



Lipotropics, Other

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

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

| Drug | Manufacturer | Indication(s) |
|--|-----------------|--|
| Apolipoprotein B Synthesis Inhibitors | | |
| lomitapide (Juxtapid™) ¹ | Aegerion | Reduction of LDL-C, total cholesterol, apolipoprotein 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 |
| Bile Acid Sequestrants | | |
| cholestyramine ² | generic | <ul style="list-style-type: none"> ▪ Primary hypercholesterolemia ▪ Relief of pruritus associated with partial biliary obstruction |
| colesevelam (WelChol®) ³ | 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®) ⁴ | generic | <ul style="list-style-type: none"> ▪ Primary hypercholesterolemia |
| Cholesterol Absorption Inhibitors | | |
| ezetimibe (Zetia®) ⁵ | Merck | <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™) ⁶ | Lupin | <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™) ⁷ | Santarus | |
| fenofibrate (Lipofen™) ⁸ | Kowa | |
| fenofibrate (Lofibra®) ⁹ | generic | |
| fenofibrate (Tricor®) ¹⁰ | Abbvie, generic | |
| fenofibrate (Triglide™) ¹¹ | Shionogi | <ul style="list-style-type: none"> ▪ Primary hyperlipidemia or mixed dyslipidemia ▪ Severe hypertriglyceridemia (≥ 500 mg/dL) |
| fenofibric acid (Fibracor™) ¹² | AR Scientific | |
| fenofibric acid (Trilipix™) ¹³ | Abbvie | |
| gemfibrozil ¹⁴ | 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®) ¹⁵ | Abbvie | <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®) ¹⁶ | 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®) ¹⁷ | 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®) ¹⁸ | GSK | <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.

OVERVIEW

Many clinical trials have demonstrated that high serum concentrations of low-density lipoprotein cholesterol (LDL-C) are major risk factors for coronary heart disease (CHD). Likewise, numerous studies have shown that lowering LDL-C levels reduces the risk for CHD. The Adult Treatment Panel (ATP) III guidelines from the National Cholesterol Education Program (NCEP) recommend a goal for LDL-C-lowering therapy in high risk patients of LDL-C <100 mg/dL. For patients with multiple CHD risk factors, LDL-C goals are <130 mg/dL. The goal for patients with no or one risk factor is to lower LDL-C <160 mg/dL.¹⁹

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.²⁰ 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 hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (“statins”) are the only class to demonstrate clear improvements in overall mortality in primary and secondary prevention. 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.

As a result of clinical data published and/or presented since the 2001 ATP III guidelines [including the Heart Protection Study (HPS) and PROVE IT], the NCEP issued additional guidance in 2004. The 2004 guidance suggests that an LDL-C goal of <70 mg/dL be considered as an option for high risk patients, especially those with established CVD (cardiovascular disease) and multiple major and/or uncontrolled risk factors for CHD and/or metabolic syndrome. For high risk patients with LDL-C 70 to 100 mg/dL, the 2004 NCEP guidance recommends that fibric acids and nicotinic acid be considered, either as monotherapy or in combination with statins, in the presence of elevated TG and/or low HDL-C.²¹

For the first time, ATP III included non-HDL-C, the sum of very low-density lipoprotein (VLDL) and LDL-C, as a secondary target of therapy in patients with elevated levels of TG. The non-HDL-C goal is 30 mg/dL higher than the corresponding LDL-C goal.²²

ATP III notes that, while there is significant interest in the potential benefit of increasing HDL-C, there was not, at the time these guidelines were published, enough data to definitively recommend a goal for raising HDL-C. ATP III did, however, suggest that fibric acids or nicotinic acid are alternatives to statin therapy in patients with LDL-C 100 to 130 mg/dL and low HDL-C.²³ Based on data from the HPS, the 2004 NCEP guidance indicates that, in patients with low HDL-C, fibric acids or nicotinic acid should be used in combination with a LDL-C-lowering drug, rather than as monotherapy.²⁴

For patients with LDL-C levels >130 mg/dL, standard doses of statins may be insufficient to achieve the goal of <100 mg/dL. In these cases, the statin dose may have to be increased or a second agent, such as a bile acid sequestrant, cholesterol absorption inhibitor, or nicotinic acid, may be added.²⁵

The 2003-2004 National Health and Nutrition Examination Survey (NHANES) showed that 85 to 89 percent of persons without CVD or related comorbidities were at recommended levels for LDL-C, non-HDL-C, HDL-C, and TG.²⁶ However, only 36 to 37 percent of those with CVD or related comorbidities were at recommended levels for LDL-C and non-HDL-C, and only 17 percent were at recommended levels for all lipids.

A 2011 scientific statement on hypertriglyceridemia from the American Heart Association (AHA), recommends 100 mg/dL as the new optimal fasting triglyceride level to replace 150 mg/dL.²⁷ The statement focuses on intensive therapeutic lifestyle change (e.g., diet and exercise) and less emphasis on medications to reduce triglycerides and risk, for most patients. This scientific statement is not intended to serve as a guideline but to complement the future Adult Treatment Panel IV (ATP IV) of the National Cholesterol Education Program (NCEP) guidelines.

The AHA/ACCF 2011 guidelines for the secondary prevention and risk reduction for patients atherosclerotic vascular disease recommend an adequate dose of statin to reduce LDL-C to < 100 mg/dL, to achieve at least a 30 percent reduction of LDL-C, and to lower non-HDL-C to < 130 mg/dL in patients who have TG ≥ 200 mg/dL.²⁸ Patients who have triglycerides > 500 mg/dL should be started on fibrate therapy in addition to statin therapy to prevent acute pancreatitis. If treatment with a statin (including trials of higher-dose statins and higher-potency statins) does not achieve goal levels, intensification of LDL-C-lowering drug therapy with a bile acid sequestrant or niacin is reasonable. For

patients who do not tolerate statins, LDL-C–lowering therapy with bile acid sequestrants and/or niacin is reasonable. The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants and/or niacin. For patients who continue to have an elevated non-HDL-C while on adequate statin therapy, the use of niacin or fibrate or fish oil may be reasonable.

In 2012, the American Association of Clinical Endocrinologists (AACE) published guidelines for the management of dyslipidemia and prevention of atherosclerosis.²⁹ 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) of 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.^{30,31} The more severe form, homozygous familial hypercholesterolemia (HoFH) is rare, occurring in about one out of a million people in the US. 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 US. 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.³² 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 ten 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 8 and 9 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.³³ Microsomal triglyceride transfer protein (MTP) transfers triglycerides onto apoB, during the production of VLDL, a precursor to LDL.³⁴

Lomitapide (Juxtapid) directly binds and inhibits MTP, preventing the synthesis of apo-B in enterocytes and hepatocytes.³⁵ 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.

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 15 to 30 percent although they have little, if any, effect on TG or HDL-C. The complementary mechanisms of action of bile acid sequestrants and statins makes them well suited for combination therapy. Combinations of bile acid sequestrants with non-

statin lipotropics may be useful in patients who are intolerant to statin therapy.³⁶ 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.³⁷

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.³⁸ 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.^{39,40,41,42} This effect is most significant in patients with diabetes or metabolic syndrome.⁴³ 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.^{44,45} 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.⁴⁶ 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.⁴⁷ 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.⁴⁸ 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. The ATP III states that fibric acids may have a role as adjuncts, especially with statins, in the treatment of patients with high TG and low HDL-C. Caution should be observed when using a statin and gemfibrozil together due to an increased risk of myositis and rhabdomyolysis. Concomitant gemfibrozil and statin use is considered a relative contraindication.⁴⁹ 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.^{50,51}

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.⁵² 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.⁵³ Niacin has been shown to reduce the risk of CHD as monotherapy and in combination with statins.^{54,55,56} It also leads to regression of carotid atherosclerosis when given with statins in a small study.^{57,58} Niacin caused regression of coronary lesions and reduced cardiovascular events in another small study when given in combination with cholestyramine and gemfibrozil.⁵⁹

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.⁶⁰ 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 ($p=0.80$).^{61,62} 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.⁶³

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.⁶⁴ 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.⁶⁵ 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 \geq 500 mg/dL.

Icosapent ethyl (Vascepa) is an ethyl ester of EPA only.⁶⁶ 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.⁶⁷

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.⁶⁸ 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™) ⁶⁹ | 7 | 39.7 | Major: M1 and M3 (CYP 3A4) | urine: 59.5 feces: 33.4 |
| Bile Acid Sequestrants | | | | |
| cholestyramine ⁷⁰ | not absorbed | -- | -- | feces |
| colesevelam (Welchol) ⁷¹ | not absorbed | -- | -- | feces |
| colestipol ⁷² | not absorbed | -- | -- | feces |
| Cholesterol Absorption Inhibitors | | | | |
| ezetimibe (Zetia) ⁷³ | 35-60 | 22 | ezetimibe glucuronide | urine: 11 feces: 78 |
| Fibric Acids | | | | |
| fenofibrate (Antara, Fenoglide, Lipofen, Lofibra, Tricor, Triglide) <small>74, 75, 76, 77, 78, 79 80</small> | unknown | 16-23 | fenofibric acid (active component); glucuronide conjugate | urine: 60 feces: 25 |
| fenofibric acid (Fibracor) ⁸¹ | unknown | 20 | glucuronide conjugate | urine |
| fenofibric acid (Trilipix) ⁸² | 81 | 20 | glucuronide conjugate | urine |
| gemfibrozil ⁸³ | 100 | 1.5 | 3 metabolites | urine: 70 feces: 6 |
| Niacin | | | | |
| niacin ER (Niaspan) ⁸⁴ | 60-76 | -- | many metabolites | predominantly urine |
| niacin IR (Niacor) ⁸⁵ | 88 | 0.3-0.75 | nicotinuric acid | urine |
| Omega-3 Fatty Acids | | | | |
| icosapent ethyl (Vascepa®) ⁸⁶ | -- | 89 | acetyl Coenzyme A | hepatic |
| omega-3-acid ethyl esters (Lovaza) ⁸⁷ | unknown | -- | -- | -- |

Fenofibrate micronized 67 mg capsule (Lofibra, generic) has been shown to provide similar therapeutic effects to fenofibrate “non-micronized” 100 mg capsule.^{88,89} All currently available fenofibrate products at the highest available dose produce similar plasma concentrations as the fenofibrate 200 mg capsules in single dose studies.^{90,91,92} Lipofen 150 mg capsules have been shown to be equivalent to Tricor 160 mg tablets under low-fat and high-fat fed conditions.⁹³ Fenoglide 120 mg tablets have been shown to be equivalent to fenofibrate 130 mg capsules under high-fat conditions.⁹⁴ Trilipix 135 mg capsules are equivalent to micronized fenofibrate 200 mg capsules administered under fed conditions.⁹⁵ Fibracor 105 mg tablets are equivalent to fenofibrate tablets (TriCor) 145 mg under fasted conditions.⁹⁶

CONTRAINDICATIONS/WARNINGS

Bile acid sequestrants, cholestyramine, colestipol, and colesevelam (Welchol), are contraindicated in patients with dysbetalipoproteinemia and/or TG > 400 mg/dL.⁹⁷ Colesevelam is contraindicated in patients with bowel obstruction and in patients with hypertriglyceridemia-induced pancreatitis.⁹⁸ Cholestyramine is contraindicated in complete biliary obstruction.⁹⁹

The combination of ezetimibe (Zetia) and a statin is contraindicated in patients with acute liver disease or unexplained persistent elevations in serum transaminases.¹⁰⁰

Fenofibrate products (Antara, Fenoglide, Lofibra, Lipofen, Tricor, Triglide) and fenofibric acid (Fibracor, Trilipix) are contraindicated in patients with hepatic or severe renal dysfunction including primary biliary cirrhosis or persistent liver enzyme elevations or preexisting gallbladder disease.^{101,102,103,104,105,106,107} Gemfibrozil is contraindicated in severe renal or hepatic impairment, including primary biliary cirrhosis, and combination therapy with repaglinide. The use of fibric acids is not recommended in nursing mothers, and it is considered a contraindication for use of Fibracor, 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 postmarketing in patients on fenofibrate therapy.¹⁰⁸ 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 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.¹⁰⁹ Monitor liver function tests in all patients during therapy, at approximately six-month intervals, or when clinically indicated.¹¹⁰ 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.¹¹¹ 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-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.^{112,113} 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.¹¹⁴

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.¹¹⁵ 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.

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 4 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, colestevlam 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.¹¹⁶

Lomitapide (Juxtapid) is contraindicated in patients who are pregnant.¹¹⁷ 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. 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). 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.¹¹⁸ 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 for deficiencies in these nutrients.

Risk Evaluation and Mitigation Strategy (REMS)

Due to the risk of hepatotoxicity, lomitapide (Juxtapid) is only available through a restricted program under the REMS.^{119,120} The goal of the REMS is to educate prescribers the risk of hepatotoxicity 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. Providers must 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) ¹²¹ | 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 |
| Bile Acid Sequestrants | | | | | | |
| cholestyramine, colestipol ^{122, 123, 124} | | reduced bioavailability of ezetimibe | reduced bioavailability of fenofibrate or fenofibric acid | reduced absorption of niacin | -- | -- |
| colesevelam (WelChol) ^{125, 126} | | reduced bioavailability of ezetimibe | reduced bioavailability of fenofibrate or fenofibric acid | -- | -- | -- |
| Cholesterol Absorption Inhibitors | | | | | | |
| ezetimibe (Zetia) ¹²⁷ | reduced bioavailability of ezetimibe | | increased ezetimibe concentration with risk of cholelithiasis | -- | -- | -- |
| Fibric Acids | | | | | | |
| fenofibrate (Antara, Fenoglide, Lipofen, Lofibra, Tricor, Triglide) ^{128, 129, 130, 131, 132, 133} | reduced bioavailability of fenofibrate | increased ezetimibe concentration with risk of cholelithiasis | | -- | -- | increased risk of myopathy and rhabdomyolysis |
| fenofibric acid (Fibricor) ¹³⁴ | reduced bioavailability of fenofibric acid | increased ezetimibe concentration | | -- | -- | increased risk of myopathy and rhabdomyolysis |
| fenofibric acid (Trilipix) ¹³⁵ | reduced bioavailability of fenofibric acid | increased ezetimibe concentration | | -- | -- | increased risk of myopathy and rhabdomyolysis |
| gemfibrozil ¹³⁶ | 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) ¹³⁷ | administration with cholestyramine or colestipol reduces absorption of niacin | -- | -- | | -- | increased risk of myopathy |
| niacin IR (Niacor) ¹³⁸ | -- | -- | -- | | -- | increased risk of myopathy |
| Omega-3 Fatty Acids | | | | | | |
| icosapent ethyl (Vascepa®) ¹³⁹ | -- | -- | -- | -- | | -- |
| omega-3-acid ethyl esters (Lovaza) ¹⁴⁰ | -- | -- | -- | -- | | -- |

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

Diltiazem, mycophenolate - The bile acid sequestrants reduce the absorption of diltiazem and mycophenolate, regardless of the time of administration of the interacting drugs relative to each other.^{141,142} 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.¹⁴³

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.^{144,145}

Colesevelam reduces levels of cyclosporine, glimepiride, glipizide, glyburide, levothyroxine, olmesartan, and oral contraceptives containing ethinyl estradiol and norethindrone.¹⁴⁶ 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.¹⁴⁷

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.¹⁴⁸

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.¹⁴⁹

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

Warfarin – Concomitant administration of fibric acids and warfarin increases the INR and the risk of bleeding.^{150,151,152,153,154}

Cyclosporine – Concomitant use of cyclosporine and fenofibrate or fenofibric acid (Fibracor, Trilipix) may decrease renal function.^{155,156,157}

Oral hypoglycemics – The concurrent use of gemfibrozil with glyburide (Diabeta[®], Glynase[®]), pioglitazone (Actos[®]) or rosiglitazone (Avandia[®]) may result in enhanced hypoglycemic effect.^{158,159,160,161} The use of gemfibrozil with repaglinide (Prandin[®]) is contraindicated due to a significant increase in serum concentrations of the oral hypoglycemic.¹⁶²

Colchicine – Myopathy, including rhabdomyolysis, have been reported with concurrent use of fenofibrate and colchicine. Use caution when prescribing both agents.¹⁶³

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).¹⁶⁴ 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.¹⁶⁵

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.^{166,167}

lomitapide (Juxtapid)¹⁶⁸

CYP3A4 inhibitors - Concomitant use of strong CYP3A4 inhibitors (boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir) 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, tipranavir/ritonavir, 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.¹⁶⁹ Simvastatin dose should not exceed 20 mg daily or 40 mg daily for patient 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) – Coadministration 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.

ADVERSE EFFECTS

| Drug | Abd. Pain | Back pain | Headache | Abnormal LFTs | Constipation | Dyspepsia |
|--|--------------|--------------|--------------|---------------|--------------|----------------|
| Apolipoprotein B Synthesis Inhibitors | | | | | | |
| lomitapide (Juxtapid) ¹⁷⁰ | 34 | 14 | 10 | 21 | 21 | 38 |
| Bile Acid Sequestrants | | | | | | |
| cholestyramine ¹⁷¹ | reported | nr | nr | nr | common | reported |
| colesevelam (Welchol) ¹⁷² | 5 (5) | 3 (6) | 3.9 (3.1) | nr | 11 (7) | 8 (3) |
| colestipol ¹⁷³ | reported | reported | reported | reported | common | reported |
| Cholesterol Absorption Inhibitors | | | | | | |
| ezetimibe (Zetia) ¹⁷⁴ | 3 (2.8) | 4 (4) | nr | nr | nr | nr |
| Fibric Acids | | | | | | |
| fenofibrate (Antara, Fenoglide, Lofibra, Lipofen, Tricor, Triglide) ^{175, 176, 177, 178, 179} | 4.6 (4.4) | 3.4 (2.5) | 3.2 (2.7) | 2-8 (1.4) | 2.1 (1.4) | reported |
| fenofibric acid (Fibracor) ¹⁸⁰ | 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) ¹⁸¹ | 4.6 (4.4) | 3.4 (2.5) | 3.2 (2.7) | 7.5 (1.4) | 2.1 (1.4) | 3.7 |
| gemfibrozil ¹⁸² | 9.8 (5.6) | nr | 1.2 (1.1) | 1 | 1.4 (1.3) | 19.6 (11.9) |
| Niacin | | | | | | |
| niacin ER (Niaspan) ¹⁸³ | 2-5 (3) | nr | 8-11 (15) | reported | nr | 2-5 (8) |
| niacin IR (Niacor) ¹⁸⁴ | nr | nr | reported | reported | nr | reported |
| Omega-3 Fatty Acids | | | | | | |
| icosapent ethyl (Vascepa®) ¹⁸⁵ | nr | nr | nr | nr | nr | nr |
| omega-3-acid ethyl esters (Lovaza) ¹⁸⁶ | 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.

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.¹⁸⁷ Colesevelam can increase TG in combination with insulin or sulfonylureas.¹⁸⁸ In the diabetes trials, the overall incidence of hypoglycemia was three percent in patients on colesevelam versus 2.3 percent in placebo-treated patients.¹⁸⁹

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.¹⁹⁰

Fibric acids: Fibric acids may cause cholelithiasis. Fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide) and fenofibric acid (Fibracor, Trilipix) may also cause myositis, myopathy and rhabdomyolysis; this risk may be further increased when given concomitantly with statins.^{191,192,193,194}

Fenofibrate use is associated with reversible elevations in serum creatinine. The clinical significance of this is unknown.¹⁹⁵ 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).¹⁹⁶ 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.

Lomitapide:¹⁹⁷ Other commonly reported adverse reactions were gastrointestinal in nature, reported by 93 percent of patients on lomitapide in clinical trials. Other adverse effects reported include influenza (21 percent), decreased weight (24 percent), chest pain (24 percent), fatigue (17 percent), and pharyngolaryngeal pain (14 percent).

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.^{198,199}

Omega-3-acids: Arthralgia has been reported with icosapent ethyl (Vascepa) use.²⁰⁰

SPECIAL POPULATIONS

Pediatrics

Many of the products in the Other Lipotropics category do not have safety and effectiveness data in the pediatric population. Limited data are available for use in children for cholestyramine and colestipol.²⁰¹ Pediatric patients have been reported to experience hyperchloremic metabolic acidosis or gastrointestinal obstruction with the use of cholestyramine.²⁰² 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.²⁰³ 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.²⁰⁴ Safety and efficacy of fibric acids (fenofibrate, fenofibric acid, and

gemfibrozil), lomitapide (Juxtapid), omega-3-acid ethyl esters (Lovaza) and icosapent ethyl (Vascepa) have not been established in pediatrics.^{205,206}

In a multicenter, 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.²⁰⁷ 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).^{208,209} 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<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

Most of the products in this class are Pregnancy Category C. The exceptions include cholestyramine and colesevelam (Welchol) which are non-absorbable and therefore considered Pregnancy Class B. Niacin is Pregnancy Category A for recommended daily allowance nutrient amounts; however, for the treatment of hyperlipidemia, niacin is considered Pregnancy Category C. Lomitapide (Juxtapid) is Pregnancy Category X, therefore contraindicated during pregnancy.²¹⁰ 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.

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.^{211,212,213,214,215,216}

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.²¹⁷

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.

Lomitapide (Juxtapid) is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C).²¹⁸ 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).²¹⁹

DOSAGES

| Drug | Availability | Dose | Comments |
|--|--|--|---|
| Apolipoprotein B Synthesis Inhibitors | | | |
| lomitapide (Juxtapid) ²²⁰ | 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. |
| Bile Acid Sequestrants | | | |
| cholestyramine ²²¹ | powder | One to two packets or scoopfuls twice daily | Mix with two to six ounces of water or pulpy fruit (applesauce) |
| colesevelam (WelChol) ²²² | 625 mg tablets 1,875 and 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 ²²³ | 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) ²²⁴ | 10 mg tablets | 10 mg daily | Take with or without food |

Dosages (continued)

| Drug | Availability | Dose | Comments |
|---|--|---------------------------------------|--|
| Fibric Acids | | | |
| fenofibrate ²²⁵ | generic and Lofibra: 67, 134, 200 mg capsules | 67-200 mg daily | Must be taken with food |
| | generic and Lofibra: 54, 160 mg tablets | 54-160 mg daily | Must be taken with food |
| fenofibrate (Antara) ²²⁶ | 43, 130 mg capsules | 43–130 mg daily | Take without regard to meals |
| fenofibrate (Fenoglide) ²²⁷ | 40, 120 mg tablets | 40-120 mg daily | Take with food |
| fenofibrate (Lipofen) ²²⁸ | 50, 150 mg capsules | 50-150 mg daily | Take with food |
| fenofibrate (Tricor) ²²⁹ | 48, 145 mg tablets | 48-145 mg daily | Take without regard to meals |
| fenofibrate (Triglide) ²³⁰ | 50, 160 mg tablets | 50-160 mg daily | Take without regard to meals |
| fenofibric acid (Fibracor) ²³¹ | 35, 105 mg tablets | 35-105 mg daily | Take without regard to meals |
| fenofibric acid (Trilipix) ²³² | 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) ²³³ | 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) ²³⁴ | 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®) ²³⁵ | 1 g capsules | 2 g twice daily | Take with food Swallow capsules whole |
| omega-3-acid ethyl esters (Lovaza) ²³⁶ | 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.

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, there have been no published clinical outcomes studies of colesevelam (Welchol), colestipol, or omega-3-acid ethyl esters (Lovaza). Though there are cardiovascular outcomes studies with EPA and DHA, they do not use the specific formulation for omega-3-acid ethyl esters (Lovaza).²³⁷

Ezetimibe (Zetia) has been shown to provide additional LDL-C lowering when added to simvastatin (Zocor) or atorvastatin (Lipitor®), as well as other statin therapy.^{238,239,240,241,242,243} The effect of ezetimibe on CV morbidity and mortality has not been determined. **A large clinical trial is underway to evaluate the potential CV benefits of ezetimibe.**²⁴⁴

Clinical trials for fenofibric acid (Fibracor) have used fenofibrate and at dosages equivalent to 105 mg fenofibric acid (Fibracor).²⁴⁵

The effect of fenofibrates on coronary heart disease morbidity and mortality and non-CV mortality has not been established.^{246,247,248,249,250}

No incremental benefit of niacin ER (Niaspan) co-administered with simvastatin or lovastatin on cardiovascular morbidity and mortality over and above that demonstrated for niacin, simvastatin, or lovastatin monotherapy has been established.²⁵¹

The effects of icosapent ethyl (Vascepa) and omega-3-acid ethyl esters (Lovaza) on CV mortality and morbidity in patients with severe hypertriglyceridemia have not been determined.^{252,253}

The effect of lomitapide on CV morbidity and mortality has not been determined.²⁵⁴ The safety and effectiveness of lomitapide have not been established in patients with hypercholesterolemia who do not have HoFH. Due to paucity of data, an open-label study for lomitapide has been included.

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.²⁵⁵ 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.²⁵⁶ 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/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.²⁵⁷ 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.²⁵⁸ 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.

ezetimibe (Zetia) and simvastatin

The ENHANCE trial, a two-year, randomized, double-blind, multicenter study of 720 patients with heterozygous familial hypercholesterolemia (HeFH) compared ezetimibe/simvastatin 10/80 mg versus simvastatin 80 mg.^{259,260} The study showed no significant difference between ezetimibe/simvastatin versus simvastatin in the primary endpoint of carotid intima media thickness (IMT), measured at three sites in the carotid arteries, using ultrasound imaging. The change in mean carotid IMT after two years was 0.0111 ± 0.0038 mm versus 0.0058 ± 0.0037 mm, for the combination product versus simvastatin alone ($p = 0.29$). Ezetimibe/simvastatin reduced LDL-C to a greater degree, 58 percent compared to simvastatin 41 percent, ($p < 0.01$), after two years of treatment. There was a between group difference of 16.5 percent ($p < 0.01$) for LDL-C lowering when comparing the simvastatin group to the ezetimibe/simvastatin group. This was not a clinical outcomes study, yet it generated attention since carotid ultrasound imaging can be a predictor of cardiac events, and the study results were delayed in being released. The American College of Cardiology (ACC) and American Heart Association (AHA) released recommendations regarding the use of products containing ezetimibe and considers it a reasonable option for patients who are currently on a high-dose statin but are not at LDL-C goal, cannot tolerate statins, or can only tolerate a low-dose statin.²⁶¹ The National Institute for Health and Clinical Excellence (NICE) guidelines echo these recommendations.²⁶²

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.²⁶³ 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).^{264,265} 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 patient at moderately high/high risk of coronary heart disease with LDL-C levels higher than the NCEP ATP III 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.²⁶⁶ 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.

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.^{267,268} 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 end point of definite CHD death and/or definite nonfatal MI; this reflected a 24 percent reduction in definite CHD death and a 19 percent reduction in nonfatal MI. The cumulative seven-year incidence of the primary end point was seven percent in the cholestyramine group and 8.6 percent in the placebo group. In addition, the incidence rates were reduced for new positive exercise tests (by 25 percent compared to placebo; $p < 0.001$) and new onset angina (by 20 percent; $p < 0.01$). The incidence of coronary bypass surgery was similar in each group. The risk of death from all causes was reduced by seven percent ($p = \text{NS}$) in the cholestyramine group; the magnitude of this decrease was less than for CHD end points because of a greater number of violent and accidental deaths in the cholestyramine group.

cholestyramine, gemfibrozil, and niacin 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.²⁶⁹ 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, sulfonyleurea, and insulin

Efficacy of colesevelam in type 2 diabetes mellitus was evaluated in three double-blind, placebo-controlled trials in combination with metformin, sulfonyleurea, or insulin.²⁷⁰ 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.²⁷¹ 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).²⁷² 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.²⁷³ 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. A total of 170 patients with type 2 diabetes mellitus in the FIELD cohort were randomly assigned to micronized fenofibrate 200 mg day or placebo in a double-blind fashion and showed that carotid intima media thickness (CIMT) and the augmentation index at second and fifth year visits increased similarly in both treatment groups.²⁷⁴

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.²⁷⁵ 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.²⁷⁶ 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 were reviewed.²⁷⁷ 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.^{278,279} 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.²⁸⁰ At the conclusion of the study, all participants were given the opportunity to receive gemfibrozil for an additional 3.5 years.²⁸¹ 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.²⁸² Three-hundred and eleven of these patients were randomized to receive gemfibrozil 1,200 mg/day and 317 subjects to receive placebo over five years in double-blind fashion. The primary end-point, a composite of fatal and non-fatal MI and cardiac deaths, did not differ significantly between the placebo and gemfibrozil groups. The same was true for total mortality. In the study, data were not evaluated for several key prognostic factors, including the presence, and between group distribution, of the true prevalence of CHD, extent of coronary artery obstructions, and degree of left ventricular dysfunction.

A 13-year post trial follow-up of the Helsinki Heart Study compared 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 ($p = 0.05$).²⁸³

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.²⁸⁴ 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; $p = 0.004$).^{285,286}

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.²⁸⁷ 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 III, 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).²⁸⁸ Patients ($n = 702$) on a stable diet were randomized to icosapent ethyl 4 or 2 g per day or placebo. The primary end point 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.²⁸⁹ 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.

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.²⁹⁰ 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).²⁹¹ 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).^{292,293} 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.²⁹⁴ 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.²⁹⁵ Data from 53 trials ($n=16,802$) using fibric acids and 30 trials ($n=4,749$) using niacin were included in the meta-analysis. Fibric acids included agents which have never been available in the US in addition to gemfibrozil and fenofibrate. Niacin products included immediate-, sustained-, and extended-release formulations. Reductions in LDL-C and TG were 36 and eight percent for fibric acids and 20 and 14 percent for niacin, respectively. Increases in HDL-C were 10 and 16 percent for fibric acids and niacin, respectively. Relative risk reduction for major cardiac events was 25 and 27 percent for fibric acids and niacin, respectively.

A pooled meta-analysis of 10 long-term, randomized, placebo-controlled, clinical trials of fenofibrate, gemfibrozil, bezafibrate, and fenofibrate evaluated these agents role in prevention of CV events.²⁹⁶ 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.²⁹⁷ 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.²⁹⁸ 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 2009.²⁹⁹ 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.³⁰⁰ 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 2010.³⁰¹ 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).³⁰² 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^{303,304,305,306,307}

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 ^{308,309,310,311} cholestyramine, colestipol, colesvelam (Welchol) | -9 to -13 | -12 to -30 | +3 to +9 | 0 to +25 |
| Cholesterol Absorption Inhibitors ³¹² ezetimibe (Zetia) | -12 to -14 | -13 to -20 | +1 to +5 | -5 to -11 |
| Fibric Acids ^{313,314,315,316,317,318,319,320,321,322,323,324,325,326,327} fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide) gemfibrozil | -4 to -26 | -27 to +9 | +6 to +18 | -29 to -54 |
| fenofibric acid (Fibracor) | -9 to -22 | -31 to +45 | +10 to +23 | -24 to -54 |
| fenofibric acid (Trilipix) ³²⁸ | -12 | -5 | +16 | -31 |
| lomitapide (Juxtapid) ³²⁹ | -36 | -40 | -7 | -45 |
| niacin ER (Niaspan) ^{330,331} | -3 to -10 | -14 to +2 | +18 to +26 | -13 to -29 |
| niacin IR (Niacor) ³³² | -10 to -20 | -10 to -20 | +20 to +35 | -30 to -70 |
| omega-3-acid ethyl esters (Lovaza) ³³³ | -10 | +45 | +9 | -45 |
| icosapent ethyl (Vascepa) ³³⁴ | -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). Other agents, however, have a role in the treatment of patients who require combination therapy or who are unable to tolerate the statins.

The bile acid sequestrant, cholestyramine, has been shown to reduce major coronary events and CHD deaths. The bile acid sequestrants are effective in lowering LDL-C and raising HDL-C; they do not lower TG levels. They can be used in combination with statins. Patients generally have poor compliance to bile acid sequestrants because of the side effect profile. Colesevelam (WelChol) provides an alternative to cholestyramine and colestipol with a potential lower incidence of GI effects. Colesevelam (Welchol) 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 CV events and CHD mortality 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 and, possibly, total mortality. 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, ezetimibe (Zetia) has not been shown to reduce CV morbidity or mortality. Large clinical outcomes trials are underway to assess potential CV benefits, beyond treatment with a statin alone. 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.

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.

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

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

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