Therapeutic Class Overview
Omega-3 Fatty Acids

Therapeutic Class

- **Overview/Summary:** This overview will focus on the omega-3 fatty acids products, which include icosapent ethyl (Vascepa®) and omega-3-acid ethyl esters (Lovaza®, Omtryg®). The agents are Food and Drug (FDA)-approved as an adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia, defined as 500 mg/dL or more.[1-3] Icosapent ethyl is an ethyl ester of eicosapentaenoic acid (EPA), while omega-3-acid ethyl esters is a mixture of ethyl esters or free fatty acids primarily composed of EPA and docosahexaenoic acid (DHA). Each omega-3 acid ethyl esters capsule contains at least 900 mg of ethyl esters of omega-3 fatty acids sourced from fish oil, which are predominantly EPA (approximately 465 mg) and DHA (approximately 375 mg). Icosapent ethyl is a newer omega-3 fatty acid formulation that also contains EPA obtained from fish oil; however, it contains at least 96% EPA and does not contain DHA. Studies suggest that this formulation does not cause significant increases in low density lipoprotein cholesterol (LDL-C) which has been associated with large doses of omega-3-acid ethyl esters.[1-4] The exact mechanism by which the agents reduce triglyceride levels is not completely understood. Inhibition of acyl-coenzyme A:1,2-diacylglycerol acyltransferase, increased mitochondrial and hepatic peroxisomal beta-oxidation, decreased hepatic lipogenesis, and increased plasma lipoprotein lipase activity are potential mechanisms of action that have been proposed.[1-4]

Table 1. Current Medications Available in the Therapeutic Class[1-3]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
icosapent ethyl (Vascepa®)	Adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia	Capsule: 1 gram	-
omega-3-acid ethyl esters (Lovaza®*, Omtryg®)	Adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia	Capsule: 1 gram (Lovaza®) 1.2 gram (Omtryg®)	a

* Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Safety and efficacy of omega-3 fatty acids have been evaluated in several clinical trials.[5-27]
  - Most studies have demonstrated that icosapent ethyl and prescription omega-3 acid ethyl esters can effectively lower triglycerides, as well as positively impact other lipid/lipoprotein parameters when used as monotherapy or in combination with fenofibrate or statins.[5-23]
  - Other studies have suggested no difference between omega-3 fatty acids and placebo or dietary therapy for the reducing the rate of graft occlusion, restenosis and cardiac events or revascularizations.[24-26]
  - In another study, omega-3 acid ethyl esters significantly reduced the risk of death, nonfatal myocardial infarction, and nonfatal stroke compared to vitamin E in patients who have experienced a recent myocardial infarction.[27]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[28-34]
  - Recommendations in clinical guidelines regarding the use of omega-3 fatty acids are varied.
  - In general, therapeutic lifestyle changes, including diet, exercise, and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia.

- When LDL lowering is required, initial treatment with a statin is recommended and considered first line therapy for patients with established coronary heart disease (CHD) or CHD equivalents.
- Older guidelines suggest omega-3 fatty acids may reduce the risk of cardiovascular disease and may be reasonable for cardiovascular disease risk reduction while newer guidelines do not address the use or recommend against the use of omega-3 fatty acids for reducing the risk of cardiovascular disease due to limited data.

· Other Key Facts:[1-3]
- Dosing recommendations are similar for both icosapent ethyl and omega-3-acid ethyl esters, with 2 grams twice daily being recommended (2.4 grams twice daily for Omtryg®).
  - Omega-3-acid ethyl esters may be given once daily at a dose of 4 or 4.8 grams, respectively.
- All omega-3 fatty acid products should be taken with food.
- These agents are considered safe, with very minimal side effects.
- Omega-3-acid ethyl esters and icosapent ethyl have not been studied in renal or hepatic impairment.
- Currently, only Lovaza® (omega-3-acid ethyl esters) is available generically.

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Therapeutic Class Review
Omega-3 Fatty Acids

Overview/Summary

This review will focus on the omega-3 fatty acids products, which include icosapent ethyl (Vascepa®) and omega-3-acid ethyl esters (Lovaza®, Omtryg®). The agents are Food and Drug (FDA)-approved as an adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia, defined as 500 mg/dL or more.[1-3] Icosapent ethyl is an ethyl ester of eicosapentaenoic acid (EPA), while omega-3-acid ethyl esters is a mixture of ethyl esters or free fatty acids primarily composed of EPA and docosahexaenoic acid (DHA). Each omega-3 acid ethyl esters capsule contains at least 900 mg of ethyl esters of omega-3 fatty acids sourced from fish oil, which are predominantly EPA (approximately 465 mg) and DHA (approximately 375 mg). Icosapent ethyl is a newer omega-3 fatty acid formulation that also contains EPA obtained from fish oil; however, it contains at least 96% EPA and does not contain DHA. Studies suggest that this formulation does not cause significant increases in LDL-C which has been associated with large doses of omega-3-acid ethyl esters.[1-4] The exact mechanism by which the agents reduce triglyceride levels is not completely understood. Inhibition of acyl-coenzyme A:1,2-diacylglycerol acyltransferase, increased mitochondrial and hepatic peroxisomal beta-oxidation, decreased hepatic lipogenesis, and increased plasma lipoprotein lipase activity are potential mechanisms of action that have been proposed.[1-4]

Safety and efficacy of the omega-3 fatty acids have been evaluated in several clinical trials.[5-27] Most studies have demonstrated that icosapent ethyl and prescription omega-3 acid ethyl esters can effectively lower triglycerides, as well as positively impact other lipid/lipoprotein parameters when used as monotherapy or in combination with fenofibrate or statins.[5-23] Other studies have suggested no difference between omega-3 fatty acids and placebo or dietary therapy for the reducing the rate of graft occlusion, restenosis and cardiac events or revascularizations.[24-26] In another study, omega-3 acid ethyl esters significantly reduced the risk of death, nonfatal myocardial infarction, and nonfatal stroke compared to vitamin E in patients who have experienced a recent myocardial infarction.[27] Recommendations in clinical guidelines regarding the use of omega-3 fatty acids are varied. In general, therapeutic lifestyle changes, including diet, exercise, and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL lowering is required, initial treatment with a statin is recommended and considered first line therapy for patients with established coronary heart disease (CHD) or CHD equivalents. Older guidelines suggest omega-3 fatty acids may reduce the risk of cardiovascular disease and may be reasonable for cardiovascular disease risk reduction while newer guidelines do not address the use or recommend against the use of omega-3 fatty acids for reducing the risk of cardiovascular disease due to limited data.[28-34]

Dosing recommendations are similar for both icosapent ethyl and omega-3-acid ethyl esters. Icosapent ethyl is dosed at 2 grams twice a day. Omega-3-acid ethyl esters is dosed at 2 or 2.4 grams twice a day for Lovaza® and Omtryg®, respectively. Additionally, omega-3-acid ethyl esters may be given once daily at a dose of 4 or 4.8 grams, respectively. All omega-3 fatty acid products should be taken with food. These agents are considered safe, with very minimal side effects.[1-4] Omega-3-acid ethyl esters and icosapent ethyl have not been studied in renal or hepatic impairment. Currently, only Lovaza® (omega-3-acid ethyl esters) is available generically.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
icosapent ethyl (Vascepa®)	Antilipemic	-
omega-3-acid ethyl esters (Lovaza®*, Omtryg®)	Antilipemic	a

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-3]

Indication	icosapent ethyl	omega-3-acid ethyl esters
Adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia	a	a

Pharmacokinetics

Absorption
After oral administration, icosapent ethyl is de-esterified during the absorption process and the active metabolite EPA is absorbed in the small intestine. Omega-3-acid ethyl esters (EPA and DHA) were absorbed when administered as ethyl esters orally. Increases of DHA content were less marked and not dose-dependent when administered as ethyl esters.

Icosapent ethyl was only studied when taken when or following a meal. Omega-3-acid ethyl esters was administered under fasted condition, on average the peak and total exposure were lower by up to 20 to 80-fold, respectively, for total plasma EPA, and lower by up to two to four-fold, respectively, for total plasma DHA, in comparison to those observed under fed condition (high-fat high-calorie meal). Both icosapent ethyl and Omega-3-acid ethyl esters should be taken with food.

Distribution
The majority of EPA circulating in plasma is incorporated in phospholipids, triglycerides and cholesteryl esters, and <1% is present as the unesterified fatty acid. Greater than 99% of unesterified EPA is bound to plasma proteins.

Metabolism
PA is mainly metabolized by the liver via beta-oxidation similar to dietary fatty acids. Beta oxidation splits the long carbon chain of EPA into acetyl Coenzyme A, which is converted into energy via the Krebs cycle. Cytochrome P450-mediated metabolism is a minor pathway of elimination of EPA.

Elimination
The plasma elimination half-life of EPA is approximately 89 hours.

Clinical Trials

The safety and efficacy of omega-3 fatty acids have been evaluated in several clinical trials and are outlined in Table 3.[5-27] Clinical trials have demonstrated that icosapent ethyl and prescription omega-3 acid ethyl esters can effectively lower triglycerides, as well as positively impact other lipid/lipoprotein parameters when used as monotherapy or in combination with fenofibrate or statins.[5-23] Other studies have suggested no difference between omega-3 fatty acids and placebo or dietary therapy for the reducing the rate of graft occlusion, restenosis and cardiac events or revascularizations.[24-26]

The GISSI-Prevenzione trial demonstrated the beneficial effects of omega-3 acid ethyl esters in patients who have experienced a recent myocardial infarction; omega-3 acid ethyl esters significantly reduced the risk of death, nonfatal myocardial infarction, and nonfatal stroke compared to vitamin E.[27]

Table 3. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Bays et al[5] MARINE Icosapent ethyl 4 g/day (2 g twice daily) vs icosapent ethyl 2 g/day (1 g twice daily) vs placebo twice daily (Icosapent ethyl is referred to by the investigational name AMR101 in this trial)	DB, MC, PC, RCT Adults >18 years of age with TG levels of ≥500 and ≤2000 mg/dL	N=229 4 to 6 week wash-out (any lipid-altering drug therapy other than statins and ezetimibe were discontinued) 2 to 3 week qualifying period 12 weeks of treatment	Primary: Placebo-corrected median percentage of change in TG from baseline to week 12 Secondary: Percent change from baseline in VLDL-C, apo B, and lipoprotein-associated phospholipase A_2; safety	Primary: Icosapent ethyl 4 g/day reduced placebo-corrected median TG levels by 33.1% (P<0.0001); icosapent ethyl 2 g/day reduced placebo-corrected median TG levels by 19.7% (P=0.0051). Secondary: Neither icosapent ethyl 4 g/day nor 2 g/day significantly increased the LDL cholesterol levels. Icosapent ethyl 4 g/day significantly reduced non-HDL-C by 17.7% (P<0.0001), lipoprotein-associated phospholipase A_2 by 13.6% (P=0.0003), very low density lipoprotein–TG by 25.8% (P=0.0023), and apo B by 8.5% (P=0.0019). Icosapent ethyl 2 g/day significantly reduced non-HDL-C by 8.1% (P=0.0182). Both icosapent ethyl doses significantly reduced VLDL-C and TC, with no significant effect on HD-C. The incidence of treatment-emergent adverse events was generally similar across the three treatment groups.
Ballantyne et al[6] ANCHOR Icosapent ethyl 4 g/day (2 g twice daily) vs icosapent ethyl 2 g/day (1 g twice daily) vs placebo twice daily	DB, MC, PC, RCT Patients >18 years of age and at high risk for CV disease with residually high TG levels (≥200 and <500 mg/dL) despite LDL-C control (≥40 and <100 mg/dL) with statin therapy	N=702 4 to 6 week wash-out (any lipid-altering drug therapy other than statins were discontinued) 2 to 3 week qualifying period	Primary: Median percent change in TG levels from baseline versus placebo at 12 weeks Secondary: Median placebo-adjusted percent change in non-HDL-C, LDL-C, apo B, VLDL, and lipoprotein-	Primary: Icosapent ethyl 4 and 2 g/day significantly decreased TG levels by 21.5% (P<0.0001) and 10.1% (P=0.0005), respectively. Secondary: Icosapent ethyl 4 and 2 g/day significantly decreased non-HDL-C by 13.6% (P<0.0001) and 5.5% (P=0.0054), respectively. Icosapent ethyl 4 g/day produced greater TG and non-HDL-C decreases in patients with higher-efficacy statin regimens and greater TG decreases in patients with higher baseline TG levels. Icosapent ethyl 4 g/day decreased LDL-C by 6.2% (P=0.0067) and decreased apo B (9.3%), TC (12.0%), VLDL-C (24.4%), lipoprotein-associated phospholipase A_2 (19.0%), and hsCRP (22.0%) versus placebo (P<0.001 for all comparisons). Icosapent ethyl was generally well tolerated, with safety profiles similar to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(Icosapent ethyl is referred to by the investigational name AMR101 in this trial)		12 weeks of treatment	associated phospholipase A_2; safety	placebo.
Shearer et al[7] Extended-release niacin (ERN, Niaspan 2g/day) vs P-OM3 (Lovaza, 4g/day) vs combination ERN and P-OM3 vs dual placebo All patients took aspirin 81 mg prior to dinner	DB, PC, RCT Patients age 40 to 69 years; BMI 25 to 40 kg/m^2; fasting TG, 150 to 750 mg/dL; HDL-C >10 mg/dL; and the ratio of TG/HDL-C >3.5	N=60 6-week, diet-stabilization, dual-placebo, run-in phase 16 weeks of treatment	Primary: Least squares mean changes, adjusted for baseline in non-HDL-C, HDL-C, TG, augmentation index, and reactive hyperemia index Secondary: Changes in TG:HDL, TC, LDL-C, VLDL-C, and lipoprotein subfractions	Primary: Significant improvements occurred in non-HDL-C, HDL-C, TG, and augmentation index with ERN treatment; TG with P-OM3 treatment; and HDL-C and TG with combination treatment. The TG reduction with combination treatment was greater than P-OM3 alone but was not greater than ERN (P=0.09). Secondary: No significant change from baseline in any group was observed for TC and LDL-C. Combination treatment had the greatest impact on lipoprotein subfractions, where improvements in particle density were observed. ERN significantly reduced the AI, a marker of vascular stiffness, by 3.5 units. No effect on this measure was observed in either P-OM3 or combination treatments. No significant effect of either agent (singly or combined) was observed on endothelial function measured by reactive hyperemia index or on blood pressure.
Pownall et al[8] Omega-3 acid ethyl esters (Omacor*) 4 g per day vs placebo	DB, PC, PG, RCT Patients with severe hypertriglyceridemia (TG ≥500 mg/dL but <2,000 mg/dL)	N=40 12 weeks	Primary: Effect on TG, lipid profile, and lipid composition Secondary: Not reported	Primary: Median TG levels were reduced 38.9% from baseline in the omega-3 acid ethyl ester group compared to 7.8% with placebo (P=0.001). Omega-3 acid ethyl esters also significantly reduced TC (-9.9%; P=0.004) and VLDL-C (-29.2%; P=0.001) and significantly increased LDL-C (16.7%; P=0.007) from baseline. HDL-C increased in patients receiving omega-3 acid ethyl esters (5.9%; P=0.057 vs baseline and P=0.023 vs placebo) and decreased in patients receiving placebo (-5.9%; P value not significant vs baseline).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
McKeone et al[9] Omega-3 acid ethyl esters (Omacor*) 4 g per day vs placebo	DB, PC, RCT Patients with severe hypertriglyceridemia (TG ≥500 mg/dL but <2,000 mg/dL)	N=40 12 weeks	Primary: Effect on TG and serum phospha-tidylcholine Secondary: Changes in lipid profile	Primary: Treatment with omega-3 acid ethyl esters significantly reduced TG levels by 26% compared to a 7% increase for placebo. Incorporation of eicosapentaenoic and docosahexaenoic acid into the serum phosphatidylcholine occurred within 6 weeks and was usually accompanied by a reduction in plasma TG. Secondary: Omega-3 acid ethyl esters also significantly reduced VLDL-C (28%) and TC (11%), and increased HDL-C (14%). None of these parameters significantly changed in the placebo group.
Calabresi et al[10] Omega-3 acid ethyl esters (Omacor*) 4 g per day for 8 weeks vs placebo for 8 weeks	DB, RCT, XO Patients with familial combined hyperlipidemia	N=14 26 weeks	Primary: Changes in lipid profile and LDL-C subclass distribution Secondary: Safety	Primary: Omega-3 acid ethyl esters significantly lowered plasma TG and VLDL-C by 27 and 18%, respectively (both P<0.05) compared to baseline. TC and HDL-C did not change but LDL-C and apo B increased by 21% (P=0.05) and 6% compared to baseline (P<0.05). Omega-3 acid ethyl esters treatment caused a redistribution of LDL-C subclasses towards less dense lipoprotein particles (possibly indicative of a less atherogenic LDL-C profile); however, the average LDL-C size did not change. Secondary: Omega-3 acid ethyl esters were well tolerated with no reports of drug-related adverse events or negative safety parameters (e.g., glucose, uric acid, liver enzymes, kidney function, and platelet count).
Calabresi et al[11] Omega-3 acid ethyl esters (Omacor*) 4 g per day for 8 weeks	DB, RCT, XO Patients with familial combined hyperlipidemia	N=14 20 weeks	Primary: Changes in lipid profile, LDL-C and HDL-C subclass distribution	Primary: Plasma TG were 44% lower and LDL-C and apo B were 25 and 7% higher after omega-3 acid ethyl esters than placebo (P<0.05 for all). HDL-C was higher (8%) after omega-3 acid ethyl esters than placebo but this difference did not reach statistical significance (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo for 8 weeks			Secondary: Not reported	Omega-3 acid ethyl esters caused a selective increase of the more buoyant HDL_2-C subfraction; plasma HDL_2-C and total mass increased by 40% (P<0.05) and 26%, respectively, whereas HDL_3-C and total mass decreased by 4% (P>0.05) and 6%. The plasma concentration of the HDL-bound antioxidant enzyme paraoxonase increased by 10% after omega-3 acid ethyl esters (P<0.05). Secondary: Not reported
Bays et al[12] Omega-3 acid ethyl ester (Lovaza®) 4 g/day vs placebo All patients received atorvastatin 10 mg/day for 8 weeks, 20 mg for 4 weeks, and 40 mg for 4 weeks.	DB, MC, PC, RCT Patients 18 to 79 years of age with hypercholesterolemia (non-HDL-C >160 mg/dL and TG 250 to 599 mg/dL)	N=245 16 weeks	Primary: Percent change in non-HDL-C level between baseline and week eight Secondary: Percent changes in non-HDL-C level between baseline and the end of treatment with atorvastatin at 20 mg and 40 mg, percent changes in TC, HDL-C, LDL-C, VLDL-C, TG, apo AI and apo B concentrations	Primary: After eight weeks of therapy, the median percent change in non-HDL-C was -40.2% in the omega-3 acid ethyl ester group and -33.7% in the placebo group (90% CI, -7.2 to -2.9; P<0.001). Secondary: Omega-3 acid ethyl ester significantly reduced non-HDL-C compared to placebo during the atorvastatin 20 mg phase (-7.9%; 90% CI, -9.1 to -4.9; P<0.001) and atorvastatin 40 mg phase (-4.1%, 90% CI, -6.8 to -2.4; P<0.001). There was no significant difference in the percentage of patients who achieved LDL-C goals with omega-3 acid ethyl ester (85.7%) or placebo groups (91.5%; P=0.20). There was no significant difference in the percentage of patients who achieved non-HDL-C goals with omega-3 acid ethyl ester (88.7%) or placebo groups (87.8%; P>0.99). Treatment with omega-3-acid ethyl esters with all doses of atorvastatin significantly reduced TC (P<0.001), TC:HDL-C (P<0.001), TG (P<0.001), VLDL-C (P<0.001), RLP-C (P<0.001) and increased HDL-C (P<0.001) compared to treatment with placebo with all doses of atorvastatin. There was no significant difference in LDL-C, apo AI, or apo B between the treatment groups. There was no significant difference in adverse events among the treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				groups.
Durrington et al[13] Phase I Omega-3 acid ethyl esters (Omacor*) 2 g BID for 24 weeks vs placebo for 24 weeks All patients received simvastatin. Phase II Omega-3 acid ethyl esters (Omacor*) 2 g BID and simvastatin 10 to 40 mg QD for 24 weeks	DB, RCT Patients ≤75 years of age with established CHD who were already receiving treatment with simvastatin 10 to 40 mg daily and who had TG >203 mg/dl	N=59 48 weeks	Primary: Percent change in TG and VLDL-C, as well as effects on other lipid parameters Secondary: Not reported	Primary: Serum TG and VLDL-C significantly decreased with omega-3 acid ethyl esters compared to baseline or placebo (20 to 30% reduction; P<0.0005 and 30 to 40% reduction; P<0.005, respectively). There were no adverse effects on other lipid parameters with omega-3 acid ethyl esters, including LDL-C and HDL-C. There were no significant adverse events with omega-3 acid ethyl esters. Secondary: Not reported
Nordoy et al[14] Omega-3 acid ethyl esters (Omacor*) 4 g per/day vs placebo All patients received simvastatin 20 mg QD.	DB, PC, RCT Patients 25 to 60 years of age with combined hyperlipidemia receiving simvastatin 20 mg for 5 to 10 weeks	N=41 5 weeks	Primary: Lipid and lipoprotein parameters Secondary: Not reported	Primary: The addition of omega-3 acid ethyl esters to simvastatin therapy led to an increase in EPA (P<0.0002) and DHA (P<0.0003) and reduction in linoleic acid (P=0.001). The addition of omega-3 acid ethyl esters to simvastatin led to a reduction in TC (P=0.052) and TG (P<0.001). There was no significant effect on HDL-C with omega-3 acid ethyl esters. There was no effect on apo A1 or apo B with the addition of omega-3 acid ethyl esters to simvastatin; however, there was a significant reduction in the concentration of apo E (P=0.035). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Davidson et al[15] Omega-3-acid ethyl ester (Lovaza®) 4 g/day vs placebo All patients were receiving simvastatin 40 mg/day.	DB, MC, PC, PG, RCT Adult patients who have received ≥8 weeks of stable statin therapy and have a mean fasting TG ≥200 and <500 mg/dL and mean LDL-C below or within 10% NCEP ATP III goal	N=254 16 weeks (includes 8 weeks OL treatment with simvastatin)	Primary: Change in non-HDL-C Secondary: Changes in TG, VLDL-C, LDL-C, HDL-C, TC and apo B; adverse events	Primary: At the end of treatment, the median percent change in non-HDL-C was significantly greater with omega-3-acid ethyl esters compared to placebo (-9.0 vs -2.2%; P<0.001). Secondary: Treatment with omega-3-acid ethyl esters was associated with significant reductions in TG (2.9 vs 6.3%), VLDL-C (27.5 vs 7.2%) and TC:HDL-C ratio (9.6 vs 0.7%), and a significant increase in HDL-C (3.4 vs -1.2%) (*P*<0.001 for all). Adverse events reported by at least one percent of patients treated with omega-3-acid ethyl esters that occurred with a higher frequency than those receiving simvastatin monotherapy were nasopharyngitis (3.3%), upper respiratory tract infection (3.3%), diarrhea (2.5%) and dyspepsia (2.5%). There was no significant difference in the frequency of adverse events between treatment groups. No serious adverse events were considered treatment related.
Maki et al[16] COMBOS Omega-3-acid ethyl esters (Lovaza®) 4 g/day vs placebo All patients received simvastatin 40 mg/day.	DB, PC, RCT Patients 18 to 79 years of age who had been receiving stable dose statin therapy for ≥8 weeks prior to trial enrollment	N=256 8 weeks	Primary: Non-HDL-C levels Secondary: TG, VLDL-C, LDL-C and HDL-C levels	Primary: Use of omega-3-acid ethyl esters and placebo in patients with a baseline LDL-C in the lowest (<80.4 mg/dL), middle (80.4 to <99.0 mg/dL) and highest (≥99.0 mg/dL) tertiles achieved a percent change from baseline in non-HDL-C of the following: -5 vs 0%, -13 vs -4% and -11 vs -2% (P values not reported). Secondary: Use of omega-3-acid ethyl esters and placebo in patients with a baseline LDL-C in the lowest, middle and highest tertiles achieved a percent change from baseline in TG of the following: -27 vs -8%, -32 vs -5% and -30 vs -6% (P values not reported). Use of omega-3-acid ethyl esters and placebo in patients with a baseline LDL-C in the lowest, middle and highest (≥99.0 mg/dL) tertiles achieved a percent change from baseline in VLDL-C of the following: -27 vs -7%, -28 vs -10% and -29 vs -7% (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Use of omega-3-acid ethyl esters and placebo in patients with a baseline LDL-C in the lowest, middle and highest tertiles achieved a percent change from baseline in LDL-C of the following: 9.5 vs 1.1%, -0.9 vs -3.8% and -6.4 vs -4.5% (P values not reported). The baseline LDL-C tertile had a significant interaction with treatment for the LDL-C response (P=0.022). Use of omega-3-acid ethyl esters and placebo in patients with a baseline LDL-C in the lowest, middle and highest tertiles achieved a percent change from baseline in HDL-C of the following: 4 vs -1%, 2 vs -1% and 4 vs -1% (P values not reported).
Bays et al[17] COMBOS Omega-3-acid ethyl esters (Lovaza®) 4 g/day plus simvastatin 40 mg/day Patients who received placebo in the COMBOS trial were switched to OL treatment with omega-3-acid ethyl esters plus simvastatin (Switchers). Those who received omega-3-acid ethyl esters plus simvastatin in the COMBOS trial were maintained on current therapy (Nonswitchers) All patients continued therapeutic lifestyle changes diet.	ES, OL of COMBOS Patients 18 to 79 years of age who had been receiving stable dose statin therapy for ≥8 weeks prior to trial enrollment	N=188 Up to 24 months	Primary: The difference between Nonswitchers and Switchers in median percent change in non-HDL-C from COMBOS end of treatment to month four Secondary: Difference in the median percent change in non-HDL-C from COMBOS end of treatment to month 12 and 24; the change in non-HDL-C from COMBOS baseline to months four, 12	Primary: The percent change in non-HDL-C from COMBOS end of treatment to month four revealed a greater response among Switchers when compared to Nonswitchers. At month four, the median percent change in non-HDL-C from the end of DB treatment was -9.4% in Switchers and 0.9% in Nonswitchers (P<0.001). Secondary: After 12 and 24 months of treatment, the median percent change in non-HDL-C from COMBOS end of treatment in Nonswitchers vs Switchers was -0.2 vs -0.64% (P=0.027) and 1.6 vs -6.3% (P=0.004). Reductions in non-HDL-C were maintained throughout the trial. After four, 12 and 24 months of treatment, the median percent change in non-HDL-C from COMBOS baseline in the total population was -8.3, -7.3 and -8.9%, respectively (P<0.001 for all). After four, 12 and 24 months of treatment, the median percent change in non-HDL-C from COMBOS baseline in Nonswitchers vs Switchers was -5.4 vs -10.3% (P=0.062), -6.6 vs -8.1% (P=0.604) and -7.8 vs -9.0% (P=0.496). Consistent with the non-HDL-C response, comparisons of the changes from the COMBOS end of treatment to months four, 12 and 24 in TG and other lipoprotein lipid parameters generally revealed greater reductions in Switchers vs Nonswitchers. The comparisons of the change from COMBOS baseline to these same endpoints reveled generally nonsignificant differences between the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			and 24 and from COMBOS end of treatment to months four, 12 and 24; percent changes in TC, HDL-C, LDL-C, VLDL-C, TG and TC:HDL-C for the same time points; HbA_{1c} levels	two groups. Median percent reductions from COMBOS baseline in TG, TC and VLDL-C in the total population were maintained at months four, 12 and 24 of treatment (P<0.001 for all). Omega-3-acid ethyl esters produced small median percent increases from baseline LDL-C levels at months four, 12 and 24. Among the subset of patients who had HbA_{1c} measured at baseline (n=38), the median absolute change in HbA_{1c} after 24 months of treatment was 0.1% (P value not reported).
Maki et al[18] Omega-3 acid ethyl esters (Lovaza®) 4 g/day vs placebo All patients received simvastatin 20 mg/day.	RCT, XO Patients 18 to 79 years of age with mixed dyslipidemia (TG 200 to 600 mg/dL and non-HDL-C above NCEP ATP III goal)	N=40 12 weeks	Primary: Lipid and lipoprotein parameters Secondary: Not reported	Primary: Treatment with omega-3 acid ethyl esters resulted in a -40% reduction in non-HDL-C compared to -34% with placebo (P<0.001). Treatment with omega-3 acid ethyl esters resulted in significantly greater changes in other lipid parameters compared to placebo, including VLDL-C (-42 vs -22%, respectively), TG (-44 vs -29%, respectively), TC (-31 vs -26%, respectively), and HDL-C (-16 vs -11%, respectively; P<0.05 for all). There was no significant difference in LDL-C with omega-3 acid ethyl esters (-37%) and placebo (-38%; P=0.433). Treatment with omega-3 acid ethyl esters resulted in significantly greater changes in other lipoprotein parameters compared to placebo, including apo B (-32 vs -28%, respectively), TC:HDL-C ratio (-39 vs -33%, respectively), and TG:HDL-C ratio (-51 vs -37%, respectively). There was no significant difference in apo AI levels with omega-3 acid ethyl esters (0.9) and placebo (4.3%; P=0.667). Secondary: Not reported
Peters et al[19] Omega-3 PUFA	DB, MC, PC, RCT HIV-infected adult patients receiving	N=48 12 weeks	Primary: Change in baseline mean fasting TG,	Primary: Omega-3 PUFA reduced TG by a mean of 1.75 mmol/L vs a 0.41 mmol/L increase with placebo (baseline-corrected percentage change related to placebo 95% CI, -69.48 to -6.53; P=0.019).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo All patients were allowed to receive fenofibrate or niacin.	HAART therapy and a fasting TG level 3.39 to 11.3 mmol/L		biochemical and virologic safety parameters Secondary: Safety	No effect was observed on biochemical or virologic safety parameters. Secondary: No severe treatment-emergent adverse events occurred. Mild to moderate treatment-emergent adverse events were reported in 20 and 19 patients receiving omega-3 PUFA and placebo. Most treatment-emergent adverse events were gastrointestinal-related and included diarrhea, nausea, and flatulence.
Roth et al[20] <u>Phase I</u> Fenofibrate 130 mg (FENO) QD and omega-3 acid ethyl esters 4 g (P-OM3) QD for 8 weeks vs fenofibrate 130 mg (FENO) QD and placebo for 8 weeks <u>Phase II</u> Fenofibrate 130 mg (FENO) QD and omega-3 acid ethyl esters 4 g (P-OM3) QD for 8 weeks	DB, MC, PC, RCT Patients 18 to 79 years of age with Fredrickson type IV dyslipidemia, BMI 25 to 43 kg/m^2, and TG 500 to 1,300 mg/dL	N=167 16 weeks	Primary: Median percent change in TG Secondary: Additional lipid and cardiovascular risk factors	Primary: After eight weeks of therapy, median TG values were reduced from 649.5 to 267.5 mg/dL (-60.8%) with P-OM3 + FENO and from 669.3 to 310 mg/dL (-53.8%) with FENO monotherapy (P=0.059). There was no significant difference between the treatment groups (P=0.059). Secondary: LDL-C was significantly increased with P-OM3 + FENO compared to FENO monotherapy (48.2 vs 39.0%, respectively; P=0.030). There was no significant difference in non-HDL-C among the treatment groups (-8.2% for P-OM3 + FENO vs -7.1% for FENO; P=0.767). There was a greater reduction in VLDL-C with P-OM3 + FENO than with FENO monotherapy (-57.6 vs -47.6%, respectively; P=0.016). There was a greater reduction in RLP-C with P-OM3 + FENO than with FENO monotherapy (-72.0 vs -62.1%; P=0.029). In the first eight week ES, the addition of P-OM3 to FENO monotherapy significantly reduced TGs compared to the end of the DB treatment period (-17.5%; P=0.003). In the first eight week ES, the addition of P-OM3 to FENO monotherapy significantly increased LDL-C (+8.1%; P=0.001) compared to the group previously receiving P-OM3 + FENO (+0.4%). There was no significant change

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				in non-HDL-C following the addition of P-OM3 to FENO. VLDL-C and RLP-C were significantly reduced by the addition of P-OM3 (-15.4%; P=0.030 and -25.8%; P=0.035, respectively). There was no significant difference in final lipid results for those who received P-OM3 + FENO for 16 weeks and those in which P-OM3 was added to FENO monotherapy during the OL phase of the study. In the pooled analysis of all patients enrolled in the eight week OL extension phase, the overall reductions of TGs and VLDL-C were -60.0 and -56.5%, respectively (P<0.001 for both). Non-HDLC and TC were also significantly reduced (P<0.001) over the 16 week treatment period in the pooled analysis. LDL-C increased 52.2% (P<0.001). There was no significant change in apo B at the end of the 16 week treatment study (P=0.544). The treatments were generally well tolerated and there was no significant difference in the safety profiles. The most adverse events were upper respiratory infection, nausea, diarrhea, constipation, gastroenteritis, dyspepsia, and headache.
Koh et al[21] Omega-3 fatty acids 2 g/day vs fenofibrate 160 mg/day vs placebo	PC, PG, RCT, SB Patients with primary hypertriglyceridemia (>150 mg/dL)	N=50 2 months	Primary: Change in baseline lipid profile; change in baseline vasomotor function, hsCRP, and fibrinogen; change in baseline adiponectin, HbA_{1c}, and insulin resistance Secondary: Not reported	Primary: Placebo treatment significant reduced TG and TG:HDL-C, but increased LDL-C from baseline. Omega-3 fatty acids significantly reduced TG and TG:HDL-C from baseline. Fenofibrate significantly reduced T C, TG, apo B, TG:HDL-C, and non-HDL-C, and increased HDL-C and apo AI from baseline. Effects of fenofibrate on TC and T G were both significant compared to placebo (P<0.05). The magnitude of change in HDL-C, apo AI, TG:HDL-C, and non-HDL-C were significantly different when omega-3 fatty acids and fenofibrate therapy were compared, but both treatments resulted in comparable improvements in TG (P<0.05). Placebo did not significantly improve flow-mediated dilator response to hyperemia, but omega-3 fatty acids and fenofibrate significantly improved flow-mediated dilator response to hyperemia after two months when compared to baseline (P<0.001), and when compared to placebo (P<0.001). Brachial artery dilator responses to nitroglycerin were not significantly different between any of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the therapies. Placebo and omega-3 fatty acids did not significantly change hsCRP and fibrinogen levels relative to baseline measurements. Fenofibrate significantly reduced hsCRP and fibrinogen levels after two months compared to baseline (P<0.001) or when compared to placebo (P<0.05). Omega-3 fatty acids did not significantly change insulin, plasma adiponectin levels, or insulin sensitivity compared to placebo. Compared omega-3 fatty acids, fenofibrate significantly decreased fasting insulin (P=0.023) and increased plasma adiponectin (P=0.002) and insulin sensitivity (P=0.015). Secondary: Not reported
Stalenhoef et al[22] Omega-3 acid ethyl esters (Omacor*) 4 g per day vs gemfibrozil 1,200 mg per day	DB, DD, RCT Patients with primary hyper-triglyceridemia	N=28 12 weeks	Primary: Change in lipid profile, LDL-C subfraction profile Secondary: Not reported	Primary: Both omega-3-acid ethyl esters and gemfibrozil resulted in similar and significant decreases in serum TG, VLDL-TG and VLDL-C concentrations and increases in HDL-C and LDL-C (P=0.05 to P<0.001 from baseline and P=0.29 to P=1.00 between groups). Both therapies resulted in a more buoyant LDL-C subfraction profile (P=0.05 for omega-3-acid ethyl esters, P<0.01 for gemfibrozil and P=0.09 between groups in favor of gemfibrozil). Secondary: Not reported
van Dam et al[23] Omega-3 acid ethyl esters (Omacor*) 4 g/day vs gemfibrozil 1,200 mg/day	DB, RCT Patients with hypertriglyceridemia (TG >400 mg/dL)	N=89 12 weeks	Primary: Percent change in TG Secondary: Percent change in TC, HDL-C, VLDL-C	Primary: The mean percent change in TG was -28.9% with omega-3 acid ethyl esters and -51.2% with gemfibrozil (P=0.007). Secondary: The mean percent change in HDL-C and TC were 1.2 and -10.2%, respectively, with omega-3 acid ethyl esters and 27.9 and -13.0%, respectively, with gemfibrozil (P=0.012 and P=0.513, respectively). The mean percent change in VLDL-C was -11.8% with omega-3 acid ethyl esters and -19.4% with gemfibrozil (P=0.494).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Trials Assessing Cardiovascular Outcomes				
Eritsland et al[24] Omega-3 acid ethyl esters (Omacor*) 4 g/day vs dietary therapy	RCT Patients admitted for coronary artery bypass grafting without concomitant cardiac surgery	N=610 1 year	Primary: Graft occlusion Secondary: Not reported	Primary: After one year of therapy, the vein graft occlusion rate per distal anastomoses was 27% in the group receiving omega-3 acid ethyl esters compared to 33% in the control group (OR, 0.77, 95% CI, 0.60 to 0.99; P=0.034). In the omega-3 acid ethyl esters group, 43% of the patients had 21 vein grafts occluded compared to 51% of the patients in the control group (OR, 0.72, 95% CI, 0.51 to 1.01; P=0.05). Secondary: Not reported
Johansen et al[25] Omega-3 acid ethyl esters (Omacor*) 3 g BID vs placebo	DB, PC, RCT Patients who were scheduled for elective coronary angioplasty for one or more lesions in native coronary arteries who had not undergone prior angioplasty	N=500 6 months	Primary: Restenosis Secondary: Not reported	Primary: Restenosis occurred in 40.6% of the treated stenoses in the 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). One or more restenoses occurred in 45.9% of patients treated with omega-3 acid ethyl esters compared to 44.8% of patients receiving placebo (OR, 1.05; 95% CI 0.69 to 1.59; P=0.82). Secondary: Not reported
Nilsen et al[26] Omega-3 acid ethyl esters (Omacor*) 3 g BID vs placebo	PC, RCT Patients >18 years of age with acute MI	N=300 Up to 2 years	Primary: Cardiac events and revascularizations Secondary: Not reported	Primary: Of the patients receiving omega-3 acid ethyl esters, 28% experienced at least one cardiac event compared to 24% of patients in the placebo group (P=0.74). There was no significant difference between the groups with regards to the number, type, or severity of cardiac events. There was no significant difference in the number of revascularizations with omega-3 acid ethyl esters or placebo (HR, 0.92; 95% CI 0.61 to 1.38).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
GISSI-Prevenzione Investigators[27] Omega-3 acid ethyl esters 1 g/day vs vitamin E 300 mg/day vs omega-3 acid ethyl esters 1 g/day vitamin E 300 mg/day vs no treatment	MC, OL, RCT Patients surviving a recent (≤3 months) MI	N=11,324 3.5 years	Primary: Cumulative rate of all-cause death, nonfatal MI and nonfatal stroke; cumulative rate of cardiovascular death, nonfatal MI, nonfatal stroke Secondary: Analyses of components of primary end points and main causes of death, adverse events	Primary: Treatment with omega-3 PUFA, but not vitamin E, significantly lowered the risk of the composite of death, nonfatal MI and nonfatal stroke (RR, 10%; 95% CI, 1 to 18; P=0.048 by 2-way analysis and RR, 15%; 95% CI, 2 to 26; P=0.023 by 4-way analysis). Treatment with omega-3 PUFA decreased the risk of the composite of cardiovascular death, nonfatal MI and nonfatal stroke (RR, 11%; 95% CI, 1 to 20; P=0.053 by 2-way analysis and RR, 20%; 95% CI, 5 to 32; P=0.008 by 4-way analysis). The effect of the combined treatment with omega-3 PUFA and vitamin E was similar to that for omega-3 PUFA for the primary end point (RR, 14%; 95% CI, 1 to 26) and for fatal events (RR, 20%; 95% CI, 5 to 33). Secondary: Analyses of the individual components of the main end point showed that the decrease in mortality (20% for total deaths [P value not reported], 30% for cardiovascular deaths [P=0.0242] and 45% for sudden deaths [P=0.010]) which was obtained with omega-3 PUFA accounted for all of the benefit seen in the combined end point. There was no difference across the treatment groups for nonfatal cardiovascular events. At one year and at the end of the trial, 11.6 and 28.5% of patients receiving omega-3 PUFA and 7.3 and 26.2% of those receiving vitamin E, respectively, had permanently stopped taking the study drug. Side effects were reported as a reason for discontinuing therapy for 3.8% of patients in the omega-3 PUFA groups and 2.1% of those in the vitamin E groups. Overall, gastrointestinal disturbances and nausea were the most frequently reported side effects (4.9 and 1.4% with omega-3 PUFA and 2.9 and 0.4% with vitamin E, respectively; P values not reported).

*Omacor was renamed to Lovaza in August 2007.

Drug regimen abbreviations: BID=twice daily, QD=once daily
Study abbreviations: DB=double-blind, ES=extension study, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, SB=single-blind, XO=crossover
Miscellaneous abbreviations: apo=apolipoprotein, BMI=body mass index, CHD=coronary heart disease, CI=confidence interval, CRP=C-reactive protein, CV=cardiovascular, DHA=docosahexaenoic acid, EPA=eicosapentaenoic acid, HAART=high active antiretroviral therapy, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, HIV=human immunodeficiency virus, HR=hazard ratio, hsCRP=high sensitivity C reactive protein, LDL-C=low-density lipoprotein cholesterol, MI=myocardial infarction, NCEP ATP=National Cholesterol Education Program Adult Treatment Panel, OR=odds ratio, PUFA=polyunsaturated fatty acids, RLP-C=remnant like particle cholesterol, RR=relative risk, TC=total cholesterol, TG=triglycerides, VLDL-C=very low-density lipoprotein cholesterol

Special Populations

Table 4. Special Populations[1-3]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
icosapent ethyl	No overall differences in safety or effectiveness were observed between these subjects and younger adult subjects. Safety and effectiveness in pediatric patients have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Yes
omega-3-acid ethyl esters	Safety and efficacy findings in subjects older than 60 years did not appear to differ from those of subjects younger than 60 years. Safety and effectiveness in pediatric patients have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Yes

Adverse Drug Events

Table 5. Adverse Events[1-3]

Adverse Event	Icosapent ethyl	Omega-3-acid ethyl esters
Arthralgia	2.3	-
Constipation	-	a
Dyspepsia	-	3
Eructation	-	4
Gastrointestinal disorder	-	a
Increased ALT and AST	-	a
Pruritus	-	a
Rash	-	a
Taste perversion	-	4
Vomiting	-	a

ALT=alanine transaminase, AST=aspartate transaminase

Contraindications

Table 6. Contraindications[1-3]

Contraindication	Icosapent ethyl	Omega-3-acid ethyl esters
Known hypersensitivity to the agent or any component	a	a

Warnings and Precautions

Table 7. Warnings and Precautions[1-3]

Warning/Precautions	Icosapent ethyl	Omega-3-acid ethyl esters
Atrial fibrillation or flutter; there is a possible association with atrial fibrillation or flutter. This agent is not indicated for the treatment of atrial fibrillation or flutter.		a
Hepatic impairment; ALT and AST levels should be monitored periodically.	a	a
Fish allergies; it is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to the drug.	a	a
LDL-C levels increased; monitor levels periodically during therapy.		a

ALT=alanine transaminase, AST=aspartate transaminase, LDL-C=low density lipoprotein cholesterol

Drug Interactions

No clinically significant interactions are associated with omega-3-acid ethyl esters or icosapent ethyl.[1-3]

Dosage and Administration

Patients should be placed on an appropriate lipid lowering diet before initiating therapy with omega-3-acid ethyl esters, and this diet should be continued throughout treatment. In addition, laboratory studies should be performed to determine that the lipids are consistently abnormal before initiating therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients and control of any medical problems such as diabetes and hypothyroidism that are contributing to the lipid abnormalities. Other agents known to exacerbate hypertriglyceridemia should be discontinued or changed if possible prior to consideration of triglyceride lowering drug therapy.[1-3]

Table 8. Dosing and Administration[1-3]

Generic Name	Adult Dose	Pediatric Dose	Availability
Icosapent ethyl	Adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia: Capsule: 2 grams BID with food	Safety and effectiveness in pediatric patients have not been established.	Capsule: 1 gram
Omega-3-acid ethyl esters	Adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia: Capsule (Lovaza®): 2 grams BID or 4 grams QD with food Capsule (Omtryg®): 2.4 grams BID or 4.8 grams QD with food	Safety and effectiveness in pediatric patients have not been established.	Capsule: 1 gram (Lovaza®) 1.2 gram (Omtryg®)

BID=twice daily, QD=once daily

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Cardiology/ American Heart Association Task Force on Practice Guidelines: **Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013)**[28]	Statin treatment · The panel makes no recommendations for or against specific low density lipoprotein cholesterol (LDL-C) or non-high density lipoprotein cholesterol (HDL-C) targets for the primary or secondary prevention of arteriosclerotic cardiovascular disease (ASCVD). · High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age that have clinical ASCVD, unless contraindicated. · In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated. · In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it. · Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required): use high-intensity statin therapy unless contraindicated. For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity. · For individual's ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction. · For individuals ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a nonstatin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and consider patient preferences. · Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus. · High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated. · In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy. · Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated 10-year ASCVD risk ≥7.5% should be treated with moderate- to high-intensity statin therapy. · It is reasonable to offer treatment with a moderate intensity statin to adults 40 to 75 years of age, with LDL-C 70 to 189 mg/dL, without clinica ASCVD or diabetes and an estimated 10-year ASCVD risk of 5.0 to <7.5%. · Before initiating statin therapy for the primary prevention of ASCVD in adults with LDL-C 70 to 189 mg/dL without clinical ASCVD or diabetes it is reasonable for clinicians and patients to engage in a discussion which

Clinical Guideline	Recommendations
	considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment. · In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk based treatment decision is uncertain, additional factors may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preference. Statin safety · To maximize the safety of statins, selection of the appropriate statin and dose in men and nonpregnant/nonnursing women should be based on patient characteristics, level of ASCVD risk, and potential for adverse effects. · Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin associated adverse effects are present. · Characteristics predisposing individuals to statin adverse effects include, but are not limited to: o Multiple or serious comorbidities, including impaired renal or hepatic function. o History of previous statin intolerance or muscle disorders. o Unexplained alanine transaminase elevations >3 times upper limit of normal. o Patient characteristics or concomitant use of drugs affecting statin metabolism. o >75 years of age. · Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to: o History of hemorrhagic stroke. o Asian ancestry. · Creatine kinase should not be routinely measured in individuals receiving statin therapy. · Baseline measurement of creatinine kinase is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy. · During statin therapy, it is reasonable to measure creatinine kinase in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue. · Baseline measurement of hepatic transaminase levels should be performed before initiating statin therapy. · During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark colored urine or yellowing of the skin or sclera). · Decreasing the statin dose may be considered when two consecutive values of LDL-C levels are <40 mg/dL. · It may be harmful to initiate simvastatin at 80 mg daily or increase the dose

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	of simvastatin to 80 mg daily. · Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines. Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events. · For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for human immunodeficiency virus (HIV). A review of the manufacturer's prescribing information may be useful before initiating any cholesterol-lowering drug. · It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm: o To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy. o If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating creatinine kinase, creatinine, and a urinalysis for myoglobinuria. · If mild to moderate muscle symptoms develop during statin therapy: o Discontinue the statin until the symptoms can be evaluated. o Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases). o If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy. o If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin. o Once a low dose of a statin is tolerated, gradually increase the dose as tolerated. o If, after two months without statin treatment, muscle symptoms or elevated creatinine kinase levels do not resolve completely, consider other causes of muscle symptoms listed above. o If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose. · For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for nonstatin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy.

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	Monitoring and optimizing statin therapy · Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within four to 12 weeks after initiation or dose adjustment, and every three to 12 months thereafter. Other safety measurements should be measured as clinically indicated. · The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated. · Individuals who have a less-than anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed: o Reinforce medication adherence. o Reinforce adherence to intensive lifestyle changes. o Exclude secondary causes of hyperlipidemia. · It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring: o High-intensity statin therapy generally results in an average LDL-C reduction of ≥50% from the untreated baseline; o Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30 to <50% from the untreated baseline; o LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards. · Individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less than-anticipated therapeutic response, addition of a nonstatin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. · Higher-risk individuals include: o Individuals with clinical ASCVD <75 years of age. o Individuals with baseline LDL-C ≥190 mg/dL. o Individuals 40 to 75 years of age with diabetes mellitus. o Preference should be given to non-statin cholesterol-lowering drugs shown to reduce ASCVD events in controlled trials. · In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use non-statin cholesterol lowering drugs that have been shown to reduce ASCVD events in controlled trials if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. Non statin safety · Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiating niacin, and again during up-titration to a maintenance dose and every six months thereafter. · Niacin should not be used if: o Hepatic transaminase elevations are higher than two to three times upper limit of normal. o Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur.

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	o New-onset atrial fibrillation or weight loss occurs. · In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiating niacin therapy. · To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to: o Start niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated. o Take niacin with food or premedicating with aspirin 325 mg 30 minutes before niacin dosing to alleviate flushing symptoms. o If an extended-release preparation is used, increase the dose of extended-release niacin from 500 mg to a maximum of 2,000 mg/day over four to eight weeks, with the dose of extended release niacin increasing not more than weekly. o If immediate-release niacin is chosen, start at a dose of 100 mg three times daily and up-titrate to 3 g/day, divided into two or three doses. · Bile acid sequestrants should not be used in individuals with baseline fasting triglyceride levels ≥300 mg/dL or type III hyperlipoproteinemia, because severe triglyceride elevations might occur. · A fasting lipid panel should be obtained before bile acid sequestrants are initiated, three months after initiation, and every six to 12 months thereafter. · It is reasonable to use bile acid sequestrants with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in four to six weeks after initiation. Discontinue the bile acid sequestrants if triglycerides exceed 400 mg/dL. · It is reasonable to obtain baseline hepatic transaminases before initiating ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent alanine transaminase elevations >3 times upper limit of normal occur. · Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. · Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are >500 mg/dL, are judged to outweigh the potential risk for adverse effect. · Renal status should be evaluated before fenofibrate initiation, within three months after initiation, and every six months thereafter. Assess renal safety with both a serum creatinine level and an estimated glomerular filtration rate based on creatinine. · Fenofibrate should not be used if moderate or severe renal impairment, defined as estimated glomerular filtration rate <30 mL/min per 1.73 m^2, is present. · If estimated glomerular filtration rate is between 30 and 59 mL/min per 1.73 m^2, the dose of fenofibrate should not exceed 54 mg/day. · If, during follow-up, the estimated glomerular filtration rate decreases persistently to ≤30 mL/min per 1.73 m^2, fenofibrate should be discontinued. o If eicosapentaenoic acid and/or docosahexanoic acid are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.

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National Cholesterol Education Program: **Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report (2002)**[29]	General recommendations · With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of evidence is only moderate at present. National Cholesterol Education Program supports the American Heart Association's recommendation that fish be included as part of a CHD risk reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. · Initiate LDL lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. · Statins should be considered as first line drugs when LDL lowering drugs are indicated to achieve LDL-C treatment goals. · After six weeks if LDL-C goal is not achieved, intensify LDL lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Statins · Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. Bile acid sequestrants · Bile acid sequestrants should be considered as LDL lowering therapy for patients with moderate elevations in LDL-C, for younger patients with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy and for patients needing only modest reductions in LDL-C to achieve target goals. · Bile acid sequestrants should be considered in combination therapy with statins in patients with very high LDL-C levels. Nicotinic acid · Nicotinic acid should be considered as a therapeutic option for higher risk patients with atherogenic dyslipidemia. · Nicotinic acid should be considered as a single agent in higher risk patients with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol lowering drugs in higher risk patients with atherogenic dyslipidemia combined with elevated LDL-C levels. · Nicotinic acid should be used with caution in patients with active liver disease, recent peptic ulcer, hyperuricemia, gout and type 2 diabetes. · High doses of nicotinic acid (>3 g/day) generally should be avoided in patients with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. Fibric acid derivatives (fibrates) · Fibrates can be recommended for patients with very high TG to reduce risk for acute pancreatitis. · They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL). · Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia.

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	· They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia. Omega-3 fatty acids · Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]) have two potential uses. · In higher doses, DHA and EPA lower serum TGs by reducing hepatic secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. · Recent trials also suggest that relatively high intakes of omega-3 fatty acids (1 to 2 g/day) in the form of fish, fish oils or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1 to 2 g/day) for either primary or secondary prevention.
National Institute for Health and Clinical Excellence: **Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease (2014)[30]**	· Be aware that when deciding on lipid modification therapy for the prevention of cardiovascular disease (CVD), drugs are preferred for which there is evidence in clinical trials of a beneficial effect on CVD morbidity and mortality · When a decision is made to prescribe a statin use a statin of high intensity and low acquisition cost. Lipid Measurement and Referral: · Measure both total and high-density lipoprotein (HDL) cholesterol to achieve the best estimate of CVD risk. · Before starting lipid modification therapy for the primary prevention of CVD, take at least one lipid sample to measure a full lipid profile. This should include measurement of total cholesterol, HDL cholesterol, non-HDL cholesterol and triglyceride concentrations. A fasting sample is not needed. · Use the clinical findings, lipid profile and family history to judge the likelihood of a familial lipid disorder rather than the use of strict lipid cut-off values alone. · Exclude possible common secondary causes of dyslipidemia (such as excess alcohol, uncontrolled diabetes, hypothyroidism, liver disease and nephrotic syndrome) before referring for specialist review. · Consider the possibility of familial hypercholesterolemia if they have a total cholesterol concentration >7.5 mmol/L and a family history of premature coronary heart disease. · Arrange for specialist assessment of people with a total cholesterol concentration of more than 9.0 mmol/L or a non-HDL cholesterol concentration of more than 7.5 mmol/L even in the absence of a first-degree family history of premature coronary heart disease. · Refer for urgent specialist review if a person has a triglyceride concentration of more than 20 mmol/L that is not a result of excess alcohol or poor glycemic control. · In people with a triglyceride concentration between 10 and 20 mmol/L: o Repeat the triglyceride measurement with a fasting test (after an

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	interval of five days, but within two weeks) and o Review for potential secondary causes of hyperlipidemia and o See specialist advice if the triglyceride concentration remains above 10 mmol/L · In people with a triglyceride concentration between 4.5 and 9.9 mmol/L: o Be aware that the CVD risk may be underestimated by risk assessment tools and o Optimize the management of other CVD risk factors present and o Seek specialist advice if non-HDL cholesterol concentration is more than 7.5 mmol/litre. Statins for the prevention of CVD: · The decision whether to start statin therapy should be made after an informed discussion between the clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as potential benefits from lifestyle modifications, informed patient preference, comorbidities, polypharmacy, general frailty and life expectancy. · Before starting statin treatment perform baseline blood tests and clinical assessment, and treat comorbidities and secondary causes of dyslipidemia. Include smoking status, alcohol consumption, blood pressure, body mass index or other obesity measure, total cholesterol, non-HDL cholesterol, HDL cholesterol, triglyceride level, glycosylated hemoglobin (HbA_{1c}),renal function and estimated glomerular filtration rate (eGFR), transaminase levels, and thyroid stimulating hormone in the assessment. Statins for the Primary Prevention of CVD: · Before offering statin treatment for primary prevention, discuss the benefits of lifestyle modification and optimize the management of all other modifiable CVD risk factors if possible. · Recognize that people may need support to change their lifestyle. To help them do this, refer them to programs such as exercise referral schemes. · Offer people the opportunity to have their risk of CVD assessed again after they have tried to change their lifestyle. · If lifestyle modification is ineffective or inappropriate, offer statin treatment after risk assessment. · Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. · For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Be aware of factors that may make treatment inappropriate. Statins for the Secondary Prevention of CVD: · Start statin treatment in people with CVD with atorvastatin 80 mg. Use a lower dose of atorvastatin if there are potential drug interactions, high risk of adverse effects, or patient preference. · Do not delay statin treatment in secondary prevention to manage modifiable risk factors. · If a person has acute coronary syndrome, do not delay statin treatment. Take a lipid sample on admission and about three months after the start of treatment.

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	Statins for the Primary Prevention of CVD for People with Type 1 Diabetes: · Consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes. · Offer statin treatment for the primary prevention of CVD to adults with type 1 diabetes who are older than 40 years, have had diabetes for more than 10 years, have established nephropathy, or have other CVD risk factors. · Start treatment for adults with type 1 diabetes with atorvastatin 20 mg. Statins for the Primary Prevention of CVD in People with Type 2 Diabetes: · Offer atorvastatin 20 mg for the primary prevention of CVD to people with type 2 diabetes who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. Statins for People with CKD: · Offer atorvastatin 20 mg for the primary or secondary prevention of CVD to people with CKD o Increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and eGFR is 30 mL/min/1.73 m^2 or more. o Agree the use of higher doses with a renal specialist if eGFR is less than 30 mL/min/1.73 m^2. Follow-up of People Started on Statin Therapy: · Measure total cholesterol, HDL cholesterol and non-HDL cholesterol in all people who have been started on high-intensity statin treatment at three months of treatment and aim for a greater than 40% reduction in non-HDL cholesterol. · If a greater than 40% reduction in non-HDL cholesterol is not achieved, discuss adherence to lifestyle modifications and drug therapy, timing of dose. o Consider increasing the dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement. · Provide annual medication reviews for people taking statins. · Discuss with people who are stable on a low- or middle-intensity statin the likely benefits and potential risks of changing to a high-intensity statin when they have a medication review and agree with the person whether a change is needed. Monitoring Statin Therapy for Adverse Effects: · Advise people who are being treated with a statin that other drugs, some foods (e.g., grapefruit juice) and some supplements may interfere with statins and to always consult the patient information leaflet, a pharmacist or prescriber for advice when starting other drugs or thinking about taking supplements. · Remind the person to restart the statin if they stopped taking it because of drug interactions or to treat intercurrent illnesses. · Before offering a statin, ask the person if they have had persistent generalized unexplained muscle pain, whether associated or not with previous lipid-lowering therapy. If they have, measure creatine kinase levels.

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	o If creatine kinase levels are more than five times the upper limit of normal, re-measure creatine kinase after seven days. If creatine kinase levels are still five times the upper limit of normal, do not start statin treatment. o If creatine kinase levels are raised but less than five times the upper limit of normal, start statin treatment at a lower dose. · Advise people who are being treated with a statin to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, measure creatine kinase. · If people report muscle pain or weakness while taking a statin, explore other possible causes of muscle pain or weakness and raised creatine kinase if they have previously tolerated statin therapy for more than three months. · Do not measure creatine kinase levels in asymptomatic people who are being treated with a statin. · Measure baseline liver transaminase before starting a statin. Measure liver transaminase within three months of starting treatment and at 12 months, but not again unless clinically indicated. · Do not routinely exclude from statin therapy people who have liver transaminase levels that are raised but are less than three times the upper limit of normal. · Do not stop statins because of an increase in blood glucose level or HbA_{1c}. · Statins are contraindicated in pregnancy and women of childbearing potential should be advised of the potential teratogenic risk of statins and to stop taking them if pregnancy is a possibility. o Advise women planning pregnancy to stop taking statins three months before they attempt to conceive and to not restart them until breastfeeding is finished. Intolerance to Statin Therapy: · If a person is not able to tolerate a high-intensity statin aim to treat with the maximum tolerated dose. · Tell the person that any statin at any dose reduces CVD risk. If someone reports adverse effects when taking high-intensity statins discuss the following possible strategies with them: o stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin and o reducing the dose within the same intensity group and o changing the statin to a lower intensity group. · Seek specialist advice about options for treating people at high risk of CVD such as those with CKD, type 1 diabetes, type 2 diabetes or genetic dyslipidemias, and those with CVD, who are intolerant to three different statins. Fibrates for Preventing CVD: · Do not routinely offer fibrates for the prevention of CVD to people who are being treated for primary or secondary prevention, or people with CKD or diabetes type 1 or 2. Nicotinic Acid for Preventing CVD: · Do not offer nicotinic acid (niacin) for the prevention of CVD to people who are being treated for primary or secondary prevention, or people with CKD

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	or diabetes type 1 or 2. Bile Acid Sequestrants (Anion Exchange Resins) for Preventing CVD: · Do not offer bile acid sequestrants for the prevention of CVD to people who are being treated for primary or secondary prevention, or people with CKD or diabetes type 1 or 2. Omega-3 Fatty Acid Compounds for Preventing CVD: · Do not offer omega-3 fatty acid compounds for the prevention of CVD to people who are being treated for primary or secondary prevention, or people with CKD or diabetes type 1 or 2. · Tell people that there is no evidence that omega-3 fatty acid compounds help to prevent CVD. Omega-3 Fatty Acid Compounds for Preventing CVD: · Do not offer the combination of a bile acid sequestrant (anion exchange resin), fibrate, nicotinic acid or omega-3 fatty acid compound with a statin for the primary or secondary prevention of CVD. Ezetimibe for Preventing CVD: · People with primary hypercholesterolemia should be considered for ezetimibe treatment.
American Association of Clinical Endocrinologists: **Guidelines for the management of dyslipidemia and prevention of atherosclerosis (2012)**[31]	· Aggressive lipid-modifying therapy is recommended to lower LDL-C to <100 mg/dL in patients with average or elevated LDL-C. This has been shown to reduce vascular mortality in patients at high risk. · An LDL-C goal <70 mg/dL is recommended as an appropriate goal for *all* patients with established CAD. Current evidence indicates that LDL-C can be aggressively lowered with statin therapy regardless of baseline levels and suggests that there is no threshold below which LDL-C lowering ceases to be effective. · Patients for whom aggressive therapy is recommended: o Patients undergoing coronary artery bypass graft. o Patients with acute coronary syndrome. o Certain healthy and functional older patients at high risk. · Statins are the drug of choice for LDL-C reduction on the basis of findings from morbidity and mortality outcome trials. Agents currently available are atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and pitavastatin. · Fibrates are recommended for treatment of severe hypertriglyceridemia (triglycerides >500 mg/dL). Adjunct use of 2 to 4 g of omega 3 acids can be used, if necessary, to achieve satisfactory triglyceride lowering. · Niacin is recommended for reducing triglycerides, increasing HDL-C, and reducing LDL-C. Adjunct use of 2 to 4 g of omega-3 fish oil can be used, if necessary, to achieve satisfactory triglyceride lowering. · Bile acid sequestrants are recommended for reducing LDL-C and apo B and modestly increasing HDL-C, but they may increase triglycerides. Bile acid sequestrants have a glucose-lowering effect; colesevelam is now also approved for treatment of type 2 diabetes. Available agents in this drug class are cholestyramine, colestipol, and colesevelam. · Cholesterol absorption inhibitors are effective as monotherapy in reducing LDL-C and apo B. Combination therapy with statins is recommended because current research indicates that this enhances these benefits and

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	further improves the beneficial effects of statins on triglycerides and HDL-C. It is uncertain whether cholesterol absorption inhibitor therapy has a direct benefit on reducing cardiovascular events. · Combination therapy be considered in the following circumstances: o When the cholesterol level is markedly increased and monotherapy does not achieve the therapeutic goal. o When mixed dyslipidemia is present. o Niacin or fibrates in combination with statins may be appropriate options for many patients with hypertriglyceridemia and associated low HDL-C. o To reduce the risk of dosage-related adverse effects. · Recommendations for lipid management in children include: o Colesevelam has been approved for patients older than 8 years. o Atorvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin have been approved for the treatment of familial hypercholesterolemia in patients 10 years or older. o Cholestyramine may also be used in children.
American Heart Association/American College of Cardiology/National Heart, Lung, and Blood Institute: **American Heart Association/American College of Cardiology Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update (2011)**[32]	Lipid management · Goal: treatment with statin therapy; use statin therapy to achieve LDL-C of <100 mg/dL; for very high risk patients an LDL-C <70 mg/dL is reasonable; if TG are ≥200 mg/dL, non-HDL-C should be <130 mg/dL, whereas non-HDL-C <100 mg/dL for very high risk patients is reasonable. · Lifestyle modifications (daily physical activity and weight management) are strongly recommended for all patients. · In addition to lifestyle modifications, statin therapy should be prescribed in the absence of contraindications or documented adverse events. · An adequate dose of statin should be used that reduces LDL-C to <100 mg/dL and achieves ≥30% lowering of LDL-C. · Patients who have TG ≥200 mg/dL should be treated with statins to lower non-HDL-C to <130 mg/dL. · Patients who have TG >500 mg/dL should be started on fibrate therapy in addition to statin therapy to prevent acute pancreatitis. · If treatment with a statin does not achieve the goal selected for an individual patient, intensification of LDL-C-lowering drug therapy with a bile acid sequestrant or niacin is reasonable. · For patients who do not tolerate statins, LDL-C-lowering therapy with bile acid sequestrants and/or niacin is reasonable. · It is reasonable to treat very high risk patients with statin therapy to lower LDL-C to <70 mg/dL. · In patients who are at very high risk and who have TG ≥200 mg/dL, a non-HDL-C goal of <100 mg/dL is reasonable. · The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants, and/or niacin. · For patients who continue to have an elevated non-HDL-C while on adequate statin therapy, niacin or fibrate therapy or fish oil may be reasonable. · For all patients, it may be reasonable to recommend omega-3 fatty acids from fist or fish oil capsules (1 g/day) for cardiovascular disease risk reduction.
Institute for Clinical Systems Improvement:	Clinical highlights · Initiate a statin with patients who have a history of CHD or CHD risk equivalents.

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Lipid Management in Adults (2011)[33]	· Establish lipid goals based on risk level. · Instruct patients on healthy lifestyle and adjunctive measures. · Patient adherence with recommended therapy should be reinforced during scheduled follow-up. · An LDL goal <70 mg/dL can be considered for patients with established CAD, non-cardiac atherosclerosis, or CAD equivalent. Ongoing drug therapy · The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). · Combination therapy can be considered on an individual basis. · No primary prevention trials have addressed pharmacologic lipid treatment in patients at low risk for CHD, and there is no evidence to support drug treatment in this population. · Primary prevention trials of pharmacologic lipid-lowering have not shown a decrease in mortality, although most have shown about a 30% reduction in CHD events. Monotherapy · Patients with risk factors for CHD but no history of disease who receive lipid-lowering therapy are likely to experience a decreased risk of CHD. · Patients with a history of CHD often benefit from statin therapy, and trials have consistently shown a decrease in risk of death from CHD. · The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). · Statins are the drugs of choice for lowering LDL-C, and aggressive treatment with statins should be pursued. Statins also have a modest effect on reducing TG and increasing HDL-C. · Several trials with clinical endpoints support the use of statins in primary and secondary prevention. · If a patient is intolerant to a statin, patients should try another statin before ruling all of them out. · Incidence of muscle symptoms or signs is the most prevalent and important adverse effect of statin therapy. · Specific statin and dose should be selected based on cost and amount of lipid-lowering required. · If patients are unable to take a statin, then bile acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available. · Many crystalline (immediate-release) and sustained-release preparations of niacin are available over-the-counter. The extended-release preparation of niacin is a prescription drug. Niacin exerts favorable effects on all lipids and lipoproteins, and is good for mixed hyperlipidemia. · Long-term use of niacin is usually limited for many patients due to side effects (e.g., flushing and pruritus, liver toxicity, gastrointestinal complaints, etc). · Combination therapy with niacin and a statin may increase the risk of myopathy based on early experience with lovastatin. · Prior to initiating a fibric acid (gemfibrozil, fenofibrate, and fenofibrate micronized), lifestyle therapies should be intensified for moderately

Clinical Guideline	Recommendations
	elevated TG. With fibric acids, TG are reduced 30 to 50%, HDL-C is increased 10 to 20%, TC is reduced 5 to 20% in patients without elevated TG, and the effect on LDL-C is variable. Fibric acids are good for severe hypertriglyceridemia (>500 mg/dL) in patients at risk for pancreatitis and for prevention of CHD (not proven for fenofibrate). · Myositis, cholelithiasis, and cholecystitis can occur with fibric acid, and caution should be exercised with a history of liver disease. · The long-term effects of ezetimibe on cardiovascular morbidity and mortality are unknown. Ezetimibe is associated with a LDL-C lowering of about 18%, and additive LDL-C lowering occurs when used in combination with a statin. · The short-term tolerability of ezetimibe is similar to placebo, and the long-term safety is unknown. · Bile acid sequestrants reduce LDL-C by 15 to 30% and TG may increase 15%; therefore, are these agents are useful for patients with moderately elevated LDL-C. The effects of the bile acid sequestrants are apparent within one week and maximum at two to three weeks. Bile acid sequestrants are good for combination therapy and are most potent with a statin. · Bile acid sequestrants are not systemically absorbed; therefore, side effects are limited to the gastrointestinal tract. In addition, drug interactions are minimized by taking other medications one hour before the sequestrant or four hours after. <u>Combination therapy</u> · It has become common practice to adjust medication therapy, including using combinations of medications, to achieve LDL-C goals. Common combinations include statin/fibrate, statin/niacin, and statin/ezetimibe. o A fibrate is commonly added to a statin, which results in enhanced lowering of LDL-C, as well as a higher incidence of myopathy. o No published clinical trial to date has evaluated the clinical benefit of combination therapy with a statin and niacin on vascular events. o The addition of ezetimibe to a statin significantly improves LDL-C over either agent alone. To date no large clinical trials have been completed evaluating this combination therapy compared to statin monotherapy on clinical vascular endpoints. · Combinations of lipid-lowering agents do not improve clinical outcomes more than statin monotherapy. · Combination therapy can be considered on an individual basis, but the additional cost, complexity, and risk for side effects argue against routine use until further trials indicate what groups of patients might benefit. · There are negative trials of cholesterylester transfer protein inhibitors when used in combination with statins. · No randomized-controlled trials looking at clinical vascular endpoints are available for other agents such as fish oils or bile-acid sequestrants used in combination therapy. <u>Lifestyle modifications</u> · Patients who are overweight should be advised to reduce their caloric intake to achieve weight loss. · Patients should follow a diet and exercise program for a reasonable amount of time to determine whether their LDL-C level is lowered to the target range.

Clinical Guideline	Recommendations
	· A diet low saturated and trans fats, and high in soluble fiber, with consideration given to adding two grams of plant sterol/stanol is recommended. · Vitamin E supplementation should not be used. · Light to moderate consumption of alcohol may lower CHD rates. · Omega-3 fatty acids should be recommended in patients with dyslipidemia (one gram of EPA/DHA by capsule supplement, or by eating at least two servings per week of fatty fish).
European Society of Cardiology and Other Societies: **Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2012)**[34]	Drugs · Currently available lipid-lowering drugs include statins, fibrates, bile acid sequestrants, niacin, and selective cholesterol absorption inhibitors (e.g., ezetimibe). · Statins, by reducing LDL-C, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. · Statins should be used as the drugs of first choice in patients with hypercholesterolemia or combined hyperlipidemia. · Selective cholesterol absorption inhibitors are not used as monotherapy to decrease LDL-C. · Bile acid sequestrants also decrease TC and LDL-C, but tend to increase TG. · Fibrates and niacin are used primarily for TG lowering and increasing HDL-C, while fish oils (omega-3 fatty acids) in doses of 2 to 4 g/day are used for TG lowering. · Fibrates are the drugs of choice for patients with severely elevated TG, and prescription omega-3 fatty acids might be added if elevated TG is not decreased adequately. Drug combinations · Patients with dyslipidemia, particularly those with established CVD, diabetes, or asymptomatic high risk patients, may not always reach treatment targets; therefore, combination treatment may be needed. · Combinations of a statin and a bile acid sequestrants or a combination of a statin and ezetimibe can be used for greater reduction in LDL-C than can be achieved with either agent used as monotherapy. · Another advantage of combination therapy is that lower doses of statins can be utilized, thus reducing the risk of adverse events associated with high dose statin therapy. However, statins should be used in the highest tolerable dose to reach LDL-C target level before combination therapy is initiated. · Combinations of niacin and a statin increase HDL-C and decrease TG better than either drug used as monotherapy, but flushing is the main adverse event with niacin, which may affect compliance. · Fibrates, particularly fenofibrate, may be useful, not only for decreasing TG and increasing HDL-C, but can further lower LDL-C when administered in combination with a statin. · If target levels cannot be reached with maximal doses of lipid-lowering therapy or combination therapy, patients will still benefit from treatment to the extent to which dyslipidemia has been improved. In these patients, increased attention to other risk factors may help to reduce total risk.

Conclusions

Icosapent ethyl (Vascepa®) and omega-3-acid ethyl esters (Lovaza®, Omtryg®) are FDA-approved as an adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia, defined as 500 mg/dL or more. Omega-3-acid ethyl esters is a mixture of ethyl esters or free fatty acids primarily composed of EPA DHA, while icosapent ethyl is an ethyl ester of EPA. Icosapent ethyl does not contain DHA. Studies suggest that this formulation does not cause significant increases in LDL-C which has been associated with large doses of omega-3-acid ethyl esters.[1-4]

Recommendations in clinical guidelines regarding the use of omega-3 fatty acids are varied. In general, therapeutic lifestyle changes, including diet, exercise, and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL lowering is required, initial treatment with a statin is recommended and considered first line therapy for patients with established coronary heart disease (CHD) or CHD equivalents. Older guidelines suggest omega-3 fatty acids may reduce the risk of cardiovascular disease and may be reasonable for cardiovascular disease risk reduction, while newer guidelines do not address the use or recommend against the use of omega-3 fatty acids for reducing the risk of cardiovascular disease due to limited data.[28-34]

Dosing recommendations are similar for both icosapent ethyl and omega-3-acid ethyl esters. Icosapent ethyl is dosed at 2 grams twice a day. Omega-3-acid ethyl esters is dosed at 2 or 2.4 grams BID for Lovaza® and Omtryg®, respectively. Additionally, omega-3-acid ethyl esters may be given once daily at a dose of 4 or 4.8 grams, respectively. All omega-3 fatty acid products should be taken with food. These agents are considered safe, with very minimal side effects. Omega-3-acid ethyl esters and icosapent ethyl have not been studied in renal or hepatic impairment. Currently, only Lovaza® (omega-3-acid ethyl esters) is available generically.

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