



Lipotropics, Statins Therapeutic Class Review (TCR)

October 29, 2015

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MagellanRx
MANAGEMENTSM

AGENTS

Drug	Manufacturer
amlodipine / atorvastatin (Caduet [®]) ¹	generic; Pfizer
atorvastatin (Lipitor [®]) ²	generic; Pfizer
ezetimibe / atorvastatin (Liptruzet [®]) ³	Merck Sharp and Dohme
ezetimibe / simvastatin (Vytorin [®]) ⁴	Merck Sharp and Dohme
fluvastatin (Lescol [®]) ⁵	generic; Novartis
fluvastatin ER (Lescol XL [®]) ⁶	generic; Novartis
lovastatin ⁷	generic
lovastatin ER (Altoprev [®]) ⁸	Shionogi
niacin ER / lovastatin (Advicor [®]) ⁹	Abbvie
niacin ER / simvastatin (Simcor [®]) ¹⁰	Abbvie
pitavastatin (Livalo [®]) ¹¹	Kowa
pravastatin (Pravachol [®]) ¹²	generic; BMS
rosuvastatin (Crestor [®]) ¹³	AstraZeneca
simvastatin (Zocor [®]) ¹⁴	generic; Merck Sharp and Dohme

In June, 2015 Merck notified the FDA that Liptruzet has been discontinued. In January 2014, Merck voluntarily recalled all lots of Liptruzet due to a packaging defect. Merck expected that the supply would be depleted and decided not to resupply the product.

Abbvie has voluntarily discontinued all strengths of niacin ER-lovastatin (Advicor) and niacin ER-simvastatin (Simcor). Supply of these agents will be available until the end of 2015.

FDA-APPROVED INDICATIONS

Indications	fluvastatin (Lescol) fluvastatin ER (Lescol XL) ^{15,16}	lovastatin ¹⁷	lovastatin ER (Altprev) ¹⁸	niacin ER/lovastatin (Advicor) ^{19*}	pravastatin (Pravachol) ²⁰
Primary hypercholesterolemia ▪ Heterozygous familial and nonfamilial Reduce: Total-C, LDL-C, TG and ApoB	X	X	X	X	X
Heterozygous familial hypercholesterolemia ▪ pediatric	X 10–16 years	X 10–17 years	--	--	X 8 years and older
Mixed dyslipidemia <i>Fredrickson Type</i> ▪ II _a and II _b Reduce: Total-C, LDL-C, TG and ApoB	X	X To reduce total-C, LDL-C	X	X	X
Increase HDL-C	X	--	X	X	X
Hypertriglyceridemia <i>Fredrickson Type IV</i>	--	--	--	X	X
Primary dysbetalipoproteinemia <i>Fredrickson Type III</i>	--	--	--	--	X
Homozygous familial hypercholesterolemia	--	--	--	--	--
Atherosclerosis ▪ slow progression	X	X	X	--	X

* Niacin ER/lovastatin (Advicor) is indicated in hypertriglyceridemia (Fredrickson Types IV and V).

FDA-Approved Indications (continued)

Indications	fluvastatin (Lescol) fluvastatin ER (Lescol XL)	lovastatin	lovastatin ER (Altoprev)	niacin ER/lovastatin (Advicor)*	pravastatin (Pravachol)
CVD <ul style="list-style-type: none"> primary prevention of coronary events 	--	Reduces risk of MI, unstable angina, coronary revascularization	Reduces risk of MI, unstable angina, coronary revascularization	--	Reduces risk of MI, myocardial revascularization, CV mortality
CHD <ul style="list-style-type: none"> secondary prevention of coronary events 	Reduces risk of coronary revascularization	--	--	--	Reduces risk of MI, myocardial revascularization, CV mortality, stroke/TIA

* Niacin ER/lovastatin (Advicor) is indicated in hypertriglyceridemia (Fredrickson Types IV and V).

FDA-Approved Indications (continued)

Indications	atorvastatin (Lipitor), amlodipine/ atorvastatin (Caduet)** 21,22	pitavastatin (Livalo) ²³	rosuvastatin (Crestor)*** ²⁴	simvastatin (Zocor) ²⁵	ezetimibe / atorvastatin, ezetimibe/ simvastatin (Liptruzet, Vytorin) ^{26,27}	niacin ER/ simvastatin (Simcor) ²⁸
Primary hypercholesterolemia ▪ Heterozygous familial and nonfamilial Reduce: Total-C, LDL-C, TG and ApoB	X	X	X	X	X	X
Heterozygous familial hypercholesterolemia ▪ pediatric	X 10–17 years; not Caduet	--	X 10–17 years	X 10–17 years	--	--
Mixed dyslipidemia <i>Fredrickson Type</i> ▪ II _a and II _b Reduce: Total-C, LDL-C, TG and ApoB	X	--	X	X	X	X
Increase HDL-C	X	X	X	X	X	X
Hypertriglyceridemia <i>Fredrickson Type IV</i>	X	--	X	X	--	X
Primary dysbetalipoproteinemia <i>Fredrickson Type III</i>	X	--	X	X	--	--
Homozygous familial hypercholesterolemia	X	--	X	X	X	--
Atherosclerosis ▪ slow progression	--	--	X	--	--	--

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

***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., HTN, low HDL-C, smoking, or a family history of CAD).

FDA-Approved Indications (continued)

Indications	atorvastatin (Lipitor), amlodipine/ atorvastatin (Caduet)**	pitavastatin (Livalo)	rosuvastatin (Crestor)***	simvastatin	ezetimibe / atorvastatin, ezetimibe/ simvastatin (Vytorin)	niacin ER/ simvastatin (Simcor)
CVD <ul style="list-style-type: none"> primary prevention of coronary events 	Reduces risk of MI, stroke, revascularization, angina	--	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 revascularization in high risk patients	--	--
CHD <ul style="list-style-type: none"> 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 total mortality risk by reducing CHD death, MI, stroke, and revascularization	--	--

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

***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., HTN, low HDL-C, smoking, or a family history of CAD).

OVERVIEW

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.²⁹ Clinical findings support the use of statins to prevent both nonfatal and fatal atherosclerotic cardiovascular disease (ASCVD) events.³⁰ 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 revascularizations compared with placebo.^{31,32} 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.

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.^{33,34,35,36} 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. 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.

As stated in the 2013 ACC/AHA Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults guideline, clinical ASCVD includes acute coronary syndromes (ACS), or a history of myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral arterial disease (PAD) presumed to be of atherosclerotic origin.³⁷ Until recently, 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.³⁸ 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 with 1 target lower than another is unknown. In addition, potential adverse effects from multidrug therapy that might be needed to achieve a specific goal have not been considered. However, percent reduction in LDL-C is appropriate as an indication of response and adherence to therapy. It is estimated that these new guidelines may increase the number of adults in the United States who would be eligible for statin therapy by 12.8 million, with the increase seen mostly among older adults without CVD as compared to the ATP III guidelines.³⁹

Clinical studies clearly show that ASCVD events are reduced by using the maximum tolerated statin intensity in predefined groups shown to benefit from statin therapy. Four benefit groups are identified in which the potential for an ASCVD risk reduction benefit clearly exceeds the potential for adverse effects.⁴⁰ These groups include adults with clinical ASCVD, those with primary elevations of LDL-C ≥ 190 mg/dL, those who are 40 to 75 years of age with diabetes with LDL-C 70 to 189 mg/dL, and those without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL-C 70 to 189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher. ASCVD prevention benefit of statin therapy may be less

clear in selected individuals who do not fall into 1 of the 4 benefit groups. For these patients, additional factors influencing ASCVD risk, such as primary LDL-C ≥ 160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD, high-sensitivity C-reactive protein > 2 mg/L, coronary artery calcium (CAC) score ≥ 300 Agatston units or ≥ 75 percentile for age, sex, and ethnicity, ankle-brachial index (ABI) < 0.9 , or elevated lifetime risk of ASCVD should be considered to evaluate the appropriateness of statin therapy. The guidelines recommend against routine use of carotid intima media thickness (CIMT); it should only be used as a research tool. For the primary prevention of ASCVD in individuals without clinical ASCVD and LDL-C 70 to 189 mg/dL, the estimated absolute 10-year risk of ASCVD (defined as nonfatal MI, CHD death, nonfatal and fatal stroke) should be used to guide the initiation of statin therapy. The 2013 guidelines no longer use the National Cholesterol Education Program (NCEP) Expert Panel on Diagnosis, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) algorithm for risk assessment because ATP III is derived in an exclusively White sample population and has a limited scope of the outcome in determining CHD alone.⁴¹ The new guidelines focus on the large proportion of the adult population without clinical signs or symptoms of ASCVD who merit evaluation for the primary prevention of ASCVD. They do not apply to those with clinically-manifest ASCVD, who require secondary prevention approaches. These guidelines recommend use of the race- and sex-specific Pooled Cohort Equations to predict 10-year risk for a first hard ASCVD event in non-Hispanic African-Americans and non-Hispanic Whites, 40 to 79 years of age. The variables that were determined to have statistical merit in these pooled cohort equations are age, total cholesterol, HDL-cholesterol, systolic blood pressure, diabetes (yes or no), and current smoking status (yes or no). They also suggest that if, after quantitative risk assessment, a risk based treatment decision is uncertain, assessment of 1 or more of the following: family history, hs-CRP, CAC score, or ABI may be considered to inform treatment decision making. It is reasonable to assess traditional ASCVD risk factors every 4 to 6 years in adults 20 to 79 years of age who are free from ASCVD and to estimate 10-year ASCVD risk every 4 to 6 years in adults 40 to 79 years of age without ASCVD.

ACC/AHA classifies the intensity of statin therapy based on the average expected LDL-C response to a specific statin and dose.⁴² High-intensity statin therapy on average lowers LDL-C by approximately $\geq 50\%$, moderate-intensity therapy lowers LDL-C by approximately 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. The ACC/AHA guidelines recommend high-intensity statin therapy for patients age 21 to 75 years with clinical ASCVD, patients with LDL-C ≥ 190 mg/dL, and for patients with diabetes and an estimated 10-year ASCVD risk $\geq 7.5\%$.⁴³ Moderate-intensity statin therapy is appropriate in those with clinical ASCVD who are not candidates for high-intensity therapy, for patients who are older than 75 years, and in diabetic patients age 40 to 75 years.

The 2014 AHA primary prevention of stroke guidelines 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. ACC/AHA recommends statin therapy for primary prevention in patients with a high 10-year risk of a CV event.⁴⁴

In 2012, the American Association of Clinical Endocrinologists (AACE) published guidelines for the management of dyslipidemia and prevention of atherosclerosis.⁴⁵ AACE recommends aggressive lipid-modifying therapy to lower LDL-C to <100 mg/dL in patients with average or elevated LDL-C and <70 mg/dL for all patients with established CAD. Statins are the drug of choice for LDL-C reduction. AACE supports the use of apolipoprotein B (apo B) in evaluating lipid status. They recommend an optimal apo B <90 mg/dL for patients at risk of CAD, while patients with established CAD or diabetes who have 1 or more additional risk factors should have an apo B <80 mg/dL. The MERCURY II trial demonstrated that aggressive LDL-C reduction in CHD patients can also reach targets for recommended apolipoprotein B (apo B) levels.⁴⁶ Patients appropriate for aggressive therapy are those undergoing coronary artery bypass graft (CABG) or with acute coronary syndrome (ACS). These guidelines address the unique challenges associated with atherosclerosis and heart disease in women and recommend pharmacotherapy, preferably with a 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 also includes guidance for lipid screening in the pediatric populations and recommend that children older than 2 years and adolescents older than 16 years be evaluated every 3 to 5 years and every 5 years, respectively, if they have CAD risk factors or a family history of premature CAD or dyslipidemia.

The National Lipid Association (NLA) published Parts 1 and 2 of their new recommendations for patient-centered management of dyslipidemia.^{47,48} 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 HIV/AIDS and rheumatoid arthritis, and those at risk based on ethnicity or race, such as Hispanics, African Americans and South Asians. The NLA outlines special considerations to take in to account when treating these specific patient populations.

The American Academy of Pediatrics (AAP) endorsed 2012 guidelines by the NHLBI on cardiovascular health and risk reduction in children and adolescents which outlines age appropriate lipid screening in the pediatric population.⁴⁹ NHLBI recommends a fasting lipid profile in children age 1 to 4 years, only if the child is positive for familial hypercholesterolemia (FH), the child has a parent with dyslipidemia, or if the child has any other risk factors or high-risk condition. 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.

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.⁵⁰ 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 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 with an initial goal in LDL-C reduction by at least 50%.⁵¹ 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 apoB and non-HDL-C have not been defined for FH. Initial drug monotherapy for those with FH includes high-intensity statin therapy (rosuvastatin or atorvastatin). If LDL-C goal is not met 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, cardiovascular and all-cause mortality has shown to occur even with modest LDL-C reduction. The addition of ezetimibe to statin therapy may provide an additional 10% to 15% LDL-C reduction. Other agents such as bile acid sequestrants, niacin, and fibrates result in only modest LDL-C-reducing effects in patients with HoFH. Four-drug combination therapy with the addition of lomitapide 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.⁵² The NHLBI sponsored Multi-Ethnic Study on Atherosclerosis (MESA) study is investigating buildup of measureable artery-hardening calcium and statin therapy outcomes, in patients who met the same criteria as the JUPITER study.⁵³ 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.⁵⁴ Coronary artery calcium (CAC) scores were stratified by scores of 0, 1 to 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.

PHARMACOLOGY^{55,56,57,58 59 60 61 62,63,64,65,66,67}

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 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.^{68,69}

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.^{70,71} The REVERSAL trial investigators found that a reduction in LDL-C and CRP leads to a slowing in progression of atherosclerosis.⁷² 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.⁷³ 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/atorvastatin (Liptruzet) and ezetimibe/simvastatin (Vytorin) are the combination of two lipid-lowering therapies which work together to lower LDL-C. Niacin ER/lovastatin (Advicor) and niacin ER/simvastatin (Simcor) provide beneficial effects on HDL-C and lower TG and 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.⁷⁴ 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, Liptruzet, 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.

Niacin (nicotinic acid) inhibits lipolysis in adipocytes and possibly inhibits hepatic TG production resulting in a reduction in the synthesis of VLDL-C and clearance of LDL-C. It may involve several actions including partial inhibition of the release of free fatty acids from adipose tissue, and increased lipoprotein lipase activity. Niacin decreases the rate of hepatic synthesis of VLDL and LDL-C. The combination products, niacin ER/lovastatin (Advicor) or niacin ER/simvastatin (Simcor), combine the efficacy of a statin with the beneficial effects of extended-release niacin for those patients failing monotherapy.⁷⁵

PHARMACOKINETICS^{76,77,78,79,80,81,82,83,84,85,86,87,88,89,90}

Drug	Bioavailability	Time to Peak Plasma Levels (hr)	Half-life (hr)	Excretion (%)	Circulating active metabolites
amlodipine and atorvastatin (Caduet)	64–90%	6–12	30–50	Urine: 70	No
	~14%; first pass metabolism	1–2	14	Urine: <2	Yes
atorvastatin (Lipitor)	~14%; first pass metabolism	1–2	14	Urine: <2	Yes
ezetimibe and atorvastatin (Liptruzet)	--	4–12	22	Urine: 11 Feces: 78	Yes
	~14%; first pass metabolism	1–2	14	Urine: <2	Yes
ezetimibe and simvastatin (Vytorin)	--	4–12	22	Urine: 11 Feces: 78	Yes
	<5% of oral dose reaches general circulation; first pass metabolism	4	3	Urine: 13 Feces: 60	Yes
fluvastatin (Lescol) (Lescol XL)	24%; first pass metabolism	<1	3	Urine: 5	No
	29%; first pass metabolism	3	9	Feces: 90	
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
niacin ER and lovastatin (Advicor)	72%	5	<1	Urine: 60	Yes
	<5% of oral dose reaches general circulation; first pass metabolism	2	4.5	Urine: 10 Feces: 83	Yes
niacin ER and simvastatin (Simcor)	dose dependent and variable; first pass metabolism	5	<1	Urine: 54	Yes
	<5% of oral dose reaches general circulation; first pass metabolism	4	4.2–4.9	Urine: 13 Feces: 60	Yes
pitavastatin (Livalo)	51%	1	12	Urine: 15 Feces: 79	Yes
pravastatin	17%; first pass metabolism	1–1.5	77	Urine: 20 Feces: 70	Yes
rosuvastatin (Crestor)	20%	3–5	19	Feces: 90	Yes
simvastatin	<5% of oral dose reaches general circulation; first pass metabolism	4	3	Urine: 13 Feces: 60	Yes

Atorvastatin and amlodipine (Caduet), ezetimibe and atorvastatin (Liptruzet), ezetimibe and simvastatin (Vytorin), niacin ER and lovastatin (Advicor), and niacin ER and simvastatin (Simcor) pharmacokinetic profiles are not affected by concurrent administration of the individual components.⁹¹

CONTRAINDICATIONS/WARNINGS^{92,93,94,95 96 97 98 99,100,101,102,103,104}

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 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.¹⁰⁵ The mechanism by which the statins cause myopathy and rhabdomyolysis is unknown.^{106,107,108}

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 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.¹⁰⁹ 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 initiated on an interacting drug that is contraindicated or is associated with a maximum dose for simvastatin, that 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.^{110,111,112} 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.

There have been rare reports of immune-mediated necrotizing myopathy (IMNM) associated with statin use. IMNM is characterized by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin therapy; muscle biopsy showing necrotizing myopathy without significant inflammation; and improvement with immunosuppressive agents.

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

for myopathy with coadministration of simvastatin with lipid-modifying doses of niacin-containing products observed in Chinese patients applies to other Asian patients.

The concomitant use of statins and cyclosporine may increase the risk of myopathy/rhabdomyolysis. Co-administration of pitavastatin (Livalo) or ezetimibe/simvastatin (Vytorin) with cyclosporine is contraindicated.¹¹³ Use of ezetimibe/atorvastatin (Liptruzet) with cyclosporine should be avoided. Dose reductions are recommended for the other statins when used concurrently with cyclosporine. Pitavastatin (Livalo) has not been studied with the protease inhibitor combination lopinavir/ritonavir so should not be used concurrently.

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) study randomized 3,414 patients with established CVD and atherogenic dyslipidemia to simvastatin (or simvastatin plus ezetimibe) at a dose sufficient to maintain LDL-C at 40-80 mg/dL and patients were randomized to receive extended-release niacin or matching placebo.¹¹⁴ Although niacin was effective at raising HDL-C and lowering triglycerides, the trial was halted early due to the lack of incremental benefit on CV risk reduction (including myocardial infarctions and stroke) in the extended-release niacin plus simvastatin arm versus simvastatin alone ($p=0.80$).^{115,116} In addition, a small, unexplained, increase in the rate of ischemic stroke was observed in the simvastatin plus extended-release niacin arm compared to simvastatin alone (29 patients versus 18 patients, respectively; $p=0.11$). Eight of the ischemic strokes in the simvastatin plus extended-release niacin group occurred in participants who had stopped taking their niacin for at least 2 months and up to 4 years before their stroke; therefore, it is unclear whether niacin contributed to this imbalance in ischemic stroke. The authors note study limitations such as: the findings may not be applicable to all patients with coronary disease or all patients with low HDL-C levels; it remains unclear whether other populations may benefit from such treatment; it is unclear if in the 94% of patients who were taking statins at study entry had more stable plaques, which are less likely to rupture, and therefore at lower risk of subsequent cardiovascular events; low percentage of women enrolled (15%); low rate of ethnic minorities (8%); and the 36-month follow-up period may not have been an adequate duration to show a clinical treatment effect of niacin. The AIM-HIGH trial was funded by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institute of Health (NIH) with additional support from Abbott Laboratories. The FDA will update the public with any new recommendations or conclusions when its review of the AIM-HIGH trial data is complete.¹¹⁷ Niacin ER (Niaspan®) and niacin ER containing products (Advicor, Simcor) are contraindicated in patients with chronic liver disease, active peptic ulcer disease, or arterial bleeding. Niacin should be used with caution in patients predisposed to gout.¹¹⁸ Niacin ER (Niaspan) can cause hyperglycemia, so serum glucose levels should be monitored in patients with diabetes particularly during the first few months of therapy.

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

DRUG INTERACTIONS^{119,120,121,122,123,124,125,126,127,128,129,130,131}

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, 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 CYP 3A4 include: fluvastatin (Lescol/Lescol XL), pitavastatin (Livalo), pravastatin, and rosuvastatin (Crestor).

Concomitant administration with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, erythromycin, clarithromycin, telithromycin and nefazodone) is contraindicated with lovastatin (Advicor, Altoprev) and simvastatin (Simcor, Vytorin, Zocor) containing products.

Atorvastatin also interacts with CYP450 3A4 inhibitors but to a lesser degree, as it undergoes less first-pass metabolism.¹³² 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. Atorvastatin should be used with caution with the HIV protease inhibitors lopinavir plus ritonavir and at the lowest dose necessary. Caution should also be used in patients taking clarithromycin, itraconazole, or HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir 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 CYP450 2C9 so its levels may be increased by CYP450 2C9 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.

Rosuvastatin dose should be 10 mg daily if given concomitantly with lopinavir/ritonavir or 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 resulted in no effect on digoxin plasma concentrations.

Simvastatin dose is 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 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.

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.

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

Atorvastatin, rosuvastatin and simvastatin are substrates for certain transporter proteins, including the hepatic uptake transporter organic anion-transporting polypeptide 1B1 (OATP1B1). Concomitant use of rosuvastatin with drugs that are inhibitors of these transporter proteins, such as cyclosporine and certain HIV protease inhibitors may result in increased rosuvastatin plasma concentrations and increased risk of toxicity. Rosuvastatin is also a substrate for efflux transporter breast cancer resistance protein (BCRP). Concomitant use of rosuvastatin with drugs that are inhibitors of BCRP may result in increased exposure to rosuvastatin.

Drug	amiodarone	cyclosporine	diltiazem	Erythromycin	gemfibrozil (fabric acid derivatives)	HIV protease inhibitors	itraconazole (azole antifungals)	nefazodone	niacin	verapamil	warfarin
atorvastatin (Lipitor, Caduet)	--	X	X	X	X	X	X	--	X	--	--
ezetimibe / atorvastatin (Liptruzet)	--	X	X	X	X	X	X	--	X	--	X
ezetimibe / simvastatin (Vytorin)	X	X	X	X	X	X	X	X	X	X	X
fluvastatin (Lescol, Lescol XL)	--	--	--	--	--	--	--	--	--	--	--
lovastatin lovastatin ER (Altoprev) niacin ER/ lovastatin (Advicor)	X	X	--	X	X	X	X	X	--	X	--
pravastatin	--	--	--	--	X	--	--	--	--	--	--
pitavastatin (Livalo)	--	X	--	X	X	X	X	--	X	--	--
rosuvastatin (Crestor)	--	X	--	--	X	X	--	--	X	--	X
simvastatin niacin ER/ simvastatin (Simcor)	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) and niacin ER and simvastatin (Simcor) have 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.

ADVERSE EFFECTS^{133,134,135,136,137,138,139,140,141,142,143,144,145}

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 / atorvastatin (Liptruzet)	3.5 (3.1)	3 (2)	6.8 (6.3)	4.7 (4.3)	4 (3.5)	reported	reported	reported
ezetimibe / simvastatin (Vytorin)	3.6 (2.3)	reported	reported	reported	reported	reported	6.8 (6.4)	reported
fluvastatin (Lescol)	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
niacin ER / lovastatin (Advicor)	3	4	6	3	7	5	9	reported
niacin ER / simvastatin (Simcor)	reported	3.5	3 (2.9)	4	3.2 (4.2)	reported	4.5 (4.6)	reported
pitavastatin (Livalo)	1.9–3.1 (1.4)	nr	1.5–2.6 (1.9)	nr	nr	reported	reported	nr
pravastatin	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)	2.7–12.7 (2.6-12.1)	2.4 (1.8)	nr	nr	2.4 (2.3)	reported	3.1-8.5 (5-5.3)	nr
simvastatin	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/Lescol XL), pravastatin, and simvastatin were rarely (<2%) discontinued due to adverse effects. Rosuvastatin (Crestor) 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.

Adverse events data for atorvastatin/amlodipine (Caduet) have been evaluated in 1,092 patients with hypertension and hyperlipidemia. Adverse events were mostly mild or moderate in severity with no unusual adverse events reported. Specific incidences have not been reported with atorvastatin/amlodipine. The combination tablet is not expected to have more adverse effects than single entity administration.

In clinical trials, 6% to 8% of patients on niacin ER/lovastatin (Advicor) withdrew from therapy due to flushing.¹⁴⁶ Overall, 53% to 83% of patients will experience flushing associated with the niacin component in niacin ER/lovastatin. In a controlled study, flushing occurred in up to 59% of patients treated with niacin ER/simvastatin (Simcor) and resulted in study discontinuation for 6% of patients. Aspirin or another NSAID may be taken with niacin ER/lovastatin or niacin ER/simvastatin therapy to reduce the incidence of flushing. The other most common adverse events, in addition to headache, nausea, and diarrhea, in a 6-month study comparing niacin ER/simvastatin to simvastatin, were pruritus and back pain (3.2% incidence for each).

After completing a 12-week randomized, double-blind, placebo-controlled, factorial, 10-armed study comparing ezetimibe 10 mg/simvastatin 10, 20, 40, or 80 mg; simvastatin 10, 20, 40, or 80 mg; ezetimibe 10 mg; or placebo, 768 patients with primary hypercholesterolemia entered a 48-week extension, with randomized, blinded, reassignment of the simvastatin 10 mg, ezetimibe, and placebo groups to 1 of the ezetimibe/simvastatin groups.¹⁴⁷ Patients previously on ezetimibe/simvastatin combination therapy, or simvastatin 20 mg, 40 mg, and 80 mg monotherapy, continued the same therapies in the 7-arm extension study. Adverse events were assessed during the 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.

Arthralgia, fatal and non-fatal hepatic failure, hepatitis, jaundice, depression, and sleep disorders have been identified during post approval use of rosuvastatin (Crestor). 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 U.S. market in 2001, there is likely reporting bias with rosuvastatin as it entered the U.S. market in 2003. In summary, the occurrence of serious adverse events such as myopathy and rhabdomyolysis are extremely rare with all statins including rosuvastatin.^{148,149,150,151,152}

Several meta-analyses and systematic reviews have evaluated statin use and the overall risk of cancer.^{153,154,155,156,157} There is no convincing evidence that statins increase or decrease the incidence of cancer.

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.^{158,159,160} However, there was a decrease in a pre-specified secondary endpoint of atherosclerotic disease events. SEAS found an increase in various types of cancer and deaths in patients taking simvastatin/ezetimibe. An interim analysis of the ongoing CV trials with simvastatin/ezetimibe (Vytorin), SHARP and IMPROVE-IT, did not show a significant increase in cancer ($p=0.61$).¹⁶¹ 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.^{162,163,164} Final analysis of SHARP and IMPROVE-IT was consistent with the interim results, reporting no increase in cancer risk.^{165,166}

The 7-year SEARCH trial included the number of major CV events (MI, revascularization, and CV death) in patients with prior MIs.¹⁶⁷ There were 6,031 patients taking 80 mg of simvastatin compared to 6,033 patients taking 20 mg of simvastatin. FDA's report 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%]). Twenty-two patients (0.4%) in the 80 mg group versus zero 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.

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

Hyperglycemia has been reported with statins.¹⁶⁸

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.^{169,170,171} 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 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/m², 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 (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.¹⁷²

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.¹⁷³ 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).¹⁷⁴ 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.¹⁷⁵

FDA also reviewed the 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.¹⁷⁶ 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.¹⁷⁷ 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.¹⁷⁸

Cognitive Adverse Events

The FDA reviewed the AERS database, the published medical literature (case reports and observational studies), and randomized clinical trials to evaluate the effect of statins on cognition.¹⁷⁹

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^{180,181}

Drug	Marked increases (3X ULN) in serum transaminases (%)
atorvastatin (Lipitor, Caduet)	0.7
ezetimibe / atorvastatin (Liptruzet)	0.6
ezetimibe / simvastatin (Vytorin)	1.8
Fluvastatin (Lescol)	1.1
fluvastatin XL (Lescol XL)	1.9
lovastatin, lovastatin ER (Altoprev)	1.9
niacin ER / lovastatin (Advicor)	1
niacin ER / simvastatin (Simcor)	0-1
pitavastatin (Livalo)	0-0.5
pravastatin	< 1.2
rosuvastatin (Crestor)	1.1
simvastatin	1

Liver enzyme elevation rates are obtained from product information and clinical trials and therefore, 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.¹⁸² 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^{183,184,185,186,187,188,189,190,191,192,193,194,195}

Pediatrics

Several statins have been approved for use in patients 10 (8 years of age for pravastatin) to 17 years of age boys and girls (at least 1 year post-menarche). Atorvastatin (Lipitor), fluvastatin (Lescol/Lescol XL), lovastatin, pravastatin, rosuvastatin (Crestor), and simvastatin have been approved for the adjunctive management of Heterozygous Familial Hypercholesterolemia (HeFH) in addition to diet.¹⁹⁶ 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.¹⁹⁷ The minimum goal of therapy is to achieve LDL-C < 130 mg/dL. Very little data are known for children less than 8 years old.

In 2011, 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 screening in the pediatric population.¹⁹⁸ NHLBI recommends a fasting lipid profile in children age 1 to 4 years, only if the child is familial hypercholesterolemia positive, the child has a parent with dyslipidemia, or if the child has any other risk factors or high-risk condition. 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 cardiovascular disease. The guideline also identifies age-specific strategies to reduce risk factors and manage cardiovascular disease in children and adolescents. Most children with high cholesterol 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.

A 2011 familial hypercholesterolemia (FH) consensus statement from the National Lipid Association (NLA) calls for awareness and provides recommendations for screening, diagnosis, and treatment of FH in pediatrics and adults.¹⁹⁹ The clinical guidance recommends universal screening for all pediatrics ages 9 to 11 years old. Screening is also recommended in patients beginning at age 2, in the presence of a family history of premature CVD or highly elevated cholesterol levels. 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%. The NLA FH consensus statement was supported by an unrestricted grant funding from manufacturers.

The AHA 2015 Agenda for Familial Hypercholesterolemia states long-term follow-up of adolescents started on statins suggests excellent safety and much lower event rates than for their affected

parents.²⁰⁰ Early treatment is critical because atherosclerosis begins early in life. However, there are no data to inform pediatric treatment goals, 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.

Safety and effectiveness of pitavastatin (Livalo), lovastatin ER (Altoprev), niacin ER/lovastatin (Advicor), niacin ER/simvastatin (Simcor), atorvastatin/amlodipine (Caduet), ezetimibe/atorvastatin (Liptruzet), and ezetimibe/simvastatin (Vytorin) have not been established in pediatric patients.

Pregnancy

All statin-containing products are Pregnancy Category X.

Race

The 2013 ACC/AHA practice guidelines recommend the use of the race- and sex-specific Pooled Cohort Equations to predict 10-year risk for a first hard ASCVD event in non-Hispanic, African Americans, and non-Hispanic Whites, 40 to 79 years of age.²⁰¹

In a prospective, open-label, blinded endpoint trial, pravastatin 10 to 20 mg daily plus diet therapy was compared to diet therapy alone in 7,832 Japanese patients with hypercholesterolemia but without a history of CHD or stroke.²⁰² During the follow-up period of 5.3 years, the primary endpoint of first occurrence of CHD was significantly lower in the pravastatin group (66 events versus 101 events; HR 0.67; 95% CI, 0.49 to 0.91; p=0.01). Mean LDL-C reductions were 3.2% in the diet group and 18% in the diet plus pravastatin group.

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.²⁰³ 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.

In an open-label randomized trial in the U.S. 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.²⁰⁴ 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.²⁰⁵

A 12-week randomized, open-label, parallel group study compared the efficacy and safety of rosuvastatin (Crestor) 10 mg once daily to atorvastatin (Lipitor) 10 mg once daily in 1,482 adults in China, Hong Kong, Korea, Malaysia, Taiwan, and Thailand, with primary hypercholesterolemia and elevated cardiovascular risk (greater than 20%/10 years, type 2 diabetes, or a history of CHD).²⁰⁶ The percentage of patients achieving LDL-C goal, based on the 1998 European Joint Task Force, was significantly higher in the

rosuvastatin group versus atorvastatin group, 79.5% versus 69.4%, respectively ($p < 0.0001$). Both agents were well-tolerated and had a similar adverse event profile.

A post-hoc analysis of the GREACE study investigated the extent in vascular event reduction by statin treatment according to gender.²⁰⁷ 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 (hazard ratio [HR] 0.46; 95% CI, 0.24-0.87; $p = 0.003$) and of 50% in men (HR 0.5; 95% CI, 0.32-0.7; $p < 0.001$). 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.

The Heart Protection Study 2 (HPS2) identified that the incidence of myopathy is higher in Chinese compared with non-Chinese patients taking simvastatin 40 mg coadministered with lipid-modifying doses of a niacin-containing product.²⁰⁸ Because the risk for myopathy is dose-related, Chinese patients should not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products. It is unknown if this risk applies to other Asian patients.

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

The JUPITER trial evaluated rosuvastatin in the primary prevention of MI, stroke, arterial revascularization, hospitalization for unstable angina, and cardiovascular death.²⁰⁹ It included 12,683 whites and 5,117 nonwhites with LDL levels < 130 mg/dL and high-sensitivity C-reactive protein (hsCRP) levels ≥ 2 mg/L. In patients randomized to rosuvastatin 20 mg, a 45% reduction in the primary endpoint among whites (HR 0.55; 95% CI, 0.43-0.69) and a 37% reduction was seen among nonwhites (HR 0.63; 95% CI, 0.41-0.99). Blacks (HR 0.65; 95% CI, 0.35-1.22) and Hispanics (HR 0.58; 95% CI 0.25-1.39) had similar risk reductions. Among nonwhites in the placebo group, the stroke rate exceeded the MI rate (0.44 versus 0.2 per 100 person-years); however, among whites the stroke rate was less than the MI rate (0.31 versus 0.42 per 100 person-years). Nonwhites had higher death rates than whites (2.25 versus 0.93 per 100 person-years); however, all-cause mortality was similar with rosuvastatin treatment in both participant groups.

Hepatic/Renal Impairment

Statins are contraindicated in patients with active liver disease.

SHARP, a double-blind study included 9,438 CKD patients, of which 3,056 were on dialysis, that were randomized to receive 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).^{210,211,212} 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 ($p = 0.0022$). Ezetimibe/simvastatin also resulted in average LDL-C differences of 43 mg/dL (1.1 mmol/L) at 1 year and 33 mg/dL (0.85 mmol/L) at 2.5 years, compared to placebo. 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).

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

DOSAGES^{213,214,215,216,217,218,219,220,221,222,223,224,225}

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 – 10 mg/80 mg daily	--	10 mg daily of atorvastatin	amlodipine / atorvastatin combination tablets: 2.5 mg/10 mg, 2.5 mg/20 mg, 2.5 mg/40 mg, 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg
atorvastatin (Lipitor)	10–40 mg daily	10–80 mg daily	ages 10–17: 10–20 mg daily	10 mg daily	10, 20, 40, 80 mg tablets
ezetimibe / atorvastatin (Liptruzet)	10 mg/10 mg – 10 mg/20 mg daily	10 mg/10 mg – 10 mg/80 mg daily	--	10 mg/10 mg daily	ezetimibe / atorvastatin combination tablets: 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg
ezetimibe / simvastatin (Vytorin)	10 mg/10 mg – 10 mg/20 mg daily	10 mg/10 mg – 10 mg/40 mg daily	--	10 mg/10 mg daily	ezetimibe / simvastatin combination tablets: 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg
fluvastatin (Lescol)	20–40 mg daily	20–80 mg daily	ages 10–16: 20 mg daily to 40 mg twice daily	40 mg twice daily	20, 40 mg capsules
fluvastatin XL (Lescol XL)	80 mg daily	80 mg daily	ages 10–16: 80 mg daily	80 mg daily	80 mg tablet
lovastatin	20 mg daily with evening meal	10–80 mg daily	ages 10–17: 10–40 mg daily	40 mg daily	10, 20, 40 mg tablets
lovastatin ER (Altoprev)	20–60 mg daily	10–60 mg daily	--	40 mg daily	20, 40, 60 mg tablets
niacin ER / lovastatin (Advicor)	500 mg/20 mg at bedtime	500 mg/20 mg–2,000 mg/40 mg at bedtime	--	1,000 mg/40 mg daily	niacin ER / lovastatin combination tablets: 500 mg/20mg, 750mg/20mg, 1,000mg/20 mg, 1,000/40mg
niacin ER / simvastatin (Simcor)	500 mg/20 mg at bedtime	500 mg/20 mg–2,000 mg/40 mg at bedtime	--	1,000 mg/20 mg daily	niacin ER/simvastatin combination tablets: 500 mg/20 mg, 500 mg/40 mg, 750 mg/20 mg, 1,000 mg/20 mg, 1,000 mg/40 mg

Dosages (continued)

Drug	Usual Starting Dose	Adult Dosing Range	Pediatric Dosing Range	Approximate Equivalent Dose (based on LDL-C lowering)	Availability
pitavastatin (Livalo)	2 mg daily	1–4 mg daily	--	2 mg daily	1, 2, 4 mg tablets
pravastatin	40 mg daily	10–80 mg daily	ages 8–13: 20 mg daily ages 14–18: 40 mg daily	40 mg daily	10, 20, 40, 80 mg tablets
rosuvastatin (Crestor)	10–20 mg daily	5–40 mg daily	ages 10–17: 5–20 mg daily	5 mg daily	5, 10, 20, 40 mg tablets
simvastatin	10–40 mg daily in the evening	5–40 mg daily	ages 10-17 years: 10–40 mg daily	20 mg daily	5, 10, 20, 40, 80 mg tablets

DOSING CONSIDERATIONS^{226,227,228,229,230,231,232,233,234,235,236,237,238,239}

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.

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.
- Clarithromycin, itraconazole, or in combination with fosamprenavir, or ritonavir plus darunavir or fosamprenavir or saquinavir: do not exceed atorvastatin 20 mg daily. The lowest dose necessary should be used.
- Avoid in patients taking the HIV protease inhibitor tipranavir plus ritonavir.
- Do not exceed atorvastatin 40 mg in patients taking nelfinavir.
- Reduce dose when used with niacin.
- Avoid large quantities of grapefruit juice (>1 quart daily).

ezetimibe / atorvastatin (Liptruzet)

- Swallow tablets whole; do not crush, dissolve, or chew.
- No dosage adjustment is recommended in renal insufficiency.
- Bile acid sequestrants: Dosing of ezetimibe/atorvastatin should occur either at least 2 hours before or at least 4 hours after administration of a bile acid sequestrant.
- Avoid use with cyclosporine and gemfibrozil.
- Avoid use with HIV protease inhibitors tipranavir plus ritonavir.
- Use caution when administering with fibrates.
- Avoid large quantities of grapefruit juice (>1.2 liters daily).
- Reduce dose when used with niacin.

ezetimibe / simvastatin (Vytorin)

- Homozygous Familial Hypercholesterolemia (HoFH): 10 mg/40 mg in the evening.
- In patients with chronic kidney disease and estimated glomerular filtration rate <60 mL/min/1.73 m², the dose of ezetimibe/simvastatin is 10/20 mg/day in the evening.
- Bile Acid Sequestrants: administer Vytorin either 2 hours before or 4 hours after administration of a bile acid sequestrant.
- Fibrates: should be avoided.
- Gemfibrozil: concomitant administration is contraindicated.

- Niacin >1 gm 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 mg/20 mg daily.
- Due to increased risk for myopathy, Chinese patients should not receive Vytorin 10 mg/80 mg 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, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, and nefazodone). Contraindicated with gemfibrozil, cyclosporine, or danazol.

fluvastatin (Lescol, 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: boceprevir and telaprevir; and 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 gm daily: use caution with concurrent administration.
- Reduce lovastatin dose with concomitant ranolazine.
- Renal insufficiency (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.

niacin ER / lovastatin (Advicor)

- For niacin ER/lovastatin, 2 tablets of 500 mg/20 mg are not interchangeable with 1,000 mg/40 mg. When converting patients on Niaspan to niacin ER/lovastatin, an equivalent niacin dosage can be started (mg per mg). If the patient has been on any other niacin product, therapy with niacin ER/lovastatin should be initiated at the lowest dose and titrated upward every 4 weeks as needed to achieve treatment goals. If niacin ER/lovastatin therapy is interrupted for more than 7 days, initiate therapy at niacin ER/lovastatin 500 mg/20 mg to minimize adverse effects.
- Avoid with cyclosporine and gemfibrozil.
- Colchicine, fibrates, or niacin >1 g daily: use caution with concurrent administration.
- Danazol, diltiazem, or verapamil: do not exceed lovastatin 20 mg daily.
- Amiodarone: do not exceed lovastatin 40 mg daily.
- Reduce lovastatin dose with concomitant ranolazine.
- Avoid large quantities of grapefruit juice (>1 quart daily).
- Renal insufficiency: use caution.

niacin ER / simvastatin (Simcor)

- Dosages > 2,000 mg/40 mg per day are not recommended.
- If therapy is discontinued for > 7 days, re-titration as tolerated.
- Amlodipine, amiodarone, or ranolazine: do not exceed 1,000 mg/20 mg daily.
- Due to an increased risk for myopathy, in Chinese patients taking simvastatin 40 mg coadministered with lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing use caution when administering niacin ER/simvastatin in doses that exceed 1,000/20 mg/day to Chinese patients. The cause of the increased risk of myopathy is not known. It is also unknown if the risk for myopathy with coadministration of simvastatin with lipid-modifying doses of niacin-containing products observed in Chinese patients applies to other Asian patients.
- Concomitant administration of strong CYP3A4 inhibitors is contraindicated.
- Concomitant administration of gemfibrozil, cyclosporine, or danazol is contraindicated.
- Concomitant administration of verapamil or diltiazem is contraindicated.
- Fenofibrate: combination with niacin ER/simvastatin should be avoided.
- Severe renal impairment: do not initiate therapy unless patient has already tolerated treatment with simvastatin at 10 mg daily or higher.

pitavastatin (Livalo)

- 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 30–59 and 15–29 mL/min/1.73 m², 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 gm daily: use caution with concurrent administration.

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)

- Asian patients: consider starting dose of 5 mg daily.
- Homozygous Familial Hypercholesterolemia (HoFH): starting dose is 20 mg daily.
- Heterozygous Familial Hypercholesterolemia (HeFH): maximum dose is 20 mg daily.
- Cyclosporine: use 5 mg only.
- Gemfibrozil: combination should be avoided; if used, do not exceed rosuvastatin 10 mg daily.
- Severe renal impairment (CrCL < 30mL/min/1.73m²) 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[®]) or atazanavir/ritonavir: do not exceed 10 mg daily.
- Use caution when used in combination with niacin (> 1g/day) or fenofibrate.

simvastatin (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.²⁴⁰ 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.
 - 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.
- 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).^{241,242,243} 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), ezetimibe/atorvastatin (Liptruzet) or for the combinations of niacin ER/lovastatin (Advicor), niacin ER/simvastatin (Simcor), or 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:²⁴⁴ The Treating to New Targets study evaluated the efficacy and safety of lowering LDL-C to less than 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 less than 130 mg/dL were then randomized to atorvastatin 10 or 80 mg daily. Overall, atorvastatin reduced LDL-C by 35% with a mean LDL-C achieved in the atorvastatin 80 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 myocardial infarction (MI), resuscitation after cardiac arrest, or fatal or nonfatal stroke. The event rate was 8.7% and 10.9% for the atorvastatin 80 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 noncardiovascular deaths in the atorvastatin 80 mg group. In specifically evaluating cerebrovascular events, the atorvastatin 80 mg group had fewer cerebrovascular events (hazard ratio [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; $p = 0.02$).²⁴⁵ 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 and 10 mg groups, respectively (HR=0.75; 95% CI, 0.58 to 0.97, $p = 0.026$).²⁴⁶ 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; $p < 0.0001$).²⁴⁷ 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 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).²⁴⁸ A history of HF was present in 7.8% of patients. A known ejection fraction less than 30% and advanced HF were exclusion criteria for the study. A predefined secondary endpoint of the study was hospitalization for HF. The incidence of hospitalization for HF 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 or older with stable CHD.²⁴⁹ 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).²⁵⁰ 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 (eGFRs) (HR 1.32; 95% CI, 1 to 1.72; p<0.05). Compared with 10 mg of atorvastatin, 80 mg of atorvastatin reduced 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:²⁵¹ As part of a larger study with 19,342 hypertensive patients with multiple risk factors for CHD, patients (n=10,305) with total-C less than 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:²⁵² 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.²⁵³ 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.²⁵⁴ 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, 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 ($n=13$; relative risk, 2.03; 95% CI, 1.05 to 3.93; $p=0.04$). Atorvastatin reduced the rate of all cardiac events combined (relative risk, 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:²⁵⁵ 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 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.²⁵⁶

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.²⁵⁷ Hemorrhagic stroke was more frequent in subjects who had a hemorrhagic stroke on study entry, in men, and with advanced age.

ASPEN:²⁵⁸ 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:²⁵⁹ 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:²⁶⁰ 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 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).²⁶¹ 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.²⁶² Low on-treatment TG (<150 mg/dl) was associated with reduced CHD risk compared with higher TG in univariate analysis (hazard ratio [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.²⁶³ 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; $p=0.014$).

atorvastatin (Lipitor) versus rosuvastatin (Crestor)

SATURN:²⁶⁴ 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 ($p=0.07$).

atorvastatin (Lipitor) versus simvastatin (Zocor)

IDEAL:²⁶⁵ 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 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; $p=0.03$).²⁶⁶

simvastatin / ezetimibe (Vytorin)

Several studies with surrogate endpoints have compared the combination of ezetimibe and simvastatin to its individual components, atorvastatin, and rosuvastatin.^{267,268,269,270,271,272,273} 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.²⁷⁴

SEAS: A double-blind trial involving 1,873 patients with mild to moderate, asymptomatic aortic stenosis randomized patients to 40 mg of simvastatin plus 10 mg of ezetimibe or placebo daily.²⁷⁵ The primary outcome was a composite of major CV events, including death from CV causes, aortic-valve replacement, nonfatal MI, hospitalization for unstable angina pectoris, heart failure, coronary-artery bypass grafting, percutaneous coronary intervention, and nonhemorrhagic stroke. Secondary outcomes were events related to aortic-valve stenosis and ischemic CV events. During a median follow-up of 52.2 months, the primary outcome occurred in 35.3% in the ezetimibe/simvastatin group and in 38.2% in the placebo group (HR in the ezetimibe/simvastatin group, 0.96; 95% CI, 0.83 to 1.12; p=0.59). There was no significant difference between the 2 groups in the secondary outcome of aortic-valve-related events, including aortic-valve replacement, death from CV causes, and hospitalization for HF as a consequence of progression of aortic stenosis (HR, 0.97; 95% CI, 0.83 to 1.14 [p=0.73]). However, aortic-valve replacement, the principal component of the secondary composite outcome, was performed in 28.3% in the ezetimibe/simvastatin group and in 29.9% in the placebo group (HR 1; 95% CI, 0.84 to 1.18; p=0.97). The primary endpoint of major CV events was not significantly reduced in ezetimibe/simvastatin compared to placebo. Fewer patients had ischemic CV events in the ezetimibe/simvastatin group compared to the placebo group (HR 0.78; 95% CI, 0.63 to 0.97; p=0.02), mainly due to the smaller number of patients who underwent CABG. Cancer occurred more frequently in the ezetimibe/simvastatin group (p=0.01). 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).²⁷⁶ 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.²⁷⁷ Final analysis of SHARP and IMPROVE-IT was consistent with the interim results, reporting no increase in cancer risk.^{278, 279}

SHARP: In a double-dummy study, patients (n=9,438) with advanced CKD with no known history of MI or coronary revascularization were randomized in a ratio of 4:4:1 to daily ezetimibe 10 mg plus simvastatin 20 mg, matching placebo, or simvastatin 20 mg (with the latter arm re-randomized at 1 year to ezetimibe 10 mg plus simvastatin 20 mg versus placebo).^{280,281} 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).

fluvastatin (Lescol)

LIPS study:²⁸² 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.²⁸³ 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:²⁸⁴ 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 less than 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.²⁸⁵ 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 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.

niacin ER / lovastatin (Advicor)

No large clinical outcomes trials have been performed with the combination of niacin ER and lovastatin. Short-term comparison trials with atorvastatin and simvastatin have been completed.^{286,287}

niacin ER / simvastatin (Simcor)

No large clinical outcomes trials have been performed with the combination of niacin ER and simvastatin. This combination product has been compared to simvastatin.^{288,289}

pitavastatin (Livalo)

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.^{290,291,292,293,294,295} In addition, an open-label Japanese study found a similar percentage change in nonculprit coronary plaque volume in patients taking pitavastatin and atorvastatin.²⁹⁶

pravastatin (Pravachol)

ALLHAT-LLT study:²⁹⁷ 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, Blacks, 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.²⁹⁸ 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.²⁹⁹ The rates of death from all cardiovascular causes (pravastatin: 7.6%; placebo: 9%; 0.81 [95% CI, 0.68-0.96] $p = 0.01$) and death from any cause (18.7% for pravastatin versus 20.5% for placebo; 0.88 [95% CI, 0.79-0.99]; $p = 0.03$) were lower in the pravastatin group over the total follow-up period. Deaths from CHD were fewer in the pravastatin group (5.1%; 0.78 [95% CI, 0.64-0.96; $p = 0.02$]) compared to placebo group (6.3%). There were no excess deaths from non-cardiovascular causes or incident cancers.

rosuvastatin (Crestor)

Short-term trials have been published comparing LDL-C reductions of rosuvastatin, atorvastatin, pravastatin, and simvastatin.^{300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315} Rosuvastatin has also been compared to atorvastatin in a short-term trial comparing the effect on HDL-C.³¹⁶

ASTEROID:³¹⁷ 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 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:^{318,319} 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.³²⁰ 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, 0.30 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; $p = 0.44$).³²¹ 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.³²²

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.³²³ Compared with placebo, rosuvastatin patients who achieved LDL-C less than 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 less than 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 found a 65% reduction in CV events in the rosuvastatin group who achieved both LDL-C less than 1.8 mmol/L (70 mg/dL) and hsCRP less than 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 less than 1.8 mmol/L (70 mg/dL) and hsCRP less than 1 mg/L, a 79% reduction (HR 0.21; 95% CI, 0.09 to 0.52) was noted.

AURORA:³²⁴ 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; $p = 0.51$).

simvastatin (Zocor)

Heart Protection Study (HPS) Collaborative Group:³²⁵ 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 ($n = 5,963$).³²⁶ 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 ($p=0.001$).³²⁷ 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 (RR) in the rate of first major vascular event (95% CI, 15 to 29; $p<0.0001$).³²⁸ 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, 1.25–1.99, 2–2.99, 3–4.99, 5–7.99, and ≥ 8 mg/L).³²⁹ 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.³³⁰ 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, 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 (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.³³¹ 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, myocardial infarction, 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; $p=0.10$). Two (0.03%) cases of myopathy were reported in patients taking simvastatin 20 mg versus 53 (0.9%) cases in the 80 mg group.

Summary of Large Clinical Trials

Drug	Primary Prevention	Secondary Prevention
atorvastatin (Lipitor)	ASCOT-LLA ³³² , CARDS ³³³	MIRACL ³³⁴ , GREACE ³³⁵ , PROVE IT-TIMI 22 ³³⁶ , TNT ³³⁷ , IDEAL ³³⁸ , ASPEN ³³⁹ , SPARCL ³⁴⁰
ezetimibe/simvastatin (Vytorin)	--	IMPROVE-IT ³⁴¹
fluvastatin (Lescol)	--	LIPS ³⁴²
lovastatin	AFCAPS/TexCAPS ³⁴³	--
pitavastatin (Livalo)	--	--
pravastatin	WOSCOPS ³⁴⁴ , PROSPER ³⁴⁵ , ALLHAT ³⁴⁶ , MEGA ³⁴⁷	CARE ³⁴⁸ , LIPID ³⁴⁹ , PROSPER ³⁵⁰ , PACT ³⁵¹ , PROVE IT-TIMI 22 ³⁵²
rosuvastatin (Crestor)	JUPITER ³⁵³	--
simvastatin	HPS ³⁵⁴	4S ³⁵⁵ , HPS ³⁵⁶ , Phase Z of A to Z ³⁵⁷ , IDEAL ³⁵⁸

IMPROVE-IT was presented at the 2014 AHA Scientific Sessions. It 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).³⁵⁹ 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%).

LDL-C Reductions

360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384, 385, 386,387,388,389,390

Drug	<25% decrease	25-35% decrease	36-45% decrease	46-50% decrease	51-60% decrease
atorvastatin (Lipitor, Caduet)	--	10 mg	10–20 mg	40 mg	80 mg
ezetimibe / atorvastatin (Liptruzet)	--	--	--	--	10 mg/10 mg–10 mg/80 mg
ezetimibe / simvastatin (Vytorin)	--	--	10 mg/10 mg	10 mg/10 mg–10 mg/20 mg	10 mg/20 mg–10 mg/80 mg
fluvastatin (Lescol)	20–40 mg	40–80 mg	80 mg	--	--
fluvastatin XL (Lescol XL)	--	80 mg	80 mg	--	--
lovastatin	10–20 mg (including 20 mg every other day)	20–40 mg (including 20 mg every other day)	40 – 80mg	--	--
lovastatin ER (Altoprev)	10 mg	10–40 mg	40–60 mg	--	--
niacin ER / lovastatin (Advicor)	--	1,000 mg/20 mg	1,000 mg/40 mg - 2,000 mg/40 mg	--	--
niacin ER / simvastatin (Simcor)*	1,000 mg/20 mg - 2,000 mg/40 mg	--	--	--	--
pitavastatin (Livalo)	--	--	2–4 mg	--	--
pravastatin	10–20 mg	20–40 mg	80 mg	--	--
rosuvastatin (Crestor)	--	--	5–10 mg	10 mg	10–40 mg
simvastatin	5 mg	5–20 mg	20–80 mg	80 mg**	--

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

*These results show the additional LDL-C lowering for either treatment-naïve patients or after receiving simvastatin 20 mg or 40 mg.

**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.³⁹¹ 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.

Effects on TG and HDL-C ^{392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416}

Drug	Triglyceride change (%)	HDL-C change (%)
atorvastatin (Lipitor, Caduet) 10–80 mg	-17 to -37	-0.1 to 9
ezetimibe / atorvastatin (Liptruzet)	-30 to -40	7 to 9
ezetimibe / simvastatin (Vytorin) 10mg/10mg–10 mg/80 mg	-23 to -35	6 to 12
fluvastatin (Lescol) 10–80 mg	- 2.7 to - 23	-3 to 9
fluvastatin XL (Lescol XL) 80 mg	-19 to -25	7 to 11
lovastatin 20–80 mg	-6 to -27	3 to 10
lovastatin ER (Altoprev) 10–60 mg	-10 to -33	6 to 13
niacin ER / lovastatin (Advicor) 1,000 mg/ 20 mg–2,000mg/40mg	-29 to -49	17 to 32
niacin ER / simvastatin (Simcor) 1,000 mg/ 20 mg–2,000 mg/40 mg	-23 to -38	15 to 29
pitavastatin (Livalo) 2–4 mg	-14 to -22	2 to 7
pravastatin 10–80 mg	-9 to -24	2 to 12
rosuvastatin (Crestor) 5–40 mg	-10 to -35	8 to 14
simvastatin 5–80 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.⁴¹⁷ 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 2006.⁴¹⁸ Intensive dose therapy with atorvastatin (Lipitor) 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%.⁴¹⁹

A meta-analysis of 15 randomized controlled statin trials through May 2006 looked at gender specific incidence of cardiovascular events.⁴²⁰ 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.

Treatment with ezetimibe 10 mg/day or placebo added to current statin therapy was compared in a meta-analysis of five randomized controlled trials with at least 6 weeks duration in 5,039 adults with hypercholesterolemia.⁴²¹ 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 (3.4; 95% CI, 2, 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.⁴²² 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.⁴²³ 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.⁴²⁴ 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, 0.6-0.84 mmol/L), and reduced the risk of MI (OR 0.83; 95% CI, 0.77-0.91) and stroke (OR 0.82; 95% CI, 0.71-0.95). Although there was no effect on mortality among patients with chronic CAD (OR 0.96; 95% CI, 0.8-1.14), all-cause mortality was reduced in patients with ACS treated with more intensive statin regimens (OR 0.75; 95% CI, 0.61-0.93) 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 use 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.⁴²⁵ The study pooled 19 trials (n=63,899) for all-cause mortality and found a RR 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).

A meta-analysis of 11 prospective randomized controlled statin trials in 65,229 patients, without baseline CVD history and with data on all-cause mortality were identified in Medline and Cochrane databases (January 1970-May 2009).⁴²⁶ Effect estimates were pooled using a random-effects model meta-analysis, with heterogeneity assessed with the I^2 statistic. A total of 2,793 deaths occurred. The use of statins in this high-risk primary prevention setting was not associated with a statistically significant reduction in the risk of all-cause mortality (RR, 0.91; 95% CI, 0.83-1.01). There was no statistical evidence of heterogeneity among studies ($I^2 = 23\%$; 95% CI, 0-61%; p=0.23).

Some uncertainties remain regarding the benefit of statins in the prevention of CV events in women compared to men.⁴²⁷ 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.⁴²⁸ However, statins did not reduce all-cause mortality in women compared to men (RR 0.92 [95% CI, 0.76-1.13] versus RR 0.79 [95% CI, 0.72-0.87]) or stroke (RR 0.92 [95% CI, 0.76-1.1] versus RR 0.81 [95% CI, 0.72-0.92]). 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.⁴²⁹ 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).⁴³⁰ 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).⁴³¹ 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.

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, CV risk assessment, obesity, and lifestyle. It emphasizes 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 $\geq 50\%$, moderate-intensity therapy lowers LDL-C by approximately 30% to $< 50\%$, and lower-intensity statin therapy lowers LDL-C by $< 30\%$. 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 new algorithms to estimate 10-year ASCVD risk.

Parts 1 and 2 of the National Lipid Association (NLA) recommendations for the management of dyslipidemia that 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) be based on LDL-C levels, not genetic abnormality or other clinical features. Initial goal is to reduce LDL-C reduction by at least 50%, which can be followed by targets of 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). 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. There is not consistent and compelling evidence to 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. But, addition of a non-statin drug may be considered to further lower LDL-C. **The addition of ezetimibe to simvastatin (Vytorin) showed a modest benefit in reducing CV events over simvastatin alone post acute coronary syndrome (ACS).**

The other statin combination agents [niacin ER/lovastatin (Advicor), niacin ER/simvastatin (Simcor) and atorvastatin/amlodipine (Caduet)], and ezetimibe/atorvastatin (Liptruzet), have not been proven to offer a substantial benefit on CV morbidity and mortality over and above that of the statin component.

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