Lipotropics, Statins Review

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Lipotropics, Statins Review

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 of the statins have trials documenting 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 cardiovascular events, many patients are not on lipid-lowering therapy or are not at LDL-C goals.[1,2]

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 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.[3]

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. Recent findings suggest that the 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.[4] The PROVE IT-TIMI 22 investigators recently published findings indicating that lower CRP levels (< 2 mg/L) are associated with improvement in cardiovascular event-free survival.[5] The correlation among CRP levels, LDL-C reduction, and cardiovascular disease requires further investigation.

Several combination products have recently been marketed. Caduet® (amlodipine / atorvastatin) is designed to treat two indications - hypertension and hyperlipidemia – which are often seen in the coronary heart disease (CHD) patient. Vytorin™ (ezetimibe / simvastatin) is the combination of two lipid-lowering therapies which work together to lower LDL-C. Advicor™ (niacin ER / lovastatin) provides beneficial effects on HDL-C and lowers 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 be responsible for the treatment of angina.[6] Amlodipine given with atorvastatin (Caduet) in a single tablet treats both hypertension and hypercholesterolemia for patients in whom calcium channel blocker therapy and lipid lowering therapy are desired.

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

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. A combination product, Advicor™, is available which combines the efficacy of a statin, lovastatin, with the beneficial effects of extended release niacin for those patients failing monotherapy.[7]

Agents and Dosage Forms

Drug	Manufacturer	Availability
amlodipine / atorvastatin (Caduet)	Pfizer	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®)	Pfizer	10, 20, 40, 80 mg tablets
ezetimibe / simvastatin (Vytorin)	Merck-Schering-Plough	ezetimibe / simvastatin combination tablets: 10mg/10mg, 10mg/20mg, 10mg/40mg, 10mg/80mg
fluvastatin (Lescol®)	Novartis	20, 40 mg capsules
fluvastatin XL (Lescol XL®)	Novartis	80 mg tablet
lovastatin (Mevacor®)	generic	10, 20, 40 mg tablets
lovastatin ER (Altoprev®)	Sciele Pharma	20, 40, 60 mg tablets
niacin ER / lovastatin (Advicor™)	Kos	niacin ER / lovastatin combination tablets: 500mg/20mg, 750mg/20mg, 1,000mg/20 mg, 1,000/40mg
pravastatin (Pravachol®)	generic, Bristol-Myers Squibb	10, 20, 40 tablets 80 mg tablets (Pravachol only)
rosuvastatin (Crestor®)	AstraZeneca	5, 10, 20, 40 mg tablets
simvastatin (Zocor®)	generic	5, 10, 20, 40, 80 mg tablets

Indications

Indications	atorvastatin (Lipitor), amlodipine/ atorvastatin (Caduet)*	ezetimibe/ simvastatin (Vytorin)	fluvastatin (Lescol)	fluvastatin (Lescol XL)	lovastatin	lovastatin ER (Altoprev)	niacin ER/ lovastatin (Advicor)	pravastatin (Pravachol)	rosuvastatin (Crestor)	simvastatin (Zocor)
Primary hypercholesterolemia ♦ Heterozygous familial and nonfamilial Reduce: Total-C, LDL-C, TG and ApoB	X	X	X		X	X	X	X	X	X
Heterozygous familial hypercholesterolemia ♦ pediatric	X 10-17 years; not Caduet		X 10-16 years	X 10-16 years	X 10-17 years			X 8 years and up		X 10-17 years
Mixed dyslipidemia *Fredrickson Type* ♦ II_a and II_b Reduce: Total-C, LDL-C, TG and ApoB	X		X	X	X To reduce total-C, LDL-C	X	X	X	X	X
Increase HDL-C	X	X	X	X		X	X	X	X	X
Hypertriglyceridemia *Fredrickson Type* IV	X							X	X	X
Primary dysbetalipoproteinemia *Fredrickson Type* III	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 II Diabetics without CHD Reduces risk of MI, stroke, CHF hospitalization, angina and revascularization in CHD patients		Reduces risk of coronary revascularization	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 and vasospastic angina.

Pharmacokinetics

Drug	Bioavailability	Time to Peak Plasma Levels (hr)	t ½ (hr)	Excretion (%)	Circulating active metabolites
amlodipine and	64-90%	6-12	30-50	Urine: 70	No
atorvastatin (Caduet)[8]	~14%; first pass metabolism	1-2	14	Urine: <2	Yes
atorvastatin (Lipitor)[9]	~14%; first pass metabolism	1-2	14	Urine: <2	Yes
ezetimibe and	--	4-12	22	Urine: 11 Feces: 78	Yes
simvastatin (Vytorin)[10,11]	<5% of oral dose reaches general circulation; first pass metabolism	4	3	Urine: 13 Feces: 60	Yes
fluvastatin (Lescol)[12]	24%; first pass metabolism	< 1	3	Urine: 5 Feces: 90	No
(Lescol XL)[13]	29%; first pass metabolism	3	9		
lovastatin[14]	<5% of oral dose reaches general circulation; first pass metabolism	2-4	--	Urine: 10 Feces: 83	Yes
lovastatin ER (Altoprev)[15]	<5% of oral dose reaches general circulation; first pass metabolism	14.2	--	Urine: 10 Feces: 83	Yes
niacin ER and	72 %	5	<1	Urine: 60	Yes
lovastatin (Advicor)[16]	<5% of oral dose reaches general circulation; first pass metabolism	2	4.5	Urine: 10 Feces: 83	Yes
pravastatin (Pravachol)[17]	17%; first pass metabolism	1-1.5	77	Urine: 20 Feces: 70	Yes
rosuvastatin (Crestor)[18]	20%	3-5	19	Feces: 90	Yes
simvastatin (Zocor)[19]	<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), and niacin ER and lovastatin (Advicor) pharmacokinetic profiles are not affected by concurrent administration of the individual components.[20,21,22,23]

Recent 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. Criteria for study inclusion in this review are the following: English language, human studies, analyze the data consistently with the study question, randomly allocate participants to comparison groups, include follow-up (endpoint assessment) of at least 80 percent of those entering the investigation, and have clearly stated, predetermined outcome measure of known or probable clinical importance. Studies were determined to be free of bias. Unbiased studies were then reviewed for validity and importance. The majority of clinical drug trials are sponsored and/or funded by pharmaceutical manufacturers. While objective criteria were used to ensure that the studies included are free of bias, the potential influence of manufacturer sponsorship/funding must be considered.

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) 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 in some studies, 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. A few clinical trials comparing cardiovascular outcomes with different statins are available.

atorvastatin (Lipitor)

TNT study:[24] 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 this 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 the 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 death from CHD, nonfatal 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 a reduction in cerebrovascular events (hazard ration (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; $p=0.02$).[25] 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 0.58–0.97, $p=0.026$).[26] Beneficial effects were seen in the 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 vs. 13 percent, respectively; HR 0.71; 95% CI 0.61-0.84; p<0.0001).[27] 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 this study.

ASCOT-LLA study:[28] 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 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:[29] The effectiveness of atorvastatin in the primary prevention of cardiovascular events in type II diabetics was studied in 2,838 patients. This 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.[30] Patients were randomized to atorvastatin 10 mg daily or placebo. The trial was halted two years earlier than predicted when atorvastatin was found to reduce the rate of the first occurrence of acute cardiac event, coronary revascularization or stroke compared to placebo (rate 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 rate of stroke by 48 percent by atorvastatin 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 II diabetes on hemodialysis to assess the efficacy and safety of atorvastatin 20 mg daily versus placebo.[31] 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 percent confidence interval, 0.68 to 0.99; p=0.03). Atorvastatin did not have a significant effect on combined cerebrovascular events or total mortality.

SPARCL:[32] In this 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. This 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 reduction in the risk of major cardiovascular events associated with atorvastatin was 3.5 percent (hazard ratio, 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.

ASPEN:[33] In this 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 0.3 percent compared to placebo 1.1 percent (p<0.0001). The composite endpoint rates were 13.7 and 15 percent for atorvastatin and placebo groups, respectively (HR 0.90; 95% CI 0.73-1.12); 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 0.59-1.15). 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 0.74-1.28). The relative risk reductions for fatal and nonfatal MI did not achieve statistical significance (27 percent overall; p=0.10).

<u>atorvastatin (Lipitor) versus pravastatin (Pravachol)</u>

REVERSAL study:[34] This 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:[35] 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 (HR=0.72; 95% CI, 0.58 to 0.89; p=0.003).[36]

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.

atorvastatin (Lipitor) and simvastatin (Zocor)

IDEAL:[37] This 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 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, 0.78-1.01, 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, 0.78-0.98; 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, 0.71-0.98; 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.[38] 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.[39] 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 vs. 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.[40] Similar findings have been reported elsewhere.[41,42]

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.[43] 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 this study.

The combination of ezetimibe/simvastatin was compared with rosuvastatin in a six-week, double-blind trial in 2,959 patients with hypercholesterolemia.[44] 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 vs. 46 to 57 percent, p=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=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.

<u>fluvastatin (Lescol)</u>

LIPS study:[45] Fluvastatin 80 mg (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.[46] During the four-year follow-up period, fluvastatin significantly decreased total-C, LDL-C, and decreased the risk of first adverse atherosclerotic cardiac events by 30 percent.

ALERT study:[47] 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 did reduce 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.[48] 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 0.63-0.99; p=0.036) and in cardiac death and nonfatal MI (HR=0.71; 95% CI 0.55-0.93, 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.[49]

pravastatin (Pravachol)

ALLHAT-LLT study:[50] This 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 II 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.

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.[51,52,53,54,55,56,57,58,59,60,61,62,63,64,65]

ASTEROID: In this prospective, randomized, open-label, blinded endpoint trial, rosuvastatin 40 mg daily was administered to 507 patients.[66] 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 a LDL-C 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 this study, large number of patients not completing the study, and the fact that the manufacturer funded this study.

simvastatin (Zocor)

Heart Protection Study (HPS) Collaborative Group:[67] 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 strokes. All patient types, including females and the elderly, were enrolled. In this 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 vs. 25.2 percent; p<0.0001). Similar results were seen in the diabetic population (n=5,963).[68] 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).[69] Of the 3,500 patients with baseline LDL-C below 100 mg/dL, the simvastatin patients were observed to have similar risk reductions as compared to the simvastatin patients with higher baseline LDL-C. 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.

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.[70] 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, 0.57-1.00; 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 of CHD	Secondary Prevention of CHD
atorvastatin (Lipitor)	ASCOT[71], CARDS[72]	GREACE[73], TNT[74], IDEAL[75]
fluvastatin (Lescol)	--	LIPS[76]
lovastatin	AFCAPS/TexCAPS[77]	--
pravastatin (Pravachol)	WOSCOPS[78], ALLHAT[79]	CARE[80], LIPID[81], PACT[82]
rosuvastatin (Crestor)	--	--
simvastatin (Zocor)	HPS[83]	4S[84], HPS[85], IDEAL[86]

Special Populations

Recently, data in the Japanese population has become available. 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.[87] 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 vs. 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 and rosuvastatin over six weeks.[88] 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.

For rosuvastatin (Crestor), Asian patients should start on 5 mg daily and should not exceed 20 mg daily.[89]

Pediatrics

Several statins have been approved for use in adolescent boys and girls (at least one year post-menarche). Atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin have been approved for the adjunctive management of Heterozygous Familial Hypercholesterolemia (HeFH) in addition to diet.[90,91,92,93,94,95,96] Statin therapy for HeFH is generally initiated when the LDL-C levels are greater than 190 mg/dL or when the LDL-C is 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. Very little data are known for children less than eight years old.

LDL-C Reductions[97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,,115,116,117,118,119,120,121,122,123]

Drug	<25% decrease	25-35% decrease	36-45% decrease	46-50% decrease	51-60% decrease
atorvastatin (Lipitor, Caduet)	--	10mg	10 - 20mg	40 - 80mg	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	--	--
pravastatin (Pravachol)	10 - 20mg	20 - 40mg	80mg	--	--
rosuvastatin (Crestor)	--	--	5-10mg	10mg	10 - 40mg
simvastatin (Zocor)	5mg	5 - 20mg	20 - 80mg	80mg	--

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

Effects on TG and HDL-C
124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145

Drug	Triglyceride decrease (%)	HDL-C increase (%)
atorvastatin (Lipitor, Caduet) 10 - 80mg	- 17 - 37	(0.1) - 9
ezetimibe / simvastatin (Vytorin) 10mg/10mg – 10mg/80mg	- 23 - 35	6 - 12
fluvastatin (Lescol) 10 - 80mg	- 2.7 - 23	(3) - 9
fluvastatin XL (Lescol XL) 80mg	- 19 - 25	7 - 11
lovastatin 20 - 80mg	- 6 - 27	3 - 10
lovastatin ER (Altoprev) 10 - 60 mg	- 10 - 33	6 - 13
niacin ER / lovastatin (Advicor) 1,000mg/20mg - 2,000mg/40mg	- 29 - 49	17-32
pravastatin (Pravachol) 10 - 80mg	- 9 - 24	2 - 12
rosuvastatin (Crestor) 5 - 40mg	- 10 - 35	8 - 14
simvastatin (Zocor) 5 - 80mg	- 9 - 34	3 - 16

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

Adverse Drug Reactions[146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165]

The adverse effects below are indicated as relative to placebo control where the rate of events in placebo control groups equals one. * = reported.

Drug	Myalgia	Abd Pain	Diarrhea	Dyspepsia	Nausea	Rash	Headache	Fatigue
atorvastatin (Lipitor)	0-5.1	4-5.4	0-3.5	0.3-3.2	*	1.6-5.6	0.4-2.4	1.2-2
ezetimibe / simvastatin (Vytorin)	1.2	*	*	*	*	*	1.1	*
fluvastatin (Lescol)	1.1	1.3	1.2	2.5	1.6	1	1.1	1.2
fluvastatin XL (Lescol XL)	0.8	1	0.8	1.1	1.3	0.7	0.6	0.7
lovastatin	0.2-1.8	1.3-1.6	0.3-1.1	0.5-0.8	0.8-1	1.1-1.9	0.8-1.3	0.9-1.2
lovastatin ER (Altoprev)	0.2	*	0.5	*	*	*	1.2	<1
niacin ER / lovastatin (Advicor)	*	*	*	*	*	*	*	*
pravastatin (Pravachol)	2.7	0.8	1.1	2.9	1.0	3.6	1.6	1.1
rosuvastatin (Crestor)	2.2	*	1.2	1.1	1.1	*	1.1	1
simvastatin (Zocor)	0.9	1	0.8-1.6	1.2	0.7	0-1	0.7	0.2

Adverse effects are taken from product information and clinical trials and therefore, should not be considered comparative.

Adverse reaction data for 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.[166] Specific incidences have not been reported with Caduet. 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 Advicor withdrew from therapy due to flushing.[167] Aspirin may be taken with Advicor therapy to reduce the incidence of flushing. Overall, 53 to 83 percent of patients will experience flushing associated with the niacin in Advicor.[168]

Rosuvastatin safety has been a subject of debate. The FDA initially evaluated the pre-marketing studies (over 12,000 patients) and found no difference in the incidence of myopathy or rhabdomyolysis cases or serious renal adverse effects compared to any of the other statins. Another post-marketing review by the FDA in response to a petition by Public Citizen was published in March 2005 and had similar findings.[169] The FDA reviewed the claims by Public Citizen and analyzed the pre- and post-marketing studies and Adverse Event Reports. The FDA concluded that rosuvastatin does not have compelling evidence demonstrating an adverse effect profile different from any other statin. The FDA also indicated that the occurrence of dose-related proteinuria is mild, transient proteinuria, and there is no evidence of an increased risk of serious renal adverse effects associated with rosuvastatin.[170]

A recent article cited an increased rate of serious adverse events based on the number of reported Adverse Drug Events.[171] 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.[172,173]

In clinical trials, atorvastatin, fluvastatin, pravastatin, and simvastatin were rarely (less than two percent) discontinued due to adverse reactions. Rosuvastatin was discontinued in 3.7 percent of patients in clinical trials.[174] Lovastatin was discontinued in 4.6 percent of patients in trials.

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 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.[175,176,177]

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.[178,179] Drug interactions with CYP450 3A4 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 Pregnancy Category X.

Patients with active liver disease are generally not appropriate candidates for statin therapy.

Liver Function/Safety [180,181,182,183,184,185,186,187,188,189,190,191]

Drug	Persistent increases (3X ULN) in serum transaminases (%)	Liver Function Testing Recommendations
atorvastatin (Lipitor, Caduet)	0.7-2.3	before initiation, 12 weeks after initiation or elevation in dose, and semi-annually
ezetimibe / simvastatin (Vytorin)	1.8 - 3.6	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 - 1.3	before initiation, 12 weeks after initiation or elevation in dose
fluvastatin XL (Lescol XL)	1.8-4.9	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)
pravastatin (Pravachol)	≤ 1.2	before initiation and prior to dose elevation
rosuvastatin (Crestor)	0.4	before initiation, 12 weeks after initiation or elevation in dose, and semi-annually
simvastatin (Zocor)	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 taken from product information and clinical trials and therefore, should not be considered comparative.

Dosages

Drug	Usual Starting Dose	Dosing Range	Pediatric Dosing Range	Approximate Equivalent Dose (based on LDL-C lowering)
amlodipine / atorvastatin (Caduet)	5 mg/10 mg daily	2.5 mg/10 mg – 10 mg/80 mg daily	--	10 mg daily of atorvastatin
atorvastatin (Lipitor)	10 – 40 mg daily	10 – 80 mg daily	ages 10-17: 10 – 20 mg daily	10 mg daily
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
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
fluvastatin XL (Lescol XL)	80 mg daily	80 mg daily	ages 10-16: 80 mg daily	80 mg daily
lovastatin	20 mg daily with evening meal	10 – 80 mg daily	ages 10-17: 10 – 40 mg daily	40 mg daily
lovastatin ER (Altoprev)	20 – 60 mg daily	10 – 60 mg daily	--	40 mg daily
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
pravastatin (Pravachol)	40 mg daily	10 – 80 mg daily	ages 8-13: 20 mg daily ages 14-18: 40 mg daily	40 mg daily
rosuvastatin (Crestor)	5 – 20 mg daily	5 – 40 mg daily	--	5 mg daily
simvastatin (Zocor)	5 – 40 mg daily	5 – 80 mg daily	ages 10-17: 10 – 40 mg daily	20 mg daily

For Advicor, two tablets of 500mg/20mg are not interchangeable with 1,000mg/40mg.[192] When converting patients on Niaspan to Advicor, an equivalent niacin dosage can be started (mg per mg); however, if the patient has been on any other niacin product, therapy with Advicor should be initiated at the lowest dose and titrated upward every four weeks as needed to achieve treatment goals. If Advicor therapy is interrupted for more than seven days, initiate therapy at Advicor 500 mg/20 mg to minimize side effects.

Dosing Considerations[193,194,195,196,197,198,199,200,201,202,203]

Drug	Dosing Considerations
amlodipine / atorvastatin (Caduet)	Caduet may be substituted for the individual agents after titration Dosage should be individualized for tolerance of both amlodipine and atorvastatin
atorvastatin (Lipitor)	Avoid administering with fibrates
ezetimibe / simvastatin (Vytorin)	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 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
lovastatin (Mevacor)	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: use 10 to 20 mg daily 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)	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
pravastatin (Pravachol)	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 to 20 mg only 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
simvastatin (Zocor)	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: initiate therapy at 5 mg daily

Drug Interactions

All of the currently available statins are extensively metabolized by the CYP450 3A4 isoenzyme system except fluvastatin, pravastatin, and rosuvastatin.

Simvastatin (Zocor, Vytorin) dose is 5 to 10 mg daily when given with danazol, gemfibrozil, or cyclosporine.[204,205] Maximum dose for lovastatin is 20 mg daily with danazol, gemfibrozil, or cyclosporine.[206] Simvastatin must not exceed 20 mg daily when given concurrently with amiodarone and 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 package inserts for Zocor, Vytorin, lovastatin, and Altoprev for full details on drug interactions.

The combination of amlodipine and atorvastatin (Caduet) has not been studied for drug interactions.[218]

Drug	**amiodarone**	**cyclosporine**	**digoxin**	**erythromycin**	**gemfibrozil (fibric acid derivatives)**	**HIV protease inhibitors**	**itraconazole (azole antifungals)**	**nefazodone**	**niacin**	**omeprazole, cimetidine, ranitidine**	**OCs**	**verapamil**	**warfarin**
atorvastatin (Lipitor, Caduet)[207,208]	--	X	X	X	X	--	X	--	X	--	X	--	--
ezetimibe / simvastatin (Vytorin)[209]	X	X	X	X	X	X	X	X	X	--	--	X	X
fluvastatin (Lescol, Lescol XL)[210,211]	--	--	X	--	--	--	--	--	--	X	--	--	--
lovastatin[212] lovastatin ER (Altoprev)[213] niacin ER/ lovastatin (Advicor)[214]	X	X	--	X	X	X	X	X	--	--	--	X	--
pravastatin (Pravachol)[215]	--	--	--	--	X	--	--	--	--	--	--	--	--
rosuvastatin (Crestor)[216]	--	X	--	--	X	--	--	--	--	--	--	--	X
simvastatin (Zocor)[217]	X	X	X	X	X	X	X	X	X	--	--	X	X

Conclusion

Any of the HMG-CoA reductase inhibitors can safely lower LDL-C by the 30 percent required in most patients to reach goal.[219]

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. Advicor combines the beneficial effects of niacin on HDL-C and triglycerides and lowers LDL-C with lovastatin. Caduet, a combination product, is available to enhance patient compliance by providing antihypertensive therapy in combination with lipid reduction therapy.

Recently, new trials have confirmed the benefits of reducing LDL-C levels below 100 mg/dL per ATP III recommendations.[220,221,222] For high-risk patients including those with CHD, diabetes or two CHD risk equivalents, a target of LDL-C of less than 70 mg/dL should now be considered reasonable.[223,224] This 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.[225] For patients with peripheral arterial disease (PAD), PAD guidelines recommend a LDL-C goal of less than 100 mg/dL. Although, for patients at very high risk of an ischemic event, a LDL-C goal of less than 70 mg/dL may be desired.[226] Despite the mounting evidence that lower LDL-C levels are better, lower doses of statins are still used more frequently than high doses.[227] 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.[228] For coronary death or MI, intensive lipid lowering was associated with 16 percent odds reduction ($p<0.000001$).

A recent meta-analysis evaluated data from 13 statin studies that included a total of 90,056 patients. This 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.[229]

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

References

[1] Thom T, Haase N, Rosamond W, et al. Heart Disease and Stroke Statistics—2006 Update. A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. 2006;113;85-151.

[2] Yan AT, Yan RT, Tan M, et al. Contemporary Management of Dyslipidemia in High-Risk Patients: Targets Still Not Met. Am J Med. 2006; 119, 676-683.

[3] The Lovastatin Study Group IV. A multicenter comparison of lovastatin and probucol for treatment of severe primary hypercholesterolemia. Am J Cardiol. 1990; 66(8):22B-30B.

[4] Nissen SE, Tuzcu EM, Schoenhagen P, et al for the REVERSAL Investigators. Statin Therapy, LDL Cholesterol, C-Reactive Protein, and Coronary Artery Disease. N Engl J Med. 2005; 352:29-38.

[5] Ridker PM, Cannon CP, Morro, et al for the PROVE IT–TIMI 22 Investigators. C-Reactive Protein Levels and Outcomes after Statin Therapy. N Engl J Med. 2005; 352:20-28.

[6] Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to update the 1999 Guidelines for the Management of Patients with Chronic Stable Angina). 2002. Available at http://www.americanheart.org/downloadable/heart/1044991838085StableAnginaNewFigs.pdf. Accessed December 18, 2006.

[7] National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 2001.
[8] Caduet [package insert]. New York, NY; Pfizer; October 2005.
[9] Lipitor [package insert]. New York, NY; Pfizer; June 2006.
[10] Vytorin [package insert]. North Wales, PA; Merck/Schering-Plough Pharmaceuticals; May 2006.
[11] Zetia [package insert]. North Wales, PA; Merck/Schering-Plough Pharmaceuticals; 2006
[12] Lescol [package insert]. East Hanover, NJ; Novartis Pharmaceutical Corporation; January 2005.
[13] Lescol XL [package insert]. East Hanover, NJ; Novartis Pharmaceutical Corporation; January 2005.
[14] Mevacor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[15] Altoprev [package insert]. Weston, FL; Andrx Laboratories; August 2004.
[16] Advicor [package insert]. Miami FL; Kos Pharmaceuticals; 2005.
[17] Pravachol [package insert]. Princeton, NJ; Bristol-Myers Squibb; December 2004.
[18] Crestor [package insert]. Wilmington, DE; AstraZeneca; 2005.
[19] Zocor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[20] Caduet [package insert]. New York, NY; Pfizer; October 2005.
[21] Vytorin [package insert]. North Wales, PA; Merck/Schering-Plough Pharmaceuticals; 2006.
[22] Advicor [package insert]. Miami FL; Kos Pharmaceuticals; 2005.
[23] Migoya EM, Bergman A, Hreniuk D, et al. Bioequivalence of an ezetimibe/simvastatin combination tablet and coadministration of ezetimibe and simvastatin as separate tablets in healthy subjects. Int J Clin Pharmacol Ther. 2006; 44(2):83-92.
[24] LaRosa JC, Grundy SM, Waters DD, et al for the Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005; 352(14):1425-35.

[25] Waters DD, LaRosa JC, Barter, P, et al. Effects of high-dose atorvastatin on cerebrovascular events in patients with stable coronary disease in the TNT (treating to new targets) study. J Am Coll Cardiol. 2006; 48(9):1793-9.

[26] Shepherd J, Breazna A, Barter P, et al for the Treating to New Targets Study. Effect of Lowering LDL Cholesterol Substantially Below Currently Recommended Levels in Patients With Coronary Heart Disease and Diabetes. Diabetes Care. 2006; 29:1220 – 1226.
[27] Deedwania P, Barter P, Carmena R, et al for the Treating to New Targets Investigators. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. Lancet. 2006; 368(9539):919-28.
[28] Sever PS, Dahlö B, Poulte NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomized controlled trial. Lancet. 2003; 361:1149-58.
[29] Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004; 364(9435):685-96.
[30] Thomason MJ, Colhoun HM, Livingstone SJ, et al. Baseline characteristics in the Collaborative AtoRvastatin Diabetes Study (CARDS) in patients with Type 2 diabetes. Diabet Med. 2004; 21(8):901-5.
[31] Wanner C, Krane V, Marz W, et al for the German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005; 353:238-48.
[32] Amarenco P, Bogousslavsky J, Callahan A 3rd, et al for the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006; 355(6):549-59.
[33] Knopp RH, d'Emden M, Smilde JG, et al. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care. 2006; 29(7):1478-85.
[34] Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA. 2004; 291(9):1071-80.
[35] Cannon CP, Braunwald E, McCabe CH, et al. Comparison of intensive and moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004; 350(15):14-95-1504.
[36] Ray KK, Cannon CP, McCabe CH, et al for the PROVE IT-TIMI 22 Investigators. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. J Am Coll Cardiol. 2005; 46(8):1405-10.
[37] Pedersen TR, Faergeman O, Kastelein JJ, et al for the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs. usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA. 2005; 294(19):2437-45.
[38] Caduet [package insert]. New York, NY; Pfizer; October 2005.
[39] Bays HE, Ose L, Fraser N, et al for the Ezetimibe Study Group. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clin Ther. 2004; 26(11):1758-73.

[40] Feldman T, Koren M, Insull W Jr, et al. Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals. Am J Cardiol. 2004; 93(12):1481-6.
[41] Goldberg AC, Sapre A, Liu J, et al. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc. 2004; 79(5):620-9.
[42] Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol. 2002; 40(12):2125-34.
[43] Ballantyne CM, Abate N, Yuan Z, et al. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia. The Vytorin Versus Atorvastatin (VYVA) Study. Am Heart J. 2005; 149:464-73.

[44] Catapano AL, Davidson MH, Ballantyne CM, et al. Lipid-altering efficacy of the ezetimibe/simvastatin single tablet versus rosuvastatin in hypercholesterolemic patients. Curr Med Res Opin. 2006;22(10):2041-53.

[45] Serruys P, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. JAMA. 2002; 287:3215-3222.
[46] Saia F, de Feyter P, Serruys PW, et al. Effect of fluvastatin on long-term outcome after coronary revascularization with stent implantation. Am J Cardiol. 2004; 93(1):92-5.
[47] Holdaas H, Fellstrom B, Jardine AG, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. Lancet. 2003; 361(9374):2024-31.
[48] Holdaas H, Fellstrom B, Cole E, et al for the Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators. Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study. Am J Transplant. 2005; 5(12):2929-36.
[49] Bays HE, Dujovne CA, McGovern ME, et al. Comparison of Once-Daily, Niacin Extended-Release/lovastatin with standard doses of atorvastatin and simvastatin (the Advicor versus other Cholesterol-Modulating agents trial evaluation [ADVOCATE]). Am J Cardiol. 2003; 91; 667-72.
[50] ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs. usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 2002; 288:2998-3007.
[51] Olsson AG, Pears J, McKellar J, et al. Effect of rosuvastatin on low-density lipoprotein cholesterol in patients with hypercholesterolemia. Am J Cardiol. 2001; 88(5):504-8.
[52] Schneck DW, Knopp RH, Ballantyne CM, et al. Comparative effects of rosuvastatin and atorvastatin across their dose ranges in patients with hypercholesterolemia and without active arterial disease. Am J Cardiol. 2003; 91(1):33-41.
[53] Stein EA, Strutt K, Southworth H, et al. Comparison of rosuvastatin versus atorvastatin in patients with heterozygous familial hypercholesterolemia. Am J Cardiol. 2003; 92(11):1287-93.
[54] Paoletti R, Fahmy M, Mahla G, et al. Rosuvastatin demonstrates greater reduction of low-density lipoprotein cholesterol compared with pravastatin and simvastatin in hypercholesterolaemic patients: a randomized, double-blind study. J Cardiovasc Risk. 2001; 8(6):383-90.
[55] Blasetto JW, Stein EA, Brown WV, et al. Efficacy of rosuvastatin compared with other statins at selected starting doses in hypercholesterolemic patients and in special population groups. Am J Cardiol. 2003; 91(5A):3C-10C.
[56] Shepherd J, Hunninghake DB, Barter P, et al. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of rosuvastatin with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. Am J Cardiol. 2003; 91(5A):11C-17C.
[57] Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). Am J Cardiol. 2003; 92(2):152-60.
[58] Schwartz GG, Bolognese MA, Tremblay BP, et al. Efficacy and safety of rosuvastatin and atorvastatin in patients with hypercholesterolemia and a high risk of coronary heart disease: a randomized, controlled trial. Am Heart J. 2004; 148(1):e4.
[59] Strandberg TE, Feely J, Sigurdsson EL for the DISCOVERY study group. Twelve-week, multicenter, randomized, open-label comparison of the effects of rosuvastatin 10 mg/d and atorvastatin 10 mg/d in high-risk adults: a DISCOVERY study. Clin Ther. 2004; 26(11):1821-33.
[60] Schuster H, Barter PJ, Stender S, et al for the Effective Reductions in Cholesterol Using Rosuvastatin Therapy I study group. Effects of switching statins on achievement of lipid goals: Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY I) study. Am Heart J. 2004; 147(4):705-13.
[61] Stender S, Schuster H, Barter P, et al for the MERCURY I Study Group. Comparison of rosuvastatin with atorvastatin, simvastatin and pravastatin in achieving cholesterol goals and improving plasma lipids in hypercholesterolaemic patients with or without the metabolic syndrome in the MERCURY I trial. Diabetes Obes Metab. 2005; 7(4):430-8.
[62] Olsson AG, Istad H, Luurila O, et al for the Rosuvastatin Investigators Group. Effects of rosuvastatin and atorvastatin compared over 52 weeks of treatment in patients with hypercholesterolemia. Am Heart J. 2002; 144(6):1044-51.
[63] Ballantyne CM, Bertolami M, Hernandez Garcia HR, et al. Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapY (MERCURY) II. Am Heart J. 2006; 151(5):e1-9.

[64] Stalenhoef AF, Ballantyne CM, Sarti C, et al. A comparative study with rosuvastatin in subjects with metabolic syndrome: results of the COMETS study. Eur Heart J. 2005; 26(24):2664-72.
[65] Milionis HJ, Rizos E, Kostapanos M, et al. Treating to target patients with primary hyperlipidaemia: comparison of the effects of ATOrvastatin and ROSuvastatin (the ATOROS study). Curr Med Res Opin. 2006;22(6):1123-31.
[66] Nissen SE, Nicholls SJ, Sipahi I, et al for the ASTEROID Investigators. Effect of Very High-Intensity Statin Therapy on Regression of Coronary Atherosclerosis. The ASTEROID Trial. JAMA. 2006; 295: 1556 – 1565.
[67] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. Lancet. 2002; 360:7-22.
[68] Collins R, Armitage J, Parish S, et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial. Lancet. 2003; 361(9374):2005-16.
[69] Collins R, Armitage J, Parish S, et al. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet. 2004; 363(9411):757-67.
[70] de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs. a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004; 292(11):1307-16.
[71] Sever PS, Dahlö B, Poulte NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomized controlled trial. Lancet. 2003; 361:1149-58.
[72] Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004; 364(9435):685-96.
[73] Athyros VG, Papageorgiou AA, Mercouris BR, et al. Treatment with atorvastatin to the National Cholesterol Educational Program versus usual care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary heart-disease evaluation (GREACE) study. Current Medical Research and Opinion. 2002; 18:220-228.
[74] LaRosa JC, Grundy SM, Waters DD, et al for the Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005; 352(14):1425-35.
[75] Pedersen TR, Faergeman O, Kastelein JJP, et al for the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-Dose Atorvastatin vs. Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction. The IDEAL Study: A Randomized Controlled Trial. JAMA. 2005; 294:2437-2445.
[76] Serruys P, de Feyter P, Macay C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. JAMA. 2002; 287:3215-3222.
[77] Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998; 279:1615-1622.
[78] Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995; 333:1301-1307.
[79] ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs. usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 2002; 288:2998-3007.
[80] Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med. 1996; 335:1001-1009.
[81] The LIPID Study Group (Long-term Intervention with Pravastatin in Ischemic Disease). Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998; 339:1349-1357.
[82] Thompson PL, Meredith I, Amerena J, et al. Effect of pravastatin compared with placebo initiated within 24 hours of onset of acute myocardial infarction or unstable angina: the Pravastatin in Acute Coronary Treatment (PACT) trial. Am Heart J. 2004; 148(1):e2.
[83] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. Lancet. 2002; 360:7-22.
[84] Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). Lancet. 1994; 344:1383-1389.
[85] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. Lancet. 2002; 360:7-22.
[86] Pedersen TR, Faergeman O, Kastelein JJP, et al for the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-Dose Atorvastatin vs. Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction. The IDEAL Study: A Randomized Controlled Trial. JAMA. 2005; 294:2437-2445.

[87] Nakamura H, Arakawa K, Itakura H, et al for the MEGA Study Group. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet. 2006; 368(9542):1152-63.

[88] Lloret R, Ycas J, Stein M, et al for the STARSHIP Study Group. Comparison of rosuvastatin versus atorvastatin in Hispanic-Americans with hypercholesterolemia (from the STARSHIP trial). Am J Cardiol. 2006;98(6):768-73.

[89] Crestor [package insert]. Wilmington, DE; AstraZeneca; 2005.
[90] Lipitor [package insert]. New York, NY; Pfizer; June 2006.
[91] Lescol [package insert]. East Hanover, NJ; Novartis Pharmaceutical Corporation; January 2005.
[92] Lescol XL [package insert]. East Hanover, NJ; Novartis Pharmaceutical Corporation; January 2005.
[93] Mevacor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[94] Pravachol [package insert]. Princeton, NJ; Bristol-Myers Squibb; December 2004.
[95] Zocor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[96] Clauss SB, Holmes KW, Hopkins P, et al. Efficacy and safety of lovastatin therapy in adolescent girls with heterozygous familial hypercholesterolemia. Pediatrics. 2005; 116(3):682-8.
[97] Lipitor [package insert]. New York, NY; Pfizer; June 2006.
[98] Lescol [package insert]. East Hanover, NJ; Novartis Pharmaceutical Corporation; January 2005.
[99] Lescol XL [package insert]. East Hanover, NJ; Novartis Pharmaceutical Corporation; January 2005.
[100] Mevacor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[101] Pravachol [package insert]. Princeton, NJ; Bristol-Myers Squibb; December 2004.
[102] Zocor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[103] Altoprev [package insert]. Weston, FL; Andrx Laboratories; August 2004.
[104] Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes. The MIRACL Study: A Randomized Controlled Trial. JAMA. 2001; 285(13):1711-1718.
[105] McKenney JM. The lipid-lowering formulary. Am J Managed Care. 1996; 2(Suppl):S48-S58.
[106] Herd JA, Ballantyne CM, Farmer JA, et al. Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS]). Am J Cardiol. 1997; 80:278-286.
[107] Ballantyne CM, Pazzucconi F, Pinto X, et al. Efficacy and tolerability of fluvastatin extended-release delivery system: a pooled analysis. Clin Ther. 2001; 23(2):177-192.
[108] Blankenhorn DH, Azen SP, Kramsch DM, et al. Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS). The MARS Research Group. Ann Intern Med. 1993; 119:969-976.
[109] Crouse JR, Lukacsko P, Niecestro R, et al. Dose response, safety and efficacy of an extended-release formulation of Lovastatin in adults with hypercholesterolemia. Am J Cardiol. 2002; 89:226-228.
[110]Davidson MH, Lukacsko P, Sun JX, et al. A multiple-dose pharmacodynamic, safety, and pharmacokinetic comparison of extended- and immediate-release formulations of lovastatin. Clin Ther. 2002; 24:112-125.
[111] Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995; 333:1301-1307.
[112] Stein E, Plotkin D, Bays H, et al. Effects of simvastatin (40 and 80mg/day) in patients with mixed hyperlipidemia. Am J Cardiol. 2000; 86:406-411.
[113] MAAS Investigators. Effect of simvastatin on coronary atheroma: The Multicentre Anti-Atheroma Study (MAAS). Lancet. 1994; 344: 633-638.
[114] Bays HE, Dujovne CA, McGovern ME, et al. Comparison of Once-Daily, niacin Extended-Release/lovastatin with standard doses of atorvastatin and simvastatin (the Advicor versus other Cholesterol-Modulating agents trial evaluation [ADVOCATE]). Am J Cardiol. 2003; 91; 667.
[115] Crestor [package insert]. Wilmington, DE; AstraZeneca; 2005.
[116] Vytorin [package insert]. North Wales, PA; Merck/Schering-Plough Pharmaceuticals; 2006.
[117] Advicor [package insert]. Miami FL; Kos Pharmaceuticals; 2005.
[118] Jones PH, McKenney JM, Karalis DG, et al. Comparison of the efficacy and safety of atorvastatin initiated at different starting doses in patients with dyslipidemia. Am Heart J. 2005; 149(1):e1.
[119] Bays HE, Ose L, Fraser N, et al for the Ezetimibe Study Group. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clin Ther. 2004; 26(11):1758-73.
[120] Ballantyne CM, Blazing MA, King TR, et al. Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolemia. Am J Cardiol. 2004 Jun 15;93(12):1487-94.
[121] Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA. 2004; 291(9):1071-80.
[122] ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs. usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 2002; 288:2998-3007.
[123] Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol. 2002; 40(12):2125-34.
[124] Lipitor [package insert]. New York, NY; Pfizer; June 2006.
[125] Lescol [package insert]. East Hanover, NJ; Novartis Pharmaceutical Corporation; January 2005.
[126] Lescol XL [package insert]. East Hanover, NJ; Novartis Pharmaceutical Corporation; January 2005.
[127] Mevacor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[128] Pravachol [package insert]. Princeton, NJ; Bristol-Myers Squibb; December 2004.

[129] Zocor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[130] Altoprev [package insert]. Weston, FL; Andrx Laboratories; August 2004.
[131] Blankenhorn DH, Azen SP, Kramsch DM, et al. Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS). The MARS Research Group. Ann Intern Med. 1993; 119:969-976.
[132] Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998; 279:1615-1622.
[133] Downs JR, Beere PA, Whitney E, et al. Design & rationale of the Air Force/Texas coronary atherosclerosis prevention study (AFCAPS/TexCAPS). Am J Cardiol. 1997; 80:287-293.
[134] Stein E, Plotkin D, Bays H, et al. Effects of simvastatin (40 and 80mg/day) in patients with mixed hyperlipidemia. Am J Cardiol. 2000; 86:406-411.
[135] MAAS Investigators. Effect of simvastatin on coronary atheroma: The Multicentre Anti-Atheroma Study (MAAS). Lancet. 1994; 344: 633-638.
[136] Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). Lancet. 1994; 344:1383-1389.
[137] Crestor [package insert]. Wilmington, DE; AstraZeneca; 2005.
[138] Olsson AG, Eriksson M, Johnson O, et al. A 52-week, multicenter, randomized, parallel-group, double-blind, double-dummy study to assess the efficacy of atorvastatin and simvastatin in reaching low-density lipoprotein cholesterol and triglyceride targets: the treat-to-target (3T) study. Clin Ther. 2003; 25(1):119-38.
[139] Vytorin [package insert]. North Wales, PA; Merck/Schering-Plough Pharmaceuticals; 2006.
[140] Advicor [package insert]. Miami FL; Kos Pharmaceuticals; 2005.
[141] Bays HE, Ose L, Fraser N, et al for the Ezetimibe Study Group. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clin Ther. 2004; 26(11):1758-73.
[142] Ballantyne CM, Blazing MA, King TR, et al. Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolemia. Am J Cardiol. 2004 Jun 15;93(12):1487-94.
[143] Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA. 2004; 291(9):1071-80.
[144] ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs. usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 2002; 288:2998-3007.
[145] Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol. 2002; 40(12):2125-34.
[146] Lipitor [package insert]. New York, NY; Pfizer; June 2006.
[147] Lescol [package insert]. East Hanover, NJ; Novartis Pharmaceutical Corporation; January 2005.
[148] Lescol XL [package insert]. East Hanover, NJ; Novartis Pharmaceutical Corporation; January 2005.
[149] Mevacor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[150] Pravachol [package insert]. Princeton, NJ; Bristol-Myers Squibb; December 2004.
[151] Zocor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[152] Altoprev [package insert]. Weston, FL; Andrx Laboratories; August 2004.
[153] Pfeffer MA, Keech A, Sacks FM, et al. Safety and tolerability of pravastatin in long-term clinical trials. Prospective Pravastatin Pooling Project. Circulation. 2002; 105:r95-r100.
[154] Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes. The MIRACL Study: A Randomized Controlled Trial. JAMA. 2001; 285(13):1711-1718.
[155] Herd JA, Ballantyne CM, Farmer JA, et al. Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS]). Am J Cardiol. 1997; 80:278-286.
[156] Ballantyne CM, Pazzucconi F, Pinto X, et al. Efficacy and tolerability of fluvastatin extended-release delivery system: a pooled analysis. Clin Ther. 2001; 23(2):177-192.
[157] Blankenhorn DH, Azen SP, Kramsch DM, et al. Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS). The MARS Research Group. Ann Intern Med. 1993; 119:969-976.
[158] Crouse JR, Lukacsko P, Niecestro R, et al. Dose response, safety and efficacy of an extended-release formulation of Lovastatin in adults with hypercholesterolemia. Am J Cardiol. 2002; 89:226-228.
[159]Davidson MH, Lukacsko P, Sun JX, et al. A multiple-dose pharmacodynamic, safety, and pharmacokinetic comparison of extended- and immediate-release formulations of lovastatin. Clin Ther. 2002; 24:112-125.
[160] Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995; 333:1301-1307.
[161] Stein E, Plotkin D, Bays H, et al. Effects of simvastatin (40 and 80mg/day) in patients with mixed hyperlipidemia. Am J Cardiol. 2000; 86:406-411.
[162] MAAS Investigators. Effect of simvastatin on coronary atheroma: The Multicentre Anti-Atheroma Study (MAAS). Lancet. 1994; 344: 633-638.

[163] Crestor [package insert]. Wilmington, DE; AstraZeneca; 2005.
[164] Vytorin [package insert]. North Wales, PA; Merck/Schering-Plough Pharmaceuticals; 2006.
[165] Advicor [package insert]. Miami FL; Kos Pharmaceuticals; 2005.
[166] Caduet [package insert]. New York, NY; Pfizer; October 2005.
[167] Rubenfire M; Impact of Medical Subspecialty on Patient Compliance to Treatment Study Group. Safety and compliance with once-daily niacin extended-release/lovastatin as initial therapy in the Impact of Medical Subspecialty on Patient Compliance to Treatment (IMPACT) study. Am J Cardiol. 2004; 94(3):306-11.
[168] Advicor [package insert]. Miami FL; Kos Pharmaceuticals; 2005.
[169] FDA Docket No. 2004P-0113/CP1. Available at http://www.fda.gov/cder/drug/infopage/rosuvastatin/crestor_CP.pdf. Accessed December 18, 2006.
[170] FDA Docket No. 2004P-0113/CP1. Available at http://www.fda.gov/cder/drug/infopage/rosuvastatin/crestor_CP.pdf. Accessed December 18, 2006.
[171] Alsheikh-Ali AA, Ambrose MS, Kuvin JT, et al. The Safety of Rosuvastatin as used in common clinical practice. A Postmarketing Analysis. Circulation. 2005; 111: 3051 - 3057.
[172] Grundy SM. The Issue of Statin Safety. Circulation. 2005; 111: 3016 - 3019.
[173] Bays H. Statin Safety: Overview and Assessment of the data – 2005. Am J Cardiol. 2006; 97(suppl):6-26C.
[174] Crestor [package insert]. Wilmington, DE; AstraZeneca; 2005.
[175] Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA Reductase Inhibitors. Ann Pharmacother. 2001; 35: 1096-107.
[176] Thompson PD, Clarkson P, Karas RH, et al. Statin-associated myopathy. JAMA. 2003; 289:1681-90.
[177] Bays H. Statin Safety: Overview and Assessment of the data – 2005. Am J Cardiol. 2006; 97(suppl):6-26C.
[178] Pasternak RC, Smith SC, Bairey-Merz CN, et al. ACC/AHA/NHLBI Advisory on the Use and Safety of Statins. J Am Coll Cardiol. 2002; 40:568-73.
[179] Grundy SM. The Issue of Statin Safety. Circulation. 2005; 111:3016-3019.
[180] Lipitor [package insert]. New York, NY; Pfizer; June 2006.
[181] Lescol [package insert]. East Hanover, NJ; Novartis Pharmaceutical Corporation; January 2005.
[182] Mevacor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[183] Pravachol [package insert]. Princeton, NJ; Bristol-Myers Squibb; December 2004.
[184] Zocor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[185] Lescol XL [package insert]. East Hanover, NJ; Novartis Pharmaceutical Corporation; January 2005.
[186] Altoprev [package insert]. Weston, FL; Andrx Laboratories; August 2004.
[187] Crestor [package insert]. Wilmington, DE; AstraZeneca; 2005.
[188] Newman CB, Palmer G, Silbershatz H, et al. Safety of atorvastatin derived from analysis of 44 completed trials in 9,416 patients. Am J Cardiol. 2003; 92(6):670-6.
[189] Vytorin [package insert]. North Wales, PA; Merck/Schering-Plough Pharmaceuticals; 2006.
[190] Advicor [package insert]. Miami, FL; Kos Pharmaceuticals; 2005.
[191] de Denus S, Spinler SA, Miller K, et al. Statins and liver toxicity: a meta-analysis. Pharmacotherapy. 2004; 24(5):584-91.
[192] Advicor [package insert]. Miami FL; Kos Pharmaceuticals; 2005.
[193] Lipitor [package insert]. New York, NY; Pfizer; June 2006.
[194] Lescol [package insert]. East Hanover, NJ; Novartis Pharmaceutical Corporation; January 2005.
[195] Mevacor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[196] Pravachol [package insert]. Princeton, NJ; Bristol-Myers Squibb; December 2004.
[197] Zocor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[198] Lescol XL [package insert]. East Hanover, NJ; Novartis Pharmaceutical Corporation; January 2005.
[199] Altoprev [package insert]. Weston, FL; Andrx Laboratories; August 2004.
[200] Crestor [package insert]. Wilmington, DE; AstraZeneca; 2005.
[201] Vytorin [package insert]. North Wales, PA; Merck/Schering-Plough Pharmaceuticals; 2006.
[202] Advicor [package insert]. Miami, FL; Kos Pharmaceuticals; 2005.
[203] Caduet [package insert]. New York, NY; Pfizer; October 2005.
[204] Zocor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[205] Vytorin [package insert]. North Wales, PA; Merck/Schering-Plough Pharmaceuticals; 2006.
[206] Mevacor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[207] Lipitor [package insert]. New York, NY; Pfizer; June 2006.
[208] Caduet [package insert]. New York, NY; Pfizer; October 2005.
[209] Vytorin [package insert]. North Wales, PA; Merck/Schering-Plough Pharmaceuticals; 2006.
[210] Lescol [package insert]. East Hanover, NJ; Novartis Pharmaceutical Corporation; January 2005.
[211] Lescol XL [package insert]. East Hanover, NJ; Novartis Pharmaceutical Corporation; January 2005.
[212] Mevacor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[213] Altoprev [package insert]. Weston, FL; Andrx Laboratories; August 2004.
[214] Advicor [package insert]. Miami FL; Kos Pharmaceuticals; 2005.
[215] Pravachol [package insert]. Princeton, NJ; Bristol-Myers Squibb; December 2004.

[216] Crestor [package insert]. Wilmington, DE; AstraZeneca; 2005.
[217] Zocor [package insert]. Whitehouse Station, NJ; Merck; 2005.
[218] Caduet [package insert]. New York, NY; Pfizer; October 2005.
[219] Grundy SM, Cleeman JI, Bairy Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation. 2004; 110:227-239.
[220] Grundy SM, Cleeman JI, Bairy Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation. 2004; 110:227-239.
[221] Kent SM, Coyle LC, Flaherty PJ, et al. Marked low-density lipoprotein cholesterol reduction below current national cholesterol education program targets provides the greatest reduction in carotid atherosclerosis. Clin Cardiol. 2004; 27(1):17-21.
[222] O'Keefe JH, Cordain L, Harris WH. Optimal low density lipoprotein is 50 to 75 mg/dL. Lower is better and physiologically normal. J Am Coll Cardiol. 2004; 43:2142-6.
[223] Grundy SM, Cleeman JI, Bairy Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation. 2004; 110:227-239.
[224] Smith SC, Allen J, Blair SN, et al. AHA/ACC Guidelines for Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease: 2006 Update. Circulation. 2006; 113:2363-2372.
[225] Smith SC, Allen J, Blair SN, et al. AHA/ACC Guidelines for Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease: 2006 Update. Circulation. 2006; 113:2363-2372.
[226] Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic): A Collaborative Report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society for Vascular Medicine and Biology, and the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). American College of Cardiology Web Site. Available at: http://www.acc.org/clinical/guidelines/pad/index.pdf. Accessed August 22, 2006.
[227] Yan AT, Yan RT, Tan M, et al. Contemporary Management of Dyslipidemia in High-Risk Patients: Targets Still Not Met. Am J Med. 2006; 119, 676-683.
[228] Cannon CP, Steinberg BA, Murphy SA, et al. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol. 2006;48(3):438-45.
[229] Baigent C, Keech A, Kearney PM, et al for the Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005; 366(9493):1267-78.