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

Final Report

September 2005

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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INTRODUCTION

Coronary heart disease (CHD) continues to be the leading cause of mortality and a significant cause of morbidity among North Americans. In 1999, CHD claimed 529,659 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 is directly related to 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.

Six statins are available in the US and Canada:

Atorvastatin (Lipitor)
Fluvastatin (Lescol, Lescol XL)
Lovastatin (Mevacor, Altocor)
Pravastatin (Pravachol)
Rosuvastatin (Crestor)
Simvastatin (Zocor)

Fluvastatin (Lescol XL) and lovastatin (Altocor) are available in extended-release as well as immediate-release forms. 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. Taking a statin at bedtime or with the evening meal improves its ability to lower LDL. 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 Program (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, angina, CHD mortality, all-cause mortality, stroke, or need for revascularization (coronary artery bypass graft, angioplasty, or stenting)?

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

5. Are there differences in the safety of statins 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:
    a. Patients with diabetes
    b. Patients with HIV
    c. Organ transplant recipients
    d. Patients at high risk for myotoxicity
    e. Patients at high risk for hepatotoxicity
    f. 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 (2004, Issue 4), Medline (1966-February Week 1 2005), EMBASE (1980-February 4, 2005), PreMEDLINE (through February 9, 2005), 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 6.0).

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.

For clinical efficacy, we included randomized clinical trials. Good-quality trials of one statin against another statin were considered to provide the best evidence for comparing efficacy

in lowering LDL-c, raising HDL-c, and in reaching NCEP goals. While head-to-head trials were considered the best evidence for long-term health outcomes, they were scarce so we relied heavily on placebo-controlled trials. For adverse effects, we evaluated data from head-to-head trials, long-term placebo-controlled single drug trials, and observational cohort studies that reported elevations in liver enzymes, myotoxicity, or drug-drug interactions. We also evaluated systematic reviews that included primarily short-term placebo-controlled single drug trials. 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).[5, 6] 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 assessed whether the doses of compared statins were equipotent and whether they were standard doses by current standards. 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 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 7,859 citations. We identified 170 potentially relevant articles. Of these, 124 randomized controlled trials provided usable data, as did 6 observational studies and eight systematic reviews. Forty-two 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 two short-term (6 weeks) trials.

Detailed Assessment

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

We identified 60 randomized controlled trials comparing the LDL-c lowering ability of two or more statins in patients with baseline LDL-c $\leq$250mg/dl (Evidence Table 1).[7-66] In 35 of these trials, the percentage of patients reaching their NCEP goal was also evaluated. There were 35 double-blinded, 22 unblinded, two single-blinded studies, and one study entitled “blinded”,

with no specifics given (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.[40] One trial looked at the effects of switching to rosuvastatin midway through the trial.[56] 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. These 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 $\geq$350 to 400mg/dl and those receiving drugs with the potential for drug interaction with statins. 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 more recent meta-analysis of placebo-controlled trials.[67] 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[17, 48, 50, 53]

(2) In an open-label, fair-quality study, lovastatin 20mg daily produced a lower- than-expected reduction in LDL-c (21%).[27] 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 shows an LDL-c reduction of 60% in patients receiving atorvastatin 80mg daily. However, this reduction comes from data involving only 23 patients. The five 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%-39%	39% (37%)	22
20mg	42.1%-46.1%	43%	8
40mg	47.2%-51.3%	50%	5
80mg	46.3%-54%	60% (57%)	6
Fluvastatin			
20mg	17%-21.8%	22% (18%) β	5
40mg	22%-26%	25% β	6
80mg	29.6%-30.6%+	36% (31%)++ β	2
80mg XL*	--	35% β	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%) α	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	43%-50%	52%	9
20mg	51.6%-52.4%	55%	3
40mg	55%-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

Comparisons of high-potency statins

Three studies directly compared atorvastatin 80mg to simvastatin 80mg daily.[29, 33, 35] At a dose of 80mg daily for each statin, atorvastatin reduced LDL-c by 53.6% compared to 48.1% for simvastatin ($p \leq 0.001$).[29] A greater number of patients in the atorvastatin 80mg as opposed to the simvastatin 80mg group reported clinical adverse effects, primarily gastrointestinal-diarrhea (23% vs 11.9%; $p<0.001$). There was no significant difference in withdrawal rates due to adverse effects between groups. 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,[35] 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[33] was an open-label trial designed to compare rosuvastatin to other statins (atorvastatin, simvastatin, and pravastatin). One hundred sixty-five patients were randomized to atorvastatin 80 and 163 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.

Seven trials[20, 33, 47, 54, 56, 57, 61] and two meta-analyses[13, 68] have compared rosuvastatin to atorvastatin (see Table 2, below).

Table 2. Trials of rosuvastatin vs. atorvastatin

Study, reference	Doses	N screened/ N randomized	Design	Duration	Patients
Davidson 2002[20] (AstraZeneca Study 24)	Rosuva 5,10 mg Atorva 10 mg	1,888/519	Double-blind Fixed dose	12 weeks	LDL 160-250 mg/dL 85% white
Schwartz 2004[57]	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 43% over age 65 91% white
Olsson 2002[47] (AstraZeneca Study 26)	Rosuva 5, 10-80 mg Atorva 10-80 mg	1,521/412	Double-blind 12-wk at fixed dose, then titration to goal S	1 year	LDL 160-250 mg/dL 100% white
Schneck 2003[54] (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	LDL 160-250 mg/dL 25% over age 65 88% white
Schuster 2004[56]	Rosuva 10 mg Atorva 10 or 20 mg	6508 screened/ 3161 randomized (2043 rosuva or atorva)	Open-label 8 week at fixed dose; then either remained on current statin or switched to rosuvastatin for 8 weeks	16 weeks total	Fasting LDL ≥115 mg/dL 57.6 % male Atherosclerosis or diabetes
Jones 2003[33] (AstraZeneca Study 65) STELLAR Trial	Rosuva 10, 20, 40, 80 mg Atorva 10, 20, 40, 80 mg	Not reported/ 2431 (1764 rosuva or atorva)	Open-label	6 weeks	Baseline LDL about 190 mg/dL 86% white
Strandberg 2004[61]	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	LDL >135 mg/dL in statin-naive patients; >120 mg/dL in patients using the starting dose of another lipid-lowering drug. Atherosclerosis or diabetes

Four trials concerned patients who had few or no risk factors for CAD[20, 33, 47, 54] and 3 trials enrolled patients at high risk for cardiovascular disease.[56, 57, 61] The 2 trials concerning high-risk patients were published more recently and are described in detail below. All studies comparing rosuvastatin to atorvastatin that reported LDL-c reductions at 12 weeks[13, 20, 47, 57, 61] had similar results, whether or not they included patients at high risk for CHD.

All of the trials had 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. Four trials reported the number screened. In three of these, 27% to 31% of the screened subjects were admitted to the trial.[57] 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). 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[57]. 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 (38.8%, 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.

Comparative data from head-to-head controlled trials on the safety and efficacy for higher doses of rosuvastatin (20-40mg) are sparse.[33, 54] Only small numbers of patients took rosuvastatin 20mg or 40mg, and very few were observed for longer than 6 weeks.

The largest trial was a 6-week open label trial (STELLAR) in which about 300 patients took rosuvastatin 40mg/day or higher. 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.[69]

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 3):

Table 3. Equivalent doses of statins for LDL-c lowering*

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

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

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.*

Table 4. Achieving Target LDL-cholesterol goals

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

(From ATP-III. Table VI-3-1. Page VI-19.[3] Optional goals from ATP-III supplement not shown.)

Thirty-five 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. In a majority of the studies, the doses compared were not equivalent. 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),[42] 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.[56] 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.[68] 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).[70]

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 are approximately equivalent, 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.[67] 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)[14, 18, 29, 32, 35, 46] but in 12 others, there was no significant difference between the two on this measure.[7, 15, 17, 19, 25, 28, 30, 34, 50, 51, 64, 66]

Two studies that compared atorvastatin to simvastatin were designed to measure HDL-c raising as a primary outcome.[10, 36] 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.[10] 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,[36] 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.[13, 20, 33, 47, 54, 57, 61] However, the results were mixed. Four studies reported greater increases in HDL-c with rosuvastatin 5 or 10mg than with atorvastatin 10mg.[13, 20, 57, 61] 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,[33] 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.[16] Rosuvastatin 10mg was better than pravastatin 20mg in this same study[16] and equivalent in two others.[49, 56]

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

- There are no head-to-head trials of equivalent doses of different statins for reducing coronary events.
    - In a head-to-head trial in post-myocardial infarction patients, **atorvastatin 80mg** reduced all-cause mortality and CV events. For every 25 patients treated with **atorvastatin 80mg** instead of **pravastatin 40mg**, one coronary event was prevented.

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

  In patients who have never had coronary disease:

  - **Pravastatin** reduced all-cause mortality and CV events in high-risk patients.
  - **Lovastatin** reduced CV events in patients at average risk.
  - **Atorvastatin** reduced CV events in high-risk patients and patients with diabetes.
  - **Simvastatin** reduced CV events in patients with diabetes.
  - **Atorvastatin** and **simvastatin** reduced the risk of cardiovascular events in high-risk patients who had LDL levels that would once have been considered to be acceptable.
  - There are no studies of **fluvastatin** or **rosuvastatin** with CHD endpoints in patients who have never had coronary disease.

  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 studies of **rosuvastatin** with CHD endpoints in patients with coronary disease.

Detailed Assessment

There is only one head-to-head trial comparing the ability different statins to reduce the risk of coronary events, stroke, or death (PROVE-IT).[72]

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 19 placebo-controlled trials and one head-to-head trial: 13 studies in outpatients,[73-85] and 7 studies in inpatients with acute MI or unstable angina.[72, 86-91] 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.[92-103] 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[93, 100] 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).[104-109]
- *Miscellaneous Trials*. Three additional trials with clinical outcomes did not fit the criteria for the other categories.[42, 110, 111]

Studies with Primary CHD Endpoints

The major trials are summarized briefly in Tables 5 (outpatient studies) and 6 (inpatient studies) below and in more detail in Evidence Table 2.

The GREACE,[112] ALLIANCE,[113] and Treating to New Targets (TNT)[114] 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 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§
AFCAPS Lovastatin 20mg-40mg (Good)	Average risk, no history of CAD/ 1.1%	150	5.2	25%	**37%**	49
WOSCOPS Pravastatin 40mg (Good)	High risk, no history of CAD/ 1.5%	192	4.9	16%	**31%**	44
LIPID Pravastatin 40mg (Good)	History of CAD/ 2.6%	150	6.1	25%	24%	164
CARE Pravastatin 40mg (Good)	History of CAD/ 2.6%	139	5	28%	**24%**	41
4S Simvastatin 20mg (Good)	History of CAD/ 5.2%	187	5.4	35%	**34%**	11
Riegger et al Fluvastatin 40mg (Fair)	Symptomatic CAD/ 2.8%	198	1	26.9%	38%	Results not significant
HPS Simvastatin 40mg (Good)	History of CVD, diabetes, or noncoronary vascular disease/ 2.1%	131	5.5	30%	**27%**	32
ASCOT Atorvastatin 10mg (Fair-Good)	HTN plus CHD risk factors/ 0.9%	133	3.3	35%	**29%**	94
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
PROSPER Pravastatin 40mg (Good)	70-82 years old, history of CHD or risk factors/ 5.2%	147	3.2	27%	**15%**	24
ALERT Fluvastatin 40 mg (Good)	Patients with renal transplant 1.0%	4.1	5.1	32%	Primary endpoint not significant (p=0.139), but 35% reduction in cardiac	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§
					deaths or non-fatal MI	
CARDS Atorvastatin 10 mg (Good)	Type 2 diabetes, no history of CVD 2.3%	117	3.9	36%	**37%**	31
PREVEND IT Pravastatin 40 mg (Fair)	Average risk, persistent microalbuminuria 0.8%	174	3.8	25%	13%	Results not significant

*__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 and WOSCOPS recruited patients without a history of CHD (primary prevention). One evaluated lovastatin (AFCAPS/TexCAPS) and the other pravastatin (WOSCOPS).[78, 84] 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,[84] 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. The next four studies in Table 5 recruited patients with documented CHD. Two of them (LIPID, CARE)[74, 82] evaluated pravastatin (n=13,173), one (4S)[80] evaluated simvastatin (n=4,444), and one evaluated fluvastatin[81] compared to placebo. 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.[115]

In Riegger et al,[81] 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. The last seven 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.[75, 116] 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.[117] 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)[118] 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).

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.[83, 119, 120] 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.

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).[77] 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 –0.37; 95% CI –0.52, -0.17). The reduction in all-cause mortality was not significant (relative risk –0.27; 95% CI –0.48, 1.00; p=0.059). The average reduction in LDL-c was 40%.

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.[73] 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.[85] 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[76] 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).

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,[79, 121] but there was no effect on the renal endpoints of graft loss, doubling of serum creatinine, or decline in GFR.[122]

Studies in Inpatients with Acute Coronary Syndrome

Head-to-Head Trial. The only head-to-head study of statins with health outcomes is the Pravastatin or Atorvastatin Evaluation and Infection Therapy--Thrombolysis in Myocardial Infarction (PROVE-IT) trial (Table 6 and Evidence Table 2).[72] In PROVE-IT, 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.

Table 6. Inpatient trials of acute MI or unstable angina.

Trial (Quality)	Population	Baseline LDL	Study Duration	% LDL reduction	Reduction in Coronary events (%)	NNT to prevent a coronary event*
Cannon et al 2004 PROVE-IT[72] (Fair)	Hospitalized for an acute coronary syndrome (MI or high-risk angina) in the preceding 10 days, but stable.	Median (interquartile range): prava 106 (87-127) mg/dL; atorva 106 (89-128) mg/dL	2 years (range 18 to 36 months)	2985 patients who had not previously receive statin therapy: 22% prava vs 51% atorva at 30 days (p<0.001)	15%	25
de Lemos 2004 A to Z Trial (Phase Z)[89] (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[91] (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[86] (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[87] (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[90] (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)[88] (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

Placebo-Controlled Trials. There are six placebo-controlled trials in patients with acute MI or unstable angina (Table 6[86-91]): 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).

The L-CAD study established that patients with acute coronary syndrome benefit from statin treatment.[86] 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[88] 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[91] 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,[90] 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.

FLORIDA[87] 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[89] 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.[92-103] (A head-to-head trial[45] 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 7 (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 7. 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[92]	Spontaneous report	Trend
ACAPS/Lovastatin[93]	Secondary endpoint	Reduction in major cardiovascular events
CCAIT/Lovastatin[94]	Spontaneous report	Trend
MARS/Lovastatin[95]	Spontaneous report	Trend
REGRESS/Pravastatin[100]	Pre-specified	Reduction in PTCA
PLAC-I/Pravastatin[96]	Pre-specified	Reduction in MI
PLAC-II/Pravastatin[97]	Pre-specified	Reduction in combined: nonfatal MI and death
KAPS/Pravastatin[98]	Spontaneous report	Trend
Sato, et al/Pravastatin[99]	Pre-specified	Reduction in overall death
MAAS/Simvastatin[101]	Spontaneous report	Trend
CIS/Simvastatin[102]	Spontaneous report	Trend
SCAT/Simvastatin[103]	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 8 and Evidence Table 6) includes placebo-controlled trials in revascularized patients (CABG, PTCA, or coronary stent).[104-109, 111] 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).[106] 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 6). In these trials, pravastatin and fluvastatin had statistically significant effects on prespecified coronary disease outcomes.

Table 8. Post-revascularization trials

Study/ drug, patients	Clinical Endpoint	Clinical Events
FLARE/ *Fluvastatin 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.[111, 123] 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.

Miscellaneous Studies. Three trials that reported clinical outcomes did not fit the criteria for the other categories (Table 9 and Evidence Table 6).[42, 110, 124]

The Target Tangible study[42] 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 9. 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 Multicenter 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

- 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 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[125] 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.

Recent trials, especially PROSPER, have confirmed that statins are beneficial in the elderly. For women, however, the results of the recent major trials are mixed. There was no suggestion of a benefit among women in ASCOT and PROSPER. However, 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.[126, 127] 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.

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.[128]

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.[129, 130] 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.[131-135] 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.[129] These studies are important because they demonstrate that the maximum (80mg) doses of simvastatin and lovastatin are well tolerated.

A subgroup analysis[128] 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.[70] 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

- 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 had average overall rates of adverse effects.
- 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.

Detailed Assessment

5a. Myotoxicity and hepatic enzymes (general population)

Myopathy

Three reviews[136-138] evaluated the safety profile of statins. Five reviews assessed myotoxicity with the statins.[139-142] One of these[141] 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[143] or rhabdomyolysis[140] with statins.

Magnitude of Risk. Although CPK elevations are common, the risk of symptomatic myopathy is low. Gaist and colleagues[143] 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.[142]

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.[136] 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.[139, 141, 144, 145]

A retrospective analysis of all domestic and foreign reports of statin-associated rhabdomyolysis has been released by the Food and Drug Administration.[140] 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.

Another review of reports to the FDA's MedWatch database limited to events associated with atorvastatin or simvastatin was published in April 2003.[146] The analysis was limited to adverse reactions that affected major organ systems (muscle toxicity, hepatotoxicity, pancreatic toxicity, and bone marrow toxicity). 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.[147] 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.

Elevations of liver enzymes

All of the statins are rarely associated with clinically important elevation in liver transaminase levels (>3X ULN), occurring in approximately 1% of patients. The risk increases with increasing doses.[138] In order to answer whether there are differences in risk of liver toxicity between statins, we reviewed the adverse effects of the 53 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, with the exception of one study comparing atorvastatin 80mg to simvastatin 80mg daily.[29] In this study, there was a significantly higher incidence of transaminase elevation in the atorvastatin group compared to simvastatin.

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,[110] and MIRACL,[90] 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,[113] 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,[114] 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).

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,[77] 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.[148] 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.[149] 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.[136, 150-155] Briefly, simvastatin, lovastatin, and atorvastatin are all metabolized in the liver via the cytochrome P450 3A4 (CYP 3A4) isoenzyme system. As a result, all three agents are susceptible to drug interactions when administered concomitantly with agents known to inhibit metabolism via CYP 3A4 (Table 10). The use of the agents listed in Table 10 increase statin concentrations and, theoretically, the possibility for adverse effects. Table 10 does not include all drugs capable of inhibiting metabolism via the CYP 3A4 isoenzyme system.

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 11). 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 10. 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 11. 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. Fluvastatin and pravastatin at 40mg daily have also been shown to be safe in cyclosporine-managed transplant recipients.[79, 156, 157]

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.[158] 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.[159] One small study[160] 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.

There are no clinical studies of rosuvastatin in organ transplant patients. 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.

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. Reduced renal function would be expected to accentuate the toxicity from atorvastatin, lovastatin, and simvastatin.

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.

We identified one small (N=20), placebo-controlled crossover trial of pravastatin for lipid-lowering in patients receiving protease inhibitors.[161] 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.

There are two retrospective studies in which patients with HIV received a statin for the management of their hyperlipidemia.[162, 163] In one,[163] 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,[162] 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.[164] 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.[145]

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.[147] 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.[147] 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[165] 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[141] 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.[140] The authors cite a reference[166] 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[136] 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.[167] 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).[168] 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).[169] 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,[141] 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.[170] 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 12 summarizes the level and direction of evidence for each key question.

Table 12. Summary of evidence

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.
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 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.

Key Question	Level of Evidence	Conclusion
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
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.

Key Question	Level of Evidence	Conclusion
b. Special populations: Patients with diabetes	Good	There are good efficacy data for people with diabetes. Studies that included people with diabetes had average overall rates of adverse effects.
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.

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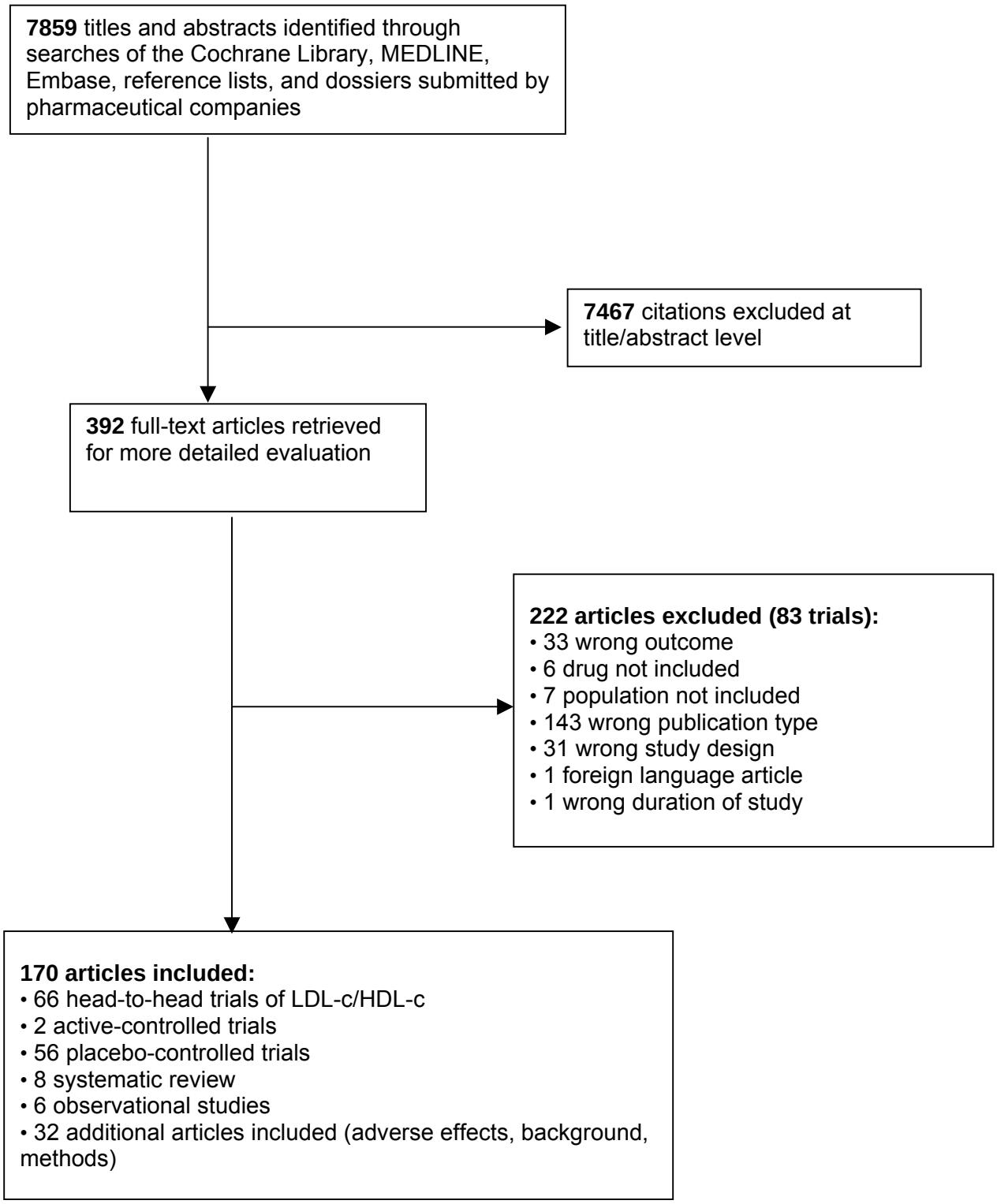
Figure 1. Literature Search Results



Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Atorvastatin vs. Lovastatin				
Davidson et al. 1997 R (3:1), DB, MC, PC, not ITT 1,049 patients randomized (n= 789 atorva, 260 lova) 52 weeks Parke-Davis Pharmaceuticals	Men and women 18-80 years with LDL ≥160 mg/dl and ≥145 mg/dl after 2 weeks dietary phase. Mean baseline LDL-c 189-192 mg/dl	NCEP step 1 diet and atorva 10 mg qd or lova 20 mg qd for 52 weeks; or placebo for 16 weeks, then atorva 10 mg qd or lova 20 mg qd for 36 weeks. Doses doubled at 22 weeks if LDL-c goals (based upon their risk factors) not achieved.	Efficacy analysis for 970 patients. **LDL-c reduction from baseline at week 16:** atorva 10 mg: 36% lova 20 mg: 27% placebo unchanged (p<0.05 vs. lova or placebo) **LDL-c reduction from baseline at week 52:** atorva: 37% (27% had dose doubled) lova: 29% (49% had dose doubled) (p<0.05 vs. lovastatin) **HDL at week 16:** atorva and lova both increased 7% (p NS) **HDL at week 52:** atorva and lova both increased 7% (p NS) **Trigs:** atorva reduction 16%; lova reduction 8% (p<0.05) **Achieved LDL-c goal:** atorva 78% vs. lova 63%	Adverse drug events (ADEs) similar across groups. Only those ADEs occurring ≥2% were reported. Withdrawal due to ADEs occurred in 3% of atorva vs. 4% of lova patients; 8% of atorva vs. 7% of lova patients had a serious ADE (no details provided), including 1 patient developing pancreatitis in atorva group. Elevation in ALT >3x ULN occurred in 1 (0.1%) atorva, 3 (1.2%) lova, and 1 (0.7%) placebo patients. No patient experienced an increase in creatine kinase (CK) of >10 times ULN. Equivalent doses not compared.
Atorvastatin vs. Pravastatin				
Bertolini et al. 1997 R (3:1), DB, MC, not ITT 305 patients randomized (n= 227 atorva, 78 prava) 1 year 2 authors employed by Parke-Davis Pharmaceuticals.	Men and women 18-80 years with LDL-c 160-250 mg/dl. Mean baseline LDL-c 195 mg/dl	6 week dietary phase NCEP step 1 diet and atorva 10 mg qd or prava 20 mg qd. If LDL-c remained ≥130 mg/dl at weeks 4 and 10, doses were doubled at week 16.	Efficacy analysis for 299 patients **LDL-c reduction from baseline at week 16:** atorva 10 mg: 35% prava 20 mg: 23% (p≤0.05) **LDL-c reduction from baseline at week 52:** atorva: 35% (24% had dose doubled) prava: 23% (64% had dose doubled) (p≤0.05). **HDL:** atorva increased 7%, prava increased 10% (NS) **Trigs:** atorva reduction 14%, prava reduction 3% (p≤0.05). **Achieved LDL-c goal:** atorva 71% vs. prava 26%	Severe adverse drug events (ADEs) similar for atorva (7%) and prava (9%); 7 patients in the atorva and 2 in the prava group withdrawn from study as a result of a severe ADE (no details). No patient in either group had clinically important elevations in AST, ALT or CK. Equivalent doses not compared.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Assman et al. 1999 R (3:1), DB, MC, not ITT 297 patients randomized (n= 224 atorva, 73 prava) 52 weeks 2 authors employed by Parke-Davis Pharmaceuticals.	Men or women 18-80 years with an LDL-c 160-250 mg/dl during dietary phase. Mean baseline LDL-c 201 mg/dl.	6-week dietary and placebo phase. NCEP step 1 diet. Mild to moderate CHD risk (dose level 1: LDL-c goal <130 mg/dl): 10 mg qd atorva (n=145) vs. prava 20 mg qd (n=27). Severe CHD risk (dose level 2: LDL-c goal <115 mg/dl): atorva 20 mg qd (n=79) vs. prava 40 mg qd (n=46). If goal not reached, dose doubled at week 4, and again at week 8 and week 16. Maximum doses: atorva 80 mg qd, prava 40 mg qd.	Efficacy analysis for 279 patients. **LDL-c reduction from baseline at 1 year:** atorva: 39% (p< 0.05) prava: 29% **HDL:** atorva increased 7% prava increased 9% (NS) **Trigs:** atorva reduction 13% (p<0.05) prava reduction 8% **Achieved LDL-c goal at last visit:** atorva\= 51% vs. prava 20% (p=0.0001) 35% atorva (20 mg-17%, 40 mg-12%, 80 mg-5%) vs. 88% prava (40 mg-88%) patients had doses doubled at least once.	9 patients (4%) in atorva group withdrew as a result of ADEs vs. 2 patients (3%) in prava group. 2 patients receiving atorva (unknown dose) experienced an elevation in ALT >3 X upper limit of normal. No patient on prava experienced an elevation. Most commonly reported ADE with atorva was myalgia and rash each reported by 4 patients. Most common ADE with prava was arthralgia in 2 patients. (unknown doses) 35% of atorva vs. 63% of prava patients categorized in the severe CHD risk or dose level II. Equivalent doses not compared.
Nissen et al, 2004 R, DB, MC, PC 657 patients randomized 18 months Funded by Pfizer	Men and women aged 30 to 75 years who required coronary angiography for a clinical indication and demonstrated at least 1 obstruction with angiographic luminal diameter narrowing of 20% or more. Lipid criteria required an LDL-c level between 125 mg/dL and 210 mg/dL after 4 to 10 week washout period. Mean baseline LDL-c atorva 80mg: 150.2 mg/dL prava 40mg: 150.2 mg/dL	Atorva 80 mg daily or prava 40 mg daily.	Efficacy analysis on 502 patients. LDL-c reduction from baseline at 18 months: Atorva 80 mg: 46.3% (p<0.001) Prava 40 mg: 25.2% HDL-c increase from baseline at 18 months: Atorva 80 mg: 2.9% Prava 40 mg: 5.6% (p=0.06) Trigs reduction from baseline at 18 months: Atorva 80 mg: 20.0% (p<0.001) Prava 40 mg: 6.8%	6.7% of prava and 6.4% of atorva group discontinued drug for adverse events. Most common reason was musculoskeletal complaints (3.4% prava, 2.8% atorva). Equivalent doses not compared

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Atorvastatin vs. Simvastatin				
Dart A et al. 1997 R (3:1), DB, MC, not ITT 177 patients randomized (n= 132 atorvastatin, 45 simvastatin) 1 year Support and contribution by Parke-Davis Pharmaceutical Research Division	Men or women 18-80 years with an LDL-c 160-300 mg/dl during the dietary phase. Mean baseline LDL-c 208-214 mg/dl	6-week dietary and placebo phase. NCEP step 1 diet and atorvastatin 10 mg qd or simvastatin 10 mg qd. Doses were doubled at week 16 if LDL-c was not ≤ 130 mg/dl.	Efficacy analysis for 177 patients. **LDL-c reduction from baseline at week 16:** Atorvastatin 10 mg: 37% Simvastatin 10 mg: 30% ($p<0.05$) **LDL-c reduction from baseline at week 52:** Atorvastatin: 38% (48% had dose doubled) Simvastatin: 33% (62% had dose doubled) ($p\leq0.05$) **HDL at week 16:** Atorvastatin increased 7% Simvastatin increased 7% (p NS) **HDL at week 52:** Atorvastatin increased 7% Simvastatin increased 7% (p NS) **Trigs:** Atorvastatin reduction 21% Simvastatin reduction 12% ($p\leq0.05$) **Achieved LDL-c goal:** atorva 46% vs. simva 27%	No clinically significant changes in ALT, AST or CK in either group. No differences in percentages of reported ADE between groups. None of the serious ADEs in either group thought to be due to the statin. Most common ADE with atorvastatin was myalgia (3%). Most common ADE with simvastatin was arthralgia (7%) and chest pain (4%). 2 patients in each group withdrawn as a result of ADEs. Details only provided for 1 patient on atorvastatin who reported excessive sweating possibly related to treatment. No other details on ADEs provided. Equivalent doses not compared.
Crouse et al. 1999 R, OL, MC, not ITT 846 patients randomized 12 weeks Merck supported and participated in study.	Men or women Mean baseline LDL-c 212.7 mg/dl	4-week dietary run-in phase, then: atorva 20 mg qd (n=210) or atorva 40 mg qd (n=215) or simva 40 mg qd (n=202) or simva 80 mg qd (n=215)	*Efficacy analysis for 842 patients.* **LDL-c reduction from baseline at 12 weeks:** atorva 20 mg: 45% * atorva 40 mg: 51.1% simva 40 mg: 42.7% simva 80 mg: 49.2% (*p<0.05 atorva 20 vs. simva 40) **HDL-c increase from baseline at 12 weeks:** atorva 20 mg: 4% atorva 40 mg: 3% simva 40 mg: 6.7% * simva 80 mg: 6.6% * (*p<0.01 atorva vs. simva) **Trig reduction from baseline at 12 weeks:** atorva 20 mg: 23.3% atorva 40 mg: 29.6% * simva 40 mg: 23% simva 80 mg: 25.2% (*p<0.01 atorva 40 vs. simva 80)	No safety data or details on patient population provided in this trial. Primary endpoint in this study was effects of atorva or simva on HDL and Apolipoprotein A-1. Dose equivalence Atorva 20 mg > or ≈ Simva 40 mg. Atorva 40 mg = Simva 80 mg

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Marz et al. 1999 R (2:1) OL, MC, not ITT 2,856 patients randomized (n= 1897 atorva, 959 simva) 14 weeks Sponsored by Parke-Davis and Pfizer	Men or women 35-75 years with CHD and LDL-c ≥130 mg/dl after the diet phase. <u>Mean baseline LDL-c</u> 186-188 mg/dl	6-week diet phase then atorva 10 mg qd or simva 10 mg qd. Doses were doubled at weeks 5 and/or 10 if LDL-c was ≥ 100 mg/dl.	Number of patients in efficacy analysis not specified. **LDL-c reduction from baseline at week 14:** atorva 10 mg: 37.6% simva 10 mg: 31.9% (p<0.001) **Overall LDL-c reduction:** 188-105 mg/dl in atorva vs. 186-112 mg/dl in simva group. (p<0.001) 38% atorva vs. 54% simva users increased to 40 mg qd.	ADEs were similar between groups occurring in 36.3% in the atorva vs. 35.7% in the simva group. Withdrawal due to ADE were similar between groups. Serious ADEs occurred in 2% atorva vs. 3% simva (NS). No differences in elevation in ALT or AST or CK during the trial between groups. <u>Dose equivalence</u> Atorvastatin 20 mg qd ≈ simvastatin 40 mg qd.
Paragh et al, 2004 R, OL, crossover, ITT not stated 49 patients randomized (50% to simvastatin and 50% to atorvastatin) 10 months (3 mos./drug) Industry role, if any, not specified	Men or women 25-70 years with Frederickson IIa and IIb hyperlipoproteinaemia with LDL-c >158 ml/dL and trigs <398 mg/dL. **Mean baseline LDL-c:** Simvastatin 20 mg: 182 mg/dL Atorvastatin 10 mg: 174 mg/dL	8-week NCEP Step 1 dietary run-in then randomized to simva 20 mg/d or atorv 10 mg/d for 3 months. Followed by 8-week washout period, then switched to alternate drug in corresponding dose for 3 months.	**% LDL-c reduced from baseline after 3 months:** Simva 20 mg: -18.5% Atora 10 mg: -28.9% (p<0.001 for baseline vs. 3 month levels; p<0.001 for simva vs. atorva) % **HDL-c increased from baseline after 3 months:** Simva 20 mg/d: +3.8% Atorva 10 mg/d: + 9.2% (p=not significant(n.s.) for baseline vs. 3 month levels; p=n.s. for simva vs.atorva) **% Trig level decreased from baseline after 3 months:** Simva 20 mg/d: -15.2 % Atorva 10 mg/d: -29.5% (p<0.01 for baseline vs. 3 month levels; p=n.s. for simva vs. atorva) **% patients reaching target LDL-c levels**: Simva 20 mg/d: 28% Atorva 10 mg/d: 44% (no p-values given)	No serious adverse events reported nor discussed in detail. No changes in physical examination findings or laboratory values occurred.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Van Dam et al. 2000 R, SB, MC, not ITT 378 patients randomized (n= 185 atorvastatin, 193 simvastatin) 8 weeks Supported by Parke-Davis and Pfizer Pharmaceuticals. One author employed by Parke-Davis.	Men or women 18-80 years currently treated with simvastatin 20 or 40 mg qd and LDL-c levels > 100 mg/dl. Mean baseline LDL-c Simvastatin 20 mg: 138 mg/dl Simvastatin 40 mg: 145 mg/dl	4-week simvastatin run-in phase followed by randomization as follows: Simvastatin 20 mg users: Atorvastatin 20 mg or simvastatin 20 mg. Simvastatin 40 mg users: Atorvastatin 40 mg or simvastatin 40mg	Efficacy analysis for 324 patients. **Additional reduction in LDL-c when switching from simvastatin to:** (p<0.05) Atorva 20 mg: 14± 14% Simva 20 mg: 3.3 ± 14%(p) Atorva 40 mg: 2.85 ±12.7% Simva 40 mg: 14.6 ± 15.2% (p) **HDL:** (p>0.05) Atorva 20 mg: reduction 1.41 ± 10.3% Simva 20 mg: increased 0.49 ± 10.8% Atorva 40 mg: reduction 1.07 ± 11.8% Simva 40 mg: increased 2.76 ± 10.4 **Trigs:** (p>0.05) Atorva 20 mg: reduction 10.9% ± 25% Simva 20 mg: reduction 4.21 ± 32.5% Atorva 40 mg: reduction 0.85 ± 36% Simva 40 mg: increased 8.4 ± 36.6% **Achieved NCEP LDL-c goal:** 28% atorva vs. 13% simva	Total 71 ADEs for 54 of 185 atorva patients vs. total 39 ADEs for 32 of 193 simva patients (p=0.005). Although not much detail provided, most frequent ADEs were myalgia and headache. Myalgia was reported most commonly in atorva group. No mention if ADEs reported more often in the higher-dose groups. No reports of elevations in ALT, AST or CK during the study. Overall, HDL reduced 1.3% in atorva vs. increased 1.3% in simva group (p=0.04). Triglycerides reduced by 7.5% in atorva vs. increased 5.6% in simva group (p=0.005). Equivalent doses not compared.
Farnier et al. 2000 **R (2:1:2), OL, MC, ITT** 272 patients randomized (n= 109 atorvastatin, 163 simvastatin) 12 weeks Supported by grant from Parke-Davis.	Men or women 18-70 years with elevated LDL-c. Mean baseline LDL-c Atorvastatin 10 mg: 247 ± 45 mg/dl Simvastatin 10 mg: 242 ± 47 mg/dl Simvastatin 20 mg: 237 ± 39 mg/dl.	6-week placebo-dietary run-in phase then randomized to: Atorvastatin 10 mg, simvastatin 10 mg or simvastatin 20 mg qd for 6 weeks.	Efficacy analysis for 272 patients. **LDL-c reduction from baseline at 6 weeks:** Atorva 10 mg: 37% Simva 10 mg: 28.9% Simva 20 mg: 33.8% (90% CI 0.66-5.7 atorva 10 mg vs. simva 20 mg) **HDL:** (NS Atorva 10 mg vs. simva 20 mg) atorva 10 mg increased 5.7% simva 10 mg increased 2.2% simvastatin 20 mg increased 3% **Trigs:** (NS atorva 10 vs. simva 20) atorva 10 mg reduction 19.2% simva 10 mg reduction 4.6% simva 20 mg reduction 16%	Authors report no difference in incidence of ADEs between groups (atorva 10 mg = 11.9% vs. simva 10 mg =5.5% vs. simva 20 mg = 3.7%). Few details provided. One patient in atorva group had an increase in ALT >3x ULN. No elevation in CK reported. Dose equivalence atorvastatin 10 mg qd ≈ simva 20 mg qd

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Recto et al. 2000 R, OL, MC, crossover, not ITT 258 (?) patients (n= 125 atorva, 126 simva) 12 weeks Study supported by grant from Merck.	Men or women 21-70 years with an LDL-c ≥ 130 mg/dl and trigs ≤ 350 mg/dl. Mean baseline LDL-c 193.4 mg/dl	4-week dietary and placebo run-in phase, then randomized to: atorva 10 mg or simva 20 mg qd or to a higher dose atorva 20 or simva 40 mg qd for 6 weeks. Followed by 1-week washout period, then switched to alternate drug in corresponding dose for 6 weeks.	Efficacy analysis for 251 patients. **LDL-c reduction from baseline at 6 weeks:** atorva 10 mg: 36.7% ± 13.3 simva 20 mg: 34.8% ± 14 atorva 20 mg: 42.1% ± 15.6 simva 40 mg: 41% ± 15.9 (p>0.05 for atorva 10 mg vs. simva 20 mg, and atorva 20 mg vs. simva 40 mg) **HDL:** (p>0.05) Atorva 10 mg increased 8.1 % Atorva 20 mg increased 8.5% Simva 20 mg increased 8.7 % Simva 40 mg increased 9.3 % **Trigs:** (p>0.05) Atorva 10 mg reduction 22% Atorva 20 mg reduction 25% Simva 20 mg reduction 21.5% Simva 40 mg reduction 21.4%	No differences in ADEs reported between groups. 1 patient in simva 20 mg group withdrawn due to ADE vs. 2 in atorva 10 mg and 3 in atorva 20 mg group. 2 serious ADEs in atorva 20 mg group. Myalgia occurred in 1 simva 20 mg vs. 2 atorva 10 mg patients. One patient in simva 40 mg group experienced elevation in ALT >3x ULN. Dose equivalence Atorva 10 mg qd ≈ simva 20 mg qd. Atorva 20 mg ≈ simva 40 mg qd.
Insull et al. 2001 R, OL, MC, not ITT 1,424 patients randomized (n= 730 atorva, 694 simva) First 6 weeks of planned 54 weeks Supported by grant from Parke-Davis.	Men or women 18-80 years with or without CHD and with or without Type 2 DM with elevated LDL. Mean baseline LDL-c Atorva 181.2 mg/dl Simva 181.9 mg/dl	8-week dietary run-in with NCEP step 1 or 2 diet. Eligible patients randomized to: atorva 10 mg qd or simva 10 mg qd.	Efficacy analysis for 1,378 patients. **LDL-c reduction from baseline at 6 weeks:** atorva 10 mg: 37.2% simva 10 mg: 29.6% (p<0.0001) **Reaching NCEP goal at 6 weeks:** atorva 10 mg: 55.6% simva 10 mg: 38.4% (p<0.0001) **HDL increased:** Atorva: 7.4% Simva: 6.9% (NS) **Trigs reduction:** Atorva: 27.6% Simva: 21.5% (p<0.0001)	No differences in treatment-related ADEs: atorva 5.8% vs. simva 2.9%. No reports of myopathy. 2 atorva patients had elevated ALT or AST >3x ULN. Equivalent doses not compared.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Illingworth et al. 2001 R, DB, MC, not ITT 826 patients randomized (n= 408 atorva, 405 simva) 36 weeks 5 authors employed by Merck. Merck assisted in preparation of manuscript.	Men or women 21-70 years with elevated cholesterol. <u>Mean baseline LDL-c</u> Atorva 206 mg/dl Simva 209 mg/dl	4-week dietary run-in phase followed by randomization to 6 weeks of: atorva 20 mg or simva 40 mg qd, then 6 weeks of atorva 40 mg or simva 80 mg qd. If CK ≤ 5x ULN, patients were eligible for 24 weeks of atorva or simva 80 mg qd.	Efficacy analysis for 813 patients. **LDL-c reduction from baseline at 6 weeks:** atorva 20 mg= 46.1% vs. simva 40 mg= 42.4% **LDL-c reduction from baseline at 2nd 6 weeks:** atorva 40 mg= 51.3% vs. simva 80 mg= 48.8% **LDL-c reduction from baseline at 36 weeks:** atorva 80 mg= 53.6% vs. simva 80mg= 48.1% (p≤ 0.001 for all 3 comparisons) **HDL increased:** **Week 6:** atorva 20 mg= 7.3% vs. simva 40 mg= 8.5% (NS) **Week 12:** atorva 40 mg= 6.4% vs. simva 80 mg= 9.7% (p<0.001) **Week 18-36:** atorva 80 mg= 3% vs. simva 80 mg= 7.5% (p<0.001) **Trigs reduction:** atorva 20 mg= 23.6% vs. simva 40 mg= 22.4% atorva 40 mg= 31.6% vs. simva 80 mg= 25.9% atorva 80 mg= 31.3% vs. simva 80 mg= 23.6% (p≤ 0.05 for all 3 comparisons)	HDL elevation was primary endpoint. ADEs similar during first 12 weeks of study. At end of 24-week period, 23.4% of atorva 80 mg vs. 11.9% of simva 80 mg experienced an ADE. (p<0.001). Difference due primarily to GI ADE (diarrhea). More in atorva 80 mg group (12.2%) vs. simva 80 mg group (3.9%) experienced laboratory ADEs (p<0.001). More discontinued treatment due to laboratory ADEs in atorva 80 mg (4.1%) vs. simva 80 mg group (0.8%) (p<0.001). Clinically significant elevations (>3x ULN) in ALT and AST observed significantly more often in atorva 80 mg vs. simva 80 mg group. ALT elevations especially prominent in women in atorva group. No myopathy reported in any group. A significantly higher number of women randomized to the atorva group.
Branchi et al. 2001 R, OL, not ITT 200 patients randomized (n= 100 atorva, 100 simva) Up to 6 months Role and source of funding not reported.	Men or women with hypercholesterolemia not controlled with diet. <u>Mean baseline LDL-c</u> Atorva 228.2 mg/dl Simva 235.1 mg/dl	8-week dietary run-in, then randomization to: atorva 10 mg or simva 20 mg qd.	Efficacy analysis for 199 patients. **LDL-c reduction from baseline at 2 months:** **a**torva: 148.7 mg/dl (34.8%) simva: 158.4 mg/dl (32.6%)(NS) **HDL increase from baseline at 2 months (n=235, adjusted for baseline values):** **a**torva: 4.3% simva: 9.0% (p<0.05) **Trigs reduction from baseline at 2 months:** atorva: 27.4% simva: 24.8% (NS)	Significant number withdrew from treatment after 2 months. 46 required an increase in dose (20 atorva vs. 26 simva); 10 refused to continue; 8 stopped treatment during a recent illness. No differences in ADEs noted. 55 atorva vs. 58 simva patients completed 6 months of follow up. Responses similar to that seen at 2 months observed. HDL still significantly increased in the simva vs. atorva group. <u>Dose equivalence</u> Atorvastatin 10 mg qd ≈ simvastatin 20 mg qd
Karalis et al. 2002 R, OL, MC, not ITT 1,732 patients randomized 6 weeks Pfizer supported and participated in the trial.	Men and women 18-80 years with LDL-c ≥190 mg/dl if no risk factors, or ≥160 mg/dl if 2 or more risk factors, or ≥130 mg/dl for those with CHD. <u>Mean baseline LDL-c</u> 178-182 mg/dl	4-week dietary run-in followed by randomization to: atorva 10 mg qd (n=650) or atorva 80 mg qd (n=216) or simva 20 mg qd (n=650) or simva 80 mg qd (n=216)	Efficacy analysis for 1694 patients. **LDL-c decrease from baseline at 6 weeks:** atorva 10 mg= 37% vs. simva 20 mg = 35% (p<0.025) atorva 80 mg= 53% vs. simva 80 mg= 47% (p<0.0001) **HDL increase from baseline:** atorva 10 mg= 5% vs. simva 20 mg= 6% atorva 80 mg= 2% vs. simva 80 mg= 6% (p<0.0001) **Trigs reduction from baseline:** atorva 10 mg= 18% vs. simva 20 mg= 14% (p<0.025) atorva 80 mg= 28% vs. simva 80 mg= 23% (p<0.025)	Patients in atorva 80 mg vs. simva 80 mg group reported higher incidence of ADEs (46% vs. 39%) and discontinuation due to ADEs (8% vs. 5%) . Neither of these differences was statistically significant. <u>Dose equivalence</u> Atorva 10 mg>Simva 20 mg. Atorva 80 mg>Simva 80 mg.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Kastelein et al, 2000 **R, DB, PC** 826 patients (n=406 atorva, 405 simva) 36 weeks Supported by a grant from Merck Research Laboratories	Men and women with LDL-c >160 mg/dL and triglycerides <350 mg/d <u>Mean baseline LDL-c</u> simva: 208.7 mg/dL atorva: 205.8 mg/dL	Atorva 20 mg qd for 6 weeks, then 40 mg qd or simva 40 mg qd for 6 weeks then 80 mg qd.	**Increase in HDL-c (average of results from weeks 6 and 12):** **s**imva 9.1% vs atorva 6.8% (p<0.001) simvastatin 80mg: 9.7% atorvastatin 40mg: 6.4% (p<0.001) simva 40mg vs atorva 20mg (NS, percent change not reported)	No difference between the 2 drugs in tolerability profile after 12 weeks of treatment. <u>Dose equivalence</u> simva 80mg >atorva 40mg simva 40mg ≈ atorva 20mg
Olsson et al. 2003 R(1:1), DB, MC, ITT 1087 patients randomized (n= 552 atorva, 535 simva) 52 weeks Supported by Pfizer.	White men and women 35-75 years with cardiovascular disease and LDL-c <u>></u> 155 mg/dl (4.0 mmol/L) <u>Mean baseline LDL-c</u> 5.19 mmol/L (calculated 200 mg/dl)	Dietary counseling during 4-week run-in phase. Patients on lipid-lowering therapy added 4-week washout period, then randomized to: atorvastatin 20 mg or simvastatin 20 mg, both titrated to 40 mg. Dose doubled at week 8 for patients not meeting NCEP target.	Efficacy analysis for 1087 patients. **LDL-c reduction at 8 (and 52) weeks:** atorva: 46%* (49%*) simva: 40% (44%) (*p<.001 vs. simva) **HDL increase at 8 (and 52) weeks:** atorva: -0.1%* (6.3%) simva: 3.3% (8.3%) (*p<.001 vs. simva) **Trigs reduction at 8 (and 52) weeks:** atorva: 23%* (24%*) simva: 14% (16%) (*p<.001 vs. simva) **Achieved NECP LDL-c goal at 8 (and 52) weeks:** atorva: 45%* (61%*) simva: 24% (41%) (*p<.001 vs. simva) 45% atorva vs. 24% simva patients remained at 20 mg	ADE comparable between groups. 12 (2.2%) atorva and 13 (2.4%) simva patients had muscular symptoms (e.g., myalgia, myositis). 1 serious drug-related ADE in simva patient, with exacerbation of arm fascitis. Withdrawals due to ADE: 20/556 (3.6%) atorva vs. 14/537 (2.6%) simva. 6 withdrawals serious, with atorva heart failure, cerebral infarction and 2 malignancies; and simva acute MI and chest pain. No significant changes in either group for S-ALT, S-AST or CK. 1 patient in each group withdrawn due to elevated liver aminotransferase.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Kadikoylu et al, 2003 R, DB 61 patients randomized (n=35 atorva, 26 simva) 24 weeks Funding not reported	Men and women with at least 2 coronary risk factors and LDL-c levels >130 mg/dL. Mean baseline LDL-c atorva: 168.5 mg/dL simva: 172.1 mg/dL	Atorva 10 mg qd or simva 10 mg qd . When target level of LDL-c was not reached at 12 weeks according to ATP-III, dosage was increased to 20 mg qd.	**LDL-c goal reached at 24 weeks (all patients):** atorva: 85.7% simva: 84.6% (NS) **Diabetics only (n=23):** atorva: 64.3% simva: 55.6% (NS) **LDL-c reduction from baseline at 24 weeks:** atorva: 38.6% simva: 33.6% (NS) **HDL-c increase from baseline at 24 weeks:** atorva: 12.6% simva: -0.6% (NS) **Trigs change from baseline at 24 weeks:** atorva: -15.8% simva:+2.0% (NS)	Adverse effects seen in 5 patients (14.2%) atorva and 3 patients (11.5%) in simva group (headache, diarrhea, constipation, myalgia). Elevations in ALT>3 times the upper limit of normal and in CK >5 times the upper limit of normal did not occur. No discontinuations due to adverse effects; no significant differences between groups in adverse effects, adverse effects not dose-related. Equivalent doses not compared
Ballantyne et al, 2003 R, DB, MC 917 patients randomized(n=464 atorva, 453 simva) 24 weeks Supported by a grant from Merck	Men and women 21-75 with LDL-c >130 mg/dL in CHD patients, >160 mg/dL in patients without CHD and with 2 or more risk factors, and >190 mg/dL in patients without CHD and with <2 risk factors; patients with diabetes were considered CHD equivalents; eligible LDL-c was >130 mg/dL in patients with HDL-c <40 mg/dL (men) and <50 mg/dL (women) plus 2 risk factors. All had triglyceride levels <400 mg/dL. Mean baseline LDL-c atorva: 187.5 mg/dL simva:190.3 mg/dL	Atorva 80 mg qd or simva 80 mg qd for 24 weeks.	**Increase in HDL-c from baseline, average of weeks 18 and 24** **Patients with baseline HDL-c <40mg/dL (n=267):** atorva: 2.1% simva: 5.4% (NS) **Patients with baseline HDL-c ≥40mg/dL (n=650):** atorva: 2.1% simva: 5.43% (NS) **Patients without metabolic syndrome (n=437):** atorva: 2.8% simva: 5.6% (NS)	No difference between groups in number of drug-related clinical gastrointestinal adverse events. Most common GI adverse events were diarrhea (simva 1.3%; atorva 3.0%), constipation (simva 1.3%; atorva 1.5%), and nausea (simva 1.8%; atorva 0.9%). Most common drug-related muscular AEs resulting in discontinuation were myalgia, arthralgia, muscular weakness, muscular cramp, musculoskeletal stiffness, and body ache. Patients treated with atorva more likely to have elevations in ALT >3 times the upper limit of normal (difference -2.4%; 95% CI -4.3 to -0.7; p=0.007) Equivalent doses not compared

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Chan, et al, 2004 R, Blinded, SC 10 week dietary run-in; 18 weeks of treatment. 120 patients (n=60 simva; n=60 atorva) No industry support mentioned	Men and women 20-75 with Type 2 diabetes with mixed hyperlipidaemia (serum trig 203.7-398.6 mg/dL and LDL-c >=131.5 mg/dL) <u>Mean baseline LDL -c:</u> atorva: 171.3 mg/dL simva: 160.5 mg/dL	10 week NIH NCEP Step 1 dietary run-in and patients on lipid-lowering drugs did a 4 week wash-out before starting. atorva: 10 mg/d for 9 weeks then increased to 20 mg/d for 9 weeks simva: 20 mg/d for 9 weeks and then increased to 40 mg/d for 9 weeks.	**% patients reaching the LDL-c target (<100 mg/dL)** atorva: 74.1% simva: 75.4% **% patients reaching the TG target (151 mg/dL):** atorva: 27.8% simva: 35.1% **% patients reaching both targets:** atorva: 22.2% simva: 29.8% **LDL-c Change from baseline (approx. from table):** atorva 10 mg:-37% atorva 20mg:-28% simva 20mg:-42% simva 40 mg:-40% **HDL-c Change from baseline (approx. from table):** atorva 10 mg:+4% atorva 20mg:<=+1.0% simva 20mg:+4% simva 40 mg:+4.5% **Trig change from baseline (approx. from table):** atorva 10 mg:-20% atorva 20mg:-25% simva 20mg:-20% simva 40 mg:-25% *no p-values given*	No adverse events discussed in detail. Atorva: 5 patients withdrew (8.3%) Simva: 7 patients withdrew (11.7%) reason stated for both groups withdrawals: "mainly because of non-compliance" Overall drug compliance was 91.5%. No subject developed a significant rise in liver enzymes or in CPK during study.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Atorvastatin vs. Multiple Statins				
Hunninghake et al. 1998 R, OL, MC, not ITT 344 patients randomized (n= 85 atorva, 82 fluva, 83 lova, 87 simva) 54 weeks Funded by Parke-Davis. One author employed by Parke-Davis.	Men or women 18-80 years at risk for CHD and elevated cholesterol. <u>Mean baseline LDL-c</u> Atorva 205 mg/dl Fluva 201 mg/dl Lova 206 mg/dl Simva 210 mg/dl	8-week optional dietary phase, 4-week dietary run-in followed by randomization to atorva 10 mg, fluva 20 mg, lova 20 mg or simva 10 mg qd. Doses titrated at 12-week intervals until LDL-c goal achieved or maximum dosage reached (atorva 80 mg, fluva 40 mg , lova 80 mg, simva 40 mg qd). If goal not reached with statin, colestipol added. Colestipol added = atorva 2%, fluva 67%, lova 24%, simva 24%.	Efficacy analysis for 337 patients (median dose/day). **LDL reduction from baseline at 54 weeks :** atorva 10 mg: 36% fluva 40 mg: 22%* lova 40 mg: 28%* simva 20 mg: 33% **HDL increase at 54 weeks:** atorva 9 % fluva 6 % lova 10% simva 11% **TRIGS reduction at 54 weeks:** atorva 20% fluva +2%* lova 16% simva 11% **Achieved LDL-c goal at 54 weeks:** atorva 95% vs. fluva 60%,* lova 77%,* simva 83%.* (*p<0.05 vs. atorva).	ADEs similar across treatment groups prior to addition of colestipol to statin therapy at 24 weeks. At 54 weeks there were more ADEs in the fluva and lova groups than in the atorva or simva groups primarily GI in nature. Withdrawal for ADEs were 3% atorva, 4% fluva, 8% lova and 5% simva. One lova-treated patient experienced an elevation in ALT >3x ULN. Other clinically insignificant elevations in ALT or AST occurred in all groups. One patient receiving fluva experienced acute pancreatitis. No myopathy observed. No details on ADE and statin dose. <u>Equivalent doses not compared; treat to target</u>.
Brown et al. 1998 R, OL, MC, not ITT 318 patients randomized (n= 80 atorva, 80 fluva, 81 lova, 77 simva) 54 weeks Study funded by Parke-Davis. One author employed by Parke-Davis.	Men and women 18-80 years with documented CHD and LDL-c 130-250 mg/dl. <u>Mean baseline LDL-c</u> 173 mg/dl	Optional 8-week dietary phase, 4-week dietary run-in, then randomization to: atorva 10 mg, fluva 20 mg, lova 20 mg, or simva 10 mg qd. Doses could be titrated at 12-week intervals until LDL-c goal or maximum dose reached (atorva 80 mg, fluva 40 mg, lova 80 mg, or simva 40 mg qd). If goal not reached with statin, colestipol added (atorva 8%, fluva 76%, lova 15%, simva 33%).	Efficacy analysis for 308 patients (median dose/day). **LDL reduction from baseline at 54 weeks:** atorva 20 mg: 41% fluva 80 mg +colestipol 20 g: 30%* lova 80 mg: 41% simva 40 mg: 37% **HDL increase at 54 weeks:** atorva: 7% fluva: 7% lova: 12% simva: 11% **Trigs reduction at 54 weeks:** atorva: 19% vs. fluva: 2%,* lova: 14%, simva: 15% **Achieved LDL-c goal at 54 weeks:** atorva 83% vs. fluva 50%*, lova 81%, simva 75% (*p<0.05 vs. atorva)	ADEs similar across treatment groups at 54 weeks, except fluvastatin where patients also receiving colestipol experienced a 2-fold increase in GI ADEs. Withdrawal for ADEs similar among groups, included 3 atorva, 4 fluva, and 2 each for lova and simva. 1 lova patient experienced pancreatitis. Two fluva patients had elevations in either ALT or AST >3x ULN. No myopathy observed. No details on ADEs and statin dose. <u>Equivalent doses not compared; treat to target.</u>

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Jones et al. 1998 **Jones et al. 2004** R, OL, MC, not ITT 534 patients randomized 8 weeks Study funded by Parke-Davis. Parke-Davis Research played role in some portion of the study.	Men or women 18-80 years with LDL ≥ 160 mg/dl. Mean baseline LDL-c Range 192-244 mg/dl	6-week dietary run-in phase, then randomization to one of 15 treatment groups: atorva 10, 20, 40, 80 mg fluva 20 or 40 mg lova 20, 40, or 80 mg prava 10, 20 or 40 mg simva 10, 20 or 40 mg qd.	Efficacy analysis for 522 patients. **LDL reduction from baseline at 8 weeks:** atorva 10 mg: 38% (n=73) / atorva 20 mg: 46% (n=51) atorva 40 mg: 51% (n=61) / atorva 80 mg: 54% (n=10) fluva 20 mg: 17% (n=12) / fluva 40 mg: 23% (n=12) lova 20 mg: 29% (n=16) / lova 40 mg: 31% (n=16) lova 80 mg: 48% (n=11) prava 10 mg: 19% (n=14) / prava 20 mg: 24% (n=41) prava 40 mg: 34% (n=25) simva 10 mg: 28% (n=70) / simva 20 mg: 35% (n=49) simva 40 mg: 41% (n=61) **HDL increase:** All similar (ranging from 3% ot 9%), except atorva 80 mg and fluva 40 mg, with reduction in HDL. Simva 40 mg increase significantly greater than atorva. **Trigs reduction:** All similar, except atorva 40 mg produced a greater reduction.	ADEs similar across treatment groups. 1 patient on atorva 20 mg developed myalgia judged unrelated to treatment. No clinically important elevations in liver transaminase or CK. Dose equivalence Atorvastatin 10 mg ≈ lovastatin 40 mg ≈ pravastatin 40 mg ≈ simvastatin 20 mg qd. Atorvastatin 20 mg ≈ lovastatin 80 mg ≈ simvastatin 40 mg qd.
Wolffenbuttel et al. 1998 R, OL, MC. cross-over, ITT 78 patients 4 weeks on each treatment Supported by Parke-Davis; one author employed by Parke-Davis.	Men and women 18-70 years with LDL-c 160-240 mg/dl. Mean baseline LDL-c 215 mg/dl	4-week dietary run-in then randomized to: atorva 5 mg or atorva 20 mg or simva 10 mg or prava 20 mg qd for 4 weeks. After washout, patients were switched to alternate treatment.	Efficacy analysis for 78 or 76 patients. **LDL-c reduction from baseline:** atorva 5 mg: 27% atorva 20 mg 44% (p<0.05 vs. simva and prava) prava 20 mg 24% simva 10 mg 28% **HDL increase from baseline:** atorva 5 mg 2% atorva 20 mg 8% prava 20 mg 3% simva 10 mg 1% (NS) **Trigs reduction from baseline:** atorva 5 mg 16% atorva 20 mg 23% (p<0.05 vs. simva and prava) prava 20 mg 11% simva 10 mg 8%	ADEs were similar between groups and no serious ADEs or withdrawal from groups as a result of ADEs were reported. Dose equivalence Atorvastatin 5 mg = pravastatin 20 mg = simvastatin 10 mg qd

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Gentile et al. 2000 R, OL, MC, not ITT 412 patients randomized 24 weeks Supported in part (60%) by MURST, Italy.	Men and women 50-65 years with type 2 diabetes mellitus and LDL-c >160 mg/dl Mean baseline LDL-c 199-218 mg/dl	6-week dietary run-in phase followed by randomization to: atorva 10 mg qd lova 20 mg qd prava 20 mg qd simva 10 mg qd or placebo for 24 weeks.	Efficacy analysis for 409 patients **LDL-c reduction from baseline:** atorva 37% (*p<0.05 vs. other statins) lova 21% prava 23% simva 26% placebo 1% **HDL increase from baseline:** atorva 7.4% lova 7.2% prava 3.2% (p<0.05 vs. other statins) simva 7.1% placebo 0.5% **Trigs reduction from baseline:** atorva 24% (p<0.05 vs. other statins) lova 11% prava 12% simva 14% placebo 1%	ADEs similar for all groups. Withdrawal for ADEs: 1 atorva, 1 lova and 1 prava patient. No clinically important elevation in ALT, AST or CK observed in any group. Equivalent doses not compared.
Andrews et al. 2001 R (4:1:1:1:1), OL, MC, not ITT 3,916 patients randomized 54 weeks Supported by grant from Pfizer. One Pfizer employee acknowledged for analysis and interpretation of data.	Men and women 18-80 years with elevated cholesterol, with or without CHD. Mean baseline LDL-c 176-179 mg/dl	Randomization to: Atorva 10 mg qd Fluva 20 mg qd Lova 20 mg qd Prava 20 mg qd or Simva 10 mg qd for 54 weeks. Doses were doubled until LDL-c goal or maximum doses were reached.	**Efficacy analysis for 3,757 patients (mean dose).** LDL-c reduction from baseline at 54 weeks: atorva (24 mg) 42% (p<0.01 vs. other statins) fluva (62 mg) 29% lova (52 mg) 36% prava (31 mg) 28% simva (23 mg) 36% HDL increase from baseline at 54 weeks (NS): atorva 5% fluva 6% lova 5% prava 6% simva 6% Trigs reduction from baseline at 54 weeks: atorva 19% (p<0.01 vs other statins) fluva 7% lova 12% prava 9% simva 13% Achieved LDL-c goal at 54 weeks (p not reported): atorva 76% fluva 37% lova 49% prava 34% simva 58%	ALT elevation >3x ULN occurred in 10 (0.5%) atorva patients vs. 1 patient each (0.2%) in fluva, prava and simva groups. None in lova. Withdrawal due to ADEs occurred in 7% atorva vs. 13% fluva vs. 8% lova vs. 4% prava vs. 8% simva patients. Myalgia occurred similarly in all groups. Serious treatment related ADEs occurred in 2 atorva patients (elevated CK , muscle cramps and rash) and 1 patient in simva (gastroenteritis). No details on dose for withdrawals or serious ADEs. Questionable why doses were not doubled for more patients to reach NCEP goals. Equivalent doses not compared.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Schaefer et al. 2004 R, OL, MC, ITT crossover design 196 patients studied: 99 patients randomized and 97 controls 36 weeks Supported by investigator-initiated research contracts from Parke-Davis/Pfeixer, and Otsuka America Pharmaceuticals, Inc.	Men and women with a mean age of 61.4 years with CHD and with LDL-c >130 mg/dl while off lipid-lowering drugs for 6 weeks. Mean baseline LDL-c : Not reported	4 week dietary run-in, then randomization to a dosing schedule that increased every 4 weeks (12 weeks total): fluva: 20 mg/d; 40 mg/d; 80 mg/d prava: 20 mg/d; 40 mg/d (8 weeks at this max dose) lova: 20 mg/d; 40 mg/d; 80 mg/d simva: 20 mg/d; 40 mg/d (8 weeks at this max dose) atorva: 20 mg/d; 40 mg/d; 80 mg/d for all 97 controls After the 12th week, an 8 week placebo period occurred. Then the patients were crossed over between atorv and another statin for 12 weeks (dosage increased every 4 weeks as before). 36 weeks total	*% change in lipoproteins data includes pre- and post-crossover data combined.* Mean % change in fasting lipoproteins after treatment (p-values are for paired comparisons between same doses of statins): **fluva 20/40/80 vs atorva 20/40/80:** LDL-c: -8%,-17%,-22% vs -34%,-45%,-51% (all have p<0.0001) HDL-c: +3%,+3%,+3% vs +2%,+6%,+1% (p not stated) trigs: -5%,-1%, 0% vs -20% (p<0.05), -25% (p<0.001), -33% (p<0.0001) **lova 20/40/80 vs atorva 20/40/80:** LDL-c: -20%,-28%,-31% vs -38%,-45%,-53% (all have p<0.0001) HDL-c: +4%,+3%,+9% vs +8% (p<0.01),+3% (p not stated),+1% (p not stated) trigs: -10%,-17%,-19% vs -27%,-32%,-32% (all have p<0.01) **prava 20/40/40 vs atorva 20/40/80:** LDL-c: -22%,-24%,-26% vs -39%,-46%,-50% (all have p<0.0001) HDL-c: +9%,+10%,+11% vs +8%,+5%,+6% (p not stated for any) trigs**:** -4%,-2%,-5% vs -9% (p not stated),-18% (p<0.05), -21% (p<0.05) **simva 20/40/40 vs atorva 20/40/80:** LDL-c: -28%,-39%,-39% vs -40% (p<0.001), -47% (p<0.01), -51%(p<0.001) HDL-c: +9%,+7%,+10% vs +5%,+5%,+4% (p not stated for any) trigs: -5%,-17%,-15% vs -27%(p<0.0001), -25%(p not stated)	No safety data (adverse events and withdrawals) reported or discussed.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Fluvastatin vs. Lovastatin				
Nash 1996 R, OL, MC, ITT 137 patients randomized 8 weeks Funded by Sandoz Pharmaceuticals.	Men or women previously controlled on lovastatin 20 mg qd (LDL-c <150 mg/dl). After dietary washout phase, LDL-c required >160 mg/dl, trigs <350 mg/dl. <u>Mean baseline LDL-c</u> Not reported	6-week dietary/placebo washout period then randomization to: fluva 20 mg qd or lova 20 mg qd. After 4 weeks, fluva was increased to 40 mg qd.	Efficacy analysis for 137 patients. **LDL-c reduction from baseline at 8 weeks:** fluva: men and women 26% lova: men 29%, women 26% (NS) **HDL-c increase from baseline at 8 weeks (NS):** fluva: men: 7 %, women 8% lova: men 7%, women 4% **Trigs reduction from baseline at 8 weeks:** fluva: men 14%, women 10% lova: men 12%, women 20% **Achieved LDL-c goal (<160 mg/dl) at 4 weeks:** fluva: 85% lova: 91% (NS) **Achieved LDL-c goal (<160 mg/dl) at 8 weeks:** fluva: 89% lova: 91% (NS)	Myalgia occurred in 1 fluva vs. 2 lova patients. Musculoskeletal abnormalities existed significantly more often as a background medical condition in the lova group. 5 fluva and 1 lova patient experienced an increase in ALT or AST >3x ULN. No details on what dose of fluva patients experienced these ADEs.
Berger et al. 1996 R, OL, MC, ITT 270 patients randomized 6 weeks Sponsored by Merck and Co.	Age ≥20 years, 45% male, with serum triglyceride levels <400 mg/dl, not following cholesterol-reducing diet, and (a) LDL-c ≥190 mg/dl and ≤2 CHD risk factors, or (b) ≥160 mg/dl and ≥2 CHD risk factors, or (c) ≥130 mg/dl and definite CHD. <u>Mean baseline LDL-c</u> 187 mg/dl	5-week diet-only run-in phase, then randomization to: fluva 20 mg qd or lova 20 mg qd	Efficacy analysis for 270 patients. **LDL-c reduction from baseline:** fluva: 18% lova: 28% (p≤0.001) **HDL-c increase from baseline:** fluva and lova: ~8% (NS) **Trigs reduction from baseline:** fluva: 9% lova: 10% (NS) **Achieved NCEP LDL-c goal:** fluva: 24% lova: 37% (p=0.02)	Withdrawals due to AEs: 8 fluva vs. 3 lova. Serious AEs (not considered drug related): 3 fluva vs. 5 lova. Total AEs: 54% fluva vs. 47% lova.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Davidson et al, 2003 R, DB, MC, PC, 838 patients randomized (n=337 fluva, 501 lova) 6 weeks 3 authors from Merck	Men and women >20 years with TG level ≤ 4.5 mmol/L and one of the following LDL-c levels after 6-week run-in on NCEP Step I diet: (1) > 3.4 mmol/L with evidence of CHD or other atherosclerotic disease; (2) >4.1 mmol/L with >2 other CHD risk factors but no CHD or other atherosclerotic disease; (30 >4.9 mmol/L without CHD or other atherosclerotic disease and <2 other CHD risk factors. Mean baseline LDL-c fluva 20 mg: 181.7 mg/dL fluva 40 mg: 189.5 mg/dL lova 10 mg: 189.5 mg/dL lova 20 mg: 189.5 mg/dL lova 40 mg: 185.6 mg/dL	Fluva 20 or 40 mg qd or lova 10, 20, or 40 mg qd for 6 weeks.	**LDL-c reduction from baseline at 6 weeks:** fluva 20 mg: 18.8% fluva 40 mg: 22.6% lova 10 mg: 21.6% (p<0.05 vs fluva 20 mg) lova 20 mg: 27.3% (p<0.001 vs fluva 20 mg, p<0.05 vs fluva 40 mg) lova 40 mg: 31.8% (p <0.001 vs fluva 40 mg) **HDL-c increase from baseline at 6 weeks** (NS): fluva 20 mg: 3.5% fluva 40 mg: 4.3% lova 10 mg: 4.9% lova 20 mg: 5.7% lova 40 mg: 6.1% **Trigs reduction from baseline at 6 weeks** (NS): fluva 20 mg: 3.3% fluva 40 mg: 11.4% lova 10 mg: 6.4% lova 20 mg: 5.7% lova 40 mg: 11.3%	No significant differences between treatments in any AE reported. Most common were GI disturbances, flatulence in 16 (3.2%) lova and 19 (5.6%) fluva patients 21 (4.2%) lova and 22 (6.5%) fluva patients withdrew due to adverse effects. 4 lova and 4 fluva patients reported serious adverse effects; only one (fecal occult blood/gastric ulcer in 1 patient treated with fluva 20mg considered treatment related. Dose equivalence lova 20 mg > fluva 40 mg
Fluvastatin vs. Pravastatin				
Jacotot et al. 1995 R, DB, MC, both ITT and on treatment analysis 134 patients randomized 16 weeks Funding and participation by Sandoz Pharmaceuticals.	Men and women 18-75 years with LDL≥160 mg/dl and trigs ≤400 mg/dl Mean baseline LDL-c Fluva 216.4 mg/dl Prava 226.9 mg/dl	6-week dietary/placebo run-in phase then, randomization to: fluva 40 mg qd or prava 20 mg qd for 4 weeks. Doses doubled at 4 weeks and study continued another 12 weeks.	Efficacy analysis for 134 patients. **LDL-c reduction from baseline at 16 weeks:** fluva 40 mg bid: 29.6% prava 40 mg qd: 26.1% (NS) **HDL-c increase from baseline at 16 weeks:** fluva 40 mg bid: 7.5% prava 40 mg qd: 9% (p<0.001) **Trigs reduction from baseline at 16 weeks:** fluva 40 mg bid: 14.9% prava 40 mg qd: 2.8% (p<0.001)	6 patients withdrew from study due to ADEs (3 in each group). No patient withdrew due to myopathic complaints or liver ADEs. More GI ADEs in fluva group. No patient experienced clinically significant elevation in ALT, AST or CK. Dose equivalence Fluvastatin 40 mg ≈ pravastatin 20 mg qd. Fluvastatin 40 mg bid ≈ pravastatin 40 mg qd.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Fluvastatin vs. Simvastatin				
Ose et al. 1995 R, DB, MC, ITT 432 patients randomized 6 weeks Funded by Merck.	Men and women 70 years of age or less and a total cholesterol >250 mg/dl. Mean baseline LDL-c 213-232 mg/dl w/o CHD 247-267 mg/dl with CHD	4-week dietary/placebo run-in, then randomized to: fluva 20 or 40 mg qd, or simva 5 or 10 mg qd for 6 weeks.	Efficacy analysis for 432 patients. **LDL-c reduction from baseline at 6 weeks:** fluva 20 mg: 21.8% fluva 40 mg: 25.9% simva 5 mg: 25.7% (p<0.01 vs fluva 20 mg) simva 10 mg: 29.9% (p<0.01 vs fluva 20 mg, p<0.05 vs fluva 40 mg) **HDL-c increase from baseline at 6 weeks:** fluva 20 mg: 6.3% fluva 40 mg: 13% simva 5 mg: 10.1% simva 10 mg: 12.2% (p<0.01 vs fluva 20 mg) **Trigs reduction from baseline at 6 weeks:** fluva 20 mg: 10% fluva 40 mg: 12.8% simva 5 mg: 11.5% simva 10 mg: 14.5% **Achieved NCEP LDL-c goal:** fluva 20 mg: 12% fluva 40 mg: 21% simva 5 mg: 24% (p<0.05 vs fluva 20 mg) simva 10 mg: 25% (p<0.01 vs fluva 20 mg)	Number of patients reporting ADEs similar across all groups. GI ADEs were more frequent in fluva vs. simva groups, especially at 40 mg qd dose. One fluva patient had ALT >3x ULN. Dose equivalence Fluvastatin 40 mg qd = simvastatin 5 mg qd for reducing LDL-c. Fluvastatin 40 mg qd = simvastatin 10 mg qd for NCEP goal reached.
Schulte et al. 1996 R, DB 120 patients randomized 10 weeks Funded by Astra.	Men and women 26-74 years with LDL-c >185 mg/dl and trigs <300 mg/dl. Median baseline LDL-c Fluva 218.5 mg/dl Simva 211.5 mg/dl	4-week dietary run-in phase and randomized to: fluva 40 mg qd or simva 20 mg qd for 4 weeks. After 4 weeks, dose was doubled and continued for 6 more weeks.	Unclear if all patients included in efficacy analysis: **LDL-c reduction from baseline at 4 and 10 weeks:** fluva 40 mg: 23.8% simva 20: 23.6% fluva 80 mg: 30.6% simva 40 mg: 34.4% (NS at 4 or 10 weeks) **HDL-c increase from baseline at 4 and 10 weeks:** fluva 40 mg: 7.1% simva 20 mg: 8% fluva 80 mg: 13.1% simva 40 mg: 12.3% (NS at 4 or 10 weeks) **Trigs reduction from baseline at 4 and 10 weeks:** fluva 40 mg: 2.1% simva 20 mg: +1% fluva 80 mg: 1.2% simva 40 mg: 2.3% (NS at 4 or 10 weeks)	Clinically insignificant differences in ADE. One patient in each group had elevations in AST or ALT >3x ULN. No clinically significant increase in CK was observed. Dose equivalence Fluvastatin 40 mg qd = simvastatin 20 mg qd. Fluvastatin 80 mg qd = simvastatin 40 mg qd.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Sigurdsson et al. 1998 R, DB, MC, not ITT 113 patients randomized 16 weeks Funded by grant from Merck. One author employed by Merck. Merck also supplied lovastatin and placebo.	Men or women with CHD. <u>Mean baseline LDL-c</u> 185-187 mg/dl	8-week dietary and 2 week-placebo run-in phase, then randomized to: fluva 20 mg qd or simva 20 mg qd for 16 weeks. Doses could be doubled at week 10 if TC >200 mg/dl at week 6.	Efficacy analysis for 110 patients. **LDL-c reduction from baseline at 16 weeks:** fluva: 25.3% simva: 39.9% (p<0.001) **HDL-c increase from baseline at 16 weeks:** fluva: 8.8% simva: 11.1% (NS) **Trigs reduction from baseline at 16 weeks:** fluva: 23.1% simva: 22.5% (NS) **Achieved LDL-c <200 mg/dl:** 49.1% fluva vs. 87.3% simva (p<0.001) 63% fluva patients vs. 18% simva patients increased dose to 40 mg qd (p<0.001)	ADEs similar between groups, with a trend to more GI ADEs in the fluva vs. simva group (8 vs. 4). The difference was not significant. No clinically important elevations in ALT, AST, or CK. <u>Nonequivalent doses compared, treat to target.</u>
Lovastatin Extended Release vs. Lovastatin Immediate Release				
Lukacsko et al, 2004 179 patients randomized (n= 90 lova ER, 89 lova IR) 12 weeks; crossover Funded by Andrx Laboratories, and all authors employed by same.	Men and women ages 21 to 70 with a TG level less than 350 mg/dL and plasma LDL-c within the following parameters: >100 mg/dl for patients with a history of CHD, peripheral vascular disease (PVD), or cerebrovascular disease (CVD); 130 mg/dl or higher for patients without a history of CHD, PVD, or CVD, but with 2 or more risk factors for heart disease; or 160 mg.dl or higher for patients without a history of CHD, PVD, or CVD, but with less than 2 risk factors for heart disease. <u>Mean baseline LDL-c</u> 182.5 mg/dl lova ER; 174.7 mg/dl lova IR	Lovastatin 20mg ER once daily vs lovastatin 20 mg IR once daily	Efficacy analysis for 179 patients. **LDL-c reduction from baseline at week 12 (from baseline to endpoint for treatment periods 2 and 4 combined, results for separate treatment periods not reported):** Lova ER: 26.4% Lova IR: 23.1% (difference -3.3%; p=0.0028; 95% CI -5.43% to -1.15%) **HDL-c increase from baseline to endpoint for treatment periods 2 and 4 combined (12 week treatment periods, results for separate treatment periods not reported):** Lova ER: 4.1% Lova IR: 4.3% (difference -0.2%; p=0.8584)	No apparent trends by treatment in the incidence of treatment emergent signs and symptoms. Serious adverse events reported by 5 patients receiving ER lova (6 events: cholecystitis, accidental injury, cerebral ischemia, angina pectoris, enlarged uterine fibroids, and back pain), and 2 patients receiving IR lova (increased knee pain due to degenerative joint disease, and MI). <u>Dose equivalence</u>: lova ER > lova IR

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Lovastatin vs. Pravastatin				
McPherson et al. 1992 R, DB, MC, not ITT 217 patients randomized 8 weeks Merck funded the study.	Men and women 18-75 years with LDL-c ≥190 mg/dl with no risk factors or ≥ 160 mg/dl in those with 2+ risk factors. Mean baseline LDL-c 209-211 mg/dl	6-week dietary/placebo and washout phase followed by randomization to: lova 20 mg qd (n=73) or prava 10 mg qd (n=74) or prava 20 mg qd (n=70)	Efficacy analysis for 201 patients. **LDL-c reduction from baseline at 8 weeks:** lova 20 mg: 28% prava 10 mg: 24.5% prava 20 mg: 28.4% (all NS) **HDL-c increase from baseline at 8 weeks (p not reported):** lova 20 mg: 8.7% prava 10 mg: 10.8% prava 20 mg: 5.4% **Trigs reduction from baseline at 8 weeks:** lova 20 mg: 6.8% prava 10 mg: 0.9% prava 20 mg: 4.9% **High risk meeting NCEP goal:** lova: 29%, prava 10 mg: 25%, prava 20 mg: 26% (NS) **Moderate risk meeting NCEP goal:** lova 74%, prava 10 mg: 53%, prava 20 mg: 68% (NS)	Adverse effects not different between groups. Difference in LDL-c lowering greater at 4 weeks in lova vs. prava 10 mg groups, however was not different at 8 weeks. LDL-c lowering in lova vs. prava 20 mg groups not different at any time. Dose equivalence lova 20 mg = prava 20 mg ≈ prava 10 mg.
The Lovastatin Pravastatin Study Group 1993 R, DB, MC, not ITT 672 patients randomized 18 weeks Merck supported and participated in trial.	Men and women 25-75 years with hypercholesterolemia Mean baseline LDL-c 194-196 mg/dl	7-week dietary/placebo run-in phase followed by randomization to: lova 20 mg qd (n=339) or prava 10 mg qd (n=333) for 6 weeks. Then doses doubled to lova 40 mg qd or prava 20 mg qd for 6 weeks, then doubled to lova 80 mg (40 mg bid) qd or prava 40 mg qd for the remaining 6 weeks.	Unclear number of patients in efficacy analysis. 91% of patients completed trial. **LDL-c reduction from baseline at 6, 12 and 18 weeks:** lova 20 mg: 28% vs. prava 10 mg: 19% lova 40 mg: 33% vs. prava 20 mg: 25% lova 80 mg: 39% vs. prava 40 mg: 27% (p<0.01 all comparisons) **HDL-c increase from baseline at 18 weeks:** lova 80 mg: 19% prava 40 mg: 16% (NS) **Trigs reduction from baseline at 18 weeks:** lova 80 mg: 22% prava 10 mg: 15% (p<0.05)	No differences between groups for ADEs. No cases of myopathy reported. Liver transaminase levels >3x ULN occurred in one lova vs. 2 prava patients. Equivalent doses not compared.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Weir et al. 1996 R, DB, MC, not ITT 426 patients randomized 12 weeks Merck participated in study.	Men and women 20-65 years with hypercholesterolemia <u>Mean baseline LDL-c</u> Lova 195 mg/dl Prava 202 mg/dl	6-week dietary/placebo run-in followed by randomization to: lova 40 mg qd (n=211) or prava 40 mg qd (n=215).	Efficacy analysis for 423 patients. **LDL-c reduction from baseline at 12 weeks:** lova: 27.9% prava: 23.6% (NS) **HDL-c increase from baseline at 12 weeks:** lova: 8.5% prava: 8.2% (NS) **Trigs reduction from baseline at 12 weeks:** lova: 6% prava: 8.6% (NS) **Achieved NECP LDL-c goal:** lova 45% vs. prava 26% (p<0.001)	Primary endpoint was quality of life. No difference in quality of life between groups. No significant differences in ADEs or laboratory ADEs between groups. <u>Dose equivalence</u> Lova 40 mg = prava 40 mg qd.
Strauss et al. 1999 R, SB, Crossover, not ITT 31 patients randomized 12 weeks Merck and Bristol Myers Squibb provided active drug only.	Men and women with hypercholesterolemia <u>Mean baseline LDL-c</u> 185 mg/dl	4-week dietary run-in followed by randomization to: lova 10 mg qd or prava 10 mg qd for 4 weeks. Then a 4 week washout period followed by crossover to alternate statin for 4 weeks.	Efficacy analysis for 30 patients. **LDL-c reduction from baseline at 4 weeks:** lova: 24% prava: 19% (NS) **HDL-c increase from baseline at 4 weeks:** lova: 0.9% prava: 1.6% (NS) **Trigs reduction from baseline at 4 weeks:** lova: 15.3% prava: 19.4% (NS)	There were no differences in ADEs between groups. No cases of myopathy or clinical significant elevation in ALT or AST observed. <u>Dose equivalence</u> Lova 10 mg = prava 10 mg qd.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Lovastatin vs. Simvastatin				
Farmer et al. 1992 R, DB, MC, not ITT 544 patients randomized 24 weeks 3 primary authors employed by Merck.	Men and women 30-85 years with hypercholesterolemia <u>Mean baseline LDL-c</u> 191.4-193.4 mg/dl	6-week baseline dietary-placebo phase followed by randomization to: lova 20 mg qd (n=137) or lova 40 mg qd (n=134) or simva 10 mg qd (n=134) or simva 20 mg qd (n=135) for 24 weeks.	Efficacy analysis for 540 patients. **LDL-c reduction from baseline at 24 weeks:** lova 20 mg: 25.4% lova 40 mg: 31.2% simva 10 mg: 27.5% (NS) simva 20 mg: 34.7% (p<0.05) **HDL-c increase from baseline at 24 weeks:** lova 20 mg: 4.2% lova 40 mg: 7.4% simva 10 mg: 4.6% (NS) simva 20 mg: 4.6 (NS) **Trigs reduction from baseline at 24 weeks:** lova 20 mg: 10.5% lova 40 mg: 10.3% simva 10 mg: 3.9% (no significance reported) simva 20 mg: 10.3% (NS) **Achieved NCEP LDL-c goal (p not reported):** lova 20 mg: 33% lova 40 mg: 51% simva 10 mg: 41% simva 20 mg: 61%	No difference in ADEs between groups. Withdrawal for clinical or laboratory ADEs not different between groups. 1 patient in lova 40 mg group had ALT 3x ULN. <u>Dose equivalence</u> lova 20 mg = simva 10 mg qd lova 40 mg < or ≈ simva 20 mg qd.
Frohlich et al. 1993 R, DB, MC, not ITT 298 patients randomized 18 weeks Merck funded the study. Authors thanked Merck for coordination of data and their biostatistics groups.	Men and women 18-70 years with total cholesterol of 240-300 mg/dl (stratum 1) or >300 mg/dl (stratum 2) <u>Mean baseline LDL-c</u> Stratum 1: 200 mg/dl Stratum 2: 282-291 mg/dl	6-week dietary, 4 week-dietary-placebo run-in phase, then randomized to: lova 20 mg (n=149) or simva 10 mg (n=146). Doses doubled at 6 and 12 weeks if TC <u>></u>200 mg/dl	Efficacy analysis for 296 patients. **LDL-c reduction from baseline at 18 weeks:** Stratum 1 (mean dose): lova 50 mg qd: 34.3% simva 26.4 mg qd 34.6% (NS) Stratum 2 (mean dose): lova 71.7 mg qd: 37.2% simva 36.9 mg qd.: 37.1% (NS) **HDL-c increase from baseline at 18 weeks:** Stratum 1 (mean dose): lova 50 mg qd: 2.7% simva 26.4 mg qd 7.0% (NS) Stratum 2 (mean dose): lova 71.7 mg qd: 8.8% simva 36.9 mg qd: 5.3% (NS)	Patients in Stratum 2 experienced more laboratory ADEs in lova group vs. simva group (8.3% vs 0% , p<0.05). There were said to be minor and well within normal ranges. No other safety differences between groups. 1 major laboratory ADE occurred in lova group in Stratum 2, thought not to be drug-related. <u>Dose equivalence</u> lova 20 mg = simva 10 mg lova 80 mg = simva 40 mg qd

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Pravastatin vs. Simvastatin				
Malini et al. 1991 R, OL, ITT 100 patients randomized 6 weeks Industry support not reported.	Men and women 18-70 years with total cholesterol ≥240 mg/dl Mean baseline LDL-c Prava 205 mg/dl Simva 209 mg/dl	4-week dietary-placebo run in phase then randomized to: prava 10 mg qd (n=50) or simva 10 mg qd (n=50)	Efficacy analysis for 100 patients. **LDL-c reduction from baseline at 6 weeks:** prava: 21.8% simva 10 mg: 33.1% (p<0.01) **HDL-c increase from baseline at 6 weeks:** prava: 7% simva: 10% (p<0.05) **Trigs reduction from baseline at 6 weeks:** prava: 5.8% simva: 12.3% (p<0.01)	ADEs were reported in 4 prava patients vs. 2 simva patients. No patient withdrew from the study due to ADEs. Dose equivalence Equivalent doses not compared.
Lefebvre et al. 1992 R, DB, MC, not ITT 291 patients randomized 6 weeks Study supported by Merck.	Men and women 18-79 years with total cholesterol ≥240 mg/dl Mean baseline LDL-c Prava 219 mg/dl Simva 223 mg/dl	4-week dietary-placebo run-in phase, then randomized to: prava 10 mg qd (n=141) or simva 10 mg qd (n=142)	Efficacy analysis for 283 patients. **LDL-c reduction from baseline at 6 weeks:** prava: 22% simva:32% (p<0.01) **HDL-c increase from baseline at 6 weeks:** prava: 5% simva: 7% (p=0.06) **Trigs reduction from baseline at 6 weeks:** prava: 6% simva: 13% (p<0.05)	ADEs similar between groups. No patient experienced a clinically significant increase in liver transaminases or CK. Authors report 9 laboratory ADEs in simva vs. 2 in prava groups. Details not provided for all incidents. Equivalent doses not compared.
Lintott et al. 1993 R, DB, MC, not ITT 48 patients randomized 24 weeks Study supported by Merck.	Men or women with hypercholesterolemia Mean baseline LDL-c Prava 243 mg/dl Simva 250 mg/dl	6-week dietary-placebo phase then, randomization to: prava 10 mg qd (n=24) or simva 10 mg qd (n=24) for 6 weeks. At 12 and 18 weeks, doses doubled if LDL-c was >130 mg/dl to a maximum of 40 mg qd. At week 18, all patients switched to simva at 18-week dose.	Efficacy analysis for 47 patients. **LDL-c reduction from baseline at 6 weeks:** prava: 17% simva: 29% (no p-value provided) **LDL-c reduction from baseline at 18 weeks:** prava: 27% simva: 38% (p=0.001) **HDL-c increase from baseline at 18 weeks:** prava: 7% simva: 11% (NS) **Trigs reduction from baseline at 18 weeks:** prava: unchanged at 18 weeks simva: 11.8% 18/24 simva vs. 22/23 prava users titrated to maximum dose.	One simva patient experienced significant elevation in CK after beginning rigorous exercise program the day before. Simva was stopped and restarted with no further incident. One prava patient developed a rash and was withdrawn. Titrate to target, nonequivalent doses compared.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Lambrecht et al. 1993 R, DB, MC, not ITT 210 patients randomized 6 weeks Industry support not reported.	Men or women 18-70 years with total cholesterol ≥250 mg/dl Mean baseline LDL-c Prava 214 mg/dl Simva 219 mg/dl	4-week dietary-placebo run-in phase, then randomized to: prava 20 mg qd (n=105) or simva 20 mg qd (n=105) for 6 weeks.	Efficacy analysis for 200 patients. **LDL-c reduction from baseline at 6 weeks:** prava: 29% simva: 38% (p<0.01) **HDL-c increase from baseline at 6 weeks:** prava: 7.3% simva: 6.7% (NS) **Trigs reduction from baseline at 6 weeks:** prava: 10.9% simva: 14.3% (NS) **Achieved LDL-c <160 mg/dl:** 78% simva vs. 64% prava (p=0.06) **Achieved LDL-c <130 mg/dl:** 46% simva vs. 19% prava (p<0.01)	ADEs similar between groups. 3 ADEs reported >1%: myalgia (1.9%) and dyspepsia (1.9%) in simva group, and flatulence (1.9%) in prava group. 3 patients withdrawn due to ADEs: 1 in simva (malaise) and 2 in prava (malaise, nausea and palpitations; and flatulence) group. None of the events was considered serious. No clinically important changes in liver transaminases or CK. Nonequivalent doses compared.
Sweany et al., 1993 R, DB, MC, not ITT 550 patients 18 weeks Merck funded and participated in study.	Men and women 18-71 years with LDL-c ≥160 mg/dl Mean baseline LDL-c Prava 212 mg/dl Simva 207 mg/dl	6-week dietary/placebo run-in phase, then randomized to: prava 10 mg qd (n=275) or simva 10 mg qd (n=275) for 6 weeks. Doses doubled if LDL-c at weeks 6 and 12 were >130 mg/dl, up to a maximum of 40 mg qd for each statin.	Efficacy analysis number of patients not reported. **LDL-c reduction from baseline at 6 weeks:** prava: 19% simva: 30% (p<0.01) **LDL-c reduction from baseline at 18 weeks:** (mean dose) prava 32 mg/d: 26% simva 27 mg/d: 38% (p<0.01) **HDL-c increase from baseline at 18 weeks:** prava 12% simva 15% (p<0.05) **Trigs reduction from baseline at 18 weeks:** prava 14% simva 18% (p<0.05) **Achieved LDL-c <130 mg/dl** 65% simva vs. 39% prava	5 patients in each group withdrew due to ADEs. Reasons in prava group: headache and tinnitus, rash, abdominal pain, GI complaints and dizziness. Reasons in simva group: GI in 3 patients, headache, and diarrhea and sinus tachycardia. Myalgia reported by 1 simva and 3 prava users. 1 prava patient stopped due to myalgia and muscle cramps with CK 3-10x ULN. CK elevation in other myalgia reports not clinically significant. 2 simva patients had CK elevation > 10x ULN, attributed to exercise (simva continued without further problems). No clinically significant elevations in AST or ALT. Nonequivalent doses compared. Treat to target.
Douste-Blazy et al. 1993 R, DB, MC, not ITT 273 patients randomized 6 weeks Study supported by Merck.	Men and women 22-75 years with an LDL-c ≥160 mg/dl Mean baseline LDL-c Prava 222 mg/dl Simva 224 mg/dl	4-week placebo/dietary run-in phase followed by randomization to: prava 20 mg qd (n=136) or simva 10 mg qd (n=137) for 6 weeks.	Efficacy analysis for 268 patients. **LDL-c reduction from baseline at 6 weeks:** prava: 25% simva: 28.3% (p<0.01) **HDL-c increase from baseline at 6 weeks:** prava: 6.1% simva: 6.3% (NS) **Trigs reduction from baseline at 6 weeks:** prava: 12.9% simva: 13.8% (NS) **Achieved LDL-c <130 mg/dl:** 16% prava vs. 22% simva **Achieved LDL-c <160 mg/dl:** 53% prava vs. 60% simva	Reported ADEs were similar between groups. Two patients in each group stopped the statin due to ADEs and were not serious. No patient withdrew due to a laboratory ADE. Dose equivalence prava 20 mg ≈ or < simva 10 mg qd.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Stalenhoef et al. 1993 R, DB, MC, not ITT 48 patients randomized 18 weeks Industry involvement not reported.	Men and women with primary hypercholesterolemia LDL-c >180 mg/dl <u>Mean baseline LDL-c</u> 316 mg/dl	6-week dietary/placebo run-in period followed by randomization to: prava 10 mg qd (n=24) or simva 10 mg qd (n=24) for 6 weeks. Doses doubled at 12 and 18 weeks to a maximum 40 mg qd.	Efficacy analysis for 46 patients. **LDL-c reduction from baseline at 18 weeks:** prava 40 mg: 33% (mean doses) simva 40 mg: 43% (p<0.01) **HDL-c increase from baseline at 18 weeks:** prava: 6% simva: 8% (NS) **Trigs reduction from baseline at 18 weeks:** prava: 13% simva: 15% (NS)	Two patients withdrew due to ADEs. No details provided. No clinically significant increases in ALT/AST or CK. <u>Nonequivalent doses compared.</u>
Steinhagen-Thiessen 1994 R, DB, MC, not ITT 281 patients randomized 12 weeks Study supported by Merck.	Men or women 21-71 years with total cholesterol 220-280 mg/dl. <u>Mean baseline LDL-c</u> 174-176 mg/dl	4-week dietary/placebo run-in period followed by randomization to: prava 10 mg qd (n=138) or simva 5 mg qd (n=143) for 6 weeks. At 6 weeks, simva increased to 10 mg qd.	Efficacy analysis for 273 patients. **LDL-c reduction from baseline at 6 weeks:** prava 10 mg: 17.7% simva 5 mg: 23.3% (p<0.01) **LDL-c reduction from baseline at 12 weeks:** prava 10 mg: 16.5% simva 10 mg: 26.8% (p<0.01) **HDL-c increase from baseline at 12 weeks:** prava 10 mg: 8.3% simva 10 mg: 8.1% (NS) **Trigs reduction from baseline at 12 weeks:** prava 10 mg: 4.2% simva 10 mg: 9.5% (NS) **Achieved LDL-c <130 mg/dl:** prava 10 mg: 32-33% vs. simva 5 mg: 45% vs. simva 10 mg 59%	Most common treatment-related ADE was musculoskeletal complaints in simva group vs. digestive disturbances in prava group. 3 patients withdrew due to ADEs: 1 rash and 1 hepatitis (patient later found to be Hep B positive) in simva group, both judged unrelated to treatment. No details on 3rd withdrawal. 1 prava patient with CK elevation >10x ULN. No further details provided. <u>Dose equivalence</u> Simvastatin 5 and 10 mg > prava 10 mg qd
Sasaki et al. 1997 R, OL, C, not ITT 74 patients randomized 16 weeks Industry involvement not reported.	Men or women with total cholesterol <u>></u>220 mg/dl. <u>Mean baseline LDL-c</u> 177.7 mg/dl	Observation period (duration not stated), then randomization to: prava 10 mg qd or simva 5 mg qd for 8 weeks - then switched to alternate statin for another 8 weeks.	Efficacy analysis for 72 patients. **LDL-c reduction from baseline at 8 weeks:** prava: 23.1% simva: 31.1% (p<0.05) **HDL-c increase from baseline at 8 weeks:** prava: 6.6% simva: 7.9% (NS) **Trigs reduction from baseline at 8 weeks:** prava: 5.8% simva: 13% (NS) **Achieved LDL-c goal:** prava: 44.4% vs simva: 63.9% (p<0.05)	No differences between groups. No clinically important laboratory changes. <u>Dose equivalence</u> Simvastatin 5 and 10 mg > prava 10 mg qd

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Rosuvastatin vs Atorvastatin				
Davidson et al, 2002 R, DB, MC, PC. 519 patients randomized (n=132 placebo, 129 rosuva 5mg, 130 rosuva 10mg, 128 atorva 10mg) 12 weeks Supported by a grant from AstraZeneca	Men and women age 18 and older with fasting LDL-c ≥ 160 mg/dL and <250 mg/dL and fasting triglycerides ≤ 400 mg/dL, and a score of 28 or less on section 1 of the Eating Pattern Assessment Tool (indicating compliance with NCEP step I diet). Mean baseline LDL-c rosuva 5mg: 188 mg/dL rosuva 10mg: 185 mg/dL atorva 10mg: 186 mg/dL	6-week dietary run-in with NCEP Step 1 diet 12 week trial with NCEP Step 1 diet and rosuvastatin 5 or 10 mg, atorvastatin 10 mg, or placebo once a day	**LDL-c reduction from baseline at week 12:** rosuva 5 mg: 40% (p< 0.01 vs atorva) rosuva 10 mg: 43% (p<0.001 vs atorva) atorva 10 mg: 35% **HDL-c increase from baseline at week 12:** rosuva 5 mg: 13% (p< 0.01 vs atorva) rosuva 10 mg: 12% (p< 0.05 vs atorva) atorva 10 mg: 8% **Triglycerides reduction from baseline at week 12:** rosuva 5 mg: 17% rosuva 10 mg: 19% atorva 10 mg: 19%	Withdrawals due to adverse events: 4 (3.1%) atorva, 6 (4.7%) rosuva 5mg, 4 (3.1%) rosuva 10mg. No clinically significant elevations in CK or ALT/AST. Types and incidences of adverse events similar across all treatment groups. Adverse events related to study treatment: 18 rosuva 5mg (14.1%), 17 rosuva 10mg (13.2%), 25 atorva (19.7%). Most frequently reported were constipation, flatulence, nausea, and myalgia. Serious adverse events in 5 (3.9%) atorva patients (angina, coronary vascular disorder, tooth disorder, pathologic fracture, hypertension, cholelithiasis, ileus, and pneumonia); 3 (2.3%) rosuva 5mg patients (angina, heart failure, meningitis, bone disorder, infection), 0 in rosuva 10mg group. No serious adverse event was considered by the investigators to be related to study drug. Equivalent doses not compared

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Schwartz et al, 2004 R, DB, MC 382 patients randomized 24 week treatment period Supported by AstraZeneca	Patients aged >18 years, with LDL-C levels >=160 and< 250 mg/dL, and trig levels <=400 mg/dL, and documented atherosclerosis, Type 2 diabetes, or both, assessed. Patients with score of <=28 on Eating Pattern Assessment Tool, fasting LDL-C levels >160mg/dL and trig levels <400 mg/dL at 2 consecutive measurements were randomized. Mean baseline LDL-c levels: Rosuv 5/20/80: 188 mg/dL Rosuv 10/40/80: 186 mg/dL Atorv 10/40/80: 188 mg/dL	After a 6 week dietary lead-in, treatment for the first 12 weeks: rosuv 5 mg (n=127) once daily or rosuv 10 mg (n=128) once daily or atorv 10 mg (n=128) once daily If LDL-c remained >50 mg/dl, then the doses were uptitrated at weeks 12 and 18 to: rosuv 5 mg became 20 mg and then 80 mg (rosuv 5/20/80) rosuv 10 mg became 40 mg and then 80 mg (rosuv 10/40/80) atorv 10 mg became 40 mg and then 80 mg (atorv 10/40/80)	**% LDL-c reduction from baseline at 12 and 18 weeks**: rosuv 5/20/80: -39.8%(p<0.01), -51.6%(p<0.01 vs atorv) rosuv 10/40/80: -47.1%(p<0.001), -58.8%(p<0.001 vs atorv) atorv 10/40/80: -35.0%, -47.2% **% HDL-c increase at 12 and 18 weeks**: rosuv 5/20/80: +6.6% (p<0.01),+8.3%(p<0.001 vs atorv) rosuv 10/40/80: +7.7%(p<0.001),+10%(p<0.001 vs atorv) atorv 10/40/80: +2.7%,+1.4% **% trig reduction at 12 and 18 weeks:** (no p-values stated for any of these %) rosuv 5/20/80: -17.4%, -20.7% rosuv 10/40/80: -19.8%, -22.9% atorv 10/40/80: -17.8%, -22.1% **% of patients meeting the ATP III LDL-c goal of <100 mg/dL at 12 weeks:** Rosuv 5 mg/d: 34.6% (p=0.002 vs atorv) Rosuv 10mg/d: 59.4% (p<0.001 vs atorv) Atorv 10 mg/d: 16.5% **% of patients meeting the ATP III LDL-c goal of <100 mg/dL at 18 weeks:** Rosuv 20 mg/d: 72.4% (p=0.035 vs atorv) Rosuv 40mg/d: 88.3% (p<0.001 vs atorv) Atorv 40 mg/d: 60.6%	"Although adverse events were frequently reported in these high-risk patients, they were generally mild and not attributed to trial medication." Most common AEs pharyngitis, pain, myalgia **Any adverse event (AE):** rosuv 5/20/80: n=116 (91%) rosuv 10/40/80: n=113 (88%) atorv 10/40/80: n=101 (80%) **AEs considered treatment-related:** rosuv 5/20/80: n=36 (28%) rosuv 10/40/80: n=38 (30%) atorv 10/40/80: n=35 (28%) **Serious AEs:** rosuv 5/20/80: n=12 (9%) rosuv 10/40/80: n=8 (6%) atorv 10/40/80: n=7 (6%) **Withdrawals due to AEs:** rosuv 5/20/80: n=5 (4%) rosuv 10/40/80: n=7 (6%) atorv 10/40/80: n=6 (5%)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Strandberg et al, 2004 **R (2:1), OL, MC, 2-arm study, ITT** 1024 patients randomized (n=686 to rosuv 10 mg/d, n=338 to atorv 10 mg/d) 12 weeks Supported by a grant from AstraZeneca	Men and women >=18 years with LDL-c level >135 mg/dL for statin-naïve patients or >120 mg/dL in patients using the starting dose of another lipid-lowering drug. They had to be at high risk for CHD and have primary hypercholesterolemia. Mean baseline LDL-c rosuva 10mg: 174 mg/dL atorva 10mg: 170 mg/dL	rosuv 10 mg/d atorv 10 mg PO OD optional extension period for rosuv pts who did not have access to drug commercially, and for atorv pts who did not achieve the 1998 JTF goal for LDL-c after 12 weeks. Rosuv could be up-titrated at 12 wk intervals to 20 mg/d and then to 40 mg/d to achieve the 1998 JTF LDL-c goal (1998 target of <116 mg/dL; JTF 2003 target of <97 mg/dL).	Efficacy analysis for 911 patients (rosuv 10mg/d, n= 627; atorv 10mg/d, n= 284) **LDL-c levels at 12 weeks:** rosuv 10 mg: 89 mg/dL atorv 10 mg: 104 mg/dL % **LDL-c reduction from baseline at 12 weeks:** rosuv 10 mg: -46.92 % change (p< 0.05 vs. atorv) atorv 10 mg: -38.07 % change from baseline % **HDL-c increase 12 weeks after baseline:** rosuv 10 mg: 4.00 % increase (p<0.05 vs. atorv) atorv 10 mg: 1.88 increase **% decrease in trig levels at 12 weeks:** rosuv 10 mg: -14.55% (p<0.05 vs. atorv) atorv 10 mg: -13.98% **% patients reaching JTF LDL-c targets after 12 weeks:** (1998 target of <116 mg/dL; 2003 target of <97 mg/dL) rosuv: 83.4%; ~73% (p<0.001 vs. atorv) atorv: 68.3%; ~51.1%	**Patients experiencing any AE (estimated from graph)**: Rosuv ~38% (n=261) Atorv ~37% (n=125). Rosuv: 1 patient had melena (later diagnosed as duodenal ulcer); 1 patient having a history of peptic ulcer disease and receiving concmitant treatment with a NSAID (diclofenac) had vomiting; 1 patient had myopathy accompanied by increased creatine levels Atorv: 1 patient had proteinuria found to be non-treatment related **AE's in rosuv vs. atorv:** *n=AE incidence (%)/ n=led to discontinuation (%)* muscle pain/myalgia: 18(2.6%)/ 13(1.9%) vs. 4(1.2%)/ 3(0.9%) nausea: 12(1.7%)/ 7(1.0%) vs.5(1.5%)/ 3(0.9%) increased ALT: 11(1.6%)/ 2(0.3%) vs. 1(0.3%)/ 0(0%) increased AST: 8(1.2%)/ 0(0%) vs. 3(0.9%)/ 0(0%) increased creatine kinase (CK): 6(0.9%)/ 0(0%) vs. 6(1.8%)/ 1(0.3%) headache: 6(0.9%)/ 2(0.3%) vs. 4(1.2%)/ 3(0.9%) **Total withdrawals due to AEs (some patients experienced >1 adverse event):** Rosuv: n=24 (3.5%) Atorv: n=10 (3.0%)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Olsson et al, 2002 R, DB, MC 412 patients randomized (n=138 rosuva 5mg, 134 rosuva 10mg, 140 atorva 10mg) 52 weeks Supported by a grant from AstraZeneca	Men and women age 18 and older with LDL-c level between 160 and <250 mg/dL and an EPAT score 28 or less. <u>Mean baseline LDL-c</u> rosuva 5mg: 188.0 mg/dL rosuva 10mg:185.9 mg/dL atorva 10mg: 188.1mg/dL	5 or 10 mg rosuva or 10 mg atorva for 12 weeks, then titrated up to 80 mg if NCEP ATP-II LDL-c goal not met, for a total of 52 weeks.	**LDL-c reduction from baseline at 12 weeks:** rosuva 5 mg: 46% (p<0.001 vs atorva) rosuva 10 mg: 50% (p<0.001 vs atorva) atorva 10 mg: 39% **Percentage of patients achieving NCEP ATP-II LDL-c goal at 12 weeks:** rosuva 5 mg: 86% rosuva 10 mg: 89% atorva 10 mg: 73% (NS) **Percentage of patients achieving NCEP ATP-II LDL-c goal at 52 weeks:** rosuva 5 mg: 88% rosuva 10 mg: 98% atorva 10 mg: 87% (NS) **HDL-c increase from baseline at 12 weeks:** rosuva 5 mg: 6% (NS vs atorva) rosuva 10 mg: 8% (NS vs atorva) atorva 10 mg: 6% **Trigs reduction from baseline at 12 weeks:** rosuva 5 mg: 15% (NS vs atorva) rosuva 10 mg: 19% (NS vs atorva) atorva 10 mg: 16%	Adverse events considered to be treatment related occurred in 29% of rosuva 5mg, 27% rosuva 10mg, and 35% atorva 10mg patients. Most frequently reported were myalgia and GI complaints. Serious adverse events leading to withdrawal: rectal hemorrhage (rosuva 10mg(, serum creatinine elevation (rosuva 10mg), ALT/AST elevations (atorva 10mg). Total 28 withdrawals due to adverse events. Of these 5 rosuva 5mg, 5 rosuva 10mg, and 8 atorva 10mg had adverse events considered treatment-related. <u>Equivalent doses not compared</u>

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Schneck et al, 2003 R, DB, MC 374 patients randomized (n=165 atorva, 209 rosuva) 6 weeks Supported by AstraZeneca Pharmaceuticals	Men and women age 18 and older with hypercholesterolemia and without active arterial disease within 3 months of study entry or uncontrolled hypertension; LDL-c ≥ 160 mg/dL but <250 mg/dL, triglycerides <400 mg/dL, and Eating Pattern Assessment Tool (to assess adherence to NCEP Step I diet) score of 28 or less. <u>Mean baseline LDL-c</u> atorva: 10mg 38.2%; 20mg:43.3%; 40mg 48.4%; 80 mg 53.5% rosuva: 5mg 41.5%; 10mg 46.6%; 20mg 51.7%; 40mg 56.8%; 80mg 61.9%	Atorva 10, 20, 40, or 80 mg qd or rosuvastatin 5, 10, 20, 40, or 80 mg qd for 6 weeks.	**Reduction in LDL-c from baseline at 6 weeks:** atorva: 10mg 38.2%; 20mg:43.3%; 40mg 48.4%; 80 mg 53.5% rosuva: 5mg 41.5%; 10mg 46.6%; 20mg 51.7%; 40mg 56.8%; 80mg 61.9% (p<0.001 difference vs atorva across dose range) **Increase in HDL-c from baseline at 6 weeks:** atorva: 10mg 5.0%; 20mg 7.6%; 40mg 4.1%; 80mg 2.1% rosuva: 5mg 7.4%; 10mg 6.0%; 20mg 9.1%; 40mg: 12.3%; 80mg 9.6% (NS) **Reduction in trigs from baseline at 6 weeks:** atorva: 10mg: 17.5%; 20mg 25.6%; 40mg 27.2%; 80mg 34.5% rosuva: 5mg 23.1%; 10mg 22.1%; 20mg 18.4%; 40mg 25.7%; 80mg 19.7% (NS)	Any adverse event: 51.2% rosuva vs 47.9% atorva (NS); no consistent relation in occurrence of individual treatment-emergent adverse events to doses of either drug. Withdrawals due to adverse events infrequent (1 patient each in rosuva 10 mg, 20 mg, 80 mg groups, atorva 10 mg 40 mg, and 80 mg groups). Most common adverse events pharyngitis, headache, and pain. <u>Dose equivalence (LDL-c lowering)</u> rosuva 5mg > atorva 20mg rosuva 10mg > atorva 20mg rosuva 20mg > atorva 40mg rosuva 40mg > atorva 80mg

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Rosuvastatin vs Multiple Statins				
Jones et al, 2003 (STELLAR) R, OL, MC 2431 patients randomized (n=643 rosuva, 641 atorva, 655 simva, 492 prava) 6 weeks Supported by AstraZeneca	Men and nonpregnant women age 18 or older with LDL-c >=160 and <250 mg/dL. Triglyceride levels <400 mg/dL. Mean baseline LDL-c (mg/dL) rosuva: 10mg 188; 20mg 187; 40mg 194 atorva: 10mg 189; 20mg 190; 40mg 189; 80mg 190 simva: 10mg 189; 20mg 189; 40mg 187; 80mg 190 prava: 10mg 189; 20mg 187; 40mg 190	Rosuvastatin 10, 20, 40, or 80 mg; atorvastatin 10, 20, 40, or 80 mg; simvastatin 10, 20, 40, or 80 mg; pravastain 10, 20, or 40 mg all once daily for 6 weeks.	**LDL-c reduction from baseline at week 6:** rosuva: 10mg 45.8%; 20mg 52.4%; 40mg 55% atorva: 10mg 36.8%; 20mg 42.6^; 40mg 47.8%; 80mg 51.1% simva: 10mg 28.3%; 20mg 35.0%; 40mg 38.8%; 80mg 45.8% prava: 10mg 20.1%; 20mg 24.4%; 40mg 29.7% equivalent doses: rosuva 10mg > atorva 20mg (p=0.026) and simva 40mg (p<0.001) rosuva 20mg > atorva 40mg (p<0.002) and simva 80mg (p<0.001) rosuva 40mg >atorva 80mg (p=0.006) **HDL-c increase from baseline at week 6:** rosuva: 10mg 7.7%; 20mg 9.5%; 40mg 9.6% atorva: 10mg 5.7%; 20mg 4.8%; 40mg 4.4% 80mg 2.1% simva: 10mg 5.3%; 20mg 6.0%; 40mg 5.2%; 80mg 6.8% prava: 10mg 3.2%; 20mg 4.4%; 40mg 5.6% equivalent doses: rosuva 10 mg = atorva 20 mg rosuva 10mg = simva 40 mg rosuva 20 mg > atorva 40mg (p<0.002) rosuva 20 mg = simva 80 mg **Trigs reduction from baseline at week 6:** rosuva: 10mg 19.8%; 20mg 23.7%; 40mg 26.1% atorva: 10mg 20.0%; 20mg 22.6%; 40mg 26.8%; 80mg 28.2% simva: 10mg 11.9%; 20mg 17.6%; 40mg 14.8%; 80mg 18.2% prava: 10mg 8.2%; 20mg 7.7%; 40mg 13.2%	Withdrawals due to adverse events: 23/643 rosuva (3.6%), 25/641 atorva (3.9%), 19/655 simva (2.9%), 11/492 prava (2.2%); 46% of all patients reported adverse events, 29 patients had serious adverse events. 2 rosuva 80mg patients developed acute renal failure of uncertain etiology. Most common adverse events pain, pharyngitis, myalgia, headache. Dose equivalence (LDL-c lowering) rosuva 10mg > atorva 20mg and simva 40mg rosuva 20mg > atorva 40mg and simva 80mg rosuva 40mg >atorva 80mg

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Blasetto et al, 2003; Shepherd et al, 2003 R, DB, MC 5 trials prospectively designed to allow pooling 1687 patients randomized (n=394 rosuva 5 mg, 392 rosuva 10 mg, 396 atorva 10 mg, 250 simva 20 mg, 255 prava 20 mg) 12 weeks Supported by AstraZeneca	Men and women age 18 or older with LDL-c ≥ 160 mg/dL and <250 mg.dL and triglyceride levels ≤ 400 mg/dL Mean baseline LDL-c 3 pooled trials of rosuva vs atorva: rosuva 5mg: 188 mg/dL rosuva 10mg: 185 mg/dL atorva 10mg: 187 mg/dL 2 pooled trials of rosuva vs prava and simva: rosuva 5mg: 189 mg/dL rosuva 10mg: 187 mg/dL simva 20mg: 188 mg/dL prava 20mg: 189 mg/dL	Rosuva 5 mg or 10 mg; atorva 10 mg; simva 20 mg; prava 20 mg	**3 pooled trials of rosuva vs atorva:** LDL-C reduction from baseline at week 12: rosuva 5mg: 41.9% (p<0.001 vs atorva); rosuva 10mg: 46.7% (p<0.001 vs atorva); atorva 10mg: 36.4% HDL-c increase from baseline at week 12: rosuva 5mg: 8.2% (p<0.01 vs atorva); rosuva 10mg: 8.9% (p<0.001 vs atorva); atorva 10mg: 5.5% Trigs decrease from baseline at week 12: rosuva 5mg: 16.4%; rosuva 10mg: 19.2%; atorva 10mg: 17.6% (NS) Achieved ATP-III LDL-c goal at week 12: rosuva 10 mg: 76% atorva 10 mg: 53% (p<0.001) **2 pooled trials of rosuva vs prava and simva:** LDL-C reduction from baseline at week 12: rosuva 5mg: 40.6% (p<0.001 vs simva and prava); rosuva 10mg: 48.1% (p<0.001 vs simva and prava); prava 20mg 27.1%; simva 20mg 35.7% HDL-c increase from baseline at week 12: rosuva 5mg: 6.9%; rosuva 10mg: 9.1% (p<0.05 vs simva and prava); prava 20mg 6.2%; simva 20mg 6.2% Trigs decrease from baseline at week 12: rosuva 5mg: 14.9%; rosuva 10mg: 20.2% (p<0.01 vs simva and prava); prava 20mg 12.2%; simva 20mg 12.4%	No information on adverse events. Equivalent doses not compared

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Brown et al. 2002 R, DB, MC, not ITT 477 patients randomized (n= 239 rosuva, 118 prava vs. 120 simva) 52 weeks 3 authors employed by AstraZeneca	Men and women ≥18 years with LDL-c ≥160 and <250 mg/dl, and triglyceride levels <=400 mg/dL Mean baseline LDL-c rosuva 5mg: 187.3 mg/dL rosuva 10mg: 187.0 mg/dL prava: 188.5 mg/dL simva: 188.0 mg/dL	6-week dietary run-in with NCEP Step 1 diet, then: rosuva 5 mg or rosuva 10 mg or prava 20 mg or simva 20 mg for 12 weeks. Then 40-week titration period to reach NCEP (ATP 2) targets or maximum dose of rosuva 80 mg, prava 40 mg or simva 80 mg.	Efficacy analysis for 471 patients. **LDL-c reduction at 12 weeks:** rosuva 5 mg: 39% (p<0.001 vs prava 20 mg; p<0.05 vs simva 20mg) rosuva 10 mg: 47% (p <0.001 vs prava 20 mg, ≤0.001 vs simva 20 mg) prava 20 mg: 27% simva 20 mg: 35% **HDL increase at 12 weeks:** rosuva 5 mg: 8.2% rosuva 10 mg: 11.9% (p<0.05 vs prava 20 mg) prava 20 mg: 8% simva 20 mg: 9% **Trigs reduction at 12 weeks:** rosuva 5 mg: 17.6% (p<0.05 vs simva 20 mg) rosuva 10 mg: 21.5% (p<0.01 vs prava 20 mg, p≤0.001 vs simva 20 mg) prava 20 mg: 11% simva 20 mg: 10% **Achieved ATP III LDL-c goal at 12 weeks:** rosuva 5 mg: 78% rosuva 10 mg: 88% prava 20 mg: 51% simva 20 mg: 63% (p-values not reported)	Withdrawals due to treatment-related adverse events:7 rosuva 5 mg, 7 rosuva 10 mg, 6 prava, 7 simva. 1 serious AE identified with treatment: simva patient with asthenia and chest pain, resolved with no change in treatment. Transient elevations in ALT >3x ULN without symptoms: 2 rosuva 5 mg, 0 rosuva 10 mg, 5 prava, 2 simva Increased laboratory. Equivalent doses not compared

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Paoletti et al. 2001 R, DB, MC, ITT 502 patients randomized 12 weeks Sponsored by and one author employed by AstraZeneca	Men and women age≥18 years with hypercholesterolaemia, fasting LDL-c ≥160 and <250 mg/dl, fasting trig ≤400 mg/dl Mean baseline LDL-c 189 mg/dl	Screening phase, then randomization to: rosuva 5 or 10 mg prava 20 mg or simva 20 mg or for 12 weeks	Efficacy analysis for 495 patients. **LDL-c reduction from baseline at 12 weeks:** rosuva 5 mg: 42% (p<0.001 vs prava, p<0.005 vs simva) rosuva 10mg: 49% (p<0.001 vs prava, p<0.001 vs simva) prava: 28% simva: 37% **HDL-c increase from baseline at 12 weeks:** rosuva 5 mg: 6% rosuva 10mg: 7% prava: 4% simva: 4% (NS) **Trigs reduction from baseline at 12 weeks:** rosuva 5 mg: 12% rosuva 10mg: 18% prava: 13% simva: 14% (NS) **Achieved NCEP ATP II LDL-c goal:** rosuva 5 mg: 71% rosuva 10mg: 87% prava: 53% simva: 64% (NS)	Serious AEs in 4 (3.5%) rosuva 10 mg patients (life-threatening cerebral hemorrhage, life threatening myocarcdial infarction, syncope, and cholecystitis plus cholelithiasis). No serious AEs considered by the investigator to be related to study treatment. Withdrawal due to AEs: rosuva 5 mg: 2 (1.6%) chest pain and infection, migraine rosuva 10 mg: 6 (5.2%) cerebral hemorrhage, diarrhea, CK increase and myalgia, headache and edema, urticaria) prava: 3 (2.2%) vasodilation and abdominal pain, dyspepsia, conjunctivitis) simva: 1 (0.8%) abdominal pain. ADEs: prava 19/136 (14%) vs simva 23/129 (18%). Most common ADEs: constipation (3 vs. 2), diarrhea ((1 vs. 1),, dyspepsia (2 vs. 3), pruritus (1 vs. 4), abdominal pain (2 vs. 4). ALT elevation in 2 simva, 3 rosuva 5 mg, and 1 rosuva 1 mg patients. No clinically significant ALT or CK elevations. Equivalent doses not compared

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments

Schuster et al. 2004
R,OL,MC,ITT
 	
5-arm trial that included statin switching (to rosuvastatin) at 8 weeks
 	
3140 patients randomized
16 weeks of treatment
 	
Sponsored by Astra Zeneca
	Patients aged >=18 years, with CHD or other atherosclerotic disease, type 2 diabetes, a CHD risk >20% over 10 years, with LDL-c levels>=115 mg/dL and trig <400 mg/dL; LDL-c measurements had to be within 15% of each other during the lead-in period.
	
	Baseline LDL-c levels:
	Rosuv 10 mg: 164.9 mg/dL
	Atorva 10 mg: 162.2 mg/dL
	Atorva 20 mg: 167.5 mg/dL
	Simva 20 mg: 165.5 mg/dL
	Prava 40 mg: 163.8 mg/dL
		6 week dietary lead-in phase, then randomization to 5 arm trial system
		(drug a for 8 weeks then drug b or c for eight additional weeks):
		rosuv 10 mg (n=538), to rosuv 10 mg (n=521);
		
		atorva 10 mg (n=529), to rosuv 10 mg (n=276) or atorva 10 mg (n=240);
		
		atorva 20 mg (n=925), to rosuv 10 mg (n=293), rosuv 20 mg (n=305), or atorva 20 mg (n=299);
		
		simva 20 mg (n=543), to rosuv 10 mg (n=277) or simva 20 mg (n=250);
		
		prava 40 mg (n=521), to rosuv 10 mg (n=253) or prava 40 mg (n=253).
			% LDL-c reduction from baseline to 8 weeks:
			Rosuv 10 mg (n=521): -47.0%
			Atorva 10 mg (n=240): -37.2%
			Atorva 20 mg (n=299): -43.7%
			Simva 20 mg (n=250): -35.4%
			Prava 40 mg (n=253): -31.0%
			(p<0.0001 for all comparisons vs rosuva 10 mg)
			
			% HDL-c increase from baseline to 8 weeks:
			Rosuv 10 mg (n=521): +9.2%
			Atorva 10 mg (n=240): +6.8% (p<0.01 vs rosuva 10 mg)
			Atorva 20 mg (n=299): +5.7% (p<0.0001 vs rosuva 10 mg)
			Simva 20 mg (n=250): +8.0% (NS vs rosuva 10 mg)
			Prava 40 mg (n=253): +7.6% (NS vs rosuva 10 mg)
			% trig reduction from baseline to 8 weeks**:**
			Rosuv 10 mg (n=521): -18.9% (p<0.01 vs rosuva 10 mg)
			Atorva 10 mg (n=240): -15.9% (NS vs rosuva 10 mg)
			Atorva 20 mg (n=299): -18.3% (NS vs rosuva 10 mg)
			Simva 20 mg (n=250): -13.5% (p<0.01 vs rosuva 10 mg)
			Prava 40 mg (n=253): -10.5% (p<0.0001 vs rosuva 10 mg)
			Proportion of patients achieving the ATP III LDL-c goals at week 8:
			Rosuv 10mg (n=538): 80%
			Atorva 10 mg (n=529): 63% (p<0.0001 vs rosuva 10 mg)
			Atorva 20 mg (n=925): 74% (p<0.01 vs rosuva 10 mg)
			Simva 20 mg (n=543): 54% (p<0.0001 vs rosuva 10 mg)
			Prava 40 mg (n=521): 45% (p<0.0001 vs rosuva 10 mg)
				"Occurrence of deaths, serious adverse events (SAE's), and withdrawals due to adverse events (AE's) were low, with no differences noted among the treatment groups." 8 patients died during the trial, but those deaths occurred from "causes that would be expected in such a patient population (i.e., cardivascular events=4, malignancy=2, pneumonia=1, and subdural hematoma=1". No treatment-related AE's leading to death nor any treatment-related SAE's are reported. SAE's or AE's are not always categorized by drug type.
				
				Myalgia - reported in 1.9% of patients in period 1 and 0.9% of patients in period 2.
				No cases of myopathy were reported (creatine kinase >10 times ULN and muscle symptoms).
				Atorva 20 mg and rosuv 10 mg each had 1 case of asymptomatic increase in creatine kinase >10 times ULN; both resolved during continued study treatment.
				No patients had increases in hepatic transaminases >3 times ULN and >= consecutive measurements.

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline
Studies in outpatients						
Downs JR, etal. 1998 Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)	Randomized, double-blind, placebo-controlled, intention to treat analysis	6605 healthy men (43-73 yrs) & postmenopausal women (55-73 yrs) without CHD with average TC, LDL-c and below average HDL-c	Lovastatin 20 mg qpm or placebo qpm. Lovastatin increased to 40 mg qpm if LDL-c >110 mg/dl (2.84 mmol/l).	5.2 years	150 ±17 mg/dl (3.88 mmol/l)	25% (at 1 year)
Colhoun 2004 Collaborative Atorvastatin Diabetes Study (CARDS)	Randomized, double-blind, placebo-controlled, multicenter	2838 men and women with no history of cardiovascular disease, LDL of 4.14 or lower, fasting triglyceride of 6.78 or less, and at least one of the following: retinopathy, albuminuria, current smoking, or hypertension.	Atorvastatin 10 mg/day or placebo	median 3.9 years	117 +32 mg/dl	36% (95% CI 37% to 35%)
Shepherd J., et al. 1995 West of Scotland Coronary Prevention Study Group (WOSCOPS)	Randomized, double-blind, placebo-controlled, intention to treat analysis	6595 Scottish men (45-64 years) with no history of MI and elevated cholesterol	Pravastatin 40 mg qpm or placebo qpm.	4.9 years	192 ± 17 mg/dl (5 mmol/l)	26% in the on-treatment group, 16% in the intent to treat population
The Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group 1998 Colquhoun, 2004 Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)	Randomized, double-blind, placebo-controlled, intention to treat analysis	9014 men & women 31-75 years with a history of either MI or hospitalization for unstable angina.	Pravastatin 40 mg qpm or placebo qpm.	6.1 years	150 mg/dl 3.88 (mmol/l) (median)	25% vs. placebo

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death	All Cause Mortality	Major Coronary Events
Studies in outpatients					
Downs JR, etal. 1998 Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)	**Fatal or nonfatal MI:** RRR=40% ARR=1.2 events/100 ppl p=0.002 95% CI 17-57% NNT=86	**Unstable angina:** RRR=32% ARR=0.8 events/100 ppl p=0.02 95% CI 5-51% NNT=122	There were not enough fatal cardiovascular or CHD events to perform survival analysis.	80 in lovastatin vs. 77 placebo (NS)	**Primary endpoint: First acute major event (fatal or nonfatal MI, unstable angina, or sudden cardiac death** RRR=37% ARR=2 events/100 ppl p<0.001 5% CI 21-50% NNT=49
Colhoun 2004 Collaborative Atorvastatin Diabetes Study (CARDS)	**Any acute cardiovascular disease event:** 9.4% atorva vs 13.4% placebo. Hazard ratio=0.68 (95% CI 0.55, 0.85)	Not reported	Not reported	4.3% atorva vs 5.8% placebo. Hazard ratio=0.73 (95% CI 0.52, 1.01)	**Primary endpoint (acute coronary event, coronary revascularization, stroke):** 5.8% atorva vs 9.0% placebo. Hazard ratio=0.63 (95% CI 0.48, 0.83) **Acute coronary events:** 3.6% atorva vs 5.5% placebo. Hazard ratio=0.64 (95% CI 0.45, 0.91)
Shepherd J., et al. 1995 West of Scotland Coronary Prevention Study Group (WOSCOPS)	**Nonfatal MI:** RRR=31% ARR=1.9 95% CI 15-45% NNT=54	Not reported	**Death from all cardiovascular causes:** RRR=32% ARR 0.7/100 ppl p=0.033 95% CI 3-53% NNT=142	RRR=22% ARR 0.9/100 ppl p=0.051 95% CI 0-40 NNT=112	**Primary endpoint: nonfatal MI or death:** RRR=31% ARR=2.2/100 ppl p<0.001 95% CI 17-43% NNT=44
The Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group 1998 Colquhoun, 2004 Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)	**Fatal or nonfatal MI:** RRR=29% ARR=2.8/100 ppl p<0.001 95% CI 18-38% NNT=36	**Unstable angina:** RRR=12% ARR=2.2/100 ppl 95% CI 4-19% NNT=45	**Primary endpoint: Death due to CHD:** RRR=24% ARR=1.9/100 ppl p<0.001 95% CI 12-35% NNT=52	RRR=22% ARR 3/100 ppl p<0.001 95% CI 13-31 NNT=33	**Death due to CHD or nonfatal MI:** RRR=24% ARR=3.5/100 ppl p<0.001) 95% CI 15-32% NNT=28

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Studies in outpatients			
Downs JR, etal. 1998 Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)	Not reported	RRR=33% ARR=1.5 events/100 ppl p=0.001 95% CI 15-48% NNT=65	Lovastatin reduced the incidence of first acute major coronary events, MI, unstable angina, coronary revascularization procedures, coronary and cardiovascular events compared to placebo.
Colhoun 2004 Collaborative Atorvastatin Diabetes Study (CARDS)	1.5% atorva vs 2.8% placebo. Hazard ratio=0.52 (95% CI 0.31, 0.89)	1.7% atorva vs 2.4% placebo. Hazard ratio=0.69 (95% CI 0.41, 1.16)	
Shepherd J., et al. 1995 West of Scotland Coronary Prevention Study Group (WOSCOPS)	46 in pravastatin vs. 51 in placebo (NS)	RRR=37% ARR=0.9/100 ppl p=0.009 95% CI 11-56% NNT=112	Pravastatin reduced the incidence of coronary events (nonfatal MI and CHD death), death from all CHD and cardiovascular causes, need for revascularization and nonfatal MI compared to placebo. There was a trend to reduced all-cause mortality in pravastatin vs. placebo.
The Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group 1998 Colquhoun, 2004 Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)	RRR=19% ARR=0.8/100 ppl p=0.48 95% CI 0-34% NNT=127	RRR=20% ARR=3/100 ppl p<0.001 95% CI 10-28% NNT=34	Pravastatin reduced the incidence of death from CHD, overall mortality, fatal and nonfatal MI and need for revascularization compared to placebo.

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline
Studies in outpatients						
Sacks FM., et al. 1996 Cholesterol and Recurrent Events Trial (CARE)	Randomized, double-blind, placebo-controlled, intention to treat analysis	4159 men and postmenopausal women 21-75 years with an acute MI 3-20 months prior to randomization	Pravastatin 40 mg qpm or placebo qpm.	5 years (median)	139 mg/dl (3.4 mmol/l)	32% (28% vs. placebo)
Scandinavian Simvastatin Survival Study Group 1994 Scandinavian Simvastatin Survival Study (4S)	Randomized, double-blind, placebo-controlled, intention to treat analysis	4444 men and women 35-70 years with a history of angina pectoris or acute MI	Simvastatin 20 mg qpm or placebo qpm	5.4 years (median)	187 mg/dl (4.87 mmol/l)	35%
Riegger G. et al.. 1998	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	365 men or women 40-70 years with stable symptomatic CHD as assessed by exercise ECG and an LDL-c >160 mg/dl (4.1 mmol/L)	Fluvastatin 40 mg qpm or placebo qpm. If LDL-c was not reduced 30% or more, fluvastatin was increased to 40 mg bidl	1 year	198 mg/dl (5.1 mmol/L)	26.90%

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death	All Cause Mortality	Major Coronary Events
Studies in outpatients					
Sacks FM., et al. 1996 Cholesterol and Recurrent Events Trial (CARE)	**Fatal or nonfatal MI:** RRR=25% ARR=2.4/100 ppl p=0.006 95% CI 8-39% NNT=41	Not reported	**Death due to CHD:** RRR=20% ARR=1.1/100 ppl p=0.1 95% CI (-)5-39% NNT=89	RRR=9% ARR=0.7/100 ppl p=0.37 95% CI (-)12-26% NNT=128	**Primary endpoint: *Death from CHD or nonfatal MI:*** RRR=24% ARR=3 p=0.003 95% CI 9-36% NNT=33
Scandinavian Simvastatin Survival Study Group 1994 Scandinavian Simvastatin Survival Study (4S)	Not reported separately	Not reported	**Death due to CHD:** RRR=42% ARR=3.5/100 ppl 95% CI 27-54% NNT=28	**Primary endpoint: Total mortality:** RRR=30% ARR=3.3/100 ppl p=0.0003 95% CI 15-42% NNT=30	**CHD Death, nonfatal MI, resuscitated cardiac arrest:** RRR=34% ARR=8.5/100 ppl p<0.00001 95% CI 25-41% NNT=12
Riegger G. et al.. 1998	3 cardiac events occurred in the fluvastatin vs. 10 in the placebo group (p<0.05, ARR=4/100 persons, NNT=25).				

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Studies in outpatients			
Sacks FM., et al. 1996 Cholesterol and Recurrent Events Trial (CARE)	RRR=31%, ARR=1.1/100 ppl, p=0.03, 95% CI 3-52, NNT=86	RRR=27% ARR=4.7/100 ppl p<0.001 95% CI 15-37% NNT=41	Pravastatin reduced the incidence of the combined primary endpoint of nonfatal MI and death due to CHD. Stroke and need for revascularization was also reduced in the pravastatin compared to placebo group. Overall mortality and mortality from noncardiovascular causes was not reduced. The reduction in coronary events was greater in women and those with higher baseline LDL-c.
Scandinavian Simvastatin Survival Study Group 1994 Scandinavian Simvastatin Survival Study (4S)	**Post-hoc analysis: fatal and nonfatal cerebrovascular events:** RRR=30% ARR=1.2/100 ppl p=0.024 95% CI 4-48% NNT=80	RRR=37% ARR=5.9/100 ppl p<0.00001 95% CI 26-46% NNT=17	Simvastatin reduced the incidence of the primary endpoint of total mortality of which CHD death accounted for a reduction of 42% vs. placebo. Simvastatin also reduced the incidence of major coronary events, as defined in this trial, need for revascularization and combined fatal and nonfatal stroke. The risk for these events was reduced in women and in those over 60 years.
Riegger G. et al.. 1998			Fluvastatin resulted in a significant reduction in cardiac events compared to placebo in patients with CHD and elevated LDL-c. Just over 20% of patients withdrew because of noncompliance or lack of cooperation with similar distribution in each group. Fair in quality for assessment of differences in clinical events between groups.

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline
Studies in outpatients						
Heart Protection Study Collaborative Group 2002, 2004 Heart Protection Study (HPS)	Randomized, double-blind, placebo-controlled, intention to treat analysis	20,536 Men or women 40-80 years with a total cholesterol of >135 mg/dl and a substantial 5 year risk for death from coronary heart disease based on their past medical history.	Simvastatin 40 mg qd or placebo qd.	5 years	131 mg/dl (3.4 mmol/L)	29.5% (calculated)
Shepherd 2002, 1999 Prospective Study of Pravastatin in the Elderly (PROSPER) Scotland, Ireland, The Netherlands	Randomized, double-blind, placebo controlled, intention-to-treat analysis	5804 men and women age 70-82 with pre-existing vascular disease or raised risk due to smoking, hypertension or diabetes.; cholesterol 155-350 mg/dl, triglycerides $\leq$530 mmol/L and good cognitive function.	Pravastatin 40 mg/day or placebo	3.2 years	3.8 mmol/L (calculated = 148.2 mg/dL)	34% from baseline and placebo at 3 months (2.5 /3.8 mmol/L).

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death	All Cause Mortality	Major Coronary Events
Studies in outpatients					
Heart Protection Study Collaborative Group 2002, 2004 Heart Protection Study (HPS)	**Nonfatal MI:** RRR=38% ARR=2.1/100 ppl pp<0.0001 95% CI 30-46, NNT=47	**Admission for unstable or worsening angina:** RRR=14% ARR=3.5/200 ppl p=0.0003 95% CI not given NNT=28	**Admission for unstable or worsening angina:** RRR=14% ARR=3.5/100 ppl p=0.0003, 95% CI not given, NNT=28	**Primary endpoint:** RRR=13%, ARR=1.75/100 ppl, p=0.0003, 95% CI 6-19%, NNT=57	**Death due to CHD or nonfatal MI:** RRR=27% ARR=3.1/100 ppl p<0.0001, 95% CI 21-33% NNT=32
Shepherd 2002, 1999 Prospective Study of Pravastatin in the Elderly (PROSPER) Scotland, Ireland, The Netherlands	**Nonfatal MI** RRR= 14% ARR=1 events/100 ppl p= .10 95% CI = -3-28% NNT=100	NR	**CHD Death** RRR= 24% ARR= 0.9 events/ 100 ppl p= .043 95% CI = 1-42% NNT= 111	RRR= 3% ARR= 0.2 events/ 100 ppl p= 0.74 95% CI = -14-17% NNT= 500	**All cardiovascular events** RRR= 15% ARR= 2.3events/100 ppl p= .012 95% CI = 3-25% NNT= 43 **Transient ischemic attacks** RRR= 25% ARR= 0.8 events/ 100 ppl p=0.051 95% CI = 0-45% NNT= 125

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Studies in outpatients			
Heart Protection Study Collaborative Group 2002, 2004 Heart Protection Study (HPS)	RRR=25%, ARR=1.37/100 ppl, p<0.0001, 95% CI 15-34, NNT=72 (Ischemic stroke accounted for this difference).	RRR=24% ARR=2.6/100 ppl p<0.0001 95% CI 17-30 NNT=38	Coronary or vascular death, nonfatal MI, stroke and need for coronary revascularization reduced for simvastatin group compared to placebo in patients at high risk for CV death. Subanalysis of patients at LDL-c levels <100 mg/dl showed a reduction of to 65 mg/dl (mean) produced a reduction in risk about as great as those at higher LDL-c. CV events were reduced in the simvastatin vs. placebo groups regardless of prerandomization LDL-c lowering response. Simvastatin reduced incidence of the primary endpoint of total mortality, with a CHD death reduction of 42% vs. placebo. Simvastatin reduced incidence of major coronary events. The risk for these events was reduced in women and in those over 60 years.
Shepherd 2002, 1999 Prospective Study of Pravastatin in the Elderly (PROSPER) Scotland, Ireland, The Netherlands	**Fatal stroke** RRR= -57% ARR= -0.3 events/ 100 ppl p= .19 95% CI = -208-20% NNT= -333 **Nonfatal stroke** RRR= 2% ARR= 0.1 event/ 100 ppl p= 0.85 95% CI = -26-24% NNT= 1000	RRR= 18% ARR= 0.3 events/ 100 ppl p= .36 95% CI = -26-46% NNT= 333	Subgroup analysis shows greater statin effect reducing CHD death and nonfatal MI in men than in women, and in secondary prevention than in primary prevention.

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline
Studies in outpatients						
ALLHAT Officers and Coordinators 2002 Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)	Randomized, open-label vs. usual care, intention-to-treat analysis	10,355 people age 55+ with stage 1 or 2 hypertension and 1+ CHD risk factor; for those with no known CHD: LDL-C 120-189 mg/dL; for those with known CHD: LDL-C 100-129 mg/dL; triglyceride lower than 350 mg/dL.	Pravastatin 40 mg/day or usual care	4.8 years (max=7.8)	145.55 mg/dL (calculated = 3.73 mmol/L)	**Year 2** - base = 23.8% - usual = 16.5% **Year 4** - base = 28.2% - usual = 16.7% **Year 6** - base = 28.6% - usual = 11.9% (calculated from table - figured different in text)
Sever 2003 Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm (ASCOT-LLA) UK, Sweden, Norway, Denmark, Finland, Ireland	Randomized, double-blind (inadequate information), placebo-controlled, intention-to-treat analysis	10,305 people with no history of CHD, total cholesterol concentration ≤ 6.5 mmol/L (calculated = 253 mg/dL), age 40-79, with untreated hypertension or treated hypertension with systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or both; plus 3+ CV risk factors, including male sex, age 55+, and family history.	Atorvastatin 10 mg/day or placebo	3.3 years (median)	3.4 mmol/L (calculated = 133 mg/dL)	**6 months** - base = 35.8% - placebo = 35.9% **Year 2** - base = 34.9% - placebo = 33.5% **Year 3** - base = 33.7% - placebo = 30.9%

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death	All Cause Mortality	Major Coronary Events
Studies in outpatients					
ALLHAT Officers and Coordinators 2002 Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)	**6-Year Rate** **Fatal CHD & Nonfatal MI** RRR= 9% (11% calculated) ARR= 1.1 events/ 100 ppl p= .16 95% CI = -4-21% NNT= 91	NR	**6-Year Rate** **CVD Deaths** RRR= 1% (3% calculated) ARR= 0.2 events/ 100 ppl p= .91 95% CI = -16-16% NNT= 500 **CHD Deaths** RRR= 1% (5% calculated) ARR= 0.2 events/ 100 ppl p= .96 95% CI = -24-20% NNT= 500	**6-Year Rate** **RRR= 1% (3% calculated)** ARR= 0.4 events/ 100 ppl p= .88 95% CI = -11-11% NNT= 250	**6-Year Rate** **Heart failure (hospitalized or fatal)** RRR= 1% (3% calculated) ARR= 0.2 events/ 100 ppl p= .89 95% CI = -18-17% NNT= 500
Sever 2003 Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm (ASCOT-LLA) UK, Sweden, Norway, Denmark, Finland, Ireland	**Primary endpoint:** **Nonfatal MI plus fatal CHD** RRR= 36% ARR= 1.1 events/ 100 ppl p= .0005 95% CI = 17-50% NNT= 91	**Unstable angina** RRR= 13% ARR= 0.1 events/ 100 ppl p= .6447 95% CI = -57-51% NNT= 1000	**CV mortality** RRR= 10% ARR= 0.2 events/ 100 ppl p= .5066 95% CI = -23-34% NNT= 500	RRR= 13% ARR= 0.5 events/ 100 ppl p= .1649 95% CI = -6-29% NNT= 200	**Total coronary events** RRR= 29% ARR= 1.4 events/ 100 ppl p= .0005 95% CI =14-41% NNT= 96

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Studies in outpatients			
ALLHAT Officers and Coordinators 2002 Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)	**6-Year Rate** **Fatal & nonfatal** RRR= 9% ARR= 0.5 events/ 100 ppl p= .31 95% CI = -9-25% NNT= 200	NR	
Sever 2003 Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm (ASCOT-LLA) UK, Sweden, Norway, Denmark, Finland, Ireland	**Fatal & nonfatal** RRR= 27% ARR= 0.7 events/ 100 ppl p= .0236 95% CI = 4-44% NNT= 142	**Total CV events & procedures** RRR= 21% ARR= 2.0 events/ 100 ppl p= .0005 95% CI =10-31% NNT= 50	

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline
Studies in outpatients						
Holdaas et al. 2003 (ALERT)	Randomized, double-blind, intention-to-treat analysis for all randomized	2100 patients of renal or renal/pancreas transplant 6+ months prior w/ stable graft function, total serum cholesterol 4.0-9.0 mmol/L (calculated 154-347 mg/dl). Exclude those using a statin, with familial hypercholesterolemia, life expectancy <1 year, and acute rejection episode in previous 3 months.	Fluvastatin 40 mg daily vs. placebo; dose doubled after 2+ years.	5.1 years	4.1 mmol/L (calculated 158 mg/dl)	32% in 5.1 years mean follow-up
Asselbergs et al 2004 Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT)	Randomized, active and placebo-controlled, double-blind, single center	864 residents of one city in the Netherlands, ages 28-75 with persistent microalbuminuria, blood pressure <160/100 mm Hg, and no use of antihypertensive medicaiton, and a total cholesterol level <309 mg/dL, or <193 mg/dL in case of previous myocardial infarction, and no use of lipid-lowering medication.	Pravastatin 40 mg or matching placebo and fosinopril 20 mg or matching placebo.	46 $\pm$ 7 months	174 $\pm$ 37	pravastatin vs placebo 3 months: 30% vs % 1 year: 25% vs 3% 2 years: 25% vs 3% 3 years: 25% vs 0% 4 years: 25% vs 3%

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death	All Cause Mortality	Major Coronary Events
Studies in outpatients					
Holdaas et al. 2003 (ALERT)	Total events RRR = 17%, p=.139 NS Definite nonfatal MI RRR= 32%, p= .05 ARR= 1.9 events/100 ppl 95% CI= 0-60% NNT= 47		**Cardiac death** RRR= 38%, p= .031 ARR= 1.7 events/100 ppl 95% CI= 4-60% NTT= 41		
Asselbergs et al 2004 Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT)	1.8% vs 3.5% (NS)	Not reported	0.9% vs 0.9% (NS)	Not reported	Not reported

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Studies in outpatients			
Holdaas et al. 2003 (ALERT)		CABG or PCI RRR= 11%, p= NS	Rate of total adverse events similar for fluvastatin 40 mg, 80 mg, and placebo groups. Over study period, 14% of placebo group admitted to other lipid-lowering treatments, mostly statins, along with 7% of fluvastatin group. Other concurrent medications similar in both groups: ciclosporin (all), steroids (81%), beta blockers and calcium antagonists (95%), and aspirin (34%)
Asselbergs et al 2004 Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT)	1.6% vs 0.9% (NS)	Not reported	

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline
Studies in inpatients with unstable angina or acute coronary syndrome						
Cannon et al 2004 PROVE-IT	Randomized, head-to-head, double-blind	4162 men and women age 18 or older who had been hospitalized for an acute coronary syndrome (MI or high-risk angina) in the preceding 10 days, but stable. Total cholesterol level 240 mg/dL or less. If receiving long-term lipid-lowering therapy, total cholesterol level 200 mg/dL or less.	pravastatin 40 mg vs atorvastatin 80 mg.	2 years (range 18 to 36 months)	Median (interquartile range): prava 106 (87-127) mg/dL; atorva 106 (89-128) mg/dL	2985 patients who had not previously received statin therapy: 22% prava vs 51% atorva at 30 days (p<0.001)
de Lemos 2004 A to Z Trial (Phase Z)	Randomized, double-blind, placebo-controlled, multicenter	4497 men and women ages 21-80 with either non-ST-elevation acute coronary syndrome or ST elevation MI with a total cholesterol level of 250 mg or lower.	Early intensive statin treatment (simvastatin 40 mg for 30 days and then simvastatin 80 mg there after) vs less aggressive strategy (placebo for 4 months and then simvastatin 20 mg thereafter)	Median 721 days (range 6 months to 24 months)	Median 112 (25th-75th percentiles 94-131)	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)
Thompson et al 2004 PACT	Randomized, double-blind, placebo-controlled, multicenter	3408 men and women age 18 to 85 within 24 hours of onset of acute MI or unstable angina.	pravastatin 40 mg (20 mg for those subjects enrolled in the early stages of the study) for 4 weeks.	4 weeks	Not reported. Mean total cholesterol 219	Not reported

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death	All Cause Mortality	Major Coronary Events
Studies in inpatients with unstable angina or acute coronary syndrome					
Cannon et al 2004 PROVE-IT	death or MI: 18% reduction (p=0.06)	recurrent unstable angina: 29% reduction in atorva group (p=0.02)	prava vs atorva 22.3% vs 19.7% (p=0.029)	28% reduction in atorva group (p=0.07)	infrequent, but rates did not differ significantly between groups
de Lemos 2004 A to Z Trial (Phase Z)	Hazard ratio 0.96 (95% CI 0.61, 1.02)	Not reported	Hazard ratio 0.75 (95% CI 0.57, 1.00)	Hazard ratio 0.79 (0.61, 1.02)	**Primary end point (cardiovascular death, myocardial infarction, readmission for acute coronary syndrome, or stroke):** Hazard ratio 0.89 (95% CI 0.76, 1.04; p=0.14)
Thompson et al 2004 PACT	nonfatal only: 0.8% vs 0.9% (NS) fatal and nonfatal: 3.8% vs 3.7% (NS)	new unstable angina: 2.4% vs 2.2% (NS) recurrent unstable angina: 4.7% vs 5.2% (NS)	Fatal MI: 0.8% vs 0.9% (NS) Death excluding fatal MI: 0.6% vs 1.3% (NS)	1.4% vs 2.2% (NS)	11.6% vs 12.4% (NS)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Studies in inpatients with unstable angina or acute coronary syndrome			
Cannon et al 2004 PROVE-IT	14% reduction in atorva group (p=0.04)		
de Lemos 2004 A to Z Trial (Phase Z)	Hazard ratio 0.79 (95% CI 0.48, 1.30)	Hazard ratio 0.93 (95% CI 0.73, 1.20)	
Thompson et al 2004 PACT	NR	NR	

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline
Studies in inpatients with unstable angina or acute coronary syndrome						
Arntz et.al 2000 L-CAD	Randomized, double-blind, vs standard care, intention-to-treat	126 men and women with total cholesterol >200 to <400 mg/dl and LDL cholesterol >130 to <300 mg/dl with an acute MI and/or who underwent emergency PTCA due to severe or unstable angina pectoris.	pravastatin 20 to 40 mg vs usual care; started on average 6 days after MI or PTCA	2 years	prava vs usual care 176 mg/dL (131-240) vs 172 mg/dL (132-239)	prava vs usual care 28% vs no change
Liem et al 2002 FLORIDA	Randomized, double-blind, placebo-controlled,	540 men and women with an MI and total cholesterol taken at admission or within 24 hours after onset of symptoms was 6.5mmol/L or higher; eligibility also required one of the following: new or markedly increased chest pain lasting longer than 30 minutes, or a new pathological Q wave.	fluvastatin 80 mg	1 year	135 mg/dl vs 139 mg/dl	fluva vs placebo: 21% decrease vs 9% increase
Schwartz et al. 2001 MIRACL	Randomized, double-blind, placebo-controlled	Men and women age 18 or older with unstable anginal or non-Q-wave MI.	atorvastatin 80 mg	16 weeks	124 mg/dL	atorva vs placebo: 40% decrease vs 12% increase (adjusted mean)
Den Hartog et al. 2001 (Pilot Study)	Pilot study; randomized, double-blind, placebo controlled.	99 men and women with acute MI or unstable angina who were hospitalized for less than 48 hours.	pravastatin 40 mg	3 months	4.51 mmol/dL	25%

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death	All Cause Mortality	Major Coronary Events
Studies in inpatients with unstable angina or acute coronary syndrome					
Arntz et.al 2000 L-CAD	1 in usual care group.			2 deaths in each group.	1 ischemic stroke in each group
Liem et al 2002 FLORIDA				2.6% vs 4.0% (p not reported, NS?)	
Schwartz et al. 2001 MIRACL	No significant differences			No significant differences	
Den Hartog et al. 2001 (Pilot Study)	2/50 vs 1/49 (NS)	24/50 vs 21/49 (NS)	2/50 vs 2/49		

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Studies in inpatients with unstable angina or acute coronary syndrome			
Arntz et.al 2000 L-CAD	11/70 prava vs 24/56 usual care (15.7% vs 42.9%)		
Liem et al 2002 FLORIDA			
Schwartz et al. 2001 MIRACL			
Den Hartog et al. 2001 (Pilot Study)	11/50 vs 9/49 (NS)		

Evidence Table 3. Internal validity

Study or Author Year	Randomly assigned?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?	Patient unaware of treatment?
Studies from Evidence Table 1							
Davidson 1997	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
Bertolini 1997	Yes	Not reported	Yes, not much detail	Yes	Yes	Yes	Yes
Assman 1999	Yes	Not reported	Yes	Yes	No details given	No details given	No details given
Dart 1997	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
Marz 1999	Yes	Not reported	Yes	Yes	Yes-serious adverse effects	No	No
Van Dam 2000	Yes-computer lists (adequate)	Not reported	No-patient risk factors Yes-lipoprotein levels	Yes	Yes	Yes	No
Farnier 2000	Yes	Not reported	Yes	Yes	Yes	No	No
Recto 2000	Yes	Not reported	Yes	Yes	No	No	No

Evidence Table 3. Internal validity

Study or Author Year	Intention-to-treat analysis?	Maintained comparable groups?	Reported attrition, crossovers, adherence, and contamination?	Different or overall high loss to follow-up?	Score (good/ fair/ poor)
Studies from Evidence Table 1					
Davidson 1997	Unsure	Yes	Attrition-yes, crossovers-no, adherence-yes, contamination-no	No	Fair-LDL lowering Poor-safety (no details on serious adverse effects and dropouts)
Bertolini 1997	No	Yes	Attrition-reported but no details on reasons for withdrawal. Crossovers-no, adherence to treatment-yes, contamination-no.	No	Fair-LDL lowering Poor-safety (no details on serious adverse effects and dropouts)
Assman 1999	No	Yes	Attrition: yes, but no details on reasons for withdrawal crossovers-no, adherence-yes, and contamination-no	No	Fair-poor-LDL no details on blinding, Poor-safety no details on dose related adverse effects
Dart 1997	No	Yes	Attrition-reported but no details on reasons for withdrawal. Crossovers-no, adherence to treatment-no, contamination-no.	No	Fair-LDL lowering Poor-safety (no details on serious adverse effects, dose and dropouts)
Marz 1999	Do not know	Yes	Attrition-reported, crossovers-no, adherence-no, contamination-no	No	Fair-LDL-lowering, Fair-safety although no details on dose at which adverse effects occurred.
Van Dam 2000	No	Were not the same to start with for risk factors. Lipoprotein levels-yes	Attrition-no reasons for withdrawal given. Crossovers-no, adherence to treatment-yes, contamination-no	No	Fair-poor-LDL single-blinded, not intent to treat, 14% loss to follow up, Poor-safety no details on dose related adverse effects or withdrawals.
Farnier 2000	Yes	Yes	Attrition reported for adverse effects but no details for other reasons for withdrawal. crossovers-no, adherence-yes, contamination-no	No	Fair-poor-LDL lowering, open-label, no details on withdrawal. Poor-safety-minimal details provided on adverse effects for each group.
Recto 2000	No	Yes	Attrition-yes, crossovers-yes, adherence-not reported, contamination-N/A	No	Fair-LDL lowering. Fair-safety included details on withdrawal and adverse effects.

Evidence Table 3. Internal validity

Study or Author Year	Randomly assigned?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?	Patient unaware of treatment?
Insull 2001	Yes	Not reported	Yes	Yes	No	No	No
Illingworth 2001	Yes	Not reported	More women in the atorva group	Yes	Yes	Yes	Yes
Branchi 2001	Yes	Not reported	Not enough detail given	Yes	Not reported	Not reported	Not reported
Karalis 2002	Method not reported	Not reported	some differences- more men in atorva 10mg than simva 20mg, and BP higher in simva vs atorva	Yes	Yes	Not reported	No
Olsson 2003	Method not reported	Not reported	Yes	Yes	Yes	Yes	Yes
Hunninghake 1998	Yes	Not reported	Yes	Yes	No	No	No
Brown 1998	Yes	Not reported	Yes	Yes	No	No	No
Jones 1998	Yes	Not reported	Yes-not much detail. LDL-c slightly lower for 3 of 4 atorva groups.	Yes	No	No	No
Wolffenbuttel 1998	Yes	Not reported	N/A cross-over trial	Yes	No	No	No

Evidence Table 3. Internal validity

Study or Author Year	Intention-to-treat analysis?	Maintained comparable groups?	Reported attrition, crossovers, adherence, and contamination?	Different or overall high loss to follow-up?	Score (good/ fair/ poor)
Insull 2001	No	Yes	Attrition-no, crossovers-no, adherence-no, contamination-no	Do not know	Poor-equivalent doses not compared. Fair-safety although short-term study.
Illingworth 2001	No	More women in the atorva group	Attrition-only reported for adverse effects; Crossovers-no; Adherence-no; Contamination-no	Do not know	Fair-LDL-lowering, Fair-good-safety
Branchi 2001	No	Not enough detail provided-age, etc.	Attrition-yes, crossovers-no, adherence-no, contamination-yes	No	Fair-poor-LDL lowering unsure of blinding, comparable groups, study planned up to 6 months, but high drop out. Poor-safety not enough detail provided.
Karalis 2002	No	Not enough detail provided	No	Not reported	Poor- differences at baseline, randomization and allocation methods not reported, not ITT, withdrawals not clear.
Olsson 2003	No	Yes	Attrition and adherence yes, others no	No	Fair
Hunninghake 1998	No	Yes	Attrition-not reported, crossovers-no, adherence-yes, contamination-no	No	Fair-LDL lowering equivalent doses not compared, treat to target. Safety-poor no details on reasons for withdrawal due to adverse effects or doses.
Brown 1998	No	Yes	Attrition-only reported for adverse effects, crossovers-no, adherence-yes-contamination-no	No	Fair-LDL lowering equivalent doses not compared, treat to target. Safety-poor no details on reasons for withdrawal due to adverse effects or doses.
Jones 1998	No	Yes, but LDL-c lower for 3 of 4 atorva groups	Attrition-yes, crossovers-no, adherence-no, contamination-no	No	Fair-poor LDL lowering. Small sample size in certain groups and LDL-c was lower for 3 out of 4 atorva groups. Fair-poor-safety. Eight patients lost to follow up.
Wolffenbuttel 1998	No	N/A-cross-over	Attrition-yes, crossovers-yes, adherence-no, contamination-no	No	Fair-LDL lowering, Fair-poor safety. Short-term trial using relatively low statin doses.

Evidence Table 3. Internal validity

Study or Author Year	Randomly assigned?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?	Patient unaware of treatment?
Gentile 2000	Yes	Not reported	Yes	Yes	No	No	No
Andrews 2001	Yes	Not reported	Yes	Yes	No	No	No
Nash 1996	Yes	Not reported	No-higher rate of musculo-skeletal conditions in lova group.	Yes	No	No	No
Berger 1996	Method not reported	Not reported	Yes	Yes	No	No	No
Jacotot 1995	Yes	Not reported	Yes, for height, weight, BMI	Yes	Yes	Yes	Yes
Ose 1995	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
Schulte 1996	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
Sigurdsson 1998	Method not reported	Not reported	Simva group slightly older (61.4 years vs 59.3 years, p=0.059)	Yes	Yes	Not reported	Yes
Schaefer 2003	Method not reported	Not reported - open label	Yes	Yes	No - open label	Not reported - open label	No - open label

Evidence Table 3. Internal validity

Study or Author Year	Intention-to-treat analysis?	Maintained comparable groups?	Reported attrition, crossovers, adherence, and contamination?	Different or overall high loss to follow-up?	Score (good/ fair/ poor)
Gentile 2000	No	Yes	Attrition-yes, crossovers-no, adherence-no, contamination-yes	No	Fair-poor LDL lowering. Nonequivalent doses compared. Fair-safety
Andrews 2001	No	Yes	Attrition-yes, crossovers-no, adherence-no, contamination-no	High loss to follow up or drop outs ranging from 14-24% of each group.	Poor-high early withdrawal rate, no reasons noted. LDL-c for Simva not as great as atorva and % meeting LDL-c also lower, possible that doses of simva not titrated properly? For safety - unknown what doses for serious adverse effects.
Nash 1996	Yes	No-higher musculoskeletal conditions in lova.	Attrition-yes, crossovers-no, adherence-yes, contamination-no	No	Fair-LDL lowering. Poor-safety since higher rate of musculo-skeletal conditions in lova group. Also no doses at which adverse effects in fluva group occurred.
Berger 1996	Yes	Yes	No	Not clear	Fair
Jacotot 1995	Yes and on treatment analysis too.	Yes	Attrition-yes, crossovers-no, adherence-no, contamination-no	No	Fair-LDL lowering. Fair-safety although no doses provided at which adverse effects occurred.
Ose 1995	No	Yes	Attrition-yes, crossovers-no, adherence-yes, contamination-no	No	Fair-LDL lowering. Fair-safety.
Schulte 1996	Unable to determine	Yes	Attrition-no, crossovers-no, adherence-yes, contamination-no	Unable to determine the number completing study	Fair-poor-LDL lowering: Drop outs and loss to follow up not given. Fair-poor safety:not sure how many actually dropped out due to adverse effects.(?2)
Sigurdsson 1998	Yes	Yes	Attrition yes, others no.	No	Fair
Schaefer 2003	Yes	Not reported	Attrition - no; crossovers - no; adherence - no; contamination - no.	Not reported	Fair/poor-LDL lowering: No drop-out data nor loss to follow-up data given. Poor - safety: no data given on any adverse effects nor on withdrawals due to adverse effects.

Evidence Table 3. Internal validity

Study or Author Year	Randomly assigned?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?	Patient unaware of treatment?
Chan 2004	Study states "blindly randomized," but no details given.	Study states "blindly randomized," but no details given.	Yes	Yes	Study states "blindly randomized," but no details given.	Study states "blindly randomized," but no details given.	Study states "blindly randomized," but no details given.
Schuster 2004	Yes	Not reported	Yes	Yes	No - open label	Not reported - open label	No - open label
Schwartz 2004	Yes	Not reported	Yes	Yes	Yes	Not reported	Yes
Paragh 2004	Yes, though method not reported	Not reported	Not reported	Yes	No - open label	Not reported - open label	No - open label
Strandberg 2004	Yes	Not reported	Yes	Yes	No - open label	Not reported - open label	No - open label

Evidence Table 3. Internal validity

Study or Author Year	Intention-to-treat analysis?	Maintained comparable groups?	Reported attrition, crossovers, adherence, and contamination?	Different or overall high loss to follow-up?	Score (good/ fair/ poor)
Chan 2004	Not clear	Not reported	Attrition - yes; crossovers - no; adherence - yes; contamination - no.	No (atorv: 5 withdrawals (8.3%) and simva 7 withdrawals (11.7%))	Poor to fair
Schuster 2004	Yes	Not reported	Attrition -yes; crossovers - no; adherence - yes; contamination - no.	No	Fair
Schwartz 2004	Yes	Not reported	Attrition -yes; crossovers - yes; adherence - no; contamination - no.	No	Fair - This study was designed to look at paraoxonase activity. Poor - safety. No specific details about adverse events or withdrawals given.
Paragh 2004	Not clear	N/A - it was a crossover study.	Attrition - no; crossovers - no; adherence - no; contamination - no.	Not reported	Poor to fair. Poor - safety. No specific details about adverse events or withdrawals given.
Strandberg 2004	Yes	Not reported	Attrition - yes; crossovers - no; adherence - no; contamination - no.	No.	Fair

Evidence Table 3. Internal validity

Study or Author Year	Randomly assigned?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?	Patient unaware of treatment?
Studies from Evidence Table 2							
AFCAPS 1998	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
CARDS Colhoun 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PREVEND IT Asselbergs 2004	Yes	Not reported	Appear similar	Yes	Yes	No details given	Yes
A to Z de Lemos 2004	Yes	Yes	More simvastatin patients had prior MI (18% vs 16%, p=0.05), otherwise similar	Yes	Yes	No details given	Yes
PACT Thompson 2004	Method not reported	Not reported	Higher total cholesterol in placebo group, more placebo patients on HRT, and more prava patients on anticoagulants.	Yes	Yes	Yes	Yes
WOSCOPS 1995	Yes	Yes	Yes	Yes	Yes	Yes	Yes
HPS	NR	Adequate; centralized	Unclear; "good balance" indicated; data NR	Yes	Yes	Yes	Yes

Evidence Table 3. Internal validity

Study or Author Year	Intention-to-treat analysis?	Maintained comparable groups?	Reported attrition, crossovers, adherence, and contamination?	Different or overall high loss to follow-up?	Score (good/ fair/ poor)
Studies from Evidence Table 2					
AFCAPS 1998	Yes	Yes	Attrition-yes, crossovers-no actual numbers provided, adherence-yes and contamination-no actual numbers provided.	No	Good
CARDS Colhoun 2004	4 patients not included, but able to calculate	Yes	attrition, adherence yes, others no.	No	Good
PREVEND IT Asselbergs 2004	Yes	Yes	Yes	No	Fair
A to Z de Lemos 2004	Yes	Yes	Attrition yes,	No	Fair
PACT Thompson 2004	2.5% lost to followup not included in analysis, but possible to calculate ITT results	Unable to assess	Attrition, adherence yes, others no.	No, 2.5% overall, 45 in each group.	Fair-Poor
WOSCOPS 1995	Both intention to treat and on treatment analysis	Yes	Attrition-yes, crossovers-no, adherence-no details and contamination-no	No	Good
HPS	Yes	NR	Attrition=13.9%; Crossovers NR; Adherence (>/= 80%)=82%; Contamination=4002(19.5%) taking non-study statin	No	Good

Evidence Table 3. Internal validity

Study or Author Year	Randomly assigned?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?	Patient unaware of treatment?
Holdaas	NR	Adequate; serially-numbered identical medication packs	Yes	Yes	Yes	Yes	Yes
ALLHAT-LLC *(open trial)*	Adequate; computer-generated scheme	adequate; centralized	Yes	Yes	No	No	No
ASCOT	NR	NR	Yes	Yes	Yes	Yes	Yes
LIPID 1998	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
CARE 1996	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4S 1994	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PROSPER	Adequate; computer-generated scheme	Adequate; centralized	Yes	Yes	Yes	Yes	Yes
Arntz et al 2000 L-CAD	Method not reported	Not reported	Yes	Yes	Yes	Yes	Yes

Evidence Table 3. Internal validity

Study or Author Year	Intention-to-treat analysis?	Maintained comparable groups?	Reported attrition, crossovers, adherence, and contamination?	Different or overall high loss to follow-up?	Score (good/ fair/ poor)
Holdaas	Yes	NR	Attrition=314 (14.9%); others NR	No	Good
ALLHAT-LLC *(open trial)*	Yes	NR	Attrition unclear; Crossover(years 2/4/6): 8.2%/17.1%/26.1%; Adherence(years 2/4/6): 87%/80%/77%; Contamination NR	No	Fair-Good
ASCOT	Yes	NR	Attrition unclear; others NR	No	Fair-Good
LIPID 1998	Yes	Yes	Attrition: yes, crossovers-no, adherence-no, and contamination-yes	No	Good
CARE 1996	Yes	Yes	Attrition: yes, crossovers-no, adherence-no, and contamination-yes	No	Good
4S 1994	Yes	Yes	Attrition-yes, crossovers-no, adherence-reported as good with no details provided, and contamination-no.	No	Good
PROSPER	Yes	NR	Attrition=1449(24.9%); Adherence (average)=94%; others NR	NR	Good
Arntz et al 2000 L-CAD	Yes- able to calculate		Attrition yes, others no	Yes: 9 patients in control group withdrew consent after learning treatment assignment.	Fair

Evidence Table 3. Internal validity

Study or Author Year	Randomly assigned?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?	Patient unaware of treatment?
Cannon et al 2004 PROVE-IT	Method not reported	Not reported	History of peripheral arterial disease more common in prava group, uneven treatment group sizes.	Yes	Yes	Not reported	Yes
Liem et al 2002 FLORIDA	Method not reported	Not reported	Yes	Yes	States "double blind," but no details.	Not reported	States "double blind," but no details.
Schwartz et al 2001 MIRACL	Method not reported	Not reported	Yes	Yes	Yes	Yes	Yes
Den Hartog (Pilot Study)	Yes	Not reported	Some differences	Yes	Yes	Not reported	Yes
Studies from Evidence Table 6: Post-revascularization							
LIPS	NR	Adequate; serially-numbered identical medication packs	No, more fluva patients with diabetes mellitus (14.2% vs 9.8%; p<0.05)	Yes	Yes	Yes	Yes

Evidence Table 3. Internal validity

Study or Author Year	Intention-to-treat analysis?	Maintained comparable groups?	Reported attrition, crossovers, adherence, and contamination?	Different or overall high loss to follow-up?	Score (good/ fair/ poor)
Cannon et al 2004 PROVE-IT	Not clear	Yes	Attrition yes, others no	No.	Fair
Liem et al 2002 FLORIDA	Yes	Yes	Attrition and adherence yes, crossover and contamination no	No	Fair
Schwartz et al 2001 MIRACL	Yes	Yes	Attrition yes, others no	No	Fair
Den Hartog (Pilot Study)	Yes	No	Attrition yes, others no	No, 2 placebo vs 0 prava lost to followup. High discontinuation rate (22%) and more placebo patients discontinued overall (26.5% vs 16%)	Poor
Studies from Evidence Table 6: Post-revascularization					
LIPS	Yes	NR	Attrition= 124(7.4%); others NR	No	Fair

Evidence Table 4. External validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
Studies from Evidence Table 1			
Davidson 1997	Men and women 18-80 years with elevated cholesterol.	Not reported	Impaired hepatic or renal function, Type I DM, uncontrolled DM, any unstable medical condition, noncompliant, enrolled in another trial, taking a drug with a potential for interaction. No numbers provided for exclusion.
Bertolini 1997	Men and women 18-80 years with elevated cholesterol.	Not reported	Pregnant or breastfeeding women, uncontrolled hypothyroidism, hypertension, DM, or other endocrine disorder, impaired hepatic or renal function, more than 14 alcoholic drinks per week, taking a drug with the potential for interaction with statins. No numbers provided for exclusion.
Assman 1999	Men and women 18-80 years with elevated cholesterol.	Not reported	Pregnant or breastfeeding women, BMI >32, impaired hepatic function, CK elevation, more than 14 alcoholic drinks per week, s/p MI, PTCA, CABG within the last 3 months or severe or unstable angina, uncontrolled hypertension. No numbers provided for exclusion.
Dart 1997	Men and women 18-80 years with elevated cholesterol.	Not reported	Pregnant or breastfeeding women, uncontrolled hypothyroidism, hypertension, DM, or other endocrine disorder, impaired hepatic or renal function, BMI>32, more than 14 alcoholic drinks per week, taking a drug with the potential for interaction with statins. No numbers provided for exclusion
Marz 1999	Men and women 35-75 years with CHD and elevated LDL-c	Not reported	4,097 patients were screened. After the 6 week diet phase, 2,856 patients met the inclusion criteria. Pregnant or breastfeeding women, uncontrolled hypothyroidism, hypertension, DM, or other endocrine disorder, impaired hepatic or renal function, BMI>32, s/p MI, PTCA, CABG, CVA within the last 3 months, moderate to severe CHF, severe hyperlipidemia or hypertriglyceridemia, secondary hyperlipidemia, more than 14 alcoholic drinks per week, taking a drug with the potential for interaction with statins. Other drugs that were not allowed included NSAIDs and digitalis. No numbers provided for exclusion
Van Dam 2000	Men or women 18-80 years currently treated with simvastatin 20 or 40 mg qd and LDL-c levels of > 100 mg/dl.	Not reported	Pregnant or breastfeeding women, BMI >32, impaired hepatic function, CK elevation, more than 4 alcoholic drinks per day, s/p MI, PTCA, CABG, CVA within the last 3 months, secondary hyperlipidemia, taking a drug with the potential for interaction with statins. No numbers provided for exclusion.
Farnier 2000	Men or women 18-70 years with elevated LDL-c	Not reported	331 patients entered prerandomization dietary placebo run-in phase, and 272 were randomized. Pregnant or breastfeeding women, BMI >32, impaired hepatic function, CK elevation, more than 4 alcoholic drinks per day, s/p MI, PTCA, CABG, CVA within the last 3 months, secondary hyperlipidemia, taking a drug with the potential for interaction with statins. No numbers provided for exclusion at each step.

Evidence Table 4. External validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup
Studies from Evidence Table 1			
Davidson 1997	Not reported, although Parke-Davis Pharmaceutical is listed as a contributor.	Yes	52 weeks. At 16 weeks, 16 (12%) from placebo, 50 (7%) from atorvastatin, and 15 (8%) from lovastatin had withdrawn. At 52 weeks, 130 patients had withdrawn. No details on number from each group or reasons for withdrawal were given.
Bertolini 1997	Not reported, although 2 of the authors are employed by Parke-Davis Pharmaceuticals	Yes	52 weeks. Withdrawal for adverse effects was reported 19% vs. 26% in the atorvastatin vs. pravastatin group (p>0.05). No details on number dropping out of the study for other reasons.
Assman 1999	Not reported, although 2 of the authors are employed by Parke-Davis Pharmaceuticals	Yes	52 weeks. Withdrawal for adverse effects was reported, but no information on dose or type of AE. No details on number dropping out of the study for other reasons.
Dart 1997	Study supported by Parke-Davis Pharmaceutical Research as well as listed as a contributor.	Yes	52 weeks. Withdrawal for adverse effects was reported , but no information on dose or type of AE. No details on number dropping out of the study for other reasons.
Marz 1999	Study sponsored by Parke-Davis and Pfizer. Employees of these companies were thanked for their continuous scientific support and provision of logistics.	Yes	14 weeks. Withdrawal from study was detailed (e.g. AE or other) and was 9% in both groups.
Van Dam 2000	Study financially supported by Parke-Davis and Pfizer.	Yes	8 weeks. 14% of the randomized patients were not available for follow up. No reasons were given.
Farnier 2000	Study financially supported by Parke-Davis and Pfizer.	Yes	12 weeks. 2 patients withdrew due to AE, no other details given on dropouts.

Evidence Table 4. External validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
Recto 2000	Men or women 21-70 years with an LDL >130 mg/dl	Not reported	
Insull 2001	Men or women 18-80 years with elevated LDL-c	Not reported	Unknown number of patients beginning 8-week dietary phase. 1424 patients randomized and 1378 patients included in efficacy analysis. Pregnant or breastfeeding women, BMI >32, impaired hepatic function, CK elevation, s/p MI, PTCA, CABG, CVA or unstable angina within the last 1 month, secondary hyperlipidemia, significant medical or psychological abnormality, participation in another study, taking a drug with the potential for interaction with statins. No numbers provided for exclusion at each step.
Illingworth 2001	Men or women 21-70 years with an elevated LDL-c	Not reported	826 patients randomized. Efficacy analysis performed on 813 patients. Patients receiving immunosuppressants, azole antifungals, or anticoagulants were excluded. No numbers provided for exclusion at each step.
Branchi 2001	Men or women with elevated cholesterol	Not reported	200 patients randomized, analysis performed on 199 patients. Patients with hepatic or renal impairment, uncontrolled Type 2 DM, Type 1 DM were excluded. No numbers provided for exclusion at each step.
Hunninghake 1998	Men or women 18-80 years at risk for CHD and elevated cholesterol.	Not reported	344 patients randomized, efficacy analysis performed on 337 patients. Pregnancy or breast-feeding, secondary hyperlipoproteinemia, uncontrolled endocrine disorders, hepatic or renal impairment, MI, CABG, PTCA, unstable angina 1 month prior to screening, participation in another study, uncontrolled type 2 DM, type 1 DM, taking a drug with the potential for interaction with statins. No numbers provided for exclusion at each step.
Brown 1998	Men or women 18-80 years with CHD and elevated LDL-c	Not reported	318 randomized, efficacy analysis performed on 308 patients. Pregnancy or breast-feeding, secondary hyperlipoproteinemia, uncontrolled endocrine disorders, hepatic or renal impairment, MI, CABG, PTCA, unstable angina 1 month prior to screening, participation in another study, uncontrolled type 2 DM, type 1 DM, taking a drug with the potential for interaction with statins. No numbers provided for exclusion at each step.
Jones 1998	Men or women 18-80 years with elevated cholesterol	Not reported	534 randomized, efficacy analysis performed on 522 patients. Secondary hyperlipidemia, type 1 or uncontrolled type 2 DM, hepatic or renal impairment, uncontrolled HTN, BMI >32 kg/m, MI, CABG, PTCA unstable angina within 3 months of study, hypersensitivity to statins, taking a drug with the potential for interaction with statins. No numbers provided for exclusion at each step.
Wolffenbuttel 1998	Men and women 18-70 years with an LDL-c between 160 and 240 mg/dl.	Not reported	78 patients randomized and included in the intention to treat analysis. Untreated HTN, BMI >30 kg/m, DM or other metabolic or endocrine disease, renal or hepatic impairment. No numbers provided for exclusion at each step.

Evidence Table 4. External validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup
Recto 2000	Study financially supported by Merck. Simva and placebo were supplied by Merck.	Yes	6 weeks each treatment. 11 patients withdrew from the study although it was not reported at what time period during the study they withdrew.
Insull 2001	Study supported by Parke-Davis.	Yes	8 weeks dietary run-in. 1424 patients randomized but only 1378 were included in the efficacy analysis at 6 weeks.
Illingworth 2001	5 of the authors were employed by Merck. Merck employees were thanked for their assistance in preparation of the manuscript.	Yes	4-week dietary run-in. 826 patients randomized, 813 analyzed at 36 weeks.
Branchi 2001	Not reported	Yes	8-week dietary run-in. 200 patients randomized, 1 lost to follow up
Hunninghake 1998	Funded by Parke-Davis. One author was employed by Parke-Davis	Yes	Optional 8-week dietary phase, 4-week dietary run-in phase 344 randomized, but 337 included in efficacy analysis.
Brown 1998	Funded by Parke-Davis. One author was employed by Parke-Davis	Yes	Optional 8-week dietary phase, 4-week dietary run-in phase 318 randomized, but 308 included in efficacy analysis.
Jones 1998	Funded by Parke-Davis. Parke-Davis employees did participate in some portion of the study.	Yes	6-week dietary run-in phase 534 randomized, but 522 included in efficacy analysis.
Wolffenbuttel 1998	Funded by Parke-Davis. One author was employed by Parke-Davis	Yes	4-week dietary and placebo run-in. 78 patients were randomized, 78 were analyzed after both treatments

Evidence Table 4. External validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
Gentile 2000	Men and women 50-65 years with type 2 DM and elevated cholesterol.	Not reported	412 patients randomized but only409 patients included in the efficacy analysis. Secondary causes of hyperlipidemia, type 1 DM, elevated CK, BMI >32 kg/m, uncontrolled HTN, MI, CABG, PTCA or established CAD, sensitivity to statins, or taking drugs with the potential for interaction with statins.
Andrews 2001	Men and women 18-80 years with or without CHD and elevated cholesterol	Not reported	7,542 patients screened and 3,916 patients randomized to study. Only 3,262 patients completed study. Patients with active liver disease, hepatic impairment, uncontrolled type 1 or 2 DM, or serum creatinine >2 mg/dl.
Nash 1996	Men and women controlled on lovastatin 20 mg qd.	Not reported	363 patients screened, 137 patients randomized. (Were large numbers of patients not randomized because their LDL-c upon washout was <160 mg/dl?) Homozygous familial hypercholesterolemia, MI, unstable angina, major surgery or PTCA 6 months prior to study, secondary causes of hyperlipidemia (alcoholism, DM, thyroid disease), pregnant or lactating women and those women who were unwilling to use alternate forms of birth control other than the pill.
Jacotot 1995	Men and women 18-75 years with hypercholesterolemia.	Not reported	134 randomized. Analysis included both on treatment and intention to treat population. Severe forms of hypercholesterolemia and those with impaired renal function were excluded. No details provided on numbers and reasons for excluding patients.
Ose 1995	Men and women 70 years or less with hypercholesterolemia	Not reported	432 patients randomized. Analysis for LDL-c reduction did not include 17 patients due to missing or inappropriately done labs. Older than 70, secondary hypercholesterolemia, unstable angina, MI or CABG within 2 months, trigs >350 mg/dl, women not using birth control, history of substance abuse, hepatic or renal impairment, baseline elevations in CK, uncontrolled DM.
Schulte 1996	Men and women 26-74 years with LDL-c>185 mg/dl and trigs <300 mg/dl.	Not reported	120 patients randomized, unclear number completing study. Active liver or gallbladder disease, elevated aminotransferases or other severe disabling disease, women with childbearing potential, drug or alcohol abuse problems, musculoskeletal diseases, or taking drugs with the potential for interaction with statins. No details provided on numbers and reasons for excluding patients.

Evidence Table 4. External validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup
Gentile 2000	MURST funded 60% of study. Otherwise not reported.	Yes	6-week dietary run-in phase 412 randomized, but 409 included in efficacy analysis.
Andrews 2001	Study was funded by Pfizer. One employee of Pfizer was acknowledged for their analysis and interpretation of the data.	Yes	3916 randomized to study, 3262 completed study. Data from 3757 was analyzed.
Nash 1996	Study funded by Sandoz Pharmaceuticals	Yes	6-week dietary/placebo washout period, 137 patients randomized and completed the study. 8 week study.
Jacotot 1995	Sandoz funded and participated in trial.	Yes	134 randomized. 16 weeks. 11 patients withdrew during trial
Ose 1995	Funded by Merck	Yes	432 patients randomized and followed for 6 weeks.
Schulte 1996	Funded by Astra	Yes	120 patients randomized, unknown completing 10 week study.

Evidence Table 4. External validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
Strandberg 2004	911 men and women >=18 years at high risk for CHD and with primary hypercholesterolemia. Included patients on a starting dose of a lipid-lowering therapy (ie, atorva 10 mg/d, fluva 20 mg/d, prava 20 mg/d, or simva 20 mg/d) who had not yet reached the 1998 JTF goal for LDL-c. Additional inclusion criteria: risk for CHD >20%/10 years in asymptomatic individuals with type 2 diabetes or a history of CHD or other established atherosclerotic disease; or an LDL-c level >135 mg/dL in statin-naive patients or >120 mg/dL in patients using a starting dose of another lipid-lowering drug.	Number recruited not reported; 1024 patients randomized to treatment; 911 patients were in the ITT analysis.	A history of serious adverse events or hypersensitivity to an hMG-CoA reductase inhibitor other than the study drugs; active hepatic disease; homozygous or heterozygous familial hypercholesterolemia (FH); unstable angina; elevated serum creatinine concentration (>220 micromol/L [2.5 mg/dL]) or treatment with a disallowed drug, such as those with known interactions with statins (ie, cyclosporine).
Chan 2004	120 Men and women aged 20-75 years with Type 2 diabetes and with mixed hyperlipidemia (serum trig = 2.3-4.5 mmol/L and LDL-c >= 3.4 mmol/L).	NR/120 randomized	Not reported
Paragh 2004	49 men and women with Frederickson IIa and Ibis hyperlipoproteinaemia with serum trig <4.5 mmol/L and LDL-c >4.1mmol/L	Not reported/49 entered study	Patients with diabetes mellitus, previous myocardial infarction, coronary heart disease, liver disease, renal dysfunction (serum creatinine >130 micromol/L) alcoholism, smoking habit, drug addiction, pregnancy, lactation, malignant disease, or had previously received lipid reducing therapy.

Evidence Table 4. External validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup
Strandberg 2004	Supported by grants from AstraZeneca Pharmaceuticals, UK.	Yes	12 week treatment (n=911, ITT) with an optional 36 week follow-up period for select patients from each group (n=387)
Chan 2004	Not reported	Not reported	18 weeks. Withdrawals (atorva n=5 (8.3%) and simva n=7 (11.7%)) reported as due to non-compliance. No data given on specific adverse events or on withdrawals.
Paragh 2004	Funded by grants from ETT and OTKA Hungary	Yes	8 months (3 months of treatment, then a 2 month washout period, and then each group was switched over to the corresponding drug for 3 months). No withdrawals were reported, and the study also stated that there were no serious adverse events.

Evidence Table 4. External validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
Schaefer 2003	Patients with a serum LDL-c of>130 mg/dL while off lipid-lowering medication for >=6 weeks (including anion exchange resins, statins, fibric acid derivatives, fish oil, or niacin-containing products) and with evidence of established CHD (coronary artery bypass grafting, angioplasty, documented myocardial infarction, significant coronary artery stenosis as assessed by angiography of >50%, or significantly decreased cardiac perfusion based on cardiac imaging, with and without exercise.	NR/ 99 patients randomized + 97 controls without CHD (196 people total enrolled)	Evidence of renal impairment, hyperthyroidism, or liver disfunction based on clinical chemistry testing, or had previous adverse reactions to statins.
Schuster 2004	Patients aged >=18 years with a history of CHD or other established atherosclerotic disease, Type 2 diabetes, or a CHD risk >20% over 10 years, with fasting levels of LDL-c >=115 mg/dL and trigs <400 mg/dL; LDL-c measurements had to be within 15% of each other during the lead-in period.	NR/6508 patients entered dietary phase/3140 randomized	Pregnant and lactating women, women not using reliable contraception, patients with a history of homozygous familial hypercholesterolemia or known type III hyperlipoproteinemia, with active arterial disease (eg, unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, or coronary revascularization procedure within 2 months of screening), uncontrolled hypertension, active liver disease or hepatic dysfunction (hepatic transaminases or bilirubin levels >=1.5 times upper limit of normal [ULN]), unexplained serum creatine kinase elevation >3 times ULN, and serum creatinine >220 micromol/L.
Schwartz 2004	Patients aged >=18 years with type 2 diabetes mellitus or documented atherosclerosis (ie, a history of peripheral vascular disease, coronary artery disease, or cerebrovascular disease). LDL-c levels were >=160 and <250 mg/dL; and trig levels were <= 400 mg/dL.	NR/1233 enrolled in dietary phase/ 383 were randomized.	Pregnant women, patients currently taking concomitant drugs known to affect the lipid profile or to present a potential safety concern, a history of active arterial disease (eg, unstable angina, myocardial infarction, transient ischemic attack, or cerebrovascular accident) or coronary revascularization procedure within 3 months of trial entry, heterozygous or homozygous familial hypercholesterolemia, uncontrolled hypertension, uncontrolled hyperthyroidism, history of malignancy, active liver disease or disfunction indicated by AST or ALT of >= 1.5 times the upper limit of normal (ULN), serum creatine kinase >3 times ULN, serum creatinine >2.5mg/dL, or uncontrolled diabetes (fasting serum glucose >9.99 mmol/L or hemoglobin A1c>9% recorded during the lead-in period).

Evidence Table 4. External validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup
Schaefer 2003	Funded by investigator-initiated research contracts from Parke-Davis/Pfizer and Otsuka America Pharmaceuticals.	Not reported	36 weeks total. Crossover - patients who had received atorv in the first part of the trial were randomized to a different statin, and those who had not been on atorv received in in the second period of testing.
Schuster 2004	Funded by Astra Zeneca, UK. Three authors are employed directly by AstraZeneca, UK.	Not reported	16 weeks. Groups were split at 8 weeks into groups that either stayed on the original drug or went onto a low dose of rosuv.
Schwartz 2004	Supported by AstraZeneca, Delaware. 4 of 7 authors are Astra Zeneca employees.	Not reported	24 weeks. Doses were up-titrated at 12 and 18 weeks if LDL-c remained >50mg/dL.

Evidence Table 4. External validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
Studies from Evidence Table 2			
CARDS Colhoun 2004	2838 men and women with no history of cardiovascular disease, LDL of 4.14 or lower, fasting triglyceride of 6.78 or less, and at least one of the following: retinopathy, albuminuria, current smoking, or hypertension.	4053 screened, 2841 randomized.	Past history of myocardial infarction, angina, coronary vascular surgery, cerebrovascular accident, or severe peripheral vascular disease (defined as warranting surgery).
PREVEND IT Asselbergs 2004	864 residents of one city in the Netherlands, ages 28-75 with persistent microalbuminuria, blood pressure <160/100 mm Hg, and no use of antihypertensive medication, and a total cholesterol level <309 mg/dL, or <193 mg/dL in case of previous myocardial infarction, and no use of lipid-lowering medication.	40,856 screened, 864 randomized	Creatinine clearance <60% of the normal age-adjusted value and use of ACE inhibitors or angiotensin II receptor antagonists.
A to Z de Lemos 2004	4497 men and women ages 21-80 with either non-ST-elevation acute coronary syndrome or ST elevation MI with a total cholesterol level of 250 mg or lower.	Not reported, 4497 randomized	Receiving statin therapy at the time of randomization, if coronary bypass graft surgery was planned, or if percutaneous coronary intervention was planned within the first 2 weeks after enrollment.
PACT Thompson 2004	3408 men and women age 18 to 85 within 24 hours of onset of acute MI or unstable angina.	Not reported, 3408 randomized	Taking statin therapy before their event, participation in any other clinical trial or the taking of an investigational drug within the previous 30 days, planned coronary revascularization or cardiac transplantation, severe renal or hepatic disease or other severe disease, drug- or alcohol-related problems, gastrointestinal disease or a history of gastrointestinal surgery that might affect drug absorption, and known hypersensitivity or previous serious adverse reactions to statin therapy. Women of childbearing potential also excluded.

Evidence Table 4. External validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup
Studies from Evidence Table 2			
CARDS Colhoun 2004	Partly funded by Pfizer	Yes	Median duration of followup 3.9 years. 1421 atorvastatin, 1398 placebo completed followup for morbidity.
PREVEND IT Asselbergs 2004	Dutch Kidney Foundation, Netherlands Heart Foundation, and Bristol-Myers Squibb	Yes	4 years.
A to Z de Lemos 2004	Funded by Merck	Yes	Up to 24 months. Treatment was discontinued prematurely in 34% of simvastatin only group and 32% of those in placebo first group. Median followup period was 721 days; 22 patients in each treatment group were lost to followup.
PACT Thompson 2004	Supported by Bristol-Myers Squibb	Yes	30 days; 85 patients (2%) lost to followup

Evidence Table 4. External validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
AFCAPS/TexCAPS 1998	Healthy men 45-73 years of age and postmenopausal women 55-73 years with average cholesterol levels and no history of a MI.	780,000 patients estimated to be eligible based upon age.	102,800 attended screening, 6,605 patients were randomized. No additional details provided on numbers and reasons for excluding patients.
WOSCOPS 1995	Men, 45-64 years of age with high cholesterol and no history of MI.	160,000 men	160,000 recruited, 81,161 men attended first visit, 20,914 attended the second visit, 13,654 attended the third visit, 6,595 patients were randomized. No additional details provided on numbers and reasons for excluding patients.
HPS	Men and women, aged 40-80 with elevated total cholesterol ($\geq$135 mg/dl) and substantial 5-year risk of death due to history of coronary disease, occlusive disease of noncoronary arteries, diabetes mellitus, or treated hypertension.	20,536	63,603 attended screening in UK, 32,145 started run-in. Ineligible were those already indicated by personal physician for statin therapy, those with chronic liver disease, evidence of abnormal liver, severe renal disease or impaired renal function, inflammatory muscle disease, evidence of muscle problems; concurrent treatment with cyclosporine, fibrates, high-dose niacin; child-bearing potential; severe heart failure; any life-threatening condition other than vascular disease or diabetes, and conditions that might limit long-term compliance. Four-week placebo run-in to measure compliance for long-term study.
Holdaas	Men and women aged 30-75 who received renal or renal/pancreas transplants $\geq$ 6 months prior, with stable graft function. All using cyclosporine. Total cholesterol 4-9 mmol/L (154-347 mg/dl).	2102	Patients (number screened NR) in northern Europe, UK and Canada. Excluded for recent MI, or MI > 6 months prior if total cholesterol not within 4-7 mmol/L; already taking statins; familial hypercholesterolemia, acute rejection episodes in previous 3 months, or predicted life expectancy $\leq$ 1 year.

Evidence Table 4. External validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup
AFCAPS/TexCAPS 1998	Three of the primary authors are employees of Merck and Co. Two other authors are consultants, speakers and/or funded researchers of Merck and Co. Supported by a research grant from Merck and Co. Spectrum Pharmaceuticals assisted in conducting the trial and Merck and Co helped design the trial and manage the data.	yes-primary prevention	5.2 years: 29% of lovastatin recipients withdrew vs. 37% of placebo recipients by the end of the trial. Patients in the placebo group were more likely to be withdrawn as a result of developing CHD or starting lipid-lowering therapy. The discontinuation rates were similar for other reasons in both groups.
WOSCOPS 1995	Role unknown. Supported by a research grant from Bristol-Myers Squibb.	yes-primary prevention	4.9 years: placebo vs prava recipient % withdrawals - cumulative withdrawal rates At 1 year: 14.9 vs 15.5%; year 2: 19.1 vs 19.4%; year 3: 22.5 vs 22.7%; year 4: 25.2 vs 24.7~~%,~~ year 5: 30.8 vs 29.6%.
HPS	UK Medical Research Council; British Heart Foundation; Merck & Co; Roche	Yes	5 years (mean)
Holdaas	Novartis Pharma AG	Yes	5.1 years (mean)

Evidence Table 4. External validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
ALLHAT-LLT	Age ≥55 with stage 1 or 2 hypertension and ≥1 CHD risk factor; for those with no known CHD: LDL-C 120-189 mg/dL; for those with known CHD: LDL-C 100-129 mg/dL; triglyceride lower than 350 mg/dL.	10,355	Open-label lipid-lowering arm of larger trial in USA. Excluded for current lipid-lowering therapy, large doses of niacin, probucol use, known intolerance or contraindications to statins, significant liver or kidney disease, or known secondary cause of hyperlipidemia. Enrollment discouraged for those whose personal physician already recommended cholesterol-lowering medications.
ASCOT	Men and women aged 40-79, no history of CHD, untreated hypertension, total cholesterol concentration <6.5 mmol/L (253 mg/dL), or treated hyper-tension with systolic blood pressure >140 mm Hg, diastolic blood pressure > 90 mm Hg, plus ≥3 CV risk factors	10.305	Lipid-lowering arm of larger trial in UK, Ireland and Scandinavia. Excluded for previous MI, currently treated angina, CV event within 3 months, triglycerides >4.5 mmol/L, heart failure, uncontrolled arrhythmias or any clinically important hematological or biochemical abnormality on routine screening.
LIPID 1998	Men and women ages 31-75 years with a broad range of cholesterol levels and a history of an acute MI or admission for unstable angina in the prior 3 months to 3 years.	An unreported number of patients were invited to participate.	11,106 patients were recruited and registered. Of those, 9,014 patients were randomized. 2,092 (18%) patients were not randomized (1,333 (12%) were ineligible and 759 (6.8%) did not choose to continue with study.
CARE 1996	Men and postmenopausal women 21-75 years of age with average cholesterol levels and a history of an acute MI 3-20 months prior to randomization	An unreported number of patients were invited to participate.	4,159 patients were enrolled and randomized into the study. No additional details provided on numbers and reasons for excluding patients.

Evidence Table 4. External validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup
ALLHAT-LLT	National Heart, Lung, and Blood Institute; Pfizer; AstraZeneca; Bristol-Myers Squibb	Yes	4.8 years (mean)
ASCOT	Pfizer, New York, NY, USA; Servier Research Group; Leo Laboratories	Yes	3.3 years (median)
LIPID 1998	Bristol-Myers Squibb provided study medication but was not involved with the study design, management of the study or analyzing the data.	Yes-providers were instructed to continue with usual care of the patient including open-label lipid lowering medication if indicated.	6.1 years: 19% of pravastatin recipients and 24% of placebo recipients discontinued their study medication. The majority of placebo recipients discontinued their treatment assignments to begin therapy with open-label lipid lowering medication.
CARE 1996	Bristol-Myers Squibb provides study medication, monitors case report forms and supporting documentation to meet regulatory requirements for clinical trials but remains blinded to treatment assignment. They have no access to the data on lipid changes or end points. Bristol-Myers Squibb provided a research grant.	Yes-patients with normal total cholesterol levels.	5 years: 6% of those taking pravastatin discontinued their study medication vs. 14% of those taking placebo. 8% of placebo vs. 2% of pravastatin began taking open-label lipid lowering medication.

Evidence Table 4. External validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
4S 1994	Men and women ages 35-70 years with elevated cholesterol and a history of angina pectoris or an acute MI	An unreported number of patients were invited for a brief overview of the study.	7,027 patients were recruited during the 8 week dietary phase of the study. 4,444 patients were enrolled if they were compliant and met the lipid entry criteria. No additional details provided on numbers and reasons for excluding patients.
PROSPER	Men and women aged 70-82 with pre-existing vascular disease or raised risk due to smoking, hypertension or diabetes.; cholesterol 155-350 mg/dl (4-9 mmol/L), triglycerides <530 mmol/L and good cognitive function	5804	Patients (number screened NR) from Scotland, Ireland, and the Netherlands. Excluded for CV event ≤6 months, any overnight surgery, poor cognitive function, NYHA class III or IV, history of malignancy within 5 years significant arrhythmia, implanted pacemaker, organ transplant recipient, current lipid-lowering treatment or cyclosporin use, current alcohol or drug abuse, any medical condition or travel that prevents optimal participation; abnormal lab findings, including for hemoglobin, thyroid stimulating hormone, glucose, platelet count, white blood cell count, serum creatinine, aminos.
Arntz et al 2000 L-CAD	Inpatients with acute MI or unstable angina	870 screened/735 eligible/135 enrolled	> age 75, diabetes, postcoronary artery bypass graft, known malignant disease, serious kidney or liver dysfunction, or women of child-bearing age not using a reliable form of contraception.
Cannon et al 2004 PROVE-IT	Inpatients with acute MI or unstable angina	# screened, eligible not reported, 4162 enrolled	Coexisting condition that shortened expected survival to less than 2 years, were receiving therapy with any statin at a dose of 80 mg per day at the time of their index event or lipid lowering therapy with fibric acid derivatives or niacin that could not be discontinued before randomization, had received drugs that are strong inhibitors of cytochrome P-450 3A4 whithink the month before randomization or were likely to require such treatment during the study period, had undergone PTCA with the previous 6 months (other than for the qualifying event) or CABG surgery within the previous 2 months or were scheduled to undergo bypass surgery in response to the index event, had factors that might prolong the QT interval, had obstructive hepatobiliary disease or other serious hepatic disease, unexplained elevation in creatinine kinase level that was more than 3 times the ULN and that was not related to MI, or a creatinine level of more than 2.0 mg per deciliter.

Evidence Table 4. External validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup
4S 1994	A member of the project steering committee worked closely with the study monitors at Merck Research Labs in Scandinavia. Merck also provided support with a research grant.	In 1994, there was no evidence to support that lowering LDL-c with a statin lowered the risk of CHD. Yes, although this issue was discussed at length.	5.4 years: 13% of placebo recipients vs. 10% of simvastatin recipients discontinued their medication at the end of the follow up period. Withdrawals prior to trial end were not provided.
PROSPER	Bristol-Myers Squibb, USA	Yes	3.2 years (mean)
Arntz et al 2000 L-CAD	Supported in part by a grant from Bristol-Myers Squibb.	Yes	
Cannon et al 2004 PROVE-IT	Supported by Bristol-Myers Squibb and Sankyo		

Evidence Table 4. External validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
Liem et al 2002 FLORIDA	Inpatients with acute MI or unstable angina	# screened, eligible not reported/ 540 enrolled	< age 18, use of lipid-lowering agents within the previous 3 months, high triglyceride level, known familial dyslipidemia, severe renal failure, known hepatic disease, signs and symptoms of severe failure (NYHA Class IV), a scheduled PTCA or CABG, and comedication that influences the sT-segment (digoxin, quinidine or tricyclic antidepressants).
Schwartz et al 2001 MIRACL	Inpatients with acute MI or unstable angina	# screened, eligible not reported/ 3086 enrolled	Total cholesterol level at screening >270 mg/dL, if coronary revascularization was planned or anticipated at the time of screening, evidence of Q-wave acute MI within the preceding 3 months; CABG within preceding 3 months, PTCA within preceding 6 months, left bundle-branch block or paced ventricular rhythm, severe heart failure (NYHA class IIIb or IV), concurrent treatment with other lipid-regulating agents (except niacin 500 mg/day), vitamin E (except at doses 400 IU/day or less), or drugs associated with rhabdomyolysis in combination with statins, severe anemia, renal failure requiring dialysis, hepatic dysfunction (alanine aminotransferase greater than 2 times ULN), insulin-dependent diabetes, pregnancy or lactation.
Den Hartog (Pilot Study)	Inpatients with acute MI or unstable angina	# screened, eligible not reported, 100 enrolled, 99 randomized.	History of hypersensitivity to statins or formulation components, severe heart failure or cardiomyopathy, significant liver disease, significant gastrointestinal disease or abdominal surgery that might adversely influence drug absorption, substance or alcohol abuse, history or present use of any other lipid-lowering or investigational agent, uncontrolled diabetes, thyroid disease, severe renal impairment, dysproteinemia, and primary muscle disease.
Studies from Evidence Table 6: Post-revascularization			
LIPS	Men and women aged 18-80, with successful revascularization; total cholesterol 3.5-7.0 mmol/L (135-270 mg/dl), triglycerides <400 mg/dl before index procedure.	1677	Patients (number screened NR) from seven countries in Europe, plus UK, Canada, and Brazil. Excluded for sustained systolic blood pressure >180 mm Hg and diastolic blood pressure >100 mm Hg despite therapy; LVEF <30%; history of previous revascularization, severe valvular disease, idiopathic cardiomyopathy or congenital heart disease, severe renal dysfunction, obesity, or malignant or other disease with life expectancy <4 years.

Evidence Table 4. External validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup
Liem et al 2002 FLORIDA	Study financed by an unrestricted grant from AstraZeneca.	Yes	
Schwartz et al 2001 MIRACL	Supported by a grant from Pfizer Inc. Pfizer provided the atorvastatin and matching placebo used.	Yes	
Den Hartog (Pilot Study)	Not reported	Yes	
Studies from Evidence Table 6: Post-revascularization			
LIPS	Novartis Pharma AG	Yes	3.9 years (median)

Evidence Table 5. Atherosclerotic progression trials

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

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

Evidence Table 5. Atherosclerotic progression trials

Author Year Study Name	Primary Endpoint Results (clinical health outcome only)	Clinical Outcomes Measured	Clinical Outcome Results	Comments/Conclusions
Herd et al. 1997 Lipoprotein and Coronary Atherosclerosis Study (LCAS)	N/A	Any cardiac, cerebrovascular, peripheral vascular, and fatal events. Also time to first CABG, PTCA, MI, hospitalization for USA or all-cause mortality	Any cardiac morbid or fatal event occurred in 12.7% of fluvastatin vs. 18.9% placebo. Time to these events showed a trend towards benefit with fluvastatin. Need for revascularization was reduced with fluvastatin 8.9% vs. 13.4% with placebo. No statistical significance provided.	LCAS was not designed with sufficient power to detect differences in clinical events. However, there was a trend observed in favor of fluvastatin. In this study, there were 909 patients screened, but only 429 randomized. The major reasons were for lipid ineligibility and lack of cooperation. There were some minor difference in baseline characteristics between groups. Fair-poor in quality to determine differences in clinical events.
Furberg et al. 1994 Asymptomatic Carotid Artery Progression Study (ACAPS)	N/A	One of the secondary endpoints in the trial was to determine the treatment effects on major atherosclerotic events.	5 (all nonfatal MI) major cardiovascular events occurred in the lovastatin vs. 14 in the lovastatin-placebo groups (4-CHD deaths, 5-strokes, 5-nonfatal MI). p=0.04, ARR=2 events/100 persons, NNT=5. Overall mortality: One death in lovastatin vs. 8 deaths in lovastatin-placebo groups p=0.02, ARR 1.5 events/100 persons, NNT=65. All 6 cardiovascular deaths occurred in lovastatin-placebo groups.	The secondary objective of major atherosclerotic events was significantly reduced in the lovastatin vs. the lovastatin-placebo groups in patients with early carotid atherosclerosis. Fair-good in quality to determinine differences in clinical events.
Waters et al. 1994 The Canadian Coronary Atherosclerosis Intervention Trial (CCAIT)	N/A	Cardiac and noncardiac events, mortality and revascularization were reported in the safety analyis.	Patients had one or more events: lovastatin 14 patients (2 deaths from cardiac causes, 5 MI, 8 USA), placebo 18 patients (1 death from cardiac causes, 6 MI, 13 USA) (NS)	CCAIT was not designed with sufficient power to detect differences in clinical events. However, there was a trend in favor of lovastatin. Mean lovastatin dose=36 mg/d and 69% met NCEP goal). Fair-poor in quality to assess differences in clinical events.

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

Evidence Table 5. Atherosclerotic progression trials

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction from baseline	Primary Endpoint
Blankenhorn et al. 1993 The Monitored Atherosclerosis Regression Study (MARS)	Randomized, double-blind placebo-controlled, not intent to treat analysis	270 men or women younger than 70 years and CHD in 2 coronary segments 50% or >	Lovastatin 80 mg qpm or placebo qpm.	2.2 years	151 mg/dl (3.91 mmol/L)	38%	Per-patient change in percent diameter stenosis between groups as determined by quantitative coronary angiography.
Jukema et al. 1995 The Regression Growth Evaluation Statin Study (REGRESS)	Randomized, double-blind, placebo-controlled, not intent to treat analysis	885 men with clinical evidence of CHD and TC 155-310mg/dl (4-8 mmol/L)	Pravastatin 40 mg qpm or placebo qpm.	2 years	166 mg/dl (4.3 mmol/L)	29%	Change in average mean segment diameter per patient and change in average minimun obstruction diameter per patient determined by coronary arteriography.
Pitt et al. 1995 Pravastatin Limitation of Atherosclerosis in Coronary Arteries (PLAC- I)	Randomized, double-blind, placebo-controlled, not intent to treat analysis	408 men or women with CHD as evidenced by 1 or > stenosis ≥50% or recent MI or PTCA and LDL-c ≥130 mg/dl	Pravastatin 40 mg qpm or placebo qpm.	3 years	164 mg/dl (4.24 mmol/L)	28%	Change in average MLD and change in percent diameter stenosis as determined by coronary arteriography.

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

Evidence Table 5. Atherosclerotic progression trials

Author Year Study Name	Primary Endpoint Results (clinical health outcome only)	Clinical Outcomes Measured	Clinical Outcome Results	Comments/Conclusions
Blankenhorn et al. 1993 The Monitored Atherosclerosis Regression Study (MARS)	N/A	Cardiac and noncardiac events, mortality and coronary revacularization were reported in the safety analysis.	22 lovastatin vs. 31 placebo recipients had one or more of the following: MI, PTCA, CABG, CHD death or hospitalization for USA. (NS) Also no difference in overall death.	MARS was not designed with sufficient power to detect differences in clinical events. However there was a trend in favor of lovastatin. Fair-poor in quality to assess differences in clinical events.
Jukema et al. 1995 The Regression Growth Evaluation Statin Study (REGRESS)	N/A	Prespecified clinical events: Fatal and nonfatal MI, CHD death, nonscheduled PTCA or CABG, Stroke or TIA, and all-cause death.	After 2 years of treatment, 89% of pravastatin vs. 81% of placebo recipients were free from clinical events (p=0.002). Although nonsignificant, there were 12 nonfatal MI in the placebo vs. 7 in the pravastatin groups (ARR 1.2/100 persons, NNT=83). Unscheduled PTCA were reduced significantly in the pravastatin vs. placebo groupg (p=0.004, RRR=57%, ARR 5.8/100 persons, NNT=17).	REGRESS prespecified analysis of clinical events. The only signficant difference in individual events was the reduced need for unscheduled PTCA in the pravastatin vs. placebo groups. This signficant reduction accounted for the overall reduction in new clinical events in the pravastatin group. Difficult to tell if intent to treat population was included in overall clinical event analysis. Fair in quality to assess differences in clinical events.
Pitt et al. 1995 Pravastatin Limitation of Atherosclerosis in Coronary Arteries (PLAC- I)	N/A	Prespecified clinical events: Fatal and nonfatal MI, nonfatal infarction or CHD death, nonfatal infarction or death from any cause and total clinic events (nonfatal MI, nonfatal completed stroke, death PTCA and CABG).	There were 17 MI in placebo vs. 8 in pravastatin ($P \leq 0.05$, RRR=60%, ARR=4.5/100 persons, NNT=22). Although not statistically significant, there were 37 PTCA in placebo vs. 25 in pravastatin. A total of 81 events occurred in placebo vs. 55 in pravastatin (NS).	PLAC-1 prespecified analysis of clinical events. The only significant difference in individual events was a reduction in the rate of MI in the pravastatin vs. placebo groups. All randomized patients were included in the clinical event analysis. Fair in quality to assess differences in clinical events, although a relatively small study population.

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

Evidence Table 5. Atherosclerotic progression trials

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction from baseline	Primary Endpoint
Crouse et al. 1995 Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II)	Randomized, double-blind, placebo-controlled, not intent to treat analysis	Men and women with CHD as evidenced by ≥ stenosis of 1 or > coronary artery or history of MI with elevated LDL-c.	Pravastatin 20 mg qpm or placebo qpm. If LDL-c was not <110 mg/dl pravastatin was increased to 40 mg qpm.	3 years	167.5 mg/dl (4.33 mmol/L)	28%	Change in the mean of the maximal IMT measurement across time determined by B-mode ultrasonography.
Salonen et al. 1995 Kuopio Atherosclerosis Prevention Study (KAPS)	Randomized, double-blind, placebo-controlled, not intent to treat analysis	Men 44-65 years with LDL-c≥4 mmol/L (155 mg/dl). Only 10% had history of MI (Primary prevention study)	Pravastatin 40 mg qpm or placebo qpm.	3 years	185 mg/dl (4.8 mmol/L)	27.40%	Rate of carotid atherosclerotic progression measured as the linear slope over annual ultrasound examinations in the average of maximum carotid IMT of the far wall of up to 4 arterial segments.
Sato et al. 2001	Randomized, unblinded, intent to treat analysis for clinical events	329 men and women <70 years with CHD documented by coronary angiography with normal cholesterol.	Pravastatin 10 mg qpm.	2 years	200 mg/dl (TC) (5.2 mmol/L). LDL-c not provided	8.5% (TC)	Mean segment diameter and minimum obstruction diameter were used to evaluate progression as assessed by coronary angiography.

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

Evidence Table 5. Atherosclerotic progression trials

Author Year Study Name	Primary Endpoint Results (clinical health outcome only)	Clinical Outcomes Measured	Clinical Outcome Results	Comments/Conclusions
Crouse et al. 1995 Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II)	N/A	Prespecified clinical events: Fatal coronary events or nonfatal MI, all-cause mortality, all deaths plus nonfatal MI.	For the combined endpoint of nonfatal MI and any death, there was a significant reduction in the pravastatin vs. placebo group (5 vs. 13, respectively). P=0.04,RRR=61%, ARR=1/100 persons, NNT=10	PLAC-II prespecified analysis of clinical events. The only significant difference was in the combined endpoint of nonfatal MI plus any deaths. Not much detail provided in clinical event section, for observation of other clinical events that were not signficantly reduced with pravastatin. Fair-poor in quality to assess difference in clinical events. Small sample size.
Salonen et al. 1995 Kuopio Atherosclerosis Prevention Study (KAPS)	N/A	Clinical events were reported spontaneously.	The number of cardiovascular events reported during the trial were not statistically significantly different between groups. However, there was a trend to less clinical cardiovascular events in the pravastatin group, primarily MI.	KAPS was not designed to sufficiently determine differences in clinical cardiac events between groups. However, there was a trend in favor of pravastatin. Fair-poor in quality to determine differences in clinical events between groups.
Sato et al. 2001	N/A	Prespecified clinical events: Fatal and nonfatal MI, CHD death, nonscheduled PTCA or CABG, Stroke or TIA, and all-cause death. (using criteria defined by REGRESS)	The incidence of clinical events was lower in the pravastatin groups vs. placebo but this difference was not significant. All-cause mortality was significantly reduced in the pravastatin vs. placebo groups (p=0.043)	Prespecified clinical events. There was a trend to a reduction in clinical cardiac events in the pravastatin vs. placebo groups, however the difference was not significant. There was a significant reduction in overall mortality with pravastatin vs. placebo. Fair in quality to assess difference in clinical events. Small sample size.

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

Evidence Table 5. Atherosclerotic progression trials

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction from baseline	Primary Endpoint
Simoons 1994 Multicentre Anti-Atheroma Study	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	404 men and women 30-67 years with 2 or > coronary artery segments occluded and hyper-cholesterolemia	Simvastatin 20 mg qpm or placebo qpm.	4 years	169 mg/dl (4.38 mmol/L)	31%	Per-patient average of mean lumen diameters of all coronary segments(diffuse atherosclerosis) and the per-patient average of MLD of all segments that were atheromatous at baseline, follow up or both (focal atherosclerosis) as assessed by coronary angiography.
Bestehorn et al. 1997 Multicenter Coronary Intervention Study (CIS)	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	254 men 30-55 years with at least 3 coronary segments with a lumen diameter of $\geq$20% and TC of 207-350 mg/dl.	Simvastatin 20 mg qpm or placebo qpm. Simvastatin was increased to 40 mg qpm if LDL-c>90 mg/dl	2.3 years	164.5 mg/dl (4.25 mmol/L)	35%	Global change score and the per-patient mean change in MLD as assessed by coronary angiography.
Teo et al. 2000 The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT)	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	460 men and women 21 year or >, atherosclerosis in 3 or > coronary segments, TC 160-240 mg/dl	Simvastatin 10 mg qpm or placebo qpm and enalapril 2.5 mg bid or placebo (2X2). Simvastatin could be titrated to 40 mg qpm.	47.8 months	130 mg/dl (3.36 mmol/L)	30.50%	Changes in absolute mean segment lumen diameter, absolute minimum segment lumen diameter, and maximum percent lumen diameter stenosis.

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Evidence Table 5. Atherosclerotic progression trials

Author Year Study Name	Primary Endpoint Results (clinical health outcome only)	Clinical Outcomes Measured	Clinical Outcome Results	Comments/Conclusions
MAAS Investigators 1994 Multicentre Anti-Atheroma Study	N/A	Clinical events were reported spontaneously.	After 4 years, there was no difference in clinical events between groups. There were a greater number of MI in the simvastatin vs placebo groups. There were more revascularizations in the placebo vs. simvastatin groups. Neither of these were statistically different. Overall, there were 40 cardiac events in the simvastatin vs. 51 in the placebo groups (NS).	There were no stastical differences in clinical events in the simvastain vs. placebo groups. Fair to poor in quality to assess differences in clinical event due to duration of trial, however was a relatively small sample size.
Bestehorn et al. 1997 Multicenter Coronary Intervention Study (CIS)	N/A	Clinical events were reported spontaneously.	There were no significant differences in clinical events with simvastatin vs. placebo. Overall, there were 15 events in the simvastatin and 19 in the placebo groups.	There were no stastical differences in clinical events in the simvastain vs. placebo groups. Fair to poor in quality to assess differences in clinical event due to duration of trial, however was a relatively small sample size.
Teo et al. 2000 The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT)	N/A	Prespecified clinical events: death, MI, stroke, hospitalization for angina, revascularization and cancer.	The only signficant difference in clinical events between simvastatin and placebo was a reduction in the number of revascularizations (6 vs. 12%, p=0.020and angioplasties (3 vs. 9% p=0.02).	There was a significant reduction in revascularization, specifically angioplasty in the simvastatin vs. placebo. No differences were noted in any other clinical events. Fair in quality to assess diffferences in clinical events since clinical events were prespecified.

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

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction	Primary Endpoint
Serruys PW. et al. 1999 Fluvastatin Angiographic Restenosis Trial (FLARE)	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	1054 men or women with symptomatic or ischaemia producing coronary lesions amenable to angioplasty and an LDL-c <230 mg/dl (6 mmol/L)	Fluvastatin 40 mg bid or placebo bid	40 weeks	153 mg/dl (3.96 mmol/L)	33%	Angiographic restenosis as assessed by quantitative coronary angiography as the loss of MLD during followup.
Weintraub WS. et al. 1994 The Lovastatin Restenosis Trial	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	404 men or women in whom angioplasty of a native vessel with a stenosis of 50-99% was successful.	Lovastatin 40 mg bid or placebo bid.	6 months	130 mg/dl (3.4 mmol/L)	42%	Extent of restenosis of the index lesion as assessed by angiography.
The Post Coronary Artery Bypass Graft Trial 1997 Post Coronary Artery Bypass Graft Trial (PCABG)	Randomized, intent to treat analysis for clinical events	1351 men or women 21-74 years with history of CABG 1-11 years prior and a baseline LDL-c of 130-175 mg/dl and at least 1 patent graft as seen on angiography	Aggressive LDL-c lowering with lovastatin 40 mg qpm titrated to 80 mg qpm (goal LDL-c < 85) or moderate LDL-c lowering with lovastatin 2.5 mg qpm titrated to 5 mg qpm (goal LDL-c <140 mg/dl). Warfarin 1 mg qd or placebo qd (titrated to 4 mg qd or INR of 2 or >) (2X2 design)	4.3 years	154 mg/dl (4 mmol/L)	37-40% yearly in the aggressive group. 13-15% yearly in the moderate group	Mean percentage per patient of grafts with a decrease of 0.6 mm or > in lumen diameter of initially patent grafts as assessed by angiography

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Primary Endpoint Results (provided only if it is a clinical health outcome)	Other Clinical Outcomes Measured	Other Clinical Outcome Results	Comments/Conclusions
Serruys PW. et al. 1999 Fluvastatin Angiographic Restenosis Trial (FLARE)	N/A	*Prespecified clinical endpoints:* Death, MI, CABG or re-intervention	Major cardiac events occurred in 92 fluvastatin vs. 99 placebo recipients (p=0.74). When death and MI were combined, there was a significant reduction in the fluvastatin vs. placebo groups (p=0.03 ARR=2.5/100 persons NNT=39)	Although not sufficiently powered to determine differences in clinical events, the combined endpoint of death/MI was significantly reduced in the fluvastatin vs. placebo groups s/p successful balloon angioplasty. The composite of major clinical events which included death/MI/CABG/re-intervention was not different between groups (p=0.74). Fair-poor in quality for assessment of differences in clinical events between groups (relatively short follow up period, insufficiently powered).
Weintraub WS. et al. 1994 The Lovastatin Restenosis Trial	N/A	Clinical events were spontaneously reported.	There were no differences in the rate of death, stroke, CABG, re-intervention (angioplasty) between groups. There was a trend towards more MI in the lovastatin vs. placebo groups (p=0.058)	There was no difference in the rate of restenosis between groups. There was also no difference in the rate of major clinical cardiac events in the lovastatin vs. placebo groups. There was a trend towards more MI in the lovastatin vs. placebo groups. Fair-poor in quality for assessment of differences in clinical events between groups (relatively short followup period, small sample size).
The Post Coronary Artery Bypass Graft Trial 1997 Post Coronary Artery Bypass Graft Trial (PCABG)	N/A	*Prespecified clinical endpoints as a composite and individually:* Death from cardiovascular or unknown causes, nonfatal MI, stroke, CABG or PTCA	There were no differences in the composite or individual clinical outcomes between treatments. There was a 29% reduction of revascularization in the aggressive lovastatin group vs. the moderate lovastatin group but did not reach statistical significance criteria in this study (p=0.03)	There was a significant difference in the rate of atherosclerotic progression favoring aggressive LDL-c lowering with lovastatin. There were no differences in composite or individual clinical outcomes between groups. There was a trend toward the aggressive lovastatin group in reducing revascularization. Fair in quality to assess differences in degree of LDL-c lowering and its effect on clinical outcomes, although no difference was noted.

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction	Primary Endpoint
Kleeman A. et al. 1999 The Cholesterol Lowering Atherosclerosis Trial (CLAPT)	Randomized, unblinded treatment, blinded angiographic endpoint, intent to treat for clinical events.	226 men 18-70 years scheduled for PTCA with a second vessel stenosis of >20% and LDL-c >135 mg/dl	Lovastatin 20 mg qpm or usual care. Lovastatin was titrated up to 80 mg qpm for LDL-c >120 mg/dl	2 years	181 mg/dl (4.7 mmol/L)	29%	Angiographic progression and restenosis. Change in mean segment diameter (diffuse coronary atherosclerosis) of nondilated and dilated segments and MLD (focal coronary atherosclerosis) of dilated lesions at 2 years as assessed by angiography
Bertrand ME. et al. 1997 Prevention of Restenosis by Elisor after Transluminal Coronary Angioplasty (PREDICT)	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	695 men or women 25-75 years and TC 200-310 mg/dl who had undergone successful PTCA	Pravastatin 40 mg qpm or placebo qpm	6 months	155 mg/dl (4 mmol/L)	23%	Minimum lumen diameter as assessed by coronary angiography

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Primary Endpoint Results (provided only if it is a clinical health outcome)	Other Clinical Outcomes Measured	Other Clinical Outcome Results	Comments/Conclusions
Kleeman A. et al. 1999 The Cholesterol Lowering Atherosclerosis Trial (CLAPT)	N/A	*Pre-specified or defined clinical events:* MI, re-PTCA, PTCA of another lesion, or death	There were 62 serious clinical events in lovastatin vs. 75 in usual care (NS). The only significant difference was a reduction in the 2nd or 3rd re-PTCA favoring lovastatin (p=0.02)	There were no differences in the rate of clinical events in the lovastatin vs. placebo groups with the exception of 2nd or 3rd re-PTCA (p=0.02). Fair in quality to assess differences in clinical events between groups. (small sample size, unblinded)
Bertrand ME. et al. 1997 Prevention of Restenosis by Elisor after Transluminal Coronary Angioplasty (PREDICT)	N/A	Secondary endpoints: restenosis rate and clinical events (death, MI, target vessel revascularization)	There were no differences in clinical restenosis or events between groups (80 events in placebo vs. 74 events in pravastatin)	There were no differences in the rate of clinical events or clinical restenosis in the pravastatin (74 events) vs. placebo (80 events) groups (death, MI, CABG, re-PTCA of target lesion). Fair in quality to assess differences in clinical events between groups (Relatively short follow up period)

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction	Primary Endpoint
Flaker GC. et al. 1999 Subgroup of CARE	Randomized, double-blind, placebo-controlled, intent to treat analysis. (Subgroup analysis of revascularized patients in CARE)	2245 men or women with history of MI and <240 mg/dl and revascularization	Pravastatin 40 mg qpm or placebo qpm	5 years	138.4 mg/dl (3.6 mmol/L)	28%	Reduction in clinical cardiovascular events (CHD death or nonfatal MI, fatal and nonfatal MI, revascularizations and stroke)
Pitt B. et al. 1999 The Atorvastatin vs. Revascularization Treatment (AVERT)*	Randomized, unblinded, intent to treat analysis for clinical events	341 men or women 18-80 years with 50% stenosis of 1 or > coronary arteries and an LDL-c ≥115 mg/dl	Atorvastatin 80 mg qpm or PTCA	18 months	Approximately 140-148 mg/dl (3.6-3.8 mmol/L)	46% (22% of all patients were on lipid-lowering drugs prior to randomization with no washout)	Reduction in ischemic events: death from cardiac causes, resuscitation after cardiac arrest, nonfatal MI, CVA, CABG, PTCA, or hospitalization for angina.

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Primary Endpoint Results (provided only if it is a clinical health outcome)	Other Clinical Outcomes Measured	Other Clinical Outcome Results	Comments/Conclusions
Flaker GC. et al. 1999 Subgroup of CARE	Pravastatin reduced the incidence of CHD death or nonfatal MI (RRR=36%, 95% CI 17-51%, p<0.001), fatal or nonfatal MI (RRR=39%, 95% CI 16-55%, p<0.002), and stroke (RRR=39%, 95% CI 3-62, p=0.037). There was a trend towards benefit with pravastatin in reducing repeat revascularization (RRR=18%, 95% CI 1-33%, p=0.068)	Subgroup analysis of CARE of revascularized patients.	See primary endpoint results.	Pravastatin significantly reduced clinical events (CHD death, nonfatal MI and stroke) in previously revascularized patients. There was a trend to reduced revascularizations in the pravastatin vs. placebo groups. Good in quality to assess differences in clinical events between groups.
Pitt B. et al. 1999 The Atorvastatin vs. Revascularization Treatment (AVERT)*	22 (13%) of the atorvastatin vs. 37 (21%) of the angioplasty group experienced ischemic events (p=0.048) NS as adjusted for interim analysis. Events making up the majority of the trend in favor of atorvastatin: CABG and hospitalization for angina	Time to first ischemic event	Time to first ischemic event was longer in the atorvastatin vs. angioplasty group (p=0.03 95% CI 5-67 RRR=36%)	Unequal baseline characteristics between groups (sex, antiplatelets/anticoagulants, and location of target lesion). Approximately 70% of patients in the angioplasty group received a statin. Mean LDL-c 119 mg/dl in angioplasty group vs. 77 mg/dl in atorvastatin group. There was a trend in reduction in clinical events with atorvastatin vs. angioplasty, however CABG and hospitalization for angina accounted primarily for this difference. Angioplasty was the main variable in this study. Poor in quality for assessment of differences in clinical events between groups.

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction	Primary Endpoint
Marz W. et al. 1999 The Target Tangible Trial (TT)*	Randomized, unblinded, intent to treat analysis for clinical events	2856 men or women 35-70 years with CHD and an LDL-c ≥130 mg/dl	Atorvastatin 10 to 40 mg qpm or simvastatin 10-40 mg qpm	14 weeks	188 mg/dl (4.9 mmol/L	Atorvastatin 10 mg=37.6% vs simvastatin 10 mg=31.9%	Safety (adverse events and laboratory events) and efficacy (LDL-c reduction)
Pravastatin Multinational Study Group 1993*	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	1062 men or women 20-69 years with 2 or > risk factors and a TC of 200-300 mg/dl (5.2-7.8 mmol/L)	Pravastatin 20 mg qpm or placebo. After 13 weeks, pravastatin could be doubled to 40 mg qpm	26 weeks	181 mg/dl (4.69 mmol/L)	26.01%	Change in serum lipids (TC, LDL-c, HDL-c, triglycerides)
Serruys PW. et al. 2002 Lescol Intervention Prevention Study (LIPS)	Randomized, double-blind, intention-to-treat analysis for all randomized	1677 Men or women 18-80 years status post successful percutaneous coronary intervention (PCI) and TC between 135 and 270 mg/dl (calculated 3.5-7.0 mmol/L).	Fluvastatin 40 mg bid or placebo bid	3.9 years	131 mg/dl (3.4 mmol/L)	27% (median)	Survival time free of major coronary events (any death, nonfatal MI, repeat revascularization). Divergence seen at 1.5 years.

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Primary Endpoint Results (provided only if it is a clinical health outcome)	Other Clinical Outcomes Measured	Other Clinical Outcome Results	Comments/Conclusions
Marz W. et al. 1999 The Target Tangible Trial (TT)*	Serious adverse events were not different between groups. Serious cardiovascular adverse events occurred in 19 atorvastatin vs. 21 simvastatin patients (p<0.05 if 1-sided test applied).	N/A	N/A	Serious cardiovascular adverse events were significantly higher in the simvastatin vs. atorvastatin group, p<0.05 if the 1-sided test is used.
Pravastatin Multinational Study Group 1993*	N/A	Reported clinical events as part of safety analysis, although cardiovascular events were predefined as fatal or requiring prolonged hospitalization.	Significantly more serious cardiovascular events were reported in the placebo (13) vs. pravastatin (1) groups (p<0.001 ARR 2.2/100 persons NNT=44)	There was a significant reduction in serious cardiovascular events in the pravastatin vs. placebo groups. Fair in quality to assess differences in clinical events between groups (relatively short follow up period).
Serruys PW. et al. 2002 Lescol Intervention Prevention Study (LIPS)	Time to major coronary events was 1558 days in the fluvastatin vs. 1227 days in the placebo group (p=0.01). 181 (21.4%) of fluvastatin vs. 222 (26.7%) of placebo recipients (p=0.01, 95% CI 0.64-0.95, ARR 5.2/100 persons, NNT=19)	Major coronary events excluding repeat revascularizations occurring within the first 6 months	Rate of major coronary events (excluding repeat revascularizations) diverged at 6 months and showed an extended event-free survival time in the fluvastatin vs. placebo groups (p<0.001, 95% CI 0.54-0.84)	Time to major coronary events was significantly prolonged in the fluvastatin vs. placebo group. Adverse effects were not statistically different between groups. Fair-good in quality for assessment of differences in clinical events between groups (Number of diabetics was not equal between groups).

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty

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

1. 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.

2. 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.

3. 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.

4. 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.

5. 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.

6. 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.

7. 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.

8. 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.

9. 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.

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11. 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.

12. 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.

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

14. 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.

15. 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.

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17. 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.

18. 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.

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21. 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.

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31. 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.

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