


Department of Vermont Health Access

***Therapeutic Class Review
Omega-3-Acid Ethyl Esters***

Overview/Summary

There are several classes of medications used to alter lipids including the hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), fibric acid derivatives, bile acid sequestrants and nicotinic acid (niacin). Each medication class differs with respect to the mechanism by which they alter lipids, as well as to what degree; therefore, Food and Drug Administration (FDA) approved indications for a particular medication class are influenced by the underlying lipid abnormality.

Modifications in lipids can also be effected by a number of dietary approaches or specific dietary supplements. Like medication classes, these modalities also differ with respect to their mechanism of action and to the degree and type of lipid modification.¹ Rich sources of omega-3-fatty acids come from fatty fish and plant sources, and fish oil as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). When administered at high doses they can reduce levels of triglycerides (TGs) by approximately 50%.¹⁻³ The mechanism by which this occurs is thought to be caused by the inhibition of very low density lipoprotein cholesterol (LDL-C) synthesis.¹ In general, omega-3-fatty acids have no effect on LDL-C, but large doses have been shown to reciprocally increase LDL-C levels in patients with hypertriglyceridemia.³ More recent clinical trials suggest that relatively high doses of omega-3-fatty acids, in the form of fish, fish oils or high-linolenic acid oils, will reduce the risk for major coronary events in persons with established coronary heart disease.³⁻⁵

Lovaza[®] (omega-3-acid ethyl esters) is the only FDA approved prescription omega-3-acid ethyl esters available. It is approved as adjunct therapy to diet to reduce TGs in adults with severe (≥ 500 mg/dL) hypertriglyceridemia.⁶ Lovaza[®] is available as a capsule, containing approximately 375 and 465 mg of DHA and EPA. Of note, there are several over-the-counter products containing omega-3-acid ethyl esters that are marketed as nutritional supplements. These products do not have FDA approved indications and may not contain the same amounts of the active ingredient.^{6,7}

In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia.^{3,5,8} When LDL lowering is required, initial treatment with a statin, a bile acid sequestrant or niacin is recommended.¹ However, in general, the statins are considered first line therapy for decreasing LDL-C levels.^{3,5,8,9} If after six weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a bile acid sequestrant or niacin should be considered. Omega-3-acid ethyl esters represent an alternative to fibric acid derivatives and niacin for the treatment of hypertriglyceridemia.³

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Omega-3-acid ethyl esters (Lovaza [®])	Omega-3-acid ethyl esters	-

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications⁶

Generic Name	Adjunct to Diet to Reduce Triglyceride Levels in Adult Patients with Severe (≥ 500 mg/dL) Hypertriglyceridemia
Omega-3-acid ethyl esters	✓

In addition to its Food and Drug Administration approved indication, omega-3-acid ethyl esters have the potential to be used off-label for the treatment of coronary arteriosclerosis, familial combined hyperlipidemia, heart failure and hyperlipidemia with triglyceride levels < 500 mg/dL.¹⁰

Pharmacokinetics

No clinically significant pharmacokinetic data for omega-3-acid ethyl esters is reported.^{6,10}

Clinical Trials

Clinical trials demonstrating the safety and efficacy of omega-3-acid ethyl esters in its Food and Drug Administration approved indication are outlined in Table 3.¹¹⁻²¹ In general, omega-3-acid ethyl esters consistently demonstrated “superiority” over placebo in the management of hypertriglyceridemia and combined hyperlipidemia.¹¹⁻¹⁴ When added to hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) therapy in patients with hyperlipidemia, omega-3-acid ethyl esters produce further beneficial modifications in lipid parameters.¹⁵⁻¹⁹ In a direct comparison of omega-3-acid ethyl esters and gemfibrozil in patients with primary hypertriglyceridemia, changes in lipid parameters were similar between the two treatments.²⁰

In an open-label, 3.5 year trial of patients with a previous myocardial infarction, treatment with omega-3-acid ethyl esters significantly decreased the risk of the composite of death, nonfatal myocardial infarction or nonfatal stroke ($P=0.148$ or $P=0.023$).²¹ Even though guidelines recognize the potential of omega-3-acid ethyl esters in reducing the risk for major coronary events in persons with established coronary heart disease, the effect of omega-3-acid ethyl esters on cardiovascular mortality and morbidity in patients with elevated triglycerides has not been determined.³⁻⁶

Table 3. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hypercholesterolemia				
Pownall et al ¹¹ Omega-3-acid ethyl esters (Omacor [®] *) 4 g/day vs placebo	DB, PC, PG, RCT Patients with severe hypertriglyceridemia (TG ≥500 but <2,000 mg/dL)	N=40 12 weeks (includes a 6 week run in period)	Primary: Effect on TG, lipid profile and lipid composition Secondary: Not reported	Primary: Median TG levels were reduced 38.9% from baseline with omega-3-acid ethyl ester compared to 7.8% with placebo (<i>P</i> =0.001). Omega-3-acid ethyl esters also significantly reduced TC (-9.9%; <i>P</i> =0.004) and VLDL-C (-29.2%; <i>P</i> =0.001) and significantly increased LDL-C (16.7%; <i>P</i> =0.007) from baseline. HDL-C increased with omega-3-acid ethyl esters (5.9%; <i>P</i> =0.057 vs baseline and <i>P</i> =0.023 vs placebo) and decreased with placebo (-5.9%; <i>P</i> value not significant vs baseline). Secondary: Not reported
McKeone et al ¹² Omega-3-acid ethyl esters (Omacor [®] *) 4 g/day vs placebo	DB, PC, RCT Patients with severe hypertriglyceridemia (TG ≥500 but <2,000 mg/dL)	N=40 12 weeks (includes a 6 week run-in period)	Primary: Effect on TG and serum phosphatidylcholine Secondary: Changes in lipid profile	Primary: Treatment with omega-3-acid ethyl esters significantly reduced TG levels by 26% compared to a 7% increase with placebo (<i>P</i> values not reported). Incorporation of EPA and DHA into the serum phosphatidylcholine occurred within six 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%) (<i>P</i> values not reported). None of these parameters significantly changed with placebo (<i>P</i> values not reported).
Calabresi et al ¹³ Omega-3-acid ethyl esters (Omacor [®] *) 4 g/day vs placebo	DB, RCT, XO Patients with familial combined hyperlipidemia	N=14 26 weeks (includes a 4 week run in period and 6 week follow-up period after treatment)	Primary: Changes in lipid profile and LDL-C subclass distribution Secondary: Safety	Primary: Omega-3-acid ethyl esters significantly reduced plasma TG and VLDL-C by 27 and 18%, respectively (both <i>P</i> <0.05) compared to baseline. TC and HDL-C did not change, but LDL-C and apo B increased by 21 (<i>P</i> =0.05) and 6% compared to baseline (<i>P</i> <0.05). Omega-3 acid ethyl esters 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:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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, platelet count).
<p>Calabresi et al¹⁴</p> <p>Omega-3-acid ethyl esters (Omacor^{®*}) 4 g/day</p> <p>vs</p> <p>placebo</p>	<p>DB, RCT, XO</p> <p>Patients with familial combined hyperlipidemia</p>	<p>N=14</p> <p>20 weeks (includes a 4 week run-in period)</p>	<p>Primary: Changes in lipid profile, LDL-C and HDL-C subclass distribution</p> <p>Secondary: Not reported</p>	<p>Primary: Plasma TG were 44% lower and LDL-C and apo B were 25 and 7% higher with omega-3-acid ethyl esters compared to placebo (all $P<0.05$). HDL-C was higher (8%) with omega-3-acid ethyl esters compared to placebo, but the difference was not significant ($P>0.05$).</p> <p>Omega-3-acid ethyl esters caused a selective increase of the more buoyant HDL2-C subfraction; plasma HDL2-C and total mass increased by 40 ($P<0.05$) and 26% (P values not reported), respectively, whereas HDL3-C and total mass decreased by 4 ($P>0.05$) and 6% (P values not reported). The plasma concentration of the HDL-bound antioxidant enzyme paraoxonase increased by 10% with omega-3-acid ethyl esters ($P<0.05$).</p> <p>Secondary: Not reported</p>
<p>Bays et al¹⁵</p> <p>Omega-3-acid ethyl ester (Lovaza[®]) 4 g/day</p> <p>vs</p> <p>placebo</p> <p>All patients received OL atorvastatin 10 to 40 mg/day.</p> <p>After 8 weeks of therapy the initial 10 mg/day dose was increased to 20 (12 weeks) then 40 mg (16 weeks).</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 18 to 79 years of age who were medically stable with a non-HDL-C concentration >160 mg/dL and a TG concentration 250 to 599 mg/dL at the end of a diet run in period</p>	<p>N=245</p> <p>20 weeks</p>	<p>Primary: Percent change in non-HDL-C at week eight</p> <p>Secondary: Percent changes in non-HDL-C at weeks 12 and 16; changes from baseline in TC, HDL-C, LDL-C, VLDL-C, TG, apo A-I and apo B</p>	<p>Primary: After eight weeks, the median change from baseline in non-HDL-C was -40.2 and -33.7% with omega-3-acid ethyl esters and placebo (difference, -6.5%; 90% CI, -7.2 to -2.9; $P<0.001$).</p> <p>Secondary: Reductions in non-HDL-C with omega-3-acid ethyl esters remained significant compared to placebo after 12 (difference, -7.9%; 90% CI, -9.1 to -4.9; $P<0.001$) and 16 weeks (difference, -4.1%; 90% CI, -6.8 to -2.4; $P<0.001$).</p> <p>Treatment with omega-3-acid ethyl esters produced consistent and significant reductions in mean TC ($P<0.001$ for all doses of atorvastatin), TC:HDL-C ($P<0.001$ for all doses of atorvastatin), TG ($P<0.001$ for all doses of atorvastatin) and VLDL-C ($P<0.001$ for all doses of atorvastatin) compared to placebo. The median percent increase from baseline in HDL-C was also greater with omega-3-acid ethyl esters with all three atorvastatin doses compared to placebo (combination with atorvastatin 10 mg; $P=0.001$,</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>combination with atorvastatin 20 and 40 mg; $P<0.001$). The median percent change from baseline in LDL-C, apo A-I and apo B was not significantly different between the two treatment groups, except for a greater reduction in apo B with combination therapy with atorvastatin 20 mg/day (-36.8 vs -33.6%; difference, 3.2%; $P=0.005$).</p>
<p>Davidson et al¹⁶</p> <p>Omega-3-acid ethyl ester (Lovaza[®]) 4 g/day</p> <p>vs</p> <p>placebo</p> <p>All patients were receiving simvastatin 40 mg/day.</p>	<p>DB, MC, PC, PG, RCT</p> <p>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</p>	<p>N=254</p> <p>16 weeks (includes 8 weeks OL treatment with simvastatin)</p>	<p>Primary: Change in non-HDL-C</p> <p>Secondary: Changes in TG, VLDL-C, LDL-C, HDL-C, TC and apo B; adverse events</p>	<p>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%; $P<0.001$).</p> <p>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).</p> <p>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.</p>
<p>Maki et al¹⁷</p> <p>COMBOS</p> <p>Omega-3-acid ethyl esters (Lovaza[®]) 4 g/day</p> <p>vs</p> <p>placebo</p> <p>All patients received simvastatin 40 mg/day.</p>	<p>DB, PC, RCT</p> <p>Patients 18 to 79 years of age who had been receiving stable dose statin therapy for ≥ 8 weeks prior to trial enrollment</p>	<p>N=256</p> <p>8 weeks</p>	<p>Primary: Non-HDL-C levels</p> <p>Secondary: TG, VLDL-C, LDL-C and HDL-C levels</p>	<p>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).</p> <p>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).</p> <p>Use of omega-3-acid ethyl esters and placebo in patients with a baseline</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>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% (<i>P</i> values not reported).</p> <p>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% (<i>P</i> values not reported). The baseline LDL-C tertile had a significant interaction with treatment for the LDL-C response (<i>P</i>=0.022).</p> <p>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% (<i>P</i> values not reported).</p>
<p>Bays et al¹⁸</p> <p>Omega-3-acid ethyl esters (Lovaza[®]) 4 g/day plus simvastatin 40 mg/day</p> <p>Patients who received placebo in the COMBOS trial were switched to OL treatment with omega-3-acid ethyl esters plus simvastatin (Switchers).</p> <p>Those who received omega-3-acid ethyl esters plus simvastatin in the COMBOS trial¹⁷ were maintained on current therapy (Nonswitchers)</p> <p>All patients continued therapeutic lifestyle changes</p>	<p>ES, OL of COMBOS¹⁷</p> <p>Patients 18 to 79 years of age who had been receiving stable dose statin therapy for ≥ 8 weeks prior to trial enrollment</p>	<p>N=188</p> <p>Up to 24 months</p>	<p>Primary: The difference between Nonswitchers and Switchers in median percent change in non-HDL-C from COMBOS end of treatment to month four</p> <p>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</p>	<p>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 (<i>P</i><0.001).</p> <p>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% (<i>P</i>=0.027) and 1.6 vs -6.3% (<i>P</i>=0.004).</p> <p>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 (<i>P</i><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% (<i>P</i>=0.062), -6.6 vs -8.1% (<i>P</i>=0.604) and -7.8 vs -9.0% (<i>P</i>=0.496).</p> <p>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</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
diet.			from COMBOS baseline to months four, 12 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	<p>lipoprotein lipid parameters generally revealed greater reductions in Switchers vs Nonswitchers. The comparisons of the change from COMBOS baseline to these same endpoints revealed generally nonsignificant differences between the 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.</p> <p>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).</p>
<p>Maki et al¹⁹</p> <p>Omega-3-acid ethyl esters (Lovaza[®]) 4 g/day</p> <p>vs</p> <p>placebo</p> <p>All patients received simvastatin 20 mg/day.</p>	<p>DB, PC, RCT, XO</p> <p>Patients 18 to 19 years of age with mixed dyslipidemia (mean fasting TG concentration of 200 to 600 mg/dL and a non-HDL-C concentration higher than the person's NCEP ATP III goal) at the end of a 5 week diet lead in period</p>	<p>N=40</p> <p>12 weeks</p>	<p>Primary: Changes in lipid profile</p> <p>Secondary: Not reported</p>	<p>Primary: Omega-3-acid ethyl esters resulted in a 40% decrease from baseline in non-HDL-C concentration compared to a decrease of 34% with placebo ($P<0.001$).</p> <p>Significantly greater alterations from baseline ($P<0.05$ for all) were also achieved with omega-3-acid ethyl esters compared to placebo for VLDL-C (-42 vs -22%), TG (-44 vs -29%), TC (-31 vs -26%) and HDL-C (16 vs 11%) concentrations.</p> <p>Significantly greater alterations from baseline were also observed with omega-3-acid ethyl esters compared to placebo for apo B (-32 vs -28%), TC:HDL-C (-39 vs -33%) and TG:HDL-C (-51 vs -37%) (P values not reported).</p> <p>LDL-C concentration was reduced by a similar degree with omega-3-acid ethyl esters compared to placebo (-37 vs -38%; $P=0.433$). Similar results were observed with changes in apo A-I concentrations (0.9 vs 4.3%; $P=0.667$).</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Stalenhoef et al²⁰</p> <p>Omega-3-acid ethyl esters (Omacor*) 4 g/day</p> <p>vs</p> <p>gemfibrozil 1,200 mg/day</p>	<p>DB, DD, RCT</p> <p>Patients with primary hypertriglyceridemia</p>	<p>N=28</p> <p>12 weeks</p>	<p>Primary: Change in lipid profile, LDL-C subfraction profile</p> <p>Secondary: Not reported</p>	<p>Not reported</p> <p>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).</p> <p>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).</p> <p>Secondary: Not reported</p>
Hypercholesterolemia Clinical Outcome Trials				
<p>No authors listed²¹</p> <p>Omega-3 PUFA 1 g/day (specific product not named but provided 850 to 882 mg EPA and DHA as ethyl esters in the average ratio of 1:2)</p> <p>vs</p> <p>vitamin E 300 mg/day</p> <p>vs</p> <p>omega-3 PUFA and vitamin E</p> <p>vs</p> <p>no treatment</p>	<p>MC, OL, RCT</p> <p>Patients surviving a recent (≤ 3 months) MI</p>	<p>N=11,324</p> <p>3.5 years</p>	<p>Primary: Cumulative rate of all-cause death, nonfatal MI and nonfatal stroke; cumulative rate of cardiovascular death, nonfatal MI, nonfatal stroke</p> <p>Secondary: Analyses of components of primary end points and main causes of death, adverse events</p>	<p>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).</p> <p>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).</p> <p>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).</p> <p>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.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>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; <i>P</i> values not reported.).</p>

*Agent not available in the United States.

Drug regimen abbreviations: DHA=docosahexaenoic acid, EPA=eicosapentaenoic acid, PUFA=polyunsaturated fatty acids

Study abbreviations: CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RR=relative risk, XO=crossover

Miscellaneous abbreviations: apo A-1=apolipoprotein A-1, apo B=apolipoprotein B, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NCEP ATP III=National Cholesterol Education Program Adult Treatment Panel III, TC=total cholesterol, TG=triglycerides, VLDL-C=very low-density lipoprotein cholesterol

Special Populations**Table 4. Special Populations⁶**

Generic Name	Population and Precaution				
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Omega-3-acid ethyl esters	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown; use with caution.

Adverse Drug Events**Table 5. Adverse Drug Events⁶**

Adverse Event	Omega-3-Acid Ethyl Esters
Constipation	✓
Dyspepsia	3
Eructation	4
Gastrointestinal disorder	✓
Increased alanine transaminase and aspartate transaminase	✓
Pruritis	✓
Rash	✓
Taste perversion	4
Vomiting	✓

✓ Percent not specified.

Contraindications/Precautions

Omega-3-acid ethyl esters is contraindicated in patients with known hypersensitivity to the agent or any component of the preparation.⁶

In patients with hepatic dysfunction, alanine aminotransferase and aspartate aminotransferase levels should be monitored periodically during treatment with omega-3-acid ethyl esters. In addition, low density lipoprotein cholesterol and triglyceride levels should be periodically measured.⁶

Lovaza[®] contains ethyl esters of omega-3 fatty acids obtained from the oil of several fish sources. It is not known whether patients with fish and/or shellfish allergies are at increased risk of an allergic reaction to the agent. Lovaza[®] should be used with caution in patients with known hypersensitivity to fish and/or shellfish.⁶

Drug Interactions

No clinically significant drug interactions are associated with omega-3-acid ethyl esters.²²

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.⁶

Table 6. Dosing and Administration⁶

Generic Name	Adult Dose	Pediatric Dose	Availability
Omega-3-acid ethyl esters	<u>Adjunct to diet to reduce triglyceride levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia:</u> Capsule: 4 g/day administered QD or in divided doses (2 g BID)	Safety and efficacy in children have not been established.	Capsule: 1 g

BID=twice daily, QD=once daily

Clinical Guidelines

Current guidelines are summarized in Table 7. The guidelines addressing the management of hypercholesterolemia are presented globally, addressing the role of various medication classes in the management of this disease.

Table 7. Clinical Guidelines

Clinical Guideline	Recommendations
National Cholesterol Education Program: Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004) ²³	<ul style="list-style-type: none"> • Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low density lipoprotein cholesterol (LDL-C) lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥ 30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statin) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥ 160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • Fibrates may have an adjunctive role in the treatment of patients with high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of coronary heart disease (CHD) risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <p><u>Treatment of heterozygous familial hypercholesterolemia</u></p> <ul style="list-style-type: none"> • Begin LDL-C lowering drugs in young adulthood. • TLC indicated for all persons.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • Statins, first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid). <p><u>Treatment of homozygous familial hypercholesterolemia</u></p> <ul style="list-style-type: none"> • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). <p><u>Treatment of familial defective apolipoprotein B-100</u></p> <ul style="list-style-type: none"> • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. <p><u>Treatment of polygenic hypercholesterolemia</u></p> <ul style="list-style-type: none"> • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
<p>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)¹</p>	<p><u>General recommendations</u></p> <ul style="list-style-type: none"> • 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. <p><u>Statins</u></p> <ul style="list-style-type: none"> • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. <p><u>Bile acid sequestrants</u></p> <ul style="list-style-type: none"> • 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. <p><u>Nicotinic acid</u></p>

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • 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. <p><u>Fibric acid derivatives (fibrates)</u></p> <ul style="list-style-type: none"> • 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. • They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia. <p><u>Omega-3 fatty acids</u></p> <ul style="list-style-type: none"> • 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.
<p>American Heart Association/American College of Cardiology/National Heart, Lung, and Blood Institute: American Heart Association/American College of Cardiology</p>	<p><u>Lipid management</u></p> <ul style="list-style-type: none"> • For patients without atherosclerotic disease, including those with other risk factors, recommendations of the National Cholesterol Education Program guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non-HDL-C include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy). • If TGs are ≥500 mg/dL, therapeutic options to prevent pancreatitis are

Clinical Guideline	Recommendations
<p>Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)⁴</p>	<p>fibrate or niacin before LDL lowering therapy. Treat LDL-C to goal after TG lowering therapy.</p> <ul style="list-style-type: none"> Dietary supplement niacin must not be used as a substitute for prescription niacin. <p><u>All patients with coronary and other atherosclerotic vascular disease</u></p> <ul style="list-style-type: none"> In addition to other lifestyle modifications, increased consumption of omega-3 fatty acids in the form of fish or in capsule form (1 g/day) for risk reduction is encouraged. For treatment of elevated TGs, higher doses are usually necessary for risk reduction.
<p>Institute for Clinical Systems Improvement: Lipid Management in Adults (2009)⁵</p>	<ul style="list-style-type: none"> Diet and exercise are the cornerstones of treatment for asymptomatic patients with dyslipidemia. TLC may include diet, aerobic exercise, weight management, smoking cessation, evaluation of alcohol consumption, sterol and stanol ester nutritional supplement and fish oil (EPA-DHA). Omega-3 fats do not affect LDL levels but may help protect the heart in other ways. Trials have suggested that omega-3 fats reduce the risk of heart attack and death from heart disease for those who already have heart disease. No primary prevention trials have addressed pharmacologic lipid treatment in persons at low risk for CHD. The incidence of CHD in men <40 years and premenopausal women is very low, and drug treatment in these groups is discouraged. Primary prevention trials of pharmacologic lipid lowering have not shown a decrease in mortality, although most trials have shown a 30% reduction in CHD events. Trial populations have consisted mostly of middle-aged men, some with other risk factors. Similar benefit in higher-risk women can be assumed but has not been demonstrated. <p><u>Monotherapy</u></p> <ul style="list-style-type: none"> 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. Specific statin and dose should be selected based on cost and amount of lipid lowering required. Based on the information above, for patients with established CHD or CHD risk equivalents, the use of a statin is recommended. Statin are the drugs of choice for lowering LDL-C, and aggressive treatment should be pursued. Statins also have a modest effect on reducing TGs and increasing HDL-C. Several trials with clinical endpoints support the use of statins in primary and secondary prevention. In patients receiving a statin who experience myalgias, it is recommended that a lower dose or another statin be tried. A 10 to 14 day vacation from a statin can also be considered as a diagnostic maneuver to see if myalgia symptoms abate. The evidence is inconclusive at this time for treating myalgia with Vitamin D and coenzyme Q. If patients are intolerant to a statin, they should try the other statins in reduced doses before the medication class is deemed inappropriate.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • If patients are unable to take a statin, bile acid sequestrants, niacin, fibric acid derivatives and ezetimibe are available. • The bile acid sequestrants reduce LDL-C, but they can increase TGs so should only be used as monotherapy in patients with a baseline TG \leq200 mg/dL. • Niacin has a greater effect on HDL-C than other currently available lipid medications. To improve tolerability and compliance, doses of niacin need to be titrated. • Fibric acid derivatives have a variable effect on LDL-C. Fenofibrate may be more effective at lowering LDL-C than gemfibrozil. They are usually reserved for hypertriglyceridemia or for an isolated low HDL-C. • Ezetimibe mainly reduces LDL-C, with minimal effect on TGs or HDL-C. No clinical outcome trials are currently available, but ezetimibe appears useful for reducing LDL-C in patients who cannot take a statin and in combination with other LDL reducing medications. <p><u>Combination therapy</u></p> <ul style="list-style-type: none"> • Although combination therapy is not supported by outcome-based trials, some high risk patients will require combination therapy. These patients will most likely have CHD. • Using low doses of two complementary agents can often reduce LDL-C to a greater extent than a higher dose of either agent, with fewer side effects and possibly less cost. • In very resistant cases, triple therapy may be required. • Combination of a cholesterol lowering drug with a TG lowering drug to achieve the non-HDL-C goal may be most warranted in patients with established coronary artery disease who are a very high risk of recurrent coronary events. • Combining nicotinic acid with a statin is favorable for improving LDL-C, HDL-C and TGs. • Use of fibric acid derivatives leads to effective decreases in TGs and increased HDL-C, but the effect on LDL-C is varied. • An increased incidence of severe myopathy has been reported when a statin was combined with nicotinic acid or fibric acid derivatives. • In general, the combination of a statin and a fibric acid derivative raises the risk of myopathy and rhabdomyolysis. <p><u>Aspirin</u></p> <ul style="list-style-type: none"> • Dosage appears unimportant, usually ranging from 60 mg every other day up to 325 mg/day. • Secondary prevention trials have demonstrated reduced cardiovascular and cerebrovascular endpoints. • Primary prevention trials in patients not selected for cardiovascular risk factors have shown minimal benefit. • Patients with hyperlipidemia are at intermediate risk and may derive greater benefit from aspirin than the lower risk populations evaluated in primary prevention trials. The recommendation of aspirin in hyperlipidemic patients is supported by this reasoning, and by the low cost and risk of this therapy.
<p>American Heart Association: Drug Therapy of High</p>	<ul style="list-style-type: none"> • For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily,

Clinical Guideline	Recommendations
Risk Lipid Abnormalities in Children and Adolescents: A Scientific Statement From the American Heart Association (2007)²⁴	<p>usually at bedtime.</p> <ul style="list-style-type: none"> For patients with high risk lipid abnormalities, the presence of additional risk factors or high risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. Additional research regarding drug therapy of high risk lipid abnormalities in children is needed to evaluate the long term efficacy and safety and impact on the atherosclerotic disease process. Niacin is rarely used to treat the pediatric population. Given the reported poor tolerance, the potential for very serious adverse effects, and the limited available data, niacin cannot be routinely recommended but may be considered for selected patients. This guideline does not contain recommendations regarding the use of omega-3 acid ethyl esters.
European Society of Cardiology and Other Societies: Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2007)⁹	<ul style="list-style-type: none"> Statins are first line drugs for lowering LDL-C. Bile acid sequestrants can serve as effective lipid lowering alternatives. Bile acid sequestrants tend to increase TG; therefore, should only be used when TG are <180 mg/dL or given in conjunction with TG lowering agents. Niacin is considered an effective lipid lowering agent but flushing may limit use. Niacin is more effective in increasing HDL-C than fibrates. When TGs are 450 to 900 mg/dL, either fibrates or statins may be used as first line drugs, and niacin is considered a good drug for selected patients. Fish oils are also TG lowering agents and might be useful as a third line therapy for patients with hypertriglyceridemia resistant to or intolerant of fibrates or niacin or in combination with other TG lowering drugs. Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.

Conclusions

Modifications in lipids can also be effected by a number of dietary approaches or specific dietary supplements. Like medication classes, these modalities also differ with respect to their mechanism of action and to the degree and type of lipid modification.¹ Rich sources of omega-3-fatty acids come from fatty fish and plant sources, and fish oil as eicosapentaenoic and docosahexaenoic acid. When administered at high doses they can reduce levels of triglycerides (TGs).¹⁻³ The mechanism by which this occurs is thought to be through inhibition of the synthesis of very low density lipoprotein cholesterol. More recent clinical trials have suggested that relatively high intakes of omega-3-fatty acids in the form of fish, fish oils or high-linolenic acid oils will reduce the risk for major coronary events in persons with established coronary heart disease.³⁻⁵

Lovaza[®] (omega-3-acid ethyl esters) is the only Food and Drug Administration (FDA) approved prescription omega-3-acid ethyl esters available. Specifically, the agent is to be used as adjunct to diet to reduce TGs in adults with severe (≥ 500 mg/dL) hypertriglyceridemia.⁶ There are several over-the-counter products containing omega-3 fatty acids that are marketed as nutritional supplements; however, these products do not have FDA approved indications and may not contain the same amounts of the active ingredient.^{6,7}

Clinical trial data has consistently demonstrated that omega-3-acid ethyl esters are “superior” over placebo for the management of hypertriglyceridemia and combined hyperlipidemia.¹¹⁻²¹ In line with treatment guidelines, the majority of clinical trials evaluated omega-3-acid ethyl esters in patients already receiving a hydroxymethylglutaryl coenzyme A reductase inhibitors (statins). When added to statin therapy, omega-3-acid ethyl esters produced further beneficial modifications in lipid parameters.¹⁵⁻¹⁹ The evidence demonstrating the potential of omega-3-acid ethyl esters in reducing the risk for major coronary events in persons with established coronary heart disease is not well established at this time.³⁻⁶ Data from a long term, open label trial, revealed that treatment with omega-3-acid ethyl esters significantly decreased the risk of the composite of death, nonfatal myocardial infarction or nonfatal stroke in patients with a previous myocardial infarction.²¹

Therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia.^{3,5,8} In general, the omega-3-acid ethyl esters are not considered first line treatment options. They represent an alternative to fibric acid derivatives and niacin for the treatment of hypertriglyceridemia.³

Appendix I: Utilization Within This Drug Class for DVHA: January 1, 2011 to June 30, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Lovaza	19	31	100%	\$9,631.50	\$310.69
Class Total:	19	31	100%	\$9,631.50	\$310.69

Recommendations

No changes to the Department of Vermont Health Access (DVHA) approval criteria for omega-3-acid ethyl esters (see below) are proposed.

Lovaza[®]

- The patient has been started and stabilized on this medication (Note: samples are not considered adequate justification for stabilization.)
OR
- The patient has triglyceride levels > 500 mg/dL
AND
- The patient has a documented contraindication, side effect, allergy, or treatment failure to a fibric acid derivative and niacin.

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