



# Lipotropics, Statins

## Therapeutic Class Review (TCR)

### February 1, 2013

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## AGENTS

Drug	Manufacturer
amlodipine / atorvastatin (Caduet <sup>®</sup> )	Pfizer, generic
atorvastatin (Lipitor <sup>®</sup> )	Pfizer, generic
ezetimibe / simvastatin (Vytorin <sup>™</sup> )	Merck
fluvastatin (Lescol <sup>®</sup> )	Novartis
fluvastatin XL (Lescol XL <sup>®</sup> )	Novartis
lovastatin (Mevacor <sup>®</sup> )	generic
lovastatin ER (Altoprev <sup>®</sup> )	Shionogi
niacin ER / lovastatin (Advicor <sup>™</sup> )	Abbott
niacin ER / simvastatin (Simcor <sup>®</sup> )	Abbott
pitavastatin (Livalo <sup>®</sup> )	Eli Lilly
pravastatin (Pravachol <sup>®</sup> )	generic
rosuvastatin (Crestor <sup>®</sup> )	AstraZeneca
simvastatin (Zocor <sup>®</sup> )	generic

## FDA-APPROVED INDICATIONS

Indications	fluvastatin (Lescol) fluvastatin ER (Lescol XL) <sup>1,2</sup>	lovastatin <sup>3</sup>	lovastatin ER (Altprev) <sup>4</sup>	niacin ER/lovastatin (Advicor) <sup>5*</sup>	pravastatin (Pravachol) <sup>6</sup>
Primary hypercholesterolemia ▪ Heterozygous familial and nonfamilial Reduce: Total-C, LDL-C, TG and ApoB	X	X	X	X	X
Heterozygous familial hypercholesterolemia ▪ pediatric	X 10-16 years	X 10-17 years			X 8 years and older
Mixed dyslipidemia <i>Fredrickson Type</i> ▪ II <sub>a</sub> and II <sub>b</sub> Reduce: Total-C, LDL-C, TG and ApoB	X	X To reduce total-C, LDL-C	X	X	X
Increase HDL-C	X		X	X	X
Hypertriglyceridemia <i>Fredrickson Type IV</i>				X	X
Primary dysbetalipoproteinemia <i>Fredrickson Type III</i>					X
Homozygous familial hypercholesterolemia					
Atherosclerosis ▪ slow progression	X	X	X		X

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

**FDA-Approved Indications (continued)**

Indications	fluvastatin (Lescol) fluvastatin ER (Lescol XL)	lovastatin	lovastatin ER (Altoprev)	niacin ER/lovastatin (Advicor)*	pravastatin (Pravachol)
CVD ▪ primary prevention of coronary events		Reduces risk of MI, unstable angina, coronary revascularization	Reduces risk of MI, unstable angina, coronary revascularization		Reduces risk of MI, myocardial revascularization, CV mortality
CHD ▪ secondary prevention of coronary events	Reduces risk of coronary revascularization				Reduces risk of MI, myocardial revascularization, CV mortality, stroke/TIA

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

**FDA-Approved Indications (continued)**

Indications	atorvastatin (Lipitor), amlodipine/ atorvastatin (Caduet)** 7,8	pitavastatin (Livalo) <sup>9</sup>	rosuvastatin (Crestor) <sup>10</sup>	simvastatin <sup>11</sup>	ezetimibe/ simvastatin (Vytorin) <sup>12</sup>	niacin ER/ simvastatin (Simcor) <sup>13</sup>
Primary hypercholesterolemia ▪ Heterozygous familial and nonfamilial Reduce: Total-C, LDL-C, TG and ApoB	X	X	X	X	X	X
Heterozygous familial hypercholesterolemia ▪ pediatric	X 10-17 years; not Caduet		X 10-17 years	X 10-17 years		
Mixed dyslipidemia <i>Fredrickson Type</i> ▪ II <sub>a</sub> and II <sub>b</sub> Reduce: Total-C, LDL-C, TG and ApoB	X		X	X	X	X
Increase HDL-C	X	X	X	X	X	X
Hypertriglyceridemia <i>Fredrickson Type IV</i>	X		X	X		X
Primary dysbetalipoproteinemia <i>Fredrickson Type III</i>	X		X	X		
Homozygous familial hypercholesterolemia	X		X	X	X	
Atherosclerosis ▪ slow progression			X			

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

\*\*\*High risk=patients with increased risk of CV disease based on age 50 years (men) and 60 years (women), hsCRP 2 mg/dL, and presence of at least one additional CV risk factor e.g. HTN, low HDL-C, smoking, or a family history of CAD.

**FDA-Approved Indications (continued)**

Indications	atorvastatin (Lipitor), amlodipine/ atorvastatin (Caduet)**	pitavastatin (Livalo)	rosuvastatin (Crestor)	simvastatin	ezetimibe/ simvastatin (Vytorin)	niacin ER/ simvastatin (Simcor)
CVD <ul style="list-style-type: none"> <li>primary prevention of coronary events</li> </ul>	Reduces risk of MI, stroke, revascularization, angina		Reduces risk of MI, stroke, revascularization, in patients without clinically evident CHD, but with multiple risk factors	Reduces total mortality risk by reducing CHD death, MI, stroke, & revascularization in high risk patients		
CHD <ul style="list-style-type: none"> <li>secondary prevention of coronary events</li> </ul>	Reduces risk of MI, stroke in Type 2 Diabetics without CHD; Reduces risk of MI, stroke, CHF hospitalization, angina, and revascularization in CHD patients			Reduces total mortality risk by reducing CHD death, MI, stroke, & revascularization		

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

\*\*\*High risk=patients with increased risk of CV disease based on age 50 years (men) and 60 years (women), hsCRP 2 mg/dL, and presence of at least one additional CV risk factor e.g. HTN, low HDL-C, smoking, or a family history of CAD.

## OVERVIEW

The 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, have become standard treatment in lowering cholesterol levels. Several statin trials document reduced morbidity and mortality with use. All statins lower low-density lipoprotein cholesterol (LDL-C), although to differing degrees, in a dose-related manner.<sup>14</sup> Despite the well-documented benefits of statins in reducing the risk of cardiovascular events, many patients are not on lipid-lowering therapy or are not at LDL-C goals.<sup>15,16,17</sup>

The Adult Treatment Panel (ATP) III guidelines from the National Cholesterol Education Program (NCEP) recommend a goal LDL-C of <100 mg/dL for high risk patients; a goal LDL-C of <70 mg/dL is a therapeutic option in those at very high risk, especially those with established cardiovascular disease (CVD) and multiple major and/or uncontrolled risk factors for coronary heart disease (CHD) and/or metabolic syndrome is reasonable.<sup>18,19,20,21</sup> For moderately high-risk persons (2+ risk factors and 10-year risk 10 to 20 percent), the recommended LDL-C goal is <130 mg/dL, but an LDL-C goal <100 mg/dL is a therapeutic option particularly for those with a baseline LDL-C of 100 to 129 mg/dL. Finally, those with 0–1 risk factor have a goal LDL cholesterol of <160 mg/dL.

For patients with atherosclerotic ischemic stroke or TIA and without known CHD, a target LDL-C reduction of at least 50 percent or a target LDL-C level of less than 70 mg/dL is recommended.<sup>22</sup> Patients with ischemic stroke or TIA with elevated cholesterol or comorbid CAD should be otherwise managed according to NCEP III guidelines.

A 2011 scientific statement on hypertriglyceridemia from the AHA, recommends 100 mg/dL as the new optimal fasting triglyceride level to replace 150 mg/dL.<sup>23</sup> The statement focuses on intensive therapeutic lifestyle change (e.g. diet and exercise) and less emphasis on medications to reduce triglycerides and risk, for most patients. This scientific statement is not intended to serve as a guideline but to complement the future Adult Treatment Panel IV (ATP IV) of the National Cholesterol Education Program (NCEP) guidelines.

The American Heart Association/American College of Cardiology Foundation (AHA/ACCF) 2011 guidelines for the secondary prevention and risk reduction for patients with atherosclerotic vascular disease recommend an adequate dose of statin to reduce LDL-C to <100 mg/dL, to achieve at least a 30 percent reduction of LDL-C, and to lower non-HDL-C to <130 mg/dL in patients who have triglycerides (TG) ≥200 mg/dL.<sup>24</sup> Patients who have TG >500 mg/dL should be started on fibrate therapy in addition to statin therapy to prevent acute pancreatitis. If treatment with a statin (including trials of higher-dose statins and higher-potency statins) does not achieve goal levels, intensification of LDL-C-lowering drug therapy with a bile acid sequestrant or niacin is reasonable. The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants and/or niacin. For patients who continue to have an elevated non-HDL-C while on adequate statin therapy, the use of niacin, fibrate, or fish oil may be reasonable.

In 2012, the American Association of Clinical Endocrinologists (AACE) published guidelines for the management of dyslipidemia and prevention of atherosclerosis.<sup>25</sup> AACE recommends aggressive lipid-modifying therapy to lower LDL-C to <100 mg/dL in patients with average or elevated LDL-C and <70 mg/dL for all patients with established CAD. Statins are the drug of choice for LDL-C reduction. AACE supports the use of apolipoprotein B (apo B) in evaluating lipid status. They recommend an optimal apo B <90 mg/dL for patients at risk of CAD, while patients with established CAD or diabetes who have

one or more additional risk factors should have an apo B <80 mg/dL. The MERCURY II trial demonstrated that aggressive LDL-C reduction in CHD patients can also reach targets for recommended apolipoprotein B (apo B) levels.<sup>26</sup> Patients appropriate for aggressive therapy are those undergoing coronary artery bypass graft (CABG) or with acute coronary syndrome (ACS). These guidelines address the unique challenges associated with atherosclerosis and heart disease in women and recommend pharmacotherapy, preferably with a statin, for all women at high risk regardless of LDL-C level and for those at intermediate risk with LDL-C > 130 mg/dL. AACE also includes guidance for lipid screening in the pediatric populations and recommend that children older than two years and adolescents older than 16 years be evaluated every three to five years and every five years, respectively, if they have CAD risk factors or a family history of premature CAD or dyslipidemia.

The American Academy of Pediatrics (AAP) endorsed 2012 guidelines by the National Heart, Lung and Blood Institute (NHLBI) on cardiovascular health and risk reduction in children and adolescents which outlines age appropriate lipid screening in the pediatric population.<sup>27</sup> NHLBI recommends a fasting lipid profile in children age one to four years, only if the child is familial hypercholesterolemia (FH) positive, the child has a parent with dyslipidemia, or if the child has any other risk factors or high-risk condition. All children should be screened for high cholesterol at least once between the ages of nine and 11 years, and again between ages 17 and 21 years. It is anticipated that a universal screening will more accurately identify children who are at high risk of cardiovascular disease. The guideline also identifies age-specific strategies to reduce risk factors and manage cardiovascular disease in children and adolescents. Most children with high cholesterol would be referred to lifestyle modifications including diet and physical activity. Less than one percent of children, primarily those with genetic dyslipidemias, would qualify for cholesterol-lowering medications. In addition to lifestyle interventions, the use of lipid-lowering medications is recommended in general in ages ten years and older if LDL-C is:  $\geq 190$  mg/dL,  $\geq 160$  mg/dL with family history of early heart disease or one high- or two moderate-level additional risk factors, or  $\geq 130$  mg/dL if diabetes mellitus is present. The initial LDL-C goal is less than 160 mg/dL, but LDL-C as low as 130 or even 110 mg/dL is warranted if strong CVD family history is present. Drug therapy may be considered for children ages eight and nine years with LDL-C persistently  $> 190$  mg/dL combined with a strong family history of early CVD or additional risk factors.

A 2011 familial hypercholesterolemia (FH) consensus statement from the National Lipid Association (NLA) calls for awareness and provides recommendations for screening, diagnosis, and treatment of FH in pediatrics and adults.<sup>28</sup> The clinical guidance recommends universal screening for all pediatric patients' ages nine to eleven years old. Screening is also recommended in patients beginning at age two years, in the presence of a family history of premature CVD or highly elevated cholesterol levels. In adults, universal screening is recommended by age 20 years. Drug therapy in both pediatrics and adults is recommended if LDL-C  $\geq 190$  mg/dL or non-HDL-C  $\geq 220$  mg/dL, after diet and lifestyle modification (maximum of three months). High-dose statin therapy is recommended as first-line for cardiovascular prevention in FH, with the goal of reducing LDL cholesterol by 50 percent. In adults, even more aggressive treatment goals (e.g. LDL-C goal  $< 100$  mg/dL), is an option for higher-risk patients e.g. clinically evident coronary disease, diabetes, family history of premature CV disease, or current smokers. Patients treated with a statin who achieved a 50 percent reduction in LDL-C but whose LDL-C levels remain above 160 mg/dL may need other agents, e.g., ezetimibe (Zetia®), niacin ER (Niaspan®), or bile-acid sequestrants. However, since cardiovascular-disease-prevention outcomes studies are lacking with these agents when used in combination with statins, high-dose statins are preferred to combination therapy. The potential risks of high-dose statin therapy should be weighed against their

potential benefit. The NLA FH consensus statement was supported by an unrestricted grant funding from manufacturers.

Many have questioned which patients with normal LDL-C levels would benefit most from statins' cardio-protective effects. The JUPITER trial reported that patients with a high C-Reactive Protein (CRP) level, a marker for circulating inflammatory cytokines, benefited from statin therapy.<sup>29</sup> The NHLBI sponsored Multi-Ethnic Study on Atherosclerosis (MESA) study is investigating buildup of measureable artery-hardening calcium and statin therapy outcomes, in patients who met the same criteria as the JUPITER study.<sup>30</sup> Coronary heart disease and cardiovascular disease event rates and multivariable-adjusted hazard ratios were compared in 950 participants from the MESA study that met all criteria for entry into the JUPITER trial.<sup>31</sup> Coronary artery calcium (CAC) scores were stratified by scores of zero, one to 100, and greater than 100. Median follow-up was 5.8 years. Of the patients (47 percent) in the MESA JUPITER population that had CAC scores of zero, rates of coronary heart disease events were 0.8 per 1000 person-years. Seventy-four percent of all coronary events were in the 239 (25%) of participants with CAC scores of more than 100 (20.2 per 1000 person-years). In the total study population, presence of CAC was associated with a hazard ratio of 4.29 (95% CI 1.99-9.25) for coronary heart disease, and of 2.57 (1.48-4.48) for cardiovascular disease. High-sensitivity C-reactive protein (hsCRP) was not associated with either disease after multivariable adjustment. The authors concluded that CAC seems to further stratify risk in patients eligible for JUPITER, and could be used to target subgroups of patients who are expected to derive the most, and the least, absolute benefit from statin treatment.

## PHARMACOLOGY

Statins competitively inhibit HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, which is an early rate-limiting step in cholesterol biosynthesis. The inhibition of cholesterol biosynthesis reduces cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and increases the uptake of circulating LDL particles. Additionally, the statins work to reduce LDL-C production by inhibiting the synthesis of very low density lipoprotein (VLDL-C), the LDL-C precursor. HMG-CoA reductase inhibitors decrease LDL-C, VLDL-C, triglycerides (TG), and increase high density lipoprotein cholesterol (HDL-C). Marked response usually occurs within two weeks with maximum response occurring within four to six weeks. In early studies with some agents, daily doses given in the evening were more effective than when given in the morning, perhaps because cholesterol is synthesized mainly at night.<sup>32,33</sup>

Other beneficial effects of the statins in reducing the risk of cardiovascular events may be through an independent anti-inflammatory effect unrelated to LDL-C reduction. Reduction in C-reactive protein (CRP) levels may lead to a decrease in cardiovascular event risk.<sup>34,35</sup> The REVERSAL trial investigators found that a reduction in LDL-C and CRP leads to a slowing in progression of atherosclerosis.<sup>36</sup> The PROVE IT-TIMI 22 investigators published findings indicating that lower CRP levels (< 2 mg/L) are associated with improvement in cardiovascular event-free survival.<sup>37</sup> The correlation among CRP levels, LDL-C reduction, and cardiovascular disease requires further investigation.

Several combination products have been marketed. Amlodipine/atorvastatin (Caduet) is designed to treat two indications - hypertension and hyperlipidemia - which are often seen in the coronary heart disease (CHD) patient. Ezetimibe/simvastatin (Vytorin) is the combination of two lipid-lowering therapies which work together to lower LDL-C. Niacin ER/lovastatin (Advicor) and niacin ER/simvastatin (Simcor) provide beneficial effects on HDL-C and lower TG and LDL-C.

Amlodipine (Norvasc<sup>®</sup>, Caduet) inhibits calcium ions from moving across the cell membrane. The limitation of calcium entering into the cells causes a decrease in mechanical contraction of myocardial and smooth muscle, thereby causing dilation of systemic arteries and a decrease in total peripheral resistance, systemic blood pressure, and the afterload of the heart. The reduction in afterload, which results in a decrease in myocardial oxygen consumption, is thought to attenuate the signs and symptoms of angina.<sup>38</sup> 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<sup>®</sup>, Vytorin) inhibits cholesterol absorption along the brush border of the small intestine. This leads to a decrease in the delivery of intestinal cholesterol to the liver, reduction of hepatic cholesterol stores, and an increase in cholesterol clearance from the blood. Ezetimibe inhibits absorption of both dietary cholesterol and cholesterol in bile. Ultimately, ezetimibe reduces total cholesterol (total-C), LDL-C, TG, apolipoprotein B, and increases HDL-C in patients with hypercholesterolemia. When ezetimibe is administered with a statin, further reductions in the lipid profile occur.

Niacin (nicotinic acid) inhibits lipolysis in adipocytes and possibly inhibits hepatic TG production resulting in a reduction in the synthesis of VLDL-C and clearance of LDL-C. It may involve several actions including partial inhibition of the release of free fatty acids from adipose tissue, and increased lipoprotein lipase activity. Niacin decreases the rate of hepatic synthesis of VLDL and LDL-C. The combination products, niacin ER/lovastatin (Advicor) or niacin ER/simvastatin (Simcor), combine the efficacy of a statin with the beneficial effects of extended-release niacin for those patients failing monotherapy.<sup>39</sup>

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) study randomized 3,414 patients with established CVD and atherogenic dyslipidemia to simvastatin (or simvastatin plus ezetimibe) at a dose sufficient to maintain LDL-C at 40-80 mg/dL and patients were randomized to receive extended-release niacin or matching placebo.<sup>40</sup> Although, niacin was effective at raising HDL-C and lowering triglycerides, the trial was halted early due to the lack of incremental benefit on CV risk reduction (including myocardial infarctions and stroke) in the extended-release niacin plus simvastatin arm versus simvastatin alone ( $p=0.80$ ).<sup>41,42</sup> In addition, a small, unexplained, increase in the rate of ischemic stroke was observed in the simvastatin plus extended-release niacin arm compared to simvastatin alone (29 patients versus 18 patients, respectively;  $p=0.11$ ). Eight of the ischemic strokes in the simvastatin plus extended-release niacin group occurred in participants who had stopped taking their niacin for at least two months and up to four years before their stroke. Therefore, it is unclear whether niacin contributed to this imbalance in ischemic stroke. The authors note study limitations such as: the findings may not be applicable to all patients with coronary disease or all patients with low HDL-C levels; it remains unclear whether other populations may benefit from such treatment; it is unclear if in the 94 percent of patients who were taking statins at study entry had more stable plaques, which are less likely to rupture, and therefore at lower risk of subsequent cardiovascular events; low percentage of women enrolled (15 percent); low rate of ethnic minorities (eight percent); and the 36 month follow-up period may not have been an adequate duration to show a clinical treatment effect of niacin. The AIM-HIGH trial was funded by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institute of Health (NIH) with additional support from Abbott Laboratories. The FDA plans to conduct a review of AIM-HIGH.<sup>43</sup>

## PHARMACOKINETICS

Drug	Bioavailability	Time to Peak Plasma Levels (hr)	t <sub>1/2</sub> (hr)	Excretion (%)	Circulating active metabolites
amlodipine and atorvastatin (Caduet) <sup>44</sup>	64-90%	6-12	30-50	Urine: 70	No
	~14%; first pass metabolism	1-2	14	Urine: <2	Yes
atorvastatin (Lipitor) <sup>45</sup>	~14%; first pass metabolism	1-2	14	Urine: <2	Yes
ezetimibe and simvastatin (Vytorin) <sup>46,47</sup>	--	4-12	22	Urine: 11 Feces: 78	Yes
	<5% of oral dose reaches general circulation; first pass metabolism	4	3	Urine: 13 Feces: 60	Yes
fluvastatin (Lescol) <sup>48</sup> (Lescol XL) <sup>49</sup>	24%; first pass metabolism	< 1	3	Urine: 5 Feces: 90	No
	29%; first pass metabolism	3	9		
lovastatin <sup>50</sup>	<5% of oral dose reaches general circulation; first pass metabolism	2-4	--	Urine: 10 Feces: 83	Yes
lovastatin ER (Altoprev) <sup>51</sup>	<5% of oral dose reaches general circulation; first pass metabolism	14.2	--	Urine: 10 Feces: 83	Yes
niacin ER and lovastatin (Advicor) <sup>52</sup>	72 %	5	<1	Urine: 60	Yes
	<5% of oral dose reaches general circulation; first pass metabolism	2	4.5	Urine: 10 Feces: 83	Yes
niacin ER and simvastatin (Simcor) <sup>53</sup>	dose dependent and variable; first pass metabolism	5	<1	Urine: 54	Yes
	<5% of oral dose reaches general circulation; first pass metabolism	4	4.2 to 4.9	Urine: 13 Feces: 60	Yes
pitavastatin (Livalo) <sup>54</sup>	51%	1	12	Urine: 15 Feces: 79	Yes
pravastatin <sup>55</sup>	17%; first pass metabolism	1-1.5	77	Urine: 20 Feces: 70	Yes
rosuvastatin (Crestor) <sup>56</sup>	20%	3-5	19	Feces: 90	Yes
simvastatin <sup>57</sup>	<5% of oral dose reaches general circulation; first pass metabolism	4	3	Urine: 13 Feces: 60	Yes

Atorvastatin and amlodipine (Caduet), ezetimibe and simvastatin (Vytorin), niacin ER and lovastatin (Advicor), and niacin ER and simvastatin (Simcor) pharmacokinetic profiles are not affected by concurrent administration of the individual components.<sup>58,59,60,61,62</sup>

## CONTRAINDICATIONS/WARNINGS<sup>63,64,65 66 67 68 69,70,71,72,73,74</sup>

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

Patients with active liver disease, with or without unexplained transaminase elevations are not appropriate candidates for statin therapy. **There have been rare postmarketing reports of fatal and**

non-fatal hepatic failure in patients taking statins. If serious symptomatic liver injury and/or hyperbilirubinemia occur statin therapy should be stopped immediately. Do not restart unless an alternate etiology is found.

Skeletal muscle abnormalities related to statin usage range from mild myalgia to myopathy. Myopathy is defined as muscle symptoms including muscle pain, tenderness, or weakness plus the elevation of creatine kinase above ten times the upper limit of normal (ULN). Rhabdomyolysis is the presence of myopathy and the elevation of creatinine and often myoglobinuria. While myalgias are common with statin use, myopathy and/or rhabdomyolysis are a rare, yet serious concern.<sup>75</sup> The mechanism by which the statins cause myopathy and rhabdomyolysis is unknown.<sup>76,77,78</sup>

All statins carry a potential risk of myopathy and/or rhabdomyolysis. On June 8, 2011 FDA notified healthcare professionals and patients of new safety recommendations for the highest approved dose (80 mg) of simvastatin based on review of data from a large clinical trial called Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) and other sources, that there is an increased risk of muscle injury compared to patients taking lower simvastatin doses or other statin drugs.<sup>79</sup> Due to this increased risk of myopathy, including rhabdomyolysis, the 80 mg dose of simvastatin must be reserved for patients who have been on this dose chronically (e.g.,  $\geq 12$  months) without evidence of muscle toxicity. If, however, a patient who is currently tolerating the 80 mg dose of simvastatin needs to be initiated on an interacting drug that is contraindicated or is associated with a maximum dose for simvastatin, that patient should be switched to an alternative statin with less potential for the drug-drug interaction. All statins have a warning in the prescribing information stating that myopathy and rhabdomyolysis have been reported with statin use. There is increased risk of myopathy and rhabdomyolysis associated with statin therapy in the following cases: advanced age (especially  $> 65$  years), perioperative periods, multiple medications, multiple chronic disease states including uncontrolled hypothyroidism and renal impairment, drug interactions, high statin dose, and concurrent therapy with fibrates and/or higher dose niacin.<sup>80,81,82</sup> Drug interactions with CYP3A4 inhibitors and concurrent therapy with fibrates may increase the risk of rhabdomyolysis. Consult the individual prescribing information for specific contraindications, drug interactions and dose reductions.

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

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

Niacin ER (Niaspan<sup>®</sup>) and niacin ER containing products (Advicor, Simcor) are contraindicated in patients with chronic liver disease, active peptic ulcer disease, or arterial bleeding. Niacin should be used with caution in patients predisposed to gout.<sup>83</sup> Niacin ER (Niaspan) can cause hyperglycemia, so serum glucose levels should be monitored in patients with diabetes particularly during the first few months of therapy.

The concomitant use of statins and cyclosporine may increase the risk of myopathy/rhabdomyolysis. Co-administration of pitavastatin (Livalo) or ezetimibe/simvastatin (Vytorin) with cyclosporine is contraindicated.<sup>84</sup> Dose reductions are recommended for the other statins when used concurrently with cyclosporine. Pitavastatin (Livalo) has not been studied with the protease inhibitor combination lopinavir/ritonavir so should not be used concurrently.

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

## DRUG INTERACTIONS<sup>85,86,87 88 89 90 91,92,93,94,95,96</sup>

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

### P450 Enzymes

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

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

Atorvastatin also interacts with CYP450 3A4 inhibitors but to a lesser degree, as it undergoes less first-pass metabolism.<sup>97</sup> Exposure to atorvastatin is significantly increased by the hepatitis C protease inhibitor, telaprevir as well as by various combinations of HIV protease inhibitors. Atorvastatin use should be avoided with telaprevir and with the HIV protease inhibitors tipranavir plus ritonavir. Atorvastatin should be used with caution with the HIV protease inhibitors lopinavir plus ritonavir and at the lowest dose necessary. Caution should also be used in patients taking clarithromycin, itraconazole, or HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir and the dose of atorvastatin should not exceed 20 mg. The dose of atorvastatin should not exceed 40 mg daily if coadministered with nelfinavir.

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

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

Fluvastatin is primarily metabolized by CYP450 2C9 so its levels may be increased by CYP450 2C9 inhibitors, but there appear to be less drug interactions. Pitavastatin, pravastatin, and rosuvastatin are not metabolized by the CYP450 enzymes to a clinically significant extent.

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

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

## Cardiovascular agents

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

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

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

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

## Colchicine

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

## Cyclosporine

Cyclosporine coadministration can increase statin exposure.

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

## Other lipid-lowering agents

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

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

## Miscellaneous

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

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

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

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

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

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

Drug	amiodarone	cyclosporine	diltiazem	Erythromycin	gemfibrozil (fabric acid derivatives)	HIV protease inhibitors	itraconazole (azole antifungals)	nefazodone	niacin	verapamil	warfarin
atorvastatin (Lipitor, Caduet) <sup>98,99</sup>	--	X	X	X	X	X	X	--	X	--	--
ezetimibe / simvastatin (Vytorin) <sup>100</sup>	X	X	X	X	X	X	X	X	X	X	X
fluvastatin (Lescol, Lescol XL) <sup>101,102</sup>	--	--	-	--	--	--	--	--	--	--	--
lovastatin <sup>103</sup> lovastatin ER (Altoprev) <sup>104</sup> niacin ER/ lovastatin (Advicor) <sup>105</sup>	X	X	-	X	X	X	X	X	--	X	--
pravastatin <sup>106</sup>	--	--	-	--	X	--	--	--	--	--	--
pitavastatin (Livalo) <sup>107</sup>	--	X	-	X	X	X	X	--	X	--	--
rosuvastatin (Crestor) <sup>108</sup>	--	X	-	--	X	X	--	--	X	--	X
simvastatin <sup>109</sup> niacin ER/ simvastatin (Simcor) <sup>110</sup>	X	X	X	X	X	X	X	X	X	X	X

X = drug-drug interaction has been reported

The combination of amlodipine and atorvastatin (Caduet) and niacin ER and simvastatin (Simcor) have not been studied for drug interactions, although studies have been conducted for the individual components.

## ADVERSE EFFECTS

Drug	Myalgia	Abd Pain	Diarrhea	Dyspepsia	Nausea	Rash	Headache	Fatigue or Malaise
atorvastatin (Lipitor) <sup>111</sup>	5.6 (1.1)	0-3.8 (0.7)	0-3.8 (1.5)	1.3-2.8 (4.1)	reported	1.1-3.9 (0.7)	2.5-16.7 (7)	reported
ezetimibe / simvastatin (Vytorin) <sup>112</sup>	3.6 (2.3)	reported	reported	reported	reported	reported	6.8 (6.4)	reported
fluvastatin (Lescol) <sup>113</sup>	5 (4.5)	4.9 (3.8)	4.9 (4.2)	7.9 (3.2)	3.2 (2)	reported	8.9 (7.8)	2.7 (2.3)
fluvastatin XL (Lescol XL) <sup>114</sup>	3.8 (4.5)	3.7 (3.8)	3.3 (4.2)	3.5 (3.2)	2.5 (2)	reported	4.7 (7.8)	1.6 (2.3)
lovastatin <sup>115</sup>	1.8-3 (1.7)	2-2.5 (1.6)	2.2-2.6 (2.3)	1-1.6 (1.9)	1.9-2.5 (2.5)	0.8-1.3 (0.7)	2.1-3.2 (2.7)	reported
lovastatin ER (Altoprev) <sup>116</sup>	3	reported	3	reported	reported	reported	7	reported
niacin ER / lovastatin (Advicor) <sup>117</sup>	3	4	6	3	7	5	9	reported
niacin ER / simvastatin (Simcor) <sup>118</sup>	reported	3.5	3 (2.9)	4	3.2 (4.2)	reported	4.5 (4.6)	reported
pitavastatin (Livalo) <sup>119</sup>	1.9-3.1 (1.4)	nr	1.5-2.6 (1.9)	nr	nr	reported	reported	nr
pravastatin <sup>120</sup>	0.6-2.7 (0-1)	2-5.4 (3.9-6.9)	2-6.2 (1.9-5.6)	2-2.9 (0.7-1.9)	2.9-7.3 (3.4-7.1)	1.3-3.4 (0.9-1.1)	1.7-6.2 (0.2-3.9)	1.9-3.8 (1-3.4)
rosuvastatin (Crestor) <sup>121</sup>	2.7-12.7 (2.6-12.1)	2.4 (1.8)	nr	nr	2.4 (2.3)	reported	3.1-8.5 (5-5.3)	nr
simvastatin <sup>122</sup>	3.7 (3.2)	3.2 (3.2)	1.9 (2.5)	1.1	1.3 (1.9)	0.6 (0.6)	0.7	reported

nr=not reported. Adverse effects are indicated as percentage occurrence. Adverse effects data are compiled from package inserts and cannot be considered comparative or all inclusive. Incidences for the placebo group are indicated in parentheses.

In clinical trials, atorvastatin (Lipitor), fluvastatin (Lescol/Lescol XL), pravastatin, and simvastatin were rarely (less than two percent) discontinued due to adverse effects. Rosuvastatin (Crestor) was discontinued in 1.4 percent of patients in clinical trials.<sup>123</sup> Pitavastatin (Livalo) was discontinued in 3.6 percent of patients in clinical trials.<sup>124</sup> Lovastatin was discontinued in 4.6 percent of patients in trials.

Adverse events data for atorvastatin/amlodipine (Caduet) have been evaluated in 1,092 patients with hypertension and hyperlipidemia. Adverse events were mostly mild or moderate in severity with no unusual adverse events reported.<sup>125</sup> Specific incidences have not been reported with atorvastatin/amlodipine. The combination tablet is not expected to have more adverse effects than single entity administration.

In clinical trials, six to eight percent of patients on niacin ER/lovastatin (Advicor) withdrew from therapy due to flushing.<sup>126</sup> Overall, 53 to 83 percent of patients will experience flushing associated with

the niacin component in niacin ER/lovastatin.<sup>127</sup> In a controlled study, flushing occurred in up to 59 percent of patients treated with niacin ER/simvastatin (Simcor) and resulted in study discontinuation for six percent of patients.<sup>128</sup> Aspirin or another NSAID may be taken with niacin ER/lovastatin or niacin ER/simvastatin therapy to reduce the incidence of flushing. The other most common adverse events, in addition to headache, nausea, and diarrhea, in a six-month study comparing niacin ER/simvastatin to simvastatin, were pruritus and back pain (3.2 percent incidence for each).

After completing a 12-week randomized, double-blind, placebo-controlled, factorial, 10-armed study comparing ezetimibe 10 mg/simvastatin 10, 20, 40, or 80 mg; simvastatin 10, 20, 40, or 80 mg; ezetimibe 10 mg; or placebo, 768 patients with primary hypercholesterolemia entered a 48-week extension, with randomized, blinded, reassignment of the simvastatin 10 mg, ezetimibe, and placebo groups to one of the ezetimibe/simvastatin groups.<sup>129</sup> Patients previously on ezetimibe/simvastatin combination therapy, or simvastatin 20, 40, and 80 mg monotherapy continued the same therapies in the 7-arm extension study. Adverse events were assessed during the extension phase. Ezetimibe/simvastatin and simvastatin monotherapy groups generally had a similar incidence of all clinical adverse events (73 versus 69 percent), treatment-related adverse events (14 versus 11 percent), clinical serious adverse events (5.2 versus 2.6 percent), treatment-related serious adverse events (0.2 versus zero percent), discontinuations due to all clinical adverse events (4.5 versus 2.6 percent), and discontinuations due to treatment-related adverse events (2.8 versus 2.2 percent), respectively.

An article cited an increased rate of serious adverse events based on the number of voluntarily reported adverse drug events for rosuvastatin (Crestor).<sup>130</sup> Use of voluntarily reported cases without assessment of causality is not a proper method to assess the rate of an adverse events associated with a drug. Due to the heightened awareness of serious adverse events following the removal of cerivastatin (Baycol®) from the US market in 2001, there is likely reporting bias with rosuvastatin as it entered the US market in 2003. In summary, the occurrence of serious adverse events such as myopathy and rhabdomyolysis are extremely rare with all statins including rosuvastatin.<sup>131,132,133,134,135</sup>

Several meta-analyses and systematic reviews have evaluated statin use and the overall risk of cancer.<sup>136,137,138,139,140</sup> There is no convincing evidence that statins increase or decrease the incidence of cancer.

The Simvastatin and Ezetimibe in Aortic Stenosis Study (SEAS) trial, a randomized, double-blind, placebo-controlled, multicenter, 52.2-month study of 1,873 patients with mild to moderate aortic stenosis, found no reduction in the primary endpoint of major cardiovascular events with simvastatin/ezetimibe (Vytorin) compared to placebo.<sup>141,142,143</sup> However, there was a decrease in a pre-specified secondary endpoint of atherosclerotic disease events. SEAS found an increase in various types of cancer and deaths in patients taking simvastatin/ezetimibe. An interim analysis of the ongoing CV trials with simvastatin/ezetimibe (Vytorin), SHARP and IMPROVE-IT, did not show a significant increase in cancer ( $p=0.61$ ).<sup>144</sup> Based on review of SEAS and interim data from IMPROVE-IT and SHARP, the FDA believes it is unlikely that simvastatin/ezetimibe (Vytorin) or ezetimibe (Zetia) increase the risk of cancer or cancer-related death.<sup>145,146,147</sup> Final analysis of SHARP was consistent with the interim results, reporting no increase in cancer risk.<sup>148</sup>

The seven-year SEARCH trial included the number of major CV events (MI, revascularization, and CV death) in patients with prior MIs.<sup>149</sup> There were 6,031 patients taking 80 mg of simvastatin compared to 6,033 patients taking 20 mg of simvastatin. FDA's report revealed that more patients in the high

dose simvastatin arm developed myopathy versus patients in the simvastatin 20 mg arm (52 [0.9 percent] cases compared to one case [0.02 percent]). Twenty-two patients (0.4 percent) in the 80 mg group versus zero patients in the 20 mg group developed rhabdomyolysis. There were no fatalities related to rhabdomyolysis. The risks for myopathy and rhabdomyolysis with simvastatin 80 mg were highest in the first 12 months of treatment, five per 1,000 person-years and two per 1,000 person-years, respectively, and decreased to one per 1,000 person-years and 0.4 per 1,000 person-years after that.

## **Increases in glycosylated hemoglobin (HbA1c,) fasting plasma glucose, and Diabetes Mellitus**

Hyperglycemia has been reported with statins.<sup>150</sup>

FDA's review of the results from the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) reported a 27 percent increase in investigator-reported diabetes mellitus in rosuvastatin-treated patients compared to placebo-treated patients.<sup>151</sup> In an analysis of JUPITER the risk of developing diabetes with statin therapy was limited to patients already at a high risk for developing diabetes (e.g. with impaired fasting glucose, metabolic syndrome, severe obesity, or elevated HbA1c).<sup>152</sup> However, in these high-risk patients as well as the entire study population, the CV benefits of rosuvastatin for primary prevention exceeded the risk of diabetes. High-dose atorvastatin had also been associated with worsening glycemic control in the Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis In Myocardial Infarction 22 (PROVE-IT TIMI 22) substudy.<sup>153</sup>

FDA also reviewed the published medical literature. A meta-analysis which included 13 statin trials (n=91,140), reported that statin therapy was associated with a nine percent increased risk for incident diabetes (odds ratio [OR] 1.09; 95% confidence interval [CI] 1.02-1.17), with little heterogeneity (I<sup>2</sup>=11 percent) between trials.<sup>154</sup> Another meta-analysis of six statin trials (n=57,593) reported a small increase in diabetes risk (relative risk [RR] 1.13; 95% CI 1.03-1.23), with no evidence of heterogeneity across trials.<sup>155</sup> A recent study using data from the Women's Health Initiative, reported that statin use conveys an increased risk of new-onset diabetes in postmenopausal women, and noted that the effect appears to be a medication class effect, unrelated to potency or to individual statin.<sup>156</sup>

## **Cognitive adverse events**

FDA reviewed the AERS database, the published medical literature (case reports and observational studies), and randomized clinical trials to evaluate the effect of statins on cognition.<sup>157</sup>

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

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

**Liver Function/Safety**<sup>158,159,160,161,162,163,164,165,166,167,168,169,170,171</sup>

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

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

Hepatic failure has been reported during post marketing experience of some statins and should be considered a class effect.<sup>172,173,174,175,176,177</sup>

In February 2012, the FDA removed recommendations for routine monitoring of liver enzymes from all statin drug labels.<sup>178</sup> Based on available data, FDA has determined that all currently marketed statins appear to be associated with a very low risk of serious liver injury and that routine periodic monitoring of serum alanine aminotransferase (ALT) does not appear to detect or prevent serious liver injury in association with statins. Healthcare professionals should perform liver enzyme tests before initiating statin therapy and as clinically indicated thereafter. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment, therapy should be interrupted. If an alternate etiology is not found, the statin should not be restarted.

**SPECIAL POPULATIONS**<sup>179,180,181 182 183 184 185,186,187,188,189,190</sup>**Pediatrics**

Several statins have been approved for use in adolescent boys and girls (at least one year post-menarche). Atorvastatin (Lipitor), fluvastatin (Lescol/Lescol XL), lovastatin, pravastatin, rosuvastatin (Crestor), and simvastatin have been approved for the adjunctive management of Heterozygous Familial Hypercholesterolemia (HeFH) in addition to diet.<sup>191,192,193,194,195,196,197,198</sup> Statin therapy for HeFH is generally initiated when the LDL-C levels are  $\geq 190$  mg/dL or when the LDL-C is  $\geq 160$  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.<sup>199</sup> The minimum goal of therapy is to achieve LDL-C  $< 130$  mg/dL. Very little data are known for children less than eight years old.

In 2011 the National Heart, Lung and Blood Institute (NHLBI) published guidelines on cardiovascular health and risk reduction in children and adolescents in which they outline age appropriate lipid screening in the pediatric population.<sup>200</sup> NHLBI recommends a fasting lipid profile in children age one to four years, only if the child is familial hypercholesterolemia positive, the child has a parent with

dyslipidemia, or if the child has any other risk factors or high-risk condition. All children should be screened for high cholesterol at least once between the ages of nine and 11 years, and again between ages 17 and 21 years. It is anticipated that a universal screening will more accurately identify children who are at high risk of cardiovascular disease. The guideline also identifies age-specific strategies to reduce risk factors and manage cardiovascular disease in children and adolescents. Most children with high cholesterol would be referred to lifestyle modifications including diet and physical activity. Less than one percent of children, primarily those with genetic dyslipidemias, would qualify for cholesterol-lowering medications.

A 2011 familial hypercholesterolemia (FH) consensus statement from the National Lipid Association (NLA) calls for awareness and provides recommendations for screening, diagnosis, and treatment of FH in pediatrics and adults.<sup>201</sup> The clinical guidance recommends universal screening for all pediatrics ages nine to 11 years old. Screening is also recommended in patients beginning at age two, in the presence of a family history of premature CVD or highly elevated cholesterol levels. Drug therapy in both pediatrics and adults is recommended if LDL-C  $\geq$ 190 mg/dL or non-HDL-C  $\geq$ 220 mg/dL, after diet and lifestyle modification (maximum of three months). High-dose statin therapy is recommended as first-line for cardiovascular prevention in FH, with the goal of reducing LDL cholesterol by 50 percent. The NLA FH consensus statement was supported by an unrestricted grant funding from manufacturers. The NHLBI is expected to release an updated Pediatrics Cardiovascular Risk Reduction Initiative in 2011.

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

## Pregnancy

All statin-containing products are Pregnancy Category X.

## Race

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

An open-label trial with 696 Hispanic patients at medium to high risk for CHD compared the mean LDL-C reductions with atorvastatin (Lipitor) and rosuvastatin (Crestor) over six weeks.<sup>203</sup> Patients were randomized to atorvastatin or rosuvastatin 10 or 20 mg daily. Both doses of rosuvastatin were associated with greater reductions in LDL-C compared to atorvastatin. Comparing the 10 mg doses of each, rosuvastatin produced significantly greater reductions in LDL-C (45 percent rosuvastatin, 36 percent atorvastatin,  $p<0.0001$ ). For the 20 mg doses, rosuvastatin (50 percent) reduced LDL-C to a greater degree than atorvastatin (42 percent,  $p<0.0001$ ). Achievement of the target levels of LDL-C of less than 100 mg/dL was reported for 74 and 91 percent for the rosuvastatin 10 and 20 mg doses and 52 and 62 percent for atorvastatin 10 and 20 mg doses, respectively. Adverse events were similar between the groups.

In an open-label randomized trial in the US and Canada, 740 patients of South-Asian origin with hypercholesterolemia received rosuvastatin (Crestor) 10 or 20 mg or atorvastatin (Lipitor) 10 or 20 mg daily.<sup>204</sup> A total of 66 percent of patients were considered as being high risk for CAD. LDL-C decreased by 45 percent with rosuvastatin 10 mg versus 40 percent with atorvastatin 10 mg ( $p=0.0023$ ) and by 50 percent with rosuvastatin 20 mg versus 47 percent with atorvastatin 20 mg ( $p=NS$ ). Most patients reached LDL-C goals, and both drugs were well tolerated. According to the prescribing information for rosuvastatin (Crestor), Asian patients should start on 5 mg daily.<sup>205</sup>

A 12-week randomized, open-label, parallel group study compared the efficacy and safety of rosuvastatin (Crestor) 10 mg once daily to atorvastatin (Lipitor) 10 mg once daily in 1,482 adults in China, Hong Kong, Korea, Malaysia, Taiwan, and Thailand, with primary hypercholesterolemia and elevated cardiovascular risk (greater than 20 percent/ten years, type 2 diabetes, or a history of CHD).<sup>206</sup> The percentage of patients achieving LDL-C goal, based on the 1998 European Joint Task Force, was significantly higher in the rosuvastatin group versus atorvastatin group, 79.5 percent versus 69.4 percent, respectively ( $p<0.0001$ ). Both agents were well-tolerated and had a similar adverse event profile.

A post-hoc analysis of the GREACE study investigated the extent in vascular event reduction by statin treatment according to gender.<sup>207</sup> From a total of 1,600 patients with stable CHD, 624/176 and 632/168 were men/women on atorvastatin (Lipitor) or on usual care, respectively. During the three year follow-up, comparison of atorvastatin treatment with usual care demonstrated a relative risk reduction (RRR) of the primary end point (all vascular events) of 54 percent in women (hazard ratio [HR] 0.46, 95% CI, 0.24-0.87,  $p=0.003$ ) and of 50 percent in men (HR 0.5, 95% CI, 0.32-0.7,  $p<0.001$ ). The fall in LDL-C levels played the key role in end point reduction in both genders. However, in men there was an additional benefit related to the atorvastatin-induced increase in HDL-C and estimated glomerular filtration rate (eGFR), while in women end points were related to a substantial TG reduction.

The ongoing Heart Protection Study 2 (HPS2) identified that the incidence of myopathy is higher in Chinese compared with non-Chinese patients taking simvastatin 40 mg co-administered with lipid-modifying doses of a niacin-containing product.<sup>208,209</sup> Because the risk for myopathy is dose-related, Chinese patients should not receive simvastatin 80 mg co-administered with lipid-modifying doses of niacin-containing products. It is unknown if this risk applies to other Asian patients.

Plasma concentrations of pitavastatin are lower (about 21 percent for C<sub>max</sub> and five percent for AUC) in healthy Black or African American subjects compared with healthy Caucasian patients.<sup>210</sup> In pharmacokinetic comparison between Caucasian volunteers and Japanese volunteers, there were no significant differences in C<sub>max</sub> and AUC.

The JUPITER trial evaluated rosuvastatin in the primary prevention of MI, stroke, arterial revascularization, hospitalization for unstable angina, and cardiovascular death.<sup>211</sup> It included 12,683 whites and 5,117 nonwhites with LDL levels  $<130$  mg/dL and high-sensitivity C-reactive protein (hsCRP) levels  $\geq 2.0$  mg/L. In patients randomized to rosuvastatin 20 mg, a 45 percent reduction in the primary end point among whites (HR 0.55, 95% CI 0.43-0.69) and a 37 percent reduction was seen among nonwhites (HR 0.63, 95% CI 0.41-0.99). Blacks (HR 0.65, 95% CI 0.35-1.22) and Hispanics (HR 0.58, 95% CI 0.25-1.39) had similar risk reductions. Among nonwhites in the placebo group, the stroke rate exceeded the MI rate (0.44 versus 0.20 per 100 person-years); however among whites the stroke rate was less than the MI rate (0.31 versus 0.42 per 100 person-years). Nonwhites had higher

death rates than whites (2.25 versus 0.93 per 100 person-years); however, all-cause mortality was similar with rosuvastatin treatment in both participant groups.

Disposition of statins including rosuvastatin, involves OATP1B1 and other transporter proteins.<sup>212</sup> Higher plasma concentrations of rosuvastatin have been reported in very small groups of patients (n=3 to 5) who have two reduced function alleles of the gene that encodes OATP1B1 (SLCO1B1 521T>C). The frequency of this genotype (e.g. SLCO1B1 521 C/C) is generally lower than five percent in most racial/ethnic groups. The impact of this polymorphism on efficacy and or safety of rosuvastatin has not been clearly established.

## Hepatic/Renal Impairment

Statins are contraindicated in patients with active liver disease.

SHARP, a double-blind study included 9,438 CKD patients, of which 3,056 were on dialysis, that were randomized to receive daily ezetimibe 10 mg plus simvastatin 20 mg, matching placebo, or simvastatin 20 mg (with the latter arm re-randomized at one year to ezetimibe 10 mg plus simvastatin 20 mg versus placebo).<sup>213,214,215</sup> After a median follow-up of 4.9 years, patients that received ezetimibe/simvastatin combination experienced a 17 percent reduction in major atherosclerotic events (defined as the combination of MI, coronary death, ischemic stroke, or any revascularization procedure) compared to placebo ( $p=0.0022$ ). Ezetimibe/simvastatin also resulted in average LDL-C differences of 43 mg/dL (1.1 mmol/L) at one year and 33 mg/dL (0.85 mmol/L) at 2.5 years, compared to placebo. Ezetimibe/simvastatin was not associated with any excess of myopathy, hepatic toxicity, or biliary complications compared to placebo, or compared to simvastatin alone (at one year).

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

**DOSAGES**<sup>216,217,218,219,220,221,222,223,224,225,226,227</sup>

Drug	Usual Starting Dose	Adult Dosing Range	Pediatric Dosing Range	Approximate Equivalent Dose (based on LDL-C lowering)	Availability
amlodipine / atorvastatin (Caduet)	5 mg/10 mg daily	2.5 mg/10 mg – 10 mg/80 mg daily	--	10 mg daily of atorvastatin	amlodipine / atorvastatin combination tablets: 2.5mg/10mg, 2.5mg/20mg, 2.5mg/40mg, 5mg/10mg, 5mg/20mg, 5mg/40mg, 5mg/80mg, 10mg/10mg, 10mg/20mg, 10mg/40mg, 10mg/80mg
atorvastatin (Lipitor)	10 – 40 mg daily	10 – 80 mg daily	ages 10-17: 10 – 20 mg daily	10 mg daily	10, 20, 40, 80 mg tablets
ezetimibe / simvastatin (Vytorin)	10 mg/10 mg – 10 mg 20 mg daily	10 mg/10 mg – 10 mg/40 mg daily	--	10 mg/10 mg daily	ezetimibe / simvastatin combination tablets: 10mg/10mg, 10mg/20mg, 10mg/40mg, 10mg/80mg
fluvastatin (Lescol)	20 – 40 mg daily	20 – 80 mg daily	ages 10-16: 20 mg daily to 40 mg twice daily	40 mg twice daily	20, 40 mg capsules
fluvastatin XL (Lescol XL)	80 mg daily	80 mg daily	ages 10-16: 80 mg daily	80 mg daily	80 mg tablet
lovastatin	20 mg daily with evening meal	10 – 80 mg daily	ages 10-17: 10 – 40 mg daily	40 mg daily	10, 20, 40 mg tablets
lovastatin ER (Altoprev)	20 – 60 mg daily	10 – 60 mg daily	--	40 mg daily	20, 40, 60 mg tablets
niacin ER / lovastatin (Advicor)	500 mg/20 mg at bedtime	500 mg/20 mg – 2,000 mg/40 mg at bedtime	--	1,000 mg/40 mg daily	niacin ER / lovastatin combination tablets: 500mg/20mg, 750mg/20mg, 1,000mg/20 mg, 1,000/40mg
niacin ER / simvastatin (Simcor)	500 mg/20 mg at bedtime	500 mg/20 mg – 2,000 mg/40 mg at bedtime	--	1,000 mg/20 mg daily	niacin ER/simvastatin combination tablets: 500mg/20mg, 750mg/20mg, 1,000mg/20mg, 500mg/40mg, 1,000mg/40mg
pitavastatin (Livalo)	2 mg daily	1 – 4 mg daily	--	2 mg daily	1, 2, 4 mg tablets

**Dosages (continued)**

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

## DOSING CONSIDERATIONS<sup>228,229,230,231,232,233,234,235,236,237,238,239,240</sup>

### amlodipine/atorvastatin (Caduet)

- Caduet may be substituted for the individual agents after titration.
- Dosage should be individualized for tolerance of both amlodipine and atorvastatin.
- No dosage adjustment is needed with renal impairment.

### atorvastatin (Lipitor)

- Use caution when administering with fibrates.
- No dosage adjustment is recommended in renal insufficiency.
- Severe hepatic disease: adjust dosage.
- Avoid use with cyclosporine and gemfibrozil.
- Clarithromycin, itraconazole, or in combination with fosamprenavir, or ritonavir plus darunavir or fosamprenavir or saquinavir: do not exceed atorvastatin 20 mg daily. The lowest dose necessary should be used.
- Avoid in taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir.
- Do not exceed atorvastatin 40 mg in patients taking nelfinavir.
- Reduce dose when used with niacin.
- Avoid large quantities of grapefruit juice (>1 quart daily).

### ezetimibe / simvastatin (Vytorin)

- Homozygous Familial Hypercholesterolemia (HoFH): 10mg/40 mg in the evening.
- In patients with chronic kidney disease and estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup>, the dose of ezetimibe/simvastatin is 10/20 mg/day in the evening.
- Bile Acid Sequestrants: administer Vytorin either two hours before or four hours after administration of a bile acid sequestrant.
- Fibrates - should be avoided.
- Gemfibrozil: concomitant administration is contraindicated.
- Niacin >1 gm daily - Caution should be used.
- Cyclosporine or danazol: concomitant administration is contraindicated.
- Strong CYP3A4 inhibitors: concomitant administration is contraindicated.
- Diltiazem or verapamil: do not exceed 10/10 mg daily.
- Amiodarone, amlodipine, or ranolazine: do not exceed 10 mg/20 mg daily.
- Due to increased risk for myopathy, Chinese patients should not receive Vytorin 10 mg/80 mg co-administered with lipid-modifying doses of niacin-containing products (≥1 g/day niacin). It is not known if this risk of myopathy observed in Chinese patients applies to other Asian patients.
- High dose simvastatin: potential increased risk of myopathy with the 80 mg dose of simvastatin compared to lower doses of simvastatin and possibly other statin drugs.

- Due to the increased risk of myopathy, including rhabdomyolysis, use of the 80 mg dose of simvastatin should be restricted to patients who have been taking ezetimibe/simvastatin 10/80 mg chronically (e.g., for  $\geq 12$  months) without evidence of muscle toxicity.
- New patients should not be started on ezetimibe/simvastatin 10/80 mg.
- Place patients who do not meet their LDL-C goal on ezetimibe/simvastatin 10/40 mg on alternative LDL-C lowering treatment(s) that provides greater LDL-C lowering.
- Follow the recommendations in the simvastatin-containing products labels regarding drugs that may increase the risk for muscle injury when used with simvastatin.
- Switch patients who need to be initiated on a drug that interacts with simvastatin to an alternative statin with less potential for the drug-drug interaction.
- Contraindicated with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone). Contraindicated with gemfibrozil, cyclosporine, or danazol.

### fluvastatin (Lescol, Lescol XL)

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

### lovastatin (Mevacor), lovastatin ER (Altoprev)

- Contraindicated with azole antifungals: itraconazole, ketoconazole, and posaconazole.
- Contraindicated with macrolide antibiotics: erythromycin, clarithromycin, and telithromycin.
- Contraindicated with HIV protease inhibitors; the hepatitis C protease inhibitors: boceprevir and telaprevir; and nefazodone.
- Avoid with cyclosporine and gemfibrozil.
- Danazol, diltiazem, or verapamil: do not exceed 20 mg daily.
- Amiodarone: do not exceed 40 mg daily.
- Avoid large quantities of grapefruit juice ( $>1$  quart daily).
- Colchicine, fibrates, or niacin  $>1$  gm daily: use caution with concurrent administration.
- Reduce lovastatin dose with concomitant ranolazine.
- Renal insufficiency (CrCL  $< 30$  mL/min): use caution with doses above 20 mg daily.
- *lovastatin ER only* - Elderly and complicated medical conditions including diabetes: use 20 mg at bedtime.

### niacin ER / lovastatin (Advicor)

- For niacin ER/lovastatin, two tablets of 500mg/20mg are not interchangeable with 1,000mg/40mg.<sup>241</sup> When converting patients on Niaspan to niacin ER/lovastatin, an equivalent niacin dosage can be started (mg per mg). If the patient has been on any other niacin product,

therapy with niacin ER/lovastatin should be initiated at the lowest dose and titrated upward every four weeks as needed to achieve treatment goals. If niacin ER/lovastatin therapy is interrupted for more than seven days, initiate therapy at niacin ER/lovastatin 500 mg/20 mg to minimize adverse effects.

- Avoid with cyclosporine and gemfibrozil.
- Colchicine, fibrates, or niacin >1 gm daily: use caution with concurrent administration.
- Danazol, diltiazem, or verapamil: do not exceed lovastatin 20 mg daily.
- Amiodarone: do not exceed lovastatin 40 mg daily.
- Reduce lovastatin dose with concomitant ranolazine.
- Avoid large quantities of grapefruit juice (>1 quart daily).
- Renal insufficiency: use caution.

### niacin ER / simvastatin (Simcor)

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

### pitavastatin (Livalo)

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

## pravastatin (Pravachol)

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

## rosuvastatin (Crestor)

- Asian patients: consider starting dose of 5 mg daily.
- Homozygous Familial Hypercholesterolemia (HoFH): Starting dose is 20 mg daily.
- Heterozygous Familial Hypercholesterolemia: Maximum dose is 20 mg daily.
- Cyclosporine: use 5 mg only.
- Gemfibrozil: combination should be avoided; if used, do not exceed rosuvastatin 10 mg daily.
- Severe renal impairment (CrCL < 30mL/min/1.73m<sup>2</sup>) not on hemodialysis: initiate therapy at 5 mg daily; do not exceed 10 mg daily.
- Rosuvastatin 40 mg should be limited only to patients who fail to achieve LDL-C goals with rosuvastatin 20 mg daily.
- Lopinavir / ritonavir (Kaletra<sup>®</sup>) or atazanavir/ritonavir: do not exceed 10 mg daily.
- Use caution when used in combination with niacin (> 1g/day) or fenofibrate.

## simvastatin (Zocor)

- HoFH: use 40 mg daily in evening.
- HeFH: maximum 40 mg/day.
- Recommended starting dose for patients at high risk of CHD is 40 mg/day.
- Fibrates: combination should be avoided.
- Diltiazem or verapamil: do not exceed 10 mg daily.
- Amiodarone, amlodipine, or ranolazine: do not exceed 20 mg daily.
- Severe renal impairment (CrCL < 10 mL/min): initiate therapy at 5 mg daily with close monitoring.
- Due to increased risk of myopathy, do not co-administer simvastatin 40 mg lipid-modifying doses of niacin-containing products ( $\geq 1$  g/day niacin) in Chinese patients, use caution in administering simvastatin > 20 mg per day in Chinese patients taking lipid-modifying doses of niacin-containing products.<sup>242</sup> It is not known if this risk of myopathy observed in Chinese patients applies to other Asian patients.
- High dose simvastatin: potential increased risk of myopathy with the 80 mg dose of simvastatin compared to lower doses of simvastatin and possibly other statin drugs.
- Due to the increased risk of myopathy, including rhabdomyolysis, use of the 80 mg dose of simvastatin should be restricted to patients who have been taking simvastatin 80 mg chronically (e.g., for  $\geq 12$  months) without evidence of muscle toxicity.
- New patients should not be started on simvastatin 80 mg.

- Place patients who do not meet their LDL-C goal on simvastatin 40 mg on alternative LDL-C lowering treatment(s) that provides greater LDL-C lowering.
- Follow the recommendations in the simvastatin-containing products labels regarding drugs that may increase the risk for muscle injury when used with simvastatin. Switch patients who need to be initiated on a drug that interacts with simvastatin to an alternative statin with less potential for the drug-drug interaction.
- Severe renal impairment: do not initiate therapy unless patient has already tolerated treatment with simvastatin at 10 mg daily or higher.
- Concomitant administration of gemfibrozil, cyclosporine, or danazol is contraindicated.
- Concomitant administration of strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone) is contraindicated.
- Avoid large quantities of grapefruit juice (>1 quart daily).

## CLINICAL TRIALS

### Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials for FDA-approved indications are considered the most relevant in this category. Clinical outcome trials rather than surrogate markers as trial primary outcome parameters are considered the most relevant in this class. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Numerous short-term trials comparing agents for the reduction in LDL-C, changes in the various lipid parameters, and other surrogate markers have been published. No cardiovascular outcomes studies have been published for pitavastatin (Livalo) or for the combinations of niacin ER/lovastatin (Advicor), niacin ER/simvastatin (Simcor), or atorvastatin/amlodipine (Caduet). Many of the large clinical trials evaluating cardiovascular events and the use of statins have used placebo as a comparison or different dose (high dose versus low dose) comparisons. Large cardiovascular outcomes trials for primary and secondary prevention are summarized at the end of this section.

### atorvastatin (Lipitor)

TNT study:<sup>243</sup> The Treating to New Targets study evaluated the efficacy and safety of lowering LDL-C to less than 100 mg/dL in patients with stable CHD. In the randomized, double-blind study, 10,001 patients with CHD were enrolled and followed for a mean of 4.9 years. Initially, all patients underwent eight weeks of open-label atorvastatin 10 mg daily. Those patients with LDL-C less than 130 mg/dL

were then randomized to atorvastatin 10 or 80 mg daily. Overall, atorvastatin reduced LDL-C by 35 percent with a mean LDL-C achieved in the atorvastatin 80 and 10 mg groups of 77 mg/dL and 101 mg/dL, respectively. The primary outcome measure was the occurrence of a first major cardiovascular event, defined as death from CHD, nonfatal nonprocedural-related myocardial infarction (MI), resuscitation after cardiac arrest, or fatal or nonfatal stroke. The event rate was 8.7 and 10.9 percent for the atorvastatin 80 and 10 mg groups, respectively ( $p < 0.001$ ). This study was not powered to detect a difference in overall mortality between the two doses of atorvastatin. There were more noncardiovascular deaths in the atorvastatin 80 mg group. In specifically evaluating cerebrovascular events, the atorvastatin 80 mg group had fewer cerebrovascular events (hazard ratio (HR)=0.77, 95% CI, 0.64 to 0.93;  $p = 0.007$ ) and stroke (HR=0.75, 95% CI, 0.59 to 0.96;  $p = 0.02$ ).<sup>244</sup> The incidence of hemorrhagic strokes was similar between the groups. Evaluating the diabetic population ( $n = 1,501$ ) enrolled in TNT, a primary outcome measure occurred in 13.8 and 17.9 percent of the atorvastatin 80 and 10 mg groups, respectively (HR=0.75; 95% CI, 0.58 to 0.97,  $p = 0.026$ ).<sup>245</sup> Beneficial effects were seen in diabetics in the high dose atorvastatin group for cerebrovascular events and any cardiovascular events. For patients with metabolic syndrome, high-dose atorvastatin significantly reduced the primary outcome measure compared to the low-dose atorvastatin group (9.5 versus 13 percent, respectively; HR=0.71; 95% CI, 0.61 to 0.84;  $p < 0.0001$ ).<sup>246</sup> Adverse events and discontinuation rates were significantly higher in the high-dose atorvastatin group (both  $p < 0.001$ ). Five cases of rhabdomyolysis were reported, with two patients in the high-dose atorvastatin group and three patients in the low-dose atorvastatin group. Liver enzyme elevation, defined as two measurements greater than three times the upper limit of normal for ALT, AST, or both within four to 10 days, occurred more frequently in the high-dose atorvastatin group (1.2 versus 0.2 percent,  $p < 0.001$ ). The manufacturer of atorvastatin funded the study.

A subgroup analysis of the TNT study evaluated the effect of high-dose atorvastatin for heart failure (HF).<sup>247</sup> A history of HF was present in 7.8 percent of patients. A known ejection fraction less than 30 percent and advanced HF were exclusion criteria for the study. A predefined secondary end point of the study was hospitalization for HF. The incidence of hospitalization for HF was 2.4 percent for atorvastatin 80 mg and 3.3 percent for atorvastatin 10 mg (HR=0.74, 95% CI, 0.59 to 0.94,  $p = 0.0116$ ). In the patients with a history of HF, the incidence of HF-related hospitalization was 10.6 percent in the atorvastatin 80 mg group and 17.3 percent in the atorvastatin 10 mg group (HR=0.59, 95% CI, 0.4 to 0.88;  $p = 0.008$ ). The rates of hospitalization for HF were much lower among patients without a history of HF [1.8 percent in the 80 mg group and 2 percent in the 10 mg group (HR=0.87, 95% CI, 0.64 to 1.16,  $p = 0.34$ )]. In a post-hoc analysis, this benefit of reduced hospitalizations for HF was only seen in patients with a history of HF.

A pre-specified secondary analysis of the TNT study assessed the effect of high-dose atorvastatin 80 mg daily or low-dose atorvastatin 10 mg daily in 3,809 patients aged 65 years or older with stable CHD.<sup>248</sup> The absolute risk was reduced by 2.3 percent and relative risk by 19 percent for major cardiovascular events in favor of the high-dose atorvastatin group (HR=0.81, 95% CI, 0.67 to 0.98,  $p = 0.032$ ). Among the components of the composite outcome, the mortality rates from CHD, nonfatal non-procedure-related MI, and fatal or nonfatal stroke (ischemic, embolic, hemorrhagic, or unknown origin) were all lower in older patients who received high-dose atorvastatin, although the difference was not statistically significant for each individual component. The improved clinical outcome was not associated with persistent elevations in creatine kinase (CK) levels.

Further analysis of the TNT data evaluated patients with CAD, type 2 diabetes, with or without chronic kidney disease (CKD).<sup>249</sup> Renal data was available for 1,431 patients of the 1,501 patients with diabetes. Of the 546 patients with diabetes and CKD, 17.4 percent experienced a major CV event compared to 13.4 percent of 885 patients with diabetes and normal estimated glomerular filtration rate (eGFRs) (HR 1.32; 95% CI, 1 to 1.72;  $p < 0.05$ ). Compared with 10 mg of atorvastatin, 80 mg of atorvastatin reduced the relative risk of major CV events by 35 percent in patients with diabetes and CKD (20.9 percent versus 13.9 percent, respectively, HR 0.65; 95% CI, 0.43 to 0.98;  $p = 0.04$ ) and by 10 percent in patients with diabetes and normal eGFR (14.1 percent versus 12.8 percent, respectively, HR 0.90; 95% CI, 0.63 to 1.29;  $p = 0.56$ ). Over 4.8 years, the number needed to treat was 14 to prevent one major CV event. Both treatments were well tolerated.

ASCOT-LLA study:<sup>250</sup> As part of a larger study with 19,342 hypertensive patients with multiple risk factors for CHD, patients ( $n = 10,305$ ) with total-C less than 235 mg/dL were enrolled in the lipid-lowering arm and were randomized to atorvastatin 10 mg daily or placebo in a double-blind manner. The primary endpoint of the lipid-lowering trial was non-fatal MI and fatal CHD. After a median follow-up of 3.3 years, the trial was stopped early due to significantly lower event rate in the atorvastatin group ( $p = 0.0005$ ). Atorvastatin reduced the relative risk of nonfatal MI and fatal CHD by 36 percent over the study period. Stroke, a secondary endpoint, was reduced by approximately 27 percent with atorvastatin ( $p = 0.024$ ).

CARDS:<sup>251</sup> The effectiveness of atorvastatin in the primary prevention of cardiovascular events was evaluated in 2,838 patients with type 2 diabetes. The trial was a multicenter, double-blind, randomized trial enrolling patients ages 40 to 75 years who did not have a history of cardiovascular disease, near normal values for LDL-C ( $< 160$  mg/dL, baseline mean 119 mg/dL) and TG ( $< 600$  mg/dL, baseline mean 172 mg/dL). Patients also had at least 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.<sup>252</sup> Patients were randomized to atorvastatin 10 mg daily or placebo. The trial was halted two years earlier than expected when atorvastatin was found to reduce the relative risk of the first occurrence of acute cardiac event, coronary revascularization or stroke compared to placebo (relative risk reduction 37 percent [95% CI, -52 to -17],  $p = 0.001$ ). Looking at the endpoints individually found that the event rate of acute coronary heart disease events was reduced by 36 percent, coronary revascularizations by 31 percent, and stroke by 48 percent by atorvastatin ( $p = 0.016$ ) compared to placebo. Atorvastatin was well tolerated in the trial over a median of 3.9 years.

A multicenter, double-blind, randomized trial enrolled 1,255 patients with type 2 diabetes on hemodialysis to assess the efficacy and safety of atorvastatin 20 mg daily versus placebo.<sup>253</sup> 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 1.1;  $p = 0.37$ ). Atorvastatin had no effect on death from cardiac causes, nonfatal MI, and nonfatal stroke. More patients died of stroke in the atorvastatin group ( $n = 27$ ) than in the placebo group ( $n = 13$ ; relative risk, 2.03; 95% CI, 1.05 to 3.93;  $p = 0.04$ ). Atorvastatin reduced the rate of all cardiac events combined (relative risk, 0.82; 95% CI, 0.68 to 0.99;  $p = 0.03$ ). Atorvastatin did not have a significant effect on combined cerebrovascular events or total mortality.

SPARCL:<sup>254</sup> In a multicenter, randomized, double-blind trial, atorvastatin 80 mg daily and placebo were compared for efficacy in reducing the risk of secondary stroke. Patients ( $n = 4,731$ ) had a history of

stroke or TIA within one to six months before study entry, and LDL-C levels were between 100 to 109 mg/dL. Contemporary management with antiplatelet and antihypertensive agents was permitted. The study population had no known CHD. After a median of 4.9 years of follow-up, the rates of fatal and nonfatal strokes were 11.2 and 13.1 percent for atorvastatin and placebo, respectively ( $p=0.03$ ). The five-year absolute risk reduction of major cardiovascular events associated with atorvastatin was 3.5 percent (HR=0.80; 95% CI, 0.69 to 0.92;  $p=0.002$ ). Hemorrhagic stroke was slightly higher in the atorvastatin group; however, the incidence of fatal hemorrhagic stroke was similar between the two groups. There was no significant difference in total mortality between the groups. Baseline LDL-C levels were similar between the groups (132.7 versus 133.7 mg/dL); however, the mean LDL-C during the trial was 73 mg/dL and 129 mg/dL for the atorvastatin and placebo groups, respectively ( $p<0.001$ ). Liver enzyme elevation was more common with atorvastatin. The discontinuation rate was higher in the atorvastatin group (17.5 versus 14.5 percent). Five cases of rhabdomyolysis were reported, with two patients in the atorvastatin group and three patients in the placebo group. After 4.9 years, at each level of LDL-C reduction, subjects with HDL-C value above the median or systolic blood pressure (BP) below the median had greater reductions in stroke and major CV events and those with a reduction in triglycerides above the median or diastolic BP below the median showed similar trends.<sup>255</sup>

A post-hoc analysis of the SPARCL trial suggested a higher incidence of hemorrhagic stroke (2.3 percent atorvastatin versus 1.4 percent placebo; HR: 1.68, 95% CI, 1.09 to 2.59;  $p=0.0168$ ) but reduced risk of ischemic stroke in the patients treated with atorvastatin 80 mg.<sup>256</sup> Hemorrhagic stroke was more frequent in subjects who had a hemorrhagic stroke on study entry, in men, and with advanced age.

ASPEN:<sup>257</sup> In a double-blind, placebo-controlled study, the effect of atorvastatin 10 mg on the incidence of cardiovascular events in type 2 diabetics with lower levels of LDL-C than the current guidelines was determined. Patients ( $n=2,410$ ) were randomized to atorvastatin 10 mg daily or placebo for four years. The primary composite endpoint consisted of cardiovascular death, nonfatal MI, nonfatal stroke, revascularization, CABG, resuscitated cardiac arrest, and worsening or unstable angina requiring hospitalization. The mean reduction of LDL-C was 29 percent over four years compared to placebo ( $p<0.0001$ ). The composite endpoint rates were 13.7 and 15 percent for atorvastatin and placebo groups, respectively (HR=0.90; 95% CI, 0.73 to 1.12); the difference did not achieve statistical significance. In the patient subgroup with prior MI or interventional procedure, the composite endpoint rates were 26.2 and 30.8 percent for atorvastatin and placebo, respectively (HR=0.82, 95% CI, 0.59 to 1.15). In patients without a history of MI or interventional procedure, there was no significant difference between the two groups (10.4 percent for atorvastatin; 10.8 percent for placebo; HR=0.97; 95% CI, 0.74 to 1.28). The relative risk reductions for fatal and nonfatal MI did not achieve statistical significance (27 percent overall;  $p=0.1$ ).

### **atorvastatin (Lipitor) versus pravastatin (Pravachol)**

REVERSAL study:<sup>258</sup> The 18-month randomized, double-blind, active-controlled, multicenter trial enrolled 654 patients to compare the effect of moderate lipid lowering therapy with pravastatin 40 mg daily to intensive lipid-lowering therapy with atorvastatin 80 mg daily on coronary artery atheroma burden and progression. Baseline mean LDL-C was 150.2 mg/dL in both treatment groups and was reduced to 110 mg/dL in the pravastatin group and to 79 mg/dL in the atorvastatin group ( $p<0.001$ ). Progression of coronary atherosclerosis occurred in the pravastatin group (2.7 percent;  $p=0.001$ ) compared with baseline. Progression did not occur in the atorvastatin group (-0.4 percent;  $p=0.98$ )

compared with baseline. For patients with CHD, intensive lipid-lowering treatment with atorvastatin reduced progression of coronary atherosclerosis compared with pravastatin.

PROVE IT-TIMI 22 study:<sup>259</sup> The authors enrolled 4,162 patients who had been hospitalized for acute coronary syndrome (ACS) within the preceding ten days and compared 40 mg of pravastatin daily (standard therapy) with 80 mg of atorvastatin daily (intensive therapy) in a double-blind, double-dummy fashion. The primary endpoint was a composite of death from any cause, MI, unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. Mean follow-up was 24 months. The median LDL-C level achieved during treatment was 95 mg/dL in the pravastatin group and 62 mg/dL in the atorvastatin group ( $p < 0.001$ ). After 30 days, the composite endpoint occurred in three and 4.2 percent of the atorvastatin and pravastatin patients, respectively (HR=0.72; 95% CI, 0.58 to 0.89;  $p = 0.003$ ).<sup>260</sup> Primary composite endpoint rates (death or major cardiovascular event) at two years were 26.3 percent in the pravastatin group and 22.4 percent in the atorvastatin group (95% CI, 5 to 26;  $p = 0.005$ ). Among ACS patients, an intensive lipid-lowering statin regimen provides greater protection against death or major cardiovascular events than does a standard regimen. These findings indicate that such patients benefit from early and continued lowering of LDL-C to levels substantially below current target levels.

The PROVE IT-TIMI 22 trial evaluated 4,162 patients hospitalized for ACS and randomized to atorvastatin 80 mg or pravastatin 40 mg daily.<sup>261</sup> The relationship between on-treatment levels of TG and LDL-C and the composite end point of death, MI, and recurrent ACS were assessed 30 days after initial presentation. Low on-treatment TG ( $< 150$  mg/dl) was associated with reduced CHD risk compared with higher TG in univariate analysis (hazard ratio [HR] 0.73, 95% CI, 0.62 to 0.87;  $p < 0.001$ ) and in adjusted analysis (HR 0.80, 95% CI 0.66 to 0.97;  $p = 0.025$ ). For each 10 mg/dL decrease in on-treatment TG, the incidence of death, MI, and recurrent ACS was lower by 1.6 percent or 1.4 percent after adjustment for LDL-C or non-high-density lipoprotein cholesterol and other covariates ( $p < 0.001$  and  $p = 0.01$ , respectively). Lower CHD risk was also observed with TG  $< 150$  mg/dl and LDL-C  $< 70$  mg/dl (HR 0.72, 95% CI, 0.54 to 0.94;  $p = 0.017$ ) or low on-treatment TG, LDL-C, and C-reactive protein ( $< 2$  mg/L) (HR 0.59, 95% CI, 0.41 to 0.83;  $p = 0.002$ ) compared with higher levels of each variable in adjusted analysis.

A double-blind, randomized trial of 893 ambulatory CAD patients (30 percent female) aged 65 to 80 years with one or more episode of myocardial ischemia that lasted three or more minutes during 48 hour ambulatory ECG at screening, compared atorvastatin 80 mg daily to pravastatin 40 mg daily with a 12 month follow-up.<sup>262</sup> The primary efficacy parameter (absolute change from baseline in total duration of ischemia at month 12) was significantly reduced in both groups at three and 12 months (both  $p < 0.001$  for each treatment group) with no significant difference between the treatment groups. Atorvastatin patients experienced greater LDL-C reductions than the pravastatin group, a trend toward fewer major acute cardiovascular events (HR=0.71, 95% CI, 0.46 to 1.09,  $p = 0.114$ ), and a significantly greater reduction in all-cause death (HR= 0.33, 95% CI, 0.13 to 0.83;  $p = 0.014$ ).

### **atorvastatin (Lipitor) versus rosuvastatin (Crestor)**

SATURN:<sup>263</sup> In an effort to compare the effect of maximum doses of atorvastatin and rosuvastatin on the progression of coronary atherosclerosis as measured by intravenous ultrasound (IVUS), this double-blind clinical trial randomized 1,039 patients with coronary disease to receive atorvastatin 80 mg or rosuvastatin 40 mg daily. After 104 weeks of therapy, the LDL-C was 62.6 mg/dL in the rosuvastatin group versus 70.2 mg/dL in the atorvastatin group ( $p = 0.01$ ) and the HDL-C was 50.4 versus

48.6 mg/dL, respectively ( $p=0.01$ ). There was no significant difference in the primary efficacy end point, percent atheroma volume (PAV), which decreased by 0.99 percent (95% [CI],  $-1.19$  to  $-0.63$ ) with atorvastatin and by 1.22 percent (95% CI,  $-1.52$  to  $-0.9$ ) with rosuvastatin ( $p=0.17$ ). Regression of PAV was reported in 63.2 percent of patients with atorvastatin and 68.5 percent with rosuvastatin ( $p=0.07$ ). The authors concluded that although no difference between the agents was found, the study does show that high-dose, intensive statin therapy can promote regression of atherosclerotic plaque.

### **atorvastatin (Lipitor) versus simvastatin (Zocor)**

IDEAL:<sup>264</sup> The study was a prospective, randomized, open-label, blinded endpoint trial evaluating atorvastatin 80 mg daily and simvastatin 20 mg daily for occurrence of coronary death, nonfatal MI, or cardiac resuscitation over a median of 4.8 years. A total of 8,888 North European patients with a history of MI were enrolled. A majority of patients were on statin therapy at baseline (simvastatin 50 percent, pravastatin 10 percent, and atorvastatin 11 percent). Baseline LDL-C levels were 121 mg/dL. Dose adjustments were permitted in the simvastatin group if total cholesterol was greater than 190 mg/dL after 24 weeks. For the atorvastatin group, if the LDL-C was less than 40 mg/dL, atorvastatin dose was reduced to 40 mg daily. After five years, the mean LDL-C levels were 80 and 100 mg/dL for atorvastatin and simvastatin, respectively. Major coronary event defined as CHD death, nonfatal MI, and cardiac resuscitation occurred in 9.3 percent of the atorvastatin patients and 10.4 percent of the simvastatin patients (HR=0.89; 95% CI, 0.78 to 1.01,  $p=0.07$ ). The rates of composite endpoint of CHD death, nonfatal MI, cardiac resuscitation, and stroke were lower with atorvastatin (HR=0.87; 95% CI, 0.78 to 0.98;  $p=0.02$ ). A significant reduction in nonfatal MI in favor of atorvastatin was observed (7.2 percent simvastatin; six percent atorvastatin; HR=0.83; 95% CI, 0.71 to 0.98;  $p=0.02$ ). All cause mortality and cardiovascular mortality were similar in both groups. Discontinuation rate due to adverse effects was higher in the atorvastatin group (9.6 versus 4.2 percent,  $p<0.001$ ). Liver enzyme elevation was reported more frequently with atorvastatin ( $p<0.001$ ). An analysis of heart failure (HF) in secondary prevention showed that atorvastatin 80 mg was associated with a 26 percent decrease in new HF events compared with simvastatin 20 to 40 mg (HR 0.74, 95% CI, 0.57 to 0.97,  $p=0.03$ ). Atorvastatin tended to be associated with fewer HF events in those with HF at baseline ( $n=537$ , HR 0.65, 95% CI, 0.38 to 1.11,  $p=0.11$ ) and those without HF at baseline ( $n=8,351$ , HR 0.8, 95% CI, 0.59 to 1.09,  $p=0.15$ ). Also, HF without preceding MI ( $n=187$ ) was decreased (HR 0.73, 95% CI, 0.54 to 0.97,  $p=0.03$ ).<sup>265</sup>

### **atorvastatin plus amlodipine (Caduet)**

No large clinical outcomes trials have been performed with the combination of atorvastatin and amlodipine. Short-term comparison trials with atorvastatin and amlodipine have been completed.<sup>266</sup>

### **ezetimibe plus simvastatin (Vytorin)**

Several studies with surrogate endpoints have compared the combination of ezetimibe and simvastatin to its individual components, atorvastatin, and rosuvastatin.<sup>267,268,269,270,271,272,273</sup>

ENHANCE: A two-year, randomized, double-blind, multicenter study of 720 patients with heterozygous familial hypercholesterolemia (HeFH) compared ezetimibe/simvastatin 10/80 mg versus simvastatin 80 mg.<sup>274,275</sup> The study showed no significant difference between ezetimibe/simvastatin versus simvastatin in the primary surrogate endpoint of carotid intima media thickness (IMT), measured at three sites in the carotid arteries, using ultrasound imaging. The change in mean carotid IMT after two

years was 0.0111+/-0.0038 mm versus 0.0058+/-0.0037 mm, for the combination product versus simvastatin alone (p=0.29). Ezetimibe/simvastatin reduced LDL-C to a greater degree, 58 percent compared to simvastatin 41 percent, (p<0.01), after two years of treatment. There was a between group difference of 16.5 percent (p<0.01) for LDL-C lowering when comparing the simvastatin group to the ezetimibe/simvastatin group. This was not a clinical outcomes study, yet it generated attention since carotid ultrasound imaging can be a predictor of cardiac events, and the study results were delayed in being released. The American College of Cardiology (ACC) and American Heart Association (AHA) have released recommendations regarding the use of products containing ezetimibe and consider it a reasonable option for patients who are currently on a high-dose statin but are not at LDL-C goal, cannot tolerate statins, or can only tolerate a low-dose statin.<sup>276</sup> The National Institute for Health and Clinical Excellence (NICE) guidelines echo these recommendations.<sup>277</sup>

SEAS: A double-blind trial involving 1,873 patients with mild to moderate, asymptomatic aortic stenosis randomized patients to 40 mg of simvastatin plus 10 mg of ezetimibe or placebo daily.<sup>278</sup> The primary outcome was a composite of major CV events, including death from CV causes, aortic-valve replacement, nonfatal MI, hospitalization for unstable angina pectoris, heart failure, coronary-artery bypass grafting, percutaneous coronary intervention, and nonhemorrhagic stroke. Secondary outcomes were events related to aortic-valve stenosis and ischemic CV events. During a median follow-up of 52.2 months, the primary outcome occurred in 35.3 percent in the ezetimibe/simvastatin group and in 38.2 percent in the placebo group (HR in the ezetimibe/simvastatin group, 0.96; 95% CI, 0.83 to 1.12; p=0.59). There was no significant difference between the two groups in the secondary outcome of aortic-valve-related events, including aortic-valve replacement, death from CV causes, and hospitalization for HF as a consequence of progression of aortic stenosis [HR, 0.97; 95% CI, 0.83 to 1.14 (p=0.73)]. However, aortic-valve replacement, the principal component of the secondary composite outcome, was performed in 28.3 percent in the ezetimibe/simvastatin group and in 29.9 percent in the placebo group (HR 1; 95% CI, 0.84 to 1.18; p=0.97). The primary endpoint of major CV events was not significantly reduced in ezetimibe/simvastatin compared to placebo. Fewer patients had ischemic CV events in the ezetimibe/simvastatin group compared to the placebo group (HR 0.78; 95% CI, 0.63 to 0.97; p=0.02), mainly due to the smaller number of patients who underwent CABG. Cancer occurred more frequently in the ezetimibe/simvastatin group (p=0.01). An interim analysis of the ongoing CV trials with simvastatin/ezetimibe (Vytorin), SHARP and IMPROVE-IT, did not show a significant increase in cancer (p=0.61).<sup>279</sup> Based on review of SEAS and interim data from IMPROVE-IT and SHARPS, the FDA believes it is unlikely that simvastatin/ezetimibe (Vytorin) or ezetimibe (Zetia) increase the risk of cancer or cancer-related death.<sup>280</sup> Final analysis of SHARP was consistent with the interim results, reporting no increase in cancer risk.<sup>281</sup>

SHARP: In a double-dummy study, patients (n=9,438) with advanced CKD with no known history of MI or coronary revascularization were randomized in a ratio of 4:4:1 to daily ezetimibe 10 mg plus simvastatin 20 mg, matching placebo, or simvastatin 20 mg (with the latter arm re-randomized at one year to ezetimibe 10 mg plus simvastatin 20 mg versus placebo).<sup>282,283</sup> A total of 3,056 patients in the study were on dialysis. After a median follow-up of 4.9 years, patients that received ezetimibe/simvastatin combination experienced a 17 percent reduction in major atherosclerotic events (defined as the combination of MI, coronary death, ischemic stroke, or any revascularization procedure) compared to placebo (p=0.0022). Compared with placebo, ezetimibe/simvastatin resulted in average LDL-C differences of 43 mg/dL at one year and 33 mg/dL at 2.5 years. Ezetimibe/simvastatin was not associated with any excess of myopathy, hepatic toxicity, or biliary complications compared to

placebo, or compared to simvastatin alone (at one year). There was no difference in incidence of cancer between groups (9.5 percent for each).

### **ezetimibe/simvastatin (Vytorin) versus atorvastatin (Lipitor)**

Adults at high cardiovascular risk with hypercholesterolemia and LDL-C  $\geq 100$  and  $\leq 160$  mg/dL (n=250), pretreated with atorvastatin 20 mg were randomized to ezetimibe/simvastatin 10/40 mg or atorvastatin 40 mg for six weeks.<sup>284</sup> Switching to ezetimibe/simvastatin resulted in significantly greater changes in LDL-C (-26.81 versus -11.81 percent), total cholesterol (-15.97 versus -7.73 percent), non-HDL-C (-22.5 versus -10.88 percent), Apo B (-17.23 versus -9.53 percent), and Apo A-I (2.56 versus -2.69 percent) compared to doubling the atorvastatin dose (all  $p \leq 0.002$ ), but not HDL-C, triglycerides, or hs-CRP. Significantly more subjects achieved LDL-C  $< 70$  mg/dL (29 versus 5 percent) or  $< 100$  mg/dL (69 versus 41 percent) after switching to ezetimibe/simvastatin compared to doubling the atorvastatin dose (all  $p < 0.001$ ). The overall safety profile appeared generally comparable between treatment groups.

### **fluvastatin (Lescol)**

LIPS study:<sup>285</sup> Fluvastatin 40 mg twice daily was compared to placebo in a randomized, double-blind trial in 1,677 patients with stable or unstable angina or ischemia following a successful percutaneous coronary intervention (PCI). Primary efficacy was determined by survival time free from cardiac death, nonfatal MI, or repeat procedure. Both groups were similarly matched at baseline including a mean LDL-C of 131 mg/dL with the exception that the fluvastatin group had significantly more diabetic patients than the placebo group (14.2 versus 9.8 percent, respectively). After nearly four years, fluvastatin was found to have a significantly longer event-free time compared to placebo ( $p=0.01$ ). The fluvastatin group had a 21.4 percent incidence of events over four years compared to the placebo group with 26.7 percent (5.3 percent absolute risk reduction). Therapy was well tolerated. At the end of follow-up, 10.7 percent of fluvastatin patients and 24 percent of placebo patients were taking other lipid lowering therapies.

As part of the LIPS study, the impact of long-term fluvastatin treatment on cardiac events was evaluated in 847 stent-treated patients with average cholesterol levels.<sup>286</sup> During the four-year follow-up period, fluvastatin significantly decreased total-C, LDL-C, and decreased the relative risk of first adverse atherosclerotic cardiac events by 30 percent.

ALERT study:<sup>287</sup> 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 a mean follow-up of 5.1 years, fluvastatin reduced LDL-C by 32 percent. The risk reduction of the composite outcome was not significant. Fluvastatin reduced the number of cardiac deaths and non-fatal MIs compared to the placebo group ( $p=0.005$ ). In a two-year, open-label extension of the ALERT trial, 1,652 patients who completed the first part of the ALERT trial continued fluvastatin XL 80 mg daily.<sup>288</sup> The mean LDL-C at the end of the trial was 98 mg/dL. After a mean follow-up period of 6.7 years, patients had a reduced risk of the first major cardiac event (HR=0.79; 95% CI, 0.63 to 0.99;  $p=0.036$ ) and in

cardiac death and nonfatal MI (HR=0.71; 95% CI, 0.55 to 0.93, p=0.014). Both groups were similar for total mortality and graft loss.

### **niacin ER / lovastatin (Advicor)**

No large clinical outcomes trials have been performed with the combination of niacin ER and lovastatin. Short-term comparison trials with atorvastatin and simvastatin have been completed.<sup>289,290</sup>

### **niacin ER / simvastatin (Simcor)**

No large clinical outcomes trials have been performed with the combination of niacin ER and simvastatin. This combination product has been compared to simvastatin.<sup>291,292</sup>

### **pitavastatin (Livalo)**

No large clinical outcomes trials have been performed with pitavastatin. Pitavastatin has been compared to pravastatin, simvastatin, and atorvastatin in patients with primary hyperlipidemia or mixed dyslipidemia, in non-inferiority trials, extension study, as well as in a long-term post-marketing study.<sup>293,294,295,296,297,298</sup>

JAPAN ACS:<sup>299</sup> This was a randomized, open-label, blinded end-point, parallel group, multicenter Japanese study. A total of 307 ACS patients undergoing intravascular ultrasound (IVUS) guided percutaneous coronary intervention were randomized; 252 patients had evaluable IVUS examinations at baseline and 8 to 12 months follow-up. Patients were randomized to 4 mg/day pitavastatin or 20 mg/day atorvastatin with a primary end point of percentage change in nonculprit coronary plaque volume. Pitavastatin 4 mg and atorvastatin 20 mg similarly reduced nonculprit coronary plaque volume post-ACS. The mean percentage change in plaque volume was -16.9 +/- 13.9 percent and -18.1 +/- 14.2 percent (p=0.5) in the pitavastatin and atorvastatin arms, respectively. This was associated with negative vessel remodeling.

A 12-week, active-controlled double-blind, double-dummy trial compared the efficacy of pitavastatin to simvastatin in patients (n=857) with primary hypercholesterolemia or combined dyslipidemia.<sup>300</sup> Patients were randomized to one of four groups: pitavastatin 2 mg, pitavastatin 4 mg, simvastatin 20 mg or simvastatin 40 mg, given daily. Pitavastatin 2 mg showed significantly greater reductions of LDL-C (39 versus 35 percent; p=0.014), non-HDL-C (p=0.021) and TC (p=0.041) compared with simvastatin 20 mg and led to more patients achieving the European Atherosclerosis Society (EAS) LDL-C treatment target. Pitavastatin 4 mg showed similar effects on all lipid parameters compared to simvastatin 40 mg. The reductions in LDL-C were 44 and 43 percent, respectively. The safety profiles of pitavastatin and simvastatin were similar at the two dose levels.

### **pravastatin (Pravachol)**

ALLHAT-LLT study:<sup>301</sup> The study investigated the effects of pravastatin and usual care on all-cause mortality in 10,355 patients with moderate hypercholesterolemia and hypertension over almost five years. The multicenter, non-blinded study randomized patients with LDL-C of 120 to 180 mg/dL to pravastatin 40 mg daily or usual care. Subjects included all patient subtypes including females, Blacks, Hispanics, patients with a history of CHD, and those with type 2 diabetes. Of the usual care group, 17.1 percent used statins at year four, and 26.1 percent used statins at year six. The LDL-C levels were reduced by 28 percent with pravastatin compared to 11 percent with usual care for those who had LDL-C determinations. All-cause mortality and CHD event rates were similar between the two groups.

Secondary endpoints of nonfatal MI or fatal CHD events combined, cause-specific mortality, and cancer were similar between the two groups.

The WOSCOPS study was a randomized primary prevention trial comparing pravastatin to placebo over five years in a large cohort of men with hyperlipidemia (TC > 250 mg/dL) and no prior history of MI.<sup>302</sup> The combined outcome of death from definite coronary heart disease or definite nonfatal MI was reduced from 7.9 to 5.5 percent ( $p < 0.001$ ). A ten-year follow-up of the trial showed a significant reduction in coronary events.<sup>303</sup> The rates of death from all cardiovascular causes [pravastatin: 7.6 percent; placebo: 9 percent; 0.81 (95% CI, 0.68-0.96)  $p = 0.01$ ] and death from any cause (18.7 percent for pravastatin versus 20.5 percent for placebo; 0.88 (95% CI, 0.79-0.99);  $p = 0.03$ ) were lower in the pravastatin group over the total follow-up period. Deaths from CHD were fewer in the pravastatin group [5.1 percent; 0.78 (95% CI, 0.64-0.96)  $p = 0.02$ ] compared to placebo group (6.3 percent). There were no excess deaths from non-cardiovascular causes or incident cancers.

### rosuvastatin (Crestor)

Short-term trials have been published comparing LDL-C reductions of rosuvastatin, atorvastatin, pravastatin, and simvastatin.<sup>304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319</sup> Rosuvastatin has also been compared to atorvastatin in a short-term trial comparing the effect on HDL-C.<sup>320</sup>

ASTEROID:<sup>321</sup> In a prospective, randomized, open-label, blinded endpoint trial, rosuvastatin 40 mg daily was administered to 507 patients. All patients underwent a baseline intravascular ultrasound (IVUS) of a single coronary vessel. After two years of rosuvastatin therapy, patients underwent a repeat IVUS to determine a change in atherosclerosis burden. A total of 349 patients had two sets of IVUS. LDL-C levels were 130.4 mg/dL at baseline and decreased to a mean of 60.8 mg/dL during the study ( $p < 0.001$ .) Over 75 percent of the population achieved LDL-C levels below 70 mg/dL. HDL-C levels increased from a mean of 43.1 mg/dL to 49 mg/dL. The primary endpoint was change in percent atheroma volume in the 10 mm-segment with the greatest disease severity at baseline and the change in normalized total atheroma volume for the entire artery. The change in the percent atheroma volume was reduced by a mean of 0.98 percent ( $p < 0.001$  versus baseline); this represents a median reduction of 9.1 percent in atheroma volume in the 10 mm-segment identified at baseline. Regression in percent atheroma volume occurred in 63.6 percent of patients and 36.4 percent showed progression. For the normalized total atheroma volume for the artery, a median reduction of 6.8 percent was observed. It is important to note the open-label design of the study, large number of patients not completing the study, and the fact that the manufacturer funded the study.

METEOR:<sup>322</sup> A randomized, double-blind, placebo-controlled, multicenter study assessed whether rosuvastatin 40 mg could slow progression and/or cause regression of carotid intima-media thickness (CIMT) over two years in 984 patients in low risk individuals with subclinical atherosclerosis. Among participants in the rosuvastatin group, the mean baseline LDL-C level of 155 mg/dL declined to 78 mg/dL, a mean reduction of 49 percent ( $p < 0.001$  versus placebo). The change in maximum CIMT for the 12 carotid sites was -0.0014 mm/year (95% CI, -0.0041 to 0.0014) for the rosuvastatin group versus 0.0131 mm/year (95% CI, 0.0087 to 0.0174) for the placebo group ( $p < 0.001$ ). Serious rosuvastatin cardiovascular adverse events were observed in 0.86 percent of patients, although this was not statistically significant. Other adverse events were similar for rosuvastatin and placebo. Though rosuvastatin reduced the rate of progression of maximum CIMT over two years, rosuvastatin did not induce disease regression.

JUPITER:<sup>323,324</sup> A randomized, double-blind, placebo-controlled, multicenter study assessed rosuvastatin 20 mg versus placebo in the primary prevention of CV events. A total of 17,802 patients with normal to low LDL-C and elevated levels of high-sensitivity C-reactive protein (hsCRP) were enrolled to determine if long-term treatment with rosuvastatin would reduce the rate of first major CV events in patients with LDL-C <130 mg/dL who are at high vascular risk due to an enhanced inflammatory response indicated by hsCRP levels  $\geq$  2 mg/L. The trial was stopped early after a median follow-up of 1.9 years based on evidence of a reduction in CV morbidity and mortality among patients who received rosuvastatin compared to placebo.<sup>325</sup> Rosuvastatin reduced LDL-C and hsCRP levels by 50 and 37 percent, respectively. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (HR for rosuvastatin, 0.56; 95% CI, 0.46 to 0.69;  $p < 0.00001$ ), with corresponding rates of 0.17 and 0.37 for MI (HR 0.46; 95% CI, 0.3 to 0.7;  $p = 0.0002$ ), 0.18 and 0.34 for stroke (HR 0.52; 95% CI, 0.34 to 0.79;  $p = 0.002$ ), 0.41 and 0.77 for revascularization or unstable angina (HR 0.53; 95% CI, 0.4 to 0.7;  $p < 0.00001$ ), 0.45 and 0.85 for the combined end point of MI, stroke, or death from CV causes (HR 0.53; 95% CI, 0.4 to 0.69;  $p < 0.00001$ ), and 1 and 1.25 for death from any cause (HR, 0.8; 95% CI, 0.67 to 0.97;  $p = 0.02$ ). The decrease in stroke risk was due to a 51 percent relative reduction in the rate of ischemic stroke (HR, 0.49; 95% CI, 0.30 to 0.81;  $p = 0.004$ ), with no difference in the rates of hemorrhagic stroke between the active and placebo groups (HR, 0.67; 95% CI, 0.24 to 1.88;  $p = 0.44$ ).<sup>326</sup> There was not a significant increase in myopathy or cancer in the rosuvastatin group, but there was a significantly higher incidence of physician-reported diabetes. The five-year number needed to treat (NNT) for JUPITER to prevent one CV event was 25 patients or 95 patients over two years.<sup>327</sup>

In a prospective analysis of 87 percent of the full cohort of JUPITER, the effects of rosuvastatin 20 mg versus placebo on rates of non-fatal MI, non-fatal stroke, admission for unstable angina, arterial revascularization, or CV death (pre-specified endpoints) during a maximum follow-up of five years (median 1.9 years) was assessed.<sup>328</sup> Compared with placebo, rosuvastatin patients who achieved LDL-C less than 1.8 mmol/L (70 mg/dL) had a 55 percent reduction in CV events (HR 0.45, 95% CI, 0.34 to 0.6,  $p < 0.0001$ ), and those achieving hsCRP less than 2 mg/L had a 62 percent reduction (HR 0.38, 95% CI, 0.26 to 0.56,  $p < 0.0001$ ). Although LDL-C and hsCRP reductions were only weakly correlated in individual patients, the analysis found a 65 percent reduction in CV events in the rosuvastatin group who achieved both LDL-C less than 1.8 mmol/L (70 mg/dL) and hsCRP less than 2 mg/L (adjusted HR 0.35, 95% CI, 0.23 to 0.54), versus a 33 percent reduction in those who achieved one or neither target (HR 0.67, 95% CI, 0.52 to 0.87) ( $p < 0.0001$  for all treatment groups). In participants who achieved LDL-C less than 1.8 mmol/L (70 mg/dL) and hsCRP less than 1 mg/L, a 79 percent reduction (HR 0.21, 95% CI, 0.09 to 0.52) was noted.

AURORA:<sup>329</sup> A randomized, double-blind, prospective, multicenter study of 2,776 patients who were undergoing maintenance hemodialysis compared rosuvastatin 10 mg daily to placebo. The combined primary end point was death from CV causes, nonfatal MI, or nonfatal stroke. Secondary end points included death from all causes and individual cardiac and vascular events. After three months, the mean reduction in LDL-C levels was 43 percent in patients receiving rosuvastatin, from a mean baseline level of 100 mg/dL. However rosuvastatin had no significant effect on the composite primary end point of death from CV causes, nonfatal MI, or nonfatal stroke. During a median follow-up period of 3.8 years, 396 patients in the rosuvastatin group and 408 patients in the placebo group reached the primary end point (9.2 and 9.5 events per 100 patient-years, respectively; HR for the combined end point in the rosuvastatin group versus the placebo group, 0.96; 95% CI, 0.84 to 1.11;  $p = 0.59$ ).

Rosuvastatin had no effect on individual components of the primary end point. There was also no significant effect on all-cause mortality (13.5 versus 14 events per 100 patient-years; HR 0.96; 95% CI, 0.86 to 1.07;  $p=0.51$ ).

### **simvastatin (Zocor)**

Heart Protection Study (HPS) Collaborative Group:<sup>330</sup> A five-year trial to evaluate the effect of simvastatin 40 mg daily compared to matching placebo enrolled 20,536 patients with CHD, other arterial disease, or diabetes for the effects of simvastatin on mortality, coronary event rates, major vascular events and stroke. All patient types, including females and the elderly, were enrolled. In the double-blind study, compliance rates were evaluated and found to be approximately 82 percent in the simvastatin group after five years of therapy. All-cause mortality was significantly lower in the simvastatin group (12.9 percent) compared to the placebo group (14.7 percent), with reduction in mortality seen in both vascular and nonvascular causes ( $p=0.0003$ ). The percent of patients experiencing a first major vascular event (coronary event, stroke, or revascularization) was significantly lower in the simvastatin group (19.8 versus 25.2 percent;  $p<0.0001$ ). Similar results were seen in the diabetic population ( $n=5,963$ ).<sup>331</sup> 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 ( $p=0.001$ ).<sup>332</sup> Of the 3,500 patients with baseline LDL-C below 100 mg/dL, simvastatin-treated patients were observed to have similar risk reductions as compared to simvastatin-treated patients with higher baseline LDL-C levels. In patients with peripheral arterial disease (PAD), simvastatin was associated with a highly significant 22 percent relative reduction (RR) in the rate of first major vascular event (95% CI, 15 to 29,  $p<0.0001$ ).<sup>333</sup> No significant differences in muscle symptoms or discontinuations due to muscle symptoms were observed between the two groups. The incidence of elevated liver enzymes was not significantly different between simvastatin and placebo groups. In a subgroup analysis of HPS, patients were divided into six groups based on CRP levels (<1.25, 1.25-1.99, 2-2.99, 3-4.99, 5-7.99, and  $\geq 8$  mg/L).<sup>334</sup> The primary endpoint for this intent-to-treat subgroup analyses was major vascular events (composite of coronary death, myocardial infarction, stroke, or revascularization). Simvastatin had a significant 24 percent (95% CI, 19 to 28) proportional reduction in the incidence of first major vascular event after randomization (19.8 percent allocated simvastatin versus 25.2 percent allocated placebo). There was no evidence that the proportional reduction in this endpoint, or its components, differed with baseline CRP concentration (trend  $p=0.41$ ). Even in patients with baseline CRP under 1.25 mg/L, major vascular events were significantly reduced by 29 percent (99% CI, 12 to 43,  $p<0.0001$ ). No significant heterogeneity in the relative risk reduction was observed between the subgroups defined by the combination of low or high baseline concentrations of LDL cholesterol and CRP ( $p=0.72$ ). There was benefit in patients with low LDL-C and low CRP (27 percent relative reduction, 99% CI, 11 to 40,  $p<0.0001$ ).

The effects of early intensive therapy or delayed initiation and less intensive therapy of simvastatin following an ACS event were investigated in the phase Z of the A to Z trial.<sup>335</sup> The randomized, double-blind trial allocated patients to either (early therapy) simvastatin 40 mg daily for one month followed by simvastatin 80 mg daily ( $n=2,265$ ) or (delayed therapy) placebo for four months followed by simvastatin 20 mg daily ( $n=2,232$ ). The composite of cardiovascular death, nonfatal MI, rehospitalization for ACS, or stroke occurred in 14.4 and 16.7 percent of the early and delayed therapy, respectively. This difference was not statistically significant ( $p=0.14$ ). The only significant difference

between the early and delayed therapy in individual endpoints was in cardiovascular death, which occurred in 5.4 and 4.1 percent of patients, respectively (HR=0.75; 95% CI, 0.57 to 1; p=0.05). Myopathy (CPK > 10 times upper limit of normal) 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.

A double-blind randomized trial studied the efficacy and safety of more intensive statin treatment in patients at high cardiovascular risk.<sup>336</sup> Patients (n=12,064) with a history of MI who were either currently on or had clear indication for statin therapy and had a total cholesterol concentration of at least 3.5 mmol/L if already on a statin or 4.5 mmol/L if not were randomized to either 80 mg or 20 mg simvastatin daily. Participants were assessed at 2, 4, 8, and 12 months and then every 6 months until final follow-up. The primary endpoint was major vascular events, defined as coronary death, myocardial infarction, stroke, or arterial revascularization. During a mean follow-up of 6.7 years, simvastatin 80 mg produced an average 0.35 mmol/L greater reduction in LDL cholesterol compared with simvastatin 20 mg. Major vascular events occurred in 24.5 percent of participants on simvastatin 80 mg compared to 25.7 percent of those on simvastatin 20 mg, corresponding to a six percent reduction (risk ratio 0.94, 95% CI, 0.88 to 1.01; p=0.10). Two (0.03 percent) cases of myopathy were reported in patients taking simvastatin 20 mg versus 53 (0.9 percent) cases in the 80 mg group.

## Summary of Large Clinical Trials

Drug	Primary Prevention	Secondary Prevention
atorvastatin (Lipitor)	ASCOT-LLA <sup>337</sup> , CARDS <sup>338</sup>	MIRACL <sup>339</sup> , GREACE <sup>340</sup> , PROVE IT-TIMI 22 <sup>341</sup> , TNT <sup>342</sup> , IDEAL <sup>343</sup> , ASPEN <sup>344</sup> , SPARCL <sup>345</sup>
ezetimibe/simvastatin (Vytorin)	--	--
fluvastatin (Lescol)	--	LIPS <sup>346</sup>
lovastatin	AFCAPS/TexCAPS <sup>347</sup>	--
pitavastatin (Livalo)	--	--
pravastatin	WOSCOPS <sup>348</sup> , PROSPER <sup>349</sup> , ALLHAT <sup>350</sup> , MEGA <sup>351</sup>	CARE <sup>352</sup> , LIPID <sup>353</sup> , PROSPER <sup>354</sup> , PACT <sup>355</sup> , PROVE IT-TIMI 22 <sup>356</sup>
rosuvastatin (Crestor)	JUPITER <sup>357</sup>	--
simvastatin	HPS <sup>358</sup>	4S <sup>359</sup> , HPS <sup>360</sup> , Phase Z of A to Z <sup>361</sup> , IDEAL <sup>362</sup>

## LDL-C Reductions<sup>363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392</sup>

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

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

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

\*\* Per FDA safety communication in March 2010, simvastatin 80 mg has the potential increased risk of myopathy compared with lower doses of simvastatin and possibly other drugs in the statin class.

### Effects on TG and HDL-C<sup>393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416</sup>

Drug	Triglyceride change (%)	HDL-C change (%)
atorvastatin (Lipitor, Caduet) 10 - 80mg	- 17 to - 37	- 0.1 to 9
ezetimibe / simvastatin (Vytorin) 10mg/10mg – 10mg/80mg	- 23 to - 35	6 to 12
fluvastatin (Lescol) 10 - 80mg	- 2.7 to - 23	- 3 to 9
fluvastatin XL (Lescol XL) 80mg	- 19 to - 25	7 to 11
lovastatin 20 - 80mg	- 6 to - 27	3 to 10
lovastatin ER (Altoprev) 10 - 60 mg	- 10 to - 33	6 to 13
niacin ER / lovastatin (Advicor) 1,000mg/20mg - 2,000mg/40mg	- 29 to - 49	17 to 32
niacin ER / simvastatin (Simcor) 1,000mg/20mg - 2,000mg/40mg	- 23 to - 38	15 to 29
pitavastatin (Livalo) 2 - 4mg	-14 to -22	2 to 7
pravastatin 10 - 80mg	- 9 to - 24	2 to 12
rosuvastatin (Crestor) 5 - 40mg	- 10 to - 35	8 to 14
simvastatin 5 - 80mg	- 9 to - 34	3 to 16

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

## META-ANALYSIS

A meta-analysis evaluated the trials (TNT, IDEAL, AtoZ, and PROVE IT/TIMI-22) comparing the intensive lipid-lowering with moderate statin therapy in a total of 27,548 patients.<sup>417</sup> A pooled analysis for intensive lipid-lowering was associated with 16 percent odds reduction ( $p < 0.000001$ ) for coronary death or MI.

A meta-analysis of 27,548 patients with ACS or stable CAD from four randomized, controlled trials comparing intensive to moderate dose statin therapy was done from 1995 to 2006.<sup>418</sup> Intensive dose therapy with atorvastatin (Lipitor) or simvastatin 80 mg was associated with better reductions in CV death (OR=0.86, 95% CI, 0.75 to 0.99,  $p=0.031$ ), MI (OR=0.84, 95% CI, 0.76 to 0.93,  $p < 0.001$ ), and stroke (OR=0.82, 95% CI, 0.72 to 0.94,  $p=0.004$ ). However, intensive dose therapy was also associated with an increased risk for any adverse event (OR=1.44, 95% CI, 1.33 to 1.55,  $p < 0.001$ ) and an increased risk for LFT and CK elevations.

A meta-analysis evaluated data from 13 statin studies that included a total of 90,056 patients. The meta-analysis included large statin trials beginning with 4S, published in 1994, and concluding with CARDS, published in 2004. Assuming appropriate adherence and achievement of approximately 39 mg/dL (1 mmol/L) reduction in LDL-C, statins can reduce the five-year incidence of major coronary events and revascularization by approximately 20 percent.<sup>419</sup>

A meta-analysis of atorvastatin (Lipitor) and simvastatin across all dose combinations in terms of changes in TC, LDL-C, TG, and HDL-C was conducted from 17 published trials and one unpublished trial.<sup>420</sup> Atorvastatin was two to four times as potent as simvastatin in reducing TC, LDL-C, and TG. Simvastatin was more effective than atorvastatin in increasing HDL-C.

A meta-analysis of 15 randomized controlled statin trials through May 2006 looked at gender specific incidence of cardiovascular events.<sup>421</sup> Cardiovascular events were reduced in men (RR= 0.76, 95% CI, 0.7 to 0.81) and women (RR=0.79, 95% CI, 0.69 to 0.9). Reductions in mortality, MI, and stroke predominantly contributed to the reduction in cardiovascular events in men on statins, but women did not have a reduction in mortality or stroke.

Treatment with ezetimibe (Zetia) 10 mg/day or placebo added to current statin therapy was compared in a meta-analysis of five randomized controlled trials with at least six weeks duration in 5,039 adults with hypercholesterolemia.<sup>422</sup> The weighted mean difference between treatments significantly favored the ezetimibe/statin combination over placebo/statin for total cholesterol [-16.1 percent (95% CI, -17.3 to -14.8),  $p < 0.0001$ ], LDL-C [-23.6 percent (95% CI, -25.6 to -21.7),  $p < 0.0001$ ] and HDL-C [1.7 percent (95% CI, 0.9 to 2.5),  $p < 0.0001$ ]. The relative risk of reaching the LDL-C treatment goal was significantly higher for patients on ezetimibe/statin relative to those on placebo/statin [3.4 (2, 5.6),  $p < 0.0001$ ]. In pre-defined sub-group analyses of studies in patients with CHD, the weighted mean difference between treatments remained significantly in favor of ezetimibe/statin ( $p < 0.0001$ ) for total cholesterol and LDL-C but was no longer significant for HDL-C. Elevations in liver enzymes did not differ significantly between groups.

A systematic overview of 18 randomized controlled trials of combination statin and ezetimibe trials was performed to assess risk in 14,471 patients.<sup>423</sup> Compared with statin monotherapy, combination therapy did not result in significant absolute increases in risks of myalgias (risk difference -0.033, 95% CI, -0.06 to -0.01), creatine kinase increases (risk difference 0.011, 95% CI, -0.02 to 0.04), rhabdomyolysis (risk difference -0.003, 95% CI, -0.01 to 0.004), transaminase increases (risk difference -0.003, 95% CI, -0.01 to 0.005), gastrointestinal adverse events (risk difference 0.005, 95% CI, -0.03 to 0.04), or discontinuations because of an adverse event (risk difference -0.005, 95% CI, -0.03 to 0.02). This systematic review showed that the addition of ezetimibe to statin therapy did not increase the risk of myalgias, creatine kinase levels, rhabdomyolysis, transaminase levels, gastrointestinal adverse events, or discontinuations due to an adverse event.

A meta-analysis compared the overall efficacy of statins on cardiac morbidity and mortality in hypertensive and non-hypertensive patients enrolled in major randomized clinical trials including the ASCOT-LLA and ALLHAT-LLT trials.<sup>424</sup> Statin therapy decreased cardiac death by 24 percent (RR 0.76, 95% CI, 0.71 to 0.82). There was no evidence of difference in RR estimates for hypertensive (RR 0.78, 95% CI 0.72 to 0.84) and non-hypertensive (RR 0.76, 95% CI 0.72 to 0.8) patients. This study showed that statin therapy decreases CV morbidity and mortality to the same extent in hypertensive and non-hypertensive patients.

A meta-analysis of randomized controlled trials comparing different intensities of statin therapy was conducted to evaluate the evidence for aggressive LDL-C lowering in CAD patients.<sup>425</sup> A search of electronic databases including, MEDLINE, EMBASE, Cochrane Central Registry of Controlled Trials, and Web of Science for randomized controlled trials published up to July 19, 2007, identified studies that compared statin regimens of different intensities in adults with CAD and that reported CV events or mortality. Seven trials consisting of 20,395 patients were included. As expected, more intensive statin

regimens compared to less intensive regimens further reduced LDL-C levels (0.72 mmol/L reduction, 95% CI, 0.6-0.84 mmol/L), and reduced the risk of MI (OR 0.83, 95% CI, 0.77-0.91) and stroke (OR 0.82, 95% CI, 0.71-0.95). Although there was no effect on mortality among patients with chronic CAD (OR 0.96, 95% CI, 0.8-1.14), all-cause mortality was reduced in patients with ACS treated with more intensive statin regimens (OR 0.75, 95% CI, 0.61-0.93) compared with lower intensity regimens. Intensive regimens were associated with small absolute increases in rates of drug discontinuation (2.5 percent), elevated levels of aminotransferases (1 percent), and myopathy (0.5 percent). In addition, there was no difference in non-CV mortality. This meta-analysis shows the use of more intensive statin regimens in patients with established CAD. The study does not find sufficient evidence to treat to particular LDL-C targets, using combination lipid-lowering therapy to achieve these targets, or for using more intensive regimens in patients without established CAD.

A meta-analysis of 20 randomized trials of at least 12-months duration in predominantly primary prevention populations showed that statins are effective in primary prevention of CV events.<sup>426</sup> The study pooled 19 trials (n=63,899) for all-cause mortality and found a RR 0.93 (95% CI, 0.87 to 0.99, p=0.03). Eighteen trials (n=59,469) assessed CV deaths (RR 0.89, 95% CI, 0.81 to 0.98, p=0.01). Seventeen trials (n=53,371) found an RR of 0.85 (95% CI, 0.77 to 0.95, p=0.004) for major CV events, and 17 trials (n=52,976) assessed MIs (RR 0.77, 95% CI, 0.63 to 0.95, p=0.01). Incidence of cancer or rhabdomyolysis were not elevated in 10 trials (n=45,469).

A meta-analysis of 11 prospective randomized controlled statin trials in 65,229 patients, without baseline CVD history and with data on all-cause mortality were identified in Medline and Cochrane databases (January 1970-May 2009).<sup>427</sup> Effect estimates were pooled using a random-effects model meta-analysis, with heterogeneity assessed with the I<sup>2</sup> statistic. A total of 2,793 deaths occurred. The use of statins in this high-risk primary prevention setting was not associated with a statistically significant reduction in the risk of all-cause mortality (RR, 0.91; 95% CI, 0.83-1.01). There was no statistical evidence of heterogeneity among studies (I<sup>2</sup> = 23 percent; 95% CI, zero-61 percent; p=0.23).

Uncertainties remain regarding the benefit of statins in the prevention of CV events in women compared to men. A meta-analysis, identified eleven trials including 43,193 patients with CV disease, of which 20.6 percent were women. This study reported a similar reduction in risk of CV events in all outcomes for women and men.<sup>428</sup> However, statins did not reduce all-cause mortality in women compared to men (RR 0.92 [95% CI 0.76-1.13] versus RR 0.79 [95% CI 0.72-0.87]) or stroke (RR 0.92 [95% CI 0.76-1.1] versus RR 0.81 [95% CI 0.72-0.92]). Possible study limitations include potential for omission of pertinent studies due to the literature search confined to PubMed and English language, and data being extracted by a single investigator.<sup>429,430</sup> Another recent meta-analysis evaluating the benefit of statins in primary and secondary prevention, included 18 randomized clinical trials of statins with sex-specific outcomes (n=141,235; 40,275 women). This analysis reported similar reduction in CV event rate in women and men receiving statins (OR: 0.81, 95% CI: 0.75 to 0.89; p<0.0001, and OR: 0.77, 95% CI: 0.71 to 0.83, p<0.0001, respectively).<sup>431</sup> All-cause mortality was also lower with statin therapy both in women and men without significant interaction by gender (p=0.44).

## SUMMARY

The Adult Treatment Panel (ATP) III guidelines consider lipid-lowering therapy to be part of treatment of patients with or at risk for cardiovascular disease. Any of the HMG-CoA reductase inhibitors can safely lower LDL-C by the 30 percent required in most patients to reach goal.

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

Statins have demonstrated clear improvements in primary and secondary prevention of cardiovascular events. They have shown a decrease in the incidence of myocardial infarction, stroke, need for revascularization, angina hospitalization, cardiovascular mortality, and overall mortality; however, questions still remain regarding the benefit of statins in the prevention of cardiovascular events in women compared to men. Combination therapy may avoid the increase in adverse effects often seen with higher doses of statins. The statin combination agents [niacin ER/lovastatin (Advicor), niacin ER/simvastatin (Simcor) and atorvastatin/amlodipine (Caduet)], and ezetimibe/simvastatin (Vytorin) have not been proven to offer a substantial benefit on cardiovascular morbidity and mortality over and above that of the statin component.

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