OPTUMRx

Therapeutic Class Overview

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

INTRODUCTION

- Cardiovascular disease (CVD) is the leading cause of death worldwide and accounts for nearly 1 in 3 deaths in the United States (US). Key cardiovascular (CV) risk factors include smoking, physical inactivity, obesity, hypercholesterolemia, poor nutrition, hypertension, and diabetes mellitus *(American Heart Association [AHA] 2019)*.
- Serum cholesterol is known to be related to atherosclerotic CVD (ASCVD), with low-density lipoprotein cholesterol (LDL-C) being the dominant form of atherogenic cholesterol. LDL-C is a primary cause of atherosclerosis, but other major contributing risk factors include cigarette smoking, hypertension, dysglycemia, and other lipoprotein abnormalities *(Grundy et al 2018).*
- Almost 40% of American adults have total cholesterol serum levels of 200 mg/dL or higher and nearly 1 in 3 have elevated levels of LDL-C (≥ 130 mg/dL) *(AHA 2019)*.
- Familial hypercholesterolemia (FH) is a common and serious genetic condition resulting in severely elevated cholesterol concentrations and increased risk of premature coronary heart disease (CHD) (*Goldberg et al 2011*). Patients can have homozygous FH (HoFH) or heterozygous FH (HeFH). HeFH is estimated to occur in 1 in 200 to 250 adults in the US; HoFH is much rarer with an estimated prevalence of 1:300,000 to 1:400,000, but homozygous patients are more adversely affected by the condition *(Rosenson and Durrington 2019).*
- Alirocumab and evolocumab are fully human monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is an enzyme that leads to the degradation of hepatocyte LDL-C receptors (LDLR), which results in increased LDL-C levels; by inhibiting PCSK9, LDLR recycling is preserved, and LDL-C levels are subsequently reduced *(Navarese et al 2015*). The PCSK9 inhibitors are administered subcutaneously (SC) every 2 weeks or once monthly.
- Current guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) *(Grundy et al 2018)*, American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) *(Jellinger et al 2017)*, and the National Lipid Association (NLA) *(Jacobson et al 2015, Orringer et al 2017)* all recommend maximally-tolerated statins as first-line therapy for hypercholesterolemia or CVD, with ezetimibe and the PCSK9 inhibitors being potential adjunctive agents for patients not achieving adequate LDL-C lowering; however, there is no consensus on goal LDL-C levels.
- Medispan class: Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Praluent (alirocumab)	-
Repatha (evolocumab)	-

(Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Praluent (alirocumab)	Repatha (evolocumab)
To reduce the risk of myocardial infarction (MI), stroke, and unstable angina (UA) requiring hospitalization in adults with established CVD	✔	
As an adjunct to diet, alone or in combination with other lipid lowering therapies (eg, statins, ezetimibe) for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C	✔	✔
As an adjunct to diet and other lipid lowering therapies (eg, statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional lowering of LDL-C		✔
To reduce the risk of MI, stroke, and coronary revascularization in adults with established CVD		✔

(Prescribing information: Praluent 2019, Repatha 2019)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The efficacy of alirocumab was evaluated in the ODYSSEY program, which consisted of 10 phase 3, multi-center (MC), double-blind (DB), randomized controlled trials (RCTs) *(Praluent Food and Drug Administration [FDA] Briefing Information).*
  - Patients with HeFH and/or high or very high CV risk were enrolled in 9 of the 10 trials. Eight trials evaluated alirocumab in patients receiving background statin therapy (typically at maximally tolerated doses), whereas 2 trials evaluated alirocumab as monotherapy, including in statin-intolerant patients (ie, ODYSSEY ALTERNATIVE). Ezetimibe was the comparator in the 5 active-controlled (AC) trials, whereas the other 5 trials were placebo-controlled (PC) *(Praluent FDA Briefing Information).*
- The efficacy of evolocumab was evaluated in the PROFICIO program, which consisted of 8 phase 3, MC, DB, RCTs *(Repatha FDA Briefing Information*).
  - In most of the trials, patients with HeFH, HoFH, or primary hyperlipidemia were randomized to receive evolocumab or placebo, and received background statin therapy in both treatment arms, ranging from moderate-intensity statin therapy (eg, atorvastatin 10 mg) to high-intensity statin therapy (eg, atorvastatin 80 mg). In 2 trials, evolocumab was compared to ezetimibe as monotherapy, including in statin-intolerant patients (ie, GAUSS-2 and -3) *(Repatha FDA Briefing Information).*

Familial hypercholesterolemia (FH)

- ODYSSEY FH I-II and HIGH FH compared the efficacy of alirocumab with placebo in patients with HeFH for a 24-week duration. In FH I-II, patients were initiated on alirocumab 75 mg SC every 2 weeks (Q2W) with an up-titration dosing strategy, whereas patients in HIGH FH were initiated on alirocumab 150 mg SC Q2W with no up-titration (*Kastelein et al 2015*).
  - ODYSSEY FH I-II were 2 identical, PC, RCTs evaluating alirocumab in 735 patients with HeFH and LDL-C > 70 mg/dL with a history of CVD or LDL-C > 100 mg/dL without history of CVD. Patients had a mean baseline LDL-C level of 140 mg/dL while receiving statin therapy; 85% of patients received high-intensity statin therapy, and 60% received ezetimibe. After 24 weeks of treatment, alirocumab reduced LDL-C by 58% and 51% in FH I and FH II, respectively, compared to placebo ($p < 0.0001$) *(Kastelein et al 2015*).
  - ODYSSEY HIGH FH evaluated alirocumab in 107 patients with HeFH and LDL-C > 160 mg/dL. Patients had a mean baseline LDL-C of approximately 200 mg/dL while receiving statin therapy; about 70% of patients were receiving high-intensity statins (eg, atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily). Compared to placebo, alirocumab reduced LDL-C by 39% at 24 weeks ($p < 0.0001$) *(Ginsberg et al 2016*).
- ODYSSEY ESCAPE was a DB, PC, RCT that randomized patients with HeFH who were undergoing lipoprotein apheresis to alirocumab 150 mg SC Q2W (n = 41) or placebo (n = 21) for 18 weeks. Patients were treated in combination with their usual apheresis schedule for 6 weeks. At week 6, the mean percent change from baseline in pre-apheresis LDL-C was -53.7% in alirocumab-treated patients vs 1.6% in placebo-treated patients; subsequently, apheresis was discontinued in 63.4% of alirocumab-treated patients, and the rate was at least halved in 92.7% *(Moriarty et al 2016).*
- In RUTHERFORD-2, patients with HeFH were randomized to receive evolocumab 140 mg SC Q2W (n = 111), evolocumab 420 mg SC every 4 weeks (Q4W) (n = 110), or placebo (n = 110) for 12 weeks. Patients had a mean baseline LDL-C level of 155 mg/dL while receiving statin therapy; 87% of patients were receiving high-intensity statin therapy, and 62% of patients were receiving ezetimibe. Compared to placebo, evolocumab 140 mg SC Q2W lowered LDL-C by 59% and evolocumab 420 mg SC Q4W by 61% at 12 weeks ($p < 0.0001$) *(Raal et al 2015a).*
- The TESLA Part B trial randomized 50 patients with HoFH on stable lipid-lowering therapy (LLT) to evolocumab 420 mg SC Q4W (n = 33) or placebo (n = 17) for 12 weeks. Patients in the evolocumab group had a mean baseline LDL-C of 356 mg/dL; those in the placebo group had a mean baseline LDL-C of 336 mg/dL. Treatment with evolocumab reduced LDL-C by 23.1%, whereas patients treated with placebo had an increase in LDL-C by 7.9% (treatment difference -30.9%; $p < 0.0001$); however, the mean on-treatment LDL-C remained significantly elevated at 271 mg/dL *(Raal et al 2015b).*
- Alirocumab has not been evaluated in patients with HoFH.

Patients with hypercholesterolemia not adequately controlled on other LLTs

- ODYSSEY COMBO I and II were 2 similarly designed 24-week, DB, RCTs in high CVD risk patients who were inadequately controlled with maximally tolerated statin therapy. Patients were included if they had a history of CVD with LDL-C ≥ 70 mg/dL, or LDL-C ≥ 100 mg/dL and CHD risk equivalents. In COMBO I, patients were randomized to alirocumab 75 mg SC Q2W (n = 209) or placebo (n = 107), whereas in COMBO II, patients were randomized to alirocumab 75 mg SC Q2W (n = 479) or ezetimibe 10 mg daily (QD) (n = 241). Both studies employed the up-titration protocol *(Cannon et al 2015, Kereiakes et al 2015).*
  - In COMBO I, 78.2% of patients had a history of CHD, 43.0% had CHD risk equivalents, and 43.0% had type 2 diabetes mellitus (T2DM). All patients but 1 received statin therapy, with 62.7% receiving high-dose statin therapy. From a baseline of 100.3 mg/dL for patients with alirocumab and 104.6 mg/dL for patients with placebo, alirocumab reduced LDL-C by 45.9% compared with placebo ($p < 0.0001$) *(Kereiakes et al 2015).*
  - In COMBO II, 75.6% of patients had CHD, 31.0% had CHD risk equivalents, and 30.7% had T2DM. All patients but 1 received statin therapy, with 66.7% receiving high-dose statin therapy. From a mean baseline of 109.0 mg/dL for patients with alirocumab and 105.0 mg/dL for patients with ezetimibe, alirocumab reduced LDL-C by 29.8% compared with ezetimibe ($p < 0.0001$) *(Cannon et al 2015).*
- ODYSSEY OPTIONS I and II were 24-week, DB, RCTs evaluating alirocumab in combination with atorvastatin or rosuvastatin in patients with hypercholesterolemia who were inadequately controlled (very high CV risk and LDL-C ≥ 70 mg/dL or high CV risk and LDL-C ≥ 100 mg/dL). In ODYSSEY OPTIONS I, 355 patients on atorvastatin 20 or 40 mg at baseline were randomized to (1) add alirocumab 75 mg SC Q2W with up-titration per ODYSSEY protocol, (2) add ezetimibe 10 mg QD, (3) double their atorvastatin dose, or (4) switch to rosuvastatin. In ODYSSEY OPTIONS II, 305 patients on rosuvastatin 10 or 20 mg were randomized to (1) add alirocumab 75 mg SC Q2W with up-titration per ODYSSEY protocol, (2) add ezetimibe 10 mg QD, or (3) double their rosuvastatin dose *(Bays et al 2015, Farnier et al 2016, Robinson et al 2014a).*
  - In OPTIONS I, among patients receiving atorvastatin 20 and 40 mg, greater LDL-C reduction was achieved with add-on alirocumab (44.1%, 54.0%), compared with add-on ezetimibe (20.5%, 22.6%), doubling atorvastatin dose (4.8%, 5.0%), or switching to rosuvastatin (21.4%; $p < 0.001$ for all comparisons) *(Robinson et al 2014a, Bays et al 2015).*
  - In OPTIONS II, in patients receiving rosuvastatin 10 mg, greater LDL-C reduction was achieved with add-on alirocumab (50.3%) compared with add-on ezetimibe (14.4%), or doubling the rosuvastatin dose (16.3%) ($p < 0.0001$ for all comparisons). In the rosuvastatin 20 mg group, the addition of alirocumab reduced LDL-C by 36.3%, but the comparisons with the ezetimibe and double rosuvastatin groups did not reach statistical significance *(Farnier et al 2016).*
- LAPLACE-2 was a phase 3 study evaluating evolocumab in combination with various statin regimens. Patients with different LDL-C levels and different background LLT were first randomized to 1 of 5 open-label (OL) statin regimens (atorvastatin 80 mg, rosuvastatin 40 mg, atorvastatin 10 mg, rosuvastatin 5 mg, or simvastatin 40 mg) for 4 weeks, and then randomized to evolocumab 140 mg SC Q2W or 420 mg SC Q4W (n = 1117), ezetimibe 10 mg QD (n = 221; patients receiving atorvastatin only), or placebo (n = 558) for 12 weeks. Compared with placebo, evolocumab further reduced LDL-C by at least 60% in all statin groups; compared with ezetimibe, evolocumab further reduced LDL-C by approximately 40% in patients receiving low-dose and high-dose atorvastatin (*Robinson et al 2014b*).
- Alirocumab was evaluated specifically in patients with diabetes in ODYSSEY DM-INSULIN and ODYSSEY DM-DISLIPIDEMIA *(Leiter et al 2017, Ray et al 2018).*
  - ODYSSEY DM-INSULIN was a 24-week, DB, PC, RCT in patients with type 1 diabetes mellitus (T1DM) (n = 71) or T2DM (n = 441) treated with insulin and not controlled on maximally-tolerated statin therapy. Patients were randomized to receive alirocumab 75 mg SC Q2W with an up-titration strategy or placebo. Alirocumab reduced LDL-C from baseline to week 24 by 49% and 47.8% vs placebo in patients with T2DM and T1DM, respectively (both $p < 0.0001$). Glycated hemoglobin (HbA1c) and fasting blood glucose levels remained stable and treatment-emergent adverse effects (TEAEs) were comparable across the groups *(Leiter et al 2017).*
  - ODYSSEY DM-DISLIPIDEMIA was a 24-week, OL, RCT in patients with T2DM and mixed dyslipidemia (defined as non-HDL-C ≥ 100 mg/dL and triglycerides ≥ 150 mg/dL but < 500 mg/dL) not adequately controlled despite maximally tolerated statin therapy. Patients were randomized to receive alirocumab (n = 276) or usual care (n = 137). Alirocumab reduced non-HDL-C by 37.3% vs 4.7% with usual care ($p < 0.0001$). No clinically meaningful effect was seen on HbA1c or change in number of glucose-lowering agents. The rate of TEAEs was similar between the groups *(Ray et al 2018).*

Monotherapy and patients unable to tolerate statin therapy

- ODYSSEY MONO was a 24-week, DB, AC, RCT comparing alirocumab monotherapy with ezetimibe in patients with hypercholesterolemia. Patients were randomized to receive alirocumab 75 mg SC Q2W (n = 52) with the option to titrate to 150 mg Q2W, or ezetimibe 10 mg QD (n = 51). At 24 weeks, alirocumab reduced LDL-C from baseline by 47.2% vs 15.6% for ezetimibe (treatment difference: -31.6%; p < 0.0001). Adverse effects (AEs) were similar between the groups *(Roth and McKenney 2015).*
- MENDEL-2 was a 12-week, DB, AC, PC, RCT comparing evolocumab monotherapy with ezetimibe or placebo in patients with hypercholesterolemia. Patients were randomized to receive evolocumab 140 mg SC Q2W (n = 153) or 420 mg SC Q4W (n = 153), ezetimibe 10 mg QD (n = 154), or placebo (n = 155). Evolocumab reduced LDL-C from baseline by 55% to 57% more than placebo and 38% to 40% more than ezetimibe (p < 0.001 for all comparisons). TEAEs and muscle-related AEs were comparable across the groups *(Koren et al 2014b).*
- ODYSSEY ALTERNATIVE was a 24-week, DB, AC, RCT comparing alirocumab with ezetimibe and atorvastatin in statin-intolerant patients. Patients were randomized to receive alirocumab 75 mg SC Q2W (n = 126) with the option to titrate to 150 mg, ezetimibe 10 mg QD (n = 125), or atorvastatin 20 mg QD (n = 63) (validation arm). Alirocumab reduced LDL-C by 45% from baseline vs 14.6% for ezetimibe (treatment difference -30.4%; p < 0.0001). Alirocumab was better-tolerated than atorvastatin in patients in terms of muscle-related TEAEs (32.5% vs 46.0%; p = 0.042) *(Moriarty et al 2015).*
- GAUSS-2 and -3 both compared evolocumab with ezetimibe in statin-intolerant patients *(Nissen et al 2016, Stroes et al 2014)*.
  - GAUSS-2 was a 12-week, DB, PC, AC trial with patients randomized to evolocumab 140 mg SC Q2W + placebo orally QD (n = 103), evolocumab 420 mg SC Q4W + placebo orally daily (n = 102), or ezetimibe 10 mg orally QD + placebo SC Q2W or Q4W (n = 102). Evolocumab reduced LDL-C from baseline by 53% to 56%, corresponding to treatment differences vs ezetimibe of 37% and 39% (p < 0.001). Muscle-related TEAEs occurred in 12% of evolocumab-treated patients vs 23% of ezetimibe-treated patients *(Stroes et al 2014).*
  - GAUSS-3 was a 24-week, 2-stage RCT in patients with a history of intolerance to 2 or more statins (N = 511). Phase A used a 24-week crossover protocol with atorvastatin or placebo to identify patients experiencing muscle-related AEs only to atorvastatin. In Phase B, patients experiencing intolerance only to atorvastatin were randomized to ezetimibe 10 mg QD (n = 73) or evolocumab 420 mg SC Q4W (n = 145) for 24 weeks. From baseline, evolocumab reduced LDL-C by 52.8% vs 16.7% for ezetimibe (treatment difference: -36.1%; p < 0.001). Muscle-related AEs were reported in 20.7% of evolocumab-treated patients and 28.8% of ezetimibe-treated patients *(Nissen et al 2016).*

Longer term efficacy and safety

- ODYSSEY LONG TERM was a 78-week, DB, PC, RCT in which high CVD risk patients who were receiving maximally tolerated statin therapy and had an LDL-C ≥ 70 mg/dL were randomized to receive alirocumab 150 mg SC Q2W (n = 1553) or placebo (n = 788) (*Robinson et al 2015*).
  - Compared with placebo, alirocumab reduced LDL-C by 61.9% at 24 weeks (p < 0.001); LDL-C reduction was sustained through 78 weeks (56.0% vs placebo; p < 0.001).
  - In a post hoc analysis, patients treated with alirocumab had a lower rate of adjudicated composite CVD events (ie, CHD death, nonfatal MI, ischemic stroke, or UA requiring hospitalization) compared with placebo (1.7% vs 3.3%, respectively; hazard ratio [HR] 0.52; 95% confidence interval [CI], 0.31 to 0.90; p = 0.02). However, there was no difference when including all positively adjudicated CVD events (ie, congestive heart failure requiring hospitalization, ischemia-driven coronary revascularization) (4.6% vs 5.1%, respectively; p = 0.68).
  - The frequency of AEs was similar in both groups (81.0% vs 82.5%, respectively), as were discontinuation rates (7.2% vs 5.8%, respectively).
- The OSLER studies enrolled 4465 patients who had completed a phase 2 or phase 3 trial with evolocumab, and randomly assigned them to OL evolocumab plus standard of care (SOC) or SOC alone. OSLER-1 enrolled patients from phase 2 trials to receive evolocumab 420 mg SC Q4W, whereas OSLER-2 enrolled patients from phase 3 trials to receive evolocumab 140 mg SC Q2W or 420 mg SC Q4W depending on patient choice. The parent trials included patients on statin therapy (70.1%), as well as patients who were statin intolerant or were not on other LLTs *(Koren et al 2014a, Sabatine et al 2015).*
  - Compared with SOC alone, evolocumab reduced LDL-C by 58.8% at 24 weeks (p < 0.001); LDL-C reduction was sustained through 48 weeks (58.4% vs SOC; p < 0.001).

- In a prespecified exploratory analysis, patients treated with evolocumab had a lower rate of CVD events (ie, death, MI, UA requiring hospitalization, coronary revascularization, stroke, transient ischemic attack [TIA], heart failure requiring hospitalization) (0.95% vs 2.18% with SOC; HR 0.47; 95% CI, 0.28 to 0.78; p = 0.003).
- The frequency of AEs was similar in both groups (69.2% vs 64.8%, respectively), as were serious AEs (7.5% in each group). Although uncommon overall, neurocognitive AEs were more frequent with evolocumab (0.9% vs 0.3% with SOC).
- In 5-year results from OSLER-1, evolocumab demonstrated sustained mean LDL-C reductions over time, with patients maintaining a 56% reduction from baseline at year 5. Evolocumab was not associated with an increase in AEs or neutralizing antibodies over time *(Koren et al 2018 [abstract])*.

- DESCARTES was a 52-week RCT comparing evolocumab with placebo in 901 hypercholesterolemic patients with a range of CVD risk. Prior to the treatment phase, patients were assigned to 1 of 4 background LLT groups in a 4- to 12-week OL run-in period: diet alone, diet with atorvastatin 10 mg QD, diet with atorvastatin 80 mg QD, or diet with atorvastatin 80 mg QD and ezetimibe 10 mg QD. Patients were intensified to the next level of background LLT if they did not reach their LDL-C goal per current guidelines (Adult Treatment Panel [ATP] III). After the run-in period, patients were then randomized in a 2:1 ratio to evolocumab 420 mg SC Q4W (n = 599) or placebo (n = 302). After 52 weeks, evolocumab reduced LDL-C in all 4 LLT groups compared with placebo (55.7%, 61.6%, 56.8%, 48.5%, respectively; p < 0.001 for all comparisons) *(Blom et al 2014).*

Cardiovascular outcomes

- FOURIER, a DB, PC, RCT, was the first completed CV outcomes trial for the PCSK9 inhibitors. The trial enrolled 27,564 high-risk patients with CVD and LDL-C levels ≥ 70 mg/dL while receiving optimized LLT (99.7% of patients were receiving moderate- or high-intensity statins). Patients were randomized to receive evolocumab (either 140 mg SC Q2W or 420 mg SC Q4W) or placebo, while remaining on their baseline LLT. The primary endpoint was a composite of CV death, MI, stroke, hospitalization for UA, and coronary revascularization *(Sabatine et al 2017)*.
  - At 48 weeks, the least-squares mean (LSM) percentage reduction in LDL-C levels with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg/dL to 30 mg/dL (p < 0.001).
  - The composite endpoint occurred in 9.8% of evolocumab-treated patients vs 11.3% of placebo-treated patients (treatment difference of 1.5%; HR 0.85; 95% CI, 0.79 to 0.92; p < 0.001) during a median follow-up period of 26 months. The benefit was driven by reduction of MI, stroke, and coronary revascularization; no benefit was identified in CV death or death from any cause.
- ODYSSEY OUTCOMES was a DB, PC, RCT enrolling 18,924 patients who had experienced an acute coronary syndrome (ACS) between 1 to 12 months prior and had inadequate control of their lipids (eg, LDL-C ≥ 70 mg/dL) despite maximally-tolerated statin therapy. Patients were randomized to receive alirocumab (75 mg or 150 mg SC Q2W) or placebo in addition to their baseline LLT to treat to an LDL-C target of 25 to 50 mg/dL. The primary endpoint was a composite of CHD death, non-fatal MI, ischemic stroke, and UA requiring hospitalization. Median follow-up was 2.8 years *(Schwartz et al 2018).*
  - Compared to placebo, alirocumab reduced the overall risk of the primary composite outcome (alirocumab: 9.5% vs placebo: 11.1%; HR 0.85; 95% CI, 0.78 to 0.93; p = 0.0003) and was associated with a lower risk of non-fatal MI (alirocumab: 6.6% vs placebo: 7.6%; HR 0.86; 95% CI, 0.77 to 0.96; p = 0.006), ischemic stroke (alirocumab: 1.2% vs placebo: 1.6%; HR 0.73; 95% CI, 0.57 to 0.93; p = 0.01), and UA (alirocumab: 0.4% vs placebo: 0.6%; HR 0.61; 95% CI, 0.41 to 0.92; p = 0.02).
    - For the primary composite endpoint, the absolute benefit of alirocumab was greater among patients with a baseline LDL-C level ≥ 100 mg/dL (HR 0.76; 95% CI, 0.65 to 0.87) compared to patients with lower baseline levels; however, the analysis on this subgroup was not prespecified.
  - Alirocumab was associated with a lower risk of all-cause mortality (alirocumab: 3.5% vs placebo: 4.1%; HR 0.85; 95% CI, 0.73 to 0.98; nominal p = 0.026), and there were also numerically fewer CHD deaths (alirocumab: 2.2% vs placebo: 2.3%; HR 0.92; 95% CI, 0.76 to 1.11; p = 0.38).
  - In a prespecified analysis of 8242 patients eligible for ≥ 3 years follow-up, alirocumab reduced death (HR 0.78; 95% CI, 0.65 to 0.94; p = 0.01). A post hoc analysis found that patients with baseline LDL-C ≥ 100 mg/dL had a greater absolute risk of death and a larger mortality benefit from alirocumab (HR 0.71; 95% CI, 0.56 to 0.90; *p*interaction = 0.007). Patients who achieved lower LDL-C values at 4 months (down to ~ 30 mg/dL) appeared to be at lower risk of subsequent death. (*Steg et al 2019*).

Meta-analyses

A Cochrane Review meta-analysis of 20 studies (N = 67,237) comparing PCSK9 inhibitors with placebo (13 RCTs), ezetimibe (2 RCTs), or ezetimibe and statins (5 RCTs) was conducted to quantify short-, medium-, and long-term effects of PCSK9 inhibitors on lipid parameters and on the incidence of CVD *(Schmidt et al 2017)*.
  - At 24 weeks, PCSK9 inhibitors decreased LDL-C by 53.86% vs placebo, 30.20% vs ezetimibe, and 39.20% vs ezetimibe and statins.
  - Compared with placebo, PCSK9 inhibitors decreased the risk of CVD events, with a risk difference (RD) of 0.91% (odds ratio [OR] 0.86; 95% CI, 0.80 to 0.92). Compared with ezetimibe and statins, PCSK9 inhibitors appeared to have a stronger protective effect on CVD risk, although with considerable uncertainty (RD 1.06%; OR 0.45; 95% CI, 0.27 to 0.75).
  - Compared with placebo, PCSK9 inhibitors probably had little or no effect on mortality (RD 0.03%; OR 1.02; 95% CI, 0.91 to 1.14).
- A meta-analysis was conducted on 35 RCTs comparing treatment with a PCSK9 inhibitor to no PCSK9 inhibitor in adults with hypercholesterolemia (N = 45,539). Compared with no PCSK9 inhibitor use, treatment with a PCSK9 inhibitor was associated with a statistically significant reduction in MI (PCSK9 inhibitor: 2.3% vs control: 3.6%; OR 0.72; 95% CI, 0.64 to 0.81), stroke (1.0% vs 1.4%; OR 0.80; 95% CI, 0.67 to 0.96), and coronary revascularization (4.2% vs 5.8%; OR 0.78; 95% CI, 0.71 to 0.86). Use of a PCSK9 inhibitor was not significantly associated with a decrease in all-cause mortality (1.9% vs 2.2%; OR 0.71; 95% CI, 0.47 to 1.09) or CV mortality (1.1% vs 1.3%; OR 1.01; 95% CI, 0.85 to 1.19) *(Karatasakis et al 2017)*.
- In an updated meta-analysis involving 62,281 patients from 28 RCTs, the CV outcomes of PCSK9 inhibitor therapy (N = 33,204) vs placebo (N = 29,077) were assessed (*Casula et al 2019*). Results revealed no significant difference in all-cause mortality between the groups (OR 0.93; 95% CI, 0.85 to 1.03). However, PCSK9 inhibitor therapy was associated with a significant reduction in CV events as compared to placebo (OR 0.83; 95% CI, 0.78 to 0.87). Additionally, the occurrence of stroke and MI were significantly reduced with the PCSK9 inhibitors. CV mortality was not significantly different between the groups (OR 0.94; 95% CI, 0.83 to 1.07)

CLINICAL GUIDELINES

- The updated ACC/AHA (2018) treatment guidelines for hypercholesterolemia emphasize reducing the risk of ASCVD through lipid management. In patients with clinical ASCVD, LDL-C should be reduced with high-intensity or maximally tolerated statin therapy. In very high risk ASCVD, an LDL-C threshold of 70 mg/dL should be utilized to consider the addition of non-statins to maximally tolerated statin therapy. If the addition of ezetimibe does not decrease LDL-C levels < 70 mg/dL, the addition of a PCSK9 inhibitor is reasonable. Similarly, in patients with severe primary hypercholesterolemia (LDL-C ≥ 190 mg/dL), high-intensity statin therapy should be initiated, but if the LDL-C level remains ≥ 100 mg/dL, adding ezetimibe may be reasonable. If the LDL-C level on statin plus ezetimibe remains ≥ 100 mg/dL and the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered. The guideline notes that long-term safety (> 3 years) with the PCSK9 inhibitors is uncertain and cost-effectiveness is low at mid-2018 prices *(Grundy et al 2018)*.
- The NLA guideline (2015) recommends that the central focus of pharmacotherapy in hypercholesterolemia be moderate- or high-intensity statin therapy, and acknowledges that RCT evidence is limited in guiding combination drug therapy in patients receiving maximally tolerated statin therapy whose atherogenic cholesterol remains elevated above treatment goals *(Jacobson et al 2015)*.
  - The NLA Expert Panel evidence-based recommendations on treatment with PCSK9 inhibitors are summarized in Table 3. Patients with ASCVD and/or additional risk factors who have not met their LDL-C goals should be considered for adjunct therapy with a PCSK9 inhibitor; it is emphasized that clinicians should reinforce the importance of statin therapy and attention to lifestyle therapy with each patient visit *(Orringer et al 2017)*.

Table 3. 2017 NLA expert panel PCSK9 inhibitor recommendations

Disorder	LDL-C/Non-HDL-C for threshold for Rx (mg/dL)
ASCVD + additional risk factors	≥ 70/ ≥ 100
Progressive ASCVD	≥ 70/ ≥ 100
LDL-C ≥ 190, age 40 to 79 with no uncontrolled risk factors or key additional risk markers	≥ 100/ ≥ 130
LDL-C ≥ 190, age 40 to 79 with uncontrolled risk factors or key additional risk	≥ 70/ ≥ 100

markers	
LDL-C ≥ 190, age 18 to 39 with uncontrolled risk factors or key additional risk markers or FH causing mutation	≥ 100/ ≥ 130
HoFH phenotype	≥ 70/ ≥ 100
ASCVD + statin intolerance	Clinical judgment

- The AACE/ACE guidelines recommend LDL-C treatment goals based on ASCVD risk categories. Target LDL-C levels range from < 130 mg/dL for patients at low CV risk with zero ASCVD risk factors, to < 55 mg/dL for patients considered at extreme risk with progressive ASCVD. Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. PCSK9 inhibitors should be considered as adjunct therapy in patients with FH or clinical CVD who are unable to reach their LDL-C goals with maximally tolerated statin therapy *(Jellinger et al 2017).*

SAFETY SUMMARY

- Warnings/precautions
  - Hypersensitivity reactions (eg, pruritus, rash, urticaria), including some serious events (eg, hypersensitivity vasculitis, hypersensitivity reactions requiring hospitalization), have been reported with alirocumab and evolocumab treatment.
- Adverse effects
  - Alirocumab and evolocumab are generally well-tolerated. The most common AEs include nasopharyngitis, injection site reactions, and influenza.
- Low LDL-C levels (ie, LDL-C < 25 mg/dL) were frequently encountered with alirocumab and evolocumab in clinical trial experience; however, symptoms associated with abetalipoproteinemia, a familial condition with minimal or nonexistent LDL-C levels (eg, fat malabsorption syndromes, hepatic steatosis, progressive neurologic degenerative disease, retinitis pigmentosa, acanthocytosis), were not observed *(McKenney 2015).* Rates of overall AEs, serious AEs, and neurocognitive AEs among patients achieving very low LDL-C levels were similar to those among the overall group *(Robinson et al 2015, Sabatine et al 2015, Sabatine et al 2017).* The long-term effects of very low LDL-C levels by alirocumab or evolocumab are unknown *(Praluent Prescribing Information 2019, Repatha Prescribing Information 2019).*
- Neurocognitive AEs occurred infrequently, but more often in patients treated with alirocumab (1.2% vs 0.5% with placebo) and evolocumab (0.9% vs 0.3% with placebo) in longer-term safety analyses *(Robinson et al 2015, Sabatine et al 2015).*
  - The EBBINGHAUS trial evaluated cognitive function in 1204 patients enrolled in the FOURIER trial and identified no important cognitive differences between patients treated with evolocumab vs placebo over a median follow-up of 19 months *(Giugliano et al 2017).*
  - A meta-analysis of 14 Phase 2 and 3 alirocumab trials found no significant differences in rates of patient-reported neurocognitive TEAEs between alirocumab and controls (placebo or ezetimibe). No association was found between neurocognitive TEAEs and LDL-C < 25 mg/dL *(Harvey et al 2018).*
- There are no data available on use of alirocumab or evolocumab in pregnant or lactating women to inform a drug-associated risk.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Praluent (alirocumab)	Single-dose pre-filled syringe: 75 mg/mL, 150 mg/mL Single-dose pre-filled pen: 75 mg/mL, 150 mg/mL	SC	Starting dose: 75 mg every 2 weeks or 300 mg every 4 weeks If LDL-C response is inadequate, the dosage may be adjusted to the maximum dose of 150 mg every 2	The safety and efficacy of alirocumab have not been established in the pediatric population.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			weeks HeFH patients undergoing LDL apheresis: 150 mg every 2 weeks; can be administered without regard to timing of apheresis	
Repatha (evolocumab)	Single-dose pre-filled syringe: 140 mg/mL Single-dose pre-filled autoinjector: 140 mg/mL Single-dose pre-filled cartridge with on-body infusor: 420 mg/3.5 mL	SC	Established ASCVD or primary hyperlipidemia: 140 mg every 2 weeks or 420 mg once monthly HoFH: 420 mg once monthly	The safety and efficacy of evolocumab in combination with diet and other LDL-C lowering therapies in adolescents with HoFH were established based on data from a 12-week, PC trial that included 10 adolescents (ages 13 to 17 years old) with HoFH. Safety and effectiveness have not been established in pediatric patients with HoFH who are younger than 13 years old. Safety and effectiveness have not been established in pediatric patients with primary hyperlipidemia or HeFH.

See the current prescribing information for full details

CONCLUSION

- CVD is the leading cause of death worldwide *(AHA 2019)*. Serum cholesterol is known to be related to ASCVD, with LDL-C being the dominant form of atherogenic cholesterol *(Grundy et al 2018).*
- Alirocumab and evolocumab are fully human monoclonal antibodies that inhibit PCSK9, leading to substantial LDL-C reduction *(Navarese et al 2015*). The PCSK9 inhibitors are administered SC every 2 weeks or once monthly.
  - Alirocumab is indicated as an adjunct to diet, alone or in combination with other LLTs (eg, statins, ezetimibe) for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C and to reduce the risk of MI, stroke, and UA requiring hospitalization in adults with established CVD.
  - Evolocumab is indicated as an adjunct to diet, alone or in combination with other LLTs (eg, statins, ezetimibe) for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C; as an adjunct to diet and other LLTs (eg, statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional lowering of LDL-C; and to reduce the risk of MI, stroke, and coronary revascularization in adults with established CVD.
- The efficacy and safety of alirocumab and evolocumab have been demonstrated across numerous clinical trials in various patient populations. The PCSK9 inhibitors offer substantial LDL-C lowering and both have been shown to reduce CV events in high-risk patients, although benefit on mortality is still unclear.
- Alirocumab and evolocumab are generally well-tolerated. The most common AEs include nasopharyngitis, injection site reactions, and influenza.
  - Low LDL-C levels (ie, LDL-C < 25 mg/dL) were frequently encountered with alirocumab and evolocumab in clinical trial experience; however, rates of overall AEs, serious AEs, and neurocognitive AEs among these patients were similar to those among the overall group. The long-term effects of very low LDL-C levels by alirocumab or evolocumab are still unknown.

- Current guidelines from the ACC/AHA *(Grundy et al 2018)*, AACE/ACE *(Jellinger et al 2017)*, and the NLA *(Jacobson et al 2015, Orringer et al 2017)* all recommend maximally-tolerated statins as first-line therapy, with ezetimibe and the PCSK9 inhibitors as potential second-line agents for patients not achieving adequate LDL-C lowering. Patients with ASCVD or at high risk for ASCVD may benefit from more aggressive LDL-C targets; however, there is no consensus on goal LDL-C levels.

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