

Lipotropics, Statins Review

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Together, we can do more.

Lipotropics, Statins Review

Agents

Drug	Manufacturer
amlodipine / atorvastatin (Caduet)	Pfizer
atorvastatin (Lipitor [®])	Pfizer
ezetimibe / simvastatin (Vytorin [™])	Merck-Schering-Plough
fluvastatin (Lescol [®])	Novartis
fluvastatin XL (Lescol XL [®])	Novartis
lovastatin (Mevacor [®])	generic
lovastatin ER (Altoprev [®])	Sciele Pharma
niacin ER / lovastatin (Advicor [™])	Abbott
niacin ER / simvastatin (Simcor [®])	Abbott
pravastatin (Pravachol [®])	generic
rosuvastatin (Crestor [®])	AstraZeneca
simvastatin (Zocor [®])	generic

Pravastatin / buffered aspirin (Pravigard PAC) is no longer available.

FDA-Approved Indications

Indications	atorvastatin (Lipitor), amlodipine/atorvastatin (Caduet)*	ezetimibe/simvastatin (Vytorin)	fluvastatin (Lescol) fluvastatin ER (Lescol XL)	lovastatin	lovastatin ER (Altoprev)	niacin ER/lovastatin (Advicor) **	niacin ER/simvastatin (Simcor)	pravastatin (Pravachol)	rosuvastatin (Crestor)	simvastatin
Primary hypercholesterolemia ♦ Heterozygous familial and nonfamilial Reduce: Total-C, LDL-C, TG and ApoB	X	X	X	X	X	X	X	X	X	X
Heterozygous familial hypercholesterolemia ♦ pediatric	X 10-17 years; not Caduet		X 10-16 years	X 10-17 years				X 8 years and older		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 To reduce total-C, LDL-C	X	X	X	X	X	X
Increase HDL-C	X	X	X		X	X	X	X	X	X
Hypertriglyceridemia <i>Fredrickson Type IV</i>	X					X	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	X	X			X	X	
CHD ♦ primary prevention of coronary events	Reduces risk of MI, stroke, revascularization, angina			Reduces risk of MI, unstable angina, coronary revascularization	Reduces risk of MI, unstable angina, coronary revascularization			Reduces risk of MI, myocardial revascularization, CV mortality		Reduces total mortality risk by reducing CHD death, MI, stroke, & revascularization in high risk patients
CHD ♦ secondary prevention of coronary events	Reduces risk of MI, stroke in Type 2 Diabetics without CHD Reduces risk of MI, stroke, CHF hospitalization, angina and revascularization in CHD patients		Reduces risk of coronary revascularization					Reduces risk of MI, myocardial revascularization, CV mortality, stroke/TIA		Reduces total mortality risk by reducing CHD death, MI, stroke, & 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.

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

Overview

The 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, have become standard treatment in lowering cholesterol levels. Several statins 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. Despite the well-documented benefits of statins in reducing the risk of cardiovascular events, many patients are not on lipid-lowering therapy or are not at LDL-C goals.^{1,2}

The Adult Treatment Panel (ATP) III guidelines from the National Cholesterol Education Program (NCEP) recommend a goal for LDL-C-lowering therapy in high risk patients of LDL-C <100 mg/dL, with LDL-C of <70 mg/dL as a therapeutic option in those at very high risk.^{3,4,5} For patients with multiple CHD risk factors, LDL-C goals are <100 mg/dL or <130 mg/dL, depending on the patient's 10-year risk for CHD events based on Framingham risk scoring. The goal for patients with no or one risk factor is to lower LDL-C <160 mg/dL.⁶

As a result of clinical data published and/or presented since the 2001 ATP III guidelines, the NCEP issued additional guidance in 2004. The 2004 guidance suggests that an LDL-C goal of <70 mg/dL be considered as an option for high-risk patients, especially those with established CVD (cardiovascular disease) and multiple major and/or uncontrolled risk factors for CHD and/or metabolic syndrome.^{7,8,9}

The new target of LDL-C of less than 70 mg/dL also extends to those patients who have a baseline LDL-C of less than 100 mg/dL.¹⁰ For all patients with peripheral arterial disease (PAD), PAD guidelines recommend a LDL-C goal of less than 100 mg/dL. For patients at very high risk of an ischemic event, a LDL-C goal of less than 70 mg/dL may be desired.¹¹ High risk patients with normal LDL-C values can even benefit from statin use.¹²

Pharmacology

The 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 two weeks with maximum response occurring within four to six 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.^{13,14}

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. The REVERSAL trial investigators found that a reduction in LDL-C and CRP leads to a slowing in progression of atherosclerosis.¹⁵ 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.¹⁶ 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 two indications - hypertension and hyperlipidemia – which are often seen in the coronary heart disease (CHD) patient. Ezetimibe / simvastatin (Vytorin) is 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.¹⁷ Amlodipine given with atorvastatin (Caduet) in a single tablet treats both hypertension and hypercholesterolemia for patients in whom calcium channel blocker therapy and lipid lowering therapy are desired.

Ezetimibe (Zetia[®], Vytorin) inhibits cholesterol absorption along the brush border of the small intestine. This leads to a decrease in the delivery of intestinal cholesterol to the liver, reduction of hepatic cholesterol stores and an increase in cholesterol clearance from the blood. Ezetimibe inhibits absorption of both dietary cholesterol and cholesterol in bile. Ultimately, ezetimibe reduces total cholesterol (total-C), LDL-C, TG, apolipoprotein B, and increases HDL-C in patients with hypercholesterolemia. When ezetimibe (Zetia) 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) are available, which combine the efficacy of a statin with the beneficial effects of extended release niacin for those patients failing monotherapy.^{18,19}

Pharmacokinetics

Drug	Bioavailability	Time to Peak Plasma Levels (hr)	t ½ (hr)	Excretion (%)	Circulating active metabolites
amlodipine and atorvastatin (Caduet) ²⁰	64-90%	6-12	30-50	Urine: 70	No
atorvastatin (Lipitor) ²¹	~14%; first pass metabolism	1-2	14	Urine: <2	Yes
ezetimibe and simvastatin (Vytorin) ^{22,23}	~14%; first pass metabolism	1-2	14	Urine: <2	Yes
ezetimibe and simvastatin (Vytorin) ^{22,23}	--	4-12	22	Urine: 11 Feces: 78	Yes
simvastatin (Vytorin) ^{22,23}	<5% of oral dose reaches general circulation; first pass metabolism	4	3	Urine: 13 Feces: 60	Yes
fluvastatin (Lescol) ²⁴ (Lescol XL) ²⁵	24%; first pass metabolism	< 1	3	Urine: 5 Feces: 90	No
fluvastatin (Lescol) ²⁴ (Lescol XL) ²⁵	29%; first pass metabolism	3	9		
lovastatin ²⁶	<5% of oral dose reaches general circulation; first pass metabolism	2-4	--	Urine: 10 Feces: 83	Yes
lovastatin ER (Altoprev) ²⁷	<5% of oral dose reaches general circulation; first pass metabolism	14.2	--	Urine: 10 Feces: 83	Yes
niacin ER and lovastatin (Advicor) ²⁸	72 %	5	<1	Urine: 60	Yes
niacin ER and lovastatin (Advicor) ²⁸	<5% of oral dose reaches general circulation; first pass metabolism	2	4.5	Urine: 10 Feces: 83	Yes
niacin ER and simvastatin (Simcor) ²⁹	dose dependent and variable; first pass metabolism	5	<1	Urine: 54	Yes
niacin ER and simvastatin (Simcor) ²⁹	<5% of oral dose reaches general circulation; first pass metabolism	4	4.2 to 4.9	Urine: 13 Feces: 60	Yes
pravastatin ³⁰	17%; first pass metabolism	1-1.5	77	Urine: 20 Feces: 70	Yes
rosuvastatin (Crestor) ³¹	20%	3-5	19	Feces: 90	Yes
simvastatin ³²	<5% of oral dose reaches general circulation; first pass metabolism	4	3	Urine: 13 Feces: 60	Yes

Atorvastatin and amlodipine (Caduet), 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.^{33,34,35,36,37}

Contraindications/Warnings

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 ten times the upper limit of normal (ULN). Rhabdomyolysis is the presence of myopathy and the elevation of creatinine and often myoglobinuria. The mechanism by which the statins cause myopathy and rhabdomyolysis is unknown.^{38,39,40}

All statins have had reports of myopathy and/or rhabdomyolysis. 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: age > 80 years, perioperative periods, multiple medications, multiple chronic disease states, drug interactions, and concurrent therapy with fibrates and/or higher dose niacin.^{41,42} Drug interactions with CYP450 3A4 inhibitors and concurrent therapy with fibric acid derivatives may increase the risk of rhabdomyolysis. Consult the individual prescribing information for specific drug interactions and dose reductions.

All statin-containing products are contraindicated in pregnancy.

Patients with active liver disease and unexplained transaminase elevations are not appropriate candidates for statin therapy.

Niacin ER (Niaspan) is 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.⁴³ Niacin ER (Niaspan) can cause hyperglycemia so serum glucose levels should be monitored in diabetic patients particularly during the first few months of therapy.⁴⁴

Drug Interactions

All of the currently available statins are extensively metabolized by the CYP450 3A4 isoenzyme system except fluvastatin (Lescol/Lescol XL), pravastatin, and rosuvastatin (Crestor).

Simvastatin (Zocor, Vytorin, Simcor) dose is 5 to 10 mg daily when given with danazol, gemfibrozil, or cyclosporine.^{45,46,47} Maximum dose for lovastatin is 20 mg daily with danazol, gemfibrozil, or cyclosporine.⁴⁸ Simvastatin must not exceed 20 mg daily when given concurrently with amiodarone or verapamil, whereas lovastatin dose must not exceed 20 to 40 mg daily. Avoid concurrent administration of simvastatin or lovastatin and the following: itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, and large quantities of grapefruit juice. See prescribing information for full details on drug interactions.

Atorvastatin (Lipitor) also interacts with CYP450 3A4 inhibitors but to a lesser degree, as it undergoes less first-pass metabolism.⁴⁹ Fluvastatin (Lescol/Lescol XL) is primarily metabolized by CYP450 2C9 so its levels may be increased by CYP450 2C9 inhibitors, but there appear to be less drug interactions.⁵⁰ Pravastatin and rosuvastatin (Crestor) are not metabolized by the CYP450 enzymes.

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 in the individual components.^{63 64}

Drug	amiodarone	cyclosporine	digoxin	erythromycin	gemfibrozil (fibric acid derivatives)	HIV protease inhibitors	itraconazole (azole antifungals)	nefazodone	niacin	omeprazole, cimetidine, ranitidine	Oral contraceptives	verapamil	warfarin
atorvastatin (Lipitor, Caduet) ^{51,52}	--	X	X	X	X	X	X	--	X	--	X	--	--
ezetimibe / simvastatin (Vytorin) ⁵³	X	X	X	X	X	X	X	X	X	--	--	X	X
fluvastatin (Lescol, Lescol XL) ^{54,55}	--	--	X	--	--	--	--	--	--	X	--	--	--
lovastatin ⁵⁶ lovastatin ER (Altoprev) ⁵⁷ niacin ER/lovastatin (Advicor) ⁵⁸	X	X	--	X	X	X	X	X	--	--	--	X	--
pravastatin ⁵⁹	--	--	--	--	X	--	--	--	--	--	--	--	--
rosuvastatin (Crestor) ⁶⁰	--	X	--	--	X	X	--	--	--	--	--	--	X
simvastatin ⁶¹ niacin ER/simvastatin (Simcor) ⁶²	X	X	X	X	X	X	X	X	X	--	--	X	X

Adverse Effects

Drug	Myalgia	Abd Pain	Diarrhea	Dyspepsia	Nausea	Rash	Headache	Fatigue or Malaise
atorvastatin (Lipitor) ⁶⁵	5.6 (1.1)	0-3.8 (0.7)	0-3.8 (1.5)	1.3-2.8 (4.1)	reported	1.1-3.9 (0.7)	2.5-16.7 (7)	reported
ezetimibe / simvastatin (Vytorin) ⁶⁶	3.5 (2.9)	reported	reported	reported	reported	reported	6.8 (6.4)	reported
fluvastatin (Lescol) ⁶⁷	5.0 (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) ⁶⁸	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 ⁶⁹	1.8-3.0 (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) ⁷⁰	3	reported	3	reported	reported	reported	7	reported
niacin ER / lovastatin (Advicor) ⁷¹	3	4	6	3	7	5	9	reported
niacin ER / simvastatin (Simcor) ⁷²	reported	3.5	3.0 (2.9)	4	3.2 (4.2)	reported	4.5 (4.6)	reported
pravastatin ⁷³	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) ⁷⁴	2.8 (1.3)	≥ 2	3.4 (2.9)	3.4 (3.1)	3.4 (3.1)	≥ 2	5.5 (5)	reported
simvastatin ⁷⁵	1.2 (1.3)	3.2 (3.2)	1.9 (2.5)	1.1	1.3 (1.9)	0.6 (0.6)	0.7	reported

Adverse effects are reported as a percentage. Adverse effects data are obtained taken from prescribing information and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses.

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 severity with no unusual adverse events reported.⁷⁶ 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, six to eight percent of patients on niacin ER/lovastatin (Advicor) withdrew from therapy due to flushing.⁷⁷ Overall, 53 to 83 percent of patients will experience flushing associated with the niacin in niacin ER/lovastatin.⁷⁸ In a controlled study, flushing occurred in up to 59 percent of patients treated with niacin ER/simvastatin (Simcor) and resulted in study

discontinuation for six percent of patients.⁷⁹ Aspirin or another NSAID may be taken with niacin ER/lovastatin (Advicor) or niacin ER/simvastatin (Simcor) therapy to reduce the incidence of flushing. The other most common adverse events in addition to headache, nausea, and diarrhea in a six-month study comparing niacin ER/simvastatin (Simcor) to simvastatin were pruritis and back pain (3.2 percent incidence for each).

An article cited an increased rate of serious adverse events based on the number of voluntarily reported adverse drug events for rosuvastatin (Crestor).⁸⁰ Use of voluntarily reported cases without assessment of causality is not a proper method to assess the rate of an adverse event associated with a drug. Due to the heightened awareness of serious adverse events following the removal of cerivastatin (Baycol[®]) from the US market in 2001, there is likely reporting bias with rosuvastatin as it entered the US market in 2003. In summary, the occurrence of serious adverse events such as myopathy and rhabdomyolysis are extremely rare with all statins including rosuvastatin.^{81,82,83}

In a meta-analysis of 26 large randomized controlled trials with mean duration of follow-up of at least one year, statins did not reduce the incidence of cancer (OR, 1.02, 95% CI, 0.97 to 1.07) or cancer deaths (OR, 1.01, 95% CI, 0.93 to 1.09).⁸⁴ The statins, primarily low to intermediate doses, had no effect on any type of cancer and did not affect the risk of cancer.

In clinical trials, atorvastatin (Lipitor), fluvastatin (Lescol/Lescol XL), pravastatin, and simvastatin were rarely (less than two percent) discontinued due to adverse reactions. Rosuvastatin (Crestor) was discontinued in 3.1 percent of patients in clinical trials.⁸⁵ Lovastatin was discontinued in 4.6 percent of patients in trials.

Liver Function/Safety^{86,87,88,89,90,91,92,93,94,95,96,97,98}

Drug	Persistent increases (3X ULN) in serum transaminases (%)	Liver Function Testing Recommendations
atorvastatin (Lipitor, Caduet)	0.7	before initiation, 12 weeks after initiation or elevation in dose, and semi-annually
ezetimibe / simvastatin (Vytorin)	1.8	before initiation, and when clinically indicated. The 10 mg/80 mg dose requires testing three months after initiation and periodically thereafter.
fluvastatin (Lescol)	1.1	before initiation, 12 weeks after initiation or elevation in dose
fluvastatin XL (Lescol XL)	1.9	before initiation, 12 weeks after initiation or elevation in dose
lovastatin, lovastatin ER (Altoprev)	1.9	before initiation for patients with a history of liver disease or for doses ≥ 40 mg, then as clinically necessary.
niacin ER / lovastatin (Advicor)	1	before initiation, every 6-12 weeks after initiation for six months, then periodically (every six months)
niacin ER / simvastatin (Simcor)	1	before initiation, every 12 weeks after initiation for six months, then periodically (every six months)
pravastatin	≤ 1.2	before initiation and when clinically indicated
rosuvastatin (Crestor)	1.1	before initiation, 12 weeks after initiation or elevation in dose, and semi-annually
simvastatin	1	before initiation, and when clinically indicated. The 80 mg dose requires testing three months after initiation and periodically thereafter.

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

Special PopulationsPediatrics

Several statins have been approved for use in adolescent boys and girls (at least one year post-menarche). Atorvastatin (Lipitor), fluvastatin (Lescol/Lescol XL), lovastatin, pravastatin, and simvastatin have been approved for the adjunctive management of Heterozygous Familial Hypercholesterolemia (HeFH) in addition to diet.^{99,100,101,102,103,104,105} Statin therapy for HeFH is generally initiated when the LDL-C levels are equal to or greater than 190 mg/dL or when the LDL-C is equal to or greater than 160 mg/dL in the presence of at least two more cardiovascular event risk factors or for the patient with a known family history of premature CHD.¹⁰⁶ The minimum goal of therapy is to achieve LDL-C of less than 130 mg/dL. Very little data are known for children less than eight years old.

The safety and effectiveness of lovastatin ER (Altoprev), niacin ER/lovastatin (Advicor), niacin ER/simvastatin (Simcor), rosuvastatin (Crestor), atorvastatin/amlodipine (Caduet) and ezetimibe/simvastatin (Vytorin) have not been established in pediatric patients.

Pregnancy

All statin-containing products are Pregnancy Category X.

Race

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.¹⁰⁷ 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, 0.49-0.91; p=0.01). The mean LDL-C reductions were 3.2 percent in the diet group and 18 percent 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 six weeks.¹⁰⁸ 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 percent rosuvastatin, 36 percent atorvastatin, p<0.0001). For the 20 mg doses, rosuvastatin (50 percent) reduced LDL-C to a greater degree than atorvastatin (42 percent, p<0.0001). Achievement of the target levels of LDL-C of less than 100 mg/dL was reported for 74 and 91 percent for the rosuvastatin 10 and 20 mg doses and 52 and 62 percent for atorvastatin 10 and 20 mg doses, respectively. Adverse events were similar between the groups.

In an open-label, randomized trial in the US and Canada, 740 patients of South-Asian origin with hypercholesterolemia, received rosuvastatin (Crestor) 10 or 20 mg or atorvastatin (Lipitor) 10 or 20 mg daily.¹⁰⁹ A total of 66 percent of patients were considered as being high risk for CAD. LDL-C decreased by 45 percent with rosuvastatin 10 mg versus 40 percent with atorvastatin 10 mg (p=0.0023) and by 50 percent with rosuvastatin 20 mg versus 47 percent with atorvastatin 20 mg (p=NS). There was no significant difference in the doses for LDL-C reduction and both drugs were well tolerated.

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 of South-Asia origin with primary hypercholesterolemia and elevated cardiovascular risk (greater than 20 percent/ten years, type 2 diabetes, or a history of coronary heart disease).¹¹⁰ 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 percent versus 69.4 percent, p<0.0001). Both agents were well-tolerated and had a similar adverse event profile.

For rosuvastatin (Crestor), Asian patients should start on 5 mg daily.¹¹¹

Hepatic/Renal

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

Dosages

Drug	Usual Starting Dose	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: 2.5mg/10mg, 2.5mg/20mg, 2.5mg/40mg, 5mg/10mg, 5mg/20mg, 5mg/40mg, 5mg/80mg, 10mg/10mg, 10mg/20mg, 10mg/40mg, 10mg/80mg
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 / simvastatin (Vytorin)	10 mg/10 mg – 10 mg/40 mg daily	10 mg/10 mg – 10 mg/80 mg daily	--	10 mg/10 mg daily	ezetimibe / simvastatin combination tablets: 10mg/10mg, 10mg/20mg, 10mg/40mg, 10mg/80mg
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: 500mg/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, 750 mg/20 mg, 1,000 mg/20 mg
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)	5 – 20 mg daily	5 – 40 mg daily	--	5 mg daily	5, 10, 20, 40 mg tablets
simvastatin	5 – 40 mg daily	5 – 80 mg daily	ages 10-17: 10 – 40 mg daily	20 mg daily	5, 10, 20, 40, 80 mg tablets

Dosing Considerations^{112,113,114,115,116,117,118,119,120,121,122}

amlodipine/atorvastatin (Caduet):

- Caduet may be substituted for the individual agents after titration
- Dosage should be individualized for tolerance of both amlodipine and atorvastatin
- Renal impairment: no dosage adjustment is needed

atorvastatin (Lipitor)

- Avoid administering with fibrates
- No dosage adjustment is recommended in renal insufficiency
- Severe hepatic disease: adjust dosage

ezetimibe / simvastatin (Vytorin)

- Homozygous Familial Hypercholesterolemia (HoFH): 10mg/40 mg or 10mg/80 mg per day in the evening
- Severe renal impairment: do not start Vytorin unless patient has tolerated more than simvastatin 5 mg daily
- Gemfibrozil or other fibrates or niacin >1 gm daily - not recommended to use in combination – do not exceed 10 mg/10 mg daily
- Cyclosporine or danazol: use 10 mg/10 mg daily only; do not start Vytorin unless patient has tolerated more than simvastatin 5 mg daily
- Amiodarone or verapamil: do not exceed 10 mg/20 mg daily

fluvastatin (Lescol, Lescol XL)

- Don't crush, chew, break tablets; do not open 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

- Cyclosporine or danazol: dosing range is 10 to 20 mg daily
- Amiodarone or verapamil: do not exceed 40 mg daily
- Gemfibrozil, fibrates, or niacin >1 gm daily: do not exceed 20 mg daily
- Renal insufficiency (CrCl < 30 mL/min): use caution with doses above 20 mg daily

lovastatin ER (Altoprev)

- Elderly and complicated medical conditions including diabetes: use 20 mg at bedtime
- Cyclosporine: do not begin Altoprev; consider immediate release lovastatin
- Amiodarone and verapamil: do not exceed 20 mg daily
- Gemfibrozil, fibrates, or niacin >1 gm daily: do not exceed 20 mg daily
- Renal insufficiency (CrCl < 30 mL/min): use caution with doses above 20 mg daily

niacin ER / lovastatin (Advicor)

- For niacin ER/lovastatin (Advicor), two tablets of 500mg/20mg are not interchangeable with 1,000mg/40mg.¹²³ When converting patients on Niaspan to niacin ER/lovastatin (Advicor), an equivalent niacin dosage can be started (mg per mg); however, if the patient has been on any other niacin product, therapy with niacin ER/lovastatin (Advicor) should be initiated at the lowest dose and titrated upward every four weeks as needed to achieve treatment goals. If niacin ER/lovastatin (Advicor) therapy is interrupted for more than seven days, initiate therapy at niacin ER/lovastatin (Advicor) 500 mg/20 mg to minimize adverse effects.
- Combination with gemfibrozil and fibrates should be avoided if possible; if benefits outweigh risks, consider niacin ER/lovastatin dosage not exceeding 1,000/20 mg daily
- Cyclosporine: do not exceed niacin ER/lovastatin 1,000/20 mg daily
- Renal insufficiency: use caution

pravastatin

- Patients with significant renal or hepatic impairment: use 10 mg daily to start
- Cyclosporine: use 10 to 20 mg daily

rosuvastatin (Crestor)

- Use rosuvastatin 5 mg for patients requiring less aggressive lipid lowering goals or higher risk for myopathy including concurrent cyclosporine, Asian patients, and patients with renal impairment
- Asian patients: use 5 mg
- Cyclosporine: use 5 mg only
- Gemfibrozil: do not exceed 10 mg daily
- Severe renal impairment (CrCl < 30mL/min): use 5 to 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[®]): do not exceed 10 mg daily

simvastatin

- HoFH: use 40 mg daily in evening or 80 mg per day in divided doses
- Gemfibrozil: do not exceed 10 mg daily
- Cyclosporine or danazol: use 5 to 10 mg daily only
- Amiodarone or verapamil: do not exceed 20 mg daily
- Severe renal impairment (CrCl < 10 mL/min): initiate therapy at 5 mg daily with close monitoring

niacin ER / simvastatin (Simcor)

- Gemfibrozil: do not exceed 10 mg daily
- Cyclosporine or danazol: do not exceed 10 mg daily

- Amiodarone or verapamil: do not exceed 20 mg daily
- Severe renal impairment: do not initiate therapy unless patient has already tolerated treatment with simvastatin at 10 mg daily or higher.

Clinical Trials

Search Strategies

Articles were identified through searches performed on PubMed, www.ifpma.org/clinicaltrials, and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials for FDA-approved indications are considered the most relevant in this category. 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 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

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 rosuvastatin (Crestor) or the combinations of simvastatin and ezetimibe (Vytorin), niacin ER/lovastatin (Advicor), niacin ER/simvastatin (Simcor) or atorvastatin and 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:¹²⁴ 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 eight 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 percent 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 percent 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 two 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).¹²⁵ 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 percent of the atorvastatin 80 and 10 mg groups, respectively (HR=0.75; 95% CI, 0.58 to 0.97, p=0.026).¹²⁶ 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 percent, respectively; HR=0.71; 95% CI, 0.61 to 0.84; p<0.0001).¹²⁷ 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 two patients in the high-dose atorvastatin group and three patients in the low-dose atorvastatin group. Liver enzyme elevation, defined as two measurements greater than three times the upper limit of normal for ALT, AST, or both within four to 10 days, occurred more frequently in the high-dose atorvastatin group (1.2 versus 0.2 percent, 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).¹²⁸ A history of HF was present in 7.8 percent of patients. A known ejection fraction less than 30 percent and advanced HF were exclusion criteria for the study. A predefined secondary end point of the study was hospitalization for HF. The incidence of hospitalization for HF was 2.4 percent for atorvastatin 80 mg and 3.3 percent for atorvastatin 10 mg (HR=0.74, 95% CI, 0.59 to 0.94, p=0.0116). The treatment effect of the higher dose was more marked in patients with a history of HF: 17.3 percent versus 10.6 percent in the 10 and 80 mg arms, respectively (HR=0.59, 95% CI, 0.4 to 0.88; p=0.009). The rates of hospitalization for HF were much lower among patients without a history of HF [1.8 percent in the 80 mg group and 2.0 percent 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.¹²⁹ The absolute risk was reduced by 2.3 percent and relative risk by 19 percent 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 CK levels.

ASCOT-LLA study:¹³⁰ 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 percent over the study period. Stroke, a secondary endpoint, was reduced by approximately 27 percent with atorvastatin (p=0.024).

CARDS:¹³¹ The effectiveness of atorvastatin in the primary prevention of cardiovascular events in type 2 diabetics was studied in 2,838 patients. 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 LDL-C values (<160 mg/dL, baseline mean 119 mg/dL) and TG (<600 mg/dL, baseline mean 172 mg/dL). Patients also had at least one of the

following risk factors: a history of retinopathy, albuminuria, current smoking, or hypertension. The mean duration of diabetes was six years upon study entry.¹³² Patients were randomized to atorvastatin 10 mg daily or placebo. The trial was halted two 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 percent [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 percent, coronary revascularizations by 31 percent, and stroke by 48 percent by atorvastatin ($p=0.016$) compared to placebo. Atorvastatin was well tolerated in this 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.¹³³ The primary endpoint was the composite of cardiac death, nonfatal MI, and stroke. After four weeks, the mean LDL-C was reduced by 42 percent in the atorvastatin group; placebo group had a 1.3 percent reduction in LDL-C. After a median of four years, 469 patients reached the composite endpoint (atorvastatin, $n=226$; placebo $n=243$; [relative risk, 0.92; 95% CI, 0.77 to 1.10; $p=0.37$). Atorvastatin had no effect on the individual components of the endpoint except the relative risk for stroke was 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:¹³⁴ 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 one to six 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 percent for atorvastatin and placebo, respectively ($p=0.03$). The five-year absolute risk reduction of major cardiovascular events associated with atorvastatin was 3.5 percent (HR=0.80; 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 two 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 percent). Five cases of rhabdomyolysis were reported, with two patients in the atorvastatin group and three patients in the placebo group.

A post-hoc analysis of the SPARCL trial suggested a higher incidence of hemorrhagic stroke but reduced risk of ischemic stroke in the patients treated with atorvastatin 80 mg.¹³⁵ Hemorrhagic stroke was more frequent in subjects who had a hemorrhagic stroke on study entry, in men, and with advanced age.

ASPEN:¹³⁶ 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 four 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

percent over four years compared to placebo ($p < 0.0001$). The composite endpoint rates were 13.7 and 15 percent for atorvastatin and placebo groups, respectively (HR=0.90; 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 percent 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 two groups (10.4 percent for atorvastatin; 10.8 percent 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 percent overall; $p = 0.10$).

atorvastatin (Lipitor) versus pravastatin (Pravachol)

REVERSAL study:¹³⁷ 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 percent; $p = 0.001$) compared with baseline. Progression did not occur in the atorvastatin group (-0.4 percent; $p = 0.98$) 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:¹³⁸ The authors enrolled 4,162 patients who had been hospitalized for acute coronary syndrome (ACS) within the preceding ten 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 three and 4.2 percent of the atorvastatin and pravastatin patients, respectively (HR=0.72; 95% CI, 0.58 to 0.89; $p = 0.003$).¹³⁹ Primary end point rates at two years were 26.3 percent in the pravastatin group and 22.4 percent in the atorvastatin group, reflecting a 16 percent reduction in the hazard ratio in favor of atorvastatin ($p = 0.005$). 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.

A double-blind, randomized trial of 893 ambulatory CAD patients (30 percent female) aged 65 to 80 years with one or more episode of myocardial ischemia that lasted three 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.¹⁴⁰ The primary efficacy parameter (absolute change from baseline in total duration of ischemia at month 12) was significantly reduced in both groups at three 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) and simvastatin (Zocor)

IDEAL:¹⁴¹ 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 percent, pravastatin 10 percent, and atorvastatin 11 percent). 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 five 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 percent of the atorvastatin patients and 10.4 percent of the simvastatin patients (HR=0.89; 95% CI, 0.78 to 1.01, p=0.07). The rates of composite of the CHD death, nonfatal MI, cardiac resuscitation, and stroke was 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 percent simvastatin; six percent 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 percent, p<0.001). Liver enzyme elevation was reported more frequently with atorvastatin (p<0.001).

atorvastatin plus amlodipine (Caduet)

In a double-blind, placebo-controlled study, 1,660 patients with hypertension and hyperlipidemia were evaluated following therapy with amlodipine, atorvastatin, or the combination of amlodipine and atorvastatin.¹⁴² Many patients had significant risk factors for CHD including diabetes (15 percent), smoking history (22 percent), and family history of CHD (14 percent). All dose strengths and possible combinations were evaluated. After eight weeks, all the combination doses of amlodipine and atorvastatin demonstrated reductions in systolic and diastolic blood pressure and LDL-C in a dose-related manner compared to placebo. No trend in modification of response of either drug was seen with the combination.

ezetimibe plus simvastatin (Vytorin)

No clinical outcomes trials with the combination of ezetimibe and simvastatin have been published to date. Short-term comparison trials utilizing LDL-C reduction as the method for comparison have been performed.

A total of 1,528 patients with primary hyperlipidemia were enrolled in a randomized, multicenter, double-blind, placebo-controlled trial comparing the efficacy and safety of ezetimibe/simvastatin combination tablet and monotherapy with ezetimibe and simvastatin.¹⁴³ After a six to eight week washout period, patients with LDL-C between 145 and 250 mg/dL were randomized to one of ten groups for 12 weeks. Groups were ezetimibe/simvastatin 10/10, 10/20, 10/40, or 10/80 mg; simvastatin 10, 20, 40, or 80 mg; ezetimibe 10 mg; or placebo daily. The groups were similar at baseline. The pooled data from the ezetimibe/simvastatin groups demonstrated greater reductions in LDL-C than the simvastatin or ezetimibe monotherapy groups (p<0.001). Reductions in LDL-C for the combination groups ranged from 44.6 to 60.2 percent. More patients in the combination groups achieved LDL-C levels of less than 100 mg/dL compared to simvastatin (78.6 versus 45.8 percent, p<0.001). Combination therapy had a similar safety profile to that of simvastatin. In another clinical trial, the combination of ezetimibe and

simvastatin has been shown to have a higher rate of ATP III goal attainment with a lower simvastatin dose and fewer dose titrations.¹⁴⁴ Similar findings have been reported elsewhere.^{145,146}

VYVA study: A total of 1,902 adult patients with CHD or CHD risk equivalents and elevated cholesterol were enrolled in a multicenter, double-blind, six-week trial comparing all doses of atorvastatin and ezetimibe/simvastatin.¹⁴⁷ Following a four week placebo and diet run-in phase, patients were randomized to one of eight arms: atorvastatin 10, 20, 40, and 80 mg daily or ezetimibe/simvastatin 10/10, 10/20, 10/40, and 10/80 mg daily. Primary endpoint was the change in LDL-C, TG, and HDL-C following the six-week treatment period. Atorvastatin reduced LDL-C by 36 to 53 percent (mean 45.3 percent) whereas ezetimibe/simvastatin reduced LDL-C by 47 to 59 percent (mean 53.4 percent). When equal doses of statins were compared (atorvastatin 10 mg versus ezetimibe/simvastatin 10/10 mg), the combination product produced significantly greater reductions in LDL-C ($p<0.001$). Reductions in TG were similar in all comparisons. For HDL-C, ezetimibe/simvastatin 10/40 and 10/80 mg were associated with higher HDL-C levels than atorvastatin 40 and 80 mg. CRP levels were similar between the two drug groups. Goal attainment for LDL-C occurred more frequently in the group receiving ezetimibe/simvastatin (89.7 versus 81.1 percent, $p<0.001$). More liver enzyme elevations were observed in the atorvastatin groups. The manufacturers of ezetimibe/simvastatin sponsored the study.

A double-blind, randomized, multicenter study compared ezetimibe/simvastatin 10/20 mg daily versus atorvastatin 10 or 20 mg daily or ezetimibe/simvastatin 10/40 mg daily versus atorvastatin 40 mg daily in 1,229 adult patients with hypercholesterolemia and type 2 diabetes.¹⁴⁸ The primary endpoint was LDL-C reduction. LDL-C levels were reduced significantly more with ezetimibe/simvastatin 10/20 mg (53.6 percent, 95% CI, 55.4% to 51.8%) than with atorvastatin 10 mg (38.3 percent, 95% CI, 40.1 to 36.5 percent, $p<0.001$) or atorvastatin 20 mg (44.6 percent, 95% CI, 46.4 to 42.8 percent, $p<0.001$), and with ezetimibe/simvastatin 10/40 mg (57.6 percent, 95% CI, 59.4 to 55.8 percent) versus atorvastatin 40 mg (50.9 percent, 95% CI, 52.7 to 49.1 percent, $p<0.001$). More patients on ezetimibe/simvastatin reached the secondary endpoint of LDL-C reduction to less than 70 mg/dL ($p<0.001$ for all dose comparisons) compared to atorvastatin monotherapy. Ezetimibe/simvastatin 10/20 mg reduced high-sensitivity C-reactive protein and TG levels significantly more than atorvastatin 10 mg ($p=0.02$), with comparable reductions at other doses. Both treatments were generally well tolerated.

The combination of ezetimibe/simvastatin was compared with rosuvastatin in a six-week, double-blind trial in 2,959 patients with hypercholesterolemia.¹⁴⁹ Randomization was performed according to stratification by LDL-C to the following doses: ezetimibe/simvastatin 10/20 mg, 10/40 mg, or 10/80 mg daily or rosuvastatin 10, 20, or 40 mg daily. The combination reduced the LDL-C levels to the greatest extent at all dosing levels (52 to 61 percent versus 46 to 57 percent, $p\leq 0.001$). Significantly more patients, including high-risk patients, achieved LDL-C levels of less than 70 mg/dL in the combination group compared to rosuvastatin ($p<0.001$, $p\leq 0.005$). HDL-C increases were similar between the treatment groups as were adverse effects, with the exception of proteinuria, more commonly reported with rosuvastatin 10 mg and 40 mg use.

Recently, the ENHANCE trial, a two-year, randomized, double-blind, multicenter study of 720 patients with heterozygous familial hypercholesterolemia compared ezetimibe/simvastatin 10/80 mg versus simvastatin 80 mg.¹⁵⁰ The study showed no significant difference between ezetimibe/simvastatin versus simvastatin in the primary endpoint of carotid intima media thickness (IMT), measured at three sites in the carotid arteries, using ultrasound imaging.¹⁵¹ The

change in mean carotid IMT after two years was 0.0111 mm versus 0.0058 mm, for the combination product versus simvastatin alone ($p=0.29$). Ezetimibe/simvastatin reduced LDL-C to a greater degree, 58 percent compared to simvastatin 41 percent, ($p<0.01$), after two years of treatment. This was not a clinical outcomes study, yet it generated attention since carotid ultrasound imaging can be a predictor of cardiac events, and the study results were delayed in being released. The American College of Cardiology (ACC) and American Heart Association (AHA) have released recommendations regarding the use of products containing ezetimibe and consider it a reasonable option for patients who are currently on a high-dose statin but are not at LDL-C goal, cannot tolerate statins, or can only tolerate a low-dose statin.¹⁵² The National Institute for Health and Clinical Excellence (NICE) guidelines echo these recommendations.¹⁵³ The full ENHANCE study results will be released at the ACC meeting in March 2008.

fluvastatin (Lescol)

LIPS study:¹⁵⁴ 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 percent, respectively). After nearly four 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 percent incidence of events over four years compared to the placebo group with 26.7 percent (5.3 percent absolute risk reduction). Therapy was well tolerated. At the end of follow-up, 10.7 percent of fluvastatin patients and 24 percent 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.¹⁵⁵ During the four-year follow-up period, fluvastatin significantly decreased total-C, LDL-C, and decreased the relative risk of first adverse atherosclerotic cardiac events by 30 percent.

ALERT study:¹⁵⁶ The effects of fluvastatin were evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 2,102 renal transplant patients over five to six years. All patients had stable graft function and were on cyclosporine. Patients were given fluvastatin 40 mg daily or placebo. After two years, the dose of fluvastatin was doubled in 65 percent 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 over five years, fluvastatin reduced LDL-C by 32 percent. 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 two-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.¹⁵⁷ 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.^{158,159}

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.^{160,161}

pravastatin (Pravachol)

ALLHAT-LLT study:¹⁶² 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 five 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 percent used statins at year four, and 26.1 percent used statins at year six. The LDL-C levels were reduced by 28 percent with pravastatin compared to 11 percent with usual care for those who had LDL-C determinations. All-cause mortality and CHD event rates were similar between the two groups. Secondary endpoints of nonfatal MI or fatal CHD events combined, cause-specific mortality, and cancer were similar between the two groups.

The WOSCOPS study was a randomized primary prevention trial comparing pravastatin to placebo over five years in a large cohort of men with hyperlipidemia (TC > 250 mg/dL) and no prior history of MI.¹⁶³ The combined outcome of death from definite coronary heart disease or definite nonfatal MI was reduced from 7.9 to 5.5 percent (p<0.001). A ten-year follow-up of the trial showed a significant reduction in coronary events.¹⁶⁴ In the long-term follow-up, the risk of death from CHD or nonfatal MI was 10.3 percent versus 8.6 percent, in placebo versus the pravastatin group, respectively, (p=0.02). The rates of death from cardiovascular causes (p=0.01) and death from any cause (p=0.03) were reduced over the entire follow-up period. There were no excess deaths from non-cardiovascular causes or incident cancers.

rosuvastatin (Crestor)

Currently, no long-term clinical outcome trials have been published with rosuvastatin. Short-term trials have been published comparing LDL-C reductions of rosuvastatin, atorvastatin, pravastatin, and simvastatin.^{165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180} Rosuvastatin has also been compared to atorvastatin in a short-term trial comparing the effect on HDL-C.¹⁸¹

ASTEROID: In a prospective, randomized, open-label, blinded endpoint trial, rosuvastatin 40 mg daily was administered to 507 patients.¹⁸² All patients underwent a baseline intravascular ultrasound (IVUS) of a single coronary vessel. After two years of rosuvastatin therapy, patients underwent a repeat IVUS to determine a change in atherosclerosis burden. A total of 349 patients had two sets of IVUS. LDL-C levels were 130.4 mg/dL at baseline and decreased to a mean of 60.8 mg/dL during the study (p<0.001.) Over 75 percent 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 primary endpoint was change in percent atheroma volume in the 10 mm-segment with the greatest disease severity at baseline and the change in normalized total atheroma volume for the entire artery. The change in the percent atheroma volume was reduced by a mean of 0.98 percent (p<0.001 versus baseline); this represents a median reduction of 9.1 percent in atheroma volume in the 10 mm-segment identified at baseline. Regression in percent atheroma volume occurred in 63.6 percent of patients and 36.4 percent showed progression. For the normalized total atheroma volume for the artery, a median reduction of 6.8 percent was observed. 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.

METEOR study:¹⁸³ A randomized, double-blind, placebo-controlled, multicenter study assessed whether 40 mg rosuvastatin therapy could slow progression and/or cause regression of carotid intima-media thickness (CIMT) over two years in 984 patients in low risk individuals with subclinical atherosclerosis. Among participants in the rosuvastatin group, the mean baseline LDL-C level of 155 mg/dL declined to 78 mg/dL, a mean reduction of 49 percent ($p < 0.001$ versus placebo). The change in maximum CIMT for the 12 carotid sites was -0.0014 mm/year (95% CI, -0.0041 to 0.0014) for the rosuvastatin group versus 0.0131 mm/year (95% CI, 0.0087 to 0.0174) for the placebo group ($p < 0.001$). Serious rosuvastatin cardiovascular adverse events were observed in 0.86 percent of patients. Though rosuvastatin reduced the rate of progression of maximum CIMT over two years, rosuvastatin did not induce disease regression.

simvastatin (Zocor)

Heart Protection Study (HPS) Collaborative Group:¹⁸⁴ A five-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 patient types, including females and the elderly, were enrolled. In the double-blind study, compliance rates were evaluated and found to be approximately 82 percent in the simvastatin group after five years of therapy. All-cause mortality was significantly lower in the simvastatin group (12.9 percent) compared to the placebo group (14.7 percent), with reduction in mortality seen in both vascular and nonvascular causes ($p = 0.0003$). The percent 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 percent; $p < 0.0001$). Similar results were seen in the diabetic population ($n = 5,963$).¹⁸⁵ Simvastatin produced a 25 percent reduction in the incidence of first stroke and a 24 percent 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 percent risk reduction in the rate of any major vascular event ($p = 0.001$).¹⁸⁶ 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 percent relative reduction (RR) in the rate of first major vascular event (95% CI, 15 to 29, $p < 0.0001$).¹⁸⁷ No significant differences in muscle symptoms or discontinuations due to muscle symptoms were observed between the two groups. The incidence of elevated liver enzymes was not significantly different between simvastatin and placebo groups.

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.¹⁸⁸ 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 four 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 percent 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 percent of patients, respectively (HR=0.75; 95% CI, 0.57 to 1.00; $p = 0.05$). Myopathy (CPK > 10 times upper limit of normal (ULN)) occurred in 0.4 percent of simvastatin patients receiving 80 mg daily ($p = 0.02$), whereas no patients receiving lower doses of simvastatin and only one patient taking placebo had evidence of myopathy.

Summary of Large Clinical Trials

Drug	Primary Prevention	Secondary Prevention
atorvastatin (Lipitor)	ASCOT-LLA ¹⁸⁹ , CARDS ¹⁹⁰	MIRACL ¹⁹¹ , GREACE ¹⁹² , PROVE IT-TIMI 22 ¹⁹³ , TNT ¹⁹⁴ , IDEAL ¹⁹⁵ , ASPEN ¹⁹⁶ , SPARCL ¹⁹⁷ ,
ezetimibe/simvastatin (Vytorin)	--	--
fluvastatin (Lescol)	--	LIPS ¹⁹⁸
lovastatin	AFCAPS/TexCAPS ¹⁹⁹	--
pravastatin	WOSCOPS ²⁰⁰ , PROSPER ²⁰¹ , ALLHAT ²⁰² , MEGA ²⁰³	CARE ²⁰⁴ , LIPID ²⁰⁵ , PROSPER ²⁰⁶ , PACT ²⁰⁷ , PROVE IT-TIMI 22 ²⁰⁸
rosuvastatin (Crestor)	--	--
simvastatin	HPS ²⁰⁹	4S ²¹⁰ , HPS ²¹¹ , Phase Z of A to Z ²¹² , IDEAL ²¹³

LDL-C Reductions^{214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241, 242}

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

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.

Effects on TG and HDL-C ^{243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265}

Drug	Triglyceride change (%)	HDL-C change (%)
atorvastatin (Lipitor, Caduet) 10 - 80mg	- 17 to - 37	- 0.1 to 9
ezetimibe / simvastatin (Vytorin) 10mg/10mg – 10mg/80mg	- 23 to - 35	6 to 12
fluvastatin (Lescol) 10 - 80mg	- 2.7 to - 23	- 3 to 9
fluvastatin XL (Lescol XL) 80mg	- 19 to - 25	7 to 11
lovastatin 20 - 80mg	- 6 to - 27	3 to 10
lovastatin ER (Altoprev) 10 - 60 mg	- 10 to - 33	6 to 13
niacin ER / lovastatin (Advicor) 1,000mg/20mg - 2,000mg/40mg	- 29 to - 49	17 to 32
niacin ER / simvastatin (Simcor) 1,000mg/20mg - 2,000mg/40mg	- 23 to - 38	15 to 29
pravastatin 10 - 80mg	- 9 to - 24	2 to 12
rosuvastatin (Crestor) 5 - 40mg	- 10 to - 35	8 to 14
simvastatin 5 - 80mg	- 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.²⁶⁶ A pooled analysis for intensive lipid-lowering was associated with 16 percent odds reduction ($p < 0.000001$) for coronary death or MI.

A meta-analysis of 27,548 patients with ACS or stable CAD from four randomized, controlled trials comparing intensive to moderate dose statin therapy was done from 1995 to 2006.²⁶⁷ 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 five-year incidence of major coronary events and revascularization and by approximately 20 percent.²⁶⁸

A meta-analysis of atorvastatin (Lipitor) and simvastatin across all dose combinations in terms of changes in TC, LDL-C, TG, and HDL-C was conducted from 17 published and one unpublished trials.²⁶⁹ Atorvastatin was two to four times as potent as simvastatin in reducing TC, LDL-C, and TG. Simvastatin was more effective than atorvastatin in increasing HDL-C.

A meta-analysis of 15 randomized controlled statin trials through May 2006 looked at gender specific incidence of cardiovascular events.²⁷⁰ Cardiovascular events were reduced in men (RR= 0.76, 95% CI, 0.70 to 0.81) and women (RR=0.79, 95% CI, 0.69 to 0.90). 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 (Zetia) 10 mg/day or placebo added to current statin therapy was compared in a meta-analysis of five randomized controlled trials with at least six weeks duration, in 5,039 adults with hypercholesterolemia.²⁷¹ The weighted mean difference between treatments significantly favored the ezetimibe/statin combination over placebo/statin for total cholesterol (-16.1 percent (95% CI, -17.3 to -14.8), $p < 0.0001$), LDL-C (-23.6 percent (95% CI, -25.6 to -21.7), $p < 0.0001$) and HDL-C (1.7 percent (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 (2.0, 5.6), $p < 0.0001$). In pre-defined subgroup 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.

Summary

Lipid-lowering therapy is considered part of treatment of patients with or at risk for cardiovascular disease. Any of the HMG-CoA reductase inhibitors can safely lower LDL-C by the 30 percent required in most patients to reach goal. Though rosuvastatin (Crestor) and ezetimibe/simvastatin (Vytorin) are able to achieve intense LDL-C reductions, clinical outcomes trials are lacking.

In those patients who require more significant reductions in LDL-C, the use of combination therapy with a lipotropic agent of a different class is often indicated. Combination therapy may avoid the increase in adverse effects often seen with higher doses of the HMG-CoA reductase inhibitors. Simvastatin in combination with ezetimibe (Vytorin) achieves lipid reduction similar to other products within this class. Niacin ER/lovastatin (Advicor) and niacin ER/simvastatin (Simcor) combine the beneficial effects of niacin on HDL-C and triglycerides and lower LDL-C with the statin component. Amlodipine/atorvastatin (Caduet), a combination product, is available to enhance patient compliance by providing antihypertensive therapy in combination with atorvastatin. Clinical outcomes trials are lacking for these combination products.

The benefits of reducing LDL-C levels below 100 mg/dL per ATP III recommendations have been established. For high-risk patients including those with CHD, diabetes, ACS, or two CHD risk equivalents, a target of LDL-C of less than 70 mg/dL should be considered reasonable. The new target of LDL-C of less than 70 mg/dL also extends to those patients who have a baseline LDL-C of less than 100 mg/dL. For all patients with peripheral arterial disease (PAD), PAD guidelines recommend a LDL-C goal of less than 100 mg/dL or less than 70 mg/dL if at higher

risk. High risk patients with normal LDL-C values can even benefit from statin use. Despite the mounting evidence that lower LDL-C levels are better, lower doses of statins are still used more frequently than high doses.

Due to equivalent efficacy at equipotent doses, PDL status should be based on relative safety and patient tolerance.

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