (aged ≥12 years). The primary endpoint was percent change in LDL-C from baseline at 12 weeks.

With the exception of THOMAS-2[24] and TESLA part B,[26] the 12-week trials were double-blind, randomized, placebo- or ezetimibe-controlled, and evaluated evolocumab in 4 different patient populations.[25,27-29] Of these, LAPLACE-2 was distinctive in that it included 24 different treatment arms; patients were first randomized to receive either a moderate or high intensity statin, then after 4 weeks were randomized to evolocumab (140 mg every 2 weeks or 420 mg every 4 weeks), or placebo or ezetimibe.[28] The co-primary endpoints of the 12-week trials (except THOMAS-2 and TESLA part B) were percent change from baseline in LDL-C at week 12 and mean percent change from baseline in LDL-C at weeks 10 and 12.[24-29] The 52-week study (DESCARTES) was a placebo-controlled trial evaluating evolocumab in 4 different patient populations.[30] The primary endpoint of the 52-week trial was percent change from baseline in LDL-C at week 52.

Like alirocumab, evolocumab was found to be efficacious in all of the phase 3 trials with significant reductions in LDL-C compared to placebo and to ezetimibe.[23-29] Though most of the trials involving evolocumab were shorter than the phase 3 trials of alirocumab, the magnitude of LDL-C reduction observed in evolocumab phase 3 trials was also substantial, ranging from -37.6% (with no background LLT) to -76.3% (with high intensity statin therapy).

Table 3. Selected phase 3 trials evaluating evolocumab.

| Study | Population | Interventions | Mean % change from baseline in LDL-C: treatment difference (95% CI) | |
|---|---|---|---|---|
| | | | vs. placebo | vs. ezetimibe |
| 6-week trial | | | | |
| THOMAS-1[24] | n=149<br>On stable dose of statin with or without ezetimibe and LDL-C ≥85 mg/dL and TG ≤400 mg/dL | • Evo 140 mg q2w (autoinjector or PFS)<br>• Placebo<br>*Background statin therapy | Week 6<br>• Autoinjector: -63.4% (-68.7, -58.2)<br>• PFS: -59.7 (-64.8, -54.7) | Not applicable |
| 12-week trials | | | | |
| THOMAS-2[24] | n=164<br>On stable dose of statin with or without ezetimibe and LDL-C ≥85 mg/dL and TG ≤400 mg/dL | • Evo 420 mg q4w (autoinjector or AMD)<br>• Placebo | Week 12<br>• Autoinjector: -64.5% (-69.2, -59.8)<br>• AMD: -67.9 (-72.6, -63.2) | Not applicable |
| RUTHERFORD-2[25] | n=329<br>HeFH with LDL-C ≥100 mg/dL, on stable dose of statin with or without ezetimibe for 4 weeks | • Evo 140 mg q2w or 420 mg q4w<br>• Placebo<br>*Background statin therapy | Week 12<br>• Evo q2w: -59.2% (-65.1, -53.4)<br>• Evo q4w: -61.3% (-69.0, -53.6) | Not applicable |
| TESLA part B[26] | n=49<br>HoFH (aged ≥12 years) with LDL-C ≥131 mg/dL on stable LLT, TG ≤174 mg/dL, BW ≥40 kg | • Evo 420 mg q4w<br>• Placebo<br>*Background LLT | Week 12<br>• Evo q4w: -30.9% (-43.9, -18.0) | Not applicable |
| MENDEL-2[27] | n=614<br>Low CV risk (Framingham score ≤10%, LDL-C ≥100 and <190 mg/dL, no LLT 3 months prior) | • Evo 140 mg q2w or 420 mg q4w<br>• Ezetimibe 10 mg/d<br>• Placebo<br>*No background LLT | Week 12<br>• Evo q2w: -57.1% (-61.1, -53.1)<br>• Evo q4w: -54.8% (-58.5, -51.1) | Week 12<br>• Evo q2w: -39.3% (-43.3, -35.3)<br>• Evo q4w: -37.6% (-41.2, -33.9) |
| LAPLACE-2[28] | n=1896<br>Primary hypercholesterolemia and mixed dyslipidemia, no previous statin intolerance<br><br>LDL-C ≥80 mg/dL if on intensive statin; LDL-C ≥100 mg/dL if on non-intensive statin; LDL-C ≥150 mg/dL if not on statin | • Evo 140 mg q2w or 420 mg q4w<br>• Ezetimibe 10 mg/d<br>• Placebo<br>*Background statin therapy | Week 12, high intensity statin[a]<br>Atorvastatin + q2w<br>• -76.3% (-86.9, -65.7)<br>Atorvastatin + q4w<br>• -70.5% (-79.8, -61.2)<br>Rosuvastatin + q2w<br>• -68.3% (-77.0, -59.6)<br>Rosuvastatin + q4w<br>• -55.0% (-65.3, -44.7) | Week 12, high intensity statin[a]<br>Atorvastatin + q2w<br>• -47.2% (-57.5, -36.9)<br>Atorvastatin + q4w<br>• -38.9% (-48.2, -29.6) |
| | | | Week 12, moderate intensity statin[a]<br>Atorvastatin + q2w<br>• -71.4% (-77.6, -65.3)<br>Atorvastatin + q4w<br>• -59.2% (-65.9, -52.4)<br>Simvastatin + q2w<br>• -70.6% (-76.7, -64.4)<br>Simvastatin + q4w<br>• -60.4% (-69.1, -51.7)<br>Rosuvastatin + q2w | Week 12, moderate intensity statin[a]<br>Atorvastatin + q2w<br>• -39.6% (-45.8, -33.4)<br>Atorvastatin + q4w<br>• -41.1% (-47.8, -34.4) |

| Study | Population | Interventions | Mean % change from baseline in LDL-C: treatment difference (95% CI) | |
|---|---|---|---|---|
| | | | vs. placebo | vs. ezetimibe |
| | | | • -68.2% (-74.7, -61.7) Rosuvastatin + q4w<br>• -64.5% (-70.8, -58.1) | |
| GAUSS-2[29] | n=307<br>Hypercholesterolemia and documented statin intolerance | • Evo 140 mg q2w or 420 mg q4w<br>• Ezetimibe 10 mg/d<br>• Placebo<br>*No statin therapy | Week 12<br>• Evo q2w: -56.1% (-59.9, -52.4)<br>• Evo q4w: -52.6% (-55.7, -49.5) | Week 12<br>• Evo q2w: -38.1% (-43.7, -32.4)<br>• Evo q4w: -37.6% (-42.2, -32.9) |
| 52-week trial | | | | |
| DESCARTES[30] | n=901<br>Hypercholesterolemia, LDL-C ≥75 mg/dL, on background LLT based on NCEP ATP III risk<br>-Diet (no drug) therapy<br>-Low-dose drug therapy<br>-High-dose drug therapy<br>-Maximal drug therapy | • Evo 420 mg q4w<br>• Placebo<br>*Background LLT | Week 52[b]<br>• Evo: -55.7% ± 4.2<br>• Evo + atorvastatin 10 mg/d: -61.6% ± 2.6<br>• Evo + atorvastatin 80 mg/d: -56.8% ± 5.3<br>• Evo + atorvastatin 80 mg/d + ezetimibe: -48.5% ± 5.2 | Not applicable |

[a]High intensity statins: atorvastatin 80 mg/d, rosuvastatin 40 mg/d; moderate intensity statins: atorvastatin 10 mg/d, simvastatin 40 mg/d, rosuvastatin 5 mg/d
[b]p<0.001 for all comparisons; 95% confidence intervals not reported
AMD=automated minidoser; BW=body weight; CV=cardiovascular; d=day; Evo=evolocumab; HeFH=heterozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; LLT=lipid-lowering therapy; NCEP ATP III=Third report of the National Cholesterol Education Program Adult Treatment Panel; PFS=prefilled syringe; q2w=every 2 weeks; q4w=every 4 weeks; TG=triglycerides

*Studies of clinical outcomes*

Since the approval of these drugs, 4 trials have been conducted evaluating the effects of PCSK9 inhibitors on cardiovascular outcomes: FOURIER, SPIRE-1 and SPIRE-2, and ODYSSEY OUTCOMES.[31-33] The FOURIER trial, published in May 2017, investigated the effects of evolocumab on cardiovascular outcomes including myocardial infarction (MI), stroke, and coronary revascularization.[31] SPIRE-1 and -2 were parallel trials designed to evaluate the effect of bococizumab on incident cardiovascular events.[32] These trials were stopped prematurely when the manufacturer chose to discontinue further development of the drug. Available data from SPIRE-1 and -2 were published in March 2017. The ODYSSEY OUTCOMES trial was designed to evaluate the effects of alirocumab on cardiovascular events; though not yet published, the study has been completed and results were presented earlier this year at the American College of Cardiology (ACC) Annual Scientific Meeting.[33] The FOURIER trial and the ODYSSEY OUTCOMES trial will be discussed in further detail below.

*FOURIER*

The FOURIER trial was a double-blind, multinational trial involving patients aged 40 to 85 years with clinically evident ASCVD, defined as a history of MI, non-hemorrhagic stroke, or symptomatic peripheral arterial disease, and additional risk factors for cardiovascular disease.[31] Risk factors included diabetes, age ≥65 at randomization, MI or non-hemorrhagic stroke within 6 months of screening, current daily cigarette smoking, most recent HDL-C <40 mg/dL for men and <50 mg/dL for women, or most recent LDL-C ≥130 mg/dL or non-HDL-C ≥160 mg/dL. Patients were randomized to receive either evolocumab (140 mg every 2 weeks or 420 mg every 4 months, according to patient preference) or placebo and were stratified according to final screening LDL-C level (<85 mg/dL or ≥85 mg/dL). The primary endpoint was a composite of

cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. A central committee that was blinded to study group assignments and lipid levels adjudicated the efficacy endpoints.

A total of 27,654 patients were randomized in the FOURIER trial, 13,784 to evolocumab and 13,780 to placebo.[31] Baseline characteristics between the groups were similar; the mean age was 63 years, and 24.6% of the study population were female. Approximately 81.1% of the study population had a history of MI; 19.4% had a history of non-hemorrhagic stroke, and 13.2% had symptomatic peripheral artery disease. The median time from the most recent MI was ~3.4 years, and the median time from the most recent stroke was ~3.2 years. The median LDL-C was 92 mg/dL. At baseline, 69.3% of the patients were taking a high intensity statin; most of the remainder (~30%) were taking a moderate intensity statin. Approximately 5.2% were also taking ezetimibe. Most patients were also using another secondary preventive agent, such as antiplatelet therapy (92.3%), a beta-blocker (75.6%), or an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (78.2%).

The median duration of follow-up was 26 months.[31] Premature study discontinuation occurred at a rate of 12.5% (similar between groups). The primary endpoint occurred in 9.8% (n=1,344) of the evolocumab group and 11.3% (n=1,563) of the placebo group (hazard ratio [HR] 0.85, 95% CI 0.79 to 0.92). The magnitude of risk reduction of the primary endpoint appeared to increase over time, from 12% (95% CI 3 to 20) in the first year to 19% (95% CI 11 to 27) in the second year. With regard to the individual components of the primary endpoint, significant reductions were observed in MI (HR 0.73, 95% CI 0.65 to 0.82), stroke (HR 0.79, 95% CI 0.66 to 0.95) and coronary revascularization (HR 0.78, 95% CI 0.71 to 0.86). Though not statistically significant, increases in the risk of cardiovascular death and all-cause mortality were observed with evolocumab (cardiovascular: HR 1.05, 95% CI 0.88 to 1.25; all-cause: HR 1.04, 95% CI 0.91 to 1.19). No significant differences were observed between groups in the overall rates of adverse events (77.4% in both groups), serious adverse events (24.8% treatment vs. 24.7% placebo), or drug-related adverse events thought to lead to study discontinuation (1.6% treatment vs. 1.5% placebo). However, injection site reactions were more common with evolocumab vs. placebo (2.1% vs. 1.6%, $p<0.001$).

The FOURIER trial was a robust study, involving a large and diverse sample.[31] However, the duration of follow-up was relatively short, and absolute differences in event rates were small (absolute risk reductions: MI: 1.2%; stroke: 0.4%; coronary revascularization: 1.5%). Despite these limitations, the Food and Drug Administration (FDA) granted approval of evolocumab for reduction in the risk of MI, stroke, and coronary revascularization in adults with established cardiovascular disease based on the FOURIER trial.[10]

*ODYSSEY OUTCOMES*

The ODYSSEY OUTCOMES investigators sought to evaluate the effects of alirocumab on cardiovascular morbidity and mortality after recent acute coronary syndrome (ACS) in patients with elevated cholesterol levels despite intensive or maximally tolerated statin therapy.[33] ODYSSEY OUTCOMES was a double-blind, multinational trial involving patients aged ≥40 years with history of acute MI or unstable angina within 1 to 12 months prior to randomization. Patients had to be taking atorvastatin 40 to 80 mg daily, rosuvastatin 20 to 40 mg daily, or a maximally tolerated dose of either statin for ≥2 weeks, and have inadequate control of lipids (LDL-C ≥70 mg/dL, non-HDL-C ≥100 mg/dL, or apolipoprotein B ≥80 mg/dL). Patients were randomized to receive alirocumab 75 or 150 mg every 2 weeks or placebo. The primary outcome was time to first occurrence of CHD death, non-fatal MI, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization. Like the FOURIER trial, outcomes in this study were adjudicated by a separate committee, blinded to treatment assignment and lipid levels.

A total of 18,924 patients were randomized in ODYSSEY OUTCOMES, 9,462 to alirocumab and 9,462 to placebo.[33] Patients were followed for a median period of 2.8 years. Study discontinuation rates were similar

between groups; 14.2% in the alirocumab group and 15.8% in the placebo group prematurely discontinued treatment. Baseline characteristics were similar between groups; the median age was 58 years, and approximately 25% of the study population were female. Approximately 18.9 to 19.5% of patients had a history of MI; 24.1% were current smokers, 28.5 to 29.1% had diabetes, and 63.9 to 65.6% had hypertension. The median time from index ACS to randomization was 2.6 months in both groups. The majority had either a non-ST segment-elevated MI (48.4 to 48.7%) or ST segment-elevated MI (34.2 to 35.0%). The median LDL-C at baseline was 87 mg/dL in both groups; however, 92.5% of the study population met the inclusion criterion of LDL-C ≥70 mg/dL. Most patients (~89%) were taking high-dose atorvastatin or rosuvastatin at baseline; the remainder were taking a lower dose of either drug. Approximately 3% of patients were taking ezetimibe. Most patients were also using another secondary preventive agent, such as antiplatelet therapy (~96%), a beta-blocker (84.5%), or an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (~78%).

With regard to the primary endpoint, major cardiovascular events occurred in 9.5% of the alirocumab group and 11.1% of the placebo group (HR 0.85, 95% CI 0.78 to 0.93).[33] Significant reductions were observed in non-fatal MI (HR 0.86, 95% CI 0.77 to 0.96), ischemic stroke (HR 0.73, 95% CI 0.57 to 0.93), and unstable angina (HR 0.61, 95% CI 0.41 to 0.92), comparing alirocumab to placebo. A reduction was also observed in CHD death, though the difference was not statistically significant (HR 0.92, 95% CI 0.76 to 1.11). Though not a component of the primary outcome, the investigators also reported a significant reduction in all-cause mortality favoring alirocumab (HR 0.85, 95% CI 0.73 to 0.98).

With regard to safety, the occurrence of treatment-emergent adverse events was similar between groups.[33] The overall occurrence was reported in 75.8% of the alirocumab group and 77.1% of the placebo group (p=not reported). Serious events were reported in 23.3% of the alirocumab group and 24.9% of the placebo group (p=not reported). A significant difference was observed in the incidence of injection site reactions, with a higher rate reported in the alirocumab group compared to the placebo group (3.8% vs. 2.1%; HR 1.82, 95% CI 1.54 to 2.17).

The data from the ODYSSEY OUTCOMES trial are impressive; however, it is important to note that these findings, as reported, are not peer-reviewed.[32] Also, further details of the study (e.g., aspects of the methodology, results, and the sponsor's interpretation of findings) are not yet available.

*ACC and NLA recommendations*

In 2017, following the publication of FOURIER, the NLA updated their recommendations on the use of PCSK9 inhibitors in adults, and the ACC issued a focused update on the role of non-statin therapies for LDL-C-lowering in the management of ASCVD risk.[34,35] The latter was endorsed by the NLA.

In their 2015 guideline on the management of dyslipidemia, the NLA made recommendations on PCSK9 inhibitors in the following populations: patients with ASCVD meeting certain thresholds of LDL-C levels (e.g., ≥100 mg/dL or ≥70 mg/dL), patients with HeFH but without ASCVD, and high or very-high-risk patients with statin intolerance.[36] In contrast, the 2017 NLA recommendations are specific to the following 4 populations: 1) patients with stable ASCVD; 2) patients with progressive ASCVD; 3) patients with LDL-C ≥190 mg/dL (including polygenic hypercholesterolemia, HeFH, and HoFH); and 4) patients at very high risk for ASCVD with statin intolerance. For patients with stable ASCVD, the NLA states that PCSK9 inhibitor therapy should be considered, particularly if patients are on maximally-tolerated statin therapy with or without ezetimibe. With regard to progressive ASCVD, the NLA states that this was not an inclusion criterion for the FOURIER trial; however, the Expert Panel still recommends that PCSK9 inhibitor therapy be considered to further reduce LDL-C in patients with progressive ASCVD on maximally-tolerated statin therapy with or without ezetimibe. In patients with LDL-C ≥190 mg/dL, the NLA advises consideration for PCSK9 inhibitor therapy according to presence of ASCVD risk factors or other key risk markers, or genetic confirmation of FH.

(ASCVD risk factors include uncontrolled hypertension, diabetes, current cigarette use, and family history of premature ASCVD; additional key risk markers include coronary calcium ≥300 Agatston units, lipoprotein A ≥50 mg/dL, high-sensitivity C-reactive protein ≥2 mg/L, or chronic kidney disease with albumin-creatinine ratio ≥30 mg/g). In patients at very high risk for ASCVD with statin intolerance, the NLA maintains their recommendations from 2015: PCSK9 inhibitor therapy may be considered in selected patients who require substantial additional atherogenic cholesterol lowering despite use of other LLT. A summary of these recommendations is in Table 4. Of note, the NLA emphasizes that all patients who are considered for PCSK9 inhibitor therapy should undergo screening for secondary causes of hypercholesterolemia, such as hypothyroidism, nephrotic syndrome, obstructive liver disease, and drug therapy.

Table 4. 2017 NLA recommendations on the use of PCSK9 inhibitors.[34,36]

| Condition | LDL-C / Non-HDL-C threshold (mg/dL) | Evidence | |
|---|---|---|---|
| | | Strength[a] | Quality[b] |
| ASCVD + additional risk factors[c] | ≥70 / ≥100 | A | High |
| Progressive ASCVD | ≥70 / ≥100 | B | Moderate |
| LDL-C ≥190, age 40-79 years<br>• No uncontrolled risk factors[c] or key additional risk markers[d] | ≥100 / ≥130 | B | Moderate |
| LDL-C ≥190, age 40-79 years<br>• Uncontrolled risk factors[c] or key additional risk markers[d] | ≥70 / ≥100 | B | Moderate |
| LDL-C ≥190, age 18-39 years<br>• Uncontrolled risk factors[c] or key additional risk markers[d] or FH causing mutation | ≥100 / ≥130 | E | Low |
| Homozygous FH | ≥70 / ≥100 | B | Moderate |
| ASCVD + statin intolerance | Clinical judgment | C | Low |

[a]Strength of evidence: A=strong recommendation; B=moderate recommendation; C=weak recommendation; D=Recommend against; E=expert opinion
[b]Quality rating: high=well-designed, well-executed randomized controlled trials that adequately represent populations to which the results are applied and directly assess effects on health outcomes, well-conducted meta-analyses; moderate=randomized controlled trials with minor limitations affecting confidence in or applicability of results, well-designed, well-executed non-randomized controlled trials and observational studies; low=randomized controlled trials with major limitations, non-randomized controlled trials and observational studies with major limitations affecting confidence in or applicability of results
[c]Uncontrolled hypertension, diabetes, current cigarette smoking, family history of premature ASCVD
[d]Coronary calcium ≥300 Agatston units, lipoprotein A ≥50 mg/dL, high-sensitivity C-reactive protein ≥2 mg/L, or chronic kidney disease with albumin-creatinine ratio ≥30 mg/g
ASCVD=atherosclerotic cardiovascular disease; FH=familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; Non-HDL-C=non-high-density lipoprotein cholesterol

In 2016, the ACC published an Expert Consensus Decision Pathway to guide use of non-statin therapies for lowering LDL-C in the 4 statin benefit groups that were identified in the 2013 ACC/American Heart Association (AHA) guideline.[3,35,37] These groups include 1) patients with clinical ASCVD; 2) patients with LDL-C ≥190 mg/dL (not due to secondary causes); 3) patients aged 40 to 75 years with diabetes mellitus and LDL-C 70 to 189 mg/dL; and 4) patients aged 40 to 75 years with no diabetes, but with LDL-C 70 to 189 mg/dL and predicted 10-year ASCVD risk ≥7.5%. In the 2017 update, the ACC modified their recommendations for patients with ASCVD, with baseline LDL-C 70 to 189 mg/dL while on maximally-tolerated statin therapy.[35] Previously, they stated it is reasonable to consider addition of ezetimibe as the initial agent and a PCSK9 inhibitor as the second agent; in the 2017 update, the ACC states that either ezetimibe or a PCSK9 inhibitor can be added.[35,37] If the patient requires >25% additional lowering of LDL-C, a PCSK9 inhibitor may be preferred as the initial non-statin agent. (Conversely, if the patients requires <25% additional lowering of LDL-C, ezetimibe may be preferred). Pharmacologic recommendations for the other statin benefit groups appear to be unchanged – generally, PCSK9 inhibitors are second-line to statins and are recommended

as optional interventions to consider among several others, including ezetimibe, bile acid sequestrants (in ezetimibe-intolerant patients), and agents for FH (mipomersen, lomitapide, and LDL apheresis).

*Discussion*

In summary, the PCSK9 inhibitors represent the most novel class of LLT.[2,5] Several trials have been conducted evaluating the 2 available agents, alirocumab and evolocumab, with most evaluating changes in LDL-C as a primary endpoint.[12-30] Recently, data on the effects of these agents on clinical outcomes have become available with the publication of the FOURIER trial in 2017 and presentation of the ODYSSEY OUTCOMES trial at the ACC annual meeting earlier this year.[31,33] Both studies were randomized, multicenter, double-blind, placebo-controlled trials with a composite primary outcome. There were slight differences between the 2 in terms of the study populations and the components of the primary outcome. For example, the FOURIER trial included patients aged 40 to 85 years with ASCVD (median time from most recent MI or stroke: 3.2 to 3.4 years) with LDL-C ≥70 mg/dL on statin therapy with or without ezetimibe; >27,000 patients were followed for a median of 2.2 years.[31] In contrast, the ODYSSEY OUTCOMES trial included patients aged ≥40 years with ACS 1 to 12 months prior to randomization, on statin therapy with or without ezetimibe; ~19,000 patients were followed for a median of 2.8 years.[33] In the FOURIER trial, statistically significant reductions were observed with evolocumab in MI, stroke, and coronary revascularization; in the ODYSSEY OUTCOMES trial, significant reductions were observed with alirocumab in non-fatal MI, ischemic stroke, unstable angina, and all-cause mortality.[31,33] Following the publication of the FOURIER trial, the FDA approved an additional indication for evolocumab; it remains to be seen whether a similar indication will be granted for alirocumab.[10]

Despite the fact that both trials were large and well-designed, they are not without limitations.[31,33] Consensus statements and guidelines have been issued by the ACC and NLA, respectively, which have been revised in consideration of the FOURIER trial data;[34-37] however, while recognized as second-line to statins in the management of dyslipidemia, the PCSK9 inhibitors are not strongly recommended for all patients as an initial add-on among the second-line options.[34,35] Based on the 2017 publications, both the NLA and ACC suggest that PCSK9 inhibitors be strongly considered only in patients with ASCVD and risk factors, already on maximally tolerated statin therapy, and requiring (substantial) further LDL-C reduction.

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