Drug Class Review
on
HMG-CoA Reductase Inhibitors (Statins)

Final Report Update 4

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A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). The Drug Effectiveness Review Project governance group elected to proceed with another full update of this report. Please see timeline on the DERP website for details on the date of its release. Prior versions of this report can be accessed at the DERP website.

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INTRODUCTION

In the United States, coronary heart disease (CHD) and cardiovascular disease (CVD) account for nearly 40% of all deaths each year. Coronary heart disease (CHD) continues to be the leading cause of mortality and a significant cause of morbidity among North Americans. In 2003, CHD claimed 653,000 lives, translating into about one out of every five deaths in the United States.[1] High levels of cholesterol, or hypercholesterolemia, are an important risk factor for CHD. The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors, also known as statins, are the most effective class of drugs for lowering serum low-density lipoprotein cholesterol (LDL-c) concentrations. They are first-line agents for patients who require drug therapy to reduce serum LDL-c concentrations.

The statins work by blocking an enzyme, HMG-CoA reductase that is the rate-limiting step in the manufacture of cholesterol. Statins reduce LDL-cholesterol, total cholesterol, and triglycerides and slightly increase high-density lipoprotein (HDL-c). Statins may also have anti-inflammatory effects. A recent good-quality systematic review found that all statins are equally effective at lowering C-reactive protein levels, but do not affect fibrinogen or several other markers of inflammation.[2] No study has evaluated whether the effect of statins on any marker is related to their effect on cardiovascular outcomes.

The third report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III {ATP-III}) was released in September 2002,[3] and updated in August 2004 to include evidence from more recent trials.[4] The report stresses that the intensity of treatment should be directed by the degree of cardiovascular risk. Target LDL-c levels depend on the patient's risk of heart disease, medical history, and initial LDL-c level. For most patients who are prescribed a statin, the target will be <130mg/dL or <100mg/dL. In ATP-III, patients who have type 2 diabetes without CHD; peripheral or carotid vascular disease; and patients who have multiple risk factors and a 10-year risk of CHD > 20% are said to have "CHD equivalents," meaning that the criteria for using drug therapy and the LDL target (<100mg/dL) is the same as for patients who have a history of CHD. An LDL-C goal of <70mg/dL for high-risk patients is a therapeutic option. Factors that place patients in the category of *very high risk* favor a decision to reduce LDL-C levels to <70mg/dL. These factors are the presence of established CVD plus (1) multiple major risk factors (especially diabetes), (2) severe and poorly controlled risk factors (especially continued cigarette smoking), (3) multiple risk factors of the metabolic syndrome (especially high triglycerides >200mg/dL plus non-HDL-C >130mg/dL with low HDL-C {<40mg/dL}), and (4) patients with acute coronary syndromes. The optional goal of <70mg/dL does not apply to individuals who are not high risk.

The 2006 update of the American Heart Association /American College of Cardiology consensus statement on secondary prevention states, "…low-density lipoprotein cholesterol (LDL-C) should be <100 mg/dL for all patients with CHD and other clinical forms of atherosclerotic disease, but in addition, it is reasonable to treat to LDL-C <70 mg/dL in such patients." They assigned this recommendation a grade of II-1 meaning "…there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment [but the]…weight of evidence/opinion is in favor of usefulness/efficacy." The AHA/ACC guidelines qualify this recommendation as follows:

When the <70-mg/dL target is chosen, it may be prudent to increase statin therapy in a graded fashion to determine a patient's response and tolerance. Furthermore, if it is not possible to attain LDL-C <70 mg/dL because of a high baseline LDL-C, it generally is possible to achieve LDL-C reductions of >50% with either statins or LDL-C–lowering drug combinations. Moreover, this guideline for patients with atherosclerotic disease does not modify the recommendations of the 2004 ATP III update for patients without atherosclerotic disease who have diabetes or multiple risk factors and a 10-year risk level for CHD >20%. In the latter 2 types of high-risk patients, the recommended LDL-C goal of <100 mg/dL has not changed. Finally, to avoid any misunderstanding about cholesterol management in general, it must be emphasized that a reasonable cholesterol level of <70 mg/dL does not apply to other types of lower-risk individuals who do not have CHD or other forms of atherosclerotic disease; in such cases, recommendations contained in the 2004 ATP III update still pertain." 5

Six statins are available in the US and Canada:

- Atorvastatin (Lipitor)
- Fluvastatin (Lescol), fluvastatin extended release (Lescol XL)
- Lovastatin (Mevacor), lovastatin extended release (Altoprev)
- Pravastatin (Pravachol)
- Rosuvastatin (Crestor)
- Simvastatin (Zocor)

Fluvastatin and lovastatin are available in extended-release as well as immediate-release forms. In August 2004, the name of the extended release formulation of lovastatin was changed to Altoprev. Lovastatin and pravastatin are natural statins found in fungi; simvastatin is a semisynthetic statin based on lovastatin; and atorvastatin, fluvastatin, and rosuvastatin are fully synthetic.

Usual starting doses are rosuvastatin 10mg, atorvastatin 10mg, pravastatin 40mg, and 20mg of the other statins. The maximum daily dose for rosuvastatin is 40mg. For all other statins, the maximum FDA-approved daily dose is 80mg. For lovastatin and pravastatin, the maximum dose usually is prescribed as 40mg twice a day.

Scope and Key Questions

The purpose of this review is to compare the efficacy and adverse effects of different statins. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to clinicians, patients. The participating organizations approved the following key questions to guide this review:

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?

   b. Is there a difference in the ability of a statin to achieve National Cholesterol Education Panel (NCEP) goals?
2. How do statins compare in their ability to raise HDL-c?
3. 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)?
4. Are there differences in the
   a. Effectiveness of statins in different demographic groups (age, sex, race)?
   b. Safety of statins in different demographic groups?
5. Are there differences in the safety of statins
   a. In the general population
   b. When used in special populations or with other medications (drug-drug interactions)? In addressing this question, we focused on the following populations and adverse effects:
      i. Patients with diabetes
      ii. Patients with HIV
      iii. Organ transplant recipients
      iv. Patients at high risk for myotoxicity
      v. Patients at high risk for hepatotoxicity
      vi. Patients using fibrates (gemfibrozil, fenofibrate) or niacin

The choice of key questions reflects the view that the following criteria may be used to select a statin: (1) the ability to lower LDL-c, (2) the ability to raise HDL-c, (3) the amount of information on cardiovascular outcomes available for each statin, (4) adverse effects, and (5) effects in demographic subgroups and in patients with concurrent medical conditions and drug therapies.

METHODS

Literature Search

To identify articles relevant to each key question, we searched the Cochrane Library (2006, Issue 1), Medline (1966-March Week 5 2006), EMBASE (1980-February 4, 2005), PreMEDLINE (through April 10, 2006), and reference lists of review articles. In electronic searches, we combined terms for the included medications with terms for relevant research designs (see Appendix A for complete search strategy). Pharmaceutical manufacturers were invited to submit dossiers, including citations. All citations were imported into an electronic database (EndNote 9.0).

Eligibility Criteria and Study Selection

Studies that met the following eligibility criteria were included in the review:

Population. Eligible populations consisted of adults (age ≥18 years) targeted for primary or secondary prevention of CHD or non-coronary forms of atherosclerotic disease with or without hypercholesterolemia. We excluded trials focusing on children and on rare, severe forms of hypercholesterolemia (LDL-c ≥250mg/dl). We included trials in inpatients with acute coronary syndrome and trials of patients undergoing revascularization if the statin was continued after hospital discharge and if health outcomes were reported.

Drugs. Trials of atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and/or simvastatin were included. We included studies that used one of three different strategies for dosing: fixed doses, single-dose titration, or treat (titrate dose) to a target LDL-c. We excluded multi-interventional therapies where the effect of the statin could not be separated out.

Outcomes. For clinical efficacy, we included studies that reported one or more of the following as primary, secondary, or incidentally reported outcomes:

Intermediate outcome measures. LDL-c reduction or the percent of patients meeting NCEP goals; HDL-c raising.

Health outcomes. Nonfatal myocardial infarction, angina, cardiovascular death, all-cause mortality, stroke, and need for revascularization (coronary artery bypass graft, angioplasty, and stenting).

We excluded studies that did not provide original data (e.g., editorials, letters), were shorter than 4 weeks in duration, did not have an English-language title or abstract, or were published only in abstract form.

We used head-to-head trials to compare the efficacy and adverse effects of different statins in a defined populations. Most head-to-head trials compare the short-term effects of different statins on LDL-c and HDL-c and on adverse events. Long-term head-to-head trials were scarce, so we relied heavily on placebo-controlled single drug trials to determine which statins have been proven to reduce mortality and the incidence of cardiovascular events. We used randomized trials as well as observational cohort studies to estimate the incidence of complications of statin therapy such as rhabdomyolysis as well as the incidence of elevations in liver enzymes or creatitine phospokinase levels. For drug interactions, we also included observational studies and individual case reports, because patients who are receiving drugs with a potential for interaction are often excluded from clinical trials. Although they do not provide comparative data, case reports were included because they may provide insight into more rare, significant interactions.

All titles and, if available, abstracts were reviewed for eligibility using the above criteria. Full-text articles of included titles and abstracts were retrieved and a second review for eligibility was conducted.

Data Abstraction

One reviewer abstracted the following data from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled,

and lost to follow-up, method of outcome ascertainment, and results for each outcome (nonfatal myocardial infarction (MI), new CHD (new angina or unstable angina), CHD mortality, all-cause mortality, stroke or TIA, and need for revascularization). Since several of the trials grouped some of these events and referred to them as major coronary events, we also included it as a category of cardiovascular health outcomes. We recorded intention-to-treat results if available.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B. These criteria are based on those developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).[6, 7] For Key Question 3, we rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories were rated poor quality; trials meeting all criteria were rated good quality; the remainder were rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population and how similar patients were to the target population in whom the intervention will be applied. We also recorded the funding source and role of the funder.

Dosing strategies can also affect applicability of these studies to practice. In fixed-dose studies, we note whether the doses are used in current practice and compare the rates of side effects when the dosages of the compared statins reduced LDL-c to a similar degree. We note when the dosages of the compared drugs differ in the extent to which they reduced LDL-c. For studies that titrated doses, we examined whether the methods used to decide when and how much to increase the doses were applied equally to the statins under study.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reported the range of estimates of LDL-c and HDL-c changes for each dosage of each drug. When possible, we also calculated pooled estimates of LDL-c reduction by drug and dosage. We considered the quality of the studies and heterogeneity across studies in study design, patient population, interventions, and outcomes, in order to determine whether meta-analysis could be meaningfully performed. If meta-analysis could not be performed, we summarized the data qualitatively.

RESULTS

Results of literature searches are shown in Figure 1. Searches identified 8,667 citations. We retrieved 438 potentially relevant articles for review. Of these, 113 randomized controlled trials and 77 additional publications (other study designs, background) were included. Excluded trials are listed in Appendix C.

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

Summary of the Evidence

- For patients who require LDL-c reductions of up to 35% to meet their goal, any of the statins are effective.
- In patients requiring an LDL-c reduction of 35% to 50% to meet the NCEP goal, atorvastatin 20mg or more, lovastatin 80mg, rosuvastatin 10mg or more, and simvastatin 20mg or more daily are likely to meet the goal.
- Among high-potency statins,
  - Atorvastatin 80mg daily and rosuvastatin 20mg or more reduced LDL-C by 50% or more.
  - Atorvastatin 80mg had a higher rate of some adverse effects (GI disturbances and transaminase elevation) than simvastatin 80mg daily in a trial in which the LDL lowering of atorvastatin was greater than that of simvastatin.
  - Adverse event rates in patients using rosuvastatin 40mg were similar to rates in patients using atorvastatin 80mg in short-term trials.

Detailed Assessment

1a. Are there doses for each statin that produce similar percent reduction in LDL-c between statins?

We identified 68 randomized controlled trials comparing the LDL-c lowering ability of two or more statins in patients with baseline LDL-c <250mg/dl (Evidence Table 1).[8-50 51-56] In 39 of these trials, the percentage of patients reaching their NCEP goal was also evaluated. There were 37 double-blinded, 27 open-label, and two single-blinded studies. One study was entitled "blinded", but no specifics were given, and in another, no information on blinding was reported (See Evidence Table 1, column 1). Dosing strategies varied between trials. Some studies titrated to a maximum recommended daily dose (titrate to target) while others compared fixed statin doses. One trial compared extended release lovastatin with the immediate-release form.[41] One trial looked at the effects of switching to rosuvastatin midway through the trial.[57] Most of the trials had fair internal validity.

The trials included men and women ages 18 and older who completed a minimum 4-week placebo/dietary run-in phase after which those meeting LDL-c criteria were randomized. Most trials excluded patients with secondary hypercholesterolemia (uncontrolled diabetes, thyroid disease, or other endocrine condition), pregnant or lactating women, kidney or liver impairment, baseline creatine kinase (CK) elevation, triglycerides ≥350 to 400mg/dl and those

receiving drugs with the potential for drug interaction with statins. One trial was conducted in African-Americans,[52] and two in patients with type 2 diabetes.[56, 58] The duration of the clinical trials varied from 4 weeks to 18 months. In the majority of the trials the efficacy analyses were performed on a smaller number of patients than were randomized (that is, the trials did not use intention-to-treat statistics).

Table 1 shows the percent LDL-c lowering from baseline for trials of a particular statin dose (rather than mean or median statin doses). Our estimates, which were based on direct head-to-head trials, were consistent with the estimates from a 2003 meta-analysis of placebo-controlled trials.[59] With only a few exceptions, the mean percent LDL-c reduction for a particular statin dose varied little across studies and was consistent with the information in the package insert. The exceptions were:

(1) Some poorly reported and poor-quality trials had discrepant results[48, 60-62]

(2) In an open-label, fair-quality study, lovastatin 20mg daily produced a lower- than-expected reduction in LDL-c (21%).[28] 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) The manufacturer's prescribing information reports an LDL-c reduction of 60% in patients receiving atorvastatin 80mg daily. However, this reduction comes from data involving only 23 patients. The six trials that assessed the LDL-c lowering ability of atorvastatin 80mg daily included a total of 1758 patients randomized to atorvastatin and had reductions of 46%-54%.

Table 1. 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 (and from ATP-III[3] if available)	Number of clinical trials**
Atorvastatin			
10mg	28.9%-40.2%	39% (37%)	22
20mg	38.4%-46.1%	43%	8
40mg	45.1%-51.3%	50%	5
80mg	46.3%-54%	60% (57%)	6
Fluvastatin			
20mg	17%-21.8%	22% (18%) $^{\beta}$	5
40mg	22%-26%	25% $^{\beta}$	6
80mg	29.6%-30.6%$^{+}$	36% (31%)$^{++}$ $^{\beta}$	2
80mg XL*	--	35% $^{\beta}$	0
Lovastatin			
10mg	21.6%-24%	21%	2
20mg	21%-29%	27% (24%)	8
40mg	27.9%-33%	31%	5
80mg	39%-48%	42% (40%) $^{\alpha}$	2
Pravastatin			
10mg	18%-24.5%	22%	9
20mg	23%-29%	32% (24%)	11
40mg	25.2%-34%	34%	8
80mg*	--	37% (34%)	0
Rosuvastatin			
5mg	39.1%-46%	45%	6
10mg	37.1%-50.6%	52%	9
20mg	45.7%-52.4%	55%	3
40mg	53.6%-58.8%	63%	3

Statin dose per day	Range of percent LDL-c lowering from comparative clinical trials	Mean percent LDL-c lowering from manufacturers prescribing information (and from ATP-III[3] if available)	Number of clinical trials**
Simvastatin 10mg	26%-33.1%	30%	17
20mg	18.5%-40%	38% (35%)	17
40mg	34.3%-43%	41%	7
80mg	43%-48.8%	47% (46%)	5

*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; total number of clinical trials will be more than the number of included trials because some trials studied more than two statins.
+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

From the trials summarized in Table 1, we determined the following approximate equivalent daily doses for statins with respect to their LDL-c lowering abilities (Table 2):

Table 2. Doses of statins that result in similar percent reductions in LDL-c*

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

*estimates based on results of head-to-head trials (Evidence Table 1)

Comparisons of high-potency statins

Atorvastatin, simvastatin, and rosuvastatin are considered high potency statins because they can lower LDL-c more than 40%. We compared efficacy and adverse events in head-to-head trials of high-potency statins.

Atorvastatin vs simvastatin. Twenty-three studies have compared atorvastatin to simvastatin (Evidence Table 1).[8, 11, 16, 17, 19, 20, 26, 28-31, 33, 35-37, 43, 46, 50, 51, 60, 61, 63, 64] Seven of these included patients with CHD or CHD equivalents (e.g., diabetes).[8, 11, 17, 28, 31, 46, 60] At doses below 80 mg, rates of adverse events and withdrawals due to adverse events were similar in patients taking atorvastatin or simvastatin.

Three studies directly compared atorvastatin 80mg to simvastatin 80mg daily:[30, 34, 36] In the first study, atorvastatin 80mg reduced LDL-c by 53.6% compared to 48.1% for simvastatin 80mg($p \leq 0.001$).[30] Compared to the simvastatin 80mg groups, a greater number of patients in the atorvastatin 80mg groups reported clinical adverse effects, primarily gastrointestinal-diarrhea (23% vs 11.9%; $p<0.001$). There was no significant difference between atorvastatin 80mg and simvastatin 80mg in withdrawal rates due to adverse effects. Withdrawal from the study due to adverse laboratory events occurred more often in the atorvastatin 80mg compared to the

simvastatin 80mg daily group (4% vs 0.8%; p<0.05). Clinically important ALT (alanine aminotransaminase) elevation (> 3 times the upper limit of normal {ULN}) 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 the second study,[36] 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. This study was unblinded and did not use intention-to-treat statistics. Mean baseline LDL-c in the atorvastatin 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.

The STELLAR trial[34] was a fair to poor quality open-label trial designed to compare rosuvastatin to other statins (atorvastatin, simvastatin, and pravastatin). One hundred sixty-seven patients were randomized to atorvastatin 80 and 165 to simvastatin 80mg. Baseline LDL levels were similar in both groups (190mg/dL). The mean percent change in LDL level after 6 weeks was 51% in the atorvastatin group and 46% in the simvastatin group, a difference (5.3 percentage points) similar to those found in the two other studies comparing atorvastatin 80mg to simvastatin 80mg. The proportion of patients who withdrew because of adverse events was 3.6% in both groups.

Atorvastatin vs rosuvastatin. Thirteen trials[21, 34, 47, 52-54, 56-58, 65-68] and two meta-analyses[14, 69] have compared rosuvastatin to atorvastatin (see Table 3, below, and Evidence Table 1).

Table 3. Trials comparing atorvastatin to rosuvastatin

Study, reference	Drugs, doses	N screened/ randomized	Design	Duration	Mean Baseline LDL-c	Other patient characteristics
Berne 2005 (URANUS)[58]	Rosuva 10 to 40 mg Atorva 10 to 80 mg	NR/ 469	Double-blind Fixed dose for 4 weeks, then titration to goal	16 weeks	165.6 mg/.dL	Type 2 diabetes
Davidson 2002[21] (AstraZeneca Study 24)	Rosuva 5,10 mg Atorva 10 mg	1,888/ 519	Double-blind Fixed dose	12 weeks	186.5 mg/dL	
Ferdinand 2006[52]	Rosuva 10, 20 mg Atorva 10, 20 mg	2,385/ 774	Open-label Fixed dose	6 weeks	190.6 mg/dL	African Americans
Fonseca 2005[53]	Rosuva 10 mg Atorva 10 mg	1,644/ 1,124	Open-label Fixed dose	12 weeks	173 mg/dL (statin naïve patients) 163 mg/dL (others)	
Jones 2003[34] (STELLAR)	Rosuva 10, 20, 40, 80 mg Atorva 10, 20, 40, 80 mg	NR/ 2431 (1284 rosuva or atorva)	Open-label	6 weeks	189.1 mg/dL	
Jukema 2005[54]	Rosuva 10, 20, 40 mg Atorva 20, 40, 80 mg	# screened NR/ 461	Open-label Fixed dose for 6 weeks, then dose increased every 6 weeks	18 weeks	141 mg/dL	Established cardiovascular disease
Olsson 2002[47] (AstraZeneca Study 26)	Rosuva 5, 10-80 mg Atorva 10-80 mg	1,521/ 412	Double-blind 12 weeks at fixed dose, then titration to goal	52 weeks	187.4 mg/dL	
Schneck 2003[65] (AstraZeneca Study 33)	Rosuva 5, 10, 20, 40, 80 mg Atorva 10, 20, 40, 80 mg	# screened NR/ 978 eligible/ 374 enrolled.	Double-blind Fixed dose	6 weeks	189 mg/dL	
Schuster 2004 (MERCURY I)[57]	Rosuva 10 or 20 mg Atorva 10 or 20 mg	6508/ 3161 (2043 rosuva or atorva)	Open-label 8 week at fixed dose; then either remained on current statin or switched to rosuvastatin for 8	16 weeks	165.1 mg/dL	History of CHD or CHD risk >20% over 10 years, atherosclerosis or diabetes

Study, reference	Drugs, doses	N screened/ randomized	Design	Duration	Mean Baseline LDL-c	Other patient characteristics
			weeks			
Schwartz 2004[66]	Rosuva 5, 10-80 mg Atorva 10-80 mg	1,233/ 383	Double-blind 12-wk at fixed dose, then forced titration	24 weeks		Atherosclerosis or diabetes
Strandberg 2004[67]	Rosuva 10 mg Atorva 10 mg	NR/ 1024	Open-label 12-wk at fixed dose, then titration to ATPII goal if needed	12 weeks plus optional 36 week follow-up	>135 mg/dL in statin-naive patients; >120 mg/dL in patients using the starting dose of another lipid-lowering drug.	History of CHD or CHD risk >20% over 10 years, atherosclerosis or diabetes
Stalenhoef 2005 (COMETS)[68]	Rosuva 10 mg Atorva 10 mg	1338/ 401	Double-blind Fixed dose	12 weeks	169.7 mg/dL	Metabolic syndrome
Wolfenbuttel 2005[56]	Rosuva 10, 20, 40 mg Atorva 20, 40, 80 mg	416/ 263	Open-label Fixed dose for 6 weeks, then dose increased every 6 weeks	18 weeks	169 mg/dL	Type 2 diabetes

Six trials concerned patients who had few or no risk factors for CAD[21, 34, 47, 52, 53, 65] and 7 trials enrolled patients at high risk for cardiovascular disease.[54, 56-58, 66-68] All studies comparing rosuvastatin to atorvastatin that reported LDL-c reductions at 12 weeks[14, 21, 47, 66, 67] had similar results, whether or not they included patients at high risk for CHD.

Trial designs included a 6-week run-in period. Only subjects who complied with an American Heart Association Step1 diet for 6 weeks but still met the LDL-c requirements were randomized. Two trials allowed patients to enter the study without run-in period if they were currently on another statin.[53, 67] Eight trials reported the number screened. The percentage of patients enrolled after screening ranged from 27.1% to 68.4%.

The Strandberg study included patients with hypertension (73%), diabetes (26.9%), other atherosclerotic disease (28%), or CHD. On average, rosuvastatin 10mg reduced LDL-c more than atorvastatin 10mg (46.9% vs. 38%, $p<0.05$). There was no comparison of rosuvastatin 10 mg to a higher dose of atorvastatin in this trial. At week 12, the 387 patients who had not reached their LDL-C goal (based on the 1998 Second Joint Task Force of European and Other Societies on Coronary Prevention {JTF} targets) were switched to rosuvastatin from atorvastatin, and had their dosage of rosuvastatin increased until their goal was met (only 12 patients titrated up to the maximum daily dose of 40mg for rosuvastatin). About 3.5 % of the rosuvastatin group (including those occurring during the 36-week extension period) and 3.0% of the atorvastatin group withdrew due to adverse events.

Schwartz et al also enrolled patients who had diabetes or were at high cardiovascular risk.[66] Of 383 patients enrolled, 3.7% had diabetes alone, 85.4% had atherosclerosis alone (i.e., a history of peripheral vascular disease, coronary artery disease, or cerebrovascular disease), and 11% had both diabetes and atherosclerosis. Although the trial was designed to compare rosuvastatin 80mg to atorvastatin 80mg over 24 weeks, results at weeks 12 and 18, before patients were titrated to 80mg, are also available. Rosuvastatin 5mg daily (39.8%, $p<0.01$) had a significant difference in reducing LDL-c levels compared to the equivalent dose of atorvastatin 10mg (35%) at 12 weeks. The 18-week analysis in this study compared rosuvastatin 20mg and rosuvastatin 40mg to atorvastatin 40mg. Through 12 weeks, similar proportions of patients taking rosuvastatin 10mg and atorvastatin 10mg withdrew because of adverse events. There was no comparison of equipotent doses of atorvastatin and rosuvastatin in this trial.

The largest head-to-head trial that included higher doses of rosuvastatin was a 6-week open label trial (STELLAR) in which about 300 patients took rosuvastatin 40mg/day or higher.[34] Rosuvastatin 80mg/day had unacceptably high rates of serious adverse events. Rosuvastatin 40mg, atorvastatin 80mg, and simvastatin 80mg had similar rates of withdrawal and of serious adverse events (pravastatin 80mg was not included). A post hoc subanalysis of 811 patients in the STELLAR trial with metabolic syndrome had results similar to the overall sample.[70]

Recent open-label trials of atorvastatin versus rosuvastatin were conducted in African Americans,[52] patients with type 2 diabetes,[56, 58] and patients with established cardiovascular disease.[54] In African Americans, rosuvastatin 10 mg lowered LDL-c more than atorvastatin 10 mg, but not atorvastatin 20 mg. This is similar to results of other studies. In patients with type 2 diabetes and established cardiovascular disease, the percent LDL-c lowering with rosuvastatin and atorvastatin was similar to that found in other studies, and patients taking rosuvastatin had greater LDL-c reductions.

1b. Do statins differ in the ability to achieve National Cholesterol Education Program goals?

The ability of an agent to achieve NCEP goals is another factor in choosing between statins. The ATP III includes a table that is helpful in determining how much reduction is needed to achieve LDL-cholesterol goals (see Table 4, below). The 2004 supplement to ATP-III stresses that the goals are *minimums.* According to the 2004 supplement to ATP-III and in the 2006 AHA/ACC guidelines, a target of <70 mg/dL is a reasonable clinical option for patients who have known coronary artery disease.

Table 4. Achieving Target LDL-cholesterol goals

Baseline LDL-c	**130**	**160**	**190**	**220**
_____(Percent Reduction to Achieve Target Goals)_____				
Target LDL-C < 70 mg/dL	43%	56%	63%	68%
Target LDL-C < 100 mg/dL	23%	38%	47%	55%
Target LDL-C < 130		19%	32%	41%
Target LDL-C < 160			16%	27%

(Based on ATP-III. Table VI-3-1. Page VI-19.[3])

Thirty-nine reports measured the percentage of patients meeting their National Cholesterol Education Program (NCEP) LDL-c treatment goals. Many of the studies compared the efficacy of the usual starting doses of the compared drugs, rather than the efficacy and adverse events when the drugs were tailored over time.

Problems in dosing limit the validity of many of these trials. Frequently, less potent starting doses of several statins (lovastatin, pravastatin, and simvastatin) were compared to more potent doses of atorvastatin. For example, in one open-label study (Target-Tangible),[43] 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 because the dosage was not yet approved by the FDA. In 10 studies, 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 seven studies, it is unclear why clinicians did not titrate the dosage as aggressively in the compared groups.

In those that studied tailored doses, the maximum dose was often lower than the maximum approved dose available today. In the Treat-to-Target (3T) Study, a 52-week, multicenter, randomized, head-to-head trial, once-daily oral treatment with 20mg atorvastatin was compared to 20mg simvastatin.[46] At 8 weeks, reductions in LDL-c were -46% for atorvastatin vs -40% for simvastatin ($p< 0.001$). The dose was doubled after 12 weeks if the target NCEP level of LDL-c<100 mg/dL was not reached at 8 weeks. Fewer atorvastatin patients needed to have their dose doubled; nevertheless a greater percentage of atorvastatin patients reached the LDL-c target after 52 weeks (61% vs 41%; $p< 0.001$). However, the simvastatin 80mg dose, which was approved later, was not evaluated in the study.

One open-label study compared rosuvastatin 10mg to different dosages of other statins (atorvastatin 10mg, atorvastatin 20mg, simvastatin 20mg, pravastatin 40mg) for eight weeks, and then looked at the effects of switching from rosuvastatin to a different statin for another eight weeks.[57] More patients achieved their ATP III goal on rosuvastatin 10mg (80%) than on the other statins studied.

In a meta-analysis of three 12-week randomized trials of rosuvastatin versus atorvastatin 76% of patients taking rosuvastatin 10mg reached their ATP III goal, versus 53% of those taking atorvastatin 10mg.[69] In the same publication, in a pooled analysis of 2 trials of rosuvastatin versus simvastatin and pravastatin, percentages of patients reaching their goal were 86% for rosuvastatin 10mg, 64% for simvastatin 20mg, and 49% for pravastatin 20mg. Results for rosuvastatin 5mg are not reported in this meta-analysis. The only one-year head-to-head study of rosuvastatin versus atorvastatin[47] was conducted in 3 phases: a 6-week run-in period, a 12-week fixed-dose comparison of rosuvastatin (5 or 10mg) or atorvastatin 10mg; and a 40-week titration period in which the dose of rosuvastatin or atorvastatin could be doubled until the NCEP-II goal or a dose of 80mg was reached. At 52 weeks, the percentage of patients meeting their goal was not significantly different among the three groups (88% of patients starting at rosuvastatin 5mg, 98% of those starting at rosuvastatin 10mg, and 87% of those starting at atorvastatin 10mg). Excluding results for 80mg of rosuvastatin, results are similar (89% of those starting at rosuvastatin 5mg and 98% of those starting at rosuvastatin 10mg reached their goal).

In other studies of atorvastatin lasting one year or longer, percentages of patients meeting their NCEP goal ranged from 46% to 61% for 10-40mg, and 51%-95% for 10-80mg.

In the head-to-head trials, 1.2% of patients taking rosuvastatin 40mg developed dipstick-positive proteinuria, versus 0.3% for atorvastatin 80mg, and 0% for simvastatin 80mg and pravastatin 40mg.[71] The clinical importance of this renal effect is not known, but, as a precaution, the rosuvastatin product label recommends dose reduction from 40mg in patients with unexplained persistent proteinuria.

Key Question 2. How do statins compare in their ability to increase HDL-c?

Summary of the Evidence

- When statins are provided in doses that reduce LDL-c by equivalent amounts, a similar percent increase in HDL-c can be achieved.
- There is conflicting evidence about simvastatin vs atorvastatin, with some studies finding no difference and others finding simvastatin superior.
- Some studies found greater increases in HDL-c with rosuvastatin compared with atorvastatin, while other studies found no difference.

Detailed Assessment

A previous meta-analysis of placebo-controlled trials estimated that, on average, statins increased HDL-c by 3mg/dL (0.07 mmol/l, 95% CI 0.06 to 0.08 mmol/l), with no detectable effect of dose.[59] In our review of 57 head-to-head trials, statins raised HDL-c levels from 0 to 19%, with the great majority between 5% and 9% (Evidence Table 1). While most found no significant difference in HDL-c-raising among the statins, there were some exceptions.

In six head-to-head studies of LDL-c lowering, simvastatin increased HDL-c more than atorvastatin (10 to 80mg)[16, 19, 30, 33, 36, 46] but in 12 others, there was no significant difference between the two on this measure.[8, 17, 20, 26, 29, 31, 35, 50, 60, 61, 63, 64]

Two studies that compared atorvastatin to simvastatin were designed to measure HDL-c raising as a primary outcome.[11, 37] A 24-week study of 917 patients randomized to atorvastatin 80mg or simvastatin 80mg reported only an average of the increase at weeks 18 and 24, separately by baseline HDL-c level.[11] The average increase was the same in patients with baseline HDL-c above and below 40 mg/dL: 2.1% for patients randomized to atorvastatin and 5.4% for those randomized to simvastatin. These differences were not statistically significant. In the other study reporting HDL-c as a primary outcome,[37] 826 patients were randomized to atorvastatin (20mg per day for 6 weeks, then 40mg per day) or simvastatin (40mg/day for 6 weeks, then 80mg/day) for 36 weeks. The primary endpoint was the average of results from weeks 6 and 12. The mean percent increase in HDL-c was greater in the simvastatin group (9.1% vs. 6.8%, $p<0.001$). The difference was greater at higher doses. HDL-c increased by 9.7% and 6.4% in the simvastatin 80mg and atorvastatin 40mg groups, respectively. At lower doses, the difference was not significant (percent change not reported). Results are not reported beyond 12 weeks.

Seven short-term head-to-head studies reported HDL-c increases with rosuvastatin compared with atorvastatin.[14, 21, 34, 47, 65-67] However, the results were mixed. Four studies reported greater increases in HDL-c with rosuvastatin 5 or 10mg than with atorvastatin 10mg.[14, 21, 66, 67] A fifth study of fair quality reported no difference between the two at the same doses.[47]

One study that increased the statin dosages every four weeks compared the HDL-c raising ability of atorvastatin to four other statins (not including rosuvastatin). Atorvastatin 20mg increased HDL-c levels more than lovastatin 20mg ($p<0.01$). In this study, atorvastatin did not show a significant difference compared to the other statins (besides lovastatin) in increasing HDL-c levels.

Five trials evaluated rosuvastatin compared to multiple statins in their abilities to increase HDL-c levels. In the STELLAR trial,[34] HDL-c increases were greater with rosuvastatin 20mg compared with atorvastatin 40mg (9.5% vs 4.4%, $p<0.002$), but there was no significant difference between rosuvastatin 20mg and simvastatin 80mg (9.5% vs 6.8%), or between rosuvastatin 10mg and atorvastatin 20mg (7.7% vs 4.8%) or simvastatin 40mg (5.2%). Three head-to-head trials compared rosuvastatin to other statins for HDL-c raising. In one, the increase in HDL-c with rosuvastatin 10mg was equivalent to simvastatin 20mg.[18] Rosuvastatin 10mg was better than pravastatin 20mg in this same study[18] and equivalent in another.[49, 57]

Key Question 3. How do statins compare in their ability to reduce the risk of nonfatal myocardial infarction, angina, CHD mortality, all-cause mortality, stroke or need for revascularization (coronary artery bypass graft, angioplasty or stenting)?

Summary of the Evidence

- Information from head-to-head trials is limited.
  - There is no information from head-to-head trials in patients who have never had coronary disease or coronary disease equivalents.
  - *In patients with known coronary heart disease:*
    - In patients who had a recent myocardial infarction, high dose **atorvastatin 80mg** daily reduced all-cause mortality and CV events compared with **pravastatin 40 mg** daily (PROVE-IT). For every 25 patients treated with **atorvastatin 80mg** instead of **pravastatin 40mg**, one coronary event was prevented.
    - In patients who had a history of myocaridal infarction (IDEAL), high-dose **atorvastatin (80 mg)** and **simvastatin (20 mg)** did not differ in the primary endpoint (coronary death, hospitalization for nonfatal acute MI, or cardiac arrest with resuscitation). More high-dose atorvastatin patients discontinued due to adverse events (9.6% vs. 4.2%, $p<0.001$), and there were more cases of elevated liver enzymes and myalgia with high-dose atorvastatin.

- The amount of information on cardiovascular outcomes available from placebo-controlled trials for each statin differs substantially.

  In patients with known coronary heart disease:
  - **Simvastatin** reduced all-cause mortality and CV events.
  - **Pravastatin** reduced all-cause mortality and CV events.
  - **Fluvastatin** reduced coronary events when started after percutaneous coronary intervention.
  - Studies of angiographic progression of atherosclerotic plaques provide fair-quality but indirect evidence that **lovastatin** is effective in preventing CV events in patients with CHD. This finding is weakened because of possible reporting bias (see below.)
  - There are no completed studies of **rosuvastatin** with CHD endpoints in patients with coronary disease.

Detailed Assessment

Head-to-head trials

There are only two head-to-head trials comparing the ability different statins to reduce the risk of coronary events, stroke, or death (PROVE-IT[72] and IDEAL[73], see Evidence Table 2).

These studies compared high-dose atorvastatin to usual-dose pravastatin or simvastatin in patients with a history of MI. A third head-to-head trial compared intensive atorvastatin to a control group of diet and low-dose lovastatin if needed in patients with stable coronary artery disease; the primary outcome measure in this trial was ischemia on ambulatory ECG.[74] There are no head-to-head trials comparing high-doses of different statins for reducing coronary events, and there are no head-to-head primary prevention trials.

In the Pravastatin or Atorvastatin Evaluation and Infection Therapy--Thrombolysis in Myocardial Infarction (PROVE-IT) trial,[72] 4,162 patients who had been hospitalized in the previous 10 days for an acute coronary syndrome (MI or unstable angina) were randomized to treatment with atorvastatin 80mg daily or pravastatin 40mg daily. Most patients were men (78%) aged 45 to 70 who had risk factors for CVD (diabetes, hypertension, smoking, or prior heart attack). Patients who were already using a high dose of a statin (80mg) were excluded from the study. While hospitalized, about 69% of patients underwent PCI (stent or PTCA) prior to randomization. Before randomization, half of the subjects had LDL levels between 87 and 127mg/dL, and half were higher or lower than that.

Atorvastatin 80mg reduced LDL by an average of 40 points. Pravastatin 40mg reduced LDL by only 10 points. The reason is that pravastatin had no effect on LDL levels in patients who were taking similar doses of a statin before their MI, while atorvastatin 80mg reduced LDL by about 32% in these subjects.

After an average of 2 years of follow-up (range 18 to 36 months), fewer atorvastatin patients had a major cardiovascular event (26.3% vs 22.4%; p=0.005). Major events were defined as all-cause mortality, MI, documented unstable angina requiring hospitalization, revascularization with either PTCA or CABG, and stroke. The atorvastatin group also had better outcomes on the components of the primary endpoint, including death or MI (18% reduction, p=0.06), recurrent unstable angina, (29% reduction, p=0.02), CHD death (22.3% vs 19.7%; p=0.029), all-cause mortality (28% reduction; p=0.07), and need for revascularization (14% reduction, p=0.04).

The benefit of atorvastatin 80mg on cardiovascular events was significantly greater only in patients with no prior statin use. Among patients with prior statin use (25.5% of atorvastatin patients vs 24.9% of pravastatin patients), 2-year event rates were 27.5% for atorvastatin and 28.9% for pravastatin. In contrast, among patients with no prior statin use, event rates were 20.6% for atorvastatin and 25.5% for pravastatin, respectively.

It is likely that the superior results of intensive therapy with atorvastatin were due to additional LDL-lowering. But the authors note that it is also possible that the superior anti-inflammatory effect of the higher-dose statin is responsible for the superior results in that group. C-reactive protein levels fell in both groups, but they fell more in the atorvastatin group.

In patients who have an acute MI and are not already taking a statin, atorvastatin 80mg was better then pravastatin 40mg. Pravastatin at any dose cannot achieve as much LDL reduction as atorvastatin 80mg. PROVE-IT does not indicate whether atorvastatin would be better than other statins that reduce LDL to a similar degree.

In the fair-quality IDEAL trial,[73] post-myocardial infarction patients were randomized to high-dose atorvastatin (80 mg) vs usual-dose simvastatin. Patients who had previously taken a statin were eligible provided they had not been titrated to a dose higher than the equivalent of simvastatin 20 mg; 50% of those enrolled were taking simvastatin prior to randomization. The study was open-label with blinded endpoint classification. The median time since MI was 21 to 22 months, and 11% of patients were within 2 months of their MI. The starting dose of

simvastatin was 20 mg; 23% of patients were taking 40 mg by the end of the study. The LDL-c reduction was greater at 12 weeks in the atorvastatin group (49% vs 33%).

After a median followup of 4.8 years, there was no difference between treatment groups on the primary endpoint (coronary death, hospitalization for nonfatal acute MI, or cardiac arrest with resuscitation). The primary endpoint occurred in 10.4% of simvastatin versus 9.3% of atorvastatin patients (Hazard Ratio 0.89; 95% CI 0.78, 1.01). There was no difference in CV mortality or all-cause mortality, but a reduction in nonfatal MI (0.83; 95% CI 0.71, 0.98) and in major coronary events and stroke (HR 0.87; 95% CI 0.78, 0.98) was shown. More high-dose atorvastatin patients discontinued due to adverse events (4.2% vs 9.6%, p<0.001), and there were more cases of elevated liver enzymes and myalgia with high-dose atorvastatin. There were no differences in the rate of myopathy or rhabdomyolysis.

Several factors might help explain the discrepant results of PROVE-IT and IDEAL:

(1) All subjects in PROVE-IT had acute coronary syndrome, whereas only 11% of those in IDEAL had had a recent MI.

(2) The definition of the primary endpoint differed in the two trials. In IDEAL, the reduction in LDL-c (49%) with atorvastatin was slightly less than expected, and adherence in the atorvastatin group was not as good as in the simvastatin group (89% vs 95%).[73]

In a fair-quality, one-year trial in patients with stable CAD, intensive atorvastatin (up to 80 mg, to a target of LDL-c <80 mg/dL) was not more effective than a control group of diet plus low-dose lovastatin (5 mg if needed, to a target of LDL-c <130 mg/dL) for reducing the number of ischemic episodes as measured on ambulatory ECG, patient-reported angina frequency, and nitroglycerin consumption.[74] There was a reduction in the number of ischemic episodes in both groups, but no difference between groups. There was no significant difference in major clinical events between groups after one year, but the number of events was small and the study was powered to detect a difference in ischemia, not clinical events.

Placebo-controlled trials

Many trials comparing a statin to placebo or, in a few instances, to non-pharmacologic treatments, reported health outcomes. These trials indicate which statins have been proven to reduce the risk of cardiovascular events in various patient populations. We examined the included trials in four categories.

- *Studies with Primary CHD Endpoints*. This group includes 20 placebo-controlled trials and two head-to-head trials: 15 studies in outpatients,[73, 75-88] and 7 studies in inpatients with acute MI or unstable angina.[72, 89-94] The primary endpoint in these trials was a reduction in cardiovascular health outcomes.
  - *Outpatient Studies*. Enrollment was in excess of 4,000 patients with an average follow-up period of 5 years. All of the trials were good or fair quality and were considered the best evidence for demonstrating a reduction in cardiovascular health outcomes with statins.
  - *Inpatient Studies*. These include studies of patients hospitalized with acute MI or unstable angina. There is one head-to-head trial of intensive atorvastatin therapy compared with a standard dose of pravastatin. Six other trials

compared a statin to placebo or usual care. No study in this group was rated good quality.

- *Studies of the Progression of Atherosclerosis with Secondary or Incidental CHD Endpoints* are placebo-controlled trials in which the primary endpoint was progression of atherosclerosis measured by angiography or B-mode ultrasonography.[95-106] 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[96, 103] of these trials enrolled more than 500 patients. The others ranged from 151 to 460 included patients. As evidence regarding reduction in CHD events, these trials were fair or fair-to-poor in quality.
- *Revascularization Studies with Restenosis or Clinical Outcome Endpoints* are trials of the use of statins to prevent restenosis after coronary revascularization (CABG, PTCA, or coronary stent).[107-112]
- *Miscellaneous Trials*. Three additional trials with clinical outcomes did not fit the criteria for the other categories.[43, 113, 114]

Studies with Primary CHD Endpoints

The major trials are summarized briefly in Tables 5 (outpatient studies) and 7 (inpatient studies) below and in more detail in Evidence Table 2.

The GREACE,[115] ALLIANCE,[116] and Treating to New Targets (TNT)[117] trials did not meet inclusion criteria for our efficacy analysis, but they provide information about safety of high-dose atorvastatin and are discussed under Key Question 4.

Table 5. Outpatient and community-based placebo-controlled trials with CHD endpoints

Trial (Quality)	Risk Status/ Average annual event rate in placebo group	Baseline LDL (mg/dL)	Study Duration (years)	% LDL reduction	Reduction in Coronary events (relative risk reduction)*	NNT to prevent a coronary event§
Trials of atorvastatin						
ASCOT Atorvastatin 10mg (Fair-Good)	HTN plus CHD risk factors/ 0.9%	133	3.3	35%	**29%**	94
CARDS Atorvastatin 10 mg (Good)	Type 2 diabetes, no history of CVD 2.3%	117	3.9	36%	**37%**	31
4D (Wanner, 2005) (Fair)	Type 2 diabetes, receiving dialysis 39%	126	4.0	42%	18% (including PTCA and CABG)	18
Trials of fluvastatin						
ALERT Fluvastatin 40 mg (Good)	Patients with renal transplant 1.0%	160	5.1	32%	Primary endpoint not significant (p=0.139), but 35% reduction in cardiac deaths or non-fatal MI	Results not significant
Riegger et al Fluvastatin 40mg (Fair)	Symptomatic CAD/ 2.8%	198	1	26.9%	38%	Results not significant
Trials of lovastatin						
AFCAPS Lovastatin 20mg-40mg (Good)	Average risk, no history of CAD/ 1.1%	150	5.2	25%	**37%**	49
Trials of pravastatin						
ALLHAT-LLC Pravastatin 40mg (Fair-Good)	Hypertensive moderately high LDL-c and at least one additional CHD risk factor/ 1.7%	145	4.8	24%	9%	Results not significant

Trial (Quality)	Risk Status/ Average annual event rate in placebo group	Baseline LDL (mg/dL)	Study Duration (years)	% LDL reduction	Reduction in Coronary events (relative risk reduction)*	NNT to prevent a coronary event§
CARE Pravastatin 40mg (Good)	History of CAD/ 2.6%	139	5	28%	**24%**	41
LIPID Pravastatin 40mg (Good)	History of CAD/ 2.6%	150	6.1	25%	24%	164
PREVEND IT Pravastatin 40 mg (Fair)	Average risk, persistent microalbuminuria 0.8%	174	3.8	25%	13%	Results not significant
PROSPER Pravastatin 40mg (Good)	70-82 years old, history of CHD or risk factors/ 5.2%	147	3.2	27%	**15%**	24
WOSCOPS Pravastatin 40mg (Good)	High risk, no history of CAD/ 1.5%	192	4.9	16%	**31%**	44
Trials of simvastatin						
4S Simvastatin 20mg (Good)	History of CAD/ 5.2%	187	5.4	35%	**34%**	11
HPS Simvastatin 40mg (Good)	History of CVD, diabetes, or noncoronary vascular disease/ 2.1%	131	5.5	30%	**27%**	32

***Bold** indicates statistically significant results; §Not adjusted for length of trial or for baseline risk.
HTN=hypertension. CVD=cardiovascular disease. CAD=coronary artery disease.

Studies in Outpatients

Primary Prevention. AFCAPS (lovastatin) and WOSCOPS (pravastatin) recruited patients without a history of CHD (primary prevention).[80, 86] In AFCAPS/TexCAPS, lovastatin reduced the incidence of new cardiovascular events by 37%, or one for every 49 subjects (men and women) treated.

In WOSCOPS,[86] pravastatin 40mg reduced coronary events by 31%, or one 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.

In WOSCOPS, but not AFCAPS/TexCAPS, statin therapy reduced coronary disease deaths. 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=0.051). The absolute risks of coronary disease death were 1.3% for subjects in the pravastatin group and 1.9% in the placebo group (NNT=163). In AFCAPS/TexCAPS, 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 (p=NS). There was no difference in all-cause mortality.

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 in the first place. The reduction in CHD deaths was actually comparable in the two studies but, in AFCAPS/TexCAPS, it did not reach statistical significance due to the lower number of events.

Secondary Prevention. Four placebo-controlled trials recruited patients with documented CHD. Two of them (LIPID, CARE)[76, 84] evaluated pravastatin (n=13,173), one (4S)[82] evaluated simvastatin (n=4,444), and one evaluated fluvastatin.[83]

Pravastatin and simvastatin significantly reduced the incidence of major coronary events, including overall mortality in LIPID and 4S. In 4S, the 8-year probability of survival was 87.6% in the placebo group and 91.3% in the simvastatin group. The risk of stroke was also reduced in CARE and 4S. In a *post hoc* subanalysis of 2,073 patients in the LIPID trial with both low LDL-C and low HDL-C, pravastatin was associated with a relative risk reduction of 27% (95% CI, 8% to 42%), a 4% absolute risk reduction, and an NNT of 22 to prevent one CHD event over 6 years.[118]

In Riegger et al,[83] patients who had stable angina were randomized to fluvastatin or placebo. The primary endpoint included cardiac death, nonfatal myocardial infarction, and unstable angina pectoris. By 1 year, there were fewer primary events in the fluvastatin group. However, excluding unstable angina, the relative risk of cardiac death and nonfatal myocardial infarction was not significantly reduced with fluvastatin (RR 0.38; 95% CI, 0.09 to 1.68).

Studies enrolling mixed populations or subjects with coronary risk equivalents.

Nine trials in Table 5 extended these results to patient populations who were excluded from the earlier trials. In the Heart Protection Study (HPS), 20,536 men and women aged 40 to 80 years were randomized to simvastatin 40mg or placebo for an average of 5.5 years.[77, 119] This study targeted individuals in whom the risk and benefits of cholesterol lowering were uncertain (women, those over 70 years, those with diabetes, those with non-coronary vascular disease, and those with average or below average cholesterol).

The overall LDL reduction was 30%. This figure results from a true intention-to-treat analysis: that is, it includes patients who never took simvastatin or who quit taking it by the end of the study. In the subset of patients who took simvastatin for the entire study period, the LDL reduction was 40%.

Simvastatin reduced all-cause mortality from 14.7% to 12.9% (a 13% reduction). Simvastatin also reduced the risk of major coronary events (NNT=32 after 5 years) and of

stroke.[120] In subgroups, simvastatin 40mg was effective in primary prevention of CHD in patients with diabetes (NNT=24 to prevent a major event in 5 years)[121] and in patients who had a history of peripheral or carotid atherosclerosis but not CHD. It was also effective in patients who had a baseline LDL<116 mg/dl (both patients with and without diabetes).

To address concerns about the potential hazards of lowering cholesterol, data from the HPS were analyzed to determine the effect of lowering cholesterol on cause-specific mortality, site-specific cancer incidence, and other major morbidity.[122] There was no evidence of any adverse effect of lowering cholesterol for 5 years on non-vascular morbidity or mortality. There was no increased risk of non-vascular mortality (RR 0.95; 95% CI 0.85, 1.07) or cancer incidence (RR 1.00; 95% CI 0.91, 1.11).

ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-lowering Arm) was a randomized, double-blind, placebo-controlled, fair-to-good quality trial of atorvastatin 10mg in 10,305 patients with well-controlled hypertension, total cholesterol concentrations less than 251 mg/dL, and an average of 3.7 CVD risk factors.[123, 124] ASCOT-LLA was terminated after a median of 3.3 years of follow-up because a statistically significant benefit emerged in the primary endpoint, non-fatal myocardial infarction (including silent MI) and fatal CHD. Treatment with atorvastatin 10mg per day for 1 year reduced LDL by 35%, from 133mg/dL to 87mg/dL. By the end of follow-up (about 3.3 years), LDL was 89mg/dL in the patients still taking atorvastatin versus 127mg/dL in the control group.

There were 100 primary endpoint events in the atorvastatin group (100/5168, or 1.9%) and 150 events in the placebo group (3%). The event rate in the placebo group corresponds to a 10-year coronary event rate of 9.4%. Over 3.3 years, the NNT to prevent one nonfatal MI or death from CHD was 94 (p=0.005). Atorvastatin increased the chance of remaining free of MI for 3.3 years from 95% to 97%.

For the secondary and tertiary endpoints, strokes were reduced (NNT 158, p<0.02), as were cardiovascular procedures, total coronary events, and chronic stable angina. All-cause mortality was 3.6% for atorvastatin vs. 4.1% for placebo (p=0.1649). Atorvastatin did not reduce cardiovascular mortality (1.4% vs. 1.6%), development of diabetes, development of renal impairment, peripheral vascular disease, heart failure (0.8 vs. 0.7), or unstable angina.

In ALLHAT-LLC (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack—Lipid-lowering Arm), a fair-to-good quality, open-label randomized trial, 10,355 hypertensive patients, aged 55 and older, were randomized to pravastatin 40mg or to usual care.[75] Nearly half the subjects were women, 35% had diabetes, 15% had a history of CHD, and about 35% were African-American. Pravastatin reduced LDL-c from 145.6mg/dL at baseline to 111mg/dL after 2 years, a 24% reduction. However, because the control group was usual care instead of placebo, 10% of control patients were taking a lipid-lowering drug by year 2, and, by year 6, 28.5% of control subjects were taking a lipid-lowering drug. Thus the control group had a mean reduction in LDL-c concentration of 11% over the course of the study.

In ALLHAT-LLC, pravastatin did not reduce all-cause mortality or cardiovascular event rates. The reason for the lack of benefit of pravastatin in ALLHAT-LLC is unclear. The high proportion of women and the high rate of use of statins in the control group are possible explanations.

The PROSPER trial (good-quality) was designed to examine the benefits of statin therapy in women and in the elderly.[87] High-risk men and women were randomized to pravastatin 40mg or to placebo. Before treatment, the mean LDL was 147mg/dL. Overall, pravastatin reduced the composite primary endpoint (CHD death, nonfatal MI, fatal/nonfatal stroke) from 16.2% in the

placebo group to 14.1% (p=0.014; NNT=48). There was also a reduction in transient ischemic attacks, but not in strokes, in the pravastatin group. There was no effect on all-cause mortality, which was 10.5% in the placebo group vs. 10.3% in the pravastatin group (hazard ratio 0.97, CI 0.83-1.14). The reduction in coronary heart disease deaths in the pravastatin group (4.2% vs. 3.3%, p=0.043) was balanced by an increase in cancer deaths (3.1% vs. 4%, p=0.082).

Pravastatin was more effective in men than in women. There were more women (n=3,000) than men (n=2,804) in the study. The baseline risk in men was higher: in the placebo group, almost 20% of men and 13% of women had an event (CHD death, nonfatal MI, or stroke) over the 3 years of the study. For men, there was a statistically significant reduction in the primary endpoint (hazard ratio 0.77, CI 0.65-0.92) and a number-needed-to-treat of 26. For women, there was no apparent effect (hazard ratio 0.96, CI 0.79-1.18). PROSPER recruited a select group of elderly subjects. Of 23,770 people who were screened, 16,714 were ineligible or refused to participate.

The PREVEND-IT trial[78] was a population-based (N=864), randomized, placebo controlled trial with a 2 X 2 factorial design. Residents of one city in the Netherlands with persistent microalbuminuria were randomized to fosinopril and pravastatin for the prevention of cardiovascular morbidity and mortality. In the pravastatin 10mg versus placebo arm, there was no reduction in urinary albumin excretion and no significant reduction in cardiovascular events after an average 46 months of follow-up (hazard ratio 0.87; 95% CI, 0.49 to 1.57). In a subgroup analysis of 286 patients with the metabolic syndrome (33% of the total group),[125] the unadjusted hazard ratio was non-significant (0.48; 95% CI 0.21, 1.07). However, when adjusted for age and sex, there was a significant reduction in cardiovascular events in the pravastatin group (HR 0.39; 0.17, 0.89).The ALERT trial established the efficacy and safety of fluvastatin in patients who have undergone renal transplant. Fluvastatin was superior to placebo in reducing cardiac deaths or non-fatal MI,[81, 126, 127] but there was no effect on the renal endpoints of graft loss, doubling of serum creatinine, or decline in GFR.[128]

Patients with diabetes. CARDS (Collaborative Atorvastatin Diabetes Study) was a good-quality, multicenter, randomized, placebo-controlled trial of atorvastatin 10mg for primary prevention of cardiovascular disease in 2838 patients with type 2 diabetes without elevated cholesterol levels (mean LDL <107 mg/dL).[79] Patients had no history of cardiovascular disease but at least one of the following risk factors: retinopathy, albuminuria, current smoking, or hypertension. After 3.9 years of follow-up, there was a significant reduction in cardiovascular events (relative risk reduction –0.37; 95% CI –0.52, -0.17). The reduction in all-cause mortality was not significant (relative risk reduction –0.27; 95% CI –0.48, 1.00; p=0.059). The average reduction in LDL-c was 40%.

CARDS was the first trial of a statin specifically designed to assess primary prevention of cardiovascular disease in patients with diabetes. Three other placebo-controlled trials with CHD outcomes have enrolled patients with diabetes and performed subgroup analyses on this population (Table 7). The HPS was the largest of these, including 5963 patients with diabetes. In the HPS, there was a 27% reduction in risk of major coronary events (first nonfatal MI or coronary death), similar to the reduction in risk in the overall population of high-risk patients. The reduction in risk for stroke (24%) in patients with diabetes was also similar to the reduction in the overall high-risk group. Among the 2912 patients with diabetes who did not have known coronary or other occlusive arterial disease at study entry, there was a 33% reduction in first major vascular events (95% CI 17% to 46%, p=0.0003).

In the subgroup of patients with type 2 diabetes in ASCOT-LLA,[129] atorvastatin lowered the risk of cardiovascular events to a similar extent in patients with and without diabetes. Non-fatal MI and fatal CHD were also reduced in patients with diabetes, but the incidence of stroke was not. In LIPS, there was a reduction in coronary events (cardiac death, nonfatal MI, CABG, or repeat PCI) with fluvastatatin 80 mg in patients with diabetes who had undergone successful PCI.

Table 6. Placebo-controlled trials in patients with diabetes with CHD endpoints

Study	Patients (N, mean baseline LDL-c, other risk factors)	Drug, dose	Relative Risk (95% CI)
CARDS	2838 <107 mg/dL At least one: Retinopathy, albuminuria, current smoking, or hypertension.	Atorvastatin 10 mg	0.63 (0.48, 0.83)
HPS (Subgroup analysis)	5963 125 mg/dL Vascular disease (51%), treated Hypertension (40%), current Smoking (13%)	Simvastatin 40 mg	0.73 (0.62, 0.85)
ASCOT-LLA (Subgroup analysis),[129]	2532 127.4 mg/dL No history of CHD Smoking (20%)	Atorvastatin 10 mg	0.77 (0.61, 0.96)
LIPS (Subgroup analysis)[130]	202 126 mg/dL Post-PCI	Fluvastatin 80 mg	0.49 (0.29, 0.84)
4D[88]	1255 121 mg/dL Undergoing maintenance hemodialysis	Atorvastatin 20 mg	0.92 (0.77, 1.10)

Table 6 also shows the 4D trial, [88] in which patients with type 2 diabetes who were receiving maintenance hemodialysis were randomized to atorvastatin 20 mg or placebo. After 4 years of followup, there was no difference between atorvastatin and placebo on the primary endpoint, a composite of cardiac death, fatal stroke, nonfatal MI, nonfatal stroke. There was an *increase* in fatal strokes in the atorvastatin group— although this is likely to be a chance finding— and no effect on any individual component of the primary endpoint.

Studies in Inpatients with Acute Coronary Syndrome

There are six placebo-controlled trials in patients with acute MI or unstable angina (Table 7[89-94]): they included pravastatin 20 to 40mg (three trials), atorvastatin 80mg, fluvastatin 80mg,

and simvastatin 20 to 80mg. One was rated fair-to-poor quality, and the rest were rated fair (see Evidence Tables 3 and 4 for details of quality ratings).

Table 7. Inpatient trials of acute MI or unstable angina (statins vs placebo or usual care)

Trial (Quality)	Population	Baseline LDL	Study Duration	% LDL reduction	Reduction in Coronary events (%)	NNT to prevent a coronary event*
de Lemos 2004 A to Z Trial (Phase Z)[92] (Fair)	Either non-ST-elevation acute coronary syndrome or ST elevation MI with a total cholesterol level of 250 mg or lower.	Median 112 mg/dL (25th-75th percentiles 94-131 mg/dL)	Median 721 days (range 6 months to 24 months)	simvastatin first vs placebo first 1 month: 39% vs +10% (p<0.001) 4 months: 45% vs +12% (p<0.001) 8 months: 44% vs 31% (p<0.001) 24 months: 41% vs 27% (p<0.001)	11%	Results not significant
Thompson et al 2004 PACT[94] (Fair-Poor)	Within 24 hours of onset of acute MI or unstable angina.	Not reported. Mean total cholesterol 219 mg/dL	4 weeks	Not reported	-7%	Results not significant
Arntz et al 2000 L-CAD[89] (Fair)	Acute MI and/or underwent emergency PTCA due to severe or unstable angina pectoris.	prava vs usual care 176 mg/dL (131-240) vs 172 mg/dL (132-239)	2 years	Prava vs usual care 28% vs no change	59%	4
Liem et al 2002 FLORIDA[90] (Fair)	MI and one of the following: new or markedly increased chest pain lasting longer than 30 minutes, or a new pathological Q-wave.	135 mg/dL vs 139 mg/dL	1 year	Fluva vs placebo: 21% decrease vs 9% increase	5%	Results not significant
MIRACL[93] (Fair)	Unstable angina or non-Q-wave MI.	124 mg/dL	16 weeks	Atorva vs placebo: 40% decrease vs 12% increase (adjusted mean)	15%	39
Den Hartog (Pilot Study)[91] (Poor)	Acute MI or unstable angina, hospitalized for less than 48 hours.	174 mg/dL	3 months	25%	Not reported	Results not significant

*NNTs are not adjusted for length of trial, and are not directly comparable due to differences among trials

The L-CAD study established that patients with acute coronary syndrome benefit from statin treatment.[89] In L-CAD, 126 patients were randomized to pravastatin 20 or 40mg or usual care an average of 6 days after an acute MI or emergency PTCA due to severe or unstable angina. After 2 years of follow-up, there were fewer major coronary events in the pravastatin group (22.9% vs 52%, p=0.005). There was no difference in all-cause mortality, but each group had only 2 deaths.

An earlier pilot study[91] of pravastatin 40mg versus placebo enrolled patients hospitalized for less than 48 hours with acute MI or unstable angina. After 3 months, there was no significant difference on any clinical endpoint, although there was a 25% reduction in LDL-c in the pravastatin group.

PACT[94] assessed outcomes at 30 days in patients with acute MI or unstable angina randomly assigned to receive pravastatin 20 to 40mg or placebo within 24 hours of the onset of chest pain. This study was rated fair to poor because of some differences in groups at baseline (higher total cholesterol in placebo group, more placebo patients on hormone replacement therapy, and more pravastatin patients on anticoagulants) and no reporting of randomization and allocation concealment methods. The primary endpoint (composite of death, recurrence of MI, or readmission to hospital for unstable angina) occurred in 12% of patients. There was no significant reduction in the primary endpoint (relative risk reduction 6.4%; 95% CI, –1.4% to 3.0%), or on any individual component of the primary endpoint.

In MIRACL,[93] a short-term (16 weeks) placebo-controlled trial of atorvastatin 80mg in patients with unstable angina or non-Q-wave MI, there was a significant reduction in major coronary events (death, nonfatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic MI requiring emergency rehospitalization) in the atorvastatin group (17.4% vs 14.8%). There were no differences between groups on the individual components MI or all-cause mortality, although the study was not powered to detect a difference on these endpoints.

FLORIDA[90] was a placebo-controlled trial of fluvastatin 80mg in 540 patients with an acute MI plus hypercholesterolemia and new or markedly increased chest pain or a new pathological Q wave. At one year of follow-up, there was no difference between groups in the occurrence of major coronary events.

The A to Z trial[92] compared early intensive statin treatment (simvastatin 40mg for 30 days and then simvastatin 80mg thereafter) to a less aggressive strategy (placebo for 4 months and then simvastatin 20mg thereafter) in patients with either non-ST-elevation acute coronary syndrome or ST elevation MI with a total cholesterol level of 250mg or lower. Patients were followed for up to 24 months. Despite greater lowering of LDL in the early intensive group, there were no differences between the early intensive and less aggressive groups on the primary endpoint (cardiovascular death, myocardial infarction, readmission for acute coronary syndrome, or stroke), or on any individual component of the primary outcome.

Nine patients in the simvastatin only group developed myopathy (creatine kinase (CK) level >10 times the ULN with associated muscle symptoms) while taking 80mg, versus one patient in the placebo first group (p=0.02). Three of these nine had CK levels higher than 10,000 units/L and met the definition for rhabdomyolysis. The rate of myopathy was high, despite the exclusion of patients at increased risk of myopathy due to renal impairment or concomitant therapy with agents known to enhance myopathy risk, or for having a prior history of nonexercise-related elevations in creatine kinase level or nontraumatic rhabdomyolysis.

The lack of effect of more intensive treatment in this trial may have been due to several factors. The "early intensive" group started with only 40mg of simvastatin, and did not increase to 80mg for 30 days. Patients who were taking statin therapy at the time of their myocardial infarction (at randomization) were excluded. The study authors report that the trial had less statistical power than originally planned due to a lower than expected number of end points and a higher than expected rate of study drug discontinuation.

The large randomized trials summarized above provide strong evidence about the balance of benefits and harms from statin therapy. Because they were analyzed on an intention-to-treat basis, the benefits (reductions in coronary events, strokes, and, in some studies, mortality) in subjects who tolerated and complied with medication are diluted by the lack of benefit in subjects who discontinued medication because of side effects or did not complete the study for other reasons. Moreover, the mortality results of the trials indicate clearly that, for the enrolled subjects, and the duration of the trials, statins are beneficial. The balance of benefits and harms of statin drugs over a longer time than the trials have observed remains unclear.

Studies of the Progression of Atherosclerosis with Secondary or Incidental CHD Endpoints

Twelve studies of the effects of statins on progression of atherosclerosis also reported rates of coronary or cardiovascular events.[95-106] (A head-to-head trial[131] of the effect of atorvastatin 80mg versus pravastatin 40mg on progression of atherosclerosis did not meet inclusion criteria because it did not report health outcomes; this study did meet inclusion criteria for Key Question 1, however. See Evidence Table 1.) 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. In 6 of the 12 trials clinical outcomes were not a pre-planned endpoint (they were "spontaneously reported"), and sample sizes were relatively small.

Table 8 (and Evidence Table 5) summarize the results of these studies. The number of trials and patients studied for each statin are as follows: fluvastatin (one, n=429), lovastatin (three, n=1,520), pravastatin (five, n=2,220), and simvastatin (three, n=1,118). The information about fluvastatin was inconclusive and the other three are already known to be effective from better studies.

In general, most trials in which CHD events were not a prespecified endpoint found 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 significant reduction in one of the components of CHD events. While consistent, the results of these studies are difficult to interpret because of possible reporting bias. That is, these trials were more likely to report a result if it was statistically significant or indicated a trend favoring treatment. Similar trials of progression of atherosclerosis that found no trend probably did not report coronary events. For this reason, we did not conduct a meta-analysis to pool the results of these studies.

Table 8. Studies of atherosclerotic progression that reported CHD outcomes

Author or Study Acronym/Statin	Pre-specified Clinical Event or Spontaneous Report*	Significant Reduction in Clinical Event or Trend Towards Statin
LCAS/Fluvastatin[95]	Spontaneous report	Trend
ACAPS/Lovastatin[96]	Secondary endpoint	Reduction in major cardiovascular events
CCAIT/Lovastatin[97]	Spontaneous report	Trend
MARS/Lovastatin[98]	Spontaneous report	Trend
REGRESS/Pravastatin[103]	Pre-specified	Reduction in PTCA
PLAC-I/Pravastatin[99]	Pre-specified	Reduction in MI
PLAC-II/Pravastatin[100]	Pre-specified	Reduction in combined: nonfatal MI and death
KAPS/Pravastatin[101]	Spontaneous report	Trend
Sato, et al/Pravastatin[102]	Pre-specified	Reduction in overall death
MAAS/Simvastatin[104]	Spontaneous report	Trend
CIS/Simvastatin[105]	Spontaneous report	Trend
SCAT/Simvastatin[106]	Pre-specified	Reduction in revascularization

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

Revascularization Studies with Restenosis or Clinical Outcome Endpoints

This group (Table 9 and Evidence Table 6) includes placebo-controlled trials in revascularized patients (CABG, PTCA, or coronary stent).[107-112, 114] The primary endpoint in five of the trials was the rate of restenosis. A reduction in clinical outcomes was the primary outcome in the sixth study (subgroup analysis of CARE).[109] Most of the studies were fair or fair-to-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 and the studies were not powered to assess these types of events.

The number of studies and patients per statin are as follows: fluvastatin (two, n=2086), lovastatin (three, n=1,981), pravastatin (two, n=2,940, data on 2,245 patients already included in CARE results in Table 5). In these trials, pravastatin and fluvastatin had statistically significant effects on prespecified coronary disease outcomes.

Table 9. Post-revascularization trials

Study/ drug, patients	Clinical Endpoint	Clinical Events
FLARE/ *Fluvastatin 40mg twice daily vs. placebo to reduce restenosis after successful single-lesion PTCA*	Prespecified 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%; log rank 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).
Weintraub et al/ *Lovastatin 40mg twice daily vs. placebo to reduce restenosis after PTCA.*	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 40mg (aggressive) vs. lovastatin 2.5 mg titrated to target; before and after CABG*	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=0.03, which was NS by study criteria for multiple comparisons)
CLAPT/ *Lovastatin plus diet vs. lovastatin, before and after PTCA.*	Pre-specified endpoint of MI, revascularization, or death.	No effect on restenosis; significant reduction in 2nd or 3rd re-PTCA (p=0.02).
PREDICT/ *Pravastatin 40mg vs. placebo after PTCA.*	Secondary endpoint of death, myocardial infarction, target vessel revascularization	No effect on restenosis or on clinical endpoints.
CARE (subgroup)/ *Pravastatin vs. placebo in patients with CABG and/or PTCA*	Primary endpoint coronary heart disease death or nonfatal MI	Reduction in primary endpoint (RRR 36%, CI 17 to 51, p = 0.001)
LIPS/ *Fluvastatin vs. placebo in patients who had PCI and average cholesterol values.*	Primary endpoint cardiac death, nonfatal MI, CABG, or repeat PCI.	For primary endpoint, relative risk {RR}, 0.78; 95% confidence interval {CI}, 0.64-0.95; *P* = .01

PTCA=percutaneous transluminal coronary angioplasty; NS=non-significant; MI=myocardial infarction; CABG= coronary artery bypass graft; PCI=percutaneous coronary intervention.

In the Lescol Intervention Prevention Study (LIPS), patients who had undergone angioplasty or other percutaneous coronary intervention (PCI) were randomized to fluvastatin 40mg bid or placebo for 4 years.[114, 132] One hundred eighty-one (21.4%) of 844 patients in the fluvastatin group and 222 (26.7%) of 833 patients in the placebo group had at least one major adverse cardiac event, defined as cardiac death, nonfatal MI, or a reintervention procedure. There was a 22% (p=0.0127) reduction in major coronary events (cardiac death, nonfatal MI, CABG or repeat PCI). The number needed to treat was 19 (21.4% in fluvastatin group vs. 26.7% in placebo group). Patients with diabetes and those with multi-vessel disease experienced a comparable or greater benefit with fluvastatin than other subjects.

Two subgroup analyses of the LIPS trial have recently been published; one in patients with type 2 diabetes[130] (discussed above) and another in patients with renal dysfunction.[133] Fluvastatin reduced major coronary events in these subgroups.

Miscellaneous Studies. Three trials that reported clinical outcomes did not fit the criteria for the other categories (Table 10 and Evidence Table 6).[43, 113, 134]

The Target Tangible study[43] randomized patients with coronary heart disease (n=2,856), including some who had been revascularized, to an initial dose of 10mg of either atorvastatin or simvastatin, after which the dosage was increased to achieve an LDL<100mg/dl. The study was open-label, but serious adverse events were classified by a safety committee 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 (A-2%, S-3%, NS), and withdrawal rates were similar for atorvastatin and simvastatin. The article states (page 10), "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 one-sided t-test was applied (p<0.05, Table III)." However, Table III of the article (p10) does not support this statement. This table shows that the number of these serious cardiovascular events was 11 (0.0058) in the atorvastatin group and seven (0.0073) in the simvastatin group, 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 the study was of short duration, 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 10. Miscellaneous trials reporting clinical outcomes

Study/drug, patients	Clinical Endpoint	Clinical Events
AVERT/ Atorvastatin vs. PTCA in stable, low-risk CAD patients	Primary endpoint included cardiac events and revascularization procedures.	No difference.
Target Tangible/ Atorvastatin vs. simvastatin safety trial	Clinical endpoints reported in safety analysis.	See text (above.)
Pravastatin Multinational Study Group / Pravastatin 20mg (dose could be increased) vs. placebo, subjects at high-risk for CAD.	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).

Key Question 4. Are there differences in the efficacy or safety of statins in different demographic groups (age, sex, race)?

Summary of Evidence

- There is good evidence from randomized trials that women and the elderly benefit from statin therapy.
- Data about efficacy and safety in African-Americans, Hispanics, and other ethnic groups are weaker.
  - There is no evidence that one statin is safer than another in these groups.

- A pharmacokinetic study conducted in the US demonstrated an approximate 2-fold elevation in median exposure of rosuvastatin in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese, or Asian-Indian origin) compared with a White control group. The rosuvastatin label has been revised to note that this increase should be considered when making rosuvastatin dosing decisions for Asian patients.

4a. Efficacy in Demographic Subgroups

Detailed Assessment

Women and the elderly

Although women and the elderly were under-represented in the early major trials, a meta-analysis[135] suggested that statins are equally efficacious in men, women, and the elderly. This meta-analysis evaluated the effect of statins on the risk of coronary disease from the first five large, long-term, primary and secondary prevention trials (see Evidence Table 2). Women accounted for an average of 17% of subjects and individuals age 65 and older accounted for an average of 29% (range 21%-39%) (WOSCOPS did not enroll women or anyone 65 years or older). The risk reduction in major coronary events was 29% (95% CI 13%-42%) in women, 31% (95% CI 26%-35%) for men, 32% (95% CI 23%-39%) in those over age 65 and 31% (95% CI 24%-36%) in those younger than age 65. In the Heart Protection Study, simvastatin reduced cardiovascular events among women generally and particularly in women with diabetes, who benefited dramatically (NNT 23 to prevent one major vascular event).

A systematic review and meta-analysis of lipid-lowering drug trials for the prevention of CHD events and death in women included 9 trials of statins that enrolled 16,486 women.[136, 137] Four additional studies, including 1,405 women, that used lipid-lowering therapy other than statins, were included in the analysis. For secondary prevention, lipid-lowering therapy reduced risk of CHD mortality (summary RR 0.74; 95% CI 0.55-1.00), nonfatal MI (summary RR 0.73; 95% CI 0.59-0.90), and CHD events (summary RR 0.80; 95% CI 0.71-0.91), but not total mortality (summary RR 1.00; 95% CI 0.77-1.29). In primary prevention studies, there was insufficient evidence of reduced risk of any clinical outcome in women, because of the small number of events in the trials. Sensitivity analyses including only studies using statins did not significantly affect the summary risk estimates.

Recent trials, especially PROSPER, have confirmed that statins are beneficial in the elderly.

African American, Hispanic, and Other Ethnic Groups

African Americans have the greatest overall CHD mortality and the highest out-of-hospital coronary death rates of any other ethnic group in the US.[3] Other ethnic and minority groups in the United States include Hispanics, Native Americans, Asian and Pacific Islanders, and South Asians. However, these groups are underrepresented in randomized clinical trials reporting reductions in clinical outcomes. As a result there is no evidence to answer whether or not statins differ in their ability to reduce clinical events in the African American, Hispanic or other ethnic groups. Significant numbers of African American and Hispanic patients participated

in AFCAPS/TexCAPS, but the investigators did not analyze events by racial group. In EXCEL, lovastatin 20mg, 40mg, and 80mg daily reduced LDL-c by similar percentages in blacks and in whites.[138]

4b. Safety in Demographic Subgroups

All of the statins used in the major long-term randomized trials were tolerated equally well among men, women, and healthy elderly subjects. These results apply to patients who met the eligibility criteria for the trials: in general, patients with liver disease and other serious diseases were excluded from these trials. Also, most of the patients in the trials took fixed doses of statins that were less than the maximum doses.

In a large, observational study of lovastatin, men, women, and the elderly experienced similar rates of adverse effects.[139, 140] The Expanded Clinical Evaluation of Lovastatin (EXCEL) Study was a 4-year study of the tolerability of lovastatin 20mg, 40mg, or 80mg daily in 8,245 patients, including over 3,000 women.[141-145] The rates of myopathy and liver enzyme elevations increased with increasing doses of lovastatin, but did not differ among men, women, and healthy elderly subjects. A meta-analysis of randomized trials of simvastatin 80mg involving 2,819 subjects (Worldwide Expanded Dose Simvastatin Study Group) had similar results.[139] These studies are important because they demonstrate that the maximum (80mg) doses of simvastatin and lovastatin are well tolerated.

A subgroup analysis[138] from the EXCEL Study examined the efficacy and safety of lovastatin versus placebo in 459 African-Americans. The endpoints in the trial were reduction in total cholesterol, LDL-c, triglycerides, and an increase in HDL-c. With regard to safety, there was a significantly higher incidence of CK elevation in African-Americans compared to white Americans in both placebo and lovastatin treatment groups. However, no cases of myopathy, defined as CK elevations>10 times ULN, occurred in African-Americans. There were no other safety differences between lovastatin and placebo in African-Americans or Caucasians.

In premarketing studies, Japanese and Chinese patients living in Singapore had higher levels of rosuvastatin in blood than Caucasians living in Europe.[146] The FDA asked the manufacturer to perform an appropriately conducted pharmacokinetic study of Asians residing in the United States. The study demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese, or Asian-Indian origin) compared with a Caucasian control group. The rosuvastatin label has been revised to note that this increase should be considered when making rosuvastatin dosing decisions for Asian patients.

Key Question 5. Are there differences in the safety of statins?

Summary of Evidence

- There is insufficient evidence to determine which statin or statins are safer with regard to muscle and liver toxicity.
- Studies that included people with diabetes did not have higher rates of adverse effects than other studies.
- In theory, **pravastatin, fluvastatin, and rosuvastatin** have the lowest potential for interactions 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 and is the safest choice in those patients receiving potent CYP inhibitors. Experts recommend starting with pravastatin and fluvastatin and using the lowest dose possible. Although there is no proof from clinical studies that these recommendations are correct, on ethical grounds low-dose pravastatin and fluvastatin probably cannot be tested in a good-quality controlled study against high doses of other statins.
  - In one small placebo-controlled crossover trial in HIV-infected patients receiving protease inhibitors, **pravastatin** reduced total cholesterol levels by 18.3%, but mean LDL-c and HDL levels did not change significantly after 8 weeks. Adverse events were similar to placebo. Muscle aches characterized as "severe" developed in two subjects, but neither discontinued therapy.
- Four studies evaluating the benefit of **atorvastatin** 80mg daily in reducing coronary heart disease on health outcomes observed a significantly higher rate of substantial elevations in liver transaminases in the **atorvastatin** groups in comparison to angioplasty, usual care, placebo, or pravastatin 40mg. The clinical significance of asymptomatic liver enzyme elevations from statins has been questioned, however.

Detailed Assessment

A postmarketing analysis of adverse event data reported to the FDA compared events reported in the first year of use of rosuvastatin to events reported for atorvastatin, simvastatin, and pravastatin during the same period and during their first years of marketing.[147] Data from the first year of use of cerivastatin was also included. The primary analysis was a composite endpoint of rhabdomyolysis, proteinuria, nephropathy, or renal failure. Secondary analyses of overall adverse event rates and specific adverse events were also conducted.

In the concurrent time period analysis, the rate of rosuvastatin-associated adverse events (composite endpoint) was significantly higher than simvastatin, pravastatin, and atorvastatin. In the analysis of the first year of marketing, the rate of rosuvastatin-associated adverse events was significantly higher than pravastatin and atorvastatin, but not simvastatin. Events with rosuvastatin were less frequent compared with the first year of marketing of cerivastatin. In secondary analyses, the rate of all adverse events was significantly higher with rosuvastatin than with simvastatin, pravastatin, and atorvastatin. Results for both the concurrent time period and first-year of marketing analyses were similar. For serious adverse events, the rate for rosuvastatin was significantly lower than simvastatin and cerivastatin, but was significantly higher than atorvastatin or pravastatin.

This observational study was limited in that it was not possible to compare adverse event rates for different statins at comparable LDL-c lowering doses. Also, the time period in which each drug was studied may have influenced results. Certain adverse events may not be recognized as being related to a particular class of drugs for some time, leading to underreporting for older drugs. Publicity and heightened public awareness may also lead to overreporting of events for newer drugs.

A systematic review and meta-analysis of 18 randomized placebo-controlled trials compared adverse event rates for the different statins.[148] Over 85% of the data came from trials

of simvastatin and pravastatin. For overall adverse events, the number needed to harm compared with placebo was 197. Serious events (CPK > 10 times ULN or rhabdomyolysis) were infrequent (NNH=3400 for myopathy and 7428 for rhabdomyolysis).[148]

5a. Myotoxicity and hepatic enzymes (general population)

Myopathy

Three reviews[149-151] evaluated the safety profile of statins. Five reviews assessed myotoxicity with the statins.[152-155] One of these[154] focused on the combination of statins and fibrates.

In addition to the reviews of safety with statins, we reviewed the 60 head-to-head statin LDL-c lowering trials to determine whether there were any significant differences in myotoxicity and/or elevation of liver enzymes. We also included two observational studies of myopathy[156] or rhabdomyolysis[153] with statins.

Magnitude of Risk. Although CPK elevations are common, the risk of symptomatic myopathy is low. Gaist and colleagues[156] 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. Using diagnostic visit codes recorded by participants in the U.K. General Practice Research Database, they identified and verified cases of symptomatic myopathic pain. A potential case of myopathy was confirmed with the clinician when the patient presented at least two of the following criteria: (1) clinical diagnosis of myopathy confirmed by the general practitioner; (2) muscle weakness, muscle pain, or muscle tenderness (two of these symptoms); and (3) creatine kinase concentration above the reference limit. By this definition, 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. 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.

In a systematic review, the incidence of myalgia in clinical trials ranged from 1% to 5% and was not significantly different from placebo. However, a review of two databases in the same review found that myalgia (defined as muscle pain without elevated CK levels) contributed to 19% to 25% and 6% to 14% of all adverse events associated with statin use.[155]

Myotoxicity of Different Statins. All of the available statins (simvastatin, lovastatin, atorvastatin, fluvastatin, pravastatin, rosuvastatin), when administered alone, have been associated with infrequent myotoxic adverse effects ranging from myalgia, and myopathy to rhabdomyolysis.[149] 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.[152, 154, 157, 158]

A retrospective analysis of all domestic and foreign reports of statin-associated rhabdomyolysis has been released by the Food and Drug Administration.[153] 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. This report does not provide information about the relative incidence of rhabdomyolysis associated with different statins, because the number of patients taking each statin was not available.

Another review of reports to the FDA's MedWatch database limited to events associated with atorvastatin or simvastatin was published in April 2003.[159] The analysis was limited to adverse reactions that affected major organ systems (muscle toxicity, hepatotoxicity, pancreatic toxicity, and bone marrow toxicity). Analyses were adjusted for dose but not LDL-c lowering. Between November 1997 and April 2000, there were 1,828 adverse event reports affecting major organ systems associated with the use of atorvastatin, and 1,028 reports associated with simvastatin. Muscle-related events were more likely with atorvastatin (dose adjusted OR 1.7, 95% CI, 1.6 to 1.8; $p<0.001$). Reports of myalgias were more likely with atorvastatin, but rhabdomyolysis-associated reports were more likely with simvastatin (dose adjusted OR 2.4, 95% CI, 2.1 to 2.7; $p<0.001$).

From these studies, 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.

Another observational study used claims data from 11 US managed health care plans to estimate the incidence of rhabdomyolysis leading to hospitalization in patients treated with different statins and fibrates, alone and in combination.[160] Fluvastatin and lovastatin were excluded from the analysis because usage was very low. There were 16 cases of rhabdomyolysis leading to hospitalization with statin monotherapy in 252,460 patients contributing 225,640 person-years of observation. Incidence rates for monotherapy with atorvastatin, pravastatin, and simvastatin were similar.

In our review of 60 head-to-head comparative statin LDL-c lowering trials, we did not find any differences in rates of muscle toxicity between statins. In the ASTEROID trial, a study of regression of atherosclerosis, there were no cases of rhabdomyolysis in 507 patients taking rosuvastatin 40 mg for 24 months.[161] (This trial is not included in our efficacy analysis because health outcomes were not reported.)

Elevations of liver enzymes

All of the statins are rarely associated with elevations in liver transaminase levels (>3X ULN), occurring in approximately 1% of patients. The clinical significance of asymptomatic liver enzyme elevations from statins has been questioned, however. The risk increases with increasing doses.[151] In order to answer whether there are differences in risk of liver toxicity

between statins, we reviewed the adverse effects of the head-to-head statin LDL-c lowering trials and did not find any significant difference in the rate of clinically relevant elevation in liver enzymes between statins. The exception was one study comparing atorvastatin 80mg to simvastatin 80mg daily[30] in which there was a significantly higher incidence of transaminase elevation in the atorvastatin group compared to simvastatin. The reduction in LDL-c was greater with atorvastatin 80 mg compared with simvastatin 80 mg (53.6% vs 48.1%; p<0.001) in this same study.

We also reviewed 29 trials reporting cardiovascular health outcomes for significant differences in elevation of liver enzymes between statins and placebo or a non-drug intervention.

In the PROVE-IT trial,[72] more patients in the atorvastatin 80mg group had elevations in ALT levels than those in the pravastatin 40mg group (3.3% vs 1.1%, p<0.001).

In AVERT,[113] and MIRACL,[93] 2% and 2.5% of patients in the atorvastatin 80mg daily group experienced clinically important elevations in the liver transaminases which were significantly greater than those in the angioplasty or placebo groups.

In GREACE, there were 5 patients out of 25 who received atorvastatin 80mg daily that experienced clinically significant increases in liver function tests. In all cases, the transaminase elevations were reversible upon discontinuation or reduction in dose of atorvastatin. There were no significant differences in transaminase elevation (>3 times the ULN) with other statins versus 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.

In the ALLIANCE study,[116] the incidence of abnormal AST or ALT levels (>3 times the ULN) in patients taking atorvastatin 80mg was 0.7% (8 patients) and 1.3% (16 patients), respectively. Laboratory testing was not conducted in the usual care group

In the Treating to New Targets (TNT) Study,[117] patients with stable coronary disease were randomized to atorvastatin 80mg (intensive lipid lowering) or 10mg. Sixty of 4,995 patients given atorvastatin 80mg had a persistent elevation in liver enzymes (2 consecutive measurements >3 times the ULN), compared with nine of 5,006 patients given 10mg of atorvastatin (1.2% vs 0.2%; p<0.001).

In the ASTEROID trial, [161] 1.8% of patients had elevated ALT levels (>3 times the ULN), and 1.2% had elevated creatine kinase levels greater than 5 times the ULN. There were no elevations of creatine kinase greater than 10 times the ULN.

5b. Myotoxicity and hepatic enzymes (special populations)

Patients with diabetes

There are no data to support any special safety concerns in patients with diabetes receiving statins. There are no prospective, head-to-head controlled clinical trials comparing the benefits or harms of different statins in patients with diabetes.

In the Heart Protection Study (HPS, simvastatin), substantial elevations of liver enzymes and creatinine kinase (CK) were not significantly higher in patients with diabetes. Moreover, taking simvastatin for five years did not adversely affect glycemic control or renal function. It

should be noted, however, that the HPS had a run-in period in which patients who had liver or muscle enzyme elevations were excluded prior to randomization.

In CARDS,[79] there was no difference between atorvastatin and placebo in the frequency of adverse events or serious adverse events, including myopathy, myalgia, rise in creatinine phosphokinase, and discontinuation from treatment for muscle-related events. There were no cases of rhabdomyolysis.

A 4-month, head-to-head trial of extended release fluvastatin 80mg versus atorvastatin 20mg was conducted in 100 patients with type 2 diabetes and low serum HDL levels.[162] The study was designed to measure the metabolic effects of the statins and did not measure clinical endpoints. There were no significant changes in serum creatinine phosphokinase or liver enzymes, and no major adverse events after 4 months of treatment.

A 48-week trial assessed efficacy and safety of long-term treatment with fluvastatin in patients with chronic renal disease and hyperlipidemia.[163] Patients with diabetic nephropathy (N=34) or chronic glomerulonephritis (N=46) were randomized to fluvastatin 20mg plus dietary therapy, or dietary therapy alone. Over 48 weeks of treatment, there were no significant differences between fluvastatin and placebo groups in serum creatinine concentration, creatinine clearance, or 24-hour urinary albumin excretion rates.

The Atorvastatin as Prevention of CHD Endpoint in NIDDM trial (ASPEN) is ongoing.

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.[149, 164-169] 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 11). The use of the agents listed in Table 11 increases statin concentrations and, theoretically, the possibility for adverse effects. Table 11 does not include all drugs capable of inhibiting metabolism via the CYP 3A4 isoenzyme system.

The significance of interactions with many drugs that inhibit CYP 3A4 is not known; examples include diltiazem, verapamil, and fluoxetine. Fluvastatin is primarily metabolized via CYP 2C9 and is vulnerable to interactions with drugs known to inhibit CYP 2C9 metabolism (Table 12). Only about 10% of rosuvastatin is metabolized, primarily through the CYP 2C9 system. Pravastatin is not significantly metabolized via the CYP isoenzyme system and is therefore not affected by drugs inhibiting metabolism via these pathways.

Table 11. Potent Inhibitors of CYP 3A4

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

*Published reports of rhabdomyolysis exist in patients receiving concomitant statin.

Table 12. Drugs Known to Inhibit Metabolism Via CYP 2C9

Amiodarone	Fluoxetine	Omeprazole
Azole Antifungals	Fluvoxamine	TMP/SMX
Cimetidine	Metronidazole	Zafirlukast

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 20mg and 10mg daily, respectively, has been shown to be safe in transplant patients receiving cyclosporine.[170, 171] Fluvastatin and pravastatin at 40mg daily have also been shown to be safe in cyclosporine-managed transplant recipients.[81, 172-175] Rosuvastatin 10 mg was studied in a 6-week cohort study of 21 cardiac transplant recipients receiving standard immunosuppressive therapy.[176] The patients' lipid levels were above target values on the highest tolerated doses of other statins. After 6 weeks, there were no statistically significant changes in creatine kinase levels or AST. There was no clinical evidence of myositis in any patient. One patient had myalgia and 2 patients were withdrawn because of mild elevation of creatine kinase (324 U/liter at 3 weeks and 458 U/liter at 6 weeks). In a premarketing study, cyclosporine had a clinically significant effect on the pharmacokinetics of rosuvastatin in heart transplant patients. The product label recommends limiting the dose of rosuvastatin to 5mg in patients taking cyclosporine.

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.[177] The patient with rhabdomyolysis was receiving simvastatin 20mg daily. No rhabdomyolysis was seen in 39 patients receiving simvastatin 10mg daily. A review of studies involving fluvastatin (up to 80mg daily) in organ transplant patients receiving cyclosporine, identified no cases of rhabdomyolysis.[178] One small study[179] 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 of statins for transplant patients is similar to that of the general population. Pravastatin and fluvastatin have the least potential for significant interaction with cyclosporine. 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 could theoretically be increased.

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 these patients.

Although data specifically addressing the combination of the protease inhibitors with the statins are limited, it is known that simvastatin, lovastatin, and atorvastatin are metabolized by CYP 3A4 to some degree. Fluvastatin and, partly, rosuvastatin are 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.

A small (N=20), placebo-controlled crossover trial of pravastatin for lipid-lowering was conducted in patients receiving protease inhibitors.[180] Mean LDL-c levels at baseline were 134mg/dL; mean total cholesterol was 218mg/dL, and mean HDL-c was 36mg/dL. Pravastatin reduced total cholesterol levels by 18.3%, but mean LDL-c and HDL levels did not change significantly after 8 weeks. With pravastatin, one subject had an asymptomatic increase in CK >2 times ULN, and another subject had an asymptomatic increase in CK >3 times ULN. Two placebo patients also had asymptomatic CK increases. With pravastatin, mild myalgia developed in one subject. Muscle aches characterized as "severe" developed in two subjects, but neither discontinued therapy. There were no myalgias in any subject in the placebo group.

A trial of pravastatin 40 mg (n=86) versus fenofibrate (n=88) in patients with HIV, 47% of whom were using protease inhibitors. Patients were randomized to either pravastatin or fenofibrate for 12 weeks; those who did not meet lipid goals after 12 weeks were then switched to combination therapy with both treatments. Safety was assessed through 48 weeks.[181] One pravastatin- and three fenofibrate-treated patients discontinued treatment in the first 12 weeks due to myalgias, elevated CK, pancreatitis, and asymptomatic elevation in lipase. Three subjects discontinued combination therapy between weeks 12 and 28 for elevations in lipase and thrombocytopenia. There were no reports of rhabdomyolysis or clinical hepatitis during the 48-week study period.

There are two retrospective studies in which patients with HIV received a statin for the management of their hyperlipidemia.[182, 183] In one,[183] a total of 30 patients were identified (five pravastatin, 13 lovastatin, 10 simvastatin, two atorvastatin) and followed for an average of almost 9 months. The mean statin dose was 23mg daily. Twenty-seven out of 30 patients received a protease inhibitor along with the statin. Two patients (one lovastatin, one simvastatin) experienced an increase in liver transaminases 3 or more times ULN. Both patients were

asymptomatic and continued therapy. One patient developed an increase in CK of 5.4 times normal and myalgias. He was receiving lovastatin 40mg daily, niacin, and either saquinavir-ritonavir or nelfinavir-delavirdine as part of a blinded study. Another patient on lovastatin 20mg daily and ritonavir reported diffuse myalgias but no CK was measured. His lovastatin was reduced to 10mg daily.

In a second observational study,[182] 25 HIV-positive patients were treated with either fluvastatin 20-40mg or pravastatin 10-20mg and followed for 12 weeks for effects on lipids and interaction with indinivir. Both fluvastatin and pravastatin significantly lowered total cholesterol, but there was a significant change from baseline on LDL-c only in the fluvastatin group (30.2% reduction). HDL-c levels were not affected in either group. Neither drug had an effect on plasma indinivir levels.

A trial in HIV seronegative volunteers evaluated the potential interaction between protease inhibitors and statins.[184] Three groups were randomized to receive pravastatin, simvastatin, or atorvastatin (40mg/day for each) on days 1 to 4 and 15 to 18. On days 4 to18, they also received dual protease inhibitors (ritonavir 400mg bid plus saquinavir 400mg bid). Sixty-seven volunteers were randomized and 56 completed the study. Area under the curve concentrations of pravastatin declined ($p=0.005$) while concentrations of simvastatin increased 30-fold in patients taking ritonavir and saquinavir ($p<0.001$). Concentrations of atorvastatin also increased ($p<0.001$), though to a lesser degree. The authors concluded from these 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.

Two groups of experts have made recommendations regarding the use of statins in HIV-infected individuals receiving protease inhibitors, 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 (http://wwwhivatis.org and http://www.aactg.s-3.com/ann.htm).

Safety of Statin-Fibrates Combination (Myopathy). Myopathy and rhabdomyolysis have also been reported in patients receiving monotherapy with fibrates, 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.[158]

In a retrospective cohort study of 252,460 patients using claims data from 11 managed health care plans, 24 cases of hospitalized rhabdomyolysis occurred during treatment.[160] The average incidence of rhabdomyolysis requiring hospitalization was 0.44 per 10,000 (95% CI, 0.20 to 0.84) and was similar for atorvastatin, pravastatin, and simvastatin. When taken in combination with a fibrate, statins were associated with an incidence of hospitalized rhabdomyolysis of 5.98 (95% CI, 0.72 to 216) per 10,000. The study of health plan claims data referred to above reported cases of rhabdomyolysis with the combination of a statin and a fibrate.[160] The cohort represented 7,300 person-years of combined therapy with statins and fibrates (gemfibrozil or fenofibrate). There were 8 cases of rhabdomyolysis with combination

therapy. Incidence rates per 10,000 person-years were 22.45 (95% CI, 0.57 to 125) for atorvastatin combined with fenofibrate, 18.73 (95% CI, 0.47 to104) for simvastatin combined with gemfibrozil, and 1,035 (95% CI, 389 to 2117) for cerivastatin plus gemfibrozil. There were no cases with pravastatin; fluvastatin and lovastatin were excluded from the analysis because usage was very low.

A review of the FDA's adverse event reporting system[185] found fewer reports of rhabdomyolysis associated with fenofibrate than gemfibrozil when used in combination with a statin (8.6 vs 0.58 per million prescriptions dispensed, excluding cerivastatin). Patients with most of these conditions or circumstances have been excluded from randomized trials or carefully screened and observed for a length of time prior to randomization, making it difficult to assess the balance of benefits and harms.

A prospective observational cohort study followed 252 patients who were prescribed a statin combined with gemfibrozil for a mean of 2.36 years (range 6 weeks to 8.6 years). Creatine kinase levels, aminotransferase levels, and any reports of muscle soreness or weakness were monitored. One presumed case of myositis occurred in a patient who took simvastatin for one year. The patient had previously taken pravastatin combination therapy for four years without incident. An asymptomatic 5-fold rise in ALT (alanine aminotransferase) was observed in one patient, and 2 other patients had an ALT elevation between 2 and 3 times the ULN. The statin involved in these cases is not specified.

A systematic review by Shek[154] identified 36 trials that combined a statin with a fibrate in the management of hypercholesterolemia. The majority of studies used gemfibrozil (n=20, 63% of patients), with the most common dose being 1200mg. Ten studies used bezafibrate, two used fenofibrate, one used clofibrate, one used ciprofibrate, one used both bezafibrate and ciprofibrate, one used bezafibrate or fenofibrate, and one used gemfibrozil or ciprofibrate.

No reports of rhabdomyolysis were observed in the 1,674 patients receiving the combination of a statin and fibrate. 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. All but two of these studies used gemfibrozil; the others used bezafibrate plus simvastatin 20mg and fenofibrate plus pravastatin 20mg or simvastatin 10mg. 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, and 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 29 published case reports of rhabdomyolysis secondary to the combination of statins and fibrates. Gemfibrozil was the fibrate used in each case. The statins used were lovastatin in 21 cases, simvastatin in four, cerivastatin in three, and atorvastatin in one. They 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.[153] The authors cite a reference[186] in which it is suggested that the hydrophilic properties of pravastatin account for the reduced risk of muscle toxicity while all other statins (with the exception of rosuvastatin) 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[149] 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.

A pooled analysis evaluated the frequency of creatine kinase (CK) elevations in trials in which fluvastatin was administered in combination with fibrates.[187] Of 1,017 patients treated with combination therapy, 493 received bezafibrate, 158 fenofibrate, and 366 gemfibrozil; mean exposure time was 37.6 weeks and ranged from 0.7 to 118.3 weeks. Results are not reported separately by type of fibrate. Five of 1,017 patients (0.5%) had CK elevations ≥ 5 times the ULN; 2 of these were ≥ 10 times the ULN. There were no significant differences in the frequency of creatine kinase elevations among the group on combination therapy and patients taking placebo, fibrates only, or fluvastatin only.

Because of the nature of adverse effect reporting and the available evidence, whether one statin is safer than the other with regard to combination therapy with fibrates is unknown. The Food and Drug Administration has approved the following recommendations when combining fibric acid derivatives or niacin with a statin:

- **Atorvastatin:** Weigh the potential benefits and risks and closely monitor patients on combined therapy.
- **Fluvastatin**: The combination with **fibrates** should generally be avoided.
- **Pravastatin:** Avoid the combination with **fibrates** unless the benefit outweighs the risk of such therapy.
- **Simvastatin**: Avoid the combination with **gemfibrozil** unless the benefit outweighs the risk and limit doses to 10mg if combined with **gemfibrozil**.
- **Lovastatin**: Avoid the combination with **fibrates** unless the benefit outweighs the risk and limit doses to 20mg if combined with **fibrates**.
- **Rosuvastatin**: Avoid the combination with **fibrates** unless the benefit outweighs the risk and limit doses to 10mg if combined with **gemfibrozil**.

Safety of Statin-Thiazolidinediones Combination. A recent study reviewed the FDA's adverse event reporting database for events reported to the FDA between 1990 and March 2002 in which simvastatin or atorvastatin was listed as a suspect in causing adverse events, and in which antidiabetic medications were listed as co-suspects or concomitant medications. Analysis was limited to adverse events affecting major organ systems (muscles, liver, pancreas, and bone marrow).[188] Atorvastatin-associated adverse event reports were more likely to list concomitant thiazolidinediones compared with simvastatin-associated adverse event reports (3.6% vs 1.6%, respectively; OR 2.3, 95% CI,1.7 to 3.2, $p<0.0001$). Muscle toxicity was the most common adverse event, followed by liver-related events.

A 24-week, placebo-controlled trial examined the effect of adding simvastatin to patients with type 2 diabetes who were taking a thiazolidinedione (pioglitazone or rosiglitazone).[189] There were 2 cases of asymptomatic CPK elevations ≥10 times the ULN in the simvastatin group (1.7%), no elevations in ALT or aspartate aminotransferase (AST), and no differences in tolerability between patients taking pioglitazone and those taking rosiglitazone.

Safety of Statin and Fibrate Combination (Elevation of Liver Enzymes). In the systematic review by Shek in 2001,[154] 8 patients, in three of the 36 included studies, discontinued the combination therapy due to significant elevation in liver transaminases (ALT and 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.

A retrospective database analysis evaluated the risk of elevated liver enzymes in patients who were prescribed a statin.[190] Changes in liver transaminases at 6 months were compared in 3 cohorts: patients with elevated baseline enzymes (AST>40 iu/l or ALT >35 iu/l) who were prescribed a statin (n=342), patients with normal transaminases who were prescribed a statin (n=1,437), and patients with elevated liver enzymes who were not prescribed a statin (n=2,245). Patients with elevated liver enzymes at baseline had a higher incidence of mild/moderate and severe elevations after 6 months, whether or not they were prescribed a statin. Those with elevated liver enzymes at baseline who were prescribed a statin had a higher incidence of mild-moderate, but not severe, elevations at 6 months than those with normal transaminases who were prescribed a statin. Most patients in this study were prescribed atorvastatin or simvastatin (5 patients were prescribed fluvastatin); there was no difference in results according to the type of statin prescribed.

SUMMARY OF EVIDENCE

Table 13 summarizes the level and direction of evidence for each key question.

Table 13. Summary of the evidence by key question

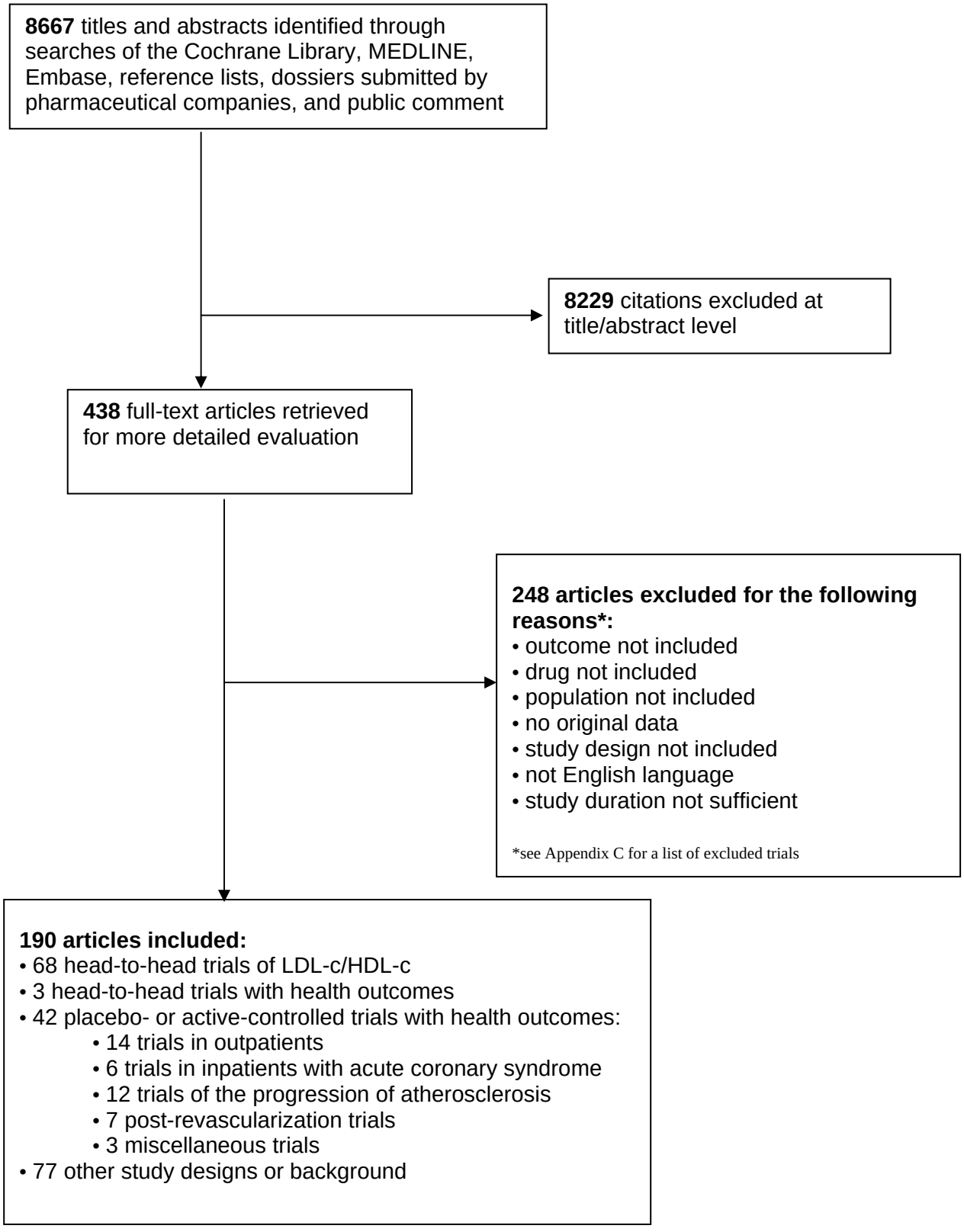
Key Question	Level of Evidence	Conclusion
1. How do statins compare in their ability to reduce LDL-c?	Fair.	The ideal study would be a double-blind, intention-to-treat randomized trial in which equipotent doses of different statins were compared with regard to LDL-lowering, withdrawals, and adverse effects. No studies met these stringent criteria.
a. Are there doses for each statin that produce similar percent reduction in LDL-c between statins?	Fair-to-good	Results of a large number of trials are generally consistent with information from the manufacturer. When statins are provided in doses that are approximately equipotent, a similar percent reduction in LDL-c can be achieved.

Key Question	Level of Evidence	Conclusion
b. Is there a difference in the ability of a statin to achieve National Cholesterol Education Program (NCEP) goals?	Good for most comparisons (see text).	For patients who require LDL-c reductions of up to 35% to meet their goal, any of the statins are effective. In patients requiring an LDL-c reduction of 35% to 50% to meet the NCEP goal, atorvastatin 20mg or more, lovastatin 80mg, rosuvastatin 10mg or more, and simvastatin 20mg or more daily are likely to meet the goal. Atorvastatin 80mg daily and rosuvastatin 20mg or more can reduce LDL-C by 50% or more. Based on fair-quality studies, atorvastatin 80mg daily resulted in 5 to 6 additional percentage points of LDL reduction than simvastatin 80 mg (53%-54% vs. 47%-48%), but had significantly higher rates of some adverse events. In short-term (6 weeks) studies rosuvastatin 40mg had greater reduction in LDL-c than atorvastatin 80mg with similar frequency of adverse events.
2. How do statins compare in their ability to raise HDL-c?	Fair-to-good	When statins are provided in doses that are approximately equipotent, a similar percent increase in HDL-c can be achieved. There is conflicting evidence about simvastatin vs atorvastatin, with some studies finding no difference and others finding simvastatin superior. Some studies found greater increases in HDL-c with rosuvastatin compared with atorvastatin, while other studies found no difference.
3. How do statins compare in their ability to reduce the risk of nonfatal myocardial infarction, angina, CHD mortality, all-cause mortality, stroke or need for revascularization (coronary artery bypass graft, angioplasty or stenting)?	NA	There are no controlled trials comparing equivalent doses of two or more statins to reduce the risk of coronary events, stroke, or death.
Which statins have been shown to reduce all-cause mortality?	Good.	Patients who have never had CHD: pravastatin (high-risk patients), simvastatin (mixed populations) Patients with CHD: atorvastatin (post-MI), pravastatin, simvastatin.
Which statins have been shown to reduce cardiovascular mortality?	Good.	Patients who have never had CHD: Pravastatin, simvastatin Patients with CHD: simvastatin, atorvastatin
Which statins have been shown to reduce CHD events?	Fair-to-good.	Patients who have never had CHD: atorvastatin (high-risk patients, patients with diabetes), lovastatin (average-risk patients), pravastatin (high-risk patients), simvastatin (mixed populations) Patients with CHD: atorvastatin, simvastatin, pravastatin. Patients after PTCA: fluvastatin, pravastatin.
Which statins have been shown to reduce strokes?	Good.	Atorvastatin, pravastatin, simvastatin
Patients with diabetes	Good	There are good efficacy data for people with diabetes. Atorva 10 mg reduced cardiovascular events in a primary prevention trial of patients with diabetes (CARDS), and simvastatin 40 mg reduced cardiovascular events in patients with diabetes (HPS). In a subgroup analysis of the LIPS

Key Question	Level of Evidence	Conclusion
		trial, there was a reduction in coronary events (cardiac death, nonfatal MI, CABG, or repeat PCI) with fluvastatatin 80 mg in patients with diabetes who had undergone successful PCI. Studies that included people with diabetes had rates of adverse effects similar to other studies.
4.a. Are there differences in effectiveness of statins in different demographic groups (age, sex, race)?	Good (elderly, women) Poor (African Americans, Hispanics, and other ethnic groups)	The benefits of statins have been documented in women and the elderly. There are almost no data about African Americans, Hispanics, or other ethnic groups. There are no data from clinical trials comparing the efficacy of different statins in women, the elderly, or African Americans.
4.b. Are there differences in safety of statins in different demographic groups (age, sex, race)?	Poor	There are no data from clinical trials comparing the safety of different statins in women, the elderly, or African Americans. A pharmacokinetic study of rosuvastatin conducted in the US demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese, or Asian-Indian origin) compared with a Caucasian control group.
5. Are there differences in the safety of statins?		
a. General population	Good	Although CPK elevations are common, the risk of symptomatic myopathy is low. All of the available statins (simvastatin, lovastatin, atorvastatin, fluvastatin, pravastatin, rosuvastatin), when administered alone, have been associated with infrequent myotoxic adverse effects ranging from myalgia, and myopathy to rhabdomyolysis. Two meta-analyses of clinical trials found rates of elevated transaminases (liver function tests) to be no higher among patients taking statins than among those receiving placebo. There is no evidence that elevated transaminases associated with statin use increase the risk of clinically significant liver failure. In a trial of two doses of atorvastatin, the incidence of persistent elevations in liver aminotransferase levels 2 per 1000 in patients taking atorvastatin 10mg daily, versus 1.2 per 1000 in patients taking 80mg daily. There is insufficient evidence to determine which statin or statins are safer with regard to muscle toxicity or elevated liver enzymes. Among high potency statins, at doses below 80 mg, rates of adverse events and withdrawals due to adverse events were similar in patients taking atorvastatin or simvastatin. Atorvastatin 80mg had a higher rate of some adverse effects (GI disturbances and transaminase elevation) than simvastatin 80mg daily in a trial in which the LDL lowering of atorvastatin was greater than that of simvastatin. Adverse event rates in patients using rosuvastatin 40mg were similar to rates in patients using atorvastatin 80mg in short-term trials.

Key Question	Level of Evidence	Conclusion
b. Special populations: Patients with diabetes	Good	Studies that included people with diabetes had rates of adverse effects similar to other studies.
Patients with HIV and transplant patients	One fair-quality observational study; one small trial (pravastatin) case reports; expert opinion; pharmacology.	In theory, pravastatin, fluvastatin, and rosuvastatin have the lowest potential for interactions 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 (Table 12) and pravastatin has the lowest potential for drug interactions and is the safest choice in those patients receiving potent CYP inhibitors. Experts recommend starting with pravastatin and fluvastatin and using the lowest dose possible. Although there is no proof from clinical studies that these recommendations are correct, on ethical grounds low-dose pravastatin and fluvastatin probably cannot be tested in a good-quality controlled study against high doses or other statins.
Drug interactions	Fair	The combination of any statin with fibrates and to a lesser extent niacin, can result in a higher risk for myopathy or rhabdomyolysis.

Figure 1. Literature Search Results



REFERENCES

1. American Heart Association. Heart and Stroke Statistics 2006 Update. *Available at: http://www.americanheart.org/downloadable/heart/1140534985281Statsupdate06book.pdf.* 2006.
2. Balk EM, Lau J, Goudas LC, et al. Effects of statins on nonlipid serum markers associated with cardiovascular disease: a systematic review. *Annals of Internal Medicine.* 2003;139(8):670-682.
3. National Cholesterol Education Program. *Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)*: National Institutes of Health; September 2002. NIH 02-5215.
4. Grundy SM, Cleeman JI, Bairey Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation.* 2004;110(2):227-239.
5. Smith Jr MD SC, ScD JAR, PED SNB. AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update. *JACC.* 2006;47:2130-2139.
6. Anonymous. *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews CRD Report Number 4 (2nd edition).* York, UK: NHS Centre for Reviews and Dissemination; 2001. 4 (2nd edition).
7. Harris RP, Helfand M, Woolf SH, et al. Current methods of the U.S. Preventive Services Task Force: a review of the process. *Am. J. Prev. Med.* 2001 2001;20(3S):21-35.
8. Andrews TC, Ballantyne CM, Hsia JA, Kramer JH. Achieving and maintaining National Cholesterol Education Program low-density lipoprotein cholesterol goals with five statins. *American Journal of Medicine.* 2001;111(3):185-191.
9. Anonymous. A multicenter comparative trial of lovastatin and pravastatin in the treatment of hypercholesterolemia. The Lovastatin Pravastatin Study Group. [see comments]. *American Journal of Cardiology.* 1993;71(10):810-815.
10. Assmann G, Huwel D, Schussman KM, et al. Efficacy and safety of atorvastatin and pravastatin in patients with hypercholesterolemia. *European Journal of Internal Medicine.* 1999;10(1):33-39.
11. Ballantyne CM, Blazing MA, Hunninghake DB, et al. Effect on high-density lipoprotein cholesterol of maximum dose simvastatin and atorvastatin in patients with hypercholesterolemia: Results of the Comparative HDL Efficacy and Safety Study (CHESS). *American Heart Journal.* 2003;146(5):862-869.
12. Berger ML, Wilson HM, Liss CL. A Comparison of the Tolerability and Efficacy of Lovastatin 20 mg and Fluvastatin 20 mg in the Treatment of Primary Hypercholesterolemia. *Journal of Cardiovascular Pharmacology & Therapeutics.* 1996;1(2):101-106.
13. Bertolini S, Bon GB, Campbell LM, et al. Efficacy and safety of atorvastatin compared to pravastatin in patients with hypercholesterolemia. *Atherosclerosis.* 1997;130(1-2):191-197.
14. Blasetto JW, Stein EA, Brown WV, Chitra R, Raza A. Efficacy of rosuvastatin compared with other statins at selected starting doses in hypercholesterolemic patients and in special population groups. *American Journal of Cardiology.* 2003;91(5A):3C-10C; discussion 10C.

15. Branchi A, Fiorenza AM, Torri A, et al. Effects of low doses of simvastatin and atorvastatin on high-density lipoprotein cholesterol levels in patients with hypercholesterolemia. *Clinical Therapeutics.* 2001;23(6):851-857.
16. Branchi A, Fiorenza AM, Torri A, et al. Effects of atorvastatin 10 mg and simvastatin 20 mg on serum triglyceride levels in patients with hypercholesterolemia. *Current Therapeutic Research, Clinical & Experimental.* 2001;62(5):408-415.
17. Brown AS, Bakker-Arkema RG, Yellen L, et al. Treating patients with documented atherosclerosis to National Cholesterol Education Program recommended low density lipoprotein cholesterol goals with atorvastatin, fluvastatin, lovastatin and simvastatin. *Journal of the American College of Cardiology.* 1998;32(3):665-672.
18. Brown WV, Bays HE, Hassman DR, et al. Efficacy and safety of rosuvastatin compared with pravastatin and simvastatin in patients with hypercholesterolemia: a randomized, double-blind, 52-week trial. *American Heart Journal.* 2002;144(6):1036-1043.
19. Crouse JRI, Frohlich J, Ose L, Mercuri M, Tobert JA. Effects of high doses of simvastatin and atorvastatin on high density lipoprotein cholesterol and apolipoprotein A I. *American Journal of Cardiology.* 1999;83(10):1476-1477, A1477.
20. Dart A, Jerums G, Nicholson G, et al. A multicenter, double blind, one year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia. [see comments]. *American Journal of Cardiology.* 1997;80(1):39-44.
21. Davidson M, Ma P, Stein EA, et al. Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia. *American Journal of Cardiology.* 2002;89(3):268-275.
22. Davidson M, McKenney J, Stein E, et al. Comparison of one year efficacy and safety of atorvastatin versus lovastatin in primary hypercholesterolemia. *American Journal of Cardiology.* 1997;79(11):1475-1481.
23. Davidson MH, Palmisano J, Wilson H, Liss C, Dicklin MR. A Multicenter, Randomized, Double-Blind Clinical Trial Comparing the Low-Density Lipoprotein Cholesterol-Lowering Ability of Lovastatin 10, 20, and 40 mg/d with Fluvastatin 20 and 40 mg/d. *Clinical Therapeutics.* 2003;25(11):2738-2753.
24. Douste-Blazy P, Ribeiro VG, Seed M, et al. Comparative study of the efficacy and tolerability of simvastatin and pravastatin in patients with primary hypercholesterolaemia. *Drug Invest.* 1993;6:353-361.
25. Farmer JA, Washington LC, Jones PH, Shapiro DR, Gotto AM, Mantell G. Comparative effects of simvastatin and lovastatin in patients with hypercholesterolemia. *Clinical Therapeutics.* 1992;14(5):708-717.
26. Farnier M, Portal JJ, Maigret P. Efficacy of atorvastatin compared with simvastatin in patients with hypercholesterolemia. *Journal of Cardiovascular Pharmacology & Therapeutics.* 2000;5(1):27-32.
27. Frohlich J, Brun LD, Blank D, et al. Comparison of the short term efficacy and tolerability of lovastatin and simvastatin in the management of primary hypercholesterolemia. *Canadian Journal of Cardiology.* 1993;9(5):405-412.
28. Gentile S, Turco S, Guarino G, et al. Comparative efficacy study of atorvastatin vs simvastatin, pravastatin, lovastatin and placebo in type 2 diabetic patients with hypercholesterolaemia. *Diabetes Obesity & Metabolism.* 2000;2(6):355-362.

29. Hunninghake D, Bakker-Arkema RG, Wigand JP, et al. Treating to meet NCEP recommended LDL cholesterol concentrations with atorvastatin, fluvastatin, lovastatin, or simvastatin in patients with risk factors for coronary heart disease. *Journal of Family Practice.* 1998;47(5):349-356.

30. Illingworth RD, Crouse IJ, Hunninghake DB, et al. A comparison of simvastatin and atorvastatin up to maximal recommended doses in a large multicenter randomized clinical trial. *Curr. Med. Res. Opin.* 2001;17(1):43-50.

31. Insull W, Kafonek S, Goldner D, Zieve F. Comparison of efficacy and safety of atorvastatin (10mg) with simvastatin (10mg) at six weeks. ASSET Investigators. *American Journal of Cardiology.* 2001;87(5):554-559.

32. Jacotot B, Benghozi R, Pfister P, Holmes D. Comparison of fluvastatin versus pravastatin treatment of primary hypercholesterolemia. French Fluvastatin Study Group. *American Journal of Cardiology.* 1995;76(2):54A-56A.

33. Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). [see comments]. [erratum appears in Am J Cardiol 1998 Jul 1;82(1) 128]. *American Journal of Cardiology.* 1998;81(5):582-587.

34. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *American Journal of Cardiology.* 2003;92(2):152-160.

35. Kadikoylu G, Yukselen V, Yavasoglu I, Bolaman Z. Hemostatic effects of atorvastatin versus simvastatin. *Annals of Pharmacotherapy.* 2003;37(4):478-484.

36. Karalis DG, Ross AM, Vacari RM, Zarren H, Scott R. Comparison of efficacy and safety of atorvastatin and simvastatin in patients with dyslepidemia with and without coronary heart disease. *American Journal of Cardiology.* 2002;89(6):667-671.

37. Kastelein JJ, Isaacsohn JL, Ose L, et al. Comparison of effects of simvastatin versus atorvastatin on high density lipoprotein cholesterol and apolipoprotein A I levels. *American Journal of Cardiology.* 2000;86(2):221-223.

38. Lambrecht LJ, Malini PL, Berthe C, et al. Efficacy and tolerability of simvastatin 20 mg vs pravastatin 20 mg in patients with primary hypercholesterolemia. *Acta Cardiologica.* 1993;48(6):541-554.

39. Lefebvre P, Scheen A, Materne P, et al. Efficacy and tolerability of simvastatin and pravastatin in patients with primary hypercholesterolemia (multicountry comparative study). *American Journal of Cardiology.* 1992;70(15):1281-1286.

40. Lintott CJ, Scott RS, Sutherland WH, Bremer JM. Treating hypercholesterolaemia with HMG CoA reductase inhibitors a direct comparison of simvastatin and pravastatin. *Australian & New Zealand Journal of Medicine.* 1993;23(4):381-386.

41. Lucasko P, Walters EJ, Cullen EI, Niecestro R, Friedhoff LT. Efficacy of once-daily extended-release lovastatin compared to immediate-release lovastatin in patients with cholesterolemia. *Curr. Med. Res. Opin.* 2004;20(1):13-18.

42. Malini PL, Ambrosioni E, De Divitiis O, Di Somma S, Rosiello G, Trimarco B. Simvastatin versus pravastatin efficacy and tolerability in patients with primary hypercholesterolemia. *Clinical Therapeutics.* 1991;13(4):500-510.

43. Marz W, Wollschlager H, Klein G, Neiss A, Wehling M. Safety of low density lipoprotein cholestrol reduction with atorvastatin versus simvastatin in a coronary heart

disease population (the TARGET TANGIBLE trial). *American Journal of Cardiology.* 1999;84(1):7-13.

44. McPherson R, Bedard J, Connelly PW, et al. Comparison of the short term efficacy and tolerability of lovastatin and pravastatin in the management of primary hypercholesterolemia. *Clinical Therapeutics.* 1992;14:276-291.

45. Nash DT. Meeting national cholesterol education goals in clinical practice a comparison of lovastatin and fluvastatin in primary prevention. *American Journal of Cardiology.* 1996;78(6A):26-31.

46. Olsson AG, Eriksson M, Johnson O, et al. A 52-week, multicenter, randomized, parallel-group, double-blind, double-dummy study to assess the efficacy of atorvastatin and simvastatin in reaching low-density lipoprotein cholesterol and triglyceride targets: The Treat-to-Target (3T) Study. *Clinical Therapeutics.* 2003;25(1):119-138.

47. Olsson AG, Istad H, Luurila O, et al. Effects of rosuvastatin and atorvastatin compared over 52 weeks of treatment in patients with hypercholesterolemia. *American Heart Journal.* 2002;144(6):1044-1051.

48. Ose L, Scott R, Brusco O, et al. Double blind comparison of the efficacy and tolerability of simvastatin and fluvastatin in patients with primary hypercholesterolaemia. *Clinical Drug Investigation.* 1995;10:127-138.

49. Paoletti R, Fahmy M, Mahla G, Mizan J, Southworth H. Rosuvastatin demonstrates greater reduction of low-density lipoprotein cholesterol compared with pravastatin and simvastatin in hypercholesterolaemic patients: a randomized, double-blind study. *Journal of Cardiovascular Risk.* 2001;8(6):383-390.

50. Recto CSI, Acosta S, Dobs A. Comparison of the efficacy and tolerability of simvastatin and atorvastatin in the treatment of hypercholesterolemia. *Clinical Cardiology.* 2000;23(9):682-688.

51. Bays HE, McGovern ME. Time as a variable with niacin extended-release/lovastatin vs. atorvastatin and simvastatin. *Preventive Cardiology.* 2005;8(4):226-233.

52. Ferdinand KC, Clark LT, Watson KE, et al. Comparison of efficacy and safety of rosuvastatin versus atorvastatin in African-American patients in a six-week trial. *American Journal of Cardiology.* Jan 15 2006;97(2):229-235.

53. Fonseca FAH, Ruiz A, Cardona-Munoz EG, et al. The DISCOVERY PENTA study: a DIrect Statin COmparison of LDL-C Value--an Evaluation of Rosuvastatin therapY compared with atorvastatin. *Current Medical Research & Opinion.* Aug 2005;21(8):1307-1315.

54. Jukema JW, Liem A-H, Dunselman PHJM, van der Sloot JAP, Lok DJA, Zwinderman AH. LDL-C/HDL-C ratio in subjects with cardiovascular disease and a low HDL-C: results of the RADAR (Rosuvastatin and Atorvastatin in different Dosages And Reverse cholesterol transport) study. *Current Medical Research & Opinion.* Nov 2005;21(11):1865-1874.

55. Saklamaz A, Comlekci A, Temiz A, et al. The beneficial effects of lipid-lowering drugs beyond lipid-lowering effects: a comparative study with pravastatin, atorvastatin, and fenofibrate in patients with type IIa and type IIb hyperlipidemia. *Metabolism: Clinical & Experimental.* May 2005;54(5):677-681.

56. Wolffenbuttel BHR, Franken AAM, Vincent HH, Dutch Corall Study G. Cholesterol-lowering effects of rosuvastatin compared with atorvastatin in patients with type 2 diabetes -- CORALL study. *Journal of Internal Medicine.* Jun 2005;257(6):531-539.

57. Schuster H, Barter PJ, Stender S, et al. Effects of switching statins on achievement of lipid goals: Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY I) study. *American Heart Journal.* 2004;147(4):705-712.
58. Berne C, Siewert-Delle A, investigators Us. Comparison of rosuvastatin and atorvastatin for lipid lowering in patients with type 2 diabetes mellitus: results from the URANUS study. *Cardiovasc Diabetol.* 2005;4(7):1-11.
59. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *Bmj.* 2003:1423-1427.
60. Chan WB, Ko GTC, Yeung VTF, et al. A comparative study of atorvastatin and simvastatin as monotherapy for mixed hyperlipidaemia in Type 2 diabetic patients. *Diabetes Res. Clin. Pract.* 2004;66(1):97-99.
61. Paragh G, Torocsik D, Seres I, et al. Effect of short term treatment with simvastatin and atorvastatin on lipids and paraoxonase activity in patients with hyperlipoproteinaemia. *Curr. Med. Res. Opin.* 2004;20(8):1321-1327.
62. Schaefer EJ, McNamara JR, Tayler T, et al. Comparisons of effects of statins (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin) on fasting and postprandial lipoproteins in patients with coronary heart disease versus control subjects. *American Journal of Cardiology.* 2004;93(1):31-39.
63. van Dam M, Basart DCG, Janus C, et al. Additional efficacy of milligram-equivalent doses of atorvastatin over simvastatin. *Clinical Drug Investigation.* 2000;19(5):327-334.
64. Wolffenbuttel BH, Mahla G, Muller D, Pentrup A, Black DM. Efficacy and safety of a new cholesterol synthesis inhibitor, atorvastatin, in comparison with simvastatin and pravastatin, in subjects with hypercholesterolemia. *Netherlands Journal of Medicine.* 1998;52(4):131-137.
65. Schneck DW, Knopp RH, Ballantyne CM, McPherson R, Chitra RR, Simonson SG. Comparative effects of rosuvastatin and atorvastatin across their dose ranges in patients with hypercholesterolemia and without active arterial disease. *American Journal of Cardiology.* 2003;91(1):33-41.
66. Schwartz GG, Bolognese MA, Tremblay BP, et al. Efficacy and safety of rosuvastatin and atorvastatin in patients with hypercholesterolemia and a high risk of coronary heart disease: a randomized, controlled trial. *American Heart Journal.* 2004;148(1):H1-H9 (e4).
67. Strandberg TE, Feely J, Sigurdsson EL. Twelve-week, multicenter, randomized, open-label comparison of the effects of rosuvastatin 10 mg/d and atorvastatin 10 mg/d in high-risk adults: A DISCOVERY study. *Clinical Therapeutics.* 2004;26(11):1821-1833.
68. Stalenhoef A, Ballantyne C, Sarti C, al. e. A COmparative study with rosuvastatin in subjects with METabolic Syndrome: results of the COMETS study. *Eur Heart J.* 2005;26:2664-2672.
69. Shepherd J, Hunninghake DB, Barter P, McKenney JM, Hutchinson HG. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of rosuvastatin with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. *American Journal of Cardiology.* 2003;91(5A):11C-17C; discussion 17C-19C.
70. Deedwania PC, Hunninghake DB, Bays HE, et al. Effects of rosuvastatin, atorvastatin, simvastatin, and pravastatin on atherogenic dyslipidemia in patients with characteristics of the metabolic syndrome. *American Journal of Cardiology.* 2005;95(3):360-366.

71. Vidt DG, Cressman MD, Harris S, Pears JS, Hutchinson HG. Rosuvastatin-induced arrest in progression of renal disease. *Cardiology.* 2004;102(1):52-60.
72. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes.[see comment]. *New England Journal of Medicine.* Apr 8 2004;350(15):1495-1504.
73. Pedersen TR, Faergeman O, Kastelein JJP, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial.[see comment]. *JAMA.* Nov 16 2005;294(19):2437-2445.
74. Stone PH, Lloyd-Jones DM, Kinlay S, et al. Effect of intensive lipid lowering, with or without antioxidant vitamins, compared with moderate lipid lowering on myocardial ischemia in patients with stable coronary artery disease: the Vascular Basis for the Treatment of Myocardial Ischemia Study. *Circulation.* Apr 12 2005;111(14):1747-1755.
75. Allhat Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT).[see comment]. *JAMA.* Dec 18 2002;288(23):2998-3007.
76. Tonkin A, Alyward P, Colquhoun D, Glasziou P, et al. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of intial cholesterol levels. *New England Journal of Medicine.* 1998;339(19):1349-1357.
77. Anonymous. MRC/BHF Heart Protection Study of cholesterol lowering therapy and of antioxidant vitamin supplementation in a wide range of patients at increased risk of coronary heart disease death early safety and efficacy experience. *European Heart Journal.* 1999;20(10):725-741.
78. Asselbergs FW, Diercks GFH, Hillege HL, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation.* 2004;110(18):2809-2816.
79. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. *Lancet.* 2004;364(9435):685-696.
80. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. [see comments]. *Journal of the American Medical Association.* 1998;279(20):1615-1622.
81. Holdaas H, Fellstr AmB, Jardine AG, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet.* 2003;361(9374):2024-2031.
82. Pedersen TR. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994;344(8934):1383-1389.
83. Riegger G, Abletshauser C, Ludwig M, et al. The effect of fluvastatin on cardiac events in patients with symptomatic coronary artery disease during one year of treatment. *Atherosclerosis.* 1999;144(1):263-270.

84. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *New England Journal of Medicine.* 1996;335(14):1001-1009.

85. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial.[see comment]. *Lancet.* Apr 5 2003;361(9364):1149-1158.

86. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *New England Journal of Medicine.* 1995;333(20):1301-1307.

87. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial.[comment]. *Lancet.* 2002;360(9346):1623-1630.

88. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *The New England journal of medicine.* 2005;353(3):238-248.

89. Arntz HR, Agrawal R, Wunderlich W, et al. Beneficial effects of pravastatin (+/- colestyramine/niacin) initiated immediately after a coronary event (the randomized Lipid-Coronary Artery Disease [L-CAD] Study). *American Journal of Cardiology.* 2000;86(12):1293-1298.

90. Liem AH, van Boven AJ, Veeger NJ, et al. Effect of fluvastatin on ischaemia following acute myocardial infarction: a randomized trial. *European Heart Journal.* 2002;23(24):1931-1937.

91. Den Hartog FR, Van Kalmthout PM, Van Loenhout TT, Schaafsma HJ, Rila H, Verheugt FW. Pravastatin in acute ischaemic syndromes: results of a randomised placebo-controlled trial. *International Journal of Clinical Practice.* 2001;55(5):300-304.

92. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *Journal of the American Medical Association.* 2004;292(11):1307-1316.

93. Schwartz GG, Olsson Ag, Ezekowitz Md, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes the MIRACL study a randomized controlled trial. [see comments]. *Journal of the American Medical Association.* 2001;285(13):1711-1718.

94. Thompson PL, Meredith I, Amerena J, Campbell TJ, Sloman JG, Harris PJ. Effect of pravastatin compared with placebo initiated within 24 hours of onset of acute myocardial infarction or unstable angina: the Pravastatin in Acute Coronary Treatment (PACT) trial. *American Heart Journal.* 2004;148(1):e2.

95. Herd JA, Ballantyne CM, Farmer JA, et al. Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS]). *American Journal of Cardiology.* 1997;80(3):278-286.

96. Furberg CD, Adams HPJ, Applegate WB, et al. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. *Circulation.* 1994;90(4):1679-1687.

97. Waters D, Higginson L, Gladstone P, et al. Effects of monotherapy with an HMG CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial

quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial. *Circulation.* 1994;89(3):959-968.

98. Blankenhorn DH, Azen SP, Kramsch DM, et al. Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS). The MARS Research Group. [see comments]. *Annals of Internal Medicine.* 1993;119(10):969-976.

99. Pitt B, Mancini GB, Ellis SG, Rosman HS, Park JS, McGovern ME. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): reduction in atherosclerosis progression and clinical events. PLAC I investigation. *Journal of the American College of Cardiology.* 1995;26(5):1133-1139.

100. Crouse JR, Byington RP, Bond MG, et al. Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II). *American Journal of Cardiology.* 1995;75(7):455-459.

101. Salonen R, Nyyssonen K, Porkkala E, et al. Kuopio Atherosclerosis Prevention Study (KAPS). A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. *Circulation.* 1995;92(7):1758-1764.

102. Sato S, Kobayashi T, Awata N, et al. Randomized, controlled trial of secondary prevention of coronary sclerosis in normocholesterolemic patients using pravastatin: Two-year follow-up of the prevention of coronary sclerosis study. *Current Therapeutic Research, Clinical & Experimental.* 2001;62(6):473-485.

103. Jukema JW, Bruschke AV, van Boven AJ, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). *Circulation.* 1995;91(10):2528-2540.

104. Simoons MI, Saelman JPM, Deckers JW, et al. Effect of simvastatin on coronary atheroma The Multicentre Anti Atheroma Study (MAAS). *Lancet.* 1994;344(8923):633-638.

105. Bestehorn HP, Rensing UFE, Roskamm H, et al. The effect of simvastatin on progression of coronary artery disease. *European Heart Journal.* 1997;18(2):226-234.

106. Teo KK, Burton JR, Buller CE, et al. Long term effects of cholesterol lowering and angiotensin converting enzyme inhibition on coronary atherosclerosis The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). *Circulation.* 2000;102(15):1748-1754.

107. Anonymous. The effect of aggressive lowering of low density lipoprotein cholesterol levels and low dose anticoagulation on obstructive changes in saphenous vein coronary artery bypass grafts. The Post Coronary Artery Bypass Graft Trial Investigators. [see comments]. [erratum appears in N Engl J Med 1997 Dec 18;337(25) 1859]. *New England Journal of Medicine.* 1997;336(3):153-162.

108. Bertrand ME, McFadden EP, Fruchart JC, et al. Effect of pravastatin on angiographic restenosis after coronary balloon angioplasty. The PREDICT Trial Investigators. Prevention of Restenosis by Elisor after Transluminal Coronary Angioplasty. *Journal of the American College of Cardiology.* 1997;30(4):863-869.

109. Flaker GC, Warnica JW, Sacks FM, et al. Pravastatin prevents clinical events in revascularized patients with average cholesterol concentrations. Cholesterol and Recurrent Events CARE Investigators. *Journal of the American College of Cardiology.* 1999;34(1):106-112.

110. Kleemann A, Eckert S, von Eckardstein A, et al. Effects of lovastatin on progression of non dilated and dilated coronary segments and on restenosis in patients after PTCA. The cholesterol lowering atherosclerosis PTCA trial (CLAPT). [see comments]. *European Heart Journal.* 1999;20(19):1393-1406.

111. Serruys PW, Foley DP, Jackson G, et al. A randomized placebo controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty; final results of the fluvastatin angiographic restenosis (FLARE) trial. *European Heart Journal.* 1999;20(1):58-69.

112. Weintraub WS, Boccuzzi SJ, Klein JL, et al. Lack of effect of lovastatin on restenosis after coronary angioplasty. Lovastatin Restenosis Trial Study Group. *New England Journal of Medicine.* 1994;331(20):1331-1337.

113. Pitt B, Waters D, Brown WV, et al. Aggressive lipid lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. [see comments]. *New England Journal of Medicine.* 1999;341(1):70-76.

114. Serruys PWJC, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial.[see comment]. *JAMA.* Jun 26 2002;287(24):3215-3222.

115. Athyros VG, Papageorgiou AA, Mercouris BR, etal. Treatment with atorvastatin to the National Cholesterol Education Program goal versus "usual" care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary heart-disease Evaluation (GREACE) Study. *Curr. Med. Res. Opin.* 2002;18(4):220-228.

116. Koren MJ, Hunninghake DB, Investigators A. Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the alliance study. *Journal of the American College of Cardiology.* 2 2004;44(9):1772-1779.

117. LaRosa JC. Is aggressive lipid-lowering effective and safe in the older adult? *Clinical Cardiology.* Sep 2005;28(9):404-407.

118. Colquhoun D, Keech A, Hunt D, et al. Effects of pravastatin on coronary events in 2073 patients with low levels of both low-density lipoprotein cholesterol and high-density lipoprotein cholesterol: Results from the LIPID study. *European Heart Journal.* 2004;25(9):771-777.

119. Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial.[comment]. *Lancet.* 2002;360(9326):7-22.

120. Collins R, Armitage J, Parish S, Sleight P, Peto R, Heart Protection Study Collaborative G. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions.[see comment]. *Lancet.* 2004;363(9411):757-767.

121. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet.* 2003;361(9374):2005-2016.

122. Heart Protection Study Collaborative G. The effects of cholesterol lowering with simvastatin on cause-specific mortality and on cancer incidence in 20,536 high-risk people: a randomised placebo-controlled trial [ISRCTN48489393]. *BMC Med.* 2005;3:6.

123. Sever PS, Dahlof B, Poulter NR, et al. Rationale, design, methods and baseline demography of participants of the Anglo-Scandinavian Cardiac Outcomes Trial. ASCOT investigators. *Journal of Hypertension.* 2001;19(6):1139-1147.
124. Sever PS, Dahlof B, Poulter NR, et al. Anglo-Scandinavian Cardiac Outcomes Trial: a brief history, rationale and outline protocol. *Journal of Human Hypertension.* 2001;15(Suppl 1):S11-12.
125. Geluk CA, Asselbergs FW, Hillege HL, et al. Impact of statins in microalbuminuric subjects with the metabolic syndrome: a substudy of the PREVEND Intervention Trial.[see comment]. *European Heart Journal.* Jul 2005;26(13):1314-1320.
126. Jardine AG, Holdaas H, Fellstrom B, et al. Fluvastatin prevents cardiac death and myocardial infarction in renal transplant recipients: Post-hoc subgroup analyses of the ALERT study. *American Journal of Transplantation.* 2004;4(6):988-995.
127. Holdaas H, Fellstrom B, Cole E, et al. Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study. *American Journal of Transplantation.* Dec 2005;5(12):2929-2936.
128. Fellstrom B, Holdaas H, Jardine AG, et al. Effect of fluvastatin on renal end points in the Assessment of Lescol in Renal Transplant (ALERT) trial. *Kidney International.* 2004;66(4):1549-1555.
129. Sever PS, Poulter NR, Dahlof B, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial--lipid-lowering arm (ASCOT-LLA).[see comment]. *Diabetes Care.* May 2005;28(5):1151-1157.
130. Arampatzis CA, Goedhart D, Serruys PW, et al. Fluvastatin reduces the impact of diabetes on long-term outcome after coronary intervention--a Lescol Intervention Prevention Study (LIPS) substudy.[see comment]. *American Heart Journal.* Feb 2005;149(2):329-335.
131. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial.[see comment]. *JAMA.* Mar 3 2004;291(9):1071-1080.
132. Serruys P, De Feyter PJ, Benghozi R, Hugenholtz PG, Lesaffre E. The Lescol(R) Intervention Prevention Study (LIPS): A double-blind, placebo-controlled, randomized trial of the long-term effects of fluvastatin after successful transcatheter therapy in patients with coronary heart disease. *International Journal of Cardiovascular Interventions.* 2001;4(4):165-172.
133. Lemos PA, Serruys PW, de Feyter P, et al. Long-term fluvastatin reduces the hazardous effect of renal impairment on four-year atherosclerotic outcomes (a LIPS substudy). *American Journal of Cardiology.* Feb 15 2005;95(4):445-451.
134. Anonymous. Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mm/l (200 - 300 mg/dl) plus 2 additional risk factors. The Pravastatin Multinational Study Group for Cardiac Risk Patients.[see comment]. *American Journal of Cardiology.* Nov 1 1993;72(14):1031-1037.
135. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *Journal of the American Medical Association.* 1999;282(24):2340-2346.

136. Grady D, Chaput L, Kristof M. Diagnosis and treatment of coronary heart disease in women: systematic reviews of evidence on selected topics. *Evid Rep Technol Assess (Summ).* May 2003(81):1-4.

137. Walsh JME, Pignone M. Drug Treatment of Hyperlipidemia in Women. *Journal of the American Medical Association.* 2004;291(18):2243-2252.

138. Prisant LM, Downton M, Watkins LO, et al. Efficacy and tolerability of lovastatin in 459 African Americans with hypercholesterolemia. *American Journal of Cardiology.* 1996;78(4):420-424.

139. Davidson MH, Stein EA, Hunninghake DB, et al. Lipid-altering efficacy and safety of simvastatin 80 mg/day: worldwide long-term experience in patients with hypercholesterolemia. *Nutrition Metabolism & Cardiovascular Diseases.* 2000;10(5):253-262.

140. Dujovne CA, Chremos AN, Pool JL, et al. Expanded clinical evaluation of lovastatin (EXCEL) study results IV. Additional perspectives on the tolerability of lovastatin. *American Journal of Medicine.* 1991;91(1 Suppl 2):25S-30S.

141. Bradford RH, Shear CL, Chremos AN, et al. Expanded clinical evaluation of lovastatin (EXCEL) study design and patient characteristics of a double blind, placebo controlled study in patients with moderate hypercholesterolemia. *American Journal of Cardiology.* 1990;66(8):44B-55B.

142. Bradford RH, Shear CL, Chremos AN, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. [see comments]. *Archives of Internal Medicine.* 1991;151(1):43-49.

143. Bradford RH, Shear CL, Chremos AN, et al. Expanded clinical evaluation of lovastatin (EXCEL) study results III. Efficacy in modifying lipoproteins and implications for managing patients with moderate hypercholesterolemia. *American Journal of Medicine.* 1991;91(1 Suppl 2):18S-24S.

144. Bradford RH, Downton M, Chremos An, et al. Efficacy and tolerability of lovastatin in 3390 women with moderate hypercholesterolemia. *Annals of Internal Medicine.* 1993;118(11):850-855.

145. Bradford RH, Shear Cl, Chremos An, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results two year efficacy and safety follow up. *American Journal of Cardiology.* 1994;74(7):667-673.

146. FDA Center for Drug Evaluation and Research. Medical review of rosuvastatin. *Available at:http://www.fda.gov/cder/foi/nda/2003/21-366_Crestor.htm.* 2003.

147. Alsheikh-Ali AA, Ambrose MS, Kuvin JT, Karas RH. The safety of rosuvastatin as used in common clinical practice: a postmarketing analysis.[see comment]. *Circulation.* Jun 14 2005;111(23):3051-3057.

148. Silva MA, Swanson AC, Gandhi PJ, Tataronis GR. Statin-related adverse events: a meta-analysis. *Clinical Therapeutics.* Jan 2006;28(1):26-35.

149. Bottorff M. 'Fire and forget?' - Pharmacological considerations in coronary care. *Atherosclerosis.* 1999;147(SUPPL. 1):S23-S30.

150. Davidson MH. Safety profiles for the HMG-CoA reductase inhibitors: treatment and trust. *Drugs.* 2001;61(2):197-206.

151. Maron DJ, Fazio S, Linton MF. Current perspectives on statins. *Circulation.* 2000;101(2):207-213.

152. Ucar M, Mjorndal T, Dahlqvist R. HMG-CoA reductase inhibitors and myotoxicity. *Drug Safety.* 2000;22(6):441-457.
153. Omar MA, Wilson JP. FDA adverse effects reports on statin-associated rhabdomyolysis. *Annals of Pharmacotherapy.* 2002;36(2):288-295.
154. Shek A, Ferrill MJ. Statin-fibrate combination therapy. *Annals of Pharmacotherapy.* 2001;35(7-8):908-917.
155. Thompson PD, Clarkson P, Karas RH. Statin-Associated Myopathy. *Journal of the American Medical Association.* 2003;289(13):1681-1690.
156. Gaist D, Rodriguez LA, Huerta C, Hallas J, Sindrup SH. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. *Epidemiology.* 2001;12(5):565-569.
157. Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors.[erratum appears in Ann Pharmacother 2001 Oct;35(10):1296]. *Annals of Pharmacotherapy.* Sep 2001;35(9):1096-1107.
158. Shepherd J. Fibrates and statins in the treatment of hyperlipidaemia: an appraisal of their efficacy and safety. *European Heart Journal.* 1995;16(1):5-13.
159. Abourjaily HM, Alsheikh-Ali AA, Karas RH. Comparison of the frequency of adverse events in patients treated with atorvastatin or simvastatin. *American Journal of Cardiology.* 2003;91(8):999-1002, A1007.
160. Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *Journal of the American Medical Association.* 2004;292(21):2585-2590.
161. Nissen S, Nicholls S, Sipahi I, al. e. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA.* 2006;295(13):1556-1565.
162. Bevilacqua M, Guazzini B, Righini V, Barrella M, Toscano R, Chebat E. Metabolic effects of fluvastatin extended release 80 mg and atorvastatin 20 mg in patients with type 2 diabetes mellitus and low serum high-density lipoprotein cholesterol levels: A 4-month, prospective, open-label, randomized, blinded - End point (probe) trial. *Current Therapeutic Research, Clinical & Experimental.* 2004;65(4):330-344.
163. Yasuda G, Kuji T, Hasegawa K, et al. Safety and efficacy of fluvastatin in hyperlipidemic patients with chronic renal disease. *Ren. Fail.* 2004;26(4):411-418.
164. Bays HE, Dujovne CA. Drug interactions of lipid-altering drugs. *Drug Safety.* 1998;19(5):355-371.
165. Gruer PJ, Vega JM, Mercuri MF, Dobrinska MR, Tobert JA. Concomitant use of cytochrome P450 3A4 inhibitors and simvastatin. *American Journal of Cardiology.* 1999;84(7):811-815.
166. Beaird SL. HMG-CoA reductase inhibitors: assessing differences in drug interactions and safety profiles. *Journal of the American Pharmaceutical Association.* 2000;40(5):637-644.
167. Davidson MH, Dicklin MR, Maki KC, Kleinpell RM. Colesevelam hydrochloride: a non-absorbed, polymeric cholesterol-lowering agent. *Expert Opinion on Investigational Drugs.* 2000;9(11):2663-2671.
168. White CM. An evaluation of CYP3A4 drug interactions with HMG-CoA reductase inhibitors. *Formulary.* 2000;35(4):343-352.

169. Worz CR, Bottorff M. The role of cytochrome P450-mediated drug-drug interactions in determining the safety of statins. *Expert Opinion on Pharmacotherapy.* 2001;2(7):1119-1127.
170. Wenke K, Meiser B, Thiery J, Reichart B. Impact of simvastatin therapy after heart transplantation an 11-year prospective evaluation. *Herz.* Aug 2005;30(5):431-432.
171. Imamura R, Ichimaru N, Moriyama T, et al. Long term efficacy of simvastatin in renal transplant recipients treated with cyclosporine or tacrolimus. *Clinical Transplantation.* Oct 2005;19(5):616-621.
172. Christians U, Jacobsen W, Floren LC. Metabolism and drug interactions of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in transplant patients: are the statins mechanistically similar? *Pharmacology & Therapeutics.* 1998;80(1):1-34.
173. O'Rourke B, Barbir M, Mitchell AG, Yacoub MH, Banner NR. Efficacy and safety of fluvastatin therapy for hypercholesterolemia after heart transplantation: Results of a randomised double blind placebo controlled study. *International Journal of Cardiology.* 2004;94(2-3):235-240.
174. Tokumoto T, Tanabe K, Ishida H, et al. Impact of fluvastatin on hyperlipidemia after renal transplantation. *Transplantation Proceedings.* Sep 2004;36(7):2141-2144.
175. Holdaas H, Fellstrom B, Jardine AG, et al. Beneficial effect of early initiation of lipid-lowering therapy following renal transplantation. *Nephrology Dialysis Transplantation.* May 2005;20(5):974-980.
176. Samman A, Imai C, Straatman L, Frolich J, Humphries K, Ignaszewski A. Safety and efficacy of rosuvastatin therapy for the prevention of hyperlipidemia in adult cardiac transplant recipients. *Journal of Heart & Lung Transplantation.* Aug 2005;24(8):1008-1013.
177. Ballantyne CM, Bourge RC, Domalik LJ, et al. Treatment of hyperlipidemia after heart transplantation and rationale for the Heart Transplant Lipid registry. *American Journal of Cardiology.* 1996;78(5):532-535.
178. Jardine A, Holdaas H. Fluvastatin in combination with cyclosporin in renal transplant recipients: a review of clinical and safety experience. *Journal of Clinical Pharmacy & Therapeutics.* 1999;24(6):397-408.
179. Romero R, Calvino J, Rodriguez J, Sanchez-Guisande D. Short-term effect of atorvastatin in hypercholesterolaemic renal-transplant patients unresponsive to other statins. *Nephrology Dialysis Transplantation.* 2000;15(9):1446-1449.
180. Stein JH, Merwood MA, Bellehumeur JL, et al. Effects of pravastatin on lipoproteins and endothelial function in patients receiving human immunodeficiency virus protease inhibitors. *American heart journal.* 2004;147(4):E18.
181. Aberg JA, Zackin RA, Brobst SW, et al. A randomized trial of the efficacy and safety of fenofibrate versus pravastatin in HIV-infected subjects with lipid abnormalities: AIDS Clinical Trials Group Study 5087. *AIDS Research & Human Retroviruses.* Sep 2005;21(9):757-767.
182. Benesic A, Zilly M, Kluge F, et al. Lipid lowering therapy with fluvastatin and pravastatin in patients with HIV infection and antiretroviral therapy: Comparison of efficacy and interaction with indinavir. *Infection.* 2004;32(4):229-233.
183. Penzak SR, Chuck SK. Hyperlipidemia associated with HIV protease inhibitor use: Pathophysiology, prevalence, risk factors and treatment. *Scandinavian Journal of Infectious Diseases.* 2000;32(2):111-123.

184. Fichtenbaum CJ, Gerber JG, Rosenkranz SL, et al. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. *AIDS.* 2002;16(4):569-577.
185. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *American Journal of Cardiology.* Jan 1 2005;95(1):120-122.
186. Wiklund O, Angelin B, Bergman M, et al. Pravastatin and gemfibrozil alone and in combination for the treatment of hypercholesterolemia. *American Journal of Medicine.* 1993;94(1):13-20.
187. Farnier M, Salko T, Isaacsohn JL, Troendle AJ, Dejager S, Gonasun L. Effects of baseline level of triglycerides on changes in lipid levels from combined fluvastatin + fibrate (bezafibrate, fenofibrate, or gemfibrozil). *American Journal of Cardiology.* 2003;92(7):794-797.
188. Alsheikh-Ali AA, Karas RH. Adverse events with concomitant use of simvastatin or atorvastatin and thiazolidinediones. *American Journal of Cardiology.* 2004 Jun 1 2004;93(11):1417-1418.
189. Lewin AJ, Kipnes MS, Meneghini LF, et al. Effects of simvastatin on the lipid profile and attainment of low-density lipoprotein cholesterol goals when added to thiazolidinedione therapy in patients with type 2 diabetes mellitus: A multicenter, randomized, double-blind, placebo-controlled trial. *Clinical Therapeutics.* 2004;26(3):379-389.
190. Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with Elevated Liver Enzymes Are Not at Higher Risk for Statin Hepatotoxicity. *Gastroenterology.* 2004;126(5):1287-1292.

Appendix A. Search strategy

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1       exp lovastatin/ or "lovastatin".mp.
2       simvastatin.mp.
3       Pravastatin/ or "pravastatin".mp
4       (atorvastatin or fluvastatin or rosuvastatin).mp.
5       statins.mp. or exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
6       1 or 2 or 3 or 4 or 5
7       Drug Evaluation/ or drug evaluation studies.mp.
8       comparative study/
9       7 or 8
10      6 and 9
11      limit 10 to human
12      limit 11 to english language
13      11 not 12
14      limit 13 to abstracts
15      12 or 14
16      6
17      limit 16 to (human and english language and (clinical trial or
        clinical trial, phase i or clinical trial, phase ii or clinical trial,
        phase iii or clinical trial, phase iv or controlled clinical trial or
        meta analysis or multicenter study or randomized controlled trial))
18      exp clinical trials/ or clinical trial$.tw.
19      exp cohort studies/
20      (cohort stud$ or longitudinal stud$ or prospective stud$).tw. (33965)
21      18 or 19 or 20
22      6 and 21
23      limit 22 to (human and english language)
24      17 or 23
25      15 or 24
```

Appendix B. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, birth dates or weekdays
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers

On-site computer based system with a randomization sequence that is not readable until allocation
Other approaches sequence to clinicians and patients
Inferior approaches to concealment of randomization:
Use of alternation, case record numbers, birth dates or week days
Open random numbers lists
Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results and adverse events.

5. Are the primary studies summarized appropriately?

   The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).
   For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Appendix C. Excluded trials

Aguilar-Salinas CA, Gomez-Perez FJ, Posadas-Romero C, et al. Efficacy and safety of atorvastatin in hyperlipidemic, type 2 diabetic patients. A 34-week, multicenter, open-label study. *Atherosclerosis.* 2000;152(2):489-496.

Akiyama T, Ishii T, Imanishi M, Nishioka T, Matsuura T, Kurita T. Efficacy and safety of treatment with low-dose fluvastatin in hypercholesterolemic renal transplant recipients. *Transplantation Proceedings.* 2001;33(3):2115-2118.

Alnaeb ME, Youssef F, Mikhailidis DP, Hamilton G. Short-term lipid-lowering treatment with atorvastatin improves renal function but not renal blood flow indices in patients with peripheral arterial disease. *Angiology.* Jan-Feb 2006;57(1):65-71.

Amarenco P, Bogousslavsky J, Callahan AS, et al. Design and baseline characteristics of the stroke prevention by aggressive reduction in cholesterol levels (SPARCL) study. *Cerebrovascular Diseases.* 2003;16(4):389-395.

Andrews TC, Raby K, Barry J, et al. Effect of cholesterol reduction on myocardial ischemia in patients with coronary disease. [see comments]. *Circulation.* 1997;95:324-328.

Anonymous. Pravastatin use and risk of coronary events and cerebral infarction in japanese men with moderate hypercholesterolemia: the Kyushu Lipid Intervention Study. *Journal of Atherosclerosis & Thrombosis.* 2000;7(2):110-121.

Anonymous. The effects of pravastatin on hospital admission in hypercholesterolemic middle-aged men: West of Scotland Coronary Prevention Study. *Journal of the American College of Cardiology.* 1999;33(4):909-915.

Arnadottir M, Eriksson LO, Germershausen JI, Thysell H. Low dose simvastatin is a well tolerated and efficacious cholesterol lowering agent in ciclosporin treated kidney transplant recipients double blind, randomized, placebo controlled study in 40 patients. *Nephron.* 1994;68:57-62.

Athyros VG, Papageorgiou AA, Hatzikonstandinou HA, et al. Safety and efficacy of long term statin fibrate combinations in patients with refractory familial combined hyperlipidemia. *American Journal of Cardiology.* 1997;80:608-613.

Baldassarre D, Veglia F, Gobbi C, et al. Intima-media thickness after pravastatin stabilizes also in patients with moderate to no reduction in LDL-cholesterol levels: the carotid atherosclerosis Italian ultrasound study. *Atherosclerosis.* 2000;151(2):575-583.

Baldini F, Di Giambenedetto S, Cingolani A, Murri R, Ammassari A, De Luca A. Efficacy and tolerability of pravastatin for the treatment of HIV-1 protease inhibitor-associated hyperlipidaemia: a pilot study. *AIDS.* 2000;14(11):1660-1662.

Ballantyne CM, Lipka LJ, Sager PT, et al. Long-term safety and tolerability profile of ezetimibe and atorvastatin coadministration therapy in patients with primary hypercholesterolaemia. *International Journal of Clinical Practice.* 2004;58(7):653-658.

Ballantyne CM, McKenney J, Trippe BS. Efficacy and safety of an extended-release formulation of fluvastatin for once-daily treatment of primary hypercholesterolemia. *American Journal of Cardiology.* 2000;86(7):759-763.

Barter PJ, O'Brien RC. Achievement of target plasma cholesterol levels in hypercholesterolaemic patients being treated in general practice. *Atherosclerosis.* 2000;149:199-205.

Bays HE, Dujovne CA, McGovern ME, et al. Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (the advicor versus other cholesterol-modulating agents trial evaluation [ADVOCATE]). *American Journal of Cardiology.* 2003;91(6):667-672.

Beishuizen ED, Jukema JW, Tamsma JT, et al. No effect of statin therapy on silent myocardial ischemia in patients with type 2 diabetes without manifest cardiovascular disease. *Diabetes Care.* Jul 2005;28(7):1675-1679.

Best JD, Nicholson GC, O Ndn, et al. Atorvastatin and simvastatin reduce elevated cholesterol in non insulin dependent diabetes. *Diabetes, Nutrition and Metabolism Clinical and Experimental.* 1996;9:74-80.

Branchi A, Fiorenza AM, Rovellini A, et al. Lowering effects of four different statins on serum triglyceride level. *European Journal of Clinical Pharmacology.* 1999;55:499-502.

Briguori C, Colombo A, Airoldi F, et al. Statin administration before percutaneous coronary intervention: impact on periprocedural myocardial infarction.[see comment]. *European Heart Journal.* Oct 2004;25(20):1822-1828.

Bruckert E, Lievre M, Giral P, et al. Short-term efficacy and safety of extended-release fluvastatin in a large cohort of elderly patients. *American Journal of Geriatric Cardiology.* 2003;12(4):225-231.

Burton JR, Teo KK, Buller CE, et al. Effects of long term cholesterol lowering on coronary atherosclerosis in patient risk factor subgroups: the Simvastatin/enalapril Coronary Atherosclerosis Trial (SCAT). *Canadian Journal of Cardiology.* 2003;19(5):487-491.

Byington RP, Davis BR, Plehn JF, et al. Reduction of stroke events with pravastatin: the Prospective Pravastatin Pooling (PPP) Project. *Circulation.* 2001;103(3):387-392.

Byington RP, Evans GW, Espeland MA, et al. Effects of lovastatin and warfarin on early carotid atherosclerosis sex specific analyses. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. *Circulation.* 1999;100:e14-17.

Campeau L, Hunninghake DB, Knatterud GL, et al. Aggressive cholesterol lowering delays saphenous vein graft atherosclerosis in women, the elderly, and patients with associated risk factors. NHLBI post coronary artery bypass graft clinical trial. Post CABG Trial Investigators. *Circulation.* 1999;99(25):3241-3247.

Capone D, Stanziale P, Gentile A, Imperatore P, Pellegrino T, Basile V. Effects of simvastatin and pravastatin on hyperlipidemia and cyclosporin blood levels in renal transplant recipients. *American Journal of Nephrology.* 1999;19:411-415.

Cheung RC, Morrell JM, Kallend D, Watkins C, Schuster H. Effects of switching statins on lipid and apolipoprotein ratios in the MERCURY I study. *International Journal of Cardiology.* Apr 20 2005;100(2):309-316.

Crisby M, Nordin-Fredriksson G, Shah PK, Yano J, Zhu J, Nilsson J. Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: implications for plaque stabilization. *Circulation.* 2001;103(7):926-933.

Derosa G, Cicero AEG, Bertone G, Piccinni MN, Ciccarelli L, Roggeri DE. Comparison of fluvastatin + fenofibrate combination therapy and fluvastatin monotherapy in the treatment of combined hyperlipidemia, type 2 diabetes mellitus, and coronary heart disease: A 12-month, randomized, double-blind, controlled trial. *Clinical Therapeutics.* 2004;26(10):1599-1607.

Derosa G, Mugellini A, Ciccarelli L, Rinaldi A, Fogari R. Effects of orlistat, simvastatin, and orlistat + simvastatin in obese patients with hypercholesterolemia: A randomized, open-label trial. *Current Therapeutic Research, Clinical & Experimental.* 2002;63(9):621-633.

Dupuis J, Tardif JC, Cernacek P, Theroux P. Cholesterol reduction rapidly improves endothelial function after acute coronary syndromes. The RECIFE (reduction of cholesterol in ischemia and function of the endothelium) trial. *Circulation.* 1999;99(25):3227-3233.

Feillet C, Farnier M, Monnier LH, et al. Comparative effects of simvastatin and pravastatin on cholesterol synthesis in patients with primary hypercholesterolemia. *Atherosclerosis.* 1995;118:251-258.

Giral P, Bruckert E, Jacob N, Chapman MJ, Foglietti MJ, Turpin G. Homocysteine and lipid lowering agents. A comparison between atorvastatin and fenofibrate in patients with mixed hyperlipidemia. *Atherosclerosis.* 2001;154:421-427.

Goldberg RB, Mellies MJ, Sacks FM, et al. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The Care Investigators. *Circulation.* 1998;98(23):2513-2519.

Gotto AM, Jr., Whitney E, Stein EA, et al. Application of the National Cholesterol Education joint European treatment criteria and clinical benefit in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *European Heart Journal.* 2000;21(19):1627-1633.

Gotto AMJ, Boccuzzi SJ, Cook JR, et al. Effect of lovastatin on cardiovascular resource utilization and costs in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). AFCAPS/TexCAPS Research Group. *American Journal of Cardiology.* 2000;86:1176-1181.

Gotto AMJ, Whitney E, Stein EA, et al. Relation between baseline and on treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Circulation.* 2000;101:477-484.

Holmberg B, Brannstrom M, Bucht B, et al. Safety and efficacy of atorvastatin in patients with severe renal dysfunction. *Scand J Urol Nephrol.* 2005;39(6):503-510.

Jayaram S, Jain MM, Naikawadi AA, Gawde A, Desai A. Comparative evaluation of the efficacy, safety, and tolerability of rosuvastatin 10 mg with atorvastatin, 10 mg in adult patients with hypercholesterolaemia: The first Indian study. *Journal of the Indian Medical Association.* 2004;102(1):48-52.

Kent SM, Coyle LC, Flaherty PJ, Markwood TT, Taylor AJ. Marked Low-Density Lipoprotein Cholesterol Reduction below Current National Cholesterol Education Program Targets Provides the Greatest Reduction in Carotid Atherosclerosis. *Clinical Cardiology.* 2004;27(1):17-21.

Kosoglou T, Statkevich P, Meyer I, et al. Effects of ezetimibe on the pharmacodynamics and pharmacokinetics of lovastatin. *Current Medical Research and Opinion.* 2004;20(6):955-965.

Lawrence JM, Reid J, Taylor GJ, Stirling C, Reckless JPD. The effect of high dose atorvastatin therapy on lipids and lipoprotein subfractions in overweight patients with type 2 diabetes. *Atherosclerosis.* 2004;174(1):141-149.

Lins RL, Matthys KE, Billiouw JM, et al. Lipid and apoprotein changes during atorvastatin up-titration in hemodialysis patients with hypercholesterolemia: A placebo-controlled study. *Clinical Nephrology.* 2004;62(4):287-294.

Mauger J-F, Couture P, Paradis M-E, Lamarche B. Comparison of the impact of atorvastatin and simvastatin on apoA-I kinetics in men. *Atherosclerosis.* 2005;178(1):157-163.

McGwin G, Jr., Modjarrad K, Hall TA, Xie A, Owsley C. 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors and the presence of age-related macular degeneration in the Cardiovascular Health Study. *Arch. Ophthalmol.* Jan 2006;124(1):33-37.

McGwin G, Jr., Xie A, Owsley C. The use of cholesterol-lowering medications and age-related macular degeneration. *Ophthalmology.* Mar 2005;112(3):488-494.

Mukamal KJ, Girotra S, Mittleman MA. Alcohol consumption, atherosclerotic progression, and prognosis among patients with coronary artery bypass grafts. *American Heart Journal.* Feb 2006;151(2):368-372.

Raggi P, Davidson M, Callister TQ, et al. Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES). *Circulation.* Jul 26 2005;112(4):563-571.

Ridker PM, Morrow DA, Rose LM, Rifai N, Cannon CP, Braunwald E. Relative efficacy of atorvastatin 80 mg and pravastatin 40 mg in achieving the dual goals of low-density lipoprotein cholesterol <70 mg/dl and C-reactive protein <2 mg/l: an analysis of the PROVE-IT TIMI-22 trial. *Journal of the American College of Cardiology.* May 17 2005;45(10):1644-1648.

Stein E, Stender S, Mata P, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: Efficacy and safety of ezetimibe co-administered with atorvastatin. *American Heart Journal.* 2004;148(3):447-455.

Stender S, Schuster H, Barter P, Watkins C, Kallend D, Group MIS. Comparison of rosuvastatin with atorvastatin, simvastatin and pravastatin in achieving cholesterol goals and improving plasma lipids in hypercholesterolaemic patients with or without the metabolic syndrome in the MERCURY I trial.[erratum appears in Diabetes Obes Metab. 2005 Jul;7(4):460]. *Diabetes, Obesity & Metabolism.* Jul 2005;7(4):430-438.

Tveit A, Grundtvig M, Gundersen T, et al. Analysis of pravastatin to prevent recurrence of atrial fibrillation after electrical cardioversion. *American Journal of Cardiology.* 2004;93(6):780-782.

van Dam MJ, Penn HJ, den Hartog FR, et al. A comparison of the efficacy and tolerability of titrate-to-goal regimens of simvastatin and fluvastatin: a randomized, double-blind study in adult patients at moderate to high risk for cardiovascular disease. *Clinical Therapeutics.* 2001;23(3):467-478.

Vernaglione L, Cristofano C, Muscogiuri P, Chimienti S. Does Atorvastatin Influence Serum C-Reactive Protein Levels in Patients on Long-Term Hemodialysis? *American Journal of Kidney Diseases.* 2004;43(3):471-478.

Zhang B, Noda K, Matsunaga A, Kumagai K, Saku K. A comparative crossover study of the effects of fluvastatin and pravastatin (FP-COS) on circulating autoantibodies to oxidized LDL in patients with hypercholesterolemia. *Journal of Atherosclerosis & Thrombosis.* 2005;12(1):41-47.