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Omega-3 Fatty Acids for Hypertriglyceridemia: Focus on Epanova®

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Hypertriglyceridemia, defined as a fasting triglyceride (TG) concentration >150 mg/dL, is common in the United States, affecting an estimated 31.4% of Americans over the age of 20 years.[1] Hypertriglyceridemia is frequently associated with metabolic syndrome and other lipid abnormalities that are linked to coronary artery diseases (CAD), putting patients at an increased risk for cardiovascular morbidity and mortality.[2] Hypertriglyceridemia is the third leading cause of pancreatitis, behind gallstones and alcohol abuse, and is estimated to cause between 1% and 4% of acute pancreatitis cases. Severe hypertriglyceridemia, defined as TG >500 mg/dL and which carries the greatest risk of causing acute pancreatitis, has risen in prevalence to ~4 million Americans by most recent estimates.[3]

Common causes of hypertriglyceridemia include obesity, hypothyroidism, and diabetes mellitus. Diets consisting of a high carbohydrate content and alcohol intake can also be significant modifiable risk factors for hypertriglyceridemia.[4] The National Cholesterol Education Program (NCEP) recommends that triglyceride reduction is the primary treatment goal for patients with severe hypertriglyceridemia (TG >500 mg/dL).[5] The current mainstay of treatment, as recommended by the American Heart Association (AHA), for isolated severe hypertriglyceridemia is therapeutic lifestyle changes (i.e., low-fat/low-carbohydrate diet, reduced alcohol intake, 30 minutes of aerobic exercise ≥5 days/week) and omega-3 essential fatty acids, which are metabolized into docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).[5] These omega-3 long chain fatty acids are considered essential since they are not synthesized endogenously. Typical dietary foods that contain these two omega-3 fatty acids include plant oils and fish. Over-the-counter supplements are also available containing DHA and EPA, but the manufacturing of such supplements is often poorly regulated leading some clinicians to avoid recommending these supplements to patients.[6]

IN THIS ISSUE

Several prescription omega-3 fatty acids are now available in the U.S., including Lovaza, Omtryg, and Vascepa. In May 2014, a new omega-3 fatty acid formulation was approved under the brand name Epanova®. This article will review prescription-only omega-3 fatty acids for severe hypertriglyceridemia with a focus on the newly-approved product Epanova®.

Pharmacology of Omega-3 Fatty Acids

The active molecules of omega-3 fatty acids are EPA and DHA. While the exact mechanisms of DHA and EPA are not completely understood, their beneficial effects are thought to be due to some combination of changed cell and tissue behavior, oxidation of LDL, direct effects via intracellular fatty acid receptors, and changes made in the composition of the cell membranes of phospholipids.[12] The full mechanism of Epanova® is also not completely understood. However, proposed mechanisms of this drug include decreased lipogenesis in the liver, increased mitochondrial and peroxisomal β-oxidation in the liver (used for fatty acid metabolism), inhibition of acyl-CoA: 1,2-diacylglycerol acyltransferase (catalyzes the formation of triglycerides from Acyl Co-A and diacylglycerol), and increased plasma lipoprotein lipase activity.[7] DHA and EPA are also poor substrates for enzymes that promote triglyceride synthesis.

The fatty acid ethyl esters (present in Lovaza® and Omtryg®) require pancreatic enzyme hydrolysis catalyzed through carboxyl ester lipase. Thus, the absorption of these compounds is highly dependent on administration with fatty meal contents.[4] Icosapent ethyl esters (present in Vascepa®) contain high-purity EPA ethyl esters that break down to EPA alone, which may be responsible for the lack of an increase in LDL observed with Vascepa® use.[8] As with ethyl esters, Vascepa® also requires co-administration with fatty meals for maximum absorption. On the other hand, omega-3 fatty-carboxylic acids (present in Epanova®) are not dependent on pancreatic enzyme activity, and thus have improved oral bioavailability compared with ethyl esters and do not require co-administration with fatty meals.[13]

Maximum concentrations are seen 5 to 8 hours after dosing for EPA and 5 to 9 hours after dosing for DHA. Epanova® achieves steady-state concentrations of DHA and EPA after two weeks of repeated dosing. Epanova® has been shown to have an increased systemic exposure of EPA by ~140% when given with fatty meals, but no change in exposure of total DHA.[7]

Proposed Benefits of Omega-3s

Omega-3 fatty acids are thought to have cardio-protective effects other than lowering triglycerides, such as lowering of both systolic and diastolic blood pressure, antithrombotic and anti-inflammatory effects, and improvement of endothelial function. However, data supporting omega-3 fatty acids and their effects on CV events or mortality, as well as their effects on the risk of pan-

Table 1 | Comparison of current FDA-approved omega-3 fatty acid medications.[6-11]

Drug	FA Type	Dosage	Cost[a]	Advantages	Disadvantages
Epanova®	Omega-3 carboxylic acid	2 or 4 g once daily	Pricing not yet available	• Take without regard to meals • Increased bioavailability vs. Lovaza®	• May increase LDL
Lovaza®	Omega-3 ethyl ester	4 g daily or 2 g twice daily	~$230	• Take without regard to meals	• May increase LDL • May increase symptomatic atrial fibrillation/ flutter
Omtryg®	Omega-3 acid ethyl esters	4.8 g daily or 2.4 g twice daily	Pricing not yet available		• May increase LDL • May increase symptomatic atrial fibrillation/ flutter • Must be taken with meals
Vascepa®	Icosapent ethyl ester	2 g twice daily	~$230	• Does not increase LDL	• Must be taken with meals

*Approximate average cash price, per 1-month supply. **FA =** fatty acid; **LDL =** low-density lipoprotein.

creatitis has not been established.[6-9] Thus, many of these surrogate outcomes (blood pressure reduction, improvement of endothelial function, anti-inflammatory, and antithrombotic effects) have had their benefits questioned without hard outcome data. Both DHA and EPA agents have been found to have a reduction in triglycerides, however DHA treatment alone has been associated with increases in LDL and HDL concentrations compared with EPA treatment alone.[4] **Table 1** shows a comparison of the various FDA-approved omega-3 fatty acid products.

Clinical Trials of Epanova®

ECLIPSE Trial

The Epanova® Compared to Lovaza® In a Pharmacokinetic Single-dose Evaluation (ECLIPSE) Trial compared the bioavailability of EPA and DHA between Lovaza® and Epanova®.[13] This trial was an open-label, randomized, single-dose, four-way crossover bioavailability study that compared the two drugs when administered during periods of low-fat and high-fat consumptions. Patients were randomly assigned to one of two treatment sequences as summarized in the **Figure**. The crossover washout period between each phase was 7 days and during each phase the patients took their medications for a duration of 4 days. The primary outcome measures was the area under the plasma concentration time curve from 0 to 24 hours (AUC_{0-24}). Inclusion criteria for this trial were age ≥18 years, a BMI between 25 and 35 kg/m^2, and a patient willingness to maintain their current activity level and follow therapeutic lifestyle changes during screening and crossover treatment washouts. The washout periods for EPA or DHA supplements or fish oil was 60 days to ensure the data would not be skewed by patients already treating elevated triglycerides. Baseline demographic characteristics included 77% of patients being men with an average age of 54 years; 67% of patients were African American or Black.[13]

Epanova® (low-fat diet) → Lovaza® (low-fat diet) → Epanova® (high-fat diet) → Lovaza® (high-fat diet)

or

Lovaza® (low-fat diet) → Epanova® (low-fat diet) → Lovaza® (high-fat diet) → Epanova® (high-fat diet)

Figure | Treatment arms from the ECLIPSE Trial.[13]

The results showed that Epanova® had a 4-fold greater bioavailability for the EPA and DHA compounds when compared to Lovaza® during low-fat diet consumption periods. Epanova® showed an AUC_{0-24} during low-fat diet of 3123.7 nmol·h/mL, compared to 735.2 nmol·h/mL for Lovaza®, and an AUC_{0-24} of 4938.5 nmol·h/ mL when given during a high-fat diet versus 3953.71 nmol·h/mL for Lovaza®. The study also showed that Epanova® had a greater bioavailability when given with a high fat period (AUC_{0-24}, 4938.5 nmol·h/mL) than Epanova® during a low-fat period (AUC_{0-24}, 3123.7 nmol·h/mL).[13]

EVOLVE Trial

The EpanoVa fOr Lowering Very high triglyceridEs (EVOLVE) trial was a multinational, double-blind, randomized, parallel, four arm, outpatient study that evaluated the safety and lipid-altering efficacy of 12 weeks of treatment of Epanova® compared to olive oil ("placebo") in 399 patients with severe hypertriglyceridemia.[3] Both placebo and treatment groups received the recommended therapeutic lifestyle changes from the National Cholesterol Education Program Adult Treatment Panel III guidelines. Inclusion criteria were age ≥18 years, BMI ≥20 kg/m^2, a mean serum TG ≥500 mg/dL but ≤2000 mg/dL, and either untreated dyslipidemia or a stable dose of a statin, cholesterol absorption inhibitor (CAI), or combination of the two.[3] Subjects also had their consumption of fish limited to no more than twice per week throughout the study. A two-week washout was used for subjects who were on bile acid sequestrants, fibrates, niacin, or other lipid-altering supplements. Patients were randomly assigned to one of 4 treatment arms: olive oil 4 grams daily (n=99), Epanova® 2 grams daily with 2 grams olive oil daily (n=100), Epanova® 3 grams daily with 1 gram olive oil (n=101), or Epanova® 4 grams daily (n=99). The primary endpoint was percent change in fasting serum TG concentration from baseline after 12 weeks of treatment. Patients enrolled in this trial were predominantly male (77%) and white (92%), with an average age of 52 years and average weight of 93.5 kg at baseline; 67% had pre-existing hypertension and 57% were obese at baseline.

By the end of 12 weeks of treatment, the group receiving Epanova® 4 grams daily had an average decrease in TG concentration by 30.9% from a baseline of 655 mg/dL ($p<0.001$), where-

Table 2 | Summary of Epanova® clinical trials.[3,13,14]

Study	Design	Treatment Arms	Primary Endpoints	Conclusions
ECLIPSE[13]	• 4 way cross-over • Open-label • Single dose • Randomized • Bioavailability study	• Epanova® 4 g/d with low-fat diet • Epanova® 4g/d with high-fat diet • Lovaza® 4g/d with low-fat diet • Lovaza® 4g/d with high-fat diet	AUC_{0-24} • Epanova® low fat diet: 3123.7 nmol·h/mL • Epanova® high fat diet: 4938.5 nmol·h/mL • Lovaza® low fat diet: 735.2 nmol·h/mL • Lovaza® high fat diet: 3953.8 nmol·h/mL	• Epanova® has superior bioavailability to Lovaza® when given during low fat diets and during high fat diets • Epanova® and Lovaza® both have peak bioavailability during high fat diets • Epanova® when given during a low fat diet has a bioavailability over four times greater than Lovaza® during low fat dieting
EVOLVE[3]	• 12 weeks • Randomized • Double-blind • Placebo-controlled	• OO 4g/d • Epanova® 2g/d + OO 2g/d • Epanova® 3g/d + OO 1g/d • Epanova® 4g/day	TG % Reduction: • OO 4 g/d: 4.3% • Epanova® 2 g/d + OO 2 g/d: 25.9% • Epanova® 3 g/d + OO 1 g/d: -25.5% • Epanova® 4 g/day: 30.9%	• 2, 3, and 4 gram doses of Epanova® resulted in significantly reduced TG in all patients vs. control (olive oil) • 4 gram daily dose resulted in highest (30.9%) TG reduction
ESPRIT[14]	• Double-blind • Randomized • Controlled • Parallel-group	• OO 4 g daily • OO 2 g daily + Epanova® 2 g daily • Epanova® 4 g daily	Reduction in Non-HDL-Cholesterol: • OO 4 g/d: 0.9% • OO 2 g/d + Epanova® 2 g/d: 3.9% • Epanova® 4 g/d: 6.9%	• Epanova® 2grams daily and 4 grams daily resulted in statistically significant decreases in non-HDL cholesterol in patients already optimized on statin therapy

OO = olive oil; **TG =** triglyceride; **g/d =** grams per day; **AUC_{0-24} =** area under plasma concentration time curve from 0-24 hours.

as the group assigned to Epanova® 3 grams daily had a 25.5% decrease from a baseline of 728 mg/dL ($p<0.01$). The group assigned to Epanova® 2 grams daily had a 25.9% decrease from a baseline TG of 717 mg/dL ($p<0.01$), and the control group receiving 4 grams olive oil daily had an average decrease of 4.3% from a baseline TG of 682 mg/dL.[3]

ESPRIT Trial

The randomized, double-blind, controlled, parallel-group ESPRIT trial was aimed at answering whether Epanova® reduced triglycerides in patients with hypertriglyceridemia who were already being treated with a maximum statin dose (at or near their current LDL goal) or a statin in addition to ezetimbe.[14] After a 6-week lead-in period of optimal dose statin therapy or statin therapy in addition to ezetimbe, all patients (n=647) underwent therapeutic lifestyle changes in accordance with the National Cholesterol Educational Program. Patients with fasting TG concentration <500 and ≥200 mg/dL were randomly assigned to 6 weeks of treatment with Epanova® 2 grams daily in addition to 2 grams of olive oil daily, Epanova® 4 grams daily, or olive oil 4 grams daily.[14] The primary endpoint was the percent change in non-HDL from baseline until the end of treatment. Patients were continued on their same dose of statin and their same diets initiated during the lead-in period.

After 6 weeks of treatment, patients assigned to the control arm (olive oil) achieved a nonsignificant 0.9% reduction in non-HDL concentration from a baseline of 135 mg/dL, those assigned to 2 grams of Epanova® daily achieved a 3.9% reduction in non-HDL concentration from a baseline of 140 mg/dL ($p=0.05$), and those assigned to 4 grams of Epanova® daily achieved a 6.9% reduction in non-HDL concentration from a baseline of 139 mg/dL ($p=0.001$). This trial also showed an average reduction of TG of 14.6% ($p=0.01$) for the 2 gram daily dose of Epanova® and 20.6% ($p=0.001$) for the 4 gram daily dose of Epanova®, whereas the control group achieved a 5.9% reduction in TG concentration from baseline. The 2 gram dose of Epanova® also resulted in a 4.6% increase in LDL concentration ($p=0.025$), whereas the 4 gram dose of Epanova® was associated with a 1.3% increase in LDL concentration ($p=0.65$) and the control group had an average increase in LDL of 1.1% [14]

Adverse Reactions

The most common side effects observed in clinical trials were gastrointestinal disorders and these occurrences remained fairly consistent across each dosage of Epanova®. In placebo-controlled trials, Epanova® 2 grams daily was associated most commonly with diarrhea (7%), nausea (4%), abdominal pain or discomfort (3%), and eructation (3%). Epanova® 4 grams daily was associated with diarrhea (15%), nausea (6%), abdominal pain or discomfort (5%), and eructation (3%). Other long-term reported side effects included constipation, vomiting, fatigue, nasopharyngitis, arthralgia, and dysgeusia.[8] **Table 3** summarizes the major side effects associated with both strengths of Epanova® and placebo.

Dosing and Administration

Epanova® is administered at a dosage of 2 grams or 4 grams once daily. The capsules are commercially-available in 1-gram formulations of red/brown coated, soft-gelatin capsules with the imprint of OME1. These dosages should be individualized based on the patient's response and tolerability to the medication. Cur-

Table 3 | Incidence of major side effects in Epanova® trials.[7]

Side Effects	Olive Oil (Control)	Epanova® 2 g daily	Epanova® 4 g daily
Diarhea	2%	7%	15%
Nausea	1%	4%	6%
Abdominal pain or discomfort	2%	3%	5%
Eructation	<1 %	3%	3%

rent guidelines do not recommend a specific titration schedule. Epanova® is recommended to be taken without regard to meals, but has been shown to have increased bioavailability when taken with food, specifically with high-fat meals. Patients should be advised to swallow the capsules whole and not break, crush, dissolve, or chew the capsules.[7]

Drug Interactions

Throughout all of the trials for Epanova®, patients were excluded if they were currently taking anticoagulant or antiplatelet medications. Various published studies show that omega-3 fatty acids can increase bleeding time in these patients. The increased bleeding time was shown not to exceed normal limits and did not lead to clinically significant bleeds, but patients taking Epanova® and anticoagulant or antiplatelet drugs should be monitored more carefully.[7]

Conclusion

The various omega-3 fatty acid drugs have all shown to statistically decrease TG concentration following relatively short-term use. However, long-term data are currently lacking, as are data on whether these TG changes have clinically important effects on hard outcomes. Omega-3 fatty acids have not been shown to decrease risk for pancreatitis or cardiovascular morbidity or mortality, but these drugs are very well tolerated with very few drug interactions and have adverse effects limited to relatively mild gastrointestinal upset. All of these products essentially break down to EPA and DHA or EPA without DHA (in the case of Vascepa®). The carboxylic acid form of Epanova® is unique in that it allows for increased bioavailability versus the other three agents. Since treatment of hypertriglyceridemia includes therapeutic lifestyle changes such as implementation of a low-fat diet, the improved bioavailability of Epanova® when taken with a low-fat diet may be a possible advantage over other prescription agents in this class which all typically require high-fat meals for maximal absorption. Further research is needed to determine whether Epanova® has a place in the long-term treatment of patients with hypertriglyceridemia and, importantly, whether treatment with Epanova® may have beneficial effects on important clinical outcomes such as cardiovascular morbidity or mortality.

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Alirocumab (Praluent®), a PCSK9 Inhibitor for Reducing Cardiovascular Risk: Balancing Efficacy and Expenditures

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Atherosclerotic cardiovascular disease (ASCVD) remains the most common cause of death in the United States, contributing to about 610,000 deaths each year.[1] The pathophysiology of ASCVD is multifactorial; however the processes of atherosclerosis of arterial vessel walls and subsequent thrombosis are the primary causes of premature mortality and disability-adjusted life years in developing countries.[2,3] Several modifiable risk factors contribute to ASCVD, including tobacco use, physical inactivity, hypertension, nutrition, and dyslipidemia.[1] Dyslipidemia encompasses a broad spectrum of lipid abnormalities, but the elevation of lipoprotein (LDL-C) remains the primary target of pharmacotherapy and lifestyle interventions. Several randomized controlled trials have demonstrated an association between reduced LDL-C and decreased ASCVD morbidity and mortality across the spectrum of baseline LDL-C concentrations >70 mg/dL.[2-5] Current United States and European guidelines recommend that LDL-C lowering be targeted with lifestyle modification and pharmacotherapy.

Both the 2011 European Society of Cardiology/European Atherosclerosis (ECS/EAS) and 2013 American Heart Association/American College of Cardiology (ACC/AHA) lipid guidelines recommend statin drugs to lower LDL-C and risk for

ASCVD or its associated outcomes.[3,5] Statin drugs remain the preferred pharmacotherapy for primary and secondary prevention of ASCVD due to their overwhelming body of evidence, generally high tolerability, and robust efficacy. However, some patients cannot tolerate statins or do not achieve adequate LDL-C lowering with statin monotherapy, potentially putting them at residual risk for adverse outcomes associated with ASCVD. Thus, patients with very high ASCVD risk, and those with lower risk who are unable to tolerate statins, may need additional or alternative therapies to statins to optimize ASCVD risk reduction. Until recently, non-statin cholesterol-lowering agents have demonstrated limited efficacy beyond LDL-C-lowering.[5] However, the July 24, 2015 approval of the first proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor, alirocumab (Praluent®), may provide an efficacious option for patients who need additional non-statin therapy to reduce major adverse cardiovascular outcomes. The purpose of this article is to review the pharmacology, pharmacokinetics, pharmacoeconomics, and clinical trial data of alirocumab for LDL-C lowering in individuals with high risk of atherosclerotic cardiovascular disease.

Pharmacology & Pharmacokinetics

Alirocumab is a fully human monoclonal antibody that specifically binds to and inhibits PCSK9.[6,7] PCSK9 is a serine protease that binds to the low-density lipoprotein receptor (LDLR) on the surface of hepatocytes promoting the degradation of the LDLR. The LDLR enables hepatic uptake of LDL-C reducing the circulating concentrations of LDL-C in the blood. By inhibiting the process of PCSK9, alirocumab maintains LDLR functionality and results in a lower circulating LDL-C concentration.[6,7]

Pharmacokinetic properties of alirocumab are summarized in **Table 1**. In clinical trials, no relevant metabolism was observed in cytochrome P450 enzymes or transporter proteins such as P-gp and OATP.[7] At low concentrations, alirocumab is eliminated through saturable binding to PCSK9; at higher concentrations, alirocumab is eliminated largely through a non-saturable proteolytic pathway. The pharmacokinetic properties of alirocumab are unchanged by mild-to-moderate hepatic impairment, however alirocumab has not been studied in patients with severe hepatic impairment. Renal function is not expected to impact the pharmacokinetics of alirocumab. Alirocumab is thought to break down into inactive polypeptides and amino acids. The mean half-life of alirocumab at steady state is 17-20 days. Pharmacokinetic parameters do no significantly differ based on administration site.[8] No clinically significant drug interactions have been documented between alirocumab and other medications, including statins.[7,9-13]

Table 1 | Pharmacokinetics of alirocumab.[7-8]

Parameter	Alirocumab
F	85%
T_{max}	3-7 days
$T_{1/2}$	17-20 days
Vd	0.04-0.05 L/kg
C_{max}	Abdomen: 8.18 mg/L Upper arm: 6.77 mg/L Thigh: 7.13 mg/L
Metabolism	Saturable binding to target and non-saturable proteolytic pathway

F = bioavailability (subcutaneous); **T_{max}** = time to reach maximum concentration; **$T_{1/2}$** = half-life; **Vd** = volume of distribution; **C_{max}** = maximum concentration.

Clinical Trials

Alirocumab has been studied in the ODYSSEY series of trials (**Table 2**), the largest of which was the ODYSSEY LONG TERM trial.[9-10] ODYSSEY LONG TERM was a multicenter, double-blind, active comparator, intention-to-treat, randomized controlled trial evaluating 2341 participants with either heterozygous familial hypercholesterolemia (as determined by genotyping or clinical criteria), established coronary heart disease, or ≥1 coronary heart disease risk equivalent(s). Participants were ≥18 years of age and had an LDL-C ≥70 mg/dL at baseline. All participants were required to be receiving maximally-tolerated doses of statin therapy with or without triglyceride-lowering therapy (e.g., a fibrate) for ≥4 weeks (≥6 weeks for fenofibrate) prior to enrollment.[9-10] Pre-trial therapy (i.e., statin ± fibrate) was continued throughout the course of the trial.

After a 3-week screening period, participants were randomly assigned to receive either alirocumab 150 mg subcutaneously every 2 weeks or an identical placebo solution (in addition to their statin/triglyceride therapy). All patients were instructed to follow a therapeutic lifestyle change diet or an equivalent diet for the duration of the study.[9] Patients were to return to the study site at weeks 4, 8, 12, 16, 24, 36, 52, 64, and 78, and again 8 weeks after the end of the double-blind period (i.e., at week 86) for a safety assessment. No significant differences in baseline characteristics were observed between participants receiving alirocumab or placebo. Participants were, on average, 60 years of age and the majority were white (alirocumab, 92.8% and placebo, 92.6%). Most patients had diagnosed coronary heart disease (alirocumab, 67.9% and placebo, 70.1%). All participants were required to be on a statin; however, only ~47% of patients in each arm were on a high-intensity statin as defined by the 2013 ACC/AHA guidelines.[5,9]

The primary endpoint was the percentage change in calculated LDL-C concentration from baseline to week 24. Participants continued for a total of 78 weeks to assess the continued efficacy and safety of alirocumab after the primary endpoint was assessed. The mean percent reduction in calculated LDL-C from baseline to week 24 was 61% with alirocumab versus 0.8% with placebo, for a between-group difference of −61.9% (95% CI -64.3% to -59.4%; p<0.001) favoring alirocumab.[9] The mean absolute LDL-C concentration at week 24 was 48 mg/dL in the alirocumab group (from a baseline mean LDL-C of 122.7 mg/dL) and 119 mg/dL in the placebo group (from a baseline LDL-C of 121.9 mg/dL). Alirocumab reduced fasting triglycerides by 15.6% compared to a 1.8% increase in placebo-treated patients, for a between-group difference of 17.3% (95% CI -20.1% to -14.6%; p<0.001). These reductions in LDL-C and triglycerides were comparable to smaller trials in the ODYSSEY series.[9-13] A *post-hoc* analysis conducted on the ODYSSEY LONG TERM data revealed a reduction in composite cardiovascular events in participants receiving alirocumab. The rate of major adverse cardiovascular events (death from heart disease, nonfatal myocardial infarction, stroke, or unstable angina) was 1.7% in the alirocumab-treated group and 3.3% in placebo-treated patients (HR 0.52; 95% CI 0.31 to 0.90).[9] The trial was not originally designed to assess this composite outcome. Additional information about the cardiovascular outcomes of alirocumab is expected in 2017 with the publication of the ODYSSEY OUTCOMES trial.

Table 2 | Summary of alirocumab phase 3 trials in participants with elevated ASCVD Risk.[9-13]

Study	Trial Arms	Endpoints	Results/Conclusions
ODYSSEY LONG TERM[9,10] (n=2341)	• Alirocumab 150 mg **and** statin therapy ± triglyceride therapy (n=1553) • Placebo **and** statin therapy ± triglyceride therapy (n=788)	Primary: • Percent change in LDL-C from baseline to week 24 Secondary: • Safety and efficacy at 78 weeks • Reductions in other lipids at week 24	Percent change in LDL-C: • 61% reduction in alirocumab group (baseline LDL-C: 122 mg/dl with week 24 LDL-C: 48 mg/dl) • 0.8% increase in placebo arm Efficacy at 78 weeks: • 54.4% reduction from baseline in LDL-C for alirocumab-treated patients Reductions in other lipids: • 15.6% reduction in fasting TGs in alirocumab group at week 24 • 1.8% increase in fasting TGs in placebo group at week 24
ODYSSEY COMBO II[11] (n=720)	• Alirocumab 75 mg **and** statin therapy for 12 weeks, then alirocumab 150 mg **and** statin therapy until week 24 (n=479) • Ezetimibe 10 mg **and** statin therapy until week 24 (n=241)	Primary: • Percent change in LDL-C from baseline to week 24 Secondary: • Reductions in other lipids at week 24	Percent change in LDL-C: • 50.6% reduction in alirocumab group (baseline LDL-C: 108 mg/dl with week 24 LDL-C: 49.4 mg/dl) • 20.7% reduction in the ezetimibe group Reductions in other lipids: • 13% reduction in fasting TGs in alirocumab group at week 24 • 12.8% reduction in fasting TGs in ezetimibe group at week 24
ODYSSEY COMBO I[12] (n=316)	• Alirocumab 75 mg **and** statin therapy for 12 weeks, then alirocumab 150 mg **and** statin therapy until week 24 (n=479) • Placebo **and** statin therapy for 24 weeks (n=241)	Primary: • Percent change in LDL-C from baseline to week 24 Secondary: • Safety and efficacy at 52 weeks • Reductions in other lipids	Percent change LDL-C: • 46.3% reduction in alirocumab group (baseline LDL-C: 100 mg/dL vs. week 24 LDL-C: 51 mg/dL) • 2.3% reduction in the placebo arm Reductions in other lipids: • 6% reduction in fasting TGs in alirocumab group • 5.4% reduction in fasting TGs in placebo group (p=0.87 comparing groups
ODYSSEY OPTIONS I[13] (n=355)	Participants on atorvastatin (ATV) 20 mg at baseline (n=169) • Alirocumab 75 mg or 150 mg (if needed in the prescribers opinion) + ATV 20 mg (n=57) • Ezetimibe + ATV 20 mg (n=55) • ATV 40 mg (n=57) Participants on ATV 40 mg at baseline (n=186) • Alirocumab 75 mg or 150 mg (if needed in the prescribers opinion) + ATV 40 mg (n=47) • Ezetimibe + ATV 40 mg (n=47) • Rosuvastatin 40 mg (n=45)	Primary: • Percent change in LDL-C from baseline to week 24	Percent change in LDL-C in patients on atorvastatin 20 mg at baseline: • Alirocumab 75/150 mg + ATV 20 mg: 44% reduction • Ezetimibe + ATV 20 mg: 20.5% reduction • ATV 40 mg: 5% reduction Percent change in LDL-C in patients on atorvastatin 40 mg at baseline: • Alirocumab 75/150 mg + ATV 40 mg: 54% reduction • Ezetimibe + ATV 40 mg: 22.6% reduction • Rosuvastatin 40 mg: 21.4% reduction

Data from individuals with familial hypercholesterolemia were excluded from these studies. **ATV =** atorvastatin; **LDL-C** = low-density lipoprotein cholesterol; **TG** = triglyceride.

Table 3 | Adverse events in 9 placebo-controlled alirocumab trials.[7]

Adverse Event	Placebo (n=1276)	Alirocumab (n=2476)
Nasopharyngitis	11.1%	11.3%
Injection site reactions	5.1%	7.2%
Influenza	4.6%	5.7%
Urinary tract infection	4.6%	4.8%
Diarrhea	4.4%	4.7%
Bronchitis	3.8%	4.3%
Myalgia	3.4%	4.2%
Muscle Spasm	2.4%	3.1%
Sinusitis	2.7%	3.0%
Cough	2.3%	2.5%
Confusion	1.3%	2.1%
Musculoskeletal pain	1.6%	2.1%

Adverse Events

Adverse events from alirocumab placebo-controlled trials are summarized in **Table 3**. The most common adverse reactions observed in clinical trials of alirocumab included nasopharyngitis (11.3%), injection site reactions (7.2%), and influenza (5.7%). Instances of myalgia were greater in the alirocumab group (4.2%) versus placebo (3.4%).[7] Adverse reactions lead to the discontinuation of alirocumab in 5.3% of patients compared to a 5.1% discontinuation rate in patients receiving placebo.[7] Allergic reactions were reported marginally more frequently in patients treated with alirocumab (8.6%) compared to placebo (7.8%) in pooled trial data (**Table 4**).[7] After 78 weeks of therapy, 0.5% of patients treated with alirocumab experienced general allergic adverse events (vs. 0.4% of placebo-treated patients).[9] Fewer than 0.1% of patients experienced rash, vasculitis, and laryngeal edema.[10] Neurocognitive events were reported in 0.8% of patients treated with alirocumab and 0.7% of patients treated with placebo.[7] In a pooled analysis of clinical trial data, 4.8% of patients treated with alirocumab developed anti-drug antibodies (vs. 0.6% in placebo).[7] The long-term consequences of anti-drug antibodies when using alirocumab are unknown; however, alirocumab has demonstrated continued efficacy at 78 weeks of therapy.[7,9]

Precautions & Contraindications

No interactions were observed between alirocumab and the cytochrome P450 system or drug transport proteins (such as P-glycoprotein and OATP) in pooled clinical trial data.[7,9-13] Human data on the use of alirocumab in pregnancy are not available at present. Animal data suggest that alirocumab crosses the placental barrier, however no fetal adverse effects have observed in doses 10 times higher than 150 mg every 2 weeks.[7] Whether alirocumab is excreted in human milk or affects human milk production is not known.[7] Alirocumab is contraindicated in individuals with a history of serious allergic reactions to alirocumab.[7]

Dosing & Administration

Alirocumab is supplied as a 75-mg and 150-mg prefilled syringe for administration. Alirocumab is administered via a subcutaneous injection into the thigh, abdomen, or upper arm following aseptic technique.[7,8] Treatment should be initiated at 75 mg administered subcutaneously every two weeks.[7] After 4 to 8 weeks of therapy, LDL-C should be reassessed. If the patient requires additional LDL-C lowering, the dose may be titrated to 150 mg subcutaneously every 2 weeks. Alirocumab should be stored in a refrigerator. If a dose is missed, the patient should be instructed to administer the dose within 7 days from the missed dose and resume the original schedule.

Pharmacoeconomics

PCSK9 inhibitors like alirocumab have demonstrated efficacy and safety in numerous clinical trials, however significant concern has been voiced on the economic impact these drugs will have on the health system. The annual wholesale acquisition cost for one year of treatment with alirocumab is estimated to be $14,600.[14] Some estimates suggest that as many as 2.6 million persons will receive these drugs in 5 years with an annualized cost of $21.6 billion to the health-system.[14] A pharmacoeconomic analysis evaluating the secondary prevention of major adverse cardiac events in statin-intolerant patients found that PCSK9 inhibitors resulted in a gain of 790,400 quality-adjusted life years (QALYs) at an incremental cost effectiveness ratio (ICER) of $506,000/QALY when compared to statins. Although the determination of relative "cost effectiveness" based on the ICER measurement differs depending on specific situations, cutoffs of $50,000 to $100,000/QALY are often used (somewhat arbitrarily) to define cost-effectiveness.[15] Thus, alirocumab may not be considered cost-effective at the current estimated costs. Due to the lack of adequate trial data on mortality, this estimate is based on a population model and existing LDL-C lowering efficacy and subsequent analyses. Using a more precise estimate of morbidity/mortality benefit, such as one derived directly from outcomes trials with these agents, may result in different conclusions on cost-effectiveness of these agents.[14,15]

Summary

Alirocumab (Praluent®) is the first PCSK9 inhibitor with an FDA-approved indication for LDL-C lowering in individuals with clinical ASCVD. PCSK9 inhibitors are poised to become an alternative for patients who have inadequate response to, or are not able to tolerate, statin therapy. Clinical trials have shown significant reductions in LDL-C following 24-weeks of therapy with

Table 4 | General allergic adverse events comparing placebo- and alirocumab-treated patients.[9-10]

Allergic Event	Placebo (n=788)	Alirocumab (n=788)
Asthma	1 (0.1%)	3 (0.2%)
Angioedema	0	1 (<0.1%)[a]
Drug hypersensitivity	0	1 (<0.1%)
Hypersensitivity vasculitis	0	1 (<0.1%)[a]
Rash	0	1 (<0.1%)[b]
Laryngeal edema	0	1 (<0.1%)[b]

[a]One participant receiving alirocumab experienced both angioedema and hypersensitivity vasculitis.
[b]Another participant receiving alirocumab experienced both rash and laryngeal edema.

alirocumab, and additional clinical trials evaluating cardiovascular outcomes are ongoing. Alirocumab has been well-tolerated in clinical trials, with a low incidence of hypersensitivity reactions. Alirocumab's high cost presents a unique challenge to the health-system and third-party payers must balance rising expenditures with the ability to potentially reduce the morbidity and mortality of the single most common cause of death in the United States.

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Editor's Corner

Empagliflozin May Reduce Cardiovascular Morbidity and Mortality

A recent study published in the *New England Journal of Medicine* investigated the effects of empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, on cardiovascular (CV) morbidity and mortality in patients with type 2 diabetes.

The study included adult patients with type 2 diabetes with a history of CV disease. Patients had an HbA1c of at least 7% and were continued with standard of care therapy. Seven-thousand twenty-eight patients were randomized to receive either 10 mg or 25 mg of empagliflozin or placebo daily. Primary outcome was composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke.

At study end, the incidence of the primary outcome was significantly less in the empagliflozin group than in the placebo group (10.5% vs. 12.1%; HR 0.86, p=0.04 for superiority). Empagliflozin also resulted in a significantly lower risk of CV-related death, all-cause mortality, and hospitalization for heart failure. Serious adverse events occurred at similar rates in both groups; however, genital infections were reported higher in the empagliflozin group.

The results of the study provide an intriguing insight into the benefits of empagliflozin on clinical outcomes. Whether this benefit is a class effect still remains to be determined. However, studies with canagliflozin (CANVAS) and dapagliflozin (DECLARE-TIMI 58) are currently underway, and may offer additional information regarding SGLT2 inhibitors' potential place in therapy for the treatment of type 2 diabetes.

For additional information:

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015;373:2117-2128.

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