Lipotropics, Other Review

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FDA-Approved Indications

Agents in this class are indicated as adjuncts to dietary modifications for the treatment of various dyslipidemias.

Drug	Manufacturer	Indication(s)
BILE ACID SEQUESTRANTS		
cholestyramine	generic	- Primary hypercholesterolemia - Relief of pruritus associated with partial biliary obstruction
colesevelam (WelChol®)	Daiichi Sankyo	- Hypercholesterolemia, Fredrickson type IIa (monotherapy or in combination with a statin) - Glycemic control in adults with type 2 diabetes mellitus
colestipol (Colestid®)	generic	- Primary hypercholesterolemia
CHOLESTEROL ABSORPTION INHIBITORS		
ezetimibe (Zetia®)	Merck/Schering-Plough	- Primary hypercholesterolemia (monotherapy or in combination with a statin) - Mixed hyperlipidemia (in combination with fenofibrate) - Homozygous familial hypercholesterolemia (adjunctive therapy) - Homozygous familial sitosterolemia
FIBRIC ACIDS		
fenofibrate (Lofibra®)	generic	- Primary hypercholesterolemia or mixed dyslipidemia, Fredrickson Types IIa and IIb - Hypertriglyceridemia, Fredrickson Types IV and V hyperlipidemia
fenofibrate (Antara™)	Oscient	
fenofibrate (Lipofen™)	Proethic	
fenofibrate (Tricor®)	Abbott	
fenofibrate (Triglide™)	Sciele	
fenofibrate (Fenoglide™)	Sciele	
gemfibrozil	generic	- Hypercholesterolemia, Fredrickson type IIb (in patients without history of, or symptoms of existing, CHD) - Hypertriglyceridemia, Fredrickson Types IV and V hyperlipidemia
NIACIN		
niacin ER (Niaspan®)	Abbott	- Primary hypercholesterolemia or mixed dyslipidemia, Fredrickson Types IIa and IIb (monotherapy or, if monotherapy inadequate, in combination with lovastatin) - Primary hypercholesterolemia or patients with a history of CAD and hypercholesterolemia (in combination with a bile acid sequestrant) - Hypertriglyceridemia, Fredrickson type IV and V (adjunctive therapy) - Patients with a history of MI and hypercholesterolemia
niacin IR (Niacor®)	Upsher-Smith	- Primary hypercholesterolemia (monotherapy or in combination with bile-acid binding resin) - Hypertriglyceridemia, Types IV and V hyperlipidemia for those who present risk of pancreatitis (adjunctive therapy)
OMEGA-3 FATTY ACIDS		
omega-3-acid ethyl esters (Lovaza®)	Reliant	- Treatment of hypertriglyceridemia in adults with TG ≥ 500 mg/dL

Overview

Many clinical trials have demonstrated that high serum concentrations of low-density lipoprotein cholesterol (LDL-C) are major risk factors for coronary heart disease (CHD). Likewise, numerous studies have shown that lowering LDL-C levels reduces the risk for CHD. The Adult Treatment Panel (ATP) III guidelines from the National Cholesterol Education Program (NCEP) recommend a goal for LDL-C-lowering therapy in high risk patients of LDL-C <100 mg/dL. For patients with multiple CHD risk factors, LDL-C goals are <100 mg/dL or <130 mg/dL, depending on the patient's 10-year risk for CHD events based on Framingham risk scoring. The goal for patients with no or one risk factor is to lower LDL-C <160 mg/dL.[1]

The current standard for the treatment of elevated LDL-C is therapy with one of the hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors ("statins") which, as a class, can lower LDL-C by up to 55 percent in a dose-related fashion. Statins typically have relatively minor effects on triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C), reducing TG by 7 to 30 percent and increasing HDL-C by 5 to 15 percent.

As a result of clinical data published and/or presented since the 2001 ATP III guidelines [including the Heart Protection Study (HPS) and PROVE IT], the NCEP issued additional guidance in 2004. The 2004 guidance suggests that an LDL-C goal of <70 mg/dL be considered as an option for high-risk patients, especially those with established CVD (cardiovascular disease) and multiple major and/or uncontrolled risk factors for CHD and/or metabolic syndrome. For high risk patients with LDL-C 70 to 100 mg/dL, the 2004 NCEP guidance recommends that fibric acids and nicotinic acid be considered, either as monotherapy or in combination with statins, in the presence of elevated TG and/or low HDL-C.[2]

For the first time, ATP III included non-HDL-C, the sum of very low-density lipoprotein (VLDL) and LDL-C, as a secondary target of therapy in patients with elevated levels of triglycerides. The non-HDL-C goal is 30 mg/dL higher than the corresponding LDL-C goal.[3]

ATP III notes that, while there is significant interest in the potential benefit of increasing HDL-C, there was not, at the time these guidelines were published, enough data to definitively recommend a goal for raising HDL-C. ATP III did, however, suggest that fibric acids or nicotinic acid are alternatives to statin therapy in patients with LDL-C 100 to 130 mg/dL and low HDL-C.[4] Based on data from the HPS, the 2004 NCEP guidance indicates that, in this patient group, fibric acids or nicotinic acid should be used in combination with a LDL-C-lowering drug, rather than as monotherapy.[5]

For patients with LDL-C levels >130 mg/dL, standard doses of statins may be insufficient to achieve the goal of <100 mg/dL. In these cases, the statin dose may have to be increased or a second agent, such as a bile acid sequestrant, cholesterol absorption inhibitor or nicotinic acid, may be added.[6]

Pharmacology

Several non-statin classes of lipotropics are considered in this review.

Bile Acid Sequestrants

The bile acid sequestrants, cholestyramine, colestipol and colesevelam (WelChol), bind bile acids in the intestine to form an insoluble complex which is excreted in the feces thereby

interrupting enterohepatic circulation. As the bile acid pool becomes depleted, the hepatic enzyme cholesterol, 7 α-hydroxylase, is upregulated. Upregulation of 7 α-hydroxylase increases the conversion of cholesterol to bile acids with a resulting increase in demand for cholesterol in the liver cells. The hepatic demand for cholesterol causes a dual effect of 1) increasing transcription and activity of the cholesterol biosynthetic enzyme, HMG-CoA reductase and 2) increasing the number of hepatic LDL-C receptors. These compensatory mechanisms increase clearance of LDL-C from the blood, resulting in decreased serum LDL-C levels. In patients with partial biliary obstruction, the reduction of serum bile acid levels reduces excess bile acids deposited in the dermal tissue with resultant decrease in pruritus.

Bile acid sequestrants can reduce LDL-C levels by 15 to 30 percent although they have little, if any effect on TG or HDL-C. The complementary mechanisms of action of bile acid sequestrants and statins makes them well suited for combination therapy. Combinations of bile acid sequestrants with non-statin lipotropics may be useful in patients who are intolerant to statin therapy.[7] Cholestyramine has been shown to reduce the number of cardiovascular events, but colestipol or colesevelam do not have clinical outcomes data.

The mechanism of action of colesevelam (Welchol) in glycemic control is unknown.

Cholesterol Absorption Inhibitors

During normal digestion, bile acids are secreted into the intestines. Bile acids emulsify the fat and lipid materials present in food, thus facilitating absorption. A major portion of the bile acids is absorbed from the intestinal tract and returned to the liver via the enterohepatic circulation. Ezetimibe (Zetia) inhibits cholesterol absorption along the brush border of the small intestine. This leads to a decrease in the delivery of intestinal cholesterol to the liver, reduction of hepatic cholesterol stores and an increase in cholesterol clearance from the blood. The molecular target of ezetimibe has been shown to be the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. Ezetimibe inhibits absorption of both dietary cholesterol and cholesterol in bile. Ultimately, ezetimibe reduces total cholesterol (total-C), LDL-C, TG and apolipoprotein B and increases HDL-C in patients with hypercholesterolemia. When ezetimibe is administered with a statin, further beneficial effects on the lipid profile occur.

Addition of ezetimibe to stable bile acid sequestrant therapy has been shown to reduce total-C by 18 percent, TG by 14 percent and LDL-C by 19 percent after three to four months. The combination had no effect on HDL-C and was well tolerated.[8]

Fibric acids

The effects of the fibric acids, fenofibrate and gemfibrozil, have been explained by the activation of peroxisome proliferator activated receptor alpha (PPARα). Through this mechanism, these agents increase lipolysis and elimination of TG-rich particles from plasma by activating lipoprotein lipase and reducing production of apoproteins C-III (an inhibitor of lipoprotein lipase activity). The resulting fall in TG produces an alteration in the size and composition of LDL-C from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation) to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of apoproteins A-I and A-II as well as HDL-C. Fenofibrate also reduces serum uric acid levels by increasing urinary excretion of uric acid.

Fibric acids have been shown to reduce the risk of CHD in patients with high TG and low HDL-C.[9,10] This effect is most significant in patients with diabetes or metabolic syndrome.[11] The ATP III states that fibric acids may have a role as adjuncts, especially with statins, in the treatment of patients with high TG and low HDL-C. Caution should be observed when using a statin and gemfibrozil together due to an increased risk of myositis and rhabdomyolysis. Fenofibrate does not interfere with statin metabolism and, therefore, may be less likely to increase the risk for myopathy in patients treated with moderate doses of statins.[12,13]

Niacin (nicotinic acid)

Niacin (nicotinic acid) inhibits lipolysis in adipocytes and possibly inhibits hepatic TG production resulting in a reduction in the synthesis of VLDL that is available for conversion to LDL-C. It may involve several actions including partial inhibition of the release of free fatty acids from adipose tissue and increased lipoprotein lipase activity. Niacin also increases HDL-C by reducing the hepatic uptake of HDL-C. Nicotinic acid increases HDL-C levels by 15 to 35 percent.[14] Immediate-release niacin (Niacor) is available with a prescription. It is also generically available without a prescription. Due to intolerance, patients often have to take aspirin prior to each dose to reduce the vasodilation and flushing associated with immediate-release niacin. To increase tolerance, a film-coated, extended-release niacin (Niaspan) has been developed.

Combination therapy with niacin and statins yields a significant reduction in LDL-C and increase in HDL-C.[15] Niacin has been shown to reduce the risk of CHD as monotherapy and in combination with statins.[16,17,18] It also leads to regression of carotid atherosclerosis when given with statins.[19] Niacin caused regression of coronary lesions and reduced cardiovascular events when given in combination with colestipol and gemfibrozil. [20]

Omega-3 Fatty Acids

Omega-3-acid ethyl esters (Lovaza™), formerly known as Omacor®, is a combination of ethyl esters – eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These two fatty acids are found in fish oil and have been shown to be a contributing factor in the beneficial effects of frequent consumption of oily fish.[21] The mechanism of action of omega-3-acid ethyl esters is not completely understood. It is thought that the omega-3-acid ethyl esters may reduce the synthesis of TG by the liver. Beneficial effects on lipids by omega-3-acid ethyl esters include reduced TG and VLDL and increases in HDL-C.[22] Elevations in LDL-C and non-HDL-C may also be observed. EPA and DHA have also been shown to demonstrate anti-inflammatory and cardioprotective effects including possible antiarrhythmic effects and changes in heart rate variability. Omega-3-acid ethyl esters have been shown to reduce TG by up to 44 percent in adults with baseline TG ≥500 mg/dL.

Pharmacokinetics

Drug	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion (%)
BILE ACID SEQUESTRANTS				
cholestyramine[23]	not absorbed	--	--	feces
colesevelam (Welchol)[24]	not absorbed	--	--	feces
colestipol[25]	not absorbed	--	--	feces
CHOLESTEROL ABSORPTION INHIBITORS				
ezetimibe (Zetia)[26]	35-60	22	ezetimibe glucuronide	urine: 11 feces: 78
FIBRIC ACIDS				
fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide)[27,28,29,30,31,32 33]	unknown	16-23	fenofibric acid (active component); glucuronide conjugate	urine: 60 feces: 25
gemfibrozil[34]	100	1.5	3 metabolites	urine: 70 feces: 6
NIACIN				
niacin ER (Niaspan)[35]	60-76	--	many metabolites	predominantly urine
niacin IR (Niacor)[36]	88	0.3-0.75	nicotinuric acid	urine
OMEGA-3 FATTY ACIDS				
omega-3-acid ethyl esters (Lovaza)[37]	unknown	--	--	--

Fenofibrate micronized 67 mg capsule (Lofibra, generic) has been shown to provide similar therapeutic effects to fenofibrate "non-micronized" 100 mg capsule.[38,39] All currently available fenofibrate products at the highest available dose produce similar plasma concentrations as the fenofibrate 200 mg capsules in single dose studies.[40,41,42] Lipofen 150 mg capsules have been shown to be equivalent to Tricor 160 mg tablets under low-fat and high-fat fed conditions.[43] Fenoglide 120 mg tablets have been shown to be equivalent to fenofibrate 130 mg capsules under high-fat conditions.[44]

Contraindications/Warnings

Bile acid sequestrants, cholestyramine, colestipol, and colesevelam (Welchol), are contraindicated in patients with dysbetalipoproteinemia and/or TG >400 mg/dL. Colesevelam (Welchol) is contraindicated in patients with bowel obstruction and in patients with hypertriglyceridemia-induced pancreatitis.[45] Cholestyramine is contraindicated in complete biliary obstruction.[46]

The combination of ezetimibe (Zetia) and a statin is contraindicated in patients with acute liver disease or unexplained persistent elevations in serum transaminases.[47]

Fenofibrate products (Antara, Fenoglide, Lipofen, Tricor, Triglide) are contraindicated in patients with hepatic or severe renal dysfunction including primary biliary cirrhosis or persistent liver enzyme elevations or preexisting gallbladder disease.[48,49,50,51,52] Gemfibrozil is contraindicated in severe renal or hepatic impairment.

Niacin (Niaspan) is contraindicated in patients with chronic liver disease, active peptic ulcer disease, or arterial bleeding. Severe gout is considered a warning in patients on niacin.[53]

Omega-3-acid ethyl esters (Lovaza) should not be used in patients with a known history of sensitivity or allergy to fish.[54]

Drug Interactions

Drug	Bile Acid Sequestrants	Cholesterol Absorption Inhibitor	Fibric Acids	Niacin	Omega-3 Fatty Acids	Statins
BILE ACID SEQUESTRANTS						
cholestyramine, colestipol[55,56,57]		reduced bioavailability of ezetimibe	reduced bioavailability of fenofibrate	reduced absorption of niacin	--	--
colesevelam (WelChol)[58,59]		reduced bioavailability of ezetimibe	reduced bioavailability of fenofibrate	--	--	--
CHOLESTEROL ABSORPTION INHIBITORS						
ezetimibe (Zetia)[60]	reduced bioavailability of ezetimibe		increased ezetimibe concentration with risk of cholelithiasis	--	--	--
FIBRIC ACIDS						
fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide)[61,62,63,64,65,66]	reduced bioavailability of fenofibrate	increased ezetimibe concentration with risk of cholelithiasis		--	--	increased risk of myopathy and rhabdomyolysis
gemfibrozil[67]	--	increased ezetimibe concentration with risk of cholelithiasis		--	--	increased risk of myopathy and rhabdomyolysis
NIACIN						
niacin ER (Niaspan)[68]	administration with cholestyramine or colestipol reduces absorption of niacin	--	--		--	increased risk of myopathy
niacin IR (Niacor)[69]	--	--	--		--	increased risk of myopathy
OMEGA-3 FATTY ACIDS						
omega-3-acid ethyl esters (Lovaza)[70]	--	--	--	--		--

OTHER DRUGS

Bile Acid Sequestrants – cholestyramine, colestipol and colesevelam (WelChol)

Diltiazem, mycophenolate - The bile acid sequestrants reduce the absorption of diltiazem and mycophenolate, regardless of the time of administration of the interacting drugs relative to each other.[71,72] The concomitant use of mycophenolate with the bile acid sequestrants is not recommended.

Cholestyramine, colestipol – Since cholestyramine and colestipol may bind other drugs given concurrently, it is recommended that patients take other drugs at least one hour before or four to six hours after cholestyramine (or as great an interval as possible) to avoid impeding their absorption.[73] In addition to binding drugs, cholestyramine can reduce serum levels of warfarin by interfering with its enterohepatic circulation; dosage adjustments may be necessary.[74] Chronic use of cholestyramine or colestipol may interfere with normal fat digestion and absorption and thus may prevent absorption of fat-soluble vitamins such as A, D, E and K. Chronic use of cholestyramine can result in a folate deficiency. Supplementation may be necessary.[75,76]

Colesevelam (Welchol) reduces levels of glyburide, levothyroxine, and oral contraceptives containing ethinyl estradiol and norethindrone.[77] Colesevelam may also interact with patient taking concomitant therapy with phenytoin, warfarin, or other narrow therapeutic index drugs. Colesevelam can increase TG in combination with insulin or sulfonylureas.[78]

Cholesterol Absorption Inhibitor – ezetimibe (Zetia)

Cyclosporine – Using cyclosporine and ezetimibe (Zetia) together may result in increased plasma levels of both drugs; the mechanism of this interaction is unknown.[79]

Fibric Acids – fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide) and gemfibrozil

Warfarin – Concomitant administration of fibric acids and warfarin increases the INR and the risk of bleeding.[80,81,82]

Cyclosporine – Concomitant use of cyclosporine and fenofibrate may decrease renal function.[83]

Oral hypoglycemics – The concurrent use of gemfibrozil with glyburide, pioglitazone (Actos®) or rosiglitazone (Avandia®) may result in enhancement of the hypoglycemic effect[84,85,86,87]. The use of gemfibrozil with repaglinide (Prandin®) is contraindicated due to a significant increase in serum concentrations of the oral hypoglycemic.[88]

Adverse Effects

Drug	Abd. Pain	Back pain	HA	Abnormal LFTs	Constipation	Dyspepsia
BILE ACID SEQUESTRANTS						
cholestyramine[89]	reported	nr	nr	nr	common	reported
colesevelam (Welchol)[90]	5 (5)	3 (6)	6 (8)	nr	11 (7)	8 (3)
colestipol[91]	reported	reported	nr	reported	common	reported
CHOLESTEROL ABSORPTION INHIBITORS						
ezetimibe (Zetia)[92]	3 (2.8)	4 (4)	nr	nr	nr	nr
FIBRIC ACIDS						
fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide)[93,94,95,96,97,98]	4.6 (4.4)	3.4 (2.5)	3.2 (2.7)	2-8 (1.4)	2.1 (1.4)	reported
gemfibrozil[99,100]	9.8 (5.6)	nr	1.2 (1.1)	1	1.4 (1.3)	19.6 (11.9)
NIACIN						
niacin ER (Niaspan)[101]	2-5 (3)	nr	8-11 (15)	reported	nr	2-5 (8)
niacin IR (Niacor)[102]	nr	nr	reported	reported	nr	reported
OMEGA-3 FATTY ACIDS						
omega-3-acid ethyl esters (Lovaza)[103]	nr	2.2 (1.3)	nr	reported	reported	3.1 (2.6)

nr= not reported
Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses.

Bile acid sequestrants: Less flatulence, constipation, dyspepsia, and other gastrointestinal effects have been reported with colesevelam than with cholestyramine and colestipol. However, no direct comparisons are available.[104] Colesevelam can increase TG in combination with insulin or sulfonylureas.[105]

Fibric acids: Fibric acids may cause cholelithiasis. Fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide) may also cause myositis, myopathy and rhabdomyolysis; this risk may be

further increased when given concomitantly with statins.[106,107]

Niacin: Flushing has been reported to occur in up to 88 percent of patients receiving niacin ER (Niaspan). Hyperglycemia and/or hyperuricemia (and/or gout) have also been associated with the use of niacin.[108,109]

Special Populations

Pediatrics

Many of the products in the Other Lipotropics category do not have safety and effectiveness data in the pediatric population. Limited data are available for use in children for cholestyramine and colestipol.[110] Pediatric patients have been reported to experience hyperchloremic metabolic acidosis or gastrointestinal obstruction with the use of cholestyramine.[111] Ezetimibe (Zetia) has been used in a limited number of children ages 10 years and older but the safety and effectiveness have not been established in patients less than 10 years of age.[112] Niacin has been used safely for the treatment of nutritional deficiencies; however, the safety and effectiveness of niacin for the treatment of hyperlipidemias have not been established in pediatrics.[113] The safety and efficacy of fibric acids (fenofibrate and gemfibrozil), have not been established in pediatrics. Omega-3-acid ethyl esters (Lovaza) have not been studied in children.[114]

Pregnancy

Most of the products in this class are Pregnancy Category C. The exceptions include cholestyramine and colesevelam, which are non-absorbable and therefore considered Pregnancy Class B. Niacin is Pregnancy Category A for recommended daily allowance nutrient amounts; however, for the treatment of hyperlipidemia, niacin is considered Pregnancy Category C.

Other Populations

Fenofibrates should be dose adjusted in renal or hepatic impairment, unless severe, where use is contraindicated. Ezetimibe (Zetia) is not recommended in moderate to severe hepatic impairment. Niacin containing products should be used with caution in patients with renal impairment.

Dosages

Drug	Availability	Dose	Comments
BILE ACID SEQUESTRANTS			
cholestyramine	powder	One to two packets or scoopfuls twice daily	Mix with two to six ounces of water or pulpy fruit (applesauce)
colesevelam (WelChol)	625 mg tablets	Hyperlipidemia or Type 2 DM: 3,750 mg daily in one or two divided doses	May be increased to 4,375 mg daily Take with meals
colestipol	1 gm tablets	2 gm once or twice daily	Increase by 2 gm at one- to two-month intervals to a maximum of 16 gm daily
	5 gm/tsp granules	5-30 gm daily	Increase daily dose by 5 gm at one- to two-month intervals
CHOLESTEROL ABSORPTION INHIBITORS			
ezetimibe (Zetia)	10 mg tablets	10 mg daily	Take with or without food
FIBRIC ACIDS			
fenofibrate	generic and Lofibra: 67, 134, 200 mg capsules	67-200 mg daily	Must be taken with food
	generic and Lofibra: 54, 160 mg tablets	54–160 mg daily	Must be taken with food
fenofibrate (Antara)[115]	43, 130 mg capsules	43–130 mg daily	Take without regard to meals
fenofibrate (Fenoglide)[116]	40, 120 mg tablets	40-120 mg daily	Take with food
fenofibrate (Lipofen)	50, 150 mg capsules	50-150 mg daily	Must be taken with food
fenofibrate (Tricor)	48, 145 mg tablets	48-145 mg daily	Take without regard to meals
fenofibrate (Triglide)	50, 160 mg tablets	50-160 mg daily	Take without regard to meals
gemfibrozil	600 mg tablets	600 mg twice daily	Given 30 minutes prior to meal
NIACIN			
niacin ER (Niaspan)	500, 750, 1,000 mg tablets	500 - 2,000 mg at bedtime	Titrate dose up every four weeks May pre-administer aspirin to reduce flushing Take at bedtime after low-fat snack
niacin IR (Niacor)	500 mg tablets	1 – 2 gm twice or three times daily	May pre-administer aspirin to reduce flushing Take at bedtime after low-fat snack
OMEGA-3 FATTY ACIDS			
omega-3-acid ethyl esters (Lovaza)	1 gm capsules	4 gm daily in one or two divided doses	Take with meal(s)

Fenofibrate micronized 67 mg capsule (Lofibra, generic) has been shown to provide similar therapeutic effects to fenofibrate "non-micronized" 100 mg capsule.[117,118] All currently available fenofibrate products at the highest available dose produce similar plasma concentrations as the fenofibrate 200 mg capsules in single dose studies.[119,120,121]

Regular and extended-release formulations of niacin are not interchangeable.

There are three combination statin products, ezetimibe/simvastatin (Vytorin), niacin ER/simvastatin (Simcor®) and niacin ER/lovastatin (Advicor®). They are not discussed in this review.

Clinical Trials

Search Strategies

Articles were identified through searches performed on PubMed, www.ifpma.org/clinicaltrials, and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

The effects of the drugs in this class on lipids are well documented. To date, however, there have been no published clinical outcomes studies of colesevelam (Welchol), colestipol, ezetimibe (Zetia) or omega-3-acid ethyl esters (Lovaza). Though there are cardiovascular outcomes studies with EPA and DHA, they do not use the specific formulation for omega-3-acid ethyl esters (Lovaza).

Ezetimibe (Zetia) has been shown to provide additional LDL-C lowering when added to simvastatin (Zocor) or atorvastatin (Lipitor®), as well as other statin therapy.[122,123,124,125,126] Clinical trials evaluating cardiovascular morbidity and mortality have not yet been published with ezetimibe (Zetia) alone or in combination with a statin at this time.

colesevelam (Welchol) and ezetimibe (Zetia)

A randomized, double-blind, placebo-controlled, parallel group, multicenter study compared colesevelam 3.8 gm/day plus ezetimibe 10 mg daily to placebo plus ezetimibe 10 mg daily in 86 patients for six weeks.[127] The primary endpoint was the mean percentage change in LDL-C reduction and secondary endpoints were mean absolute change in LDL-C, mean absolute and mean percentage change in HDL-C, non-HDL-C, TC, apo A-I and apo B, and mean absolute change and percentage changes in TG and CRP. Colesevelam plus ezetimibe produced a mean percentage change in LDL-C of -32.3 percent versus -21.4 percent with ezetimibe monotherapy ($p<0.0001$). The combination therapy was significantly more effective than

ezetimibe alone in reducing TC, non-HDL-C, and apo-B and increasing apo A-I (p<0.005 for all). Neither regimen significantly increased TG (p=NS). Both treatment arms were generally well tolerated.

ezetimibe/simvastatin (Vytorin) and fenofibrate

A randomized, double-blind, placebo-controlled, parallel arm, multicenter trial compared ezetimibe/simvastatin 10/20 mg plus fenofibrate 160 mg, ezetimibe/simvastatin 10/20 mg, fenofibrate 160 mg, and placebo in a 3:3:3:1 ratio for 12 weeks in 611 patients.[128] The primary endpoint was to evaluate the LDL-C reduction of ezetimibe/simvastatin plus fenofibrate versus fenofibrate monotherapy. LDL-C was reduced significantly (p<0.05) with ezetimibe/simvastatin plus fenofibrate (-45.8 percent) compared with fenofibrate (-15.7 percent) but not compared to ezetimibe/simvastatin (-47.1 percent). HDL-C and apo A-I were significantly increased with ezetimibe/simvastatin plus fenofibrate (18.7 percent and 11.1 percent) compared with ezetimibe/simvastatin (9.3 percent and 6.6 percent) or placebo (1.1 percent and 1.6 percent) but not compared to fenofibrate (18.2 percent and 10.8 percent). TG, non-HDL-C and apo-B were significantly reduced with ezetimibe/simvastatin plus fenofibrate (-50.0 percent, -50.5 percent, and -44.7 percent) versus all other treatment arms. Treatments were well-tolerated.

ezetimibe (Zetia)/atorvastatin (Lipitor) versus atorvastatin (Lipitor)

A double-blind, placebo-controlled, multicenter trial randomized 148 patients with primary hypercholesterolemia and CHD to ezetimibe 10 mg and atorvastatin 10 mg combination therapy versus atorvastatin 10 mg monotherapy, for six weeks.[129] The primary endpoint was the mean percentage change in LDL-C from baseline to the end of study. The combination therapy resulted in greater adjusted mean change in LDL-C compared to monotherapy, -50.5 percent versus -36.5 percent, (p<0.0001), equating to an additional 14.1 percent reduction in LDL-C (95% CI, -17.90 to -10.19). Patients receiving combination therapy were 12 times more likely to reach LDL-C targets (OR 12.1, 95% CI 5.8 to 25.1, p<0.0001) compared with monotherapy. The incidence of adverse events was similar in both groups.

ezetimibe (Zetia) and simvastatin

Recently, the ENHANCE trial, a two-year, randomized, double-blind, multicenter study of 720 patients with heterozygous familial hypercholesterolemia compared ezetimibe/simvastatin 10/80 mg versus simvastatin 80 mg.[130] The study showed no significant difference between ezetimibe/simvastatin versus simvastatin in the primary endpoint of carotid intima media thickness (IMT), measured at three sites in the carotid arteries, using ultrasound imaging.[131] The change in mean carotid IMT after two years was 0.0111 mm versus 0.0058 mm, for the combination product versus simvastatin alone (p=0.29). Ezetimibe/simvastatin reduced LDL-C to a greater degree, 58 percent compared to simvastatin 41 percent, (p<0.01), after two years of treatment. This was not a clinical outcomes study, yet it generated attention since carotid ultrasound imaging can be a predictor of cardiac events, and the study results were delayed in being released. The American College of Cardiology (ACC) and American Heart Association (AHA) have released recommendations regarding the use of products containing ezetimibe and consider it a reasonable option for patients who are currently on a high-dose statin but are not at LDL-C goal, cannot tolerate statins, or can only tolerate a low-dose statin.[132] The National Institute for Health and Clinical Excellence (NICE) guidelines echo these recommendations.[133] The full ENHANCE study results will be released at the ACC meeting in March 2008. Three large scale, clinical outcomes studies (IMPROVE-IT, SHARP, and SEAS) are underway, with results expected in two to three years.

cholestyramine

The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), a multicenter, double-blind study, tested the efficacy of cholesterol lowering in reducing risk of CHD.[134,135] In this study, 3,806 asymptomatic middle-aged (35 to 59 years) men with primary hypercholesterolemia were randomized to receive cholestyramine 24 g/day or placebo for an average of 7.4 years. Both groups followed a moderate cholesterol-lowering diet. The cholestyramine group experienced average reductions in total-C of 13.4 percent and in LDL-C of 20.3 percent. The cholestyramine group experienced a 19 percent reduction in risk ($p<0.05$) of the primary composite end point of definite CHD death and/or definite nonfatal MI; this reflected a 24 percent reduction in definite CHD death and a 19 percent reduction in nonfatal MI. The cumulative seven-year incidence of the primary end point was seven percent in the cholestyramine group and 8.6 percent in the placebo group. In addition, the incidence rates were reduced for new positive exercise tests (by 25 percent compared to placebo; $p<0.001$) and new onset angina (by 20 percent; $p<0.01$). The incidence of coronary bypass surgery was similar in each group. The risk of death from all causes was reduced by seven percent (p=NS) in the cholestyramine group; the magnitude of this decrease was less than for CHD end points because of a greater number of violent and accidental deaths in the cholestyramine group.

cholestyramine, gemfibrozil, and niacin

A randomized, double-blind, placebo-controlled trial assessed the effects of gemfibrozil, niacin and cholestyramine on the composite outcome of MI, transient ischemic attack or stroke, cardiovascular death, cardiovascular procedures or hospitalization for angina.[136] A total of 143 military retirees with low HDL-C (mean 34 mg/dL) and documented CAD enrolled and were randomized to the combination of therapy or placebos. Active treatment included gemfibrozil 600 mg twice daily, niacin 500 mg titrated to 3,000 mg daily, and cholestyramine 2 gm titrated to 16 gm daily. Aggressive dietary and lifestyle changes were followed for six months prior to randomization. Cardiac angiography was performed at baseline and after 30 months of follow-up. The active treatment group experienced a total-C reduction of 20 percent (95% CI 14.8 to 24.3 percent), LDL-C reduction of 26 percent (95% CI 19.1 to 33.7 percent), TG reduction of 50 percent (95% CI 40.5 to 59.2 percent) and an increase in HDL-C of 36 percent (95% CI 28.4 to 43.5 percent). The composite endpoint was reached by 26.4 percent of the placebo group compared to 12.7 percent of the active treatment group, an absolute difference of 13.7 percent (95% CI 0.9 to 26.5 percent). There were no significant differences in the individual clinical event rates between the two small groups. On repeat cardiac angiography, the active treatment group was observed to have slight regression, whereas the placebo group experienced progression over the 30 months. Flushing, skin rash, and GI intolerance were more common in the active treatment group, and flushing problems could have lead to the possibility of unblinding.

colesevelam (Welchol) and meformin, sulfonylurea, and insulin

The efficacy of colesevelam in type 2 diabetes mellitus was evaluated in three double-blind placebo controlled trials in combination with metformin, sulfonylurea, or insulin.[137] A total of 1,018 patients with baseline HbA1c of 7.5 to 9.5 percent took colesevelam 3.75 mg/day as three tablets twice daily with meals or as six tablets with dinner for 26 weeks. In all three trials, HbA1c was reduced by 0.5 percent compared to placebo, ($p<0.001$ for all comparisons). Colesevelam increased TG levels in patients taking concurrent insulin or sulfonylurea but not in the metformin study.

A randomized, double-blind, placebo-controlled study evaluated colesevelam 3.75 mg/day versus placebo in 65 patients for 12 weeks.[138] These type 2 diabetic patients were already on metformin and/or sulfonylurea and continued on these agents through the study. The primary endpoint of reduction in HbA1c from baseline to week 12 was 0.5 percent for colesevelam versus placebo (p=0.007). There were no significant changes in weight or hypoglycemia between groups. The colesevelam group had a higher incidence of constipation.

fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide)

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, 9,795 patients with type 2 diabetes and no signs of prior CV disease were randomized to fenofibrate 200 mg/day or placebo for a median of five years.[139] Patients were 50 to 75 years, had total-C of 116 to 251 mg/dL and did not take statin therapy prior to study enrollment. In the double-blind trial, the primary outcome of coronary events (CHD death and non-fatal MI), occurred in 5.9 and 5.2 percent of placebo and fenofibrate groups, respectively, for a relative risk reduction of 11 percent (p=0.16). The fenofibrate group had a 24 percent relative risk reduction for MI with a nonsignificant increase in CHD mortality. The excess of CHD deaths in the fenofibrate group (110 versus 93 events in the placebo group) was mostly due to an increase in sudden cardiac death (70 versus 64 events, respectively). The secondary endpoint of total CV events (CV mortality, MI, stroke and coronary and carotid revascularization) occurred in 12.5 percent of patients in the fenofibrate group and 13.9 percent of patients in the placebo group (p=0.035). This reduction was primarily related to a 24 percent relative risk reduction in the incidence of MI (p=0.010) and 21 percent relative risk reduction in coronary revascularization (p=0.003). There was a significant 11 percent reduction in the secondary outcomes (HR 0.89, 0.80 to 0.99, p=0.04). There was a non-significant 11 percent (HR 1.11, 0.95, 1.29, p=0.41 and 19 percent (HR 1.19, 0.90, 1.57, p=0.22) increase in total and coronary heart disease mortality, respectively, with fenofibrate compared to placebo. By the end of the study, twice as many patients in the placebo group (32 percent) were receiving statins than in the fenofibrate group (16 percent; p<0.0001). After adjusting for statin use, investigators estimated that fenofibrate reduced the risk of CHD events by 19 percent (p=0.01) and of total CV disease events by 15 percent (p=0.004). Fenofibrate was also associated with less progression of albuminuria (p=0.002). Fenofibrate was well tolerated with a discontinuation rate similar to placebo. Nonsignificant increases in pancreatitis and pulmonary embolism were reported in the fenofibrate group.

gemfibrozil

The Helsinki Heart Study, a randomized, double-blind primary prevention study, found that gemfibrozil 1,200 mg/day was associated with a significant reduction in total plasma TG and a significant increase in HDL-C in men aged 40 to 55 years old (n=4,081) compared to placebo.[140,141] Over the five-year study period, there was a 34 percent relative risk reduction (p<0.02) in the incidence of cardiac endpoints (MI and cardiac death) with the use of gemfibrozil compared to placebo.[142] At the conclusion of this study, all participants were given the opportunity to receive gemfibrozil for an additional 3.5 years.[143] After the additional open-label period, there was no significant difference in CV or all-cause mortality between the two groups.

During screening for the Helsinki Heart Study, approximately 600 dyslipidemic individuals were detected who exhibited signs and symptoms of possible CHD; these subjects were excluded from the primary study.[144] Three-hundred and eleven of these patients were randomized to receive gemfibrozil 1,200 mg/day and 317 subjects to receive placebo over five years in double-blind fashion. The primary end-point, a composite of fatal and non-fatal MI and cardiac deaths,

did not differ significantly between the placebo and gemfibrozil groups. The same was true for total mortality. In the study, data were not evaluated for several key prognostic factors, including the presence, and between group distribution, of the true prevalence of CHD, extent of coronary artery obstructions and degree of left ventricular dysfunction.

A 13 year post trial follow-up of the Helsinki Heart Study compared the CHD, cancer, and all-cause mortality among the original gemfibrozil and original placebo groups. Gemfibrozil had a 23 percent relative risk reduction of CHD mortality compared to placebo, (p=0.05).[145]

In the double-blind Veterans' Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) study, 2,531 men with CHD, mean HDL-C of 31.5 mg/dL and mean LDL-C of 111 mg/dL were randomized to gemfibrozil 1,200 mg/day or placebo.[146] The primary study outcome was nonfatal MI or death from coronary causes. At one year, the mean total-C was four percent lower, HDL-C six percent higher and TG 31 percent lower in the active treatment than the placebo group; there was no between group difference in LDL-C. After a median follow-up of 5.1 years, a primary event occurred in 17.3 percent of patients in the gemfibrozil group and 21.7 percent of patients in the placebo group, a significant relative risk reduction of 22 percent (95% CI 7 to 35 percent; p=0.006). There was also a 24 percent relative risk reduction in the secondary composite endpoint of death from CHD, nonfatal MI and stroke (p<0.001 compared to placebo). There were no significant differences between groups in the incidences of coronary revascularization, hospitalization for unstable angina, death from any cause and cancer. Subsequent predefined subanalyses showed a reduced incidence in the primary outcome in patients with chronic renal insufficiency (25 percent relative risk reduction; p=0.02)[147] and in patients with diabetes (32 percent relative risk reduction; p=0.004).[148]

niacin

The Coronary Drug Project was a nine-year, double-blind study conducted by the NHLBI to assess the long-term efficacy and safety of several lipid-influencing drugs (conjugated estrogens 2.5 or 5 mg/day, clofibrate 1.8 gm/day, dextrothyroxine 6 mg/day, niacin 3 gm/day or placebo) in 8,341 men aged 30 to 64 years with documented previous MI.[149] The two estrogen regimens and dextrothyroxine were discontinued early because of adverse effects. No evidence of efficacy was found for the clofibrate treatment. Niacin treatment showed modest benefit in decreasing nonfatal recurrent MI but did not decrease total mortality. After a mean follow-up of 15 years, mortality from all causes in each of the drug groups, except for niacin, was similar to that in the placebo group; mortality in the niacin group was 11 percent lower than in the placebo group (52 versus 58.2 percent; p=0.0004), as reported.

niacin ER (Niaspan)

In a double-blind, randomized, placebo-controlled trial, niacin ER 1,000 mg daily was added to statin therapy in 167 patients with CAD and low HDL-C (< 45 mg/dL).[150] Patients were initially started on niacin ER 500 mg and then titrated to 1,000 mg daily after one month. A total of 149 patients completed the study. Baseline carotid intima-media thickness (CIMT), LDL-C (mean 89 mg/dL), and HDL-C (mean 40 mg/dL) were comparable in the two groups. After 12 months, HDL-C increased by 21 percent in the niacin group. The mean CIMT increased significantly in the placebo group (p<0.001) but was unchanged in the niacin group. The difference in the CIMT progression was not statistically significant (p=0.08). Cardiovascular event rates were similar in the small trial (3.8 percent in the niacin group and 9.6 percent in the statin-only group; p=0.20).

omega-3-acid ethyl esters (Lovaza)/simvastatin versus simvastatin

A randomized, double-blind, placebo-controlled, parallel group trial compared the combination of omega-3 acid ethyl esters 4 gm daily and simvastatin 40 mg per day with simvastatin 40 mg per day monotherapy, in 254 patients with persistent high TG (200 to 499 mg/dL).[151,152] Patients were treated with eight weeks of open-label simvastatin 40 mg daily prior to randomization to control their LDL-C to no greater than 10 percent above NCEP ATP III goal and remained on this dose throughout the study. After the initial open-label phase, patients were then randomized to either omega-3-acid ethyl esters or placebo for an additional eight weeks. Combination therapy versus monotherapy resulted in a median percentage change in TG of -29.5 percent versus -6.3 percent, respectively, ($p<0.0001$). The mean percentage change in HDL-C was +3.4 percent for combination therapy versus -1.2 percent for monotherapy, ($p<0.05$). The mean percentage change in LDL-C was +0.7 percent for the combination group and -2.8 percent for monotherapy, ($p=0.05$).

Meta-analysis

The fibric acids were compared to niacin in a meta-analysis evaluating lipid parameter effects and risk reductions for major cardiac events.[153] Data from 53 trials (n=16,802) using fibric acids and 30 trials (n=4,749) using niacin were included in the meta-analysis. Fibric acids included agents which have never been available in the US in addition to gemfibrozil and fenofibrate. Niacin products included immediate-, sustained-, and extended-release formulations. Reductions in LDL-C and TG were 36 and eight percent for fibric acids and 20 and 14 percent for niacin, respectively. Increases in HDL-C were 10 and 16 percent for fibric acids and niacin, respectively. Relative risk reduction for major cardiac events was 25 and 27 percent for fibric acids and niacin, respectively.

Effects on Lipids for Selected Agents[154,155,156,157,158]

While outcomes data are lacking for many of the non-statin lipotropics, the effects of these agents on the lipid profile are well documented and may serve as an indirect indicator of the efficacy.

Drug	TC (% change)	LDL-C (% change)	HDL-C (% change)	TG (% change)
Bile Acid Sequestrants[159,160,161,162] cholestyramine, colestipol, colesevelam (Welchol)	-9 to -13	-12 to -30	+3 to +9	0 to +25
Cholesterol Absorption Inhibitors[163] ezetimibe (Zetia)	-12 to -13	- 18	+ 1	- 8
Fibric Acids[164,165,166,167,168,169,170,171,172,173,174,175,176,177,178] fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide) gemfibrozil	-4 to -26	-27 to +9	+ 6 to +18	- 29 to -54
niacin ER (Niaspan)[179,180]	- 3 to -10	-14 to +2	+ 18 to +26	-13 to -29
niacin IR (Niacor)[181]	-10 to -20	-10 to -20	+ 20 to + 35	-30 to -70
omega-3-acid ethyl esters (Lovaza)[182]	-10	+45	+9	-45

Summary

The preponderance of outcomes data support the use of statins as the primary agents for LDL-C-reduction therapy. Other agents, however, have a role in the treatment of patients who require combination therapy or who are unable to tolerate the statins.

The bile acid sequestrant, cholestyramine, has been shown to reduce major coronary events and CHD deaths. The bile acid sequestrants are effective in lowering LDL-C and raising HDL-C; they do not lower TG levels. They can be used in combination with statins. Patients generally have poor compliance to bile acid sequestrants because of the side effect profile. Colesevelam (WelChol) provides an alternative to cholestyramine and colestipol with a potential lower incidence of GI effects. Colesevelam (Welchol) is now FDA approved for glycemic control in type 2 diabetes mellitus. Colesevelam (Welchol) only provides modest HbA1c reductions and can provide an option in patients who are almost at HbA1c goal who also require lipid lowering.

To date, ezetimibe (Zetia) has not been shown to reduce CV morbidity or mortality. It does reduce LDL-C, both when given alone and, particularly, in combination with a statin.

Fibric acids have been shown to reduce CV morbidity and mortality in both primary and secondary prevention trials.[183,184] They lower TG levels and raise HDL-C levels to a greater extent than do the statins. Depending on the specific type of dyslipidemia, the fibric acids may lower total-C and LDL-C, although not as significantly as the statins. The fibric acids should be considered as an alternative agent to the statins for specific lipid disorders or can be used as

add-on therapy with caution, considering the increased risk of myopathy. Fenofibrate is less likely to interact with statins compared to gemfibrozil.

Niacin has been shown to reduce major coronary events and, possibly, total mortality. Compared to immediate release niacin (Niacor), niacin ER (Niaspan) may increase compliance and reduce the incidence of flushing.

Omega-3-acid ethyl esters (Lovaza) reduce TG in patients with very high TG (>500 mg/dL). Several forms of omega-3 fatty acids are sold over-the-counter; however, the high concentration of EPA and DHA in a single capsule, low daily capsule count, and data from large clinical trials with the Lovaza formulation make it unique.[185] In addition, omega-3-acid ethyl esters (Lovaza) does not increase the risk of rhabdomyolysis in combination with statins.

Each class of non-statin lipotropics provides a unique option for use in patients who cannot reach target lipid levels on statin monotherapy or who do not tolerate statins. While there are not outcomes data for each class, their effects on lipids profiles are clearly substantiated.

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