

Therapeutic Class Overview

Omega-3 Fatty Acids

INTRODUCTION

- The independent relationship of triglycerides (TGs) to the risk of future cardiovascular disease (CVD) events has long been controversial (*Miller et al 2011*).
- Rich sources of omega-3-fatty acids come from fatty fish and plant sources, and fish oil contains eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).
 - Omega-3-fatty acids can reduce TG levels by approximately 27 to 45% (*Jellinger et al 2017*).
 - Select clinical trials suggest that relatively high doses of omega-3-fatty acids, in the form of fish, fish oils, or high-linolenic acid oils, reduce the risk for major coronary events in persons with established coronary heart disease; however, the overall body of literature does not offer convincing evidence that fish oil supplements are beneficial for preventing CVD or improving outcomes (*Abdelhamid et al 2018, National Cholesterol Education Program [NCEP] 2002, Smith et al 2011, Manson 2019*).
 - A 2018 large-scale randomized controlled trial (RCT) with Vascepa (icosapent ethyl) demonstrated a significant reduction in cardiovascular events when added to statin therapy in patients with elevated TG levels despite statin therapy (*Bhatt et al 2018*).
- The scope of this review will focus on Lovaza (omega-3-acid ethyl esters), Vascepa (icosapent ethyl), and Epanova (omega-3-carboxylic acids), which are all prescription omega-3 fatty acids **Food and Drug Administration (FDA)**-approved as adjunct therapy to diet to reduce TGs in adults with severe (≥ 500 mg/dL) hypertriglyceridemia.
 - Lovaza (omega-3-acid ethyl esters) is available as a 1 gram soft-gelatin capsule, containing approximately 375 mg and 465 mg of DHA and EPA, respectively.
 - Vascepa (icosapent ethyl) is available as a soft-gelatin capsule, containing icosapent ethyl, an esterified formulation of EPA. Vascepa contains $\geq 96\%$ EPA (*LexiComp 2019*).
 - Epanova (omega-3 carboxylic acids) coated, soft-gelatin capsules contain at least 850 mg of polyunsaturated fatty acids, including multiple omega-3 fatty acids (predominantly EPA and DHA). **Epanova was approved by the FDA in 2014, but has not been marketed to date (Anon 2019)**.
 - Omtryg and Triklo (omega-3-acid ethyl esters) have been discontinued.
 - Of note, there are several over-the-counter products containing omega-3 fatty acids that are marketed as nutritional supplements. These products do not have FDA-approved indications and may not contain the same amount of the active ingredient (*LexiComp 2019*).
- Omega-3 fatty acids have the potential to be used off-label for the treatment of coronary arteriosclerosis, familial combined hyperlipidemia, heart failure, and hyperlipidemia with TG levels < 500 mg/dL (*Micromedex 2019*).
- The 2018 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Management of Blood Cholesterol provides recommendations based on a patient's overall atherosclerotic CVD (ASCVD) risk to guide appropriate treatment. Primary therapies in reducing ASCVD risk are adherence to a heart-healthy lifestyle and statin therapy. Omega-3 fatty acids and fibrates are recommended in patients with TGs ≥ 500 mg/dL, but neither agent is considered a low-density lipoprotein cholesterol (LDL-C)-lowering drug (*Grundy et al 2018*). Recent ACC/AHA recommendations on non-statin use do not consider the use of omega-3 fatty acids as they did not include therapies for severe hypertriglyceridemia (*Lloyd-Jones et al 2016, Lloyd-Jones et al 2017*).
- The National Lipid Association recommends omega-3 fatty acids, fibric acid derivatives, or niacin as first-line agents for patients with TG levels ≤ 1000 mg/dL. These agents may also be considered for patients with contraindications or intolerance to statin therapy (*Jacobson et al 2015*).
- The Endocrine Society Clinical Practice Guidelines state that omega-3 fatty acids, fibrates, and niacin may be considered as monotherapy or in combination with statins in patients with TG levels that are moderate (200 to 999 mg/dL, based on the Endocrine Society criteria) to severe (1000 to 1999 mg/dL, based on the Endocrine Society criteria) (*Berglund et al 2012*).
- The American Association of Clinical Endocrinologists and American College of Endocrinology recommend prescription omega-3 fatty acids 2 to 4 g for severe hypertriglyceridemia (TG > 500 mg/dL) (*Jellinger et al 2017*).
- Medi-Span Class: Antihyperlipidemics – Misc.

Table 1. Medications Included Within Class Review

Drug*	Generic Availability
Epanova (omega-3-carboxylic acids)†	-
Lovaza (omega-3-acid ethyl esters)*	✓
Vascepa (icosapent ethyl)	-

Omtryg and Triklo (omega-3-acid ethyl esters) are no longer marketed.

*Lovaza was initially marketed in the United States as Omacor.

†Epanova was approved by the FDA in 2014; no product launch date is available.

(Drugs@FDA 2019 Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019; Anon 2019; Reliant Pharmaceuticals 2007)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Epanova (omega-3-carboxylic acids capsule)	Lovaza (omega-3-acid ethyl esters capsule)	Vascepa (icosapent ethyl capsule)
Adjunctive treatment to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia	✓	✓	✓

(Prescribing information: Epanova 2017, Lovaza 2019, Vascepa 2017)

- 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

- There are currently no head-to-head efficacy trials comparing Epanova (omega-3-carboxylic acids), Lovaza (omega-3-acid ethyl esters), or Vascepa (icosapent ethyl). One study compared the effects of an acylglycerol omega-3 formulation, which is often available in non-prescription omega-3 supplements to Lovaza. In this double-blind (DB) trial in patients with TG concentrations of 150 to 500 mg/dL, 120 patients were randomized to 5563 mg acylglycerol omega-3 daily, Lovaza 4 g daily, or placebo (olive oil). Both omega-3 groups had decreased TG concentrations compared with placebo ($p < 0.001$), but no difference was found between active treatments (28% reduction with acylglycerol omega-3 and 22% with Lovaza; $p = 0.785$). Because patients included in this study had mild to moderate elevations in TG levels at baseline, it is unclear if the acylglycerol omega-3 formulation would have similar results in patients with severe hypertriglyceridemia (Hedengran et al 2015).
- The EVOLVE study was a 12-week, DB, placebo (olive oil)-controlled, RCT that evaluated the safety and lipid-altering efficacy of Epanova (omega-3-carboxylic acids) in 399 adult patients with average serum TG concentrations of ≥ 500 mg/dL but < 2000 mg/dL at screening (1 and 2 weeks before random assignment). Patients were either treatment-naïve for dyslipidemia or using a stable (for at least 6 weeks before the first qualifying lipid measurement) dosage of a statin, cholesterol absorption inhibitor (CAI), or their combination. They were randomized to 1 of 4 treatment groups: placebo (olive oil) ($n = 99$), or Epanova 2 g ($n = 100$), 3 g ($n = 101$), or 4 g ($n = 99$). The Epanova 3 g group demonstrated a lower TG reduction than the other two active treatment groups. Treatment with Epanova 2 g and Epanova 4 g compared to placebo led to statistically significant reductions in fasting TG levels ($p < 0.01$ and $p < 0.001$, respectively) and in non-high-density lipoprotein cholesterol (HDL-C) levels ($p < 0.05$ and $p < 0.01$, respectively). However, there was a statistically significant increase in LDL-C levels in both active treatment groups ($p < 0.001$ for both) (Kastelein et al 2014).
- The ESPRIT trial was a 6-week, DB, parallel-group trial of 647 diet-stable patients with fasting TG levels ≥ 200 mg/dL and < 500 mg/dL (treated with a maximally tolerated dose of statin or statin with ezetimibe) and at high risk for CVD who were randomized to receive placebo (olive oil) capsules ($n = 216$), Epanova 2 g daily ($n = 215$), or Epanova 4 g daily ($n = 216$).

= 216) to assess the TG and non-HDL-C lowering efficacy of adding Epanova to existing statin therapy. Compared to placebo, both the Epanova 2 g and 4 g treatment groups demonstrated significant reductions in non-HDL-C levels ($p < 0.05$ for both) and TG levels ($p < 0.001$ for both). LDL-C was significantly increased compared to placebo in the Epanova 2 g group only ($p < 0.025$) (Maki et al 2013).

- Lovaza (omega-3-acid ethyl esters) and Vascepa (icosapent ethyl) (studied under the investigational name, AMR-101) were consistently associated with decreases in TG levels from baseline compared to placebo in studies of hypertriglyceridemia (Ballantyne et al 2012, Bays et al 2011, Bays Maki et al 2010, Bays McKenny et al 2010, Calabresi et al 2000, Calabresi et al 2004, Davidson et al 2007, Durrington et al 2001, Eritsland et al 1996, GISSI-Prevenzione Investigators 1999, Johansen et al 1999, Koh et al 2012, Macchia et al 2013, Maki et al 2008, Maki et al 2010, McKeone et al 1997, Nilsen et al 2001, Nordoy et al 1998, Peters et al 2012, Pownall et al 1999, Risk and Prevention Study Collaborative Group et al 2013, Roth et al 2009, Stalenhoef et al 2000, Van Dam et al 2001).
- In select placebo-controlled trials, Lovaza (omega-3-acid ethyl esters) was associated with an increase in LDL-C levels from baseline compared to placebo (Bays Maki et al 2010, Calabresi et al 2000, Calabresi et al 2004, Koh et al 2012, Maki et al 2010, Pownall et al 1999, Roth et al 2009, Stalenhoef et al 2000).
- Lovaza (omega-3-acid ethyl esters) was generally associated with an additive decrease in TGs and total cholesterol (TC) levels when added to a regimen containing a statin or a fibric acid derivative (Bays Maki et al 2010 COMBOS, Bays McKenny et al 2010, Davidson et al 2007, Durrington et al 2001, Maki et al 2008, Maki et al 2010 COMBOS, Nordoy et al 1998, Peters et al 2012, Roth et al 2009).
- When compared in head-to-head trials, Lovaza (omega-3-acid ethyl esters) was associated with similar decreases in cholesterol parameters from baseline compared to fenofibrate. When compared to gemfibrozil, 1 DB RCT demonstrated similar significant decreases in TGs and an increase in HDL and LDL cholesterol concentrations. However, a second RCT demonstrated that Lovaza (omega-3-acid ethyl esters) was associated with a significantly smaller decrease in TG levels from baseline (-28.9 vs -51.2% , respectively; $p = 0.007$). TC was decreased 10.2% with Lovaza, and 13.0% with gemfibrozil ($p = 0.51$) (Koh et al 2012, Stalenhoef et al 2000, Van Dam et al 2001).
- In placebo-controlled trials, Vascepa (icosapent ethyl) was not associated with an increase in LDL-C levels from baseline compared to placebo (Ballantyne et al 2012, Bays et al 2011).
- Outcomes data with Lovaza (omega-3-acid ethyl esters) have demonstrated mixed results when evaluating reduction in the risk of cardiovascular events.
 - The GISSI-Prevenzione trial demonstrated the beneficial effects of omega-3 acid ethyl esters in patients who have experienced a recent myocardial infarction (MI); omega-3-acid ethyl esters significantly reduced the risk of death, nonfatal MI, and nonfatal stroke compared to vitamin E. Treatment with omega-3 poly unsaturated fatty acids (PUFA), but not vitamin E, significantly lowered the risk of the composite of death, nonfatal MI, and nonfatal stroke (relative risk [RR], 0.10; 95% confidence interval [CI], 0.01 to 0.18; $p = 0.048$ by 2-way analysis and RR, 0.15; 95% CI, 0.20 to 0.25; $p = 0.023$ by 4-way analysis) (GISSI-Prevenzione Investigators 1999).
 - An RCT comparing Lovaza (omega-3-acid ethyl esters) to dietary therapy in patients admitted for coronary artery bypass grafting demonstrated a lower incidence of vein graft occlusion in the treatment group. After 1 year of therapy, the vein graft occlusion rate per distal anastomoses was 27% in the group receiving Lovaza (omega-3-acid ethyl esters) compared to 33% in the control group (odds ratio [OR], 0.77; 95% CI, 0.60 to 0.99; $p = 0.034$) (Eritsland et al 1996).
 - An RCT comparing Lovaza (omega-3-acid ethyl esters) to placebo in patients who were scheduled for elective coronary angioplasty demonstrated no difference in the rate of restenosis. This event occurred in 40.6% of the treated stenoses in the Lovaza (omega-3-acid ethyl esters) group and in 35.4% of the treated stenoses in the placebo group (OR, 1.25; 95% CI, 0.87 to 1.80; $p = 0.21$) (Johansen et al 1999).
 - An RCT comparing Lovaza (omega-3-acid ethyl esters) to placebo in patients with an acute MI demonstrated no difference in the rate of cardiovascular events and revascularizations. Of the patients receiving Lovaza (omega-3-acid ethyl esters), 28% experienced at least 1 cardiac event compared to 24% of patients in the placebo group ($p = 0.74$). There was no significant difference between the groups concerning the number, type, or severity of cardiac events (Nilsen et al 2001).
 - The Risk and Prevention Study compared Lovaza (omega-3-acid ethyl esters) to placebo in patients evaluated to be at a high cardiovascular risk and demonstrated no difference in the rate of death, nonfatal MI, and nonfatal stroke. The primary endpoint occurred in 1478 of 12,505 patients included in the analysis (11.8%), of whom 733 of 6239 (11.7%) had received omega-3 PUFA and 745 of 6266 (11.9%) had received placebo (hazard ratio [HR], 0.97; 95% CI, 0.88 to 1.08; $p = 0.58$) (Risk and Prevention Study Collaborative Group et al 2013).

- An RCT comparing Lovaza (omega-3-acid ethyl esters) to placebo in patients with confirmed symptomatic paroxysmal atrial fibrillation (AF) that required cardioversion, who had at least 2 episodes of AF in the 6 months before randomization, or both, demonstrated no significant difference in the rate of recurrence of symptomatic AF. At 12 months, 56 of 297 participants (18.9%) in the placebo group and 69 of 289 participants (24%) in the omega-3 PUFA group had a recurrent symptomatic AF (HR, 1.28; 95% CI, 0.90 to 1.83; $p = 0.17$) (*Macchia et al 2013*).
- Additionally, 1 large trial (VITAL), enrolling over 25,000 participants, studied the effects of omega-3 fatty acids and vitamin D supplementation vs placebo for reduction of cardiovascular events and cancer. Enrolled patients were at least 60 years of age (at least 65 years for women) with no significant cardiovascular or cancer history. Omega-3 supplementation use provided 840 mg omega-3 fatty acids (460 mg EPA and 380 mg DHA [as Omacor]). After a median of 5.3 years, no significant reductions in cardiovascular events (HR 0.92; 95% CI, 0.80 to 1.06) or cancer (HR 1.03; 95% CI, 0.93 to 1.13) vs placebo were seen (*Manson 2019*).
- The multicenter, randomized, DB, placebo-controlled REDUCE-IT trial (N = 8179) evaluated the effect of Vascepa (icosapent ethyl) on ischemic events in patients with elevated TGs despite statin therapy and established CVD (70.7%) or other risk factors (eg, diabetes). The primary endpoint was a composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. After a median follow-up of 4.9 years, a primary endpoint event was observed in 17.2% of patients in the Vascepa (icosapent ethyl) group vs 22.0% of patients in the placebo group (HR, 0.75; 95% CI, 0.68 to 0.83; $p < 0.001$). The number needed to treat to avoid 1 primary endpoint event was 21 (95% CI, 15 to 33). Vascepa (icosapent ethyl) was also associated with a significant reduction in the key secondary endpoint (composite of cardiovascular death, nonfatal MI, or nonfatal stroke; HR, 0.74; 95% CI, 0.65 to 0.83; $p < 0.001$) (*Bhatt et al 2018*).
- Additionally, a formulation of icosapent ethyl has been marketed in Japan since 1994 under the trade name Epadel (ethyl-eicosapentaenoic acid, the active metabolite of icosapent ethyl). Published studies have evaluated this formulation as an adjunctive therapy with estriol and statins in the cardiovascular outcomes of this agent.
 - In a prospective, observational, 48-week trial, Epadel (ethyl-eicosapentaenoic acid) 1800 mg daily added to estriol 2 mg daily was compared to estriol 2 mg daily alone. TC decreased significantly from baseline in both groups. Serum levels of TGs decreased significantly from 194.5 to 141.5 mg/dL (-27.2%; $p = 0.001$) in the study group but increased slightly from 192.9 to 207.4 mg/dL (+7.5%) in the control group at week 48 in the women whose level of TGs was not < 150 mg/dL (*Kurabayashi et al 2000*).
 - In an open-label (OL) trial, 900 to 1800 mg/day of Epadel (ethyl-eicosapentaenoic acid) was administered to patients with hyperlipidemia who had been treated with statins for an average of 30 months. Serum TC and TG concentrations were significantly decreased 3 months after the administration of Epadel (ethyl-eicosapentaenoic acid) (from 5.63 to 5.02 mmol/L, $p < 0.05$; from 2.07 to 1.08 mmol/L; $p < 0.01$, respectively) (*Nakamura et al 1999*).
 - In the Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS), a prospective, OL, blinded endpoint trial, 18,645 patients were randomly assigned to receive either 1800 mg of Epadel (ethyl-eicosapentaenoic acid) daily with a statin or statin therapy alone. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal MI, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. At a mean follow-up of 4.6 years, the primary endpoint occurred less frequently in the Epadel (ethyl-eicosapentaenoic acid) group compared to the control group (262 [2.8%] vs 324 [3.5%], respectively; RR, 0.19; $p = 0.011$) (*Yokoyama et al 2007*).
 - Seven sub-analyses have been published of the JELIS study.
 - The reduction in cardiovascular risk was greater in the Epadel (ethyl-eicosapentaenoic acid) group compared to the control group in patients unable to attain LDL-C and/or HDL-C goals (-38% reduced risk; $p = 0.007$), those with peripheral artery disease (HR, 0.44; 95% CI, 0.19 to 0.97; $p = 0.041$), those with preexisting coronary artery disease (CAD) and a TC ≥ 250 mg/dL (8.7% vs 10.7%, respectively; HR, 0.77, 95% CI, 0.63 to 0.96; $p = 0.017$) and regardless of the number of cardiovascular risk factors (hypercholesterolemia, obesity, high TG or low HDL-C, diabetes, and hypertension) ($p < 0.05$ for all comparisons) (*Ishikawa et al 2010, Matsuzaki et al 2009, Saito et al 2008 Sasaki et al 2012*).
 - The use of Epadel (ethyl-eicosapentaenoic acid) was associated with a significantly greater decrease in CAD compared to the control group in patients with impaired glucose metabolism, but not normoglycemic patients ($p = 0.048$ and $p = 0.062$, respectively) (*Oikawa et al 2009*).
 - Adherence to $\geq 80\%$ of the medication regimen was associated with a decreased incidence of cardiovascular endpoints compared to those exhibiting $< 80\%$ adherence to study medications ($p = 0.041$) (*Origasa et al 2010*).
 - The incidence of secondary stroke was lower in the Epadel (ethyl-eicosapentaenoic acid) group compared to the control group (6.8 vs 10.5%, respectively; HR, 0.80; 95% CI, 0.64 to 0.997; $p = 0.047$); however, there was no

difference between groups in the incidence of primary stroke (1.5 vs 1.3%, respectively; HR, 1.08; 95% CI, 0.95 to 1.22; p = 0.244) (*Tanaka et al 2008*).

- A Cochrane systematic review of 79 RCTs examined the effects of fish- and plant-based omega-3 fatty acids on CVD. Increased intake of EPA or DHA had little or no effect on all-cause mortality or cardiovascular events; however, evidence included in this review was primarily from supplement trials (*Abdelhamid et al 2018*). Another meta-analysis of omega-3 fatty acids found no evidence of reduction in coronary heart disease events or major vascular events in patients at risk for cardiovascular events (*Aung et al 2018*).

CLINICAL GUIDELINES

- The 2018 ACC/AHA guidelines emphasize adherence to lifestyle and to statin therapy before considering the addition of an LDL-lowering nonstatin drug. Omega-3 fatty acids and fibrates are recommended in patients with TGs \geq 500 mg/dL (*Grundy et al 2018*).
- Other guidelines (**National Lipid Association and the American Association of Clinical Endocrinologists/American College of Endocrinology**) suggest a potential role for other lipid-lowering therapies when treating hypertriglyceridemia including fibric acid derivatives, niacin, and omega-3 fatty acids (*Jacobson et al 2015, Jellinger et al 2017*).

SAFETY SUMMARY

- Omega-3 fatty acids have precautions for use in patients with hepatic impairment and fish allergy; **these agents may also prolong bleeding time**. Lovaza (omega-3 acid ethyl esters) and Epanova (omega-3-carboxylic acids) may be associated with increases in LDL-C. Additionally, Lovaza has a possible association with atrial fibrillation or flutter.
- The most common adverse reactions associated with Lovaza (incidence > 3% and greater than placebo) were eructation, dyspepsia, and taste perversion.
- The most common adverse reactions with Epanova (incidence \geq 3% and greater than placebo) were eructation, nausea, diarrhea, and abdominal pain. Additional adverse reactions include vomiting, flatulence, and taste perversion.
- The most common adverse reaction associated with Vascepa (incidence > 2% and greater than placebo) was arthralgia.

DOSING AND ADMINISTRATION

- Prior to initiating therapy, TG levels should be assessed. Other causes of TG elevation (eg, diabetes mellitus, hypothyroidism, or medications) should be identified and managed.
- Patients should be placed on an appropriate lipid-lowering diet prior to receiving treatment and should continue diet during therapy.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Epanova (omega-3-carboxylic acids)	Coated soft gelatin capsule	Oral	Once daily	Administered without regard to meals in clinical trials
Lovaza (omega-3-acid ethyl esters)	Soft gelatin capsule	Oral	Once daily or in 2 divided doses	Administered with meals in clinical trials
Vascepa (icosapent ethyl)	Soft gelatin capsule	Oral	In two divided doses	Should be administered with food

See the current prescribing information for full details

CONCLUSION

- Prescription omega-3 fatty acids are approved by the FDA for the treatment of severe hypertriglyceridemia. There is a generic formulation of Lovaza (omega-3-acid ethyl esters) currently available. **Although approved in 2014, Epanova has not been marketed to date.**

- In patients with an elevated TG level (≥ 500 mg/dL), a fibric acid derivative or niacin should be initiated before LDL-C lowering therapy to prevent pancreatitis. Omega-3 fatty acids represent an alternative to fibric acid derivatives and niacin for the treatment of hypertriglyceridemia. Select clinical trials suggest that relatively high doses of omega-3-fatty acids, in the form of fish, fish oils or high-linolenic acid oils, will reduce the risk for major coronary events in persons with established coronary heart disease; however, the overall body of literature does not offer convincing evidence that fish oil supplements are beneficial for preventing CVD or improving outcomes.
- Clinical trials have demonstrated that prescription omega-3 acid ethyl esters can effectively lower TGs, as well as positively affect other lipid/lipoprotein parameters when used as monotherapy or in combination with fenofibrate or statins.
- In select placebo-controlled trials, both Lovaza (omega-3-acid ethyl esters) and Epanova (omega-3 carboxylic acids) were associated with an increase in LDL-C levels from baseline compared to placebo.
- In placebo-controlled trials, Vascepa (icosapent ethyl) was not associated with an increase in LDL-C levels from baseline compared to placebo.
- Select cardiovascular outcomes studies have suggested a decrease in cardiovascular outcomes with Lovaza (omega-3 acid ethyl esters) and Vascepa (icosapent ethyl); however, certain trials have demonstrated no benefit compared to a control group.
- Epanova (omega-3-carboxylic acids) is the first FDA-approved prescription omega-3 in free fatty acid form, which produces higher bioavailability than esterified forms. Unlike the other prescription omega-3 fatty acids, Epanova can be taken without regard to meals. It has a similar safety profile as the existing available products.
- The 2018 ACC/AHA guidelines emphasize adherence to lifestyle and to statin therapy before considering the addition of an LDL-lowering nonstatin drug. Omega-3 fatty acids are a reasonable addition for patients with persistently elevated severe hypertriglyceridemia, along with implementing a very low-fat diet (*Grundy et al 2018*).

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