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

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Cathy Kelley, PharmD
Mark Helfand, MD, MPH

Oregon Evidence-based Practice Center
Oregon Health & Science University

TABLE OF CONTENTS

INTRODUCTION

Coronary heart disease (CHD) continues to be the leading cause of mortality and a significant cause of morbidity among Americans. In 1999, CHD claimed 529,659 lives, translating into about 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 LDL-cholesterol concentrations. They are first-line agents for patients who require drug therapy to reduce serum LDL-cholesterol concentrations.

The statins work by blocking an enzyme in the body called HMG-CoA reductase. This enzyme is the rate-limiting step in the manufacture of cholesterol. Statins reduces LDL-cholesterol, total cholesterol, and triglycerides and slightly increases high density lipoprotein (HDL-c).

The third report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) was released in September, 2002.[2] The report stresses that the intensity of treatment is directly related to the degree of cardiovascular risk. In ATP-III, patients who have Type II 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 (<100 mg/dL) is the same as for patients who have a history of CHD.

Description of the Statins

Five statins are available in the U.S.—atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. Fluvastatin and lovastatin are also available in extended-release forms. Rosuvastatin is not approved yet. Lovastatin and pravastatin are natural statins found in fungi; simvastatin is a semisynthetic statin based on lovastatin, and atorvastatin and fluvastatin are fully synthetic.

The usual starting dose of atorvastatin is 10 mg.. The usual starting dose of the other statins is 20 mg. Taking a statin at bedtime or with the evening meal improves its ability to lower LDL. For all the statins, the maximum FDA-approved daily dose is 80 mg. For lovastatin and pravastatin, the maximum dose is usually prescribed as 40 mg twice a day.

FDA information

Recent changes to the product labels of atorvastatin, lovastatin, and simvastatin: add an indication in children and adolescents with a familial dyslipidemia and add more detailed warnings about liver enzyme elevation and skeletal muscle damage that are standard for statins.

Recent changes to the fluvastatin and lovastatin product labels pertain to the pharmacokinetics of extended-release fluvastatin (Lescol XL) and extended-release lovastatin (Altocor).

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 developed the scope of the review by writing 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 an Oregon Health Resources Commission subcommittee for lipid-lowering therapies, comprised of local experts (pharmacists, primary care clinicians, and a cardiologist) and representatives of the public. In consultation with the subcommittee, we selected the following key questions to guide this review:

1. How do statins compare in their ability to reduce LDL-c?
    a. Are there doses for each statin that produce similar percent reduction in LDL-c between statins?
    b. Is there a difference in the ability of a statin to achieve National Cholesterol Education Panel (NCEP) goals?
2. How do statins compare in their ability to reduce the risk of nonfatal myocardial infarction, CHD (angina), CHD mortality, all-cause mortality, stroke, or need for revascularization (coronary artery bypass graft, angioplasty, or stenting)?
3. Are there differences in efficacy or safety of statins in different demographic groups (age, sex, race)?
4. Are there differences in the safety of statins when used in special populations? In addressing this question, we reviewed to focus on the following populations and adverse effects:
    a. Diabetics
    b. Patients with HIV
    c. Organ transplant recipients
    d. Patients at high risk for myotoxicity
    e. Patients at high risk for hepatotoxicity

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 amount of information on cardiovascular outcomes available for each statin, (3) adverse effects, and (4) 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 (2003, Issue 1), MEDLINE (1966-May, 2003), EMBASE (1980-May, 2003), 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). Subcommittee members were invited to provide additional citations. Pharmaceutical manufacturers were invited to submit dossiers, including citations, using a protocol issued by the State of Oregon (http://www.ohppr.state.or.us/index.htm). All citations were imported into an electronic database (EndNote 5.0).

The update search used the names of each statin (atorvastatin OR fluvastatin OR lovastatin OR pravastatin OR simvastatin) and was limited by relating to the concept of controlled trials. This search identified 107 citations published in 2002 or 2003. Of these, 21 were controlled trials that had an included population, intervention, and outcome measure and provided original data. We also identified 11 potentially eligible reviews and meta-analyses. In addition, a separate search for rosuvastatin studies identified 10 controlled trials, of which 7 were head-to-head trials or meta-analyses. [3-7] Several of the head-to-head rosuvastatin trials included 2 or more active controls (e.g., pravastatin and simvastatin), making them included head-to-head trials even though rosuvastatin itself is not examined in the update.

Eligibility Criteria and Study Selection

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

Population. Adults (age ≥ 20 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 rare, severe forms of hypercholesterolemia (LDL-c ≥ 250mg/dl). We excluded trials in inpatients with acute coronary syndrome, but included 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, 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.

Health outcomes. Nonfatal myocardial infarction, CHD (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 and in reaching NCEP goals. We excluded trials that reported *only* angiographic results.

For adverse effects, we included randomized clinical trials plus observational cohort studies that reported hepatotoxicity, myotoxicity, or drug-drug interactions. 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 followup, 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, which were submitted to the Health Resources Commission in December 2001. 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).[8, 9] For key question 2, 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 followup; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories were rated poor quality; trials which met 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

Searches identified 3047 citations: 740 from the Cochrane Library, 1178 from Medline, 1080 from Embase, 15 from reference lists, and 34 from pharmaceutical company submissions. We identified 988 potentially relevant randomized controlled trials and 118 controlled clinical trials. Of these, 67 randomized controlled trials provided usable data and are included in evidence tables.

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

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

We identified 44 randomized clinical trials comparing the LDL-c lowering ability of two or more statins in patients with baseline LDL-c ≤250mg/dl (Evidence Table 1). In 25 of these trials, the percentage of patients reaching their NCEP goal was also evaluated. There were 24 [4, 5, 10-31] double-blinded, 18 [32-34 35-49] unblinded and two[50, 51] single-blinded studies. Dosing strategies varied between trials. Some studies titrated to a maximum recommended daily dose (titrate to target) while others compared a single statin dose with or without dose titration. In the majority of the trials the efficacy analyses were performed on a smaller number of patients than those randomized (that is, the trials did not use intention-to-treat statistics). Most of the trials had fair internal validity.

The trials included men and women ages 18 to 80 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 ≥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 1 year.

Table 1 (below) 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 comparator (head-to-head) trials, were consistent with the estimates from a more recent meta-analysis of placebo-controlled trials.[52] 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) In an open-label, poor-quality study of 10 patients using lovastatin 40mg,[53] the mean percent reduction in LDL-c was higher than expected (48%). This study did not use intention-to-treat statistics.

(2) In an open-label, fair-quality study, lovastatin 20mg daily produced a lower-than-expected reduction in LDL-c (21%).[38] 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.

(3,4) In a poor-to-fair-quality trial comparing fluvastatin 20 and 40mg to simvastatin 20 and 40mg, fluvastatin produced reductions in LDL-c that were consistent with the package insert information, but reductions in LDL-c with simvastatin were less than expected (23.6% with 20mg daily and 34.4% with 40mg daily).[14] We were unable to determine the number of patients completing the study and it was unclear whether intention-to-treat analysis was used.

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

Table 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 if available)	Number of clinicaltrials**
Atorvastatin			
10mg	34.2%-38%	39% (37%)	12
20mg	42.1%-46.1%	43%	4
40mg	51%-51.3%	50%	2
80mg	53.6%-54%	60% (57%)	3
Fluvastatin			
20mg	17%-21.8%	22% (18%) β	4
40mg	22%-26%	25% β	5
80mg	29.6%-30.6% +	36% (31%)++ β	2
80mg XL*	--	35% β	0
Lovastatin			
10mg	24%	21%	1
20mg	21%-29%	27% (24%)	7
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%)	9
40mg	25.6%-34%	34%	6
80mg*	--	37% (34%)	0
Simvastatin			
10mg	26%-33.1%	30%	16
20mg	23.6%-40%	38% (35%)	11
40mg	34.3%-43%	41%	5
80mg	43%-48.8%	47% (46%)	4

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

Two studies directly compared atorvastatin 80mg to simvastatin 80mg daily.[10, 34] The first study, by Illingworth and colleagues,[10] randomized 826 patients with hypercholesterolemia to atorvastatin 20mg or simvastatin 40mg daily for 6 weeks; followed by atorvastatin 40mg or simvastatin 80mg daily for 6 weeks; then atorvastatin 80mg or simvastatin 80mg daily for the remaining 24 weeks. Mean baseline LDL-c was 206mg/dl in the atorvastatin versus 206mg/dl in the simvastatin group. The study was double-blind but did not use intention-to-treat statistics. At a dose of 80mg daily for each statin, atorvastatin reduced LDL-c by 53.6% compared to 48.1% for simvastatin ($p \leq 0.001$). With regard to safety, a greater number of patients in the atorvastatin 80mg as opposed to the simvastatin 80mg group ($p<0.001$) reported clinical adverse effects (primary gastrointestinal-diarrhea). There was no significant difference in withdrawal rates due to adverse effects between groups. With regard to laboratory safety, a greater number of patients in the atorvastatin 80mg versus the simvastatin 80mg daily group experienced adverse laboratory events ($p<0.001$). Furthermore, withdrawal from the study due to adverse laboratory events occurred more often in the atorvastatin 80mg compared to the simvastatin 80mg daily group ($p<0.05$). Clinically important ALT elevation (> 3 times the upper limit of normal) occurred statistically more often in the atorvastatin 80mg compared to the simvastatin 80mg group (17 vs. 2 cases, respectively, $p=0.002$) and was especially pronounced in women (there were statistically more women randomized to atorvastatin than simvastatin). Aminotransferase elevation generally occurred within 6 to 12 weeks after initiation of the 80mg statin dose.

In the second study,[34] Karalis and colleagues randomized 1,732 patients with hypercholesterolemia to treatment with atorvastatin 10mg or 80mg daily or simvastatin 20mg or 80mg daily for 6 weeks. In this study, a total of 432 patients received either atorvastatin or simvastatin at a dose of 80mg daily. Mean baseline LDL-c in the atorvastatin 80mg daily group was 179mg/dl and 178mg/dl in the simvastatin 80mg daily group. This study was unblinded and did not use intention-to-treat statistics. At a dose of 80mg daily for each statin, LDL-c was reduced by 53% in the atorvastatin versus 47% in the simvastatin group ($p<0.0001$). With regard to safety at the 80mg dosage for each statin, atorvastatin was associated with a higher incidence of adverse effects compared to simvastatin (46% vs. 39%) and a higher rate of study discontinuation due to adverse effects (8% vs. 5%). However, neither of these differences was statistically significant.

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

Table 2. Equivalent doses of statins

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

1b. Is there a difference in the ability of a statin to achieve National Cholesterol Education Panel 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 (Table 3).

Table 3. Achieving Target LDL-cholesterol goals

Baseline LDL-c	130	160	190	220
(Percent Reduction to Achieve Target Goals)				
Target LDL-C < 100	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.)

Twenty-six reports measured the percentage of patients meeting their National Cholesterol Education Panel (NCEP) LDL-c treatment goals. These trials are summarized in Table 3.1. 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)[32], 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. In 10 studies in Table 3.1, the inferior drug appears not to have been titrated to its maximum daily dosage. Seven of the 10 studies that had this flaw were reported to be double-blinded; in these, it is unclear why clinicians did not titrate the dosage as aggressively in the compared groups.

In those that studied tailored doses, the maximum dose was often lower than the maximum approved dose. The recent Treat-to-Target (3T) Study had this flaw. It was a 52-week, multicenter, randomized, head-to-head study of once-daily oral treatment with 20 mg atorvastatin or 20 mg simvastatin.[31] 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 National Cholesterol Education Program level of LDL-C (<=2.6 mmol/L [100 mg/dL]) was not reached at 8 weeks. Fewer atorvastatin patients needed to have their dose doubled; nevertheless more atorvastatin patients reached the LDL-C target after 52 weeks (61% vs 41%; $P < 0.001$). However, the simvastatin 80 mg dose was not evaluated in the study.

Some recent studies designed to evaluate rosuvastatin indirectly compared atorvastatin 10 mg, simvastatin 20 mg, and pravastatin 20 mg. In a meta-analysis of five 12-week randomized trials, the mean percent reduction from baseline in the LDL cholesterol/HDL cholesterol ratio was 39% in patients treated with atorvastatin 10 mg, 39% for simvastatin 20 mg, and 30% for pravastatin 20 mg.[3] In these trials, 53% of patients taking atorvastatin 10 mg reached their ATP III goal, versus 64% for simvastatin 20 mg and 49% for pravastatin 20 mg.[54] The ATP III goals differ from the older NCEP goals. Nevertheless, comparing these results to those of the direct comparisons of atorvastatin and simvastatin, it is clear that simvastatin performed better and atorvastatin worse in studies conducted by the maker of rosuvastatin.

Summary

There is fair-to-good-quality evidence that, when statins are provided in doses that are approximately equivalent, a similar percent reduction in LDL-c and percent of patients meeting LDL-c goals can be achieved. For patients who require LDL-c reductions of up to 40% to meet their goal, any of the statins are effective. There is also fair-to-good-quality evidence that, in patients requiring an LDL-c reduction of 40% or greater to meet their NCEP goal, only atorvastatin 20mg or more, lovastatin 80mg, and simvastatin 20mg or more daily are likely to meet the goal. There is fair evidence that in patients requiring greater than a 50% reduction in LDL-c, only atorvastatin 80mg daily has demonstrated the ability to achieve that goal, but it had a higher rate of some adverse effects (GI disturbances and transaminase elevation) than simvastatin 80mg daily.

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

There are no controlled trials comparing the ability of two or more statins to reduce the risk of coronary events, stroke, or death. On the other hand, many trials comparing a statin to placebo or, in a few instances, to nonpharmacologic treatments, reported these 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 three tiers.

- The first tier included nine placebo-controlled trials. The primary endpoint in these trials was a reduction in cardiovascular health outcomes. Enrollment was in excess of 4,000 patients with an average followup period of 5 years. All of the trials were good quality and were considered the best evidence for demonstrating a reduction in cardiovascular health outcomes with statins.
- The second tier consisted of placebo-controlled trials in which the primary endpoint was progression of atherosclerosis measured by angiography or B-mode ultrasonography.[55-66] 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[56, 63] 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.
- The third tier contained trials of using statins to prevent restenosis after coronary revascularization (CABG or PTCA).[67-72] Other studies that reported health outcomes that did not fit into the first two tiers were included in this tier as "miscellaneous" trials.[32, 73-75]

First Tier

The major trials are summarized briefly in Table 4 below and in more detail in Evidence Table 2.

Table 4. Major trials with CHD endpoints

Trial	Risk Status	Baseline LDL	Study Duration (years)	% LDL reduction	Reduction in Coronary events (%)	NNT to prevent a coronary event*
AFCAPS lovastatin	Average risk, no history of CAD	150	5.2	25%	37%	49.19
WOSCOPS pravastatin	High risk, no history of CAD	192	4.9	16%	31%	44.21
LIPID pravastatin	History of CAD	150	6.1	25%	24%	163.7
CARE pravastatin	History of CAD	139	5	28%	24%	
4S simvastatin	History of CAD	187	5.4	35%	34%	11
HPS simvastatin	History of CVD or diabetes	131	5.5	30%	27%	32
ASCOT atorvastatin	HTN plus CHD risk factors	133	3.3	35%	29%	94
ALLHAT-LLC pravastatin	Mostly primary prevention	145	4.8	24%	9%	Results not significant
PROSPER pravastatin	70-82 years old, history of CHD or risk factors	147	3.2	27%	15%	24

*Not adjusted for length of trial.
HTN=hypertension. CVD=cardiovascular disease. CAD=coronary artery disease.

<u>Primary Prevention.</u> The first two studies recruited patients without a history of CHD (primary prevention). One evaluated lovastatin (AFCAPS/TexCAPS)[76] and the other pravastatin (WOSCOPS).[77] 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,[77] 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 value .051). The absolute risks of coronary disease death were 1.3% for subjects in the lovastatin 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 (not significant). 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.

Secondary Prevention. The next three studies in Table 4 recruited patients with documented CHD. Two of them (LIPID, CARE)[78, 79] evaluated pravastatin (n=13,173) and the other (4S)[80] simvastatin (n=4,444) 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.

More recent studies. The last four trials in Table 4 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 40 mg qpm or placebo for an average of 5.5 years.[81-83] This study targeted individuals in whom the risk and benefits of cholesterol lowering were uncertain (women, those over 70 years, diabetics, those with non-coronary vascular disease, and those with average or below average cholesterol).

The overall LDL reduction of 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 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. In subgroups, simvastatin 40 mg was effective in primary prevention of CHD in patients with diabetes (NNT=24 to prevent a major event in 5 years)[84] 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 diabetics and nondiabetics.)

ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-lowering Arm) was a randomized, double-blind, placebo-controlled, good-quality trial of atorvastatin 10 mg 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.[85-87] ASCOT-LLA is best viewed as a primary prevention population with CHD equivalents. ASCOT-LLA was terminated after a median of 3.3 years of followup because a statistically significant benefit emerged in the primary endpoint, non-fatal myocardial infarction (including silent MI) and fatal CHD. Treatment with atorvastatin 10 mg qd for 1 year reduced LDL by 35%, from 133 mg/dL to 87 mg/dL. By the end of followup (about 3.3 years), LDL was 89 mg/dL in the patients still taking atorvastatin versus 127 mg/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, but not all-cause mortality (3.6% for atorvastatin vs. 4.1% for placebo, p=0.1649), 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.

About 24.5% of the subjects in ASCOT were diabetics and 19% were women. Atorvastatin did not reduce MI and CVD death in diabetes (3.0% vs. 3.6%, p=0.4253). In women, there was no indication of a benefit (1.9% vs. 1.8%, p=0.7692); when compared to the results for men, women in the placebo group had a much lower rate of events. Most other subgroup analyses were statistically significant and, except for diabetics and women, the point estimates of the non-significant subgroup analyses were similar to that of the whole sample.

In ALLHAT-LLC (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack—Lipid-lowering Arm), a fair-quality, open-label randomized trial, 10,355 hypertensive patients, aged 55 and older, were randomized to pravastatin 40 mg or to usual care.[88] Nearly half the subjects were women, 35% were diabetic, 15% had a history of CHD, and about 35% were black. Pravastatin reduced LDL-c from 145.6 mg/dL at baseline to 111 mg/dL after 2 years, a 24% reduction. However, because the control group was usual care instead of placebo, 90% 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.[89] High risk men and women were randomized to pravastatin 40 mg qhs or to placebo. Before treatment, the mean LDL was 147 mg/dL. Overall, pravastatin improved 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. PROPSER also had a pre-randomization run-in period during which noncompliant subjects were excluded from randomization. Of 7,056 subjects who entered the run-in period, 5,804 (82%) were randomized.

Second Tier

The second tier includes studies of the effects of statins on progression of atherosclerosis that also reported rates of coronary or cardiovascular events.[55-66] 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 preplanned endpoint (they were "spontaneously reported"), and sample sizes were relatively small.

Table 5 (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, Tier-1 studies.

In general, those trials in which CHD events were not an endpoint did not find a difference between groups. There was usually a trend towards a reduction in clinical events in favor of the statin. In the trials in which CHD events were a secondary endpoint, there was usually a reduction in one of the clinical events. While consistent, the results of these studies are difficult to interpret because of possible publication bias. Similar trials of progression of atherosclerosis which found no trend probably did not report coronary events, making this a biased sample of studies. For this reason, we did not conduct a meta-analysis to pool the results of these studies.

Table 5. 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	Spontaneous report	Trend
ACAPS/Lovastatin	Secondary endpoint	Reduction in major cardiovascular events
CCAIT/Lovastatin	Spontaneous report	Trend
MARS/Lovastatin	Spontaneous report	Trend
REGRESS/Pravastatin	Pre-specified	Reduction in PTCA
PLAC-I/Pravastatin	Pre-specified	Reduction in MI
PLAC-II/Pravastatin	Pre-specified	Reduction in combined: nonfatal MI and death
KAPS/Pravastatin	Spontaneous report	Trend
Sato, etal/Pravastatin	Pre-specified	Reduction in overall death
MAAS/Simvastatin	Spontaneous report	Trend
CIS/Simvastatin	Spontaneous report	Trend
SCAT/Simvastatin	Pre-specified	Reduction in revascularization

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

Third Tier

The third tier (Table 6 and Evidence Table 6) includes placebo-controlled trials in revascularized patients (CABG, PTCA, or coronary stent.).[67-72] 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). Most of the studies were fair or fair-to-poor in quality for the question of whether treatment with a statin is associated with a reduction in clinical cardiovascular outcomes in patients with CHD. Sample sizes were relatively small and the studies were not powered to assess these types of events.

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

Table 6. 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*	Pre-specified composite clinical endpoint of death, myocardial infarction, coronary artery bypass graft surgery or re-intervention.	No effect on restenosis or on the preplanned composite clinical end-point at 40 weeks (22.4% vs 23.3%; logrank P=0.74). Incidence of total death and myocardial infarction was lower in the fluvastatin group (1.4%) vs. 4.0%; log rank P=0.025).
Weintraub WS.,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 qd (aggressive) vs. lovastatin 2.5 mg qd 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=.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

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.[90, 91] 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 1 major adverse cardiac event. 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.) Diabetics and patients with multivessel disease experienced a comparable or greater benefit with fluvastatin than other subjects.

<u>Miscellaneous Studies.</u> Five trials that reported clinical outcomes did not fit the criteria for the three tiers (Table 7 and Evidence Table 6).[32, 73-75, 92] In one of these trials, Riegger et al,[75], 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 (Table 7). Another trial of fluvastatin established its efficacy and safety in patients who have undergone renal transplant.[92]

The Target Tangible study[32] 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," meaning the patients and investigators/clinicians knew which medication was given. However, 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 (p10) that "Serious cardiovascular events (including angina pectoris, myocardial infarction, and cerebral ischemia) were more frequent in the simvastatin group (19 patients, 2%) than in the atorvastatin group (21 patients, 1.0%) if the one-sided t-test was applied (p<0.05, Table III)." However, Table III of the article (p10) does not support this statement. The Table shows that the number of these serious cardiovascular events was 11 (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 of the short duration of the study, the investigators did not interpret any of the cardiovascular events to be related to therapy. The study was rated fair-to-poor quality because of the lack of blinding and the lack of clarity of the statistical analysis.

Table 7. 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.)
Riegger G., etal Fluvastatin 40mg vs. placebo in patients with symptomatic CAD.	Primary endpoint included cardiac death, nonfatal myocardial infarction, unstable angina pectoris	3 events in the fluvastatin group vs. 10 in the placebo group (p<0.05, ARR=4/100 persons, NNT=25).
Pravastatin Multinational Study Group/ Pravastatin 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).
Holdaas H. etal Fluvastatin vs. placebo in renal transplant patients	cardiac death, non-fatal myocardial infarction (MI), or coronary intervention procedure	After a mean follow-up of 5.1 years, risk reduction with fluvastatin for the primary endpoint (risk ratio 0.83 [95% CI 0.64-1.06], p=0.139) was not significant, although there were fewer cardiac deaths or non-fatal MI (70 vs 104, 0.65 [0.48-0.88] p=0.005) in the fluvastatin group than in the placebo group.

Summary

In placebo-controlled trials, several statins have been shown to reduce coronary events. No good-quality studies directly compared the ability of different statins to reduce coronary disease events.

The amount of information on cardiovascular outcomes available for each statin differs substantially. The major (first tier) trials provide good-quality evidence that atorvastatin, lovastatin, pravastatin and simvastatin reduce cardiovascular events. Atorvastatin and simvastatin both reduced cardiovascular events in patients who had LDL levels that would once have been considered to be acceptable. For pravastatin, there is good evidence for both primary and secondary prevention and for reduction of all-cause mortality in primary prevention. For simvastatin, there is good evidence for reducing cardiovascular events and all-cause mortality for both primary and secondary prevention.

The angiographic studies (Tier 2) provide fair-quality evidence that lovastatin is effective in secondary prevention, but little other information, because (1) there were no statistically significant findings for statins other than lovastatin, pravastatin, and simvastatin, which are already known to reduce cardiac events; (2) the studies had inadequate power to assess clinical outcomes, and (3) there is a high probability of publication bias. The post-revascularization studies (Tier 3) and miscellaneous studies provide fair evidence about fluvastatin and additional support for pravastatin.

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

3a. Efficacy in Demographic Subgroups

Women and the Elderly

Although women and the elderly were under-represented in the early major trials, a meta-analysis[93] and an observational study[94] suggested that statins are equally efficacious in men, women, and the elderly. The meta-analysis[93] evaluated the effect of statins on the risk of coronary disease from the first five large, long-term, primary and secondary prevention trials (see Evidence Table 2). Women accounted for an average of 17% of subjects and individuals age 65 and older accounted for an average of 29% (range 21%-39%) (WOSCOPS did not enroll women or anyone 65 years or older). The risk reduction in major coronary events was 29% (95% CI 13%-42%) in women, 31% (95% CI 26%-35%) for men, 32% (95% CI 23%-39%) in those over age 65 and 31% (95% CI 24%-36%) in those younger than age 65.

In the observational study, elderly patients with a history of CHD residing in a long-term care facility were followed for a mean of 36 months.[94] In patients receiving statins, there was a significantly lower rate of new coronary events compared to those not receiving lipid-lowering therapy (46% vs. 72%, respectively. P<0.0001). When the risk reduction was assessed by age group (e.g., 60-70, 71-80, etc.), the benefit observed in the statin recipients was consistent for all ages, including those age 91 to 100. More patients in the statin group smoked and had hypertension. No information was provided on which statins were utilized in the study.

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 diabetic women, who benefitted dramatically (NNT 23 to prevent one major vascular event).

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.[95] 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 20 mg, 40 mg, and 80 mg daily reduced LDL-c by similar similar percentages in blacks and in whites.[96]

3b. 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.[97, 98] The Expanded Clinical Evaluation of Lovastatin (EXCEL) Study was a 4-year study of the tolerability of lovastatin 20 mg, 40 mg, or 80 mg daily in 8,245 patients, including over 3,000 women.[99-103] 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 80 mg involving 2,819 subjects (Worldwide Expanded Dose Simvastatin Study Group) had similar results.[97] These studies are important because they demonstrate that the maximum (80 mg) doses of simvastatin and lovastatin are well-tolerated.

A subgroup analysis[96], 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 the upper limit of normal, occurred in African-Americans. There were no other safety differences between lovastatin and placebo in African-Americans or Caucasians.

Summary

There is good evidence from randomized trials that women and the elderly benefit from statin therapy. While it is clear from the Heart Protection Study that women can benefit, in most of the trials risk reduction was smaller or nil in women, possibly because there were fewer women and they were at lower risk than the men. 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.

4. Are there differences in the safety of statins when used in special populations?

Diabetics

There are no prospective, controlled clinical trials assessing the benefits or harms of different statins in patients with diabetes. In the Heart Protection Study (HPS, simvastatin), substantial elevations of liver enzymes and creatine kinase were not significantly higher in diabetics. 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.

Ongoing studies of the efficacy and safety of statins in diabetics include the Atorvastatin as Prevention of CHD Endpoint in NIDDM trial (ASPEN, atorvastatin), and the Collaborative Atorvastatin Diabetes Study (CARDS, atorvastatin.) There are no data to support any special safety concerns in diabetic patients receiving statins.

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.[104-110] 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 8). The use of the agents listed in Table 8 increase statin concentrations and, theoretically, the possibility for adverse effects. Table 8 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 9). Pravastatin is not significantly metabolized via the CYP isoenzyme system and is therefore not affected by drugs inhibiting metabolism via these pathways.

Table 8. 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 9. 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[92] and pravastatin at 40mg daily have also been shown to be safe in cyclosporine-managed transplant recipients.[111]

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.[112] 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.[113] One small study[114] involving atorvastatin (10mg/day) in 10 renal-transplant recipients taking cyclosporine observed a significant benefit with regard to lipid levels and no cases of myopathy or rhabdomyolysis.

In summary, based upon pharmacologic information, case reports, and small series of patients when used in the lowest doses, the safety profile of statins for transplant patients is similar to that of the general population. Pravastatin and fluvastatin have the least potential for significant interaction with cyclosporine. If a known inhibitor of CYP 3A4 is given to a transplant patient receiving cyclosporine and a statin metabolized by CYP 3A4 (atorvastatin, lovastatin, simvastatin), the risk for rhabdomyolysis could theoretically be increased. 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 date, there are no prospective, randomized clinical trials evaluating the benefit of statins in HIV infected patients.

Although data specifically addressing the combination of the protease inhibitors with the statins are lacking, it is known that simvastatin, lovastatin, and atorvastatin are metabolized by CYP 3A4 to some degree. Fluvastatin is metabolized by CYP 2C9 and pravastatin is not metabolized by the CYP isoenzyme system. Therefore, potential exists for increased concentrations of simvastatin, lovastatin, or atorvastatin when used in combination with the protease inhibitors, especially ritonavir. The increased concentration of statins may result in an increased risk for myopathy and rhabdomyolysis. The risk may be even greater in those HIV-infected patients receiving protease inhibitors plus other known inhibitors of CYP 3A4.

There is one retrospective study[115] in which patients with HIV received a statin for the management of their hyperlipidemia. 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 the upper limit of normal. Both patients were asymptomatic and continued therapy. One patient developed an increase in creatine kinase of 5.4 times normal and myalgias. He was receiving lovastatin 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.

An abstract presented during the 7th Conference on Retroviruses and Opportunistic Infections in February, 2000 evaluated the potential interaction between protease inhibitors and statins. In this study, HIV seronegative volunteers were randomized to receive pravastatin 40mg/d, simvastatin 40mg/d, or atorvastatin 40mg/d on days 1 to 4 and 15 to 18. On days 5 to18, volunteers received dual protease inhibitors (ritonavir 400mg bid plus saquinavir 400mg bid). Investigators noted a 31.6-fold increase in simvastatin and a 4.5-fold increase in atorvastatin median estimated area under the curve concentrations (AUC_{0-24}) when used in combination with ritonavir and saquinavir. Median estimated AUC_{0-24} decreased nonstatistically in those subjects receiving dual protease inhibitors with pravastatin. 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 (http://www.retroconference.org).

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).

Are there differences in safety between statins with regard to myopathy and hepatoxicity?

Three reviews[107, 116, 117] evaluated the safety profile of statins. Two other reviews assessed myotoxicity with the statins[118, 119] and one systematic review[120] focused on the combination of statins and fibrates.

In addition to the reviews of safety with statins, we reviewed the 40 head-to-head statin LDL-c lowering trials to determine whether there were any significant differences in myotoxicity and/or hepatotoxicity. We also included two observational studies regarding myopathy[121] or rhabdomyolysis[119] with statins.

Magnitude of Risk. Although the absolute risk of myopathy is low, because of the wide use of lipid-lowering therapy there are good data about its frequency. Gaist and colleagues[121] conducted a population-based observational study in which three cohorts of patients were identified. The first cohort consisted of patients (n=17,219) who had received at least one prescription for lipid-lowering drugs. The second cohort consisted of patients (n=28,974) who had a diagnosis of hyperlipidemia but did not receive lipid-lowering drugs. The third cohort consisted of people (n=50,000) from the general population without a diagnosis of hypercholesterolemia. The incidence of myopathy in the lipid-lowering group was 2.3 per 10,000 person-years (95% CI 1.2-4.4) versus none per 10,000 person-years in the nontreated group (95% CI 0-0.4) and 0.2 per 10,000 person-years (95% CI 0.1-0.4) in the general population. In patients using fibrates or statins compared to nonusers, the relative risk of myopathy was 42.2 per 10,000 (95% CI 11.6-170.5) and 7.6 per 10,000 (95% CI 1.4-41.3), respectively. The authors concluded that the relative risk for myopathy is significantly increased when lipid-lowering drugs are used, especially fibrates. However, the absolute risk is very small. In 17,086 person-years of statin treatment, there were only two cases of myopathy. In this study, rates of myotoxicity were not differentiated between statins.

Myotoxicity of Different Statins. All of the available statins (simvastatin, lovastatin, atorvastatin, fluvastatin, pravastatin), when administered alone, have been associated with infrequent myotoxic adverse effects ranging from myalgia, and myopathy to rhabdomyolysis.[107] 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.[118, 120, 122, 123]

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

For example, the actual exposure (denominator) of a population to a statin is not known, so the true incidence rates of an adverse effect cannot be determined. Furthermore, the number of reported cases (numerator) may be underestimated.

In our review of the 40 head-to-head comparative statin LDL-c lowering trials, we did not find any differences in rates of muscle toxicity between statins.

Safety of Statin-Fibrate Combination (Myopathy). Myopathy and rhabdomyolysis have also been reported in patients receiving monotherapy with fibrates (gemfibrozil), especially in patients with impaired renal function. Although the mechanism of the interaction is not completely known, the combination of any statin with gemfibrozil and to a lesser extent niacin, can result in a higher risk for myopathy or rhabdomyolysis.[123]

A systematic review by Shek[120] identified 36 trials that combined a statin with a fibrate in the management of hypercholesterolemia. No reports of rhabdomyolysis were observed in the 1,674 patients receiving the combination. A total of 19 (1.14%) patients withdrew secondary to myalgia or CK elevation. Two patients (0.12%) developed myopathy (defined as myalgia with CK >10 X the upper limit of normal [ULN])and 33 (1.9%) patients experienced other muscle symptoms including myalgia, musculoskeletal pain or weakness, or myositis. There were 35 reports (2.1%) of subclinical elevation of CK (<10X ULN) in 16 of the included studies. Some of the studies did not report whether the CK elevation was symptomatic or if treatment was discontinued as a result. In one of the included studies, a patient tolerated the combination of pravastatin and gemfibrozil for 4 years, then developed myopathy with clinically important elevation in CK after being switched to simvastatin,

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

The authors of the systematic review found no case reports of severe myopathy or rhabdomyolysis in patients receiving pravastatin or fluvastatin combined with a fibrate. However, cases of pravastatin or fluvastatin combined with a fibrate resulting in rhabdomyolysis have been reported. [119] The authors cite a reference[124] in which it is suggested that the hydrophilic properties of pravastatin account for the reduced risk of muscle toxicity while all other statins are lipophilic. The suggested mechanism responsible for this difference is that lipophilic drugs are metabolized by the liver to more hydrophilic compounds while hydrophilic agents are more likely to be renally excreted unchanged[107] and have a lower risk for drug interactions. With regard to fluvastatin, it has been suggested that in patients with more severe, mixed hyperlipidemia, maximum doses of fluvastatin may not achieve desired LDL-c goals and may be switched to a more potent LDL-c lowering statin prior to using combination therapy. The authors conclude that the theoretical advantage of pravastatin has not been adequately addressed in comparative statin trials and requires further investigation.

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

- Atorvastatin: Closely monitor patients on combined therapy with gemfibrozil or niacin[125]
- Fluvastatin or pravastatin: Avoid the combination with gemfibrozil unless the benefit outweighs the risk of such therapy.[126, 127]
- Simvastatin or lovastatin: Limit doses of simvastatin to 10mg qd and lovastatin to 20mg qd if combined with gemfibrozil or niacin.[128, 129]

Hepatotoxicity of Statins. All of the statins are rarely associated with clinically important elevation in liver transaminase levels (>3X ULN), occurring in approximately 1% of patients. The risk increases with increasing doses.[117] In order to answer whether there are differences in risk of liver toxicity between statins, we reviewed the adverse effects of the 40 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.[10] In this study, there was a significantly higher incidence of transaminase elevation in the atorvastatin group compared to simvastatin.

We also reviewed the 27 trials reporting cardiovascular health outcomes for significant differences in hepatotoxicity between statins and placebo or a non-drug intervention. Two other studies reporting cardiovascular outcomes were reviewed for adverse effects (MIRACL[130] and GREACE[131]). The MIRACL and GREACE trials were excluded from the efficacy analysis because of study population (MIRACL-acute coronary syndromes) and because the effect of the statin could not be separated out from another intervention (GREACE-University Clinic vs. usual care). In AVERT,[73] and MIRACL,[130] there were 2 and 2.5% of patients in the atorvastatin 80mg daily group who experienced clinically important elevations in the liver transaminases which was significantly greater than that seen in the angioplasty or placebo groups. In GREACE,[131] 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 X upper limit or normal) 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.

Safety of Statin and Fibrate Combination (Hepatoxicity). In the systematic review by Shek in 2001[120], liver toxicity was addressed briefly stating that 8 patients, in three of the 36 included studies, discontinued the combination therapy due to significant elevation in liver transaminases (ALT, AST). In most of the other studies, there were only reports of subclinical (<3X ULN) elevation in ALT or AST. Conclusions regarding the safety of different statins in the liver were not made.

There is insufficient evidence to determine which statin or statins are safer with regard to muscle and liver toxicity.

SUMMARY OF EVIDENCE

Table 10 summarizes the level and direction of evidence for each key question.

Table 10. Summary of evidence

Key Question	Level of Evidence	Conclusion
1. How do statins compare in their ability to reduce LDL-c?	Overall grade--fair.	The ideal study would be a double-blinded, 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 equivalent, 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 Panel (NCEP) goals?	Good for most comparisons (see text).	For patients who require LDL-c reductions of up to 40% to meet their NCEP goal, any of the statins are effective. In patients requiring an LDL-c reduction of 40% or greater to meet their NCEP goal, only atorvastatin 20mg or more, lovastatin 80mg, and simvastatin 40mg or more daily are likely to meet the goal. Based on fair-quality studies, atorvastatin 80 mg daily resulted in 5 to 6 additional percentage points of LDL reduction than simvastatin (53%-54% vs. 47%-48%), but had significantly higher rates of some adverse events.
2. How do statins compare in their ability to reduce the risk of nonfatal myocardial infarction, CHD (angina), CHD mortality, all-cause mortality, stroke or need for revascularization (coronary artery bypass graft, angioplasty or stenting)?	N/A	There are no controlled trials comparing the ability 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.	Primary prevention: pravastatin, simvastatin Secondary prevention: pravastatin, simvastatin.
Which statins have been shown to reduce cardiovascular mortality?	Good.	Primary prevention: Pravastatin, simvastatin Secondary prevention: simvastatin
Which statins have been shown to reduce CHD events?	Fair-to-good.	Primary prevention:, atorvastatin, lovastatin, pravastatin, simvastatin Secondary prevention: simvastatin, pravastatin Secondary prevention: fluvastatin (fair evidence), lovastatin (fair evidence)

Key Question	**Level of Evidence**	**Conclusion**
Which statins have been shown to reduce strokes?	Good.	Atorvastatin, pravastatin, simvastatin
3. What is the correlation between LDL-c lowering and the risk reduction for CHD outcomes?	Poor.	While there is a relationship between LDL-lowering and outcomes in a general sense, data are insufficient to quantify it, and other effects cannot be excluded.
4. Are there differences in efficacy or safety 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 or safety of different statins in women, the elderly, or African Americans.
5. Are there differences in the safety of statins when used in special populations?		
a. Diabetics	Poor-to-good	There are good efficacy data for diabetics Studies which included diabetics had average overall rates of adverse effects.
b. Patients with HIV c. Transplant patients d. Elevated Risk for Myotoxicity e. Elevated Risk for Hepatotoxicity	One fair-quality observational study; case reports; expert opinion; pharmacology. 3 fair or fair-poor quality studies	In theory, pravastatin and fluvastatin 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 9) 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. Three studies, evaluating the benefit of atorvastatin 80 mg daily in reducing coronary heart disease health outcomes, observed a significantly higher rate of clinically important elevations in liver transaminases in the atorvastatin groups in comparison to angioplasty, usual care or placebo.

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Evidence Table 1. Trials comparing LDL-c lowering 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 (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:** atorva and lova both increased 7%. **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 (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%. **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.

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

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 (n= 224 atorva, 73 prava) 1 year 2 authors employed by Parke-Davis Pharmaceuticals.	Men or women 18-80 years with an LDL-c 160-250 mg/dl during dietary phase. <u>Mean baseline LDL-c</u> 201 mg/dl.	6-week dietary and placebo phase. NCEP step 1 diet. <u>Mild to moderate CHD risk (dose level 1: LDL-c goal <130 mg/dl):</u> 10 mg qd atorva (n=145) vs. prava 20 mg qd (n=27). <u>Severe CHD risk (dose level 2: LDL-c goal <115 mg/dl):</u> 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% prava: 29% **HDL:** atorva increased 7% prava increased 9% **Trigs:** atorva reduction 13% prava reduction 8% **Achieved LDL-c goal at last visit:** atorva\= 51% vs. prava 20% 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. <u>Equivalent doses not compared.</u>
<u>Atorvastatin vs. Simvastatin</u>				
Dart A et al. 1997 R (3:1), DB, MC, not ITT 177 patients (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. <u>Mean baseline LDL-c</u> 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 $\leq$ 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:** Atorvastatin increased 7% Simvastatin increased 7% **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. <u>Equivalent doses not compared.</u>

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Crouse et al. 1999 R, OL, MC, not ITT 846 patients 12 weeks Merck supported and participated in study.	Men or women <u>Mean baseline LDL-c</u> 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. <u>Dose equivalence</u> Atorva 20 mg > or ≈ Simva 40 mg. Atorva 40 mg = Simva 80 mg
Marz et al. 1999 R (2:1) OL, MC, not ITT 2,856 patients (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.

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

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 (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. <u>Mean baseline LDL-c</u> 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). <u>Equivalent doses not compared.</u>
Farnier et al. 2000 R (2:1:2), OL, MC, ITT 272 patients (n= 109 atorvastatin, 163 simvastatin) 12 weeks Supported by grant from Parke-Davis.	Men or women 18-70 years with elevated LDL-c. <u>Mean baseline LDL-c</u> 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. <u>Dose equivalence</u> atorvastatin 10 mg qd ≈ simva 20 mg qd

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

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 (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% **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.

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

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 (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. Mean baseline LDL-c 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% ($p \leq 0.001$ for all 3 comparisons) **HDL increased:** atorva 20 mg= 7.3% vs. simva 40 mg= 8.5% (NS) atorva 40 mg= 6.4% vs. simva 80 mg= 9.7% ($p<0.001$) 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% ($p \leq 0.05$ 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 (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. Mean baseline LDL-c 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:** atorva: 148.7 mg/dl (34.8%) simva: 158.4 mg/dl (32.6%)(NS) **HDL increase from baseline at 2 months:** atorva: 3.7% simva: 7.8% ($p<0.05$)% **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. Dose equivalence Atorvastatin 10 mg qd ≈ simvastatin 20 mg qd

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Karalis et al. 2002 R, OL, MC, not ITT 1,732 patients 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. Mean baseline LDL-c 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. Dose equivalence Atorva 10 mg>Simva 20 mg. Atorva 80 mg>Simva 80 mg.
Olsson et al. 2003 R(1:1), DB, MC, ITT 1087 patients (n= 552 atorva, 535 simva) 52 weeks Supported by Pfizer.	White men and women 35-75 years with cardiovascular disease and LDL-c > 155 mg/dl (4.0 mmol/L) Mean baseline LDL-c 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.

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
<u>Atorvastatin vs. Multiple Statins</u>				
Hunninghake et al. 1998 R, OL, MC, not ITT 344 patients (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>.

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Brown et al. 1998 R, OL, MC, not ITT 318 patients (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>

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Jones et al. 1998 R, OL, MC, not ITT 534 patients 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, 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.

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
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
Gentile et al. 2000 R, OL, MC, not ITT 412 patients 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.

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Andrews et al. 2001 R (4:1:1:1:1), OL, MC, not ITT 3,916 patients 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:** atorva 5% fluva 6% lova 5% prava 6% simva 6% **Trigs reduction from baseline at 54 weeks:** atorva 19% fluva 7% lova 12% prava 9% simva 13% **Achieved LDL-c goal at 54 weeks:** 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.

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

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 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. Mean baseline LDL-c 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:** 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 6 weeks Sponsored by Merck and Co.	Age $\geq$20 years, 45% male, with serum triglyceride levels <400 mg/dl, not following cholesterol-reducing diet, and (a) LDL-c $\geq$190 mg/dl and $\leq$2 CHD risk factors, or (b) $\geq$160 mg/dl and $\geq$2 CHD risk factors, or (c) $\geq$130 mg/dl and definite CHD. Mean baseline LDL-c 187 mg/dl	5-week diet-only run-in phase, then randomization to: fluva 20 mg qd or lova 20 mg qd	Efficacy analysis for 270 patients. **LDL-c reduction from baseline:** fluva: 18% lova: 28% ($p \leq 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.

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Fluvastatin vs. Pravastatin				
Jacotot et al. 1995 R, DB, MC, both ITT and on treatment analysis 134 patients 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.
Fluvastatin vs. Simvastatin				
Ose et al. 1995 R, DB, MC, ITT 432 patients 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% simva 10 mg: 29.9% **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% **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% simva 10 mg: 25%	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.

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Schulte et al. 1996 R, DB 120 patients 10 weeks Funded by Astra.	Men and women 26-74 years with LDL-c >185 mg/dl and trigs <300 mg/dl. <u>Median baseline LDL-c</u> 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. <u>Dose equivalence</u> Fluvastatin 40 mg qd = simvastatin 20 mg qd. Fluvastatin 80 mg qd = simvastatin 40 mg qd.
Sigurdsson et al. 1998 R, DB, MC, not ITT 113 patients 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>

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

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 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:** 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% **Moderate risk meeting NCEP goal:** lova 74%, prava 10 mg: 53%, prava 20 mg: 68%	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 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.

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

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 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 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.

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

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 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:** 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 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 $\geq$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)	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

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

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 6 weeks Industry support not reported.	Men and women 18-70 years with total cholesterol >240 mg/dl <u>Mean baseline LDL-c</u> 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. <u>Dose equivalence</u> Equivalent doses not compared.
Lefebvre et al. 1992 R, DB, MC, not ITT 291 patients 6 weeks Study supported by Merck.	Men and women 18-79 years with total cholesterol >240 mg/dl <u>Mean baseline LDL-c</u> 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% (NS) **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. <u>Equivalent doses not compared.</u>

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Lintott et al. 1993 R, DB, MC, not ITT 48 patients 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: 8.3% simva: 8.3% (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.
Lambrecht et al. 1993 R, DB, MC, not ITT 210 patients 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.

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Simvastatin-Pravastatin Study Group 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 <u>Mean baseline LDL-c</u> 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.
Douste-Blazy et al. 1993 R, DB, MC, not ITT 273 patients 6 weeks Study supported by Merck.	Men and women 22-75 years with an LDL-c ≥160 mg/dl <u>Mean baseline LDL-c</u> 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. <u>Dose equivalence</u> prava 20 mg ≈ or < simva 10 mg qd.

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

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 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 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

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Sasaki et al. 1997 R, OL, C, not ITT 74 patients 16 weeks Industry involvement not reported.	Men or women with total cholesterol >220 mg/dl. Mean baseline LDL-c 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. Dose equivalence Simvastatin 5 and 10 mg > prava 10 mg qd
Paoletti et al. 2001 R, DB, MC, ITT 265 patients 12 weeks Sponsored by and one author employed by AstraZeneca	Men and women age >18 years with hyper-cholesterolaemia, LDL-c 160-250 mg/dl, fasting trig <400 mg/dl Mean baseline LDL-c 189 mg/dl	Screening phase, then randomization to: prava 20 mg or simva 20 mg for 12 weeks	Efficacy analysis for 265 patients. **LDL-c reduction from baseline at 12 weeks:** prava: 28% simva: 37% (p<0.0001) **HDL-c increase from baseline at 12 weeks:** prava: 4% simva: 4% (NS) **Trigs reduction from baseline at 12 weeks:** prava: 13% simva: 14% (NS) **Achieved NCEP ATP II LDL-c goal:** prava: 53% vs simva: 64% (NS)	No serious AEs. Withdrawal due to AEs: prava 3 vs. 1 simva. 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 patients. No clinically significant ALT or CK elevations. Study designed for comparison to rosuvastatin 5 mg and 10 mg. Total n=502.

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day; R=randomized; ULN=upper limit of normal

Evidence Table 1. Trials comparing LDL-c lowering abilities of 2 or more statins (continued)

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (change in lipoprotein levels)	Safety/Comments
Brown et al. 2002 R, DB, MC, not ITT 238 patients (n= 118 prava vs. 120 simva) 52 weeks Trial also included rosuvastatin 5 and 10 mg groups 3 authors employed by AstraZeneca	Men and women ≥18 years with LDL-c ≥160 and <250 mg/dl. Mean baseline LDL-c prava: 188.5 mg/dl simva: 188.0 mg/dl	6-week dietary run-in with NCEP Step 1 diet, then: 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 prava 40 mg or simva 80 mg.	Efficacy analysis for 1087 patients. **LDL-c reduction at 12 (and 52) weeks:** prava: 27% (32%) simva: 35% (38%) **HDL increase at 12 (and 52) weeks:** prava: 8% (5%) simva: 9% (6%) **Trigs reduction at 12 (and 52) weeks:** prava: 11% (9%) simva: 10% (14%) **Achieved LDL-c goal (<100 mg/dl) at 52 weeks:** prava: 51% simva: 63%	Withdrawals due to treatment-related adverse events: 6 prava vs. 7 simva patients. 1 serious ADE identified with treatment: simva patient with asthenia and chest pain, resolved with no change in treatment. Transient elevations in ALT >3x ULN without symptoms: prava 5 vs. simva 2 patients. Transient elevations in AST >3x ULN: prava 4 vs. simva 2 patients. Transient elevations in CK >10x ULN without myopathy: 2 prava vs 3 simva patients. No significance tests compare groups as study focused on comparison of both to

ADEs=adverse drug effects; ALT/AST=liver transaminases; CK=creatine kinase; CO=crossover,DB=double-blind; ITT=intent-to-treat analysis; LDL-c=low density lipoprotein cholesterol; MC=multicenter; NCEP=National Cholesterol Education Panel; OL=open-label; PC=placebo-controlled; qd=once per day;
R=randomized; ULN=upper limit of normal

Evidence Table 2. Randomized controlled 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
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)
Shepherd J., etal. 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 a 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 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
Sacks FM., etal. 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)

CABG=coronary artery bypass graft, MI=myocardial infarction, PTCA=percutaneous transluminal coronary angioplasty; RRR= relative risk reduction, ARR= absolute risk reduction, NNT= number needed to treat

Evidence Table 2. Randomized controlled trials with primary coronary heart disease endpoints (continued)

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
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
Shepherd J., etal. 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 endoint: 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 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
Sacks FM., etal. 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

CABG=coronary artery bypass graft, MI=myocardial infarction, PTCA=percutaneous transluminal coronary angioplasty; RRR= relative risk reduction, ARR= absolute risk reduction, NNT= number needed to treat

Evidence Table 2. Randomized controlled trials with primary coronary heart disease endpoints (continued)

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
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.
Shepherd J., etal. 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 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.
Sacks FM., etal. 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.

CABG=coronary artery bypass graft, MI=myocardial infarction, PTCA=percutaneous transluminal coronary angioplasty; RRR= relative risk reduction, ARR= absolute risk reduction, NNT= number needed to treat

Evidence Table 2. Randomized controlled trials with primary coronary heart disease endpoints (continued)

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline
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%
Heart Protection Study Collaborative Group 2002 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)
<u>From July 2003 Update:</u>						
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).

CABG=coronary artery bypass graft, MI=myocardial infarction, PTCA=percutaneous transluminal coronary angioplasty; RRR= relative risk reduction, ARR= absolute risk reduction, NNT= number needed to treat

Evidence Table 2. Randomized controlled trials with primary coronary heart disease endpoints (continued)

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
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
Heart Protection Study Collaborative Group 2002 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
<u>From July 2003 Update:</u>					
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

CABG=coronary artery bypass graft, MI=myocardial infarction, PTCA=percutaneous transluminal coronary angioplasty; RRR= relative risk reduction, ARR= absolute risk reduction, NNT= number needed to treat

Evidence Table 2. Randomized controlled trials with primary coronary heart disease endpoints (continued)

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Scandinavian Simvastatin Survival Study Group 1994 Scandinavian Simvastatin Survival Study (4S)	**Post-hoc analysis: fatal and nonfatal cerebrovasular 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 majorcoronary 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.
Heart Protection Study Collaborative Group 2002 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.
<u>From July 2003 Update:</u>			
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.

CABG=coronary artery bypass graft, MI=myocardial infarction, PTCA=percutaneous transluminal coronary angioplasty; RRR= relative risk reduction, ARR= absolute risk reduction, NNT= number needed to treat

Evidence Table 2. Randomized controlled trials with primary coronary heart disease endpoints (continued)

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline
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 $\leq$ 6.5 mmol/L (calculated = 253 mg/dL), age 40-79, with untreated hypertension or treated hypertension with systolic blood pressure $\geq$ 140 mm Hg, diastolic blood pressure $\geq$ 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%

CABG=coronary artery bypass graft, MI=myocardial infarction, PTCA=percutaneous transluminal coronary angioplasty; RRR= relative risk reduction, ARR= absolute risk reduction, NNT= number needed to treat

Evidence Table 2. Randomized controlled trials with primary coronary heart disease endpoints (continued)

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
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

CABG=coronary artery bypass graft, MI=myocardial infarction, PTCA=percutaneous transluminal coronary angioplasty; RRR= relative risk reduction, ARR= absolute risk reduction, NNT= number needed to treat

Evidence Table 2. Randomized controlled trials with primary coronary heart disease endpoints (continued)

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
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	

CABG=coronary artery bypass graft, MI=myocardial infarction, PTCA=percutaneous transluminal coronary angioplasty; RRR= relative risk reduction, ARR= absolute risk reduction, NNT= number needed to treat

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?	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	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Unsure	Yes	Attrition-yes, crossovers-no, adherence-yes, contamination-no	No	Fair-LDL lowering Poor-safety (no details on serious ADEs and dropouts)
Bertolini 1997	Yes	Not reported	Yes, not much detail	Yes	Yes	Yes	Yes	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 ADEs and dropouts)
Assman 1999	Yes	Not reported	Yes	Yes	No details given	No details given	No details given	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 ADEs

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?	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)
Dart 1997	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	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 ADEs, dose and dropouts)
Marz 1999	Yes	Not reported	Yes	Yes	Yes-serious ADE	No	No	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 ADE occurred.
Van Dam 2000	Yes-computer lists (adequate)	Not reported	No-patient risk factors Yes-Lipo-protein levels	Yes	Yes	Yes	No	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 ADEs or withdrawals.

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?	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)
Farnier 2000	Yes	Not reported	Yes	Yes	Yes	No	No	Yes	Yes	Attrition reported for ADEs 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 ADEs for each group.
Recto 2000	Yes	Not reported	Yes	Yes	No	No	No	No	Yes	Attrition-yes, crossovers-yes, adherence-not reported, contamination-N/A	No	Fair-LDL lowering. Fair-safety included details on withdrawal and ADEs.
Insull 2001	Yes	Not reported	Yes	Yes	No	No	No	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	Yes	Not reported	More women in the atorva group	Yes	Yes	Yes	Yes	No	More women in the atorva group	Attrition-only reported for ADEs, crossovers-no, adherence-no-contamination-no	Do not know	Fair-LDL-lowering, Fair-good-safety

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?	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)
Branchi 2001	Yes	Not reported	Not enough detail given	Yes	Not reported	Not reported	Not reported	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												
Olsson 2003												

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?	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)
Hunninghake 1998	Yes	Not reported	Yes	Yes	No	No	No	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 ADE or doses.
Brown 1998	Yes	Not reported	Yes	Yes	No	No	No	No	Yes	Attrition-only reported for ADEs, 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 ADE or 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?	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)
Jones 1998	Yes	Not reported	Yes-not much detail. LDL-c slightly lower for 3 of 4 atorva groups.	Yes	No	No	No	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.
Wolffenbuttel 1998	Yes	Not reported	N/A cross-over trial	Yes	No	No	No	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.
Gentile 2000	Yes	Not reported	Yes	Yes	No	No	No	No	Yes	Attrition-yes, crossovers-no, adherence-no, contamination-yes	No	Fair-poor LDL lowering. Nonequivalent doses compared. Fair-safety

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?	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)
Andrews 2001	Yes	Not reported	Yes	Yes	No	No	No	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 ADEs.

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?	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)
Nash 1996	Yes	Not reported	No-higher rate of musculoskeletal conditions in lova group.	Yes	No	No	No	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 musculoskeletal conditions in lova group. Also no doses at which ADEs in fluva group occurred.
Berger 1996												
Jacotot 1995	Yes	Not reported	Yes, for height, weight, BMI	Yes	Yes	Yes	Yes	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 ADEs occurred.
Ose 1995	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	No	Yes	Attrition-yes, crossovers-no, adherence-yes, contamination-no	No	Fair-LDL lowering. Fair-safety.

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?	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)
Schulte 1996	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	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 ADEs.(?2)
Sigurdsson 1998												
Van Dam 2001												
McPherson 1992												
Lovastatin Pravastatin Study Group 1993												
Weir 1996												

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?	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)
Strauss 1999												
Farmer 1992												
Frohlich 1993												
Malini 1991												
Lefebvre 1992												
Lintott 1993												
Lambrecht 1993												
Simvastatin Pravastatin Study Group 1993												
Douste-Blazy 1993												
Stalenhoef 1993												

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?	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)
Steinhagen-Thiessen 1994												
Sasaki 1997												
Paoletti 2001												
Brown 2002												
Studies from Evidence Table 2 - Tier 1												
AFCAPS 1998	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Attrition-yes, crossovers-no actual numbers provided, adherence-yes and contamination-no actual numbers provided.	No	Good
WOSCOPS 1995	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Both intention to treat and on treatment analysis	Yes	Attrition-yes, crossovers-no, adherence-no details and contamination-no	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?	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)
HPS	NR	Adequate; centralized	Unclear; "good balance" indicated; data NR	Yes	Yes	Yes	Yes	Yes	NR	Attrition=13.9%; Crossovers NR; Adherence (>/= 80%)=82%; Contamination=4002(19.5%) taking non-study statin	No	Good
ALLHAT-LLC *(open trial)*	Adequate; computer-generated scheme	adequate; centralized	Yes	Yes	No	No	No	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	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes	NR	Attrition unclear; others NR	No	Fair-Good
LIPID 1998	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Attrition: yes, crossovers-no, adherence-no, and contamination-yes	No	Good
CARE 1996	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Attrition: yes, crossovers-no, adherence-no, and contamination-yes	No	Good
4S 1994	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Attrition-yes, crossovers-no, adherence-reported as good with no details provided, and contamination-no.	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?	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)
PROSPER	Adequate; computer-generated scheme	Adequate; centralized	Yes	Yes	Yes	Yes	Yes	Yes	NR	Attrition=1449(24.9%); Adherence(average)= 94%; others NR	NR	Good
<u>Studies from Evidence Table 5 - Tier 2</u>												
LCAS												
ACAPS												
CCAIT												
MARS												
REGRESS												
PLAC-I												
PLAC-II												
KAPS												
Sato												
MAAS												
CIS												
SCAT												
<u>Studies from Evidence Table 6 - Tier 3: Post-revascularization</u>												
FLARE												
Weintraub												
PCABG												
CLAPT												
PREDICT												
CARE (subgroup)												

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?	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)
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	Yes	NR	Attrition= 124(7.4%); others NR	No	Fair
<u>Studies from Evidence Table 6 - Tier 3: Miscellaneous</u>												
AVERT Target Tangible Riegger Pravastatin Multinational Study Group												
Holdaas	NR	Adequate; serially-numbered identical medication packs	Yes	Yes	Yes	Yes	Yes	Yes	NR	Attrition=314(14.9%); others NR	No	Good

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

Evidence Table 4. External Validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup	Quality Rating
Studies from E				
Davidson 1997	Not reported, although Parke-Davis Pharmaceutical is listed as a contributer.	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.	Fair-LDL lowering, Poor-safety no details on withdrawal from groups.
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.	Fair-LDL lowering, Poor-safety no details on types of events requiring withdrawal from groups.
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 ADE. No details on number dropping out of the study for other reasons.	Fair-LDL lowering, Poor-safety no details on type of ADEs or dose in which they occurred.
Dart 1997	Study supported by Parke-Davis Pharmaceutical Research as well as listed as a contributer.	Yes	52 weeks. Withdrawal for adverse effects was reported , but no information on dose or type of ADE. No details on number dropping out of the study for other reasons.	Fair-LDL lowering, Poor-safety no details on type of ADEs or dose in which they occurred.
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. ADE or other) and was 9% in both groups.	Fair-LDL-lowering, Fair-safety although no dose in which ADEs occurred was given.

Evidence Table 4. External Validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
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.
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.

Evidence Table 4. External Validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup	Quality Rating
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.	Fair-poor-LDL lowering, no reasons for withdrawal given. Poor-safety, no details on dose ADEs occurred and specific types or withdrawal for ADEs.
Farnier 2000	Study financially supported by Parke-Davis and Pfizer.	Yes	12 weeks. 2 patients withdrew due to ADE, no other details given on dropouts.	Fair-LDL lowering, Poor-safety few details on type of ADEs or dose in which they occurred.
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.	Fair-LDL lowering, Fair-safety adverse effects were detailed for drug and dosage.
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.	Poor-LDL lowering nonequivalent doses compared. Safety-poor no details on withdrawal or doses at which ADEs occurred. Short-term trial.
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.	Fair-good LDL-lowering since there were mininal exclusions, Fair-good safety
Branchi 2001	Not reported	Yes	8-week dietary run-in. 200 patients randomized, 1 lost to follow up	Fair-LDL lowering, Poor-safety no details on type of ADEs.

Evidence Table 4. External Validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
Karalis 2002			
Olsson 2003			
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	Menor 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	Quality Rating
Karalis 2002				
Olsson 2003				
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.	Fair-LDL-lowering, Poor-safety no reasons for withdrawal for ADEs and no dose in which ADEs occurred was given.
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.	Fair-LDL lowering, Poor-safety no reasons for withdrawal for ADEs and no dose in which ADEs occurred.
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.	Fair-poor-LDL lowering. Small sample size for some groups and no details on reasons for withdrawal given. Also, 3 out of 4 atorva groups started with lower LDL-c values. Poor-safety, 8 patients lost to follow up.
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	Fair-poor-diabetics excluded. Fair-poor safety. Short-term with small numbers of patients and low statin doses.

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, majorsurgery or PTCA 6 months prior to study, secondary causes of hyperlipidemia (alcholism, 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.

Evidence Table 4. External Validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup	Quality Rating
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.	Fair-LDL lowering. Fair-Safety
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.	Fair-poor-LDL lowering. High drop out or loss to follow up with no reasons for withdrawal provided. Fair-poor safety since high drop out rate for unknown reasons.
Nash 1996	Study funded by Sandoz Pharmaceuticals	Yes	6-week dietary/placebo washout period, 137 patients randomized and completed the study. 8 week study.	Poor-large numbers of patients excluded after dietary/placebo washout phase. Also DM excluded. Poor-safety:higher number of patients in lova group with musculoskeletal conditions and dose at which ADEs occurred with fluva not reported.
Jacotot 1995	Sandoz funded and participated in trial.	Yes	134 randomized. 16 weeks. 11 patients withdrew during trial	Fair-LDL lowering. Fair-Safety: no details on dose when ADEs occurred.
Ose 1995	Funded by Merck	Yes	432 patients randomized and followed for 6 weeks.	Fair-LDL lowering. Fair-safety.

Evidence Table 4. External Validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
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.
Sigurdsson 1998			
Van Dam 2001			
McPherson 1992			
Lovastatin Pravastatin Study Group 1993			
Weir 1996			
Strauss 1999			
Farmer 1992			
Frohlich 1993			
Malini 1991			

Evidence Table 4. External Validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup	Quality Rating
Schulte 1996	Funded by Astra	Yes	120 patients randomized, unknown completing 10 week study.	Fair-poor LDL lowering: unsure of number completing study. Fair-poor-safety unsure number of drop outs.
Sigurdsson 1998				
Van Dam 2001				
McPherson 1992				
Lovastatin Pravastatin Study Group 1993				
Weir 1996				
Strauss 1999				
Farmer 1992				
Frohlich 1993				
Malini 1991				

Evidence Table 4. External Validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
Lefebvre 1992			
Lintott 1993			
Lambrecht 1993			
Simvastatin Pravastatin Study Group 1993			
Douste-Blazy 1993			
Stalenhoef 1993			
Steinhagen-Thiessen 1994			
Sasaki 1997			
Paoletti 2001			
Brown 2002			
Studies from Evidence Table 2 - Tier 1			

Evidence Table 4. External Validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup	Quality Rating
Lefebvre 1992				
Lintott 1993				
Lambrecht 1993				
Simvastatin Pravastatin Study Group 1993				
Douste-Blazy 1993				
Stalenhoef 1993				
Steinhagen-Thiessen 1994				
Sasaki 1997				
Paoletti 2001				
Brown 2002				
Studies from E				

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 ciclosporin, 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.
ALLHAT-LLT	Age $\geq$55 with stage 1 or 2 hypertension and $\geq$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.

Evidence Table 4. External Validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup	Quality Rating
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 disontinuation rates were similar for other reasons in both groups.	Fair. A number of the authors were employees of Merck and Co or were consultants, speakers or had research projects funded by Merck and Co. No details given on withdrawal prior to study end.
WOSCOPS 1995	Role unknown. Supported by a research grant from Bristol-Myers Squibb.	yes-primary prevention	4.9 years: At 1 year, 14.9 vs. 15.5 % of placebo vs. pravastatin recipients withdrew. At year 2, 19.1 vs. 19.4 placebo vs pravastastin withdrew. At year 3, 22.5 vs. 22.7 placebo vs. pravastatin withdrew. At year 4, 25.2 vs. 24.7 placebo vs. pravastatin withdrew. At year 5, 30.8 vs. 29.6 placebo vs. pravastatin patients withdrew (cumulative withdrawal rates).	Fair-poor Women excluded
HPS	UK Medical Research Council; British Heart Foundation; Merck & Co; Roche	Yes	5 years (mean)	Good
ALLHAT-LLT	National Heart, Lung, and Blood Institute; Pfizer; AstraZeneca; Bristol-Myers Squibb	Yes	4.8 years (mean)	Fair-Good

Evidence Table 4. External Validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
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.

Evidence Table 4. External Validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup	Quality Rating
ASCOT	Pfizer, New York, NY, USA; Servier Research Group; Leo Laboratories	Yes	3.3 years (median)	Fair-Good
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.	Good. However no details provided on total number of patients recruited.

Evidence Table 4. External Validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
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.
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.

Evidence Table 4. External Validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup	Quality Rating
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.	Fair. No details given on recruited patients or patients withdrawn prior to study end.
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.	Fair. No details given on withdrawal prior to study end.

Evidence Table 4. External Validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
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 <u><</u>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.
<u>Studies from Evidence Table 5 - Tier 2</u>			
LCAS			
ACAPS			
CCAIT			
MARS			
REGRESS			
PLAC-I			
PLAC-II			
KAPS			
Sato			
MAAS			
CIS			
SCAT			
<u>Studies from Evidence Table 6 - Tier 3: Post-revascularization</u>			
FLARE			
Weintraub			
PCABG			
CLAPT			
PREDICT			
CARE (subgroup)			

Evidence Table 4. External Validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup	Quality Rating
PROSPER	Bristol-Myers Squibb, USA	Yes	3.2 years (mean)	Good
Studies from E				
LCAS				
ACAPS				
CCAIT				
MARS				
REGRESS				
PLAC-I				
PLAC-II				
KAPS				
Sato				
MAAS				
CIS				
SCAT				
Studies from E				
FLARE				
Weintraub				
PCABG				
CLAPT				
PREDICT				
CARE (subgroup)				

Evidence Table 4. External Validity

Study Year	Similarity of Population to Disease Population	Number recruited	Exclusion Criteria
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.
Studies from Evidence Table 6 - Tier 3: Miscellaneous			
AVERT			
Target Tangible			
Riegger			
Pravastatin Multinational Study Group			
Holdaas	Men and women aged 30-75 who received renal or renal/pancreas transplants ≥ 6 months prior, with stable graft function. All using ciclosporin. 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 ≤ 1 year.

Evidence Table 4. External Validity

Study Year	Funding Source	Control Group Standard of Care	Length of followup	Quality Rating
LIPS	Novartis Pharma AG	Yes	3.9 years (median)	Fair
Studies from E				
AVERT				
Target				
Tangible				
Riegger				
Pravastatin Multinational Study Group				
Holdaas	Novartis Pharma AG	Yes	5.1 years (mean)	Good

Evidence Table 5. Atherosclerosis 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. Atherosclerosis progression trials (continued)

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. Atherosclerosis progression trials (continued)

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. Atherosclerosis progression trials (continued)

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. Atherosclerosis progression trials (continued)

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. Atherosclerosis progression trials (continued)

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. Atherosclerosis progression trials (continued)

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction from baseline	Primary Endpoint
MAAS Investigators 1994 Multicentre Anti-Atheroma Study	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	404 men and women 30-67 years with 2 or > coronary artery segments occluded and hypercholesterolemia	Simvastatin 20 mg qpm or placebo qpm.	4 years	169 mg/dl (4.38 mmol/L)	31%	Per-patient average of mean lumen diameters of all coronary segments(diffuse atherosclerosis) and the per-patient average of MLD of all segments that were atheromatous at baseline, follow up or both (focal atherosclerosis) as assessed by coronary angiography.
Bestehorn 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 >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.

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. Atherosclerosis progression trials (continued)

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.

*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 (continued)

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).

*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 (continued)

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction	Primary Endpoint
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
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

*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 (continued)

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
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.
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)

*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 (continued)

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction	Primary Endpoint
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
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)

*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 (continued)

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
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)
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.

*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 (continued)

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction	Primary Endpoint
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.
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)

*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 (continued)

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
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.
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.

*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 (continued)

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction	Primary Endpoint
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%	Reduction in cardiac events: Death from cardiovascular cause (fatal MI, sudden cardiac death), nonfatal MI, CABG, and USA.
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)

*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 (continued)

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
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).	N/A	N/A	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.
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).

*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 (continued)

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction	Primary Endpoint
From July 2003 Update:							
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.
Holdaas H. et al. 2003	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	Major adverse cardiac event: cardiac death, nonfatal MI, coronary intervention procedure

*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 (continued)

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
From July 2003 Update:				
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).
Holdaas H. et al. 2003	**Total events** RRR = 17%, p=.139 NS **Cardiac death** RRR= 38%, p= .031 ARR= 1.7 events/100 ppl 95% CI= 4-60% NTT= 41 **Definite nonfatal MI** RRR= 32%, p= .05 ARR= 1.9 events/100 ppl 95% CI= 0-60% NTT= 47 **CABG or PCI** RRR= 11%, p= NS	Cerebrovascular events, all-cause mortality, graft loss or doubling of serum creatinine	**All-cause death** RRR= -2%, p= NS **Cerebrovascular and other vascular cause of death** RRR= -58%, p= NS **Fatal+nonfatal CBV events** RRR= -16%, p= NS **Graft loss or doubling of serum creatinine** RRR= -10%, 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%)

*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

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. Methods for Drug Class Reviews for Oregon Health Plan Practitioner-Managed Prescription Drug Plan Oregon Health & Science University Evidence-based Practice Center

Quality Criteria

Assessment of Internal Validity
To assess the internal validity of individual studies, the EPC adopted criteria for assessing the internal validity of individual studies from the US Preventive Services Task Force and the NHS Centre for Reviews and Dissemination.

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 week days
    - 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 Reports of 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?

Economic Studies

Assessment of Internal Validity

Framing

1. Was a well-defined question posed in answerable form?
2. Was a comprehensive description of the competing alternatives given?
3. Are the interventions and populations compared appropriate?
4. Is the study conducted from the societal perspective?
5. Is the time horizon clinically appropriate and relevant to the study question?

Effects

1. Are all important drivers of effectiveness included?
2. Are key harms included?
3. Is the best available evidence used to estimate effectiveness?
4. Are long-term outcomes used?

5. Do effect measures capture preferences or utilities?

Costs

1. Are costs and outcomes measured accurately?
2. Are costs and outcomes valued credibly?
3. Are costs and outcomes adjusted for differential timing?
4. Are all appropriate downstream medical costs included?
5. Are charges converted to costs appropriately?
6. Are the best available data used to estimate costs? (like first question)
7. Are all important and relevant costs and outcomes for each alternative identified?

Results

1. Are incremental cost-effectiveness ratios presented?
2. Are appropriate sensitivity analyses performed?
3. How far do study results include all issues of concern to users?

Assessment of External Validity

1. Are the results generalizable to the setting of interest in the review?