Drug Class Review

Hydroxymethylglutaryl-coenzyme A Reductase Inhibitors (statins)

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and the Medical Advisory Panel
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Objectives

The objective is to review the efficacy, safety and administration of the 5 currently available hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) in the management of hypercholesterolemia. Astra-Zeneca has filed a new drug application (NDA) for a new statin, rosuvastatin. All applicable published and unpublished data available for rosuvastatin will be included in this review.

Brand Name®	Lipitor	Lescol/Lescol XL	Mevacor/Various*	Pravachol	Crestor	Zocor
Generic Name	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvasatin	Simvastatin
Manufacturer	Pfizer	Reliant/Novartis	Merck/Various*	Bristol-Myers Squibb	Astra- Zeneca	Merck

*Lovastatin is available as a generic product and as a branded extended-release product (Altocor)

Introduction

Coronary heart disease (CHD) continues to be the leading cause of mortality and a significant cause of morbidity among Americans. In 1999, CHD claimed 529,659 lives, translating into about 1 out of every 5 deaths in the United States.[1] Elevated cholesterol, or hypercholesterolemia, is an important risk factor for CHD. The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors, also known as statins, are an important component of care in the management of hypercholesterolemia because of their effectiveness in reducing low-density lipoprotein (LDL-c), their safety and tolerability, and because of their demonstrated ability to reduce cardiovascular morbidity and mortality in clinical trials. The statins work by blocking the enzyme HMG-CoA reductase. This enzyme assists in the manufacture of cholesterol. Upon blocking HMG-CoA reductase, there is a reduction in cholesterol production. As a result of this reduction, a greater number of LDL receptors are created thereby increasing the uptake of LDL-c. As a result, treatment with statins reduces the amount of cholesterol made by the body. This reduction in cholesterol production results in reduced LDL-c, total cholesterol, and triglycerides and slightly increases high-density lipoprotein (HDL-c).

There are some that theorize that there are other effects of the statins that may be responsible for their ability to reduce morbidity and mortality from CHD. These other effects are referred to as the pleiotropic (e.g. statins effect on endothelial function, inflammation, coagulation, and plaque stability) effect of statins.[111] However, a discussion of potential statin pleiotropic effects is beyond the scope of this review.

Indications

All 5 of the statins are approved for the reduction of total cholesterol and LDL-c in patients with primary hypercholesterolemia and mixed dyslipidemias (Frederickson classification of hyperlipoproteinemias Types IIa and IIb) when diet and other nonpharmacologic measures, alone, have been inadequate. Additional indications for each statin are listed in Table 1. (Rosuvastatin is not included in Table 1 since it has not been approved by the Food and Drug Administration (FDA)).

Table 1: FDA Approved Indications for HMG-CoA RI's[2-6]

Indication	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Lipid lowering:					
TC	X	X	X	X	X
LDL-c	X	X	X	X	X
TG	X	X		X	X
Apo B	X	X		X	X
Increase HDL-c	X	X		X	X
Patients with homozygous familial hypercholesterolemia to reduce TC & LDL-c	X				X
Patients with Frederickson Type III & IV primary dysbetalipoproteinemia and elevated serum TG	X			X	X
Patients with elevated cholesterol with no evidence of CAD to reduce the risk of:					
MI				X	
Cardiovascular mortality				X	
PTCA/CABG				X	
Slowing atherosclerosis in patients with elevated cholesterol & evidence of CAD		X	X	X	
Patients with elevated cholesterol & evidence of CAD (± MI) to reduce the risk of:					
Non-fatal MI				X	X
Stroke/ TIA				X	X
PTCA/CABG				X	X
Acute coronary events					
Total mortality (by decreasing coronary death)				X	X
Patients with previous MI and normal cholesterol (below 75th percentile of population) to reduce the risk of:					
Recurrent MI				X	
PTCA/CABG				X	
Stroke /TIA				X	
Primary prevention in patients without symptomatic CAD disease who have average to moderately elevated TC & LDL-C and below average HDL-C to reduce the risk of:					
MI, unstable angina, and revascularizations			X		

ApoB= apolipoprotein B; CABG= coronary artery bypass graft; CAD= coronary artery disease; HDL-C= high-density lipoprotein cholesterol; LDL-c= low-density lipoprotein cholesterol; MI= myocardial infarction; PTCA= percutaneous transluminal coronary angioplasty; TC= total cholesterol; TIA transient ischemic attack; TG = triglycerides

Pharmacokinetics

The statins are absorbed rapidly following oral administration, with time to peak concentrations (t_{max}) within 2 - 5 hours. All of the agents may be taken without regard to meals with the exception of immediate-release (IR) and extended-release (ER) lovastatin. During fasting conditions, plasma concentrations of lovastatin (IR) were 2/3 that seen immediately after a meal. As a result, lovastatin (IR) should be taken with the evening meal. As opposed to lovastatin IR, lovastatin (ER), taken after a meal, results in a significant reduction in bioavailability. Therefore, lovastatin ER should be given at bedtime. Protein binding is high for these agents (50-99%). In general, the statins undergo extensive first-pass hepatic extraction and all except pravastatin are metabolized through the cytochrome P450 (CYP) enzyme system. The primary route of elimination for this class of drugs is biliary, while renal elimination accounts for <2 - 20% of drug elimination. Table 2 lists the relevant pharmacokinetic parameters of the six agents. At the time of this review, data for rosuvastatin on oral bioavailability, protein binding and interaction with food were not available.

Table 2. Pharmacokinetic Properties[2-8]

Parameter	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Bioavailability	14%	24%	< 5%	17%	Unknown	< 5%
Excretion: Renal Feces	 < 2% 98%	 5% 90%	 10% 83%	 20% 70%	 10% 90%	 13% 60%
Metabolic enzymes	CYP 3A4	CYP 2C9	CYP 3A4	Sulfation	CYP 2C9, 2C19	CYP 3A4
Metabolites contributing to lipid lowering effect	Yes	No	Yes	No	No	Yes
Hepatic first pass effect	20-30%	40-70%	40-70%	50-70%	Unknown	50-80%
Lipophilicity	Lipophilic	Hydrophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic

Efficacy

In order to address the question of efficacy between statins, head to head LDL-c lowering studies comparing 2 or more statins and trials reporting coronary heart disease (CHD) outcomes were included.

1. How do statins compare in their ability to reduce LDL-c?

A. **Are there doses for each statin that produce similar percent reduction in LDL-c between statins?**

A total of 42 randomized clinical trials comparing the LDL-c lowering ability of two or more statins in patients with baseline LDL-c ≤300 mg/dl were identified. In 27 of those trials, the percentage of patients reaching their National Cholesterol Education Program (NCEP) goal was also evaluated. There were 22 double-blinded, 18 unblinded, and 2 single-blinded studies. Dosing strategies varied between trials. Some studies titrated to a maximum recommended daily dose (titrate to target) while others compared a single statin dose with or without dose titration. In the majority of the trials, the efficacy analyses were performed on a smaller number of patients than those randomized (that is, the trials did not use intention to treat statistics).

The trials included men and women ages 18-80 years who completed a minimum 4-week placebo/dietary run in phase after which those meeting LDL-c criteria were randomized. These trials excluded patients with secondary causes of hypercholesterolemia (uncontrolled diabetes, thyroid disease, or other endocrine condition), pregnant or lactating women, kidney or liver impairment, baseline creatine kinase (CK) elevation, triglycerides ≥350-400 mg/dl and those receiving drugs with the potential for drug interaction with statins. The duration of the clinical trials varied from 6 weeks to 1 year.

Table 3. Trials Comparing LDL-c Lowering Abilities of 2 or more Statins

Clinical Trial	Inclusion Criteria	Treatment Groups	Results (% LDL-c lowering* and % achieving LDL-c goal**)
Atorvastatin vs. Lovastatin			
Davidson M., etal. 1997[9] **R (3:1), DB, MC** 1,049 patients 1 year (Parke-Davis participated in trial)	Men and women 18-80 years with an LDL-c ≥160 mg/dl and ≥145 mg/dl after dietary phase.	Atorva 10 mg/d or Lova 20 mg/d or Placebo for 16 weeks. Then Atorva 10 mg/d or Lova 20 mg/d for 36 weeks. Doses could be doubled at 22 weeks if LDL-c goal was not achieved.	**% LDL-c reduction:** Atorva 10 mg: 36% Lova 20 mg: 27% (p<0.05 vs. lova) **% meeting LDL-c goal:** Atorva 10 mg: 78% Lova 20 mg: 63% **Atorva 10 > Lova 20 mg** **Equivalent doses not compared, titrate to target**
Atorvastatin vs. Pravastatin			
Bertolini S., etal. 1997[10] **R (3:1), DB, MC** 305 patients 1 year (2 authors were employed by Parke-Davis)	Men and women 18-80 years with an LDL-c ≥160 mg/dl and ≤ 250 mg/dl.	Atorva 10 mg/d or Prava 20 mg/d Doses were doubled at week 16 if LDL-c was ≥130 mg/dl.	**% LDL-c reduction:** Atorva 10 mg: 35% Prava 20 mg: 23% (p≤0.05 vs. prava) **% meeting LDL-c goal:** Atorva 10 mg: 71% Prava 20 mg: 26% **Equivalent doses not compared, titrate to target**
Assman G., etal. 1999[11] **R (3:1), DB, MC**	Men and women 18-80 years with an LDL-c ≥160 mg/dl	Mild/Moderate risk level: Atorva 10 mg/d or	**% LDL-c reduction:** Atorva 39%

297 patients 1 year (2 authors were employed by Park-Davis)	and ≤ 250 mg/dl.	Prava 20 mg/d High risk level: Atorva 20 mg/d or Prava 40 mg/d Doses could be doubled at week 8 and 16, if LDL-c goal was not met, up to atorva 80 mg qd or prava 40 mg qd.	Prava 29% (p<0.0001 vs. prava) **% meeting LDL-c goal:** Atorva 51% Prava 20% **Equivalent doses not compared, titrate to target**
Atorvastatin vs. Rosuvastatin			
Davidson M., etal. 2002[12] **R, DB, MC PC** 519 patients 16 weeks (Supported by AstraZeneca)	Men and women 18 years or > with an LDL-c of ≥160 mg/dl and ≤ 250 mg/dl.	Atorva 10 mg/d or Rosuva 5 mg/d or Rosuva 10 mg/d or Placebo	**% LDL-c reduction:** Atorva 10 mg: 35% Rosuva 5 mg: 40% Rosuva 10 mg: 43% Placebo NC (p<0.01 vs. atorva) **% meeting LDL-c goal:** Atorva 10 mg: 72% Rosuva 5 mg: 84% Rosuva 10 mg: 82% Placebo: 12% **Rosuva 5 and 10 mg > Atorva 10 mg**
Atorvastatin vs. Simvastatin			
Simons LA., etal. 1998[13] **R (3:1), OL, MC** 92 patients 30 weeks (Supported by Parke-Davis)	Patients previously stable on simva 40 mg/d and an LDL-c ≥193 mg/dl. (Severe)	Simva withdrawn and randomized to: Atorva 10 mg/d or Simva 10 mg/d Doses doubled at 6 week intervals until atorva 80 mg/d or simva 40 mg/d if LDL-c ≥135 mg/dl. Cholestyramine 4 gm. could be added to simva. (84% of simva 40 mg/d patients were also on cholestyramine)	**% LDL-c reduction:** Atorva 10 mg: 33% Atorva 20 mg: 40% Mean dose: Atorva 38 mg: 45% Atorva 69 mg: 49% Simva 10 mg: 22% Simva 20 mg: 30% Simva 38 mg: 35% Simva 39 mg: 38% **% meeting LDL-c goal:** Atorva: 19% Simva: 6% **Atorva 10 mg ≅ Simva 20 mg** **Equivalent doses not compared, treat to target**
Dart A., etal. 1997[14] **R (3:1), DB, MC** 177 patients 1 year (Parke-Davis participated and supported study)	Men and women 18-80 years with an LDL-c ≥160 mg/dl and ≤ 300 mg/dl.	Atorva 10 mg/d or Simva 10 mg/d Doses were doubled at week 16 if LDL-c >130 mg/dl	**% LDL-c reduction:** Atorva 10 mg: 37% Simva 10 mg: 30% (p≤0.05 vs. simva) **% meeting LDL-c goal:** Atorva: 46% Simva: 27% **Equivalent doses not compared, titrate to target**
Crouse JR., etal. 1999[15] **R, OL, MC** 846 patients (Merck participated and supported study)	Men or women with hypercholesterolemia	Atorva 20 mg/d or Atorva 40 mg/d or Simva 40 mg/d or Simva 80 mg/d	**% LDL-c reduction:** Atorva 20 mg: 45% Atorva 40 mg: 51.1% Simva 40 mg: 42.7% Simva 80 mg: 49.2% (p<0.05 in favor of atorva 20 vs simva 40) **Atorva 20 mg > or = Simva 40 mg. Atorva 40 mg = Simva 80 mg**
Marz W., etal. 1999[16] **R (2:1), OL, MC** 2,856 patients 14 weeks (Study sponsored by Parke-Davis and Pfizer)	Men and women 35-75 years with CHD and LDL-c ≥130 mg/dl.	Atorva 10 mg/d or Simva 10 mg/d Doses were doubled at weeks 5 and/or 10 if LDL-c ≥100 mg/dl to max. of 40 mg/d.	**% LDL-c reduction:** Atorva 10 mg: 37.6% Simva 10 mg: 31.9% (p<0.001 vs. simva) **% meeting LDL-c goal:** Atorva: 67% Simva: 53% (Cumulative response was

			same in atorva 20 and simva 40 mg) **Atorva 20 mg = Simva 40 mg**
Van Dam M., etal. 2000[17] **R, SB, MC** 378 patients 8 weeks (One author was employed by Parke-Davis. Supported by Parke-Davis and Pfizer)	Men and women 18-80 years currently treated with simva 20 or 40 mg/d and LDL-c >100 mg/dl.	Past simva 20 mg users: Atorva 20 mg/d or Simva 20 mg/d Past simva 40 mg users: Atorva 40 mg/d or Simva 40 mg/d	**% LDL reduction:** **N/A (additional reductions)** **% meeting LDL-c goal:** Atorva: 28% Simva: 13% **Equivalent doses not compared.**
Farnier M., etal. 2000[18] **R (2:1:2), OL, MC** 272 patients 12 weeks (Supported by Parke-Davis)	Men and women 18-70 years with an LDL-c≥160 mg/dl.	Atorva 10 mg/d or Simva 10 mg/d or Simva 20 mg/d	**% LDL reduction:** Atorva 10 mg: 37% Simva 10 mg: 28.9 Simva 20 mg: 33.8% **% meeting LDL-c goal:** **Atorva 10 mg > Simva 20 mg**
Recto CS., etal. 2000[19] **R, OL, MC** 258 patients 12 weeks (Supported by a grant from Merck)	Men and women 21-70 years with an LDL-c ≥130 mg/dl.	Atorva 10 mg/d or Simva 20 mg/d or Atorva 20 mg/d or Simva 40 mg/d	**% LDL reduction:** Atorva 10 mg: 36.7% Atorva 20 mg: 42.1% Simva 20 mg: 34.8% Simva 40 mg: 41% (NS) **% meeting LDL-c goal:** Approximately 70% of atorva and simva patients. **Atorva 10 mg=Simva 20 mg, Atorva 20 mg=Simva 40 mg**
In sull W., etal 2001[20] **R, OL, MC** 1,424 patients First 6 weeks of planned 54week study. (Supported y Parke-Davis)	Men and women 18-80 years with or without CHD and with or without Type 2 DM with elevated LDL-c.	Atorva 10 mg/d or Simva 10 mg/d	**% LDL-c reduction:** Atorva 10 mg: 37.2% Simva 10 mg: 29.6% (p<0.0001) **% meeting LDL-c goal:** Atorva 10 mg: 55.6% Simva 10 mg: 38.4% (p<0.0001) **Equivalent doses not compared.**
Illingworth DR., etal. 2001[21] **R, DB, MC** 826 patients 36 weeks (5 authors were employees of Merck. The authors acknowledge Merck for assisting in the preparation of the manuscript)	Men and women 21-70 years with elevated cholesterol.	Atorva 20 mg/d or Simva 40 mg/d for 6 weeks, then Atorva 40 mg/d or Simva 80 mg/d for 6 weeks, then Atorva 80 mg/d or Simva 80 mg/d for 24 weeks.	**% LDL-c reduction:** Atorva 20 mg: 46.1% Simva 40 mg: 42.4% Atorva 40 mg: 51.3% Simva 80 mg: 48.8% Atorva 80 mg: 53.6% Simva 80 mg: 48.1% (p≤0.001 for all 3 comparisons vs. simva) **% meeting LDL-c goal:** Not evaluated in study. **Atorva 20 mg > Simva 40 mg, Atorva 40 mg > Simva 80 mg, Atorva 80 mg > Simva 80 mg**
Branchi A., etal. 2001[22] **R, OL** 200 patients Up to 6 months (data provided for first 2 months) (Role and source of funding not reported)	Men and women with hypercholesterolemia not controlled with diet.	Atorva 10 mg/d or Simva 20 mg/d	**% LDL-c reduction:** Atorva 10 mg: 34.8% Simva 20 mg: 32.6% (NS) **% meeting LDL-c goal:** Not evaluated in study. **Atorva 10 mg=Simva 20 mg**
Karalis DG., etal. 2002[23] **R, OL, MC** 1,732 patients 6 weeks (Pfizer supported and participated in trial)	Men and women 18-80 years with an LDL-c≥190 mg/dl if no risk factors, ≥160 mg/dl if 2 or more risk factors, and ≥130 mg/dl if CHD.	Atorva 10 mg/d or Atorva 80 mg/d or Simva 20 mg/d or Simva 80 mg/d	**% LDL-c reduction:** Atorva 10 mg: 37% * Simva 20 mg: 35% Atorva 80 mg: 53% ** Simva 80 mg: 47% (*p<0.025 vs. simva, **p<0.0001 vs. simva) **% meeting LDL-c goal:** Atorva 10 mg: 59% * Simva 20 mg: 53%

			Atorva 80 mg: 89% ** Simva 80 mg: 82% (*p<0.0125, **p=NS) **Atorva 10 mg ≥ Simva 20 mg** **Atorva 80 mg > Simva 80 mg**
Atorvastatin vs. Multiple Statins			
Hunninghake D., etal. 1998[24] **R, OL, MC** 344 patients 54 weeks (One author was employed by Parke-Davis. Supported by Parke-Davis	Men or women 18-80 years with elevated cholesterol at risk for CHD.	Atorva 10 mg/d or Fluva 20 mg/d or Lova 20 mg/d or Simva 10 mg/d Doses were titrated up to a maximum of: Atorva 80 mg/d, Fluva 40 mg/d, Lova 80 mg/d, Simva 40mg/d. Colestipol was added if needed.	**% LDL-c reduction: (Median dose/day)** Atorva 10 mg: 35% Fluva 40 mg: 22% * Lova 40 mg: 28% * Simva 20 mg: 33% (p<0.05 vs. atorva) **% meeting LDL-c goal:** Atorva 10 mg: 95% Fluva 40 mg: 60% Lova 40 mg: 77% Simva 20 mg: 83% **Atorva 10 mg = Simva 20 mg** **Atorva 10 mg > Fluva 40 mg and Lova 40 mg**
Brown AS., etal. 1998[25] **R, OL, MC** 318 patients 54 weeks (One author was employed by Parke-Davis. Supported by Parke-Davis)	Men and women 18-80 years with documented CHD and LDL-c≥130 mg/dl and ≤250 mg/dl.	Atorva 10 mg/d or Fluva 20 mg/d or Lova 20 mg/d or Simva 10 mg/d Doses were titrated up to a maximum of: Atorva 80 mg/d, Fluva 40 mg/d, Lova 80 mg/d, Simva 40mg/d. Colestipol was added if needed.	**% LDL-c reduction: (Median dose/d)** Atorva 20 mg: 41% Fluva 80 mg+Colestipol 20 g): 30% * Lova 80 mg: 41% Simva 40 mg: 37% **% meeting LDL-c goal:** Atorva 83% Fluva 50% * Lova 81% Simva 75% (p<0.05 vs. atorva) **Atorva 20 mg = Lova 80 mg = Simva 40 mg**
Jones P., etal. 1998[26] **R, OL, MC** 534 patients 8 weeks (Parke-Davis funded and participated in study)	Men and women 18-80 years with LDL-c ≥160 mg/dl.	Atorva 10 mg/d or Atorva 20 mg/d or Atorva 40 mg/d or Atorva 80 mg/d or Fluva 20 mg/d or Fluva 40 mg/d or Lova 20 mg/d or Lova 40 mg/d or Lova 80 mg/d or Prava 10 mg/d or Prava 20 mg/d or Prava 40 mg/d or Simva 10 mg/d or Simva 20 mg/d or Simva 40 mg/d or	**% LDL-c reduction:** Atorva 10 mg: 38% Atorva 20 mg: 46% Atorva 40 mg: 51% Atorva 80 mg: 54% Fluva 20 mg: 17% Fluva 40 mg: 23% Lova 20 mg: 29% Lova 40 mg: 31% Lova 80 mg: 48% Prava 10 mg: 19% Prava 20 mg: 24% Prava 40 mg: 34% Simva 10 mg: 28% Simva 20 mg: 35% Simva 40 mg: 41% **% meeting LDL-c goal:** Not evaluated in study. **Atorva 10 mg ≅ Lova 40 mg ≅ Prava 40 mg ≅ Simva 20 mg** **Atorva 20 mg ≅ Lova 80 mg ≅ Simva 40 mg**
Wolffenbuttel BHR., etal 1998[27] **R, OL, MC, CO** 78 patients 4 weeks on each treatment (One author was employed by Parke-Davis. Supported by Parke-Davis)	Men and women 18-70 years with and LDL-c 160 to 240 mg/dl.	Atorva 5 mg/d or Atorva 20 mg/d or Prava 20 mg/d or Simva 10 mg/d	**% LDL-c reduction:** Atorva 5 mg: 27% Atorva 20 mg: 44% * Prava 20 mg: 24% Simva 10 mg: 28% (*p<0.05 vs atorva 5, prava and simva) **% meeting LDL-c goal:** Not evaluated in study. **Atorva 5 mg = Prava 20 mg**

			= Simva 10 mg
Gentile S., etal. 2000[28] **R, OL, MC** 412 patients 24 weeks (Supported in part by MURST, Italy)	Men and women 50-65 years with Type 2 DM and an LDL-c >160 mg//dl.	Atorva 10 mg/d or Lova 20 mg/d or Prava 20 mg/d or Simva 10 mg/d or Placebo	**% LDL-c reduction:** Atorva 10 mg: 37% Lova 20 mg: 21% * Prava 20 mg: 23% * Simva 10 mg: 26% * Placebo: 1% (p<0.05 vs. atorva) **% meeting LDL-c goal:** Not evaluated in study. **Equivalent doses not compared.**
Andrews TC., etal. 2001[29] **R (4:1:1:1:1), OL, MC** 3,916 patients 54 weeks (One employee from Pfizer was acknowledged for analysis and interpretation of data. Supported by Pfizer)	Men and women 18-80 years with elevated cholesterol, with or without CHD.	Atorva 10 mg/d or Fluva 20 mg/d or Lova 20 mg/d or Prava 20 mg/d or Simva 10 mg Doses were titrated up to a maximum of: Atorva 80 mg/d, Fluva 80 mg/d, Lova 80 mg/d, Prava 40 mg/d or Simva 40mg/d.	**% LDL-c reduction: (Mean Dose/day)** Atorva 24 mg: 42% * Fluva 62 mg: 29% Lova 52 mg 36% Prava 31 mg: 28% Simva 23 mg: 36% (p<0.01 in favor of atorva vs. all other statins) **% meeting LDL-c goal:** Atorva 76% Fluva 37% Lova 49% Prava 34% Simva 58% **Equivalent doses not compared.**
Fluvastatin vs. Lovastatin			
Nash DT. 1996[30] **R, OL, MC** 137 patients 8 weeks (Supported by Sandoz)	Men and women previously controlled on lovastatin 20 mg/d (LDL-c <150 mg/dl).	Fluva 20 mg/d or Lova 20 mg/d After 4 weeks, Fluva was increased to 40 mg/d	**% LDL-c reduction:** Fluva 20 mg: 22-23% Fluva 40 mg: 26% Lova 20 mg: 26-29% (p not stated for comparison between Fluva 20 and Lova) **% meeting LDL-c goal:** Fluva 20 mg: 85% Fluva 40 mg: 89% Lova 20 mg:91% **Fluva 40 mg = Lova 20 mg**
Fluvastatin vs. Pravastatin			
Jacotot B., etal. 1995[31] **R, DB, MC** 134 patients 16 weeks (Participation and financial support by Sandoz)	Men and women 18-75 years with LDL-c≥160 mg/dl.	Fluva 40 mg/d or Prava 20 mg/d Doses doubled at 4 weeks.	**% LDL-c reduction:** Fluva 40 mg bid: 29.6% Prava 40 mg: 26.1% (NS) **% meeting LDL-c goal:** Not evaluated in this study. **Fluva 40 mg = Prava 20 mg** **Fluva 80 mg = Prava 40 mg**
Fluvastatin vs. Simvastatin			
Ose L., etal. 1995[32] **R, DB, MC** 432 patients 6 weeks (Supported by Merck)	Men and women 70 years or less with a TC ≥150 mg/dl.	Fluva 20 mg/d or Fluva 40 mg/d or Simva 5 mg/d or Simva 10 mg/d	**% LDL-c reduction:** Fluva 20 mg: 21.8% Fluva 40 mg: 25.9% Simva 5 mg: 25.7% Simva 10 mg: 29.9% (p≤0.05 vs simva 10 mg) **% meeting LDL-c goal:** Fluva 20 mg: 12% Fluva 40 mg: 21% Simva 5 mg: 24% Simva 10 mg: 25% **Fluva 40 mg = Simva 5 mg**
Ludwig Schulte K., etal. 1996[33] **R, DB** 120 patients 10 weeks (Supported by Astra)	Men and women 26-74 years with an LDL-c >185 mg/dl.	Fluva 40 mg/d or Simva 20 mg/d Doses were doubled at 4 weeks.	**% LDL-c reduction:** Fluva 40 mg: 23.8% Fluva 80 mg: 30.6% Simva 20 mg: 23.6% Simva 40 mg: 34.4% (NS)

			% meeting LDL-c goal: Not evaluated in study. **Fluva 40 mg = Simva 20 mg** **Fluva 80 mg = Simva 40 mg**
Sigurdsson G., etal. 1998[34] **R, DB, MC** 113 patients 16 weeks (One author was employed by Merck. Merck supported study and supplied lovastatin and placebo)	Men and women with CHD.	Fluva 20 mg/d or Simva 20 mg/d Doses could be doubled at week 10 if TC >200 mg/dl at week 6.	**% LDL-c reduction: (Mean dose/day)** Fluva 32 mg: 25.3% Simva 23 mg: 39.9% (p<0.001) **% meeting LDL-c goal:** Fluva: 49.1% Simva: 87.3% (p value not provided) **Equivalent doses not compared, treat to target.**
Van Dam MJ., etal. 2001[35] **R, DB, MC** 478 patients 18 weeks (One author employed by Merck. Supported by Merck)	Men and women 20-70 years with an LDL-c ≤232 mg/dl.	Fluva 20 mg/d or Simva 10 mg/d Doses could be doubled at weeks 6 and 12 if LDL-c goal not reached. Max. of Fluva 40 mg bid and Simva 40 mg/d	**% LDL-c reduction:** Fluva 20 mg: 19.7% Simva 10 mg: 31.5% (p<0.001) **% meeting LDL-c goal:** Fluva: 35.1% Simva: 60.8% **Equivalent doses not compared, treat to target.**
Lovastatin vs. Pravastatin			
McPherson R., etal. 1992[36] **R, DB, MC** 217 patients 8 weeks (Supported by Merck)	Men and women 18-75 years with an LDL-c ≥190 mg/dl without CHD or 2 other CHD risk factors, ≥160 mg/dl with 2 or more risk factors or definite CHD.	Lova 20 mg/d or Prava 10 mg/d or Prava 20 mg/d	**% LDL-c reduction:** Lova 20 mg: 28% Prava 10 mg: 24.5% Prava 20 mg: 28.4% (NS Lova 20 vs. Prava 20) **% meeting LDL-c goal:** High risk: Lova 10 mg: 29.2% Prava 10 mg: 24.5% Prava 20 mg: 25.6% Moderate risk: Lova 10 mg: 73.7% Prava 10 mg: 53.3% Prava 20 mg: 68.4% **Lova 20 mg = Prava 20 mg > or = Prava 10 mg**
The Lovastatin Pravastatin Study Group 1993[37] **R, DB, MC** 672 patients 18 weeks (Merck supported and participated in study)	Men and women 25-75 years with hypercholesterolemia.	Lova 20 mg/d or Prava 10 mg/d. Doses were doubled at 6 week intervals to a max. of 80 mg/d (40 mg bid) for Lova and 40 mg/d for Prava).	**% LDL-c reduction:** Lova 20 mg: 28% Lova 40 mg: 33% Lova 80 mg: 39% Prava 10 mg: 19% Prava 20 mg: 25% Prava 40 mg: 27% (p<0.01 in favor of lova) **% meeting LDL-c goal:** Not evaluated in study. **Equivalent doses not compared.**
Weir MR., etal. 1996[38] **R, DB, MC** 426 patients 12 weeks (Supported by Merck)	Men and women 20-65 years with hypercholesterolemia.	Lova 40 mg/d or Prava 40 mg/d	**% LDL-c reduction:** Lova 40 mg: 27.9% Prava 40 mg: 23.6% (NS) **% meeting LDL-c goal:** Lova: 45% Prava 26% **Lova 40 mg = Prava 40 mg**
Strauss WE., etal. 1999[39] **R, SB, CO** 31 patients 12 weeks (Merck and Bristol Myers Squibb provided active drug)	Men and women with hypercholesterolemia.	Lova 10 mg/d or Prava 10 mg/d 4 weeks on each treatment with 4 week washout.	**% LDL-c reduction:** Lova 10 mg: 24% Prava 10 mg: 19% (NS) **% meeting LDL-c goal:** Not evaluated in study. **Lova 10 mg = Prava 10 mg**
Lovastatin vs. Simvastatin			

Farmer JA., etal 1992[40] **R, DB, MC** 544 patients 24 weeks (3 primary authors employed by Merck)	Men and women 30-85 years with hypercholesterolemia	Lova 20 mg/d or Lova 40 mg/d or Simva 10 mg/d or Simva 20 mg/d	**% LDL-c reduction:** Lova 20 mg: 25.4% Simva 10 mg: 27.5% (NS) Lova 40 mg: 31.2% Simva 20 mg: 34.7% (p≤0.05 vs. lova) **% meeting LDL-c goal:** Lova 20 mg: 33% Lova 40 mg: 51% Simva 10 mg: 41% Simva 20 mg: 61% **Lova 20 mg = Simva 10 mg** **Lova 40 mg = or < Simva 20 mg**
Frohlich J., etal. 1993[41] **R, DB, MC** 298 patients 18 weeks (Merck acknowledged for their coordination of data and biostatistics group. Supported by Merck)	Men and women 18-70 years with TC 240-300 mg/dl (Stratum I) or >300 mg/dl (Stratum II).	Lova 20 mg/d or Simva 10 mg/d Doses doubled at weeks 6 and 12 if TC ≥200mg/dl.	**% LDL-c reduction:** Stratum I Mean dose/day: Lova 50 mg: 34.3% Simva 26.4 mg: 34.6% (NS) Stratum II Mean dose/day: Lova 71.7 mg: 37.2% Simva 36.9 mg: 37.1% (NS) **% meeting LDL-c goal:** Not evaluated in study **Lova 20 mg = Simva 10 mg** **Lova 40 mg = Simva 20 mg** **Lova 80 mg = Simva 40 mg**
Pravastatin vs. Simvastatin			
Malini PL., etal. 1991[42] **R, OL** 100 patients 6 weeks (Source and role of funding not provided)	Men and women 18=70 years with TC ≥240 mg/dl.	Prava 10 mg/d or Simva 10 mg/d	**% LDL-c reduction:** Prava 10 mg: 21.8% Simva 10 mg: 33.1% (p≤0.01 in favor of simva) **% meeting LDL-c goal:** Not evaluated in study. **Equivalent doses not compared.**
The European Study Group 1992[43] **R, DB, MC** 291 patients 6 weeks (Supported by Merck)	Men and women 18-79 years with TC ≥240 mg/dl.	Prava 10 mg/d or Simva 10 mg/d	**% LDL-c reduction:** Prava 10 mg: 22% Simva 10 mg: 32% (p≤0.01 in favor of simva) **% meeting LDL-c goal:** Not evaluated in study. **Equivalent doses not compared.**
Lintott DJ., etal. 1993[44] **R, DB, MC** 48 patients 24 weeks (Supported by Merck)	Men and women with hypercholesterolemia.	Prava 10 mg/d or Simva 10 mg/d Doses were doubled at weeks 12 and 18 if LDL-c was >130 mg/dl to a max. of 40 mg/d. At week18, all patients were switched to simva at the 18week dose.	**% LDL-c reduction:** Prava 10 mg: 17% Simva 10 mg: 29% (no p value provided) **% meeting LDL-c goal:** Not evaluated in study. **Equivalent doses not compared, titrate to target.**
Lambrecht LD., etal. 1993[45] **R, DB, MC** 210 patients 6 weeks (Industry involvement not reported)	Men and women 18-70 years with TC ≥250 mg/dl.	Prava 20 mg/d or Simva 20 mg/d	**% LDL-c reduction:** Prava 20 mg: 29% Simva 20 mg: 38% (p≤0.01 in favor of simva) **% meeting LDL-c goal:** LDL-c <160 mg/dl: Prava 64% Simva 78% LDL-c <130 mg/dl: Prava 19% Simva 46% **Equivalent doses not compared.**
Simvastatin-Pravastatin Study Group, 1993[46]	Men and women 18-71 years with an LDL-c ≥160 mg/dl.	Prava 10 mg/d or Simva 10 mg/d	**% LDL-c reduction: (Mean dose/day)**

R, DB, MC 550 patients 18 weeks (Merck participated and supported study)		Doses were doubled at weeks 6 and 12 if LDL-c >130 mg/dl up to max. of 40 mg/d each.	Prava 32 mg: 26% Simva 27 mg: 38% (p≤0.01 in favor of simva) **% meeting LDL-c goal:** Prava: 39% Simva 65% **Equivalent doses not compared, treat to target.**
Douste-Blazy P., etal. 1993[47] 273 patients 6 weeks (Supported by Merck)	Men and women 22-75 years with an LDL-c ≥160 mg/dl.	Prava 20 mg/d or Simva 10 mg/d	**% LDL-c reduction:** Prava 20 mg: 25% Simva 10 mg: 28.3% (p≤0.01 in favor of simva) **% meeting LDL-c goal:** LDL-c <160 mg/dl Prava 53% Simva 60% LDL-c <130 mg/dl Prava 16% Simva 22% **Prava 20 mg ≅ or < Simva 10 mg**
Stalenhoef AF., etal. 1993[48] **R, DB, MC** 48 patients 18 weeks (Industry involvement not reported)	Men and women with an LDL-c >180 mg/dl.	Prava 10 mg/d or Simva 10 mg/d Doses were doubled at 12 and 18 weeks to a max. of 40 mg/d	**% LDL-c reduction: (Mean dose/day)** Prava 40 mg: 33% Simva 40 mg: 43% (p<0.01 in favor of simva) **% meeting LDL-c goal:** **Equivalent doses not compared.**
Steinhagen-Thiessen E., 1994[49] **R, DB, MC** 281 patients 12 weeks (Supported by Merck)	Men and women 21-71 years with a TC 220-280 mg/dl.	Prava 10 mg/d or Simva 5 mg/d At 6 weeks, simva was increased to 10 mg/d.	**% LDL-c reduction:** Prava 10 mg: 17.7% Simva 5 mg: 23.3% Simva 10 mg: 26.8% (p≤0.01 in favor of simva) **% meeting LDL-c goal:** Prava 10 mg: 32-33% Simva 5 mg: 45% Simva 10 mg: 59% **Prava 10 mg < Simva 5 and 10 mg**
Sasaki S., etal. 1997[50] **R, OL, CO** 74 patients 16 weeks (Industry involvement not reported)	Men and women with TC ≥220 mg/dl.	Prava 10 mg/d or Simva 5 mg/d for 8 weeks, then alternate agent for 8 weeks.	**% LDL-c reduction:** Prava 10 mg: 23.1% Simva 5 mg: 31.1% (p<0.05 in favor of simva) **% meeting LDL-c goal:** Prava 10 mg: 44.4% Simva 5 mg: 63.9% **Prava 10 mg < Simva 5 mg**

Atorva=atorvastatin, CO=crossover, DB=double-blind, Fluva=fluvastatin, LDL-c=low density lipoprotein cholesterol, Lova=lovastatin, MC=multicenter, OL=open-label, PC=placebo-controlled, Prava=pravastatin, R=randomized, Simva=simvastatin
*LDL-c reduction noted when singe doses directly compared or when mean doses were provided.
** LDL-c goal achieved at study end (fixed dose or titrate to target)

Table 4 (below) shows the percent LDL-c lowering from baseline for trials of a particular statin dose (rather than mean or median statin doses). With only five exceptions, the mean percent LDL-c reduction for an individual statin varied little across studies and was consistent with the information in the package insert. The five exceptions included 2 studies involving lovastatin, 2 involving simvastatin, and the percent LDL-c lowering listed in the prescribing information for atorvastatin 80 mg:

(1) In an open-label, poor-quality study of 10 patients using lovastatin 40mg[26] the mean percent reduction in LDL-c was higher than expected (48%). This study did not use intention-to-treat statistics.
(2) In an open-label, fair-quality study[28], lovastatin 20mg qd produced a lower- than-expected reduction in LDL-c (21%). There were no obvious factors that may have led to a percent LDL-c reduction that was lower than expected. The other statins in the trial produced expected percent LDL-c lowering.
(3) (Exception 3 and 4) In one poor-to-fair-quality trial[33] comparing fluvastatin 20 and 40mg to simvastatin 20 and 40mg, fluvastatin produced reductions in LDL-c that were consistent with the package insert information,

but reductions in LDL-c with simvastatin were less than expected (23.6% with 20mg daily and 34.4% with 40mg daily). The number of patients completing the study was not stated and it was unclear whether intention-to-treat analysis was used.

(4) The manufacturer's prescribing information shows an LDL-c reduction of 60% in patients receiving atorvastatin 80mg daily. However, this reduction comes from data involving only 23 patients. The three trials that assessed the LDL-c lowering ability of atorvastatin 80mg daily included a total of 625 patients and had reductions of 53.6%-54%.

Table 4. Percent Reduction in LDL-c with Statins

Statin dose per day	Range of percent LDL-c lowering from comparative clinical trials	Mean percent LDL-c lowering from manufacturers prescribing information	Number of clinical trials**
Atorvastatin			
10mg	34.2%-38%	39%	13
20mg	42.1%-46.1%	43%	4
40mg	51%-51.3%	50%	2
80mg	53.6%-54%	60%	3
Fluvastatin			
20mg	17%-21.8%	22% β	4
40mg	22%-26%	25% β	5
80mg	29.6%-30.6% +	36%++ β	2
80mg XL*	--	35% β	0
Lovastatin			
10mg	24%	21%	1
20mg	21%-29%	27%	7
40mg	27.9%-33%	31%	5
80mg	39%-48%	42%α	2
Lovastatin ER			
10 mg*	--	23.8%	0
20 mg*	--	29.6%	0
40 mg*	--	35.8%	0
60 mg*	--	40.8%	0
Pravastatin			
10mg	18%-24.5%	22%	9
20mg	23%-29%	32%	9
40mg	25.6%-34%	34%	6
80mg*	--	37%	0
Rosuvastatin			
5 mg	40%	--	1
10 mg	43%	--	1

Simvastatin			
10mg	26%-33.1%	30%	16
20mg	23.6%-40%	38%	11
40mg	34.3%-43%	41%	5
80mg	43%-48.8%	47%	4

*Newly-approved dose or dosage form with no head-to-head clinical trial data against another statin.
**% LDL-c reduction in clinical trials included in table only if data provided for a specific dosage and not a mean dosage.
+Given as fluvastatin 80mg qd or 40mg bid (does not include XL product)
++Given as fluvastatin 40mg bid
α Given as lovastatin 40mg bid
β Median percent change
Lovastatin ER and fluvastatin XL are extended release products

From the trials summarized in Table 4, we determined the following approximate equivalent daily doses for statins with respect to their LDL-c lowering abilities: (Table 5)

Table 5. Equivalent Daily Doses of Statins.

Atorvastatin	*Fluvastatin*	*Lovastatin*	*Pravastatin*	*Rosuvastatin*	*Simvastatin*
--	40mg	20mg	20mg	--	10mg
10mg	80mg	40 or 80mg	40mg	5 mg	20mg
20mg	--	80mg	--	10 mg	40mg
40mg	--	--	--	--	80mg
80 mg	--	--	--	--	--

The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP-III) recognizes LDL-c to be the primary target for reducing the risk for coronary heart disease. However, evidence does exist to support an inverse relationship between raising HDL-c and lowering the risk for heart disease.[51, 107-109] High-density lipoprotein is considered, in the NCEP III guidelines, to be a strong independent risk factor for CHD. Although, the data are less consistent with regard to the benefit of triglyceride lowering and a reduction in coronary artery disease [107,109], ATP III also recognizes triglycerides to be an independent risk factor for CHD. Triglyceride lowering and HDL-c raising abilities of the statins (appendix 1) were taken from clinical trials (19 trials) in which approximately equivalent LDL-c lowering doses were compared.

In the majority of these nineteen trials (comparing equivalent LDL-c lowering doses) there was no significant difference in the ability of a particular statin to reduce triglycerides or elevate HDL-c. However in several studies, in which the equivalent LDL-c lowering doses of atorvastatin and simvastatin were compared, atorvastatin had a greater ability to reduce triglycerides vs. simvastatin and simvastatin elevated HDL-c significantly more than atorvastatin.

B. Is there a difference in the ability of a statin to achieve National Cholesterol Education Program goals?

The ability of an agent to achieve NCEP goals is another factor in choosing between statins. Twenty-seven of the 42 included trials reported the percentage of patients meeting their National Cholesterol Education Program (NCEP) LDL-c treatment goals. These 27 trials are summarized in Table 6. Most reported the overall percentage of patients reaching their goals. When this information was not provided, we recorded the percentages of patients meeting the low (LDL-c <160mg/dl), moderate (<130mg/dl), or high-risk (<100 or the European Atherosclerosis Society goal of <115mg/dl) goals. The VA/DoD guideline, for the management of hyperlipidemia, recommends an LDL-c goal of 120 mg/dl for high-risk individuals (e.g. established coronary heart disease, diabetics).

Problems in dosing limit the validity of many of these trials. In a majority of the studies, the doses compared were not equivalent (see Table 6). Frequently, less potent starting doses of several statins (lovastatin, pravastatin, and simvastatin) were compared to more potent doses of atorvastatin. When some of these studies were planned, the approximate equivalent doses for a particular statin may not have been known, or the maximum recommended dose

may have been lower. For example, in one open-label study (Target-Tangible)[16], atorvastatin 10 to 40mg showed better NCEP goal-reaching than simvastatin 10 to 40mg with similar adverse effect rates, but simvastatin 80mg was not included as a treatment option. Pravastatin 80mg daily and simvastatin 80mg daily were not approved or widely used until recently.

In 10 studies in Table 6, the inferior drug appears not to have been titrated to its maximum daily dosage. Seven of the 10 studies that had this flaw were reported to be double-blinded; in these, it is unclear why clinicians did not titrate the dosage as aggressively as in the compared groups.

Table 6. Trials Reporting Percent LDL-c Goals Achieved

Statins Directly Compared	# of studies reviewed/# of studies reporting % meeting LDL-c goal*	Daily Statin Dose Used in Clinical Trial	% of Patients Meeting NCEP goal (all risk groups)Φ	Comments
Atrovastatin vs. Fluvastatin	0/0	--		
Atorvastatin vs. Lovastatin (Davidson, 1997)	1/1	Atorva 10-20 mg Lova 10-20 mg	78% 63%Δ	**Nonequivalent doses compared. Trial conclusion: Atorva 10 or 20 mg>lova 10 or 20 mg.**
Atorvastatin vs. Pravastatin (Bertolini, 1996; Assman1999)	2/2	Atorva 10-20 mg Prava 20-40 mg (titrate to goal)	72% 26%Δ	**Nonequivalent doses compared**. **Trial conclusion: Atorva better than prava.** 24% of atorva vs. 64% of prava users took the higher dose.
		Titrate to maximum dose: Atorva 10-80 mg Prava 20-40 mg	51% 20%Δ	**Nonequivalent doses compared**. **Trial conclusion: Atorva better than prava.** (35% of atorva were on doses 20-80 mg vs. 88 % of prava received 40 mg qd)
Atorvastatin vs. Rosuvastatin Davidson, 2002	1/1	Atorva 10 mg Rosuva 5 mg Rosuva 10 mg Placebo	72% 84% 82% 12%	**Trial conclusion: Atorva < Rosuva 5 and 10 mg.**
Atorvastatin vs. Simvastatin (Dart, 1997; Simons, 1998; Marz, 1999; Van Dam, 2000; Recto, 2000; Insull, 2001; Karalis, 2002)	11/7	Atorva 10-20 mg Simva 10-20 mg (titrate to goal)	46% 27%	**Nonequivalent doses compared**. **Statistical significance not given** 48% of atorva vs. 62% of simva users doubled their dose to 20 mg daily.
		Atorva 10-80 mg Simva 10-40 mg (titrate to goal)	19% 6%Δ	**Nonequivalent doses compared. Trial conclusion: Atorva 80 mg > Simva 40 mg + resin.** 78% atorva were on 80 mg/d and 95% of simva were on 40 mg/d with 84% of those receiving cholestyramine 4 g/d.
		Atorva 10-40 mg Simva 10-40 mg (titrate to goal)	67% 53%Δ	**Nonequivalent doses compared**. **Trial conclusion: Atrova is better than simva on a mg/mg basis.** When atorva 20 mg and simva 40 mg were compared, cumulative response was the same.
		Atorva 20 or 40 mg Simva 20 or 40 mg	28% 13%Δ	**Nonequivalent doses compared**. **Trial conclusion: Atorva 20>simva 20, atorva 40>simva40.** All were on simva 20 or 40 mg qd. Randomized to simva or atorva 20 or simva or atorva 40 mg qd..
		Atorva 10 or 20 mg Simva 20 or 40 mg	70% 70%	**Equivalent doses compared**. **Trial conclusion: Atorva 10=simva20 and atorva 20=simva 40**
		Atorva 10 mg Simva 10 mg	55.6% 38.4%Δ	**Nonequivalent doses compared. Trial conclusion: Atorva 10 mg >simva 10 mg.** Recommended starting doses are Atorva 10 mg and Simva 20 mg qd.

		Atorva 10 or 80 mg Simva 20 or 80 mg	59 (10 mg)Δ or 89 (80 mg)% 53 (20 mg) or 82 (80 mg)%	**Equivalent doses compared**. **Trial conclusion: Atorva 10>simva 20, atorva 80=simva 80.** A higher number of atorva users (8% vs. 5%) withdrew due to adverse events. Not intention to treat.
Atrovastatin vs. Fluvastatin vs. Lovastatin vs. Simvastatin (Brown, 1998; Hunninghake, 1998)	2/2	Titrate to maximum dose. (Median doses): Atrova 20 mg qd Fluva 40 mg qd (max=40 mg)+colestipol 20 g Lova 80 mg qd Simva 40 mg qd	83% 50%Δ 81% 75%	**Median doses are equivalent and within the approved dose range**. **Trial conclusion: Atorva>fluva but equal to lova and simva.**
		Titrate to maximum dose. (Median doses): Atorva 10 mg qd Fluva 40 mg qd (max=40 mg) Lova 40 mg qd Simva 20 mg qd	95% 60%Δ 77%Δ 83%Δ	**Median doses were equivalent for atorva and simva, but not lova, and within the dose range. Trial conclusion: Atorva>fluva, lova and simva**.
Atorvastatin vs. Fluvastatin vs. Lovastatin vs. Pravastatin vs. Simvastatin (Andrews, 2001)	2/1	Titrate to maximum dose. (Mean dose): Atorva 24 mg Fluva 62 mg (max=80 mg) Lova 52 mg Prava 31 mg Simva 23 mg	76% 37% 49% 34% 58%	**Nonequivalent doses compared**. Patients in all groups were not titrated to their maximum doses despite % LDL goal less than 100%. Significance reported only for those patients continuing to meet LDL-c goal from 6-54 weeks and not at study completion.
Atorvastatin vs. Lovastatin vs. Pravastatin vs. Simvastatin	1/0	N/A	N/A	N/A
Atorvastatin vs. Pravastatin vs. Simvastatin	1/0	N/A	N/A	N/A
Fluvastatin vs. Lovastatin (Nash, 1996)	1/1	Fluva 40 mg Lova 20 mg	90% 90%	Equivalent doses compared. Trial conclusion: Fluva 40 mg=lova 20 mg

Fluvastatin vs. Pravastatin	1/0	N/A	N/A	N/A
Fluvastatin vs. Simvastatin (Ose, 1995; Sigurdsson, 1998; Van Dam, 2001)	4/3	Fluva 20 or 40 mg Simva 5 or 10 mg	12% (20 mg)Δ or 21% (40 mg) 24% (5 mg) or 25% (10 mg)	**Equivalent doses compared**. **Trial conclusion: Simva 5 or 10 mg=fluva 40 mg>fluva 20 mg**
		Fluva 20 –40 mg Simva 20-40 mg (titrate to goal)	49.1%Δ 87.3%	**Nonequivalent doses compared**. **Trial conclusion: Simva titrate to target >fluva.** Results reported for mean doses of fluva 32 mg qd vs. simva 23 mg qd. Could more patients in fluva group increase their dose?
		Titrate to maximum dose: Fluva 20-80 mg Simva 10-40 mg	35.1%Δ 60.8%	**Nonequivalent doses compared. Trial conclusion: Simva>fluva.** No mean or median dose given. 87.1% vs. 64.1% of patients required dose titration.
Lovastatin vs. Pravastatin (McPherson, 1992)	4/1	Lova 20 mg Prava 10 mg Prava 20 mg	29.2% (CHD) 73.7%(no CHD). 24.5% (CHD) and 53.3% (no CHD) 25.6% (CHD) and 68.4% (no CHD)	**Equivalent doses compared. Trial conclusion: Prava 10 or 20 mg=lova 20 mg.** No statistical difference for any group.
Lovastatin vs. Simvastatin (Farner, 1992; Frohlich, 1993)	2/2	Lova 20 or 40 mg Simva 10 or 20 mg	33% (20 mg) or 51% (40 mg) 41% (10 mg) or 61% (20 mg)	**Equivalent doses compared.** No statistical significance given.
		Lova 20-40 mg Simva 10-20 mg (titrate to goal)	72%, 31% 69%, 29%	**Equivalent doses compared. Trial conclusion: Lova 20 mg=simva 10 mg, lova 40 mg=simva 20 mg.** Mean doses not provided. First number represents patients starting with lower LDL-c than 2nd number. No difference noted.
Pravastatin vs. Simvastatin (Douste-Blazy, 1993; Lambrecht, 1993; Stalenhoef , 1993; Simva-Prava Study Group, 1993; Steinhagen-Thiessen, 1994; Sasaki 1997)	9/6	Prava 20 mg Simva 10 mg	16%, 53% 22%, 60%	**Equivalent doses compared. Trial conclusion: Prava 20 mg=simva 10 mg.** First number represents % achieving LDL-c <130, 2nd number <160 mg/dl No difference noted.
		Prava 20 mg Simva 20 mg	19%Δ , 64%Δ, 46%, 78%	**Nonequivalent doses compared**. **Trial conclusion: Simva 20 mg>prava 20 mg.** First number represents % achieving LDL-c <130 and 2nd number <160 mg/dl.
		Prava 10-40 mg Simva 10-40 mg	4.3% 26%	**Nonequivalent doses compared.** All but 3 of simva and 1 of prava were receiving 40 mg of their assigned statin at study completion. Only 46 patients studied. No statistical significance given.

		Titrate to maximum dose: Prava 10-40 mg Simva 10-40 mg	39%Δ, 68%Δ 65%, 84%	**Nonequivalent doses compared. Trial conclusion: Simva>prava.** First number represents % achieving LDL-c <130 and 2nd number <160 mg/dl. 66% of prava vs. 48% of simva users received the maximum dose of 40 mg qd. Could more prava patients have increased their dose?
		Prava 10 mg Simva 5-10 mg qd	59% 33%Δ	**Nonequivalent doses compared. Trial conclusion: Simva 10 mg>prava 10 mg.** Results provide for 10 mg qd of prava and simva..
		Prava 10 mg Simva 5 mg	44.4%Δ 63.9%	**Equivalent doses compared. Trial conclusion: Simva 5 mg>prava 10 mg.**

*National Cholesterol Education Panel or European Atherosclerosis Society goals [LDL<100 or 115 mg/dl (high risk), LDL<130 mg/dl (moderate risk) or LDL<160 mg/dl (low risk)]
ΦRepresents overall percentage meeting LDL-c goal if provided in trial.
+Maximum approved daily dose at the time the majority of trials were planned were atorvastatin 80 mg, fluvastatin 40-80 mg, lovastatin 80 mg, pravastatin 40 mg and simvastatin 40 mg.
Recommended starting doses are atorvastatin 10 mg qd, fluvastatin 20-40 mg qd, lovastatin 20 mg qd, pravastatin 10-40 mg qd, simvastatin 20 mg qd.
ΔStatistically significant difference (p<0.05)

Summary

There is fair-to-good-quality evidence that, when statins are provided in doses that are approximately equivalent, a similar percent reduction in LDL-c and percent of patients meeting NCEP LDL-c goals can be achieved. For patients who require LDL-c reductions of up to 40% to meet their NCEP goal, any of the statins are effective. There is also fair-to-good-quality evidence that, in patients requiring an LDL-c reduction of 40% or greater to meet their NCEP goal, only atorvastatin 20mg or more, lovastatin 80mg, and simvastatin 40mg or more daily are likely to meet the goal. There is fair[21,23] to poor[26] evidence that in patients requiring greater than a 50% reduction in LDL-c, only atorvastatin 80mg daily has demonstrated the ability to achieve that goal but with a higher risk for some adverse effects (gastrointestinal disturbances and transaminase elevation-see adverse events section). With regard to lowering triglycerides or elevating HDL-c (Appendix 1), there does not appear to be major differences between agents. However in several studies (n=200 to 1,732), atorvastatin was more effective at lowering triglycerides than simvastatin. On the other hand, simvastatin was more effective than atorvastatin at raising HDL-c in these studies.

2. How do statins compare in their ability to reduce the risk of nonfatal myocardial infarction, CHD (angina), CHD mortality, all-cause mortality, stroke or need for revascularization (coronary artery bypass graft, angioplasty or stenting)?

There are no controlled trials comparing the ability of two or more statins to reduce the risk of coronary events, stroke, or death. On the other hand, there are many trials comparing a statin to placebo or, in a few instances, to nonpharmacologic treatments. These trials were reviewed primarily to compare the amount of information on cardiovascular outcomes available for each statin.

Controlled Clinical Trials

We identified 32 randomized trials reporting cardiovascular outcomes in patients receiving a statin compared to an active or placebo control or usual care.

We examined the included trials in three tiers.

- The first tier included six (two primary prevention[51, 52] and four secondary prevention[53-55, 105]) placebo-controlled trials. The primary endpoint in these trials was a reduction in cardiovascular health outcomes. Enrollment was in excess of 4,000 patients with an average follow-up period of 5 years. All of the trials were good quality and were considered the best evidence for demonstrating a reduction in cardiovascular health outcomes with statins.

- The second tier consisted of 12[59-70] placebo-controlled trials in which the primary endpoint was progression of atherosclerosis measured by angiography or B-mode ultrasonography. In these trials, CHD events or cardiovascular morbidity and mortality was reported either as a secondary endpoint or incidentally (that is, even though it was not a predefined endpoint). In general, these studies had insufficient power to assess CHD events. Only two[60,63] of these trials enrolled more than 500 patients. The others ranged from 151 to 460 included patients. As evidence regarding reduction in health outcomes, these trials were fair or fair-to-poor in quality.
- The third tier contained seven trials[71-76,105] of using statins to prevent restenosis after coronary revascularization (CABG or PTCA). Seven other studies,[16, 78-82,104] reporting health outcomes, did not fit into the first two tiers so were included in this tier as "miscellaneous" trials.

First Tier. The six studies are summarized briefly in appendix 2. (AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study, WOSCOPS=West of Scottland Coronary Prevention Study, CARE=Cholesterol and Recurrent Events Trial, LIPD=Long-Term Intervention with Pravastatin in Ischemic Disease Study, 4S=Scandinavian Simvastastin Survival Study, HPS=Heart Protection Study)

In the first tier, all six studies were large, good-quality, multicenter trials. Two of the studies recruited patients without a history of coronary heart disease (primary prevention) and a broad range of cholesterol levels or hypercholesterolemia. One of the studies evaluated lovastatin (AFCAPS/TexCAPS)[51] and the other pravastatin (WOSCOPS)[52] with enrollment of over 6,500 patients each. In both studies, there was a reduction in risk for major coronary events (fatal or nonfatal MI, CHD, CHD death, need for revascularization).

In AFCAPS/TexCAPs, lovastatin reduced the incidence of new cardiovascular events by 37%, or 1 for every 49 subjects (men and women) treated. In WOSCOPS, pravastatin 40mg reduced coronary events by 31%, or 1 for every 44 patients (men only) treated. WOSCOPS used a stricter definition of coronary events than AFCAPS, so the relative risk reductions and numbers-needed-to-treat (NNTs) are not directly comparable.

WOSCOPS, but not AFCAPS/TexCAPS, proved that statin therapy can reduce coronary disease deaths. In AFCAPS/TexCAP, the absolute risks of fatal coronary disease events were 3.3 per 1,000 subjects in the lovastatin group and 4.5 per 1,000 in the placebo group (not significant). There was no difference in all-cause mortality. In WOSCOPS, pravastatin reduced coronary disease deaths by 33% (95% CI, 1% to 55%) and reduced all-cause mortality by 22% (95% CI 0% to 40%) a result that nearly reached statistical significance (p value .051). In AFCAPS/TexCAPS, the absolute risks of coronary disease death were 1.3% subjects in the lovastatin group and 1.9% in the placebo group (NNT=163). The different mortality results should not be taken as evidence that pravastatin and lovastatin would differ if used in subjects at similar risk. Compared with AFCAPS/TexCAPs, WOSCOPS recruited subjects who had about 4 times as high a risk of dying from coronary disease.

The remaining 4 studies in appendix 1 consist of patients with documented CHD. Two of those studies (CARE[53] and LIPID[54]) evaluated the reduction in clinical outcomes with pravastatin (n=13,173) and the other two (4S[55] and HPS[105]) simvastatin (n=24,980) compared to placebo. In all 4 of these studies, pravastatin or simvastatin significantly reduced the incidence of major coronary events, including overall mortality in LIPID, 4S and HPS. The risk of stroke was also reduced in CARE, 4S and HPS.

The Heart Protection Study (HPS) is the most recent of these mega trials to be published[56-58, 105]. More than 20,000 men and women between the ages 40-80 years who were considered to be at high risk for coronary heart disease were enrolled. This study is unique in that it targeted individuals in whom the risk and benefits of cholesterol lowering had been uncertain (women, those over 70 years, diabetics, those with non-coronary vascular disease and those with average or below average cholesterol). Patients were randomized to simvastatin 40 mg qpm or placebo for an average of 5 years. The benefit or risk of antioxidant vitamins was also assessed in this trial. Over the 5-year period, there were significant reductions in overall mortality, death from CHD, nonfatal myocardial infarction, coronary revascularization, stroke and major vascular events. These reductions were observed in women, individuals over and under 70 years, TC <200 mg/dl (5 mmol/L) and LDL-c <120 mg/dl (3 mmol/L). There was no risk or benefit of the antioxidant vitamins. Of further interest, in HPS, risk of major cardiovascular events was reduced similarly regardless of baseline LDL-c. The subgroup of patients whose mean baseline LDL-c was less than 100 mg/dl (2.6 mmol/L), and mean treatment LDL-c was 65 mg/dl (1.7 mmol/L) versus those on placebo (mean LDL-c

97 mg/dl), experienced a risk reduction nearly as great as those with higher baseline LDL-c. However, when evaluating the effect of the degree of LDL-c lowering, the reduction in cardiovascular events was similar regardless of degree of prerandomization LDL-c response (e.g. those with an LDL-c reduction of <38% on simvastatin experienced a similar risk reduction as those achieving a ≥48% response).

Second Tier. The 12 trials are summarized in appendix 3.

The second tier includes studies of the effects of statins on progression of atherosclerosis that also reported rates of coronary or cardiovascular events. In these studies, the primary endpoint was progression of atherosclerosis and all of the patients had known CHD. To answer the question of whether treatment with a statin is associated with a reduction in clinical cardiovascular outcomes in patients with CHD, these studies are considered fair or fair to poor in quality to answer this question. Six of the 12 trials spontaneously reported clinical outcomes, and sample sizes were relatively small.

Table 7 briefly summarizes the results of these studies. The number of trials and patients studied for each statin are as follows: fluvastatin (1 n=429), lovastatin (3, n=1,520), pravastatin (5, n=2,220), and simvastatin (3, n=1,118). The information about fluvastatin was inconclusive and the other 3 are already known to be effective from better, Tier-1 studies.

In general, those trials in which CHD events were not an endpoint did not find a difference between groups. However, there was a trend towards a reduction in clinical events in favor of the statin. In the trials in which CHD events were a secondary endpoint, there was usually a reduction in one of the clinical events. While consistent, the results of these studies are difficult to interpret because of possible publication bias.

Table 7. Studies of Atherosclerotic Progression Reporting CHD Outcomes.

Author or Study Aronym/Statin	Pre-specified Clinical Event or Spontaneous Report*	Significant Reduction in Clinical Event or Trend Towards Statin
LCAS/Fluvastatin[59]	Spontaneous report	Trend
ACAPS/Lovastatin[60]	Secondary endpoint	Reduction in major cardiovascular events
CCAIT/Lovastatin[61]	Spontaneous report	Trend
MARS/Lovastatin[62]	Spontaneous report	Trend
REGRESS/Pravastatin[63]	Pre-specified	Reduction in PTCA
PLAC-I/Pravastatin[64]	Pre-specified	Reduction in MI
PLAC-II/Pravastatin[65]	Pre-specified	Reduction in combined: nonfatal MI and death
KAPS/Pravastatin[66]	Spontaneous report	Trend
Sato, etal/Pravastatin[67]	Pre-specified	Reduction in overall death
MAAS/Simvastatin[68]	Spontaneous report	Trend
CIS/Simvastatin[69]	Spontaneous report	Trend
SCAT/Simvastatin[70]	Pre-specified	Reduction in revascularization

* "Spontaneous report" means that the outcome was not a pre-specified endpoint for the study but was reported anyway.

Third Tier. The 14 trials are summarized in appendix 4.

The third tier (Table 8) includes 7 placebo-controlled trials in revascularized patients (CABG or PTCA). The primary endpoint in 5 of the trials was the rate of restenosis. A reduction in clinical outcomes was the primary outcome in the 6th (subgroup analysis of CARE) and 7th studies. Most of the studies were fair or fair-poor in quality for the question of whether treatment with a statin is associated with a reduction in clinical cardiovascular outcomes in patients with CHD. Sample sizes were relatively small in the majority of the studies and were not powered to determine differences in these types of events.

The number of studies and patients per statin are as follows: fluvastatin (2, n=2086), lovastatin (3, n=1,981), pravastatin (2, n=2,940, data on 2,245 patients already included in CARE results in appendix 1). In these trials, pravastatin and fluvastatin had statistically significant effects on prespecified coronary disease outcomes.

Table 8. Post-Revascularization Trials

Study/ drug, patients	**Clinical Endpoint**	**Clinical Events**
FLARE/ fluvastatin 40 mg twice daily vs. placebo to reduce restenosis after successful single-lesion PTCA[71]	Pre-specified composite clinical endpoint of death, myocardial infarction, coronary artery bypass graft surgery or re-intervention.	No effect on restenosis or on the preplanned composite clinical end-point at 40 weeks (22.4% vs 23.3%; logrank P=0.74). Incidence of total death and myocardial infarction was lower in the fluvastatin group (1.4%) vs. 4.0%; log rank P=0.025).
LIPs/fluvastatin 40 mg bid vs. placebo in patients after percutaneous coronary intervention (PCI)[110]	Primary endpoint composite of major adverse cardiac events (cardiac death, nonfatal MI, reintervention procedure). Secondary endpoint were major coronary events excluding revascularizations occurring within 6 months of the PCI	Significant reduction in primary outcome of composite major coronary events in fluvastatin vs. placebo (21.4% vs. 26.7%, RR 0.78, 95% CI 0.64-0.95, p=0.01). Time to first event was significantly longer in the fluvastatin vs. placebo group p=0.01
Weintraub WS., et al/ lovastatin 40 mg twice daily vs. placebo to reduce restenosis after PTCA.[72]	Spontaneous report	No effect on restenosis. NS trend to more MIs in the lovastatin group; no difference in fatal or nonfatal events at six months
PCABG/ lovastatin 40 mg qd (aggressive) vs. lovastatin 2.5 mg qd titrated to target; before and after CABG[73]	Pre-specified composite clinical endpoint of death from cardiovascular disease or unknown causes, nonfatal MI, stroke, CABG, or angioplasty	No difference in composite outcome (12.6% vs. 15.3%, p=0.12). No differences in individual components except a lower rate of repeat PTCA or CABG (6.5% vs. 9.2%, P=.03) which was NS by study criteria for multiple comparisons.
CLAPT/ Lovastatin plus diet vs. lovastatin, before and after PTCA.[74]	Pre-specified secondary endpoint: MI, re-PTCA, PTCA of another lesion or death.	No effect on restenosis; The only significant reduction in clinical outcomes was a reduction in 2nd or 3rd re-PTCA favoring lovastatin (p=0.02).
PREDICT/ Pravastatin 40 mg vs. placebo after PTCA.[75]	Secondary endpoint of death, myocardial infarction, target vessel revascularization	No effect on restenosis or on clinical endpoints.
CARE/ subgroup analysis of CARE Pravastatin vs. placebo in patients with CABG and/or PTCA[76]	Primary endpoint coronary heart disease death or nonfatal MI	Reduction in primary endpoint (RRR 36%, CI 17 to 51, p = 0.001)

Miscellaneous Studies (included in the third tier trials). The 7 trials are summarized in appendix 4.

Seven trials that reported clinical outcomes did not fit the criteria for the 3 tiers (Table 9). The number of studies and patients in these studies were: atorvastatin (4, n=7883), fluvastatin (1, n=365), pravastatin (2, n=1,162), and simvastatin (1, n=2856). The only study reporting health outcomes and comparing 2 statins directly (atorvastatin and simvastatin) is the Target Tangible[16] study. In Target Tangible, patients with coronary heart disease (n=2,856), including some who had been revascularized, were randomized to an initial dose of 10 mg of either atorvastatin or simvastatin, after which the dosage was increased to achieve an LDL<100 mg/dl. The study was "open-label" however, serious adverse events were classified by a safety committee that was blinded to allocation. The primary endpoint was safety, including noncardiac and cardiac events after 14 weeks of treatment. It was not designed to determine whether simvastatin and atorvastatin differed in their effects on coronary disease events but reported them as part of their safety analysis. Total adverse effect rates, serious adverse effect rates (Atorva-2%, Simva-3%, NS), and withdrawal rates were similar for atorvastatin and simvastatin. The article states (p10) that "Serious cardiovascular events (including angina pectoris, myocardial infarction, and cerebral ischemia) were more frequent in the simvastatin group (19 patients, 2%) than in the atorvastatin group (21 patients, 1.0%) if the 1=sided t test was applied (p<0.05, Table III)." However, Table III of the article (p10) does not support this statement. The Table shows that the number of these serious cardiovascular events was 11 in the atorvastatin group and 7 in the simvastatin group; this comes to 0.0058 for atorvastatin and 0.0073 for simvastatin, which is not statistically significant. If deaths are included the probabilities of serious cardiovascular events are 0.0069 for atorvastatin and 0.013 for simvastatin, not 1% and 2% as stated in the article. Because of the short duration of the study, the investigators did not interpret any of the cardiovascular events to be related to therapy. The study was rated fair-to-poor quality because of the lack of blinding and the lack of clarity of the statistical analysis.

Table 9. Miscellaneous Trials Reporting Clinical Outcomes.

Study/ drug, patients	Clinical Endpoint	Clinical Events
AVERT/ Atorvastatin vs. PTCA in stable, low-risk CAD patients[78]	Primary endpoint included cardiac events and revascularization procedures.	No difference.
MIRACL/ Atorvastatin vs. placebo in patients with acute coronary syndromes (non-Q-wave acute MI or unstable angina)[79]	Primary endpoint included death, nonfatal MI, cardiac arrest with resuscitation or recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization.	There was no difference in death, nonfatal MI, or cardiac arrest. There was a benefit of atorvastatin in significantly reducing symptomatic ischemia requiring emergency rehospitalization (p=0.02, 95% CI 0.57-0.95, ARR=2.2/100, NNT=45)
Target Tangible/ Atorvastatin vs. simvastatin safety trial[16]	Clinical endpoints reported in safety analysis.	See text (above.)
GREACE/ Atorvastatin 80 mg daily managed in a University based clinic vs. usual care managed by community based physicians in patients with established heart disease.	Primary endpoints were death, nonfatal MI, unstable angina, congestive heart failure, revascularization and stroke.	In the atorvastatin group, there was a significant reduction in total and coronary mortality, nonfatal MI, unstable angina, revascularizations, congestive heart failure and stroke (p<0.05 for all events) (see appendix 3 for ARR, NNT)
Riegger G., etal Fluvastatin 40 mg vs. placebo in patients with symptomatic CAD.[80]	Primary endpoint included cardiac death, nonfatal myocardial infarction, unstable angina pectoris.	3 events in the fluvastatin group vs. 10 in the placebo group (p<0.05, ARR=4/100 persons, NNT=25).
Pravastatin Multinational Study Group/ Pravastatin 20 mg (dose could be increased) vs. placebo, subjects at high-risk for CAD.[81]	Reported in safety analysis after 6 months of treatment.	13 serious cardiovascular events were reported in the placebo group vs. 1 for pravastatin (p<0.001, ARR 2.2/100 persons, NNT=44).
Hartog F., etal./ Pravastatin vs. placebo in patients with acute coronary syndromes (acute MI or unstable angina)[82]	Primary endpoint was safety of pravastatin. Secondary endpoint was to assess lipid profiles and coronary events.	No difference in death or MI.

Summary

No good-quality studies directly compared the ability of different statins to reduce coronary disease events. Twenty-nine out of thirty-two studies reporting clinical events compared a statin to placebo. In another (Target-Tangible), atorvastatin was compared to simvastatin with a primary endpoint of overall safety; in the second, aggressive vs. moderate LDL-c lowering with lovastatin was compared; in the last, atorvastatin managed in a University clinic was compared to usual care (which could include lipid-lowering therapies) managed by community physicians.

The amount of information on cardiovascular outcomes available for each statin differs substantially. The first tier studies provide consistent good-quality evidence that lovastatin, pravastatin and simvastatin reduce cardiovascular events. For pravastatin and lovastatin there is fair-good and good-quality evidence for both primary and secondary prevention. For pravastatin and simvastatin there is good-quality evidence for secondary prevention. The latter two statins reduced deaths from cardiovascular and cerebrovascular disease as well.

The angiographic studies (Tier 2) provide little additional information, because: (1) there were no statistically significant findings for statins other than lovastatin, pravastatin and simvastatin (2) the studies had inadequate power to assess clinical outcomes and (3) there is a high probability of publication bias. The post-revascularization studies (Tier 3) provide fair or fair-good quality evidence for fluvastatin and additional support for pravastatin in reducing coronary events. The miscellaneous studies (Tier 3) provide fair or fair-poor evidence about atorvastatin for secondary prevention and in acute coronary syndromes. Also fair evidence for fluvastatin and additional evidence for pravastatin in reducing coronary heart disease events was presented.

Special Populations and Statin-Drug Interactions

To assess whether a particular statin is safer in a special population, a review of potential drug interactions is necessary. We identified seven non-systematic reviews pertaining to statin drug interactions.[83-89]

Briefly, simvastatin, lovastatin, and atorvastatin are all metabolized in the liver via the cytochrome P450 3A4 (CYP 3A4) isoenzyme system. As a result, all three agents are susceptible to drug interactions when administered concomitantly with agents known to inhibit metabolism via CYP 3A4 (Table 10). The use of the agents listed in Table 10 increase statin concentrations and, theoretically, the possibility for adverse effects. Table 10 does not

include all drugs capable of inhibiting metabolism via the CYP 3A4 isoenzyme system. Thus, caution should be exercised when using these or other such drugs in combination with simvastatin, lovastatin, or atorvastatin. When doing so it is generally prudent to start the statin at a low dose and titrate upward, as needed to reach LDL-c goal, while observing for any adverse or untoward effect (e.g. myopathy or myalgias). Fluvastatin is primarily metabolized via CYP 2C9 and is vulnerable to interactions with drugs known to inhibit CYP 2C9 metabolism (Table 11). Pravastatin is not significantly metabolized via the CYP isoenzyme system and is therefore not affected by drugs inhibiting metabolism via these pathways.

Table 10. Potent Inhibitors of CYP 3A4

Clarithromycin*
Erythromycin*
Cyclosporine*
Protease inhibitors (indinivir, nelfinavir, ritonavir, saquinavir, amprenavir, lopinavir/ritonavir)
Delavirdine
Itraconazole*
Fluconazole
Ketoconazole
Nefazodone*
Verapamil
Grapefruit juice

*Published reports of rhabdomyolysis exist in patients receiving concomitant statin.
Table 10 does not include all drugs capable of inhibiting metabolism via the CYP 3A4 isoenzyme system.

Table 11. Drugs Known to Inhibit Metabolism Via CYP 2C9

Amiodarone	Fluvoxamine
Azole Antifungals	Metronidazole
Omeprazole	Cimetidine
TMP/SMX	
Zafirlukast	

Recently, the FDA approved labeling changes that were recommended by the manufacturer of simvastatin. These changes were sought in response to data from a large ongoing trial in patients randomized to simvastatin 20 mg or 80 mg daily. Upon examination of the data, a higher than expected incidence of myopathy (n=6 out of 100) was observed in patients receiving simvastatin 80 mg daily in combination with amiodarone. No cases were seen in those taking amiodarone with simvastatin 20 mg daily. No case of rhabdomyolysis was seen in any of these patients. Although the exact mechanism of this interaction is not known (e.g. not known if CYP 3A4 mediated), daily doses of simvastatin should be limited to 20 mg in patients receiving amiodarone. Data are lacking to address the safety of the combination of atorvastatin, fluvastatin, lovastatin, moderate doses of simvastatin (e.g. 40 mg qd) or pravastatin with amiodarone.

It is not clear what course of action is best in patients requiring long-term therapy with amiodarone in combination with simvastatin, without adverse effects. While the manufacturer recommends limiting doses of simvastatin to 20 mg daily, the benefit of lipid control may exceed the risk of adverse events. In new patients who require amiodarone, doses of simvastatin should be limited to 20 mg daily.

Furthermore, in patients receiving any dose of verapamil in combination with simvastatin, the daily dose of simvastatin should be limited to 20 mg. This change in dosing was recommended when clinical trial data (n=approx. 25,000) involving simvastatin, were reviewed by the manufacturer. They observed a higher than expected number of patients receiving verapamil and simvastatin who developed myopathy (4/635 or 0.63%) compared to those on simvastatin without verapamil (13/21,224 or 0.061%). None of these patients developed rhabdomyolysis. The exact mechanism for the interaction is not entirely known, but can be partially explained by verapamil's ability to inhibit cytochrome P450 3A4.

It is not clear what course of action is best in patients on long-term therapy with amiodarone and/or verapamil in combination with simvastatin, without adverse effects. While the manufacturer recommends limiting doses of simvastatin to 20 mg daily, the benefit of lipid control may exceed the risk of adverse events. If amiodarone or

verapamil can safely be discontinued or changed to another agent without interactions to the statins, this is preferable. In new patients who require amiodarone and/or verapamil, doses of simvastatin should be limited to 20 mg daily. If the interaction between verapamil and simvastatin is partially explained by inhibition of statin metabolism, caution should also be exercised if considering atorvastatin or lovastatin because their metabolism is similar to simvastatin. Never the less, in patients who require statin therapy, it is prudent to avoid concomitant use of verapamil or limit the statin dose. Furthermore, since fluvastatin and pravastatin are not metabolized via CYP 3A4, they may be offer a safer alternative in patients receiving verapamil and requiring more than simvastatin 20 mg daily to meet their cholesterol goals.

Safety in Organ Transplant Recipients. The primary concern of statin therapy in organ transplant patients is the potential for a statin-drug interaction (e.g. cyclosporine). The risk for toxicity with statins in combination with cyclosporine is dose-related. Long-term, single-drug treatment of hyperlipidemia with lovastatin or simvastatin at doses not exceeding 20 mg and 10 mg daily, respectively, has been shown to be safe in transplant patients receiving cyclosporine. Fluvastatin and pravastatin at 40 mg daily have also been shown to be safe in cyclosporine managed transplant recipients. [90]

Only one case of rhabdomyolysis was identified from a heart transplant registry which included 210 patients managed with a variety of statins for 1 year.[91] The patient with rhabdomyolysis was receiving simvastatin 20 mg daily. No cases of rhabdomyolysis were seen in 39 patients receiving simvastatin 10 mg daily. A review of studies involving fluvastatin (up to 80 mg daily) in organ transplant patients receiving cyclosporine, identified no cases of rhabdomyolysis.[92] One small study[93] involving atorvastatin (10mg/day) in 10 renal-transplant recipients taking cyclosporine observed a significant benefit with regard to lipid levels and no cases of myopathy or rhabdomyolysis.

In summary, based upon pharmacologic information, case reports and small series of patients, when used in the lowest doses, the safety profile for statins in transplant patients is similar to that of the general population. Pravastatin and fluvastatin have the least potential for significant interaction with cyclosporine. Theoretically, if a known inhibitor of CYP 3A4 is given to a transplant patient receiving cyclosporine and a statin metabolized by CYP 3A4 (atorvastatin, lovastatin, simvastatin) the risk for rhabdomyolysis may be increased significantly. Reduced renal function can accentuate the toxicity from atorvastatin, lovastatin and simvastatin. If patients in this population are unable to achieve the desired LDL-c goals on fluvastatin or pravastatin, consideration can be given to the other statins. However, very close monitoring and patient education regarding the recognition of adverse effects is required.

Safety in HIV-Infected Patients. A significant proportion of HIV infected patients receiving protease inhibitors develop hyperlipidemia as an adverse effect. As a result, these patients require lipid-lowering treatment. Because of the severity of the lipid elevation, statins are often prescribed. To date, there are no prospective, randomized clinical trials evaluating the benefit of statins in HIV infected patients.

Although data specifically addressing the combination of the protease inhibitors with the statins are lacking, it is known that simvastatin, lovastatin, and atorvastatin, are metabolized by CYP 3A4 to some degree. Fluvastatin is metabolized by CYP 2C9 and pravastatin is not metabolized by the CYP isoenzyme system. Therefore, potential exists for increased concentrations of simvastatin, lovastatin, or atorvastatin when used in combination with the protease inhibitors, especially ritonavir. The increased concentration of statins may result in an increased risk for myopathy and rhabdomyolysis. The risk may be even greater in those HIV-infected patients receiving protease inhibitors plus other known inhibitors of CYP 3A4.
There is one retrospective study[94] in which patients with HIV received a statin for the management of their hyperlipidemia. A total of 30 patients were identified (5-pravastatin, 13-lovastatin, 10-simvastatin, 2 atorvastatin) and followed for an average of almost 9 months. The mean statin dose was 23 mg daily. Twenty-seven out of 30 patients received a protease inhibitor along with the statin. Two patients (1-lovastatin, 1-simvastatin) experienced an increase in liver transaminases 3 or more times the upper limit of normal. Both patients were asymptomatic and continued therapy. One patient developed an increase in creatine kinase of 5.4 times normal and myalgias. He was receiving lovastatin 40 mg daily, niacin and either saquinavir-ritonavir or nelfinavir-delavirdine as part of a blinded study. Another patient on lovastatin 20 mg daily and ritonavir reported diffuse myalgias but no CK was measured. His lovastatin was reduced to 10 mg daily.

An abstract presented during the 7th Conference on Retroviruses and Opportunistic Infections in February, 2000 evaluated the potential interaction between protease inhibitors and statins. In this study, HIV seronegative volunteers were randomized to receive pravastatin 40 mg/d, simvastatin 40 mg/d or atorvastatin 40 mg/d on days 1-4 and 15-18. On days 5-18, volunteers received dual protease inhibitors (ritonavir 400 mg bid plus saquinavir 400 mg bid). Investigators noted a 31.6 fold increase in simvastatin and a 4.5 fold increase in atorvastatin median estimated area under the curve concentrations (AUC_{0-24}) when used in combination with ritonavir and saquinavir. Median estimated AUC_{0-24} decreased nonstatistically in those subjects receiving dual protease inhibitors with pravastatin. Authors concluded from this data that simvastatin and atorvastatin either be avoided or used in lower doses in patients receiving ritonavir plus saquinavir in order to avoid potential toxicity from these agents. In addition, reduced doses of pravastatin do not appear necessary in patients receiving ritonavir plus saquinavir (http://www.retroconference.org).

Two groups of experts have made recommendations regarding the use of statins in HIV-infected individuals receiving protease inhibitor including the Adult AIDs Clinical Trials Research Group (AACTG) Cardiovascular Disease Focus Group and the Centers for Disease Control and Prevention/Department of Health and Human Services/Henry J Kaiser Foundation. Both groups have recommended avoidance of simvastatin and lovastatin in patients receiving protease inhibitors and suggest atorvastatin, fluvastatin, or pravastatin be considered as alternatives that could be used with caution. [112]

To summarize, although clinical data regarding the combination of the protease inhibitors and each statin are lacking, two expert consensus panels have recommended avoiding lovastatin or simvastatin in patients receiving protease inhibitors and using atorvastatin, fluvastatin or pravastatin with caution. However, since atorvastatin is also metabolized via CYP 3A4, it also has a similar potential to lovastatin and simvastatin for elevated serum concentrations. Therefore, should be used at the lowest possible dose or avoided if possible.

Adverse Effects

In general, the statins are well tolerated. Adverse effects are usually mild and transient and may include gastrointestinal disturbances, headache, insomnia and rash. More serious, rare adverse effects include transaminase elevation (> 3 times upper limit of normal) and creatine kinase elevation with or without muscle symptoms.

Are there differences in safety between statins with regard to myopathy and hepatoxicity? Three reviews[86, 95-96] evaluated the safety profile of statins. Two other reviews assessed myotoxicity with the statins[97-98] and one systematic review[99] focused on the combination of statins and fibrates.

In addition to the reviews of safety with statins, the 42 head-to-head statin LDL-c lowering trials were reviewed to determine whether there were any significant differences in myotoxicity and/or hepatotoxicity. Two observational studies regarding myopathy[100] or rhabdomyolysis[98] with statins were also included.

Magnitude of Risk. Although the absolute risk of myopathy is low, because of the wide use of lipid-lowering therapy there are good data about its frequency. Gaist and colleagues[100] conducted a population-based observational study in which three cohorts of patients were identified. The first cohort consisted of patients (n=17,219) who had received at least one prescription for lipid-lowering drugs. The second cohort consisted of patients (n=28,974) who had a diagnosis of hyperlipidemia but did not receive lipid-lowering drugs. The third cohort consisted of people (n=50,000) from the general population without a diagnosis of hypercholesterolemia. The incidence of myopathy in the lipid-lowering group was 2.3 per 10,000 person-years (95% CI 1.2-4.4) versus none per 10,000 person-years in the nontreated group (95% CI 0-0.4) and 0.2 per 10,000 person-years (95% CI 0.1-0.4) in the general population. In patients using fibrates or statins compared to nonusers, the relative risk of myopathy was 42.2 per 10,000 (95% CI 11.6-170.5) and 7.6 per 10,000 (95% CI 1.4-41.3), respectively. The authors concluded that the relative risk for myopathy is significantly increased when lipid-lowering drugs are used, especially fibrates. However, the absolute risk is very small. In 17,086 person-years of statin treatment, there were only two cases of myopathy. In this study, rates of myotoxicity were not differentiated between statins.

Myotoxicity of Different Statins. All of the available statins (simvastatin, lovastatin, atorvastatin, fluvastatin, pravastatin), when administered alone, have been associated with infrequent myotoxic adverse effects ranging from

myalgia, and myopathy to rhabdomyolysis.[86] Factors that may increase the risk for myopathy or rhabdomyolysis with statins are higher dosages, drug interactions, other myotoxic drugs (fibrates or niacin), increased age, hypothyroidism, surgery or trauma, heavy exercise, excessive alcohol intake, and renal or liver impairment.[97,99,101,102] All patients receiving treatment with statins should be advised to report any unexplained muscle pain, tenderness or weakness. Patients experiencing any of these symptoms should be advised to discontinue their lipid therapy immediately and providers should obtain a creatine kinase (CK) level as soon as possible, if clinically indicated. Since there can be varying degrees of myotoxicity, (e.g. myalgia-normal or slightly elevated CK, myositis-with or without CK elevation, myopathy-elevated CK {>10 times ULN}, rhabdomyolysis-myoglobinemia and myoglobinuria with an elevated CK {>10 times ULN}) the CK may not always be elevated [97]. Therefore if the CK is normal, a second trial with a statin may be appropriate with especially close monitoring and reinforcement to the patient to discontinue their lipid therapy immediately and contact their provider if muscle pain and weakness recurs.

A retrospective analysis of all domestic and foreign reports of statin-associated rhabdomyolysis has been released by the Food and Drug Administration.[98] During a 29-month period (November 1997-March 2000), there were 871 reported cases of rhabdomyolysis. The number of cases (% of total) for each statin are as follows: atorvastatin,73 (12.2%), fluvastatin, 10 (1.7%), lovastatin, 40 (6.7%), pravastatin,71 (11.8%), and simvastatin, 215 (35.8%). The report also included cerivastatin with 192 (31.9%) cases of rhabdomyolysis. In the majority of these cases, a drug with the potential for increasing the statin serum level was identified. From this study, conclusions regarding the differences in the risk of severe muscle toxicity between statins cannot be made since there are significant limitations to voluntary, spontaneous reporting systems. For example, the actual exposure (denominator) of a population to a statin is not known, so the true incidence rates of an adverse effect cannot be determined. Furthermore, the number of reported cases (numerator) may be underestimated.

In reviewing the 42 head to head comparative statin LDL-c lowering trials, no differences in the rates of muscle toxicity between statins were found. Furthermore, the American College of Cardiology, American Heart Association, and the National Heart, Lung, Blood Institute (ACC/AHA/NHLBI) recently released a clinical advisory[106] of the use and safety of statins (primarily myopathy) which states "that clinicians should consider the rates of severe myopathy as equivalent among all of the approved statins."

Safety of Statin-Fibrate Combination (Myopathy). Myopathy and rhabdomyolysis have also been reported in patients receiving monotherapy with fibrates (gemfibrozil or fenofibrate), especially in patients with impaired renal function. Although the mechanism of the interaction is not completely known, the combination of any statin with fibrates and to a lesser extent niacin, can result in a higher risk for myopathy or rhabdomyolysis.[102]

A systematic review by Shek[99] identified 36 trials that combined a statin with a fibrate in the management of hypercholesterolemia. No reports of rhabdomyolysis were observed in the 1,674 patients receiving the combination. A total of 19 (1.14%) patients withdrew secondary to myalgia or CK elevation. Two patients (0.12%) developed myopathy (defined as myalgia with CK >10 X the upper limit of normal [ULN]) and 33 (1.9%) patients experienced other muscle symptoms including myalgia, musculoskeletal pain or weakness, or myositis. There were 35 reports (2.1%) of subclinical elevation of CK (<10X ULN) in 16 of the included studies. Some of the studies did not report whether the CK elevation was symptomatic or if treatment was discontinued as a result. In one of the included studies, a patient tolerated the combination of pravastatin and gemfibrozil for 4 years, then developed myopathy with clinically important elevation in CK after being switched to simvastatin.

The authors of the systematic review admitted that there were several limitations to their findings. First, clinical trials exclude most patients that have risk factors for developing adverse outcomes. Therefore, data based on trials underestimate rates of adverse effects in a general clinic population. Also, some of the included studies did not report numbers and reasons for study withdrawal and were not of the best quality.

The authors of the systematic review found no case reports of severe myopathy or rhabdomyolysis in patients receiving pravastatin or fluvastatin combined with a fibrate. However, cases of pravastatin or fluvastatin combined with a fibrate resulting in rhabdomyolysis have been reported.[98] The authors cite a reference[103] in which it is suggested that the hydrophilic properties of pravastatin account for the reduced risk of muscle toxicity while all other statins are lipophilic. The suggested mechanism responsible for this difference is that lipophilic drugs are metabolized by the liver to more hydrophilic compounds while hydrophilic agents are more likely to be renally excreted unchanged[86] and have a lower risk for drug interactions. With regard to fluvastatin, it has been suggested

that in patients with more severe, mixed hyperlipidemia, maximum doses of fluvastatin may not achieve desired LDL-c goals and may be switched to a more potent LDL-c lowering statin prior to using combination therapy. The authors conclude that the theoretical advantage of pravastatin has not been adequately addressed in comparative statin trials and requires further investigation.

Because of the nature of adverse effect reporting and the available evidence, the answer to the question of whether one statin is safer than the other with regard to combination therapy with a fibrate is unknown. The authors of the before mentioned clinical advisory[106] on the use and safety of statins, state that it is reasonable to believe that the increase in creatine kinase, seen in trials involving lovastatin with gemfibrozil, would be similar with other statin-fibrate combinations.

The Food and Drug Administration has approved the following recommendations when combining a fibrate or niacin (≥ 1 gm/day) with a statin:

- Atorvastatin: Combination of statins and fibrates should generally be avoided. However, if combined, the risks and benefits should be carefully weighed and close monitoring for signs and symptoms of muscle pain or weakness is recommended [2].
- Fluvastatin: Combination of statins and fibrates should generally be avoided [3].
- Lovastatin: Combination of statins with fibrates or niacin (≥ 1 gm/day) should generally be avoided. However if combined, the dose of lovastatin should not exceed 20 mg daily [6].
- Pravastatin: The combined use of fibrates with pravastatin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk [5].
- Simvastatin: Combination of statins with fibrates or niacin (≥ 1 gm/day) should be avoided. However if combined, the dose of simvastatin should not exceed 10 mg daily[6].

Hepatotoxicity of Statins. All of the statins are rarely associated with clinically important elevation in liver transaminase levels (>3X ULN), occurring in approximately 1% of patients. The risk increases with increasing doses.[96] In order to answer whether there are differences in risk of liver toxicity between statins, the adverse effects of the 42 head-to-head statin LDL-c lowering trials were reviewed.

There were no significant differences in the rates of clinically relevant elevation in liver enzymes between statins with the exception of one study[21] comparing atorvastatin 80 mg to simvastatin 80 mg daily. In that study, Illingworth and colleagues[21] randomized 826 patients with hypercholesterolemia to atorvastatin 20mg or simvastatin 40mg daily for 6 weeks; followed by atorvastatin 40mg or simvastatin 80mg daily for 6 weeks; then atorvastatin 80mg or simvastatin 80mg daily for the remaining 24 weeks. Mean baseline LDL-c was 206mg/dl in the atorvastatin versus 206mg/dl in the simvastatin group. The study was double-blind but did not use intention-to-treat statistics. At a dose of 80mg daily for each statin, atorvastatin reduced LDL-c by 53.6% compared to 48.1% for simvastatin ($p \leq 0.001$). With regard to safety, a greater number of patients in the atorvastatin 80mg as opposed to the simvastatin 80mg group ($p<0.001$) reported clinical adverse effects (primary gastrointestinal-diarrhea). There was no significant difference in withdrawal rates due to adverse effects between groups. With regard to laboratory safety, a greater number of patients in the atorvastatin 80mg versus the simvastatin 80mg daily group experienced adverse laboratory events ($p<0.001$). Furthermore, withdrawal from the study due to adverse laboratory events occurred more often in the atorvastatin 80mg compared to the simvastatin 80mg daily group ($p<0.05$). Clinically important ALT elevation (> 3 times the upper limit of normal) occurred statistically more often in the atorvastatin 80mg compared to the simvastatin 80mg group (17 vs. 2 cases, respectively, $p=0.002$) and was especially pronounced in women (there were statistically more women randomized to atorvastatin than simvastatin). Aminotransferase elevation generally occurred within 6 to 12 weeks after initiation of the 80mg statin dose.

In a second study,[23] comparing maximum doses of atorvastatin and simvastatin, Karalis and colleagues randomized 1,732 patients with hypercholesterolemia to treatment with atorvastatin 10mg or 80mg daily or simvastatin 20mg or 80mg daily for 6 weeks. In this study, a total of 432 patients received either atorvastatin or simvastatin at a dose of 80mg daily. Mean baseline LDL-c in the atorvastatin 80mg daily group was 179mg/dl and 178mg/dl in the simvastatin 80mg daily group. This study was unblinded and did not use intention-to-treat statistics. At a dose of 80mg daily for each statin, LDL-c was reduced by 53% in the atorvastatin versus 47% in the simvastatin group ($p<0.0001$). With regard to safety at the 80mg dosage for each statin, atorvastatin was associated with a higher

incidence of adverse effects compared to simvastatin (46% vs. 39%) and a higher rate of study discontinuation due to adverse effects (8% vs. 5%). However, neither of these differences was statistically significant.
In addition, the 32 trials reporting cardiovascular health outcomes were examined for significant differences in hepatotoxicity between statins and placebo or a non-drug intervention. In AVERT[78], and MIRACL[79], there were 2 and 2.5% of patients in the atorvastatin 80 mg daily group who experienced clinically important elevations in liver transaminases which was significantly greater than that seen in the angioplasty or placebo groups. In GREACE[104], there were 5 patients out of 25 who received atorvastatin 80 mg daily who experienced clinically significant increases in liver function tests. In all cases (GREACE), the transaminase elevations were reversible upon discontinuation or reduction in dose of atorvastatin. In the 32 studies, there were no significant differences in transaminase elevation (> 3 X upper limit or normal) with other statins vs. placebo or non-drug interventions. However, in the majority of studies reporting health outcomes involving fluvastatin, lovastatin, pravastatin or simvastatin, the maximum daily dose was not used.

Safety of Statin and Fibrate Combination (Hepatoxicity). In the systematic review by Shek 2001[99], liver toxicity was addressed briefly stating that 8 patients, in three of the 36 included studies, discontinued the combination therapy due to significant elevation in liver transaminases (ALT, AST). In most of the other studies, there were only reports of subclinical (<3X ULN) elevation in ALT or AST. Conclusions regarding the safety of different statins in the liver were not made.

In summary, there is insufficient evidence to determine which statin or statins are safer with regard to muscle and liver toxicity.

It is recommended that liver function tests (LFTs) be monitored routinely as suggested by the drugs manufacturer (Table 12). Monitoring for rosuvastatin is not included since it is not yet available in the U.S.

Table 12. Statin LFT Monitoring Requirements[2-6] (For initiation of treatment and dose elevation)

Statin	Start	6 weeks	12 weeks	Periodically (semiannual)
Atorvastatin	X		X	X
Fluvastatin and XL	X		X*	
Lovastatin	X	X	X	X
Pravastatin* **	X			
Simvastatin	X			X**
Simvastatin 80 mg	X		X	X

* If LFT normal, no further testing is recommended.
** Periodically thereafter for the 1st year of treatment or until one year after the last elevation in dose.
***Monitor LFTs prior to dose elevation or when clinically indicated.

Dosage and Administration[2-6]

With the exception of fluvastatin 80 mg (which is administered as 40 mg twice daily), statins are dosed once daily in the evening or at bedtime. All are taken without regard to meals except lovastatin IR and ER. Lovastatin IR is recommended to be taken with the evening meal due to a reduced hypolipidemic effect under fasting conditions. Lovastatin ER is recommended to be taken at bedtime due to reduced bioavailability under fed conditions. Table 13 lists the recommended dose ranges and suggestions for dosing in special populations. Rosuvastatin is not included since it is not yet available in the U.S.

Table 13. FDA Approved Dosing Recommendations for Statins

Statin	Initial dose (range)	Adjustment for renal impairment	Adjustment/caution for severe hepatic impairment
Atorvastatin	10 mg/day (10-80)	None	Yes-increased AUC in Childs-Pugh A & B disease. Contraindicated in active liver disease and unexplained transaminase elevation. Caution in those with history of liver disease or heavy alcohol use.
Fluvastatin or Fluvastatin XL	LDL-c reduction of < 25%: 20 mg/day (20-80) LDL-c reduction of > 25%: 40 mg/d or 80 mg/d *(80 mg for fluvastatin is*	Mild/moderate - no adjustment needed; Use caution for severe renal impairment since doses 40 mg/day or > have not been studied.	Yes-contraindicated in those with active liver disease and unexplained transaminase elevation. Caution in those with history of liver disease or heavy alcohol use.

	given as 40 mg bid or 80 mg/hs for fluvastatin XL)		
Lovastatin Lovastatin ER	20 mg/day (10 – 80)* 20, 40, or 60 mg/day (10-60 mg)	CrCl < 30 ml/min use caution above 20mg/day	Yes-contraindicated in active liver disease or unexplained transaminase elevation. Caution in those with history of liver disease or heavy alcohol use.
Pravastatin	10, 20 or 40 mg/day (10 – 80)	Severe renal insufficiency -use starting dose of 10 mg/day	Yes-contraindicated in active liver disease and unexplained transaminase elevation. Caution in those with a history of liver disease, signs suggesting liver disease or heavy alcohol use
Simvastatin	20 mg/day (5 - 80)	Severe renal insufficiency- use starting dose of 5mg/day	Yes-contraindicated in active liver disease or unexplained transaminase elevation. Caution in those with history of liver disease or heavy alcohol use.

AUC = area under the curve; CrCl = creatinine clearance, ER=extended release, XL=extended release
*Doses can be given as once or twice daily.
If lovastatin or simvastatin are selected in a patient receiving cyclosporine, lovastatin should be started at 10 mg/day and simvastatin at 5 mg/day. The dose of lovastatin should not exceed 20 mg/day and simvastatin should not exceed 10 mg/day.

Summary of the Evidence

Table 14 is meant to summarize the available data on statins. It is not meant to be used as a guideline for choosing between the statins. When choosing a particular statin for a patient, clinicians should integrate the data from all of the questions addressed in this document (reduction in health outcomes, LDL-c lowering ability, concomitant medications, etc.).

Table 14. Summary of the Evidence

Question	Level of Evidence	Conclusion
How do statins compare in their ability to reduce LDL-c?	Overall grade—fair	The best study to answer this question would be a double-blind, randomized, intention-to-treat trial in which equipotent doses of statins were compared with regard to LDL-c lowering, withdrawals and adverse effects. No studies met these criteria.
Are there doses for each statin that produce similar percent reduction in LDL-c between statins?	Overall grade—fair to good	Results of a large number of trials are fairly consistent with information reported by the manufacturer. When statins are provided in doses that are approximately equivalent, a similar percent reduction in LDL-c can be achieved.
Is there a difference in the ability of a statin to achieve National Cholesterol Panel (NCEP) goals?	Overall grade—fair to good	For patients who require LDL-c reductions of up to 40% to meet their NCEP goal, any of the statins are effective. In patients requiring an LDL-c reduction of 40% or > to meet their NCEP goal, only atorvastatin 20 mg or >, lovastatin 80 mg, and simvastatin 40 mg or > daily are likely to meet the goal. Based on fair-quality studies, atorvastatin 80 mg daily resulted in 5 to 6 additional percentage points of LDL-c reduction than simvastatin 80 mg daily (53-54% vs. 47-48%), but had significantly higher rates of some adverse effects.
How do statins compare in their ability to reduce the risk of nonfatal MI, CHD (angina), CHD mortality, all-cause mortality, stroke, or need for revascularization (coronary artery bypass grafting, angioplasty or stenting)?	N/A	There are no controlled trials comparing the ability of two or more statins to reduce the risk of death, coronary events, stroke or death.
Which statins have been shown to improve CHD mortality?	Fair to good	Primary prevention: pravastatin (good evidence) Secondary prevention: pravastatin, simvastatin (good evidence), and atorvastatin (fair evidence)
Which statins have been shown to	Fair to good	Primary prevention: lovastatin and pravastatin

improve CHD events?		Secondary prevention: pravastatin and simvastatin (all good evidence), atorvastatin and fluvastatin (both fair evidence)
Which statins have been shown to reduce stroke?	Fair to good	Pravastatin and simvastatin (all good evidence), atorvastatin (fair evidence)
Are there differences in safety of statins when used in special populations? • HIV patients • Transplant patients • Drug interactions	One fair quality observational study, case reports, expert opinion, pharmacology	In theory, pravastatin and fluvastatin have the lowest potential for interaction with drugs that are potent inhibitors of CYP 3A4. Atorvastatin, lovastatin and simvastatin have the greatest potential for clinically important interactions. Fluvastatin has a potential for interaction with drugs inhibiting CYP 2C9 and pravastatin has the lowest potential for drug interactions. Experts recommend starting with pravastatin or fluvastatin and using the lowest possible dose. Although there is not adequate proof that these recommendations are correct, on ethical grounds, fluvastatin or pravastatin are unlikely to be tested in a good-quality controlled study against other statins.
Are there differences in risk for myotoxicity or hepatotoxicity between statins?	Fair quality observational study, several fair review articles. 42 comparative statin LDL-c lowering trials (generally fair in quality) 32 health outcome trials poor to good in quality	Evidence in lacking with regard to differences in the risk for muscle and hepatotoxicity among statins. However, in 3 trials evaluating cardiovascular outcomes with atorvastatin 80 mg daily, there was a higher rate of liver transaminase elevation in the atorvastatin vs. angioplasty, placebo, or usual care groups.

Summary

Statins are considered by most to be an important component of care in the management of hypercholesterolemia as a result of their effectiveness in reducing LDL-c, their safety and tolerability, and because of the demonstrated ability to reduce cardiovascular morbidity and mortality in clinical trials. All of the agents have the ability to reduce LDL-c 20-30% or more. Atorvastatin, lovastatin and simvastatin are capable of LDL-c reductions in excess of 40%. Only atorvastatin has demonstrated the ability to reduce LDL-c 50% or greater. With regard to reduction in health outcomes, lovastatin, pravastatin and simvastatin have been demonstrated in good quality clinical trials to reduce cardiovascular health outcomes. Atorvastatin and fluvastatin reduced some cardiovascular health outcomes in fair quality studies. In those patients receiving known inhibitors of CYP 3A4 and 2C9, pravastatin has the lowest potential for interaction and may be the safest choice. The choice of agent for VA National Formulary should have evidence demonstrating a reduction in cardiovascular outcomes and reduce LDL-c in the majority of veterans in order for them to meet their NCEP goals at the lowest cost. In addition, if the agent chosen to meet the criteria listed in the previous sentence has the potential for drug-drug interactions, a second agent should be allowed for those patients receiving potent CYP inhibitors.

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Appendix 1. HDL-Trig Comparison Table

Author or Study	Treatment Group(s)	HDL-c (mean % increase from baseline)	Triglycerides (mean % decrease from baseline)	Statistical Difference ($p<0.05$) (yes or no) in favor of…
Davidson M, etal. [9]	Atorva 10 mg/d vs. rosuva 5 or 10 mg/d (n=516)	Atorva 10 mg: 8 Rosuva 5 mg: 13 Rosuva 10 mg: 12	Atorva 10 mg: 19 Rosuva 5 mg: 17 Rosuva 10 mg: 19	**HDL-c: Yes** (rosuva) **Trigs: No**
Crouse JR, etal [15]	Atorva 20 or 40 mg/d or simva 40 or 80/d (n=846)	Atorva 20 mg: 4 Atorva 40 mg: 3 Simva 40 mg: 6.7 Simva 80 mg: 6.6	Atorva 20 mg: 23.3 Atorva 40 mg: 29.6 Simva 40 mg: 23 Simva 80 mg: 25.2	**HDL-c: Yes** (simva) **Trigs: Yes** (atorva 40 vs. simva 80)
Karalis DG, etal [23]	Atorva 10 or 80 mg/d or simva 20 or 80 mg/d (n=1,732)	Atorva 10 mg: 5 Atorva 80 mg: 2 Simva 20 mg: 6 Simva 80 mg: 6	Atorva 10 mg: 18 Atorva 80 mg: 28 Simva 20 mg: 14 Simva 80 mg: 23	**HDL-c: Yes** (simva 80 vs. atorva 80) **Trigs: Yes** (atorva vs corresponding dose of simva)
Branchi A, etal [22]	Atorva 10 mg vs. simva 20 mg/d (n=200)	Atorva 10 mg: 3.7 Simva 20 mg: 7.8%	Atorva 10 mg: 24.4+ Simva 20 mg: 26.1+	**HDL-c: Yes** (simva) **Trigs: No**
Illingworth DR, etal [21]	Atorva 20, 40 or 80 mg/d or simva 40 or 80 mg/d (n=826)	Atorva 20 mg: 7.3 Atorva 40 mg: 6.4 Atorva 80 mg: 3 Simva 40 mg: 8.5 Simva 80 mg: 7.5	Atorva 20 mg: 23.6+ Atorva 40 mg: 31.6+ Atorva 80 mg: 31.3+ Simva 40 mg: 22.4+ Simva 80 mg: 23.6+	**HDL-c: Yes** (simva) **Trigs: Yes** (atorva)
Farnier M, etal. [18]	Atorva 10 or simva 10 or 20 mg/d (n=272)	Atorva 10 mg: 5.7 Simva 10 mg: 2.2 Simva 20 mg: 3	Atorva 10 mg: 19.2 Simva 10 mg: 4.6 Simva 20 mg: 16	**HDL-c: No** **Trigs: Yes** (atorva) (unusual statistics used)
Brown AS, etal [25]	Atorva 10 mg, fluva 20 mg, lova 20 mg or simva 10 mg/d (n=318)	Atorva 10 mg: 9 Fluva 20 mg: 5 Lova 20 mg: 6 Simva 10 mg: 9	Atorva 10 mg: 11 Fluva 20 mg: 6 Lova 20 mg: 6 Simva 10 mg: 11	**HDL-c: No** **Trigs: No**
Hunninghake D, etal. [24]	Atorva 10 mg/ fluva 20 mg, lova 20 mg, simva 10 mg/d (n=344)	Atorva 10 mg: 4 Fluva 20 mg 5 Lova 20 mg: 5 Simva 10 mg: 6	Atorva 10 mg: 16 Fluva 20 mg 7 Lova 20 mg: 5 Simva 10 mg: 5	**HDL-c: No** **Trigs: Yes** (atorva) *(nonequal atorva and other statin doses compared)*
Wolffenbuttel BHR, etal. [27]	Atorva 5 mg or 20 mg, prava 20 mg or simva 10 mg/d (n=78)	Atorva 5 mg: 2 Atorva 20 mg 8 Prava 20 mg: 3 Simva 10 mg: 1	Atorva 5 mg: 16 Atorva 20 mg: 23 Prava 20 mg: 11 Simva 10 mg: 8	**HDL-c No** **Trigs: Yes** (atorva 20 mg vs. simva and prava) *(nonequal atorva and other statin doses compared)*
Ose L, etal. [32]	Fluva 20 or 40 mg or simva 5 or 10 mg/d (n=432)	Fluva 20 mg: 6.3 Fluva 40 mg: 13 Simva 5 mg: 10.1 Simva 10 mg: 12.2	Fluva 20 mg: 10 Fluva 40 mg: 12.8 Simva 5 mg: 11.5 Simva 10 mg: 14.5	**HDL-c: Yes** (simva 10 >fluva 20) **Trigs: Yes** (simva 10 >fluva 20) Fluva 40 and simva 10 were not different
Jacotot B, etal. [31]	Fluva 40 or 80 mg or prava 20 or 40 mg/d (n=134)	Fluva 40 mg: 4.2 Fluva 80 mg: 7.7 Prava 20 mg: 5 Prava 40 mg: 9.4	Fluva 40 mg: 14.5 Fluva 80 mg: 14.6 Prava 20 mg: 0.7 Prava 40 mg: 1.8	**HDL-c: No** **Trigs: No**
Nash DT. [30]	Fluva 20 mg or 40 mg or lova 20 mg/d (n=137)	Fluva 20 mg: 1.6 Fluva 40 mg: 7 Lova 20 mg: 7	Fluva 20 mg: 14 Fluva 40 mg: 14 Lova 20 mg: 12	**HDL-c: No** **Trigs: No**
McPherson R, etal. [36]	Lova 20 mg, prava 10 mg or 20 mg/d (n=217)	Lova 20 mg: 8.7 Prava 10 mg: 10.8 Prava 20 mg: 5.4	Lova 20 mg: 6.8 Prava 10 mg: 0.9 Prava 20 mg: 4.9	Statistics not provided for between group comparisons for HDL and Trigs

Appendix 1. HDL-Trig Comparison Table

Weir MR, etal. [38]	Lova 40 mg or prava 40 mg/d (n=426)	Lova 40 mg: 8.5 Prava 40 mg: 8.2	Lova 40 mg: -- Prava 40 mg: -- (not provided)	**HDL-c: No** **Trigs: unknown**
Strauss We, etal. [39]	Lova 10 mg or prava 10 mg/d (n=30)	Lova 10 mg: 3 Prava 10 mg: 1.1	Lova 10 mg: 9.4 Prava 10 mg: 15	**HDL-c: No** **Trigs: No**
Farmer JA, etal. [40]	Lova 20 or 40 mg or simva 10 or 20 mg/d (n=544)	Lova 20 mg: 4.2 Lova 40 mg: 7.4 Simva 10 mg: 4.6 Simva 20 mg: 4.6	Lova 20 mg: 10.5 Lova 40 mg: 10.3 Simva 10 mg: 3.9 Simva 20 mg: 10.3	**HDL-c: No** **Trigs: No**
Sasaki S, etal. [50]	Prava 10 mg or simva 5 mg/d (n=36)	Prava 10 mg: 6.6 Simva 5 mg: 7.9	Prava 10 mg: 5.8 Simva 5 mg: 13	**HDL-c: No** **Trigs: Yes** (simva)
Steinhagen-Thiessen E. etal. [49]	Prava 10 mg or simva 5 or 10 mg/d (n=281)	Prava 10 mg: 5 Simva 5 mg: 7.7 Simva 10 mg: 8.1	Prava 10 mg: 5.3 Simva 5 mg: 9.5 Simva 10 mg: 9.5	**HDL-c: No** **Trigs; No**
Douste-Blazy P, etal. [47]	Prava 20 mg or simva 10 mg/d (n=273)	Prava 20 mg: 6.1 Simva 10 mg: 6.3	Prava 20 mg: 12.9 Simva 10 mg: 13.8	**HDL-c: No** **Trigs: No**

+Median % change

Author/Year/Study Name	Study Characteristics	Number of Patients Randomized	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction from baseline	Primary Endpoint
Herd AJ., etal./1997/ L/Lipoprotein and Coronary Atherosclerosis Study (LCAS)	Randomized, double-blind, placebo-controlled, not intent to treat analysis	429	Men or women 35-75 years with ≥1 coronary atherosclerotic lesion causing 30-75% diameter stenosis	**Fluvastatin 20 mg bid** or placebo bid. Cholestyramine up to 12 g/day was given to those with LDL-c≥160 mg/dl after dietary phase.	2.5 years	146.2 ± 20.1 mg/dl (3.78 mmol/L)	22.5% (fluvastatin alone)	Within patient per-lesion change in MLD of qualifying lesion as assessed by coronary angiography.
Furberg CD., etal./ 1994/Asymptomatic Carotid Artery Progression Study (ACAPS)	Randomized, double-blind, placebo-controlled, intent to treat analysis	919	Men or women 40-79 years with early carotid atherosclerosis and elevated LDL-c	**Lovastatin 20 mg qpm** or placebo qpm. Lovastatin was titrated to 40 mg qd if LDL-c >90-100 mg/dl. Warfarin 1 mg qd or placebo qd.	3 years (last 300 randomized only received 33 months of follow up	156.6 mg/dl (4 mmol/L)	28%	Progression of a summary measure via B-mode ultrasonography: the mean of the maximum IMT measurements from the 12 walls, near and far, of the common carotid, the bifurcation, and the internal carotid arteries bilaterally measured by B-mode ultrasonography.
Waters D., etal./ 1994/The Canadian Coronary Atherosclerosis Intervention Trial (CCAIT)	Randomized, double-blind, placebo-controlled, not intent to treat analysis	331	Men or women up to 70 years at higher risk for CHD events with diffuse CHD and TC 220-300 mg/dl.	**Lovastatin 20 mg qpm** or placebo qpm. Lovastatin was titrated to 40 and then 40 mg bid if LDL-c >130 mg/dl.	2 years	173 mg/dl (4.5 mmol/L)	29%	Comparison between groups for coronary change score (per-patient mean of the MLD for all lesions measured as determined by coronary angiography
Blankenhorn DH., etal./ 1993/ The Monitored Atherosclerosis Regression Study (MARS)	Randomized, double-blind placebo-controlled, not intent to treat analysis	270	Men or women younger than 70 years and CHD in 2 coronary segments 50% or >	**Lovastatin 80 mg qpm** or placebo qpm.	2.2 years	151 mg/dl (3.91 mmol/L)	38%	Per-patient change in percent diameter stenosis between groups as determined by quantitative coronary angiography.

Jukema JW., etal./ 1995/ The Regression Growth Evaluation Statin Study (REGRESS)	Randomized, double-blind, placebo-controlled, not intent to treat analysis	885	Men with clinical evidence of CHD and TC 155-310mg/dl (4-8 mmol/L)	**Pravastatin 40 mg qpm** or placebo qpm.	2 years	166 mg/dl (4.3 mmol/L)	29%	Change in average mean segment diameter per patient and change in average minimun obstruction diameter per patient determined by coronary arteriography.
Pitt B., etal./1995/ Pravastatin Limitation of Atherosclerosis in Coronary Arteries (PLAC-1)	Randomized, double-blind, placebo-controlled, not intent to treat analysis	408	Men or women with CHD as evidenced by 1 or > stenosis ≥50% or recent MI or PTCA and LDL-c ≥130 mg/dl	**Pravastatin 40 mg qpm** or placebo qpm.	3 years	164 mg/dl (4.24 mmol/L)	28%	Change in average MLD and change in percent diameter stenosis as determined by coronary arteriography.
Crouse JR., etal./ 1995/Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II)	Randomized, double-blind, placebo-controlled, not intent to treat analysis	151	Men and women with CHD as evidenced by ≥ stenosis of 1 or > coronary artery or history of MI with elevated LDL-c.	**Pravastatin 20 mg qpm** or placebo qpm. If LDL-c was not <110 mg/dl pravastatin was increased to 40 mg qpm.	3 years	167.5 mg/dl (4.33 mmol/L)	28%	Change in the mean of the maximal IMT measurement across time determined by B-mode ultrasonography.
Salonen R., etal./ 1995/Kuopio Atherosclerosis Prevention Study (KAPS)	Randomized, double-blind, placebo-controlled, not intent to treat analysis	447	Men 44-65 years with LDL-c≥4 mmol/L (155 mg/dl). Only 10% had history of MI (Primary prevention study)	**Pravastatin 40 mg qpm** or placebo qpm.	3 years	185 mg/dl (4.8 mmol/L)	27.40%	Rate of carotid atherosclerotic progression measured as the linear slope over annual ultrasound examinations in the average of maximum carotid IMT of the far wall of up to 4 arterial segments.

Sato S., etal./2001	Randomized, unblinded, intent to treat analysis for clinical events	329	Men and women <70 years with CHD documented by coronary angiography with normal cholesterol.	**Pravastatin 10 mg qpm.**	2 years	200 mg/dl (TC) (5.2 mmol/L). LDL-c not provided	8.5% (TC)	Mean segment diameter and minimum obstruction diameter were used to evaluate progression as assessed by coronary angiography.
MAAS Investigators/ 1994/Multicentre Anti-Atheroma Study	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	404	Men and women 30-67 years with 2 or > coronary artery segments occluded and hypercholesterolemia.	**Simvastatin 20 mg qpm** or placebo qpm.	4 years	169 mg/dl (4.38 mmol/L)	31%	Per-patient average of mean lumen diameters of all coronary segments(diffuse atherosclerosis) and the per-patient average of MLD of all segments that were atheromatous at baseline, follow up or both (focal atherosclerosis) as assessed by coronary angiography.
Bestehorn HP., etal. /1997/Multicenter Coronary Intervention Study (CIS)	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	254	Men 30-55 years with at least 3 coronary segments with a lumen diameter of ≥20% and TC of 207-350 mg/dl.	**Simvastatin 20 mg qpm** or placebo qpm. Simvastatin was increased to 40 mg qpm if LDL-c>90 mg/dl	2.3 years	164.5 mg/dl (4.25 mmol/L)	35%	Global change score and the per-patient mean change in MLD as assessed by coronary angiography.
Teo KK., etal./2000/ The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT)	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	460	Men and women 21 year or >, atherosclerosis in 3 or > coronary segments, TC 160-240 mg/dl,	**Simvastatin 10 mg qpm** or placebo qpm and enalapril 2.5 mg bid or placebo (2X2). Simvastatin could be titrated to 40 mg qpm.	47.8 months	130 mg/dl (3.36 mmol/L)	30.50%	Changes in absolute mean segment lumen diameter, absolute minimum segment lumen diameter, and maximum percent lumen diameter stenosis.

BID=twice a day, CHD=coronary heart disease, IMT=intimal-medial thickness, MLD=minimum lumen diameter, MI=myocardial infarction, qpm=every evening

Primary Endpoint Results (provided only if it is a clinical health outcome)	Clinical Outcomes Measured	Clinical Outcome Results	Comments/Conclusions
N/A	Any cardiac, cerebrovascular, peripheral vascular, and fatal events. Also time to first CABG, PTCA, MI, hospitalization for USA or all-cause mortality	Any cardiac morbid or fatal event occurred in 12.7% of fluvastatin vs. 18.9% placebo. Time to these events showed a trend towards benefit with fluvastatin. Need for revascularization was reduced with fluvastatin 8.9% vs. 13.4% with placebo. No statistical significance provided.	LCAS was not designed with sufficient power to detect differences in clinical events. However, there was a trend observed in favor of fluvastatin. In this study, there were 909 patients screened, but only 429 randomized. The major reasons were for lipid ineligibility and lack of cooperation. There were some minor difference in baseline characteristics between groups. Fair-poor in quality to determine differences in clinical events.
N/A	One of the secondary endpoints in the trial was to determine the treatment effects on major atherosclerotic events.	5 (all nonfatal MI) major cardiovascular events occurred in the lovastatin vs. 14 in the lovastatin-placebo groups (4-CHD deaths, 5-strokes, 5-nonfatal MI). p=0.04, ARR=2 events/100 persons, NNT=5. Overall mortality: One death in lovastatin vs. 8 deaths in lovastatin-placebo groups p=0.02, ARR 1.5 events/100 persons, NNT=65. All 6 cardiovascular deaths occurred in lovastatin-placebo groups.	The secondary objective of major atherosclerotic events was significantly reduced in the lovastatin vs. the lovastatin-placebo groups in patients with early carotid atherosclerosis. Fair-good in quality to determinine differences in clinical events.
N/A	Cardiac and noncardiac events, mortality and revascularization were reported in the safety analyis.	Patients had one or more events: lovastatin 14 patients (2 deaths from cardiac causes, 5 MI, 8 USA), placebo 18 patients (1 death from cardiac causes, 6 MI, 13 USA) (NS)	CCAIT was not designed with sufficient power to detect differences in clinical events. However, there was a trend in favor of lovastatin. Mean lovastatin dose=36 mg/d and 69% met NCEP goal). Fair-poor in quality to assess differences in clinical events.
N/A	Cardiac and noncardiac events, mortality and coronary revacularization were reported in the safety analysis.	22 lovastatin vs. 31 placebo recipients had one or more of the following: MI, PTCA, CABG, CHD death or hospitalization for USA. (NS) Also no difference in overall death.	MARS was not designed with sufficient power to detect differences in clinical events. However there was a trend in favor of lovastatin. Fair-poor in quality to assess differences in clinical events.

N/A	Prespecified clinical events: Fatal and nonfatal MI, CHD death, nonscheduled PTCA or CABG, Stroke or TIA, and all-cause death.	After 2 years of treatment, 89% of pravastatin vs. 81% of placebo recipients were free from clinical events (p=0.002). Although nonsignificant, there were 12 nonfatal MI in the placebo vs. 7 in the pravastatin groups (ARR 1.2/100 persons, NNT=83). Unscheduled PTCA were reduced significantly in the pravastatin vs. placebo groupg (p=0.004, RRR=57%, ARR 5.8/100 persons, NNT=17).	REGRESS prespecified analysis of clinical events. The only signficant difference in individual events was the reduced need for unscheduled PTCA in the pravastatin vs. placebo groups. This signficant reduction accounted for the overall reduction in new clinical events in the pravastatin group. Difficult to tell if intent to treat population was included in overall clinical event analysis. Fair in quality to assess differences in clinical events.
N/A	Prespecified clinical events: Fatal and nonfatal MI, nonfatal infarction or CHD death, nonfatal infarction or death from any cause and total clinic events (nonfatal MI, nonfatal completed stroke, death PTCA and CABG).	There were 17 MI in placebo vs. 8 in pravastatin (P≤0.05, RRR=60%, ARR=4.5/100 persons, NNT=22). Although not statistically significant, there were 37 PTCA in placebo vs. 25 in pravastatin. A total of 81 events occurred in placebo vs. 55 in pravastatin (NS).	PLAC-1 prespecified analysis of clinical events. The only significant difference in individual events was a reduction in the rate of MI in the pravastatin vs. placebo groups. All randomized patients were included in the clinical event analysis. Fair in quality to assess differences in clinical events, although a relatively small study population.
N/A	Prespecified clinical events: Fatal coronary events or nonfatal MI, all-cause mortality, all deaths plus nonfatal MI.	For the combined endpoint of nonfatal MI and any death, there was a significant reduction in the pravastatin vs. placebo group (5 vs. 13, respectively). P=0.04,RRR=61%, ARR=1/100 persons, NNT=10	PLAC-II prespecified analysis of clinical events. The only significant difference was in the combined endpoint of nonfatal MI plus any deaths. Not much detail provided in clinical event section, for observation of other clinical events that were not signficantly reduced with pravastatin. Fair-poor in quality to assess difference in clinical events. Small sample size.
N/A	Clinical events were reported spontaneously.	The number of cardiovascular events reported during the trial were not statistically significantly different between groups. However, there was a trend to less clinical cardiovascular events in the pravastatin group, primarily MI.	KAPS was not designed to sufficiently determine differences in clinical cardiac events between groups. However, there was a trend in favor of pravastatin. Fair-poor in quality to determine differences in clinical events between groups.

N/A	Prespecified clinical events: Fatal and nonfatal MI, CHD death, nonscheduled PTCA or CABG, Stroke or TIA, and all-cause death. (using criteria defined by REGRESS)	The incidence of clinical events was lower in the pravastatin groups vs. placebo but this difference was not significant. All-cause mortality was significantly reduced in the pravastatin vs. placebo groups (p=0.043)	Prespecified clinical events. There was a trend to a reduction in clinical cardiac events in the pravastatin vs. placebo groups, however the difference was not significant. There was a significant reduction in overall mortality with pravastatin vs. placebo. Fair in quality to assess difference in clinical events. Small sample size.
N/A	Clinical events were reported spontaneously.	After 4 years, there was no difference in clinical events between groups. There were a greater number of MI in the simvastatin vs placebo groups. There were more revascularizations in the placebo vs. simvastatin groups. Neither of these were statistically different. Overall, there were 40 cardiac events in the simvastatin vs. 51 in the placebo groups (NS).	There were no stastical differences in clinical events in the simvastain vs. placebo groups. Fair to poor in quality to assess differences in clinical event due to duration of trial, however was a relatively small sample size.
N/A	Clinical events were reported spontaneously.	There were no significant differences in clinical events with simvastatin vs. placebo. Overall, there were 15 events in the simvastatin and 19 in the placebo groups.	There were no stastical differences in clinical events in the simvastain vs. placebo groups. Fair to poor in quality to assess differences in clinical event due to duration of trial, however was a relatively small sample size.
N/A	Prespecified clinical events: death, MI, stroke, hospitalization for angina, revascularization and cancer.	The only signficant difference in clinical events between simvastatin and placebo was a reduction in the number of revascularizations (6 vs. 12%, p=0.020and angioplasties (3 vs. 9% p=0.02).	There was a significant reduction in revascularization, specifically angioplasty in the simvastatin vs. placebo. No differences were noted in any other clinical events. Fair in quality to assess diffferences in clinical events since clinical events were prespecified.