



Lipotropics, Other

Therapeutic Class Review (TCR)

November 25, 2014

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, digital scanning, or via any information storage or retrieval system without the express written consent of Provider Synergies, L.L.C.

All requests for permission should be mailed to:

Attention: Copyright Administrator
Intellectual Property Department
Provider Synergies, L.L.C.
10101 Alliance Road, Suite 201
Cincinnati, Ohio 45242

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCReEditor@magellanhealth.com.

FDA-APPROVED INDICATIONS

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

Drug	Manufacturer	Indication(s)
Apolipoprotein B Synthesis Inhibitors		
lomitapide (Juxtapid™) ¹	Aegerion	Reduction of LDL-C, total cholesterol, apolipoprotein B (Apo B), and non-HDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to a low-fat diet and other lipid-lowering treatments
mipomersen (Kynamro™) ²	Genzyme	Reduction of LDL-C, total cholesterol, apolipoprotein B (Apo B), and non-HDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to diet and lipid-lowering medications
Bile Acid Sequestrants		
cholestyramine ³	generic	<ul style="list-style-type: none"> ▪ Primary hypercholesterolemia ▪ Relief of pruritus associated with partial biliary obstruction
colesevelam (WelChol®) ⁴	Daiichi Sankyo	<ul style="list-style-type: none"> ▪ Hypercholesterolemia, Fredrickson type IIa (monotherapy or in combination with a statin) ▪ Reduction of LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) after failing an adequate trial of diet therapy ▪ Glycemic control in adults with type 2 diabetes mellitus
colestipol (Colestid®) ⁵	Pfizer, generic	<ul style="list-style-type: none"> ▪ Primary hypercholesterolemia
Cholesterol Absorption Inhibitors		
ezetimibe (Zetia®) ⁶	Merck Sharp & Dohme	<ul style="list-style-type: none"> ▪ Primary hypercholesterolemia (monotherapy or in combination with a statin) ▪ Mixed hyperlipidemia (in combination with fenofibrate) ▪ Homozygous familial hypercholesterolemia (HoFH) (adjunctive therapy in combination with atorvastatin or simvastatin) ▪ Homozygous familial sitosterolemia
Fibric Acids		
fenofibrate (Antara™) ⁷	Lupin, generic	<ul style="list-style-type: none"> ▪ Primary hypercholesterolemia or mixed dyslipidemia, Fredrickson types IIa and IIb ▪ Hypertriglyceridemia, Fredrickson types IV and V hyperlipidemia
fenofibrate (Fenoglide™) ⁸	Santarus	
fenofibrate (Lipofen™) ⁹	Kowa	
fenofibrate (Lofibra®) ¹⁰	generic	
fenofibrate (Tricor®) ¹¹	Abbvie, generic	
fenofibrate (Triglide™) ¹²	Shionogi	
fenofibric acid (Fibracor™) ¹³	AR Scientific	<ul style="list-style-type: none"> ▪ Primary hyperlipidemia or mixed dyslipidemia ▪ Severe hypertriglyceridemia (≥ 500 mg/dL)
fenofibric acid (Trilipix™) ¹⁴	Abbvie, generic	<ul style="list-style-type: none"> ▪ Mixed dyslipidemia (in combination with a statin) in patients with CHD or CHD risk equivalent ▪ Primary hyperlipidemia or mixed dyslipidemia ▪ Severe hypertriglyceridemia
gemfibrozil ¹⁵	Pfizer, generic	<ul style="list-style-type: none"> ▪ Hypercholesterolemia, Fredrickson type IIb (in patients without history of or symptoms of existing CHD) ▪ Hypertriglyceridemia, Fredrickson types IV and V hyperlipidemia

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
Niacin		
niacin ER (Niaspan®) ¹⁶	Abbvie, generic	<ul style="list-style-type: none"> ▪ Primary hyperlipidemia or mixed dyslipidemia (monotherapy, or if monotherapy inadequate, in combination with lovastatin or simvastatin) ▪ Primary hyperlipidemia or patients with a history of Coronary Artery Disease (CAD) and hyperlipidemia (in combination with a bile acid sequestrant) ▪ Severe hypertriglyceridemia as adjunct in patients at risk for pancreatitis ▪ Patients with a history of myocardial infarction (MI) and hyperlipidemia
niacin IR (Niacor®) ¹⁷	Upsher-Smith	<ul style="list-style-type: none"> ▪ Primary hypercholesterolemia (monotherapy or in combination with bile-acid binding resin) ▪ Hypertriglyceridemia, types IV and V hyperlipidemia for those who present with a risk of pancreatitis (adjunctive therapy)
Omega-3 Fatty Acids		
icosapent ethyl (Vascepa®) ¹⁸	Amarin	<ul style="list-style-type: none"> ▪ Treatment of hypertriglyceridemia in adults with severe triglycerides (TG) ≥ 500 mg/dL, as adjunct to diet.
omega-3-acid ethyl esters (Lovaza®) ¹⁹	GSK, generic	<ul style="list-style-type: none"> ▪ Treatment of hypertriglyceridemia in adults with triglycerides (TG) ≥ 500 mg/dL

The effects of icosapent ethyl and omega-3-acid ethyl esters on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia have not been determined. The effect of icosapent ethyl and omega-3-acid ethyl esters on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.

The effect of lomitapide on cardiovascular morbidity and mortality has not been determined. The safety and effectiveness of lomitapide have not been established in patients with hypercholesterolemia who do not have HoFH.

The safety and effectiveness of mipomersen have not been established in patients with hypercholesterolemia who do not have HoFH. The effect of mipomersen on cardiovascular (CV) morbidity and mortality has not been determined.

The use of mipomersen as an adjunct to LDL-C apheresis is not recommended.

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). The National Health and Nutrition Examination Survey (NHANES) reported that in 2011-2012 approximately 12.9 percent of adults aged 20 years and over had high total cholesterol; which was unchanged since 2009-2010 data.²⁰ The percentage with high total cholesterol was higher in women (14.4 percent) than in men (11.1 percent). A larger percentage of Hispanic men had high total cholesterol (14.2 percent) compared with both non-Hispanic white (11.6 percent) and non-Hispanic black men (7.4 percent). The NHANES analysis was based on measured cholesterol only and does not take into account whether lipid-lowering medications were taken.

In 2013 the American College of Cardiology (ACC) and the American Heart Association (AHA), in combination with the National Heart, Lung, and Blood Institute (NHLBI), released four new consensus guidelines regarding cholesterol management, cardiovascular risk assessment, obesity, and lifestyle. ACC/AHA emphasizes lifestyle modification, including a reduced calorie diet and aerobic physical activity, as a critical component of atherosclerotic cardiovascular disease (ASCVD) risk reduction, both prior to and in conjunction with cholesterol lowering drug therapies.^{21,22,23, 24}

There is a high level of evidence supporting the use of hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (“statins”) for secondary prevention and moderate to high level of evidence for primary prevention.²⁵ As a class, they can lower LDL-C by up to 60 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 six to 30 percent and increasing HDL-C by two to 16 percent.

Non-statin therapies do not provide adequate ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD.²⁶ As demonstrated in the AIM-HIGH study, the additional reduction in non-HDL-C [as well as additional reductions in Apo B, Lp(a), and triglycerides in addition to HDL-C increases] levels with niacin therapy did not further reduce ASCVD risk in individuals treated to LDL-C levels of 40-80 mg/dL. The ACCORD trial reported that, in patients with and without clinical CVD, fenofibrate-simvastatin did not reduce the risk for CVD events compared with simvastatin alone. However, ACC/AHA recognizes that maximal statin therapy might not be adequate to lower LDL-C sufficiently to reduce ASCVD event risk in individuals with primary severe elevations of LDL-C at which time the addition of non-statin agents can be considered. As presented at the AHA Scientific Sessions in 2014, the IMPROVE-IT study reported an average additional reduction in LDL-C of 17 mg/dL with the addition of ezetimibe to simvastatin.²⁷ The primary composite endpoint of CV death, myocardial infarction (MI), unstable angina, stroke, and coronary revascularization beyond 30 days of randomization was significantly lower with ezetimibe/simvastatin as compared to simvastatin alone (32.7 versus 34.7 percent, respectively; $p=0.016$) during the seven year follow-up period, with reports of significant reduction for all endpoint components. Both treatment arms reported similar rates of CV and all-cause mortality and revascularization.

ACC/AHA no longer supports the use of the National Cholesterol Education Program Expert Panel on Diagnosis, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) algorithm for risk assessment citing that it is derived in an exclusively white sample population and the limited scope of the outcome in determining CHD alone.²⁸ Instead, they recommend use of the new race- and sex-specific Pooled Cohort Equations to estimate 10-year ASCVD risk in both white and black men and women.

ACC/AHA also no longer supports treat-to-target approach with goals such as LDL-C <70 mg/dL and <100 mg/dL for secondary and primary ASCVD prevention, respectively; rather, the guidelines advocate using the maximum tolerated statin intensity in patients identified to benefit from statin therapy.²⁹ This guideline focuses on treatments proven to reduce ASCVD events and is not intended to be a comprehensive approach to lipid management. They suggest examination of treatment of hypertriglyceridemia and use of non-HDL-C apolipoprotein B, lipoprotein-a, or LDL particles in guiding treatment decisions. Routine use of carotid intima media thickness (CIMT) is no longer recommended by the ACC/AHA. It should only be used as a research tool.

High plasma HDL cholesterol (HDL-C) is associated with reduced risk of myocardial infarction (MI), but whether this association is causal is unclear. A study published in 2012 that utilizes databases of genetic information has found that raising HDL-C levels may not affect heart disease risk.³⁰ The study reported that carriers of the *LIPG* 396Ser allele (2.6 percent frequency) had higher HDL-C (0.14 mmol/L higher, $p=8\times 10^{-13}$) but similar levels of other lipid and non-lipid risk factors for MI compared with non-carriers. This difference in HDL-C was expected to decrease risk of MI by 13 percent (odds ratio [OR] 0.87, 95% CI 0.84-0.91), but the investigators found that the 396Ser allele was not associated with risk of MI (OR 0.99, 95% CI 0.88-1.11, $p=0.85$). These data challenge the concept that raising HDL-C will uniformly translate into reductions in risk of MI.

The 2012 guidelines on the evaluation and treatment of hypertriglyceridemia by the Endocrine Society (ES) defines moderate hypertriglyceridemia as TG levels between 200-999 mg/dL, severe hypertriglyceridemia as TG levels between 1,000-1,999 mg/dL, and very severe hypertriglyceridemia as TG levels 2,000 mg/dL or greater. A high TG level is a component of metabolic syndrome, which is associated with risk for CVD.³¹ In addition, there is growing support for unadjusted elevated TG levels as an independent CVD risk factor, although the extent of direct association is unknown. The ES recommends hypertriglyceridemia screening in adults as part of a lipid panel at least every five years and suggest that use of apolipoprotein B (apoB) or lipoprotein(a) [Lp(a)] levels can be of value. Patients with primary hypertriglyceridemia should be evaluated for family history of dyslipidemia and CVD to assess genetic causes and future CVD risk. In addition to lifestyle changes, ES recommends drug therapy to reduce the risk of pancreatitis in patients with severe and very severe hypertriglyceridemia; a fibrate is considered a first-line treatment. For patients with moderate to severe hypertriglyceridemia, fibrates, niacin, and omega-3 fatty acids alone or in combination with statins may be considered. Statins should not be used alone for severe or very severe hypertriglyceridemia; however, statins may be useful for the treatment of moderate hypertriglyceridemia to modify CVD risk. Recommended treatment goal for patients with moderate hypertriglyceridemia are non-HDL-C levels of < 130 mg/dL in those with CHD and CHD Risk Equivalent (10-year risk for CHD >20%), < 160 mg/dL in those with at least two risk factors, and < 190 mg/dL in those with zero to one risk factor.³²

Studies to date have not demonstrated an overall benefit of fibrates for reduction of CV or total mortality, although post hoc subgroup analyses have reported a decrease in composite CV events with the use of fibrates in patients with moderate hypertriglyceridemia.³³ In addition, no studies using high-dose omega-3 fatty acids in hypertriglyceridemia patients have shown a beneficial cardiovascular outcome.

In 2012, the American Association of Clinical Endocrinologists (AACE) published guidelines for the management of dyslipidemia and prevention of atherosclerosis.³⁴ AACE also includes lipid screening in the pediatric populations and recommend that children older than two years and adolescents older than 16 years be evaluated every three to five years and every five years, respectively, if they have CAD risk factors or a family history of premature CAD or dyslipidemia. AACE supports the use of apolipoprotein B (apo B) in evaluating lipid status. They recommend an optimal apo B < 90 mg/dL for patients at risk of CAD, while patients with established CAD or diabetes who have one or more additional risk factors should have an apo B < 80 mg/dL. They recommend fibrates for treatment of triglycerides > 500 mg/dL. Niacin can be used for reducing triglycerides, increasing HDL-C, and reducing LDL-C. Omega-3 fish oil (2 to 4 g) can be used, as adjunct to fibrates or niacin if necessary, to achieve satisfactory triglyceride lowering. AACE recommends bile acid sequestrants for reducing LDL-C and apo B and modestly increasing HDL-C, but they may increase triglycerides. Cholesterol absorption inhibitors are effective as monotherapy in reducing LDL-C and apo B. In addition, combination therapy with statins can be used. AACE recommends pharmacotherapy for children and adolescents older than eight years who do not respond sufficiently to lifestyle modification and particularly for those with either LDL-C \geq 190 mg/dL, or LDL-C \geq 160 mg/dL and the presence of two or more cardiovascular risk factors, or a family history of premature CAD. These guidelines also address the unique challenges associated with atherosclerosis and heart disease in women. They recommend the following pharmacotherapy for all women at high risk: lipid-lowering pharmacotherapy (preferably with a statin) regardless of LDL-C level, and niacin or fibrate therapy in the presence of low HDL-C or elevated non-HDL-C; for all women at intermediate risk: lipid-lowering pharmacotherapy (preferably with a statin) in the presence of an

LDL-C level greater than 130 mg/dL, and niacin or fibrate therapy in the presence of low HDL-C or elevated non-HDL-C after LDL-C goal is reached.

Familial hypercholesterolemia is a genetic disorder that leads to accumulation of LDL particles in plasma and premature cardiovascular disease.^{35,36} The more severe form, homozygous familial hypercholesterolemia (HoFH) is rare, occurring in about one out of a million people in the U.S. In HoFH, LDL receptor activity is nearly absent and LDL-C levels commonly range between 400-1,000 mg/dL. Severe and widespread atherosclerosis affects all major arteries and children are at risk for early coronary events and valve abnormalities, particularly aortic stenosis. Historically, treating patients with HoFH has been very difficult since it is resistant to diet modifications and most medications indicated for lowering cholesterol. The less serious heterozygous familial hypercholesterolemia (HeFH) occurs in one in 500 persons in the U.S. CAD symptoms begin to manifest in the fourth and fifth decades of life, in men and women, respectively. Additional risk factors (e.g., genetic, metabolic, and environmental) can lead to variations in the clinical manifestations and severity of atherosclerotic disease of HeFH. Accumulation of cholesterol in nonvascular tissue (cornea, skin, tendons, and joints) also commonly occurs in children with HoFH, and in adults with HeFH.

In 2011, the American Academy of Pediatrics (AAP) endorsed guidelines by the National Heart, Lung, and Blood Institute (NHLBI) on cardiovascular health and risk reduction in children and adolescents that outlines age appropriate lipid screening in the pediatric population.³⁷ NHLBI recommends a fasting lipid profile in children age one to four years, only if the child is familial hypercholesterolemia (FH) positive, the child has a parent with dyslipidemia, or if the child has any other risk factors or high-risk conditions. All children should be screened for high cholesterol at least once between the ages of nine and 11 years, and again between ages 17 and 21 years. It is anticipated that a universal screening will more accurately identify children who are at high risk for cardiovascular disease. The guideline also identifies age-specific strategies to reduce risk factors and manage cardiovascular disease in children and adolescents. Most children with high cholesterol should be treated with lifestyle modifications including diet and physical activity. Less than one percent of children, primarily those with genetic dyslipidemias, may qualify for cholesterol-lowering medications. In addition to lifestyle interventions, the use of lipid-lowering medications is recommended in general in ages 10 years and greater if LDL-C is: ≥ 190 mg/dL, ≥ 160 mg/dL with family history of early heart disease or one high- or two moderate-level additional risk factors, or > 100 mg/dL if diabetes mellitus is present. The initial LDL-C goal is less than 160 mg/dL, but LDL-C as low as 130 or even 110 mg/dL is warranted if strong CVD family history is present. Drug therapy may be considered for children ages eight and nine years with LDL-C persistently > 190 mg/dL combined with a strong family history of early CVD or additional risk factors.

PHARMACOLOGY

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

Apolipoprotein B (apoB) Synthesis Inhibitors

Apolipoprotein B (apo-B) is a structural protein of VLDL and LDL.³⁸ Microsomal triglyceride transfer protein (MTP) transfers triglycerides onto apoB, during the production of VLDL, a precursor to LDL.³⁹

Lomitapide (Juxtapid) directly binds and inhibits MTP, preventing the synthesis of apo-B-containing proteins in enterocytes and hepatocytes.⁴⁰ This results in decreased synthesis of VLDL, and thereby reduced plasma LDL-C levels. MTP inhibitors are not liver-specific and thus block the secretion of both

intestinal and hepatic lipoproteins. This lack of inhibition specificity can lead to fat malabsorption in some patients.

Mipomersen is an antisense oligonucleotide, complementary to the coding region of the human messenger ribonucleic acid (mRNA) for apo B-100, the principal apolipoprotein of LDL.⁴¹ Mipomersen binds to mRNA, forming a hybridization of mipomersen to the cognate mRNA that results in RNase H-mediated degradation of the cognate mRNA thus inhibiting translation of the apo B-100 protein.

Bile Acid Sequestrants

During normal digestion, bile acids are secreted into the intestines. Bile acids emulsify the dietary fat and lipids 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. 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 12 to 30 percent and may have a small effect on HDL-C. Reports of impact on TG vary from zero to 25 percent reduction. 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.⁴² Cholestyramine has been shown to reduce the number of cardiovascular events, but colestipol or colesevelam do not have cardiovascular clinical outcomes data.

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

Cholesterol Absorption Inhibitors

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 improvements 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.⁴³

Fibric acids

The effects of the fibric acids [fenofibrate, fenofibric acid (the active metabolite of fenofibrate), and gemfibrozil], have been explained by the activation of peroxisome proliferator activated receptor alpha (PPAR α). Through this mechanism, the fibric acids increase lipolysis and elimination of TG-rich particles from plasma by activating lipoprotein lipase. Fibric acids reduce 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 PPAR α 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. Each fenofibric acid (Trilipix) delayed-release capsule contains choline fenofibrate.⁴⁴ The active moiety of Fibracor and Trilipix is fenofibric acid.

Gemfibrozil has been shown to reduce the risk of CHD in patients with high TG and low HDL-C.^{45,46,47,48} This effect is most significant in patients with diabetes or metabolic syndrome.⁴⁹ Fenofibrate did not demonstrate, in patients with type 2 diabetes, a statistically significant reduction in the risk of first nonfatal MI and CHD death in the FIELD study, although nonfatal MI was significantly reduced.^{50,51} In the lipid arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular (CV) events, nonfatal MI, or nonfatal stroke, compared with simvastatin monotherapy, suggesting against the routine use of combination therapy with fenofibrate and simvastatin to reduce CV risk in the majority of high-risk patients with type 2 diabetes.⁵² Based on results from the ACCORD Lipid trial and other clinical trials, in November 2011, the FDA informed the public that fenofibric acid (Trilipix) may not lower a patient's risk of having a myocardial infarction or stroke and is requiring the manufacturer of Trilipix to conduct a clinical trial to evaluate the CV effects of Trilipix in patients at high risk for CV disease who are already taking statins.⁵³ In addition, a subgroup analysis of ACCORD showed there was an increase in the risk for major adverse cardiac events in women, relative to men, receiving the combination therapy versus simvastatin alone.⁵⁴ The clinical significance of this subgroup finding is unclear, as this finding was not observed in a separate large randomized controlled clinical trial of fenofibrate versus placebo. Data to support the routine use of non-statin drugs in combination with statin therapy to reduce further ASCVD events are lacking; however, non-statin therapy may be considered as adjunct to statin therapy when maximum intensity statin therapy does not lower LDL-C sufficiently to reduce ASCVD event risk in individuals with primary severe elevations of LDL-C.⁵⁵ ACC/AHA advises that gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. Gemfibrozil use with simvastatin is contraindicated.⁵⁶ Fenofibrate, however, does not interfere with statin metabolism and may be less likely to increase the risk for myopathy in patients treated with moderate doses of statins.^{57,58}

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 and has shown to decrease total cholesterol by 10 percent and triglycerides by 27 percent.^{59,60} Immediate-release niacin (Niacor) is

available with a prescription. It is also available without a prescription. Due to intolerance, patients often need 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 and is available with a prescription.

Combination therapy with niacin and statins yields a significant reduction in LDL-C and increase in HDL-C.⁶¹ Niacin has been shown to reduce the risk of CHD as monotherapy and in combination with statins.^{62,63,64} It also leads to regression of carotid atherosclerosis when given with statins in a small study.^{65,66} Niacin caused regression of coronary lesions and reduced cardiovascular events in another small study when given in combination with cholestyramine and gemfibrozil.⁶⁷

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) included 3,414 patients with established CVD and atherogenic dyslipidemia. All patients received simvastatin (or simvastatin plus ezetimibe) at a dose sufficient to maintain LDL-C at 40-80 mg/dL. Patients were randomized to extended-release niacin or matching placebo.⁶⁸ Although niacin extended-release was effective at raising HDL-C and lowering triglycerides, the trial was halted early due to the lack of incremental benefit on CV risk reduction (including myocardial infarctions and stroke) in the extended-release niacin plus simvastatin arm versus simvastatin alone ($p=0.80$).^{69,70} In addition, a small, unexplained, increase in the rate of ischemic stroke was observed in the simvastatin plus extended-release niacin arm compared to simvastatin alone (29 patients versus 18 patients, respectively; $p=0.11$). Nine of the ischemic strokes in the simvastatin plus extended-release niacin group occurred in participants who had stopped taking niacin for at least two months and up to four years before their stroke. Therefore, it is unclear whether niacin contributed to this imbalance in ischemic stroke. The authors note study limitations such as: the findings may not be generalizable to all patients with coronary disease or all patients with low HDL cholesterol levels; it remains unclear whether other populations may benefit from such treatment; it is unclear if in the 94 percent of patients who were taking statins at entry at baseline had more stable plaques, less likely to rupture, and, therefore, at lower risk of subsequent cardiovascular events; low percentage of women enrolled (15 percent); low rate of ethnic minorities (eight percent); and the 36 month follow-up period may not have been an adequate duration to show a clinical treatment effect of niacin. The AIM-HIGH trial was funded by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institute of Health (NIH) with additional support from Abbott Laboratories. The FDA plans to conduct a review of AIM-HIGH.⁷¹

Omega-3 Fatty Acids

Omega-3-acid ethyl esters (Lovaza) is a combination of ethyl esters – 465 mg of eicosapentaenoic acid (EPA) and 375 mg of 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.⁷² 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.⁷³ Elevations in LDL-C and non-HDL-C may also be observed. In trials done with omega-3-acid ethyl esters (Lovaza), the median percent change in LDL-C was an increase of 49.3 percent relative to placebo. 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 4 grams per day have been shown to reduce TG by up to 45 percent in adults with baseline TG ≥ 500 mg/dL.

Icosapent ethyl (Vascepa) is an ethyl ester of EPA only.⁷⁴ Icosapent ethyl 4 grams per day has been shown to reduce TG by up to 33.1 percent in adults with baseline TG \geq 500 mg/dL while elevations of LDL-C have not been observed.⁷⁵

The use of EPA alone does not affect LDL-C like the combination of EPA and DHA can, due to an increased conversion of VLDL to LDL.⁷⁶ In the pivotal clinical trials, treatment with icosapent ethyl was not associated with elevations in LDL-C compared to placebo. The median reduction in triglycerides in omega-3-acid ethyl esters-treated patients from pivotal trials was 27 percent (33 percent relative to placebo).

PHARMACOKINETICS

Drug	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion (%)
Apolipoprotein B Synthesis Inhibitors				
lomitapide (Juxtapid) ⁷⁷	7	39.7	major: M1 and M3 (CYP 3A4)	urine: 59.5 feces: 33.4
mipomersen (Kynamro) ⁷⁸	54 to 78	1 to 2 months	oligonucleotide metabolites	urine
Bile Acid Sequestrants				
cholestyramine ⁷⁹	not absorbed	--	--	feces
colesevelam (Welchol) ⁸⁰	not absorbed	--	--	feces
colestipol ⁸¹	not absorbed	--	--	feces
Cholesterol Absorption Inhibitors				
ezetimibe (Zetia) ⁸²	35-60	22	ezetimibe glucuronide	urine: 11 feces: 78
Fibric Acids				
fenofibrate (Antara, Fenoglide, Lipofen, Lofibra, Tricor, Triglide) <small>83,84,85,86,87,88 89</small>	unknown	16-23	fenofibric acid (active component); glucuronide conjugate	urine: 60 feces: 25
fenofibric acid (Fibricor) ⁹⁰	unknown	20	glucuronide conjugate	urine
fenofibric acid (Trilipix) ⁹¹	81	20	glucuronide conjugate	urine
gemfibrozil ⁹²	100	1.5	3 metabolites	urine: 70 feces: 6
Niacin				
niacin ER (Niaspan) ⁹³	60-76	--	many metabolites	predominantly urine
niacin IR (Niacor) ⁹⁴	88	0.3-0.75	nicotinuric acid	urine
Omega-3 Fatty Acids				
icosapent ethyl (Vascepa) ⁹⁵	--	89	acetyl Coenzyme A	hepatic
omega-3-acid ethyl esters (Lovaza) ⁹⁶	unknown	--	--	--

Fenofibrate micronized 67 mg capsule (Lofibra, generic) has been shown to provide similar therapeutic effects to fenofibrate “non-micronized” 100 mg capsule.^{97,98} All currently available fenofibrate products at the highest available dose produce similar plasma concentrations as the fenofibrate 200 mg capsules in single dose studies.^{99,100,101} Lipofen 150 mg capsules have been shown to be equivalent to Tricor 160 mg tablets under low-fat and high-fat fed conditions.¹⁰² Fenoglide 120 mg tablets have been shown to be equivalent to fenofibrate 130 mg capsules under high-fat conditions.¹⁰³ Trilipix 135 mg capsules are equivalent to micronized fenofibrate 200 mg capsules administered under fed conditions.¹⁰⁴ Fibracor 105 mg tablets are equivalent to fenofibrate tablets (TriCor) 145 mg under fasted conditions.¹⁰⁵

CONTRAINDICATIONS/WARNINGS

Apolipoprotein B (apoB) Synthesis Inhibitors

Mipomersen (Kynamro) is contraindicated in patients with moderate or severe hepatic impairment, or active liver disease, including unexplained persistent elevations of serum transaminases¹⁰⁶ Mipomersen carries a black boxed warning due to the risk of hepatotoxicity resulting from increases in transaminases and hepatic steatosis. Mipomersen can increase hepatic fat, with or without concomitant increases in transaminases. Hepatic steatosis resulting from mipomersen use may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis. Transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), alkaline phosphatase, and total bilirubin should be measured prior to initial therapy. During the first year, measurement of ALT and AST should occur monthly. After the first year, these tests should be conducted every three months.

Lomitapide (Juxtapid) is contraindicated in patients who are pregnant.¹⁰⁷ Concomitant use of lomitapide with strong or moderate CYP3A4 inhibitors is also contraindicated.

Lomitapide is contraindicated in patients with moderate or severe hepatic impairment (Child Pugh category B or C) or active liver disease, including unexplained persistent abnormal liver function tests.¹⁰⁸ Lomitapide carries a boxed warning of the risk of hepatotoxicity resulting from increases in transaminases and hepatic steatosis. Although cases of hepatic dysfunction or failure have not been reported, both agents have the potential to induce steatohepatitis, which can ultimately lead to cirrhosis. Transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), alkaline phosphatase, and total bilirubin should be measured prior to initial therapy and prior to each increase in dose or on a monthly basis (whichever occurs first). After the first year of treatment, testing should continue at a minimum of every three months.

Caution should be used when lomitapide is taken with other medications that are known to be hepatotoxic (e.g., isotretinoin, amiodarone, high doses of acetaminophen (>4 g/day for ≥ three days) methotrexate, tetracyclines, and tamoxifen).¹⁰⁹ Due to the fact that alcohol may also increase levels of hepatic fat, patients should not consume more than one alcoholic beverage each day.

Due to lomitapide’s mechanism of action in the small intestine, the absorption of fat-soluble nutrients may be reduced.¹¹⁰ Patients taking lomitapide should receive daily supplements containing 400 IU vitamin E, 200 mg linoleic acid, 210 mg alpha-linolenic acid (ALA), 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA). Patients with chronic bowel or pancreatic disease may be at increased risk of deficiencies in these nutrients.

The use of mipomersen as an adjunct to LDL apheresis is not recommended.¹¹¹

Bile Acid Sequestrants

Bile acid sequestrants, cholestyramine, colestipol, and colesevelam (Welchol), are contraindicated in patients with dysbetalipoproteinemia and/or TG > 400 mg/dL.¹¹² Colesevelam is contraindicated in patients with bowel obstruction and in patients with hypertriglyceridemia-induced pancreatitis.¹¹³ Cholestyramine is contraindicated in complete biliary obstruction.¹¹⁴

Bile acid sequestrants may decrease the absorption of fat-soluble vitamins A, D, E, and K. Patients on oral vitamin supplementation should take their vitamins at least four hours prior to a bile acid sequestrant. Caution should be exercised when treating patients with a susceptibility to deficiencies of vitamin K (e.g., patients on warfarin, patients with malabsorption syndromes) or other fat-soluble vitamins. Because of its constipating effects, colesevelam is not recommended in patients with gastroparesis, other gastrointestinal motility disorders, and in those who have had major gastrointestinal tract surgery and who may be at risk for bowel obstruction.¹¹⁵

Phenylketonuric patients should be aware that colesevelam (Welchol) oral suspension contains 13.5 mg phenylalanine per 1.875 gram packet and 27 mg phenylalanine per 3.75 gram packet.

Cholesterol Absorption Inhibitors

The combination of ezetimibe (Zetia) and a statin is contraindicated in patients with acute liver disease or unexplained persistent elevations in serum transaminases.¹¹⁶

Fibric acids

Fenofibrate products (Antara, Fenoglide, Lofibra, Lipofen, Tricor, Triglide) and fenofibric acid (Fibricor, Trilipix) are contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis or persistent liver enzyme elevations or pre-existing gallbladder disease.^{117,118,119,120,121,122,123} Gemfibrozil is contraindicated in severe renal or hepatic impairment, including primary biliary cirrhosis, and combination therapy with repaglinide. Caution should be used when prescribing a statin and gemfibrozil together due to an increased risk of myositis and rhabdomyolysis. Concomitant gemfibrozil and simvastatin use is contraindicated.

The use of fibric acids is not recommended in nursing mothers, and it is considered a contraindication for use of Fibricor, Trilipix, and Fenoglide. Fenofibrates and fenofibric acid may cause venothromboembolic disease. Regular periodic monitoring of liver function should be performed for the duration of fenofibrate therapy, and therapy discontinued if enzyme levels persist above three times the upper limit of normal.

Fenofibrates and gemfibrozil can lead to cholelithiasis; therefore, these therapies should be discontinued if gallstones are found.

Reports of dramatic decreases in HDL-C levels (2 mg/dL) have occurred post-marketing in patients on fenofibrate therapy.¹²⁴ This can occur weeks to months after initiation of fenofibrate therapy. HDL-C levels return to normal once fibrate therapy is discontinued. Clinical significance is unknown, but it is recommended that HDL-C levels be monitored within the first few months of start of fibrate therapy.

Niacin (nicotinic acid)

Niacin ER (Niaspan) is contraindicated in patients with chronic liver disease, active peptic ulcer disease, or arterial bleeding. Caution should also be used when Niaspan is used in patients with unstable angina or in the acute phase of a myocardial infarction (MI), particularly when such patients are also receiving vasoactive drugs, such as nitrates, calcium channel blockers, or adrenergic blocking agents. Caution should be used with niacin in patients predisposed to gout.¹²⁵ Monitor liver function tests in all patients during therapy, at approximately six-month intervals, or when clinically indicated.¹²⁶ If transaminase levels are above three times the upper limit of normal, or clinical symptoms of hepatic dysfunction are present, niacin should be discontinued. Niacin treatment can increase fasting serum glucose levels. Frequent monitoring of blood glucose should be performed.

Due to an increased risk for myopathy in Chinese patients taking simvastatin 40 mg co-administered with lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing products, caution should be used when taking niacin ER/simvastatin (Simcor) in doses that exceed 1,000/20 mg daily to Chinese patients.¹²⁷ The cause of the increased risk of myopathy is unknown. It is also unknown whether the risk for myopathy with co-administration of simvastatin with lipid-modifying doses of niacin-containing products observed in Chinese patients applies to other Asian patients.

Omega-3 Fatty Acids

Omega-3-acid ethyl esters (Lovaza) and icosapent ethyl (Vascepa) should be used with caution in patients with a known history of sensitivity or allergy to fish and/or shellfish.^{128,129} In patients with hepatic impairment, monitor liver transaminases periodically during therapy. Lovaza may increase levels of LDL-C; therefore, periodic LDL-C monitoring during therapy is recommended.¹³⁰

A clinical study has reported a potential association between omega-3-acid ethyl esters (Lovaza) and increased recurrences of symptomatic atrial fibrillation or flutter in patients with paroxysmal or persistent atrial fibrillation, particularly within two to three months after initiation of therapy.¹³¹ This occurred in patients that had no substantial structural heart disease, were taking no anti-arrhythmic therapy (rate control permitted), and were in normal sinus rhythm at baseline.

Risk Evaluation and Mitigation Strategy (REMS)

Due to the risk of hepatotoxicity, lomitapide (Juxtapid) and mipomersen (Kynamro) are only available through a restricted program under the REMS.^{132,133} The goal of the REMS is to educate prescribers regarding the risk of hepatotoxicity, the need to monitor patients during therapy, and to restrict access to therapy with these agents to patients with a clinical or laboratory diagnosis consistent with HoFH. Only certified providers and pharmacies may prescribe and dispense lomitapide and mipomersen. Providers must complete a REMS program prescriber enrollment form, complete a prescriber training module, and submit a REMS prescription authorization form for each new prescription.

DRUG INTERACTIONS

Drug	Bile Acid Sequestrants	Cholesterol Absorption Inhibitor	Fibric Acids	Niacin	Omega-3 Fatty Acids	Statins
Apolipoprotein B Synthesis Inhibitors						
lomitapide (Juxtapid) ¹³⁴	administration with bile acid sequestrants can reduce lomitapide absorption	slight increase in ezetimibe exposure	decrease in fenofibrate, micronized exposure	increase in nicotinic acid exposure	--	increased risk of myopathy
mipomersen (Kynamro) ¹³⁵	--	--	--	--	--	--
Bile Acid Sequestrants						
cholestyramine, colestipol ^{136,137,138}		reduced bioavailability of ezetimibe	reduced bioavailability of fenofibrate or fenofibric acid	reduced absorption of niacin	--	--
colesevelam (WelChol) ^{139,140}		reduced bioavailability of ezetimibe	reduced bioavailability of fenofibrate or fenofibric acid	--	--	--
Cholesterol Absorption Inhibitors						
ezetimibe (Zetia) ¹⁴¹	reduced bioavailability of ezetimibe		increased ezetimibe concentration with risk of cholelithiasis	--	--	--
Fibric Acids						
fenofibrate (Antara, Fenoglide, Lipofen, Lofibra, Tricor, Triglide) ^{142,143,144,145,146,147}	reduced bioavailability of fenofibrate	increased ezetimibe concentration with risk of cholelithiasis		--	--	increased risk of myopathy and rhabdomyolysis
fenofibric acid (Fibricor) ¹⁴⁸	reduced bioavailability of fenofibric acid	increased ezetimibe concentration		--	--	increased risk of myopathy and rhabdomyolysis
fenofibric acid (Trilipix) ¹⁴⁹	reduced bioavailability of fenofibric acid	increased ezetimibe concentration		--	--	increased risk of myopathy and rhabdomyolysis
gemfibrozil ¹⁵⁰	reduced bioavailability of gemfibrozil when given at exact same time as colestipol	increased ezetimibe concentration with risk of cholelithiasis		--	--	increased risk of myopathy and rhabdomyolysis

Drug Interactions (continued)

Drug	Bile Acid Sequestrants	Cholesterol Absorption Inhibitor	Fibric Acids	Niacin	Omega-3 Fatty Acids	Statins
Niacin						
niacin ER (Niaspan) ¹⁵¹	administration with cholestyramine or colestipol reduces absorption of niacin	--	--		--	increased risk of myopathy
niacin IR (Niacor) ¹⁵²	--	--	--		--	increased risk of myopathy
Omega-3 Fatty Acids						
icosapent ethyl (Vascepa®) ¹⁵³	--	--	--	--		--
omega-3-acid ethyl esters (Lovaza) ¹⁵⁴	--	--	--	--		--

Other Drugs**Apolipoprotein B Synthesis Inhibitors^{155,156}****lomitapide (Juxtapid)**

CYP3A4 inhibitors – Concomitant use of strong CYP3A4 inhibitors (boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, **tipranavir/ritonavir**) and moderate CYP3A4 inhibitors (ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, verapamil) with lomitapide can significantly increase lomitapide exposure and are contraindicated. Lomitapide dose should not exceed 30 mg daily when used with weak CYP3A4 inhibitors (alprazolam, amiodarone, amlodipine, atorvastatin, cimetidine, cyclosporine, fluoxetine, ginkgo, oral contraceptives, ranitidine, ticagrelor).

Warfarin – Lomitapide increases plasma concentrations of warfarin. Monitor INR appropriately, particularly after lomitapide dosage change.

Simvastatin and lovastatin – Lomitapide increases simvastatin exposure. Reduce simvastatin dose by 50 percent when initiating lomitapide.¹⁵⁷ Simvastatin dose should not exceed 20 mg daily or 40 mg daily for patients who have been tolerant to simvastatin 80 mg daily for at least one year. Although not studied, since metabolizing enzymes are similar for lovastatin and simvastatin, lovastatin dose reduction should be considered with concomitant use of lomitapide.

P-glycoprotein Substrates (P-gp) – Co-administration of lomitapide with P-gp substrates (e.g., aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, fexofenadine, saxagliptin, sitagliptin) may increase the absorption of the P-gp substrate. Dose reduction of the P-gp substrate should be considered when used concomitantly with lomitapide.

mipomersen (Kynamro)

Mipomersen is not metabolized by CYP450 enzymes. No clinically-relevant pharmacokinetic interactions were reported between mipomersen and simvastatin, ezetimibe, or warfarin.

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.^{158,159} Concomitant use of mycophenolate with the bile acid sequestrants is not recommended.

Warfarin – Cholestyramine can reduce serum levels of warfarin by interfering with its enterohepatic circulation; dosage adjustments may be necessary.¹⁶⁰

Vitamins – 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.^{161,162}

Colesevelam reduces levels of cyclosporine, glimepiride, glipizide, glyburide, levothyroxine, olmesartan, and oral contraceptives containing ethinyl estradiol and norethindrone.¹⁶³ These agents should be administered at least four hours prior to colesevelam. Colesevelam increases the exposure of extended-release metformin. Colesevelam may also interact with concomitant therapy with phenytoin, warfarin, or other narrow therapeutic index drugs. Colesevelam can increase TG in combination with insulin or sulfonylureas.¹⁶⁴

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.¹⁶⁵

Cholesterol Absorption Inhibitor – ezetimibe (Zetia)

Cyclosporine – Using cyclosporine and ezetimibe together may result in increased plasma levels of both drugs; the mechanism of this interaction is unknown.¹⁶⁶

Fibric Acids – fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide), fenofibric acid (Fibricor, Trilipix), and gemfibrozil

Warfarin – Concomitant administration of fibric acids and warfarin increases the INR and the risk of bleeding.^{167,168,169,170,171}

Cyclosporine – Concomitant use of cyclosporine and fenofibrate or fenofibric acid (Fibricor, Trilipix) may decrease renal function.^{172,173,174}

Oral hypoglycemics – The concurrent use of gemfibrozil with glyburide (Diabeta[®], Glynase[®]), pioglitazone (Actos[®]) or rosiglitazone (Avandia[®]) may result in enhanced hypoglycemic effect.^{175,176,177,178} The use of gemfibrozil with repaglinide (Prandin[®]) is contraindicated due to a significant increase in serum concentrations of the oral hypoglycemic.¹⁷⁹

Colchicine – Myopathy, including rhabdomyolysis, has been reported with concurrent use of fenofibrate or gemfibrozil with colchicine. Use caution when prescribing both agents.^{180,181}

Statins – The concomitant administration of gemfibrozil with simvastatin is contraindicated.¹⁸²

Niacin – niacin IR and ER (Niacor and Niaspan)

Warfarin – Caution should be observed when niacin is administered concomitantly with anticoagulants. Both Niacin and Niaspan have been associated with small but statistically significant increases (mean four percent) in prothrombin time (PT).¹⁸³ Monitor INR periodically.

Lovastatin and simvastatin – Combination therapy with Niaspan and lovastatin or simvastatin should not exceed doses of 2,000 mg Niaspan and 40 mg lovastatin or simvastatin daily.¹⁸⁴

Omega-3-Fatty Acids – omega-3-acid-ethyl esters (Lovaza), icosapent ethyl (Vascepa)

Anticoagulants - Omega-3-acids may prolong bleeding time. Patients taking Lovaza or Vascepa and an anticoagulant or other drug affecting coagulation should be monitored periodically.^{185,186}

ADVERSE EFFECTS

Drug	Abd. Pain	Back pain	Headache	Abnormal LFTs	Constipation	Dyspepsia
Apolipoprotein B Synthesis Inhibitors						
lomitapide (Juxtapid) ¹⁸⁷	34	14	10	21	21	38
mipomersen (Kynamro) ¹⁸⁸	3 (1)	nr	12 (9)	12 (1)	nr	nr
Bile Acid Sequestrants						
cholestyramine ¹⁸⁹	reported	nr	nr	nr	common	reported
colesevelam (Welchol) ¹⁹⁰	5 (5)	3 (6)	3.9 (3.1)	nr	11 (7)	8 (3)
colestipol ¹⁹¹	reported	reported	reported	reported	common	reported
Cholesterol Absorption Inhibitors						
ezetimibe (Zetia) ¹⁹²	3 (2.8)	4 (4)	nr	nr	nr	nr
Fibric Acids						
fenofibrate (Antara, Fenoglide, Lofibra, Lipofen, Tricor, Triglide) ^{193,194,195,196,197}	4.6 (4.4)	3.4 (2.5)	3.2 (2.7)	2-8 (1.4)	2.1 (1.4)	reported
fenofibric acid (Fibracor) ¹⁹⁸	4.6 (4.4)	3.4 (2.5)	3.2 (2.7)	7.5 (1.4)	2.1 (1.4)	3.7
fenofibric acid (Trilipix) ¹⁹⁹	4.6 (4.4)	3.4 (2.5)	3.2 (2.7)	7.5 (1.4)	2.1 (1.4)	3.7
gemfibrozil ²⁰⁰	9.8 (5.6)	nr	1.2 (1.1)	1	1.4 (1.3)	19.6 (11.9)
Niacin						
niacin ER (Niaspan) ²⁰¹	2-5 (3)	nr	8-11 (15)	reported	nr	2-5 (8)
niacin IR (Niacor) ²⁰²	nr	nr	reported	reported	nr	reported
Omega-3 Fatty Acids						
icosapent ethyl (Vascepa®) ²⁰³	nr	nr	nr	nr	nr	nr
omega-3-acid ethyl esters (Lovaza) ²⁰⁴	nr	nr	nr	reported	reported	3.1 (2.6)

nr= not reported LFTs = liver function tests

Adverse effects are indicated as percentage occurrence. Adverse effects data are compiled from package inserts and cannot be considered comparative or all inclusive. Incidences for the placebo group are indicated in parentheses.

Apolipoprotein B Synthesis Inhibitors: Other commonly reported adverse reactions for lomitapide were gastrointestinal in nature, reported by 93 percent of patients on lomitapide in clinical trials.²⁰⁵ Other adverse effects reported include influenza (21 percent), decreased weight (24 percent), chest pain (24 percent), fatigue (17 percent), and pharyngolaryngeal pain (14 percent).

Other commonly reported adverse reaction reported for mipomersen were injection site reactions (84 percent), flu-like symptoms (30 percent), and nausea (14 percent).²⁰⁶

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.²⁰⁷ Colesevelam can increase TG in combination with insulin or sulfonylureas.²⁰⁸ In the diabetes trials, the overall incidence of hypoglycemia was three percent in patients on colesevelam versus 2.3 percent in placebo-treated patients.²⁰⁹

Cholesterol Absorption Inhibitor: Cases of myopathy and rhabdomyolysis have been reported in patients treated with ezetimibe (Zetia) co-administered with a statin and with ezetimibe administered alone. Risk for skeletal muscle toxicity increases with higher doses of statin, advanced age (>65), hypothyroidism, renal impairment, and depending on the statin used, concomitant use of other drugs.²¹⁰

Fibric acids: Fibric acids may cause cholelithiasis. Fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide) and fenofibric acid (Fibricor, Trilipix) may also cause myositis, myopathy, and rhabdomyolysis; this risk may be further increased when given concomitantly with statins.^{211,212,213,214}

Fenofibrate use is associated with reversible elevations in serum creatinine. The clinical significance of this is unknown.²¹⁵ Renal function should be monitored in patients with or at risk for renal insufficiency, such as the elderly and patients with diabetes. In a study that assessed renal outcomes in elderly adults within 90 days of a new fibrate prescription, patients who received fibrates (n=19,072) were more likely to be hospitalized for an increase in serum creatinine level (adjusted odds ratio, 2.4 [95% CI, 1.7 to 3.3]) and were more likely to consult a nephrologist (absolute risk difference, 0.15% [CI, 0.01% to 0.29%]; adjusted odds ratio, 1.3 [CI, 1.0 to 1.6]), than patients who received ezetimibe (n=61,831).²¹⁶ There were no differences between groups in the risk for all-cause mortality or receiving dialysis for severe acute kidney injury. In a subpopulation of 1,110 patients (fibrates, n=220; ezetimibe, n=890), 9.1 percent of fibrate users and 0.3 percent of ezetimibe users had an increase in serum creatinine level of at least 50 percent. Risks were greater among fibrate users with chronic kidney disease.

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.^{217,218}

Omega-3-acids: Arthralgia has been reported with icosapent ethyl (Vascepa) use.²¹⁹

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 regarding use in children for cholestyramine and colestipol.²²⁰ Pediatric patients have been reported to experience hyperchloremic metabolic acidosis or gastrointestinal obstruction with the use of cholestyramine.²²¹ Colesevelam (Welchol) is approved to reduce LDL-C in boys and postmenarchal girls, 10 to 17 years, with heterozygous familial hypercholesterolemia (HeFH) as monotherapy or in combination with a statin. Colesevelam has not been studied in children younger than 10 years of age. 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.²²² Niacin has been used safely for the treatment of nutritional deficiencies; however, safety and effectiveness of niacin for the treatment of hyperlipidemias have not been established in pediatrics.²²³ Safety and efficacy of fibric acids (fenofibrate, fenofibric acid, and gemfibrozil), lomitapide (Juxtapid), mipomersen (Kynamro), omega-3-acid ethyl esters (Lovaza) and icosapent ethyl (Vascepa) have not been established in pediatrics.²²⁴

In a multi-center, double-blind, controlled study followed by an open-label phase, 142 boys and 106 postmenarchal girls, 10 to 17 years of age, with HeFH were randomized to receive either ezetimibe co-administered with simvastatin or simvastatin monotherapy.²²⁵ The mean baseline LDL-C value was 225 mg/dL in the combination group compared to 219 mg/dL in the monotherapy group. The patients received combination of ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) or simvastatin monotherapy (10 mg, 20 mg, or 40 mg) for six weeks, co-administered ezetimibe/simvastatin 10/40 mg or simvastatin 40 mg monotherapy for the next 27 weeks, and open-label co-administered ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) for 20 weeks thereafter. At week six, the mean percent difference between treatment groups for LDL-C was -15 percent (95% CI, -18 to -12). Results at week 33 were consistent with those at week six.

The safety and efficacy of colesevelam in pediatric patients were evaluated in an eight-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter, study followed by an open-label phase, in 194 boys and postmenarchal girls 10 to 17 years of age with HeFH, taking a stable dose of an FDA-approved statin (with LDL-C >130 mg/dL) (24 percent of patients) or naïve to lipid-lowering therapy (with LDL-C >160 mg/dL) (76 percent of patients).^{226,227} The mean baseline LDL-C was approximately 199 mg/dL. During the double-blind treatment period, patients were assigned randomly to treatment: colesevelam 3.8 g/day (n=64), colesevelam 1.9 g/day (n=65), or placebo (n=65). A total of 186 patients completed the double-blind treatment period. After eight weeks of treatment, colesevelam 3.8 g/day significantly decreased plasma levels of LDL-C (-13 percent), TC (-7 percent), and significantly increased HDL-C (+6 percent) compared to placebo ($p \leq 0.05$ for all comparisons). There was a non-significant increase in TG (+5 percent) versus placebo. During the open-label treatment period, patients were treated with colesevelam 3.8 g/day. A total of 173 patients completed 26 weeks of treatment. Results at week 26 were consistent with those at week eight.

Pregnancy

Cholestyramine and colesevelam (Welchol) are non-absorbable and therefore considered Pregnancy Category B. Mipomersen (Kynamro) is also Pregnancy Category B. Niacin is Pregnancy Category A for recommended daily allowance nutrient amounts; however, for the treatment of hyperlipidemia, niacin is considered Pregnancy Category C. Lomitapide (Juxtapid) is Pregnancy Category X, therefore contraindicated during pregnancy.²²⁸ Females of reproductive potential should have a negative pregnancy test before starting lomitapide therapy and should use effective contraception during therapy. Lomitapide dosage should not exceed 30 mg daily in women also taking oral contraceptives. If vomiting or diarrhea occurs while on lomitapide, hormone absorption may be reduced, and use of additional contraceptive methods is warranted. Females on lomitapide who become pregnant should stop therapy immediately and notify their healthcare provider. The remaining products in this class are Pregnancy Category C.

Gender

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial was a double-blind, placebo-controlled study that evaluated if fenofibrate reduced major cardiovascular (CV) events in patients with type 2 diabetes and gender differences in response.²²⁹ A total of 3,657 women and 6,138 men with type 2 diabetes and not on statin therapy received either fenofibrate 200 mg/day or placebo for five years. LDL-, HDL- and non-HDL cholesterol, and apolipoproteins (apo) A-1 and B improved in both men and women (all $p < 0.001$). A greater reduction was seen in women for all measures, except apo A-1. Fenofibrate reduced total CV outcomes (CV death, fatal and non-fatal stroke, and carotid and coronary revascularization) by 30 percent in women ($p = 0.008$) and 13 percent in men ($p = 0.07$).

Hepatic/Renal Impairment

Fenofibrates (Antara, Fenoglide, Lofibra, Lipofen, Tricor, Triglide) and fenofibric acid (Fibricor, Trilipix) should be dose adjusted in renal impairment, unless severe when use is contraindicated. Their use has not been evaluated in hepatic impairment, but is contraindicated in hepatic dysfunction including patients with primary biliary cirrhosis or unexplained persistent liver function abnormalities.^{230,231,232,233,234,235}

Ezetimibe is not recommended in moderate to severe hepatic impairment.

No dosage adjustment of ezetimibe is necessary with renal impairment. When ezetimibe is given with simvastatin in patients with moderate to severe renal impairment (estimated glomerular filtration rate < 60 mL/min/1.73 m²), doses of simvastatin exceeding 20 mg should be used cautiously and with close monitoring for myopathy.²³⁶

Niacin containing products should be used with caution in patients with renal impairment. Niacin-containing products should be used with caution in patients with a past history of liver disease and in patients who consume substantial quantities of alcohol. Active liver disease, unexplained transaminase elevations, and significant or unexplained hepatic dysfunction are contraindications to the use of niacin.

Mipomersen (Kynamro) is contraindicated in patients with moderate or severe hepatic impairment, or active liver disease, including unexplained persistent elevations of serum transaminases.²³⁷ The safety and efficacy of mipomersen has not been established in patients with known renal impairment or in patients undergoing renal dialysis. It is not recommended in patients with severe renal impairment, clinically significant proteinuria, or on renal dialysis.

Lomitapide (Juxtapid) is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C).²³⁸ Lomitapide exposure is significantly increased in patients with mild hepatic impairment (Child-Pugh A) or with end-stage renal disease receiving dialysis, therefore lomitapide dosage should not exceed 40 mg daily. Although not studied, it is possible that lomitapide exposure is increased in those patients with mild, moderate, or severe renal impairment, not on dialysis; therefore, caution should be used.

Monitor liver function (ALT, AST) in patients with hepatic impairment periodically during therapy with omega-3-acid ethyl esters (Lovaza) and icosapent ethyl (Vascepa).²³⁹

DOSAGES

Drug	Availability	Dose	Comments
Apolipoprotein B Synthesis Inhibitors			
lomitapide (Juxtapid) ²⁴⁰	5, 10, 20 mg capsules	Initiate with 5 mg daily. Titrate to 10 mg daily after ≥ 2 weeks, then 4-week intervals to 20 mg, 40 mg, 60 mg. Do not exceed 60 mg per day.	Swallow capsules whole Take with water and without food, at least two hours after the evening meal.
mipomersen (Kynamro) ²⁴¹	200 mg/1 mL solution in single-use vial and prefilled syringe	200 mg once weekly as a subcutaneous injection	Do not administer intramuscularly or intravenously. Administer dose on the same day each week; if a dose is missed, the dose should be given at least three days from the next weekly dose.
Bile Acid Sequestrants			
cholestyramine ²⁴²	powder	One to two packets or scoopfuls twice daily	Mix with two to six ounces of water or pulpy fruit (applesauce)
colesevelam (WelChol) ²⁴³	625 mg tablets 3,750 mg packet powder oral suspension	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 Oral suspension may be mixed with water, fruit juice, or diet soft drinks prior to ingestion
colestipol ²⁴⁴	1 g tablets	2 g once or twice daily	Increase by 2 g at one- to two-month intervals to a maximum of 16 g daily
	5 g/tsp granules	5-30 g daily	Increase daily dose by 5 g at one- to two-month intervals
Cholesterol Absorption Inhibitors			
ezetimibe (Zetia) ²⁴⁵	10 mg tablets	10 mg daily	Take with or without food

Dosages (continued)

Drug	Availability	Dose	Comments
Fibric Acids			
fenofibrate ²⁴⁶	67, 134, 200 mg capsules	67-200 mg daily	Must be taken with food
	54, 160 mg tablets	54-160 mg daily	Must be taken with food
fenofibrate (Antara) ²⁴⁷	30, 43, 90, 130 mg capsules	30-130 mg daily	Take without regard to meals
fenofibrate (Fenoglide) ²⁴⁸	40, 120 mg tablets	40-120 mg daily	Take with food
fenofibrate (Lipofen) ²⁴⁹	50, 150 mg capsules	50-150 mg daily	Take with food
fenofibrate (Tricor) ²⁵⁰	48, 145 mg tablets	48-145 mg daily	Take without regard to meals
fenofibrate (Triglide) ²⁵¹	50, 160 mg tablets	50-160 mg daily	Take without regard to meals
fenofibric acid (Fibricor) ²⁵²	35, 105 mg tablets	35-105 mg daily	Take without regard to meals
fenofibric acid (Trilipix) ²⁵³	45, 135 mg delayed release capsules	45-135 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) ²⁵⁴	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) ²⁵⁵	500 mg tablets	1-2 g twice or three times daily	May pre-administer aspirin to reduce flushing Take at bedtime after low-fat snack
Omega-3 Fatty Acids			
icosapent ethyl (Vascepa®) ²⁵⁶	1 g capsules	2 g twice daily	Take with food Swallow capsules whole
omega-3-acid ethyl esters (Lovaza) ²⁵⁷	1 g capsules	4 g daily in one or two divided doses	Take with meal(s) Swallow capsules whole

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

Patients with end-stage renal disease on dialysis or with baseline mild hepatic impairment should not exceed lomitapide 40 mg daily.

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.

Antara 43 mg and 130 mg capsules will be discontinued and replaced by Antara 30 mg and 90 mg capsules. Dispensing of the 43 mg and 130 mg capsules can be continued until existing stock is exhausted, but not after the end of 2014 when all expiration dates of existing stock will be reached.

CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed 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, clinical outcomes have not been established for colesevelam (Welchol), colestipol, ezetimibe (Zetia), fenofibrates, lomitapide (Juxtapid), mipomersen (Kynamro), niacin ER (Niaspan), prescription strength omega-3-acid ethyl esters (Lovaza), or icosapent ethyl (Vascepa).^{258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268}

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.²⁶⁹ 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 C-reactive protein (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 total-C, 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 (Zetia) and fenofibrate

A randomized, double-blind, placebo-controlled, parallel-group, multicenter, 12-week study of 625 patients with mixed hyperlipidemia compared fenofibrate 160 mg/day, ezetimibe 10 mg/day, or the combination of fenofibrate 160 mg/day and ezetimibe 10 mg/day.²⁷⁰ At baseline and at 12 weeks, the Vertical Auto Profile II method was used to measure the cholesterol associated with two very low-density lipoprotein (VLDL) subfractions (VLDL-C1 + 2 and VLDL-C3), intermediate-density lipoproteins (IDL-C), and 4 LDL-C subfractions (LDL-C1 through LDL-C4, from most buoyant to most dense), lipoprotein (Lp) (a), and 2 HDL-C subfractions (HDL-C2 and HDL-C3). The LDL-C particle size was determined using segmented gradient gel electrophoresis. Fenofibrate reduced cholesterol mass within VLDL, IDL, and dense LDL-C (primarily LDL-C4) subfractions, and increased cholesterol mass within the more buoyant LDL-C2 subfraction, consistent with a shift to a more buoyant LDL-C peak

particle size. Ezetimibe reduced cholesterol mass within all of the apolipoprotein B-containing particles (e.g., VLDL-C, IDL-C, and LDL-C) but did not lead to a shift in the LDL-C particle size distribution profile. Co-administration of fenofibrate and ezetimibe promoted more pronounced reductions in VLDL-C, IDL-C, and LDL-C, and a preferential decrease in dense LDL-C subfractions. Fenofibrate and combination therapy promoted similar increases in HDL-C2 and HDL-C3. ezetimibe (Zetia) and simvastatin

In the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial, a randomized, multicenter, placebo-controlled study, found that intensive LDL-C lowering with the combination of ezetimibe/simvastatin 10/40 mg daily in 1,873 patients with mild to moderate aortic stenosis did not reduce the primary endpoint of major CV events.²⁷¹ Ezetimibe/simvastatin did reduce the secondary endpoint of reduction of atherosclerotic events.

SHARP: In a double-dummy study, patients (n=9,438) with advanced CKD with no known history of MI or coronary revascularization were randomized in a ratio of 4:4:1 to daily ezetimibe 10 mg plus simvastatin 20 mg, matching placebo, or simvastatin 20 mg (with the latter arm re-randomized at one year to ezetimibe 10 mg plus simvastatin 20 mg versus placebo).²⁷² A total of 3,056 patients in the study were on dialysis. After a median follow-up of 4.9 years, patients that received ezetimibe/simvastatin combination experienced a 17 percent reduction in major atherosclerotic events (defined as the combination of MI, coronary death, ischemic stroke, or any revascularization procedure) compared to placebo (p=0.0022). Compared with placebo, ezetimibe/simvastatin resulted in average LDL-C differences of 43 mg/dL at one year and 33 mg/dL at 2.5 years. Ezetimibe/simvastatin was not associated with any excess of myopathy, hepatic toxicity, or biliary complications compared to placebo, or compared to simvastatin alone (at one year). There was no difference in incidence of cancer between groups (9.5 percent for each).

ezetimibe (Zetia) and rosuvastatin (Crestor)

The ACTE study, a six-week, randomized, double-blind, parallel-group, trial of 440 patients at moderately high/high risk of coronary heart disease with LDL-C levels higher than the NCEP ATP III (<100 mg/dL for moderately high/high-risk subjects without atherosclerotic vascular disease or <70 mg/dl for high-risk subjects with atherosclerotic vascular disease) recommendations compared ezetimibe (10 mg) added to stable rosuvastatin therapy and up-titration of rosuvastatin from 5 to 10 mg or from 10 to 20 mg.²⁷³ The study demonstrated that ezetimibe added to stable rosuvastatin 5 mg or 10 mg reduced LDL-C by 21 percent, while doubling rosuvastatin to 10 mg or 20 mg reduced LDL-C by 5.7 percent (p<0.001). Compared to rosuvastatin up-titration, ezetimibe add-on achieved significantly greater attainment of LDL-C of <70 or <100 mg/dL (59.4 percent versus 30.9 percent; p<0.001), and <70 mg/dL in all subjects (43.8 percent versus 17.5 percent; p<0.001); produced significantly greater reductions in total cholesterol, non-HDL-C, and apolipoprotein B (p<0.001). Adverse experiences were comparable among the groups.

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.²⁷⁴ The primary endpoint was LDL-C reduction of ezetimibe/simvastatin plus fenofibrate versus fenofibrate monotherapy. LDL-C was reduced significantly with ezetimibe/simvastatin plus fenofibrate compared with fenofibrate (-45.8 percent versus -15.7 percent, p<0.05) but not compared to ezetimibe/simvastatin (-47.1 percent,

p>0.2). HDL-C and apo A-I were increased with ezetimibe/simvastatin plus fenofibrate (18.7 percent and 11.1 percent, respectively) compared with ezetimibe/simvastatin (9.3 percent and 6.6 percent, respectively) or placebo (1.1 percent and 1.6 percent, respectively) but not compared to fenofibrate (18.2 percent and 10.8 percent, respectively) (p values for all comparisons were p<0.01 except for ezetimibe versus placebo which was p<0.2). TG, non-HDL-C and apo-B were significantly reduced with ezetimibe/simvastatin plus fenofibrate (-50 percent, -50.5 percent, and -44.7 percent, respectively) versus all other treatment arms (p<0.01 for all comparisons). Treatments were well-tolerated.

ezetimibe/simvastatin (Vytorin) and niacin ER (Niaspan)

A 24-week, double-blind, multicenter study randomized 1,220 patients with type IIa or IIb hyperlipidemia to the combination of ezetimibe/simvastatin 10/20 mg/day and niacin ER titrated to 2 grams/day, or niacin ER titrated to 2 grams/day, or ezetimibe/simvastatin 10/20 mg/day.²⁷⁵ Combination therapy with ezetimibe/simvastatin and niacin ER resulted in significantly greater reductions in LDL-C, non-HDL-C, TG, apolipoprotein B, and lipid/lipoprotein ratios, compared with either agent alone (p<0.001). The combination increased levels of apolipoprotein A-I and HDL-C significantly more than ezetimibe/simvastatin (p<0.001). The combination reduced high-sensitivity C-reactive protein (hs-CRP) levels significantly more than niacin ER (p=0.005). Niacin ER, as well as the ezetimibe/simvastatin plus niacin ER, groups showed significantly greater study discontinuation rates, primarily due to flushing, 25 percent and 23.3 percent, respectively, compared with ezetimibe/simvastatin (9.6 percent, p<0.001). Incidences of other clinical and laboratory adverse events related to the liver, muscle, and gastrointestinal systems were similar for all groups.

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.^{276,277} A total of 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 endpoint 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 endpoint 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 endpoints because of a greater number of violent and accidental deaths in the cholestyramine group.

cholestyramine, gemfibrozil, and niacin IR (Niacor)

A randomized, double-blind, placebo-controlled trial assessed the effects of gemfibrozil, niacin immediate-release and cholestyramine on the composite outcome of MI, transient ischemic attack or stroke, cardiovascular death, cardiovascular procedures, or hospitalization for angina.²⁷⁸ A total of 143 military retirees with low HDL-C (mean 34 mg/dL) and documented CAD 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 metformin, sulfonylurea, and insulin

Efficacy of colesevelam in type 2 diabetes mellitus was evaluated in three double-blind, placebo-controlled trials in combination with metformin, sulfonylurea, or insulin.²⁷⁹ A total of 1,018 patients with baseline HbA1c of 7.5 to 9.5 percent took colesevelam 3.75 g/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 26-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluated the effects of colesevelam 3.75 g daily in 316 patients with inadequately controlled type 2 diabetes mellitus (baseline HbA1c of 8.1 percent), who were receiving metformin monotherapy or metformin combined with additional oral anti-diabetes drugs.²⁸⁰ Colesevelam lowered the mean HbA1c level by -0.54 percent compared with placebo at week 26 ($p < 0.001$). Similar results were observed in the metformin monotherapy (-0.47 percent, $p = 0.002$) and combination therapy cohorts (-0.62 percent, $p < 0.001$). Colesevelam also significantly reduced fasting plasma glucose (-13.9 mg/dL, $p = 0.01$), total-C (-7.2 percent, $p < 0.001$), LDL-C (-15.9 percent, $p < 0.001$), and apo B (-7.9 percent, $p < 0.001$). TG, HDL-C, and apolipoprotein A-I levels were not statistically significantly increased.

colesevelam (Welchol) and insulin

A 16-week, randomized, double-blind, placebo-controlled, parallel group, multicenter study of 287 patients with type 2 diabetes mellitus evaluated the efficacy and safety of colesevelam 3.75 g/day in patients already receiving insulin alone or in combination with oral antidiabetic agents with inadequate glycemic control (mean baseline HbA1c 8.3 percent).²⁸¹ The mean (SE) change in HbA1c was -0.41 percent (0.07 percent) versus 0.09 percent (0.07 percent) for colesevelam versus placebo, respectively. The treatment difference was 0.5 percent (0.09 percent) (95% CI, -0.68 to -0.32, $p < 0.001$). There was a 12.8 percent reduction in LDL-C levels in the colesevelam group versus placebo ($p < 0.001$). Median TG levels increased significantly in the colesevelam group.

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.²⁸² 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, 0.8 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, 0.9 to 1.57, $p=0.22$) increase in total mortality and CHD 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.

The SAFARI study was a randomized, double-blind, active-controlled, multicenter, 18-week (six-week diet and placebo run-in period) study of 618 patients with mixed dyslipidemia.²⁸³ Simvastatin 20 mg daily and fenofibrate 160 mg daily was compared to simvastatin monotherapy 20 mg daily to evaluate efficacy and safety. From baseline to week 12, median TG levels decreased 43 percent in the combination group and 20.1 percent in the simvastatin monotherapy group (treatment difference -23.6 percent, $p<0.001$). Mean LDL-C decreased 31.2 percent and 25.8 percent (treatment difference -5.4 percent, $p<0.001$), and HDL-C increased 18.6 percent and 9.7 percent (treatment difference 8.8 percent, $p<0.001$) in the combination group versus monotherapy group, respectively. No drug-related serious adverse experiences were observed. No cases of clinical myopathy or severe abnormalities in liver function were reported.

The lipid arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was a randomized, double-blind, multicenter study of 5,518 patients with type 2 diabetes.²⁸⁴ After one month of open-label simvastatin, patients were randomized to simvastatin plus fenofibrate 160 mg daily or simvastatin plus placebo. The mean age was 62 years, 31 percent were women, 37 percent had a prior CV event, mean systolic blood pressure was 134 mm Hg, mean HbA1c was 8.1 percent, and about 60 percent were taking a statin prior to enrollment. In the fenofibrate group, LDL-C decreased from 100 to 81 mg/dL, HDL-C increased from 38 to 41.2 mg/dL, and TG decreased from 189 to 147 mg/dL. In the placebo group, LDL-C decreased from 101 to 80 mg/dL ($p=0.16$ between groups), HDL-C increased from 38 to 40.5 mg/dL ($p=0.01$ between groups), and TG decreased from 186 to 170 mg/dL ($p<0.001$ between groups). After a mean follow-up of 4.7 years, the annual rate of the primary

outcome (first occurrence of nonfatal MI, nonfatal stroke, or death from CV causes) was 2.2 percent with fenofibrate versus 2.4 percent with placebo (HR in the fenofibrate group, 0.92; 95% CI, 0.79 to 1.08; $p=0.32$). There were also no significant differences between the two study groups with respect to any secondary outcome. Hazard ratios for the secondary outcomes, including the individual components of the primary outcome, ranged from 0.82 to 1.17 ($p \geq 0.1$ for all comparisons). Annual rates of death were 1.5 percent in the fenofibrate group and 1.6 percent in the placebo group (HR, 0.91; 95% CI, 0.75 to 1.1; $p=0.33$). In subgroup analysis, men appeared to benefit, while women appeared to be harmed from fenofibrate therapy (p for interaction= 0.01). Also, a high TG (≥ 203 mg/dL)/low HDL-C (≤ 35 mg/dL) profile appeared to non-significantly benefit (p for interaction= 0.057) the fenofibrate group versus placebo. Study drug was discontinued due to a decrease in estimated glomerular filtration rate in 2.4 percent in the fenofibrate group and 1.1 percent of placebo. Serum creatinine levels increased in the fenofibrate group soon after randomization but then remained constant, compared with placebo. There was no evidence of increased risk of myositis or rhabdomyolysis in the fenofibrate/simvastatin group. The trial was sponsored by the National Heart, Lung, and Blood Institute (NHLBI).

fenofibric acid (Trilipix)

In three 12-week, randomized, double-blind, multicenter studies of 2,698 patients with mixed dyslipidemia, efficacy and safety of fenofibric acid in combination with statins to each single agent were reviewed.²⁸⁵ Moderate doses of rosuvastatin (Crestor®) 10 mg or 20 mg, simvastatin 20 mg or 40 mg, or atorvastatin (Lipitor®) 20 mg or 40 mg were co-administered with 135 mg of fenofibric acid. In the pooled analysis, combination therapy with a low-dose and a moderate-dose statin significantly increased HDL-C (18.1 percent and 17.5 percent, respectively) and decreased TG (43.9 percent and 42 percent, respectively) compared to the corresponding dose of statin monotherapy (7.4 percent and 8.7 percent for HDL-C, -16.8 percent and -23.7 percent for TG; $p < 0.001$ for all comparisons). In addition, both doses of combination therapy resulted in mean percent decreases (33.1 percent and 34.6 percent, respectively) in LDL-C that is significantly greater than fenofibric acid monotherapy (5.1 percent, $p < 0.001$).

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.^{286,287} 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.²⁸⁸ At the conclusion of the study, all participants were given the opportunity to receive gemfibrozil for an additional 3.5 years.²⁸⁹ 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.²⁹⁰ 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 endpoint, 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 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 ($p=0.05$).²⁹¹

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.²⁹² 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 was six percent higher, and TG was 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; $p=0.02$) and in patients with diabetes (32 percent relative risk reduction; $p=0.004$).^{293,294}

icosapent ethyl (Vascepa)

MARINE: In a randomized, double-blind, multicenter, placebo-controlled study, 229 patients with severe hypertriglyceridemia (baseline triglyceride [TG] levels 500 to 2,000 mg/dL) with or without background statin therapy were randomized to icosapent ethyl 4 grams daily, icosapent ethyl 2 grams daily, or placebo for 12 weeks.²⁹⁵ Median TG level was 680 mg/dL, 657 mg/dL and 703 mg/dL in the 4-gram, 2-gram and placebo groups, respectively. The primary endpoint was placebo-corrected median percent change in TG from baseline to week 12. Icosapent ethyl resulted in a 33.1 percent reduction in the 4-gram group ($p<0.001$ versus placebo) and a 19.7 percent reduction in the 2-gram group ($p=0.0051$). Low-density lipoprotein (LDL-C) was not significantly increased in either group. The study found that patients with a higher baseline TG level demonstrated larger reductions. In those with a baseline TG >750 mg/dL, the 4 gram dosage resulted in a 45.4 percent reduction ($n=28$, $p=0.0001$) and the 2 gram dosage resulted in a 32.9 percent reduction ($n=28$, $p=0.0016$). Patients who were on concomitant statin therapy had a larger decrease in TG compared to those not treated with statins (4-gram group on statins 65 percent reduction, $p=0.0001$; 2-gram group on statins 40.7 percent reduction, $p=0.0276$ compared to 4-gram group no statin 25.8 percent reduction, $p=0.0002$; 2-gram group no statins 16.4 percent, $p=0.036$). Safety profile of icosapent ethyl was similar to placebo.

ANCHOR: The efficacy and safety of icosapent ethyl were evaluated in a phase 3, double-blind, 12-week trial in high-risk statin-treated patients with residually high TG levels (≥ 200 and <500 mg/dL) despite LDL-C control (≥ 40 and <100 mg/dL).²⁹⁶ Patients ($n=702$) on a stable diet were randomized to icosapent ethyl 4 or 2 g per day or placebo. The primary endpoint was median percent change in TG levels from baseline versus placebo. Both doses of icosapent ethyl significantly decreased TG levels by 21.5 percent ($p<0.0001$) and 10.1 percent ($p=0.0005$), respectively, and non-HDL-C by 13.6 percent ($p<0.0001$) and 5.5 percent ($p=0.0054$), respectively. Icosapent ethyl 4 g/day produced greater TG and

non-HDL cholesterol decreases in patients with higher-efficacy statin regimens and greater TG decreases in patients with higher baseline TG levels. Icosapent ethyl 4 g/day also decreased LDL-C, apolipoprotein B, total cholesterol, VLDL-C, lipoprotein-associated phospholipase A(2), and high-sensitivity C-reactive protein compared to placebo ($p < 0.001$ for all comparisons). Icosapent ethyl was generally well tolerated, with safety profiles similar to placebo.

lomitapide (Juxtapid)

The safety and effectiveness of lomitapide (as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available) were evaluated in a single-arm, open-label trial involving 29 adults with HoFH.²⁹⁷ Current lipid lowering therapy was maintained. Patients were counseled to follow a low-fat diet (<20 percent calories from fat) and to take dietary supplements. Sixty-two percent of patients were receiving apheresis. Lomitapide dose was titrated based on safety and tolerability from 5 mg to a maximum of 60 mg daily. The primary endpoint was mean percent change in LDL-C measured at week 26. Patients remained on lomitapide for an additional year to assess long-term safety. At week 26 LDL-C was reduced by 50 percent (95% CI -62 to -39; $p < 0.0001$) from baseline; LDL-C levels remained reduced by 44 percent (95% CI -57 to -31; $p < 0.0001$) at week 56 and 38 percent (-52 to -24; $p < 0.0001$) at week 78. The most common adverse events reported were gastrointestinal symptoms. Four patients had aminotransaminase levels of more than five times the upper limit of normal, which resolved after dose reduction or temporary interruption of lomitapide.

mipomersen (Kynamro)

A 26-week, double-blind, phase 3 study in patients aged 12 years and older with clinical diagnosis or genetic confirmation of homozygous familial hypercholesterolemia, who were already receiving the maximum tolerated dose of a lipid-lowering drug, were randomly assigned to mipomersen ($n=34$) 200 mg subcutaneously weekly or placebo ($n=17$).²⁹⁸ The mean age was 32 years. The primary endpoint was percentage change in LDL-C from baseline. The mean percent reduction of LDL-C was significantly greater with mipomersen (24.7 percent, 95% CI -31.6 to -17.7) than placebo (3.3 percent, -12.1 to +5.5; $p=0.0003$). The most common adverse events were injection-site reactions, reported in 76 percent of patients in mipomersen group compared to 24 percent in the placebo group. Twelve percent of patients on mipomersen and none on placebo had increases in alanine aminotransferase levels of three times or more the upper limit of normal.

niacin IR

The Coronary Drug Project was a nine-year, double-blind study conducted by the National Heart, Lung, and Blood Institute (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 MI.²⁹⁹ 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; $p=0.0004$).

niacin ER (Niaspan)

In a double-blind, randomized, placebo-controlled trial, niacin ER 1,000 mg daily (n=87) or placebo (n=80) were added to statin therapy in 167 patients with CAD and low HDL-C (< 45 mg/dL).³⁰⁰ 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); however, niacin significantly reduced the rate of IMT progression in patients without insulin resistance (p=0.026). 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).^{301,302} Patients were treated with eight weeks of open-label simvastatin 40 mg daily prior to randomization to reduce 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).

A 16-week study randomized patients with elevated non-HDL-C >160 mg/dL and TG ≥250 mg/dL, and ≤599 mg/dL levels to double-blind treatment with prescription omega-3-acid ethyl esters, 4 g/day, or placebo.³⁰³ Patients also received escalating dosages of open-label atorvastatin (weeks 0-8, 10 mg/day; weeks 9-12, 20 mg/day; weeks 13-16, 40 mg/day). Omega-3-acid ethyl esters plus atorvastatin 10, 20, and 40 mg/day reduced median non-HDL-C levels by 40.2 percent versus 33.7 percent (p<0.001), 46.9 percent versus 39 percent (p<0.001), and 50.4 percent versus 46.3 percent (p<0.001) compared with placebo plus the same doses of atorvastatin at the end of 8, 12, and 16 weeks, respectively. Omega-3-acid ethyl esters plus atorvastatin also reduced median TC, TG, and very LDL-C levels and increased HDL-C levels to a significantly greater proportion compared to placebo plus atorvastatin. At study end, percent changes from baseline LDL-C, apolipoprotein A-I, and apolipoprotein B levels were not significantly different between groups.

META-ANALYSES

Fibric acids were compared to niacin in a meta-analysis evaluating lipid parameter effects and risk reductions for major cardiac events.³⁰⁴ 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 U.S., 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.

A pooled meta-analysis of 10 long-term, randomized, placebo-controlled, clinical trials of fenofibrate, gemfibrozil, bezafibrate, and fenofibrate evaluated the role of these agents in prevention of CV events.³⁰⁵ A total of 36,489 patients were included. As expected, fibrates significantly reduced total-C and TG levels by approximately eight percent and 30 percent, respectively, and raised HDL-C by approximately nine percent compared to placebo. The odds of all-cause mortality trended higher ($p=0.08$), and the odds of non-cardiovascular mortality were significantly higher ($p=0.004$) with the use of fibrates. However, these significant differences did not persist after exclusion of trials using clofibrate as the study drug. Fibrates did not significantly reduce the odds of CV mortality ($p=0.68$), fatal MI ($p=0.76$), or stroke ($p=0.56$). On the other hand, fibrates significantly reduced the odds of nonfatal MI by about 22 percent ($p<0.00001$). The odds of developing cancer ($p=0.98$) or cancer-related deaths ($p=0.17$) were not significantly higher with the use of fibrates.

A systematic review of 18 randomized controlled trials of combination statin and ezetimibe trials was performed to assess risk in 14,471 patients.³⁰⁶ Compared with statin monotherapy, combination therapy did not result in significant absolute increases in risks of myalgias (risk difference -0.033, 95% CI, -0.06 to -0.01), creatine kinase increases (risk difference 0.011, 95% CI, -0.02 to 0.04), rhabdomyolysis (risk difference -0.003, 95% CI, -0.01 to 0.004), transaminase increases (risk difference -0.003, 95% CI, -0.01 to 0.005), gastrointestinal adverse events (risk difference 0.005, 95% CI, -0.03 to 0.04), or discontinuations because of an adverse event (risk difference -0.005, 95% CI, -0.03 to 0.02). This systematic review showed that the addition of ezetimibe to statin therapy did not increase the risk of myalgias, creatine kinase levels, rhabdomyolysis, transaminase levels, gastrointestinal adverse events, or discontinuations due to an adverse event.

An Agency for Healthcare Research and Quality (AHRQ)-funded systematic review of 98 randomized controlled trials and four nonrandomized comparative studies compared the clinical outcomes of high-dose statin monotherapy with those of statin combination therapy in adults at high risk for coronary disease.³⁰⁷ The randomized studies compared statin monotherapy with statins combined with bile-acid sequestrants, fibrates, ezetimibe, niacin, or omega-3 fatty acids. The nonrandomized comparative studies were longer than 24 weeks and reported clinical and harms outcomes. Very-low-strength evidence showed that statin–ezetimibe (two trials; $n=439$) and statin–fibrate (one trial; $n=166$) combinations did not reduce mortality more than high-dose statin monotherapy. No trials compared the effect of combination therapy versus high-dose statin monotherapy on the incidence of MI, stroke, or revascularization procedures. Although a meta-analysis of two trials that compared therapy with statin-omega 3 fatty acids to high-dose statin monotherapy demonstrated no statistically significant difference for fatal MI (odds ratio, 0.73; 95% CI, 0.34 to 1.58). Two statin–ezetimibe trials ($n=295$) demonstrated higher LDL-C goal attainment with combination therapy (odds ratio, 7.21; 95% CI, 4.3 to 12.08). Trials in lower-risk patients did not show a difference in mortality. There were no statistically significant differences in serious adverse events between combination treatment and monotherapy. Limitations of this review included short duration of trials, focus on surrogate outcomes, heterogeneous study sample, use of similar doses of statins in the combination and monotherapy groups, and few studies examined treatment combinations other than statin–ezetimibe. In this review, no firm trial evidence showed that combining a statin with another agent (bile-acid sequestrant, fibrate, ezetimibe, niacin, or omega-3 fatty acids) improved clinical outcomes (MI, stroke, or mortality) more often than high-dose statin monotherapy.

An analysis of existing published studies for dyslipidemia products marketed in the US was performed to identify trials for niacin extended-release and lovastatin (NER/L); niacin extended-release and simvastatin (NER/S); rosuvastatin (R); and, ezetimibe/simvastatin (E/S) from database inception to May, 1 2009.³⁰⁸ Demographics and changes from baseline in LDL-C and HDL-C were abstracted and HDL-C to LDL-C change (%Delta-lipids) was created for each therapy. Using a previously validated model the percent reduction in CV events was estimated for each treatment strategy. Data for 177 treatment arms (120 unique reports), accounting for drug and dose were abstracted. The range in mean +/- SD %Delta-lipids depending on drug dose was: E/S, 58 +/- 6 to 67 +/- 3; R, 51 +/- 5 to 65 +/- 5; NER/L, 33 +/- 7 to 75 +/- 7; and NER/S, 48 to 77 +/- 4. Risk reductions were greatest for NER/statin combinations, with percent risk reductions greater than 77 percent for NER/S, 2000 mg/10 mg and 83 percent NER/S, 2000 mg/40 mg. Without consideration for medication strengths, reductions in CV events ranged from 58 percent for R, 60 percent for E/S, 61 percent for NER/L, and 72 percent for NER/S. Analysis limitations include publication bias, English only search, limited published studies with NER in combination with L or S, adherent populations, and aggregation of multiple populations.

A systematic review searched the literature to identify randomized, double-blind, placebo-controlled trials examining the effect of fibrates on lipid profiles or cardiovascular outcomes.³⁰⁹ Fibrates were associated with greater reductions in total cholesterol (range: -101.3 mg/dL to -5 mg/dL) and TG (range: -321.3 mg/dL to -20.8 mg/dL), and a greater increase in HCL-C (range: +1.1 mg/dL to +17.9 mg/dL), compared to placebo, in all trials. Although not consistently, fibrates tended to be associated with a greater reduction in LCL-C (range: -76.3 mg/dL to +38.7 mg/dL) than placebo. Fibrates were better than placebo at preventing nonfatal MI (OR=0.78; 95% CI, 0.69-0.89), but not all-cause mortality (OR=1.05; 95% CI, 0.95-1.15).

A systematic review and meta-analysis searched for prospective randomized placebo-controlled fibrate trials with effect on CV outcomes published between 1950 and March 2010.³¹⁰ Medline, Embase, and the Cochrane Library were searched. Summary estimates of relative risk (RR) reductions were calculated with a random effects model. Outcomes analyzed included major CV events, coronary events, stroke, HF, coronary revascularization, all-cause mortality, CV death, non-vascular death, sudden death, new onset albuminuria, and drug-related adverse events. Eighteen trials with 45,058 patients were identified, including 2,870 major CV events, 4,552 coronary events, and 3,880 deaths. Fibrate therapy produced a 10 percent RR reduction (95% CI, 0 to 18) for major CV events (p=0.048) and a 13 percent RR reduction (95% CI, 7 to 19) for coronary events (p<0.0001), but had no benefit on stroke (-3 percent, 95% CI, -16 to 9; p=0.69). There was no effect of fibrate therapy on the risk of all-cause mortality (0 percent, 95% CI, -8 to 7; p=0.92), CV mortality (3 percent, 95% CI, -7 to 12; p=0.59), sudden death (11 percent, 95% CI, -6 to 26; p=0.19), or non-vascular mortality (-10 percent, 95% CI, -21 to 0.5; p=0.063). Fibrates reduced the risk of albuminuria progression by 14 percent (95% CI, 2 to 25; p=0.028). Serious drug-related adverse events were not significantly increased by fibrates (RR 1.21, 95% CI, 0.91 to 1.61; p=0.19), although increases in serum creatinine concentrations were common (1.99, 95% CI, 1.46 to 2.7; p<0.0001).

A meta-analysis of 11 randomized trials with 6,616 patients found niacin significantly reduced major coronary events (relative OR=25 percent, 95% CI, 13 to 35), stroke (25 percent, 95% CI, 8 to 41), and any CV events (27 percent, 95% CI, 15 to 37).³¹¹ In comparison with the non-niacin group, more patients in the niacin group showed regression of coronary atherosclerosis (relative increase 92 percent; 95% CI, 39 to 67), but the rate of patients with progression decreased by 41 percent (95% CI,

25 to 53). Similar effects of niacin were found on carotid intima thickness with a weighted mean difference in annual change of -17 microm/year (95% CI, -22 to -12).

Effects on Lipids for Selected Agents^{312,313,314,315,316}

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	total-C (% change)	LDL-C (% change)	HDL-C (% change)	TG (% change)
Bile Acid Sequestrants ^{317,318,319,320} cholestyramine, colestipol, colesevelam (Welchol)	-9 to -13	-12 to -30	+3 to +9	0 to +25
Cholesterol Absorption Inhibitors ³²¹ ezetimibe (Zetia)	-12 to -14	-13 to -20	+1 to +5	-5 to -11
Fibric Acids ^{322,323,324,325,326,327,328,329,330,331,332,333,334,335,336} fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide) gemfibrozil	-4 to -26	-27 to +9	+6 to +18	-29 to -54
fenofibric acid (Fibricor)	-9 to -22	-31 to +45	+10 to +23	-24 to -54
fenofibric acid (Trilipix) ³³⁷	-12	-5	+16	-31
lomitapide (Juxtapid) ³³⁸	-36	-40	-7	-45
mipomersen (Kynamro) ³³⁹	-21	-25	+15	-18
niacin ER (Niaspan) ^{340,341}	-3 to -10	-14 to +2	+18 to +26	-13 to -29
niacin IR (Niacor) ³⁴²	-10 to -20	-10 to -20	+20 to +35	-30 to -70
omega-3-acid ethyl esters (Lovaza) ³⁴³	-10	+45	+9	-45
icosapent ethyl (Vascepa) ³⁴⁴	-7	-5	-4	-27

SUMMARY

The preponderance of outcomes data supports the use of statins as the primary agents for LDL-C reduction therapy and for primary and secondary prevention of coronary heart disease (CHD). According to the 2013 ACC/AHA practice guidelines for the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, non-statin therapies do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD. However, ACC/AHA recognizes that maximal statin therapy might not be adequate to lower LDL-C sufficiently to reduce ASCVD event risk in individuals with primary severe elevations of LDL-C at which time the addition of non-statin agents can be considered. This guideline focuses on treatments proven to reduce ASCVD events and is not intended to be a comprehensive approach to lipid management. They suggest examination of treatment of hypertriglyceridemia and use of non-HDL-C Apo B, Lp(a), or LDL particles in guiding treatment decisions.

The 2012 Endocrine Society guideline on the evaluation and treatment of hypertriglyceridemia recommends drug therapy to reduce the risk of pancreatitis in patients with severe and very severe hypertriglyceridemia; a fibrate is considered a first-line treatment. For patients with moderate to severe hypertriglyceridemia, fibrates, niacin, and omega-3 fatty acids alone or in combination with statins may be considered. Statins should not be used alone for severe or very severe hypertriglyceridemia; however, statins may be useful for the treatment of moderate hypertriglyceridemia to modify CVD risk.

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 a small increase in HDL-C. Effect on decrease in TG levels has been reported between zero and 25 percent. 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) has also been studied in pediatrics ages 10 to 17 years of age with heterozygous familial hypercholesterolemia. In patients with type 2 diabetes mellitus, colesevelam (Welchol) only provides modest HbA1c reductions (-0.5 percent) and can provide an option in patients who are almost at HbA1c goal who also require lipid lowering.

Gemfibrozil has demonstrated reductions in risk of CHD primarily in subsets of patients with high TG, low HDL-C, and characteristics of metabolic syndrome. In the FIELD study in patients with type 2 diabetes mellitus, fenofibrate was not shown to reduce CHD disease morbidity and mortality. Fenofibrate produced a nonsignificant reduction in the primary endpoint of coronary events. Non-fatal MI and total CV events were significantly reduced, but all-cause mortality was not. In the ACCORD trial, combination of fenofibrate and simvastatin did not reduce rates of CV disease, compared to simvastatin monotherapy. The ACCORD findings do not support the routine use of combination fenofibrate and statin therapy, over statin therapy alone, to reduce CV risk in most patients with type 2 diabetes that are at high risk for CV disease. Fibrates lower TG levels and raise HDL-C levels to a greater extent than do the statins, but fibrates as a group have less favorable effects on clinical CV outcomes. Depending on the specific type of dyslipidemia, the fibrates may lower total-C and LDL-C, although not as significantly as the statins. The fibrates 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 rhabdomyolysis. Fenofibrate is less likely to interact with statins compared to gemfibrozil. Although fenofibric acid (Trilipix) is the only fibrate approved for use in combination with a statin, the use of fibrates with statins is still common in practice.

Niacin has been shown to reduce major coronary events. Compared to immediate-release niacin (Niacor), niacin ER (Niaspan) may increase compliance and reduce the incidence of flushing. In the AIM-HIGH study, there was no incremental benefit on CV risk reduction (including myocardial infarctions and stroke) when niacin ER was added to simvastatin therapy versus simvastatin therapy alone. In addition, a small, unexplained, increase in the rate of ischemic stroke was observed in the simvastatin plus extended-release niacin arm compared to simvastatin alone. OTC preparations of niacin are not federally regulated, therefore may lack nicotinic acid or be associated with an increased risk of hepatotoxicity.

Ezetimibe (Zetia) is the only available cholesterol absorption inhibitor. It inhibits intestinal absorption of both dietary and biliary cholesterol by blocking its transport at the brush border of the small intestine. To date, published trials of ezetimibe (Zetia) have not shown to reduce CV morbidity or mortality. Ezetimibe (Zetia) reduces LDL-C, both when given alone and in combination with a statin. Ezetimibe has been studied in pediatrics ages 10 to 17 years of age with heterozygous familial hypercholesterolemia.

Lomitapide (Juxtapid) and mipomersen (Kynamro) were approved for use in patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to a low-fat diet and other lipid-lowering treatments. These agents inhibit the production of apolipoprotein B which leads to a reduction in LDL-C concentration. The safety and effectiveness of lomitapide and mipomersen have not been established in patients with hypercholesterolemia who do not have HoFH.

Omega-3-acid ethyl esters (Lovaza) and icosapent ethyl (Vascepa) reduce TG in patients with very high TG (>500 mg/dL). Although EPA and DHA have shown reduction in major coronary events, the specific formulations for omega-3-acid ethyl esters (Lovaza) and icosapent ethyl (Vascepa) were not used. Several forms of omega-3 fatty acids are sold OTC; however, Lovaza has a high concentration of EPA and DHA in a single capsule. Both twice daily, low capsule count omega-3-acid ethyl esters (Lovaza) and icosapent ethyl (Vascepa) do not increase the risk of rhabdomyolysis in combination with statins. Icosapent ethyl (Vascepa) contains only EPA, while omega-3-acid ethyl esters (Lovaza) contains both EPA and DHA.

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.

REFERENCES

- 1 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 2 Kynamro [package insert]. Cambridge, MA; Genzyme; January 2013.
- 3 Questran [package insert]. Spring Valley, NY; PAR Pharmaceutical, Inc; July 2002.
- 4 Welchol [package insert]. Parsippany, NJ; Daiichi Sankyo; January 2014.
- 5 Colestid [package insert]. New York, NY; Pfizer; May 2014.
- 6 Zetia [package insert]. North Wales, PA; Merck/Schering-Plough; January 2012.
- 7 Antara [package insert]. Baltimore MD; Lupin Pharma; October 2013.
- 8 Fenoglide [package insert]. Atlanta, GA; Shionogi, October 2012.
- 9 Lipofen [package insert]. Juncos, Puerto Rico; Galephar; January 2013.
- 10 Lofibra [package insert]. Sellersville, PA; Gate Pharmaceuticals; January 2010.
- 11 Tricor [package insert]. North Chicago, IL; Abbott Laboratories; February 2013.
- 12 Triglide [package insert]. Atlanta, GA; Shionogi Pharma; January 2013.
- 13 Fibrivor [package insert]. Detroit, MI; Caraco; January 2014.
- 14 Trilipix [package insert]. North Chicago, IL; Abbott Laboratories; September 2012.
- 15 Lopid [package insert]. New York, NY; Pfizer; November 2014.
- 16 Niaspan [package insert]. Cranbury, NJ; Kos Pharmaceuticals; February 2013.
- 17 Niacor [package insert]. Minneapolis, MN; Upsher-Smith Laboratories; February 2000.
- 18 Vascepa [package insert]. Bedminster, NJ; Amarin; November 2013.
- 19 Lovaza [package insert]. Research Triangle Park, NC; GSK; May 2014.
- 20 National Center for Health Statistics Data Brief. Total and High-density Lipoprotein Cholesterol in Adults: National Health and Nutrition Examination Survey, 2011–2012. Available at: <http://www.cdc.gov/nchs/data/databriefs/db132.htm#the>. Accessed November 25, 2014.
- 21 Jensen M, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults. DOI: 10.1016/j.jacc.2013.11.004. Available at: http://jacciacccardiosource.com/acc_documents/2013_FULL_Guideline_Obesity.pdf. Accessed October 31, 2014.
- 22 Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. JACC 2013. doi: 10.1016/j.jacc.2013.11.002. Available at: http://circ.ahajournals.org/content/129/25_suppl_2/S1. Accessed October 31, 2014.
- 23 Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk. DOI: 10.1016/j.jacc.2013.11.003. Available at: http://jacciacccardiosource.com/acc_documents/2013_FULL_Guideline_Lifestyle.pdf. Accessed November 25, 2014.
- 24 Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. JACC 2013. doi: 10.1016/j.jacc.2013.11.002. Available at: http://circ.ahajournals.org/content/129/25_suppl_2/S1. Accessed November 25, 2014.
- 25 Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. JACC 2013. doi: 10.1016/j.jacc.2013.11.002. Available at: http://circ.ahajournals.org/content/129/25_suppl_2/S1. Accessed November 25, 2014.
- 26 Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. JACC 2013. doi: 10.1016/j.jacc.2013.11.002. Available at: http://circ.ahajournals.org/content/129/25_suppl_2/S1. Accessed November 25, 2014.
- 27 Available at: http://www.cardiosource.org/science-and-quality/clinical-trials/i/improve-it.aspx?w_nav=RI. Accessed November 25, 2014.
- 28 Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. doi: 10.1016/j.jacc.2013.11.005. Available at: http://jacciacccardiosource.com/acc_documents/2013_FULL_Blood_Cholesterol_GuidelineRR.pdf. Accessed November 25, 2014.
- 29 Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. JACC 2013. doi: 10.1016/j.jacc.2013.11.002. Available at: http://circ.ahajournals.org/content/129/25_suppl_2/S1. Accessed November 25, 2014.
- 30 Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomization study. Lancet online publication. doi:10.1016/S0140-6736(12)60312-2.

- 31 Berglund L, Brunzell JD, Goldberg AC, et al. Evaluation and Treatment of Hypertriglyceridemia: An Endocrine Society Clinical Practice Guideline. doi: 10.1210/jc.2011-3213. *J Clin Endocrinol Metab* 2012; 97:2969-89. Available at: <http://icem.endojournals.org/content/97/9/2969.full.pdf>. Accessed November 25, 2014.
- 32 Available at: <http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf>. Accessed November 25, 2014.
- 33 Berglund L, Brunzell JD, Goldberg AC, et al. Evaluation and Treatment of Hypertriglyceridemia: An Endocrine Society Clinical Practice Guideline. doi: 10.1210/jc.2011-3213. *J Clin Endocrinol Metab* 2012; 97:2969-89. Available at: <http://icem.endojournals.org/content/97/9/2969.full.pdf>. Accessed November 25, 2014.
- 34 Jellinger PS, Smith DA, Mehta AE, et al. American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis. *Endocrine Practice*. 2012;16(S1):1-78. Available at: <https://www.aace.com/publications/guidelines>. Accessed November 25, 2014.
- 35 Farnier M, Bruckert E. Severe familial hypercholesterolaemia: current and future management. *Arch Cardiovasc Dis*. 2012; 105(12):656-65.
- 36 Available at: <http://emedicine.medscape.com/article/121298-overview>. Accessed May 7, 2014.
- 37 Daniels SR, Benuck I, Christakis DA, et al. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Available at: http://www.nhlbi.nih.gov/guidelines/cvd_ped/peds_guidelines_sum.pdf. Accessed November 25, 2014.
- 38 Ricotta DN, Frishman W. Mipomersen: A Safe and Effective Antisense Therapy Adjunct to Statins in Patients With Hypercholesterolemia. *Cardiology in Review* 2012;20: 90–95.
- 39 Cuchel M, Bloedon LT, Szapary PO, et al. Inhibitor of microsomal triglyceride transfer protein in familial hypercholesterolemia. *NEJM*. 2007;356:148-156.
- 40 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 41 Kynamro [package insert]. Cambridge, MA; Genzyme; January 2013.
- 42 Insull W Jr. Clinical utility of bile acid sequestrants in the treatment of dyslipidemia: a scientific review. *South Med J*. 2006; 99:257-273.
- 43 Xydakis AM, Guyton JR, Chiou P, et al. Effectiveness and tolerability of ezetimibe add-on therapy to a bile acid resin-based regimen for hypercholesterolemia. *Am J Cardiol*. 2004; 94:795-797.
- 44 Trilipix [package insert]. North Chicago, IL; Abbott Laboratories; September 2012.
- 45 National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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. *Circulation*. 2002; 106:3143–3421.
- 46 Rubins HB. Triglycerides and coronary heart disease: implications of recent clinical trials. *J Cardiovasc Risk*. 2000; 7:339–345.
- 47 Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med*. 1987; 317:1237-1245.
- 48 Remick J, Weintraub H, Setton R. Fibrate therapy: an update. *Cardiol Rev*. 2008; 16(3):129–141.
- 49 Robins SJ, Rubins HB, Faas FH, et al. Veterans Affairs HDL Intervention Trial (VA-HIT). Insulin resistance and cardiovascular events with low HDL cholesterol: the Veterans Affairs HDL Intervention Trial (VA-HIT). *Diabetes Care*. 2003; 26:1513–7.
- 50 Keech A, Simes RJ, Barter P, et al for the FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomized controlled trial. *Lancet*. 2005; 366:1849-1861.
- 51 Saha SA, Kizhakepunnur LG, Bahekar A, et al. The role of fibrates in the prevention of cardiovascular disease—a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. *Am Heart J*. 2007; 154(5):943-953.
- 52 Ginsberg HN, Elam MB, Lovato LC, et al. The ACCORD study group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010; 362(17):1563-74.
- 53 U.S. Food and Drug Administration. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm278837.htm>. Accessed November 25, 2014.
- 54 The ACCORD Study Group. Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. *NEJM*. 2010; 362 (17): 1563-74.
- 55 Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *JACC* 2013. doi: 10.1016/j.jacc.2013.11.002. Available at: http://circ.ahajournals.org/content/129/25_suppl_2/S1. Accessed November 25, 2014.
- 56 Lopid [package insert]. New York, NY; Pfizer; November 2014.
- 57 Prueksaritanont T, Tang C, Qiu Y, et al. Effects of fibrates on metabolism of statins in human hepatocytes. *Drug Metab Dispos*. 2002; 30:1280–1287.
- 58 Pan WJ, Gustavson LE, Achari R, et al. Lack of a clinically significant pharmacokinetic interaction between fenofibrate and pravastatin in healthy volunteers. *J Clin Pharmacol*. 2000; 40:316–323.
- 59 National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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. *Circulation*. 2002; 106:3143–3421.
- 60 Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *JACC* 2013. doi: 10.1016/j.jacc.2013.11.002. Available at: http://circ.ahajournals.org/content/129/25_suppl_2/S1. Accessed November 25, 2014.
- 61 Bays HE, Dujovne CA, McGovern ME, et al. ADVICOR Versus Other Cholesterol-Modulating Agents Trial Evaluation. Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (the ADVICOR Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *Am J Cardiol*. 2003; 91:667–672.
- 62 Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA*. 1975; 231:360-381.
- 63 Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986; 8:1245–1255.
- 64 Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med*. 1990; 323:1289–1298.
- 65 Taylor AJ, Sullenberger LE, Hyun JL, et al. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2. A double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation*. 2004; 110:3512-3517.
- 66 Taylor AJ, Lee HJ, Sullenberger LE. The effect of 24 months of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. *Curr Med Res Opin*. 2006; 22(11):243-2250.

- 67 Whitney EJ, Krasuski RA, Personius BE, et al. A randomized trial of a strategy for increasing high-density lipoprotein cholesterol levels: effects on progression of coronary heart disease and clinical events. *Ann Intern Med.* 2005; 142:95-104.
- 68 AIM-HIGH Investigators. The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol: baseline characteristics of study participants. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: impact on Global Health outcomes (AIM-HIGH) trial. *American Heart J.* 2011; 161(3):538-43.
- 69 NIH News. Available at: <http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=2792>. Accessed November 25, 2014.
- 70 AIM-HIGH Investigators. Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy. published on-line. Available at: <http://www.nejm.org/doi/full/10.1056/NEJMoa1107579>. Accessed November 25, 2014.
- 71 Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm256841.htm>. Accessed November 25, 2014.
- 72 AHA Scientific Statement: Fish Consumption, Fish Oil, Omega-3 Fatty Acids and Cardiovascular Disease, #71-0241 *Circulation.* 2002; 106:2747-2757.
- 73 Lovaza [package insert]. Research Triangle Park, NC; GSK; May 2014.
- 74 Vascepa [package insert]. Bedminster, NJ; Amarin; November 2013.
- 75 Bays HE, Ballantyne CM, Kastelein JJ, et al. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, placebo-controlled, Randomized, double-blind, 12-week study with an open-label Extension [MARINE] trial). *Am J Cardiol.* 2011; 108(5):682-90.
- 76 Vascepa [package insert]. Bedminster, NJ; Amarin; November 2013.
- 77 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 78 Kynamro [package insert]. Cambridge, MA; Genzyme; January 2013.
- 79 Questran [package insert]. Spring Valley, NY; PAR Pharmaceutical, Inc; July 2002.
- 80 Welchol [package insert]. Parsippany, NJ; Daiichi Sankyo; January 2014.
- 81 Colestid [package insert]. New York, NY; Pfizer; May 2014.
- 82 Zetia [package insert]. North Wales, PA; Merck/Schering-Plough; January 2012.
- 83 Tricor [package insert]. North Chicago, IL; Abbott Laboratories; February 2013.
- 84 Lofibra [package insert]. Sellersville, PA; Gate Pharmaceuticals; January 2010.
- 85 Antara [package insert]. Baltimore MD; Lupin Pharma; December 2012.
- 86 Triglide [package insert]. Atlanta, GA; Shionogi; January 2013.
- 87 McKenney JM, Farnier M, Lo KW, et al. Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. *J Am Coll Cardiol.* 2006; 47:1584-1587.
- 88 Lipofen [package insert]. Juncos, Puerto Rico; Galephar; January 2013.
- 89 Fenoglide [package insert]. Atlanta, GA; Shionogi Pharma; October 2012.
- 90 Fibracor [package insert]. Philadelphia, PA; AR Scientific; March 2013.
- 91 Trilipix [package insert]. North Chicago, IL; Abbott Laboratories; September 2012.
- 92 Lopid [package insert]. New York, NY; Pfizer; November 2014.
- 93 Niaspan [package insert]. Cranbury, NJ; Kos Pharmaceuticals; February 2013.
- 94 Niacor [package insert]. Minneapolis, MN; Upsher-Smith Laboratories; February 2000.
- 95 Vascepa [package insert]. Bedminster, NJ; Amarin; November 2013.
- 96 Lovaza [package insert]. Research Triangle Park, NC; GSK; May 2014.
- 97 Lofibra [package insert]. Sellersville, PA; Gate Pharmaceuticals; January 2010.
- 98 Najib J. Fenofibrate in the treatment of dyslipidemia: a review of the data as they relate to the new supra bioavailable tablet formulation. *Clin Ther.* 2002; 24:2022-2050.
- 99 Antara [package insert]. Baltimore MD; Lupin Pharma; October 2013.
- 100 Tricor [package insert]. North Chicago, IL; Abbott Laboratories; February 2013.
- 101 Triglide [package insert]. Atlanta, GA; Shionogi; January 2013.
- 102 Lipofen [package insert]. Juncos, Puerto Rico; Galephar; January 2013.
- 103 Fenoglide [package insert]. Atlanta, GA; Shionogi Pharma; October 2012.
- 104 Trilipix [package insert]. North Chicago, IL; Abbott Laboratories; September 2012.
- 105 Fibracor [package insert]. Philadelphia, PA; AR Scientific; March 2013.
- 106 Kynamro [package insert]. Cambridge, MA; Genzyme; January 2013.
- 107 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 108 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 109 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 110 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 111 Kynamro [package insert]. Cambridge, MA; Genzyme; January 2013.
- 112 <http://emedicine.medscape.com/article/118466-treatment>. Accessed November 25, 2014.
- 113 Welchol [package insert]. Parsippany, NJ; Daiichi Sankyo; January 2014.
- 114 Questran [package insert]. Spring Valley, NY; PAR Pharmaceutical, Inc; July 2002.
- 115 Welchol [package insert]. Parsippany, NJ; Daiichi Sankyo; January 2014.
- 116 Zetia [package insert]. North Wales, PA; Merck/Schering-Plough; January 2012.
- 117 Antara [package insert]. Waltham, MA; Oscient Pharmaceuticals; July 2008.
- 118 Tricor [package insert]. North Chicago, IL; Abbott Laboratories; February 2013.
- 119 Triglide [package insert]. Atlanta, GA; Shionogi; January 2013.
- 120 Lofibra [package insert]. Sellersville, PA; Gate Pharmaceuticals; January 2010.
- 121 Fenoglide [package insert]. Atlanta, GA; Shionogi Pharma; October 2012.
- 122 Trilipix [package insert]. North Chicago, IL; Abbott Laboratories; September 2012.
- 123 Fibracor [package insert]. Philadelphia, PA; AR Scientific; March 2013.

- 124 Antara [package insert]. Baltimore MD; Lupin Pharma; October 2013.
- 125 Niaspan [package insert]. Cranbury, NJ; Kos Pharmaceuticals; February 2013.
- 126 Available at: <http://www.clinicalpharmacology.com>. Accessed November 25, 2014.
- 127 Simcor [package insert]. North Chicago, IL; Abbott; June 2011.
- 128 Lovaza [package insert]. Research Triangle Park, NC; GSK; May 2014.
- 129 Vascepa [package insert]. Bedminster, NJ; Amarin; November 2013.
- 130 Lovaza [package insert]. Research Triangle Park, NC; GSK; May 2014.
- 131 Lovaza [package insert]. Research Triangle Park, NC; GSK; May 2014.
- 132 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 133 <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM337472.pdf>. Accessed October 31, 2014.
- 134 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 135 Kynamro [package insert]. Cambridge, MA; Genzyme; January 2013.
- 136 Questran [package insert]. Spring Valley, NY; PAR Pharmaceutical, Inc; July 2002.
- 137 Colestid [package insert]. New York, NY; Pfizer; May 2014.
- 138 Tricor [package insert]. North Chicago, IL; Abbott Laboratories; February 2013.
- 139 Welchol [package insert]. Parsippany, NJ; Daiichi Sankyo; January 2014.
- 140 Tricor [package insert]. North Chicago, IL; Abbott Laboratories; February 2013.
- 141 Zetia [package insert]. North Wales, PA; Merck/Schering-Plough; January 2012.
- 142 Tricor [package insert]. North Chicago, IL; Abbott Laboratories; February 2013.
- 143 Lofibra [package insert]. Sellersville, PA; Gate Pharmaceuticals; January 2010.
- 144 Antara [package insert]. Waltham, MA; Oscient Pharmaceuticals; July 2008.
- 145 Triglide [package insert]. Atlanta, GA; Shionogi; January 2013.
- 146 Tricor [package insert]. North Chicago, IL; Abbott Laboratories; February 2013.
- 147 Fenoglide [package insert]. Atlanta, GA; Shionogi Pharma, October 2010.
- 148 Fibracor [package insert]. Philadelphia, PA; AR Scientific; March 2013.
- 149 Trilipix [package insert]. North Chicago, IL; Abbott Laboratories; September 2012.
- 150 Lopid [package insert]. New York, NY; Pfizer; September 2010.
- 151 Niaspan [package insert]. Cranbury, NJ; Kos Pharmaceuticals; February 2013.
- 152 Niacor [package insert]. Minneapolis, MN; Upsher-Smith Laboratories; February 2000.
- 153 Vascepa [package insert]. Bedminster, NJ; Amarin; November 2013.
- 154 Lovaza [package insert]. Research Triangle Park, NC; GSK; May 2014.
- 155 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 156 Kynamro [package insert]. Cambridge, MA; Genzyme; January 2013.
- 157 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 158 Turner SW, Jungbluth GL and Knuth DW. Effect of concomitant colestipol hydrochloride administration on the bioavailability of diltiazem from immediate- and sustained-release formulations. *Biopharm Drug Dispos.* 2002; 23:369-377.
- 159 Cellcept [package insert]. Nutley, NJ; Roche Laboratories; October 2005.
- 160 Jahnchen E, Meinertz T, Gilfrich HJ, et al. Enhanced elimination of warfarin during treatment with cholestyramine. *Br J Clin Pharmacol.* 1978; 5:437-440.
- 161 Questran [package insert]. Spring Valley, NY; PAR Pharmaceutical, Inc; July 2002.
- 162 Colestid [package insert]. New York, NY; Pfizer; May 2014.
- 163 Welchol [package insert]. Parsippany, NJ; Daiichi Sankyo; January 2014.
- 164 Welchol [package insert]. Parsippany, NJ; Daiichi Sankyo; January 2014.
- 165 Questran [package insert]. Spring Valley, NY; PAR Pharmaceutical, Inc; July 2002.
- 166 Zetia [package insert]. North Wales, PA; Merck/Schering-Plough; January 2012.
- 167 Tricor [package insert]. North Chicago, IL; Abbott Laboratories; February 2013.
- 168 Lopid [package insert]. New York, NY; Pfizer; November 2014.
- 169 Fenoglide [package insert]. Atlanta, GA; Shionogi Pharma; October 2012.
- 170 Trilipix [package insert]. North Chicago, IL; Abbott Laboratories; September 2012.
- 171 Fibracor [package insert]. Philadelphia, PA; AR Scientific; March 2013.
- 172 Fibracor [package insert]. Philadelphia, PA; AR Scientific; March 2013.
- 173 Antara [package insert]. Baltimore MD; Lupin Pharma; October 2013.
- 174 Trilipix [package insert]. North Chicago, IL; Abbott Laboratories; September 2012.
- 175 Ahmad S. Gemfibrozil: Interaction with glyburide (letter). *South Med J.* 1991; 84:102.
- 176 Deng L, Wang F and Li H. Effect of gemfibrozil on the pharmacokinetics of pioglitazone. *Eur J Clin Pharmacol.* 2005; 6:831-6.
- 177 Jaakkola T, Backman JT, Neuvonen M, et al. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics of pioglitazone. *Clin Pharm Ther.* 2005; 77:404-414.
- 178 Avandia [package insert]. Research Triangle Park, NC; GlaxoSmithKline; October 2008.
- 179 Prandin [package insert]. Princeton, NJ; Novo Nordisk Pharmaceuticals; June 2006.
- 180 Antara [package insert]. Baltimore MD; Lupin Pharma; October 2013.
- 181 Lopid [package insert]. New York, NY; Pfizer; November 2014.
- 182 Lopid [package insert]. New York, NY; Pfizer; November 2014.
- 183 Available at: <http://www.clinicalpharmacology.com>. Accessed November 25, 2014.
- 184 Niaspan [package insert]. Cranbury, NJ; Kos Pharmaceuticals; February 2013.
- 185 Available at: <http://www.clinicalpharmacology.com>. Accessed November 25, 2014.
- 186 Vascepa [package insert]. Bedminster, NJ; Amarin; November 2013.

- 187 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 188 Kynamro [package insert]. Cambridge, MA; Genzyme; January 2013.
- 189 Questran [package insert]. Spring Valley, NY; PAR Pharmaceutical, Inc; July 2002.
- 190 Welchol [package insert]. Parsippany, NJ; Daiichi Sankyo; January 2014.
- 191 Colestid [package insert]. New York, NY; Pfizer; May 2014.
- 192 Zetia [package insert]. North Wales, PA; Merck/Schering-Plough; January 2012.
- 193 Tricor [package insert]. North Chicago, IL; Abbott Laboratories; February 2013.
- 194 Lofibra [package insert]. Sellersville, PA; Gate Pharmaceuticals; January 2010.
- 195 Antara [package insert]. Baltimore MD; Lupin Pharma; October 2013.
- 196 Triglide [package insert]. Atlanta, GA; Shionogi; January 2013.
- 197 Fenoglide [package insert]. Atlanta, GA; Shionogi Pharma; October 2012.
- 198 Fibracor [package insert]. Philadelphia, PA; AR Scientific; March 2013.
- 199 Trilipix [package insert]. North Chicago, IL; Abbott Laboratories; September 2012.
- 200 Lipid [package insert]. New York, NY; Pfizer; November 2014.
- 201 Niaspan [package insert]. Cranbury, NJ; Kos Pharmaceuticals; February 2013.
- 202 Niacor [package insert]. Minneapolis, MN; Upsher-Smith Laboratories; February 2000.
- 203 Vascepa [package insert]. Bedminster, NJ; Amarin; November 2013.
- 204 Lovaza [package insert]. Research Triangle Park, NC; GSK; May 2014.
- 205 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 206 Kynamro [package insert]. Cambridge, MA; Genzyme; January 2013.
- 207 The Medical Letter. Colesevelam (WelChol) for hypercholesterolemia. 2000; 42:102-104.
- 208 Welchol [package insert]. Parsippany, NJ; Daiichi Sankyo; January 2014.
- 209 Welchol [package insert]. Parsippany, NJ; Daiichi Sankyo; January 2014.
- 210 Zetia [package insert]. North Wales, PA; Merck/Schering-Plough; July 2009.
- 211 Tricor [package insert]. North Chicago, IL; Abbott Laboratories; February 2013.
- 212 Triglide [package insert]. Atlanta, GA; Shionogi; January 2013.
- 213 Trilipix [package insert]. North Chicago, IL; Abbott Laboratories; September 2012.
- 214 Fibracor [package insert]. Philadelphia, PA; AR Scientific; March 2013.
- 215 Tricor [package insert]. North Chicago, IL; Abbott Laboratories; February 2013.
- 216 Zhao YY, Weir MA, Manno M, et al. New fibrate use and acute renal outcomes in elderly adults. A population-based study. *Annals*. 2012; 156(8): 560-569.
- 217 Niaspan [package insert]. Cranbury, NJ; Kos Pharmaceuticals; February 2013.
- 218 Niacor [package insert]. Minneapolis, MN; Upsher-Smith Laboratories; February 2000.
- 219 Vascepa [package insert]. Bedminster, NJ; Amarin; November 2013.
- 220 McCrindle BW, Helden E, Cullen-Dean G, et al. A Randomized Crossover Trial of Combination Pharmacologic Therapy in Children with Familial Hyperlipidemia. *Pediatric Res*. 2002; 51:715-721.
- 221 Knodel LC, Talbert RL. Adverse effects of hypolipidaemic drugs. *Med Toxicol*. 1987; 2:10-32.
- 222 Zetia [package insert]. West Wales, PA; Merck/Schering-Plough; July 2011.
- 223 Niaspan [package insert]. Miami, FL; Kos Pharmaceuticals; December 2010.
- 224 Lovaza [package insert]. Research Triangle Park, NC; GSK; May 2014.
- 225 Zetia [package insert]. North Wales, PA; Merck/Schering-Plough; January 2012.
- 226 Welchol [package insert]. Parsippany, NJ; Daiichi Sankyo; January 2014.
- 227 Stein SE, Marais AD, Szamosi T, et al. Colesevelam hydrochloride: efficacy and safety in pediatric subjects with heterozygous familial hypercholesterolemia. *J Pediatr*. 2010; 156(2):231-236.e1-3.
- 228 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 229 D'Emden MC, Jenkins AJ, Zannino D, et al. Favourable effects of fenofibrate on lipids and cardiovascular disease in women with type 2 diabetes: results from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetologia*. 2014; 57(11):2296-303. doi: 10.1007/s00125-014-3344-3.
- 230 Fibracor [package insert]. Philadelphia, PA; AR Scientific; March 2013.
- 231 Trilipix [package insert]. North Chicago, IL; Abbott Laboratories; September 2012.
- 232 Tricor [package insert]. North Chicago, IL; Abbott Laboratories; February 2013.
- 233 Lofibra [package insert]. Sellersville, PA; Gate Pharmaceuticals; January 2010.
- 234 Antara [package insert]. Baltimore MD; Lupin Pharma; October 2013.
- 235 Triglide [package insert]. Atlanta, GA; Shionogi; January 2013.
- 236 Zetia [package insert]. North Wales, PA; Merck/Schering-Plough; January 2012.
- 237 Kynamro [package insert]. Cambridge, MA; Genzyme; January 2013.
- 238 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 239 Vascepa [package insert]. Bedminster, NJ; Amarin; November 2013.
- 240 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 241 Kynamro [package insert]. Cambridge, MA; Genzyme; January 2013.
- 242 Questran [package insert]. Spring Valley, NY; PAR Pharmaceutical, Inc; July 2002.
- 243 Welchol [package insert]. Parsippany, NJ; Daiichi Sankyo; January 2014.
- 244 Colestid [package insert]. New York, NY; Pfizer; May 2014.
- 245 Zetia [package insert]. North Wales, PA; Merck/Schering-Plough; January 2012.
- 246 Lofibra [package insert]. Sellersville, PA; Gate Pharmaceuticals; January 2010.
- 247 Antara [package insert]. Baltimore MD; Lupin Pharma; August 2012.
- 248 Fenoglide [package insert]. Atlanta, GA; Shionogi Pharma; October 2012.
- 249 Lipofen [package insert]. Montgomery, AL; Kowa Pharmaceuticals; June 2008.

- 250 Tricor [package insert]. North Chicago, IL; Abbott Laboratories; February 2013.
- 251 Triglide [package insert]. Atlanta, GA; Shionogi; January 2013.
- 252 Fibricor [package insert]. Philadelphia, PA; AR Scientific; March 2013.
- 253 Trilipix [package insert]. North Chicago, IL; Abbott Laboratories; September 2012.
- 254 Niaspan [package insert]. Cranbury, NJ; Kos Pharmaceuticals; February 2013.
- 255 Niacor [package insert]. Minneapolis, MN; Upsher-Smith Laboratories; February 2000.
- 256 Vascepa [package insert]. Bedminster, NJ; Amarin; November 2013.
- 257 Lovaza [package insert]. Research Triangle Park, NC; GSK; May 2014.
- 258 Yokoyama M, Origasa H, Matsuzaki M, et al. Japan EPA Intervention Study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet*. 2007; 369(9567):1090-1098.
- 259 Tricor [package insert]. North Chicago, IL; Abbott Laboratories; February 2013.
- 260 Lopid [package insert]. New York, NY; Pfizer; November 2014.
- 261 Fenoglide [package insert]. Atlanta, GA; Shionogi Pharma; October 2012.
- 262 Trilipix [package insert]. North Chicago, IL; Abbott Laboratories; September 2012.
- 263 Fibricor [package insert]. Philadelphia, PA; AR Scientific; March 2013.
- 264 IMPROVE-IT. Available at: <http://clinicaltrials.gov/show/NCT00202878>. Accessed November 25, 2014.
- 265 Niaspan [package insert]. Cranbury, NJ; Kos Pharmaceuticals; February 2013.
- 266 Vascepa [package insert]. Bedminster, NJ; Amarin; November 2013.
- 267 Lovaza [package insert]. Research Triangle Park, NC; GSK; May 2014.
- 268 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 269 Bays H, Rhyne J, Abby S, et al. Lipid-lowering effects of colessevelam HCl in combination with ezetimibe. *Curr Med Res Opin*. 2006; 22(11):2191-2200.
- 270 Tribble DL, Farnier M, Macdonell G, et al. Effects of fenofibrate and ezetimibe, both as monotherapy and in coadministration, on cholesterol mass within lipoprotein subfractions and low-density lipoprotein peak particle size in patients with mixed hyperlipidemia. *Metabolism*. 2008; 57(6):796-801.
- 271 Rossebø AB, Pedersen TR, Boman K, et al. SEAS Investigators. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008; 359(13):1343-1356.
- 272 SHARP Collaborative Group. Study of Heart and Renal Protection (SHARP): Randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. *Am Heart J*. 2010; published online 20 September 2010.
- 273 Bays HE, Davidson MH, Massad R, et al. Safety and efficacy of EZETIMIBE added on to rosuvastatin 5 or 10 mg versus up-titration of rosuvastatin in patients with hypercholesterolemia (the ACTE Study). *Am J Cardiol*. 2011 Aug 15;108(4):523-530.
- 274 Farnier M, Roth E, Gil-Extremera B, et al. Efficacy and safety of the coadministration of ezetimibe/simvastatin with fenofibrate in patients with mixed hyperlipidemia. *Am Heart J*. 2007; 153(2):335.e1-8.
- 275 Guyton JR, Brown BG, Fazio S, et al. Lipid-altering efficacy and safety of ezetimibe/simvastatin coadministered with extended-release niacin in patients with type IIa or type IIB hyperlipidemia. *J Am Coll Cardiol*. 2008; 51(16):1564-1572.
- 276 The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA*. 1984; 251:1351-1364.
- 277 Probstfield JL, Rifkind BM. The Lipid Research Clinics Coronary Primary Prevention Trial: design, results, and implications. *Eur J Clin Pharmacol*. 1991; 40 Suppl 1:S69-S75.
- 278 Whitney EJ, Krasuski RA, Personius BE, et al. A randomized trial of a strategy for increasing high-density lipoprotein cholesterol levels: effects on progression of coronary heart disease and clinical events. *Ann Intern Med*. 2005; 142:95-104.
- 279 Welchol [package insert]. Parsippany, NJ; Daiichi Sankyo; January 2014.
- 280 Bays HE, Goldberg RB, Truitt KE, et al. Colessevelam hydrochloride therapy in patients with type 2 diabetes mellitus treated with metformin: glucose and lipid effects. *Arch Intern Med*. 2008; 168(18):1975-1983.
- 281 Goldberg RB, Fonseca VA, Truitt KE, et al. Efficacy and safety of colessevelam in patients with type 2 diabetes mellitus and inadequate glycemic control receiving insulin-based therapy. *Arch Intern Med*. 2008; 168(14):1531-1540.
- 282 Keech A, Simes RJ, Barter P, et al for the FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomized controlled trial. *Lancet*. 2005; 366:1849-1861.
- 283 Grundy SM, Vega GL, Yuan A, et al. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). *Am J Cardiol*. 2005; 95(4):462-468.
- 284 Ginsberg HN, Elam MB, Lovato LC, et al. The ACCORD study group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010; 362(17):1563-74.
- 285 Trilipix [package insert]. North Chicago, IL; Abbott Laboratories; September 2012.
- 286 Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med*. 1987; 317:1237-1245.
- 287 Manninen V, Elo O, Frick MH, et al. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA*. 1988; 260:641-651.
- 288 Manttari M, Romo M, Manninen V, et al. Reduction in Q wave myocardial infarctions with gemfibrozil in the Helsinki Heart Study. *Am Heart J*. 1990; 119:991-995.
- 289 Heinonen OP, Huttunen JK, Manninen V, et al. The Helsinki Heart Study: coronary heart disease incidence during an extended follow-up. *J Intern Med*. 1994; 235:41-49.
- 290 Frick MH, Heinonen OP, Huttunen JK, et al. Efficacy of gemfibrozil in dyslipidaemic subjects with suspected heart disease. An ancillary study in the Helsinki Heart Study frame population. *Ann Med*. 1993; 25:41-45.
- 291 Tenkanen L, Manttari M, Kovanen PT, et al. The Helsinki Heart Study. Gemfibrozil in the treatment of dyslipidemia: an 18 year mortality follow-up of the Helsinki Heart Study. *Arch Intern Med*. 2006; 166(7):743-748.
- 292 Rubins HB, Robins SJ, Collins D. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Intervention Trial Study Group. *N Engl J Med*. 1999; 341:410-418.
- 293 Tonelli M, Collins D, Robins S, et al. Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. *Kidney Int*. 2004; 66:1123-1130.

- 294 Rubins HB, Robins SJ, Collins D, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch Intern Med.* 2002; 162:2597-2604.
- 295 Bays HE, Ballantyne CM, Kastelein JJ, et al. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, placebo-controlled, Randomized, double-blind, 12-week study with an open-label Extension [MARINE] trial). *Am J Cardiol.* 2011; 108(5):682-90.
- 296 Ballantyne CM, Bays HE, Kastelein JJ, et al. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). *Am J Cardiol.* 2012; 110(7):984-92.
- 297 Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. *Lancet.* 2013; 381(9860):40-6.
- 298 Raal FJ, Santos RD, Blom DJ, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2010 Mar 20;375(9719):998-1006.
- 299 Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol.* 1986; 8:1245-1255.
- 300 Taylor AJ, Sullenberger LE, Hyun JL, et al. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2. A double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation.* 2004; 110:3512-3517.
- 301 Lovaza [package insert]. Research Triangle Park, NC; GSK; May 2014.
- 302 Davidson MH, Stein EA, Bays HE, et al; COMBination of prescription omega-3 with simvastatin (COMBOS) investigators. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. *Clin Ther.* 2007; 29(7):1354-1367.
- 303 Bays HE, McKenney J, Maki KC, et al. Effects of prescription omega-3-acid ethyl esters on non-high-density lipoprotein cholesterol when coadministered with escalating doses of atorvastatin. *Mayo Clin Proc.* 2010; 85(2):122-128.
- 304 Birjmohun RS, Hutten BA, Kastelein JJP, et al. Efficacy and Safety of High-Density Lipoprotein Cholesterol-Increasing Compounds: A Meta-Analysis of Randomized Controlled Trials. *J Am Coll Cardiol.* 2005; 45:185-197.
- 305 Saha SA, Kizhakepunnur LG, Bahekar A, et al. The role of fibrates in the prevention of cardiovascular disease—a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. *Am Heart J.* 2007; 154(5):943-953.
- 306 Kashani A, Sallam T, Bheemreddy S, et al. Review of side-effect profile of combination ezetimibe and statin therapy in randomized clinical trial. *Am J Cardiol.* 2008; 101(11):1606-1613.
- 307 Sharma M, Ansari MT, Abou-Setta AM, et al. Systematic Review: Comparative Effectiveness and Harms of Combinations of Lipid-Modifying Agents and High-Dose Statin Monotherapy. *Ann Intern Med.* 2009; 151(9): online Sep. 1, 2009. Available at <http://annals.org/article.aspx?articleid=745137>. Accessed October 23, 2013.
- 308 Charland SL, Malone DC. Prediction of cardiovascular event risk reduction from lipid changes associated with high potency dyslipidemia therapy. *Curr Med Res Opin.* 2010; 26(2):365-375.
- 309 Abourbih S, Filion KB, Joseph L, et al. Effect of fibrates on lipid profiles and cardiovascular outcomes: a systematic review. *Am J Med.* 2009; 122(10):962.e1-8.
- 310 Jun M, Foote C, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet.* 2010; 375(9729):1875-84.
- 311 Bruckert E, Labreuche J, Amarenco P. Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis. *Atherosclerosis.* 2010; 210 (2):353-361.
- 312 Hunninghake D, Insull W, Toth P, et al. Coadministration of colesvelam hydrochloride with atorvastatin lowers LDL-C additively. *Atherosclerosis.* 2001; 158:407-416.
- 313 Farnier M, Dejager S. Effect of combined fluvastatin-fenofibrate therapy compared with fenofibrate monotherapy in severe primary hypercholesterolemia. French Fluvastatin Study Group. *Am J Cardiol.* 2000; 85:53-57.
- 314 Durrington PN, Tuomilehto J, Hamann A, et al. Rosuvastatin and fenofibrate alone and in combination in type 2 diabetes patients with combined hyperlipidaemia. *Diabetes Res Clin Pract.* 2004; 64:137-151.
- 315 Capuzzi DM, Guyton JR, Morgan JM, et al. Efficacy and safety of an extended-release niacin (Niaspan): a long-term study. *Am J Cardiol.* 1998; 82:74U-81U.
- 316 Guyton JR, Blazing MA, Hagar J, et al. Extended-release niacin vs. gemfibrozil for the treatment of low levels of high density lipoprotein cholesterol. Niaspan-Gemfibrozil Study Group. *Arch Intern Med.* 2000; 160(8):1177-1184.
- 317 National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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. *Circulation.* 2002; 106:3143–3421.
- 318 Rifkind BM. The Lipid Research Clinics Coronary Primary Prevention Trial. *Drugs.* 1986; 31 Suppl 1:53-60.
- 319 Welchol [package insert]. Parsippany, NJ; Daiichi Sankyo; January 2014.
- 320 Aldridge MA, Ito MK. Colesevelam hydrochloride: a novel bile acid-binding resin. *Ann Pharmacother.* 2001; 35:898-907.
- 321 Zetia [package insert]. North Wales, PA; Merck/Schering-Plough; January 2012.
- 322 Tricor [package insert]. North Chicago, IL; Abbott Laboratories; February 2013.
- 323 Lofibra [package insert]. Sellersville, PA; Gate Pharmaceuticals; January 2010.
- 324 Antara [package insert]. Baltimore MD; Lupin Pharma; October 2013.
- 325 Triglide [package insert]. Atlanta, GA; Shionogi; January 2010.
- 326 McKenney J, Jones M, Abby S. Safety and efficacy of colesvelam hydrochloride in combination with fenofibrate for the treatment of mixed hyperlipidemia. *Curr Med Res Opin.* 2005; 21:1403-1412.
- 327 Insua A, Massari F, Rodriguez MJJ, et al. Fenofibrate of gemfibrozil for treatment of types IIa and IIb primary hyperlipoproteinemia: a randomized, double-blind, crossover study. *Endocr Pract.* 2002; 8:96-101.
- 328 De la Serna G, Cardarso G. Fenofibrate decreases plasma fibrinogen, improves lipid profile, and reduces uricemia. *Clin Pharmacol Ther.* 1999; 66:166-172.
- 329 Manninen V, Huttunen JK, Heinonen OP, et al. Relation between baseline lipid and lipoprotein values and the incidence of coronary heart disease in the Helsinki Heart Study. *Am J Cardiol.* 1989; 63:42H-47H.

- 330 Farnier M. Cerivastatin in the treatment of mixed hyperlipidemia: the RIGHT study. The Cerivastatin Study Group. Cerivastatin Gemfibrozil Hyperlipidemia Treatment. *Am J Cardiol.* 1998; 82(4B):47J-51J.
- 331 Odman B, Ericsson S, Lindmark M, et al. Gemfibrozil in familial combined hyperlipidaemia: effect of added low-dose cholestyramine on plasma and biliary lipids. *Eur J Clin Invest.* 1991; 21:344-3499.
- 332 Ros E, Zambon D, Bertomeu A, et al. Comparative study of a microporous cholestyramine analogue (filicol) and gemfibrozil for treatment of severe primary hypercholesterolemia. Short- and long-term results. *Arch Intern Med.* 1991; 151:301-305.
- 333 Insua A, Massari F, Rodriquez MJJ, et al. Fenofibrate of gemfibrozil for treatment of types IIa and IIb primary hyperlipoproteinemia: a randomized, double-blind, crossover study. *Endocr Pract.* 2002; 8:96-101.
- 334 Kaukola S, Manninen V, Malkonen M, et al. Gemfibrozil in the treatment of dyslipidaemias in middle-aged male survivors of myocardial infarction. *Acta Med Scand.* 1981; 209:69-73.
- 335 Rubins HB, Robins SJ, Collins D: Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med.* 1999; 341:410-418.
- 336 Fenoglide [package insert]. Atlanta, GA; Shionogi Pharma; October 2012.
- 337 Trilipix [package insert]. North Chicago, IL; Abbott Laboratories; September 2012.
- 338 Juxtapid [package insert]. Cambridge, MA; Aegerion; August 2014.
- 339 Kynamro [package insert]. Cambridge, MA; Genzyme; January 2013.
- 340 Niaspan [package insert]. Cranbury, NJ; Kos Pharmaceuticals; February 2013.
- 341 Guyton JR, Blazing MA, Hagar J, et al. Extended-release niacin vs. gemfibrozil for the treatment of low levels of high-density lipoprotein cholesterol. Niaspan-Gemfibrozil Study Group. *Arch Intern Med.* 2000; 160:1177-1184.
- 342 Niacor [package insert]. Minneapolis, MN; Upsher-Smith Laboratories; February 2000.
- 343 Lovaza [package insert]. Research Triangle Park, NC; GSK; May 2014.
- 344 Vascepa [package insert]. Bedminster, NJ; Amarin; November 2013.