Lipotropics, Other
Therapeutic Class Review (TCR)

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6950 Columbia Gateway Drive
Columbia, Maryland 21046

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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)
Adenosine Triphosphate-Citrate Lyase (ACL) Inhibitor		
bempedoic acid* (Nexletol®)[1]	Esperion	▪ As adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (CVD) who require additional lowering of low-density lipoprotein cholesterol (LDL-C)
ACL Inhibitor/Cholesterol Absorption Inhibitor		
bempedoic acid/ ezetimibe* (Nexlizet®)[2]	Esperion	▪ As adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or established atherosclerotic CVD who require additional lowering of LDL-C
Angiopoietin-like 3 (ANGPTL3) Inhibitor		
evinacumab-dgnb† (Evkeeza™)[3]	Regeneron	▪ As an adjunct to other LDL-C lowering therapies for the treatment of adult and pediatric patients ≥ 12 years old with homozygous familial hypercholesterolemia (HoFH)
Apolipoprotein B Synthesis Inhibitor		
lomitapide (Juxtapid®)[4]	Aegerion	▪ Reduction of LDL-C, total cholesterol (Total-C), apolipoprotein B (Apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with HoFH, as an adjunct to a low-fat diet and other lipid-lowering treatments
Bile Acid Sequestrants		
cholestyramine (Questran®, Questran® Light)[5]	generic, Par	▪ Primary hypercholesterolemia ▪ Relief of pruritus associated with partial biliary obstruction
colesevelam‡ (Welchol®)[6]	generic, Daiichi Sankyo, Cosette	▪ As adjunct to diet and exercise to reduce elevated LDL-C in adults with primary hyperlipidemia ▪ Reduction of LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with HeFH who are unable to reach LDL-C target despite adequate trial of dietary therapy and lifestyle modifications ▪ Glycemic control in adults with type 2 diabetes mellitus (T2DM)
colestipol (Colestid®)[7,8]	generic, Pharmacia/Pfizer	▪ Primary hypercholesterolemia

* Limitations of use for both bempedoic acid (Nexletol) and bempedoic acid/ezetimibe (Nexlizet) include that the effect on cardiovascular (CV) morbidity and mortality has not been determined.

† Limitations of use for evinacumab-dgnb (Evkeeza) include that (1) safety and effectiveness have not been established in patients with other causes of hypercholesterolemia, including those with HeFH; and (2) the effects on CV morbidity and mortality have not been determined.

‡ Limitations of use for colesevelam (Welchol) include that (1) it should not be used to treat type 1 diabetes mellitus or diabetic ketoacidosis; (2) its effects on cardiovascular morbidity and mortality have not been established; (3) it has not been studied in T2DM in combination with a dipeptidyl peptidase 4 (DPP4) inhibitor; (4) it has not been studied in Frederickson Type I, III, IV, and V dyslipidemias; and (5) it has not been studied in children < 10 years of age or in premenarchal girls.

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FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
Cholesterol Absorption Inhibitors		
ezetimibe (Zetia®)[9]	generic, Merck Sharp & Dohme, Organon	▪ Primary hypercholesterolemia (monotherapy or in combination with a statin) ▪ Mixed hyperlipidemia (in combination with fenofibrate) ▪ HoFH (adjunctive therapy in combination with atorvastatin or simvastatin) ▪ Homozygous familial sitosterolemia
Fibric Acids		
fenofibrate (Antara®)[10,11]	generic, Lupin	As an adjunct to diet: ▪ To reduce elevated LDL-C, Total-C, triglycerides (TG), and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia ▪ To treat adult patients with severe hypertriglyceridemia
fenofibrate (Fenoglide®)[12]	generic, Santarus	
fenofibrate (Lipofen®)[13]	Ani, Kowa	
fenofibrate[14]	generic	
fenofibrate (Tricor®)[15]	generic, Abbvie	
fenofibric acid (Fibricor®)[16]	generic§, Athena	▪ Primary hyperlipidemia or mixed dyslipidemia in adults ▪ Severe hypertriglyceridemia (≥ 500 mg/dL) in adults
fenofibric acid (Trilipix®)[17]	generic, Abbvie	▪ Primary hyperlipidemia or mixed dyslipidemia ▪ Severe hypertriglyceridemia
gemfibrozil (Lopid®)[18]	generic, Pfizer	▪ Hypercholesterolemia, Fredrickson type IIb (in patients without history of or symptoms of existing coronary heart disease [CHD]) ▪ Hypertriglyceridemia, Fredrickson types IV and V hyperlipidemia
Niacin		
niacin ER (Niaspan®)[19]	generic, Abbvie	▪ Primary hyperlipidemia or mixed dyslipidemia ▪ 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®)[20]	Redmont, Avondale	▪ 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)

§ Authorized generic (AG) available.

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FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
Omega-3 Fatty Acids		
icosapent ethyl¶ (Vascepa®)[21]	generic, Amarin	▪ As adjunct to maximally tolerated statin therapy to reduce the risk of MI, stroke, coronary revascularization, and unstable angina requiring hospitalization in adults with elevated TG levels (≥ 150 mg/dL) and – Established CVD; or – Diabetes mellitus and ≥ 2 additional risk factors for CVD ▪ As adjunct to diet, to reduce TG levels in adults with severe hypertriglyceridemia (TG ≥ 500 mg/dL)
omega-3 acid ethyl esters (Lovaza®)[22]	generic, Woodward	▪ Treatment of hypertriglyceridemia in adults with TG ≥ 500 mg/dL
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors		
alirocumab (Praluent®)[23]	Sanofi/Regeneron, Regeneron	▪ To reduce the risk of MI, stroke, and unstable angina requiring hospitalization in adults with established atherosclerotic cardiovascular disease (ASCVD) ▪ As adjunct to diet, alone or in combination with other LDL-C-lowering therapies (e.g., statins, ezetimibe), in adults with primary hyperlipidemia, including HeFH, to reduce LDL-C ▪ As an adjunct to other LDL-C-lower therapies in adults with HoFH to reduce LDL-C
evolocumab (Repatha®)[24]	Amgen	▪ To reduce the risk of MI, stroke, and coronary revascularization in adults with established CVD ▪ As adjunct to diet, alone or in combination with other LDL-lowering therapies, for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C ▪ As an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HeFH, to reduce LDL-C ▪ As an adjunct to other LDL-lowering therapies in adults and pediatric patients aged 10 years and older with HoFH to reduce LDL-C
PCSK9-Directed Small Interfering Ribonucleic Acid (siRNA)		
inclisiran‖ (Leqvio®)[25]	Novartis	▪ As an adjunct to diet and maximally tolerated statin therapy in adults with HeFH or clinical ASCVD who require additional LDL-C reduction

¶ The effects of 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 inclisiran on cardiovascular morbidity and mortality has not been determined.

The combination statin product, ezetimibe/simvastatin (Vytorin®), is not discussed in this review.

OVERVIEW

Many clinical trials have demonstrated that a high serum concentration of low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C) are major risk factors for coronary heart disease (CHD). The National Health and Nutrition Examination Survey (NHANES) reported that in 2015 to 2018, approximately 11.4% of adults in the United States (US) had high total cholesterol (≥ 240 mg/dL) and 17.2% had low HDL-C (< 40 mg/dL).[26] The prevalence of high total

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cholesterol was higher in women (12.1%) compared to men (10.5%), but the difference was not significant. The prevalence of low HDL-C was higher in men (26.6%) compared to women (8.5%). In 2015 to 2018, there were no significant race or Hispanic-origin differences in the prevalence of high total cholesterol in adults. The NHANES analysis was based on measured cholesterol only and did not consider whether lipid-lowering medications were taken. In addition, NHANES reported that the percentage of adults aged 20 and over with elevated triglycerides (TG) declined from 33.3% for 2001 to 2004 to 25.1% during 2009 to 2012.[27]

Between 2013 and 2019, the American College of Cardiology (ACC) and the American Heart Association (AHA), in combination with the National Heart, Lung, and Blood Institute (NHLBI), released 4 new consensus guidelines regarding cholesterol management, cardiovascular (CV) risk assessment, obesity, and lifestyle. ACC/AHA emphasizes lifestyle modification, including a reduced calorie diet and aerobic physical activity, as a critical component of atherosclerotic cardiovascular disease (ASCVD) risk reduction, both prior to and in conjunction with cholesterol lowering drug therapies.[28,29,30,31] Additionally, in June 2021, the AHA published a scientific statement on physical activity as a crucial component in the first-line treatment for increased blood pressure and cholesterol.[32] The statement details mild- to moderate-risk patient groups appropriate for lifestyle-only treatment of increased cholesterol as well as a description of the recommendations, usual effects, and considerations for lifestyle management with physical activity. Guidance and resources are also provided for evaluating, prescribing, counseling, and referring to assist in increased physical activity.

There is a high level of evidence supporting the use of hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors ("statins") for secondary prevention and moderate to high level of evidence for their use for primary prevention.[33] As a class, they can lower LDL-C by ≥ 50% in a dose-related fashion. Statins typically have relatively minor effects on TG and high-density lipoprotein cholesterol (HDL-C) levels, reducing TG by 7% to 30% and increasing HDL-C by approximately 5% to 15%.[34]

Many non-statin therapies do not provide adequate ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD.[35] As demonstrated in the AIM-HIGH study, the additional reduction in non-HDL-C (as well as apolipoprotein B [Apo B], lipoprotein (a) [Lp(a)], and triglycerides [TG]) levels with niacin therapy did not further reduce ASCVD risk in individuals treated to LDL-C levels of 40 to 80 mg/dL.[36] The ACCORD trial reported that, in diabetic patients with and without clinical CV disease, the addition of fenofibrate to simvastatin therapy did not reduce the risk for CV events compared with simvastatin alone.[37] However, the ACC/AHA recognizes that maximally tolerated statin therapy might not be adequate to lower LDL-C sufficiently to reduce ASCVD event risk in individuals with primary severe elevations of LDL-C (≥ 190 mg/dL) at which time the addition of non-statin agents can be considered.[38] In contrast, the IMPROVE-IT study reported an average additional reduction in LDL-C of 17 mg/dL with the addition of ezetimibe to simvastatin.[39] The primary composite endpoint of CV death, myocardial infarction (MI), unstable angina, stroke, and coronary revascularization was significantly lower with combination therapy as compared to simvastatin alone (32.7% versus 34.7%, respectively; p=0.016). A significant reduction in MI and ischemic stroke and a nonsignificant increase in risk of hemorrhagic stroke were also reported with combination therapy.

In 2015, the FDA approved alirocumab (Praluent) and evolocumab (Repatha), a new class of lipotropic agents. Both are human monoclonal antibodies that bind to proprotein convertase subtilisin/kexin type 9 (PCSK9). The FOURIER (evolocumab; n=27,564) and ODYSSEY OUTCOMES (alirocumab; n=18,924) trials reported a 15% reduction in CV risk when evolocumab (Repatha) or alirocumab (Praluent) were added to optimal statin therapy.[40,41,42] LDL-C levels were reduced by 59% and 55% with each drug, respectively.

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In addition, the EBBINGHAUS cognitive function trial, a substudy of FOURIER, also demonstrated that evolocumab had no significant effect on cognitive function compared to placebo.[43,44]

In 2022, an international panel which included clinicians, methodologists, and patients published a clinical practice guideline on the use of PCSK9 inhibitors and ezetimibe for the reduction of CV events.[45] Notably, the guideline includes mostly weak recommendations, and the authors emphasize that shared decision making must be utilized when applying the recommendations to practice. The guideline suggests that adult patients on high-intensity statin therapy with LDL-C > 70 mg/dL who are considered high-risk (15-20% five-year risk of a major cardiovascular event [MACE]) be placed on ezetimibe as a second lipid-lowering drug, and very high-risk patients (>20% five-year risk of MACE) be placed on ezetimibe first, followed by a PCSK9 inhibitor (alirocumab, evolocumab). For adults with LDL-C > 70 mg/dL who are intolerant to statins, the guideline recommends against the use of alternate lipid-lowering therapy for low-risk patients (<5% five-year risk of MACE) and moderate-risk patients (5-15% five-year risk of MACE), while high-risk and very high-risk patients should be prescribed ezetimibe first, followed by the potential addition of a PCSK9 inhibitor.

Since the release of the 2013 guidelines for the treatment of blood cholesterol to reduce atherosclerotic CV risk in adults, the ACC/AHA no longer supports the use of the National Cholesterol Education Program (NCEP) Expert Panel on Diagnosis, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) algorithm for risk assessment, citing that it is derived in an exclusively Caucasian sample population and is focused on the limited scope of CHD alone.[46,47] Instead, they recommend use of the race- and gender-specific Pooled Cohort Equations to estimate 10-year ASCVD risk in both Caucasian and African American men and women.[48] They also no longer support a treat-to-target approach with goals such as LDL-C < 70 mg/dL and < 100 mg/dL for secondary and primary ASCVD prevention, respectively; rather, the guidelines advocate using the maximum tolerated statin intensity in patients identified to benefit from statin therapy and focus on treatments proven to reduce ASCVD events. The 2018 AHA/ACC guidelines on management of blood cholesterol, published along with several other relevant professional organizations, emphasizes lifestyle therapies to reduce ASCVD risk.[49] The 2018 guidelines expand upon the use of the 10-year ASCVD risk score and advise consideration of risk-enhancing factors, such as family history of premature ASCVD, persistent LDL-C ≥ 160 mg/dL, persistent TG ≥ 175 mg/dL, metabolic syndrome, chronic kidney disease (CKD), history of preeclampsia or premature menopause, chronic inflammatory disorders, and high-risk ethnic groups, among others, when considering antilipid therapy. Coronary calcium score may also be used when uncertainty of level of ASCVD risk exists. For primary prevention, statins are recommended in patients with severe hypercholesterolemia and in adults 40 to 75 years of age with diabetes mellitus or at higher ASCVD risk. For secondary prevention, in very high-risk ASCVD patients (history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions), ACC/AHA considers the addition of ezetimibe to maximally tolerated statin therapy a reasonable option when the LDL-C level remains ≥ 70 mg/dL; if LDL-C level still remains ≥ 70 mg/dL, then a PCSK9 inhibitor can be added. For LDL-C ≥ 190 mg/dL, high-intensity statin therapy is warranted regardless of ASCVD risk score. If LDL-C remains ≥ 100 mg/dL ezetimibe should be added, and if LDL-C is still ≥ 100 mg/dL and the patient has multiple risk factors, addition of a PCSK9 inhibitor may be considered.

High plasma HDL cholesterol (HDL-C) is associated with reduced risk of MI, but whether this association is causal is unclear. A study published in 2012 that utilized databases of genetic information found that raising HDL-C levels may not affect heart disease risk.[50] The study reported that carriers of the *LIPG 396Ser* allele (2.6% frequency) had higher HDL-C (0.14 mmol/L higher; $p=8\times10^{-13}$) but similar levels of

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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% (odds ratio [OR], 0.87; 95% confidence interval [CI], 0.84 to 0.91), but the investigators found that the *396Ser* allele was not associated with risk of MI (OR, 0.99; 95% CI, 0.88 to 1.11; p=0.85). These data challenge the concept that raising HDL-C will uniformly translate into reductions in risk of MI.

The NCEP categorizes above normal serum TG levels as borderline high with levels between 150 to 199 mg/dL, high TG between 200 to 499 mg/dL, and very high TG as levels ≥ 500 mg/dL.[51] The 2012 guidelines on the evaluation and treatment of hypertriglyceridemia by the Endocrine Society (ES) state that severe and very severe hypertriglyceridemia increase the risk for pancreatitis, whereas mild or moderate hypertriglyceridemia may be a risk factor for CVD.[52] To take into account the risk for pancreatitis, the ES defines mild hypertriglyceridemia as TG levels between 150 to 199 mg/dL, moderate hypertriglyceridemia as TG levels between 200 to 999 mg/dL, severe hypertriglyceridemia as TG levels between 1,000 to 1,999 mg/dL, and very severe hypertriglyceridemia as TG levels ≥ 2,000 mg/dL. A high TG level is a component of metabolic syndrome, which is associated with risk for CVD. The ES recommends hypertriglyceridemia screening in adults as part of a lipid panel at least every 5 years and suggests that use of apo B or Lp(a) levels can be of value. Patients with primary hypertriglyceridemia should be evaluated for family history of dyslipidemia and CVD to assess genetic causes and future CVD risk. In addition to lifestyle changes, ES recommends drug therapy to reduce the risk of pancreatitis in patients with severe and very severe hypertriglyceridemia; a fibrate is considered first-line treatment. For patients with moderate to severe hypertriglyceridemia, fibrates, niacin, or omega-3 fatty acids alone or in combination with statins may be considered. Statins should not be used alone for severe or very severe hypertriglyceridemia; however, statins may be useful for the treatment of moderate hypertriglyceridemia to modify CVD risk. Recommended treatment goals for patients with moderate hypertriglyceridemia are non-HDL-C < 130 mg/dL in patients with CHD or a CHD Risk Equivalent (10-year risk for CHD > 20%), non-HDL-C < 160 mg/dL in patients with at least 2 risk factors, and non-HDL-C < 190 mg/dL in those with 0 to 1 risk factor.[53] In 2020, the ES published a clinical practice guideline focusing on lipid management in patients with endocrine disorders with the objective of preventing CV events and TG-induced pancreatitis; it also addresses whether treatment of the endocrine disorder improves lipid abnormalities as well as CV outcomes.[54] The 2020 guidance recommends drug therapy as an adjunct to diet and exercise to prevent pancreatitis in adults with fasting TG levels > 500 mg/dL. Statin therapy is recommended in addition to lifestyle changes to decrease the CV risk in adults with type 2 diabetes and other CV risk factors. Additional details on these recommendations and recommendations for type 1 diabetes mellitus, obesity, thyroid disease, excess glucocorticoids, growth hormone secretion disorders, polycystic ovary syndrome, and menopause/hormone replacement are also provided. In 2021, the ACC published an expert consensus decision pathway for the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia, defined as TG levels ≥ 175 mg/dL after a minimum of 4 to 12 weeks of lifestyle intervention, a stable dose of a maximally tolerated statin when indicated, and management of secondary causes.[55,56] ACC emphasizes the necessary lifestyle interventions for hypertriglyceridemia and recommends a low-fat diet and consideration of fibrates and prescription-grade omega 3 fatty acids. They also note that fibrates provide benefit as monotherapy but not when combined with statins.

The Fredrickson classification was adopted by the World Health Organization (WHO) and categorized dyslipidemias by patterns of elevation in lipids and lipoproteins.[57] Type I (familial hyperchylomicronemia) is characterized by elevated chylomicrons and TGs; type IIa (familial

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hypercholesterolemia) by elevated LDL-C and total cholesterol; type IIb (familial combined hyperlipoproteinemia) by elevated LDL-C, very low density lipoprotein cholesterol (VLDL-C), TGs, and total cholesterol; type III (dysbetalipoproteinemia) by elevated VLDL, chylomicron remnants, TGs, and total cholesterol; type IV (primary hypertriglyceridemia) by elevated VLDL and TGs; and type V (mixed hypertriglyceridemia) by elevated chylomicrons, VLDL, TGs, and total cholesterol. The Fredrickson classification does not directly account for HDL, and it does not distinguish among the different genes that may play a role in dyslipidemia.

Studies to date have not demonstrated an overall benefit of fibrates for reduction of CV events or total mortality; although *post-hoc* subgroup analyses have reported a decrease in composite CV events with the use of fibrates in patients with moderate hypertriglyceridemia.[58] Notably, the REDUCE-IT trial revealed that icosapent ethyl reduces CV event risk by 25%.[59]

In 2017, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) published guidelines for the management of dyslipidemia and prevention of CV disease.[60] In general, adults ≥ 20 years of age should be assessed annually for dyslipidemia; more frequent monitoring should be performed based on individual clinical circumstances. Lipid screening and management in the pediatric population is also addressed. AACE/ACE recommends screening children who are at risk for familial hypercholesterolemia (FH), defined as family history of either premature ASCVD or elevated cholesterol levels consistent with FH. At-risk children for FH should be assessed at ages > 3 years, again between ages 9 to 11 years, and again at age 18 years. Adolescents > 16 years of age with ASCVD risk factors should be evaluated every 5 years. AACE/ACE supports the use of apo B in evaluating lipids and recommends an optimal apo B < 90 mg/dL for patients at risk of CAD, while patients with established CAD or diabetes who have ≥ 1 additional risk factor have an apo B < 80 mg/dL. The 2017 AACE guidance recommends pharmacotherapy for children and adolescents > 10 years who do not respond sufficiently to lifestyle modification and for those with either LDL-C ≥ 190 mg/dL or LDL-C ≥ 160 mg/dL and the presence of ≥ 2 CV risk factors, a family history of premature CAD, or those who are obese, overweight, or insulin resistant. The 2017 guidelines also address the unique challenges associated with atherosclerosis and heart disease in women. AACE/ACE recommends 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 they recommend lipid-lowering pharmacotherapy (preferably with a statin) in the presence of an LDL-C > 130 mg/dL, as well as niacin or fibrate therapy in the presence of low HDL-C or elevated non-HDL-C after LDL-C goal is reached. In 2020, the AACE and ACE published a consensus statement algorithm for the management of dyslipidemia and prevention of CV disease to complement the 2017 AACE/ACE Guidelines for Management of Dyslipidemia and Prevention of CV Disease, and it incorporates new data not available at the time of the 2017 guidelines.[61] AACE/ACE maintains statins as primary therapy and the 2020 algorithm recommends treatment intensification with the addition of other LDL-C lowering agents (e.g., PCSK9 inhibitors, ezetimibe, colesevelam, or bempedoic acid) as needed to reach treatment goals. Although CV outcome trials (CVOTs) with colesevelam or bempedoic acid (BA) are not published, outcome trials with statins and ezetimibe or a PCSK9 inhibitor suggest further reduction in LDL-C, though any combination of drugs would provide ASCVD benefits. Thereby, the 2020 AACE/ACE algorithm advocates for progression of therapy intensity in order to reach LDL-C targets. The 2019 approval of icosapent ethyl marked the first FDA approval for a medication that lowers TGs and reduces ASCVD. As the REDUCE IT trial used for approval showed a TG decrease of only 18%, the 2020 AACE/ACE algorithm states the CV outcome benefit does not appear to

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be related to the reduction in TGs. For patients with hypertriglyceridemia who do not have established ASCVD or diabetes with ≥ 2 risk factors and are not at the TG goal of < 150 mg/dL with statin therapy, then a fibrate, omega-3 fatty acid, or niacin can be considered. In order to decrease the potential for acute pancreatitis, all patients with severe hypertriglyceridemia (> 500 mg/dL) should receive a fibrate, prescription-grade omega-3 fatty acid, and/or niacin. Niacin can be used to reduce TG and LDL-C and to increase HDL-C, although its principal role is as adjunctive therapy to reduce TG.[62] Omega-3 fish oil (2 g to 4 g) can be used as adjunct to fibrates or niacin if necessary to achieve satisfactory triglyceride lowering in patients with TG > 500 mg/dL. AACE recommends bile acid sequestrants to reduce LDL-C and apo B and to modestly increase HDL-C, but these agents may increase triglycerides and, therefore, should be used with caution in patients with TG increases. Ezetimibe is effective as monotherapy to decrease LDL-C and apo B, particularly in statin-intolerant patients. In addition, combination therapy with statins can be used. A new CV risk category of "extreme risk" was also included in the 2017 guidance. Treatment goals based on ASCVD risk are as follows.

AACE/ACE Treatment Goals[63]

Risk category	Risk factors/10-year risk	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)	TG (mg/dL)
Extreme risk	▪ Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL ▪ Established clinical cardiovascular disease in patients with DM, CKD ≥ 3, or HeFH ▪ History of premature ASCVD (< 55 years male, < 65 years female)	< 55	< 80	< 70	< 150
Very high risk	▪ Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% ▪ Diabetes with ≥ 1 risk factor(s) ▪ CKD ≥ 3 with albuminuria ▪ HeFH	< 70	< 100	< 80	< 150
High risk	▪ ≥ 2 risk factors and 10-year risk 10% to 20% ▪ Diabetes or CKD ≥ 3 with no other risk factors	< 100	< 130	< 90	< 150
Moderate risk	▪ < 2 risk factors and 10-year risk < 10%	< 100	< 130	< 90	< 150
Low risk	▪ No risk factors	< 130	< 160	not recommend-ed	< 150

In 2022, the American College of Cardiology (ACC) updated its consensus decision pathway on the use of non-statin LDL-C lowering drugs for the management of ASCVD risk.[64,65] For patients with clinical ASCVD who are at very high risk or who have familial hypercholesterolemia (FH), and who are on high-intensity statin therapy, the addition of non-statin therapy is recommended when LDL-C ≥ 55 mg/dL. For patients with clinical ASCVD who are at very high risk, have FH, or have baseline LDL-C > 190 mg/dL with

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inadequate lowering of LDL-C on maximally tolerated statin therapy alone, initial non-statin therapy should include either a PCSK9 inhibitor (alirocumab, evolocumab) or ezetimibe. The addition of bempedoic acid can be considered for patients who do not achieve ≥50% LDL-C reduction or for patients where LDL-C remains > 55 mg/dL who are receiving a maximally tolerated statin, ezetimibe, and a PCSK9 inhibitor. Patients with poor adherence to PCSK9 inhibitors or who are unable to self-inject may be initiated on inclisiran given its twice-yearly dosing and its required administration by a healthcare provider. For patients with or without clinical ASCVD who have homozygous familial hypercholesterolemia (HoFH), treatment with evinacumab, lomitapide, or LDL apheresis under the care of a lipid specialist may be considered when LDL-C lowering is inadequate with maximally tolerated statin therapy with or without ezetimibe, a PCKS9 inhibitor, and/or bempedoic acid. For patients with clinical ASCVD not at very high risk or clinical ASCVD with baseline LDL-C > 190 mg/dL without FH, it is recommended to consider the addition of non-statin therapies to maximally tolerated statin therapy for LDL-C > 70 mg/dL. For most patients with clinical ASCVD not at very high risk, ezetimibe should be the initial non-statin agent. A PCSK9 inhibitor can be added in combination with or in place of ezetimibe for patients who do not reach LDL-C goals with maximally tolerated statin-ezetimibe combination therapy. Bempedoic acid can be added for patients who achieve < 50% LDL-C reduction or for patients where LDL-C remains > 70 mg/dL. Inclisiran can be considered for patients with poor adherence to PCSK9 inhibitor therapy or for those who are unable to self-inject a PCSK9 inhibitor. Primary prevention recommendations for patients without clinical ASCVD are consistent with the 2018 ACC/AHA blood cholesterol guidelines.

The National Lipid Association (NLA) published Parts 1 and 2 of their recommendations for patient-centered management of dyslipidemia in 2014 and 2015.[66,67] Atherosclerosis develops over decades often beginning in childhood. Targeted lipid screening should begin at 2 years of age if warranted by family history; universal screening is appropriate at ages 9 to 11 years and should be repeated at age 20 years. The NLA recommends using lipid levels in conjunction with other ASCVD risk factors to assess overall risk, and supports the use of risk calculators, such as the ATP III Framingham Risk Score and the ACC/AHA Pooled Cohort Equations. The NLA considers non-HDL-C to be superior to LDL-C for predicting ASCVD event risk since non-HDL-C is better correlated with apo B and is more closely associated with the total burden of atherogenic particles. Non-HDL-C measurements are used along with LDL-C as primary targets of therapy. Triglyceride level is associated with the VLDL-C level, therefore using non-HDL-C as a target also simplifies the management of patients with high triglycerides. Desirable targets in patients with low, moderate, and high risk of an ASCVD event are non-HDL-C < 130 mg/dL and LDL-C < 100 mg/dL; in patients considered to be at very high risk target measures are < 100 mg/dL and < 70 mg/dL, respectively. The NLA advises that the intensity of risk-reduction therapy should be based on the patient's absolute risk for an ASCVD event. The NLA recommends lifestyle therapies such as diet modification and moderate physical activity before initiating drug therapy for patients at low and moderate ASCVD event risk; however, in patients at high or very high risk, drug therapy may be prescribed from the start. Moderate to high intensity statin therapy is considered first-line drug therapy. Non-statin agents, such as ezetimibe, bile acid sequestrants, fibric acids, long-chain omega-3 fatty acid concentrates, and nicotinic acid can be considered in patients with contraindications or intolerance to statins, or as an add-on to maximally tolerated statin therapy if cholesterol levels are still elevated with maximally tolerated statin doses. If very high triglycerides (≥ 500 mg/dL) exist, a triglyceride-lowering drug may be considered for first line use to prevent pancreatitis. Response and adherence to therapy should be monitored every 4 to 12 months. The NLA recommends review of both cholesterol goals and adherence to therapy with patients at each visit to identify barriers or side effects; an interdisciplinary team approach

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should be used whenever possible. Statins remain the drug therapy of choice for those with increased cardiovascular risk conditions, including HIV/AIDS and rheumatoid arthritis, and those at risk based on ethnicity or race, such as Hispanics, African Americans, and South Asians. The NLA outlines special considerations to take into account when treating these specific patient populations. In 2017, NLA published an update to the 2015 Part 2 to include new evidence on the use of PCSK9 inhibitors in adults.[68] They recommend consideration of PCSK9 inhibitors in patients with ASCVD (stable or progressive) or LDL-C ≥ 190 mg/dL (including polygenic hypercholesterolemia, HeFH, HoFH) based on factors such as age, other ASCVD risk factors, use of maximally-tolerated statin therapy ± ezetimibe, and on-treatment LDL-C or non–HDL-C levels. Subsequently, in 2019, the NLA published a statement on the enhanced value of the PCSK9 inhibitors based on CV outcomes data as well as reductions in list prices.[69] Since risk reduction is directly proportional to absolute LDL-C, patients with higher starting ASCVD risk and higher LDL-C levels generally achieved greater reduction in major vascular events when treated with anti-hyperlipidemic pharmacotherapy. Based, at least in part, on ASCVD risk phenotype and LDL-C thresholds, the NLA determined that PSCK9 inhibitors will provide reasonable value in the following 3 groups of patients on maximally tolerated statin therapy: (1) extremely high-risk (≥ 40% 10-year ASCVD risk) patients with LDL-C ≥ 70 mg/dL, including patients with extensive or active ASCVD burden and those with less extensive ASCVD plus extremely high-risk cardiometabolic risk factors; (2) very high-risk (≥ 30% to 39% 10-year ASCVD risk) patients with LDL-C ≥ 100 mg/dL; and (3) high-risk (< 30% 10-year ASCVD risk) patients with LDL-C ≥ 130 mg/dL, including patients with HeFH or severe hypercholesterolemia ≥ 220 mg/dL. It is generally advised to add ezetimibe to statin therapy before adding a PCSK9 inhibitor; however, the NLA states that adding a PCSK9 inhibitor directly to a statin may be more efficacious for select patients at very high and extremely high ASCVD risk, particularly if their LDL-C is at a lower level. In October 2019, the NLA published a statement on the use of icosapent ethyl in patients with elevated TGs and high or very-high ASCVD risk who are taking statins.[70] Based on data from the REDUCE-IT trial, the NLA recommends that patients who are 45 years or older with clinical ASCVD, and patients who are 50 years or older with diabetes requiring medication and with ≥ 1 additional risk factor (men ≥ 55 and women ≥ 65 years of age, cigarette smoker or stopped smoking within 3 months, hypertension, HDL-C ≤ 40 for men mg/dL or ≤ 50 mg/dL for women, high-sensitivity C-reactive protein [hs-CRP] > 3 mg/L, renal dysfunction with creatinine clearance [CrCl] > 30 and < 60 mL/min, retinopathy, micro- or macroalbuminuria, ankle-brachial index < 0.9 without intermittent claudication symptoms), with fasting TG between 135 to 499 mg/dL on maximally tolerated statin therapy with or without ezetimibe, are recommended to be prescribed icosapent ethyl for ASCVD risk reduction. In November 2020, the NLA published a scientific statement on coronary artery calcium (CAC) scoring from a CT scan of the heart to guide prevention of ASCVD.[71] A directly proportional relationship has been found between CAC scores and major adverse clinical ASCVD events. The 2018 AHA/ACC cholesterol guidelines state CAC scoring is reasonable in borderline or intermediate-risk individuals 40 to 75 years of age, without ASCVD or diabetes, and with an LDL-C of 70 to 189 mg/dL when the decision regarding statin use is unclear, following use of the Pooled Cohort Equations and risk-enhancing factors. As the absolute CAC score is the best predictor for absolute 5- to 10-year ASCVD event risk, it is recommended to be used for estimating the number-needed-to-treat (NNT) and for guiding drug therapy decisions. In September 2021, the NLA published a scientific statement on lipid measurement in the management of CVD. Key points include that screening with non-fasting lipids is acceptable, non-HDL-C can be measured in a fasting or non-fasting state and can guide ASCVD prevention, and LDL-C can be estimated from total cholesterol, HDL-C, and TG measurements.[72]

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In March 2017, the AHA published a Science Advisory on the use of omega-3 polyunsaturated fatty acid (PUFA) supplementation for the prevention of clinical CVD.[73] They state that PUFA supplementation is reasonable in patients with coronary heart disease (CHD) to reduce CHD-related mortality. Reduced hospitalization and improved survival have been shown in clinical studies in patients with HF and reduced left ventricular function. There are no published data to support its use in patients with diabetes, pre-diabetes, or a history of stroke, or for primary prevention of stroke or atrial fibrillation. In August 2019, the AHA released a Science Advisory on omega-3 fatty acid use for the management of hypertriglyceridemia.[74] They instruct for patients with very high TG (≥ 500 mg/dL), treatment with eicosatetraenoic acid (EPA) plus docosahexaenoic acid (DHA) at a dose of 4 grams/day reduces TG by ≥ 30% and increases LDL-C; however, EPA-only agents did not raise LDL-C in this population. For hypertriglyceridemia (TG, 200 to 499 mg/dL), EPA+DHA and EPA-only appear roughly comparable for TG lowering, resulting in a 20% to 30% reduction and no increase in LDL-C. The AHA concludes that prescription omega-3 fatty acid at doses of 4 grams/day are safe and effective for reducing TG either as monotherapy or as an adjunct to a statin.

Familial hypercholesterolemia (FH) is a genetic disorder that leads to accumulation of LDL-C particles in plasma and premature CV disease.[75,76] The more severe form, homozygous familial hypercholesterolemia (HoFH), is rare, occurring in about 1 out of a million people in the US. In HoFH, LDL receptor activity is nearly absent and LDL-C levels > 600 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 1 in 200 to 250 persons in industrialized countries. 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 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 the 2015 Agenda for Familial Hypercholesterolemia, the AHA advises that FH treatment be based on LDL-C levels, not genetic abnormality or other clinical features, with an initial goal in LDL-C reduction by at least 50%.[77] This can be followed by achieving an LDL-C < 100 mg/dL (absence of CAD or other major risk factors) or < 70 mg/dL (presence of CAD or other major risk factors). The maximal LDL-C reduction that can be tolerated with therapy is a practical target, particularly for higher-risk patients. Therapeutic targets for apo B and non-HDL-C have not been defined for FH. Initial drug monotherapy for those with FH includes high-intensity statin therapy (rosuvastatin or atorvastatin). If LDL-C goal is not met within 3 months of adherent therapy, ezetimibe should be added. If after another 3 months, LDL-C goal is still not met, the addition of a PCSK9 inhibitor, a bile acid sequestrant (colesevelam), or prescription-strength niacin should be considered. In most patients with HoFH, high dose statin therapy provides only modest reductions in LDL-C of 10% to 25%; however, reduction in CV and all-cause mortality has shown to occur even with modest LDL-C reduction. The addition of ezetimibe to statin therapy may provide an additional 10% to 15% LDL-C reduction. Other agents such as bile acid sequestrants, niacin, and fibrates result in only modest LDL-C-reducing effects in patients with HoFH. Four-drug combination therapy with the addition of lomitapide can be considered in patients with HoFH if needed. Dietary and lifestyle modifications should also be an aspect of FH treatment.

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The 2020 type 2 diabetes management algorithm by the AACE/ACE advises early and intensive management of dyslipidemia in patients with type 2 diabetes mellitus (T2DM) to decrease the risk for ASCVD.[78] Some patients may achieve lipid goals with lifestyle therapy, but most will require pharmacotherapy to reduce CV risk. Moderate- to high-intensity statin therapy is recommended as first-line lipid-lowering drug therapy unless contraindicated. PCSK9 inhibitors provide a more aggressive lipid-lowering therapy option and can provide further reduction of residual ASCVD risk in patients with clinical ASCVD and diabetes.

In 2020, the American College of Cardiology (ACC) published an expert consensus decision pathway focused on novel therapies for CV risk reduction in patients with type 2 diabetes.[79] For patients ≥ 18 years with type 2 diabetes and ≥ 1 of the following: ASCVD, heart failure (HF), diabetic kidney disease (DKD), or at high risk for ASCVD, it is recommended to concurrently optimize guideline-directed medical therapy for prevention (lifestyle, blood pressure, lipids, glucose, and antiplatelets) and initiate a sodium-glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 receptor agonist (GLP-1RA) with proven CV benefit, depending on patient-specific factors, comorbid conditions, and patient-clinician preferences and priorities.

In their 2022 Standards of Medical Care in Diabetes, the American Diabetes Association (ADA) states that it is reasonable to obtain a lipid profile at initiation of a statin or other lipid-lowering therapy, 4 to 12 weeks after initiation or a change in dose, and annually thereafter in patients on lipid-lowering therapy.[80] The ADA recommends moderate-intensity statin therapy in addition to lifestyle therapy for patients aged 40 to 75 years with diabetes without ASCVD for primary prevention (level of evidence A). For diabetes patients 20 to 39 years old with additional ASCVD risk factors, starting statin therapy in addition to lifestyle therapy may be considered (C). In patients who are higher risk, particularly with multiple ASCVD risk factors or who are 50 to 70 years of age, high-intensity statin therapy is reasonable (B). In diabetic adults with a 10-year ASCVD risk of ≥ 20%, addition of ezetimibe to maximally tolerated statin therapy may be considered for reducing LDL-C by ≥ 50% (C). For secondary prevention, patients of all ages with diabetes and ASCVD should have high-intensity statin therapy added to lifestyle therapy (A). For diabetic patients with very high risk ASCVD and LDL-C ≥ 70 mg/dL on a maximally tolerated statin dose, additional LDL-lowering therapy, such as ezetimibe or a PCSK9 inhibitor, can be considered (A). The ADA recommends against the addition of niacin (A) or a fibrate (A) to statin therapy in diabetic patients due to lack of additional benefit and advises of the increased risk of abnormal transaminase levels, myositis, and rhabdomyolysis with combination therapy with a statin and fibrate. Furthermore, the combination of a statin plus niacin may increase the risk for stroke. Based on data from the REDUCE-IT trial, the ADA now states that icosapent ethyl can be considered for reduction of CV risk in select patients (on a statin with controlled LDL-C but increased TGs) with diabetes and ASCVD or other cardiac risk factors (A).

The American Academy of Pediatrics (AAP) endorsed guidelines by the NHLBI on CV health and risk reduction in children and adolescents outlines age-appropriate lipid screening in the pediatric population.[81] NHLBI recommends a fasting lipid profile in children aged 1 to 4 years, only if the child is 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 9 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 CV disease. The guideline also identifies age-specific strategies to reduce risk factors and manage CV disease in children and adolescents. Most children with high cholesterol should be treated with lifestyle modifications including diet and physical activity. Less than 1% of children, primarily those with genetic dyslipidemias, may qualify for cholesterol-lowering

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medications. In addition to lifestyle interventions, the use of lipid-lowering medications is recommended, in general, in ages ≥ 10 years if LDL-C is ≥ 190 mg/dL, ≥ 160 mg/dL with family history of early heart disease or 1 high- or 2 moderate-level additional risk factors, or > 100 mg/dL if diabetes mellitus is present. The initial LDL-C goal is < 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.

In contrast, the US Preventive Services Task Force (USPSTF) issued a final recommendation in July 2016 regarding lipid screening in children and adolescents and states that the evidence is insufficient to weigh the risk and benefit of screening for lipid disorders in patients < 20 years.[82] An update to this recommendation is in progress.[83]

In a 2019 AHA scientific statement on cardiovascular risk reduction in high-risk pediatric patients, screening for FH through a fasting lipid panel is recommended beginning at 2 years of age for patients with a family history of premature CVD or significant hypercholesterolemia, and then every 3 to 5 years through adulthood.[84] For high-risk pediatric patients (HoFH, type 1 or 2 diabetes, end-stage renal disease, solid organ transplant vasculopathy, Kawasaki disease with persistent aneurysms), it is recommended that LDL-C be maintained ≤ 100 mg/dL. For moderate-risk pediatric patients (HeFH, severe obesity, hypertension, chronic kidney disease), it is recommended that LDL-C be maintained ≤ 130 mg/dL. For at-risk pediatric patients (obesity, white-coat hypertension, Kawasaki disease with regressed aneurysms), it is recommended that LDL-C be maintained ≤ 160 mg/dL.

Data obtained during clinical trials have demonstrated that statin efficacy does not increase proportionally with dose.[85,86] This is referred to as the rule of 6%; doubling a statin dose results in approximately an additional 6% decrease in LDL-C, although the actual percentage may vary slightly among individuals. Thus, if it is known that a patient is unlikely to meet a goal LDL-C based on this limitation of statins, the addition of a non-statin agent may be appropriate in select patients.

A trial evaluating the effects of bempedoic acid on incidence of major adverse cardiovascular events in statin intolerant patients (CLEAR Outcomes trial) is ongoing; the projected completion date is by the end of 2022.[87] Additionally, ORION-4 (NCT03705234) is an ongoing, double-blind, randomized controlled trial that aims to determine whether inclisiran reduces cardiovascular morbidity and mortality in patients with clinical ASCVD; results are expected in July 2026.[88]

PHARMACOLOGY[89,90,91,92,93,94,95,96,97,98,99]

ACL Inhibitors

Adenosine Triphosphate-Citrate Lyase (ACL) is an enzyme found upstream from 3-hydroxy-3-methyl-glutaryl-coezyme A (HMG-CoA) reductase that catalyzes the formation of acetyl-CoA and oxaloacetate from citrate.[100] Acetyl-CoA generated from this reaction then undergoes enzymatic conversion by HMG-CoA synthase and HMG-CoA reductase to form cholesterol. Bempedoic acid (Nexletol), a prodrug that is activated in the liver, lowers cholesterol synthesis and low-density lipoprotein cholesterol (LDL-C) by inhibiting ACL and upregulating LDL receptors. Bempedoic acid is also found in bempedoic acid/ezetimibe (Nexlizet), a combination ACL and cholesterol absorption inhibitor.

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ANGPTL3 Inhibitor

Angiopoietin-like 3 (ANGPTL3) is a protein expressed predominantly in the liver that is involved in the regulation of lipid metabolism through inhibition of lipoprotein lipase (LPL) and endothelial lipase (EL). By inhibiting ANGPTL3, evinacumab-dgnb (Evkeeza) results in reduction of LDL-C, HDL-C, and TG. Additionally, evinacumab-dgnb decreases LDL-C independent of the LDL receptor (LDL-R) through promotion of very low-density lipoprotein (VLDL) processing and clearance upstream of LDL formation. Inhibiting ANGPTL3 decreases TG and HDL-C through rescuing the activities of LPL and EL, respectively.

Apolipoprotein B (apo B) Synthesis Inhibitors

Apolipoprotein B (apo-B) is a structural protein of very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL).[101] Microsomal triglyceride transfer protein (MTP) transfers triglycerides onto apo B during the production of VLDL, a precursor to LDL.[102]

Lomitapide (Juxtapid) directly binds and inhibits MTP, preventing the synthesis of apo-B-containing proteins in enterocytes and hepatocytes. 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 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 (Colestid), and colesevelam (Welchol), bind bile acids in the intestine to form an insoluble complex which is excreted in the feces, thereby interrupting enterohepatic circulation. As the bile acid pool becomes depleted, the hepatic enzyme cholesterol, 7 α-hydroxylase, is upregulated. Upregulation of 7 α-hydroxylase increases the conversion of cholesterol to bile acids with a resulting increase in demand for cholesterol in the liver cells. The hepatic demand for cholesterol causes a dual effect of 1) increasing transcription and activity of the cholesterol biosynthetic enzyme, HMG-CoA reductase and 2) increasing the number of hepatic LDL-C receptors. These compensatory mechanisms increase clearance of LDL-C from the blood, resulting in decreased serum LDL-C levels. In patients with partial biliary obstruction, the reduction of serum bile acid levels reduces excess bile acids deposited in the dermal tissue with resultant decrease in pruritus.

Bile acid sequestrants can reduce LDL-C levels by 12% to 30% and may have a small effect on HDL-C. Reports of impact vary, but bile acid sequestrants may increase TGs. 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.[103] Cholestyramine has been shown to reduce the number of CV events, but colestipol or colesevelam do not have CV clinical outcomes data.

The mechanism of action of colesevelam 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,

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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 apo 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%, TG by 14%, and LDL-C by 19% after 3 to 4 months. The combination had no effect on HDL-C and was well tolerated.[104]

Fibric Acids

The effects of the fibric acids, fenofibrate (Antara, Fenoglide, Lipofen, Tricor), fenofibric acid (Fibricor, Trilipix; the active metabolite of fenofibrate), and gemfibrozil (Lopid), have been explained by the activation of peroxisome proliferator activated receptor alpha (PPARα). 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 PPARα also induces an increase in the synthesis of apoproteins A-I and A-II, as well as HDL-C. Fenofibrate also reduces serum uric acid levels by increasing urinary excretion of uric acid. Each fenofibric acid (Trilipix) delayed-release capsule contains the choline salt of fenofibric acid, which is converted to fenofibric acid in the gastrointestinal tract.[105] Fenofibric acid is thought to be more readily absorbed and less affected by food than fenofibrate.

Gemfibrozil has been shown to reduce the risk of CHD in patients with high TG and low HDL-C.[106,107,108,109] This effect is most significant in patients with diabetes or metabolic syndrome.[110] ACC/AHA advises that gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. Gemfibrozil use with simvastatin is contraindicated. 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.[111,112]

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.[113,114] In the lipid arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, the combination of fenofibrate and simvastatin did not significantly reduce the rate of fatal CV events, nonfatal MI, or nonfatal stroke, compared with simvastatin monotherapy (HR 0.92, 95% CI 0.79 to 1.08; p=0.32), 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.[115] 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 MI or stroke and required 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 were already taking statins.[116] 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.[117] The clinical significance of this subgroup finding is unclear, as this finding was not observed in a separate large randomized controlled clinical trial

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of fenofibrate versus placebo. Data to support the routine use of non-statin drugs in combination with statin therapy to reduce further ASCVD events are lacking; however, non-statin therapy may be considered as adjunct to statin therapy when maximum intensity statin therapy does not lower LDL-C sufficiently to reduce ASCVD event risk in individuals with primary severe elevations of LDL-C.[118] In April 2015, the FDA removed the indication for fenofibric acid (Trilipix) as an adjunct to diet in combination with a statin to reduce triglycerides and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.[119]

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% and has shown to decrease total cholesterol by 10% and triglycerides by 27%.[120,121] 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 niacin immediate-release. To increase tolerance, a film-coated, niacin extended-release (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.[122] Niacin has been shown to reduce the risk of CHD as monotherapy and in combination with statins.[123,124,125] It also led to regression of carotid atherosclerosis when given with statins in a small study.[126,127] Niacin caused regression of coronary lesions and reduced CV events in another small study when given in combination with cholestyramine and gemfibrozil.[128]

In April 2016, the FDA removed the indication for niacin ER (Niaspan) in combination with simvastatin or lovastatin for the treatment of primary hyperlipidemia and mixed dyslipidemia when treatment with Niaspan, simvastatin, or lovastatin monotherapy is considered inadequate.[129]

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 2 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.[130] 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. Elevations in LDL-C and non-HDL-C may also be observed. In trials done with omega-3-acid ethyl esters, the median percent change in LDL-C was an increase of 49.3% 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% in adults with baseline TG ≥ 500 mg/dL.

Icosapent ethyl (Vascepa) is an ethyl ester of EPA only. Icosapent ethyl 4 grams per day has been shown to reduce TG by up to 33.1% in adults with baseline TG ≥ 500 mg/dL while elevations of LDL-C have not been observed.[131]

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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. 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% (33% relative to placebo).

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

Alirocumab (Praluent) and evolocumab (Repatha) are human monoclonal antibodies that bind to PCSK9. PCSK9 binds to low density lipoprotein receptors (LDLR) at the surface of hepatocytes and, thereby, targets internalized LDLR for lysosomal degradation. By inhibiting the binding of PCSK9 to LDLR, these agents increase the number of LDLR available to clear LDL particles, thereby lowering LDL-C.

Significant reductions in LDL-C by approximately 40% to 60% ($p<0.0001$) have been reported for alirocumab compared with placebo. Similar reductions in non-HDL-C levels and apo B were also observed. In phase 3 clinical trials, patients treated with evolocumab experienced an average LDL-C reduction of approximately 30% to 70% ($p<0.0001$).

PCSK9-Directed Small Interfering RNA (siRNA)

Inclisiran (Leqvio) is a double-stranded small interfering ribonucleic acid (siRNA) which enters hepatocyte cells and prevents proprotein convertase subtilisin/kexin type 9 (PCKS9) translation through an RNA interference mechanism. As a result, LDL-C receptor recycling and expression is increased on the hepatocyte cell surface, LDL-C uptake is increased, and LDL-C levels in the circulation are reduced. Inclisiran contains a covalently linked ligand containing N-acetylgalactosamine residues, which facilitates uptake into hepatocytes.

Sustained reduction in LDL-C by 48% to 52% was reported in clinical trials for inclisiran when compared with placebo, along with 30% to 33% reduction in total cholesterol, 42% to 47% reduction in non-HDL-C, and 36% to 43% reduction in Apo B.

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PHARMACOKINETICS[132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155]

Drug	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion (%)
ACL Inhibitors				
bempedoic acid (Nexletol)	unknown	21	ESP15228 (active metabolite); glucuronide conjugates	urine: 70 feces: 30
ACL Inhibitor/Cholesterol Absorption Inhibitor				
bempedoic acid/ ezetimibe (Nexlizet)	unknown 35-60	21 22	ESP15228 ezetimibe glucuronide	see individual components
ANGPTL3 Inhibitor				
evinacumab-dgnb (Evkeeza)	not applicable	--	small peptides and amino acids	urine: not applicable feces: not applicable
Apolipoprotein B Synthesis Inhibitor				
lomitapide (Juxtapid)	7	39.7	major: M1 and M3 (CYP 3A4)	urine: 59.5 feces: 33.4
Bile Acid Sequestrants				
cholestyramine	not absorbed	--	--	feces
colesevelam (Welchol)	not absorbed	--		
colestipol (Colestid)	not absorbed	--		
Cholesterol Absorption Inhibitors				
ezetimibe (Zetia)	35-60	22	ezetimibe glucuronide	urine: 11 feces: 78
Fibric Acids				
fenofibrate (Antara, Fenoglide, Lipofen, Tricor)[156]	unknown	16-23	fenofibric acid (active component); glucuronide conjugate	urine: 60 feces: 25
fenofibric acid (Fibricor)	unknown	20	glucuronide conjugate	urine
fenofibric acid (Trilipix)	81	20	glucuronide conjugate	urine
gemfibrozil (Lopid)	100	1.5	3 metabolites	urine: 70 feces: 6
Niacin				
niacin ER (Niaspan)	60-76	--	many metabolites	predominantly urine
niacin IR (Niacor)	88	0.3-0.75	nicotinuric acid	urine
Omega-3 Fatty Acids				
icosapent ethyl (Vascepa)	--	89	acetyl Coenzyme A	hepatic
omega-3-acid ethyl esters (Lovaza)	unknown	--	--	--

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Pharmacokinetics (continued)

Drug	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion (%)
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors				
alirocumab (Praluent)	85	17-20 days	--	saturable binding to target (PCSK9) at low concentrations; non-saturable proteolytic pathway at higher concentrations
evolocumab (Repatha)	72	11-17 days	--	
PCSK9-Directed Small Interfering Ribonucleic Acid (siRNA)				
inclisiran (Leqvio)	unknown	9	--	urine: 16

Fenofibrate micronized 67 mg capsule has been shown to provide similar therapeutic effects to fenofibrate "non-micronized" 100 mg capsule.[157] All currently available fenofibrate products at the highest available dose produce similar plasma concentrations as the fenofibrate 200 mg capsules in single dose studies. Lipofen 150 mg capsules have been shown to be equivalent to Tricor 160 mg tablets under low-fat and high-fat fed conditions. Fenoglide 120 mg tablets have been shown to be equivalent to fenofibrate 130 mg capsules under high-fat conditions. Trilipix 135 mg capsules are equivalent to micronized fenofibrate 200 mg capsules administered under fed conditions. Fibricor 105 mg tablets are equivalent to fenofibrate tablets (Tricor) 145 mg under fasted conditions.

CONTRAINDICATIONS/WARNINGS[158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182]

Adenosine Triphosphate-Citrate Lyase (ACL) Inhibitor

There are no contraindications for use of bempedoic acid (Nexletol); however, the combination product, bempedoic acid/ezetimibe (Nexlizet) is contraindicated in patients with known hypersensitivity to ezetimibe. Products containing bempedoic acid may result in increased blood uric acid levels due to the inhibition of renal tubular organic anion transporter 2 (OAT2). In clinical trials, patients treated with bempedoic acid experienced increased uric acid levels as early as 4 weeks after starting therapy with levels remaining elevated throughout treatment. An increased risk of the development of gout was reported in patients both with and without a prior history of gout, with higher risk in patients with a previous history. Patients experiencing symptoms of hyperuricemia should contact their healthcare provider and if needed, should have their serum uric acid level assessed. Treatment with urate-lowering medications may be necessary in some patients.

An increased risk of tendon rupture or injury has also been associated with products containing bempedoic acid. In clinical trials, tendon rupture or injury affecting the rotator cuff, Achilles tendon, and biceps tendon was reported within weeks to months after initiating bempedoic acid (0.5% versus 0 of placebo patients). Patients with previous tendon disorders, renal failure, > 60 years of age, and those receiving fluoroquinolone or corticosteroid medications may be at an increased risk for tendon rupture. Patients who have a history of tendon disorders or rupture should be considered for appropriate therapeutic alternatives. Patients experiencing tendon rupture should discontinue any product containing bempedoic acid immediately. Patients should contact their healthcare provider and rest should they experience any signs or symptoms of tendinitis or tendon rupture.

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ANGPTL3 Inhibitor

Evinacumab-dgnb (Evkeeza) is contraindicated in patients with a known hypersensitivity to it or any of its excipients. If signs and symptoms of serious hypersensitivity reactions occur, such as anaphylaxis, then treatment should be discontinued, and the patient should be treated according to standard of care. Based on animal reproduction studies, evinacumab-dgnb may cause embryofetal toxicity. Patients who may become pregnant should be advised of this risk to the fetus, and a pregnancy test should be considered prior to treatment. Contraception should be used during treatment and continued for a minimum of 5 months after the last dose in patients of reproductive potential.

Apolipoprotein B (apo B) Synthesis Inhibitor

Lomitapide (Juxtapid) is contraindicated in patients with moderate or severe hepatic impairment (Child Pugh category B or C), or active liver disease, including unexplained persistent elevations of serum transaminases. Lomitapide carries a boxed warning due to the risk of hepatotoxicity resulting from increases in transaminases and hepatic steatosis. It can increase hepatic fat, with or without concomitant increases in transaminases. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be measured each month during the first year of lomitapide therapy and every 3 months thereafter.

Lomitapide is contraindicated in patients who are pregnant. It also carries a warning regarding embryofetal toxicity; females of reproductive potential should use effective contraception during and for 2 weeks following the last dose. Concomitant use of lomitapide with strong or moderate CYP3A4 inhibitors is also contraindicated.

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 ≥ 3 days], methotrexate, tetracyclines, tamoxifen). Alcohol may also increase levels of hepatic fat; therefore, patients taking lomitapide should not consume > 1 alcoholic beverage each day.

Due to lomitapide's mechanism of action in the small intestine, the absorption of fat-soluble nutrients may be reduced. 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 for deficiencies in these nutrients.

Bile Acid Sequestrants

Bile acid sequestrants, cholestyramine, colestipol (Colestid), and colesevelam (Welchol), can raise triglyceride levels and are contraindicated in patients with very high triglyceride levels (> 500 mg/dL).[183] A lipid panel, including triglycerides, should be assessed prior to initiating colesevelam therapy as well as periodically thereafter. Patients with triglycerides levels > 300 mg/dL may experience higher triglyceride level increases when receiving colesevelam therapy and may require more frequent triglyceride monitoring. Colesevelam is also contraindicated in patients with bowel obstruction and in patients with hypertriglyceridemia-induced pancreatitis. Patients who experience triglyceride levels > 500 mg/dL or symptoms of acute pancreatitis should discontinue colesevelam therapy and seek immediate medical attention. Cholestyramine is contraindicated in complete biliary obstruction.

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Because of its constipating effects, colesevelam is not recommended in patients with gastroparesis, other gastrointestinal motility disorders, and in those who have had major gastrointestinal tract surgery and who may be at risk for bowel obstruction; bowel obstruction has been reported postmarketing.

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

Cholesterol Absorption Inhibitors

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

Use of bempedoic acid/ezetimibe (Nexlizet) in patients with a known hypersensitivity to ezetimibe is contraindicated.

Fibric acids

Fenofibrate products (Antara, Fenoglide, Lipofen, Tricor), fenofibric acid (Fibricor, Trilipix), and gemfibrozil (Lopid) are contraindicated in patients with hepatic or severe renal dysfunction, including active liver disease (e.g., primary biliary cirrhosis, unexplained persistent liver function abnormalities) or pre-existing gallbladder disease, or with known hypersensitivity to the product. Fenofibrate and fenofibric acid are also contraindicated in patients with unexplained persistent liver enzyme elevations. Concomitant use of gemfibrozil with agents containing dasabuvir, repaglinide, selexipag, or simvastatin is also contraindicated. Caution should be used when prescribing a statin and a fibrate, particularly gemfibrozil, together due to an increased risk of myopathy and rhabdomyolysis.

The use of fibric acids is not recommended in nursing mothers, and it is considered a contraindication for use in Fibricor, Trilipix, and Fenoglide. Fenofibrates and fenofibric acid may cause venous thromboembolic disease. Fenofibrates have also been associated with serious drug-induced liver injury (DILI; hepatocellular, chronic active, cholestatic hepatitis, cirrhosis [in association with chronic active hepatitis]), leading to liver transplantation and death in the postmarketing setting occurring weeks to months after initiation of therapy. In some patients, DILI has been reversable with drug discontinuation. Regular periodic monitoring of liver function (serum ALT, AST, and total bilirubin) should be performed at baseline and for the duration of fenofibrate therapy, and therapy discontinued if enzyme levels persist (ALT or AST > 3 times the upper limit of normal [ULN]) or if accompanied by increased bilirubin. Therapy should also be discontinued in those who develop signs or symptoms of hepatic impairment (e.g., dark urine, abnormal stool, jaundice, malaise, abdominal pain, myalgia, weight loss, pruritus, nausea) and should not be restarted unless an alternative cause for the liver injury is identified.

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. This can occur weeks to months after initiation of fenofibrate therapy. HDL-C levels returned 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 starting fibrate therapy.

There have been postmarketing reports of anaphylaxis, angioedema, and severe cutaneous adverse drug reactions (SCAR), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and interstitial lung disease with fenofibrate. Fenofibrate should be discontinued and appropriate treatment administered if SCAR is suspected.

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Niacin (nicotinic acid)

Niacin ER (Niaspan) is contraindicated in patients with chronic liver disease, active peptic ulcer disease, or arterial bleeding. Caution should also be used when niacin ER is used in patients with unstable angina or in the acute phase of a 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. Monitor liver function tests in all patients during therapy at approximately 6-month intervals or when clinically indicated. If transaminase levels are > 3 x ULN, 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.

An increased risk for myopathy in Chinese patients taking simvastatin co-administered with lipid-modifying doses of niacin (≥ 1 g/day) has been reported.[184] Therefore, concurrent usage of simvastatin with niacin doses ≥ 1 g/day is not recommended. 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 populations.

Omega-3 Fatty Acids

Omega-3-acid ethyl esters (Lovaza) and icosapent ethyl (Vascepa) should be used with caution in patients with a known history of sensitivity or allergy to fish and/or shellfish. Patients experiencing allergic reactions should discontinue therapy and seek medical attention. In patients with hepatic impairment, monitor liver transaminases periodically during therapy. Omega-3-acid ethyl esters may increase levels of LDL-C; therefore, periodic LDL-C monitoring during therapy is recommended.

A clinical study has reported a potential association between omega-3-acid ethyl esters and increased recurrences of symptomatic atrial fibrillation or flutter in patients with paroxysmal or persistent atrial fibrillation, particularly within 2 to 3 months after initiation of therapy. 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.

Icosapent ethyl has also been associated with an increased incidence of atrial fibrillation or flutter requiring hospitalization. Patients with a prior history of atrial fibrillation or flutter have shown a higher incidence of atrial fibrillation.

An association with icosapent ethyl and increased bleeding risk has been shown. Patients taking icosapent ethyl with concurrent antithrombotic medications (e.g., aspirin, clopidogrel, warfarin) were shown to have a higher incidence of bleeding.

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

Alirocumab (Praluent) and evolocumab (Repatha) are contraindicated in patients with known hypersensitivity to alirocumab, evolocumab, respectively, or any of the product's excipients. Hypersensitivity reactions, such as angioedema, have been reported with both medications; pruritus, vasculitis, nummular eczema, and reactions requiring hospitalization have been reported with alirocumab. Discontinue if signs or symptoms of an allergic reaction occur. For evolocumab, the needle cover of the glass prefilled syringe and the prefilled autoinjector contain a derivative of latex, which may cause an allergic reaction in individuals sensitive to latex.

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PCSK9-Directed Small Interfering RNA (siRNA)

There are no contraindications or warnings/precautions for the use of inclisiran (Leqvio).

Risk Evaluation and Mitigation Strategy (REMS)

Due to the risk of hepatotoxicity, lomitapide (Juxtapid) is only available through a restricted program under the REMS.[185] The goal of the REMS is to educate prescribers regarding the risk of hepatotoxicity, the need to monitor patients during therapy, and to restrict access to therapy with these agents to patients with a clinical or laboratory diagnosis consistent with HoFH. Only certified providers and pharmacies may prescribe and dispense lomitapide. Providers must complete a REMS program prescriber enrollment form, complete a prescriber training module, submit a REMS prescription authorization form for each new prescription, and comply with state-specific prescription requirements (e.g., e-prescribing, state-specific prescription forms, fax language).

DRUG INTERACTIONS[186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212]

Drug	Bile Acid Sequestrants	Cholesterol Absorption Inhibitor	Fibric Acids	Niacin	Omega-3 Fatty Acids	Statins
ACL Inhibitor						
bempedoic acid (Nexletol)	--	--	--	--	--	increased risk of myopathy (simvastatin or pravastatin)
ACL Inhibitor/Cholesterol Absorption Inhibitor						
bempedoic acid/ezetimibe (Nexlizet)	reduced bioavailability of ezetimibe	--	increased ezetimibe concentration with risk of cholelithiasis	--	--	increased risk of myopathy (simvastatin or pravastatin)
ANGPTL3 Inhibitor						
evinacumab-dgnb (Evkeeza)	--	--	--	--	--	--
Apolipoprotein B Synthesis Inhibitor						
lomitapide (Juxtapid)	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 (Colestid)	--	reduced bioavailability of ezetimibe	reduced bioavailability of fenofibrate or fenofibric acid	reduced absorption of niacin	--	--

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Drug Interactions (continued)

Drug	Bile Acid Sequestrants	Cholesterol Absorption Inhibitor	Fibric Acids	Niacin	Omega-3 Fatty Acids	Statins
Bile Acid Sequestrants *(continued)*						
colesevelam (Welchol)	--	reduced bioavailability of ezetimibe	reduced bioavailability of fenofibrate or fenofibric acid	--	--	--
Cholesterol Absorption Inhibitors						
ezetimibe (Zetia)	reduced bioavailability of ezetimibe	--	increased ezetimibe concentration with risk of cholelithiasis	--	--	--
Fibric Acids						
fenofibrate (Antara, Fenoglide, Lipofen, Tricor)	reduced bioavailability of fenofibrate	increased ezetimibe concentration with risk of cholelithiasis	--	--	--	increased risk of myopathy and rhabdomyolysis
fenofibric acid (Fibricor, Trilipix)	reduced bioavailability of fenofibric acid	increased ezetimibe concentration	--	--	--	increased risk of myopathy and rhabdomyolysis
gemfibrozil (Lopid)	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
Niacin						
niacin ER (Niaspan)	administration with cholestyramine or colestipol reduces absorption of niacin	--	--	--	--	increased risk of myopathy
niacin IR (Niacor)	--	--	--	--	--	increased risk of myopathy
Omega-3 Fatty Acids						
icosapent ethyl (Vascepa)	--	--	--	--	--	--
omega-3-acid ethyl esters (Lovaza)	--	--	--	--	--	--
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors						
alirocumab (Praluent)	--	--	--	--	--	--
evolocumab (Repatha)	--	--	--	--	--	--

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Drug Interactions (continued)

Drug	Bile Acid Sequestrants	Cholesterol Absorption Inhibitor	Fibric Acids	Niacin	Omega-3 Fatty Acids	Statins
PCSK9-Directed Small Interfering RNA (siRNA)						
inclisiran (Leqvio)	--	--	--	--	--	--

Other Drug Interactions

Adenosine Triphosphate-Citrate Lyase (ACL) Inhibitor – bempedoic acid (Nexlizet)

Statins: Concomitant use of bempedoic acid with simvastatin or pravastatin may lead to an increased simvastatin or pravastatin concentration and increased risk of myopathy. Avoid concurrent use with simvastatin doses > 20 mg and pravastatin doses > 40 mg.

ACL Inhibitor/Cholesterol Absorption Inhibitor – bempedoic acid/ezetimibe (Nexlizet)

Cholestyramine: Concurrent use of bempedoic acid/ezetimibe and cholestyramine may decrease ezetimibe concentration. Bempedoic acid/ezetimibe should be administered ≥ 2 hours before or 4 hours after a bile acid sequestrant.

Cyclosporine: Concomitant use of bempedoic acid/ezetimibe and cyclosporine increases ezetimibe and cyclosporine concentrations. Cyclosporine levels should be monitored with concurrent use.

Fibric Acids: Fenofibrate and ezetimibe may each increase the risk of cholelithiasis. Co-administration of bempedoic acid/ezetimibe and fibrates, other than fenofibrate, is not recommended. If cholelithiasis is suspected in a patient receiving bempedoic acid/ezetimibe and fenofibrate, assess gallbladder function and consider alternative lipid-lowering therapy.

Statins: Concomitant use of bempedoic acid/ezetimibe with simvastatin or pravastatin may lead to an increased simvastatin or pravastatin concentration and increased risk of myopathy. Avoid concurrent use with simvastatin doses > 20 mg and pravastatin doses > 40 mg.

Apolipoprotein B Synthesis Inhibitor – lomitapide (Juxtapid)

CYP3A4 inhibitors: Concomitant use of strong CYP3A4 inhibitors (boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, tipranavir/ritonavir), and moderate CYP3A4 inhibitors (ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, verapamil) with lomitapide can significantly increase lomitapide exposure and is contraindicated. Lomitapide dose should not exceed 30 mg daily when used with weak CYP3A4 inhibitors (alprazolam, amiodarone, amlodipine, atorvastatin, cimetidine, cyclosporine, fluoxetine, ginkgo, ranitidine, ticagrelor); maximum dose with concomitant use of oral contraceptive is 40 mg daily. In women taking oral contraceptives, if vomiting or diarrhea occurs while on lomitapide, hormone absorption may be reduced, and use of additional contraceptive methods is warranted.

A clinically relevant drug interaction between ritonavir-boosted nirmatrelvir (Paxlovid™) and lomitapide has been identified. Ritonavir-boosted nirmatrelvir has received Emergency Use Authorization by the FDA for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (≥ 12 years old weighing ≥ 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Current guidance from the National Institutes of Health

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(NIH) suggests that lomitapide be withheld during ritonavir-boosted nirmatrelvir therapy, as well as for 2 to 3 days after completion of treatment, if clinically appropriate.

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

Statins: Lomitapide increases simvastatin exposure. Reduce simvastatin dose by 50% when initiating lomitapide. Simvastatin dose should not exceed 20 mg daily or 40 mg daily for patients who have been tolerant to simvastatin 80 mg daily for at least 1 year. Although not studied, since metabolizing enzymes are similar for lovastatin and simvastatin, lovastatin dose reduction should be considered with concomitant use of lomitapide.

Warfarin: Lomitapide increases plasma concentrations of warfarin. Monitor the international normalized ratio (INR) appropriately, particularly after lomitapide dosage change.

Bile Acid Sequestrants – cholestyramine, colestipol (Colestid), 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.[213,214] Concomitant use of mycophenolate with the bile acid sequestrants is not recommended.

Vitamins: 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. Chronic use of cholestyramine can result in a folate deficiency. Supplementation may be necessary.

Warfarin: Cholestyramine can reduce serum levels of warfarin by interfering with its enterohepatic circulation; dosage adjustments may be necessary.[215]

Other drugs: Since cholestyramine and colestipol may bind other drugs given concurrently, it is recommended that patients take other drugs at least 1 hour before or 4 to 6 hours after cholestyramine (or as great an interval as possible) to avoid impeding their absorption.

Colesevelam reduces levels of cyclosporine, glimepiride, glipizide, glyburide, levothyroxine, olmesartan, and oral contraceptives containing ethinyl estradiol and norethindrone. These agents should be administered at least 4 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 triglycerides in combination with insulin or sulfonylureas.

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.

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

Colchicine: Myopathy, including rhabdomyolysis, has been reported with concurrent use of fenofibrate or gemfibrozil with colchicine. Use caution when prescribing both agents.

Cyclosporine: Concomitant use of cyclosporine and fenofibrate or fenofibric acid (Fibricor, Trilipix) may decrease renal function.

CYP2C8 and OATP1B1 substrates: Gemfibrozil inhibits CYP2C8 and OATP1B1 and may increase exposure to substrates of these enzymes (e.g., dabrafenib, enzalutamide, loperamide, montelukast, paclitaxel, pioglitazone); dosing reductions may be necessary for the substrates. Concomitant use with the OATP1B1 substrates repaglinide and simvastatin is contraindicated.

Oral hypoglycemics: The concurrent use of gemfibrozil with glyburide (Glynase®), pioglitazone (Actos®), or rosiglitazone (Avandia®) may result in enhanced hypoglycemic effect.[216,217,218,219] The use of gemfibrozil with repaglinide (Prandin®) is contraindicated due to a significant increase in serum concentrations of the oral hypoglycemic.[220]

Statins: The concomitant administration of gemfibrozil with simvastatin is contraindicated. Concurrent use of gemfibrozil with rosuvastatin should be avoided; if concurrent use cannot be avoided, start rosuvastatin at 5 mg once daily and do not exceed 10 mg once daily.

Warfarin: Concomitant administration of fibric acids and warfarin increases the INR and the risk of bleeding.

Niacin – niacin IR and ER (Niacor and Niaspan)

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

Warfarin: Caution should be observed when niacin is administered concomitantly with anticoagulants. Niacin has been associated with small but statistically significant increases (mean 4%) in prothrombin time (PT). Monitor INR periodically.

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 and/or antiplatelet or other drug affecting coagulation should be monitored periodically for bleeding.

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors – alirocumab (Praluent), evolocumab (Repatha)

No relevant drug-drug interactions for alirocumab or evolocumab are listed in the prescribing information.

PCSK9-Directed Small Interfering RNA (siRNA)

No relevant drug-drug interactions for inclisiran (Leqvio) are listed in the prescribing information.

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ADVERSE EFFECTS[221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244]

Drug	Abdominal Pain	Back pain	Headache	Abnormal LFTs	Constipation	Dyspepsia
Adenosine Triphosphate-Citrate Lyase (ACL) Inhibitor						
bempedoic acid (Nexletol)	3.1 (2.2)	3.3 (2.2)	nr	2.1 (0.8)	nr	nr
ACL Inhibitor/Cholesterol Absorption Inhibitor						
bempedoic acid/ezetimibe (Nexlizet)	reported	reported	nr	reported	4.7 (0)	nr
ANGPTL3 Inhibitor						
evinacumab-dgnb (Evkeeza)	reported	nr	nr	nr	reported	nr
Apolipoprotein B Synthesis Inhibitor						
lomitapide (Juxtapid)	34	14	10	21	21	38
Bile Acid Sequestrants						
cholestyramine	reported	nr	nr	nr	common	reported
colesevelam (Welchol)	reported	2.3 (1.3)	3.9 (3.1)	reported	6.5-11 (2.2-7)	2.8-8.3 (1-3.5)
colestipol (Colestid)	reported	reported	reported	reported	common	reported
Cholesterol Absorption Inhibitor						
ezetimibe (Zetia)	3 (2.8)	4 (4)	nr	nr	nr	nr
Fibric Acids						
fenofibrate (Antara, Fenoglide, Lipofen, Tricor)	4.6 (4.4)	3.4 (2.5)	3.2 (2.7)	2-8 (1.4)	2.1 (1.4)	reported
fenofibric acid (Fibricor)	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)	4.6 (4.4)	3.4 (2.5)	3.2 (2.7)	7.5 (1.4)	2.1 (1.4)	3.7
gemfibrozil (Lopid)	9.8 (5.6)	nr	1.2 (1.1)	1	1.4 (1.3)	19.6 (11.9)
Niacin						
niacin ER (Niaspan)	2-5 (3)	nr	8-11 (15)	reported	nr	2-5 (8)
niacin IR (Niacor)	nr	nr	reported	reported	nr	reported
Omega-3 Fatty Acids						
icosapent ethyl (Vascepa)	reported	nr	nr	nr	reported	nr
omega-3-acid ethyl esters (Lovaza)	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.

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Adverse Effects (continued)

Drug	Abdominal Pain	Back pain	Headache	Abnormal LFTs	Constipation	Dyspepsia
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors						
alirocumab (Praluent)	nr	nr	nr	2.5 (1.8)	nr	nr
evolocumab (Repatha)	nr	2.3 to 6.2 (2.2 to 5.6)	4 to 11 (2 to 3.6)	nr	nr	nr
PCSK9-Directed Small Interfering RNA (siRNA)						
inclisiran (Leqvio)	nr	nr	nr	nr	nr	nr

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.

ACL Inhibitor: Other common adverse events reported for bempedoic acid (Nexletol) versus placebo, respectively, include upper respiratory tract infection (4.5% versus 4%), muscle spasms (3.6% versus 2.3%), hyperuricemia (3.5% versus 1.1%), bronchitis (3% versus 2.5%), pain in extremity (3% versus 1.7%), and anemia (2.8% versus 1.9%).

ACL Inhibitor/Cholesterol Absorption Inhibitor: The most common adverse events seen with bempedoic acid/ezetimibe (Nexlizet) therapy were comparable to adverse events seen in individual studies of both bempedoic acid and ezetimibe. Common adverse effects seen with bempedoic acid/ezetimibe versus placebo, respectively, but not in the individual bempedoic acid and ezetimibe trials, were urinary tract infection (5.9% versus 2.4%), nasopharyngitis (4.7% versus 0%), and constipation (4.7% versus 0%). The most common adverse event leading to treatment discontinuation with bempedoic acid/ezetimibe was oral discomfort (2% versus 0%).

ANGPTL3 Inhibitor: The most common adverse events reported with evinacumab-dgnb (Evkeeza) versus placebo, respectively, were nasopharyngitis (16% versus 13%), influenza-like illness (7% versus 6%), infusion reactions (e.g., pruritus, pyrexia, muscular weakness, nausea, nasal congestion) (7% versus 4%), dizziness (6% versus 0), rhinorrhea (5% versus 0), nausea (5% versus 2%), pain in extremity (4% versus 0), and asthenia (4% versus 0). Since evinacumab-dgnb is a therapeutic protein, there is a possibility for immunogenicity.

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

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.[245] Colesevelam can increase triglycerides in combination with insulin or sulfonylureas. In the diabetes trials, the overall incidence of hypoglycemia was 3% in patients on colesevelam versus 2.3% in placebo-treated patients.

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

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A systematic review of 18 randomized controlled trials of combination statin and ezetimibe trials was performed to assess risk in 14,471 patients.[246] Compared with statin monotherapy, combination therapy did not result in significant absolute increases in risks of myalgias, creatine kinase increases, rhabdomyolysis, transaminase increases, gastrointestinal adverse events, or discontinuations because of an adverse event. 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 adverse events.

Fibric acids: Fibric acids may cause cholelithiasis. Fenofibrate and fenofibric acid may also cause myositis, myopathy, and rhabdomyolysis; this risk may be further increased when given concomitantly with statins. Increases in liver enzymes have also been observed; increased total bilirubin has been observed in the postmarketing setting.

Fenofibrate use is associated with reversible elevations in serum creatinine. The clinical significance of this is unknown. 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 OR, 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 OR, 1.3 [CI, 1 to 1.6]), than patients who received ezetimibe (n=61,831).[247] 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% of fibrate users and 0.3% of ezetimibe users had an increase in serum creatinine level of at least 50%. Risks were greater among fibrate users with chronic kidney disease.

Niacin: Flushing has been reported to occur in up to 88% of patients receiving niacin ER. Hyperglycemia and/or hyperuricemia (and/or gout) have also been associated with the use of niacin.

Omega-3-acids: In hypertriglyceridemia clinical trials, other adverse effects for icosapent ethyl occurring ≥ 1% more than placebo were reported included arthralgia and oropharyngeal pain. Cardiovascular outcomes trials reported additional adverse effects that occurred at an incidence ≥ 1% than seen in placebo, including musculoskeletal pain, peripheral edema, constipation, gout, and atrial fibrillation. Postmarketing adverse reactions reported for icosapent ethyl include diarrhea, increased triglycerides, abdominal discomfort, and pain in the extremities.

In addition, icosapent ethyl has been associated with an increased risk of atrial fibrillation or flutter requiring hospitalization for ≥ 24 hours. In patients with either CVD or diabetes and ≥ 1 risk factor for CVD, 127 (3%) patients receiving icosapent ethyl developed atrial fibrillation or flutter requiring hospitalization versus 84 (2%) patients receiving placebo (hazard ratio [HR], 1.5; 95% CI, 1.14 to 1.98).

An increased bleeding risk has also been associated with icosapent ethyl. In clinical trials, bleeding events occurred in 482 (12%) participants receiving icosapent ethyl versus 404 (10%) of those receiving placebo. The incidence of serious bleeding events was also higher for icosapent ethyl treated patients, occurring in 111 (3%) patients versus 85 (2%) patients receiving placebo.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors: Common adverse reactions with the PCSK9 inhibitors include nasopharyngitis, injection site reactions, upper respiratory tract infection/inflammation, urinary tract infections, diarrhea, and myalgia. The most common adverse reactions observed in pediatric patients with HeFH that occurred more often with evolocumab than with

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placebo, respectively, were nasopharyngitis (12% versus 11%), headache (11% versus 2%), oropharyngeal pain (7% versus 0), influenza (6% versus 4%), and upper respiratory tract infection (6% versus 2%).

Similar incidence of neurocognitive events was reported for the PCSK9 inhibitors compared to placebo (0.8% and 0.7% of patients treated with alirocumab and placebo, respectively; ≤ 0.2% of patients treated with evolocumab or placebo).

In a cardiovascular outcomes trial with over 18,000 patients, 5.5% of patients treated with alirocumab developed anti-drug antibodies (ADA) compared with 1.6% of patients treated with placebo; consistent ADA, defined as ≥ 2 consecutive samples separated by ≥ 16 weeks, were reported in 0.7% and 0.4% of patients in each group, respectively, and neutralizing antibodies (Nab) were found in 0.5% and < 0.1% of patients in each group, respectively. While LDL-C reduction was typically similar in patients with or without ADA, some patients treated with alirocumab with persistent ADA or Nab experienced diminished LDL-C efficacy. In clinical trials, 0.1% of patients treated with evolocumab tested positive for binding antibody development; however, none of these patients who were tested further for Nab tested positive. There was no evidence that the presence of anti-drug binding antibodies impacted the pharmacokinetic profile, clinical response, or safety of evolocumab. In clinical studies of pediatric patients who received evolocumab, development of anti-evolocumab antibodies was not observed. The long-term consequences of continuing treatment in the presence of persistent Nab are unknown. The ability to detect of antibodies is dependent on several factors; therefore, comparison of the incidence of antibodies between studies or between products may be misleading.

In July 2016, the FDA approved the Pushtronex™ on-body infusion device as a single-injection option for the delivery of evolocumab (Repatha) 420 mg once monthly dose. Adverse effects reported were similar to those for the 420 mg dose delivered as 3 consecutive SC injections.[248]

PCSK9-Directed Small Interfering RNA (siRNA): The most common adverse reactions reported for inclisiran (Leqvio) versus placebo, respectively, include injection site reactions (8.2% versus 1.8%), arthralgia (5% versus 4%), urinary tract infection (4.4% versus 3.6%), diarrhea (3.9% versus 3.5%), bronchitis (4.3% versus 2.7%), pain in extremity (3.3% versus 2.6%), and dyspnea (3.2% versus 2.6%). In clinical trials, adverse reactions led to discontinuation of treatment in 2.5% of patients in the inclisiran group versus 1.9% of patients in the placebo group. The most common reason for treatment discontinuation in patients treated with inclisiran was injection site reactions.

Immunogenicity of inclisiran was evaluated in clinical trials via screening and confirmatory immunoassays for detection of anti-drug antibodies. A total of 1,830 patients were tested, and anti-drug antibodies were detected in 33 (1.8%) patients prior to receiving inclisiran, and 90 (4.9%) patients during the 18 months of treatment with inclisiran. Study data did not identify a link between the presence of anti-drug antibodies and impact on safety or efficacy of inclisiran, however long-term consequences are unknown.

SPECIAL POPULATIONS[249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272]

Pediatrics

Many of the products in the Other Lipotropics category do not have safety and effectiveness data in the pediatric population. Limited data are available regarding use in children for cholestyramine and

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colestipol.[273] Pediatric patients have been reported to experience hyperchloremic metabolic acidosis or gastrointestinal obstruction with the use of cholestyramine.[274] Evinacumab-dgnb (Evkeeza) is approved as an adjunct to other LDL-C lowering therapies in pediatric patients aged ≥ 12 years old with HoFH; safety and efficacy of evinacumab-dgnb has not been established in pediatric patients who are < 12 years of age. Colesevelam (Welchol) is approved to reduce LDL-C in boys and postmenarchal girls aged 10 to 17 years with HeFH who are unable to reach LDL-C goals despite an adequate trial of lifestyle modification. Colesevelam has not been studied in children < 10 years or in premenarchal females. Ezetimibe (Zetia) has been used in a limited number of children ages ≥ 10 years, but the safety and effectiveness have not been established in patients < 10 years of age. 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. Safety and efficacy of fibric acids (fenofibrate, fenofibric acid, and gemfibrozil), lomitapide (Juxtapid), omega-3-acid ethyl esters (Lovaza), icosapent ethyl (Vascepa), bempedoic acid (Nexletol), bempedoic acid/ezetimibe (Nexlizet), and inclisiran (Leqvio) have not been established in pediatrics.

The combination ezetimibe/simvastatin demonstrated a greater mean percent reduction in LDL-C compared to simvastatin alone (-15% [95% CI, -18 to -12]) in boys and postmenarchal girls 10 to 17 years of age.[275]

In addition, in a clinical study colesevelam 3.8 g/day significantly decreased plasma levels of LDL-C (-13%), total cholesterol (-7%), and significantly increased HDL-C (+6%) compared to placebo ($p \leq 0.05$ for all comparisons) in boys and postmenarchal girls 10 to 17 years of age.[276] Adverse reactions seen in pediatric patients, but not in adults, include headache (3.9%), creatine phosphokinase increases (2.3%), and vomiting (2.3%). The safety and efficacy of colesevelam in pediatric patients with type 2 diabetes has not been established; a 6-month randomized clinical trial which included patients ages 10 to 17 years with type 2 diabetes failed to demonstrate effectiveness with regard to glycemic improvement.[277]

The safety and efficacy of alirocumab (Praluent) in pediatric patients have not been established. The safety and efficacy of evolocumab (Repatha) for the treatment of pediatric patients ≥ 10 years of age with HoFH who require additional LDL-C lowering were established based on a trial in adults and pediatric patients ≥ 13 years old with HoFH (including 7 pediatric patients) and from open-label studies with an additional 19 pediatric patients aged ≥ 11 years. The safety and effectiveness of evolocumab have been established in pediatric patients ≥ 10 years old as an adjunct to diet and other LDL-C-lowering therapies for the treatment of HeFH based on a 24-week, randomized, placebo-controlled, double-blind trial in pediatric patients. The Pushtronex on-body infusion should only be used in children 13 to 17 years of age under adult supervision, as instructed by a healthcare professional.

Pregnancy

There are no available data on the use of bempedoic acid in pregnant women to assess risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Bempedoic acid (Nexletol) and bempedoic acid/ezetimibe (Nexlizet) should be discontinued when pregnancy is recognized unless its benefits outweigh the potential risk to the fetus.

Based on data from animal studies, evinacumab-dgnb (Evkeeza) can cause embryofetal harm when administered to a pregnant patient. Human data are not available. Patients who may become pregnant should consider having a pregnancy test prior to starting evinacumab-dgnb and should use effective contraception during treatment and for a minimum of 5 months after the last dose.

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Previously Pregnancy Category X, labeling for lomitapide (Juxtapid) has been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and states that use may cause fetal harm and therefore is contraindicated in pregnancy. Females of reproductive potential should have a negative pregnancy test before starting lomitapide therapy and should use effective contraception during therapy. Females on lomitapide who become pregnant should stop therapy immediately and notify their healthcare provider.

Previously Pregnancy Category B, labeling for colesevelam (Welchol) has been updated to comply with the PLLR and states the product is not absorbed systemically following oral administration, and maternal use is not expected to result in fetal exposure to the drug. Limited available data on the use of colesevelam are insufficient to determine a drug-associated risk of major congenital malformations or miscarriage.

Niacin is Pregnancy Category A for recommended daily allowance nutrient amounts; however, for the treatment of hyperlipidemia, niacin IR (Niacor) is considered Pregnancy Category C. Previously Pregnancy Category C, labeling for niacin extended-release (Niaspan) has been updated to comply with the PLLR and states therapy should be discontinued once pregnancy is recognized when used for treating hyperlipidemia and the risks versus benefits should be considered for use during pregnancy when used for treating hypertriglyceridemia.

Previously considered Pregnancy Category C, labeling has been updated to comply with the PLLR and advises data are insufficient for alirocumab (Praluent), evolocumab (Repatha), fenofibrate (Fenoglide, Fibricor, Tricor, Trilipix), gemfibrozil (Lopid), icosapent ethyl (Vascepa), omega-3-acid ethyl esters (Lovaza) in pregnant women to determine drug-associated fetal or maternal risks. As alirocumab and evolocumab are monoclonal antibodies, these agents are transported across the placenta and amounts increase during near term; therefore, these agents can be transmitted from the mother to the developing fetus.

The remaining products in this class are Pregnancy Category C.

The pregnancy exposure registry for alirocumab and evolocumab has been removed; however, there are pregnancy ongoing safety studies for providers to report exposure to either agent during pregnancy to the respective manufacturer.

Human data are not available for the use of inclisiran (Leqvio) in pregnancy. Given the mechanism of action of inclisiran which involves decreasing cholesterol and possibly other cholesterol-derived biologically active substances, it is possible that inclisiran could cause fetal harm when administered to pregnant patients. As such, it is generally recommended that inclisiran be discontinued during pregnancy for most patients, however providers should consider the needs of the individual patient.

Gender

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial was a double-blind, placebo-controlled study that evaluated if fenofibrate reduced major CV events in patients with type 2 diabetes and whether there were gender differences in fenofibrate response.[278] A total of 3,657 women and 6,138 men with type 2 diabetes and not on statin therapy received either fenofibrate 200 mg/day or placebo for 5 years. LDL-C, HDL-C, non-HDL-C, and apolipoproteins (apo) A-1 and B improved in both men and women (all $p<0.001$). A greater reduction was seen in women for all measures, except apo A-1. Fenofibrate reduced total CV outcomes (CV death, fatal and non-fatal stroke, and carotid and coronary revascularization) by 30% in women ($p=0.008$) and 13% in men ($p=0.07$).

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Hepatic/Renal Impairment

No dose adjustment of bempedoic acid (Nexletol) is required in patients with mild or moderate hepatic impairment. Bempedoic acid has not been studied in those with severe hepatic impairment (Child-Pugh C). Bempedoic acid/ezetimibe (Nexlizet) is not recommended with moderate to severe hepatic impairment (Child-Pugh B or C).

No dose adjustment of bempedoic acid or bempedoic acid/ezetimibe is required in patients with mild or moderate renal impairment. Data are lacking on use in patients with severe impairment and bempedoic acid has not been studied with end-stage renal disease.

Fenofibrates (Antara, Fenoglide, Lipofen, Tricor) and fenofibric acid (Fibricor, Trilipix) should be dose adjusted in renal impairment, unless severe impairment, 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.

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 [eGFR] < 60 mL/min/1.73 m^2), doses of simvastatin > 20 mg should be used cautiously and with close monitoring for myopathy.

Niacin-containing products should be used with caution in patients with renal impairment, 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 is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C). Lomitapide exposure is significantly increased in patients with mild hepatic impairment (Child-Pugh A) or with end-stage renal disease (ESRD) 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 and icosapent ethyl (Vascepa).

No dose adjustment is necessary for patients with mild to moderate hepatic or renal impairment using alirocumab or evolocumab. Neither alirocumab nor evolocumab have been studied in patients with severe hepatic or renal impairment.

No dose adjustment is necessary for patients taking inclisiran who have mild, moderate, or severe renal impairment, or mild or moderate hepatic impairment. Inclisiran has not been studied in end stage renal disease or severe hepatic impairment.

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DOSAGES[279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302]

Drug	Availability	Dose	Comments
ACL Inhibitor			
bempedoic acid (Nexletol)	180 mg tablets	180 mg once daily	Take with or without food
ACL Inhibitor/Cholesterol Absorption Inhibitor			
bempedoic acid/ ezetimibe (Nexlizet)	180 mg/10 mg tablets	180 mg/10 mg once daily	Take with or without food Swallow tablets whole
ANGPTL3 Inhibitor			
evinacumab-dgnb (Evkeeza)	345 mg/2.3 mL and 1,200 mg/8 mL of solution in single-dose vials	15 mg/kg administered by intravenous (IV) infusion over 60 minutes once monthly (every 4 weeks)	LDL-C may be measured 2 weeks from the first dose; the rate of infusion may be slowed, interrupted, or discontinued if signs of adverse reactions occur
Apolipoprotein B Synthesis Inhibitor			
lomitapide (Juxtapid)	5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 60 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 2 hours after the evening meal
Bile Acid Sequestrants			
cholestyramine (Questran, Questran Light)	powder for oral suspension†	1 to 2 packets or scoopfuls twice daily	Mix with 2 to 6 ounces of water or pulpy fruit (applesauce)
colesevelam (Welchol)	625 mg tablets	Hyperlipidemia or Type 2 DM: 3,750 mg daily in 1 or 2 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
	3,750 mg packet powder for oral suspension		
colestipol (Colestid)	1 g tablets	2 g once or twice daily	Increase by 2 g at 1- to 2-month intervals to a maximum of 16 g daily
	5 g granule packets and 7.5 g flavored granule packs (each 7.5 g packet contains 5 g colestipol hydrochloride)	5 g to 30 g daily	Increase daily dose by 5 g at 1- to 2-month intervals
Cholesterol Absorption Inhibitors			
ezetimibe (Zetia)	10 mg tablets	10 mg daily	Take with or without food

* Patients with ESRD on dialysis or with baseline mild hepatic impairment should not exceed lomitapide 40 mg daily.

† Prevalite (cholestyramine/aspartame) powder for oral suspension, by Upsher-Smith, was approved under an abbreviated new drug application (ANDA).

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Dosages (continued)

Drug	Availability	Dose	Comments
Fibric Acids			
fenofibrate	67 mg, 134 mg, 200 mg capsules	67 mg to 200 mg daily	Must be taken with food
	54 mg, 160 mg tablets	54 mg to 160 mg daily	
fenofibrate (Antara)	30 mg, 43 mg (generic only), 90 mg, 130 mg (generic only) capsules‡	30 mg to 90 mg daily	Take without regard to meals
		43 mg to 130 mg daily	
fenofibrate (Fenoglide)	40 mg, 120 mg tablets	40 mg to 120 mg daily	Take with food
fenofibrate (Lipofen)	50 mg, 150 mg capsules	50 mg to 150 mg daily	Take with food
fenofibrate (Tricor)	48 mg, 145 mg tablets	48 mg to 145 mg daily	Take without regard to meals
fenofibric acid (Fibricor)	35 mg, 105 mg tablets	35 mg to 105 mg daily	Take without regard to meals
fenofibric acid (Trilipix)	45 mg, 135 mg delayed-release capsules	45 mg to 135 mg daily	Take without regard to meals
gemfibrozil (Lopid)	600 mg tablets	600 mg twice daily	Take 30 minutes prior to meal
Niacin			
niacin ER (Niaspan)	500 mg (generic only), 750 mg (generic only), 1,000 mg tablets	500 mg to 2,000 mg at bedtime§	Titrate dose up every 4 weeks May pre-administer aspirin to reduce flushing Take at bedtime after low-fat snack
niacin IR (Niacor)	500 mg tablets	1 g to 2 g twice or 3 times daily§	May pre-administer aspirin to reduce flushing Take at bedtime after low-fat snack
Omega-3 Fatty Acids			
icosapent ethyl (Vascepa)	0.5 g and 1 g capsules	2 g twice daily	Take with food Swallow capsules whole
omega-3-acid ethyl esters (Lovaza)	1 g capsules	4 g daily in 1 or 2 divided doses	Take with meal(s) Swallow capsules whole

‡ Antara 43 mg and 130 mg capsules have been discontinued and replaced by Antara 30 mg and 90 mg capsules.

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

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Dosages (continued)

Drug	Availability	Dose	Comments
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors			
alirocumab (Praluent)	75 mg/1 mL and 150 mg/1 mL single-dose prefilled pen	75 mg subcutaneously (SC) once every 2 weeks; may be increased to a maximum of 150 mg administered every 2 weeks; an alternative starting dose of 300 mg (2 x 150 mg SC injections) may be given every 4 weeks In adults with HeFH undergoing LDL apheresis or in adults with HoFH: 150 mg SC once every 2 weeks (administer without regard to timing of apheresis)	Patients can self-administer the pen with proper training; Administration should be in the thigh, abdomen, or upper arm; rotate the injection site with each injection and inject into areas that are not tender, bruised, red, or indurated
evolocumab (Repatha)	140 mg/1 mL prefilled syringe or SureClick® auto-injector 420 mg/3.5 mL single-use Pushtronex system (on-body infusor with prefilled cartridge)‖	Established CVD or with primary hyperlipidemia or HeFH in ≥ 10 years old: 140 mg SC once every 2 weeks or 420 mg SC once monthly; HoFH (adults and ≥ 10 years old): 420 mg SC once monthly; may be increased to 420 mg every 2 weeks; and alternative starting dose is 420 mg every 2 weeks for patients on lipid apheresis (administer after the apheresis session is complete)	Patients can self-administer the pen, syringe, or Pushtronex system with proper training; administer in the thigh, abdomen, or upper arm that are not tender, bruised, red, indurated, scarred or have stretch marks; rotate the injection sites; the needle cover of the glass single-dose prefilled syringe and the single-dose prefilled autoinjector contain a derivative of latex that may cause allergic reactions in individuals sensitive to latex The 420 mg dose may be delivered via: ▪ Prefilled autoinjector or syringe – administer three 140 mg/mL injections SC consecutively within 30 minutes ▪ Pushtronex system – administer 420 mg SC dose over 5 minutes
PCSK9-Directed Small Interfering RNA (siRNA)			
inclisiran (Leqvio)	284 mg/1.5 mL single-dose prefilled syringe	284 mg SC once initially, again at 3 months, and then every 6 months in combination with maximally tolerated statin therapy	Must be administered by a healthcare professional Inject into the abdomen, upper arm, or thigh; avoid areas of active skin disease or injury (e.g., sunburn, skin rash, inflammation, infection)

‖The Repatha Pushtronex system is a single-use infusor device that is attached to the skin to provide hands-free delivery of evolocumab 420 mg in a single SC dose. Moderate physical activity can be done during the injection process (e.g., walking, reaching, bending).

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Bempedoic acid and bempedoic acid/ezetimibe are given in combination with maximally tolerated statin therapy. Lipid levels should be assessed within 8 to 12 weeks after starting therapy with bempedoic acid or bempedoic acid/ezetimibe.

Lomitapide doses should be reduced or withheld if transaminase levels increase to ≥ 3 x ULN during treatment. When levels resolve to < 3 x ULN, consider resuming lomitapide at reduced doses.

For alirocumab and evolocumab, LDL-C level should be assessed as clinically appropriate; the LDL-lowering effect may be measured as early as 4 weeks following initiation of therapy. For missed doses of alirocumab the patient should administer the injection within 7 days from the missed dose and then resume the original dosing schedule. If the missed dose is not administered within 7 days, then the patient should wait until the next dose on the original schedule. If a dose of evolocumab is missed, the patient should administer the dose as soon as possible if there are more than 7 days until the next scheduled dose or omit the missed dose and administer the next dose according to the original schedule. Alirocumab and evolocumab should be refrigerated and may be kept at room temperature in the original carton for up to 30 days. Alirocumab should be allowed to warm to room temperature for 30 to 40 minutes prior to use. If refrigerated, the Repatha Pushtronex (evolocumab) infusor should naturally reach room temperature over 45 minutes prior to use.

The LDL-C lowering effect of inclisiran may be measured as soon as 30 days after initiation and anytime thereafter, regardless of timing of doses, as clinically indicated. If a planned inclisiran dose is missed by < 3 months, inclisiran should be administered and the original dosing schedule should be maintained. If a planned inclisiran dose is missed by > 3 months, inclisiran should be restarted with a new dosing schedule (initial dose, again at 3 months, and then every 6 months). Inclisiran should be stored at controlled room temperature between 20 to 25 degrees Celsius).

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% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship funding must be considered, the studies in this review have also been evaluated for validity and importance.

The effects of the drugs in this class on lipids are well documented. To date, however, clinical outcomes have not been established for bempedoic acid (Nexletol), bempedoic acid/ezetimibe (Nexlizet), colesevelam (Welchol), colestipol (Colestid), fenofibrates, lomitapide (Juxtapid), inclisiran (Leqvio), or prescription strength omega-3-acid ethyl esters (Lovaza).[303,304,305,306,307,308,309,310,311,312]

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bempedoic acid (Nexletol)

The CLEAR trial program included four phase 3, double-blind, randomized clinical trials evaluating efficacy and safety of bempedoic acid. The CLEAR Harmony 52-week trial enrolled adults with ASCVD, HeFH, or both. Baseline LDL-C levels were ≥ 70 mg/dL while on maximally tolerated stain therapy with or without additional lipid-lowering therapies.[313] Patients were randomized to bempedoic acid 180 mg once daily (n=1,488) or matching placebo (n=742). Mean baseline LDL-C was 103.2 mg/dL. Mean age was 66.1 years. Key exclusion criteria were the use of gemfibrozil or simvastatin at doses > 40 mg per day. The use of a PCSK9 inhibitor was permitted after week 24 for patients with LDL-C > 170 mg/dL and an LDL-C increase by ≥ 25% from baseline. At week 12, bempedoic acid resulted in the mean reduction of LDL-C by 19.2 mg/dL (difference from placebo in change from baseline, -18.1%; 95% CI, -18.2 to -14; p<0.001). Significant differences in changes from baseline compared to placebo were also seen in non-high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), apolipoprotein B (apo-B), and high-sensitivity C-reactive protein (hsCRP) at week 12 (p<0.001 for all). Effect was seen through week 52 of the study. Efficacy did not depend on type or intensity of background lipid-lowering therapy.

The CLEAR Wisdom 52-week trial included adults with ASCVD, HeFH, or both. Baseline LDL-C levels were ≥ 70 mg/dL while on maximally tolerated statin therapy.[314] Patients were randomized to bempedoic acid 180 mg once daily (n=522) or matching placebo (n=257) added to maximally tolerated lipid lowering therapy. At baseline, mean LDL-C level was 120.4 mg/dL. Mean age was 64 years. At week 12, the difference in mean percent change in LDL-C from baseline between bempedoic acid and placebo was -17.4% (95% CI, -21 to -13.9; p<0.001).

The CLEAR Serenity trial assessed 345 patients with hypercholesterolemia and a history of intolerance to ≥ 2 statins. Baseline LDL-C levels were ≥ 130 mg/dL for primary prevention patients and ≥ 100 mg/dL for patients with HeFH while on maximally tolerated statin therapy.[315] Patients were randomized to bempedoic acid 180 mg or placebo once daily for 24 weeks. Stable background lipid-lowering therapy was continued. Mean age was 65.2 years and mean baseline LDL-C was 157.6 mg/dL. At week 12, bempedoic acid significantly reduced LDL-C from baseline (difference from placebo, −21.4% [95% CI, −25.1 to −17.7]; p<0.001). Significant reductions from baseline compared to placebo were also seen with non-HDL-C, TC, apo-B, and hsCRP (p<0.001 for all).

The CLEAR Tranquility trial enrolled adults with a history of statin intolerance and an LDL-C ≥ 100 mg/dL while on stable lipid-lowering therapy.[316] After a 4-week run-in period with ezetimibe 10 mg/day, patients were randomized to bempedoic acid 180 mg once daily (n=181) or placebo (n=88) as add-on to background lipid-lowering therapy that included ezetimibe 10 mg/day. The mean baseline LDL-C was 127.6 mg/dL. The mean age was 63.8 years. The change in LDL-C from baseline to week 12 was significantly greater with bempedoic acid compared to placebo (difference from placebo, -28.5% [95% CI, -34.4 to -22.5; p<0.001). Significant reductions in LDL-C with bempedoic acid compared to placebo were recorded at week 4. In addition, significant reductions from baseline compared to placebo were also observed with non-HDL-C, TC, apo-B, and hsCRP (p<0.001 for all). The study demonstrated minimal effect on triglyceride levels.

bempedoic acid (Nexletol) and bempedoic acid/ezetimibe (Nexlizet)

The efficacy and safety of bempedoic acid and bempedoic acid/ezetimibe were assessed in a phase 3, double-blind clinical trial that enrolled 301 adults with ASCVD, HeFH, or multiple CVD risk factors.[317] Patients were randomized 2:2:2:1 to once daily fixed-dose combination of bempedoic acid/ezetimibe

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180 mg/10 mg, bempedoic acid 180 mg, ezetimibe 10 mg, or placebo as add-on to stable background statin therapy for 12 weeks. The mean LDL-C was 149.8 mg/dL at baseline. At week 12, all treatment groups resulted in significant reductions in LDL-C compared to placebo (fixed-dose combination: –36.2%; bempedoic acid alone: –17.2%; ezetimibe alone: –23.2%; placebo: 1.8%; p<0.001 for all compared to placebo).

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.[318,319] 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% and in LDL-C of 20.3%. The cholestyramine group experienced a 19% reduction in risk (p<0.05) of the primary composite endpoint of definite CHD death and/or definite nonfatal MI; this reflected a 24% reduction in definite CHD death and a 19% reduction in nonfatal MI. The cumulative 7-year incidence of the primary endpoint was 7% in the cholestyramine group and 8.6% in the placebo group. In addition, the incidence rates were reduced for new positive exercise tests (by 25% compared to placebo; p<0.001) and new onset angina (by 20%; p<0.01). The incidence of coronary bypass surgery was similar in each group. The risk of death from all causes was reduced by 7% (p=not significant [NS]) in the cholestyramine group; the magnitude of this decrease was less than for CHD endpoints because of a greater number of violent and accidental deaths in the cholestyramine group.

cholestyramine, gemfibrozil, and niacin IR (Niacor)

A randomized, double-blind, placebo-controlled trial assessed the effects of gemfibrozil, niacin immediate-release, and cholestyramine on the composite outcome of MI, transient ischemic attack or stroke, CV death, CV procedures, or hospitalization for angina.[320] 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 6 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% (95% CI, 14.8 to 24.3), LDL-C reduction of 26% (95% CI, 19.1 to 33.7), triglyceride (TG) reduction of 50% (95% CI, 40.5 to 59.2), and an increase in HDL-C of 36% (95% CI, 28.4 to 43.5). The composite endpoint was reached by 26.4% of the placebo group compared to 12.7% of the active treatment group, an absolute difference of 13.7% (95% CI, 0.9 to 26.5). There were no significant differences in the individual clinical event rates between the 2 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 led to the possibility of unblinding.

colesevelam (Welchol) and metformin, sulfonylurea, and insulin

Efficacy of colesevelam in type 2 diabetes mellitus was evaluated in 3 double-blind, placebo-controlled trials in combination with metformin, sulfonylurea, or insulin.[321] A total of 1,018 patients with baseline hemoglobin A1c (HbA1c) of 7.5% to 9.5% took colesevelam 3.75 g/day as 3 tablets twice daily with meals or as 6 tablets with dinner for 26 weeks. In all 3 trials, HbA1c was reduced by 0.5% compared to placebo

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(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%), who were receiving metformin monotherapy or metformin combined with additional oral anti-diabetes drugs.[322] Colesevelam lowered the mean HbA1c level by -0.54% compared with placebo at week 26 (p<0.001). Similar results were observed in the metformin monotherapy (-0.47%, p=0.002) and combination therapy cohorts (-0.62%, p<0.001). Colesevelam also significantly reduced fasting plasma glucose (-13.9 mg/dL, p=0.01), total-C (-7.2%, p<0.001), LDL-C (-15.9%, p<0.001), and apo B (-7.9%, 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%).[323] The mean (SE) change in HbA1c was -0.41% (0.07%) versus 0.09% (0.07%) for colesevelam versus placebo, respectively. The treatment difference was 0.5% (SE, 0.09%; 95% CI, -0.68 to -0.32; p<0.001). There was a 12.8% reduction in LDL-C levels in the colesevelam group versus placebo (p<0.001). Median TG levels increased significantly in the colesevelam group.

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 6 weeks.[324] 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% versus -21.4% 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.

colesevelam (Welchol) in pediatrics

The safety and efficacy of colesevelam in pediatric patients were evaluated in an 8-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% of patients) or naïve to lipid-lowering therapy (with LDL-C > 160 mg/dL) (76% of patients).[325] 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 8 weeks of treatment, colesevelam 3.8 g/day significantly decreased plasma levels of LDL-C (-13%), total cholesterol (-7%), and significantly increased HDL-C (+6%) compared to placebo (p≤0.05 for all comparisons). There was a non-significant increase in TG (+5%) versus placebo.

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Patients were treated with colesevelam 3.8 g/day during the open-label treatment period. A total of 173 patients completed 26 weeks of treatment. Results at week 26 were consistent with those at week 8.

evinacumab-dgnb (Evkeeza)

The double-blind, placebo-controlled, phase 3, ELIPSE trial enrolled patients (n=65) ≥ 12 years of age with HoFH (based on either genetic or clinical criteria) and an LDL-C ≥ 70 mg/dL while on stable lipid-lowering therapy at maximum tolerated doses (statin, ezetimibe, PCSK9 inhibitors, lomitapide, and apheresis or combination therapy).[326,327] Patients were randomized 2:1 to receive IV evinacumab at a dose of 15 mg/kg of body weight every 4 weeks or placebo in addition to their background treatment. The mean baseline LDL-C was 255.1 mg/dL. The primary efficacy endpoint was to determine percent change in LDL-C from baseline to week 24. Evinacumab resulted in a 47.1% reduction in LDL-C from baseline compared to a 1.9% increase with placebo. The least squares mean treatment difference in LDL-C between evinacumab and placebo was -49% (95% CI, -65 to -33; p<0.0001). The LDL-C reduction with evinacumab was reported as early as week 2 of the study. LDL-C reductions were similar among those with null-null (virtually absent LDL-receptor activity) and non-null variants (impaired LDL-receptor activity). LDL-C reductions were also similar regardless of background anti-lipid therapies. Notably, HDL-C levels were reduced by 29.6% from baseline in the evinacumab group versus an increase of 0.8% in the placebo group. Adverse events occurred in 66% of evinacumab patients versus 81% of placebo patients; 2 patients (5%) in the evinacumab group experienced serious adverse events (urosepsis and suicide attempt, 1 case each). No deaths occurred.

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.[328] At baseline and at 12 weeks, the Vertical Auto Profile II method was used to measure the cholesterol associated with 2 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-C, IDL-C, and dense LDL-C (primarily LDL-C4) subfractions, and increased cholesterol mass within the more buoyant LDL-C2 subfraction, consistent with a shift to a more buoyant LDL-C peak particle size. Ezetimibe reduced cholesterol mass within all of the apolipoprotein B-containing particles (e.g., VLDL-C, IDL-C, and LDL-C) but did not lead to a shift in the LDL-C particle size distribution profile. Co-administration of fenofibrate and ezetimibe promoted more pronounced reductions in VLDL-C, IDL-C, and LDL-C, and a preferential decrease in dense LDL-C subfractions. Fenofibrate and combination therapy promoted similar increases in HDL-C2 and HDL-C3.

ezetimibe (Zetia) plus simvastatin (Zocor) versus simvastatin (Zocor) monotherapy in pediatrics

In a multi-center, double-blind, controlled study followed by an open-label phase, 142 boys and 106 postmenarchal girls, 10 to 17 years of age, with HeFH were randomized to receive either ezetimibe co-administered with simvastatin or simvastatin monotherapy.[329] 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

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received combination of ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) or simvastatin monotherapy (10 mg, 20 mg, or 40 mg) for 6 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 6, the mean percent difference between treatment groups for LDL-C was -15% (95% CI, -18 to -12). Results at week 33 were consistent with those at week 6.

fenofibrate (Antara, Fenoglide, Lipofen, Tricor)

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 5 years.[330] 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% of placebo and fenofibrate groups, respectively, for a relative risk reduction of 11% (p=0.16). The fenofibrate group had a 24% relative risk reduction for non-fatal 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% of patients in the fenofibrate group and 13.9% of patients in the placebo group (p=0.035). This reduction was primarily related to a 24% relative risk reduction in the incidence of MI (p=0.010) and 21% relative risk reduction in coronary revascularization (p=0.003). There was a significant 11% reduction in the secondary outcomes (HR 0.89, 95% CI 0.8 to 0.99, p=0.04). There was a non-significant 11% (HR 1.11, 95% CI 0.95, 1.29, p=0.41) and 19% (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%) were receiving statins than in the fenofibrate group (16%; p<0.0001). After adjusting for statin use, investigators estimated that fenofibrate reduced the risk of CHD events by 19% (p=0.01) and of total CV disease events by 15% (p=0.004). Fenofibrate was also associated with less progression of albuminuria (p=0.002). Fenofibrate was well tolerated with a discontinuation rate similar to placebo. Nonsignificant increases in pancreatitis and pulmonary embolism were reported in the fenofibrate group.

The SAFARI study was a randomized, double-blind, active-controlled, multicenter, 18-week (6-week diet and placebo run-in period) study of 618 patients with mixed dyslipidemia.[331] 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% in the combination group and 20.1% in the simvastatin monotherapy group (treatment difference-23.6%, p<0.001). Mean LDL-C decreased 31.2% and 25.8% (treatment difference -5.4%, p<0.001), and HDL-C increased 18.6% and 9.7% (treatment difference 8.8%, 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.[332] After 1 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% were women, 37% had a prior CV event, mean systolic blood pressure was 134 mm Hg, mean HbA1c was 8.1%, and about 60% were taking a statin prior to enrollment.

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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% with fenofibrate versus 2.4% 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 2 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≥0.1 for all comparisons). Annual rates of death were 1.5% in the fenofibrate group and 1.6% 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% in the fenofibrate group and 1.1% 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 3, 12-week, randomized, double-blind, multicenter studies of 2,698 patients with mixed dyslipidemia, efficacy, and safety of fenofibric acid in combination with statins to each single agent were reviewed.[333] 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% and 17.5%, respectively) and decreased TG (43.9% and 42%, respectively) compared to the corresponding dose of statin monotherapy (7.4% and 8.7% for HDL-C, -16.8% and -23.7% for TG; p<0.001 for all comparisons). In addition, both doses of combination therapy resulted in mean percent decreases (33.1% and 34.6%, respectively) in LDL-C that is significantly greater than fenofibric acid monotherapy (5.1%, 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 ages 40 to 55 years old (n=4,081) compared to placebo.[334,335] Over the 5-year study period, there was a 34% relative risk reduction (p<0.02) in the incidence of cardiac endpoints (MI and cardiac death) with the use of gemfibrozil compared to placebo.[336] At the conclusion of the study, all participants were given the opportunity to receive gemfibrozil for an additional 3.5 years.[337] After the additional open-label period, there was no significant difference in CV or all-cause mortality between the 2 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.[338] Three-hundred and eleven of these patients were randomized to receive gemfibrozil 1,200 mg/day and 317 subjects to receive placebo over 5 years in double-blind fashion. The primary endpoint, a composite of fatal and non-fatal MI and cardiac deaths, did not differ significantly between the placebo and gemfibrozil groups. The same was true for total mortality. In the study, data were not evaluated for

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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% relative risk reduction of CHD mortality compared to placebo (p=0.05).[339]

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.[340] The primary study outcome was nonfatal MI or death from coronary causes. At 1 year, the mean total-C was 4% lower, HDL-C was 6% higher, and TG was 31% 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% of patients in the gemfibrozil group and 21.7% of patients in the placebo group, a significant relative risk reduction of 22% (95% CI, 7 to 35; p=0.006). There was also a 24% 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 subanalysis showed a reduced incidence in the primary outcome in patients with chronic renal insufficiency (25% relative risk reduction; p=0.02) and in patients with diabetes (32% relative risk reduction; p=0.004).[341,342]

icosapent ethyl (Vascepa)

MARINE: In a randomized, double-blind, multicenter, placebo-controlled study, 229 patients with severe hypertriglyceridemia (baseline 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.[343] 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% reduction in the 4-gram group (p<0.001 versus placebo) and a 19.7% reduction in the 2-gram group (p=0.0051). 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% reduction (n=28, p=0.0001) and the 2-gram dosage resulted in a 32.9% 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% reduction, p=0.0001; 2-gram group on statins 40.7% reduction, p=0.0276 compared to 4-gram group no statin 25.8% reduction, p=0.0002; 2-gram group no statins 16.4%, p=0.036). Safety profile of icosapent ethyl was similar to placebo.

ANCHOR: The efficacy and safety of icosapent ethyl were evaluated in a phase 3, double-blind, 12-week trial in high-risk statin-treated patients with residually high TG levels (≥ 200 and < 500 mg/dL) despite LDL-C control (≥ 40 mg/dL and < 100 mg/dL).[344] Patients (n=702) on a stable diet were randomized to icosapent ethyl 4 g or 2 g per day or placebo. The primary endpoint was median percent change in TG levels from baseline versus placebo. Both doses of icosapent ethyl significantly decreased TG levels by 21.5% (p<0.0001) and 10.1% (p=0.0005), respectively, and non-HDL-C by 13.6% (p<0.0001) and 5.5% (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, apo B, total cholesterol, VLDL-C, lipoprotein-associated phospholipase A(2), and high-sensitivity C-reactive protein compared to

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placebo (p<0.001 for all comparisons). Icosapent ethyl was generally well tolerated, with safety profiles similar to placebo.

icosapent ethyl (Vascepa) and cardiovascular outcomes

REDUCE-IT: Icosapent ethyl effect on the risk of ischemic events was evaluated in a randomized trial in 8,179 patients on statin-therapy with triglycerides between 135 and 499 mg/dL and LDL-C between 41 and 100 mg/dL.[345] Patients also had a history of ASCVD (71%) or diabetes (29%). Patients were randomized to icosapent ethyl 4 g per day or placebo. The primary efficacy endpoint was total (first and subsequent) primary composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina. Median time of follow-up was 4.9 years. Overall, icosapent ethyl significantly reduced total primary endpoint events (17.2% with icosapent ethyl versus 22% placebo, respectively; hazard ratio [HR], 0.75 [95% CI, 0.68 to 0.83; p < 0.001]); each primary endpoint component was also reduced with icosapent ethyl.

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.[346] Current lipid-lowering therapy was maintained. Patients were counseled to follow a low-fat diet (< 20% 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% (95% CI, -62 to -39; p<0.0001) from baseline; LDL-C levels remained reduced by 44% (95% CI, -57 to -31; p<0.0001) at week 56 and 38% (95% CI, -52 to -24; p<0.0001) at week 78. The most common adverse events reported were gastrointestinal symptoms. Four patients had aminotransaminase levels > 5 times the upper limit of normal, which resolved after dose reduction or temporary interruption of lomitapide.

niacin IR

The Coronary Drug Project was a 9-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 mg 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.[347] The 2 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. Study authors state that a late benefit of niacin occurred after discontinuation of the drug that may be a result of a translation into a mortality benefit over subsequent years of the early favorable effect of niacin in decreasing nonfatal recurrent MI or a result of the cholesterol-lowering effect of niacin, or both. Mortality in the niacin group was 11% lower than in the placebo group (52% versus 58.2%; 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).[348] Patients were

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initially started on niacin ER 500 mg and then titrated to 1,000 mg daily after 1 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 2 groups. After 12 months, HDL-C increased by 21% 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% in the niacin group and 9.6% in the statin-only group; $p=0.2$).

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, with or without ezetimibe, at a dose sufficient to maintain LDL-C at 40 to 80 mg/dL. Patients were randomized to niacin extended-release (ER) or matching placebo.[349] Although niacin ER 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 MI and stroke) in the niacin ER plus simvastatin arm versus simvastatin alone ($p=0.8$).[350,351] In addition, a small, unexplained, increase in the rate of ischemic stroke was observed in the simvastatin plus niacin ER arm compared to simvastatin alone (29 patients versus 18 patients, respectively; $p=0.11$). Nine of the ischemic strokes in the simvastatin plus niacin ER group occurred in participants who had stopped taking niacin for at least 2 months and up to 4 years before their stroke. Therefore, it is unclear whether niacin contributed to this imbalance in ischemic stroke. The authors note many study limitations, such as that the findings may not be generalizable to all patients with coronary disease or all patients with low HDL-C levels. It remains unclear whether other populations may benefit from such treatment; it is unclear if in the 94% of patients who were taking statins at study entry whether or not they had more stable plaques at baseline which were less likely to rupture, and therefore, had a lower risk of subsequent CV events. The low percentage of women enrolled (15%), the low rate of ethnic minorities (8%), and the 36-month follow-up period may not have been adequate 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.[352]

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).[353,354] Patients were treated with 8 weeks of open-label simvastatin 40 mg daily prior to randomization to reduce LDL-C to no greater than 10% 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 8 weeks. Combination therapy versus monotherapy resulted in a median percentage change in TG of -29.5% versus -6.3%, respectively, ($p<0.0001$). The mean percentage change in HDL-C was +3.4% for combination therapy versus -1.2% for monotherapy, ($p<0.05$). The mean percentage change in LDL-C was +0.7% for the combination group and -2.8% 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.[355] Patients also received escalating dosages of open-label atorvastatin (weeks 0-8, 10 mg/day;

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weeks 9-12, 20 mg/day; weeks 13-16, 40 mg/day). Omega-3-acid ethyl esters plus atorvastatin 10 mg, 20 mg, and 40 mg/day reduced median non-HDL-C levels by 40.2% versus 33.7% (p<0.001), 46.9% versus 39% (p<0.001), and 50.4% versus 46.3% (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 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.

alirocumab (Praluent) versus placebo

ODYSSEY COMBO I was a multicenter, phase 3, randomized, double-blind, 52-week trial that evaluated the effect of alirocumab in patients with a history of ASCVD not at goal (LDL-C ≥ 70 mg/dL) or moderate chronic kidney disease (CKD) or diabetes with additional risk factors not at goal (LDL-C ≥ 100 mg/dL) despite maximally tolerated statin with or without other lipid-lowering therapy.[356] Patients with known HeFH or HoFH were excluded. Overall, 209 patients were randomized (2:1) to subcutaneous (SC) alirocumab and 107 to placebo. Eighty four percent had clinical ASCVD. Patients in the alirocumab group were initiated at a dose of 75 mg every 2 weeks with possible up-titration to 150 mg every 2 weeks at week 12 in patients whose LDL-C was still ≥ 70 mg/dL. After 24 weeks, the treatment difference between alirocumab and placebo in mean LDL-C percent change was 45.9% (p<0.0001). The treatment difference between alirocumab and placebo for percent change from baseline in Apo B, non-HDL-C, total cholesterol, triglyceride reductions, and HDL increase at 24 weeks were 35.8%, 37.5%, 25%, 0.6%, and 7.3%, respectively (p<0.0001 except all for triglycerides). The dose was up-titrated to 150 mg in 16% of patients treated with alirocumab for at least 12 weeks.

ODYSSEY FH I and II were both 78-week multicenter, multinational, randomized, double-blind, placebo-controlled trials in patients with HeFH not at goal (LDL-C ≥ 70 mg/dL if patient had prior CVD and ≥ 100 mg/dL if no history of CVD) despite maximally tolerated statin with or without other lipid lowering therapy.[357,358] Overall, 490 patients were assigned to alirocumab and 245 to placebo. Patients in the alirocumab group were initiated at a dose of 75 mg every 2 weeks with possible up-titration to 150 mg every 2 weeks at week 12 in patients whose LDL-C was still ≥ 70 mg/dL. After 24 weeks, the treatment difference between alirocumab and placebo in mean LDL-C percent change was 57.9% (p<0.0001) and 51.4% (p<0.0001) in FH I and II, respectively. In FH I, the treatment difference between alirocumab and placebo for percent change from baseline in Apo B, Non-HDL-C, total cholesterol, and triglyceride reductions, and HDL increase at 24 weeks were 45.8%, 52.4%, 38.7%, 16%, and 8%, respectively (p<0.0001 for all). In FH II, the treatment differences were 39.3%, 45.7%, 32.8%, 10.9%, and 6.8%, respectively (p<0.01 for all). The dose was up-titrated to 150 mg in 43.4% and 38.6% of patients treated with alirocumab for at least 12 weeks in FH I and II, respectively.

ODYSSEY High FH, with a nearly identical trial design to FH I and II, was a 78-week trial in patients with HeFH and a baseline LDL-C ≥ 160 mg/dL. Overall, 72 patients were assigned to alirocumab 150 mg every 2 weeks and 35 to placebo.[359,360,361] After 24 weeks, the treatment difference between alirocumab and placebo in mean LDL-C percent change was 39.1% (p<0.0001). The treatment difference between alirocumab and placebo for percent change from baseline in apo B, non-HDL-C, total cholesterol, and triglyceride reductions, and HDL increase at 24 weeks were 30.3%, 35.5%, 28.4%, 8.7%, and 3.7%, respectively (p<0.001 for all except triglycerides and HDL).

ODYSSEY LONG-TERM, a multinational, phase 3, randomized, double-blind, placebo-controlled, 18-month trial, evaluated the effect of alirocumab in non-familial hypercholesterolemia (non-FH) and HeFH

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ASCVD patients with high or very high cardiovascular risk not at goal (LDL-C ≥ 70 mg/dL).[362] Overall, 1,553 patients were assigned to alirocumab 150 mg every 2 weeks and 788 to placebo. Sixty-nine percent were non-FH patients with clinical ASCVD and 18% had HeFH. After 24 weeks, the treatment difference between alirocumab and placebo in mean LDL-C percent change was 61.9% (95% CI, -64.3 to -59.4; p<0.0001). The treatment difference between alirocumab and placebo for percent change from baseline in Apo B, non-HDL-C, total cholesterol, and triglyceride reductions, and HDL increase at 24 weeks were 54%, 52.3%, 37.5%, 17.3%, and 4.6%, respectively (p<0.0001).

ODYSSEY CHOICE 1 compared alirocumab 300 mg SC every 4 weeks (n=312), 75 mg every 2 weeks (n=78), and placebo (n=157) in a randomized, double-blind manner.[363,364] Included patients had inadequately controlled hypercholesterolemia and were either on maximally tolerated statin or no statin, with or without other lipid-lowering therapies. Alirocumab dosage could be adjusted to 150 mg every 2 weeks if needed after 12 weeks of therapy, based on prespecified LDL-C criteria, which occurred in approximately 20% of patient receiving alirocumab. At week 24, the treatment difference in mean percent change in LDL-C from baseline between those treated with placebo and those initially assigned to alirocumab 300 mg was -56% (97.5% CI, -62 to -49; p<0.0001); and the treatment difference between placebo and initial assignment to alirocumab 75 mg was -48% (97.5% CI, -57 to -39).

ODYSSEY HoFH (NCT03156621) compared alirocumab 150 mg every 2 weeks to placebo in a randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 3 study (n=69).[365,366] Adults who were receiving maximally tolerated doses of statins ± other lipid-lowering therapy and needed additional LDL-C reduction were enrolled. The average age was 43 years (range, 19 to 81) with the majority being women (51%) and Caucasian (78%). At baseline, in the alirocumab group (n=45), the average LDL-C was 295 mg/dL, and it was 259.6 mg/dL in the placebo group (n=24), with the majority of patients (n=67) receiving background lipid-lowering treatment of a statin (59 patients on high-intensity statin), 50 patients on ezetimibe, 10 patients receiving lomitapide, and 10 patients receiving apheresis. After 12 weeks of treatment, the primary endpoint, assessing percent reduction from baseline in LDL-C, demonstrated a least squares mean difference (LSMD) of -35.6% (alirocumab, -26.9% versus placebo, 8.6%; p<0.0001). At week 12, decreases in other atherogenic lipids were -29.8% for apolipoprotein B, -32.9% for non-HDL-C, -26.5% for total cholesterol, and -28.4% for lipoprotein(a), (all p<0.0001). No serious adverse reactions, permanent therapy discontinuations, or deaths due to adverse events occurred. The authors concluded that, in patients with HoFH, alirocumab resulted in statistically and clinically significant decreases in LDL-C and was generally well tolerated, with similar safety to that observed with placebo.

alirocumab (Praluent) versus ezetimibe (Zetia)

The ODYSSEY COMBO II trial followed an identical study design as COMBO I but included an active comparator rather than placebo. It was a 104-week, double-blind, double-dummy, active-controlled, parallel-group, phase 3 study, comparing alirocumab to ezetimibe (n=720) in high-risk patients with ASCVD and elevated LDL-C despite maximal statin treatment (n=720).[367] Patients with known He-FH or Ho-FH were excluded. Patients were randomized to SC alirocumab 75 mg every 2 weeks or oral ezetimibe 10 mg daily, both with background statin therapy. After 24 weeks, the treatment difference between alirocumab and ezetimibe in mean LDL-C percent change was 29.8% (95% CI, -34.4 to -25.3; p<0.0001) favoring alirocumab, the primary endpoint. Secondary endpoints included percent change in LDL-C at week 12 and 52, proportion of patients reaching calculated LDL-C < 70 mmol/L at week 24, and percent

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change in apolipoprotein B, non-HDL-C, total cholesterol, lipoprotein A, HDL-C, fasting triglycerides, and apolipoprotein A-1 from baseline to week 24. Nearly all secondary endpoints also demonstrated superiority of alirocumab compared to ezetimibe (p<0.0001 for all endpoints excluding triglycerides). At 104 weeks, LDL-C was reduced by 49% with alirocumab compared to 17% with ezetimibe (p<0.0001), and LDL-C < 70 mg/dL was achieved by 73% of patients treated with alirocumab versus 40% treated with ezetimibe.[368] A similar overall safety profile was seen in both treatment groups at years 1 and 2.

The ODYSSEY MONO trial, a phase 3, randomized, double-blind, double-dummy study, compared alirocumab and ezetimibe in 103 moderate risk ASCVD patients that were not on any other background lipid-lowering therapy.[369] Patients with known He-FH or Ho-FH were excluded. Patients were randomized to alirocumab 75 mg SC every 2 weeks (dose could be up titrated to 150 mg if LDL-C was ≥ 70 mg/dL at week 12) or oral ezetimibe 10 mg daily. Fourteen of the 52 patients in the alirocumab treatment arm were up titrated at 12 weeks. After 24 weeks, the treatment difference between alirocumab and ezetimibe in mean LDL-C percent change was 31.6% (95% CI, -40.2 to -23; p<0.0001).

The ODYSSEY OPTIONS I study, a phase 3, 24-week, multicenter, randomized, double-blind, active-comparator study, explored the efficacy of alirocumab in 355 HeFH and non-FH ASCVD patients at high or very high cardiovascular risk not adequately controlled on atorvastatin 20 mg to 40 mg.[370] Patients were randomized to add-on alirocumab 75 mg SC every 2 weeks (up titration to 150 mg was possible based on LDL-C level and CV risk at week 12), add-on ezetimibe 10 mg/day, doubled atorvastatin dose, or a switch to rosuvastatin 40 mg (those on atorvastatin 40 mg/day only). At 24 weeks in the patient group treated with 20 mg atorvastatin at baseline, the least squares (LS) mean (standard error [SE]) percent change in LDL-C from baseline in the add-on alirocumab group was -44.1% (±4.5%), -20.5% (±4.7%) in the ezetimibe group, and -5% (±4.6%) in the atorvastatin dose doubling group (p=0.0004 alirocumab versus ezetimibe; p<0.0001 alirocumab versus atorvastatin). At 24 weeks in the patient group treated with atorvastatin 40 mg at baseline, the LS mean (SE) percent change in LDL-C from baseline was -54% (±4.3%) in the add-on alirocumab group, -22.6% (±4.3%) in the ezetimibe group, -4.8% (±4.2%) in the atorvastatin dose doubling group, and -21.4% (±4.2%) in the rosuvastatin group (p<0.0001 for all comparisons).

alirocumab (Praluent) and cardiovascular outcomes

ODYSSEY OUTCOMES:[371,372] The impact of alirocumab on CV outcome was evaluated in the 18,924 patients on maximally tolerated statins (90% on high-intensity therapy) who had an ACS sometime during the 12 months prior to study enrollment. Patients with residual LDL-C ≥ 70 mg/dL, non-HDL-C ≥ 100 mg/dL, or apo B ≥ 80 mg/dL after 2 to 16 weeks of intensive or maximally tolerated statin therapy were randomized (1:1) to alirocumab or placebo. Patients given alirocumab started with 75 mg every 2 weeks and the dose was increased to 150 mg every 2 weeks if LDL-C remained > 50 mg/dL (n=2,615; 805 patients switched back to 75 mg). The primary composite endpoint was overall risk reduction of major adverse cardiovascular events (MACE), which included MI, ischemic stroke, death from coronary heart disease, or hospitalization due to unstable angina. After an average of 2.8 years, the incidence of MACE was reduced by 15% in patients who received alirocumab compared to placebo-treated patients (9.5% versus 11%; HR, 0.85; 95% CI, 0.78 to 0.93; p=0.0003). There was a similar decrease in all-cause mortality (HR, 0.85; 95% CI, 0.73 to 0.98; nominal p=0.026). After a mean 2.8 years, mean LDL-C was 53.3 mg/dL in the alirocumab group and 101.4 mg/dL in the placebo group, translating to a 54.7% reduction with alirocumab.

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evolocumab (Repatha) versus placebo

DESCARTES, a 52-week, phase 3, multinational, randomized, double-blind trial, evaluated the effect of evolocumab 420 mg once monthly compared to placebo (2:1) in patients 18 to 75 years of age with hyperlipidemia, an LDL cholesterol level of ≥ 75 mg/dL, and a fasting triglyceride level of ≤ 400 mg/dL who were stabilized on either diet alone, 10 mg of atorvastatin, 80 mg of atorvastatin, or 80 mg of atorvastatin plus ezetimibe (n=901).[373] The difference in LS mean reduction in LDL-C from baseline for evolocumab compared to placebo was 57% (SE, ±2.1; p<0.001) compared to placebo at 52 weeks. The treatment difference between evolocumab and placebo for percent change from baseline in Apo B, non-HDL-C, and triglycerides at 12 weeks were -44.2%, -50.3%, and -11.5%, respectively.

RUTHERFORD-2, a 12-week, multicenter, randomized, double-blind, placebo-controlled trial, evaluated the safety and efficacy of evolocumab in 329 patients with HeFH. Evolocumab (dosed either 140 mg every 2 weeks or 420 mg once monthly) was compared to placebo in patients aged 18 to 80 years who had a baseline LDL-C ≥ 100 mg/dL and were on a stable on statin (with or without other lipid-lowering therapies).[374] Compared with placebo, evolocumab twice monthly and once monthly reduced LDL-C by -59.2% (95% CI, -65.1 to -53.4; p<0.001) and 61.3% (95% CI, -69 to -53.6; p<0.001), respectively, at 12 weeks. The treatment difference between evolocumab and placebo for percent change from baseline in Apo B, non-HDL-C, and triglycerides at 12 weeks were -49.1%, -54.8%, and -19.6% in the every 2 week group and -49.4%, -55%, and -11.6% in the once monthly group, respectively (all p<0.0001 excluding triglycerides in the monthly treatment group [p=0.0214]).

TESLA (Part B), a 12-week, phase 3, multinational, randomized, double-blind, placebo-controlled trial, evaluated the efficacy of evolocumab in 49 patients with HoFH.[375] Patients aged 13 to 80 years who had a baseline LDL-C ≥ 130 mg/dL and were on lipid-lowering therapies, but not on lipid-apheresis therapy, were randomized 2:1 to evolocumab 420 mg once monthly or placebo. Compared with placebo, evolocumab reduced LDL-C by 30.9% (95% CI, -43.9 to -18; p<0.0001) at 12 weeks. The treatment difference between evolocumab and placebo for percent change from baseline in Apo B, HDL-C, and triglycerides were -23.1%, -0.1%, and 0.3, respectively (p value significant for Apo B only [p=0.0007]).

TAUSSIG (NCT01624142), a multicenter, open-label, 5-year extension trial evaluated HoFH patients treated with evolocumab as an adjunct to other lipid lowering therapies (n=106, including 14 pediatric patients between ages of 13 years and 17 years).[376] All patients started therapy with a dose of 420 mg once monthly (except for those receiving lipid apheresis at enrollment who started with 420 mg every 2 weeks). Those who were not receiving apheresis could be titrated up to 420 mg once every 2 weeks depending on LDL-C response and PCSK9 levels. Based on data from 48 patients who received 420 mg once monthly for at least 12 weeks followed by 420 mg every 2 weeks for at least 12 weeks, the average percent change from baseline in LDL-C at week 12 was -20% with dosing of 420 mg once monthly and -30% with dosing of 420 mg every 2 weeks.

HAUSER-OLE (NCT02624869), a single-arm, open-label, multicenter, 80-week study, evaluated evolocumab in pediatric patients with HoFH who were 10 years old to 17 years old.[377] Patients were required to be on a low-fat diet as well as receive background lipid-lowering therapy. A total of 12 patients received 420 mg of evolocumab SC once monthly. The average age of patients enrolled was 12 years (range, 11 to 17 years old), with the majority being Caucasian (75%); 17% of patients were female. At baseline, the median LDL-C was 398 mg/dL, and all patients were receiving a statin and ezetimibe; no patients were undergoing lipid apheresis. Diagnosis of HoFH had been based on genetic confirmation, although clinical diagnosis for enrolling was also allowed. At week 80, the median percent change in

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LDL-C from baseline was -14%, and 2 of 3 patients with < 5% LDL receptor activity demonstrated a response.

The GLACOV (Global Assessment of Plaque ReGression with a PCSK9 AntibOdy as Measured by IntraVascular Ultrasound) study randomized 968 patients with atherosclerosis to evolocumab (420 mg once per month) or placebo as add-on to background statin therapy.[378] The addition of evolocumab produced a significantly greater atheroma regression as measured by percent atheroma volume (PAV) than statin therapy alone after 76 weeks of therapy; PAV +0.05% with placebo, PAV -0.95% with evolocumab (95% CI, −1.8 to −0.64; p<0.001). The secondary measure of total atheroma volume (TAV) decreased by 0.9 mm^3 with placebo and 5.8 mm^3 with evolocumab (95% CI, −7.3 to −2.5; p<0.001). Plaque regression was seen in 64.3% compared to 47.3% of patients on evolocumab plus a statin versus statin therapy alone, the difference is significant (difference 17% [95% CI, 10.4 to 23.6]; p<0.001).

FOURIER, a double-blind, trial enrolled 27,564 adults with established CVD and LDL-C ≥ 70 mg/dL and/or non-HDL-C ≥ 100 mg/dL despite moderate to high intensity statin therapy.[379] Patients were randomized (1:1) to SC evolocumab (140 mg every 2 weeks or 420 mg once monthly) or placebo. The primary composite endpoint was time to first occurrence of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. The primary endpoint was significantly lower with evolocumab compared to placebo (4.5% versus 5.2%; HR, 0.85; 95% CI, 0.79 to 0.92; p<0.0001). This was primarily driven by the decreases in the times to first MI (HR, 0.73; 95% CI, 0.65 to 0.82), first stroke (HR, 0.79; 95% CI, 0.66 to 0.95), and first coronary revascularization (HR, 0.78; 95% CI, 0.71 to 0.86).

HAUSER-RCT (NCT02392559), a randomized, multicenter, placebo-controlled, double-blind, 24-week study assessed pediatric patients 10 years old to 17 years old with HeFH diagnosed with diagnostic criteria or by genetic testing (n=157).[380,381] All patients enrolled were also on a low-fat diet as well as optimized background lipid-lowering therapy and were randomized 2:1 to 420 mg of evolocumab SC once monthly (n=104) or placebo (n=53). The average age of patients enrolled was 14 years (range, 10 to 17 years) with the majority being female (56%) and Caucasian (85%). At baseline, the average LDL-C was 184 mg/dL, and the majority of patients were on a moderate-intensity statin (62%; high-intensity statin: 17%, ezetimibe: 13%). At week 24, the primary endpoint assessing the mean percent change in LDL-C from baseline was -44.5% in the evolocumab-treated patients compared with -6.2% in the placebo group (treatment difference, -38.3%; p<0.001) corresponding to an absolute change in LDL-C of -77.5 mg/dL for evolocumab versus -9 mg/dL for placebo (treatment different, -68.6 mg/dL; p<0.001). Secondary endpoints assessing lipids were also significantly improved with evolocumab compared to placebo. Furthermore, the frequency of adverse reactions during treatment was comparable between the 2 study arms. The authors concluded evolocumab demonstrated reductions in LDL-C as well as other lipid measures in the pediatric patients with HeFH evaluated in the study.

evolocumab (Repatha) versus ezetimibe (Zetia)

LAPLACE-2, a 12-week, randomized, double-blind trial, evaluated the effect of evolocumab (dosed either 140 mg every 2 weeks or 420 mg once monthly) compared to placebo or ezetimibe 10 mg/day in 1,899 patients with primary hypercholesterolemia and mixed dyslipidemia stabilized on moderate or high-intensity statin therapy.[382] At the mean of 10 and 12 weeks, evolocumab every 2 weeks reduced LDL-C levels by 66% (95% CI, 58 to 73) to 75% (95% CI, 65 to 84) and monthly by 63% (95% CI, 54 to 71) to 75% (95% CI, 67 to 83) compared to placebo in the moderate and high intensity statin groups. Ezetimibe reduced LDL-C values by 17% to 24% from baseline, evolocumab (every 2 weeks) reduced LDL-C values

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by 61% to 62% (p<0.001 versus ezetimibe), and evolocumab (monthly) reduced LDL-C values by 62% to 65% (p<0.001 versus ezetimibe).

MENDEL-2, a randomized, controlled, phase 3 clinical trial, studied evolocumab (dosed either 140 mg every 2 weeks or 420 mg once monthly) compared to either ezetimibe 10 mg/day or placebo as monotherapy in 614 patients, 18 to 80 years of age, with primary hypercholesterolemia, fasting LDL-C ≥ 100 mg/dL and < 190 mg/dL, and Framingham risk scores ≤ 10%.[383] At 12 weeks, average LDL-C decreased by a mean of 57% (95% CI, -59.5 to -54.6) with evolocumab every 2 weeks, 56.1% (95% CI, -58.3 to -53.9) with evolocumab once monthly, 0.1% to 1.3% (95% CI, -3.2 to 3.4; and 95% CI, -4.4 to 1.7, respectively) in placebo groups 1 and 2, and 17.8% to 18.6% (95% CI, -21 to -14.5; and 95% CI, -21.6 to -15.5, respectively) in ezetimibe groups 1 and 2 (p<0.001 evolocumab versus placebo and ezetimibe). These reductions were also significant for the mean of week 10 and week 12 compared to placebo and ezetimibe (p<0.001), the other co-primary endpoint. Significant differences were found when comparing both dosing schedules of evolocumab to placebo and ezetimibe in the following lipid parameters (apolipoprotein B, lipoprotein a, non-HDL-C, and HDL-C [p<0.02 for all comparisons]).

GAUSS-2, a 12-week, double-blind, randomized controlled trial, studied evolocumab (dosed either 140 mg every 2 weeks or 420 mg once monthly) compared to ezetimibe 10 mg/day in 307 patients with hyperlipidemia diagnosed with statin intolerance.[384] The mean percent change in LDL-C from baseline at week 12 was -55.3% to -56.1% with evolocumab and -16.6% to -19.2% with ezetimibe (treatment difference -36.9 to -38.7; p<0.001 for both comparisons). The mean percent change in LDL-C from baseline at week 10 and 12 was -52.6% to -56.1% with evolocumab and-15.1% to -18.1% with ezetimibe (treatment difference -37.6 to -38.1; p<0.001 for both comparisons). Significant differences were also seen in some secondary endpoints: apolipoprotein B, lipoprotein a, and LDL-C < 70 mg/dL (p<0.001), but not in HDL-C or apolipoprotein A-1.

GAUSS-3, a double-blind, randomized cross-over study, enrolled 491 adults with uncontrolled LDL-C and an intolerance to 2 or more statins.[385] After a 4-week washout period when all lipid-lowering agents were discontinued, patients entered the crossover phase A. Patients were randomized to atorvastatin 20 mg daily or placebo for 10 weeks, then entered a 2-week wash-out period, followed by a crossover to the alternative therapy for 10 weeks. A total of 199 patients (42.6%) experienced muscle-related adverse effects while on atorvastatin but not placebo and continued on to the 24-week, phase B portion of the study. In addition, 19 patients with a documented history of CK elevation > 10 x ULN with muscle symptoms while on statin therapy entered the study directly at phase B. In this phase, patients received either evolocumab SC 420 mg monthly or ezetimibe 10 mg daily, with corresponding opposite matching-placebo. Coprimary endpoints were mean percent change in LDL-C level from baseline to the mean of weeks 22 and 24 levels and from baseline to week 24 levels. For the mean of weeks 22 and 24, there was a mean change in LDL-C by −16.7% (95% CI, -20.5 to -12.9) for ezetimibe and -54.5% (95% CI, -57.2 to -51.8) for evolocumab. Further, with ezetimibe, at week 24 the mean percent change in LDL-C was −16.7% (95% CI, −20.8 to −12.5); with evolocumab it was −52.8% (95% CI, −55.8 to −49.8). Muscle symptoms were experienced by 28.8% of patients treated with ezetimibe and 20.7% with evolocumab.

evolocumab (Repatha) and cardiovascular outcomes and cognitive effects

In the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) double-blind study, 27,564 patients with ASCVD and LDL-C ≥ 70 mg/dL or a non-high density lipoprotein cholesterol ≥ 100 mg/dL, who were on optimal statin therapy, were randomly assigned to evolocumab (140 mg every 2 weeks or 420 mg monthly) or placebo subcutaneous

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injections.[386] Ezetimibe use was allowed but was infrequent. Median follow-up was 26 months. At 48 weeks, there was a least-squares mean percentage reduction in LDL-C levels of 59% with evolocumab compared with placebo. The primary endpoint, a composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization, occurred 15% less often with evolocumab (9.8%) than with placebo (11.3%). The key secondary composite endpoint of CV death, MI, or stroke occurred 20% less often with evolocumab versus placebo (5.9% versus 7.4%). In addition, EBBINGHAUS, a substudy that included 1,204 patients from the FOURIER study who had baseline and follow-up cognitive testing, revealed that there were no significant changes from baseline in cognitive function, as measured by spatial working memory strategy index (SWMsi) of executive function, in patients treated with either, evolocumab or placebo.[387]

inclisiran (Leqvio) versus placebo

The ORION trial series included three 18-month (median treatment duration of 77 weeks), double-blind, randomized controlled trials evaluating the efficacy and safety of inclisiran.[388] The co-primary endpoints evaluated in all 3 studies were placebo-corrected percentage change in LDL-C from baseline to day 510, and time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540. [389,390] ORION-10 enrolled 1,561 adult patients with clinical ASCVD who required additional LDL-C reduction despite maximally tolerated statin therapy with or without other lipid lowering therapy.[391] Patients were randomized 1:1 to receive either inclisiran 284 mg SC injections (n=781) or placebo (n=780) administered on days 1, 90, 270, and 450, and were stratified according to current use of statins or other lipid lowering medications. Patients who were taking a PCSK9 inhibitor within 90 days before screening were excluded from the trial. At baseline, the mean age was 66 years, 31% of patients were women, and 86% were White. At baseline, the mean LDL-C was 105 mg/dL, 89% of participants were on a statin, and 10% were on ezetimibe. At day 510, the difference from placebo in mean percentage change in LDL-C from baseline was -52.3% (95% CI, -55.7% to -48.8%; p<0.001), and the difference from placebo in time-adjusted change in LDL-C between day 90 and day 540 as compared with baseline was -53.8% (95% CI, -56.2% to -51.3%; p<0.001). The differences from placebo in mean percentage change from baseline to day 510 in total cholesterol, non-HDL-C, and Apo B were -33%, -47%, and -43%, respectively.

ORION-11 enrolled 1,617 adult patients with clinical ASCVD or with an ASCVD risk equivalent (type 2 diabetes, familial hypercholesterolemia, or 10-year risk of CV event ≥ 20%) who required additional LDL-C reduction despite maximally tolerated statin therapy with or without other lipid lowering therapy. [392] Participants were randomized 1:1 to receive inclisiran 284 mg SC injections (n=810) or placebo (n=807) on days 1, 90, 270, and 450, and were stratified according to country, current use of statin therapy, and current use of other lipid lowering therapy. Patients who were taking a PCSK9 inhibitor within 90 days before screening were excluded from the trial. The mean age at baseline was 65 years, 28% were women, and 98% were White. At baseline, mean LDL-C was 106 mg/dL, 95% of patients were taking a statin, and 7% were taking ezetimibe. At day 510, the difference from placebo in mean percent change from baseline in LDL-C was -49.9% (95% CI, -53.1% to -46.6%; p<0.001), and the difference from placebo in time-adjusted change in LDL-C between day 90 and day 540 as compared with baseline was -49.2% (95% CI, -51.6% to -46.8%; p<0.001). The differences from placebo in mean percentage change from baseline for total cholesterol, non-HDL-C, and Apo B were -30%, -44%, and -40%, respectively.

ORION-9 enrolled 482 adult patients with heterozygous familial hypercholesterolemia (HeFH) who required additional LDL-C reduction despite maximally tolerated statin therapy with or without

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additional lipid lowering therapy.[393] Patients were randomized 1:1 to receive either inclisiran 284 mg SC injections (n=242) or placebo (n=240) on days 1, 90, 270, and 450, and were stratified according to country and current use of statins or other lipid lowering medications. Patients who were taking PCSK9 inhibitors were excluded from the trial. The mean age at baseline was 56 years, 53% were women, 94% were White, and 27% had preexisting coronary heart disease. At baseline, mean LDL-C was 153 mg/dL, 90% of patients were taking a statin, and 53% were taking ezetimibe. At day 510, the difference from placebo in the mean percent change from baseline in LDL-C was -47.9% (95% CI, -53.5% to -42.3%; p<0.001), and the difference from placebo in time-adjusted change in LDL-C between day 90 and day 540 as compared with baseline was -44.3% (95% CI, -48.5% to -40.1%; p<0.001). The differences from placebo in mean percentage change from baseline for total cholesterol, non-HDL-C, and Apo B were -32%, -42%, and -36%, respectively.

META-ANALYSES

Fibric acids were compared to niacin in a meta-analysis evaluating lipid parameter effects and risk reductions for major cardiac events.[394] Data from 53 trials (n=16,802) using fibric acids and 30 trials (n=4,749) using niacin were included in the meta-analysis. Fibric acids included agents which have never been available in the U.S., in addition to gemfibrozil and fenofibrate. Niacin products included immediate-, sustained-, and extended-release formulations. Reductions in LDL-C and TG were 36% and 8% for fibric acids and 20% and 14% for niacin, respectively. Increases in HDL-C were 10% and 16% for fibric acids and niacin, respectively. Relative risk reduction for major cardiac events was 25% and 27% for fibric acids and niacin, respectively.

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.[395] 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 HDL-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 LDL-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 to 0.89), but not all-cause mortality (OR, 1.05; 95% CI, 0.95 to 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.[396] 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% RR reduction (95% CI, 0 to 18) for major CV events (p=0.048) and a 13% RR reduction (95% CI, 7 to 19) for coronary events (p<0.0001) but had no benefit on stroke (−3%; 95% CI, −16 to 9; p=0.69). There was no effect of fibrate therapy on the risk of all-cause mortality (0%; 95% CI, −8 to 7; p=0.92), CV mortality (3%; 95% CI, −7 to 12; p=0.59), sudden death (11%; 95% CI, −6 to 26; p=0.19), or non-vascular mortality (−10%; 95% CI, −21 to 0.5; p=0.063). Fibrates reduced the risk of albuminuria progression by 14% (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).

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A meta-analysis of 11 randomized trials with 6,616 patients found niacin significantly reduced major coronary events (relative OR, 25%; 95% CI, 13 to 35), stroke (25%; 95% CI, 8 to 41), and any CV events (27%; 95% CI, 15 to 37).[397] In comparison with the non-niacin group, more patients in the niacin group showed regression of coronary atherosclerosis (relative increase 92%; 95% CI, 39 to 67), but the rate of patients with progression decreased by 41% (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 µm/year (95% CI, -22 to -12).

A systematic review and meta-regression analysis was performed for fibrates, niacin, and marine-derived omega-3 fatty acids.[398] Randomized controlled trials (RCTs) reporting major vascular events were selected for inclusion (24 non-statin therapy trials and 25 statin therapy trials). Overall, the RCTs showed lowering of TGs was associated with a decreased risk for major vascular events, even with adjustments for reduction in LDL-C; however, the observed effect was less pronounced than seen with LDL-C reduction. The risk ratio (RR) for major vascular events associated with absolute reduction in lipid parameters were as follows per 1-mmol/L reduction in the lipid parameter: 0.80 (95% CI, 0.76 to 0.85; p<0.0001) for LDL-C, 0.84 (95% CI, 0.75 to 0.94; p=0.0026) for TG. The association between TG reduction and reduction in major vascular events was weaker once findings from the REDUCE-IT study (Reduction of CV Events with Icosapent Ethyl-Intervention Trial) were removed, which had results that were an outlier to the other studies. After removal of the REDUCE-IT study, the RR per 1-mmol/L reduction in LDL-C was 0.79 (95% CI, 0.76 to 0.83; p<0.0001) and 0.91 (95% CI, 0.81 to 1.006; p=0.06) for each per 1-mmol/L (0.96 per 40 mg/dL) reduction in TGs.

An October 2020 Cochrane systematic review evaluated the impact of PCSK9 inhibitors on CVD, all-cause mortality, MI, and stroke compared to placebo or active treatments in the settings of primary and secondary prevention.[399] Safety of the agents was evaluated as a secondary objective. Parallel-group and factorial RCTs with a follow-up of at least 24 weeks that evaluated adults with or without a history of CVD were included if the study compared PCSK9 alirocumab or evolocumab to placebo or active treatments (e.g., statins, ezetimibe, combination). A total of 24 studies (n=60,997) were selected for inclusion with 18 of the studies evaluating alirocumab (6 with an active treatment comparison group) and 6 studies assessing evolocumab (3 active comparison trials). In the studies, all participants were given background lipid-lowering therapy or lifestyle counseling. For the studies that were compared to placebo, follow-up ranged from 6 months to 36 months and 6 months to 12 months for studies that compared to active treatment. As the studies primarily included patients with established CVD or at high risk for CVD, there is minimal evidence in patients considered to be low or medium risk. Compared to placebo, there was high-certainty evidence that alirocumab decreased the risk of CVD events (OR, 0.87; 95% CI, 0.8 to 0.94), mortality (OR, 0.83; 95% CI, 0.72 to 0.96), MI (OR, 0.86; 95% CI, 0.79 to 0.94), and any stroke (OR, 0.73; 95% CI, 0.58 to 0.91). Compared to ezetimibe and statins, alirocumab demonstrated the following all with low certainty: CVD (OR 1.37; 95% CI, 0.65 to 2.87), mortality (OR, 0.51; 95% CI, 0.18 to 1.4; MI (OR, 1.45; 95% CI, 0.64 to 3.28), and for any stroke (OR, 0.85; 95% CI, 0.13 to 5.61). Compared to placebo, there was high-certainty evidence that evolocumab decreased the risk for CVD events (OR, 0.84; 95% CI, 0.78 to 0.91), MI (OR, 0.72; 95% CI, 0.64 to 0.82), and any stroke (OR, 0.79; 95% CI, 0.65 to 0.94), and, for mortality, the OR was 1.04 (95% CI, 0.91 to 1.19). Data were insufficient to compare evolocumab with ezetimibe and statins for stroke, and evidence was considered to be of very low certainty for a reduction in any CVD event (OR, 0.66; 95% CI, 0.14 to 3.04), for all-cause mortality (OR, 0.43; 95% CI, 0.14 to 1.30), and for MI (OR, 0.66; 95% CI, 0.23 to 1.85). Authors concluded strong evidence exists for beneficial effects of PCSK9 inhibitors for patients

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who may not be eligible for other lipid-lowering drugs as well as for those who cannot meet their lipid goals with traditional therapies; however, evidence for PCSK9 inhibitors compared with ezetimibe and statins is low to very low-certainty, and it is uncertain if these agents may be used effectively as alternative therapies. Furthermore, evidence is very limited in terms of potential safety issues for these agents. Although current evidence has not shown any adverse safety findings, it also does not demonstrate safety concerns could be found in the future. As such, careful consideration is suggested of alternative lipid-lowering therapies prior to use of PCSK9 inhibitors.

A systematic review and network meta-analysis published in 2022 investigated the efficacy of various non-statin agents added on to maximally tolerated statin therapy for reduction in LDL-C in adult patients, including statin-intolerant patients, with primary hypercholesterolemia or ASCVD.[400] The network meta-analysis included 48 randomized controlled trials and found that all non-statin medications investigated, including bempedoic acid, ezetimibe, alirocumab, evolocumab, and inclisiran, significantly reduced baseline LDL-C versus placebo in 12 weeks, regardless of other therapies used concomitantly. The PCSK9 inhibitors (evolocumab and alirocumab) were found to be the most effective agents with a mean LDL-C reduction of 64.68% (95% CI, 67.37 to 62) for evolocumab 140 mg every 2 weeks / 420 mg once monthly and a mean LDL-C reduction of 62.71% (95% CI, 67.56 to 57.87) for alirocumab 150 mg every 2 weeks. Monotherapy with alirocumab 75 mg every 2 weeks, alirocumab 300 mg once monthly, inclisiran 300 mg every 3 months to every 6 months, bempedoic acid/ezetimibe 180 mg/10 mg daily, ezetimibe 10 mg daily, and bempedoic acid 180 mg daily also significantly reduced LDL-C versus placebo.

Effects on Lipids for Selected Agents[401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455]

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. Conditions and populations in clinical trials may vary.

Effects on Lipids

Drug	total-C (% change)	LDL-C (% change)	HDL-C (% change)	TG (% change)
ACL Inhibitor bempedoic acid (Nexletol)	-11 to -18	-17 to -29	-4.5 to -5.9	-9.2 +0.4
ACL Inhibitor/Cholesterol Absorption Inhibitor bempedoic acid/ezetimibe (Nexlizet)	-27	-38	nr	nr
ANGPTL3 Inhibitor evinacumab-dgnb (Evkeeza)	-43.4 to -49.1	-47.1	-29.6	-55
Bile Acid Sequestrants cholestyramine, colestipol (Colestid), colesevelam (Welchol)	-9 to -13	-12 to -30	+3 to +9	0 to +25
Cholesterol Absorption Inhibitors ezetimibe (Zetia)	-12 to -14	-13 to -20	+1 to +5	-5 to -11
Fibric Acids fenofibrate (Antara, Fenoglide, Lipofen, Tricor) gemfibrozil (Lopid)	-4 to -26	-27 to +9	+ 6 to +18	- 29 to -54

nr = not reported

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Effects on Lipids (continued)

Drug	total-C (% change)	LDL-C (% change)	HDL-C (% change)	TG (% change)
fenofibric acid (Fibricor)	-9 to -22	-31 to +45	+10 to +23	- 24 to -54
fenofibric acid (Trilipix)	-12	-5	+16	-31
lomitapide (Juxtapid)	-36	-40	-7	-45
niacin ER (Niaspan)	-3 to -10	-14 to +2	+18 to +26	-13 to -29
niacin IR (Niacor)	-10 to -20	-10 to -20	+20 to +35	-30 to -70
omega-3-acid ethyl esters (Lovaza)	-10	+45	+9	-45
icosapent ethyl (Vascepa)	-7	-5	-4	-27
alirocumab (Praluent)	-27 to -38	-43 to -61	+4 to +9	-6 to -16
evolocumab (Repatha)	-17 to -42	-22 to -65	+4 to +9	-5 to -20
inclisiran (Leqvio)	-29.8 to -33.1	-47.9 to -52.3	+2.6 to +6.1	-7 to -12.6

nr = not reported

SUMMARY

The preponderance of outcomes data supports the use of statins as the primary agents for low-density lipoprotein cholesterol (LDL-C) reduction therapy and for primary and secondary prevention of coronary heart disease. The 2018 American College of Cardiology (ACC) and the American Heart Association (AHA) practice guidelines for the management of blood cholesterol emphasizes lifestyle therapies to reduce atherosclerotic cardiovascular disease (ASCVD) risk. In addition to the 10-year ASCVD risk score, the ACC/AHA advises consideration of risk-enhancing factors, such as family history of premature ASCVD, persistent LDL-C ≥ 160 mg/dL, persistent triglycerides (TG) ≥ 175 mg/dL, metabolic syndrome, chronic kidney disease (CKD), history of preeclampsia or premature menopause, chronic inflammatory disorders, and high-risk ethnic groups, among others, when considering anti-lipid therapy. While non-statin therapies do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD, these agents (e.g., ezetimibe, PSCK9 inhibitors) may be added to maximally tolerated statin therapy to lower LDL-C sufficiently to reduce ASCVD event risk in individuals with primary severe elevations of LDL-C.

The 2012 Endocrine Society (ES) guideline on the evaluation and treatment of hypertriglyceridemia recommends drug therapy to reduce the risk of pancreatitis in patients with severe and very severe hypertriglyceridemia; a fibrate is considered a first-line treatment. For patients with moderate to severe hypertriglyceridemia, fibrates, niacin, and omega-3 fatty acids alone or in combination with statins may be considered. Statins should not be used alone for severe or very severe hypertriglyceridemia; however, statins may be useful for the treatment of moderate hypertriglyceridemia to modify cardiovascular (CV) disease risk. The 2020 ES guidelines on lipid management in patients with endocrine disorders similarly recommends drug therapy as an adjunct to diet and exercise to prevent pancreatitis in adults with fasting TG levels > 500 mg/dL. The 2020 American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) consensus statement algorithm for the management of dyslipidemia and prevention of CV disease also addresses treatment of hypertriglyceridemia. For patients with hypertriglyceridemia who do not have established ASCVD or diabetes with ≥ 2 risk factors and are not at the TG goal of < 150 mg/dL with statin therapy, then a fibrate, omega-3 fatty acid, or niacin can be considered. In order to decrease the potential for acute pancreatitis, all patients with severe

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hypertriglyceridemia (> 500 mg/dL) should receive a fibrate, prescription-grade omega-3 fatty acid, and/or niacin. Similarly, the 2021 ACC expert consensus decision pathway for the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia emphasizes the necessary lifestyle interventions (e.g., low-fat diet) and consideration of fibrates and prescription-grade omega-3 fatty acids; they also note that fibrates provide benefit as monotherapy but not when combined with statins.

The bile acid sequestrant cholestyramine has been shown to reduce major coronary events and coronary heart disease deaths. The bile acid sequestrants are effective in lowering LDL-C and a producing a small increase in high-density lipoprotein cholesterol (HDL-C). Its effect on decreasing TG levels has been reported between 0% and 25%. Bile acid sequestrants 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 gastrointestinal effects. Colesevelam has also been studied in pediatric patients ages 10 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH). In patients with type 2 diabetes mellitus, colesevelam only provides modest hemoglobin A1c (HbA1c) reductions (-0.5%) and can provide an option in patients who are almost at HbA1c goal who also require lipid lowering. ACC downgraded their recommendations on use of bile acid sequestrants to use only as a secondary alternative in patients intolerant to ezetimibe.

Gemfibrozil (Lopid) has demonstrated reductions in risk of coronary heart disease primarily in subsets of patients with high triglycerides, 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 coronary heart disease morbidity and mortality. Fenofibrate produced a nonsignificant reduction in the primary endpoint of coronary events. Non-fatal myocardial infarction (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. Fibric acids 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 fibric acids may lower total cholesterol and LDL-C, although not as significantly as the statins. The fibric acids should be considered as an alternative agent to the statins for specific lipid disorders or can be used as add-on therapy with caution considering the increased risk of rhabdomyolysis. Fenofibrate is less likely to interact with statins compared to gemfibrozil. The FDA has removed the indication of fenofibric acid (Trilipix) use in combination with a statin; however, the use of fibrates with statins is still common in practice.

Niacin has been shown to reduce major coronary events. Compared to immediate-release niacin (Niacor), niacin extended-release (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 MIs and stroke) when niacin extended-release 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. The FDA has removed the indication for niacin extended-release (Niaspan) in combination with simvastatin or lovastatin. Over the counter (OTC) preparations of niacin are not federally regulated and, therefore, may lack nicotinic acid or be associated with an increased risk of hepatotoxicity.

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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. Ezetimibe reduces LDL-C, both when given alone and in combination with a statin. In addition, the IMPROVE-IT study reported lower CV mortality and morbidity when ezetimibe was added to statin (simvastatin) therapy as compared to a statin alone. Ezetimibe has been studied in pediatrics ages 10 to 17 years of age with HeFH.

Lomitapide (Juxtapid) is 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 has not been established in patients with hypercholesterolemia who do not have HoFH. The 2022 ACC consensus decision pathway states HoFH patients, with or without clinical ASCVD, may be candidates for lomitapide if unable to reach LDL-C goals despite maximally tolerated statin therapy with or without ezetimibe, a PCSK9 inhibitor, and/or bempedoic acid.

Omega-3-acid ethyl esters (Lovaza) and icosapent ethyl (Vascepa) reduce TG in patients with very high TGs (> 500 mg/dL). Although eicosapentaenoic acid (EPA) and docosahexaenoic acid (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 and icosapent ethyl do not increase the risk of rhabdomyolysis in combination with statins. Icosapent ethyl contains only EPA, while omega-3-acid ethyl esters contain both EPA and DHA. A 2017 Science Advisory by the AHA states that omega-3 polyunsaturated fatty acid (PUFA) supplementation is reasonable in patients with coronary heart disease (CHD) to reduce CHD-related mortality. Based on findings of the REDUCE-IT trial, icosapent ethyl has received FDA-approval as adjunct to maximally tolerated statin therapy to reduce the risk of MI, stroke, coronary revascularization, and unstable angina requiring hospitalization in adults with elevated TG levels (≥ 150 mg/dL) and established CVD or diabetes mellitus and ≥ 2 additional risk factors for CVD.

Alirocumab (Praluent) and evolocumab (Repatha) are proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Both have demonstrated significant efficacy in regard to LDL-C lowering. Both agents are indicated for use in patients with HeFH, CVD, or HoFH. Evolocumab is also indicated for use in certain pediatric patients (in pediatric patients ≥ 10 years old with HeFH and in pediatric patients ≥ 10 years old with HoFH). The AHA advises that PCSK9 inhibitors can be added to high-intensity statin plus ezetimibe therapy in patients with familial hypercholesterolemia (FH) when dual therapy does not result in desired LDL-C goal after 3 months of adherent therapy. The ACE and the AACE have also included PCSK9 inhibitors in their algorithm for use in patients with type 2 diabetes mellitus as an option as add-on to statins in patients with clinical ASCVD who are not at goal with maximally tolerated statin or in those with FH. Alirocumab and evolocumab may be dosed subcutaneously (SC) once every 2 weeks. Evolocumab is also available as a once-monthly 420 mg dose administered either as 3 consecutive SC injections (all within 30 minutes) or with the single-use Pushtronex system that delivers the 420 mg SC dose over 9 minutes. Recently, the FOURIER and ODYSSEY OUTCOMES studies reported a positive effect on CV outcomes as evidenced by a 15% reduction in the composite of CV outcomes when evolocumab or alirocumab were added to optimal statin therapy.

Bempedoic acid (Nexletol) is a first-in-class, oral adenosine triphosphate-citrate lyase (ACL) inhibitor. In February 2020, bempedoic acid and bempedoic acid/ezetimibe (Nexlizet) both received FDA approval to be used as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH

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or established ASCVD who require additional lowering of LDL-C. These agents offer another option for those requiring additional cholesterol lowering therapy for patients who are not at goal with diet and maximally tolerated statin therapy. PCSK9 inhibitors have demonstrated superior reductions in LDL-C compared to bempedoic acid, although these were not comparative clinical trials. While bempedoic acid is not associated with myalgias as seen with statin therapy, it does carry risks for hyperuricemia and tendon rupture. Although AACE/ACE maintains statins as primary therapy, their 2020 consensus statement algorithm recommends treatment intensification with the addition of other LDL-C lowering agents (e.g., PCSK9 inhibitors, ezetimibe, colesevelam, or bempedoic acid) as needed to reach treatment goals. The ACC 2022 consensus decision pathway states bempedoic acid can be added for patients who do not achieve LDL-C goals despite the addition of other non-statin agents.

In February 2021, the FDA approved another first-in-class drug, evinacumab-dgnb (Evkeeza). It is an angiopoietin-like 3 (ANGPTL3) inhibitor and is indicated as an adjunct to other LDL-C lowering therapies for the treatment of adult and pediatric patients, aged ≥ 12 years, with HoFH. As concomitant therapy, evinacumab-dgnb has shown to decrease LDL-C by almost half in a pivotal phase 3 trial after 24 weeks. Evinacumab-dgnb has a more desirable safety and tolerability profile than lomitapide, which is associated with hepatotoxicity. PCSK9 inhibitors are administered SC every 2 or 4 weeks and demonstrate higher LDL-C lowering (range, 55% to 59%) compared to evinacumab-dgnb. Therefore, the treatment hierarchy for evinacumab-dgnb in the HoFH space remains to be determined, especially since it lowers LDL-C but also lowers HDL-C. Moreover, the effects of evinacumab-dgnb on CV morbidity and mortality have not been established. However, the 2022 ACC consensus decision pathway states HoFH patients, with or without clinical ASCVD, may be candidates for evinacumab if unable to reach LDL-C goals despite maximally tolerated statin therapy with or without ezetimibe, a PCSK9 inhibitor, and/or bempedoic acid.

The FDA approved inclisiran (Leqvio), an additional first-in-class medication, in December 2021. Inclisiran is a small interfering RNA (siRNA) directed to PCSK9 and is indicated as an adjunct to diet and maximally tolerated statin therapy for adults with HeFH or clinical ASCVD who require additional LDL-C lowering. Inclisiran is available as a single SC injection administered by a healthcare professional (HCP) and is administered twice yearly after completion of two initial doses given 3 months apart. Data from 3 placebo-controlled trials and a median treatment duration of 77 weeks demonstrated a significant reduction in LDL-C by 48% to 52% with inclisiran versus placebo as add on to maximally tolerated statin therapy (with or without other lipid-modifying therapy), and a favorable safety profile with no contraindications or drug interactions. Data are not yet available regarding the effect of inclisiran on CV morbidity and mortality, and inclisiran is not yet included in most clinical practice guidelines. However, the ACC 2022 consensus decision pathway states inclisiran can be considered for patients with poor adherence to PCSK9 inhibitors or those who cannot self-inject, given that it must be administered by an HCP.

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

REFERENCES

1 Nexletol [package insert]. Ann Arbor, MI; Esperion; September 2021.
2 Nexlizet [package insert]. Ann Arbor, MI; Esperion; September 2021.

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3 Evkeeza [package insert]. Tarrytown, NY; Regeneron; February 2021.
4 Juxtapid [package insert]. Cambridge, MA; Aegerion; September 2020.
5 Questran [package insert]. Spring Valley, NY; Par; April 2016.
6 Welchol [package insert]. South Plainfield, NJ; Cosette; February 2022.
7 Colestid tablet [package insert]. New York, NY; Pfizer; May 2017.
8 Colestid granules [package insert]. New York, NY; Pfizer; April 2018.
9 Zetia [package insert]. Jersey City, NJ; Organon; June 2021.
10 Antara [package insert]. Baltimore, MD; Lupin; June 2021.
11 Fenofibrate 43 mg and 130 mg [package insert]. Weston, FL; Apotex. November 2021.
12 Fenoglide [package insert]. Bridgewater, NJ; Salix; June 2021.
13 Lipofen [package insert]. Montgomery, AL; Kowa; June 2021.
14 Fenofibrate tablet (Lofibra) [package insert]. Baltimore, MD; Lupin; December 2021.
15 Tricor [package insert]. North Chicago, IL; Abbvie; June 2021.
16 Fibricor [package insert]. Athens, GA; Athena; June 2021.
17 Trilipix [package insert]. North Chicago, IL; Abbvie; June 2021.
18 Lopid [package insert]. New York, NY; Pfizer; December 2020.
19 Niaspan [package insert]. North Chicago, IL; Abbvie; May 2022.
20 Niacor [package insert]. Birmingham, AL; Avondale; September 2017.
21 Vascepa [package insert]. Bridgewater, NJ; Amarin; September 2021.
22 Lovaza [package insert]. Wixom, MI; Woodward; February 2021.
23 Praluent [package insert]. Tarrytown, NY; Regeneron; April 2021.
24 Repatha [package insert]. Thousand Oaks, CA; Amgen; September 2021.
25 Leqvio [package insert]. East Hanover, NJ; Novartis; December 2021.
26 National Center for Health Statistics Data Brief. Total and high-density lipoprotein cholesterol in adults: United States, 2015-2018. April 2020. Available at: https://www.cdc.gov/nchs/products/databriefs.htm. Accessed October 7, 2022.
27 National Center for Health Statistics Data Brief. Trends in elevated triglyceride in adults: United States, 2001–2012. May 2015. Available at: at: https://www.cdc.gov/nchs/products/databriefs.htm. Accessed October 7, 2022.
28 Jensen M, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults. DOI: 10.1016/j.jacc.2013.11.004. Available at http://www.acc.org/guidelines#doctype=Guidelines. Accessed October 7, 2022.
29 Grundy S, Stone NJ, Baily A, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. J Am Coll Cardiol. 2018. DOI: 10.1016/j.jacc.2018.11.003. Available at http://www.acc.org/guidelines#doctype=Guidelines. Accessed October 7, 2022.
30 Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk. DOI: 10.1016/j.jacc.2013.11.003. Available at: http://www.acc.org/guidelines#doctype=Guidelines. Accessed October 7, 2022.
31 Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Circulation. 2019; 140: e596–e646. DOI: 10.1161/CIR.0000000000000678. Available at: http://www.acc.org/guidelines#doctype=Guidelines. Accessed October 7, 2022.
32 Barone Gibbs B, Hivert MF, Jerome GH, et al. Physical activity as a critical component of first-line treatment for elevated blood pressure or cholesterol: who, what, and how?: A scientific statement from the American Heart Association. Hypertension. 2021;78: e26–e37. DOI: 10.1161/HYP.0000000000000196. Available at: https://professional.heart.org/en/guidelines-and-statements/guidelines-and-statements-search. Accessed October 7, 2022.
33 Grundy S, Stone NJ, Baily A, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. J Am Coll Cardiol. 2018. DOI: 10.1016/j.jacc.2018.11.003. Available at http://www.acc.org/guidelines#doctype=Guidelines. Accessed October 7, 2022.
34 National Heart, Lung, and Blood Institute. ATP III at-a-glance: quick desk reference. 2001. Available at: https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/atp-iii-glance-quick-desk-reference. Accessed October 7, 2022.
35 Grundy S, Stone NJ, Baily A, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. J Am Coll Cardiol. 2018. DOI: 10.1016/j.jacc.2018.11.003. Available at http://www.acc.org/guidelines#doctype=Guidelines. Accessed October 7, 2022.
36 Boden WE, Probst-field JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive stating therapy. N Engl J Med. 2011; 365: 2,255-2,267. DOI: 10.1056/NEJMoa1107579.
37 Ginsberg HN, Elam MB, Lovato LC, et al. The ACCORD study group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010; 362(17): 1,563-1,574. DOI: 10.1056/NEJMoa1001282
38 Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013. DOI: 10.1016/j.jacc.2013.11.002. Available at: https://professional.heart.org/en/guidelines-and-statements/guidelines-and-statements-search. Accessed October 7, 2022.
39 Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015; 372(25): 2,387-2,397. DOI: 10.1056/NEJMoa1410489.
40 Sabine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017; 376: 1,713-1,722. DOI: 10.1056/NEJMoa1615664.
41 Repatha [package insert]. Thousand Oaks, CA; Amgen; September 2021.
42 ODYSSEY Outcomes: Results suggest use of PCSK9 inhibitor reduces CV events, LDL-C in ACS patients. Published March 10, 2018. Available at: http://www.acc.org/latest-in-cardiology/articles/2018/03/05/15/53/sat-9am-odyssey-outcomes-cv-outcomes-with-alirocumab-after-acs-acc-2018. Accessed October 7, 2022.

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.
© 2004-2022 Magellan Rx Management. All Rights Reserved.

43 Giugliano RP, Mach F, Zavitz K, et al. Design and rationale of the EBBINGHAUS trial: a phase 3, double-blind, placebo-controlled, multicenter study to assess the effect of evolocumab on cognitive function in patients with clinically evident cardiovascular disease and receiving statin background lipid-lowering therapy—A cognitive study of patients enrolled in the FOURIER trial. Clin Cardiol. 2017; 40(2): 59-65. DOI: 10.1002/clc.22678.
44 Giugliano RP, Mach F, Zavitz K, et al. Cognitive function in a randomized trial of evolocumab. N Engl J Med. 2017; 377: 633-643. DOI: 10.1056/NEJMoa1701131.
45 Hao Q, Aertgeerts B, Guyatt G, et al. PCSK9 inhibitors and ezetimibe for the reduction of cardiovascular events: a clinical practice guideline with risk-stratified recommendations. BMJ. 2022. DOI: 10.1136/bmj-2021-069066. Available at: https://www.bmj.com/content/377/bmj-2021-069066. Accessed October 7, 2022.
46 Nayor M, Vasan RS. Recent update to the US cholesterol treatment guidelines: a comparison with international guidelines. Circulation. 2016; 133(18): 1,795-1,806. DOI: 10.1161/CIRCULATIONAHA.116.021407.
47 Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013. DOI: 10.1016/j.jacc.2013.11.002. Available at: https://professional.heart.org/en/guidelines-and-statements/guidelines-and-statements-search. Accessed October 7, 2022.
48 Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk. DOI: 10.1016/j.jacc.2013.11.005. Available at: http://www.acc.org/guidelines#doctype=Guidelines. Accessed October 7, 2022.
49 Grundy S, Stone NJ, Baily A, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. J Am Coll Cardiol. 2018. DOI: 10.1016/j.jacc.2018.11.003. Available at http://www.acc.org/guidelines#doctype=Guidelines. Accessed October 7, 2022.
50 Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a Mendelian randomization study. Lancet. 2012; 380: 572-580. DOI: 10.1016/S0140-6736(12)60312-2.
51 National Heart, Lung, and Blood Institute. ATP III at-a-glance: quick desk reference. 2001. Available at: https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/atp-iii-glance-quick-desk-reference. Accessed October 7, 2022.
52 Berglund L, Brunzell JD, Goldberg AC, et al. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012; 97: 2,969-2,989. DOI: 10.1210/jc.2011-3213. Available at: https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines. Accessed October 7, 2022.
53 National Cholesterol Education Program. ATP III guidelines at-a-glance. 2001. Available at: https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/atp-iii-glance-quick-desk-reference. Accessed October 7, 2022.
54 Newman CB, Blaha MJ, Boord JB, et al. Lipid management in patients with endocrine disorders: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2020; 105(12): 3613-3682. DOI: 10.1210/clinem/dgab175. Available at: https://www.endocrine.org/clinical-practice-guidelines/lipid-management-guideline. Accessed October 7, 2022.
55 Virani SS, Morris PB, Agarwala A, et al. 2021 ACC Expert Consensus Decision Pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021; 78 (9): 960–993. DOI: 10.1016/j.jacc.2021.06.011. Available at: https://www.acc.org/Guidelines#/tab1. Accessed October 7, 2022.
56 Rubenfire M. ACC consensus on ASCVD risk reduction in hypertriglyceridemia: key points. July 28, 2021. Available at: https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2021/07/27/21/04/2021-acc-ecdp-hypertriglyceridemia. Accessed October 7, 2022.
57 Merck Manuals. Dyslipidemia. Updated September 2022. Available at: https://www.merckmanuals.com/professional/endocrine-and-metabolic-disorders/lipid-disorders/dyslipidemia. Accessed October 7, 2022.
58 Berglund L, Brunzell JD, Goldberg AC, et al. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012; 97: 2,969-2,989. DOI: 10.1210/jc.2011-3213. Available at: https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines. Accessed October 7, 2022.
59 Bhatt DL, Steg G, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med. 2019; 380(1): 11-22. DOI: 10.1056/NEJMoa1812792.
60 Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocrine Practice. 2017; 23(S2): 1-87. Available at: https://pro.aace.com/resources?keys=&disease_state_resource_cat_1%5Blipids-and-cv-health%5D=lipids-and-cv-health&field_disease_state_content_t_value%5BGuidelines%5D=Guidelines. Accessed October 7, 2022.
61 Handelsman Y, Jellinger PS, Guerin C, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the management of dyslipidemia and prevention of cardiovascular disease algorithm – 2020 executive summary. Endocrine Practice. 2020; 26(10): 1196-1224. DOI: 10.4158/CS-2020-0490. Available at: https://pro.aace.com/resources?keys=&disease_state_resource_cat_1%5Blipids-and-cv-health%5D=lipids-and-cv-health&field_disease_state_content_t_value%5BGuidelines%5D=Guidelines. Accessed October 7, 2022.
62 Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocrine Practice. 2017; 23(S2): 1-87. DOI: 10.4158/EP171764.APPGL. Available at: https://pro.aace.com/resources?keys=&disease_state_resource_cat_1%5Blipids-and-cv-health%5D=lipids-and-cv-health&field_disease_state_content_t_value%5BGuidelines%5D=Guidelines. Accessed October 7, 2022.
63 Handelsman Y, Jellinger PS, Guerin C, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the management of dyslipidemia and prevention of cardiovascular disease algorithm – 2020 executive summary. Endocrine Practice. 2020; 26(10): 1196-1224. DOI: 10.4158/CS-2020-0490. Available at: https://pro.aace.com/resources?keys=&disease_state_resource_cat_1%5Blipids-and-cv-health%5D=lipids-and-cv-health&field_disease_state_content_t_value%5BGuidelines%5D=Guidelines. Accessed October 7, 2022.
64 Writing Committee, Lloyd-Jones DM, Morris PB, et al. 2022 ACC expert consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology solution set oversight committee. J Am Coll Cardiol. 2022. 80(14):1366-1418. DOI: 10.1016/j.jacc.2022.07.006. Available at: https://www.acc.org/Guidelines. Accessed October 6, 2022.
65 Rubenfire M. 2022 ACC ECDP on Role of Nonstatin Therapies for LDL-C Lowering. August 25, 2022. Available at: https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2022/08/25/13/13/2022-acc-ecdp-on-nonstatin. Accessed October 16, 2022.

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.
© 2004-2022 Magellan Rx Management. All Rights Reserved.

66 Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 – executive summary. Journal of Clinical Lipidology. 2014: 8(5): 473–488. DOI: 10.1016/j.jacl.2014.07.007. Available at: https://www.lipid.org/practicetools/documents. Accessed October 7, 2022.
67 Jacobson TA, Maki KC, Orringer C, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 2. May 17, 2017. DOI: 10.1016/j.jacl.2015.09.002. Available at: https://www.lipid.org/practicetools/documents. Accessed October 7, 2022.
68 Orringer CE, Jacobson TA, Saseen JJ, et al. Update on the use of PCSK9 inhibitors in adults: recommendations from an expert panel of the National Lipid Association. Journal of Clinical Lipidology. 2017; 11(4): 880-891. DOI: 10.1016/j.jacl.2017.05.001. Available at: https://www.lipid.org/recommendations. AccessedOctober 7, 2022.
69 Robinson JG, Jayanna MB, Brown AS, et al. Enhancing the value of PCSK9 monoclonal antibodies by identifying patients most likely to benefit: A scientific statement from the National Lipid Association. Journal of Clinical Lipidology, 2019: 13(4); DOI: 10.1016/j.jacl.2019.05.005. Available at: https://www.lipid.org/practicetools/documents. Accessed October 7, 2022.
70 Orringer CE, Jacobson TA, Maki KC. National Lipid Association scientific statement on the use of icosapent ethyl in statin-treated patients with elevated triglycerides and high or very-high ASCVD risk. Journal of Clinical Lipidology, 2019: 13: 860-872. DOI: 10.1016/j.jacl.2019.10.014. Available at: https://www.lipid.org/practicetools/documents. Accessed October 7, 2022.
71 Orringer CE, Blaha MJ, Blankstein R, et al. The National Lipid Association scientific statement on coronary artery calcium scoring to guide preventive strategies for ASCVD risk reduction. Journal of Clinical Lipidology. 2020; 15(1): 33-60. DOI: 10.1016/j.jacl.2020.12.005. Available at: https://www.lipid.org/nla/cac-scoring-guide-prevention-ascvd. Accessed October 7, 2022.
72 Wilson PWF, Jacobson TA, Martin SS, et al. Lipid measurements in the management of cardiovascular diseases: practical recommendations. Available at: https://www.lipid.org/nla/lipid-measurements-management-cardiovascular-diseases-scientific-statement. Accessed October 7, 2022.
73 Siscovick DS, Barringer TA, Fretts AM, et al. Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease: a science advisory from the American Heart Association. Circulation. 2017; 136(14). DOI: 10.1161/CIR.0000000000000482. Available at: https://professional.heart.org/en/guidelines-and-statements. Accessed October 7, 2022.
74 Skulas-Ray AC, Wilson PWF, Harris WS, et al. Omega-3 fatty acids for the management of hypertriglyceridemia: a science advisory from the American Heart Association. Circulation. 2019; 140: e673–e691. DOI: 10.1161/CIR.0000000000000709. Available at: https://professional.heart.org/en/guidelines-and-statements. Accessed October 7, 2022.
75 Farnier M, Bruckert E. Severe familial hypercholesterolaemia: current and future management. Arch Cardiovasc Dis. 2012; 105(12): 656-665. DOI: 10.1016/j.acvd.2012.05.011.
76 Familial hypercholesterolemia. Updated December 29, 2021. Available at: http://emedicine.medscape.com/article/121298-overview. Accessed October 7, 2022.
77 Gidding SS, Champagne MA, de Ferranti SD, et al. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. Circulation. 2015; 132(22): 00-00. DOI: 10.1161/CIR.0000000000000297. Available at: http://professional.heart.org/professional/GuidelinesStatements/UCM_492626_Guidelines-Statements-Search-Page.jsp. Accessed October 7, 2022.
78 Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm. 2020 executive summary. Endocrine Practice. 2020; 26(1): 107-139. DOI: 10.4158/CS-2019-0472. Available at: https://pro.aace.com/resources?keys=&disease_state_resource_cat_1%5Bdiabetes%5D=diabetes&field_disease_state_content_t_value%5BAlgorithm%5D=Algorithm. Accessed October 7, 2022.
79 Das SR, Everett BM, et al. 2020 Expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes. Journal of the American College of Cardiology. 2020; 76: 1,117-1,145. DOI: 10.1016/j.jacc.2020.05.037. August 5, 2020. Available at: https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2020/08/04/13/05/2020-expert-consensus-type-2-diabetes. Accessed October 7, 2022.
80 American Diabetes Association. Standards of Medical Care in Diabetes—2022. Available at: https://professional.diabetes.org/content/clinical-practice-recommendations/. Accessed October 7, 2022.
81 Daniels SR, Benuck I, Christakis DA, et al. NHLBI expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: January 2012. Available at: https://www.nhlbi.nih.gov/health-pro/guidelines/current. Accessed October 7, 2022.
82 US Preventive Services Task Force. Lipid disorders in children and adolescents: Screening. August 2016. Available at: https://www.uspreventiveservicestaskforce.org/Announcements/News/Item/final-recommendation-statement-screening-for-lipid-disorders-in-children-and-adolescents. Accessed October 7, 2022.
83 US Preventive Services Task Force. Screening for lipid disorders in children and adolescents. Last updated August 12, 2021. Available at: https://www.uspreventiveservicestaskforce.org/uspstf/draft-update-summary/lipid-disorders-children-adolescents-screening. Accessed October 7, 2022.
84 De Farranti SD, Steinberger J, Ameduri R, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association. Circulation. 2019. 139(13):e603-e634. DOI: 10.1161/CIR.0000000000000618. Available at: https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2019/03/07/15/02/cardiovascular-risk-reduction-in-high-risk-pediatric. Accessed October 7, 2022.
85 Konrad RJ, Troutt JS, Cao G. Effects of currently prescribed LDL-C-lowering drugs on PCSK9 and implications for the next generation of LDL-C-lowering agents. Lipids Health Dis. 2011; 10: 38. DOI: 10.1186/1476-511X-10-38.
86 Sahebkar A, Watts GF. Managing recalcitrant hypercholesterolemia in patients on current best standard of care. Clin Lipidology. 2014; 9(2): 221-233. Available at: http://www.medscape.com/viewarticle/827299_1. Accessed October 7, 2022.
87 Evaluation of major cardiovascular events in patients with, or at high risk for, cardiovascular disease who are statin intolerant treated with bempedoic acid (ETC-1002) or placebo (CLEAR Outcomes). Updated September 10, 2022. Clinicaltrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02993406. Accessed October 18, 2022.
88 A randomized trial assessing the effects of inclisiran on clinical outcomes among people with cardiovascular disease (ORION-4). Updated September 16, 2022. Clinical Trials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03705234. Accessed October 10, 2022.
89 Nexletol [package insert]. Ann Arbor, MI; Esperion; September 2021.
90 Nexlizet [package insert]. Ann Arbor, MI; Esperion; September 2021.
91 Evkeeza [package insert]. Tarrytown, NY; Regneron; February 2021.

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.
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92 Juxtapid [package insert]. Cambridge, MA; Aegerion; September 2020.
93 Trilipix [package insert]. North Chicago, IL; Abbvie; June 2021.
94 Lopid [package insert]. New York, NY; Pfizer; December 2020.
95 Lovaza [package insert]. Wixom, MI; Woodward; February 2021.
96 Vascepa [package insert]. Bridgewater, NJ; Amarin; September 2021.
97 Praluent [package insert]. Tarrytown, NY; Regeneron; April 2021.
98 Repatha [package insert]. Thousand Oaks, CA; Amgen; September 2021.
99 Leqvio [package insert]. East Hanover, NJ; Novartis; December 2021.
100 Lemus HN, Mendivil CO. Adenosine triphosphate citrate lyase: emerging target in the treatment of dyslipidemia. J Clin Lipidol. 2015; 9(3): 384-389. DOI: 10.1016/j.jacl.2015.01.002. Available at: https://www.lipidjournal.com/article/S1933-2874(15)00038-0/fulltext. Accessed October 7, 2022.
101 Contois JH, McConnell JP, Sethi AA, et al. Apolipoprotein B and cardiovascular disease risk: position statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on best practices. Clinical Chemistry. 2009; 55(3): 407–419. DOI: 10.1373/clinchem.2008.118356.
102 Cuchel M, Bloedon LT, Szapary PO, et al. Inhibitor of microsomal triglyceride transfer protein in familial hypercholesterolemia. New Engl J Med. 2007;356:148-156. DOI: 10.1056/NEJMoa061189.
103 Insull W Jr. Clinical utility of bile acid sequestrants in the treatment of dyslipidemia: a scientific review. South Med J. 2006; 99: 257-273. DOI: 10.1097/01.smj.0000208120.73327.db.
104 Xydakis AM, Guyton JR, Chiou P, et al. Effectiveness and tolerability of ezetimibe add-on therapy to a bile acid resin-based regimen for hypercholesterolemia. Am J Cardiol. 2004; 94: 795-797. DOI: doi: 10.1016/j.amjcard.2004.06.008.
105 FDA Briefing Document. Trilipix. Application number 22-224. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022224s000_ClinPharmR_P1.pdf. Accessed October 7, 2022.
106 National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Available at: https://www.lipid.org/practicetools/guidelines/national. Accessed October 7, 2022.
107 Rubins HB. Triglycerides and coronary heart disease: implications of recent clinical trials. J Cardiovasc Risk. 2000; 7: 339–345. DOI: 10.1177/204748730000700507.
108 Frick MH, Elo O, Haapa K, et al. Helsinki heart study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. N Engl J Med. 1987; 317: 1,237-1,245. DOI: 10.1056/NEJM198711123172001.
109 Remick J, Weintraub H, Setton R. Fibrate therapy: an update. Cardiol Rev. 2008; 16(3): 129–141. DOI: 10.1097/CRD.0b013e31816b43d3.
110 Robins SJ, Rubins HB, Faas FH, et al. Veterans Affairs HDL Intervention Trial (VA-HIT). Insulin resistance and cardiovascular events with low HDL cholesterol: the Veterans Affairs HDL Intervention Trial (VA-HIT). Diabetes Care. 2003; 26: 1,513–1,517. DOI: 10.2337/diacare.26.5.1513.
111 Prueksaritanont T, Tang C, Qiu Y, et al. Effects of fibrates on metabolism of statins in human hepatocytes. Drug Metab Dispos. 2002; 30:1280–1287. DOI: 10.1124/dmd.30.11.1280.
112 Pan WJ, Gustavson LE, Achari R, et al. Lack of a clinically significant pharmacokinetic interaction between fenofibrate and pravastatin in healthy volunteers. J Clin Pharmacol. 2000; 40:316–323. DOI: 10.1177/00912700022008874.
113 Keech A, Simes RJ, Barter P, et al for the FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomized controlled trial. Lancet. 2005; 366:1849-1861. DOI: 10.1016/S0140-6736(05)67667-2.
114 Saha SA, Kizhakepunnur LG, Bahekar A, et al. The role of fibrates in the prevention of cardiovascular disease-a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. Am Heart J. 2007; 154(5): 943-953. DOI: 10.1016/j.ahj.2007.07.011.
115 Ginsberg HN, Elam MB, Lovato LC, et al. The ACCORD study group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010; 362(17):1563-74. DOI: 10.1056/NEJMoa1001282.
116 FDA Drug Safety Communication: Review update of Trilipix (fenofibric acid) and the ACCORD Lipid trial. November 2011. Updated February 13, 2018. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-review-update-trilipix-fenofibric-acid-and-accord-lipid-trial. Accessed October 7, 2022.
117 The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. New Engl J Med. 2010; 362 (17): 1563-74.
118 Grundy S, Stone NJ, Baily A, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. J Am Coll Cardiol. 2018. DOI: 10.1016/j.jacc.2018.11.003. Available at: http://www.acc.org/guidelines#doctype=Guidelines. Accessed October 7, 2022.
119 FDA. Withdrawal of approval of indications related to the coadministration with statins in applications for niacin extended-release tablets and fenofibric acid delayed-release capsules. Published April 18, 2016. Available at: https://www.federalregister.gov/documents/2016/04/18/2016-08887/abbvie-inc-et-al-withdrawal-of-approval-of-indications-related-to-the-coadministration-with-statins. Accessed October 7, 2022.
120 National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Available at: https://www.lipid.org/practicetools/guidelines/national. Accessed October 7, 2022
121 Grundy S, Stone NJ, Baily A, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. J Am Coll Cardiol. 2018. DOI: 10.1016/j.jacc.2018.11.003. Available at: http://www.acc.org/guidelines#doctype=Guidelines. Accessed October 7, 2022.
122 Bays HE, Dujovne CA, McGovern ME, et al. ADvicor versus other cholesterol-modulating agents trial evaluation. Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (the ADvicor Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). Am J Cardiol. 2003; 91: 667–672. DOI: 10.1016/s0002-9149(03)00007-9.
123 Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. JAMA. 1975; 231: 360-381.
124 Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. J Am Coll Cardiol. 1986; 8: 1245–1255. DOI: 10.1016/s0735-1097(86)80293-5.
125 Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med. 1990; 323:1289–1298. DOI: 10.1056/NEJM199011083231901.

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© 2004-2022 Magellan Rx Management. All Rights Reserved.

126 Taylor AJ, Sullenberger LE, Hyun JL, et al. Arterial biology for the investigation of the treatment effects of reducing cholesterol (ARBITER) 2. A double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. Circulation. 2004; 110: 3,512-3,517. DOI: 10.1161/01.CIR.0000148955.19792.8D.
127 Taylor AJ, Lee HJ, Sullenberger LE. The effect of 24 months of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. Curr Med Res Opin. 2006; 22(11): 243-250. DOI: 10.1185/030079906x148508.
128 Whitney EJ, Krasuski RA, Personius BE, et al. A randomized trial of a strategy for increasing high-density lipoprotein cholesterol levels: effects on progression of coronary heart disease and clinical events. Ann Intern Med. 2005; 142: 95-104. DOI: 10.7326/0003-4819-142-2-200501180-00008.
129 FDA. Withdrawal of Approval of indications related to the coadministration with statins in applications for niacin extended-release tablets and fenofibric acid delayed-release capsules. April 18, 2016. Available at: https://www.federalregister.gov/documents/2016/04/18/2016-08887/abbvie-inc-et-al-withdrawal-of-approval-of-indications-related-to-the-coadministration-with-statins. Accessed October 7, 2022.
130 AHA Scientific Statement: Fish consumption, fish oil, omega-3 fatty acids and cardiovascular disease, #71-0241 Circulation. 2002; 106: 2,747-2,757. DOI: 10.1161/CIR.0000000000000574.
131 Bays HE, Ballantyne CM, Kastelein JJ, et al. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, placebo-controlled, Randomized, double-blind, 12-week study with an open-label Extension [MARINE] trial). Am J Cardiol. 2011; 108(5): 682-690. DOI: 10.1016/j.amjcard.2011.04.015.
132 Nexletol [package insert]. Ann Arbor, MI; Esperion; September 2021.
133 Nexlizet [package insert]. Ann Arbor, MI; Esperion; September 2021.
134 Evkeeza [package insert]. Tarrytown, NY; Regneron; February 2021.
135 Juxtapid [package insert]. Cambridge, MA; Aegerion; September 2020.
136 Questran [package insert]. Spring Valley, NY; Par; April 2016.
137 Welchol [package insert]. South Plainfield, NJ; Cosette; February 2022.
138 Colestid tablet [package insert]. New York, NY; Pfizer; May 2017.
139 Zetia [package insert]. Jersey City, NJ; Organon; June 2021.
140 Tricor [package insert]. North Chicago, IL; Abbvie; June 2021.
141 Lipofen [package insert]. Montgomery, AL; Kowa; June 2021.
142 Antara [package insert]. Baltimore, MD; Lupin; June 2021.
143 Fenofibrate 43 mg and 130 mg [package insert]. Weston, FL; Apotex. November 2021.
144 Lipofen [package insert]. Montgomery, AL; Kowa; June 2021.
145 Fenoglide [package insert]. Bridgewater, NJ; Salix; June 2021.
146 Fibricor [package insert]. Athens, GA; Athena; June 2021.
147 Trilipix [package insert]. North Chicago, IL; Abbvie; June 2021.
148 Lopid [package insert]. New York, NY; Pfizer; December 2020.
149 Niaspan [package insert]. North Chicago, IL; Abbvie; May 2022.
150 Niacor [package insert]. Birmingham, AL; Avondale; September 2017.
151 Vascepa [package insert]. Bridgewater, NJ; Amarin; September 2021.
152 Lovaza [package insert]. Wixom, MI; Woodward; February 2021.
153 Praluent [package insert]. Tarrytown, NY; Regeneron; April 2021.
154 Repatha [package insert]. Thousand Oaks, CA; Amgen; September 2021.
155 Leqvio [package insert]. East Hanover, NJ; Novartis; December 2021.
156 McKenney JM, Farnier M, Lo KW, et al. Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. J Am Coll Cardiol. 2006; 47: 1,584-1,587. DOI: 10.1016/j.jacc.2005.11.072.
157 Najib J. Fenofibrate in the treatment of dyslipidemia: a review of the data as they relate to the new supra bioavailable tablet formulation. Clin Ther. 2002; 24: 2,022-2,050. DOI: 10.1016/s0149-2918(02)80095-9.
158 Nexletol [package insert]. Ann Arbor, MI; Esperion; September 2021.
159 Nexlizet [package insert]. Ann Arbor, MI; Esperion; September 2021.
160 Evkeeza [package insert]. Tarrytown, NY; Regneron; February 2021.
161 Juxtapid [package insert]. Cambridge, MA; Aegerion; September 2020.
162 Questran [package insert]. Spring Valley, NY; Par; April 2016.
163 Welchol [package insert]. South Plainfield, NJ; Cosette; February 2022.
164 Colestid tablet [package insert]. New York, NY; Pfizer; May 2017.
165 Zetia [package insert]. Jersey City, NJ; Organon; June 2021.
166 Tricor [package insert]. North Chicago, IL; Abbvie; June 2021.
167 Lipofen [package insert]. Montgomery, AL; Kowa; June 2021.
168 Antara [package insert]. Baltimore, MD; Lupin; June 2021.
169 Fenofibrate 43 mg and 130 mg [package insert]. Weston, FL; Apotex. November 2021.
170 Lipofen [package insert]. Montgomery, AL; Kowa; June 2021.
171 Fenoglide [package insert]. Bridgewater, NJ; Salix; June 2021.
172 Fibricor [package insert]. Athens, GA; Athena; June 2021.
173 Trilipix [package insert]. North Chicago, IL; Abbvie; June 2021.
174 Lopid [package insert]. New York, NY; Pfizer; December 2020.
175 Niaspan [package insert]. North Chicago, IL; Abbvie; May 2022.
176 Niacor [package insert]. Birmingham, AL; Avondale; September 2017.
177 Vascepa [package insert]. Bridgewater, NJ; Amarin; September 2021.
178 Lovaza [package insert]. Wixom, MI; Woodward; February 2021.

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179 Available at: https://www.clinicalkey.com/pharmacology/. Accessed October 7, 2022.
180 Praluent [package insert]. Tarrytown, NY; Regeneron; April 2021
181 Repatha [package insert]. Thousand Oaks, CA; Amgen; September 2021.
182 Leqvio [package insert]. East Hanover, NJ; Novartis; December 2021.
183 Hypertriglyceridemia. July 23, 2021. Available at: http://emedicine.medscape.com/article/118466-treatment. Accessed October 7, 2022.
184 Zocor [package insert]. Whitehouse Station, NJ; Merck; April 2020.
185 FDA. Approved Risk Evaluation and Mitigation Strategies (REMS). Juxtapid. Available at: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm. Accessed October 7, 2022.
186 Nexletol [package insert]. Ann Arbor, MI; Esperion; September 2021.
187 Nexlizet [package insert]. Ann Arbor, MI; Esperion; September 2021.
188 Evkeeza [package insert]. Tarrytown, NY; Regneron; February 2021.
189 Juxtapid [package insert]. Cambridge, MA; Aegerion; September 2020.
190 Questran [package insert]. Spring Valley, NY; Par; April 2016.
191 Welchol [package insert]. South Plainfield, NJ; Cosette; February 2022.
192 Colestid tablet [package insert]. New York, NY; Pfizer; May 2017.
193 Zetia [package insert]. Jersey City, NJ; Organon; June 2021.
194 Tricor [package insert]. North Chicago, IL; Abbvie; June 2021.
195 Lipofen [package insert]. Montgomery, AL; Kowa; June 2021.
196 Antara [package insert]. Baltimore, MD; Lupin; June 2021.
197 Fenofibrate 43 mg and 130 mg [package insert]. Weston, FL; Apotex. November 2021.
198 Lipofen [package insert]. Montgomery, AL; Kowa; June 2021.
199 Fenoglide [package insert]. Bridgewater, NJ; Salix; June 2021.
200 Fibricor [package insert]. Athens, GA; Athena; June 2021.
201 Trilipix [package insert]. North Chicago, IL; Abbvie; June 2021.
202 Lopid [package insert]. New York, NY; Pfizer; December 2020.
203 Niaspan [package insert]. North Chicago, IL; Abbvie; May 2022.
204 Niacor [package insert]. Birmingham, AL; Avondale; September 2017.
205 Vascepa [package insert]. Bridgewater, NJ; Amarin; September 2021.
206 Lovaza [package insert]. Wixom, MI; Woodward; February 2021.
207 Available at: https://www.clinicalkey.com/pharmacology/. Accessed October 7, 2022.
208 Praluent [package insert]. Tarrytown, NY; Regeneron; April 2021.
209 Repatha [package insert]. Thousand Oaks, CA; Amgen; September 2021.
210 Leqvio [package insert]. East Hanover, NJ; Novartis; December 2021.
211 COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov/. Updated September 26, 2022. Accessed October 18, 2022.
212 Paxlovid [Fact Sheet for Healthcare Providers]. New York, NY; Pfizer; September 2022.
213 Turner SW, Jungbluth GL and Knuth DW. Effect of concomitant colestipol hydrochloride administration on the bioavailability of diltiazem from immediate- and sustained-release formulations. Biopharm Drug Dispos. 2002; 23: 369-377. DOI: 10.1002/bdd.330.
214 Cellcept [package insert]. Nutley, NJ; Roche; December 2019.
215 Jahnchen E, Meinertz T, Gilfrich HJ, et al. Enhanced elimination of warfarin during treatment with cholestyramine. Br J Clin Pharmacol. 1978; 5: 437-440. DOI: 10.1111/j.1365-2125.1978.tb01651.x.
216 Ahmad S. Gemfibrozil: Interaction with glyburide (letter). South Med J. 1991; 84:102.
217 Deng L, Wang F and Li H. Effect of gemfibrozil on the pharmacokinetics of pioglitazone. Eur J Clin Pharmacol. 2005; 6: 831-836. DOI: 10.1007/s00228-005-0042-6.
218 Jaakkola T, Backman JT, Neuvonen M, et al. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics of pioglitazone. Clin Pharm Ther. 2005; 77: 404-414. DOI: 10.1016/j.clpt.2004.12.266.
219 Avandia [package insert]. Research Triangle Park, NC; GlaxoSmithKline; February 2019.
220 Prandin [package insert]. Princeton, NJ; Novo Nordisk; January 2019.
221 Nexletol [package insert]. Ann Arbor, MI; Esperion; September 2021.
222 Nexlizet [package insert]. Ann Arbor, MI; Esperion; September 2021.
223 Evkeeza [package insert]. Tarrytown, NY; Regneron; February 2021.
224 Juxtapid [package insert]. Cambridge, MA; Aegerion; September 2020.
225 Questran [package insert]. Spring Valley, NY; Par; April 2016.
226 Welchol [package insert]. South Plainfield, NJ; Cosette; February 2022.
227 Colestid tablet [package insert]. New York, NY; Pfizer; May 2017.
228 Zetia [package insert]. Jersey City, NJ; Organon; June 2021.
229 Tricor [package insert]. North Chicago, IL; Abbvie; June 2021.
230 Lipofen [package insert]. Montgomery, AL; Kowa; June 2021.
231 Antara [package insert]. Baltimore, MD; Lupin; June 2021.
232 Fenofibrate 43 mg and 130 mg [package insert]. Weston, FL; Apotex. November 2021.
233 Lipofen [package insert]. Montgomery, AL; Kowa; June 2021.
234 Fenoglide [package insert]. Bridgewater, NJ; Salix; June 2021.
235 Fibricor [package insert]. Athens, GA; Athena; June 2021.
236 Trilipix [package insert]. North Chicago, IL; Abbvie; June 2021.

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237 Lopid [package insert]. New York, NY; Pfizer; December 2020.
238 Niaspan [package insert]. North Chicago, IL; Abbvie; May 2022.
239 Niacor [package insert]. Birmingham, AL; Avondale; September 2017.
240 Vascepa [package insert]. Bridgewater, NJ; Amarin; September 2021.
241 Lovaza [package insert]. Wixom, MI; Woodward; February 2021.
242 Praluent [package insert]. Tarrytown, NY; Regeneron; April 2021.
243 Repatha [package insert]. Thousand Oaks, CA; Amgen; September 2021.
244 Leqvio [package insert]. East Hanover, NJ; Novartis; December 2021.
245 The Medical Letter. Colesevelam (Welchol) for hypercholesterolemia. 2000; 42: 102-104.
246 Kashani A, Sallam T, Bheemreddy S, et al. Review of side-effect profile of combination ezetimibe and statin therapy in randomized clinical trial. Am J Cardiol. 2008; 101(11):1606-1613. DOI: 10.1016/j.amjcard.2008.01.041.
247 Zhao YY, Weir MA, Manno M, et al. New fibrate use and acute renal outcomes in elderly adults. A population-based study. Annals. 2012; 156(8): 560-569. DOI: 10.7326/0003-4819-156-8-201204170-00003.
248 Clinical Trials.gov. Available at: https://clinicaltrials.gov/ct2/show/results/NCT01879319?term=evolocumab&rank=2&sect=X4387015#more. Accessed October 7, 2022.
249 Nexletol [package insert]. Ann Arbor, MI; Esperion; September 2021.
250 Nexlizet [package insert]. Ann Arbor, MI; Esperion; September 2021.
251 Evkeeza [package insert]. Tarrytown, NY; Regneron; February 2021.
252 Juxtapid [package insert]. Cambridge, MA; Aegerion; September 2020.
253 Cholestyramine. Available at: https://www.micromedexsolutions.com/micromedex2/librarian//. Accessed October 7, 2022.
254 Welchol [package insert]. South Plainfield, NJ; Cosette; February 2022.
255 Colestid tablet [package insert]. New York, NY; Pfizer; May 2017.
256 Zetia [package insert]. Jersey City, NJ; Organon; June 2021.
257 Tricor [package insert]. North Chicago, IL; Abbvie; June 2021.
258 Lipofen [package insert]. Montgomery, AL; Kowa; June 2021.
259 Antara [package insert]. Baltimore, MD; Lupin; June 2021.
260 Fenofibrate 43 mg and 130 mg [package insert]. Weston, FL; Apotex. November 2021.
261 Lipofen [package insert]. Montgomery, AL; Kowa; June 2021.
262 Fenoglide [package insert]. Bridgewater, NJ; Salix; June 2021.
263 Fibricor [package insert]. Athens, GA; Athena; June 2021.
264 Trilipix [package insert]. North Chicago, IL; Abbvie; June 2021.
265 Lopid [package insert]. New York, NY; Pfizer; December 2020.
266 Niaspan [package insert]. North Chicago, IL; Abbvie; May 2022.
267 Niacor [package insert]. Birmingham, AL; Avondale; September 2017.
268 Vascepa [package insert]. Bridgewater, NJ; Amarin; September 2021.
269 Lovaza [package insert]. Wixom, MI; Woodward; February 2021.
270 Praluent [package insert]. Tarrytown, NY; Regeneron; April 2021.
271 Repatha [package insert]. Thousand Oaks, CA; Amgen; September 2021.
272 Leqvio [package insert]. East Hanover, NJ; Novartis; December 2021.
273 McCrindle BW, Helden E, Cullen-Dean G, et al. A randomized crossover trial of combination pharmacologic therapy in children with familial hyperlipidemia. Pediatric Res. 2002; 51: 715-721. DOI: 10.1203/00006450-200206000-00009.
274 Knodel LC, Talbert RL. Adverse effects of hypolipidaemic drugs. Med Toxicol. 1987; 2: 10-32. DOI: 10.1007/BF03259858.
275 Zetia [package insert]. Jersey City, NJ; Organon; June 2021.
276 Stein SE, Marais AD, Szamosi T, et al. Colesevelam hydrochloride: efficacy and safety in pediatric subjects with heterozygous familial hypercholesterolemia. J Pediatr. 2010; 156(2): 231-236.e1-3. DOI: 10.1016/j.jpeds.2009.08.037.
277 Welchol [package insert]. South Plainfield, NJ; Cosette; February 2022.
278 D'Emden MC, Jenkins AJ, Zannino D, et al. Favourable effects of fenofibrate on lipids and cardiovascular disease in women with type 2 diabetes: results from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetologia. 2014; 57(11): 2,296-2,303. DOI: 10.1007/s00125-014-3344-3.
279 Nexletol [package insert]. Ann Arbor, MI; Esperion; September 2021.
280 Nexlizet [package insert]. Ann Arbor, MI; Esperion; September 2021.
281 Evkeeza [package insert]. Tarrytown, NY; Regneron; February 2021.
282 Juxtapid [package insert]. Cambridge, MA; Aegerion; September 2020.
283 Questran [package insert]. Spring Valley, NY; Par; April 2016.
284 Welchol [package insert]. South Plainfield, NJ; Cosette; February 2022.
285 Colestid tablet [package insert]. New York, NY; Pfizer; May 2017.
286 Zetia [package insert]. Jersey City, NJ; Organon; June 2021.
287 Tricor [package insert]. North Chicago, IL; Abbvie; June 2021.
288 Lipofen [package insert]. Montgomery, AL; Kowa; June 2021.
289 Antara [package insert]. Baltimore, MD; Lupin; June 2021.
290 Fenofibrate 43 mg and 130 mg capsule [package insert]. Weston, FL; Apotex. November 2021.
291 Lipofen [package insert]. Montgomery, AL; Kowa; June 2021.
292 Fenoglide [package insert]. Bridgewater, NJ; Salix; June 2021.
293 Fibricor [package insert]. Athens, GA; Athena; June 2021.

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294 Trilipix [package insert]. North Chicago, IL; Abbvie; June 2021.
295 Lopid [package insert]. New York, NY; Pfizer; December 2020.
296 Niaspan [package insert]. North Chicago, IL; Abbvie; May 2022.
297 Niacor [package insert]. Birmingham, AL; Avondale; September 2017.
298 Vascepa [package insert]. Bridgewater, NJ; Amarin; September 2021.
299 Lovaza [package insert]. Wixom, MI; Woodward; February 2021.
300 Praluent [package insert]. Tarrytown, NY; Regeneron; April 2021.
301 Repatha [package insert]. Thousand Oaks, CA; Amgen; September 2021.
302 Leqvio [package insert]. East Hanover, NJ; Novartis; December 2021.
303 Yokoyama M, Origasa H, Matsuzaki M, et al. Japan EPA Intervention Study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007; 369(9567): 1,090-1,098. DOI: 10.1016/S0140-6736(07)60527-3.
304 Tricor [package insert]. North Chicago, IL; Abbvie; June 2021.
305 Lopid [package insert]. New York, NY; Pfizer; December 2020.
306 Fenoglide [package insert]. Bridgewater, NJ; Salix; June 2021.
307 Trilipix [package insert]. North Chicago, IL; Abbvie; June 2021.
308 Fibricor [package insert]. Athens, GA; Athena; June 2021.
309 Niaspan [package insert]. North Chicago, IL; Abbvie; May 2022.
310 Lovaza [package insert]. Wixom, MI; Woodward; February 2021.
311 Juxtapid [package insert]. Cambridge, MA; Aegerion; September 2020.
312 Leqvio [package insert]. East Hanover, NJ; Novartis; December 2021.
313 Ray KK, Bays HE, Catapano AL, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. N Engl J Med 2019; 380: 1,022-1,032.DOI: 10.1056/NEJMoa1803917.
314 Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease. The CLEAR Wisdom randomized clinical trial. JAMA. 2019; 322(18): 1,780-1,788. DOI:10.1001/jama.2019.16585.
315 Laufs U, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. J Am Heart Assoc. 8(7); DOI:10.1161/JAHA.118.011662.
316 Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: a randomized, placebo-controlled study. Atherosclerosis. 2018; 277: 195-203. DOI: 10.1016/j.atherosclerosis.2018.06.002.
317 Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. Eur JPrev Cardiol. 2020; 27(6): 593–603. DOI: 10.1177/2047487319864671.
318 The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA. 1984; 251: 351-364. DOI: 10.1001/jama.1984.03340270029025.
319 Probstfield JL, Rifkind BM. The Lipid Research Clinics Coronary Primary Prevention Trial: design, results, and implications. Eur J Clin Pharmacol. 1991; 40 Suppl 1:S69-S75. DOI: 10.1007/BF03216294.
320 Whitney EJ, Krasuski RA, Personius BE, et al. A randomized trial of a strategy for increasing high-density lipoprotein cholesterol levels: effects on progression of coronary heart disease and clinical events. Ann Intern Med. 2005; 142: 95-104. DOI: 10.7326/0003-4819-142-2-200501180-00008.
321 Welchol [package insert]. South Plainfield, NJ; Cosette; February 2022.
322 Bays HE, Goldberg RB, Truitt KE, et al. Colesevelam hydrochloride therapy in patients with type 2 diabetes mellitus treated with metformin: glucose and lipid effects. Arch Intern Med. 2008; 168(18): 1,975-1,983. DOI: 10.1001/archinte.168.18.1975.
323 Goldberg RB, Fonseca VA, Truitt KE, et al. Efficacy and safety of colesevelam in patients with type 2 diabetes mellitus and inadequate glycemic control receiving insulin-based therapy. Arch Intern Med. 2008; 168(14): 1,531-1,540. DOI: 10.1001/archinte.168.14.1531.
324 Bays H, Rhyne J, Abby S, et al. Lipid-lowering effects of colesevelam HCl in combination with ezetimibe. Curr Med Res Opin. 2006; 22(11):2191-2200. DOI: 10.1185/030079906X148436.
325 Stein SE, Marais AD, Szamosi T, et al. Colesevelam hydrochloride: efficacy and safety in pediatric subjects with heterozygous familial hypercholesterolemia. J Pediatr. 2010; 156(2): 231-236.e1-3. DOI: 10.1016/j.jpeds.2009.08.037.
326 Raal, FJ, Rosenson, RS, Reeskamp, LF, et al. Evinacumab for homozygous familial hypercholesterolemia. N Engl J Med. 2020; 383: 711-720. DOI: 10.1056/NEJMoa2004215.
327 Rosenson, RS, Burgess, LJ, Ebenbichler, LF, et al. Evinacumab in patients with refractory hypercholesterolemia. N Engl J Med. 2020; 383: 2,307-2,319. DOI: 10.1056/NEJMoa2031049.
328 Tribble DL, Farnier M, Macdonell G, et al. Effects of fenofibrate and ezetimibe, both as monotherapy and in coadministration, on cholesterol mass within lipoprotein subfractions and low-density lipoprotein peak particle size in patients with mixed hyperlipidemia. Metabolism. 2008; 57(6): 796-801. DOI: 10.1016/j.metabol.2008.01.026.
329 Zetia [package insert]. Jersey City, NJ; Organon; June 2021.
330 Keech A, Simes RJ, Barter P, et al for the FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomized controlled trial. Lancet. 2005; 366: 1,849-1,861. DOI: 10.1016/S0140-6736(05)67667-2.
331 Grundy SM, Vega GL, Yuan A, et al. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). Am J Cardiol. 2005; 95(4): 462-468. DOI: 10.1016/j.amjcard.2004.10.012.
332 Ginsberg HN, Elam MB, Lovato LC, et al. The ACCORD study group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010; 362(17): 1,563-1,574. DOI: 10.1056/NEJMoa1001282.
333 Trilipix [package insert]. North Chicago, IL; Abbvie; June 2021.
334 Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. N Engl J Med. 1987; 317: 1,237-1,245. DOI: 10.1056/NEJM198711123172001.

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© 2004-2022 Magellan Rx Management. All Rights Reserved.

335 Manninen V, Elo O, Frick MH, et al. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. JAMA. 1988; 260: 641-651.
336 Manttari M, Romo M, Manninen V, et al. Reduction in Q wave myocardial infarctions with gemfibrozil in the Helsinki Heart Study. Am Heart J. 1990; 119: 991-995. DOI: 10.1016/s0002-8703(05)80226-1.
337 Heinonen OP, Huttunen JK, Manninen V, et al. The Helsinki heart study: coronary heart disease incidence during an extended follow-up. J Intern Med. 1994; 235: 41-49. DOI: 10.1111/j.1365-2796.1994.tb01030.x.
338 Frick MH, Heinonen OP, Huttunen JK, et al. Efficacy of gemfibrozil in dyslipidaemic subjects with suspected heart disease. An ancillary study in the Helsinki Heart Study frame population. Ann Med. 1993; 25: 41-45. DOI: 10.3109/07853899309147855.
339 Tenkanen L, Manttari M, Kovanen PT, et al. The Helsinki heart study. Gemfibrozil in the treatment of dyslipidemia: an 18 year mortality follow-up of the Helsinki Heart Study. Arch Intern Med. 2006; 166(7): 743-748. DOI: 10.1001/archinte.166.7.743.
340 Rubins HB, Robins SJ, Collins D. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs high-density lipoprotein cholesterol intervention trial study group. N Engl J Med. 1999; 341: 410-418. DOI: 10.1056/NEJM199908053410604.
341 Tonelli M, Collins D, Robins S, et al. Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. Kidney Int. 2004; 66: 1,123-1,130. DOI: 10.1111/j.1523-1755.2004.00862.x.
342 Rubins HB, Robins SJ, Collins D, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). Arch Intern Med. 2002; 162: 2,597-2,604. DOI: 10.1001/archinte.162.22.2597.
343 Bays HE, Ballantyne CM, Kastelein JJ, et al. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, plAcebo-controlled, Randomized, double-blind, 12-week study with an open-label Extension [MARINE] trial). Am J Cardiol. 2011; 108(5): 682-90. DOI: 10.1016/j.amjcard.2011.04.015.
344 Ballantyne CM, Bays HE, Kastelein JJ, et al. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). Am J Cardiol. 2012; 110(7): 984-992. DOI: 10.1016/j.amjcard.2012.05.031.
345 Bhatt DL, Steg G, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med. 2019; 380(1): 11-22. DOI: 10.1056/NEJMoa1812792.
346 Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet. 2013; 381(9860): 40-46. DOI: 10.1016/S0140-6736(12)61731-0.
347 Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. J Am Coll Cardiol. 1986; 8: 1,245-1,255. DOI: 10.1016/s0735-1097(86)80293-5.
348 Taylor AJ, Sullenberger LE, Hyun JL, et al. Arterial biology for the Investigation of the treatment effects of reducing cholesterol (ARBITER) 2. A double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. Circulation. 2004; 110: 3,512-3,517. DOI: 10.1161/01.CIR.0000148955.19792.8D.
349 AIM-HIGH Investigators. The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol: baseline characteristics of study participants. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: impact on Global Health outcomes (AIM-HIGH) trial. American Heart J. 2011; 161(3): 538-543. DOI: 10.1016/j.ahj.2010.12.007.
350 NIH News. NIH stops clinical trial on combination cholesterol treatment. May 26, 2011. Available at: http://www.nih.gov/news/health/may2011/nhlbi-26.htm. Accessed October 7, 2022.
351 AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. NEJM. 2011; 365: 2,255-2,267. DOI: 10.1056/NEJMoa1107579.
352 FDA Statement on the AIM-HIGH Trial. May 26, 2011. Available at: http://wayback.archive-it.org/7993/20161022205459/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm256841.htm. Accessed October 7, 2022.
353 Lovaza [package insert]. Wixom, MI; Woodward; February 2021.
354 Davidson MH, Stein EA, Bays HE, et al; COMBination of prescription omega-3 with simvastatin (COMBOS) investigators. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther. 2007; 29(7): 1,354-1,367. DOI: 10.1016/j.clinthera.2007.07.018.
355 Bays HE, McKenney J, Maki KC, et al. Effects of prescription omega-3-acid ethyl esters on non-high-density lipoprotein cholesterol when coadministered with escalating doses of atorvastatin. Mayo Clin Proc. 2010; 85(2): 122-128. DOI: 10.4065/mcp.2009.0397.
356 Kereiakes DJ, Robinson JG, Cannon CP, et al for the ODYSSEY COMBO I Investigators. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO I study. Am Heart J. 2015; 169(6): 906-915. DOI: 10.1016/j.ahj.2015.03.004.
357 Kastelein JJP, Robinson JG, Farnier M, et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia not adequately controlled with current lipid-lowering therapy: design and rationale of the ODYSSEY FH studies. Cardiovasc Drugs Ther. 2014; 28(3): 281-289. DOI: 10.1007/s10557-014-6523-z.
358 Praluent [package insert]. Tarrytown, NY; Regeneron; April 2021.
359 Kastelein JJP, Robinson JG, Farnier M, et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia not adequately controlled with current lipid-lowering therapy: design and rationale of the ODYSSEY FH studies. Cardiovasc Drugs Ther. 2014; 28(3): 281-289. DOI: 10.1007/s10557-014-6523-z.
360 Praluent [package insert]. Tarrytown, NY; Regeneron; April 2021.
361 FDA Briefing Information: Alirocumab Injection. The Endocrinologic and Metabolic Drugs Advisory Committee Meeting. FDA Center for Drug Evaluation and Research. Meeting date: June 9, 2015. Available at: https://www.fdanews.com/ext/resources/files/06-15/06-15-FDA-AdCom.pdf?1520849799. Accessed October 10, 2022.
362 Robinson JG, Farnier M, Krempf for the ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015; 372(16): 1,489-1,499. DOI: 10.1056/NEJMoa1501031.
363 Praluent [package insert]. Tarrytown, NY; Regeneron; April 2021.

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364 Roth EM, Moriarty PM, Bergeron J, et al. A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I. Atherosclerosis. 2016; 254: 254-262. DOI: 10.1016/j.atherosclerosis.2016.08.043.
365 Blom DJ, Harada-Shiba M, Rubba P, et al. Efficacy and safety of alirocumab in adults with homozygous familial hypercholesterolemia: The ODYSSEY HoFH trial. J Am Coll Cardiol. 2020; 76(2): 131-142. DOI: 10.1016/j.jacc.2020.05.027.
366 Praluent [package insert]. Tarrytown, NY; Regeneron; April 2021.
367 Cannon CP, Cariou B, Blom D, et al for the ODYSSEY COMBO II Investigators. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. Eur Heart J. 2015; 36(19): 1,186-1,194. DOI: 10.1093/eurheartj/ehv028.
368 El Shahawy M, Cannon CP, Clom DJ, et al. Efficacy and safety of alirocumab versus ezetimibe over 2 years (from ODYSSEY COMBO II). Am J Cardiol. 2017; 120(6): 931-939. DOI: 10.1016/j.amjcard.2017.06.023.
369 Roth EM, Taskinen MR, Ginsberg, HN, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24-week, double-blind, randomized phase 3 trial. Int J Cardiol. 2014; 176(1): 55-61. DOI: 10.1016/j.ijcard.2014.06.049.
370 Bays H, Gaudet D, Weiss R, et al. Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial. J Clin Endocrinol Metab. 2015; 100(8): 3,140-3,148. DOI: 10.1210/jc.2015-1520.
371 ODYSSEY Outcomes: Evaluation of cardiovascular outcomes after an acute coronary syndrome during treatment with alirocumab. Available at: https://clinicaltrials.gov/ct2/show/record/NCT01663402. Accessed October 10, 2022.
372 ODYSSEY Outcomes: Results suggest use of PCSK9 inhibitor reduces CV events, LDL-C in ACS patients. March 10, 2018. Available at: http://www.acc.org/latest-in-cardiology/articles/2018/03/05/15/53/sat-9am-odyssey-outcomes-cv-outcomes-with-alirocumab-after-acs-acc-2018. Accessed October 10, 2022.
373 Blom DJ, Hala T, Bolognese M, et al for the DESCARTES Investigators. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med. 2014; 370(19): 1,809-1,819. DOI: 10.1056/NEJMoa1316222.
374 Raal FJ, Stein EA, Dufourn R et al for the RUTHERFORD-2 Investigators. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet. 2015; 385(9965): 331-340. DOI: 10.1016/S0140-6736(14)61399-4.
375 Raal FJ, Honarpour N, Blom DJ et al for the TESLA Investigators. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet. 2015; 385(9965): 341-350. DOI: 10.1016/S0140-6736(14)61374-X.
376 Repatha [package insert]. Thousand Oaks, CA; Amgen; September 2021.
377 Repatha [package insert]. Thousand Oaks, CA; Amgen; September 2021.
378 Nicholls SJ, Puri R, Anderson T, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients. The GLAGOV randomized clinical trial. JAMA. Published online on November 15, 2016. DOI:10.1001/jama.2016.16951.
379 Repatha [package insert]. Thousand Oaks, CA; Amgen; September 2021.
380 Santos RD, Ruzza A, Hovingh GK, et al. Evolocumab in pediatric heterozygous familial hypercholesterolemia. N Engl J Med. 2020; 383(14): 1317-1327. DOI: 10.1056/NEJMoa2019910. Epub 2020 Aug 29.
381 Repatha [package insert]. Thousand Oaks, CA; Amgen; September 2021.
382 Robinson JG, Nedergaard BS, Rogers WJ, et al for the LAPLACE-2 Investigators. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA. 2014; 311(18): 1,870-1,882. DOI: 10.1001/jama.2014.4030.
383 Koren MJ, Lundqvist P, Bolognese M, et al for the MENDEL-2 Investigators. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol. 2014; 63(23): 2,531-2,540. DOI: 10.1016/j.jacc.2014.03.018.
384 Stroes E, Colguhoun D, Sullivan D, et al for the GAUSS-2 Investigators. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol. 2014; 63(23): 2,541-2,548. DOI: 10.1016/j.jacc.2014.03.019.
385 Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance The GAUSS-3 randomized clinical trial. JAMA. 2016; 315(15): 1,580-1,590. DOI:10.1001/jama.2016.3608.
386 Sabine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017; 376:1,713-1,722. DOI: 10.1056/NEJMoa1615664.
387 Giugliano RP, Mach F, Zavitz K, et al. Design and rationale of the EBBINGHAUS trial: a phase 3, double-blind, placebo-controlled, multicenter study to assess the effect of evolocumab on cognitive function in patients with clinically evident cardiovascular disease and receiving statin background lipid-lowering therapy—A cognitive study of patients enrolled in the FOURIER trial. Clin Cardiol. 2017; 40(2): 59-65. DOI: 10.1002/clc.22678.
388 Leqvio [package insert]. East Hanover, NJ; Novartis; December 2021.
389 Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020;382(16):1507-1519. DOI: 10.1056/NEJMoa1912387.
390 Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Eng J Med. 2020; 382: 1520-1530. DOI: 10.1056/NEJMoa1913805.
391 Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020;382(16):1507-1519. DOI: 10.1056/NEJMoa1912387.
392 Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020;382(16):1507-1519. DOI:10.1056/NEJMoa1912387.
393 Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Eng J Med. 2020; 382: 1520-1530. DOI: 10.1056/NEJMoa1913805.
394 Birjmohun RS, Hutten BA, Kastelein JJP, et al. Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2005; 45: 185-197. DOI: 10.1016/j.jacc.2004.10.031.
395 Abourbih S, Filion KB, Joseph L, et al. Effect of fibrates on lipid profiles and cardiovascular outcomes: a systematic review. Am J Med. 2009; 122(10): 962.e1-8. DOI: 10.1016/j.amjmed.2009.03.030.

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396 Jun M, Foote C, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet. 2010; 375(9729): 1,875-1,884. DOI: 10.1016/S0140-6736(10)60656-3.
397 Bruckert E, Labreuche J, Amarenco P. Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis. Atherosclerosis. 2010; 210(2): 353-361. DOI: 10.1016/j.atherosclerosis.2009.12.023.
398 Marston NA, Giugliano RP, Im K, et al. Association between triglyceride lowering and reduction of cardiovascular risk across multiple lipid-lowering therapeutic classes: a systematic review and meta-regression analysis of randomized controlled trials. Circulation. 2019; 140(16): 1,308-1,317. DOI: 10.1161/CIRCULATIONAHA.119.041998.
399 Schmidt AF, Carter JPL, Pearce LS, et al. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2020; 10(10): CD011748. DOI: 10.1002/14651858.CD011748.pub3.
400 Toth PP, Bray S, Villa G, et al. Network meta-analysis of randomized trials evaluating the comparative efficacy of lipid-lowering therapies added to maximally tolerated statins for the reduction of low-density lipoprotein cholesterol. J Am Heart Assoc. 2022;11(18):e025551. DOI:10.1161/JAHA.122.025551.
401 Welchol [package insert]. South Plainfield, NJ; Cosette; February 2022.
402 Aldridge MA, Ito MK. Colesevelam hydrochloride: a novel bile acid-binding resin. Ann Pharmacother. 2001; 35: 898-907.
403 Zetia [package insert]. Jersey City, NJ; Organon; June 2021.
404 Tricor [package insert]. North Chicago, IL; Abbvie; June 2021.
405 Lipofen [package insert]. Montgomery, AL; Kowa; June 2021.
406 Antara [package insert]. Baltimore, MD; Lupin; June 2021.
407 Fenoglide [package insert]. Bridgewater, NJ; Salix; June 2021.
408 Trilipix [package insert]. North Chicago, IL; Abbvie; June 2021.
409 Juxtapid [package insert]. Cambridge, MA; Aegerion; September 2020.
410 Niaspan [package insert]. North Chicago, IL; Abbvie;. May 2022.
411 Niacor [package insert]. Birmingham, AL; Avondale; September 2017.
412 Lovaza [package insert]. Wixom, MI; Woodward; February 2021.
413 Vascepa [package insert]. Bridgewater, NJ; Amarin; September 2021.
414 Praluent [package insert]. Tarrytown, NY; Regeneron; April 2021.
415 Repatha [package insert]. Thousand Oaks, CA; Amgen; September 2021.
416 Hunninghake D, Insull W, Toth P, et al. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL-C additively. Atherosclerosis. 2001; 158: 407-416. DOI: 10.1016/s0021-9150(01)00437-3.
417 Farnier M, Dejager S. Effect of combined fluvastatin-fenofibrate therapy compared with fenofibrate monotherapy in severe primary hypercholesterolemia. French Fluvastatin Study Group. Am J Cardiol. 2000; 85: 53-57. DOI: 10.1016/s0002-9149(99)00606-2.
418 Durrington PN, Tuomilehto J, Hamann A, et al. Rosuvastatin and fenofibrate alone and in combination in type 2 diabetes patients with combined hyperlipidaemia. Diabetes Res Clin Pract. 2004; 64: 137-151. DOI: 10.1016/j.diabres.2003.11.012.
419 Capuzzi DM, Guyton JR, Morgan JM, et al. Efficacy and safety of an extended-release niacin (Niaspan): a long-term study. Am J Cardiol. 1998; 82: 74U-81U. DOI: 10.1016/s0002-9149(98)00731-0.
420 Guyton JR, Blazing MA, Hagar J, et al. Extended-release niacin vs. gemfibrozil for the treatment of low levels of high density lipoprotein cholesterol. Niaspan-Gemfibrozil Study Group. Arch Intern Med. 2000; 160(8): 1,177-1,184. DOI: 10.1001/archinte.160.8.1177.
421 National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation. 2002; 106: 3,143–3,421.
422 Rifkind BM. The Lipid Research Clinics coronary primary prevention trial. Drugs. 1986; 31 Suppl 1: 53-60. DOI: 10.2165/00003495-198600311-00010.
423 McKenney J, Jones M, Abby S. Safety and efficacy of colesevelam hydrochloride in combination with fenofibrate for the treatment of mixed hyperlipidemia. Curr Med Res Opin. 2005; 21: 1,403-1,412. DOI: 10.1185/030079905x59157.
424 Insua A, Massari F, Rodriquez MJJ, et al. Fenofibrate of gemfibrozil for treatment of types IIa and IIb primary hyperlipoproteinemia: a randomized, double-blind, crossover study. Endocr Pract. 2002; 8: 96-101. DOI: 10.4158/EP.8.2.96.
425 De la Serna G, Cardarso G. Fenofibrate decreases plasma fibrinogen, improves lipid profile, and reduces uricemia. Clin Pharmacol Ther. 1999; 66: 166-172. DOI: 10.1053/cp.1999.v66.99709.
426 Manninen V, Huttunen JK, Heinonen OP, et al. Relation between baseline lipid and lipoprotein values and the incidence of coronary heart disease in the Helsinki Heart Study. Am J Cardiol. 1989; 63: 42H-47H. DOI: 10.1016/0002-9149(89)90115-x.
427 Farnier M. Cerivastatin in the treatment of mixed hyperlipidemia: the RIGHT study. The Cerivastatin Study Group. Cerivastatin Gemfibrozil Hyperlipidemia Treatment. Am J Cardiol. 1998; 82(4B): 47J-51J. DOI: 10.1016/s0002-9149(98)00437-8.
428 Odman B, Ericsson S, Lindmark M, et al. Gemfibrozil in familial combined hyperlipidaemia: effect of added low-dose cholestyramine on plasma and biliary lipids. Eur J Clin Invest. 1991; 21: 344-349. DOI: 10.1111/j.1365-2362.1991.tb01380.x.
429 Ros E, Zambon D, Bertomeu A, et al. Comparative study of a microporous cholestyramine analogue (filicol) and gemfibrozil for treatment of severe primary hypercholesterolemia. Short- and long-term results. Arch Intern Med. 1991; 151: 301-305.
430 Insua A, Massari F, Rodriquez MJJ, et al. Fenofibrate of gemfibrozil for treatment of types IIa and IIb primary hyperlipoproteinemia: a randomized, double-blind, crossover study. Endocr Pract. 2002; 8: 96-101. DOI: 10.4158/EP.8.2.96.
431 Kaukola S, Manninen V, Malkonen M, et al. Gemfibrozil in the treatment of dyslipidemias in middle-aged male survivors of myocardial infarction. Acta Med Scand. 1981; 209: 69-73. DOI: 10.1111/j.0954-6820.1981.tb11554.x.
432 Rubins HB, Robins SJ, Collins D: Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs high-density lipoprotein cholesterol intervention trial study group. N Engl J Med. 1999; 341: 410-418. DOI: 10.1056/NEJM199908053410604.
433 Guyton JR, Blazing MA, Hagar J, et al. Extended-release niacin vs. gemfibrozil for the treatment of low levels of high-density lipoprotein cholesterol. Niaspan-Gemfibrozil Study Group. Arch Intern Med. 2000; 160: 1,177-1,184. DOI: 10.1001/archinte.160.8.1177.

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434 Kereiakes DJ, Robinson JG, Cannon CP, et al for the ODYSSEY COMBO I Investigators. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO I study. Am Heart J. 2015; 169(6): 906-915. DOI: 10.1016/j.ahj.2015.03.004.
435 Robinson JG, Farnier M, Krempf for the ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015; 372(16): 1,489-1,499. DOI: 10.1056/NEJMoa1501031.
436 Cannon CP, Cariou B, Blom D, et al for the ODYSSEY COMBO II Investigators. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. Eur Heart J. 2015; 36(19): 1,186-1,194. DOI: 10.1093/eurheartj/ehv028.
437 Roth EM, Taskinen MR, Ginsberg, HN, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24-week, double-blind, randomized phase 3 trial. Int J Cardiol. 2014; 176(1): 55-61. DOI: 10.1016/j.ijcard.2014.06.049.
438 Bays H, Gaudet D, Weiss R, et al. Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial. J Clin Endocrinol Metab. 2015;100(8): 3,140-3,148. DOI: 10.1210/jc.2015-1520.
439 Blom DJ, Hala T, Bolognese M, et al for the DESCARTES Investigators. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med. 2014; 370(19): 1,809-1,819. DOI: 10.1056/NEJMoa1316222.
440 Raal FJ, Stein EA, Dufourn R et al for the RUTHERFORD-2 Investigators. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet. 2015; 385(9965): 331-340. DOI: 10.1016/S0140-6736(14)61399-4.
441 Raal FJ, Honarpour N, Blom DJ et al for the TESLA Investigators. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet. 2015; 385(9965): 341-350. DOI: 10.1016/S0140-6736(14)61374-X.
442 Robinson JG, Nedergaard BS, Rogers WJ, et al for the LAPLACE-2 Investigators. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA. 2014; 311(18): 1,870-1,882. DOI: 10.1001/jama.2014.4030.
443 Koren MJ, Lundqvist P, Bolognese M, et al for the MENDEL-2 Investigators. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol. 2014; 63(23): 2,531-2,540. DOI: 10.1016/j.jacc.2014.03.018.
444 Stroes E, Colguhoun D, Sullivan D, et al for the GAUSS-2 Investigators. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol. 2014; 63(23): 2,541-2,548. DOI: 10.1016/j.jacc.2014.03.019.
445 Ray KK, Bays HE, Catapano AL, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. N Engl J Med 2019; 380: 1,022-1,032. DOI: 10.1056/NEJMoa1803917.
446 Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease. The CLEAR Wisdom randomized clinical trial. JAMA. 2019; 322(18): 1,780-1,788. DOI:10.1001/jama.2019.16585.
447 Laufs U, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. J Am Heart Assoc. 8(7); DOI:10.1161/JAHA.118.011662.
448 Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: a randomized, placebo-controlled study. Atherosclerosis. 2018; 277: 195-203. DOI: 10.1016/j.atherosclerosis.2018.06.002.
449 Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. Eur J Prev Cardiol. 2020; 27(6): 593–603. DOI: 10.1177/2047487319864671.
450 Nexletol [package insert]. Ann Arbor, MI; Esperion; September 2021.
451 Nexlizet [package insert]. Ann Arbor, MI; Esperion; September 2021.
452 Raal, FJ, Rosenson, RS, Reeskamp, LF, et al. Evinacumab for homozygous familial hypercholesterolemia. N Engl J Med. 2020; 383: 711-720. DOI: 10.1056/NEJMoa2004215.
453 Leqvio [package insert]. East Hanover, NJ; Novartis; December 2021.
454 Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020;382(16):1507-1519. DOI:10.1056/NEJMoa1912387.
455 Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Eng J Med. 2020; 382: 1520-1530. DOI: 10.1056/NEJMoa1913805

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