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Therapeutic Class Review
Lipotropics – Niacin and Omega-3 Acid Ethyl Esters

I. Overview

Niacin and omega-3 acid ethyl esters are the only two agents classified as miscellaneous antilipemic agents by the American Hospital Formulary Service (AHFS).[1] Both agents are available as over-the-counter (OTC) and brand name prescription formulations.[1-5] Prescription niacin and omega-3 acid ethyl esters are approved by the Food and Drug Administration (FDA) as adjunctive agents for the treatment of hypertriglyceridemia.[2,3,5] Prescription niacin has several other FDA indications which are to manage hypercholesterolemia and mixed dyslipidemias, to reduce the risk of recurrent nonfatal myocardial infarction in patients with hypercholesterolemia, and to slow progression or promote regression of atherosclerotic disease in combination with bile acid binding resins in patients with a history of coronary artery disease and hypercholesterolemia.[3]

Niacin (nicotinic acid) is a water-soluble, B complex vitamin.[1] The exact mechanism by which niacin lowers cholesterol and triglycerides is not completely understood but is independent of the drug's role as a vitamin. Reductions in low-density lipoprotein cholesterol (LDL-C) through reduced hepatic synthesis of very low-density lipoprotein cholesterol (VLDL-C) are primarily responsible for the antilipemic effect of niacin.[1,6] Niacin may decrease production of VLDL-C by partially inhibiting mobilization of free fatty acids from adipose tissue, decreasing delivery of free fatty acids to the liver, decreasing triglyceride synthesis and altering the hepatic production of apolipoprotein B. Niacin increases high-density lipoprotein cholesterol (HDL-C) by reducing its catabolism.

Lovaza® (formerly known as Omacor®) is the only FDA-approved prescription omega-3 fatty acid product and it was first approved in 2004.[7] Each 1-g capsule contains at least 900 mg of the ethyl esters of omega-3 fatty acids, which are predominantly eicosapentaenoic acid (EPA-approximately 465 mg) and docosahexaenoic acid (DHA-approximately 375 mg).[5] The omega-3 fatty acids in this formulation are derived from a natural marine origin (eg, herring, mackerel, salmon) and through an FDA-monitored process the oil expressed from the fish carcass is purified and refined.[7] The mechanism(s) by which omega-3 fatty acids lower triglyceride levels is not completely understood but may be related to a reduction in triglyceride production and/or increase in triglyceride clearance.

OTC niacin and omega-3 acid ethyl esters are labeled as "dietary supplements" and as such, the production and marketing are not strictly regulated by the FDA in the same way as it oversees prescription products.[7,8] While dietary supplements are "generally recognized as safe", the FDA does not examine the efficacy and safety of these products or inspect or regulate manufacturing processes.[7] In addition, the FDA has imposed statutory restrictions prohibiting manufacturers of dietary supplements from claiming that their products "treat, cure, or prevent any disease" (only FDA-approved drugs can legally make such claims). Without FDA regulation, the content of nicotinic acid in niacin products is not guaranteed.[8] The American Heart Association (AHA) states that OTC "dietary supplement niacin must not be used as a substitute for prescription niacin" and "it should not be used for lowering cholesterol because of potential very serious side effects".[9] OTC omega-3 fatty acid products may also contain widely variable amounts and ratios of the active ingredients EPA and DHA.[1] The most common fish-oil capsule provides approximately 180 mg EPA and 120 mg DHA per capsule. The total EPA and DHA dose recommended for triglyceride lowering is approximately 2-4 g per day.[7] The AHA advises that therapy with EPA and DHA to lower very high triglyceride levels should be used only under a physician's care. In addition, the FDA has recommended that the dosage of EPA and DHA as a dietary supplement not exceed 2 g per day.

The miscellaneous antilipemic agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic legend products in this class. Niacin is available as OTC and prescription brand name immediate-release and sustained-release formulations. Omega-3 acid ethyl esters are also available OTC and by prescription.

Table 1. Miscellaneous Antilipemic Agents Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)
niacin	sustained-release capsule, sustained-release tablet, tablet	Niacor®, Niaspan®, Slo-Niacin®†
omega-3 acid ethyl esters	capsule	Lovaza®‡,

†Product is available over-the-counter.
‡Omacor was renamed to Lovaza in August 2007.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the miscellaneous antilipemic agents are summarized in Table 2. The decision to treat hyperlipidemia generally follows the treatment guidelines of the Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III.[10] The NCEP guidelines focus primarily on attaining goal LDL-C levels, since LDL-C is the major atherogenic lipid component. In general for every 1% reduction in LDL-C there is a 1% reduction in coronary heart disease (CHD) event rates.[6] Although LDL-C is the primary treatment target, very elevated triglycerides should also be treated to avoid pancreatitis and reduce CHD risk. Finally, consideration should be given to treating low levels of HDL-C even if the LDL-C goal has already been achieved.[10] Elevations of HDL-C by 1% result in a reduction of approximately 2% in CHD events.[6] For a more comprehensive overview of the treatment of dyslipidemias, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Miscellaneous Antilipemic Agents

Clinical Guideline	Recommendation
National Heart, Lung, and Blood Institute (NHLBI)/American College of Cardiology (ACC)/American Heart Association (AHA): **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)[10]**	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • In high-risk patients with high triglyceride (TG) or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and an LDL-lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of CHD risk, both when used alone and in combination with hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins). The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. • The use of omega-3 acid ethyl esters was not addressed in this guideline.
National Institutes of Health (NIH), National Cholesterol Education Program (NCEP): **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report (2002)[11]**	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. ATP III supports the AHA'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 low-density lipoprotein-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 6 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.

Clinical Guideline	Recommendation
	Nicotinic Acid • Nicotinic acid should be considered as a therapeutic option for higher risk persons with atherogenic dyslipidemia. • Nicotinic acid should be considered as a single agent in higher-risk persons 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 persons with atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in persons 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 persons with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. Omega-3 Fatty Acids • Omega-3 fatty acids (linolenic acid, DHA, EPA) have 2 potential uses. • In higher doses, DHA and EPA lower serum triglycerides by reducing hepatic secretion of triglyceride-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3-12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. • Recent clinical trials also suggest that relatively high intakes of omega-3 fatty acids (1-2 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 clinical trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1-2 g/day) for either primary or secondary prevention.
American Heart Association (AHA)/ American College of Cardiology (ACC) National Heart, Lung, and Blood Institute (NHLBI): **AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)**[12]	All Patients With Coronary and Other Atherosclerotic Vascular Disease • 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 triglycerides, higher doses are usually necessary for risk reduction. Lipid Management • 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 triglycerides are ≥500 mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL-lowering therapy. Treat LDL-C to goal after triglyceride-lowering therapy. • Dietary supplement niacin must not be used as a substitute for prescription niacin.
Institute for Clinical Systems Improvement (ICSI): **Healthcare Guideline: Lipid Management in Adults (2007)**[13]	• Lifestyle modifications may include fish oil (EPA and DHA). • Dietary and nondietary intake of omega-3 polyunsaturated fatty acids may reduce overall mortality and sudden death in patients with stable coronary artery disease (CAD). The guideline notes that the AHA recommends omega-3 fatty acids in patients with stable CAD and the recommended daily amount is 1 g of EPA/DHA by capsule supplement, the equivalent amount in alpha-linolenic acid (ALA) from vegetable sources or by eating at least two servings of fatty fish per week. • Statins are considered the drugs of choice for lowering LDL-C. • If patients are unable to take a statin, then bile acid sequestrants, ezetimibe, fibric acid derivatives and niacin are available. • Niacin and omega-3 fatty acids are considered treatment options after therapeutic lifestyle changes, in patients with increased LDL-C and triglycerides.

Clinical Guideline	Recommendation
	• Niacin is considered a treatment option after therapeutic lifestyle changes, in patients with increased LDL-C with or without a low HDL-C. • Niacin is considered a treatment option after therapeutic lifestyle changes, in patients with normal LDL-C and HDL-C <40 mg/dL. • Niacin and omega-3 fatty acids are considered treatment options after therapeutic lifestyle changes, in patients with increased triglycerides. • The guidelines note that niacin can elevate glucose in patients with diabetes.
American Heart Association (AHA): Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: **A Scientific Statement From the American Heart Association (2007)**[14]	• 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 Guidelines on Cardiovascular Disease Prevention in Clinical Practice: **Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies (2007)**[15]	• Statins are first-line drugs for lowering LDL-C. • Niacin is considered an effective lipid-lowering agent but flushing may limit use. • Niacin is more effective in increasing HDL-C than fibrates. • When triglycerides are between ~450-900 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 triglyceride-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 triglyceride-lowering drugs.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous antilipemic agents are summarized in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Miscellaneous Antilipemic Agents

Indications	Niacin, Extended-Release* (Niaspan®)	Niacin, Immediate-Release† (Niacor®)	Omega-3 Acid Ethyl Esters
Adjunct to diet for reduction of elevated TC, LDL-C, apo B and TG levels, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb) when the response to an appropriate diet has been inadequate	✔		
Adjunct to diet for reduction of elevated TC and LDL-C in patients with primary hypercholesterolemia when response to an appropriate diet and nonpharmacologic measures alone have been inadequate		✔	
In combination with lovastatin, treatment of primary hypercholesterolemia and mixed dyslipidemia	✔		
To reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hypercholesterolemia	✔		

Indications	Niacin, Extended-Release* (Niaspan®)	Niacin, Immediate-Release† (Niacor®)	Omega-3 Acid Ethyl Esters
In combination with a bile acid binding resin, to slow progression or promote regression of atherosclerotic disease in patients with a history of coronary artery disease and hypercholesterolemia	✔		
In combination with a bile acid binding resin as an adjunct to diet for reduction of elevated TC and LDL-C levels in adult patients with primary hypercholesterolemia, when the response to an appropriate diet or diet plus monotherapy has been inadequate	✔	✔	
Adjunctive therapy for treatment of adult patients with very high serum triglyceride levels (Fredrickson Types IV and V hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them	✔	✔	
Adjunct to diet to reduce triglyceride levels in adult patients with very high (>500 mg/dL) triglyceride levels			✔

apo B=apolipoprotein B, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides
*Slo-Niacin, an over-the-counter extended-release niacin tablet, is "suggested as a dietary supplement".[4]
†Over-the-counter immediate-release niacin is a dietary supplement.[3]

IV. Pharmacokinetics

The pharmacokinetic parameters for the miscellaneous antilipemic agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Miscellaneous Antilipemic Agents[1-5,16]

Drug	Bioavailability (%)	Time to Peak	Protein Binding (%)	Elimination	Active Metabolites	Serum Half-Life
Niacin, extended-release (Niaspan®)	60-76*	4-5 hours	Not reported	Rapidly metabolized and undergoes extensive first-pass metabolism; 60%-76% eliminated by the kidneys as unchanged drug and metabolites; up to 12% recovered as unchanged niacin after multiple dosing	Several metabolites whose activity is unknown	20-60 minutes (niacin)
Niacin, immediate-release tablet (Niacor®)	Rapid absorption from the gastrointestinal tract (% not reported)	30-60 minutes	Not reported	Rapidly metabolized and undergoes extensive first-pass metabolism; 88% eliminated by kidneys as unchanged drug and nicotinuric acid, the primary metabolite (inactive)	Unknown	20-45 minutes
Omega-3 acid ethyl esters (Lovaza®)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

*Single-dose bioavailability studies have demonstrated that the 500 mg and 1,000 mg tablet strengths are dosage form equivalent but the 500 mg and 750 mg tablets are not dosage form equivalent.

V. Drug Interactions

Drug interactions of major (Level 1) and/or moderate (Level 2) severity for niacin or omega-3 acid ethyl esters have not been reported.[17] Rare cases of rhabdomyolysis have been linked to concomitant administration of niacin (doses ≥1 g/day) and hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins). In clinical studies with a combination tablet of niacin and lovastatin, no cases of rhabdomyolysis and one suspected case of myopathy have been reported in 1,079 patients who were treated with doses up to 2,000 mg of niacin and 40 mg of lovastatin daily for periods up to 2 years. When selecting combination therapy with niacin and HMG-CoA reductase inhibitors, prescribers should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug.[2,3]

VI. Adverse Drug Events

The most common adverse events with the miscellaneous antilipemic agents are noted in Table 5. At usual antilipemic dosages, niacin is generally well tolerated and side effects have been mild and transient.[1] The most common adverse effects with niacin are gastrointestinal upset, flushing (especially of the face and neck) and pruritus. Flushing is more common with the immediate-release formulation and may be diminished by starting with a low dose, taking niacin after meals, and by pretreating with aspirin (325 mg) or ibuprofen (200 mg).[1,18] The frequency and severity of adverse hepatic effects appear to be dose related and may be increased with the sustained-release preparations.[1] Sustained-release preparations have been hepatotoxic in doses ≥2 g per day. Although uncommon, cases of severe hepatotoxicity have occurred in patients who have substituted sustained-release niacin for equivalent doses of immediate-release niacin. Therefore, different formulations should not be used interchangeably.

The American Heart Association has issued the following statement regarding niacin:

> "Niacin comes in prescription form and as 'dietary supplements.' Dietary supplement niacin must *not* be used as a substitute for prescription niacin. It should *not* be used for lowering cholesterol because of potential very serious side effects. Dietary supplement niacin is not regulated by the United States (US) Food and Drug Administration (FDA) the same way that prescription niacin is. It may contain widely variable amounts of niacin—from *none* to much more than the label states. The amount of niacin may even vary from lot to lot of the same brand."[9]

Pooled data from randomized, placebo-controlled trials have shown that prescription omega-3 acid ethyl esters (Lovaza®) are safe and well tolerated.[7] The most common adverse events were eructation, infection, flu-like syndrome, dyspepsia and taste perversion. Omega-3 acid ethyl esters should be used with caution in patients with known hypersensitivity to fish or shellfish.[1]

Table 5. Adverse Drug Events (%) Reported with the Miscellaneous Antilipemic Agents[2-5]

Adverse Event(s)	Niacin, Extended-Release (Niaspan®)	Niacin, Immediate-Release (Niacor®)	Omega-3 Acid Ethyl Esters
Cardiovascular			
Angina pectoris	-	-	1.3
Arrhythmia (including atrial fibrillation)	✔	✔	✔
Bypass surgery	-	-	✔
Cardiac arrest	-	-	✔
Chest pain	-	-	✔
Hyperlipidemia	-	-	✔
Hypertension	-	-	✔
Hypotension	✔	✔	-
Migraine	✔	-	✔
Myocardial infarction/ischemia/occlusion	-	-	✔
Orthostasis	✔	✔	-
Palpitations	✔	-	-
Peripheral vascular disorder	-	-	✔

Adverse Event(s)	Niacin, Extended-Release (Niaspan®)	Niacin, Immediate-Release (Niacor®)	Omega-3 Acid Ethyl Esters
Syncope	✔	-	✔
Tachycardia	✔	-	✔
Central Nervous System			
Depression	-	-	✔
Dizziness	✔	-	✔
Emotional lability	-	-	✔
Facial paralysis	-	-	✔
Headache	5-11	✔	-
Insomnia	✔	-	✔
Nervousness	✔	-	-
Paresthesia	✔	-	-
Vasodilatation	-	-	✔
Vertigo	-	-	✔
Dermatologic			
Acanthosis nigricans	✔	✔	-
Alopecia	-	-	✔
Dry skin	✔	✔	-
Eczema	-	-	✔
Hyperpigmentation	✔	✔	-
Mild-to-severe cutaneous flushing	✔	✔	-
Pruritus	≤6	✔	✔
Rash	0-5	-	1.8
Urticaria	✔	-	-
Sweating	✔	-	✔
Endocrine/Metabolic			
Abnormal liver function tests	✔	✔	✔
Decreased glucose tolerance	✔	✔	-
Edema (generalized)	✔	-	✔
Face edema	✔	-	-
Gout	✔	✔	-
Hyperglycemia	✔	-	✔
Hyperuricemia	✔	✔	-
Increased amylase	✔	-	-
Increased lactate dehydrogenase	✔	-	-
Peripheral edema	✔	-	-
Reductions in phosphorus	✔	-	-
Gastrointestinal			
Abdomen enlarged	-	-	✔
Abdominal pain	2-5	-	-
Anorexia	-	-	✔
Colitis	-	-	✔
Constipation	-	-	✔
Diarrhea	6-8	✔	-
Dry mouth	-	-	✔
Dyspepsia	2-5	✔	3.1
Dysphagia	-	-	✔
Eructation	✔	-	4.9
Fecal incontinence	-	-	✔
Flatulence	✔	-	-
Gastritis	-	-	✔
Gastroenteritis	-	-	✔

Adverse Event(s)	Niacin, Extended-Release (Niaspan®)	Niacin, Immediate-Release (Niacor®)	Omega-3 Acid Ethyl Esters
Hepatotoxicity	-	✔	-
Increased appetite	-	-	✔
Intestinal obstruction	-	-	✔
Jaundice	✔	✔	-
Nausea	2-8	-	-
Pancreatitis	-	-	✔
Peptic ulceration	✔	✔	-
Tenesmus	-	-	✔
Vomiting	0-8	✔	✔
Hematologic/Lymphatic			
Lymphadenopathy	-	-	✔
Prolongation prothrombin time	✔	-	-
Slight reduction platelet count	✔	-	-
Musculoskeletal			
Arthralgia	-	-	✔
Arthritis	-	-	✔
Asthenia	✔	-	✔
Back pain	-	-	2.2
Fracture	-	-	✔
Leg cramps	✔	-	-
Malaise	-	-	✔
Myalgia	✔	-	✔
Myasthenia	✔	-	-
Neck pain	-	-	✔
Pain	1-5	-	1.8
Rhabdomyolysis	-	✔	-
Rheumatoid arthritis	-	-	✔
Tendon rupture	-	-	✔
Respiratory			
Asthma	-	-	✔
Bronchitis	-	-	✔
Cough increased	-	-	✔
Dyspnea	✔	-	✔
Epistaxis	-	-	✔
Laryngitis	-	-	✔
Pharyngitis	-	-	✔
Pneumonia	-	-	✔
Rhinitis	2-5	-	✔
Sinusitis	-	-	✔
Urogenital			
Cervix disorder	-	-	✔
Endometrial carcinoma	-	-	✔
Epididymitis	-	-	✔
Impotence	-	-	✔
Other			
Body odor	-	-	✔
Cataract	-	-	✔
Chills	✔	-	✔
Cystoid macular edema	✔	✔	-
Fever	-	-	✔
Flu symptoms	-	-	3.5

Adverse Event(s)	Niacin, Extended-Release (Niaspan®)	Niacin, Immediate-Release (Niacor®)	Omega-3 Acid Ethyl Esters
Hypersensitivity reactions	✔	-	-
Infection	-	-	4.4
Neoplasm	-	-	✔
Sudden death	-	-	✔
Suicide	-	-	✔
Taste perversion	-	-	2.7
Toxoid amblyopia	✔	✔	-

- Event not reported or incidence <1%
✔ Percent not specified

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous antilipemic agents are summarized in Table 6. Both immediate-release and sustained-release niacin should be initiated at a low dose and titrated slowly according to patient tolerance and response.

Table 6. Usual Dosing for the Miscellaneous Antilipemic Agents[2-5,16]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Niacin	Hyperlipidemia: Immediate-release tablet (Niacor®): initial, 250 mg once daily following an evening meal; increase frequency and/or dose every 4-7 days to desired response or first-level therapeutic dose (1.5-2 g/day in 2 to 3 divided doses); after 2 months, may increase at 2- to 4-week intervals to 3 g/day (1 g 3 times per day); maximum: in patients with marked lipid abnormalities, a higher dose is occasionally required but generally should not exceed 6 g/day Sustained-release capsule or tablet (Niaspan®): initial, 500 mg at bedtime for 4 weeks, then 1 g at bedtime for 4 weeks; after week 8, titrate to patient response and tolerance; can increase to a maximum of 2 g/day, but only at 500 mg/day at 4-week intervals Niacin deficiency: Oral: 10-20 mg/day; maximum: 100 mg/day Note: sustained-release niacin preparations should not be substituted for equivalent doses of immediate-release niacin.	Safety and effectiveness in children have not been established.	Sustained-release capsule: 125 mg 250 mg 400 mg 500 mg Sustained-release tablet: 250 mg 500 mg 750 mg 1,000 mg Tablet: 50 mg 100 mg 250 mg 500 mg
Omega-3 acid ethyl esters	Oral: 4 g per day taken as a single 4 g dose or as two 2 g doses (2 capsules given twice daily)	Safety and effectiveness in pediatric patients <18 years of age have not been established.	Capsule: 1 g

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous antilipemic agents are summarized in Table 7.

Table 7. Clinical Efficacy Studies Using the Miscellaneous Antilipemic Agents

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Niacin Cardiovascular Outcome Trials				
CDP Research Group (1975)[19] IR niacin 3 g per day vs clofibrate 1.8 g per day vs placebo Treatment arms also included estrogens and dextrothyroxine.	DB, MC, PC, RCT Men aged 30-64 years with previous MI	N=8,341 (N=1,119 for niacin, N=2,789 for placebo) 5 years	Primary: Total mortality Secondary: Cause-specific mortality (eg, coronary mortality and sudden death), nonfatal cardiovascular events	Primary: The incidence of total mortality was comparable between niacin (24.4%), clofibrate (25.5%) and placebo (25.4%) (all *P*=NS). Secondary: Five-year rates of death due to cardiovascular disease were comparable between niacin (18.8%), clofibrate (17.3%) and placebo (18.9%) (all *P*=NS). Major cardiovascular events were reduced with niacin: CHD events by 13%, nonfatal MI by 27% and cerebrovascular events by 21%. Niacin treatment significantly reduced the incidence of nonfatal MI compared to placebo (8.9% vs 12.2%; *P*<0.004). There was no evidence of significant efficacy of clofibrate with regard to total mortality and cause-specific mortality. Treatment with niacin for 5 years lowered TC by 10% and TG levels by 26%. Treatment with clofibrate lowered TC by 7% and TG levels by 22%.
CDP Research Group (1986) [20] IR niacin 3 g per day	DB, MC, PC, RCT Men aged 30-64 years with previous MI	N=8,341 (N=1,119 for niacin, N=2,789 for placebo) 9 years	Primary: Total mortality Secondary: Cause-specific mortality (eg, coronary mortality and sudden death)	Primary: A follow-up of subjects 9 years after completion of the CDP study (total mean follow-up of 15 years) showed that niacin reduced the risk of all-cause mortality by 11% (52.0% for niacin and 58.2% for placebo; *P*=0.0004). Secondary: The survival benefit in the niacin group was primarily evident for death caused by CHD (36.5% for niacin vs 41.3% for placebo; *P*<0.05).
HATS[21] Niacin (mean dose 2.4±2.0 g per day)	DB, PC Patients with clinical coronary	N=160 3 years	Primary: Changes in lipid profile, arteriographic	Primary: The mean levels of LDL-C, HDL-C and TG were significantly changed by –42% (*P*<0.001), +26% (*P*<0.001) and –36% (*P*<0.001), respectively, in the niacin plus simvastatin group but were unaltered in the antioxidant only and placebo groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
plus simvastatin (mean dose 13±6 mg per day) vs antioxidants (total daily dose of 800 IU vitamin E, 1,000 mg vitamin C, 25 mg beta carotene and 100 µg selenium) vs niacin plus simvastatin plus antioxidants vs placebos Note: niacin was initiated as SR niacin (Slo-Niacin®) 250 mg BID and increased to 1,000 mg BID at 4 weeks. Patients whose HDL-C had not increased by 5 mg/dL at 3 months, 8 mg/dL at 8 months and 10 mg/dL at 12 months were switched to IR	disease (defined as previous MI, coronary interventions or confirmed angina) and with at least 3 stenoses of at least 30% of the luminal diameter or 1 stenosis of at least 50%, low HDL-C, normal LDL-C		evidence of change in coronary stenosis (% stenosis caused by most severe lesion in each of 9 proximal coronary segments), occurrence of first cardiovascular event (death from coronary causes, MI, stroke or revascularization) Secondary: Mean change in % stenosis in lesions of varying degrees of severity, mean change in luminal diameter in proximal lesions and all lesions	Similar changes were observed when antioxidants were added to niacin plus simvastatin. The protective increase in HDL2 (considered to be the most protective component of HDL-C) with niacin plus simvastatin (+65%) was attenuated by concurrent therapy with antioxidants (+28%; *P*=0.02). The average stenosis progressed by 3.9% with placebo, 1.8% with antioxidants (*P*=0.16 compared to placebo) and 0.7% with niacin plus simvastatin plus antioxidants (*P*=0.004) and regressed by 0.4% with niacin plus simvastatin (*P*<0.001). The frequency of the composite primary end point (death from coronary causes, MI, stroke or revascularization) was 24% with placebos, 3% with niacin plus simvastatin, 21% with antioxidants and 14% with niacin plus simvastatin plus antioxidants. The risk of the composite primary end point was 90% lower in the niacin plus simvastatin group than placebo (*P*=0.03). The risk in the other treatment groups did not differ significantly from that in the placebo group (*P* values not reported). Secondary: In general, the treatment effects observed with respect to the primary angiographic end point were confirmed for the various subcategories of stenoses and were supported by the results for the mean minimal luminal diameter.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
niacin (Niacor®) up to a maximum of 4 g per day. Niacin "placebo" tablets contained immediate-release niacin and delivered 50 mg BID.				
Zhao et al[22] Niacin (mean dose 2.4±2.0 g per day) plus simvastatin (mean dose 13±6 mg per day) vs antioxidants (total daily dose of 800 IU vitamin E, 1,000 mg vitamin C, 25 mg beta carotene and 100 µg selenium) vs niacin plus simvastatin plus antioxidants vs placebo	ES of HATS[21] (see above) Patients with clinical coronary disease (defined as previous MI, coronary interventions or confirmed angina) including 25 with diabetes mellitus with mean LDL-C 128 mg/dL, HDL-C 31mg/dL and TG 217 mg/dL	N=160 38 months	Primary: Side effects, response to question "Overall, how difficult is it to take the study medication?" Secondary: Not reported	Primary: Patients who had received niacin plus simvastatin experienced similar frequencies of clinical or laboratory side effects compared to placebo: any degree of flushing (30% vs 23%; *P*=NS), symptoms of fatigue, nausea and/or muscle aches (9% vs 5%; *P*=NS), AST ≥3 times ULN (3% vs 1%; *P*=NS), CPK ≥2 times ULN (3% vs 4%; *P*=NS), new onset of uric acid ≥7.5 mg/dL (18% vs 15%; *P*=NS), and homocysteine ≥15 µmol/L (9% vs 4%; *P*=NS). There were no side effects attributable to the antioxidant regimen. Glycemic control among diabetics declined mildly in the niacin plus simvastatin group but returned to pretreatment levels at 8 months and remained stable for the rest of the study. The niacin plus simvastatin combination regimen was repeatedly described by 91% of treated patients and 86% of placebo subjects as "very easy" or "fairly easy" to take. Secondary: Not reported
ARBITER 2[23]	DB, PC, RCT	N=167	Primary: Change in mean	Primary: After 12 months, mean CIMT increased significantly in the placebo group (0.044±0.100

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
SR niacin (Niaspan®) 1,000 mg DAILY vs placebo All patients received background statin therapy (specific statin not described).	Patients mean age 67 years (91% men) with known coronary heart disease and low levels of HDL-C (<45 mg/dL)	1 year	common CIMT after 1 year Secondary: Changes in lipid concentrations, composite of clinical cardiovascular events (including any hospitalization for an acute coronary syndrome, stroke, revascularization procedure or sudden cardiac death), adverse events	mm; *P*<0.001) and was unchanged in the niacin group (0.014±0.104 mm; *P*=0.23). The overall difference in CIMT progression between the groups was not statistically significant (*P*=0.08); however, a post hoc analysis showed that niacin significantly reduced the rate of CIMT progression in subjects without insulin resistance (*P*=0.026). Secondary: HDL-C increased 21% in the niacin group but did not change in the placebo group (*P*<0.003). Clinical cardiovascular events occurred in 3 patients treated with niacin (3.8%) and 7 patients treated with placebo (9.6%; *P*=0.20). Adherence to study medication based on pill counts ranged from 90.3% to 94.5% and was not statistically different between the placebo and niacin groups (*P* value not reported). No patient experienced significant (3 times the ULN) elevations of liver enzymes or developed myositis. At the end of the study, skin flushing was reported to have occurred in 69.2% of patients receiving niacin compared to 12.7% of patients receiving placebo (*P*<0.001).
Niacin Clinical Trials				
ADMIT[24] IR niacin (Niacor®) 3,000 mg per day or maximum tolerated dosage vs placebo	MC, PC, RCT Patients with peripheral arterial disease with or without diabetes, mean age 67 years for patients with diabetes and 65 years for those without diabetes	N=468 (N=125 patients with diabetes) Up to 60 weeks (12-week active run-in and 48-week double-	Primary: Change in lipid profile, glucose, HbA_{1c}, ALT, uric acid; hypoglycemic drug use, compliance, adverse events Secondary: Not reported	Primary: Niacin use significantly increased HDL-C by 29% and 29% and decreased TG by 23% and 28% and LDL-C by 8% and 9%, respectively, in participants with and without diabetes compared to baseline (*P*<0.001 for niacin vs placebo for all). Glucose levels were modestly increased by niacin (8.7 and 6.3 mg/dL; *P*=0.04 and *P*<0.001) in participants with and without diabetes, respectively. HbA_{1c} levels were unchanged from baseline to follow-up in participants with diabetes treated with niacin. In participants with diabetes treated with placebo, HbA_{1c} decreased by 0.3% (*P*=0.04 for difference). There were no significant differences in niacin discontinuation, niacin dosage, or

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
		blind)		hypoglycemic therapy in participants with diabetes assigned to niacin vs placebo. Secondary: Not reported
ADVENT[25] SR niacin (Niaspan®) 1,000 mg per day vs SR niacin (Niaspan®) 1,500 mg per day vs placebo	DB, PC, RCT Patients with stable type 2 diabetes, 47% were receiving concomitant statin therapy	N=148 16 weeks	Primary: Change in HDL-C, TG, HbA_{1c} Secondary: TC, LDL-C, FBG, adverse effects	Primary: Dose-dependent increases in HDL-C (13% to 19% for the 1,000 mg dose and 22% to 24% for the 1,500 mg dose; both *P*<0.05 vs placebo) and reductions in TG levels (–15% to –20% for the 1,000 mg dose; *P*=NS, and –28% to –36% for the 1,500 mg dose; *P*<0.05) were observed. Changes in HbA_{1c} levels from baseline to week 16 were no different for niacin 1,000 mg/day (7.28% and 7.35%; *P*=0.16) and placebo (7.13% and 7.11%) but were significantly different for niacin 1,500 mg/day (7.2% and 7.5%; *P*=0.048). Secondary: Mean LDL-C levels were not significantly different than baseline for the placebo and niacin 1,000 mg groups. In the niacin 1,500 mg group, LDL-C levels decreased at all time points and the difference vs placebo was statistically significant at weeks 12 and 16 (*P*<0.05). The mean changes from baseline at 16 weeks were +9%, +5% and –7% in the placebo, niacin 1,000 mg and 1,500 mg groups, respectively. Similar trends were observed for TC with mean increases of +4% in both the placebo and niacin 1,000 mg groups and a decrease of –6% in the SR niacin 1,500 mg group (*P* values not reported). In both the niacin groups, an initial rise in FBG was observed between weeks 4 and 8 which returned to baseline by week 16. Four patients in the niacin group (3 patients were receiving 1,500 mg) discontinued participation because of inadequate glucose control. Rates of adverse events other than flushing were similar for the niacin and placebo groups. Flushing was reported by about 67% of patients receiving SR niacin and about 10% of patients receiving placebo. Four patients, including 1 patient in the placebo arm, withdrew from the study due to flushing. No hepatotoxic effects or myopathy was observed.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kuvin et al[26] SR niacin (Niaspan®) initially 500 mg HS for 2 weeks then 1,000 mg HS vs placebo	PC, RCT Patients with stable coronary artery disease and LDL-C <100 mg/dL, all received concurrent statin therapy (>80% atorvastatin)	N=60 3 months	Primary: Changes in lipoproteins, HDL and LDL particle distribution and inflammatory markers Secondary: Not reported	Primary: Six patients did not complete the protocol, 2 discontinued treatment due to flushing and 4 were lost to follow-up. Niacin significantly increased total HDL-C by 7.5% and decreased TG by 15% compared to baseline (*P*<0.005 for both), whereas TC and LDL-C remained unchanged. Compared with baseline values, the addition of niacin resulted in a 32% increase in large-particle HDL (*P*<0.001) and an 8% decrease in small-particle HDL (*P*=0.0032). Addition of niacin produced an 82% increase in large-particle LDL (*P*=0.09) and a 12% decrease in small-particle LDL (*P*=0.008). Niacin also favorably altered inflammatory markers with lipoprotein-associated phospholipase A2 and CRP levels decreasing by 20% and 15%, respectively, compared to baseline (*P*<0.05 for both). No significant changes from baseline were seen in any tested parameter in subjects who received placebo. No major cardiovascular events were reported during the study in the treatment or placebo group. Secondary: Not reported
Capuzzi et al[27] SR niacin (Niaspan®) initiated at 375 mg HS for 1 week, then 500 mg HS for 1 week, then 1,000 mg HS for 1 week; dosages were titrated to 1,000 mg to 3,000 mg per day for	ES, MC, OL Patients (mean age 54 years) with primary hypercholesterol-emia who were previously enrolled in a randomized short-	N=517 Up to 96 weeks	Primary: Changes in LDL-C and apo B Secondary: Changes in TC, HDL-C, TC:HDL-C ratio, Lp(a) and TG; adverse events	Primary: Patients receiving niacin experienced significant reductions in LDL-C by 18% at week 48 and 20% at week 96. Similar reductions were seen with apo B (16% at week 48 and 19% at week 96). The percent changes achieved by both 48 and 96 weeks of therapy were statistically significant (*P*<0.001). Secondary: HDL-C significantly increased by 26% at week 48 and 28% at week 96 in patients receiving niacin. TC modestly decreased (12% and 13%, respectively), whereas the TC:HDL-C ratio decreased by almost one third (all *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks 4-96 based on clinical response and adverse events Concomitant therapy with a statin, bile acid sequestrant or both was permitted if the patient did not achieve sufficient LDL-C reduction while taking a maximally tolerated dose or 2,000 mg of SR niacin.	term study or in a placebo-only qualification clinical trial			TG and Lp(a) levels were decreased by 27% and 30%, respectively, at week 48, and by 28% and 40%, respectively, at week 96 (all *P*<0.001). SR niacin was generally well tolerated. Flushing was common (75%); however, there was a progressive decrease in flushing with time from 3.3 episodes in the first month to ≤1 episode by week 48. Aspirin was used by one third of patients before niacin dosing to minimize flushing episodes. Six percent of patients discontinued therapy due to flushing. Serious adverse events occurred in about 10% of patients; however, none were considered probably or definitely related to SR niacin. No deaths or myopathy occurred. There were statistically significant increases in alkaline phosphatase, ALT, amylase, AST, direct bilirubin, glucose, and uric acid and a decrease in phosphorus (all *P*<0.001). These changes were considered small and not likely to be biologically or clinically significant since the majority of the changes occurred within the reference values for these analytes. Six patients had AST levels >2 times the ULN and 2 patients had AST levels >3 times the ULN on niacin monotherapy. Five patients had ALT levels >2 times ULN and no patient had ALT levels >3 times ULN. Mean platelet counts decreased by 10.1% at week 48 and 14.8% at week 96, whereas leukocyte counts increased by 6.5% and 6.8%, respectively, at week 48 and week 96 of therapy (all *P*<0.0001).
Guyton et al[28] SR niacin (Niaspan®) initiated at 375 mg HS for 1 week, then 500 mg HS for 1 week, then 1,000 mg HS for 1 week; dosages were titrated to 1,000 mg to 3,000 mg per day for weeks 4-96 based on clinical response and	ES, MC, OL Patients (mean age 53 years) with primary hyperlipidemia who were previously enrolled in an RCT or in a placebo-only qualification	N=269 patients treated up to 96 weeks and a cohort of N=230 patients treated for 3 months (safety data)	Primary: Changes in TC, LDL-C, HCL-C, TG, apo B and Lp(a); safety Secondary: Not reported	Primary: The dosages of niacin attained by 269 patients were 1,000 mg (95% of patients), 1,500 mg (86%) and 2,000 mg (65%). After 96 weeks of treatment, niacin alone (median dose 2,000 mg) significantly reduced LDL-C (18%), TC (10%), and TG (26%) and increased HDL-C (32%). Apo B and Lp(a) were significantly reduced by 26% and 36%, respectively, at 48 weeks but values for these parameters were not available at 96 weeks (*P*<0.01 for all values). At 96 weeks of the study, niacin plus a statin significantly lowered LDL-C (32%), TC (24%) and TG (32%) and increased HDL-C (25%) (*P*<0.01 for all values). Apo B (26%; *P*<0.01) and Lp(a) (19%; *P*=NS) were also reduced at 48 weeks but values for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
adverse events Concomitant therapy with a statin, bile acid sequestrant or both was permitted if the patient did not achieve sufficient LDL-C reduction while taking a maximally tolerated dose or 2,000 mg of SR niacin.	clinical trial			these parameters were not available at 96 weeks. Niacin plus a bile acid sequestrant lowered LDL-C (28%) and TC (15%) and increased HDL-C (31%) (P<0.01 for all values). Niacin plus a bile acid sequestrant increased TG (5%; P=NS). Apo B and Lp(a) were significantly reduced by 19% and 24% (P<0.01), respectively, at 48 weeks but values for these parameters were not available at 96 weeks. Intolerance to flushing led 4.8% of participants (13 of 269) to discontinue SR niacin. (Combining all of the data, 7.3% of patients discontinued SR niacin due to flushing.) Other medication-related adverse events leading to discontinuation from the 96-week study included nausea (3.3% of patients) sometimes with vomiting, other gastrointestinal symptoms (1.5%) and pruritus (2.6%). One case each of acanthosis nigricans, elevated glucose, gout, headache, palpitations and shoulder pain led to patient withdrawal. Overall, 9 of 499 (2.6%) patients experienced an ALT or AST elevation >2 times ULN. Five of these patients were on combination therapy, including 4 with a statin and 1 with a bile acid sequestrant. In 5 of the 9 cases, the transaminase elevation resolved while SR niacin was continued without reduction in dose. Three cases led to SR niacin dosage reduction. One patient discontinued SR niacin because of transaminase elevations. Leg aches and myalgias with normal creatine kinase levels were described in 1 patient taking niacin with simvastatin. Secondary: Not reported
Gray et al[29] SR niacin (Slo-Niacin®) average maintenance dose of 1.67 g per day	RETRO cohort study Male veterans (mean age 61.7 years) treated for dyslipoprotein-emia with SR niacin between	N=969 1-36 months (mean 13.0 months)	Primary: Changes in lipid profile, alterations in hepatic enzymes and blood chemistry tests, hepatotoxicity Secondary: Not reported	Primary: Lipoprotein responses were dose-related and favorable. Results included the following: TC –19.1%, LDL-C –24.0%, HDL-C +5.7%, and TG –32.5% (all $P\leq$0.0035). Statistically but not clinically meaningful dose-related increases were seen in levels of liver enzymes and serum glucose (AST +29%, ALT +23%, alkaline phosphatase +25%, and glucose +7%; P=0.0001). Niacin was discontinued in 48.5% (435 of 896) of patients primarily because of adverse

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	October 1988 and October 1991			effects. The primary documented reasons for discontinuation included flushing and itching (8.9%), increased serum glucose (4.8%), gastrointestinal complaints (3.7%) and increased liver function tests (3.7%). Poor glycemic control led to discontinuation in 40.6% (43 of 106) patients with diabetes mellitus. Twenty of 896 (2.2%) and 42 of 896 (4.7%) patients met biochemical criteria for "probable" and for "possible or probable" niacin-induced hepatotoxicity, respectively. Predisposing factors included high dose, alcohol use, preexisting liver disease and concurrent oral sulfonylurea therapy. Secondary: Not reported
Knopp et al[30] IR niacin (brand not specified) TID titrated up to 1.5 g per day for weeks 4 to 8, and 3.0 g per day for weeks 9 to 16 vs SR niacin (Niaspan®) titrated up to 1.5 g HS by week 4 vs placebo	DB, MC, PG, RCT Patients with hypercholesterol-emia, average age 54 years	N=223 25 weeks (9 week lead-in period)	Primary: Change in LDL-C, FPG, uric acid, drug tolerance Secondary: Change in TC, TG, HDL-C, HDL subfractions, apo B, apo AI, apo E, and Lp(a)	Primary: LDL-C was significantly reduced by 12%, 12% and 22%, respectively, by SR niacin 1.5 g HS, IR niacin 1.5 g/day, and IR niacin 3.0 g/day, respectively, compared to placebo ($P \leq 0.05$). At equal doses of 1.5 g/day of SR niacin versus IR niacin, AST increased 5.0% vs 4.8% (P=NS), FPG increased 4.8% vs 4.5% (P=NS), and uric acid concentration increased 6% vs 16% (P=0.0001), respectively. Flushing events were more frequent with IR niacin versus SR niacin (1,905 vs 575; $P<0.001$). Flushing severity was slightly greater with SR niacin, but still well tolerated. Secondary: Compared with placebo at 8 weeks, SR niacin 1.5 g HS vs IR niacin 1.5 g/day showed comparable efficacy in lowering TC, TG, apo B, apo E and Lp(a), and raising HDL-C, HDL2-C, HDL3-C and apo AI ($P \leq 0.05$ in all instances). IR niacin 3.0 g/day produced significantly greater changes in the above lipid parameters compared to IR niacin 1.5 g/day and SR niacin 1.5 g HS ($P \leq 0.05$).
McKenney et al[31] IR niacin (generic by Rugby) administered	DB, PG, RCT Patients with LDL-C >160	N=46 36 weeks	Primary: LCL-C, HDL-C, TG, adverse events (especially	Primary: SR niacin lowered LDL-C significantly more than IR niacin at the dosage of 1,500 mg/day and above ($P<0.04$ to $P<0.001$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
BID at daily doses of 500 mg, 1,000 mg, 1,500 mg, 2,000 mg, and 3,000 mg, each for 6 weeks vs SR niacin (generic by Goldline) administered BID at daily doses of 500 mg, 1,000 mg, 1,500 mg, 2,000 mg, and 3,000 mg, each for 6 weeks	mg/dL after 1 month on an NCEP ATP III - Step 1 diet		hepatotoxicity) Secondary: Not reported	IR niacin increased HDL-C levels significantly more than SR niacin at all dosage levels (P<0.04 to P<0.001). The reduction in TG levels was similar (P=NS) between IR and SR niacin at all dosages except for the 1,000 mg dose where the IR formulation led to significantly greater reductions (P=0.009). Nine of 23 patients (39%) in the IR niacin group withdrew before completing the 3,000 mg daily dose. Four patients withdrew at the 1,000 mg dose, 1 patient at the 1,500 mg dose, 3 patients at the 2,000 mg dose and 1 patient at the 3,000 mg dose. The most common reasons for withdrawal were vasodilatory symptoms, fatigue, and acanthosis nigricans. Eighteen of 23 patients (78%) in the SR niacin group withdrew before completing the 3,000 mg daily dose. Two patients withdrew at the 1,000 mg dose, 2 patients at the 1,500 mg dose, 7 patients at the 2,000 mg dose and 7 patients at the 3,000 mg dose. The most common reasons for withdrawal were gastrointestinal tract symptoms, fatigue, and increases in liver function tests, often with symptoms of hepatic dysfunction. None of the patients taking IR niacin developed hepatotoxic effects, while 12 patients (52%) receiving SR niacin did. Secondary: Not reported
Superko et al[32] IR niacin (brand not specified) 3,000 mg per day vs SR niacin (Niaspan®) 1,500 mg per day	PC, RCT Patients with hypercholesterol-emia	N=180 plus 38 subjects from a previous trial 14 weeks	Primary: Changes in lipid profile and lipoprotein subclass distribution Secondary: Not reported	Primary: IR and SR niacin significantly decreased TG, LDL-C, apo B, and Lp(a) and significantly increased HDL-C (all P≤0.0001). Both niacin products significantly increased mean LDL peak particle diameter and percent distribution of large LDL I and IIa, with a significant decrease in small LDL IIIa, IIIb, and IVb (all P<0.05 with the exception of LDL I where P=0.12 for SR niacin 1,500 mg). In general, the effects were greater in patients with LDL pattern B (predominance of dense LDL) compared with those with LDL pattern A (predominance of buoyant LDL).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo In addition, results of 38 subjects receiving SR niacin 3,000 mg from a previous study were utilized.				Compared to the IR 3,000 mg group, SR niacin 3,000 mg produced a smaller decrease in TG (–27% vs –47%; *P*<0.001) but had similar changes in LDL-C (–20% vs –22%; *P* value not reported), apo B (–22% vs –21%; *P* value not reported), HDL-C (27% vs 28%; *P* value not reported) and LDL peak particle diameter (0.90 mm vs 0.76 mm; *P* value not reported). Secondary: Not reported
Guyton et al[33] SR niacin (Niaspan®) titrated up to 1,000 mg HS for 4 weeks, 1,500 mg HS for 4 weeks and 2,000 mg HS for 8 weeks vs gemfibrozil 600 mg BID	DB, MC, PC, RCT Patients between the ages of 21 and 75 years with an HDL-C ≤40 mg/dL, LDL-C ≤160 mg/dL or <130 mg/dL with atherosclerotic disease, TG ≤400 mg/dL	N=173 8 weeks	Primary: Effect on HDL-C Secondary: Change in other lipoproteins, adverse effects	Primary: SR niacin 1,500 mg and 2,000 mg raised HDL-C by 21% and 26%, respectively, vs 13% with gemfibrozil (*P*<0.02). Secondary: SR niacin 1,500 mg and 2,000 mg vs gemfibrozil significantly raised apo AI (9% and 11% vs 4%), reduced TC:HDL-C ratio (–17% and –22% vs –12%), reduced Lp(a) level (–7% and –20% vs no change), and had no adverse effect on LDL-C (2% and 0% change vs 9% increase; *P* values ranged from *P*<0.001 to *P*<0.02.). Triglycerides decreased by 40% with gemfibrozil vs 16% with SR niacin 1,000 mg (*P*<0.001) and 29% with niacin 2,000 mg (*P*<0.06). Effects on plasma fibrinogen levels were significantly favorable for SR niacin compared with gemfibrozil (–1% to –6% vs 5% to 9%, respectively; *P*<0.02). Flushing was significantly more frequent with SR niacin (78% of patients) compared with gemfibrozil (10% of patients) at every point (*P* values not reported). Flu syndrome occurred more frequently with SR niacin vs gemfibrozil group (*P*=0.006). Dyspepsia was a more frequent occurrence with gemfibrozil (*P*=0.009).
Omega-3 Acid Ethyl Esters Cardiovascular Outcome Trials				
GISSI-Prevenzione Investigators[34] Omega-3 PUFA	MC, OL, RCT Patients surviving a recent (≤3	N=11,324 3.5 years	Primary: Cumulative rate of all-cause death, nonfatal MI and	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
1 g daily (specific product not named but provided 850-882 mg EPA and DHA as ethyl esters in the average ratio of 1:2) vs vitamin E 300 mg daily vs omega-3 PUFA and vitamin E vs no treatment	months) MI		nonfatal stroke; cumulative rate of CV death, nonfatal MI and nonfatal stroke Secondary: Analyses of components of primary end points and main causes of death, adverse events	analysis). Treatment with omega-3 PUFA decreased the risk of the composite of CV 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 1 year and at the end of the study, 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% of omega-3 PUFA recipients and 2.9% and 0.4% of vitamin E recipients, respectively; no *P* values were reported.).
Omega-3 Acid Ethyl Esters Clinical Trials				
Pownall et al[35] Omega-3 acid ethyl esters (Omacor®*) 4 g per day vs placebo	DB, PC, PG, RCT Patients with severe hypertrigycer-idemia (TG ≥500 mg/dL but <2,000 mg/dL)	N=40 12 weeks (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 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*=NS vs baseline).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
McKeone et al[36] Omega-3 acid ethyl esters (Omacor®*) 4 g per day vs placebo	DB, PC, RCT Patients with severe hypertrigyceridemia (TG ≥500 mg/dL but <2,000 mg/dL)	N=40 12 weeks (6 week run-in period)	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 (*P* values not reported). 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%) (*P* values not reported). None of these parameters significantly changed in the placebo group (*P* values not reported).
Calabresi et al[37] (2000) Omega-3 acid ethyl esters (Omacor®*) 4 g per day for 8 weeks then crossed over to placebo vs placebo for 8 weeks then crossed over to omega-3 acid ethyl esters	DB, RCT, XO Patients with familial combined hyperlipidemia	N=14 26 weeks (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 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 (eg, glucose, uric acid, liver enzymes, kidney function, and platelet count).
Calabresi et al[38] (2004) 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 (4 week run-in period)	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 (all $P<0.05$). 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
then crossed over to placebo vs placebo for 8 weeks then crossed over to omega-3 acid ethyl esters			Secondary: Not reported	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% (no P value reported), respectively, whereas HDL3-C and total mass decreased by 4% (P>0.05) and 6% (no P value reported). 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
Davidson et al[39] Omega-3 acid ethyl ester (Lovaza®) 4 g per day plus simvastatin 40 mg per day vs placebo plus simvastatin 40 mg per day	DB, MC, PC, PG, RCT Adults (mean age 59.8 years) who had received ≥8 weeks of stable statin therapy and had mean fasting TG ≥200 mg/dL and <500 mg/dL and mean LDL-C below or within 10% NCEP ATP III goal	N=254 16 weeks (8 weeks OL treatment with simva-statin)	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 in the omega-3 acid ethyl ester plus simvastatin group than placebo plus simvastatin group (–9.0% vs –2.2%; P<0.001). Secondary: Treatment with omega-3 acid ethyl esters plus simvastatin was associated with significant reductions in TG (2.9% vs 6.3%) and VLDL-C (27.5% vs 7.2%), a significant increase in HDL-C (3.4% vs –1.2%) and a significant reduction in TC:HDL-C ratio (9.6% vs 0.7%) (all P<0.001). Adverse events reported by ≥1% of patients in the omega-3 acid ethyl esters group that occurred with a higher frequency than in simvastatin monotherapy group 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 groups and no serious adverse events were considered treatment related.
Stalenhoef et al[40] Omega-3 acid ethyl esters (Omacor*) 4 g per day vs gemfibrozil 1,200 mg	DB, DD, RCT Patients with primary hypertriglycer-idemia	N=28 12 weeks (treatment duration)	Primary: Change in lipid profile, LDL-C subfraction profile Secondary: Not reported Results regarding in	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
per day			vitro data on oxidation were not included since their clinical relevance is not known.	Secondary: Not reported

*Omacor was renamed to Lovaza in August 2007.
Drug regimen abbreviations: BID=twice daily, DHA=docosahexaenoic acid, EPA=eicosapentaenoic acid, HS=bedtime, IR=immediate release, IU=international units, PUFA=polyunsaturated fatty acids, SR=sustained release, TID=three times daily
Study abbreviations: CI=confidence interval, DB=double-blind, ES=extension study, MC=multicenter, NS=not significant, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, XO=crossover
Miscellaneous abbreviations: ADMIT=Arterial Disease Multiple Intervention Trial, ADVENT=Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial, ALT=alaninine aminotransferase, apo AI=apoliprotein AI, apo B=apolipoprotein B, apo E=apoliprotein E, ARBITER=ARterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol, AST=aspartate aminotransferase, CDP=Coronary Drug Project, CHD=coronary heart disease, CIMT=carotid intima-media thickness, CPK=creatinine phosphokinase, CRP=C-reactive protein, CV=cardiovascular, FBG=fasting blood glucose, GISSI=Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico, HATS=HDL-Atherosclerosis Treatment Study, HbA_{1c}=hemoglobin A1c, HDL=high-density lipoprotein, HDL-C=high-density lipoprotein cholesterol, LDL=low-density lipoprotein, LDL-C=low-density lipoprotein cholesterol, Lp(a)=lipoprotein(a), MI=myocardial infarction, NCEP ATP III=National Cholesterol Education Program Adult Treatment Panel III, TC=total cholesterol, TG=triglycerides, ULN=upper limit of normal, VLDL-C=very low-density lipoprotein, VLDL-TG=very low-density lipoprotein triglycerides

IX. Conclusions

Niacin and omega-3 acid ethyl esters are the only two agents classified by the American Hospital Formulary Service as miscellaneous antilipemic agents.[1] Niacin is available over the counter (OTC) in immediate-release and sustained-release formulations. Niacin is also available by prescription only as immediate-release (Niacor®) and sustained-release (Niaspan®) formulations. Omega-3 acid ethyl esters are also available OTC and by prescription only. There are no generic formulations for either legend niacin or omega-3 acid ethyl esters.

Prescription sustained-release niacin and omega-3 acid ethyl esters are approved by the Food and Drug Administration (FDA) as adjunctive therapy for the treatment of adult patients with very high triglyceride levels (>500 mg/dL).[3,5] Clinical trials have shown that both niacin and omega-3 acid ethyl esters are effective in managing hypertriglyceridemia, reducing triglyceride levels by 20%-35% and 20%-50%, respectively.[18] There are no trials comparing the safety and efficacy of niacin to omega-3 acid ethyl esters. Omega-3 acid ethyl esters may be an alternative to the fibric acid derivatives for combination use with a hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitor ("statin") because it does not increase the risk of rhabdomyolysis.[18] While established coronary and vascular disease is not an FDA-approved indication for omega-3 acid ethyl esters, for patients with these conditions the American Heart Association (AHA) encourages increased consumption of omega-3 fatty acids in the form of fish or in capsule form (1 g/day).[12]

Prescription niacin has obtained additional indications since it has been shown to have favorable effects on all plasma lipoproteins and lipids. Niacin increases HDL-C by 15%-35% and decreases TC and LDL-C by 5%-25%, changing small, dense LDL particles to large, buoyant forms. Niacin has been shown to lower the incidence of nonfatal myocardial infarction and overall mortality rates, and to slow progression or promote regression of atherosclerotic disease in combination with other antilipemic agents in patients with a history of coronary artery disease and hypercholesterolemia.[18] While statins are considered the drugs of choice for lowering LDL-C, niacin is primarily used for the management of mixed hyperlipidemia, or as a second-line agent in combination therapy for hypercholesterolemia.[10-15] There are limited head-to-head studies comparing the safety and efficacy of immediate-release to sustained-release niacin, but overall, these agents appear to be comparable in efficacy.[30-32] While flushing may be more common with the immediate-release formulation, it still occurs with the sustained-release products and may be diminished by starting with a low dose, taking after meals and by pretreating with aspirin (325 mg) or ibuprofen (200 mg). Hepatotoxicity has been reported with sustained-release preparations in doses ≥2 g per day and in situations where equivalent doses of the sustained-release product were substituted for the immediate-release formulation. Therefore, different formulations should not be used interchangeably. Due to significant safety concerns with regarding OTC niacin products, the AHA stresses that OTC dietary supplement niacin must not be used as a substitute for prescription niacin, because these agents are not regulated by the FDA in the same manner as prescription niacin, thus the amount of niacin may vary from product to product and within lots of the same brand.[9] Furthermore, the AHA states that OTC niacin should not be used for cholesterol lowering because of the potential for very serious side effects.

Therefore, the prescription immediate-release and sustained-release niacin products are comparable to each other but do offer significant clinical advantages over other brand and OTC products within the class reviewed. Given its limited FDA-approved indication and potential for off-label use, prescription omega-3 acid ethyl esters should be available for patients with very high (≥500 mg/dL) triglyceride levels through the prior-authorization process.

X. Recommendations

Prescription niacin is recommended for preferred status. Currently, Niaspan® is preferred and no changes are recommended.

No brand omega-3 acid ethyl ester is recommended for preferred status. Currently, Prior Authorization is required for Lovaza® with the following criteria and no changes are recommended.

Lovaza®

- 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.

(Note regarding fibrates: For patients receiving statin therapy, fenofibrate appears less likely to increase statin levels and thus may represent a safer choice than gemfibrozil for coadministration in this group of patients - *Am J Med* 2004;116:408-416)

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