Lipotropics, Statins
Therapeutic Class Review (TCR)

October 2, 2020

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AGENTS

Drug	Manufacturer
amlodipine / atorvastatin (Caduet®)[1]	generic, Pfizer
atorvastatin (Lipitor®)[2]	generic, Pfizer
ezetimibe / simvastatin (Vytorin®)[3]	generic, Merck Sharp and Dohme
fluvastatin[4]	generic
fluvastatin ER (Lescol XL®)[5]	generic, Novartis
lovastatin[6]	generic
lovastatin ER (Altoprev®)[7]	Covis
pitavastatin calcium (Livalo®)[8]	Kowa
pitavastatin magnesium (Zypitamag®*)[9]	Medicure
pravastatin (Pravachol®)[10]	generic; BMS
rosuvastatin (Crestor®)[11]	generic, AstraZeneca
rosuvastatin (Ezallor™ Sprinkle*)[12]	Sun
simvastatin (Flolipid*)[13]	Salerno
simvastatin (Zocor®)[14]	generic, Merck Sharp and Dohme

* Simvastatin oral suspension (Flolipid), pitavastatin tablet (Zypitamag), and rosuvastatin (Ezallor) were approved as a New Drug Application (NDA) via the 505(b)(2) pathway. A 505(b)(2) NDA is a United States (US) Food and Drug Administration (FDA) approval pathway in which at least some of the information required for approval comes from studies not conducted by or for the applicant.[15] Some of the data used for approval of Flolipid, Zypitamag, and Ezallor were derived from safety and efficacy data with simvastatin (Zocor), pitavastatin (Livalo), and rosuvastatin (Crestor), respectively.

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FDA-APPROVED INDICATIONS

Indications	atorvastatin (Lipitor), amlodipine/ atorvastatin* (Caduet)[16,17]	ezetimibe/ simvastatin (Vytorin)[18]	fluvastatin, fluvastatin ER (Lescol XL)[19,20]	lovastatin[21]	lovastatin ER (Altoprev)[22]
Primary hypercholesterolemia ▪ Heterozygous familial and nonfamilial Reduce: Total-C, LDL-C, TG and ApoB Increase: HDL-C	X	X	X	X	X
Heterozygous familial hypercholesterolemia ▪ pediatric	X 10–17 years *(Lipitor only)*	--	X 10–16 years	X 10–17 years	--
Mixed dyslipidemia *Fredrickson Type* ▪ II$_a$ and II$_b$ Reduce: Total-C, LDL-C, TG and ApoB	X	X	X	X To reduce total-C, LDL-C	X
Increase HDL-C	X	X	X	--	X
Hypertriglyceridemia *Fredrickson Type* IV	X	--	--	--	--
Primary dysbetalipoproteinemia *Fredrickson Type* III	X	--	--	--	--
Homozygous familial hypercholesterolemia	X	X	--	--	--
Atherosclerosis ▪ slow progression	--	--	X	X	X

Total-C = Total cholesterol; LDL-C = low density lipoprotein cholesterol; TG = triglycerides; ApoB = apoprotein B

* Caduet is indicated when amlodipine and atorvastatin are both appropriate. Indications for amlodipine are hypertension, chronic stable angina, vasospastic angina, and angiographically documented coronary artery disease (CAD).

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Indications	atorvastatin (Lipitor), amlodipine/ atorvastatin* (Caduet)	ezetimibe/ simvastatin (Vytorin)	fluvastatin, fluvastatin ER (Lescol XL)	lovastatin	lovastatin ER (Altoprev)
CVD ▪ primary prevention of coronary events	Reduces risk of MI, stroke, revascularization, angina	--	--	Reduces risk of MI, unstable angina, and need for coronary revascularization	Reduces risk of MI, unstable angina, coronary revascularization
CHD ▪ secondary prevention of coronary events	Reduces risk of MI, stroke in Type 2 diabetics without CHD; Reduces risk of MI, stroke, CHF hospitalization, angina, and revascularization in CHD patients	--	Reduces risk of coronary revascularization	--	--

Total-C = Total cholesterol; LDL-C = low density lipoprotein cholesterol; TG = triglycerides; ApoB = apoprotein B

* Caduet is indicated when amlodipine and atorvastatin are both appropriate. Indications for amlodipine are hypertension, chronic stable angina, vasospastic angina, and angiographically documented coronary artery disease (CAD).

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FDA-Approved Indications (continued)

Indications	pitavastatin (Livalo, Zypitamag)[23]	pravastatin (Pravachol)[24]	rosuvastatin[†] (Crestor, Ezallor Sprinkle)[25,26]	simvastatin (Flolipid, Zocor) [27,28]
Primary hypercholesterolemia ■ Heterozygous familial and nonfamilial Reduce: Total-C, LDL-C, TG and ApoB	X	X	X[‡]	X
Heterozygous familial hypercholesterolemia ■ pediatric	X 8 years and older *(Livalo only)*	X 8 years and older	X[‡] 8–17 years	X 10–17 years
Mixed dyslipidemia *Fredrickson Type* ■ II$_a$ and II$_b$ Reduce: Total-C, LDL-C, TG and ApoB	--	X	X[‡]	X
Increase HDL-C	X	X	X[‡]	X
Hypertriglyceridemia - *Fredrickson Type IV*	--	X	X	X
Primary dysbetalipoproteinemia - *Fredrickson Type III*	--	X	X	X
Homozygous familial hypercholesterolemia	--	--	X 7–17 years[§]	X
Atherosclerosis ■ slow progression	--	X	X[‡]	--
CVD ■ primary prevention of coronary events	--	Reduces risk of MI, myocardial revascularization, CV mortality	Reduces risk of MI, stroke, revascularization, in patients without clinically evident CHD, but with multiple risk factors[‡]	Reduces total mortality risk by reducing CHD death, MI, stroke, and need for revascularization in high risk patients

Total-C = Total cholesterol; LDL-C = low density lipoprotein cholesterol; TG = triglycerides; ApoB = apoprotein B

† High risk = patients with increased risk of CV disease based on age 50 years (men) and 60 years (women), hsCRP 2 mg/dL, and presence of at least 1 additional CV risk factor (e.g., hypertension, low high-density lipoprotein cholesterol (HDL-C), smoking, or a family history of premature CAD).

‡ Approval for rosuvastatin (Crestor) only

§ Rosuvastatin (Ezallor Sprinkle) is approved for use in adults only.

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FDA-Approved Indications (continued)

Indications	pitavastatin (Livalo, Zypitamag)[29]	pravastatin (Pravachol)[30]	rosuvastatin[†] (Crestor, Ezallor Sprinkle)[31,32]	simvastatin (Flolipid, Zocor) [33,34]
CHD ▪ secondary prevention of coronary events	--	Reduces risk of MI, myocardial revascularization, CV mortality, stroke/TIA	--	Reduces total mortality risk by reducing CHD death, MI, stroke, and need for revascularization

Total-C = Total cholesterol; LDL-C = low density lipoprotein cholesterol; TG = triglycerides; ApoB = apoprotein B

† High risk = patients with increased risk of CV disease based on age 50 years (men) and 60 years (women), hsCRP 2 mg/dL, and presence of at least 1 additional CV risk factor (e.g., hypertension, low high-density lipoprotein cholesterol (HDL-C), smoking, or a family history of premature CAD).

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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 from 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).[35] The prevalence of high total cholesterol in women was 12.1% compared to 10.5% in men, 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 and Hispanic-origin differences in the prevalence of high total cholesterol in adults. The NHANES analysis was based on measured cholesterol only and does 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.[36]

In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA), in combination with the National Heart, Lung, and Blood Institute (NHLBI), released 4 new consensus guidelines regarding cholesterol management, cardiovascular risk assessment, obesity, and lifestyle.[37,38,39,40] Obesity is associated with increased risk in all-cause and cardiovascular disease (CVD) mortality, and lifestyle changes that produce even modest, sustained weight loss of 3% to 5% result in clinically meaningful health benefits. In 2018, ACC/AHA, along with several other relevant professional organizations, published updated guidance on optimal lipid management.[41] ACC/AHA emphasizes lifestyle modification including a reduced calorie diet and aerobic physical activity as a critical component of ASCVD risk reduction, both prior to and in conjunction with cholesterol lowering drug therapies.

The 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, are the standard treatment in lowering cholesterol levels. Several statin trials document reduced morbidity and mortality with use. All statins lower low-density lipoprotein cholesterol (LDL-C), although to differing degrees, in a dose-related manner.[42] However, data obtained during clinical trials have demonstrated that statin efficacy does not increase proportionally with dose.[43,44] 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 another agent may be appropriate in select patients. Clinical findings support the use of statins to prevent both nonfatal and fatal atherosclerotic cardiovascular disease (ASCVD) events.[45,46] There is a high level of evidence supporting use of statins for secondary prevention and moderate to high level of evidence for primary prevention. When used for primary prevention, statins are associated with lower rates of all-cause mortality, major vascular events, and revascularization procedures compared with placebo.[47,48] Although, few studies are available that demonstrate significant additional ASCVD event reductions with non-statin cholesterol-lowering drugs, for patients with a primary LDL-C ≥ 190 mg/dL, after the maximum intensity of statin therapy has been reached, addition of a non-statin drug may be considered to further lower LDL-C.

According to the ACC/AHA, clinical ASCVD includes acute coronary syndromes (ACS), or a history of myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization,

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stroke, transient ischemic attack (TIA), or peripheral arterial disease (PAD) presumed to be of atherosclerotic origin.[49,50] Previously, a treat-to-target approach with goals such as LDL-C < 70 mg/dL and < 100 mg/dL for secondary and primary ASCVD prevention was used.[51] As of 2013, ACC/AHA guidelines no longer support this model since clinical trial data do not define an appropriate target and the expected magnitude of additional ASCVD risk reduction, nor does the model consider potential adverse effects from multidrug therapy. Conversely, percent reduction in LDL-C is appropriate as an indication of response and adherence to therapy. With the 2013 guidelines, the ACC/AHA recommended the use of the race- and sex-specific Pooled Cohort Equations (PCE) to predict 10-year risk for a first hard ASCVD event in non-Hispanic African-Americans and non-Hispanic Caucasians who are 40 to 79 years of age. Prior to this, the National Cholesterol Education Program (NCEP) Expert Panel on Diagnosis, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) algorithm was recommended for risk assessment, but it has limited use because it is based on an exclusively Caucasian sample population.[52] The 2018 ACC/AHA guidelines on management of blood cholesterol, published in collaboration with several other relevant professional organizations, emphasized lifestyle therapies to reduce ASCVD risk.[53] 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 triglycerides ≥ 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. In the 2019 ACC/AHA guideline on primary prevention of CVD, statins are recommended as first-line therapy for primary prevention of ASCVD, in patients with elevated LDL-C ≥ 190 mg/dL, adults with diabetes mellitus 40 to 75 years of age, and individuals found to be at higher ASCVD risk.[54] 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 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 proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor can be added.[55] 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; if LDL-C is still ≥ 100 mg/dL and the patient has multiple risk factors, addition of a PCSK9 inhibitor may be considered. Furthermore, the 2016 updated AHA/ACC guidelines for PAD recommend statins for all patients with lower extremity PAD.[56]

In patients with established heart failure (HF), ischemic and non-ischemic in origin, several analyses have identified an inverse relationship between cholesterol levels and CV outcome with a cutoff for total cholesterol at 190 to 200 mg/dL.[57] The role that low cholesterol, including intrinsic or as a result of antihyperlipidemic therapy, plays in HF outcomes is unclear. Two large, prospective, randomized trials revealed that statin treatment does not result in significant clinical benefit in patients with HF of either ischemic or nonischemic origin. Therefore, in their 2016 Scientific Statement on management of chronic HF, the AHA advises that the routine use of statins to treat HF of any type is not indicated beyond the current practice guidelines for the primary and secondary prevention of ASCVD. In their 2018 guidelines, ACC/AHA states moderate-intensity statin therapy may be considered to reduce the occurrence of ASCVD events in patients with HF with reduced ejection fraction attributed to ischemic heart disease who have a life expectancy of about 3 to 5 years.[58]

ACC/AHA classifies the intensity of statin therapy based on the average expected LDL-C response to a specific statin and dose.[59,60] Generally, high-intensity statin therapy on average lowers LDL-C by ≥ 50%, moderate-intensity therapy lowers LDL-C by 30% to < 50%, and lower-intensity statin therapy lowers LDL-C by < 30%. High-intensity statin therapy includes daily doses of atorvastatin 40 mg and 80 mg and rosuvastatin 20 mg and 40 mg, while moderate-intensity therapy includes daily doses of atorvastatin 10 mg and 20 mg, rosuvastatin 5 mg and 10 mg, simvastatin 20 mg to 40 mg, pravastatin 40 mg and 80 mg, lovastatin 40 mg, fluvastatin 80 mg, and pitavastatin 2 mg to 4 mg. All remaining lower dosages are classified as lower-intensity therapy.

For primary prevention of ASCVD in patients ages 40 to 75 years with LDL-C 70 to 189 mg/dL, lifestyle management alone is advised in those with low ASCVD risk (10-year risk < 5%).[61] For patients with borderline risk (10-year risk of 5% to < 7.5%), moderate-intensity statin therapy may be added if risk enhancers are present. Moderate-intensity statin therapy is recommended in patients with intermediate risk (10-year risk ≥ 7.5% to < 20%) and as initial therapy in diabetic patients (regardless of ASCVD risk). High-intensity statin therapy is recommended in high-risk (10-year risk ≥ 20%) patients and diabetic adults with multiple risk factors.

For secondary prevention in patients with clinical ASCVD, the ACC/AHA recommends high-intensity statin therapy for patients age 75 years or younger; moderate-intensity statin therapy can be used in patients in this population who are not candidates for high-intensity therapy.[62] In patients 75 years or older with clinical ASCVD, moderate- or high-intensity statin therapy may be considered after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and preferences. The addition of ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9) inhibitors to statin therapy is generally limited to secondary prevention in patients at very high-risk of new ASCVD events not controlled on maximally tolerated statin therapy alone.

The 2014 AHA primary prevention of stroke guidelines and the 2016 AHA scientific statement for stroke prevention with silent cerebrovascular disease support the use of the 2013 ACC/AHA cardiovascular risk calculator to identify individuals who could benefit from therapeutic intervention and the 2013 ACC/AHA blood cholesterol guidelines rather than the NCEP ATP III guidelines.[63] ACC/AHA recommends statin therapy for primary prevention in patients with a high 10-year risk of a CV event.

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 cardiovascular disease.[64] AACE/ACE recommends aggressive lipid-modifying therapy to lower LDL-C with statins as the drugs of choice for LDL-C reduction. They recommend LDL goals of < 55 mg/dL, < 70 mg/dL, < 100 mg/dL, and < 130 mg/dL for individuals at extreme, very high, high/moderate, and low risk for cardiovascular events, respectively. AACE supports the use of apolipoprotein B (apo B) or LDL particles, lipoprotein a (Lp[a]), and high-sensitivity C reactive protein (hsCRP) for evaluating lipid status, depending on individualized patient factors.[65] The MERCURY II trial demonstrated that aggressive LDL-C reduction in CHD patients can also reach targets for recommended apolipoprotein B (apo B) levels.[66] Patients appropriate for aggressive therapy are those undergoing coronary artery bypass graft (CABG) or with acute coronary syndrome (ACS).[67] These guidelines address the unique challenges associated with atherosclerosis and heart disease in women and recommend pharmacotherapy, preferably with a

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statin, for all women at high risk regardless of LDL-C level and for those at intermediate risk with LDL-C > 130 mg/dL.

AACE/ACE also includes guidance for lipid screening in the pediatric populations and recommend screening children who are at risk for familial hypercholesterolemia (FH) at ages > 3 years, again at ages 9 to 11 years, and again at age 18. For those > 16 years of age with ASCVD risk factors, should be evaluated every 5 years. 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 incorporate new data not available at the time of the 2017 guidelines.[68] AACE/ACE maintains statins as primary therapy and their 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. Treatment goals, based on ASCVD risk, are described in the following table.

AACE/ACE Treatment Goals[69]

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 recommended	< 150

In November 2016, The US Preventive Services Task Force (USPSTF) published final recommendations on the use of statins for primary prevention of CVD in adults.[70] USPSTF recommends a low- to moderate-dose statin for the prevention of CVD events and mortality in adults ages 40 to 75 years with

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no history of CVD, ≥ 1 CVD risk factor, and a 10-year calculated CVD event risk of ≥ 10% (Grade B). Since the likelihood of benefit is smaller, USPSTF states that clinicians may consider a low- to moderate-dose statin in adults ages 40 to 75 years with no history of CVD, ≥ 1 CVD risk factor, and a 10-year calculated CVD event risk of 7.5% to 10% (Grade C). There is insufficient evidence to assess adequately the risk versus benefits of statin use in older adults (≥ 76 years of age) without CVD history (Grade I). The USPSTF is in the process of updating these recommendations.[71]

In 2014 and 2015, the National Lipid Association (NLA) published Parts 1 and 2 of their new recommendations for patient-centered management of dyslipidemia.[72,73] They emphasize lifestyle therapies as an important aspect of ASCVD risk-reduction and provide specific advice for changes in diet and physical activity required for cardiovascular health. Atherosclerosis develops over decades often beginning in childhood. Targeted lipid screening based on family history should begin at 2 years of age, while universal screening is appropriate at ages 9 to 11 years and repeated at age 20 years. The NLA recommends lipid levels be used in conjunction with other ASCVD risk factors to assess overall risk and also support the use of risk calculators, such as the ATP III Framingham Risk Score and the ACC/AHA Pooled Cohort Equations. Even relatively small differences in cholesterol levels have an important impact on ASCVD risk if maintained over time. The NLA considers non-high density lipoprotein cholesterol (non-HDL-C) to be superior to LDL-C for predicting ASCVD event risk because non-HDL-C is more correlated with apolipoprotein B (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 very low density lipoprotein cholesterol (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 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 statin therapy, 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 cholesterol goals and adherence to therapy with patients at each visit to identify barriers or side effects; an interdisciplinary team approach should be used whenever possible. Statins remain the drug therapy of choice for those with increased cardiovascular risk conditions, including human immunodeficiency virus (HIV) infection 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.

The American Academy of Pediatrics (AAP) endorsed the 2012 guidelines by the NHLBI on CV health and risk reduction in children and adolescents that outline age appropriate lipid screening in the pediatric population.[74] NHLBI recommends a fasting lipid profile in children aged 1 to 4 years, only if

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the child is positive for FH, 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 of CVD. The guideline also identifies age-specific strategies to reduce risk factors and manage CVD in children and adolescents. Most children with high cholesterol would be referred to lifestyle modifications including diet and physical activity. Less than 1% of children, primarily those with genetic dyslipidemias, would qualify for cholesterol-lowering medications. In addition to lifestyle interventions, the use of lipid-lowering medications is recommended in general in ages 10 years and older 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 ≥ 130 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 2016, the AHA published the first scientific statement on acute MI in women.[75] They emphasized that differences in underlying causes and symptoms often lead to missed diagnoses and undertreatment. Women are more likely to have atypical symptoms (e.g., nausea, vomiting, dyspnea, indigestion, palpitations, diaphoresis, weakness, anxiety, and upper back, neck or jaw pain); shoulder and arm pain are more predictive of an ACS diagnosis for women than for men. Women are less likely to be referred for appropriate treatment during an acute MI and suffer worse outcomes than men. In addition, women with non-obstructive CAD and MI are less likely to be prescribed medications for secondary prevention of MI. Although, these gender differences exist, AHA recommends the same pharmacologic management in women and men with non-ST-elevated myocardial infarction (NSTEMI), including statins.

A 2011 familial hypercholesterolemia consensus statement from the NLA calls for awareness and provides recommendations for screening, diagnosis, and treatment of FH in pediatrics and adults.[76] The clinical guidance recommends universal screening for all pediatric patients ages 9 to 11 years old. Screening is also recommended in patients beginning at age 2 years, in the presence of a family history of premature CVD or highly elevated cholesterol levels. In adults, universal screening is recommended by age 20 years. Drug therapy in both pediatrics and adults is recommended if LDL-C ≥ 190 mg/dL or non-HDL-C ≥ 220 mg/dL, after diet and lifestyle modification (maximum of 3 months). High-dose statin therapy is recommended as first-line for cardiovascular prevention in FH, with the goal of reducing LDL cholesterol by 50%. In adults, even more aggressive treatment goals (e.g., LDL-C goal < 100 mg/dL), is an option for higher-risk patients (e.g., clinically evident coronary disease, diabetes, family history of premature CV disease, or current smokers). Patients treated with a statin who achieved a 50% reduction in LDL-C but whose LDL-C levels remain above 160 mg/dL may need other agents (e.g., ezetimibe [Zetia®], niacin ER [Niaspan®], or bile-acid sequestrants). However, since cardiovascular-disease-prevention outcomes studies are lacking with these agents when used in combination with statins, high-dose statins are preferred to combination therapy. The potential risks of high-dose statin therapy should be weighed against their potential benefit. The NLA FH consensus statement was supported by an unrestricted grant funding from manufacturers.

In 2012, the National Heart, Lung and Blood Institute (NHLBI) published guidelines on cardiovascular health and risk reduction in children and adolescents in which they outline age appropriate lipid

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screening in the pediatric population.[77] 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; earlier repeat (12 to 17 years) should be performed if new diagnosis of FH+, dyslipidemia in a parent, or other risk factors or high-risk condition in the child. It is anticipated that a universal screening will more accurately identify children who are at high risk of cardiovascular disease. NHLBI recommends a fasting lipid profile in children age 1 to 8 years, only if the child is familial hypercholesterolemia positive (FH+), the child has a parent with dyslipidemia, or if the child has any other risk factors or high-risk condition. The guideline also identifies age-specific strategies to reduce risk factors and manage cardiovascular disease in children and adolescents. Most children with high cholesterol would be referred to lifestyle modifications including diet and physical activity. Less than 1% of children, primarily those with genetic dyslipidemias, would qualify for cholesterol-lowering medications.

In the 2015 Agenda for Familial Hypercholesterolemia, the AHA advises that FH treatment is based on LDL-C levels, not genetic abnormality or other clinical features.[78] Early treatment is critical because atherosclerosis begins early in life. Aggressive pharmacological treatment for affected individuals is recommended beginning at 8 to 10 years of age; younger children should be treated only if extreme LDL-C elevation or other major risk factors suggesting premature cardiovascular disease are present. Long-term follow-up of adolescents started on statins suggests excellent safety and much lower event rates than for their affected parents. In adults, initial goal in LDL-C reduction by at least 50%. This can be followed by achieving an LDL-C of < 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. In contrast, there are no data to recommend treatment goals in pediatric patients, whether to target an LDL-C level of <100 or 130 mg/dL or to aim to achieve a 50% reduction in LDL-C from baseline. Initial drug monotherapy for those with FH includes high-intensity statin therapy (rosuvastatin or atorvastatin). If LDL-C goal is not met with 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 proprotein convertase subtilisin/kexin type 9 (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, a reduction in cardiovascular and all-cause mortality has been 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 or mipomersen can be considered in patients with HoFH if needed. Dietary and lifestyle modifications should also be an aspect of FH treatment.

Many have questioned which patients with normal LDL-C levels would benefit most from statins' cardio-protective effects. The JUPITER trial reported that patients with a high C - reactive protein (CRP) level, a marker for circulating inflammatory cytokines, benefited from statin therapy.[79] The NHLBI-sponsored Multi-Ethnic Study on Atherosclerosis (MESA) study is investigating buildup of measurable artery-hardening calcium and statin therapy outcomes, in patients who met the same criteria as the JUPITER study.[80] Coronary heart disease and cardiovascular disease event rates and multivariable-adjusted hazard ratios were compared in 950 participants from the MESA study that met all criteria for entry into the JUPITER trial.[81] Coronary artery calcium (CAC) scores were stratified by scores of 0, 1 to

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100, and >100. Median follow-up was 5.8 years. Of the patients (47%) in the MESA JUPITER population that had CAC scores of 0, rates of coronary heart disease events were 0.8 per 1,000 person-years. Seventy-four percent of all coronary events were in the 239 (25%) of participants with CAC scores of > 100 (20.2 per 1,000 person-years). In the total study population, presence of CAC was associated with a hazard ratio of 4.29 (95% confidence interval [CI], 1.99 to 9.25) for coronary heart disease, and of 2.57 (95% CI, 1.48 to 4.48) for cardiovascular disease. High-sensitivity C-reactive protein (hsCRP) was not associated with either disease after multivariable adjustment. The authors concluded that CAC seems to further stratify risk in patients eligible for JUPITER, and could be used to target subgroups of patients who are expected to derive the most, and the least, absolute benefit from statin treatment.

In their 2020 Standards of Medical Care in Diabetes, the American Diabetes Association (ADA) states that it is reasonable to obtain a lipid profile at initiation of statins 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.[82] The ADA recommends moderate- or high-intensity statin therapy in patients with diabetes based on patient age and presence of ASCVD or 10-year ASCVD risk factors. For diabetic patients 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%. 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 PCSK9 inhibitor, can be considered. The ADA recommends against the addition of niacin or a fibrate 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, combination use of a statin plus niacin may increase the risk for stroke. Based on data from the REDUCE-IT and DECLARE-TIMI 58 trials, 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 for primary and secondary prevention.

The 2020 type 2 diabetes management algorithm by the AACE/ACE advise early and intensive management of dyslipidemia in patients with type 2 diabetes mellitus to decrease the risk for ASCVD.[83] 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. Other lipid-modifying agents can be added to maximally-tolerated statin therapy.

In April 2016, the FDA announced withdrawal of approval for indications related to coadministration of niacin ER with a statin.[84] The FDA stated that available evidence no longer supports that a decrease in TG levels and/or increase in HDL-C levels by these agents in statin-treated patients results in a risk reduction in CV events. The FDA has requested that manufacturers stop marketing niacin ER for these indications.

PHARMACOLOGY[85,86,87,88,89,90,91,92,93,94,95,96,97]

Statins competitively inhibit HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, which is an early rate-limiting step in cholesterol biosynthesis. The inhibition of cholesterol biosynthesis reduces cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and increases the uptake of circulating LDL particles. Additionally, the statins work to reduce LDL-C production by inhibiting the synthesis of very low density lipoprotein (VLDL-C), the LDL-C

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precursor. HMG-CoA reductase inhibitors decrease LDL-C, VLDL-C, triglycerides (TG), and increase high density lipoprotein cholesterol (HDL-C). Marked response usually occurs within 2 weeks with maximum response occurring within 4 to 6 weeks. In early studies with some agents, daily doses given in the evening were more effective than when given in the morning, perhaps because cholesterol is synthesized mainly at night.[98,99]

Other beneficial effects of the statins in reducing the risk of cardiovascular events may be through an independent anti-inflammatory effect unrelated to LDL-C reduction. Reduction in C-reactive protein (CRP) levels may lead to a decrease in cardiovascular event risk.[100,101] The REVERSAL trial investigators found that a reduction in LDL-C and CRP leads to a slowing in progression of atherosclerosis.[102] The PROVE IT-TIMI 22 investigators published findings indicating that lower CRP levels (< 2 mg/L) are associated with improvement in cardiovascular event-free survival.[103] The correlation among CRP levels, LDL-C reduction, and cardiovascular disease requires further investigation.

Several combination products have been marketed. Amlodipine/atorvastatin (Caduet) is designed to treat 2 indications – hypertension and hyperlipidemia – which are often seen in the coronary heart disease (CHD) patient. Ezetimibe/simvastatin (Vytorin) is a combination of two lipid-lowering therapies which work together to lower LDL-C.

Amlodipine (Norvasc®, Caduet) inhibits calcium ions from moving across the cell membrane. The limitation of calcium entering into the cells causes a decrease in mechanical contraction of myocardial and smooth muscle, thereby causing dilation of systemic arteries and a decrease in total peripheral resistance, systemic blood pressure, and the afterload of the heart. The reduction in afterload, which results in a decrease in myocardial oxygen consumption, is thought to attenuate the signs and symptoms of angina.[104] Amlodipine given with atorvastatin (Caduet) in a single tablet treats both hypertension and hypercholesterolemia for patients in whom calcium channel blocker therapy and lipid lowering therapy are desired.

Ezetimibe (Zetia, Vytorin) inhibits cholesterol absorption along the brush border of the small intestine. This leads to a decrease in the delivery of intestinal cholesterol to the liver, reduction of hepatic cholesterol stores, and an increase in cholesterol clearance from the blood. Ezetimibe inhibits absorption of both dietary cholesterol and cholesterol in bile. Ultimately, ezetimibe reduces total cholesterol (total-C), LDL-C, TG, apolipoprotein B, and increases HDL-C in patients with hypercholesterolemia. When ezetimibe is administered with a statin, further reductions in the lipid profile occur.

PHARMACOKINETICS[105,106,107,108,109,110,111,112,113,114,115,116,117,118,119]

Drug	Bioavailability	Time to Peak Plasma Levels (hr)	Half-life (hr)	Excretion (%)	Circulating active metabolites
amlodipine and atorvastatin (Caduet)	64–90% ~14%; first pass metabolism	6–12 1–2	30–50 14	Urine: 70 Urine: < 2	No Yes
atorvastatin (Lipitor)	~14%; first pass metabolism	1–2	14	Urine: < 2	Yes
ezetimibe and simvastatin (Vytorin)	-- < 5% of oral dose reaches general circulation; first pass metabolism	4–12 4	22 3	Urine: 11 Feces: 78 Urine: 13 Feces: 60	Yes Yes
fluvastatin (Lescol XL)	24%; first pass metabolism 29%; first pass metabolism	< 1 3	3 9	Urine: 5 Feces: 90	No
lovastatin	< 5% of oral dose reaches general circulation; first pass metabolism	2–4	--	Urine: 10 Feces: 83	Yes
lovastatin ER (Altoprev)	< 5% of oral dose reaches general circulation; first pass metabolism	14.2	--	Urine: 10 Feces: 83	Yes
pitavastatin (Livalo, Zypitamag*)	51%	1	12	Urine: 15 Feces: 79	Yes
pravastatin (Pravachol)	17%; first pass metabolism	1–1.5	77	Urine: 20 Feces: 70	Yes
rosuvastatin (Crestor, Ezallor Sprinkle†)	20%	3–5	19	Feces: 90	Yes
simvastatin (Flolipid)	< 5% of oral dose reaches general circulation; first pass metabolism	4	3	Urine: 13 Feces: 60	Yes
simvastatin (Zocor)	< 5% of oral dose reaches general circulation; first pass metabolism	4	3	Urine: 13 Feces: 60	Yes

Atorvastatin and amlodipine (Caduet) and ezetimibe and simvastatin (Vytorin), pharmacokinetic profiles are not affected by concurrent administration of the individual components.[120]

*Each film-coated tablet of Zypitamag contains 1.026 mg, 2.053 mg, or 4.106 mg of pitavastatin magnesium, which is equivalent to 1 mg, 2 mg, or 4 mg, respectively, of pitavastatin free base.

† Each capsule of Ezallor Sprinkle contains 5.198 mg, 10.395 mg, 20.79 mg, or 41.58 mg of rosuvastatin calcium, which is equivalent to 5 mg, 10 mg, 20 mg, or 40 mg, respectively, of rosuvastatin free base.

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CONTRAINDICATIONS/WARNINGS[121,122,123,124,125,126,127,128,129,130,131,132,133]

All statin-containing products are contraindicated in pregnant or nursing women.

Patients with active liver disease, with or without unexplained transaminase elevations are not appropriate candidates for statin therapy. There have been rare post-marketing reports of fatal and non-fatal hepatic failure in patients taking statins. If serious symptomatic liver injury and/or hyperbilirubinemia occur, statin therapy should be stopped immediately. Do not restart unless an alternate etiology is found.

Skeletal muscle abnormalities related to statin usage range from mild myalgia to myopathy. Myopathy is defined as muscle symptoms including muscle pain, tenderness, or weakness plus the elevation of creatine kinase (CK) above 10 times the upper limit of normal (ULN). Rhabdomyolysis is the presence of myopathy and the elevation of creatinine and often myoglobinuria. While myalgias are common with statin use, myopathy and/or rhabdomyolysis are a rare, yet serious concern.[134] The mechanism by which the statins cause myopathy and rhabdomyolysis is unknown.[135,136,137]

All statins carry a potential risk of myopathy and/or rhabdomyolysis. In 2011, the FDA notified healthcare professionals and patients of new safety recommendations for the highest approved dose (80 mg) of simvastatin based on a review of data from a large clinical trial called Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) and other sources, that there is an increased risk of muscle injury compared to patients taking lower simvastatin doses or other statin drugs.[138] Due to this increased risk of myopathy, including rhabdomyolysis, the 80 mg dose of simvastatin must be reserved for patients who have been on this dose chronically (e.g., ≥ 12 months) without evidence of muscle toxicity. If, however, a patient who is currently tolerating the 80 mg dose of simvastatin needs to be started on a drug with a contraindication of concurrent use or dose limitation with simvastatin, the patient should be switched to an alternative statin with less potential for the drug-drug interaction. All statins have a warning in the prescribing information stating that myopathy and rhabdomyolysis have been reported with statin use. There is increased risk of myopathy and rhabdomyolysis associated with statin therapy in the following cases: advanced age (especially > 65 years), perioperative periods, multiple medications, multiple chronic disease states, including uncontrolled hypothyroidism and renal impairment, drug interactions, high statin dose, and concurrent therapy with fibrates and/or higher dose niacin.[139,140,141] Chinese patients taking simvastatin may be at increased risk for myopathy. Drug interactions with CYP3A4 inhibitors and concurrent therapy with fibric acid derivatives may increase the risk of rhabdomyolysis. Consult the individual prescribing information for specific contraindications, drug interactions, and dose reductions. The concomitant use of statins and cyclosporine may increase the risk of myopathy/rhabdomyolysis. Co-administration of pitavastatin (Livalo, Zypitamag) or ezetimibe/simvastatin (Vytorin) with cyclosporine is contraindicated.[142] Additionally, atorvastatin (Caduet, Lipitor) should be avoided in patients on cyclosporine and other agents, such as tipranavir plus ritonavir, glecaprevir plus pibrentasvir, and letermovir, when co-administered with cyclosporine.[143,144] Dose reductions are recommended for certain statins when used concurrently with cyclosporine. Pitavastatin (Livalo, Zypitamag) has not been studied with the protease inhibitor combination lopinavir/ritonavir so should not be used concurrently.

Labeling for all statins has been updated to include a warning or precaution for immune-mediated necrotizing myopathy (IMNM). Statin use has been associated with rare reports of this autoimmune

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myopathy. This condition is characterized by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin therapy; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents.

Additional information on drugs contraindicated with simvastatin and lovastatin may be found under the following section on Drug Interactions.

DRUG INTERACTIONS[145,146,147,148,149,150,151,152,153,154,155,156,157]

Drug-drug interactions that have been reported to cause an increase in statin exposure may be associated with an increased risk of myopathy.

Concomitant use of lovastatin or simvastatin (Vytorin, Flolipid, Zocor) with cobicistat-containing drugs is contraindicated due to the potential for myopathy, including rhabdomyolysis. Lovastatin and simvastatin are substrates for CYP3A4, CYP2D6, and the drug transporter P-gp. Cobicistat is an inhibitor of both enzymes and P-gp. Coadministration is expected to significantly increase simvastatin plasma concentrations.

P450 Enzymes

Many of the currently available statins are extensively metabolized by the CYP450 3A4 isoenzyme system. Those that are not metabolized by CYP3A4 include: fluvastatin (Lescol XL), pitavastatin (Livalo, Zypitamag), pravastatin, and rosuvastatin (Crestor, Ezallor Sprinkle).

Concomitant administration with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, select HIV protease inhibitors, select hepatitis C virus (HCV) protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone) is contraindicated with lovastatin (Altoprev) and simvastatin (Vytorin, Flolipid, Zocor) containing products.

Atorvastatin also interacts with CYP3A4 inhibitors but to a lesser degree, as it undergoes less first-pass metabolism.[158] Exposure to atorvastatin is significantly increased by various combinations of HIV protease inhibitors. Atorvastatin use should be avoided with the HIV protease inhibitors tipranavir plus ritonavir and the HCV protease inhibitors glecaprevir plus pibrentasvir. Atorvastatin should be used with caution with the HIV protease inhibitors lopinavir plus ritonavir, or simeprevir, and at the lowest dose necessary. Caution should also be used in patients taking clarithromycin, itraconazole, the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, or the HCV protease inhibitors elbasvir plus grazoprevir and the dose of atorvastatin should not exceed 20 mg. The dose of atorvastatin should not exceed 40 mg daily if coadministered with nelfinavir.

Limit pravastatin to 40 mg once daily with concurrent clarithromycin use.

Do not exceed fluvastatin 20 mg twice daily with concurrent fluconazole use.

Fluvastatin is primarily metabolized by CYP2C9 so its levels may be increased by CYP2C9 inhibitors, but there appear to be less drug interactions. Pitavastatin, pravastatin, and rosuvastatin are not metabolized by the CYP450 enzymes to a clinically significant extent.

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Rosuvastatin dose should be 10 mg daily if given concomitantly with lopinavir/ritonavir, atazanavir/ritonavir, or simeprevir. Pitavastatin should not be administered with lopinavir/ritonavir.

Rifampin, a CYP3A4 inducer, may significantly increase pitavastatin exposure; therefore, the dose of pitavastatin should be adjusted in patients taking rifampin. Due to the dual interaction mechanism of rifampin, simultaneous administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

Cardiovascular Agents

In studies when atorvastatin or pravastatin and digoxin were coadministered, steady state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately. Studies have shown small increases in digoxin exposure with concomitant use of simvastatin or immediate-release fluvastatin, and small decrease in digoxin levels with pitavastatin and rosuvastatin. Concomitant administration of lovastatin and digoxin has no effect on digoxin plasma concentrations.

Simvastatin dose should be limited to 20 mg daily when given concurrently with amiodarone, amlodipine, or ranolazine. Dose adjustment of lovastatin may be considered during coadministration with ranolazine.

It is also recommended that lovastatin doses should not exceed 20 mg with diltiazem or verapamil, or 40 mg with amiodarone.

Simvastatin and rosuvastatin can increase the international normalization ratio (INR) in patients receiving coumarin anticoagulants. In patients taking these medications concomitantly, INR should be determined prior to starting simvastatin or rosuvastatin and then monitored appropriately.

Colchicine

Caution should be used when prescribing atorvastatin, fluvastatin, lovastatin, pravastatin, pitavastatin, rosuvastatin, and simvastatin concurrently with colchicine.

Cyclosporine

Cyclosporine coadministration can increase statin exposure.

Concurrent use of simvastatin and pitavastatin containing products is contraindicated in patients on cyclosporine. Lovastatin and atorvastatin should be avoided in these patients. Rosuvastatin dose should be limited to 5 mg once daily; and pravastatin to 20 mg once daily; and fluvastatin to 20 mg twice daily, if given in combination with cyclosporine.

Other Lipid-lowering Agents

Concurrent use of simvastatin and pitavastatin containing products is contraindicated in patients on gemfibrozil. Use of atorvastatin, fluvastatin, lovastatin, pravastatin, and rosuvastatin should be avoided in patients on gemfibrozil. If used, the dose of rosuvastatin should not exceed 10 mg daily when given concurrently with gemfibrozil.

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All statins should be administered with caution if given concurrently with other fibrates or lipid-lowering doses (≥ 1 g/day) of niacin. A dose reduction of atorvastatin, fluvastatin, pitavastatin, and pravastatin should be considered with concurrent niacin use.

Miscellaneous

Simvastatin is contraindicated with concurrent use of danazol. Lovastatin doses should not exceed 20 mg with danazol use.

Ingestion of large quantities (> 1 quart/day) of grapefruit juice should be avoided with atorvastatin, lovastatin, and simvastatin.

Coadministration of atorvastatin and an oral contraceptive may increase exposure of norethindrone and ethinyl estradiol and should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Concomitant administration of fluvastatin and glyburide can increase glyburide exposure. Monitor blood glucose levels when fluvastatin dose is changed.

In vitro studies have demonstrated that voriconazole inhibits the metabolism of lovastatin. Adjustment of the lovastatin dose may be needed to reduce the risk of myopathy, including rhabdomyolysis, if voriconazole must be used concomitantly with lovastatin.

Atorvastatin, rosuvastatin, and simvastatin are substrates for certain transporter proteins, including the hepatic uptake transporter organic anion-transporting (OATP1B1, OATP1B3). Concomitant use of atorvastatin and rosuvastatin with drugs that are inhibitors of these transporter proteins, such as cyclosporine and certain HIV protease inhibitors, may result in increased statin plasma concentrations and increased risk of toxicity. Atorvastatin when given concomitantly with letermovir should not exceed a dosage of 20 mg, and use is not recommended if given with letermovir plus cyclosporine. Atorvastatin and rosuvastatin are also a substrate for efflux transporter breast cancer resistance protein (BCRP). Concomitant use of atorvastatin or rosuvastatin with drugs that are inhibitors of BCRP may result in increased exposure to the statin.

Rhabdomyolysis has been reported with co-administration of simvastatin (Zocor, Vytorin) and daptomycin. Each product increases the risk of myopathy and rhabdomyolysis when given alone, and this risk is increased with coadministration. Simvastatin-containing therapy should be interrupted if daptomycin is prescribed.

For complete drug-drug interaction information, see individual package inserts.

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Select Drug Interactions

Drug	amiodarone	cyclosporine	diltiazem	erythromycin	gemfibrozil (fibric acid derivatives)	HIV protease inhibitors	itraconazole (azole antifungals)	nefazodone	niacin	verapamil	warfarin
amlodipine/ atorvastatin (Caduet), atorvastatin (Lipitor)	--	X	X	X	X	X	X	--	X	--	--
ezetimibe / simvastatin (Vytorin)	X	X	X	X	X	X	X	X	X	X	X
fluvastatin, fluvastatin XL (Lescol XL)	--	--	--	--	--	--	--	--	--	--	--
lovastatin, lovastatin ER (Altoprev)	X	X	--	X	X	X	X	X	--	X	--
pitavastatin (Livalo, Zypitamag)	--	X	--	X	X	X	X	--	X	--	--
pravastatin (Pravachol)	--	--	--	--	X	--	--	--	--	--	--
rosuvastatin (Crestor)	--	X	--	--	X	X	--	--	X	--	X
simvastatin (Flolipid)	X	X	X	X	X	X	X	X	X	X	X
simvastatin (Zocor)	X	X	X	X	X	X	X	X	X	X	X

X = drug-drug interaction has been reported

The combination of amlodipine and atorvastatin (Caduet) has not been studied for drug interactions, although studies have been conducted for the individual components. Co-administration with moderate and strong CYP3A inhibitors may increase systemic exposure to amlodipine and may require dose reduction. In addition, amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when coadministered, drug levels of the immunosuppressant agent should be monitored.

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ADVERSE EFFECTS[159,160,161,162,163,164,165,166,167,168,169,170,171]

Drug	Myalgia	Abd Pain	Diarrhea	Dyspepsia	Nausea	Rash	Headache	Fatigue or Malaise
atorvastatin (Lipitor)	5.6 (1.1)	0–3.8 (0.7)	0–3.8 (1.5)	1.3–2.8 (4.1)	reported	1.1–3.9 (0.7)	2.5–16.7 (7)	reported
ezetimibe / simvastatin (Vytorin)	3.6 (2.3)	reported	reported	reported	reported	reported	6.8 (6.4)	reported
fluvastatin	5 (4.5)	4.9 (3.8)	4.9 (4.2)	7.9 (3.2)	3.2 (2)	reported	8.9 (7.8)	2.7 (2.3)
fluvastatin XL (Lescol XL)	3.8 (4.5)	3.7 (3.8)	3.3 (4.2)	3.5 (3.2)	2.5 (2)	reported	4.7 (7.8)	1.6 (2.3)
lovastatin	1.8-3 (1.7)	2–2.5 (1.6)	2.2–2.6 (2.3)	1–1.6 (1.9)	1.9–2.5 (2.5)	0.8–1.3 (0.7)	2.1–3.2 (2.7)	reported
lovastatin ER (Altoprev)	3	reported	3	reported	reported	reported	7	reported
pitavastatin (Livalo, Zypitamag)	1.9–3.1 (1.4)	nr	1.5–2.6 (1.9)	nr	nr	reported	reported	nr
pravastatin (Pravachol)	0.6–2.7 (0–1)	2–5.4 (3.9–6.9)	2–6.2 (1.9–5.6)	2–2.9 (0.7–1.9)	2.9–7.3 (3.4–7.1)	1.3–3.4 (0.9–1.1)	1.7–6.2 (0.2–3.9)	1.9–3.8 (1–3.4)
rosuvastatin (Crestor, Ezallor Sprinkle)	1.9–12.7 (1.3–12.1)	2.4 (1.8)	nr	nr	2.4–6.3 (2.3–3.1)	reported	3.1–8.5 (5–5.3)	nr
simvastatin (Flolipid)	3.7 (3.2)	3.2 (3.2)	1.9 (2.5)	1.1	1.3 (1.9)	0.6 (0.6)	0.7	reported
simvastatin (Zocor)	3.7 (3.2)	3.2 (3.2)	1.9 (2.5)	1.1	1.3 (1.9)	0.6 (0.6)	0.7	reported

nr = not reported. 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.

In clinical trials, atorvastatin (Lipitor), fluvastatin (Lescol XL), pravastatin, and simvastatin were rarely (< 2%) discontinued due to adverse effects. Rosuvastatin (Crestor, Ezallor Sprinkle) was discontinued in 1.4% of patients in clinical trials. Pitavastatin (Livalo) was discontinued in 3.6% of patients in clinical trials. Lovastatin was discontinued in 4.6% of patients in trials.

In clinical trials for atorvastatin/amlodipine (Caduet), adverse events were mostly mild or moderate in severity with no unusual adverse events reported. The combination tablet is not expected to have more adverse effects than single entity administration.

Adverse events for ezetimibe/simvastatin were assessed during a clinical trial extension phase. Ezetimibe/simvastatin and simvastatin monotherapy groups generally had a similar incidence of all clinical adverse events (73% versus 69%), treatment-related adverse events (14% versus 11%), clinical serious adverse events (5.2% versus 2.6%), treatment-related serious adverse events (0.2% versus 0%), discontinuations due to all clinical adverse events (4.5% versus 2.6%), and discontinuations due to treatment-related adverse events (2.8% versus 2.2%), respectively.

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Arthralgia, fatal and non-fatal hepatic failure, hepatitis, jaundice, depression, and sleep disorders have been identified during post approval use of rosuvastatin (Crestor, Ezallor Sprinkle). Since these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Use of voluntarily reported cases without assessment of causality is not a proper method to assess the rate of an adverse events associated with a drug. Due to the heightened awareness of serious adverse events following the removal of cerivastatin (Baycol®) from the US market in 2001, there is likely reporting bias with rosuvastatin as it entered the US market in 2003. In summary, the occurrence of serious adverse events such as myopathy and rhabdomyolysis are extremely rare with all statins including rosuvastatin.[172,173,174,175,176]

Several meta-analyses and systematic reviews have evaluated statin use and the overall risk of cancer.[177,178,179,180,181] There is no convincing evidence that statins increase or decrease the incidence of cancer.

The Simvastatin and Ezetimibe in Aortic Stenosis Study (SEAS) found an increase in various types of cancer and deaths in patients taking simvastatin/ezetimibe. [182,183,184] An interim analysis of the ongoing CV trials with simvastatin/ezetimibe (Vytorin), SHARP and IMPROVE-IT, did not show a significant increase in cancer (p=0.61).[185] Based on review of SEAS and interim data from IMPROVE-IT and SHARP, the FDA believes it is unlikely that simvastatin/ezetimibe (Vytorin) or ezetimibe (Zetia) increase the risk of cancer or cancer-related death.[186,187,188] Final analysis of SHARP and IMPROVE-IT was consistent with the interim results, reporting no increase in cancer risk.[189,190]

FDA's review of the 7-year SEARCH trial revealed that more patients in the high dose simvastatin arm developed myopathy versus patients in the simvastatin 20 mg arm (52 [0.9%] cases compared to 1 case [0.02%]).[191] Twenty-two patients (0.4%) in the 80 mg group versus 0 patients in the 20 mg group developed rhabdomyolysis. There were no fatalities related to rhabdomyolysis. The risks for myopathy and rhabdomyolysis with simvastatin 80 mg were highest in the first 12 months of treatment, 5 per 1,000 person-years, and 2 per 1,000 person-years, respectively, and decreased to 1 per 1,000 person-years and 0.4 per 1,000 person-years after that.

In clinical studies, the safety profile of pitavastatin (Livalo) in pediatric patients 8 to 16 years of age was similar to that observed in the adult population.

Increases in Glycosylated Hemoglobin (HbA1c,) Fasting Plasma Glucose, and Diabetes Mellitus

Hyperglycemia has been reported with statins.[192] The risk of statin-induced newly diagnosed diabetes mellitus is approximately 0.2% per year of treatment, depending on the underlying risk of diabetes mellitus.[193]

The rate of occurrence of new-onset diabetes (NOD) with CV event reduction among patients with coronary disease but without diabetes was evaluated in the Treating to New Targets (TNT; n=7,595) and Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL); n=7,461) trials.[194,195,196] Cardiovascular events included coronary heart disease death, MI, stroke, and resuscitated cardiac arrest. TNT randomized patients to receive atorvastatin 10 mg or 80 mg and patients were followed for an average of 5 years. IDEAL compared atorvastatin 80 mg with simvastatin 40 mg and used a prospective, randomized, open-label, blinded endpoints (PROBE) design. Similar rates of NOD occurred between

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treatment groups in patients with 0 to 1 risk factors for NOD, including fasting blood glucose > 100 mg/dL, fasting triglycerides > 150 mg/dL, body mass index > 30 kg/m^2, and history of hypertension. Among the patients with 2 to 4 NOD risk factors, NOD developed in 14.3% of patients in the atorvastatin 80 mg group and in 11.9% in the lower-dose groups (hazard ratio [HR], 1.24; 95% CI, 1.08 to 1.42; p=0.0027). The ACC/AHA guidelines state that the rate of excess diabetes varies by statin intensity, estimating 0.1 cases per 100 statin-treated individuals per year for moderate-intensity therapy and 0.3 cases per 100 individuals per year for high-intensity therapy.[197,198]

The FDA's review of the results from the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) reported a 27% increase in investigator-reported diabetes mellitus in rosuvastatin-treated patients compared to placebo-treated patients.[199] In an analysis of JUPITER the risk of developing diabetes with statin therapy was limited to patients already at a high risk for developing diabetes (e.g., with impaired fasting glucose, metabolic syndrome, severe obesity, or elevated HbA1c).[200] However, in these high-risk patients as well as the entire study population, the CV benefits of rosuvastatin for primary prevention exceeded the risk of diabetes. High-dose atorvastatin had also been associated with worsening glycemic control in the Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis In Myocardial Infarction 22 (PROVE-IT TIMI 22) substudy.[201]

FDA also reviewed published medical literature. A meta-analysis which included 13 statin trials (n=91,140), reported that statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09; 95% CI, 1.02 to 1.17), with little heterogeneity (I^2=11%) between trials.[202] Another meta-analysis of 6 statin trials (n=57,593) reported a small increase in diabetes risk (relative risk [RR], 1.13; 95% CI, 1.03 to 1.23), with no evidence of heterogeneity across trials. [203] A recent study using data from the Women's Health Initiative, reported that statin use conveys an increased risk of new-onset diabetes in postmenopausal women, and noted that the effect appears to be a medication class effect, unrelated to potency or to individual statin.[204]

Cognitive Adverse Events

The FDA reviewed the Adverse Event Reporting System (AERS) database, the published medical literature (case reports and observational studies), and randomized clinical trials to evaluate the effect of statins on cognition.[205]

Time to onset of the event was highly variable, ranging from one day to years after statin exposure and was reversible upon discontinuation of statin therapy. The review did not reveal an association between the adverse event and the specific statin, the age of the individual, the statin dose, or concomitant medication use.

Labeling of all statins includes rare post-marketing reports of cognitive impairment.

Liver Function/Safety[206,207]

Drug	Marked increases (3X ULN) in serum transaminases (%)
atorvastatin (Lipitor, Caduet)	0.7
ezetimibe / simvastatin (Vytorin)	1.8
fluvastatin	1.1
fluvastatin XL (Lescol XL)	1.9
lovastatin, lovastatin ER (Altoprev)	1.9
pitavastatin (Livalo, Zypitamag)	0 – 0.5
pravastatin (Pravachol)	< 1.2
rosuvastatin (Crestor, Ezallor Sprinkle)	1.1
simvastatin (Flolipid)	1
simvastatin (Zocor)	1

Liver enzyme elevation rates are obtained from product information and clinical trials; therefore, this data should not be considered comparative.

Hepatic failure has been reported during post-marketing experience of some statins and should be considered a class effect.

In February 2012, the FDA removed recommendations for routine monitoring of liver enzymes from all statin drug labels.[208] Based on available data, the FDA has determined that all currently marketed statins appear to be associated with a very low risk of serious liver injury and that routine periodic monitoring of serum alanine aminotransferase (ALT) does not appear to detect or prevent serious liver injury in association with statins. Healthcare professionals should perform liver enzyme tests before initiating statin therapy and as clinically indicated thereafter. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment, therapy should be interrupted. If an alternate etiology is not found, the statin should not be restarted.

SPECIAL POPULATIONS[209,210,211,212,213,214,215,216,217,218,219,220,221]

Pediatrics

Several statins have been approved for use in patients 10 (8 years of age for pravastatin and pitavastatin) to 17 years of age for both boys and girls (at least 1 year post-menarche).

Atorvastatin (Lipitor), fluvastatin (Lescol XL), lovastatin, pitavastatin calcium (Livalo), pravastatin, rosuvastatin tablets (Crestor), and simvastatin have been approved for the adjunctive management of heterozygous familial hypercholesterolemia (HeFH) in addition to diet.[222] Statin therapy for HeFH is generally initiated when the LDL-C levels are ≥ 190 mg/dL or when the LDL-C is ≥ 160 mg/dL in the presence of at least 2 more cardiovascular event risk factors or for the patient with a known family history of premature CHD.[223] The minimum goal of therapy is to achieve LDL-C < 130 mg/dL. Very little data are available for the treatment of HeFH in children < 8 years old.

In 2016 rosuvastatin (Crestor) was FDA approved for treatment of homozygous familial hypercholesterolemia (HoFH) as an adjunct to diet, either alone or with other lipid-lowering agents in pediatric patients 7 to 17 years of age

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Safety and effectiveness of pitavastatin magnesium (Zypitamag), lovastatin ER (Altoprev), rosuvastatin capsules (Ezallor Sprinkle), atorvastatin/amlodipine (Caduet), and ezetimibe/simvastatin (Vytorin) have not been established in pediatric patients.

Pregnancy

All statin-containing products are considered Pregnancy Category X; their use is contraindicated in pregnant women. As the FDA gradually approves updates to the Prescribing Information of agents in this class, labels are updated in alignment with the Pregnancy and Lactation Labeling Rule (PLLR). Due to its approval date, rosuvastatin capsules (Ezallor Sprinkle) was not assigned a Pregnancy Category. Instead its labeling includes descriptive text; like all statins, its use is contraindicated in pregnant women.

Hepatic/Renal Impairment

Statins are contraindicated in patients with active liver disease.

Please refer to the Dosing Consideration section for hepatic and renal considerations.

Race/Ethnicity

Plasma concentrations of pitavastatin are lower (about 21% for Cmax and 5% for AUC) in healthy African-American or African-American subjects compared with healthy Caucasian patients. In pharmacokinetic comparison between Caucasian volunteers and Japanese volunteers, there were no significant differences in Cmax and AUC.

According to the prescribing information for rosuvastatin (Crestor, Ezallor Sprinkle), Asian patients should start on 5 mg daily.[224]

Risk of myopathy is greater in Chinese patients when simvastatin (Zocor, Vytorin) is coadministered with lipid-modifying doses of niacin (≥ 1 g/day). Coadministration is not recommended in this population.

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DOSAGES[225,226,227,228,229,230,231,232,233,234,235,236,237,238]

Drug	Usual Starting Dose	Adult Dosing Range	Pediatric Dosing Range	Approximate Equivalent Dose (based on LDL-C lowering)	Availability
amlodipine/atorvastatin (Caduet)	5 mg/10 mg daily	2.5 mg/10 mg to 10 mg/80 mg daily	--	10 mg daily of atorvastatin	amlodipine/atorvastatin combination tablets: 2.5/10 mg (generic only), 2.5/20 mg (generic only), 2.5/40 mg (generic only), 5/10 mg, 5/20 mg, 5/40 mg, 5/80 mg, 10/10 mg, 10/20 mg, 10/40 mg, 10/80 mg
atorvastatin (Lipitor)	10 mg to 40 mg daily	10–80 mg daily	Ages 10 to 17 years: 10 mg to 20 mg daily	10 mg daily	10 mg, 20 mg, 40 mg, 80 mg tablets
ezetimibe/simvastatin (Vytorin)	10 mg/10 mg to 10 mg/20 mg daily	10 mg/10 mg to 10 mg/40 mg daily	--	10 mg/10 mg daily	ezetimibe/simvastatin combination tablets: 10/10 mg, 10/20 mg, 10/40 mg, 10/80 mg
fluvastatin	20 mg to 40 mg daily	20 mg to 80 mg daily	Ages 10 to 16 years: 20 mg daily to 40 mg twice daily	40 mg twice daily	20 mg, 40 mg capsules
fluvastatin XL (Lescol XL)	80 mg daily	80 mg daily	Ages 10 to 16 years: 80 mg daily	80 mg daily	80 mg tablet
lovastatin	20 mg daily with evening meal	10 mg to 80 mg daily	Ages 10 to 17 years: 10 mg to 40 mg daily	40 mg daily	10 mg, 20 mg, 40 mg tablets
lovastatin ER (Altoprev)	20 mg to 60 mg daily	10 mg to 60 mg daily	--	40 mg daily	20 mg, 40 mg, 60 mg tablets
pitavastatin calcium (Livalo)	2 mg daily	1 mg to 4 mg daily	Ages ≥ 8 years: 2 mg to 4 mg daily	2 mg daily	1 mg, 2 mg, 4 mg tablets
pitavastatin magnesium (Zypitamag)	2 mg daily	1 mg to 4 mg daily	--	2 mg daily	2 mg, 4 mg tablets
pravastatin (Pravachol)	40 mg daily	10 mg to 80 mg daily	Ages 8 to 13 years: 20 mg daily; ages 14 to 18 years: 40 mg daily	40 mg daily	10 mg (generic only), 20 mg, 40 mg, 80 mg (generic only) tablets

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Dosages (continued)

Drug	Usual Starting Dose	Adult Dosing Range	Pediatric Dosing Range	Approximate Equivalent Dose (based on LDL-C lowering)	Availability
rosuvastatin (Crestor)	10 mg to 20 mg daily	5 mg to 40 mg daily	*HeFH* Ages 8 to < 10 years: 5 mg to 10 mg daily; ages 10 to 17 years: 5 mg to 20 mg daily *HoFH* Ages 7 to 17 years: 20 mg daily	5 mg daily	5 mg, 10 mg, 20 mg, 40 mg tablets
rosuvastatin (Ezallor Sprinkle)	10 mg to 20 mg daily	5 mg to 40 mg daily	--	5 mg daily	5 mg, 10 mg, 20 mg, 40 mg capsules
simvastatin (Flolipid)	10 mg to 20 mg daily in the evening	5 mg to 40 mg daily	*HeFH* Ages 10 to 17 years: 10 mg to 40 mg daily	20 mg daily	20 mg/5 mL, 40 mg/5 mL oral suspension in 150 mL bottle
simvastatin (Zocor)	10 mg to 20 mg daily in the evening	5 mg to 40 mg daily	*HeFH* Ages 10 to 17 years: 10 mg to 40 mg daily	20 mg daily	5 mg (generic only), 10 mg, 20 mg, 40 mg, 80 mg tablets

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DOSING CONSIDERATIONS[239,240,241,242,243,244,245,246,247,248,249,250,251,252,253]

amlodipine/atorvastatin (Caduet)

- Caduet may be substituted for the individual agents after titration.
- Dosage should be individualized for tolerance of both amlodipine and atorvastatin.
- No dosage adjustment is needed with renal impairment.
- Concomitant use of atorvastatin and cyclosporine, tipranavir plus ritonavir, glecaprevir plus pibrentasvir, or letermovir when coadministered with cyclosporine should be avoided.
- Patients receiving lopinavir plus ritonavir, simeprevir, fibric acid derivatives, erythromycin, azole antifungals, lipid-modifying doses of niacin, or colchicine should use the lowest dose possible of atorvastatin and with caution.
- Use the lowest dose necessary, and do not exceed atorvastatin 20 mg daily in patients who are also taking clarithromycin, itraconazole, elbasvir plus grazoprevir, saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, or letermovir.
- Do not exceed 40 mg of atorvastatin in patients who are also receiving nelfinavir therapy.

atorvastatin (Lipitor)

- Use caution when administering with fibrates.
- No dosage adjustment is recommended in renal insufficiency.
- Severe hepatic disease: adjust dosage.
- Avoid use with cyclosporine and gemfibrozil.
- Concomitant use of atorvastatin and cyclosporine, tipranavir plus ritonavir, glecaprevir plus pibrentasvir, or letermovir when coadministered with cyclosporine should be avoided.
- Patients receiving lopinavir plus ritonavir, simeprevir, fibric acid derivatives, erythromycin, azole antifungals, lipid-modifying doses of niacin, or colchicine should use the lowest dose possible of atorvastatin and with caution.
- Use the lowest dose necessary and do not exceed atorvastatin 20 mg daily in patients who are also taking clarithromycin, itraconazole, elbasvir plus grazoprevir, saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, or letermovir.
- Do not exceed 40 mg of atorvastatin in patients who are also receiving nelfinavir therapy.
- Reduce dose when used with niacin.
- Avoid large quantities of grapefruit juice (> 1 quart daily).

ezetimibe/simvastatin (Vytorin)

- HoFH: 10/40 mg in the evening.
- In patients with chronic kidney disease and estimated glomerular filtration rate < 60 mL/min/1.73 m^2, the dose of ezetimibe/simvastatin is 10/20 mg/day in the evening.
- Bile Acid Sequestrants: administer ezetimibe/simvastatin either 2 hours before or 4 hours after administration of a bile acid sequestrant.
- Fibrates: should be avoided.

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- Gemfibrozil: concomitant administration is contraindicated.
- Niacin > 1 g daily – Caution should be used.
- Cyclosporine or danazol: concomitant administration is contraindicated.
- Strong CYP3A4 inhibitors: concomitant administration is contraindicated.
- Diltiazem or verapamil: do not exceed 10/10 mg daily.
- Amiodarone, amlodipine, or ranolazine: do not exceed 10/20 mg daily.
- Due to increased risk for myopathy, Chinese patients should not receive Vytorin coadministered with lipid-modifying doses of niacin-containing products (≥ 1 g/day niacin). It is not known if this risk of myopathy observed in Chinese patients applies to other Asian patients.
- High dose simvastatin: potential increased risk of myopathy with the 80 mg dose of simvastatin compared to lower doses of simvastatin and possibly other statin drugs.
- Due to the increased risk of myopathy, including rhabdomyolysis, use of the 80 mg dose of simvastatin should be restricted to patients who have been taking ezetimibe/simvastatin 10/80 mg chronically (e.g., for ≥ 12 months) without evidence of muscle toxicity.
- New patients should not be started on ezetimibe/simvastatin 10/80 mg.
- Place patients who do not meet their LDL-C goal on ezetimibe/simvastatin 10/40 mg on alternative LDL-C lowering treatment(s) that provides greater LDL-C lowering.
- Follow the recommendations in the simvastatin-containing products labels regarding drugs that may increase the risk for muscle injury when used with simvastatin.
- Switch patients who need to be initiated on a drug that interacts with simvastatin to an alternative statin with less potential for the drug-drug interaction.
- Contraindicated with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin, and nefazodone). Contraindicated with gemfibrozil, cyclosporine, or danazol.

fluvastatin, fluvastatin XL (Lescol XL)

- Cyclosporine or fluconazole: do not exceed fluvastatin 20 mg twice daily.
- Do not crush, chew, break tablets extended-release tablets; do not open immediate-release capsules.
- Renal insufficiency: very little data with doses > 40 mg daily, use with caution in severe impairment.
- Severe hepatic impairment or heavy alcohol ingestion: use caution.

lovastatin, lovastatin ER (Altoprev)

- Contraindicated with azole antifungals: itraconazole, ketoconazole, and posaconazole.
- Contraindicated with macrolide antibiotics: erythromycin, clarithromycin, and telithromycin.
- Contraindicated with HIV protease inhibitors; the hepatitis C protease inhibitors: nefazodone.
- Avoid with cyclosporine and gemfibrozil.
- Danazol, diltiazem, or verapamil: do not exceed 20 mg daily.
- Amiodarone: do not exceed 40 mg daily.

- Avoid large quantities of grapefruit juice (> 1 quart daily).
- Colchicine, fibrates, or niacin > 1 g daily: use caution with concurrent administration.
- Reduce lovastatin dose with concomitant ranolazine.
- Renal insufficiency (estimated creatine clearance [CrCl] < 30 mL/min): use caution with doses above 20 mg daily.
- Lovastatin ER only – Elderly and complicated medical conditions including diabetes: use 20 mg at bedtime.

pitavastatin (Livalo, Zypitamag)

- Doses greater than 4 mg once daily have been associated with an increased risk for severe myopathy; therefore, do not exceed 4 mg daily.
- Renal insufficiency: moderate and severe renal impairment (glomerular filtration rate 30 to 59 and 15 to 29 mL/min/1.73 m^2, respectively) and end-stage renal disease on hemodialysis initial dose is 1 mg daily; maximum dose 2 mg daily.
- Erythromycin: pitavastatin dose should be limited to 1 mg daily.
- Rifampin: pitavastatin dose should be limited to 2 mg daily.
- Avoid with gemfibrozil.
- Fibrates or niacin > 1 g daily: use caution with concurrent administration.
- Severe hepatic impairment or heavy alcohol ingestion: use caution.

pravastatin (Pravachol)

- Patients with significant renal or hepatic impairment: use 10 mg daily to start.
- Avoid use with gemfibrozil.
- Fibrates: use pravastatin with caution.
- Clarithromycin: limit pravastatin to 40 mg once daily.
- Cyclosporine: use 10 to 20 mg daily.
- Reduce dose when used with niacin.

rosuvastatin (Crestor, Ezallor Sprinkle)

- Asian patients: consider starting dose of 5 mg daily.
- HoFH: starting dose is 20 mg daily.
- HeFH: maximum dose is 20 mg daily (Crestor only).
- Cyclosporine: use 5 mg only.
- Darolutamide: maximum dose is 5 mg daily.
- Regorafenib: maximum dose is 10 mg daily.
- Sofosbuvir/velpatasvir/voxilaprevir, ledipasvir/sofosbuvir: concomitant use not recommended
- Gemfibrozil: combination should be avoided; if used, do not exceed rosuvastatin 10 mg once daily (initiate at 5 mg once daily).

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- Severe renal impairment (CrCl < 30 mL/min/1.73m^2) not on hemodialysis: initiate therapy at 5 mg daily; do not exceed 10 mg daily.
- Rosuvastatin 40 mg should be limited only to patients who fail to achieve LDL-C goals with rosuvastatin 20 mg daily.
- Lopinavir/ritonavir (Kaletra®), atazanavir/ritonavir, simeprevir, dasabuvir/ombitasvir/paritaprevir/ritonavir, elbasvir/grazoprevir, sofosbuvir/velpatasvir, or glecaprevir/pibrentasvir: do not exceed 10 mg once daily (initiate at 5 mg once daily).
- Use caution when used in combination with niacin (> 1 g/day) or fenofibrate.
- Rosuvastatin capsules (Ezallor Sprinkle) can be opened and the granules emptied onto a teaspoon of soft food such as applesauce or chocolate/vanilla flavored pudding. It should be swallowed immediately, without chewing. It can also be administered via nasogastric (NG) tube (see Prescribing Information for details).

simvastatin (Flolipid, Zocor)

- HoFH: use 40 mg daily in evening.
- HeFH: maximum 40 mg/day.
- Recommended starting dose for patients at high risk of CHD is 40 mg/day.
- Fibrates: combination should be avoided.
- Diltiazem or verapamil: do not exceed 10 mg daily.
- Amiodarone, amlodipine, or ranolazine: do not exceed 20 mg daily.
- Severe renal impairment (CrCl < 10 mL/min): initiate therapy at 5 mg daily with close monitoring.
- Due to increased risk of myopathy, do not coadminister simvastatin 40 mg lipid-modifying doses of niacin-containing products (≥ 1 g/day niacin) in Chinese patients, use caution in administering simvastatin > 20 mg per day in Chinese patients taking lipid-modifying doses of niacin-containing products.[254] It is not known if this risk of myopathy observed in Chinese patients applies to other Asian patients.
- High dose simvastatin: potential increased risk of myopathy with the 80 mg dose of simvastatin compared to lower doses of simvastatin and possibly other statin drugs.
- Due to the increased risk of myopathy, including rhabdomyolysis, use of the 80 mg dose of simvastatin should be restricted to patients who have been taking simvastatin 80 mg chronically (e.g., for ≥ 12 months) without evidence of muscle toxicity.
- New patients should not be started on simvastatin 80 mg.
- Use simvastatin oral suspension (Flolipid) 40 mg/5 mL concentration for dosages ≥ 40 mg.
- Take the oral suspension on an empty stomach.
- Place patients who do not meet their LDL-C goal on simvastatin 40 mg on alternative LDL-C lowering treatment(s) that provides greater LDL-C lowering.
- Follow the recommendations in the simvastatin-containing products labels regarding drugs that may increase the risk for muscle injury when used with simvastatin. Switch patients who need to be initiated on a drug that interacts with simvastatin to an alternative statin with less potential for the drug-drug interaction.

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- Severe renal impairment: do not initiate therapy unless patient has already tolerated treatment with simvastatin at 10 mg daily or higher.
- Concomitant administration of gemfibrozil, cyclosporine, or danazol is contraindicated.
- Concomitant administration of strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin, and nefazodone) is contraindicated.
- Avoid large quantities of grapefruit juice (> 1 quart daily).

CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials for FDA-approved indications are considered the most relevant in this category. Clinical outcome trials rather than surrogate markers as trial primary outcome parameters are considered the most relevant in this class. 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 and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are studies evaluating carotid intima media thickness (CIMT), but the American Heart Association and American College of Cardiology no longer recognizes the routine use of carotid intima media thickness (CIMT).[255,256,257] It should be reserved as a research tool. Numerous short-term trials comparing agents for the reduction in LDL-C, changes in the various lipid parameters, and other surrogate markers have been published. No cardiovascular outcomes studies have been published for pitavastatin (Livalo, Zypitamag), or for the combination of atorvastatin/amlodipine (Caduet). Many of the large clinical trials evaluating cardiovascular events and the use of statins have used placebo as a comparison or different dose (high dose versus low dose) comparisons. Large cardiovascular outcomes trials for primary and secondary prevention are summarized at the end of this section.

atorvastatin (Lipitor)

TNT study:[258] The Treating to New Targets study evaluated the efficacy and safety of lowering LDL-C to < 100 mg/dL in patients with stable CHD. In the randomized, double-blind study, 10,001 patients with CHD were enrolled and followed for a mean of 4.9 years. Initially, all patients underwent 8 weeks of open-label atorvastatin 10 mg daily. Those patients with LDL-C < 130 mg/dL were then randomized to atorvastatin 10 mg or 80 mg daily. Overall, atorvastatin reduced LDL-C by 35% with a mean LDL-C achieved in the atorvastatin 80 mg and 10 mg groups of 77 mg/dL and 101 mg/dL, respectively. The primary outcome measure was the occurrence of a first major cardiovascular event, defined as death

from CHD, nonfatal nonprocedural-related MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke. The event rate was 8.7% and 10.9% for the atorvastatin 80 mg and 10 mg groups, respectively (p<0.001). This study was not powered to detect a difference in overall mortality between the 2 doses of atorvastatin. There were more non-cardiovascular deaths in the atorvastatin 80 mg group. In specifically evaluating cerebrovascular events, the atorvastatin 80 mg group had fewer cerebrovascular events (HR, 0.77; 95% CI, 0.64 to 0.93; p=0.007) and stroke (HR, 0.75; 95% CI, 0.59 to 0.96; p=0.02).[259] The incidence of hemorrhagic strokes was similar between the groups. Evaluating the diabetic population (n=1,501) enrolled in TNT, a primary outcome measure occurred in 13.8% and 17.9% of the atorvastatin 80 mg and 10 mg groups, respectively (HR, 0.75; 95% CI, 0.58 to 0.97, p=0.026).[260] Beneficial effects were seen in diabetics in the high dose atorvastatin group for cerebrovascular events and any cardiovascular events. For patients with metabolic syndrome, high-dose atorvastatin significantly reduced the primary outcome measure compared to the low-dose atorvastatin group (9.5% versus 13%, respectively; HR, 0.71; 95% CI, 0.61 to 0.84; p<0.0001).[261] Adverse events and discontinuation rates were significantly higher in the high-dose atorvastatin group (both p<0.001). Five cases of rhabdomyolysis were reported, with 2 patients in the high-dose atorvastatin group and 3 patients in the low-dose atorvastatin group. Liver enzyme elevation, defined as 2 measurements greater than 3 times the upper limit of normal (ULN) for ALT, AST, or both within 4 to 10 days, occurred more frequently in the high-dose atorvastatin group (1.2% versus 0.2%, p<0.001). The manufacturer of atorvastatin funded the study.

A subgroup analysis of the TNT study evaluated the effect of high-dose atorvastatin for heart failure (HF).[262] A history of HF was present in 7.8% of patients. A known ejection fraction < 30% and advanced HF were exclusion criteria for the study. The incidence of hospitalization for HF, a predefined secondary endpoint, was 2.4% for atorvastatin 80 mg and 3.3% for atorvastatin 10 mg (HR, 0.74; 95% CI, 0.59 to 0.94; p=0.0116). In the patients with a history of HF, the incidence of HF-related hospitalization was 10.6% in the atorvastatin 80 mg group and 17.3% in the atorvastatin 10 mg group (HR, 0.59; 95% CI, 0.4 to 0.88; p=0.008). The rates of hospitalization for HF were much lower among patients without a history of HF (1.8% in the 80 mg group and 2% in the 10 mg group [HR, 0.87; 95% CI, 0.64 to 1.16; p=0.34]). In a post-hoc analysis, this benefit of reduced hospitalizations for HF was only seen in patients with a history of HF.

A pre-specified secondary analysis of the TNT study assessed the effect of high-dose atorvastatin 80 mg daily or low-dose atorvastatin 10 mg daily in 3,809 patients aged ≥ 65 years with stable CHD.[263] The absolute risk was reduced by 2.3% and relative risk by 19% for major cardiovascular events in favor of the high-dose atorvastatin group (HR, 0.81; 95% CI, 0.67 to 0.98; p=0.032). Among the components of the composite outcome, the mortality rates from CHD, nonfatal non-procedure-related MI, and fatal or nonfatal stroke (ischemic, embolic, hemorrhagic, or unknown origin) were all lower in older patients who received high-dose atorvastatin, although the difference was not statistically significant for each individual component. The improved clinical outcome was not associated with persistent elevations in creatine kinase (CK) levels.

Further analysis of the TNT data evaluated patients with CAD, type 2 diabetes, with or without chronic kidney disease (CKD).[264] Renal data was available for 1,431 patients of the 1,501 patients with diabetes. Of the 546 patients with diabetes and CKD, 17.4% experienced a major CV event compared to 13.4% of 885 patients with diabetes and normal estimated glomerular filtration rate (eGFR) (HR, 1.32; 95% CI, 1 to 1.72; p<0.05). Compared with 10 mg of atorvastatin, 80 mg of atorvastatin reduced

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the relative risk of major CV events by 35% in patients with diabetes and CKD (20.9% versus 13.9%, respectively; HR, 0.65; 95% CI, 0.43 to 0.98; p=0.04) and by 10% in patients with diabetes and normal eGFR (14.1% versus 12.8%, respectively; HR, 0.9; 95% CI, 0.63 to 1.29; p=0.56). Over 4.8 years, the number needed to treat was 14 to prevent 1 major CV event. Both treatments were well tolerated.

ASCOT-LLA study:[265] As part of a larger study with 19,342 hypertensive patients with multiple risk factors for CHD, patients (n=10,305) with total-C < 235 mg/dL were enrolled in the lipid-lowering arm and were randomized to atorvastatin 10 mg daily or placebo in a double-blind manner. The primary endpoint of the lipid-lowering trial was non-fatal MI and fatal CHD. After a median follow-up of 3.3 years, the trial was stopped early due to significantly lower event rate in the atorvastatin group (p=0.0005). Atorvastatin reduced the relative risk of nonfatal MI and fatal CHD by 36% over the study period. Stroke, a secondary endpoint, was reduced by approximately 27% with atorvastatin (p=0.024).

CARDS:[266] The effectiveness of atorvastatin in the primary prevention of cardiovascular events was evaluated in 2,838 patients with type 2 diabetes. The trial was a multicenter, double-blind, randomized trial enrolling patients ages 40 to 75 years who did not have a history of cardiovascular disease, near normal values for LDL-C (< 160 mg/dL, baseline mean 119 mg/dL) and TG (< 600 mg/dL, baseline mean 172 mg/dL). Patients also had at least 1 of the following risk factors: a history of retinopathy, albuminuria, current smoking, or hypertension. The mean duration of diabetes was 6 years upon study entry.[267] Patients were randomized to atorvastatin 10 mg daily or placebo. The trial was halted 2 years earlier than expected when atorvastatin was found to reduce the relative risk of the first occurrence of acute cardiac event, coronary revascularization, or stroke compared to placebo (relative risk reduction 37%; 95% CI, -52 to -17; p=0.001). Looking at the endpoints individually found that the event rate of acute coronary heart disease events was reduced by 36%, coronary revascularizations by 31%, and stroke by 48% by atorvastatin (p=0.016) compared to placebo. Atorvastatin was well tolerated in the trial over a median of 3.9 years.

A multicenter, double-blind, randomized trial enrolled 1,255 patients with type 2 diabetes on hemodialysis to assess the efficacy and safety of atorvastatin 20 mg daily versus placebo.[268] The primary endpoint was the composite of cardiac death, nonfatal MI, and stroke. After 4 weeks, the mean LDL-C was reduced by 42% in the atorvastatin group; placebo group had a 1.3% reduction in LDL-C. After a median of 4 years, 469 patients reached the composite endpoint (atorvastatin, n=226; placebo n=243; relative risk [RR], 0.92; 95% CI, 0.77 to 1.1; p=0.37). Atorvastatin had no effect on death from cardiac causes, nonfatal MI, and nonfatal stroke. More patients died of stroke in the atorvastatin group (n=27) than in the placebo group (n=13; RR, 2.03; 95% CI, 1.05 to 3.93; p=0.04). Atorvastatin reduced the rate of all cardiac events combined (RR, 0.82; 95% CI, 0.68 to 0.99; p=0.03). Atorvastatin did not have a significant effect on combined cerebrovascular events or total mortality.

SPARCL:[269] In a multicenter, randomized, double-blind trial, atorvastatin 80 mg daily and placebo were compared for efficacy in reducing the risk of secondary stroke. Patients (n=4,731) had a history of stroke or TIA within 1 to 6 months before study entry, and LDL-C levels were between 100 to 109 mg/dL. Contemporary management with antiplatelet and antihypertensive agents was permitted. The study population had no known CHD. After a median of 4.9 years of follow-up, the rates of fatal and nonfatal strokes were 11.2% and 13.1% for atorvastatin and placebo, respectively (p=0.03). The 5-year absolute risk reduction of major cardiovascular events associated with atorvastatin was 3.5% (HR, 0.8; 95% CI, 0.69 to 0.92; p=0.002). Hemorrhagic stroke was slightly higher in the atorvastatin group; however, the incidence of fatal hemorrhagic stroke was similar between the 2 groups. There was no

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significant difference in total mortality between the groups. Baseline LDL-C levels were similar between the groups (132.7 versus 133.7 mg/dL); however, the mean LDL-C during the trial was 73 mg/dL and 129 mg/dL for the atorvastatin and placebo groups, respectively (p<0.001). Liver enzyme elevation was more common with atorvastatin. The discontinuation rate was higher in the atorvastatin group (17.5% versus 14.5%). Five cases of rhabdomyolysis were reported, with 2 patients in the atorvastatin group and 3 patients in the placebo group. After 4.9 years, at each level of LDL-C reduction, subjects with HDL-C value above the median or systolic blood pressure (BP) below the median had greater reductions in stroke and major CV events and those with a reduction in triglycerides above the median or diastolic BP below the median showed similar trends.[270]

A post-hoc analysis of the SPARCL trial suggested a higher incidence of hemorrhagic stroke (2.3% atorvastatin versus 1.4% placebo; HR, 1.68; 95% CI, 1.09 to 2.59; p=0.0168) but reduced risk of ischemic stroke in the patients treated with atorvastatin 80 mg.[271] Hemorrhagic stroke was more frequent in subjects who had a hemorrhagic stroke on study entry, in men, and with advanced age.

ASPEN:[272] In a double-blind, placebo-controlled study, the effect of atorvastatin 10 mg on the incidence of cardiovascular events in type 2 diabetics with lower levels of LDL-C than the current guidelines was determined. Patients (n=2,410) were randomized to atorvastatin 10 mg daily or placebo for 4 years. The primary composite endpoint consisted of cardiovascular death, nonfatal MI, nonfatal stroke, recanalization, CABG, resuscitated cardiac arrest, and worsening or unstable angina requiring hospitalization. The mean reduction of LDL-C was 29% over 4 years compared to placebo (p<0.0001). The composite endpoint rates were 13.7% and 15% for atorvastatin and placebo groups, respectively (HR, 0.9; 95% CI, 0.73 to 1.12); the difference did not achieve statistical significance. In the patient subgroup with prior MI or interventional procedure, the composite endpoint rates were 26.2% and 30.8% for atorvastatin and placebo, respectively (HR, 0.82; 95% CI, 0.59 to 1.15). In patients without a history of MI or interventional procedure, there was no significant difference between the 2 groups (10.4% for atorvastatin; 10.8% for placebo; HR, 0.97; 95% CI, 0.74 to 1.28). The relative risk reductions for fatal and nonfatal MI did not achieve statistical significance (27% overall; p=0.1).

atorvastatin (Lipitor) versus pravastatin (Pravachol)

REVERSAL study:[273] The 18-month randomized, double-blind, active-controlled, multicenter trial enrolled 654 patients to compare the effect of moderate lipid lowering therapy with pravastatin 40 mg daily to intensive lipid-lowering therapy with atorvastatin 80 mg daily on coronary artery atheroma burden and progression. Baseline mean LDL-C was 150.2 mg/dL in both treatment groups and was reduced to 110 mg/dL in the pravastatin group and to 79 mg/dL in the atorvastatin group (p<0.001). Progression of coronary atherosclerosis occurred in the pravastatin group (2.7%; p=0.001) compared with baseline. Progression did not occur in the atorvastatin group (-0.4%; p=0.98) compared with baseline. For patients with CHD, intensive lipid-lowering treatment with atorvastatin reduced progression of coronary atherosclerosis compared with pravastatin.

PROVE IT-TIMI 22 study:[274] The authors enrolled 4,162 patients who had been hospitalized for acute coronary syndrome (ACS) within the preceding 10 days and compared 40 mg of pravastatin daily (standard therapy) with 80 mg of atorvastatin daily (intensive therapy) in a double-blind, double-dummy fashion. The primary endpoint was a composite of death from any cause, MI, unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. Mean follow-up was 24 months. The median LDL-C level achieved during treatment was 95

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mg/dL in the pravastatin group and 62 mg/dL in the atorvastatin group (p<0.001). After 30 days, the composite endpoint occurred in 3% and 4.2% of the atorvastatin and pravastatin patients, respectively (HR, 0.72; 95% CI, 0.58 to 0.89; p=0.003).[275] Primary composite endpoint rates (death or major cardiovascular event) at 2 years were 26.3% in the pravastatin group and 22.4% in the atorvastatin group (95% CI, 5 to 26; p=0.005). Among ACS patients, an intensive lipid-lowering statin regimen provides greater protection against death or major cardiovascular events than does a standard regimen. These findings indicate that such patients benefit from early and continued lowering of LDL-C to levels substantially below current target levels.

The PROVE IT-TIMI 22 trial also examined the relationship between on-treatment levels of TG and LDL-C and the composite endpoint of death, MI, and recurrent ACS 30 days after initial presentation.[276] Low on-treatment TG (< 150 mg/dl) was associated with reduced CHD risk compared with higher TG in univariate analysis (HR, 0.73; 95% CI, 0.62 to 0.87; p<0.001) and in adjusted analysis (HR, 0.8; 95% CI 0.66 to 0.97; p=0.025). For each 10 mg/dL decrease in on-treatment TG, the incidence of death, MI, and recurrent ACS was lower by 1.6% or 1.4% after adjustment for LDL-C or non-high-density lipoprotein cholesterol and other covariates (p<0.001 and p=0.01, respectively). Lower CHD risk was also observed with TG < 150 mg/dl and LDL-C < 70 mg/dl (HR, 0.72; 95% CI, 0.54 to 0.94; p=0.017) or low on-treatment TG, LDL-C, and C-reactive protein (< 2 mg/L) (HR, 0.59; 95% CI, 0.41 to 0.83; p=0.002) compared with higher levels of each variable in adjusted analysis.

A double-blind, randomized trial of 893 ambulatory CAD patients (30% female) aged 65 to 80 years with 1 or more episode of myocardial ischemia that lasted 3 or more minutes during 48 hour ambulatory ECG at screening, compared atorvastatin 80 mg daily to pravastatin 40 mg daily with a 12-month follow-up.[277] The primary efficacy parameter (absolute change from baseline in total duration of ischemia at month 12) was significantly reduced in both groups at 3 and 12 months (both p<0.001 for each treatment group) with no significant difference between the treatment groups. Atorvastatin patients experienced greater LDL-C reductions than the pravastatin group, a trend toward fewer major acute cardiovascular events (HR, 0.71; 95% CI, 0.46 to 1.09; p=0.114), and a significantly greater reduction in all-cause death (HR, 0.33; 95% CI, 0.13 to 0.83; p=0.014).

A post-hoc analysis of the GREACE study investigated the extent in vascular event reduction by statin treatment according to gender.[278] From a total of 1,600 patients with stable CHD, 624/176 and 632/168 were men/women on atorvastatin (Lipitor) or on usual care, respectively. During the 3 year follow-up, comparison of atorvastatin treatment with usual care demonstrated a relative risk reduction (RRR) of the primary endpoint (all vascular events) of 54% in women (HR, 0.46; 95% CI, 0.24 to 0.87; p=0.003) and of 50% in men (HR, 0.5; 95% CI, 0.32 to 0.7; p<0.001). The fall in LDL-C levels played the key role in endpoint reduction in both genders. However, in men there was an additional benefit related to the atorvastatin-induced increase in HDL-C and estimated glomerular filtration rate (eGFR), while in women endpoints were related to a substantial TG reduction.

atorvastatin (Lipitor) versus simvastatin (Zocor)

IDEAL:[279] The study was a prospective, randomized, open-label, blinded endpoint trial evaluating atorvastatin 80 mg daily and simvastatin 20 mg daily for occurrence of coronary death, nonfatal MI, or cardiac resuscitation over a median of 4.8 years. A total of 8,888 North European patients with a history of MI were enrolled. A majority of patients were on statin therapy at baseline (simvastatin 50%, pravastatin 10%, and atorvastatin 11%). Baseline LDL-C levels were 121 mg/dL. Dose adjustments were

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permitted in the simvastatin group if total cholesterol was greater than 190 mg/dL after 24 weeks. For the atorvastatin group, if the LDL-C was less than 40 mg/dL, atorvastatin dose was reduced to 40 mg daily. After 5 years, the mean LDL-C levels were 80 and 100 mg/dL for atorvastatin and simvastatin, respectively. Major coronary event defined as CHD death, nonfatal MI, and cardiac resuscitation occurred in 9.3% of the atorvastatin patients and 10.4% of the simvastatin patients (HR, 0.89; 95% CI, 0.78 to 1.01; p=0.07). The rates of composite endpoint of CHD death, nonfatal MI, cardiac resuscitation, and stroke were lower with atorvastatin (HR, 0.87; 95% CI, 0.78 to 0.98; p=0.02). A significant reduction in nonfatal MI in favor of atorvastatin was observed (7.2% simvastatin; 6% atorvastatin; HR, 0.83; 95% CI, 0.71 to 0.98; p=0.02). All-cause mortality and cardiovascular mortality were similar in both groups. Discontinuation rate due to adverse effects was higher in the atorvastatin group (9.6% versus 4.2%, p<0.001). Liver enzyme elevation was reported more frequently with atorvastatin (p<0.001). An analysis of heart failure (HF) in secondary prevention showed that atorvastatin 80 mg was associated with a 26% decrease in new HF events compared with simvastatin 20 to 40 mg (HR, 0.74; 95% CI, 0.57 to 0.97; p=0.03). Atorvastatin tended to be associated with fewer HF events in those with HF at baseline (n=537; HR, 0.65; 95% CI, 0.38 to 1.11; p=0.11) and those without HF at baseline (n=8,351; HR, 0.8; 95% CI, 0.59 to 1.09; p=0.15). Also, HF without preceding MI (n=187) was decreased (HR, 0.73; 95% CI, 0.54 to 0.97; p=0.03).[280]

fluvastatin

LIPS study:[281] Fluvastatin 40 mg twice daily was compared to placebo in a randomized, double-blind trial in 1,677 patients with stable or unstable angina or ischemia following a successful percutaneous coronary intervention (PCI). Primary efficacy was determined by survival time free from cardiac death, nonfatal MI, or repeat procedure. Both groups were similarly matched at baseline including a mean LDL-C of 131 mg/dL with the exception that the fluvastatin group had significantly more diabetic patients than the placebo group (14.2% versus 9.8%, respectively). After nearly 4 years, fluvastatin was found to have a significantly longer event-free time compared to placebo (p=0.01). The fluvastatin group had a 21.4% incidence of events over 4 years compared to the placebo group with 26.7% (5.3% absolute risk reduction). Therapy was well tolerated. At the end of follow-up, 10.7% of fluvastatin patients and 24% of placebo patients were taking other lipid lowering therapies.

As part of the LIPS study, the impact of long-term fluvastatin treatment on cardiac events was evaluated in 847 stent-treated patients with average cholesterol levels.[282] During the 4-year follow-up period, fluvastatin significantly decreased total-C, LDL-C, and decreased the relative risk of first adverse atherosclerotic cardiac events by 30%.

ALERT study:[283] The effects of fluvastatin were evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 2,102 renal transplant patients over 5 to 6 years. All patients had stable graft function and were on cyclosporine. Patients were given fluvastatin 40 mg daily or placebo. After 2 years, the dose of fluvastatin was doubled in 65% of the patients. Seventy-four percent of the fluvastatin patients did achieve LDL-C < 115 mg/dL. The primary endpoint was the composite endpoint of cardiac death, non-fatal MI, or coronary intervention procedure. After a mean follow-up of 5.1 years, fluvastatin reduced LDL-C by 32%. The risk reduction of the composite outcome was not significant. Fluvastatin reduced the number of cardiac deaths and non-fatal MIs compared to the placebo group (p=0.005). In a 2-year, open-label extension of the ALERT trial, 1,652 patients who completed the first part of the ALERT trial continued fluvastatin XL 80 mg daily.[284] The mean LDL-C at the end of the trial was 98 mg/dL. After a mean follow-up period of 6.7 years, patients had a reduced

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risk of the first major cardiac event (HR, 0.79; 95% CI, 0.63 to 0.99; p=0.036) and in cardiac death and nonfatal MI (HR, 0.71; 95% CI, 0.55 to 0.93, p=0.014). Both groups were similar for total mortality and graft loss.

pitavastatin (Livalo, Zypitamag)

No large clinical outcomes trials have been performed with pitavastatin. Pitavastatin has been compared to pravastatin, simvastatin, and atorvastatin in patients with primary hyperlipidemia or mixed dyslipidemia, in non-inferiority trials, extension study, as well as in a long-term post-marketing study.[285, 286,287,288,289,290,291]

pitavastatin (Livalo, Zypitamag) versus pravastatin (Pravachol) in HIV-infected patients

The INTREPID (HIV PatieNts and TREatment With Pitavastatin Versus PravastatIn for Dyslipidemia) trial was a 12-week, phase 4, double-blind, double-dummy, active-controlled, parallel-group, superiority study that enrolled 252 HIV-infected patients with dyslipidemia who had received antiretroviral therapy for at a minimum of 6 months.[292,293] Patients were randomized to once-daily pitavastatin 4 mg or pravastatin 40 mg. At week 12, L pitavastatin demonstrated superiority over pravastatin in LDL-C lowering (31.1% versus 20.9%, respectively). Decreases in secondary measures such as Apo-B and Non-HDL-C were also significantly greater for pitavastatin compared to pravastatin (Apo-B 23.3% versus 16.5%, respectively; non-HDL-C 26.9% versus 18.7%, respectively; both p<0.001) A study 40-week safety extension study that included 190 patients demonstrated that the lipid-lowering effects were maintained at week 52.[294] Adverse events were similar between the groups.

pravastatin (Pravachol)

ALLHAT-LLT study:[295] The study investigated the effects of pravastatin and usual care on all-cause mortality in 10,355 patients with moderate hypercholesterolemia and hypertension over almost 5 years. The multicenter, non-blinded study randomized patients with LDL-C of 120 to 180 mg/dL to pravastatin 40 mg daily or usual care. Subjects included all patient subtypes including females, African-Americans, Hispanics, patients with a history of CHD, and those with type 2 diabetes. Of the usual care group, 17.1% used statins at year 4, and 26.1% used statins at year 6. The LDL-C levels were reduced by 28% with pravastatin compared to 11% with usual care for those who had LDL-C determinations. All-cause mortality and CHD event rates were similar between the 2 groups. Secondary endpoints of nonfatal MI or fatal CHD events combined, cause-specific mortality, and cancer were similar between the 2 groups.

The WOSCOPS study was a randomized primary prevention trial comparing pravastatin to placebo over 5 years in a large cohort of men with hyperlipidemia (TC > 250 mg/dL) and no prior history of MI.[296] The combined outcome of death from definite coronary heart disease or definite nonfatal MI was reduced from 7.9% to 5.5% (p<0.001). A 10-year follow-up of the trial showed a significant reduction in coronary events.[297] The rates of death from all cardiovascular causes (pravastatin: 7.6%; placebo: 9%; HR, 0.81 [95% CI, 0.68 to 0.96]; p=0.01) and death from any cause (18.7% for pravastatin versus 20.5% for placebo; HR, 0.88 [95% CI, 0.79 to 0.99]; p=0.03) were lower in the pravastatin group over the total follow-up period. Deaths from CHD were fewer in the pravastatin group (5.1%; HR, 0.78 [95% CI, 0.64 to 0.96; p=0.02]) compared to placebo group (6.3%). There were no excess deaths from non-cardiovascular causes or incident cancers.

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rosuvastatin (Crestor, Ezallor Sprinkle)

Short-term trials have been published comparing LDL-C reductions of rosuvastatin, atorvastatin, pravastatin, and simvastatin.[298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313] Rosuvastatin has also been compared to atorvastatin in a short-term trial comparing the effect on HDL-C.[314]

ASTEROID:[315] In a prospective, randomized, open-label, blinded endpoint trial, rosuvastatin 40 mg daily was administered to 507 patients. A total of 349 patients underwent an intravascular ultrasound (IVUS) at baseline and after 2 years of therapy. Significant decreases in LDL-C levels were reported (p<0.001) and over 75% of the population achieved LDL-C levels below 70 mg/dL. HDL-C levels increased from a mean of 43.1 mg/dL to 49 mg/dL. The change in the percent atheroma volume was reduced by a mean of 0.98% (p<0.001 versus baseline); this represents a median reduction of 9.1% in atheroma volume in the 10 mm-segment with the greatest disease severity identified at baseline. Regression in percent atheroma volume occurred in 63.6% of patients and 36.4% showed progression. A median reduction of 6.8% was observed in the normalized total atheroma volume of the artery. It is important to note the open-label design of the study, large number of patients not completing the study, and the fact that the manufacturer funded the study.

JUPITER:[316,317] A randomized, double-blind, placebo-controlled, multicenter study assessed rosuvastatin 20 mg versus placebo in the primary prevention of CV events. A total of 17,802 patients with normal to low LDL-C and elevated levels of high-sensitivity C-reactive protein (hsCRP) were enrolled to determine if long-term treatment with rosuvastatin would reduce the rate of first major CV events in patients with LDL-C < 130 mg/dL who are at high vascular risk due to an enhanced inflammatory response indicated by hsCRP levels ≥ 2 mg/L. The trial was stopped early after a median follow-up of 1.9 years based on evidence of a reduction in CV morbidity and mortality among patients who received rosuvastatin compared to placebo.[318] Rosuvastatin reduced LDL-C and hsCRP levels by 50% and 37%, respectively. The rates of the primary endpoint were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (HR for rosuvastatin, 0.56; 95% CI, 0.46 to 0.69; p<0.00001), with corresponding rates of 0.17 and 0.37 for MI (HR, 0.46; 95% CI, 0.3 to 0.7; p=0.0002), 0.18 and 0.34 for stroke (HR, 0.52; 95% CI, 0.34 to 0.79; p=0.002), 0.41 and 0.77 for revascularization or unstable angina (HR, 0.53; 95% CI, 0.4 to 0.7; p<0.00001), 0.45 and 0.85 for the combined endpoint of MI, stroke, or death from CV causes (HR, 0.53; 95% CI, 0.4 to 0.69; p<0.00001), and 1 and 1.25 for death from any cause (HR, 0.8; 95% CI, 0.67 to 0.97; p=0.02). The decrease in stroke risk was due to a 51% relative reduction in the rate of ischemic stroke (HR, 0.49; 95% CI, 0.3 to 0.81; p=0.004), with no difference in the rates of hemorrhagic stroke between the active and placebo groups (HR, 0.67; 95% CI, 0.24 to 1.88; p=0.44).[319] There was not a significant increase in myopathy or cancer in the rosuvastatin group, but there was a significantly higher incidence of physician-reported diabetes. The 5-year number needed to treat (NNT) for JUPITER to prevent 1 CV event was 25 patients or 95 patients over 2 years.[320]

In a prospective analysis of 87% of the full cohort of JUPITER, the effects of rosuvastatin 20 mg versus placebo on rates of non-fatal MI, non-fatal stroke, admission for unstable angina, arterial revascularization, or CV death (pre-specified endpoints) during a maximum follow-up of 5 years (median, 1.9 years) was assessed.[321] Compared with placebo, rosuvastatin patients who achieved LDL-C < 1.8 mmol/L (70 mg/dL) had a 55% reduction in CV events (HR, 0.45; 95% CI, 0.34 to 0.6; p<0.0001), and those achieving hsCRP < 2 mg/L had a 62% reduction (HR, 0.38, 95% CI, 0.26 to 0.56; p<0.0001). Although LDL-C and hsCRP reductions were only weakly correlated in individual patients, the analysis

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found a 65% reduction in CV events in the rosuvastatin group who achieved both LDL-C < 1.8 mmol/L (70 mg/dL) and hsCRP < 2 mg/L (adjusted HR, 0.35; 95% CI, 0.23 to 0.54), versus a 33% reduction in those who achieved 1 or neither target (HR, 0.67; 95% CI, 0.52 to 0.87) (p<0.0001 for all treatment groups). In participants who achieved LDL-C < 1.8 mmol/L (70 mg/dL) and hsCRP < 1 mg/L, a 79% reduction (HR, 0.21; 95% CI, 0.09 to 0.52) was noted.

The JUPITER trial included 12,683 Caucasians and 5,117 non-Caucasians.[322] In patients randomized to rosuvastatin 20 mg, a 45% reduction in the primary endpoint among was seen among Caucasians (HR, 0.55; 95% CI, 0.43 to 0.69) and a 37% reduction was seen among non-Caucasians (HR, 0.63; 95% CI, 0.41 to 0.99). African-Americans (HR, 0.65; 95% CI, 0.35 to 1.22) and Hispanics (HR, 0.58; 95% CI 0.25 to 1.39) had similar risk reductions. Among non-Caucasians in the placebo group, the stroke rate exceeded the MI rate (0.44 versus 0.2 per 100 person-years); however, among Caucasians the stroke rate was less than the MI rate (0.31 versus 0.42 per 100 person-years). Non-Caucasians had higher death rates than Caucasians (2.25 versus 0.93 per 100 person-years); however, all-cause mortality was similar with rosuvastatin treatment in both participant groups.

AURORA:[323] A randomized, double-blind, prospective, multicenter study of 2,776 patients who were undergoing maintenance hemodialysis compared rosuvastatin 10 mg daily to placebo. The combined primary endpoint was death from CV causes, nonfatal MI, or nonfatal stroke. Secondary endpoints included death from all causes and individual cardiac and vascular events. After 3 months, the mean reduction in LDL-C levels was 43% in patients receiving rosuvastatin, from a mean baseline level of 100 mg/dL. However rosuvastatin had no significant effect on the composite primary endpoint of death from CV causes, nonfatal MI, or nonfatal stroke. During a median follow-up period of 3.8 years, 396 patients in the rosuvastatin group and 408 patients in the placebo group reached the primary endpoint (9.2 and 9.5 events per 100 patient-years, respectively; HR for the combined endpoint in the rosuvastatin group versus the placebo group, 0.96; 95% CI, 0.84 to 1.11; p=0.59). Rosuvastatin had no effect on individual components of the primary endpoint. There was also no significant effect on all-cause mortality (13.5 versus 14 events per 100 patient-years; HR, 0.96; 95% CI, 0.86 to 1.07; p=0.51).

rosuvastatin (Crestor, Ezallor Sprinkle) versus atorvastatin (Lipitor)

SATURN:[324] This double-blind clinical trial randomized 1,039 patients with coronary disease to receive atorvastatin 80 mg or rosuvastatin 40 mg daily. After 104 weeks of therapy, although lower LDL-C levels and higher HDL-C levels were reported in the rosuvastatin group versus the atorvastatin group (p=0.01 for each), there was no significant difference in the primary efficacy endpoint, percent atheroma volume (PAV). Regression of PAV was reported in 63.2% of patients with atorvastatin and 68.5% with rosuvastatin (p=0.07).

An open-label trial with 696 Hispanic patients at medium to high risk for CHD compared the mean LDL-C reductions with atorvastatin (Lipitor) and rosuvastatin (Crestor) over 6 weeks.[325] Patients were randomized to atorvastatin or rosuvastatin 10 or 20 mg daily. Both doses of rosuvastatin were associated with greater reductions in LDL-C compared to atorvastatin. Comparing the 10 mg doses of each, rosuvastatin produced significantly greater reductions in LDL-C (45% rosuvastatin, 36% atorvastatin; p<0.0001). For the 20 mg doses, rosuvastatin (50%) reduced LDL-C to a greater degree than atorvastatin (42%; p<0.0001). Achievement of the target levels of LDL-C of < 100 mg/dL was reported for 74% and 91% for the rosuvastatin 10 mg and 20 mg doses and 52% and 62% for atorvastatin 10 mg and 20 mg doses, respectively. Adverse events were similar between the groups.

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In an open-label randomized trial in the US and Canada, 740 patients of South-Asian origin with hypercholesterolemia received rosuvastatin (Crestor) 10 or 20 mg or atorvastatin (Lipitor) 10 or 20 mg daily.[326] A total of 66% of patients were considered as being high risk for CAD. LDL-C decreased by 45% with rosuvastatin 10 mg versus 40% with atorvastatin 10 mg (p=0.0023) and by 50% with rosuvastatin 20 mg versus 47% with atorvastatin 20 mg (p=NS). Most patients reached LDL-C goals, and both drugs were well tolerated. According to the prescribing information for rosuvastatin (Crestor), Asian patients should start on 5 mg daily.[327]

simvastatin (Zocor)

Heart Protection Study (HPS) Collaborative Group:[328] A 5-year trial to evaluate the effect of simvastatin 40 mg daily compared to matching placebo enrolled 20,536 patients with CHD, other arterial disease, or diabetes for the effects of simvastatin on mortality, coronary event rates, major vascular events and stroke. All-cause mortality was significantly lower in the simvastatin group (12.9%) compared to the placebo group (14.7%), with reduction in mortality seen in both vascular and nonvascular causes (p=0.0003). The percentage of patients experiencing a first major vascular event (coronary event, stroke, or revascularization) was significantly lower in the simvastatin group (19.8% versus 25.2%; p<0.0001). Similar results were seen in the diabetic population (n=5,963).[329] Simvastatin produced a 25% reduction in the incidence of first stroke and a 24% reduction in revascularization procedures. For patients with a history of cerebrovascular disease, there was no significant difference in recurrent strokes, but there was a 20% risk reduction in the rate of any major vascular event (p=0.001).[330] Of the 3,500 patients with baseline LDL-C below 100 mg/dL, simvastatin-treated patients were observed to have similar risk reductions as compared to simvastatin-treated patients with higher baseline LDL-C levels. In patients with peripheral arterial disease (PAD), simvastatin was associated with a highly significant 22% relative reduction in the rate of first major vascular event (95% CI, 15 to 29; p<0.0001).[331] No significant differences in muscle symptoms or discontinuations due to muscle symptoms were observed between the 2 groups. The incidence of elevated liver enzymes was not significantly different between simvastatin and placebo groups. In a subgroup analysis of HPS, patients were divided into 6 groups based on CRP levels (< 1.25, 1.25 to 1.99, 2 to 2.99, 3 to 4.99, 5 to 7.99, and ≥ 8 mg/L).[332] The primary endpoint for this intent-to-treat subgroup analyses was major vascular events (composite of coronary death, myocardial infarction, stroke, or revascularization). Simvastatin had a significant (24%; 95% CI, 19 to 28) proportional reduction in the incidence of first major vascular event after randomization (19.8% allocated simvastatin versus 25.2% allocated placebo). There was no evidence that the proportional reduction in this endpoint, or its components, differed with baseline CRP concentration (trend p=0.41). Even in patients with baseline CRP under 1.25 mg/L, major vascular events were significantly reduced by 29% (99% CI, 12 to 43; p<0.0001). No significant heterogeneity in the relative risk reduction was observed between the subgroups defined by the combination of low or high baseline concentrations of LDL cholesterol and CRP (p=0.72). There was benefit in patients with low LDL-C and low CRP (27% relative reduction; 99% CI, 11 to 40; p<0.0001).

The effects of early intensive therapy or delayed initiation and less intensive therapy of simvastatin following an ACS event were investigated in the phase Z of the A to Z trial.[333] The randomized, double-blind trial allocated patients to either (early therapy) simvastatin 40 mg daily for one month followed by simvastatin 80 mg daily (n=2,265) or (delayed therapy) placebo for 4 months followed by simvastatin 20 mg daily (n=2,232). The composite of cardiovascular death, nonfatal MI, rehospitalization for ACS, or stroke occurred in 14.4% and 16.7% of the early and delayed therapy,

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respectively. This difference was not statistically significant (p=0.14). The only significant difference between the early and delayed therapy in individual endpoints was in cardiovascular death, which occurred in 5.4% and 4.1% of patients, respectively (HR, 0.75; 95% CI, 0.57 to 1; p=0.05). Myopathy (creatine phosphokinase [CPK] > 10 times upper limit of normal) occurred in 0.4% of simvastatin patients receiving 80 mg daily (p=0.02), whereas no patients receiving lower doses of simvastatin and only 1 patient taking placebo had evidence of myopathy.

A double-blind randomized trial studied the efficacy and safety of more intensive statin treatment in patients at high cardiovascular risk.[334] Patients (n=12,064) with a history of MI who were either currently on or had clear indication for statin therapy and had a total cholesterol concentration of at least 3.5 mmol/L if already on a statin or 4.5 mmol/L if not were randomized to either 80 mg or 20 mg simvastatin daily. Participants were assessed at 2, 4, 8, and 12 months and then every 6 months until final follow-up. The primary endpoint was major vascular events, defined as coronary death, MI, stroke, or arterial revascularization. During a mean follow-up of 6.7 years, simvastatin 80 mg produced an average 0.35 mmol/L greater reduction in LDL cholesterol compared with simvastatin 20 mg. Major vascular events occurred in 24.5% of participants on simvastatin 80 mg compared to 25.7% of those on simvastatin 20 mg, corresponding to a 6% reduction (risk ratio, 0.94; 95% CI, 0.88 to 1.01; p=0.1). Two (0.03%) cases of myopathy were reported in patients taking simvastatin 20 mg versus 53 (0.9%) cases in the 80 mg group.

simvastatin oral suspension (Flolipid)

The FDA-approval for simvastatin oral suspension was based on clinical studies for simvastatin tablets (Zocor).

simvastatin / ezetimibe (Vytorin)

Several studies with surrogate endpoints have compared the combination of ezetimibe and simvastatin to its individual components, atorvastatin, and rosuvastatin.[335,336,337,338,339,340,341] Validated surrogate markers are those for which evidence has established that a drug-induced effect on the surrogate predicts the desired effect on the clinical outcome of interest.[342]

SHARP: In a double-dummy study, patients (n=9,438) with advanced CKD, of which 3,056 were on dialysis, with no known history of MI or coronary revascularization were randomized in a ratio of 4:4:1 to daily ezetimibe 10 mg plus simvastatin 20 mg, matching placebo, or simvastatin 20 mg (with the latter arm re-randomized at 1 year to ezetimibe 10 mg plus simvastatin 20 mg versus placebo).[343,344,345] A total of 3,056 patients in the study were on dialysis. After a median follow-up of 4.9 years, patients that received ezetimibe/simvastatin combination experienced a 17% reduction in major atherosclerotic events (defined as the combination of MI, coronary death, ischemic stroke, or any revascularization procedure) compared to placebo (p=0.0022). Compared with placebo, ezetimibe/simvastatin resulted in average LDL-C differences of 43 mg/dL at 1 year and 33 mg/dL at 2.5 years. Ezetimibe/simvastatin was not associated with any excess of myopathy, hepatic toxicity, or biliary complications compared to placebo, or compared to simvastatin alone (at 1 year). There was no difference in incidence of cancer between groups (9.5% for each).

The Simvastatin and Ezetimibe in Aortic Stenosis Study (SEAS), a randomized, double-blind, placebo-controlled, multicenter, 52.2-month trial of 1,873 patients with mild to moderate aortic stenosis, found no reduction in the primary endpoint of major cardiovascular events with simvastatin/ezetimibe

(Vytorin) compared to placebo.[346,347,348] However, there was a decrease in a pre-specified secondary endpoint of atherosclerotic disease events.

Summary of Large Clinical Trials

Drug	Primary Prevention	Secondary Prevention
atorvastatin (Lipitor)	ASCOT-LLA[349], CARDS[350]	MIRACL[351], GREACE[352], PROVE IT-TIMI 22[353], TNT[354], IDEAL[355], ASPEN[356], SPARCL[357]
ezetimibe/simvastatin (Vytorin)	--	IMPROVE-IT[358]
fluvastatin	--	LIPS[359]
lovastatin	AFCAPS/TexCAPS[360]	--
pitavastatin (Livalo, Zypitamag)	--	--
pravastatin	WOSCOPS[361], PROSPER[362], ALLHAT[363], MEGA[364]	CARE[365], LIPID[366], PROSPER[367], PACT[368], PROVE IT-TIMI 22[369]
rosuvastatin (Crestor, Ezallor Sprinkle)	JUPITER[370]	--
simvastatin (Flolipid, Zocor)	HPS[371]	4S[372], HPS[373], Phase Z of A to Z[374], IDEAL[375]

The IMPROVE-IT study evaluated the safety and efficacy of ezetimibe 10 mg/simvastatin 40 mg fixed-dose combination compared to simvastatin 40 mg alone in reducing CV events in 18,144 patients with recent acute coronary syndrome (ACS).[376] This study reported reductions in LDL-C as early as 1 month, and reductions in triglyceride and increases in HDL-C at 1 year. The average reduction in LDL-C with the addition of ezetimibe was 17 mg/dL. The primary composite endpoint of CV death, MI, unstable angina, stroke, and coronary revascularization beyond 30 days of randomization was significantly lower in the ezetimibe/simvastatin group compared with the simvastatin group (32.7% versus 34.7%, respectively; p=0.016) during the 7-year follow-up period, with reports of significant reduction for all endpoint components. This translates to a reduction of 2 ACS events for every 100 patients treated with combination therapy. Diabetic patients appeared to have a greater benefit with combination therapy. Incidence of cancer was similar in both groups (10.2%).

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LDL-C Reductions[377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404]

Drug	< 25% decrease	25% to 35% decrease	36% to 45% decrease	46% to 50% decrease	51% to 60% decrease
atorvastatin (Lipitor, Caduet)	--	10 mg	10 mg to 20 mg	40 mg	80 mg
ezetimibe / simvastatin (Vytorin)	--	--	10/10 mg	10/10 mg to 10/20 mg	10/20 mg to 10/80 mg
fluvastatin	20 mg to 40 mg	40 mg to 80 mg	80 mg	--	--
fluvastatin XL (Lescol XL)	--	80 mg	80 mg	--	--
lovastatin	10 mg to 20 mg (including 20 mg every other day)	20 mg to 40 mg (including 20 mg every other day)	40 mg to 80 mg	--	--
lovastatin ER (Altoprev)	10 mg	10 mg to 40 mg	40 mg to 60 mg	--	--
pitavastatin (Livalo, Zypitamag)	--	--	2 mg to 4 mg	--	--
pravastatin (Pravachol)	10 mg to 20 mg	20 mg to 40 mg	80 mg	--	--
rosuvastatin (Crestor, Ezallor Sprinkle)	--	--	5 mg to 10 mg	10 mg	10 mg to 40 mg
simvastatin (Zocor)	5 mg	5 mg to 20 mg	20 mg to 80 mg	80 mg*	--

Reductions in LDL-C are obtained from prescribing information and clinical trials and, therefore, should not be considered comparative.

* Per FDA safety communication in June 2011, simvastatin 80 mg has the potential increased risk of myopathy compared with lower doses of simvastatin and possibly other drugs in the statin class.[405] Simvastatin 80 mg dose should only be used by patients who have been taking it for 12 months or longer without ill effect. If simvastatin 40 mg is not meeting LDL cholesterol goal, therapy should be changed to a different statin rather than raising the simvastatin dose.

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Effects on TG and HDL-C [406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427]

Drug	Triglyceride change (%)	HDL-C change (%)
atorvastatin (Lipitor, Caduet) 10 mg to 80 mg	-17 to -37	-0.1 to 9
ezetimibe / simvastatin (Vytorin) 10/10 mg to 10/80 mg	-23 to -35	6 to 12
fluvastatin 10 mg to 80 mg	- 2.7 to - 23	-3 to 9
fluvastatin XL (Lescol XL) 80 mg	-19 to -25	7 to 11
lovastatin 20 mg to 80 mg	-6 to -27	3 to 10
lovastatin ER (Altoprev) 10 mg to 60 mg	-10 to -33	6 to 13
pitavastatin (Livalo, Zypitamag) 2 mg to 4 mg	-14 to -22	2 to 7
pravastatin (Pravachol) 10 mg to 80 mg	-9 to -24	2 to 12
rosuvastatin (Crestor, Ezallor Sprinkle) 5 mg to 40 mg	-10 to -35	8 to 14
simvastatin (Flolipid, Zocor) 5 mg to 80 mg	-9 to -34	3 to 16

Effects on TG and HDL-C are obtained from prescribing information and clinical trials and therefore, should not be considered comparative.

META-ANALYSIS

A meta-analysis evaluated the trials (TNT, IDEAL, AtoZ, and PROVE IT/TIMI-22) comparing the intensive lipid-lowering with moderate statin therapy in a total of 27,548 patients.[428] A pooled analysis for intensive lipid-lowering was associated with 16% odds reduction (p<0.000001) for coronary death or MI.

A meta-analysis of 27,548 patients with ACS or stable CAD from 4 randomized, controlled trials comparing intensive to moderate dose statin therapy was done from 1995 to 2006.[429] Intensive dose therapy with atorvastatin or simvastatin 80 mg was associated with better reductions in CV death (OR, 0.86; 95% CI, 0.75 to 0.99; p=0.031), MI (OR, 0.84; 95% CI, 0.76 to 0.93; p<0.001), and stroke (OR, 0.82; 95% CI, 0.72 to 0.94; p=0.004). However, intensive dose therapy was also associated with an increased risk for any adverse event (OR, 1.44; 95% CI, 1.33 to 1.55; p<0.001) and an increased risk for LFT and CK elevations.

A meta-analysis evaluated data from 13 statin studies that included a total of 90,056 patients. The meta-analysis included large statin trials beginning with 4S, published in 1994, and concluding with CARDS, published in 2004. Assuming appropriate adherence and achievement of approximately 39 mg/dL (1 mmol/L) reduction in LDL-C, statins can reduce the 5-year incidence of major coronary events and revascularization by approximately 20%.[430]

A meta-analysis of 15 randomized controlled statin trials through May 2006 looked at gender specific incidence of cardiovascular events.[431] Cardiovascular events were reduced in men (RR, 0.76; 95% CI, 0.7 to 0.81) and women (RR, 0.79; 95% CI, 0.69 to 0.9). Reductions in mortality, MI, and stroke predominantly contributed to the reduction in cardiovascular events in men on statins, but women did not have a reduction in mortality or stroke.

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Treatment with ezetimibe 10 mg/day or placebo added to current statin therapy was compared in a meta-analysis of 5 randomized controlled trials with at least 6 weeks duration in 5,039 adults with hypercholesterolemia.[432] The weighted mean difference between treatments significantly favored the ezetimibe/statin combination over placebo/statin for total cholesterol (-16.1%; 95% CI, -17.3 to -14.8; p<0.0001), LDL-C (-23.6%; 95% CI, -25.6 to -21.7; p<0.0001), and HDL-C (1.7%; 95% CI, 0.9 to 2.5; p<0.0001). The relative risk of reaching the LDL-C treatment goal was significantly higher for patients on ezetimibe/statin relative to those on placebo/statin (RR, 3.4; 95% CI, 2 to 5.6; p<0.0001). In pre-defined sub-group analyses of studies in patients with CHD, the weighted mean difference between treatments remained significantly in favor of ezetimibe/statin (p<0.0001) for total cholesterol and LDL-C but was no longer significant for HDL-C. Elevations in liver enzymes did not differ significantly between groups.

A systematic overview of 18 randomized controlled trials of combination statin and ezetimibe trials was performed to assess risk in 14,471 patients.[433] Compared with statin monotherapy, combination therapy did not result in significant absolute increases in risks of myalgias (risk difference, -0.033; 95% CI, -0.06 to -0.01), creatine kinase increases (risk difference, 0.011; 95% CI, -0.02 to 0.04), rhabdomyolysis (risk difference, -0.003; 95% CI, -0.01 to 0.004), transaminase increases (risk difference, -0.003; 95% CI, -0.01 to 0.005), gastrointestinal adverse events (risk difference, 0.005; 95% CI, -0.03 to 0.04), or discontinuations because of an adverse event (risk difference, -0.005; 95% CI, -0.03 to 0.02). This systematic review showed that the addition of ezetimibe to statin therapy did not increase the risk of myalgias, creatine kinase levels, rhabdomyolysis, transaminase levels, gastrointestinal adverse events, or discontinuations due to an adverse event.

A meta-analysis compared the overall efficacy of statins on cardiac morbidity and mortality in hypertensive and non-hypertensive patients enrolled in major randomized clinical trials including the ASCOT-LLA and ALLHAT-LLT trials.[434] Statin therapy decreased cardiac death by 24% (RR, 0.76; 95% CI, 0.71 to 0.82). There was no evidence of difference in RR estimates for hypertensive (RR, 0.78; 95% CI, 0.72 to 0.84) and non-hypertensive (RR, 0.76; 95% CI, 0.72 to 0.8) patients. This study showed that statin therapy decreases CV morbidity and mortality to the same extent in hypertensive and non-hypertensive patients.

A meta-analysis of randomized controlled trials comparing different intensities of statin therapy was conducted to evaluate the evidence for aggressive LDL-C lowering in CAD patients.[435] A search of electronic databases including, MEDLINE, EMBASE, Cochrane Central Registry of Controlled Trials, and Web of Science for randomized controlled trials published up to July 19, 2007, identified studies that compared statin regimens of different intensities in adults with CAD and that reported CV events or mortality. Seven trials consisting of 20,395 patients were included. As expected, more intensive statin regimens compared to less intensive regimens further reduced LDL-C levels (0.72 mmol/L reduction; 95% CI, 0.6 to 0.84 mmol/L), and reduced the risk of MI (OR, 0.83; 95% CI, 0.77 to 0.91) and stroke (OR, 0.82; 95% CI, 0.71 to 0.95). Although there was no effect on mortality among patients with chronic CAD (OR, 0.96; 95% CI, 0.8 to 1.14), all-cause mortality was reduced in patients with ACS treated with more intensive statin regimens (OR, 0.75; 95% CI, 0.61 to 0.93) compared with lower intensity regimens. Intensive regimens were associated with small absolute increases in rates of drug discontinuation (2.5%), elevated levels of aminotransferases (1%), and myopathy (0.5%). In addition, there was no difference in non-CV mortality. This meta-analysis shows the benefit of more intensive statin regimens in patients with established CAD. The study does not find sufficient evidence to treat to particular LDL-

C targets, using combination lipid-lowering therapy to achieve these targets, or for using more intensive regimens in patients without established CAD.

A meta-analysis of 20 randomized trials of at least 12-months duration in predominantly primary prevention populations showed that statins are effective in primary prevention of CV events.[436] The study pooled 19 trials (n=63,899) for all-cause mortality and found a RR of 0.93 (95% CI, 0.87 to 0.99; p=0.03). Eighteen trials (n=59,469) assessed CV deaths (RR, 0.89; 95% CI, 0.81 to 0.98; p=0.01). Seventeen trials (n=53,371) found an RR of 0.85 (95% CI, 0.77 to 0.95; p=0.004) for major CV events, and 17 trials (n=52,976) assessed MIs (RR, 0.77; 95% CI, 0.63 to 0.95; p=0.01). Incidence of cancer or rhabdomyolysis were not elevated in 10 trials (n=45,469).

Cardiovascular disease is the leading cause of death in women in the US.[437] A meta-analysis, identified 11 trials including 43,193 patients with CV disease, of which 20.6% were women. This study reported a similar reduction in risk of CV events in all outcomes for women and men.[438] However, statins did not reduce all-cause mortality in women compared to men (RR, 0.92 [95% CI, 0.76 to 1.13] versus RR, 0.79 [95% CI, 0.72 to 0.87]) or stroke (RR, 0.92 [95% CI, 0.76 to 1.1] versus RR, 0.81 [95% CI, 0.72 to 0.92]). Possible study limitations include potential for omission of pertinent studies due to the literature search confined to PubMed and English language, and data being extracted by a single investigator.[439] Another recent meta-analysis evaluating the benefit of statins in primary and secondary prevention, included 18 randomized clinical trials of statins with sex-specific outcomes (n=141,235; 40,275 women). This analysis reported similar reduction in CV event rate in women and men receiving statins (OR, 0.81; 95% CI, 0.75 to 0.89; p<0.0001, and OR, 0.77; 95% CI, 0.71 to 0.83; p<0.0001, respectively).[440] All-cause mortality was also lower with statin therapy both in women and men without significant interaction by gender (p=0.44).

A Cochrane database systematic review evaluated statins for primary prevention of CVD. Eighteen randomized controlled trials (19 cohorts; n=56,934; over 60% male and approximately 39% female) were included. Fourteen trials recruited patients with specific conditions (elevated lipids, diabetes, hypertension, microalbuminuria).[441] All-cause mortality was reduced by statins (OR, 0.86; 95% CI, 0.79 to 0.94), as well as combined fatal and non-fatal CVD (RR, 0.75; 95% CI, 0.7 to 0.81), combined fatal and non-fatal CHD events (RR, 0.73; 95% CI, 0.67 to 0.8), and combined fatal and non-fatal stroke (RR, 0.78; 95% CI, 0.68 to 0.89). There was also a reduction of revascularization rates (RR, 0.62; 95% CI, 0.54 to 0.72). Total cholesterol and LDL-C were reduced in all trials but there was evidence of heterogeneity of effects. Statins did not cause any serious adverse events. New-onset diabetes was observed in 1 of the 2 trials reporting this outcome (RR, 1.18; 95% CI, 1.01-1.39). The incidence of cancers, myalgia, rhabdomyolysis, liver enzyme elevation, renal dysfunction, or arthritis did not differ between the groups.

A meta-analysis to evaluate the effectiveness and safety of statins in children ages 4 to 18 years with heterozygous familial hypercholesterolemia was published in 2019.[442] In total, 9 randomized controlled trials were included in the analysis, representing 1,177 patients. Included studies compared the lipid lowering effects of statin therapies to placebo. After a median treatment duration of 24 weeks, LDL reductions were significantly greater in those treated with statin therapies (mean relative reduction, -32.15%; 95% CI, -34.9 to -29.4). This study demonstrated the lipid lowering effects of statin therapies in children with familial hypercholesterolemia and identified limited safety concerns. Due to the short term nature of the included studies, long-term pediatric studies are needed in order to establish the safety profile of extended use of statins in this population.

A 2020 network meta-analysis evaluated all-cause mortality and cardiac events between statin therapies in patients with chronic kidney disease (CKD).[443] Nineteen randomized controlled trials were included representing 45,863 patients with CKD for analysis. Compared to placebo, pravastatin 40 mg was the only statin dosage associated with a statistically significant reduction in all-cause mortality (OR, 0.75; 95% credible interval [CrI], 0.53 to 0.98). Other statins, such as atorvastatin 80 mg, fluvastatin 40 mg, rosuvastatin 10 mg, and simvastatin 40 mg did not show a benefit above placebo for mortality. Cardiac events evaluated in the analysis included death from coronary heart disease, non-fatal acute myocardial infarction, resuscitation after cardiac arrest, cardiac revascularization, and hospital admission for unstable angina. Several statin doses were shown to significantly reduce the odds for cardiac events compared to placebo, including atorvastatin 80 mg (OR, 0.72; CrI, 0.52 to 0.98), fluvastatin 40 mg (OR, 0.67; CrI, 0.43 to 0.99), lovastatin 20 mg (OR, 0.37; CrI, 0.13 to 0.92), pravastatin 40 mg (OR, 0.67; CrI, 0.51 to 0.85), and simvastatin 40 mg (OR, 0.72; CrI 0.55 to 0.92). Notably, rosuvastatin 10 mg, atorvastatin 10 mg, and simvastatin/ezetimibe 20 mg/10 mg did not demonstrate a statistically significant difference from placebo for cardiac events.

Another 2020 meta-analysis evaluated the lipid lowering effects of combination therapy with ezetimibe 10 mg and a statin compared to a doubling of the statin dose in adult patients with hypercholesterolemia.[444] Eleven randomized placebo or active controlled studies were included in the meta-analysis, representing 1,926 patients. Patients receiving combination ezetimibe and statin therapy demonstrated statistically significant decreases in LDL-C from baseline compared to double dose statin therapy (weighted mean difference [WMD], -13.14 mg/dL; 95% CI, -16.83 to -9.44; p=0.00001). Additionally, statistically significant decreases in total cholesterol were also observed in the ezetimibe and statin group (WMD, -23.79 mg/dL; 95% CI, -38.65 to -8.93; p=0.002) compared to double dose statin therapy. The analysis for total cholesterol was determined to be based on studies with a high level of heterogeneity and therefore more studies are needed to confirm this benefit. No significant differences between groups were seen for HDL-C concentrations.

SUMMARY

In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) in combination with the National Heart, Lung, and Blood Institute (NHLBI) released 4 consensus guidelines regarding cholesterol management, cardiovascular (CV) risk assessment, obesity, and lifestyle. In 2018, the ACC/AHA, along with several other relevant professional organizations, published updated guidance on optimal lipid management. These guidelines emphasize lifestyle modification, including a reduced calorie diet and aerobic physical activity, as a critical component of ASCVD risk reduction. ACC/AHA guidelines no longer support a treat-to-target approach based on LDL-C goals, rather they support treatment decisions based on patients' risk status. The guideline recommends use of maximum tolerated statin intensity and classifies intensity of statin therapy based on the average expected LDL-C response to a specific statin and dose. High-intensity statin therapy on average lowers LDL-C by approximately ≥ 50%, moderate-intensity therapy lowers LDL-C by approximately 30% to < 50%, and lower-intensity statin therapy lowers LDL-C by approximately < 30%. The guidelines identify 4 benefit groups in which the potential for an ASCVD risk reduction benefit clearly exceeds the potential for adverse effects. These guidelines also recommend algorithms to estimate 10-year ASCVD risk.

The 2017, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) guidelines for the management of dyslipidemia and prevention of cardiovascular

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disease recommends aggressive lipid-modifying therapy to lower LDL-C, with statins as the drugs of choice. They recommend LDL goals of < 55 mg/dL, < 70 mg/dL, < 100 mg/dL, and < 130 mg/dL for individuals at extreme, very high, high/moderate, and low risk for cardiovascular events, respectively. Target non-HDL-C and apo B levels are also provided. 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 incorporate new data not available at the time of the 2017 guidelines. AACE/ACE maintains statins as primary therapy, and their 2020 algorithm recommends treatment intensification with the addition of other LDL-C lowering agents as needed to reach treatment goals. Treatment goals, based on ASCVD risk, also include target triglyceride levels.

Parts 1 and 2 of the National Lipid Association (NLA) recommendations for the management of dyslipidemia outline a patient-centered approach based on atherosclerotic CVD (ASCVD) risk assessment with an emphasis on lifestyle therapies as an important aspect of ASCVD risk-reduction. The NLA recommends lipid levels be used in conjunction with other ASCVD risk factors to assess overall risk and also support the use of risk calculators, such as the ATP III Framingham Risk Score and the ACC/AHA Pooled Cohort Equations. The NLA considers non-high density lipoprotein cholesterol (non-HDL-C) to be superior to LDL-C for predicting ASCVD event risk and now uses non-HDL-C measurements along with LDL-C as primary targets of therapy. Desirable targets 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 less than 100 mg/dL and 70 mg/dL, respectively. The NLA advises that intensity of risk-reduction therapy should be based on the patient's absolute risk for an ASCVD event. The NLA recommends lifestyle therapies for patients at low and moderate ASCVD event risk. For patients at high or very high-risk moderate to high intensity statin therapy is considered first-line.

The AHA advises that treatment for familial hypercholesterolemia (FH) should be based on LDL-C levels, not genetic abnormality or other clinical features. Initial goal is to reduce LDL-C by at least 50%, which can be followed by targets of LDL-C of less than 100 mg/dL (absence of CAD or other major risk factors) or 70 mg/dL (presence of CAD or other major risk factors). Initial drug monotherapy for those with FH includes high-intensity statin therapy. If needed, the addition of ezetimibe followed by a PCSK9 inhibitor, a bile acid sequestrant, or prescription strength niacin should be considered if target LDL-C is not met. Four-drug combination therapy with the addition of lomitapide or mipomersen can be considered in patients with homozygous FH if needed. Dietary and lifestyle modifications should also be an aspect of FH treatment.

Cardiovascular outcomes trials are desired since they directly measure clinical endpoints such as stroke, myocardial infarction, or cardiac death. However, since long-term trials in large patient populations are difficult to perform, coronary atherosclerosis surrogate endpoints are often used instead. These include LDL-C, various lipid parameters, C-reactive protein (CRP), and coronary intravascular ultrasound (IVUS).

Statins have demonstrated clear improvements in primary and secondary prevention of CV events. They have shown a decrease in the incidence of myocardial infarction, stroke, need for revascularization, angina hospitalization, CV mortality, and overall mortality. Addition of a non-statin drug may be considered to further lower LDL-C, and the 2020 AACE/ACE algorithm advocates for progression of therapy intensity in order to reach LDL-C targets. The addition of ezetimibe to

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simvastatin (Vytorin) showed a modest benefit in reducing CV events over simvastatin alone post-acute coronary syndrome (ACS).

The combination agent atorvastatin/amlodipine (Caduet) has not been proven to offer a substantial benefit on CV morbidity and mortality over and above that of the statin component. In April 2016, the FDA withdrew approval for indications for coadministration of niacin ER with a statin. Available data no longer support that use of these agents together results in a risk reduction in CV events.

In August 2017, simvastatin oral suspension (Flolipid) became available as the first oral liquid statin formulation approved by the FDA. In June 2019, rosuvastatin capsules (Ezallor Sprinkles) became available; capsules may be opened and contents sprinkled onto select foods for immediate consumption or contents may be administered via nasogastric (NG) tube.

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