Drug Class Review

HMG-CoA Reductase Inhibitors (Statins) and Fixed-dose Combination Products Containing a Statin

Final Report
Update 5

November 2009

This report reviews information about the comparative effectiveness and safety of drugs within a pharmaceutical class. The report is neither a usage guideline nor an endorsement or recommendation of any drug, use, or approach. Oregon Health & Science University does not endorse any guideline or recommendation developed by users of this report.

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

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INTRODUCTION

In the United States, coronary heart disease and cardiovascular disease account for nearly 40% of all deaths each year. Coronary heart disease continues to be the leading cause of mortality and a significant cause of morbidity among North Americans. In 2006, coronary heart disease claimed 607 000 lives, translating into about 1 out of every 5 deaths in the United States.[1] High levels of cholesterol, or hypercholesterolemia, are an important risk factor for coronary heart disease. The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors, also known as statins, are the most effective class of drugs for lowering serum low-density lipoprotein cholesterol concentrations. They are first-line agents for patients who require drug therapy to reduce serum low-density lipoprotein cholesterol concentrations.

Statins work by blocking the enzyme HMG-CoA reductase, the rate-limiting step in the manufacture of cholesterol. Statins reduce low-density lipoprotein cholesterol, total cholesterol, and triglycerides and slightly increase high-density lipoprotein cholesterol. Statins may also have anti-inflammatory and other pleiotroptic[2] effects. A recent good-quality systematic review found that all statins are equally effective at lowering C-reactive protein levels, but do not affect fibrinogen or several other markers of inflammation.[3]

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[4] and updated in August 2004 to include evidence from more recent trials.[5] The report stressed that the intensity of treatment should be directed by the degree of cardiovascular risk. Target low-density lipoprotein cholesterol levels depend on the patient's risk of heart disease, medical history, and initial low-density lipoprotein cholesterol level. For most patients who are prescribed a statin, the target will be less than 130 mg/dL or less than 100 mg/dL. In the Adult Treatment Panel III, patients who have type 2 diabetes without coronary heart disease, peripheral or carotid vascular disease, and patients who have multiple risk factors and a 10-year risk of coronary heart disease of greater than 20% are said to have "coronary heart disease equivalents." This means that the criteria for using drug therapy and the low-density lipoprotein target (less than 100 mg/dL) is the same as for patients who have a history of coronary heart disease. A low-density lipoprotein cholesterol goal of less than 70 mg/dL for high-risk patients is a therapeutic option. Factors that place patients in the category of *very high risk* favor a decision to reduce low-density lipoprotein cholesterol levels to less than 70 mg/dL. These factors are the presence of established cardiovascular disease plus (1) multiple major risk factors (especially diabetes), (2) severe and poorly controlled risk factors (especially continued cigarette smoking), (3) multiple risk factors of the metabolic syndrome (triglycerides greater than 200 mg/dL plus non-high-density lipoprotein cholesterol greater than 130 mg/dL with low high-density lipoprotein cholesterol [less than 40 mg/dL]), and (4) patients with acute coronary syndromes. The optional goal of less than 70 mg/dL does not apply to individuals who are not high risk.

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

The American Heart Association/American College of Cardiology guidelines qualify this recommendation as follows:

"When the <70 mg/dL target is chosen, it may be prudent to increase statin therapy in a graded fashion to determine a patient's response and tolerance. Furthermore, if it is not possible to attain low-density lipoprotein cholesterol <70 mg/dL because of a high baseline low-density lipoprotein cholesterol, it generally is possible to achieve low-density lipoprotein cholesterol reductions of >50% with either statins or low-density lipoprotein cholesterol–lowering drug combinations. Moreover, this guideline for patients with atherosclerotic disease does not modify the recommendations of the 2004 Adult Treatment Panel III update for patients without atherosclerotic disease who have diabetes or multiple risk factors and a 10-year risk level for coronary heart disease >20%. In the latter 2 types of high-risk patients, the recommended low-density lipoprotein cholesterol goal of <100 mg/dL has not changed. Finally, to avoid any misunderstanding about cholesterol management in general, it must be emphasized that a reasonable cholesterol level of <70 mg/dL does not apply to other types of lower-risk individuals who do not have coronary heart disease or other forms of atherosclerotic disease; in such cases, recommendations contained in the 2004 Adult Treatment Panel III update still pertain."[6]

Six statins are available in the United States and Canada (Table 1).

Table 1. Included statins

Statin	Strength	Dose range	Usual starting dose
Atorvastatin (Lipitor®)	10 mg, 20 mg, 40 mg, 80mg	10-80 mg once daily	20 mg
Fluvastatin (Lescol and Lescol XL®)	20 mg, 40 mg XL, 80 mg	20-80 mg once daily or divided bid; XL once daily	20 mg
Lovastatin[a] (Mevacor and extended release Altoprev®)	20 mg, 40 mg, 20 mg, 40 mg, 60 mg	20-80 mg daily or divided bid 20-80 mg once daily Altoprev	20 mg
Pravastatin[a] (Pravachol®)	10 mg, 20 mg, 40 mg, 80 mg (also 30 mg in generic only)	10-80 mg once daily	40 mg
Rosuvastatin (Crestor®)	5 mg, 10 mg, 20 mg, 40 mg	5-40 mg once daily	10 mg
Simvastatin[a] (Zocor®)	5 mg, 10 mg, 20 mg, 40 mg, 80 mg	5-80 mg once daily	40 mg

[a] Available in generic and trade form.

Three fixed-dose combination products containing a statin and another lipid-lowering drug are available in the United States while only 1 is currently available in Canada (Table 2). There are currently 3 fixed-dose combination products on the market in the United States that combine a statin medication with either extended release niacin or ezetimibe. Niacin is vitamin B3. Although its mechanism of action is not fully understood, it believed to be effective in

improving the lipid profile by inhibiting lipolysis of adipose tissue, inhibiting hepatic synthesis of triglycerides, and likely suppressing apo A-1 hepatic removal.[7] The result of this is reduction in triglycerides, elevation of high-density lipoprotein, and reduction of low-density lipoprotein. Niacin has been shown to reduce the risk of myocardial infarction.[8] Ezetimibe inhibits the absorption of cholesterol from the small intestine by binding to the Niemann-Pick C1-Like 1 receptor on the brush border. The effect is a lowering of low-density lipoprotein cholesterol.[9]

Table 2. Included fixed-dose combination products

Fixed-dose combination product	Strength	Dose range	Usual starting dose
Lovastatin/Niacin-ER (Advicor®)	20/500 mg 20/750 mg 20/1000 mg 40/1000 mg	20/500 mg – 80/2000 mg once daily	20/500 mg
Simvastatin/Niacin-ER (Simcor®), not available in Canada	20/500 mg 20/750 mg 20/1000 mg	10/500 – 40/2000 mg	20/500 mg if niacin naive
Simvastatin/Ezetimibe (Vytorin®), not available in Canada	10/10 mg 10/20 mg 10/40 mg 10/80 mg	10/10 – 10/80 mg	10/20 mg (10/40 if need >55% LDL-C reduction)

Abbreviations: LDL-C, low-density lipoprotein cholesterol.

Purpose and Limitations of Systematic Reviews

Systematic reviews, also called evidence reviews, are the foundation of evidence-based practice. They focus on the strength and limits of evidence from studies about the effectiveness of a clinical intervention. Systematic reviews begin with careful formulation of research questions. The goal is to select questions that are important to patients and clinicians then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix A and are defined as they apply to reports produced by the Drug Effectiveness Review Project.

Systematic reviews emphasize the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality of life) are preferred over studies of intermediate outcomes (such as change in bone density). Reviews also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of *absolute risk* or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in each group, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant between groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than absolute risk reduction. Another useful measure is the *number needed to treat* (or harm). The number needed to treat is the number of patients who would need be treated with an intervention for 1 additional patient to benefit

(experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

Systematic reviews weigh the quality of the evidence, allowing a greater contribution from studies that meet high methodological standards and, thereby, reducing the likelihood of biased results. In general, for questions about the relative benefit of a drug, the results of well-executed randomized controlled trials are considered better evidence than results of cohort, case-control, and cross-sectional studies. In turn, these studies provide better evidence than uncontrolled trials and case series. For questions about tolerability and harms, observational study designs may provide important information that is not available from controlled trials. Within the hierarchy of observational studies, well-conducted cohort designs are preferred for assessing a common outcome. Case-control studies are preferred only when the outcome measure is rare and the study is well conducted.

Systematic reviews pay particular attention to whether results of *efficacy studies* can be generalized to broader applications. Efficacy studies provide the best information about how a drug performs in a controlled setting. These studies attempt to tightly control potential confounding factors and bias; however, for this reason the results of efficacy studies may not be applicable to many, and sometimes to most, patients seen in everyday practice. Most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, adherence to treatment, or severity of illness. For many drug classes, including the antipsychotics, unstable or severely impaired patients are often excluded from trials. In addition, efficacy studies frequently exclude patients who have comorbid disease, meaning disease other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that are impractical in typical practice settings. These studies often restrict options that are of value in actual practice, such as combination therapies and switching to other drugs. Efficacy studies also often examine the short-term effects of drugs that in practice are used for much longer periods. Finally, efficacy studies tend to assess effects by using objective measures that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Systematic reviews highlight studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the "average" patient than results from the highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures, such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it was neither possible nor desirable to exclude evidence based on these characteristics. Labeling a study as either an efficacy or an effectiveness study, although convenient, is of limited value; it is more useful to consider whether the patient

population, interventions, time frame, and outcomes are relevant to one's practice or to a particular patient.

Studies anywhere on the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard for determining whether characteristics of different drugs are related to their effects on disease. Systematic reviews thoroughly cover the efficacy data in order to ensure that decision makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how large the quantity, may have limited applicability to practice. Clinicians can judge the relevance of studies' results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs there exist few or no effectiveness studies and many efficacy studies. Yet clinicians must decide on treatment for patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. Systematic reviews indicate whether or not there exists evidence that drugs differ in their effects in various subgroups of patients, but they do not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these decisions must be informed by clinical judgment.

In the context of development of recommendations for clinical practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of an intervention are based on strong evidence from clinical studies. By themselves, they do not say what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is untrue. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policy. Additional criteria include acceptability to physicians and patients, potential for unrecognized harm, applicability of the evidence to practice, and consideration of equity and justice.

Scope and Key Questions

The purpose of this review is to compare the efficacy and adverse effects of different statins. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to clinicians and patients. Since the last review, the participating organizations have decided to include pediatric population and fixed-dose combination products containing a statin and another lipid-lowering drug. The participating organizations approved the following key questions to guide this review:

1. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to reduce low-density lipoprotein cholesterol?
    a. Are their doses for each statin or fixed-dose combination product containing a statin and another lipid-lowering drug that produce similar percent reduction in low-density lipoprotein cholesterol between statins?
    b. Is there a difference in the ability of a statin or fixed-dose combination product containing a statin and another lipid-lowering drug to achieve National Cholesterol Education Panel goals?

2. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to raise high-density lipoprotein cholesterol?
    a. Are there doses for each statin or fixed-dose combination product containing a statin and another lipid-lowering drug that produce similar percent increase in high-density lipoprotein cholesterol between statins?
    b. Is there a difference in the ability of a statin or fixed-dose combination product containing a statin and another lipid-lowering drug to achieve National Cholesterol Education Panel goals?

3. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to reduce the risk of nonfatal myocardial infarction, coronary heart disease (angina), coronary heart disease mortality, all-cause mortality, stroke, hospitalization for unstable angina, or need for revascularization (coronary artery bypass graft, angioplasty, or stenting)?

4. Are there differences in effectiveness of statins and fixed-dose combination products containing a statin and another lipid-lowering drug in different demographic groups or in patients with comorbid conditions (e.g., diabetes, obesity)?

5. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid-lowering drug when used in the general population of children or adults?

6. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid-lowering drug when used in special populations or with other medications (drug-drug interactions)? In addressing this question, we will focus on the following populations:
    a. Patients with HIV
    b. Organ transplant recipients
    c. Patients at high risk for myotoxicity (e.g., patients with a history of statin-associated muscle-related harms due to drug-drug/drug-food interactions, patients co-administered fibrates, patients taking potent 3A4 inhibitors, elderly patients, especially elderly females)
    d. Patients at high risk for hepatotoxicity
    e. Patients using fibrates (gemfibrozil, fenofibrate, fenofibric acid) or niacin
    f. Children with nephrotic syndrome

The choice of key questions reflects the view that the following criteria may be used to select a statin: (1) the ability to lower low-density lipoprotein cholesterol, (2) the ability to raise high-density lipoprotein cholesterol, (3) the amount of information on cardiovascular outcomes available for each statin or fixed-dose combination product containing a statin and another lipid-lowering drug, (4) adverse effects, and (5) effects in demographic subgroups and in patients with concurrent medical conditions and drug therapies.

Inclusion Criteria

Populations

- Outpatients targeted for primary or secondary prevention of coronary heart disease or non-coronary forms of atherosclerotic disease with or without hypercholesterolemia
- Inpatients with acute coronary syndrome or undergoing revascularization (if the statin was continued after hospital discharge and if health outcomes were reported)
- Adults and children with familial hypercholesterolemia (homozygous or heterozygous).
- Exclusions: Adults with rare, severe forms of hypercholesterolemia (low-density lipoprotein cholesterol greater than or equal to 250 mg/dL)

Interventions

Individual statins
Atorvastatin (Lipitor®)
Fluvastatin (Lescol®)
Fluvastatin extended release (Lescol XL®)
Lovastatin (Mevacor®)
Lovastatin extended release (Altoprev®[a])
Pravastatin (Pravachol®)
Rosuvastatin (Crestor®)
Simvastatin (Zocor®)
Fixed-dose combination products containing a statin
Lovastatin, niacin extended release (Advicor®)
Simvastatin, ezetimibe (Vytorin®[a])
Simvastatin, niacin extended release (Simcor®[a])

[a] Not available in Canada.

We did not include products that contained a statin and a non-lipid-lowering drug such as Caduet® (atorvastatin; amlodipine).

Comparators

For effectiveness and harms of individual statins:

- For Key Questions 1 and 2, head-to-head trials comparing one statin to another
- For other key questions, trials comparing a statin to placebo or another active comparator

For effectiveness and harms of fixed-dose combination products containing a statin:

- Head-to-head trials comparing one fixed-dose combination product to another
- Trials comparing a fixed-dose combination product to an individual statin, placebo, or another active comparator
- Exclusions: Trials comparing a fixed-dose combination product to the product's individual components given separately (co-administration)

Outcomes

Intermediate outcomes

- Low-density lipoprotein cholesterol-lowering ability
- High-density lipoprotein cholesterol-raising ability

Health outcomes

- Reduction in nonfatal myocardial infarction, coronary heart disease, mortality (coronary heart disease and all-cause), stroke, and need for revascularization (including coronary artery bypass grafting, angioplasty, and coronary stents)

Harms outcomes

- Overall adverse events
- Withdrawals due to adverse events
- Serious adverse events
- Specific adverse events (including, but not limited to, hepatotoxicity, myopathy, rhabdomyolysis, renal toxicity, and myalgia)

Study designs

Based on the "hierarchy of evidence" approach, controlled clinical trials and systematic reviews were considered for assessment of effectiveness, whereas for the assessment of harms, controlled clinical trials, observational studies, and systematic reviews were considered. If higher-level evidence was not available and a gap existed then the authors considered other levels of evidence. However, studies that did not provide original data (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, were excluded.

METHODS

Literature Search

To identify articles relevant to each key question, we searched the Cochrane Central Register of Controlled Trials (2nd Quarter 2009), MEDLINE (1966-June 4, 2009), PreMEDLINE (through June 4, 2009), and reference lists of review articles (see Appendix B for complete search strategies). Pharmaceutical manufacturers were invited to submit dossiers and citations. For Update 5 we received dossiers from the manufacturers of fluvastatin, rosuvastatin, and the fixed-dose combination products simvastatin/niacin extended release and simvastatin/ezetimibe. All citations were imported into an electronic database (EndNote XI).

Study Selection

Using the criteria listed above, 2 reviewers independently assessed abstracts of citations identified from literature searches for inclusion. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria.

Data Abstraction

We abstracted the following data from included trials: study design, setting, and population characteristics (including sex, age, ethnicity, and diagnosis); eligibility and exclusion criteria; interventions (dose and duration); comparisons; numbers screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome (nonfatal myocardial infarction), new coronary heart disease (new angina or unstable angina), coronary heart disease mortality, all-cause mortality, stroke or transient ischemic attack, need for revascularization, and percent change from baseline in low-density lipoprotein cholesterol and high-density lipoprotein cholesterol. 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 C. These criteria are based on those developed by the United States Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).[10, 11] For Key Question 3, we rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw in 1 or more categories were rated poor quality; trials meeting all criteria were rated good quality; the remainder were rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population and how similar patients were to the target population in whom the intervention will be applied. We also recorded the funding source and role of the funder.

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

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reported the range of estimates of low-density lipoprotein cholesterol and high-density lipoprotein cholesterol changes for each dosage of each drug. When possible, we also calculated pooled estimates of changes in lipoprotein levels by drug and dosage. We considered the quality of the studies and heterogeneity across studies in study design, patient

population, interventions, and outcomes, in order to determine whether meta-analysis could be meaningfully performed. If meta-analysis could not be performed, we summarized the data qualitatively.

In order to quantify the effects of statins on lipid levels, we conducted a meta-analysis of placebo-controlled trials of statins in children with familial hypercholesterolemia. We pooled the mean difference between groups in the change from baseline in low-density lipoprotein cholesterol and high-density lipoprotein cholesterol using a random effects model. We conducted a sensitivity analysis excluding studies rated poor quality. Data analysis was conducted using RevMan version 5.0.

Peer Review and Public Comment

Original Drug Effectiveness Review Project reports are independently reviewed and commented upon by 3 to 5 peer reviewers. Peer reviewers are identified through a number of sources, including but not limited to professional society membership, acknowledged expertise in a particular field, prominent authorship in the published literature, or recommendation by Drug Effectiveness Review Project participating organizations. A list of individuals who have acted as peer reviewers of Drug Effectiveness Review Project reports is available on the Drug Effectiveness Review Project website.

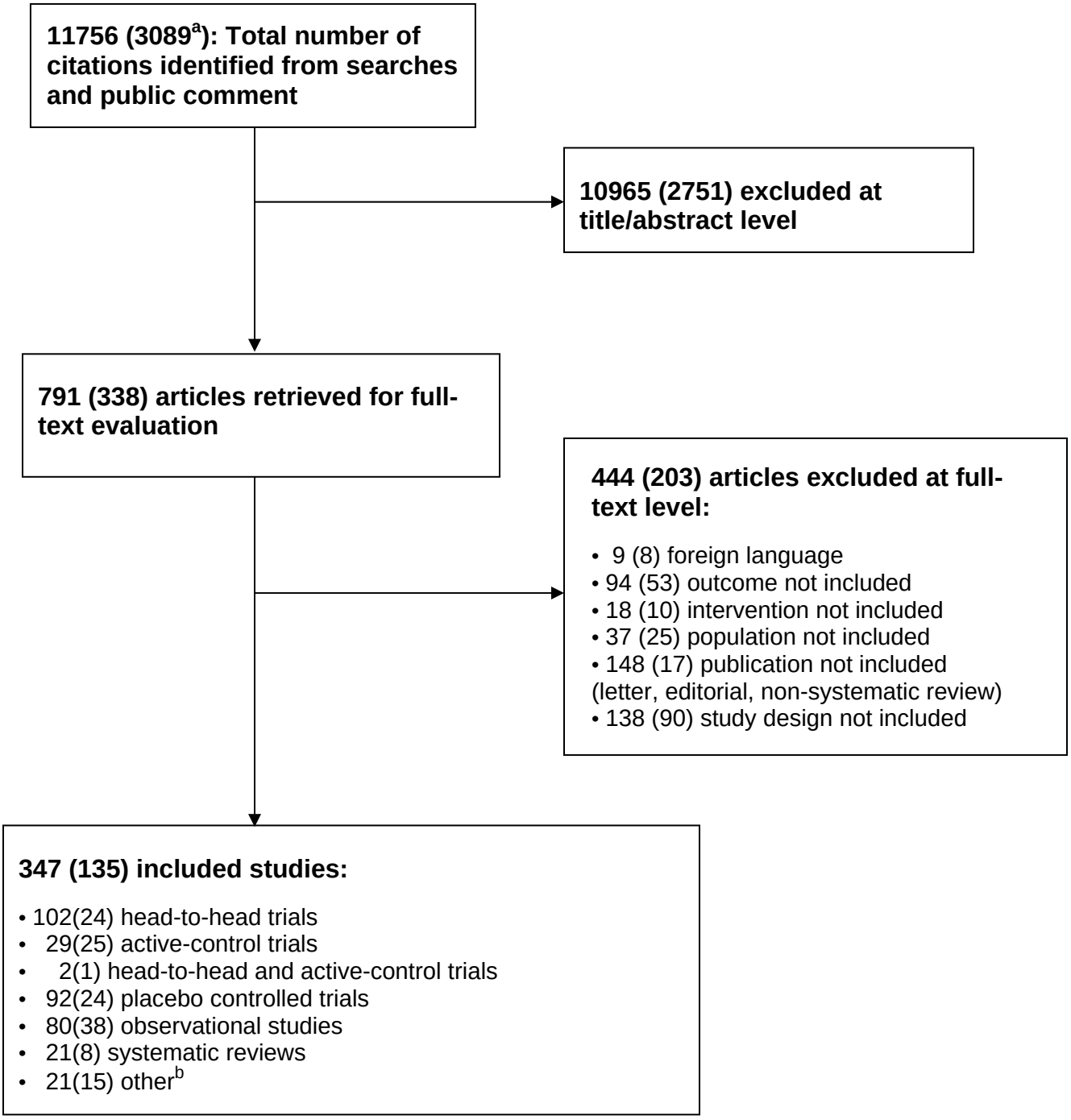
Peer reviewers have a maximum of 3 weeks for review and comment. They are asked to submit their comments in a standardized form in order to maintain consistent handling of comments across reports and to allow the Drug Effectiveness Review Project team to address all comments adequately. The Drug Effectiveness Review Project process allows for a 2-week public comment period prior to finalization of the report. Draft reports are posted on the Drug Effectiveness Review Project website and interested individuals or organizations can review the complete draft report and submit comments. Comments from peer reviewers and the public are entered into a spreadsheet and the disposition of each comment is tracked individually.

RESULTS

Overview

Results of literature searches are shown in Figure 1. Update searches identified 3089 citations. We retrieved 338 potentially relevant articles for review. Of these, 74 randomized controlled trials and 61 additional publications (other study designs) were included. Excluded trials are listed in Appendix D.

Figure 1. Results of literature search



[a] Numbers in parentheses are results of the literature search new to Update 5.
[b] Other refers to post-hoc analysis, pooled analysis and dose ranging study.

Report Organization

The results in this report are presented in two sections: one, results for adults, and two, results for children.

ADULTS

Key Question 1. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to reduce low-density lipoprotein cholesterol?

Summary of findings

- For patients who required low-density lipoprotein cholesterol reductions of up to 35% to meet their goal, any of the statins were effective.
- In patients requiring a low-density lipoprotein cholesterol reduction of 35% to 50% to meet the National Cholesterol Education Program goal, atorvastatin 20 mg or more, lovastatin 80 mg, rosuvastatin 10 mg or more, simvastatin 20 mg or more, ezetimibe-simvastatin fixed-dose combination product 10/10 mg or more, and niacin extended release-lovastatin fixed-dose combination product 1000/40 mg or 2000/40 mg daily were likely to meet the goal.
    - The niacin extended-release lovastatin fixed-dose combination product 1000/40 mg and 2000/40 mg had greater adverse events and a higher number of patients who discontinued therapy due to adverse events.
- Among high-potency and high-dose statins:
    - Atorvastatin 40 mg or 80 mg daily and rosuvastatin 20 mg or more reduced low-density lipoprotein cholesterol by 50% or more.
    - Atorvastatin 80 mg had a higher rate of some adverse effects (gastrointestinal disturbances and transaminase elevation) than simvastatin 80 mg daily in a trial in which the low-density lipoprotein lowering of atorvastatin was greater than that of simvastatin.
    - Adverse event rates in patients using rosuvastatin 40 mg were similar to rates in patients using atorvastatin 80 mg in short-term trials.
- In patients requiring a low-density lipoprotein cholesterol reduction of greater than 50%, the higher doses of ezetimibe-simvastatin at 10/40 mg and 10/80 mg were more likely to meet the National Cholesterol Education Program Adult Treatment Panel III goal than an equivalent high-potency statin.

Key Question 1a. Are there doses for each statin or fixed-dose combination product containing a statin and another lipid-lowering drug that produce similar percent reduction in low-density lipoprotein cholesterol?

Statins

We identified 88 randomized controlled trials and 2 meta-analyses[12, 13] comparing the low-density lipoprotein cholesterol-lowering ability of 2 or more statins in patients with baseline low-

density lipoprotein cholesterol less than 250 mg/dL or 6.4 mmol/L (Evidence Table 1).[14-29 30-78] In 51 of these trials, the percentage of patients reaching their National Cholesterol Education Program goal (or equivalent goal based on the country of origin of the study) was also evaluated. There were 40 double-blinded, 43 open-label, and 3 single-blinded studies, and dosing strategies varied between trials. Some studies titrated to a maximum recommended daily dose (titrate to target) while others compared fixed statin doses. One trial compared extended-release lovastatin with the immediate-release form.[63] One trial looked at the effects of switching to rosuvastatin midway through the trial.[79] Another study switched to pravastatin from simvastatin but was given a poor quality rating, thus its data was not included in this report.[80] Most of the trials had fair internal validity.

The trials included men and women ages 18 and older who met low-density lipoprotein cholesterol criteria. Many of the trials had participants initially complete a placebo/dietary run-in phase before determining low-density lipoprotein eligibility. Most trials excluded patients with secondary hypercholesterolemia (uncontrolled diabetes, thyroid disease, or other endocrine condition), pregnant or lactating women, kidney or liver impairment, baseline creatine kinase elevation, triglycerides greater than or equal to 350 to 400 mg/dL, and those receiving drugs with the potential for drug interaction with statins. Most trials were of short duration (4 to 24 weeks) although a few were significantly longer.[81] In the majority of the trials the efficacy analyses were performed on a smaller number of patients than were randomized (that is, the trials did not use intention-to-treat statistics), although some trials used modified intention-to-treat analyses requiring that post-randomization data be available in order to include the results in the analysis.

Table 3 shows the percent low-density lipoprotein cholesterol lowering from baseline for trials of a particular statin dose (rather than mean or median statin doses). Our estimates, which were based on direct head-to-head trials, were consistent with the estimates from a 2003 meta-analysis of placebo-controlled trials.[82] With only a few exceptions, the mean percent low-density lipoprotein cholesterol reduction for a particular statin dose varied little across studies and was consistent with the information in the package insert. The exceptions were:

(1) Some poorly reported and poor-quality trials had discrepant results.[70, 83-85]

(2) In an open-label, fair-quality study, lovastatin 20 mg daily produced a lower than expected reduction in low-density lipoprotein cholesterol (21%) with no obvious factors that would explain this reduction.[50] The other statins in the trial produced expected percent low-density lipoprotein cholesterol lowering.

(3) The manufacturer's prescribing information reported a low-density lipoprotein cholesterol reduction of 60% in patients receiving atorvastatin 80 mg daily. However, this reduction came from data involving only 23 patients. The 6 trials that assessed the low-density lipoprotein cholesterol-lowering ability of atorvastatin 80 mg daily included a total of 1758 patients randomized to atorvastatin and had reductions of 46% to 54%.

(4) The reductions in low-density lipoprotein reported in the manufacturer's prescribing information for rosuvastatin 10 mg, 20 mg, and 40 mg reports are greater than the ranges found in randomized controlled trials reviewed for this report.

Table 3. Percent reduction in low-density lipoprotein cholesterol with statins

Statin dose per day	Range of percent low-density lipoprotein cholesterol lowering from comparative clinical trials	Mean percent low-density lipoprotein cholesterol lowering from manufacturers prescribing information (and from the Adult Treatment Panel III[3] if available)	Number of clinical trials[a]
Atorvastatin			
10 mg	28.9%-40.2%	39% (37%)	35
20 mg	38.4%-46.1%	43%	14
40 mg	45.1%-51.3%	50%	7
80 mg	46.3%-55.4%	60% (57%)	11
Fluvastatin			
20 mg	17.0%-21.8%	22% (18%)[b]	5
40 mg	22.0%-26.0%	25%[b]	6
80 mg	29.6%-30.6%[c]	36% (31%)[b, d]	2
80 mg XL[e]	--	35%[b]	0
Lovastatin			
10 mg	21.6%-24.0%	21%	2
20 mg	21.0%-29.0%	27% (24%)	8
40 mg	27.9%-33.0%	31%	5
80 mg	39.0%-48.0%	42% (40%)[f]	2
Pravastatin			
10 mg	18.0%-24.5%	22%	10
20 mg	23.0%-29.0%	32% (24%)	12
40 mg	25.2%-34.0%	34%	10
80 mg[e]	--	37% (34%)	0
Rosuvastatin			
5 mg	39.1%-46.0%	45%	7
10 mg	37.1%-50.6%	52%	22
20 mg	45.0%-52.4%	55%	7
40 mg	53.6%-58.8%	63%	5
Simvastatin			
10 mg	26.0%-33.1%	30%	20
20 mg	18.5%-40.0%	38% (35%)	23
40 mg	34.3%-43.0%	41%	10
80 mg	43.0%-48.8%	47% (46%)	6

[a] Trials are listed in Evidence Table 1. Percent low-density lipoprotein cholesterol reduction in clinical trials included in table only if data provided for a specific dosage and not a mean dosage; total number of clinical trials will be more than the number of included trials because some trials studied more than 2 statins.
[b] Median percent change.
[c] Given as fluvastatin 80 mg once daily or 40 mg twice daily (does not include XL product).
[d] Given as fluvastatin 40 mg twice daily.
[e] Newly approved dose or dosage form with no head-to-head clinical trial data against another statin.
[f] Given as lovastatin 40 mg twice daily.

From the trials summarized in Table 3, we determined the following approximate equivalent daily doses for statins with respect to their low-density lipoprotein cholesterol-lowering abilities (Table 4).

Table 4. Doses of statins that result in similar percent reductions in low-density lipoprotein cholesterol[a]

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

[a] Estimates based on results of head-to-head trials (Evidence Table 1).

Comparisons of high-potency and high-dose statins

Atorvastatin and rosuvastatin are considered high-potency statins because they can lower low-density lipoprotein cholesterol more than 50%. High-dose simvastatin can lower low-density lipoprotein cholesterol by more than 40%. We compared efficacy and adverse events in head-to-head trials of high-potency and high-dose statins.

Atorvastatin compared with simvastatin

Thirty trials have compared atorvastatin to simvastatin (Evidence Table 1).[12, 15, 19, 26, 29, 30, 33, 38, 39, 41, 42, 48, 50-53, 55, 57-59, 65, 68, 72, 73, 83, 84, 86-89] One meta-analysis has compared atorvastatin to simvastatin.[12] Thirteen of the trials included patients with coronary heart disease or high risk of coronary heart disease including coronary heart disease equivalents such as diabetes.[12, 15, 19, 26, 30, 33, 39, 50, 53, 68, 83, 86, 87] At doses below 80 mg, rates of adverse events and withdrawals due to adverse events were similar in patients taking atorvastatin or simvastatin.

Three studies directly compared atorvastatin 80 mg to simvastatin 80 mg daily.[52, 56, 58] In the first study, atorvastatin 80 mg reduced low-density lipoprotein cholesterol by 53.6% compared with 48.1% for simvastatin 80 mg ($P \leq 0.001$).[52] Compared with the simvastatin 80 mg groups, a greater number of patients in the atorvastatin 80 mg groups reported clinical adverse effects, primarily gastrointestinal diarrhea (23% compared with 11.9%; $P<0.001$). There was no significant difference between atorvastatin 80 mg and simvastatin 80 mg in withdrawal rates due to adverse effects. Withdrawal from the study due to adverse laboratory events occurred more often in the atorvastatin 80 mg compared with the simvastatin 80 mg daily group (4% compared with 0.8%; $P<0.05$). Clinically important alanine aminotransferase elevation (greater than 3 times the upper limit of normal) occurred statistically more often in the atorvastatin 80 mg compared with the simvastatin 80 mg group (17 compared with 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 80 mg statin dose.

In the second study,[58] Karalis and colleagues randomized 1732 patients with hypercholesterolemia to treatment with atorvastatin 10 mg or 80 mg daily or simvastatin 20 mg or 80 mg daily for 6 weeks. This study was unblinded and did not use intention-to-treat statistics. Mean baseline low-density lipoprotein cholesterol in the atorvastatin group was reduced by 53% compared with 47% in the simvastatin group ($P<0.0001$). With regard to safety at the 80 mg dosage for each statin, atorvastatin was associated with a higher incidence of adverse effects compared to simvastatin (46% compared with 39%) and a higher rate of study discontinuation due to adverse effects (8% compared with 5%). However, neither of these differences was statistically significant.

The STELLAR trial[56] was a fair- to poor-quality open-label trial designed to compare rosuvastatin to other statins (atorvastatin, simvastatin, and pravastatin). One hundred sixty-seven patients were randomized to atorvastatin 80 mg and 165 to simvastatin 80 mg. Baseline low-density lipoprotein levels were similar in both groups (190 mg/dL). The mean percent change in low-density lipoprotein level after 6 weeks was 51% in the atorvastatin group and 46% in the simvastatin group, a difference (5.3 percentage points) similar to those found in the 2 other studies comparing atorvastatin 80 mg to simvastatin 80 mg. The proportion of patients who withdrew because of adverse events was 3.6% in both groups.

Atorvastatin compared with rosuvastatin

Twenty-nine trials[14-17, 19-24, 28, 43, 56, 69, 74-76, 78, 79, 86, 90-96] and 3 meta-analyses[13, 36, 97] have compared rosuvastatin to atorvastatin (see Table 5, below, and Evidence Table 1).

Table 5. Trials comparing atorvastatin to rosuvastatin

Study, reference	Drugs, doses	Number screened/ Randomized	Design	Duration	Mean baseline LDL-C	Other patient characteristics
DISCOVERY-UK 2006[19]	Rosuva 10 mg Atorva 10 mg	NR/ 1874	Open-label Fixed dose	12 weeks	174 mg/dL	Presence of diabetes and cardiovascular disease
Aszatalos 2007[14] (STELLAR)	Rosuva 40 mg Atorva 80 mg	NR/ 325	Open-label Fixed dose	6 weeks	192 mg/dL	Atherosclerosis, diabetes mellitus
Ballantyne 2006[15] (MERCURYII)	Rosuva 20 mg Atorva 10, 20 mg	NR/ 1993	Open-label, fixed dose for 8 weeks, remained on initial dose or switched to a lower or mg equivalent rosuvastatin dose for 8 weeks	16 weeks	168.1 mg/dL	CHD or CHD risk equivalents, diabetes
Berne 2005[95] (URANUS)	Rosuva 10-40 mg Atorva 10 to 80 mg	NR/ 469	Double-blind Fixed dose for 4 weeks, then titration to goal	16 weeks	165.6 mg/dL	Type 2 diabetes

Study, reference	Drugs, doses	Number screened/ Randomized	Design	Duration	Mean baseline LDL-C	Other patient characteristics
Binbrek 2006[16] (DISCOVERY ALPHA)	Rosuva 10 mg Atorva 10 mg	NR/ 1506	Open-label Fixed dose	12 weeks	170.5 mg/dL	Atherosclerosis, type 2 diabetes, family history of previous CHD
Bots 2005[86] (DUTCH DISCOVERY)	Rosuva 10 mg Atorva 10 mg	NR/ 1215 (621 rosuva, 189 atorva)	Open-label Fixed dose	12 weeks	171.6 mg/dL	Presence of diabetes, atherosclerosis disease, CHD risk, previous lipid lowering therapy
Clearfield 2006[17] (PULSAR)	Rosuva 10 mg Atorva 20 mg	NR/ 996	Open-label Fixed dose	6 weeks	165 mg/dL	Metabolic syndrome, diabetes, CHD or CHD risk equivalents
Davidson 2002[43] (AstraZeneca Study 24)	Rosuva 5,10 mg Atorva 10 mg	1888/ 519	Double-blind Fixed dose	12 weeks	186.5 mg/dL	
Faergeman 2008[20] (ECLIPSE)	Rosuva 10, 20, 40 mg Atorva 10, 20, 40, 80 mg	2696/ 1036	Open-label Flexible dose	24 weeks	188.8 mg/dL	Renal impairment, metabolic syndrome, diabetes mellitus, CHD
Ferdinand 2006[74]	Rosuva 10, 20 mg Atorva 10, 20 mg	2385/ 774	Open-label Fixed dose	6 weeks	190.6 mg/dL	African Americans
Fonseca 2005[75]	Rosuva 10 mg Atorva 10 mg	1644/ 1124	Open-label Fixed dose	12 weeks	173 mg/dL (statin naïve patients) 163 mg/dL (others)	
Insull 2007[87] (SOLAR)	Rosuva 10, 20 mg Atorva 10, 20 mg	4161/ 1632	Open-label Fixed dose for 6 wks, then dose doubled to reach NCEP ATP goal for additional 6 weeks	12 weeks	168.5 mg/dL	History of CHD or CHD risk >20% over 10 years, diabetes, hypertension
Jones 2003[56] (STELLAR)	Rosuva 10, 20, 40, 80 mg Atorva 10, 20, 40, 80 mg	NR/ 2431 (1284 rosuva or atorva)	Open-label	6 weeks	189.1 mg/dL	

Study, reference	Drugs, doses	Number screened/ Randomized	Design	Duration	Mean baseline LDL-C	Other patient characteristics
Jukema 2005[76]	Rosuva 10, 20, 40 mg Atorva 20, 40, 80 mg	NR/ 461	Open-label Fixed dose for 6 weeks, then dose increased every 6 weeks	18 weeks	141 mg/dL	Established cardiovascular disease
Kurabayashi 2008[22] (SUBARU)	Rosuva 5 mg Atorva 10 mg	NR/ 427	Open-label Fixed dose	8 weeks	106.1 mg/dL	Hypertension, diabetes and family history of coronary artery disease
Lloret 2006[23] (STARSHIP)	Rosuva 10, 20 mg Atorva 10, 20 mg	2750/ 696	Open-label Fixed dose	6 weeks	163.7 mg/dL	Hispanic, renal impairment, diabetes, hypertension, CHD or CHD risk equivalent
Mazza 2008[24]	Rosuva 10 mg Atorva 20 mg	NR/ 106	Open-label Fixed dose	48 weeks	225.3 mg/dL	
Milionis 2006[98] (ATOROS)	Rosuva 10, 20 mg Atorva 20, 40 mg	NR/ 120	Open-label Fixed dose	24 weeks	204.5 mg/dL	Hypertension, family history of CHD
Olsson 2002[69] (AstraZeneca Study 26)	Rosuva 5, 10-80 mg Atorva 10-80 mg	1521/ 412	Double-blind 12 weeks at fixed dose, then titration to goal	52 weeks	187.4 mg/dL	
Qu 2009[91]	Rosuva 10 mg Atorva 10 mg	NR/ 69	Fixed dose	12 weeks	150.4 mg/dL	Diabetes, hypertension
Rawlings 2009[28]	Rosuva 10 mg Atorva 40 mg	NR/ 30	Double blind Fixed dose	4 weeks	141 mg/dL	Caucasian men, hypertension, diabetes mellitus, myocardial infarction
Schneck 2003[92] (AstraZeneca Study 33)	Rosuva 5, 10, 20, 40, 80 mg Atorva 10, 20, 40, 80 mg	NR/ 978 eligible/ 374 enrolled	Double-blind Fixed dose	6 weeks	189 mg/dL	

Study, reference	Drugs, doses	Number screened/ Randomized	Design	Duration	Mean baseline LDL-C	Other patient characteristics
Schuster 2004[79] (MERCURY I)	Rosuva 10 or 20 mg Atorva 10 or 20 mg	6508/ 3161 (2043 rosuva or atorva)	Open-label 8 week at fixed dose; then either remained on current statin or switched to rosuvastatin for 8 weeks	16 weeks	165.1 mg/dL	History of CHD or CHD risk >20% over 10 years, atherosclerosis or diabetes
Schwartz 2004[93]	Rosuva 5,10-80 mg Atorva 10-80 mg	1233/ 383	Double-blind 12 weeks at fixed dose, then forced titration	24 weeks		Atherosclerosis or diabetes
Strandberg 2004[94]	Rosuva 10 mg Atorva 10 mg	NR/ 1024	Open-label 12 weeks at fixed dose, then titration to the Joint Task Force goal if needed	12 weeks plus optional 36 week open-label extension	>135 mg/dL in statin-naive patients; >120 mg/dL in patients using the starting dose of another lipid-lowering drug.	History of CHD or CHD risk >20% over 10 years, atherosclerosis or diabetes
Stalenhoef 2005[96] (COMETS)	Rosuva 10-20 mg Atorva 10-20 mg	1338/ 401	Double-blind; 10 mg for 6 weeks, then increased to 20 mg	12 weeks	169.7 mg/dL	Metabolic syndrome
Wolfenbuttel 2005[78]	Rosuva 10, 20, 40 mg Atorva 20, 40, 80 mg	416/ 263	Open-label Fixed dose for 6 weeks, then dose increased every 6 weeks	18 weeks	169 mg/dL	Type 2 diabetes

Abbreviations: CHD, coronary heart disease; low-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; NR, not recorded.

Nine trials concerned patients who had moderate to no risk factors for coronary artery disease[14, 43, 56, 69, 74, 75, 91, 92, 98] and 19 trials enrolled patients at high risk for cardiovascular disease.[15-17, 19-24, 28, 76, 78, 79, 86, 87, 93-96] All studies comparing rosuvastatin to atorvastatin that reported low-density lipoprotein cholesterol reductions at 12 weeks [36, 43, 69, 86, 87, 91, 93, 94] had

similar results, whether or not they included patients at high risk for coronary heart disease. There were 2 studies that provided low-density lipoprotein cholesterol data at 24 weeks[20, 98] and revealed consistency with the 12-week trial results. One trial continued for 48 weeks[24] and had an effect of 30% reduction in low-density lipoprotein with atorvastatin 20 mg compared with 44.3% reduction with rosuvastatin 10 mg. This effect was significantly different at $P<0.001$.

Most trial designs included a 6-week run-in period during which dietary counseling was provided. After this run-in period, only patients meeting low-density lipoprotein cholesterol requirements were randomized. Eight trials allowed patients to enter the study without a run-in period.[19, 22, 24, 28, 75, 86, 91, 94] Fifteen trials reported the number screened. The percentage of patients enrolled after screening ranged from 27.1% to 85.9%.

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

Schwartz et al also enrolled patients who had diabetes or were at high cardiovascular risk.[93] Of 383 patients randomized, 3.7% had diabetes alone, 85.4% had atherosclerosis alone (a history of peripheral vascular disease, coronary artery disease, or cerebrovascular disease), and 11% had both diabetes and atherosclerosis. Although the trial was designed to compare rosuvastatin 80 mg to atorvastatin 80 mg over 24 weeks, results at weeks 12 and 18, before patients were titrated to 80 mg, are also available. Rosuvastatin 5 mg daily (39.8%, $P<0.01$) had a significant difference in reducing low-density lipoprotein cholesterol levels compared to atorvastatin 10 mg (35%) at 12 weeks. The 18-week analysis in this study compared rosuvastatin 20 mg and rosuvastatin 40 mg to atorvastatin 40 mg. Through 12 weeks, similar proportions of patients taking rosuvastatin and atorvastatin withdrew because of adverse events.

A large head-to-head trial that included higher doses of rosuvastatin was a 6-week open label trial (STELLAR) in which about 300 patients took rosuvastatin 40 mg/day or higher.[56] Rosuvastatin 40 mg, atorvastatin 80 mg, and simvastatin 80 mg had similar rates of withdrawal and of serious adverse events (pravastatin 80 mg was not included). A post hoc subanalysis of 811 patients in the STELLAR trial with metabolic syndrome had results similar to the overall sample.[99] In this analysis, the low-density lipoprotein cholesterol reductions for rosuvastatin 40 mg and atorvastatin 80 mg were –55.3% and –48.8%, respectively (P=NS).

Many of the trials comparing atorvastatin and rosuvastatin were open-label and were multisite studies that pooled data, including DISCOVERY,[19] STELLAR,[14] MERCURY II,[15] SUBARU,[22] SOLAR,[87] ECLIPSE,[20] and STARSHIP.[23] One trial was single-blinded[91] and 1 study was double-blinded.[28] Recent open-label trials of atorvastatin compared with rosuvastatin were conducted in African Americans,[74] patients with type 2 diabetes,[78, 95] and patients with established cardiovascular disease.[76] In African Americans, rosuvastatin 10 mg lowered low-density lipoprotein cholesterol more than atorvastatin 10 mg, but not atorvastatin 20 mg. This is similar to results of other studies. In patients with type 2 diabetes and established cardiovascular

disease, the percent low-density lipoprotein cholesterol reduction with rosuvastatin and atorvastatin was similar to that found in other studies, and patients taking rosuvastatin had greater low-density lipoprotein cholesterol reductions.

Fixed-dose combination products containing a statin and another lipid-lowering drug

We identified 13 randomized controlled trials comparing the low-density lipoprotein cholesterol-lowering ability of a fixed-dose combination product compared with another lipid-lowering drug in patients with baseline low-density lipoprotein cholesterol less than 250 mg/dL or 6.4 mmol/L (Evidence Table 1). Of these, 10 trials involved the combination of ezetimibe and simvastatin (Vytorin): 8 trials compared to another statin,[100-107] 1 trial compared to fenofibrate,[108] and 1 trial compared to extended-release niacin.[109] One trial evaluated the low-density lipoprotein cholesterol-lowering ability of the fixed-dose combination of niacin extended-release and simvastatin (Simcor) to simvastatin[110] and 2 trials evaluated the low-density lipoprotein-lowering ability of the fixed-dose combination of niacin extended release and lovastatin (Advicor) to atorvastatin and/or simvastatin.[73, 111, 112] In 7 of these trials, the percentage of patients reaching their National Cholesterol Education Program goal was also evaluated. There were 10 double-blinded and 3 open-label studies. Dosing strategies varied between trials. Some had multiple arms comparing all doses of the fixed-dose combination product to equivalent doses of the statin while others compared a low dose of each without titration. In 1 trial, we only included the date of the fixed-dose combination of ezetimibe and simvastatin (Vytorin) to fenofibrate despite the trial also looking at the effectiveness of Vytorin added to fenofibrate, as this combination was not fixed.[108] All of the trials involving a fixed-dose combination of extended-release niacin with either simvastatin (Simcor) or lovastatin (Advicor) were titration studies. Two trials compared Vytorin to the effect of doubling the current statin dose.[105, 106] Most of the trials had fair internal validity.

Similar to the statin trials, these trials included men and women ages 18 and older who met low-density lipoprotein cholesterol criteria. Most of the trials had participants complete a placebo/dietary run-in phase before determining low-density lipoprotein eligibility, although 1 compared ezetimibe and simvastatin to doubling the current statin dose after hospitalization for an acute coronary event. Most trials excluded patients with secondary hypercholesterolemia (uncontrolled diabetes, thyroid disease, or other endocrine condition), pregnant or lactating women, kidney or liver impairment, baseline creatine kinase elevation, triglycerides greater than or equal to 350 to 400 mg/dL, and those receiving drugs with the potential for drug interaction with statins. Some trials were conducted in statin-experienced patients whereas others included only statin-naïve patients. Studies varied in the baseline risk factors of their populations. Most trials were of 12 weeks duration with a range of 6 to 24 weeks. In the majority of the trials the efficacy analyses were performed on a smaller number of patients than were randomized (that is, the trials did not use intention-to-treat statistics), although most trials used modified intention-to-treat analyses requiring that at least 1 post-randomization value be available in order to include the results in the analysis.

Table 6 shows the percent low-density lipoprotein cholesterol lowering from baseline for trials of a particular fixed-dose combination drug dose. Our estimates, which were based on direct active-control trials, were consistent with the information in the package insert. Ezetimibe-simvastatin fixed-dose combination was compared to rosuvastatin,[103] atorvastatin,[100, 101] simvastatin,[102, 104, 107] and doubling a statin dose.[105, 106] In all of these trials, participants taking

the fixed-dose combination product had a significantly greater decrease in low-density lipoprotein cholesterol compared to those taking the statin alone. In the niacin extended release fixed-dose trials, there was no significant difference in low-density lipoprotein cholesterol reduction compared to the statins except in the Bays 2003 trial[102] which obtained 42% reduction with niacin ER/lovastatin 1000/40 mg compared to simvastatin 20 mg (34%, $P<0.001$).

Table 6. Percent reduction in low-density lipoprotein cholesterol with fixed-dose combination products

Fixed-dose combination product dose per day	Range of percent LDL-C lowering from comparative clinical trials	Number of clinical trials
Ezetimibe-simvastatin (Vytorin),[100-109]		
10/10 mg	44.8%-47.2%	3
10/20 mg	30.8%-53.5%	9
10/40 mg	27.0%-55.5%	5
10/80 mg	58.6%-61.0%	4
Niacin extended-release lovastatin (Advicor)[73, 111, 112]		
1000/40 mg	30.5-39%	2
2000/20 mg	42%	1
Niacin extended-release simvastatin (Simcor)[110]		
1000/20 mg	13.1%	1
2000/40 mg	14.2%	1

Abbreviations: LDL-C, low-density lipoprotein cholesterol.

Key Question 1b. Do statins or fixed-dose combination products containing a statin and another lipid-lowering drug differ in the ability to achieve National Cholesterol Education Program goals?

The ability of an agent to achieve National Cholesterol Education Program goals is another factor in choosing between statins. The Adult Treatment Panel III includes a table that is helpful in determining how much reduction is needed to achieve low-density lipoprotein cholesterol goals (see Table 7, below). The 2004 supplement to the Adult Treatment Panel III stresses that the goals are *minimums.* According to the 2004 supplement to the Adult Treatment Panel III and in the 2006 American Heart Association/American College of Cardiology guidelines, a target of less than 70 mg/dL is a reasonable clinical option for patients who have known coronary artery disease.

Table 7. Achieving target low-density lipoprotein cholesterol goals

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

Based on the Adult Treatment Panel III. Table VI-3-1. Page VI-19.[3]
Abbreviations: LDL-C, low-density lipoprotein cholesterol.

Statins

Fifty-one reports measured the percentage of patients meeting their National Cholesterol Education Program low-density lipoprotein cholesterol treatment goals.[15-17, 19-22, 29, 86, 87, 113, 114] Additionally, 1 study reported only on the European guidelines goal attainment,[113] 1 study reported on the Japanese goal attainment,[22] and 3 reported on attainment of both the Adult Treatment Panel III and the 2003 European goals.[17, 20, 29] 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 limited the validity of many of these trials. Many compared only the low, starting doses of several statins and no study evaluated the Adult Treatment Panel III guideline achievement efficacy of rosuvastatin 5 mg. The percentage of patients achieving Adult Treatment Panel III low-density lipoprotein cholesterol <100 was 57.5% to 84.8% for rosuvastatin 10 mg; 39.2% to 62.5% for atorvastatin 10-20 mg; 35.6% to 69.7% for simvastatin 20 mg; and 30.8% for pravastatin 40 mg. Frequently, less potent starting doses of several statins (lovastatin, pravastatin, and simvastatin) were compared to more potent doses of atorvastatin or rosuvastatin. For example, in 1 open-label study (Target-Tangible),[65] atorvastatin 10 to 40 mg showed better National Cholesterol Education Program goal-reaching than simvastatin 10 to 40 mg with similar adverse effect rates, but simvastatin 80 mg was not included as a treatment option because the dosage was not yet approved by the US Food and Drug Administration. Further complicating the validity of the trial data, most of the trials evaluating the ability to achieve National Cholesterol Education Program goals were open-label and in most trials the inferior drug appeared not to have been titrated to its maximum daily dosage (See Evidence Table 1). Seven of the studies that had this flaw were reported to be double-blinded and in these 7 studies, it was unclear why clinicians did not titrate the dosage as aggressively in the compared groups.

In those that studied tailored doses, the maximum dose was often lower than the maximum approved dose available today. In the Treat-to-Target (3T) Study, a 52-week, multicenter, randomized, head-to-head trial, once-daily oral treatment with 20 mg atorvastatin was compared to 20 mg simvastatin.[68] At 8 weeks, reductions in low-density lipoprotein cholesterol were –46% for atorvastatin compared with –40% for simvastatin (P<0.001). The dose was doubled after 12 weeks if the target National Cholesterol Education Program level of

low-density lipoprotein cholesterol less than 100 mg/dL was not reached at 8 weeks. Fewer atorvastatin patients needed to have their dose doubled; nevertheless a greater percentage of atorvastatin patients reached the low-density lipoprotein cholesterol target after 52 weeks (61% compared with 41%; $P<0.001$). However, the simvastatin 80 mg dose, which was approved later, was not evaluated in the study.

In the Evaluation to Compare Lipid-lowering effects of rosuvastatin and atorvastatin (ECLIPSE) study, a 24-week, open-label, randomized, multicenter and multinational, head-to-head trial, compared rosuvastatin 10 mg to atorvastatin 10 mg.[20] At 6 weeks, 52.8% of patients on rosuvastatin and 27.6% of those on atorvastatin had reached the National Cholesterol Education Program low-density lipoprotein cholesterol goal of <100 mg/dL (2.5mmol/l). The doses were then sequentially doubled every 6 weeks until the patient was receiving rosuvastatin 40 mg or atorvastatin 80 mg, the maximal dose of each drug. At 24 weeks, 83.6% of patients on rosuvastatin and 74.6% of those on atorvastatin had reached the National Cholesterol Education Program goal of low-density lipoprotein cholesterol <100 mg/dL. Also analyzed was the percentage of very high-risk patients achieving a low-density lipoprotein cholesterol goal of <70 mg/dL (1.8mmol/L) at 24 weeks, and 38.0% of those on rosuvastatin reached this goal compared with 20.2% of those on atorvastatin.

In the STELLAR trial,[56] Adult Treatment Panel III LDL cholesterol goals were achieved by 82% to 89% of patients treated with rosuvastatin 10 to 40 mg compared with 69% to 85% of patients treated with atorvastatin 10 to 80 mg.

In a meta-analysis of three 12-week randomized trials of rosuvastatin compared with atorvastatin, 76% of patients taking rosuvastatin 10 mg reached their Adult Treatment Panel III goal compared with 53% of those taking atorvastatin 10 mg.[97] In the same publication, in a pooled analysis of 2 trials of rosuvastatin compared with simvastatin and pravastatin, percentages of patients reaching their goal were 86% for rosuvastatin 10 mg, 64% for simvastatin 20 mg, and 49% for pravastatin 20 mg. Results for rosuvastatin 5 mg are not reported in this meta-analysis. The only 1-year head-to-head study of rosuvastatin compared with atorvastatin[69] was conducted in 3 phases: a 6-week run-in period, a 12-week fixed-dose comparison of rosuvastatin (5 mg or 10 mg) or atorvastatin (10 mg), and a 40-week titration period in which the dose of rosuvastatin or atorvastatin could be doubled until the National Cholesterol Education Program-II goal or a dose of 80 mg was reached. At 52 weeks, the percentage of patients meeting their goal was 88% for patients starting at rosuvastatin 5 mg, 98% of those starting at rosuvastatin 10 mg, and 87% of those starting at atorvastatin 10 mg (no statistical analysis was performed). Excluding results for 80 mg of rosuvastatin, results were similar (89% of those starting at rosuvastatin 5 mg and 98% of those starting at rosuvastatin 10 mg reached their goal).

In other studies of atorvastatin lasting 1 year or longer, percentages of patients meeting their National Cholesterol Education Program goal ranged from 46% to 61% for 10 mg to 40 mg atorvastatin and 51% to 95% for 10 mg to 80 mg atorvastatin.

Fixed-dose combination products containing a statin and another lipid-lowering drug

Eight trials measured the percentage of patients meeting their National Cholesterol Education Program low-density lipoprotein cholesterol treatment goals. Seven of these evaluated ezetimibe and simvastatin (Vytorin) fixed-dose combination[100, 101, 103-107] and 1 evaluated the efficacy of

niacin extended-release and simvastatin (Simcor) fixed-dose combination.[110] Fewer studies reported the percentage achievement of the optional goal of <70 mg/dL low-density lipoprotein cholesterol for very high-risk patients. There was a significant difference in the ezetimibe-simvastatin fixed-dose compared to all statins at all comparable doses except for rosuvastatin, which had equal efficacy in achieving National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals at all doses except rosuvastatin 10 mg (Table 8).[103] There was no statistically significant difference in the ability of the niacin extended-release and simvastatin fixed-dose combination compared to simvastatin alone in achieving the National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals based on 1 study.[110]

Table 8. Achievement of National Cholesterol Education Program low-density lipoprotein cholesterol goals of fixed-dose combination products

Fixed-dose combination product	LDL-C < 100 mg/dL or 2.5mmol/L	LDL-C < 70 mg/dL or 1.8mmol/L	Number of trials
Ezetimibe-simvastatin (Vytorin)[100, 101, 103-107]			
10/10 mg	78%–91%	20 %	2
10/20 mg	67%–94.7%	27%–39%	4
10/40 mg	85.8%-95.6%	57-59.8%	3
10/80 mg	91%-97.5%	64%	2
Niacin extended release simvastatin (Simcor)[110]			
1000/20 mg	45%		1
2000/20 mg	58%		1

Abbreviations: LDL-C, low-density lipoprotein cholesterol.

A comparative effectiveness review and meta-analysis was recently conducted by the Agency for Healthcare Research and Quality. Its conclusions regarding combination lipid-lowering products are consistent with the results of this review.[115]

Key Question 2. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to increase high-density lipoprotein cholesterol?

Summary of findings

- When statins are provided in doses that reduce low-density lipoprotein cholesterol by equivalent amounts, a similar percent increase in high-density lipoprotein cholesterol can be achieved.
- There was conflicting evidence about simvastatin compared with atorvastatin, with some studies finding no difference and others finding simvastatin superior.

- Some studies found greater increases in high-density lipoprotein cholesterol with low-dose rosuvastatin compared with atorvastatin, while other studies found no difference.
- Amongst the high potency statins, high dose of rosuvastatin increased high-density lipoprotein cholesterol more than high dose simvastatin or atorvastatin.
- Ezetimibe-simvastatin fixed-dose combination had an equivalent effect on increasing high-density lipoprotein cholesterol as simvastatin alone.
- Ezetimibe-simvastatin was not as effective as fenofibrate or niacin in increasing high-density lipoprotein cholesterol.
- Fixed-drug combination products containing extended-release niacin with lovastatin or simvastatin were more effective in increasing high-density lipoprotein cholesterol than simvastatin 20 mg to 40 mg, but with more adverse events.

Key Question 2a. Are there doses for each statin or fixed-dose combination product containing a statin and another lipid-lowering drug that produce similar percent increase in high-density lipoprotein cholesterol between statins?

Statins

A previous meta-analysis of placebo-controlled trials estimated that, on average, statins increased high-density lipoprotein cholesterol by 3 mg/dL (0.07 mmol/l; 95% CI, 0.06 to 0.08 mmol/l), with no detectable effect of dose.[82] In our review of 77 head-to-head trials, statins raised high-density lipoprotein cholesterol levels from 0% to 19%, with the great majority between 5% and 9% (Evidence Table 1). While most found no significant difference in high-density lipoprotein cholesterol-raising among the statins, there were some exceptions.

In 6 head-to-head studies of low-density lipoprotein cholesterol lowering, simvastatin increased high-density lipoprotein cholesterol more than atorvastatin 10 to 80 mg,[38, 41, 52, 55, 58, 68] but in 14 others, there was no significant difference between the 2 on this measure.[26, 29, 30, 39, 42, 48, 51, 53, 57, 72, 83, 84, 88, 89] In the Mulder study, the simvastatin to atorvastatin switch trial (STAT), patients had received simvastatin 40 mg for at least 8 weeks prior to the screening visit and had low-density lipoprotein cholesterol levels above 2.6 mmol/L (100 mg/dL) at screening. Patients were then randomized to simvastatin 40 mg or atorvastatin 40 mg for 8 weeks, when the atorvastatin dose was increased to 80 mg while the simvastatin dose remained the same. The atorvastatin group had a 4.4% increase in high-density lipoprotein cholesterol whereas the simvastatin group had a 1.8% decrease in high-density lipoprotein cholesterol, but this was not significant. The non-equivalent dosing and patient inclusion criteria limited the utility of this finding. There was 1 meta-analysis of randomized controlled trials of atorvastatin and simvastatin which demonstrated that simvastatin was generally associated with greater increases in high-density lipoprotein cholesterol than atorvastatin, with the greatest significance at the higher doses of atorvastatin.[12]

Two studies that compared atorvastatin to simvastatin were designed to measure high-density lipoprotein cholesterol raising as a primary outcome.[33, 59] A 24-week study of 917 patients randomized to atorvastatin 80 mg or simvastatin 80 mg reported only an average of the increase at weeks 18 and 24, separately, by baseline high-density lipoprotein cholesterol level.[33] The average increase was the same in patients with baseline high-density lipoprotein cholesterol above and below 40 mg/dL: 2.1% for patients randomized to atorvastatin and 5.4% for those randomized to simvastatin. These differences were not statistically significant. In the other study

reporting high-density lipoprotein cholesterol as a primary outcome,[59] 826 patients were randomized to atorvastatin (20 mg daily for 6 weeks, then 40 mg daily) or simvastatin (40 mg daily for 6 weeks, then 80 mg daily) for 36 weeks. The primary endpoint was the average of results from weeks 6 and 12. The mean percent increase in high-density lipoprotein cholesterol was greater in the simvastatin group (9.1% compared with 6.8%; $P<0.001$). The difference was greater at higher doses. High-density lipoprotein cholesterol increased by 9.7% and 6.4% in the simvastatin 80 mg and atorvastatin 40 mg groups, respectively. At lower doses, the difference was not significant (percent change not reported). Results are not reported beyond 12 weeks.

Nine head-to-head trials (in 11 publications) reported high-density lipoprotein cholesterol increases with rosuvastatin compared with atorvastatin.[14, 17, 20, 36, 43, 56, 69, 92-94, 98] Five studies reported greater increases in high-density lipoprotein cholesterol with rosuvastatin 5 or 10 mg than with atorvastatin 10 mg.[20, 36, 43, 93, 94] A sixth study of fair quality reported no difference between the 2 drugs at the same doses.[69] Two studies reported greater increases with rosuvastatin 10 mg than with atorvastatin 20 mg (with one showing a decrease in high-density lipoprotein cholesterol).[17, 98] Two studies reported greater increases with rosuvastatin 40 mg compared with atorvastatin 80 mg.[14, 20] Six head-to-head studies comparing low-dose rosuvastatin (5 or 10 mg) to low-dose atorvastatin (10 or 20 mg) reported no significant difference in change in high-density lipoprotein cholesterol.[16, 21-24, 28, 91] Most of these trials were large multicenter and multinational trials. Interestingly, there was 1 randomized double blinded placebo-controlled trial of rosuvastatin 20 mg that reported no significant difference in high-density lipoprotein cholesterol.

Eight trials evaluated rosuvastatin compared to multiple statins in their abilities to increase high-density lipoprotein cholesterol levels. In the STELLAR trial,[56] high-density lipoprotein cholesterol increases were greater with rosuvastatin 20 mg compared with atorvastatin 40 mg (9.5% compared with 4.4%; $P<0.002$), but there was no significant difference between rosuvastatin 20 mg and simvastatin 80 mg (9.5% compared with 6.8%) or between rosuvastatin 10 mg and atorvastatin 20 mg (7.7% compared with 4.8%) or simvastatin 40 mg (5.2%). In the MERCURY II trial rosuvastatin 10 mg increased high-density lipoprotein cholesterol greater than either atorvastatin 10 mg or simvastatin 20 mg, and rosuvastatin 20 mg increased high-density lipoprotein cholesterol greater than either atorvastatin 20 mg or simvastatin 40 mg.[15] In the DISCOVERY Netherlands and the SOLAR trials, rosuvastatin 10 mg reported greater increases in high-density lipoprotein cholesterol compared to atorvastatin 10 mg and simvastatin 20 mg.[86, 87] In the DISCOVERY-UK trial,[19] atorvastatin 10 mg, rosuvastatin 10 mg, and simvastatin 20 mg all increased high-density lipoprotein cholesterol at 12 weeks, but there were no significant differences between treatment groups. The DISCOVERY Netherlands trial and the MERCURY I trial[79] showed a significant increase in high-density lipoprotein cholesterol with rosuvastatin compared to pravastatin 40 mg. The increase in high-density lipoprotein cholesterol with rosuvastatin 10 mg was not significantly different from simvastatin 20 mg in one study,[40] increased high-density lipoprotein cholesterol more than pravastatin 20 mg in the same study,[40] and not significantly different from pravastatin 20 mg in another.[71]

Fixed-dose combination products containing a statin and another lipid-lowering drug

Twelve active-control trials reported on the ability of a fixed-dose combination product to increase high-density lipoprotein cholesterol compared with another lipid-lowering drug. Nine of

the trials studied the fixed-dose combination of ezetimibe and simvastatin (Vytorin). Of these, 7 compared ezetimibe-simvastatin to another statin, 1 compared ezetimibe-simvastatin to niacin, and 1 to fenofibrate. Of the trials comparing ezetimibe-simvastatin to another statin, there were no differences between ezetimibe-simvastatin 10/10-10/80 mg and simvastatin 10-80 mg.[102, 104] There were 2 randomized open-label trials that compared ezetimibe-simvastatin to doubling the current statin dose. One study used the 10/20 mg dose of ezetimibe-simvastatin and the other used the 10/40 mg dose. In the lower dose trial, doubling the statin involved increasing simvastatin to 40 mg or atorvastatin to 20 mg, which effectively increased high-density lipoprotein cholesterol significantly greater than switching to ezetimibe-simvastatin 10/20 mg.[106] In the second trial, patients were on multiple different statin therapies at the onset of the trial and there was no difference between doubling the current statin dose and switching to ezetimibe-simvastatin 10/40 mg.[105] There were 2 trials that compared ezetimibe-simvastatin to atorvastatin. Both reported greater increases in high-density lipoprotein cholesterol with ezetimibe-simvastatin.[100, 101] Two trials compared ezetimibe-simvastatin 10/20 mg to other lipid-lowering drugs. In 1 trial the comparator was fenofibrate 160 mg and in the other trial the comparator was extended-release niacin titrated to 2000 mg per day. In both of these trials, ezetimibe-simvastatin increased high-density lipoprotein cholesterol by 8.1% to 9.3%, however the comparator had a greater effect, an increase of 18.2% for fenofibrate and 28.1% for extended-release niacin.[108, 116]

Three trials evaluated extended-release niacin fixed-dose combination products and all reported a greater ability to increase high-density lipoprotein cholesterol than a statin.[110-112] The SEACOAST trial was a randomized double-blind active-control trial comparing niacin extended release-simvastatin 1000/20 mg and 2000/20 mg to simvastatin 20 mg. The fixed-dose combination increased high-density lipoprotein cholesterol by 18.3% and 24.9% respectively, however 35.9% of those in the higher-dose niacin extended release-simvastatin group had an adverse event and 15.6% discontinued treatment because of an adverse event compared with 17.5% and 5.3% respectively in the simvastatin group. Of note, patients in the simvastatin group did receive 50 mg of immediate-release niacin with their study medication, and the niacin extended release-simvastatin group was titrated on a 4- to 12-week period.[110]

Key Question 2b. Is there a difference in the ability of a statin or fixed-dose combination product containing a statin and another lipid-lowering drug to achieve National Cholesterol Education Panel goals?

There were no differences between the fixed-dose combinations of ezetimibe and simvastatin and statin monotherapy in achieving National Cholesterol Education Program high-density lipoprotein goals.[100, 101, 103-107] In the SEACOAST I randomized double-blind active-control trial comparing the fixed-dose combination of extended-release niacin and simvastatin to simvastatin monotherapy, a significantly higher percentage of patients met the National Cholesterol Education Program Adult Treatment Panel III high-density lipoprotein cholesterol goal when taking extended-release niacin-simvastatin 2000/20 mg than when taking simvastatin 20 mg.[110]

Key Question 3. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to reduce the risk of nonfatal myocardial infarction, coronary heart disease (angina), coronary heart disease mortality, all-cause mortality, stroke, hospitalization for unstable angina, or need for revascularization (coronary artery bypass graft, angioplasty, or stenting)?

Summary of findings

- Information from head-to-head trials was limited.
  - *In patients with no known coronary heart disease:*
    - There were still no head-to-head trials of statins or fixed-dose combination products containing a statin (and another lipid-lowering drug) in this population.
  - *In patients with known coronary heart disease:*
    - In patients who had a *recent* myocardial infarction, high dose atorvastatin 80 mg daily reduced cardiovascular events compared with pravastatin 40 mg daily (PROVE-IT). For every 25 patients treated with atorvastatin 80 mg instead of pravastatin 40 mg, 1 coronary event was prevented.
    - In patients who had a *history* of myocardial infarction (IDEAL), high-dose atorvastatin (80 mg) and simvastatin (20 mg) did not differ in the primary endpoint (coronary death, hospitalization for nonfatal acute myocardial infarction, or cardiac arrest with resuscitation). More high-dose atorvastatin patients discontinued due to adverse events (9.6% compared with 4.2%; $P<0.001$), and there were more cases of elevated liver enzymes and myalgia with high-dose atorvastatin.
    - No studies of fixed-dose combination products in this population were found.
- The amount of information on cardiovascular outcomes available from placebo-controlled trials for each statin differed substantially.
  - There were no studies of fixed-dose combination products that reported cardiovascular outcomes.
  - *In patients with no known coronary disease (primary prevention):*
    - Pravastatin reduced all-cause mortality and cardiovascular events over 4.9 years in 1 trial.
    - Lovastatin reduced cardiovascular events over 5.2 years in 1 trial.
    - Rosuvastatin reduced all-cause mortality and cardiovascular events over median of 1.9 years in 1 trial.
  - *In patients with mixed populations or subjects with coronary risk equivalents:*
    - Simvastatin reduced all-cause mortality and cardiovascular events.
    - Atorvastatin and fluvastatin reduced cardiovascular events.
    - Pravastatin reduced all-cause mortality and cardiovascular events in Japanese adults.
  - *In patients with known coronary heart disease (secondary prevention):*
    - Atorvastatin reduced cardiovascular events
    - Simvastatin reduced all-cause mortality and cardiovascular events.
    - Pravastatin reduced all-cause mortality and cardiovascular events.

- Fluvastatin reduced coronary events when started after percutaneous coronary intervention.
- Studies of angiographic progression of atherosclerotic plaques provided fair-quality but indirect evidence that lovastatin is effective in preventing cardiovascular events in patients with coronary heart disease. This finding is weakened because of possible reporting bias (see below).
- There are still no completed studies of rosuvastatin with coronary heart disease endpoints in patients with coronary disease.

Detailed assessment

Head-to-head trials

There were only 2 head-to-head trials comparing the ability of different statins to reduce the risk of a second coronary event, stroke, or death (PROVE-IT[117] and IDEAL,[118] see Evidence Table 2). The purpose of both studies was to evaluate if aggressive treatment with high-dose atorvastatin to achieve low-density lipoprotein levels <100 mg/dL would provide additional benefit compared with usual-dose pravastatin or simvastatin in patients with a history of cardiovascular events. A third head-to-head trial[119] compared intensive atorvastatin to a control group of diet plus low-dose lovastatin if needed in patients with stable coronary artery disease. The primary outcome measure in this trial was ischemia on ambulatory electrocardiogram. There are still no head-to-head trials comparing high-doses of different statins for reducing coronary events and there are no head-to-head primary prevention trials.

In the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE-IT) trial,[117] 4162 patients who had been hospitalized in the previous 10 days for an acute coronary syndrome (myocardial infarction or unstable angina) were randomized to treatment with atorvastatin 80 mg daily or pravastatin 40 mg daily. Most patients were men (78%) aged 45 to 70 who also had risk factors for cardiovascular disease (diabetes, hypertension, smoking, or prior heart attack). Median baseline low-density lipoprotein was 106 mg/dL (interquartile range: 87 to 128 mg/dL). Patients who were using high statin doses (80 mg) were excluded from the study. While hospitalized, about 69% of patients underwent percutaneous coronary intervention (stent or percutaneous transluminal coronary angioplasty) prior to randomization.

Atorvastatin 80 mg reduced low-density lipoprotein by an average of 40 points (~32% reduction from baseline) yielding a median low-density lipoprotein of 62 mg/dL (interquartile range: 50-79 mg/dL) compared with pravastatin 40 mg which reduced low-density lipoprotein by about 10 points (~10% reduction from baseline) yielding a median low-density lipoprotein of 95 mg/dL (interquartile range: 79-113 mg/dL). The reason pravastatin had minimal effect on low-density lipoprotein was that patients were taking similar doses of a statin prior to their index event.

After an average of 2 years of follow-up (range 18 to 36 months), fewer atorvastatin-treated patients had a major cardiovascular event (rates, 22.4% compared with 26.3%; $P=0.005$; absolute risk reduction 3.9%; number needed to treat, 25) than those using pravastatin. Major events were defined as all-cause mortality, myocardial infarction, documented unstable angina requiring hospitalization, revascularization with either percutaneous transluminal coronary angioplasty or coronary artery bypass graft, and stroke. Looking at the individual components of the primary outcome, atorvastatin appeared to exhibit its greatest benefit in reducing recurrent

unstable angina requiring hospitalization (rates, 3.8% compared with 5.1%; *P*=0.02) and the need for revascularizations (rates, 16.3% compared with 18.8%; *P*=0.04) compared with pravastatin. There was a nonsignificant trend for all-cause mortality (rates, 2.2% compared with 3.2%; *P*=0.07) and for the combined endpoint of death or myocardial infarction (rates, 8.3% compared with 10.0%; *P*=0.06).

The benefit of atorvastatin 80 mg on cardiovascular events was greater in a subgroup of patients with higher baseline low-density lipoprotein of ≥125 mg/dL and those without prior statin use. Among patients who had used statins, the 2-year event rates were 27.5% for atorvastatin and 28.9% for pravastatin. In contrast, among patients without prior statin use, event rates were lower for atorvastatin (20.6%) compared with pravastatin (25.5%). Withdrawal rates due to any cause including adverse events were not significantly different between atorvastatin and pravastatin, but overall the rates were high at 2 years (30.4% compared with 33.0%; *P*=0.11). No cases of rhabdomyolysis were reported in either group but more atorvastatin-treated patients observed elevations in alanine aminotransferase >3 times the upper limit of normal compared with pravastatin (69 patients [3.3%] compared with 23 patients [1.1%]; *P*<0.001).

It is likely that the superior results of intensive therapy with atorvastatin were due to additional low-density lipoprotein-lowering. Pravastatin at any dose cannot achieve as much low-density lipoprotein reduction as atorvastatin 80 mg. PROVE-IT did not indicate whether atorvastatin would be better than other statins that reduce low-density lipoprotein to a similar degree.

In the fair-quality IDEAL trial,[118] post-myocardial infarction patients were randomized to high-dose atorvastatin (80 mg) compared with usual-dose simvastatin 20 mg. Patients who had previously taken a statin were eligible provided they had not been titrated to a dose higher than the equivalent of simvastatin 20 mg, and about 50% of those enrolled were taking simvastatin prior to randomization. The study was open-label with blinded endpoint classification. The median time since myocardial infarction was 21 to 22 months and 11% of patients were enrolled within 2 months of their myocardial infarction.

After a median follow-up of 4.8 years, mean low-density lipoprotein with high-dose atorvastatin was 81 mg/dL while mean low-density lipoprotein with usual-dose simvastatin was 104 mg/dL. There was no difference between treatment groups on the primary endpoint (coronary death, hospitalization for nonfatal acute myocardial infarction, or cardiac arrest with resuscitation). The primary endpoint occurred in 10.4% of simvastatin compared with 9.3% of atorvastatin patients (hazard ratio, 0.89; 95% CI, 0.78 to 1.01). There was no difference in cardiovascular mortality or all-cause mortality, but a significant reduction in nonfatal myocardial infarction (hazard ratio, 0.83; 95% CI, 0.71 to 0.98) and in major coronary events and stroke (hazard ratio, 0.87; 95% CI, 0.78 to 0.98) was shown. Post-hoc analyses adjusting for age (<65 years compared with ≥65 years) and sex showed no significant differences in treatment effects.[118, 120] More high-dose atorvastatin patients discontinued therapy due to adverse events than simvastatin-treated patients (9.6% compared with 4.2%; *P*<0.001), and there were more cases of elevated liver enzymes and myalgia with high-dose atorvastatin. No differences in the rate of myopathy or rhabdomyolysis. Several factors might help explain the discrepant results of PROVE-IT and IDEAL:

(1) All subjects in PROVE-IT had recent acute coronary syndrome, whereas only 11% of those in IDEAL had myocardial infarction within 2 months of randomization. This

(2) The definition of the primary endpoint differed in the 2 trials. In IDEAL, the reduction in low-density lipoprotein cholesterol with atorvastatin was slightly less than expected, and adherence in the atorvastatin group was not as good as in the simvastatin group (89% compared with 95%).[118]

(3) Durations of follow-up were different (2 years compared with 4.8 years).

In a fair-quality, 1-year trial in patients with stable coronary artery disease, intensive atorvastatin (up to 80 mg, to a target of low-density lipoprotein cholesterol less than 80 mg/dL) was not more effective than a control group of diet plus low-dose lovastatin (5 mg if needed, to a target of low-density lipoprotein cholesterol less than 130 mg/dL) for reducing the number of ischemic episodes as measured on ambulatory electrocardiogram, patient-reported angina frequency, and nitroglycerin consumption.[119] There was a reduction in the number of ischemic episodes in both groups, but no difference between groups. There was no significant difference in major clinical events between groups after 1 year, but the number of events was small and the study was powered to detect a difference in ischemia, not clinical events.

Placebo-controlled trials

Many trials comparing a statin to placebo or, in a few instances, to non-pharmacologic treatments, reported health outcomes. These trials indicated which statins have been proven to reduce the risk of cardiovascular events in various patient populations. We examined the included trials in 4 categories.

(1) *Studies with primary coronary heart disease endpoints*. This group included 27 placebo-controlled trials and 2 head-to-head trials: 22 studies in outpatients[118, 121-134] and 7 studies in inpatients with acute myocardial infarction or unstable angina.[81, 117, 135-146] The primary endpoint in these trials was a reduction in cardiovascular health outcomes.
   a. *Outpatient studies*. Enrollment was in excess of 4000 patients with an average follow-up period of 5 years. All of the trials were good or fair quality and were considered the best evidence for demonstrating a reduction in cardiovascular health outcomes with statins.
   b. *Inpatient studies*. These included studies of patients hospitalized with acute myocardial infarction or unstable angina. There was 1 head-to-head trial of intensive atorvastatin therapy compared with a standard dose of pravastatin. Six other trials compared a statin to placebo or usual care. No study in this group was rated good quality.

(2) *Studies of the progression of atherosclerosis with secondary or incidental coronary heart disease endpoints* are placebo-controlled trials in which the primary endpoint was progression of atherosclerosis measured by angiography or B-mode ultrasonography.[147-158] In these trials, coronary heart disease 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 coronary heart disease events. Only 2[148, 155] of these trials

enrolled more than 500 patients. The others ranged from 151 to 460 included patients. As evidence regarding reduction in coronary heart disease events, these trials were fair or fair-to-poor in quality.

(3) *Revascularization studies with restenosis or clinical outcome endpoints* are trials of the use of statins to prevent restenosis after coronary revascularization (coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or coronary stent).[159-165]

(4) *Miscellaneous trials*. Three additional trials with clinical outcomes did not fit the criteria for the other categories.[65, 166, 167]

Studies with primary coronary heart disease endpoints

The major trials are summarized briefly in Tables 9 (outpatient studies) and 11 (inpatient studies) below and in more detail in Evidence Table 2.

The GREACE,[168] ALLIANCE,[169] and Treating to New Targets (TNT)[170] trials did not meet inclusion criteria for our efficacy analysis, but they provided information about safety of high-dose atorvastatin and are discussed under Key Question 4.

Table 9. Outpatient and community-based placebo-controlled trials of statins with coronary heart disease endpoints

Trial (Quality)	Risk status/ Average annual event rate in placebo group	Baseline LDL (mg/dL)	Study duration (years)	% LDL reduction	Reduction in coronary events (relative risk reduction)[a]	Number needed to treat to prevent a coronary event[b]
Trials of atorvastatin						
ASCOT[171, 172] Atorvastatin 10 mg (Fair-Good)	HTN plus CHD risk factors/ 0.9%	133	3.3	35%	**36%**	94
CARDS[125] Atorvastatin 10 mg (Good)	Type 2 diabetes, no history of CVD 2.3%	117	3.9	36%	**37%**	31
4D[134] (Fair)	Type 2 diabetes, receiving dialysis 39%	126	4.0	42%	18% (including PTCA and CABG)	18
ASPEN[142]	Type 2 diabetes, low LDL levels	113	4.25	29%	10.4% vs. 10.8%	Results not significant
Xu[145]	Diabetes, coronary artery disease	125	1.75	24%	**37%** (including revascularization)	7
Trials of fluvastatin						
ALERT[173] Fluvastatin 40 mg (Good**)**	Patients with renal transplant 1.0%	160	5.1	32%	Primary endpoint not significant (*P*=0.139), but 35% reduction in cardiac deaths or non-fatal MI	Results not significant
Riegger[129] Fluvastatin 40 mg (Fair)	Symptomatic CAD/ 2.8%	198	1	26.9%	38%	Results not significant
Trials of lovastatin						
AFCAPS[126] Lovastatin 20 mg-40 mg (Good)	Average risk, no history of CAD/ 1.1%	150	5.2	25%	**37%**	49
Trials of pravastatin						
ALLHAT-LLC[121] Pravastatin 40 mg (Fair-Good)	Hypertensive moderately high LDL-C and at least 1 additional CHD risk factor/ 1.7%	145	4.8	24%	9%	Results not significant
CARE[122] Pravastatin 40 mg (Good)	History of CAD/ 2.6%	139	5	28%	**24%**	41
LIPID[130]; Pravastatin 40 mg (Good)	History of CAD/ 2.6%	150	6.1	25%	24%	164

Trial (Quality)	Risk status/ Average annual event rate in placebo group	Baseline LDL (mg/dL)	Study duration (years)	% LDL reduction	Reduction in coronary events (relative risk reduction)[a]	Number needed to treat to prevent a coronary event[b]
PREVEND IT[124] Pravastatin 40 mg (Fair)	Average risk, persistent microalbuminuria 0.8%	174	3.8	25%	13%	Results not significant
PROSPER[133] Pravastatin 40 mg (Good)	70-82 years old, history of CHD or risk factors/ 5.2%	147	3.2	27%	**15%**	24
WOSCOPS[132] Pravastatin 40 mg (Good)	High risk, no history of CAD/ 1.5%	192	4.9	16%	**31%**	44
MEGA[144]	40-70 yrs, bodyweight <40 kg, hypercholesterolemia, no CHD history	158	5.3	18% vs. 3%	30%	119
Trials of simvastatin						
4S[128] Simvastatin 20 mg (Good)	History of CAD/ 5.2%	187	5.4	35%	**34%**	11
Heart Protection Study[123, 174] Simvastatin 40 mg (Good)	History of CVD, diabetes, or noncoronary vascular disease/ 2.1%	131	5.5	30%	**27%**	32
Trials of rosuvastatin						
JUPITER[81] Rosuvastatin 20 mg (Good)	LDL <130 mg/dL, high-sensitivity C-reactive protein levels > 2 mg/L, no history of CVD or diabetes	108	1.9	50%	HR, 0.56 (95% CI, 0.46 to 0.69); *P*<0.00001	25

Abbreviations: CABG, Coronary artery bypass graft, CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; HTN, hypertension; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; PTCA, percutaneous transluminal coronary angioplasty.

[a] **Bolding** indicates statistically significant results.

[b] Not adjusted for length of trial or for baseline risk.

Studies in outpatients

Primary prevention

AFCAPS (lovastatin), WOSCOPS (pravastatin), and JUPITER (rosuvastatin) trials recruited patients without a history of coronary heart disease (primary prevention).[81, 126, 132] All 3 trials were rated as good quality. One new trial[143] was rated poor quality due to multiple methodologic weaknesses.

In WOSCOPS,[132] pravastatin 40 mg reduced coronary events by 31%, or 1 for every 44 patients (men only) treated (absolute risk, 5.5% compared with 7.9%) whereas in AFCAPS/TexCAPS, lovastatin reduced the incidence of new cardiovascular events by 37%, or 1 for every 49 subjects (men and women) treated (absolute risk, 6.8% compared with 10.9%). WOSCOPS used a stricter definition of coronary events, defined as the occurrence of nonfatal myocardial infarction or coronary heart disease death, than AFCAPS, which included incidence of unstable angina in their primary outcome, so the relative risk reductions and numbers-needed-to-treat were not directly comparable.

In WOSCOPS, but not AFCAPS/TexCAPS, pravastatin therapy reduced coronary disease deaths by 33% (95% CI, 1 to 55) and all-cause mortality by 22% (95% CI, 0 to 40), a result that nearly reached statistical significance (P=0.051). The absolute risks of coronary disease death were 1.3% for subjects in the pravastatin group and 1.9% in the placebo group; number needed to treat, 163. In AFCAPS/TexCAPS, the absolute risks of fatal coronary disease events were 3.3 per 1000 subjects in the lovastatin group and 4.5 per 1000 subjects in the placebo group (P=NS). There was no difference in all-cause mortality in AFCAPS/TexCAPS.

The different mortality results should not be taken as evidence that pravastatin and lovastatin would differ if used in subjects at similar risk. Compared with AFCAPS/TexCAPS, WOSCOPS recruited subjects who had about 4 times as high a risk of dying from coronary disease in the first place. The reduction in coronary heart disease deaths was actually comparable in the 2 studies, however in AFCAPS/TexCAPS, it did not reach statistical significance due to the lower number of events.

In JUPITER,[81] a large multicenter, international trial, 17 802 relatively healthy adults with lipid levels below current treatment thresholds who also had elevated C-reactive protein and who had never used lipid lowering therapy, were randomized to rosuvastatin 20 mg or placebo. The trial was initially designed to continue until 520 primary endpoints were documented but was stopped early for benefit. After a median follow-up of 1.9 years, rosuvastatin 20 mg lowered the risk for the occurrence of a first major cardiovascular event by 44% (hazard ratio, 0.56; 95% CI, 0.46 to 0.69; P<0.00001). The absolute risks observed for rosuvastatin was 1.6% compared with 2.8% (number needed to treat, ~83). All-cause mortality was reduced for rosuvastatin-treated patients (hazard ratio, 0.80; 95% CI, 0.67 to 0.97; P=0.02) but the absolute risk difference was small (2.2% compared with 2.8%; number needed to treat, ~167). Most individual components of the primary endpoint showed favorable findings for rosuvastatin in preventing coronary events, except for deaths from cardiovascular causes since these data were not reported. About 41% of patients enrolled had metabolic syndrome, 16% were smokers, and 12% reported family history of coronary disease.

Compared with WOSCOPS and AFCAPS/TexCAPS, the primary endpoint in the JUPITER trial was broader and included incidence of nonfatal myocardial infarction, nonfatal stroke, hospitalizations for unstable angina, need for revascularization, or death from cardiovascular causes. Total withdrawal rates and withdrawals due to adverse events were not reported, though there were no significant differences in the total number of reported serious adverse events between treatment groups (1352 cases with rosuvastatin compared with 1377 placebo; P=0.60). There were 19 cases of myopathy in 10 rosuvastatin-treated and 9 placebo-treated patients (P=0.82). One fatal case of rhabdomyolysis was recorded in a 90-year old patient (rosuvastatin arm) who had febrile influenza, pneumonia, and trauma-induced myopathy. There were no significant differences between rosuvastatin or placebo for elevations in alanine aminotransferase >3 times the upper limit of normal (0.3% compared with 0.2%; P=0.34) but

newly diagnosed diabetes, as reported by physicians, was more frequent with rosuvastatin (3.0% compared with 2.4%; *P*=0.01). These cases were not verified by the endpoint committee and conclusions based on these findings should be considered with caution until further studies are conducted.

Although the risk reductions were significant for rosuvastatin in preventing major cardiovascular events and deaths, the absolute risk differences between treatment groups were small. It is unknown whether these risk reductions will be maintained over longer periods of time for primary prevention since this trial (JUPITER) was stopped early. Truncated trials such as this pose a difficult challenge in determining whether treatment effects are overestimations of the "true" value. It has been shown that truncated trials stopped early for benefit are more likely to show greater treatment effects than trials that were not stopped early.[175, 176] Therefore, extrapolating results from this trial beyond about 1.9 years (to 4 or 5 years) is not recommended, as was done by the authors of the trial. Further studies longer in duration will need to be conducted to confirm the findings.

Studies enrolling mixed populations or subjects with coronary risk equivalents

Ten trials extended these results to patient populations who were excluded from the earlier trials (Table 9). In the Heart Protection Study, 20 536 men and women aged 40 to 80 years were randomized to simvastatin 40 mg or placebo for an average of 5.5 years.[123, 174] This study targeted individuals in whom the risk and benefits of cholesterol lowering were uncertain (women, those over 70 years, those with diabetes, those with non-coronary vascular disease, and those with average or below average cholesterol).

The overall low-density lipoprotein reduction was 30%. This figure resulted from a true intention-to-treat analysis, that is, it included patients who never took simvastatin or who quit taking it by the end of the study. In the subset of patients who took simvastatin for the entire study period, the low-density lipoprotein 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 (number needed to treat, 32 after 5 years) and of stroke.[177] In subgroups, simvastatin 40 mg was effective in primary prevention of coronary heart disease in patients with diabetes (number needed to treat, 24 to prevent a major event in 5 years)[178] and in patients who had a history of peripheral or carotid atherosclerosis but not coronary heart disease. Simvastatin 40 mg was also effective in patients who had a baseline low-density lipoprotein less than 116 mg/dL (both patients with and without diabetes).

To address concerns about the potential hazards of lowering cholesterol, data from the Heart Protection Study were analyzed to determine the effect of lowering cholesterol on cause-specific mortality, site-specific cancer incidence, and other major morbidity.[179] There was no evidence of any adverse effect of lowering cholesterol for 5 years on non-vascular morbidity or mortality. There was no increased risk of non-vascular mortality (relative risk, 0.95; 95% CI, 0.85 to 1.07) or cancer incidence (relative risk, 1.00; 95% CI, 0.91 to 1.11).

The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-lowering Arm (ASCOT-LLA) was a randomized, double-blind, placebo-controlled, fair-to-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 cardiovascular disease risk factors.[171, 172] The trial was terminated after a median of 3.3 years of follow-up because a statistically significant benefit was shown on the primary endpoint, non-fatal myocardial infarction (including silent myocardial infarction) and fatal coronary heart disease. Treatment with atorvastatin 10 mg per day for 1 year

reduced low-density lipoprotein by 35%, from 133 mg/dL to 87 mg/dL. By the end of follow-up (about 3.3 years), low-density lipoprotein was 89 mg/dL in the patients still taking atorvastatin compared with 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 corresponded to a 10-year coronary event rate of 9.4%. Over 3.3 years, the number needed to treat to prevent 1 nonfatal myocardial infarction or death from coronary heart disease was 94 (P=0.005). Atorvastatin increased the chance of remaining free of myocardial infarction for 3.3 years from 95% to 97%.

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

In ALLHAT-LLC (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack—Lipid-lowering Arm), a fair-to-good quality, open-label randomized trial, 10 355 hypertensive patients, aged 55 and older, were randomized to pravastatin 40 mg or to usual care.[121] Nearly half the subjects were women, 35% had diabetes, 15% had a history of coronary heart disease, and about 35% were African-American. Pravastatin reduced low-density lipoprotein cholesterol 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, 10% of control patients were taking a lipid-lowering drug by year 2, and, by year 6, 28.5% of control subjects were taking a lipid-lowering drug. Thus the control group had a mean reduction in low-density lipoprotein cholesterol 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 was unclear. The high proportion of women and the high rate of use of statins in the control group are possible explanations.

The good-quality PROSPER trial was designed to examine the benefits of statin therapy in women and in the elderly.[133] High-risk men and women were randomized to pravastatin 40 mg or to placebo. Before treatment, the mean low-density lipoprotein was 147 mg/dL. Overall, pravastatin reduced the composite primary endpoint (coronary heart disease death, nonfatal myocardial infarction, and fatal/nonfatal stroke) from 16.2% in the placebo group to 14.1% (P=0.014; number needed to treat, 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 compared with 10.3% in the pravastatin group (hazard ratio, 0.97; 95% CI, 0.83 to 1.14). The reduction in coronary heart disease deaths in the pravastatin group (4.2% compared with 3.3%; P=0.043) was balanced by an increase in cancer deaths (3.1% compared with 4%; P=0.082).

Pravastatin was more effective in men than in women. There were more women (n=3000) than men (n=2804) 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 (coronary heart disease death, nonfatal myocardial infarction, 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; 95% CI, 0.65 to 0.92; number needed to treat, 26). For women, there was no apparent effect (hazard ratio, 0.96; 95% CI, 0.79

to 1.18). PROSPER recruited a select group of elderly subjects. Of 23 770 people who were screened, 16 714 were ineligible or refused to participate.

The PREVEND-IT trial[124] was a population-based (N=864), randomized, placebo-controlled trial with a 2 X 2 factorial design. Residents of 1 city in the Netherlands with persistent microalbuminuria were randomized to fosinopril and pravastatin for the prevention of cardiovascular morbidity and mortality. In the pravastatin 10 mg compared with placebo arm, there was no reduction in urinary albumin excretion and no significant reduction in cardiovascular events after an average 46 months of follow-up (hazard ratio, 0.87; 95% CI, 0.49 to 1.57). In a subgroup analysis of 286 patients with the metabolic syndrome (33% of the total group),[180] the unadjusted hazard ratio was non-significant (hazard ratio, 0.48; 95% CI, 0.21 to 1.07). However, when adjusted for age and sex, there was a significant reduction in cardiovascular events in the pravastatin group (hazard ratio, 0.39; 95% CI, 0.17 to 0.89).

The ALERT trial established the efficacy and safety of fluvastatin in patients who had undergone renal transplant. Fluvastatin was superior to placebo in reducing cardiac deaths or non-fatal myocardial infarction,[127, 181, 182] but there was no effect on the renal endpoints of graft loss, doubling of serum creatinine, or decline in glomerular filtration rate.[173]

The MEGA study[144] enrolled Japanese adults without known coronary disease who had coronary heart disease risk equivalents or other risk factors (21% diabetes, 42% hypertension, 20% smokers). Patients were randomized to lower doses of pravastatin 10-20 mg (typical doses used in Japan) plus diet or diet alone and found 33% relative reduction in the incidence of coronary events with pravastatin over a mean follow-up of 5.3 years (hazard ratio, 0.67; 95% CI, 0.49 to 0.91; rate, 1.7% pravastatin compared with 2.55% diet alone). The primary endpoint was driven by reductions in nonfatal myocardial infarction and the need for revascularizations. All-cause mortality was lower in pravastatin-treated patients, though statistical significance was not achieved (hazard ratio, 0.72; 95% CI, 0.51 to 1.01; *P*=0.055).

Patients with diabetes. There were 8 trials[125, 134, 142, 145, 146, 178, 183, 184] evaluating long-term effectiveness of atorvastatin 10-20 mg, simvastatin 40 mg, and fluvastatin 80 mg in patients with diabetes (Table 10; Evidence Table 2).

Of the 8 trials, CARDS (Collaborative Atorvastatin Diabetes Study) was the only study designed to assess primary prevention of cardiovascular disease in patients with type 2 diabetes. Two-thousand eight-hundred thirty eight patients without elevated cholesterol levels (mean low-density lipoprotein less than 107 mg/dL), who had no history of cardiovascular disease but at least 1 of the risk factors of retinopathy, albuminuria, current smoking, or hypertension, were randomized to atorvastatin 10 mg or placebo. After 3.9 years of follow-up, there was a significant relative risk reduction of 37% in cardiovascular events but not with all-cause mortality (Table 10). The CARDS trial was stopped 2 years earlier than planned because of significant benefit at the second interim analysis.

In addition to CARDS, 3 placebo-controlled trials (HPS, ASCOT-LLA, ASPEN)[142, 178, 184] enrolled patients with type 2 diabetes with and without established cardiovascular disease, and subgroup analyses were performed for those classified as primary prevention. Overall, CARDS, HPS, and ASCOT-LLA[125, 178, 184] found the study statins to be beneficial in reducing coronary events compared with placebo in patients with type 2 diabetes with and without established cardiovascular disease (Table 10; Evidence Table 2). The HPS trial was the largest of these, including 5963 patients with diabetes. There was a 27% reduction in risk of major coronary events (first nonfatal myocardial infarction or coronary death), similar to the reduction in risk in the overall population of high-risk patients with simvastatin 40 mg. Among the 2912

patients with diabetes who did not have known coronary or other occlusive arterial disease at study entry, there was a 33% reduction in first major vascular events (95% CI, 17 to 46; *P*=0.0003). The reduction in risk for stroke (24%) in patients with diabetes was also similar to the reduction in the overall high-risk group. ASPEN was the only trial that showed a small nonsignificant reduction in the composite primary outcome of cardiovascular deaths or other cardiovascular events with atorvastatin (Table 10; Evidence Table 2). Potential reasons for not finding a significant effect may have been due to a change in study protocol within 2 years of the start of the study, enrollment of "very low risk" patients, and how the primary endpoint was defined.

There were 2 trials[145, 183] (LIPS, Xu, et al) that studied the effectiveness of fluvastatin 80 mg or atorvastatin 20 mg in patients with diabetes who had undergone percutaneous coronary interventions. Both trials observed a benefit associated with the study statins compared with placebo (Table 10; Evidence Table 2). All-cause mortality reported in 1[145] trial was not significant.

The 4D trial[134] enrolled patients with type 2 diabetes who had end-stage renal disease and were receiving maintenance hemodialysis (Table 10; Evidence Table 2). After 4 years of follow-up, there was no difference between atorvastatin 20 mg and placebo on the primary endpoint or all-cause mortality despite low-density lipoprotein of 72 mg/dL. There was also an *increase* in fatal strokes in the atorvastatin group— although this was likely to be a chance finding— and no effect on any individual component of the primary endpoint. Authors of 4D speculated that nonsignificant results for primary outcome may be related to lower baseline low-density lipoprotein levels, sicker population, and a different pathogenesis of events in this population.

One publication[146] was rated poor quality due to unclear randomization, allocation concealment, intention-to-treat analysis, and inadequate blinding.

Table 10. Placebo-controlled trials in patients with diabetes

Study/ Duration of follow-up	Patients (N, mean baseline LDL-C, other risk factors)	Drug, dose	Primary outcome (CHD endpoints)	CHD endpoints relative risk (95% CI)	All-cause mortality[a] relative risk (95% CI)
CARDS[125] 3.9 years	2838 <107 mg/dL At least 1: Retinopathy, albuminuria, current smoking, or hypertension	Atorvastatin 10 mg	Composite of acute CHD event (MI, unstable angina, acute CHD death, resuscitated cardiac arrest), coronary revascularization, or stroke.	0.63 (0.48 to 0.83)	-27% (-48 to 1.0)[b]
Heart Protection Study (HPS) (Subgroup analysis)[178] 4.8 years	5963 125 mg/dL Vascular disease (51%), treated hypertension (40%), current smoking (13%)	Simvastatin 40 mg	MI, stroke, vascular procedure, cancer or other serious adverse experience, and about the main reasons for all other hospital admissions	0.73 (0.62 to 0.85)	Not evaluated
ASCOT-LLA (Subgroup analysis)[184] 3.3 years	2532 127.4 mg/dL No history of CHD Smoking (20%)	Atorvastatin 10 mg	Total CV events (CV deaths, nonfatal MI, unstable or stable angina, life-threatening arrhythmias, nonfatal HF, nonfatal stroke, PAD, retinal vasc thrombosis, revascularization, TIA, and reversible ischemic neuro deficits	0.77 (0.61 to 0.96)	Not evaluated
ASPEN[142] 4 years	2411 113.5 mg/dL CVD history (34%), hypertension (55%), BP 133/76, smokers (12.5%)	Atorvastatin 10 mg	Composite of CV death (fatal MI, fatal stroke, sudden cardiac death, HF, or arrhythmic nonsudden cardiac death), nonfatal or silent MI, nonfatal stroke, recanalization, CABG, resusc cardiac arrest, worsening or unstable angina requiring hospitalization	HR 0.90 (0.73 to 1.12)	Not evaluated
LIPS (Subgroup analysis)[183] 3-4 years	202 126 mg/dL Post-percutaneous coronary intervention	Fluvastatin 80 mg	Composite of cardiac death (all deaths except those related to a noncardiac cause), nonfatal MI, and reinterventions (CABG, revascularization, or PCI for a new lesion)	0.49 (0.29 to 0.84)	Not evaluated
Xu, Kai 2007[145] 1.8 years	648 125 mg/dL Percutaneous coronary intervention, prior MI (42.5%), bare metal stent (81%)	Atorvastatin 20 mg	Fatal and nonfatal MI, revascularization	0.63 (0.50 to 0.79)	0.63 (0.34 to 1.1)[c]

Study/ Duration of follow-up	Patients (N, mean baseline LDL-C, other risk factors)	Drug, dose	Primary outcome (CHD endpoints)	CHD endpoints relative risk (95% CI)	All-cause mortality[a] relative risk (95% CI)
4D[134] 4 years	1255 121 mg/dL Undergoing maintenance hemodialysis	Atorvastatin 20 mg	Composite of death from cardiac causes, fatal stroke, nonfatal MI, or nonfatal stroke	0.92 (0.77 to 1.10)	0.93 (0.79 to 1.08)

Abbreviations: BP, blood pressure; CABG, Coronary artery bypass graft, CAD, coronary artery disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; HF, heart failure; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

[a] All-cause mortality was a secondary outcome.

[b] *P*=0.059.

[c] *P*=0.196.

Secondary prevention

Four placebo-controlled trials recruited patients with documented coronary heart disease while 1[141] enrolled patients with recent stroke or transient ischemic attack without history of coronary heart disease. Two trials (LIPID, CARE)[122, 130] evaluated pravastatin (N=13 173), 1 trial (4S)[128] evaluated simvastatin (N=4444), 1 trial evaluated fluvastatin,[129] and 1 trial (SPARCL)[141] evaluated atorvastatin.

Pravastatin and simvastatin significantly reduced the incidence of major coronary events, including overall mortality in LIPID and 4S. In 4S, the 8-year probability of survival was 87.6% in the placebo group and 91.3% in the simvastatin group. The risk of stroke was also reduced in CARE and 4S. In a post hoc subanalysis of 2073 patients in the LIPID trial with low low- and high-density lipoprotein cholesterol, pravastatin was associated with a relative risk reduction of 27% (95% CI, 8 to 42), a 4% absolute risk reduction, and a coronary artery disease of 22 to prevent 1 coronary heart disease event over 6 years.[185]

In Riegger et al,[129] patients who had stable angina were randomized to fluvastatin or placebo. The primary endpoint included cardiac death, nonfatal myocardial infarction, and unstable angina pectoris. By 1 year, there were fewer primary events in the fluvastatin group. However, excluding unstable angina, the relative risk of cardiac death and nonfatal myocardial infarction was not significantly reduced with fluvastatin (RR 0.38; 95% CI, 0.09 to 1.68).

In SPARCL, 4731 patients without coronary heart disease who had recent stroke or transient ischemic attack within 6 months were randomized to atorvastatin 80 mg or to placebo. By 4.9 years of follow-up (range: 4 to 6.6 years), atorvastatin significantly reduced the relative risk of fatal or nonfatal stroke by 16% (hazard ratio, 0.84; 95% CI, 0.71 to 0.99) or by a 1.9% absolute risk reduction (number needed to treat, ~53). Post-hoc analyses stratifying by type of stroke found that patients with ischemic or unclassified type benefited the most while those with hemorrhagic type were more likely to experience a harmful event (hazard ratio, 1.66; 95% CI, 1.08 to 2.55).

Even though none of the patients had established coronary disease, atorvastatin reduced the risk of major coronary events and need for revascularization, but not for death from cardiovascular disease or causes (Evidence Table 2). Deaths from any cause were also not reduced with atorvastatin (hazard ratio, 1.00; 95% CI, 0.82 to 1.21; *P*=0.98). Reductions in stroke and cardiovascular events were consistent in elderly in a post-hoc analysis.[186]

Most patients in SPARCL had prior ischemic stroke (~67%) and transient ischemic attack (~30%). About 2% of those with hemorrhagic stroke were considered to be at risk for ischemic events. About 62% of patients had hypertension, 17% had diabetes, and 19% were smokers. Most patients were naive to statin therapy.

Studies in inpatients with acute coronary syndrome

There were 6 placebo-controlled trials in patients with acute myocardial infarction or unstable angina (Table 11).[135-140] No new trials were identified for Update 5. The trials included 3 of pravastatin 20 to 40 mg and 1 each of atorvastatin 80 mg, fluvastatin 80 mg, and simvastatin 20 to 80 mg. One was rated fair-to-poor quality, and the rest were rated fair quality (see Evidence Tables 3 and 4 for details of quality ratings).

Table 11. Inpatient trials of acute myocardial infarction or unstable angina (statins compared with placebo or usual care)

Trial (Quality)	Population	Baseline LDL	Study duration	% LDL reduction	Reduction in coronary events (%)	NNT to prevent a coronary event[a]
de Lemos 2004 A to Z Trial (Phase Z)[138] (Fair)	Either non-ST-elevation acute coronary syndrome or ST elevation MI with a total cholesterol level of 250 mg or lower	Median 112 mg/dL (25th-75th percentiles 94-131 mg/dL)	Median 721 days (range 6 months to 24 months)	Simvastatin first vs. placebo first 1 month: 39% vs. +10% (*P*<0.001) 4 months: 45% vs. +12% (*P*<0.001) 8 months: 44% vs. 31% (*P*<0.001) 24 months: 41% vs. 27% (*P*<0.001)	11%	Results not significant
Thompson et al 2004 PACT[140] (Fair-Poor)	Within 24 hours of onset of acute MI or unstable angina	Not reported Mean total cholesterol 219 mg/dL	4 weeks	Not reported	-7%	Results not significant
Arntz et al 2000 L-CAD[135] (Fair)	Acute MI and/or underwent emergency PTCA due to severe or unstable angina pectoris	Pravastatin vs. usual care 176 mg/dL (131-240) vs. 172 mg/dL (132-239)	2 years	Pravastatin vs. usual care 28% vs. no change	59%	4
Liem et al 2002 FLORIDA[136] (Fair)	MI and 1 of the following: new or markedly increased chest pain lasting longer than 30 minutes, or a new pathological Q-wave	135 mg/dL vs. 139 mg/dL	1 year	Fluvastatin vs. placebo: 21% decrease vs. 9% increase	5%	Results not significant
MIRACL[139] (Fair)	Unstable angina or non-Q-wave MI	124 mg/dL	16 weeks	Atorvastatin vs. placebo: 40% decrease vs. 12% increase (adjusted mean)	16%	39
Den Hartog (Pilot Study)[137] (Poor)	Acute MI or unstable angina, hospitalized for less than 48 hours	174 mg/dL	3 months	25%	Not reported	Results not significant

Abbreviations: MI, myocardial infarction; NNT, number needed to treat; PTCA, percutaneous transluminal coronary angioplasty.
[a] Numbers needed to treat are not adjusted for length of trial and are not directly comparable due to differences among trials.

The L-CAD study established that patients with acute coronary syndrome benefit from statin treatment.[135] In L-CAD, 126 patients were randomized to pravastatin 20 or 40 mg or usual care an average of 6 days after an acute myocardial infarction or emergency percutaneous transluminal coronary angioplasty due to severe or unstable angina. After 2 years of follow-up, there were fewer major coronary events in the pravastatin group (22.9% compared with 52%; P=0.005). There was no difference in all-cause mortality, but each group had only 2 deaths.

An earlier pilot study[137] of pravastatin 40 mg compared with placebo enrolled patients hospitalized for less than 48 hours with acute myocardial infarction or unstable angina. After 3 months, there was no significant difference on any clinical endpoint, although there was a 25% reduction in low-density lipoprotein cholesterol in the pravastatin group.

PACT[140] assessed outcomes at 30 days in patients with acute myocardial infarction or unstable angina randomly assigned to receive pravastatin 20 to 40 mg or placebo within 24 hours of the onset of chest pain. This study was rated fair-to-poor quality because of some differences in groups at baseline (higher total cholesterol in placebo group, more placebo patients on hormone replacement therapy, and more pravastatin patients on anticoagulants) and no reporting of randomization and allocation concealment methods. The primary endpoint (composite of death, recurrence of myocardial infarction, or readmission to hospital for unstable angina) occurred in 12% of patients. There was no significant reduction in the primary endpoint (relative risk reduction, 6.4%; 95% CI, –1.4 to +3.0), or on any individual component of the primary endpoint.

In MIRACL,[139] a short-term (16 weeks) placebo-controlled trial of atorvastatin 80 mg in patients with unstable angina or non-Q-wave myocardial infarction, there was a significant reduction in major coronary events (death, nonfatal acute myocardial infarction, cardiac arrest with resuscitation, or recurrent symptomatic myocardial infarction requiring emergency rehospitalization) in the atorvastatin group (17.4% compared with 14.8%). There were no differences between groups on the individual components myocardial infarction or all-cause mortality, although the study was not powered to detect a difference on these endpoints.

FLORIDA[136] was a placebo-controlled trial of fluvastatin 80 mg in 540 patients with an acute myocardial infarction plus hypercholesterolemia and new or markedly increased chest pain or a new pathological Q wave. At 1 year of follow-up, there was no difference between groups in the occurrence of major coronary events.

The A to Z trial[138] compared early intensive statin treatment (simvastatin 40 mg for 30 days and then simvastatin 80 mg thereafter) to a less aggressive strategy (placebo for 4 months and then simvastatin 20 mg thereafter) in patients with either non ST elevation acute coronary syndrome or ST elevation myocardial infarction with a total cholesterol level of 250 mg/dL or lower. Patients were followed for up to 24 months. Despite greater lowering of low-density lipoprotein in the early intensive group, there were no differences between the early intensive and less aggressive groups on the primary endpoint (cardiovascular death, myocardial infarction, readmission for acute coronary syndrome, or stroke), or on any individual component of the primary outcome.

Nine patients in the simvastatin only group developed myopathy (creatine kinase level greater than 10 times the upper limit of normal with associated muscle symptoms) while taking 80 mg compared with 1 patient in the placebo first group (P=0.02). Three of the 9 in the simvastatin group had creatine kinase levels higher than 10 000 units/L and met the definition for rhabdomyolysis. The rate of myopathy was high, despite the exclusion of patients at increased risk of myopathy due to renal impairment or concomitant therapy with agents known to enhance

myopathy risk, or for having a prior history of nonexercise-related elevations in creatine kinase level or nontraumatic rhabdomyolysis.

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

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

Studies of the progression of atherosclerosis with secondary or incidental coronary heart disease endpoints

Twelve studies of the effects of statins on progression of atherosclerosis also reported rates of coronary or cardiovascular events.[147-158] A head-to-head trial[187] of the effect of atorvastatin 80 mg compared with pravastatin 40 mg on progression of atherosclerosis did not meet inclusion criteria because it did not report health outcomes. However, this study did meet inclusion criteria for Key Question 1 (see Evidence Table 1). In these studies, the primary endpoint was progression of atherosclerosis, and all of the patients had known coronary heart disease. To answer the question of whether treatment with a statin is associated with a reduction in clinical cardiovascular outcomes in patients with coronary heart disease, these studies were considered fair or fair-to-poor 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 12 and Evidence Table 5 summarize the results of these studies. The number of trials and patients studied for each statin are as follows: fluvastatin (1 trial; N=429), lovastatin (3 trials; N=1520), pravastatin (5 trials; N=2220), and simvastatin (3 trials; N=1118). The information about fluvastatin was inconclusive and the other 3 statins were already known to be effective from better studies.

In general, most trials in which coronary heart disease events were not a prespecified endpoint found a trend towards a reduction in clinical events in favor of a statin. In the trials in which coronary heart disease events were a secondary endpoint, there was usually a significant reduction in 1 of the components of coronary heart disease events. While consistent, the results of these studies are difficult to interpret because of possible reporting bias. That is, these trials may have been more likely to report a result if it was statistically significant or indicated a trend favoring treatment. Similar trials of progression of atherosclerosis that found no trend probably did not report coronary events. For this reason, we did not conduct a meta-analysis to pool the results of these studies.

Table 12. Studies of atherosclerotic progression that reported coronary heart disease outcomes

Author or study acronym Statin	Pre-specified clinical event or spontaneous report[a]	Significant reduction in clinical event or trend towards statin
LCAS Fluvastatin[147]	Spontaneous report	Trend
ACAPS Lovastatin[148]	Secondary endpoint	Reduction in major cardiovascular events
CCAIT Lovastatin[149]	Spontaneous report	Trend
MARS Lovastatin[150]	Spontaneous report	Trend
REGRESS Pravastatin[155]	Pre-specified	Reduction in percutaneous transluminal coronary angioplasty
PLAC-I Pravastatin[151]	Pre-specified	Reduction in myocardial infarction
PLAC-II Pravastatin[152]	Pre-specified	Reduction in combined: nonfatal myocardial infarction and death
KAPS Pravastatin[153]	Spontaneous report	Trend
Sato, et al Pravastatin[154]	Pre-specified	Reduction in overall death
MAAS Simvastatin[156]	Spontaneous report	Trend
CIS Simvastatin[157]	Spontaneous report	Trend
SCAT Simvastatin[158]	Pre-specified	Reduction in revascularization

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

Revascularization studies with restenosis or clinical outcome endpoints

This group (Table 13 and Evidence Table 6) included placebo-controlled trials in revascularized patients (coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or coronary stent).[159-165, 167] The primary endpoint in 5 of the trials was the rate of restenosis. A reduction in clinical outcomes was the primary outcome in the 6th study (subgroup analysis of CARE).[161] 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 coronary heart disease. 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 were as follows: fluvastatin (2 trials; N=2086), lovastatin (3 trials; N=1981), pravastatin (3 trials; N=3017; Table 9 presented data on 2245 patients already included in CARE). In these trials, pravastatin and fluvastatin had statistically significant effects on prespecified coronary disease outcomes.

Table 13. Post-revascularization trials

Study Drug, patients	Clinical endpoint	Clinical events
FLARE[163] Fluvastatin 40 mg twice daily vs. placebo to reduce restenosis after successful single-lesion PTCA	Prespecified composite clinical endpoint of death, myocardial infarction, coronary artery bypass graft surgery, or re-intervention.	No effect on restenosis or on the preplanned composite clinical end-point at 40 weeks (22.4% vs. 23.3%; log rank *P*=0.74); incidence of total death and myocardial infarction was lower in the fluvastatin group (1.4% vs. 4.0%; log rank *P*=0.025)
Weintraub 1994[164] Lovastatin 40 mg 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 6 months
PCABG[159] Lovastatin 40 mg (aggressive) vs. lovastatin 2.5 mg titrated to target; before and after CABG	Pre-specified composite clinical endpoint of death from cardiovascular disease or unknown causes, nonfatal MI, stroke, CABG, or angioplasty	No difference in composite outcome (12.6% vs. 15.3%, *P*=0.12); no differences in individual components except a lower rate of repeat PTCA or CABG (6.5% vs. 9.2%; *P*=0.03; NS by study criteria for multiple comparisons)
CLAPT[162] 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[160] Pravastatin 40 mg vs. placebo after PTCA	Secondary endpoint of death, myocardial infarction, target vessel revascularization	No effect on restenosis or on clinical endpoints.
CARE (subgroup)[161] Pravastatin vs. placebo in patients with CABG and/or PTCA	Primary endpoint coronary heart disease death or nonfatal MI	Reduction in primary endpoint (relative risk, 36; 95% CI, 17 to 51; *P*=0.001)
LIPS[167, 188] 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, 0.78; 95% CI, 0.64 to 0.95; *P*=0.01)
Kayikcioglu 2002[165] Pravastatin 40 mg and thrombolytics vs. thrombolytics in patients who under went coronary balloon angioplasty during 1st month of acute MI (6 month study)	Major adverse cardiovascular events: fatal or nonfatal MI, cardiac death, angina	No difference in reducing cardiac deaths, rate of reinfarctions, or repeat revascularizations. Rate of angina was reduced with pravastatin (30%) compared with control (59.5%), *P*=0.018

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

In the Lescol Intervention Prevention Study (LIPS), patients who had undergone angioplasty or other percutaneous coronary intervention were randomized to fluvastatin 40 mg twice daily or placebo for 4 years.[167, 188] 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, defined as cardiac death, nonfatal myocardial infarction, or a reintervention procedure. There was a 22% (*P*=0.0127) reduction in major coronary events (cardiac death, nonfatal myocardial infarction, coronary artery bypass graft or repeat percutaneous coronary intervention). The number needed to treat was 19 (21.4% in fluvastatin group compared with 26.7% in placebo group). Patients with diabetes and those with multi-vessel disease experienced a comparable or greater benefit with fluvastatin than other subjects.

Two subgroup analyses of the LIPS trial have recently been published; 1 in patients with type 2 diabetes[183] (discussed above) and another in patients with renal dysfunction.[189] Fluvastatin reduced major coronary events in these subgroups.

Miscellaneous studies

Three trials that reported clinical outcomes did not fit the criteria for the other categories (Table 14 and Evidence Table 6).[65, 166, 190]

The Target Tangible study[65] randomized patients with coronary heart disease (N=2856), including some who had been revascularized, to an initial dose of 10 mg of either atorvastatin or simvastatin, after which the dosage was increased to achieve a low-density lipoprotein less than 100 mg/dL. The study was open-label, but serious adverse events were classified by a safety committee blinded to allocation. The primary endpoint was safety, including noncardiac and cardiac events after 14 weeks of treatment. It was not designed to determine whether simvastatin and atorvastatin differed in their effects on coronary disease events but reported them as part of their safety analysis. Total adverse effect rates, serious adverse effect rates (A-2%, S-3%, NS), and withdrawal rates were similar for atorvastatin and simvastatin. The article states (page 10), "Serious cardiovascular events (including angina pectoris, myocardial infarction, and cerebral ischemia) were more frequent in the simvastatin group (19 patients, 2%) than in the atorvastatin group (21 patients, 1.0%) if the one-sided t-test was applied ($P<0.05$, Table III)." However, Table III of the article (p10) does not support this statement. This table shows that the number of these serious cardiovascular events was 11 (0.0058) in the atorvastatin group and 7 (0.0073) in the simvastatin group, which is not statistically significant. If deaths are included, the probabilities of serious cardiovascular events are 0.0069 for atorvastatin and 0.013 for simvastatin, not 1% and 2% as stated in the article. Because the study was of short duration, the investigators did not interpret any of the cardiovascular events to be related to therapy. The study was rated fair-to-poor quality because of the lack of blinding and the lack of clarity of the statistical analysis.

Table 14. Miscellaneous trials reporting clinical outcomes

Study Drug Patients	Clinical endpoint	Clinical events
AVERT[166] Atorvastatin vs. percutaneous Transluminal coronary angioplasty in stable, low-risk coronary artery disease patients	Primary endpoint included cardiac events and revascularization procedures	No difference
Target Tangible[65] Atorvastatin vs. simvastatin Safety trial	Clinical endpoints reported in safety analysis	See text (above)
Pravastatin Multinational Study Group[190] Pravastatin 20 mg (dose could be increased) vs. placebo Subjects at high-risk for coronary artery disease	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; number needed to treat, 44)

Key Question 4. Are there differences in effectiveness of statins and fixed-dose combination products containing a statin and another lipid-lowering drug in different demographic groups or in patients with comorbid conditions (e.g., diabetes, obesity)?

Summary of findings

- There was good evidence from randomized trials that women and the elderly benefit from statin therapy.
- Data about efficacy and safety in African-Americans, Hispanics, and other ethnic groups were weaker.
  - There was no evidence that one statin is safer than another in these groups.
  - A pharmacokinetic study conducted in the United States demonstrated a 2-fold higher blood level of rosuvastatin in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese, or Asian-Indian origin) compared with a White control group taking the same dose. The rosuvastatin label has been revised to note that this increase should be considered when making rosuvastatin dosing decisions for Asian patients.

Efficacy in demographic subgroups

Women and the elderly

Although women and the elderly were under-represented in the early major trials, we found 4 meta-analyses[191-194] suggesting that statins are equally efficacious in men, women, and the elderly.

One meta-analysis[191] evaluated the effect of statins on the risk of coronary disease from 5 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% of subjects with a range of 21% to 39% (WOSCOPS did not enroll women or anyone 65 years or older). The risk reduction in major coronary events was 29% (95% CI, 13 to 42) in women, 31% (95% CI, 26 to 35) for men, 32% (95% CI, 23 to 39) in those over age 65, and 31% (95% CI, 24 to 36) in those younger than age 65. Similarly, the Heart Protection Study[123, 178] found that simvastatin reduced cardiovascular events among women generally and particularly in women with diabetes, who benefited dramatically (number needed to treat, 23 to prevent 1 major vascular event).

Unlike the analysis by La Rosa and colleagues[191] that reported morbidity results, a meta-analysis by Walsh and colleagues[192] reported on total mortality, coronary heart disease mortality, and other coronary heart disease events in women with and without prior cardiovascular disease. Nine trials of statins that enrolled 16486 women and 4 additional studies that included 1405 women who used drug therapy other than statins were included in the analysis. For secondary prevention, lipid-lowering therapy reduced risk of coronary heart disease mortality (summary RR 0.74; 95% CI, 0.55 to 1.00), nonfatal myocardial infarction (summary RR 0.73; 95% CI, 0.59 to 0.90), and coronary heart disease events (summary RR 0.80; 95% CI, 0.71 to 0.91), but not total mortality (summary RR 1.00; 95% CI, 0.77 to 1.29). In primary prevention studies, there was insufficient evidence of reduced risk of any clinical outcome in women, because of the small number of events in the trials. Sensitivity analyses including only studies using statins did not significantly affect the summary risk estimates.

Two meta-analyses[193, 194] specifically evaluating statins in the elderly confirmed prior findings that these drugs are effective in this population. In particular, a hierarchial bayesian meta-analysis[193] included 9 placebo-controlled trials that enrolled 19 569 elderly patients who had a history of cardiovascular events. The pooled relative risk for all-cause mortality was 0.78 (95% CI, 0.65 to 0.89) with a posterior mean estimate of the number needed to treat of 28 (95% CI, 15 to 56) favoring statins over a mean weighted follow-up period of 4.9 years. Coronary heart disease mortality, nonfatal myocardial infarction, need for revascularization, and stroke were all statistically significantly reduced with statins compared with placebo (Evidence Table 8). Of note, the Heart Protection study (which included primary prevention population) was included in the meta-analysis but a sensitivity analysis with and without this trial showed consistent treatment effects. Statins that were included were simvastatin 20-40 mg, pravastatin 40 mg, and fluvastatin 80 mg.

African American, Hispanic, and other ethnic groups

African Americans had the greatest overall coronary heart disease mortality and the highest out-of-hospital coronary death rates of any other ethnic group in the United States.[4] Other ethnic and minority groups in the United States included 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 was 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 low-density lipoprotein cholesterol by similar percentages in blacks and in whites.[195]

In short-term head-to-head trials, reductions in low-density lipoprotein cholesterol and frequency of adverse events with rosuvastatin 10 to 20 mg and atorvastatin 10 to 20 mg in Hipanic,[23] South Asian,[196] and African American[74] patients were similar to those observed in studies conducted in primarily white non-Hispanic populations.

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 applied 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.[197, 198] 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 8245 patients, including over 3000 women.[199-203] 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 2819 subjects (Worldwide Expanded Dose Simvastatin Study Group) had similar results.[197] These studies were important because they demonstrated that the maximum (80 mg) doses of simvastatin and lovastatin were well tolerated. Similar findings were observed in 3 additional publications.[18, 194, 204]

A subgroup analysis[195] from the EXCEL Study examined the efficacy and safety of lovastatin compared with placebo in 459 African-Americans. The endpoints in the trial were reduction in total cholesterol, low-density lipoprotein cholesterol, triglycerides, and an increase in high-density lipoprotein cholesterol. With regard to safety, there was a significantly higher incidence of creatine kinase elevation in African-Americans compared to white Americans in both placebo and lovastatin treatment groups. However, no cases of myopathy, defined as creatine kinase elevations greater than 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.

In premarketing studies, Japanese and Chinese patients living in Singapore had higher levels of rosuvastatin in blood than Caucasians living in Europe.[205] The US Food and Drug Administration asked the manufacturer to perform an appropriately conducted pharmacokinetic study of Asians residing in the United States. The study demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese, or Asian-Indian origin) compared with a Caucasian control group. The rosuvastatin label noted that this increase should be considered when making rosuvastatin dosing decisions for Asian patients.

Key Question 5. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid-lowering drug when used in the general population of adults?

Summary of findings

- There was insufficient evidence to determine which statin or statins are safer with regard to muscle and liver toxicity.
- Four studies evaluating the benefit of atorvastatin 80 mg daily in reducing coronary heart disease on health outcomes observed a significantly higher rate of substantial elevations in liver transaminases in the atorvastatin groups in comparison with angioplasty, usual care, placebo, or pravastatin 40 mg. The clinical significance of asymptomatic liver enzyme elevations from statins has been questioned, however.
- Niacin extended release fixed-dose combination products cause increased adverse events leading to discontinuation of therapy compared with statin monotherapy.

Detailed assessment

Six reviews evaluated the safety profiles of statins.[206-211] In addition to the reviews of safety with statins, we reviewed the 83 head-to-head statin low-density lipoprotein cholesterol-lowering trials to determine whether there were any significant differences in adverse events. One meta-analysis of 18 randomized placebo-controlled trials comparing the adverse event rates for the different statins determined the number needed to harm compared to placebo to be 197 for overall adverse events.[211] Over 85% of the data came from trials of simvastatin and pravastatin. Serious events (creatine kinase greater than 10 times the upper limit of normal or rhabdomyolysis) were infrequent (number needed to harm, 3400 for myopathy and 7428 for rhabdomyolysis).[211] Another large meta-analysis reviewed 119 randomized controlled trials from the years 1982 to 2006 that involved 86 000 study participants.[209] Most of the data came from

trials of pravastatin and simvastatin with only 2 involving rosuvastatin. Although there was an increased incidence of myositis (odds ratio, 2.56; 95% CI, 1.12 to 5.58), they found a lower rate of discontinuance due to adverse events than that of placebo (odds ratio, 0.88; 95% CI, 0.84 to 0.93).

One meta-analysis of 4 randomized controlled trials evaluated the adverse events of intensive dose statin therapy of atorvastatin, simvastatin, or pravastatin compared to moderate dose therapy.[210] They found that the number needed to harm for any adverse event was 30 (odds ratio, 1.44; 95% CI, 1.33 to1.55). The number needed to harm for discontinuing therapy due to an adverse event was 47, for elevated transaminases was 86, and for elevation in creatine kinase greater than 10 times the upper limit of normal was 1534. There were no differences in the rate of rhabdomyolysis. From their analysis, treating 1000 patients would prevent significant health outcomes (4 cardiovascular deaths, 10 myocardial infarctions, and 6 strokes) while causing 33 adverse events: 21 adverse events requiring drug discontinuation and 12 instances of elevated liver function test values. Thus for every outcome prevented, there would be 8 adverse events of any type.[210]

A postmarketing analysis of adverse event data reported to the US Food and Drug Administration compared events reported in the first year of rosuvastatin use to events reported for atorvastatin, simvastatin, and pravastatin during the same period and during their first years of marketing.[212] Data from the first year of use of cerivastatin was also included. The primary analysis was a composite endpoint of rhabdomyolysis, proteinuria, nephropathy, or renal failure. Secondary analyses of overall adverse event rates and specific adverse events were also conducted.

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

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

Since that time, 3 additional large cohort studies have evaluated the safety of rosuvastatin compared to other statins.[213-215] No increased risk for rhabdomyolysis, acute renal failure, or significant hepatic injury was observed for rosuvastatin compared to other statins. Rhabdomyolysis was found to be rare with an incident rate of 2.9 per 10 000 person-years in 1 cohort.[214] In 16 head-to-head randomized-controlled trials, most of which were open label, adverse event rates were similar in all treatments.[15-17, 19-24, 28, 86, 87, 91, 98, 113] The Mazza 2008 open label randomized-controlled trial comparing rosuvastatin 10 or 20 mg to atorvastatin 20 mg was a 48-week study and did show a significant increase in alanine aminotransferase for atorvastatin

relative to baseline (24.6% change; $P<0.005$). The significance of asymptomatic transaminase elevation remains uncertain however.

One 24-week head-to-head randomized-controlled and open-label trial compared high-dose rosuvastatin to high-dose atorvastatin and reported adverse events.[20] They found similar adverse event rates except for an increase risk of hematuria, which was detected in 10.8% of rosuvastatin patients and 5.7% of atorvastatin patients. The clinical significance of this is uncertain. Proteinuria was similar in both groups. One meta-analysis of 25 head-to-head randomized-controlled trials of rosuvastatin compared to atorvastatin found no significant differences in adverse event rates.[13]

Myotoxicity

Five reviews[206-209, 211] evaluated the safety profile of statins. Six additional reviews specifically assessed myotoxicity with the statins.[216-220]

In addition to the reviews of safety with statins, we reviewed the 83 head-to-head statin low-density lipoprotein cholesterol-lowering trials to determine whether there were any significant differences in myotoxicity and/or elevation of liver enzymes. We also included 3 observational studies [218, 221, 222] with statins.

Magnitude of risk

Gaist and colleagues[222] conducted a population-based observational study in which 3 cohorts of patients were identified. The first cohort consisted of patients (n=17 219) who had received at least 1 prescription for lipid-lowering drugs. The second cohort consisted of patients (n=28 974) who had a diagnosis of hyperlipidemia but did not receive lipid-lowering drugs. The third cohort consisted of people (n=50 000) from the general population without a diagnosis of hypercholesterolemia. Using diagnostic visit codes recorded by participants in the U.K. General Practice Research Database, they identified and verified cases of symptomatic myopathic pain. A potential case of myopathy was confirmed with the clinician when the patient presented at least 2 of the following criteria: (1) clinical diagnosis of myopathy confirmed by the general practitioner; (2) muscle weakness, muscle pain, or muscle tenderness (2 of these symptoms); and (3) creatine kinase concentration above the reference limit. By this definition, the incidence of myopathy in the lipid-lowering group was 2.3 per 10 000 person-years (95% CI, 1.2 to 4.4) compared with none per 10 000 person-years in the non treated group (95% CI, 0 to 0.4) and 0.2 per 10 000 person-years (95% CI, 0.1 to 0.4) in the general population. In 17 086 person-years of statin treatment, there were only 2 cases of myopathy. In this study, rates of myotoxicity were not differentiated between statins.

In a systematic review, the incidence of myalgia in clinical trials ranged from 1% to 5% and was not significantly different from placebo. However, a review of 2 databases in the same review found that myalgia (defined as muscle pain without elevated creatine kinase levels) contributed to 19% to 25% and 6% to 14% of all adverse events associated with statin use.[220] In a large meta-analysis of 119 double-blind, placebo-controlled randomized-controlled trials, the odds of myalgia with statin monotherapy were no different than that of placebo (odds ratio, 1.09; 95% CI, 0.97 to 1.23).[209] There was an increased risk of myositis with an odds ratio of 2.56 (95% CI, 1.12 to 5.58).

Myotoxicity of different statins

All of the available statins (simvastatin, lovastatin, atorvastatin, fluvastatin, pravastatin, and rosuvastatin), when administered alone, have been associated with infrequent myotoxic adverse effects ranging from myalgia and myopathy to rhabdomyolysis.[206] 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.[217, 219, 223, 224]

A retrospective analysis of all domestic and foreign reports of statin-associated rhabdomyolysis has been released by the Food and Drug Administration.[218] During a 29-month period (November 1997 to March 2000) there were 871 reported cases of rhabdomyolysis. The number of cases (% of total) for each statin were as follows: atorvastatin, 73 (12.2%); fluvastatin, 10 (1.7%); lovastatin, 40 (6.7%); pravastatin, 71 (11.8%); and simvastatin, 215 (35.8%). The report also included cerivastatin with 192 (31.9%) cases of rhabdomyolysis. In the majority of these cases, a drug with the potential for increasing the statin serum level was identified. This report does not provide information about the relative incidence of rhabdomyolysis associated with different statins, because the number of patients taking each statin was not available.

Another review of reports to the US Food and Drug Administration's MedWatch database limited to events associated with atorvastatin or simvastatin was published in April 2003.[225] The analysis was limited to adverse reactions that affected major organ systems (muscle toxicity, hepatotoxicity, pancreatic toxicity, and bone marrow toxicity). Analyses were adjusted for dose but not low-density lipoprotein cholesterol lowering. Between November 1997 and April 2000, there were 1828 adverse event reports affecting major organ systems associated with the use of atorvastatin, and 1028 reports associated with simvastatin. Muscle-related events were more likely with atorvastatin (dose adjusted odds ratio, 1.7; 95% CI, 1.6 to 1.8; $P<0.001$). Reports of myalgias were more likely with atorvastatin, but rhabdomyolysis-associated reports were more likely with simvastatin (dose adjusted odds ratio, 2.4; 95% CI, 2.1 to 2.7; $P<0.001$).

Dale et al, 2007 performed a systematic review of randomized-controlled trials comparing higher with moderate intensity statin therapy. They included 9 trials with primarily high dose of atorvastatin or simvastatin to lower doses of atorvastatin, simvastatin, pravastatin, or lovastatin.[216] They evaluated hydrophilic (pravastatin) statins separately from the other more lipophilic statins and found an increase risk of significant creatinine kinase elevation but only in the lipophilic statins and not in the hydrophilic statins (relative risk, 6.09; 95% CI, 1.36 to 27.35). They did report that rosuvastatin was considered a hydrophilic statin, however no data on rosuvastatin was included in this review.

From these studies, conclusions regarding the differences in the risk of severe muscle toxicity between statins could not be made since there are significant limitations to voluntary, spontaneous reporting systems. For example, the actual exposure (denominator) of a population to a statin is not known, so the true incidence rates of an adverse effect cannot be determined. Furthermore, the number of reported cases (numerator) may be underestimated.

Another observational study used claims data from 11 United States-managed health care plans to estimate the incidence of rhabdomyolysis leading to hospitalization in patients treated with different statins and fibrates, alone and in combination.[226] Fluvastatin and lovastatin were excluded from the analysis because usage was very low. There were 16 cases of rhabdomyolysis leading to hospitalization with statin monotherapy in 252 460 patients contributing 225 640 person-years of observation. Incidence rates for monotherapy with atorvastatin, pravastatin, and simvastatin were similar.

In our review of 83 head-to-head comparative statin low-density lipoprotein cholesterol-lowering trials, we did not find any differences in rates of muscle toxicity between statins. In the ASTEROID trial, a study of regression of atherosclerosis, there were no cases of rhabdomyolysis in 507 patients taking rosuvastatin 40 mg for 24 months.[227] This trial is not included in our efficacy analysis because health outcomes were not reported.

Elevations of liver enzymes

All of the statins were rarely associated with elevations in liver transaminase levels (greater than 3 times the upper limit of normal), occurring in approximately 1% of patients. The clinical significance of asymptomatic liver enzyme elevations from statins has been questioned, however. The risk increases with increasing doses.[208] In order to answer whether there are differences in risk of liver toxicity between statins, we reviewed the adverse effects of the head-to-head statin low-density lipoprotein cholesterol-lowering trials and did not find any significant difference in the rate of clinically relevant elevation in liver enzymes between statins. The exception was 1 study comparing atorvastatin 80 mg to simvastatin 80 mg daily[52] in which there was a significantly higher incidence of transaminase elevation in the atorvastatin group compared to simvastatin. The reduction in low-density lipoprotein cholesterol was greater with atorvastatin 80 mg compared with simvastatin 80 mg (53.6% compared with 48.1%; $P<0.001$) in this same study.

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

In the PROVE-IT trial,[117] more patients in the atorvastatin 80 mg group had elevations in alanine aminotransaminase levels than those in the pravastatin 40 mg group (3.3% compared with 1.1%; $P<0.001$).

In AVERT[166] and MIRACL,[139] 2% and 2.5% of patients in the atorvastatin 80 mg daily group experienced clinically important elevations in the liver transaminases which were significantly greater than those in the angioplasty or placebo groups.

In GREACE, there were 5 patients out of 25 who received atorvastatin 80 mg 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 (greater than 3 times the upper limit of normal) with other statins compared with placebo or non-drug interventions. However, in the majority of studies reporting health outcomes involving fluvastatin, lovastatin, pravastatin, or simvastatin, the maximum daily dose was not used.

In the ALLIANCE study,[169] the incidence of abnormal aspartate aminotransferase or alanine aminotransaminase levels (greater than 3 times the upper limit of normal) in patients taking atorvastatin 80 mg was 0.7% (8 patients) and 1.3% (16 patients), respectively. Laboratory testing was not conducted in the usual care group

In the Treating to New Targets (TNT) Study,[228] patients with stable coronary disease were randomized to atorvastatin 80 mg (intensive lipid lowering) or 10 mg. Sixty of 4995 patients given atorvastatin 80 mg had a persistent elevation in liver enzymes (2 consecutive measurements greater than 3 times the upper limit of normal) compared with 9 of 5006 patients given 10 mg of atorvastatin (1.2% compared with 0.2%; $P<0.001$).

In the ASTEROID trial,[227] 1.8% of patients taking rosuvastatin 40 mg had elevated alanine aminotransaminase levels (greater than 3 times the upper limit of normal) and 1.2% had

elevated creatine kinase levels greater than 5 times the upper limit of normal. There were no elevations of creatine kinase greater than 10 times the upper limit of normal.

One meta-analysis reviewed 9 randomized-controlled trials that evaluated higher compared with lower statin doses with a mean follow-up of 48 weeks.[216] The effect of hydrophilic compared with lipophilic statin therapy were evaluated considering rosuvastatin and pravastatin as primarily hydrophilic. Dale found that more intense statin therapy increased the incidence of hepatic transaminase elevation but only with the hydrophilic statins which in this study only reviewed pravastatin date (RR, 3.54; 95% CI, 1.83 to 6.85) compared to the lipophilic statins (RR, 1.58; 95% CI, 0.81 to 3.08).

Proteinuria

In head-to-head trials, dipstick-positive proteinuria occurred in <1% of patients in all treatment groups, except for the rosuvastatin 40-mg group (1.5%). Hematuria occurred in <2.0% of patients in all treatment groups, except for the simvastatin 80 mg group (2.6%).[229] In the 24-week ECLIPSE trial, 3.2% of the rosuvastatin group and 2.0% of the atorvastatin group developed proteinuria at any time. The clinical importance of this renal effect is not known, but, as a precaution, the rosuvastatin product label recommends dose reduction from 40 mg in patients with unexplained persistent proteinuria.

Fixed-dose combination products containing a statin and another lipid-lowering agent

There were no significant differences in rates for any clinical adverse event, drug-related adverse events, or elevated creatine kinase levels across age (< 65 years compared with ≥65 years), sex, or race between patients receiving fixed-dose combination of ezetimibe-simvastatin and simvastatin monotherapy in a pooled analysis of 3 trials (12 weeks duration).[230] Consecutive elevations in aspartate aminotransferase/alanine aminotransferase ≥ 3 times the upper limit of normal were noted for the fixed-dose combination group compared with simvastatin monotherapy, but the increases were asymptomatic and reversible. We identified very little evidence of harms in the trials of the fixed dose combination product trials. The majority of trials were not longer than 12 weeks in duration.

In the SEACOAST I trial, increased efficacy of extended-release niacin-simvastatin 2000/20 mg compared with simvastatin 20 mg monotherapy came at the cost of an increased rate of adverse events, with 35.9% of the extended-release niacin-simvastatin patients reporting any adverse event and 10.9% reporting flushing compared to 17.5% and 0% respectively in the simvastatin group.[110]

Key question 6. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid-lowering drug when used in special populations or with other medications (drug-drug interactions)?

Summary of findings

- Studies that included patients with diabetes did not have higher rates of adverse events than other studies.
- In general, statin-fibrate combination increased risk of musculoskeletal-related adverse events compared with statin monotherapy.

- It appeared that the risk is greater with statin-gemfibrozil combination than with statin-fenofibrate combinations.

Detailed assessment

Myotoxicity and hepatic enzymes (special populations)

Patients with diabetes

There are no data to support any special safety concerns in patients with diabetes receiving statins. In short-term head-to-head studies of atorvastatin compared with rosuvastatin in patients with diabetes, the type and frequency of adverse events was similar to those found in studies of patients without diabetes.[78, 95, 231]

In the Heart Protection Study (HPS, simvastatin), substantial elevations of liver enzymes and creatinine kinase were not significantly higher in patients with diabetes. Moreover, taking simvastatin for 5 years did not adversely affect glycemic control or renal function. It should be noted, however, that the Heart Protection Study had a run-in period in which patients who had liver or muscle enzyme elevations were excluded prior to randomization.

In CARDS,[125] there was no difference between atorvastatin and placebo in the frequency of adverse events or serious adverse events, including myopathy, myalgia, rise in creatinine phosphokinase, and discontinuation from treatment for muscle-related events. There were no cases of rhabdomyolysis.

A 4-month, head-to-head trial of extended-release fluvastatin 80 mg compared with atorvastatin 20 mg was conducted in 100 patients with type 2 diabetes and low serum high-density lipoprotein levels.[232] The study was designed to measure the metabolic effects of the statins and did not measure clinical endpoints. There were no significant changes in serum creatinine phosphokinase or liver enzymes and no major adverse events after 4 months of treatment.

A 48-week trial assessed efficacy and safety of long-term treatment with fluvastatin in patients with chronic renal disease and hyperlipidemia.[233] Patients with diabetic nephropathy (N=34) or chronic glomerulonephritis (N=46) were randomized to fluvastatin 20 mg plus dietary therapy, or dietary therapy alone. Over 48 weeks of treatment, there were no significant differences between fluvastatin and placebo groups in serum creatinine concentration, creatinine clearance, or 24-hour urinary albumin excretion rates.

Adverse event rates were similar between atorvastatin and placebo-treated patients enrolled in the ASPEN trial.[142] Abnormal liver function tests occurred in 1.4% using atorvastatin compared with 1.2% in the placebo group. The rate of myalgia was more frequent with atorvastatin (3% compared with 1.6%; *P* value not reported). Two cases of rhabdomyolysis were reported, 1 in each treatment arm. Neither of the cases were thought to be related to the interventions.

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 7 non-systematic reviews pertaining to statin drug interactions.[206, 234-239] Briefly, simvastatin, lovastatin, and atorvastatin are all metabolized in the liver via the cytochrome P450 3A4 isoenzyme system. As a result, all 3 agents are susceptible to drug interactions when administered concomitantly with agents known to inhibit metabolism via CYP 3A4. The use of the agents listed below increases statin concentrations and, theoretically,

the possibility for adverse effects and 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. Only about 10% of rosuvastatin is metabolized, primarily through the CYP 2C9 system. Pravastatin is not significantly metabolized via the CYP isoenzyme system and is therefore not affected by drugs inhibiting metabolism via these pathways.

Statin-clopidogrel. Several pharmacokinetic studies have suggested potential drug interaction with atorvastatin (and other CYP 3A4 statins) and clopidogrel. Clopidogrel is a prodrug that requires activation via CYP 3A4/2C19.

We identified 9 publications[240-248] examining the potential drug interaction with regard to clinical outcomes. Of these, 8 studies[240, 242-248] collectively showed little difference in the risk of cardiovascular events (myocardial infarction, death, revascularization, hospitalization, etc) in patients at high risk for atherothrombotic events (with or without percutaneous coronary intervention) for those receiving statin-clopidogrel combination compared with those using statin or clopidogrel monotherapy. There was also a minimal difference in risk between groups when statins were stratified by whether they were metabolized by 3A4 or non-3A4 pathways.

Study designs were retrospective or post-hoc analyses of larger randomized trials. Each study had its limitations such as small sample size (lack of power), unknown statin doses, unclear duration of statin or clopidogrel combination therapy, potential selection bias in database studies, and unknown adherence to therapy; thus, the results should be interpreted carefully.

Statin-efavirenz. We found 1 small retrospective review (N=13)[249] that assessed the potential drug interaction with the combination of simvastatin to an efavirenz-based regimen in HIV-infected and non-infected patients. Efavirenz is a non-nucleoside reverse transcriptase inhibitor that has CYP 3A4 inductive effects and the combination with simvastatin, a 3A4 substrate, could potentially lead to less of a statin treatment effect. This study found small non-significant absolute differences in low-density lipoprotein and total cholesterol lowering effects between those using simvastatin-efavirenz and those using only statin therapy. There were no reports of myopathies or elevated liver transaminase and creatine kinase levels in the chart reviews.

Potent inhibitors of CYP 3A4 are listed below:

- 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 with Clarithromycin, Erythromycin, Cyclosporine, Itraconazole, and Nefazodone.

Drugs known to inhibit metabolism via CYP 2C9 are listed below:

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

Harms in organ transplant recipients. The main concern of statin therapy in organ transplant patients is the potential for increased musculoskeletal and hepato-toxicities from statin-drug interaction, especially for drugs that are substrates (simvastatin, lovastatin, atorvastatin) and inhibitors (cyclosporine) of the CYP 3A4 pathway.

The risk for adverse events with statins in combination with cyclosporine appears to be dose-related. Long-term, single-drug treatment of hyperlipidemia with simvastatin at doses not exceeding 10 mg daily, respectively, has been shown to be well tolerated with minimal harms in cardiac and renal transplant patients receiving cyclosporine.[250, 251] Fluvastatin 20-80 mg daily and pravastatin at 20-40 mg daily have also been shown to be relatively safe in cyclosporine-managed cardiac and renal transplant recipients.[127, 252-255] A post hoc analysis of the ALERT trial, one of the largest renal transplant trials evaluating fluvastatin, found little statistical difference between fluvastatin and placebo-treated groups with or without diabetes with regards to changes in serum creatinine, creatinine clearance, proteinuria, serious renal adverse events leading to study withdrawal, or incidence of graft loss.[256] There was also little difference in the incidence of transplant rejection within the first post-transplantation year between pravastatin and placebo-treated identified patients in a different retrospective study.[257] Rosuvastatin 10 mg (average dose) was studied in a cohort study of 21 cardiac transplant recipients receiving standard immunosuppressive therapy.[258] The patients' lipid levels were above target values on the highest tolerated doses of other statins. After 6 weeks, there were no statistically significant changes in creatine kinase levels or aspartate aminotransferase. There was no clinical evidence of myositis in any patient. One patient had myalgia and 2 patients were withdrawn because of mild elevation of creatine kinase (324 U/liter at 3 weeks and 458 U/liter at 6 weeks). In a premarketing study, cyclosporine had a clinically significant effect on the drug concentrations of rosuvastatin in heart transplant patients. The product label recommends limiting the dose of rosuvastatin to 5 mg in patients taking cyclosporine.

Only 1 case of rhabdomyolysis was identified from a heart transplant registry which included 210 patients managed with a variety of statins for 1 year.[259] The patient with rhabdomyolysis was receiving simvastatin 20 mg daily. No rhabdomyolysis was seen in 39 patients receiving simvastatin 10 mg daily. A review of studies involving fluvastatin (up to 80 mg daily) in organ transplant patients receiving cyclosporine identified no cases of rhabdomyolysis.[260] One small study[261] involving atorvastatin (10 mg/day) in 10 renal-transplant recipients taking cyclosporine observed a significant benefit with regard to lipid levels and no cases of myopathy or rhabdomyolysis.

A small prospective, single-center cohort study found that 80% of heart transplant patients who were converted from cyclosporine and high-dose fluvastatin regimen to tacrolimus

and atorvastatin 20-40 mg therapy tolerated the switch through 13 months. There were no reports of myalgias, significant elevations in creatine kinase, myopathies, or liver toxicities.[262]

Harms in HIV-infected patients: Statins and protease-inhibitors. A significant proportion of HIV-infected patients receiving protease inhibitors developed hyperlipidemia as an adverse effect. As a result, these patients required lipid-lowering treatment. Because of the severity of the lipid elevation, statins are often prescribed to these patients but little is known about the harms observed in this population.

To date, good-quality long-term clinical data evaluating the combination of the protease inhibitors with statins are limited. Pharmacokinetic studies have shown that when simvastatin or atorvastatin (CYP 3A4 substrates) are used in combination with potent CYP 3A4 inhibitors (such as ritonavir and/or saquinavir), increased drug concentrations of statins may lead to greater potential risk for myopathies and rhabdomyolysis.[263]

We identified 8 publications[25, 264-270] that reported harms in HIV-infected patients receiving combination therapy with protease inhibitors and statins or fibrates. Of these, 7[264-270] studied primarily pravastatin while 1[25] reported "combined statin" results.

Of the 7 pravastatin studies, 3 randomized trials compared pravastatin 40 mg daily with placebo in HIV-infected patients receiving a protease-inhibitor (45% to 90% were prescribed ritonavir).[266, 269, 270] Over 8-12 week period, there were no reports of myopathy or rhabdomyolysis and no significant changes in aspartate aminotransferase, alanine aminotransferase, or creatine phosphokinase levels between treatment groups or across trials. Four cases of mild to moderate myalgias were found with pravastatin than with 1 case in the placebo group.[266, 270] "Severe" muscle aches developed in 2 patients in 1 trial,[270] but neither discontinued therapy and their creatine phosphokinase levels were within normal limits. Only 1 pravastatin-treated patient withdrew from a trial because of seizure and hospitalization, which was not related to study treatment.[266]

Three open-label, randomized trials[264, 267, 268] and 1 prospective observational study[265] also found that HIV-infected patients using combination therapy with a protease-inhibitor and low-dose statin or fibrate tolerated the combination fairly well except for some gastrointestinal complaints such as nausea, dyspepsia, diarrhea, and meteorism (range: 2%-12%). There were no reports of myalgias or myositis during 48-72 weeks of follow-up and no significant elevations in creatine kinase or liver transaminases. All patients were using a protease inhibitor with about 27% to 88% using ritonavir. Totally daily doses of statins and fibrates studied were: pravastatin 10-20 mg, atorvastatin 10 mg, rosuvastatin 10 mg, fluvastatin 20-40 mg, fenofibrate 200 mg, gemfibrozil 1200 mg, and bezafibrate LA 400 mg.

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 largely based on pharmacokinetic studies and suggest using low-to mid-level doses of atorvastatin, fluvastatin, or pravastatin as alternatives (http://wwwhivatis.org and http://www.aactg.s-3.com/ann.htm).

Statins in HIV-infected patients with comorbidities. One small (N=80) retrospective chart review compared harms in HIV-positive and hepatitis C virus co-infection patients using statins compared with HIV-positive and hepatitis C virus/hepatitis B virus-negative patients using statins.[25] The purpose of the study was to evaluate whether statins increased hepatotoxicity

between the 2 groups. Most patients were middle-aged men and about 45% were taking antiretroviral therapy with a protease inhibitor. Sixty-four percent of included patients were using atorvastatin, 29% pravastatin, 5% rosuvastatin, and 2.5% simvastatin. Elevated liver enzymes (≥1.5 times the baseline values) were considered significant in this study. Overall, there were no major differences in the number of patients with liver enzymes ≥1.5 times baseline values between treatment groups. About 7.9% of co-infected patients observed a ≥1.5 time elevation in alanine aminotransferase but this was lower than alanine aminotransferase values found in hepatitis C virus/hepatitis B virus-negative group. No patients discontinued statin therapy because of liver toxicities or modified their antiretroviral therapies due to drug interactions. The results from this study should be considered with caution due to poor internal quality.

Harms of statin-fibrates combination (rhabdomyolysis and myopathy). Myopathy and rhabdomyolysis have also been reported in patients receiving monotherapy with fibrates, especially in patients with impaired renal function. Although the mechanism of the interaction is not completely known, it appears the combination of statins with fibrates, and to a lesser extent niacin, can result in a higher risk for myopathy or rhabdomyolysis. These adverse effects may also be dose-related.[206, 224, 271] The mechanism for the interaction is unclear but it is hypothesized that gemfibrozil inhibits glucuronidation of statins.

We identified 12 studies[218, 219, 226, 272-280] reporting harms with statin-fibrate combination. Of these, 8[218, 219, 226, 272, 275, 276, 278, 280] reported information on rhabdomyolysis, 3[219, 279, 280] on myopathy, and 4 studies[219, 273, 274, 277] reported data on other harms such as elevations in liver transaminase or creatine kinase levels.

Of the 8 studies that reported information on rhabdomyolysis, 1 systematic review[219] of 36 studies (ranging from 2 to 184 weeks in duration) and 2 shorter-term trials[278, 280] (12 to 22 weeks in duration) that evaluated statin-fibrate combination therapy in the management of hypercholesterolemia, reported no cases of rhabdomyolysis.

In the systematic review by Shek and colleagues,[219] the majority of included studies used gemfibrozil (total daily dose of 1200 mg; n=20, 63% of patients). Ten studies used bezafibrate, 2 used fenofibrate, 1 used clofibrate, 1 used ciprofibrate, 1 used both bezafibrate and ciprofibrate, 1 used bezafibrate or fenofibrate, and 1 used gemfibrozil or ciprofibrate. No reports of rhabdomyolysis were observed in the 1674 patients receiving statin-fibrate combination. A total of 19 (1.14%) patients withdrew secondary to myalgia or creatine kinase elevation. Two patients (0.12%) developed myopathy (defined as myalgia with creatine kinase >10 times the upper limit of normal) 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 creatine kinase (<10 times the upper limit of normal) in 16 of the included studies. All but 2 of these studies used gemfibrozil; the others used bezafibrate plus simvastatin 20 mg and fenofibrate plus pravastatin 20 mg or simvastatin 10 mg. Some of the studies did not report whether the creatine kinase elevation was symptomatic or if treatment was discontinued as a result. In 1 of the included studies, a patient tolerated the combination of pravastatin and gemfibrozil for 4 years, and then developed myopathy with clinically important elevation in creatine kinase after being switched to simvastatin.

Shek and colleagues[219] also found 29 published case reports of rhabdomyolysis secondary to statin-fibrate combination not captured in the above 36 publications. Gemfibrozil was the fibrate used in each case. Statins used were lovastatin in 21 cases, simvastatin in 4 cases, cerivastatin in 3 cases, and atorvastatin in 1 case. Time to developing rhabdomyolysis was rapid

(17% within 2 weeks and 93% within 12 weeks) and the onset of symptoms ranged from 36 hours to 36 weeks. No case reports of severe myopathy or rhabdomyolysis in patients receiving pravastatin or fluvastatin combined with a fibrate were found. Similarly, there were no reports of severe myopathy or rhabdomyolysis in a different trial evaluating combination of pravastatin and gemfibrozil.[280] However, cases of pravastatin or fluvastatin combined with a fibrate resulting in rhabdomyolysis have been reported.[218]

There were several limitations to this systematic review.[219] First, included trials tended to exclude patients who had risk factors or comorbidities for developing adverse outcomes. Therefore, data based on these trials likely underestimate rates of adverse events in the broader population. Also, some of the included studies did not report numbers and reasons for study withdrawal and were not of the best quality.

We identified 2 observational studies that found statin-fibrate combination therapy to have higher rates of rhabdomyolysis compared with statin monotherapy.[226, 272] Data collected in these studies included the time period when cerivastatin was on the market and when serious adverse events were being reported. The inclusion of cerivastatin in both studies could have inflated rates observed, so results should be considered with caution.

A retrospective cohort study of 252 460 patients using claims data from 11 managed health care plans found 24 cases of hospitalized rhabdomyolysis occurring during treatment.[226] The average incidence of rhabdomyolysis requiring hospitalization was 0.44 per 10 000 (95% CI, 0.20 to 0.84) and was similar for atorvastatin, pravastatin, and simvastatin monotherapy. When taken in combination with a fibrate, statins were associated with a higher incidence of hospitalized rhabdomyolysis of 5.98 (95% CI, 0.72 to 216) per 10 000. The study of health plan claims data referred to above reported cases of rhabdomyolysis with the combination of a statin and a fibrate.[226] The cohort represented 7300 person-years of combined therapy with statins and fibrates (gemfibrozil or fenofibrate). There were 8 cases of rhabdomyolysis with combination therapy. Incidence rates per 10 000 person-years were 22.45 (95% CI, 0.57 to 125) for atorvastatin combined with fenofibrate, 18.73 (95% CI, 0.47 to104) for simvastatin combined with gemfibrozil, and 1035 (95% CI, 389 to 2117) for cerivastatin plus gemfibrozil. There were no cases with pravastatin; fluvastatin and lovastatin were excluded from the analysis because usage was very low.

Another retrospective review from the US Food and Drug Administration's adverse events reporting system found 866 cases of rhabdomyolysis, of which 44% were related to statin-gemfibrozil combination therapy and 56% with statin monotherapy.[272] Almost half of the monotherapy cases and about 75% of combination therapy cases were believed to be from cerivastatin. When individual statins were stratified based on mono-or combination therapy, the crude reporting rates for rhabdomyolysis per an estimated 100 000 prescriptions over marketing years (1988-July 2001) was higher with statin-gemfibrozil combinations than statin monotherapy. The crude reporting rates for combination compared with monotherapy were: lovastatin (2.84 compared with 0.12), pravastatin (0.14 compared with 0.02), simvastatin (3.85 compared with 0.08), atorvastatin (0.50 compared with 0.03), fluvastatin (0.00 compared with 0.00), and cerivastatin (1248.66 compared with 1.81).

In addition to the above observational studies, we found 2 retrospective reviews using the US Food and Drug Administration's adverse event reporting system to compare rates of rhabdomyolysis between statin-fenofibrate and statin-gemfibrozil combination therapies.[275, 276] Both studies found fewer reports or lower rates of rhabdomyolysis associated with statin-fenofibrate use than statin-gemfibrozil use. The number of cases reported in the Jones study[276]

for statin-fenofibrate compared with statin-gemfibrozil was 0.58 compared with 8.6 per million prescriptions dispensed, excluding cerivastatin, whereas the odds ratio of rhabdomyolysis was 1.36 (95% CI, 1.12 to 1.71; P=0.002) for statin-fenofibrate compared with an odds ratio of 2.67 (95% CI, 2.11 to 3.30; P<0.001) for statin-gemfibrozil. Since data from the US Food and Drug Administration database are dependent on volunteer reports of adverse events, rates may be an underestimation of "actual" events for either combination therapies and results should be considered carefully.

Of the 12 publications that reported harms associated with statin-fibrate therapy, the remaining publications[273, 274, 277] showed variable rates of elevated liver transaminase or creatine kinase elevations with combination statin-fibrate usage compared with placebo, statin, or fibrate monotherapies. The evidence base was limited and results should be interpreted carefully.

A pooled analysis evaluated the frequency of creatine kinase elevations in Novartis-funded trials in which fluvastatin was administered in combination with fibrates.[274] Of 1017 patients treated with combination therapy, 493 received bezafibrate, 158 fenofibrate, and 366 gemfibrozil. Mean exposure time was 37.6 weeks and ranged from 0.7 to 118.3 weeks. Results were not reported separately by type of fibrate. Five of 1017 patients (0.5%) had creatine kinase elevations greater than or equal to 5 times the upper limit of normal; 2 of these were greater than or equal to 10 times the upper limit of normal. There were no significant differences in the frequency of creatine kinase elevations among the group on combination therapy and patients taking placebo, fibrates only, or fluvastatin only. Similarly, there were no large differences in liver function tests or creatine kinase levels found between the atorvastatin-fenofibrate treatment group and atorvastatin or fenofibrate monotherapy groups in 2 short-term (8-16 week) studies.[273, 277] There were also no deaths, no increased risk of renal failure, and no liver function tests >3 times the upper limit of normal.[273]

A prospective observational cohort study followed 252 patients who were prescribed a statin combined with gemfibrozil for a mean of 2.36 years (range 6 weeks to 8.6 years). Creatine kinase levels, aminotransferase levels, and any reports of muscle soreness or weakness were monitored. One presumed case of myositis occurred in a patient who took simvastatin for 1 year. The patient had previously taken pravastatin combination therapy for 4 years without incident. An asymptomatic 5-fold rise in alanine aminotransferase was observed in 1 patient, and 2 other patients had an alanine aminotransferase elevation between 2 and 3 times the upper limit of normal. The statin involved in these cases is not specified.

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

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

- **Rosuvastatin**: Avoid the combination with **fibrates** unless the benefit outweighs the risk and limit doses to 10 mg if combined with **gemfibrozil**.

Elevation in liver enzymes. In the systematic review by Shek in 2001,[219] 8 patients in 3 of the 36 included studies discontinued the combination therapy due to significant elevation in liver transaminases (alanine aminotransferase and aspartate aminotransferase). In most of the other studies, there were only reports of subclinical (<3 times the upper limit of normal) elevation in alanine aminotransferase or aspartate aminotransferase. Conclusions regarding the safety of different statins in the liver were not made.

A retrospective database analysis evaluated the risk of elevated liver enzymes in patients who were prescribed a statin.[281] Changes in liver transaminases at 6 months were compared in 3 cohorts: patients with elevated baseline enzymes (aspartate aminotransferase>40 IU/L or alanine aminotransferase >35 IU/L) who were prescribed a statin (n=342), patients with normal transaminases who were prescribed a statin (n=1437), and patients with elevated liver enzymes who were not prescribed a statin (n=2245). Patients with elevated liver enzymes at baseline had a higher incidence of mild/moderate and severe elevations after 6 months, whether or not they were prescribed a statin. Those with elevated liver enzymes at baseline who were prescribed a statin had a higher incidence of mild-moderate, but not severe, elevations at 6 months than those with normal transaminases who were prescribed a statin. Most patients in this study were prescribed atorvastatin or simvastatin (5 patients were prescribed fluvastatin); there was no difference in results according to the type of statin prescribed.

Harms of statin-thiazolidinediones combination. A recent nested, case-control study[282] evaluated the potential association between statin-thiazolidinedione combination and statins, thiazolidinediones, or other antidiabetic medications in patients with type 2 diabetes for muscle-related toxicities such as myopathy, myositis, rhabdomyolysis and myalgias. Of the 25 567 patients included in the analysis, about 5.7% of cases and 4.9% of controls were classified as having been *ever exposed* to statin-thiazolidinedione combination. Atorvastatin was the most commonly prescribed statin followed by simvastatin; rosiglitazone and pioglitazone were the thiazolidinediones under evaluation.

When compared with patients exposed to statin monotherapy, patients using statin-thiazolidinedione combination did not show an increased risk for muscle-related toxicities (adjusted odds ratio, 1.03; 95% CI, 0.83 to 1.26).

A different retrospective study reviewed the adverse events reported to the US Food and Drug Administration between 1990 and March 2002 in which simvastatin or atorvastatin was listed as a suspect in causing adverse events, and in which antidiabetic medications were listed as *co-suspects* or concomitant medications. Analysis was limited to adverse events affecting major organ systems (muscles, liver, pancreas, and bone marrow).[283] Atorvastatin-associated adverse event reports were more *likely* to list concomitant thiazolidinediones compared with simvastatin-associated adverse event reports (3.6% compared with 1.6%, respectively; odds ratio, 2.3; 95% CI, 1.7 to 3.2; $P<0.0001$). Muscle toxicity was the most common adverse event, followed by liver-related events.

We also found one 24-week, placebo-controlled trial examining the effect of adding simvastatin to patients with type 2 diabetes who were taking a thiazolidinedione (pioglitazone or rosiglitazone).[284] There were 2 cases of asymptomatic creatine phosphokinase elevations ≥10 times the upper limit of normal in the simvastatin group (1.7%), no elevations in alanine

aminotransferase or aspartate aminotransferase, and no differences in tolerability between patients taking pioglitazone and those taking rosiglitazone.

CHILDREN

Key Question 1. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to reduce low-density lipoprotein cholesterol?

Summary of findings

- Trials of statins in children have been conducted primarily in children with heterozygous or homozygous familial hypercholesterolemia, or other familial dyslipidemias.
- Eight trials of various statins showed improvement in low-density lipoprotein compared with placebo.
- In meta-analysis, statins reduced low-density lipoprotein cholesterol in children taking a statin by 32% (95% CI, 37 to 26).
- One trial compared ezetimibe/simvastatin to simvastatin alone and demonstrated a 54% reduction in low-density lipoprotein cholesterol for combination compared to 38% reduction for simvastatin alone.

Key Question 1a. Are there doses for each statin or fixed-dose combination product containing a statin and another lipid-lowering drug that produce similar percent reduction in low-density lipoprotein cholesterol?

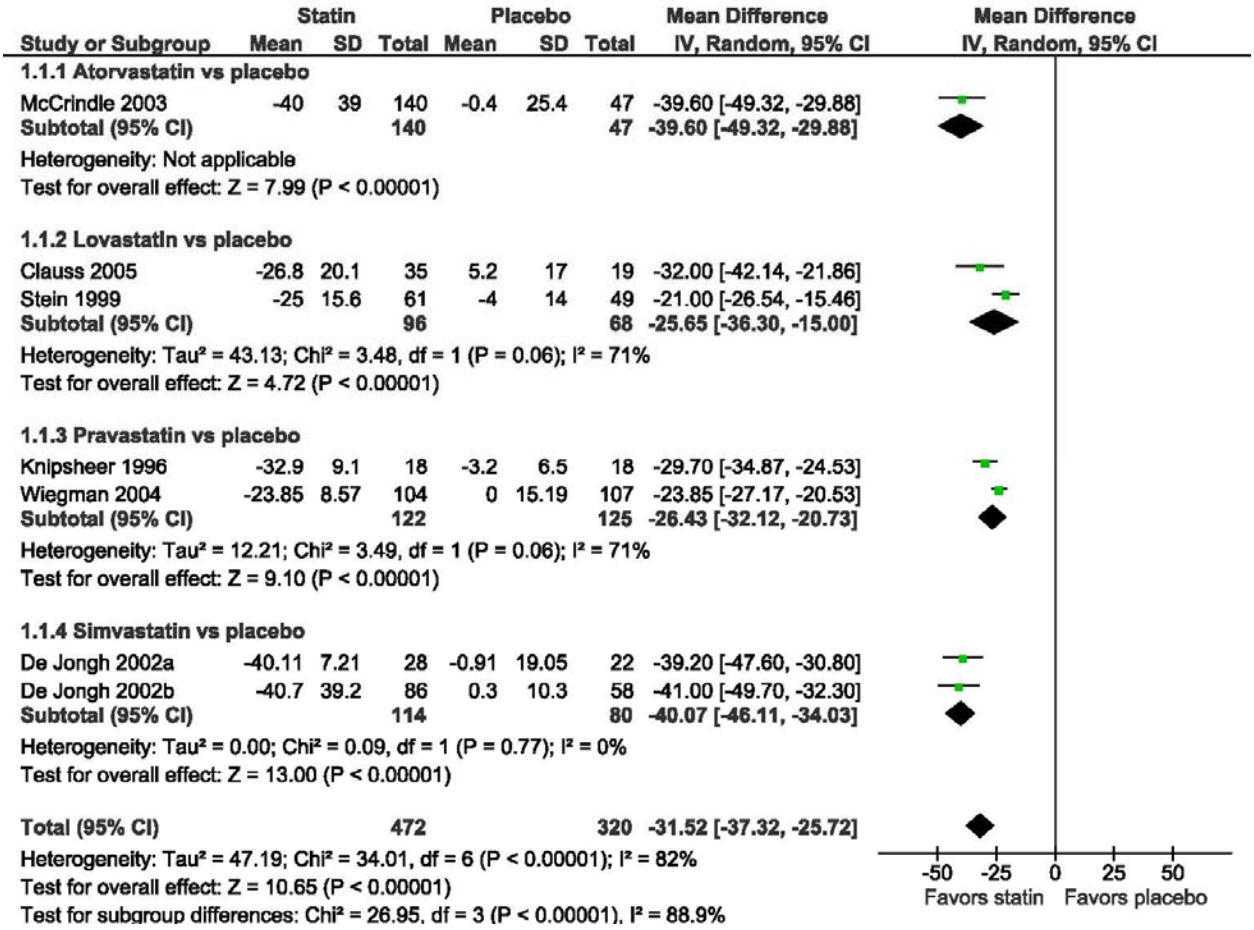
All the trials of statin drugs compared to placebo, including 1 trial of atorvastatin [285] 2 of lovastatin,[286, 287] 2 of pravastatin,[288, 289] and 3 of simvastatin,[290-292] demonstrated improvement in total cholesterol and low-density lipoprotein cholesterol among children and adolescents with familial hypercholesterolemia. For all trials, the change in total cholesterol ranged from –17% to –32% from baseline for treatment groups compared with changes of +3.6% to –2.3% for placebo groups. The decreases in low-density lipoprotein cholesterol ranged from 19% to 41% for treatment groups compared with changes of +0.67% to –3% for placebo groups.

The 1 trial of atorvastatin compared to rosuvastatin included patients with homozygous familial hypercholesterolemia. Eight of the 44 patients enrolled were under age 18 and results were not separated out by age group. The trial started with open label dose titration of rosuvastatin for 18 weeks and then randomized patients to atorvastatin or rosuvastatin (both at 80 mg/day doses) in a crossover design for 6 weeks. After the first 18-week dose titration phase, there was a 21% difference in low-density lipoprotein cholesterol levels compared to baseline ($P<0.0001$). At the end of the first 6-week period of the crossover phase there was no difference in low-density lipoprotein cholesterol from baseline between groups (19% decrease for rosuvastatin 80 mg/day and 18% decrease for atorvastatin 80 mg/day).[293]

We conducted a meta-analysis of the percent change from baseline in low-density lipoprotein levels in placebo-controlled trials (Figure 2). Seven trials provided sufficient information to be included in the meta-analysis (mean percent change from baseline and standard deviation, or data to calculate these).[285-289, 291, 292] Of these, 1 was rated good quality,[286] 1 was

rated poor quality,[291] and the rest were fair quality. A sensitivity analysis excluding the poor quality study did not change results of the meta-analysis. One study included atorvastatin,[285] 2 lovastatin,[286, 287] 2 pravastatin,[288, 289] and 2 simvastatin.[291, 292] The meta-analysis included 472 patients taking a statin and 320 taking a placebo. Overall, statins reduced low-density lipoprotein cholesterol in children taking a statin by 32% (95% CI, 37 to 26). The mean percent change from baseline was greater for atorvastatin (10 mg) and simvastatin (40 mg) than lovastatin (40 mg) and pravastatin (20 to 40 mg). These results are similar to percent reductions seen in adults at these doses. With the exception of pravastatin 20 to 40 mg compared with simvastatin 40 mg, confidence intervals for the different statins overlapped, suggesting similar percent low-density lipoprotein cholesterol lowering. However, because this body of evidence is indirect, and studies were heterogenous, it cannot be used to draw strong conclusions about the comparative effectiveness of the different statins.

Figure 2. Low-density lipoprotein cholesterol lowering in placebo-controlled trials of statins in children with familial hypercholesterolemia



Key Question 1b. Do statins or fixed-dose combination product containing a statin and another lipid-lowering drug differ in the ability to achieve National Cholesterol Education Program goals?

National Cholesterol Education Panel goals for children were updated in 2007.[294] In that guideline statement, treatment is considered for children 10 years of age or greater, preferably after the onset of menses in girls and ideally after children have reached Tanner stage II or higher. Age and low-density lipoprotein level at which statin therapy is initiated is subject to judgment about presence of risk factors that suggest familial hypercholesterolemia such as cutaneous xanthomas. Authors suggest that patient and family preferences should be considered in decision-making.[294]

In the only study of simvastatin compared to fixed dose ezetimibe/simvastatin combination (10 mg/40 mg), low-density lipoprotein cholesterol was reduced from a mean of 114 mg/dL to a mean of 103 mg/dL (change of 54%) in the ezetimibe/simvastatin group and reduced from a mean of 144 mg/dL to a mean of to 135 mg/dL (change of 38%) in the simvastatin group.[295] At the end of 33 weeks, the percentage of subjects achieving a low-density lipoprotein cholesterol <130 mg/dL were 77% in the ezetimibe/simvastatin group and 53% in the simvastatin group ($P<0.01$); the number of subjects achieving a low-density lipoprotein cholesterol level <110 mg/dL were 63% in the ezetimibe/simvastatin group and 27% in the simvastatin group ($P<0.01$).[295]

Key Question 2. How do statins and fixed-dose combination products containing a statin and another lipid lowering drug compare in their ability to raise high-density lipoprotein cholesterol?

Summary of findings

- Statins decreased high-density lipoprotein cholesterol in 1 study of atorvastatin and did not change high-density lipoprotein cholesterol in 5 other trials of statins including rosuvastatin, simvastatin, lovastatin, and pravastatin.
- Overall, the pooled result indicated that statins increased high-density lipoprotein cholesterol by 3% (95% CI, 0.6 to 5.6).

Key Question 2b. Are there doses for each statin or fixed-dose combination product containing a statin and another lipid lower drug that produce similar percent increase in high-density lipoprotein cholesterol between statins?

High-density lipoprotein cholesterol decreased in the 1 trial of atorvastatin[285] but did not change in 2 trials of lovastatin,[286, 287] 1 trial of pravastatin that reported high-density lipoprotein cholesterol,[288] and 2 trials of simvastatin.[291, 292] Overall, high-density lipoprotein cholesterol increased +1% to +11% for treatment groups compared with –1% to +4.8% for placebo groups.

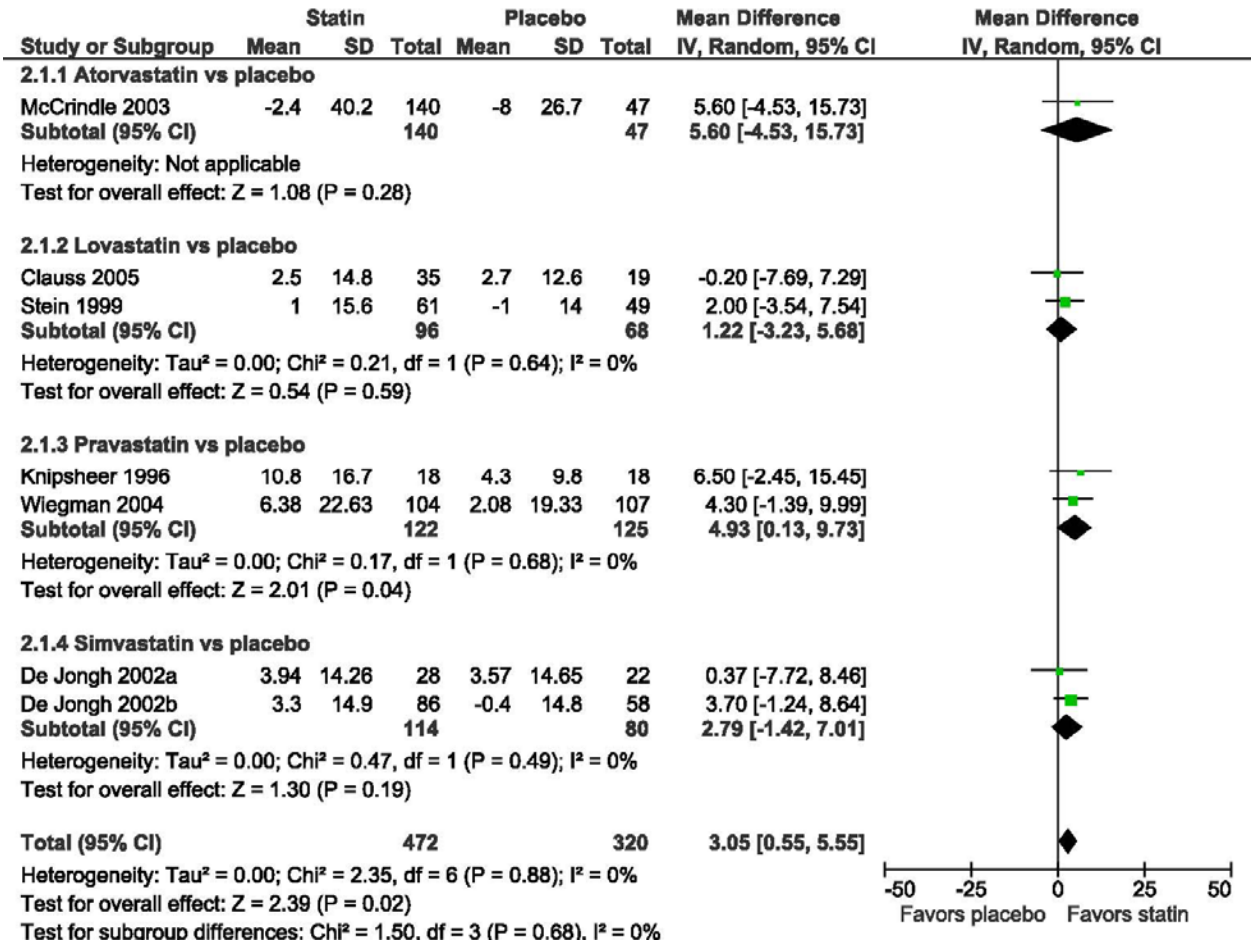
The trial of atorvastatin compared to rosuvastatin started with open-label dose titration of rosuvastatin for 18 weeks and then randomized patients to atorvastatin or rosuvastatin (both at 80 mg/day doses) in a crossover design for 6 weeks. Eight of 44 patients enrolled in the trial were under age 18; results were not separated out by age group. At the end of the initial dose titration phase (18 weeks) there was no significant difference in high-density lipoprotein levels compared

with baseline (3.1% increase in the rosuvastatin group, not significant). After 6 weeks of the crossover comparison phase (prior to crossover), there was no difference between groups in the change in high-density lipoprotein cholesterol from baseline (2.5% increase for rosuvastatin 80 mg/day and 4.9% decrease for atorvastatin 80 mg/day, *P*=0.24).[293]

The 1 trial that evaluated simvastatin compared to fixed-dose ezetimibe/simvastatin combination (10 mg/40 mg) demonstrated no change in high-density lipoprotein cholesterol.[295]

We conducted a random-effects meta-analysis of placebo-controlled trials reporting the change from baseline in high-density lipoprotein cholesterol levels in children with familial hypercholesterolemia (Figure 3). Seven trials contributed data to the meta-analysis,[285-289, 291, 292] representing 472 patients taking a statin and 320 taking a placebo. Results are shown in Figure 3. Overall, the pooled result indicated that statins increased high-density lipoprotein cholesterol by 3% (95% CI, 0.6 to 5.6). Among the individual statins, only pravastatin significantly increased high-density lipoprotein cholesterol, with a 5% change (95% CI, 0.1 to 9.7). The mean difference from placebo was nonsignificant for the other statins.

Figure 3. High-density lipoprotein cholesterol increases in placebo-controlled trials of statins in children with familial hypercholesterolemia



Key Question 3. How do statins and fixed-dose combination products containing a statin and another lipid lowering drug compare in their ability to reduce the risk of nonfatal myocardial infarction, coronary disease (angina), coronary heart disease mortality, all-cause mortality, stroke, hospitalization for unstable angina, or need for revascularization (coronary artery bypass graft, angioplasty, or stenting)?

Summary of findings

- Studies of statins in children have not been conducted with long enough follow-up to assess for outcomes related to cardiovascular mortality and morbidity.

Detailed assessment

Nonfatal myocardial infarction, coronary disease (angina), coronary heart disease mortality, all-cause mortality, stroke, hospitalization for unstable angina, or need for revascularization (coronary artery bypass graft, angioplasty, or stenting) are outcomes that occur primarily in adults. There were no studies in children that had sufficient follow-up to determine the effect of treatment with statin or fixed-dose combination products containing a statin and another lipid-lowering drug on the risk of these outcomes. However, it is generally assumed by the specialists in this area that treatment of children with familial hypercholesterolemia does postpone or prevent the onset of early cardiovascular disease. As a surrogate end-point, trials have demonstrated the effect of statins on intima-medial thickness, arterial stiffness, and endothelial function.[289]

Key Question 4. Are there differences in effectiveness of statins and fixed-dose combination products containing a statin and another lipid lowering drug in different demographic groups or in patients with comorbid conditions (e.g. diabetes, obesity)?

Summary of findings

- No trials have evaluated statins in children with diabetes or obesity. One study demonstrated 21% reduction in low-density lipoprotein with simvastatin in children with neurofibromatosis 1.

Detailed assessment

We identified no trials of statins and fixed-dose combination products in children with diabetes or obesity. One study of simvastatin compared to placebo in children with neurofibromatosis 1 demonstrated a reduction in low-density lipoprotein cholesterol (21% for simvastatin; low-density lipoprotein reduction for placebo group not reported) but no change in high-density lipoprotein.[296]

Key Question 5. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid lowering drug when used in the general population of children?

Summary of findings

- Adverse events were variably reported; methods of detection and assessment of adverse events were often not specified.
- Multiple studies reported no significant elevations in both creatine kinase and aspartate aminotransferase/alanine aminotransferase over the course of the study.
- Elevations in aspartate aminotransferase/alanine aminotransferase occurred but were either lower than 3 times the upper limit of normal or resolved with interruption/ discontinuation of medication.
- Elevations in creatine kinase occurred with simvastatin and simvastatin plus ezetimibe; all returned to normal with cessation of medication.

Detailed assessment

Information on harms of statins and fixed-dose combination products in children was obtained from randomized-controlled trials, controlled clinical trials, non-controlled case series, and case reports. Data on adverse events from clinical trials is variably reported; methods for detection and assessment of the adverse events were often not specified.

Several studies reported that aspartate aminotransferase and alanine aminotransferase remained below twice or 3 times the upper limit of normal. This was true for 24-48 weeks of treatment lovastatin,[286, 287] 28 weeks of simvastatin,[291] and 12 weeks to 2 years of treatment with pravastatin.[288, 289, 297] Reports of elevations in transaminases occurred with atorvastatin,[285] simvastatin-ezetimibe combinations,[295] and rosuvastatin (in a trial that included both adults and children with homozygous familial hypercholesterolemia).[293] In studies that reported increased transaminase levels during statin treatment, these levels returned to normal with treatment interruption or discontinuation of the statin.[285, 291, 295]

Similarly, multiple studies reported no significant elevations in creatine kinase over the study period.[285-287, 289, 293] One study reported a 1.6% incidence of creatine kinase elevation (>10 times the upper limit of normal) in the treatment (simvastatin plus ezetimibe) group compared to 9% in the control group (simvastatin alone).[295] Another study reported a single child with creatine kinase elevation (>10 times the upper limit of normal) without muscled symptoms, which occurred with concomitant administration of simvastatin and erythromycin and returned to normal after completion of the antibiotics, and 2 children with increases in creatine kinase (>5-fold the upper limit of normal) that returned to normal in repeat tests.[292]

Several studies also cited “no significant” or “no serious” adverse events, or even “no adverse events”.[286, 291, 298] Such statements in these studies lack rigorous definitions of the methods used to monitor for and detect adverse events. Other studies stated that the incidence of reporting any adverse events was equal between the treatment and control (placebo) groups[287, 288, 291] or reported the incidence of adverse events to demonstrate that point.[285, 292, 295] Treatment-related adverse effects were reported as 8.6% for lovastatin compared with 5% for placebo;[286] 4.7% compared with 3.4% (clinical) and 1.2% compared with 1.7% (laboratory);[288] 18.2% for

rosuvastatin in the open-label titration period and in the crossover period; and 2.6% for atorvastatin compared with 0% for rosuvastatin.[293]

Key Question 6. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid lowering drug when used in special populations or with other medications (drug-drug interactions)?

Summary of findings

- One study of fluvastatin in children with minimal change glomerulonephritis demonstrated decrease in total cholesterol and reported no side effects.

Detailed assessment

One study of children with minimal change glomerulonephritis (MCGN) assigned 36 patients to 20 mg of fluvastatin or dipyridamole for 2 years.[299] The main study outcome was bone mineral density, for which there was no change over the course of the study. Hematuria decreased significantly, and creatinine clearance, total protein, and albumin increased compared to baseline in the statin group, but not the dipyridamole group. Total cholesterol decreased from 4.43±0.57 mmol/L to 3.68±0.52 mmol/L and triglycerides decreased from 1.04±0.57 g/L to 0.66±0.26 g/L ($P<0.001$ compared with baseline for both; $P>0.001$ compared with dipyridamole for both after treatment). The authors observed no side effects in any of the patients over the treatment period.

SUMMARY

Table 15 summarizes the level and direction of evidence for each key question.

Table 15. Summary of the evidence by key question

Key question	Strength of evidence	Conclusion
ADULTS		
1. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to reduce low-density lipoprotein cholesterol?	Fair	The ideal study would be a double-blind, intention-to-treat randomized trial in which equipotent doses of different statins were compared with regard to low-density lipoprotein-lowering, withdrawals, and adverse effects. No studies met these stringent criteria.
a. Are their doses for each statin or fixed-dose combination product containing a statin and another lipid-lowering drug that produce similar percent reduction in low-density lipoprotein cholesterol between statins?	Fair-to-good	Results of a large number of trials are generally consistent with information from the manufacturer. When statins are provided in doses that are approximately equipotent, a similar percent reduction in low-density lipoprotein cholesterol can be achieved. In active-control trials, the fixed-dose combination of ezetimibe-simvastatin had a significant increase in low-density lipoprotein cholesterol lowering compared to statin

Key question	Strength of evidence	Conclusion
		monotherapy.
b. Is there a difference in the ability of a statin or fixed-dose combination product containing a statin and another lipid-lowering drug to achieve National Cholesterol Education Panel goals?	Good for most comparisons (see text)	For patients who require low-density lipoprotein cholesterol reductions of up to 35% to meet their goal, any of the statins are effective. In patients requiring a low-density lipoprotein cholesterol reduction of 35% to 50% to meet the National Cholesterol Education Program goal, atorvastatin 20 mg or more, lovastatin 80 mg, rosuvastatin 10 mg or more, and simvastatin 40 mg or more daily are likely to meet the goal. Atorvastatin 80 mg daily and rosuvastatin 20 mg or more can reduce low-density lipoprotein cholesterol by 50% or more. Based on fair-quality studies, atorvastatin 80 mg daily resulted in 5 to 6 additional percentage points of low-density lipoprotein reduction than simvastatin 80 mg (53% to 54% vs. 47% to 48%), but had significantly higher rates of some adverse events. In head-to-head studies rosuvastatin 40 mg had greater reduction in low-density lipoprotein cholesterol than atorvastatin 80 mg with similar frequency of adverse events. In patients requiring a low-density lipoprotein cholesterol reduction of greater than 50%, the higher doses of ezetimibe-simvastatin at 10/40 mg and 10/80 mg are more likely to meet the National Cholesterol Education Program Adult Treatment Panel III goal than an equivalent high potency statin.
2. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to raise high-density lipoprotein cholesterol?	Fair-to-good	When statins are provided in doses that are approximately equipotent for lowering LDL-C, a similar percent increase in high-density lipoprotein cholesterol can be achieved. There is conflicting evidence about simvastatin vs. atorvastatin, with some studies finding no difference and others finding simvastatin superior. Some studies found greater increases in high-density lipoprotein cholesterol with rosuvastatin compared with atorvastatin, while other studies found no difference.
3. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to reduce the risk of nonfatal myocardial infarction, coronary heart disease (angina), coronary heart disease mortality, all-cause mortality, stroke, hospitalization for unstable angina, or need for revascularization (coronary artery bypass graft, angioplasty, or stenting)?	NA	There are no controlled trials comparing equivalent doses of 2 or more statins to reduce the risk of coronary events, stroke, or death.
Which statins have been shown to reduce all-cause mortality?	Good	Patients who have never had CHD: pravastatin (high-risk patients), simvastatin (mixed populations); rosuvastatin (patients with elevated C-reactive protein) Patients with CHD: atorvastatin (post-MI), pravastatin, simvastatin

Key question	Strength of evidence	Conclusion
Which statins have been shown to reduce cardiovascular mortality?	Good	Patients who have never had CHD: Pravastatin, simvastatin Patients with CHD: simvastatin, atorvastatin
Which statins have been shown to reduce CHD events?	Fair-to-good	Patients who have never had CHD: atorvastatin (high-risk patients, patients with diabetes), lovastatin (average-risk patients), pravastatin (high-risk patients), simvastatin (mixed populations) ; rosuvastatin (patients with elevated C-reactive protein) Patients with CHD: atorvastatin, simvastatin, pravastatin. Patients after PTCA: fluvastatin, pravastatin.
Which statins have been shown to reduce strokes?	Good	Atorvastatin, pravastatin, simvastatin, rosuvastatin (patients with elevated C-reactive protein)
Patients with diabetes	Good	There are good efficacy data for people with diabetes. Atorva 10 mg reduced cardiovascular events in a primary prevention trial of patients with diabetes (CARDS), and simvastatin 40 mg reduced cardiovascular events in patients with diabetes (Heart Protection Study). In a subgroup analysis of the LIPS trial, there was a reduction in coronary events (cardiac death, nonfatal MI, CABG, or repeat PCI) with fluvastatin 80 mg in patients with diabetes who had undergone successful PCI. Studies that included people with diabetes had rates of adverse effects similar to other studies.
4. Are there differences in effectiveness of statins and fixed-dose combination products containing a statin and another lipid-lowering drug in different demographic groups or in patients with comorbid conditions (e.g., diabetes, obesity)?	Good (elderly, women)-to-Fair to 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. In short-term head-to-head trials, reductions in LDL-C and frequency of adverse events with rosuvastatin 10 to 20 mg and atorvastatin 10 to 20 mg in Hispanic, South Asian, and African American patients were similar to those observed in studies conducted in primarily white non-Hispanic populations.
Are there differences in safety of statins in different demographic groups (age, sex, race)?	Poor	There are no data from clinical trials comparing the safety of different statins in women, the elderly, or African Americans. A pharmacokinetic study of rosuvastatin conducted in the United States demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese, or Asian-Indian origin) compared with a Caucasian control group.
5. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid-lowering drug when used in the general population of children or adults?	Good for statins monotherapy Fair to poor for fixed dose combination products	Although creatine kinase elevations are common, the risk of symptomatic myopathy is low. All of the available statins (simvastatin, lovastatin, atorvastatin, fluvastatin, pravastatin, rosuvastatin), when administered alone, have been associated with infrequent myotoxic adverse effects ranging from myalgia, and myopathy to rhabdomyolysis. Two meta-analyses of clinical trials found rates of elevated transaminases (liver function tests) to be no higher among patients taking statins than among those receiving placebo. There is no evidence that elevated transaminases

Key question	Strength of evidence	Conclusion
		associated with statin use increase the risk of clinically significant liver failure. In a trial of 2 doses of atorvastatin, the incidence of persistent elevations in liver aminotransferase levels 2 per 1000 in patients taking atorvastatin 10 mg daily, vs. 1.2 per 1000 in patients taking 80 mg daily. There is insufficient evidence to determine which statin or statins are safer with regard to muscle toxicity or elevated liver enzymes. Among high potency statins, at doses below 80 mg, rates of adverse events and withdrawals due to adverse events were similar in patients taking atorvastatin or simvastatin. Atorvastatin 80 mg had a higher rate of some adverse effects (gastrointestinal disturbances and transaminase elevation) than simvastatin 80 mg daily in a trial in which the low-density lipoprotein lowering of atorvastatin was greater than that of simvastatin. Adverse event rates in patients using rosuvastatin 40 mg were similar to rates in patients using atorvastatin 80 mg in short-term trials. We identified very little evidence of harms in the trials of the fixed dose combination product trials. The majority of trials were not longer than 12 weeks in duration.
6. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid-lowering drug when used in special populations or with other medications (drug-drug interactions)? In addressing this question, we will focus on the following populations:		
Special populations: Patients with diabetes	Good	Studies that included people with diabetes had rates of adverse effects similar to other studies.
Drug interactions	Fair	The combination of any statin with fibrates, and to a lesser extent niacin, can result in a higher risk for myopathy or rhabdomyolysis.
CHILDREN		
1. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to reduce low-density lipoprotein cholesterol?	Fair-to-poor	In one head-to-head trial conducted in adults and children with homozygous familial hypercholesterolemia, atorvastatin 80 mg and rosuvastatin 80 mg were similarly efficacious for reducing low-density lipoprotein cholesterol (18% for atorvastatin, 19% for rosuvastatin). In placebo-controlled trials of atorvastatin, lovastatin, pravastatin, and simvastatin, statins reduced low-density lipoprotein cholesterol in children with familial hypercholesterolemia by 32% (95% CI, 37 to 26). In one trial, the fixed dose combination product simvastatin/ezetimibe reduced low-density lipoprotein more

Key question	Strength of evidence	Conclusion
		than simvastatin alone (54% vs. 38%). There were no trials of fluvastatin or the fixed dose combination products lovastatin/niacin extended-release or simvastatin/niacin extended-release in children.
2. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to raise high-density lipoprotein cholesterol?	Fair-to-poor	In one head-to-head trial of atorvastatin 80 mg vs. rosuvastatin 80 mg conducted in adults and children with homozygous familial hypercholesterolemia, there was no difference in high-density lipoprotein cholesterol levels after 6 weeks. In placebo-controlled trials of atorvastatin, lovastatin, pravastatin, and simvastatin, statins increased high-density lipoprotein cholesterol in children with familial hypercholesterolemia by 3% (95% CI, 0.6 to 5.6). One trial of the fixed dose combination product simvastatin/ezetimibe compared with simvastatin alone showed no change in high-density lipoprotein levels. There were no trials of fluvastatin or the fixed dose combination products lovastatin/niacin extended-release or simvastatin/niacin extended-release in children.
3. How do statins and fixed-dose combination products containing a statin and another lipid-lowering drug compare in their ability to reduce the risk of nonfatal myocardial infarction, coronary heart disease (angina), coronary heart disease mortality, all-cause mortality, stroke, hospitalization for unstable angina, or need for revascularization (coronary artery bypass graft, angioplasty, or stenting)?	Poor	No evidence in children.
4. Are there differences in effectiveness of statins and fixed-dose combination products containing a statin and another lipid-lowering drug in different demographic groups or in patients with comorbid conditions (e.g., diabetes, obesity)?	Poor	No evidence in children with diabetes or obesity. One placebo-controlled trial in children with neurofibromatosis 1 showed reduction in low-density lipoprotein levels with simvastatin, but no change in high-density lipoprotein levels.
5. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid-lowering drug when used in the general population of children or adults?	Fair-to-poor	Multiple studies reported no significant elevations in creatine kinase and AST/ALT. If AST/ALT elevations occurred, they were either lower than 3 times the upper limit of normal, or resolved with discontinuation of medication. In trials, reporting of adverse events was poor.
6. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid-lowering drug when	Poor	No comparative evidence in children.

Key question	Strength of evidence	Conclusion
used in special populations or with other medications (drug-drug interactions)?		

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CABG, coronary artery bypass graft; CHD, coronary heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty.

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Appendix A. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An **adverse event** for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a

participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report was hypothetically repeated on a collection of 100 random samples of studies, the resulting 100 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage

forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity.*

Half- life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intention to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (hear attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are

many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an ood ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/ treatment/ rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combing data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤ 0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the

included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomisation when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug’s adverse effects impact the patient’s ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance

side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measureable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix B. Search strategy

Searches on Medline, Medline-In Process amd Cochrane Central Register of Controlled Trials were repeated in May-June of 2009 and gave additional citations that were reviewed and incorporated when they met eligibility criteria.

Database: Ovid MEDLINE(R) <1996 to January Week 4 2009>
Search Strategy:
---

1 lovastatin.mp. or exp Lovastatin/ (5022)
2 simvastatin.mp. or exp Simvastatin/ (3948)
3 pravastatin.mp. or exp Pravastatin/ (2578)
4 atorvastatin.mp. (3245)
5 fluvastatin.mp. (1073)
6 rosuvastatin.mp. (726)
7 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or statin$.mp. (18571)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (20058)
9 Comparative Study/ (686468)
10 drug evaluation studies.mp. or exp Drug Evaluation/ (4285)
11 9 or 10 (689769)
12 8 and 11 (2374)
13 limit 12 to humans (2036)
14 limit 13 to english language (1761)
15 limit 13 to abstracts (1812)
16 14 or 15 (1964)
17 exp clinical trials/ or clinical trial$.mp. (380571)
18 exp Cohort Studies/ (431690)
19 (cohort stud$ or longitudinal stud$ or prospective stud$).mp. (296276)
20 17 or 18 or 19 (762070)
21 8 and 20 (5991)
22 limit 21 to humans (5938)
23 limit 21 to abstracts (5335)
24 22 or 23 (5988)
25 16 or 24 (6831)
26 (2006$ not (200601$ or 200602$)).ed. (526925)
27 (2007$ or 2008$ or 2009$).ed. (1409839)
28 26 or 27 (1936764)
29 25 and 28 (2347)
30 from 29 keep 1-2347 (2347)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <February 05, 2009>
Search Strategy:
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1 lovastatin.mp. or exp Lovastatin/ (74)
2 simvastatin.mp. or exp Simvastatin/ (233)
3 pravastatin.mp. or exp Pravastatin/ (108)
4 atorvastatin.mp. (215)
5 fluvastatin.mp. (38)
6 rosuvastatin.mp. (79)
7 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or statin$.mp. (947)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (1313)
9 Comparative Study/ (3071)
10 drug evaluation studies.mp. or exp Drug Evaluation/ (2)
11 9 or 10 (3073)
12 8 and 11 (24)
13 meta analysis.mp. or exp Meta-Analysis/ (1529)
14 multicenter study.mp. or exp Multicenter Study/ (835)
15 exp clinical trials/ or clinical trial$.mp. (6900)
16 exp Cohort Studies/ (3)
17 (cohort stud$ or longitudinal stud$ or prospective stud$).mp. (5885)
18 13 or 14 or 15 or 16 or 17 (14494)
19 12 or (8 and 18) (167)
20 limit 19 to abstracts (161)
21 from 20 keep 1-161 (161)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2008>
Search Strategy:
---

1 lovastatin.mp. or exp Lovastatin/ (1204)
2 simvastatin.mp. or exp Simvastatin/ (1167)
3 pravastatin.mp. or exp Pravastatin/ (949)
4 atorvastatin.mp. (941)
5 fluvastatin.mp. (368)
6 rosuvastatin.mp. (143)
7 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or statin$.mp. (2749)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (3802)
9 Comparative Study/ or comparative study.mp. (12886)
10 drug evaluation studies.mp. or exp Drug Evaluation/ (5646)
11 9 or 10 (18324)
12 8 and 11 (90)
13 meta analysis/ or meta analysis.mp. (1027)
14 multicenter study/ or multicenter study.mp. (6897)
15 exp clinical trials/ or clinical trial$.mp. (82715)
16 exp Cohort Studies/ (73025)
17 (cohort stud$ or longitudinal stud$ or prospective stud$).mp. (59519)
18 13 or 14 or 15 or 16 or 17 (152832)
19 12 or (8 and 18) (1240)
20 limit 19 to abstracts (1190)

21 from 20 keep 1-1190 (1190)

Database: Ovid MEDLINE(R) <1996 to January Week 4 2009>
Search Strategy:
---
1 Advicor.mp. (9)
2 Vytorin.mp. (16)
3 Simcor.mp. (3)
4 (lovastatin and niacin).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (76)
5 (simvastatin and ezetimibe).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (234)
6 (simvastatin and niacin).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (90)
7 lovastatin.mp. or exp Lovastatin/ (5022)
8 simvastatin.mp. or exp Simvastatin/ (3948)
9 niacin.mp. or exp Niacin/ (1922)
10 niacin extended release.mp. (19)
11 Niacin ER.mp. (21)
12 (niacin adj3 extend$ release).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (94)
13 ezetimibe.mp. (784)
14 Zetia.mp. (26)
15 1 or 2 or 3 or 4 or 5 or 6 (355)
16 7 or 8 (5572)
17 9 or 10 or 11 or 12 or 13 or 14 (2624)
18 16 and 17 (361)
19 15 or 18 (363)
20 from 19 keep 1-363 (363)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <February 05, 2009>
Search Strategy:
---
1 Advicor.mp. (0)
2 Vytorin.mp. (1)
3 Simcor.mp. (0)
4 (lovastatin and niacin).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2)
5 (simvastatin and ezetimibe).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (25)

6 (simvastatin and niacin).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (11)
7 lovastatin.mp. or exp Lovastatin/ (74)
8 simvastatin.mp. or exp Simvastatin/ (233)
9 niacin.mp. or exp Niacin/ (99)
10 niacin extended release.mp. (3)
11 Niacin ER.mp. (3)
12 (niacin adj3 extend$ release).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (16)
13 ezetimibe.mp. (77)
14 Zetia.mp. (1)
15 1 or 2 or 3 or 4 or 5 or 6 (34)
16 7 or 8 (284)
17 9 or 10 or 11 or 12 or 13 or 14 (170)
18 16 and 17 (35)
19 15 or 18 (35)
20 from 19 keep 1-35 (35)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2008>
Search Strategy:
---
1 Advicor.mp. (3)
2 Vytorin.mp. (2)
3 Simcor.mp. (1)
4 (lovastatin and niacin).mp. (44)
5 (simvastatin and ezetimibe).mp. (55)
6 (simvastatin and niacin).mp. (20)
7 lovastatin.mp. or exp Lovastatin/ (1204)
8 simvastatin.mp. or exp Simvastatin/ (1167)
9 niacin.mp. or exp Niacin/ (297)
10 niacin extended release.mp. (9)
11 Niacin ER.mp. (13)
12 (niacin adj3 extend$ release).mp. (42)
13 ezetimibe.mp. (118)
14 Zetia.mp. (3)
15 1 or 2 or 3 or 4 or 5 or 6 (112)
16 7 or 8 (1567)
17 9 or 10 or 11 or 12 or 13 or 14 (413)
18 16 and 17 (113)
19 15 or 18 (115)
20 from 19 keep 1-115 (115)

Appendix C. Methods used to assess quality of studies

Study quality was objectively assessed using predetermined criteria for internal validity, which were based on a combination of the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination[1, 2] criteria.

All included studies, regardless of design, were assessed for quality and assigned a rating of "good," "fair," or "poor". Studies that have a fatal flaw were rated poor quality. A fatal flaw was the failure to meet combinations of criteria that may be related to indicate the presence of bias. An example would be inadequate procedures for allocation concealment combined with important differences between groups in prognostic factors at baseline and following randomization. Studies that meet all criteria were rated good quality; the remainder were rated fair quality. As the fair-quality category was broad, studies with this rating varied in their strengths and weaknesses: The results of some fair-quality studies were *likely* to be valid, while others were only *possibly* valid. A poor-quality trial was not valid; the results were at least as likely to reflect flaws in the study design as a true difference between the compared drugs.

Criteria for assessing applicability (external validity) are also listed, although they were not used to determine study quality.

Systematic Reviews

1. Does the systematic review report a clear review question and clearly state inclusion and exclusion criteria for primary studies?

A good-quality review focuses on a well-defined question or set of questions, which ideally refer to the inclusion/exclusion criteria by which decisions are made about whether to include or exclude primary studies. These criteria would relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. A good-quality review also includes details about the process of decision-making, that is, how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

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

If details of electronic database searches and other identification strategies are given, the answer to this question usually is yes. Ideally, search terms, date restrictions, and language restrictions are presented. In addition, descriptions of hand-searches, attempts to identify unpublished material, and any contact with authors, industry, or research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only MEDLINE is searched for a systematic review about health education, then it is unlikely that all relevant studies will be located.

3. Is the validity of included studies adequately assessed?

If the review systematically assesses the quality of primary studies, it should include an explanation of the basis for determining quality (for example, method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis) and the process by which assessment is carried out (that is, how many reviewers are involved, whether the assessment is independent, and how discrepancies between reviewers are resolved). Authors

may have used either a published checklist or scale or one that they designed specifically for their review.

4. Is sufficient detail of the individual studies presented?

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

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (for example, according to sample size or according to inverse of the variance) so that studies that are thought to provide the most reliable data have greater impact on the summary statistic.

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 number, birth date, or day of week

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

Inferior approaches to concealment of randomization:

Use of alternation, case record number, birth date, or day of week

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 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 (that is, 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 follow-up or overall high loss to follow-up? (Study should give number for each group.)

Nonrandomized studies

Assessment of Internal Validity

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

2. Was there important differential loss to follow-up or overall high loss to follow-up? (Numbers should be given for 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 unbiased and accurate ascertainment of events (that is, by independent ascertainers using a validated ascertainment technique)?

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

7. Was the duration of follow-up reasonable for investigated events?

References

1. Center for Reviews and Dissemination, University of York, 2001. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. *CRD ReportNumber 4(2nd edition).*

2. Harris RP, Helfand M, Woolf SH. Current methods of the US Preventive Services Task Force: a review of the process. *American Journal of Preventive Medicine.* 2001;20(3 Suppl):21-35.

Appendix D. Excluded studies

Exclusion Codes
1=Foreign language, 2=Wrong outcome, 3=Wrong intervention, 4=Wrong population, 5=Wrong publication type, 6=Wrong study design.

Excluded studies	Exclusion code
Head-to-head trials	
Betteridge DJ, Gibson JM, Sager PT. Comparison of effectiveness of rosuvastatin versus atorvastatin on the achievement of combined C-reactive protein (<2 mg/L) and low-density lipoprotein cholesterol (< 70 mg/dl) targets in patients with type 2 diabetes mellitus (from the ANDROMEDA study). American Journal of Cardiology. Oct 15 2007;100(8):1245-1248.	2
Zhang B, Noda K, Matsunaga A, Kumagai K, Saku K. A comparative crossover study of the effects of fluvastatin and pravastatin (FP-COS) on circulating autoantibodies to oxidized LDL in patients with hypercholesterolemia. Journal of Atherosclerosis & Thrombosis. 2005;12(1):41-47.	2
Yoshino G, Kazumi T, Matsushita M, et al. Comparison of the effects of pravastatin and simvastatin in hypercholesterolemic subjects. Current Therapeutic Research, Clinical & Experimental. 1990;48(2):259-267.	4
van Dam MJ, Penn HJ, den Hartog FR, et al. A comparison of the efficacy and tolerability of titrate-to-goal regimens of simvastatin and fluvastatin: a randomized, double-blind study in adult patients at moderate to high risk for cardiovascular disease. Clinical Therapeutics. 2001;23(3):467-478.	4
Stein EA, Marais AD, Ducobu J, et al. Comparison of short-term renal effects and efficacy of rosuvastatin 40 mg and simvastatin 80 mg, followed by assessment of long-term renal effects of rosuvastatin 40 mg, in patients with dyslipidemia. Journal of Clinical Lipidology. 2007;1(4):287-299.	4
Spring S, Simon R, van der Loo B, et al. High-dose atorvastatin in peripheral arterial disease (PAD): effect on endothelial function, intima-media-thickness and local progression of PAD. An open randomized controlled pilot trial. Thrombosis & Haemostasis. Jan 2008;99(1):182-189.	6
Ridker PM, Morrow DA, Rose LM, Rifai N, Cannon CP, Braunwald E. Relative efficacy of atorvastatin 80 mg and pravastatin 40 mg in achieving the dual goals of low-density lipoprotein cholesterol <70 mg/dl and C-reactive protein <2 mg/l: an analysis of the PROVE-IT TIMI-22 trial. Journal of the American College of Cardiology. May 17 2005;45(10):1644-1648.	2
Raggi P, Davidson M, Callister TQ, et al. Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES). Circulation. Jul 26 2005;112(4):563-571.	2
Pitt B, Loscalzo J, Ycas J, Raichlen JS. Lipid levels after acute coronary syndromes.[see comment]. Journal of the American College of Cardiology. Apr 15 2008;51(15):1440-1445.	2

Excluded studies	Exclusion code
Mauger J-F, Couture P, Paradis M-E, Lamarche B. Comparison of the impact of atorvastatin and simvastatin on apoA-I kinetics in men. Atherosclerosis. 2005;178(1):157-163.	2
Kent SM, Coyle LC, Flaherty PJ, Markwood TT, Taylor AJ. Marked Low-Density Lipoprotein Cholesterol Reduction below Current National Cholesterol Education Program Targets Provides the Greatest Reduction in Carotid Atherosclerosis. Clinical Cardiology. 2004;27(1):17-21.	2
Jayaram S, Jain MM, Naikawadi AA, Gawde A, Desai A. Comparative evaluation of the efficacy, safety, and tolerability of rosuvastatin 10 mg with atorvastatin, 10 mg in adult patients with hypercholesterolaemia: The first Indian study. J Indian Med Assoc. 2004;102(1):48-52.	5
Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. American Journal of Cardiology. 1 2004;94(9):1140-1146.	6
Haasis R, Berger J. Fluvastatin vs. lovastatin in primary hypercholesterolemia. Herz Kreislauf. 1995;27(11):375-380.	1
Gagne C, Gaudet D, Bruckert E, Ezetimibe Study G. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation. May 28 2002;105(21):2469-2475.	4
Feillet C, Farnier M, Monnier LH, et al. Comparative effects of simvastatin and pravastatin on cholesterol synthesis in patients with primary hypercholesterolemia. Atherosclerosis. 1995;118:251-258.	2
Cheung RC, Morrell JM, Kallend D, Watkins C, Schuster H. Effects of switching statins on lipid and apolipoprotein ratios in the MERCURY I study. International Journal of Cardiology. Apr 20 2005;100(2):309-316.	2
Capone D, Stanziale P, Gentile A, Imperatore P, Pellegrino T, Basile V. Effects of simvastatin and pravastatin on hyperlipidemia and cyclosporin blood levels in renal transplant recipients. American Journal of Nephrology. 1999;19:411-415.	4
Branchi A, Fiorenza AM, Rovellini A, et al. Lowering effects of four different statins on serum triglyceride level. European Journal of Clinical Pharmacology. 1999;55:499-502.	2
Bots A, Kastelein J, Investigators DN. Achieving lipid goals in real life: the Dutch DISCOVERY study. Int J Clin Pract. 2005;59(12):1387-1394.	5
Best JD, Nicholson GC, O Ndn, et al. Atorvastatin and simvastatin reduce elevated cholesterol in non insulin dependent diabetes. Diabetes, Nutrition and Metabolism Clinical and Experimental. 1996;9:74-80.	4
Bertolami MC, Ramires JAF, Nicolau JC, Novazzi JP, Bodanese LC, Giannini SD. Open, randomized, comparative study of atorvastatin and simvastatin, after 12 weeks treatment, in patients with hypercholesterolemia alone or with combined hypertriglyceridemia. Revista Brasileira de Medicina. 2002;59(8):577-584.	1

Excluded studies	Exclusion code
Barter PJ, O'Brien RC. Achievement of target plasma cholesterol levels in hypercholesterolaemic patients being treated in general practice. Atherosclerosis. 2000;149:199-205.	3
Ballantyne CM, McKenney J, Trippe BS. Efficacy and safety of an extended-release formulation of fluvastatin for once-daily treatment of primary hypercholesterolemia. American Journal of Cardiology. 2000;86(7):759-763.	6
Rosuvastatin shows superiority to atorvastatin in lowering cholesterol in type 2 diabetes. British Journal of Cardiology. 2004;11:188%N 183."	5
Active- control trials	
Bays H. Combination niacin and statin therapy compared with monotherapy. Cardiology Review. 2003;20(11):34-37.	3
Zeman M, Zak A, Vecka M, Romaniv S. Long-lasting combination treatment of mixed hyperlipoproteinaemias with statins and fibrates. Casopis Lekaru Ceskych. 2003;142(8):500-504.	1
Wiklung O, Angelin B, Fager G, et al. Treatment of familial hypercholesterolaemia: A controlled trial of the effects of pravastatin or cholestyramine therapy on lipoprotein and apoliprotein levels. J Intern Med. 1990;228(3):241-247.	4
Widimsky J, Hulinsky V, Balazovjech I, Lanska V. The long-term treatment of combined hyperlipidemia in CHD patients with a combination of fluvastatin and fenofibrate. Vnitrni Lekarstvi. 1999;45(4):210-216.	1
Stein E, Stender S, Mata P, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: Efficacy and safety of ezetimibe co-administered with atorvastatin. American Heart Journal. 2004;148(3):447-455.	3
Nagai R, Izumi T, Kurabayashi M, et al. Rationale and design of a study to examine lower targets for low-density lipoprotein-cholesterol and blood pressure in coronary artery disease patients. Circulation Journal. Apr 2008;72(4):515-520.	5
Kosoglou T, Statkevich P, Meyer I, et al. Effects of ezetimibe on the pharmacodynamics and pharmacokinetics of lovastatin. Curr Med Res Opin. 2004;20(6):955-965.	6
Kastelein JJ, Akdim F, Stroes ES, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. The New England journal of medicine. 2008;358(14):1431-1443.	4
Hunninghake DB, McGovern ME, Koren M, et al. A dose-ranging study of a new, once-daily, dual-component drug product containing niacin extended-release and lovastatin. Clinical Cardiology. Mar 2003;26(3):112-118.	6
Hogue J-C, Lamarche B, Tremblay AJ, Bergeron J, Gagne C, Couture P. Differential effect of atorvastatin and fenofibrate on plasma oxidized low-density lipoprotein, inflammation markers, and cell adhesion molecules in patients with type 2 diabetes mellitus. Metabolism: Clinical & Experimental. Mar 2008;57(3):380-386.	3

Excluded studies	Exclusion code
Harikrishnan S, Rajeev E, Tharakan J, et al. Efficacy and safety of combination of extended release niacin and atorvastatin in patients with low levels of high density lipoprotein cholesterol.[see comment]. Indian Heart Journal. May-Jun 2008;60(3):215-222.	3
Hajer GR, Dallinga-Thie GM, van Vark-van der Zee LC, Visseren FLJ. The effect of statin alone or in combination with ezetimibe on postprandial lipoprotein composition in obese metabolic syndrome patients. Atherosclerosis. Jan 2009;202(1):216-224.	3
Hajer GR, Dallinga-Thie GM, van Vark-van der Zee LC, Olijhoek JK, Visseren FLJ. Lipid-lowering therapy does not affect the postprandial drop in high density lipoprotein-cholesterol (HDL-c) plasma levels in obese men with metabolic syndrome: a randomized double blind crossover trial. Clin Endocrinol. Dec 2008;69(6):870-877.	3
Giral P, Bruckert E, Jacob N, Chapman MJ, Foglietti MJ, Turpin G. Homocysteine and lipid lowering agents. A comparison between atorvastatin and fenofibrate in patients with mixed hyperlipidemia. Atherosclerosis. 2001;154:421-427.	6
Franceschini G, Calabresi L, Colombo C, Favari E, Bernini F, Sirtori CR. Effects of fenofibrate and simvastatin on HDL-related biomarkers in low-HDL patients. Atherosclerosis. Dec 2007;195(2):385-391.	3
Derosa G, Mugellini A, Ciccarelli L, Rinaldi A, Fogari R. Effects of orlistat, simvastatin, and orlistat + simvastatin in obese patients with hypercholesterolemia: A randomized, open-label trial. Current Therapeutic Research, Clinical & Experimental. 2002;63(9):621-633.	6
Cannon CP, Giugliano RP, Blazing MA, et al. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. American Heart Journal. Nov 2008;156(5):826-832.	6
Campeau L, Hunninghake DB, Knatterud GL, et al. Aggressive cholesterol lowering delays saphenous vein graft atherosclerosis in women, the elderly, and patients with associated risk factors. NHLBI post coronary artery bypass graft clinical trial. Post CABG Trial Investigators. Circulation. 1999;99(25):3241-3247.	2
Berhanu P, Kipnes MS, Khan MA, et al. Effects of pioglitazone on lipid and lipoprotein profiles in patients with type 2 diabetes and dyslipidaemia after treatment conversion from rosiglitazone while continuing stable statin therapy.[erratum appears in Diab Vasc Dis Res. 2006 Sep;3(2):71]. Diabetes & Vascular Disease Research. May 2006;3(1):39-44.	6
Bays HE, Dujovne CA, McGovern ME, et al. Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (the advicor versus other cholesterol-modulating agents trial evaluation [ADVOCATE]). American Journal of Cardiology. 2003;91(6):667-672.	3

Excluded studies	Exclusion code
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Baldassarre S, Scruel O, Deckelbaum RJ, Dupont IE, Ducobu J, Carpentier YA. Beneficial effects of atorvastatin on sd LDL and LDL phenotype B in statin-naive patients and patients previously treated with simvastatin or pravastatin. International Journal of Cardiology. Oct 10 2005;104(3):338-345.	6
Avisar I, Brook JG, Wolfovitz E. Atorvastatin monotherapy vs. combination therapy in the management of patients with combined hyperlipidemia. European Journal of Internal Medicine. May 2008;19(3):203-208.	3
Arca M, Montali A, Pigna G, et al. Comparison of atorvastatin versus fenofibrate in reaching lipid targets and influencing biomarkers of endothelial damage in patients with familial combined hyperlipidemia. Metabolism: Clinical & Experimental. Nov 2007;56(11):1534-1541.	4
Alrasadi K, Awan Z, Alwaili K, et al. Comparison of treatment of severe high-density lipoprotein cholesterol deficiency in men with daily atorvastatin (20 mg) versus fenofibrate (200 mg) versus extended-release niacin (2 g). American Journal of Cardiology. Nov 15 2008;102(10):1341-1347.	4
Airan-Javia SL, Wolf RL, Wolfe ML, Tadesse M, Mohler E, Reilly MP. Atheroprotective lipoprotein effects of a niacin-simvastatin combination compared to low- and high-dose simvastatin monotherapy. American Heart Journal. Apr 2009;157(4):687.e681-688.	3

Appendix E. Black box warnings for US Food and Drug Administration-approved drugs

No boxed warnings were found for any of the included drugs.

Drug Class Review

HMG-CoA Reductase Inhibitors (Statins) and Fixed-dose Combination Products Containing a Statin

Final Report Update 5
Evidence Tables

November 2009

This report reviews information about the comparative effectiveness and safety of drugs within a pharmaceutical class. The report is neither a usage guideline nor an endorsement or recommendation of any drug, use, or approach. Oregon Health & Science University does not endorse any guideline or recommendation developed by users of this report.

Update 4: August 2006
Update 3: September 2005
Update 2: March 2004
Update 1: July 2003
Original Report: April 2002
The literature on this topic is scanned periodically.

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
	Atorvastatin vs. Lovastatin		
Davidson et al. 1997 R (3:1), DB, MC, PC, not ITT 1,049 patients randomized (n= 789 aorta, 260 lova) 52 weeks	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	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.	NCEP step 1 diet and aorta 10 mg qd or lova 20 mg qd for 52 weeks; or placebo for 16 weeks, then aorta 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.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Davidson et al. 1997 R (3:1), DB, MC, PC, not ITT 1,049 patients randomized (n= 789 aorta, 260 lova) 52 weeks	Efficacy analysis for 970 patients. **LDL-c reduction from baseline at week 16:** aorta 10 mg: 36% lova 20 mg: 27% placebo unchanged (p<0.05 vs. lova or placebo) **LDL-c reduction from baseline at week 52:** aorta: 37% (27% had dose doubled) lova: 29% (49% had dose doubled) (p<0.05 vs. lovastatin) **HDL at week 16:** aorta and lova both increased 7% (p NS) **HDL at week 52:** aorta and lova both increased 7% (p NS) **Trigs:** aorta reduction 16%; lova reduction 8% (p<0.05) **Achieved LDL-c goal:** aorta 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 aorta vs. 4% of lova patients; 8% of aorta vs. 7% of lova patients had a serious ADE (no details provided), including 1 patient developing pancreatitis in aorta group. Elevation in ALT >3x ULN occurred in 1 (0.1%) aorta, 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.

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

Clinical Trial	Funding Source
Davidson et al. 1997 R (3:1), DB, MC, PC, not ITT 1,049 patients randomized (n= 789 aorta, 260 lova) 52 weeks	Parke-Davis Pharmaceuticals

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
	Atorvastatin vs. Pravastatin		
Assman et al. 1999 R (3:1), DB, MC, not ITT 297 patients randomized (n= 224 aorta, 73 parva) 52 weeks	Men or women 18-80 years with an LDL-c 160-250 mg/dl during dietary phase. Mean baseline LDL-c 201 mg/dl.	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.	6-week dietary and placebo phase. NCEP step 1 diet. Mild to moderate CHD risk (dose level 1: LDL-c goal <130 mg/dl): 10 mg qd aorta (n=145) vs. parva 20 mg qd (n=27). Severe CHD risk (dose level 2: LDL-c goal <115 mg/dl): aorta 20 mg qd (n=79) vs. parva 40 mg qd (n=46). If goal not reached, dose doubled at week 4, and again at week 8 and week 16. Maximum doses: aorta 80 mg qd, parva 40 mg qd.
Bertolini et al. 1997 R (3:1), DB, MC, not ITT 305 patients randomized (n= 227 aorta, 78 parva) 1 year	Men and women 18-80 years with LDL-c 160-250 mg/dl. Mean baseline LDL-c 195 mg/dl	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.	6 week dietary phase NCEP step 1 diet and aorta 10 mg qd or parva 20 mg qd. If LDL-c remained ≥130 mg/dl at weeks 4 and 10, doses were doubled at week 16.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Assman et al. 1999 R (3:1), DB, MC, not ITT 297 patients randomized (n= 224 aorta, 73 parva) 52 weeks	Efficacy analysis for 279 patients. **LDL-c reduction from baseline at 1 year:** aorta: 39% (p< 0.05) parva: 29% **HDL:** aorta increased 7% parva increased 9% (NS) **Trigs:** aorta reduction 13% (p<0.05) parva reduction 8% **Achieved LDL-c goal at last visit:** aorta\= 51% vs. parva 20% (p=0.0001) 35% aorta (20 mg-17%, 40 mg-12%, 80 mg-5%) vs. 88% parva (40 mg-88%) patients had doses doubled at least once.	9 patients (4%) in aorta group withdrew as a result of ADEs vs. 2 patients (3%) in parva group. 2 patients receiving aorta (unknown dose) experienced an elevation in ALT >3 X upper limit of normal. No patient on parva experienced an elevation. Most commonly reported ADE with aorta was myalgia and rash each reported by 4 patients. Most common ADE with parva was arthralgia in 2 patients. (unknown doses) 35% of aorta vs. 63% of parva patients categorized in the severe CHD risk or dose level II. Equivalent doses not compared.
Bertolini et al. 1997 R (3:1), DB, MC, not ITT 305 patients randomized (n= 227 aorta, 78 parva) 1 year	Efficacy analysis for 299 patients **LDL-c reduction from baseline at week 16:** aorta 10 mg: 35% parva 20 mg: 23% (p≤0.05) **LDL-c reduction from baseline at week 52:** aorta: 35% (24% had dose doubled) parva: 23% (64% had dose doubled) (p≤0.05). **HDL:** aorta increased 7%, parva increased 10% (NS) **Trigs:** aorta reduction 14%, parva reduction 3% (p≤0.05). **Achieved LDL-c goal:** aorta 71% vs. parva 26%	Severe adverse drug events (ADEs) similar for aorta (7%) and parva (9%); 7 patients in the aorta and 2 in the parva group withdrawn from study as a result of a severe ADE (no details). No patient in either group had clinically important elevations in AST, ALT or CK. Equivalent doses not compared.

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

Clinical Trial	Funding Source
Assman et al. 1999 R (3:1), DB, MC, not ITT 297 patients randomized (n= 224 aorta, 73 parva) 52 weeks	2 authors employed by Parke-Davis Pharmaceuticals.
Bertolini et al. 1997 R (3:1), DB, MC, not ITT 305 patients randomized (n= 227 aorta, 78 parva) 1 year	2 authors employed by Parke-Davis Pharmaceuticals.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Deedwania P, et al 2007 R (1:1), DB, MC, ITT 893 patients randomized (n (mITT)= 446 (408) aorta, 445 (396) parva) 52 weeks	Men and women 65 to 85, history of CAD, baseline LDL-C levels between 100 mg/dL and 250 mg/dL, and 1 episode of myocardial ischemia with a total duration of 3 minutes	Atrial fibrillation and heart failure NYHA III and IV	4-6 week washout period, then randomized in a double-blind fashion to atorvastatin 80 mg/d or pravastatin 40 mg/d and were followed up for 12 months.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Deedwania P, et al 2007 R (1:1), DB, MC, ITT 893 patients randomized (n (mITT)= 446 (408) aorta, 445 (396) parva) 52 weeks	**LDL-c change from baseline:** 3 months aorta -56.3 vs.. Prava -32.1 (p < 0.001) 12 months aorta -55.4 vs.. Prava -32.4 (p < 0.001) **HDL-c change from baseline:** 3 months aorta 2.2 vs. Prava 5.8 (p < 0.001) 12 months aorta 5.0 vs. Prava 7.6 (p = 0.009) **MACE aorta vs parva at one year n(%)** Major Adverse Cardiovascular Events 36 (8.1) vs. 50 (11.2) (p = 0.114) Cardiovascular death 4 (0.9) vs. 10 (2.2) Nonfatal myocardial infarction 16 (3.6) vs. 16 (3.6) Resuscitated cardiac arrest 1 (0.2) vs. 1 0 (0.0) Urgent coronary revascularization 20 (4.5) vs. 29 (6.5) Hospitalized for unstable angina 14 (3.1) vs. 22 (4.9) Stroke 1 (0.2) vs. 3 (0.7) **all-cause mortality at 12 months** aorta(1.3% incidence [6 deaths]) vs. parva (4.0% incidence [18 deaths]) (HR, 0.33; 95% CI, 0.13 to 0.83; p= 0.014)	aorta vs. parva n(%) Patients ≥ 1 adverse event, 273 (61.2) vs. 287 (64.5) (p = 0.31) Patients who discontinued study drug due to AEs, 48 (10.8) vs. 46 (10.3) (p = 0.84) Patients w/ serious AEs 90 (20.2) vs. 103 (23.1) (p = 0.28) Patients with ALT or AST 3 x upper limit of normal, 19 (4.3) vs. 1 (0.2) (p < 0.001)

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

Clinical Trial	Funding Source
Deedwania P, et al 2007 R (1:1), DB, MC, ITT 893 patients randomized (n (mITT)= 446 (408) aorta, 445 (396) parva) 52 weeks	Pfizer, Inc.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Murakami T, et al 2006 RCT, DB, MC, not ITT 41 patients randomized (n= 11 aorta, 18 parva analyzed) 26 weeks	Clinical indications for cholesterol lowering therapy without DM (HBA1C $\leq$ 5.8) **Baseline LDL-c** aorta 192(67.1) parva 143(30.5) **Baseline HDL-c** aorta 52.3 (11.4) parva 47.6 (14.4)	Drugs that effect glucose tolerance, disturbed liver and/or renal functions	Atorvastatin 5-10 mg/day vs. pravastatin 10-20 mg/day for 3-6 months
Nissen et al, 2004 R, DB, MC, PC 657 patients randomized 18 months	Men and women aged 30 to 75 years who required coronary angiography for a clinical indication and demonstrated at least 1 obstruction with angiographic luminal diameter narrowing of 20% or more. Lipid criteria required an LDL-c level between 125 mg/dL and 210 mg/dL after 4 to 10 week washout period. Mean baseline LDL-c aorta 80mg: 150.2 mg/dL parva 40mg: 150.2 mg/dL	Not reported	Atorva 80 mg daily or parva 40 mg daily.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Murakami T, et al 2006 RCT, DB, MC, not ITT 41 patients randomized (n= 11 aorta, 18 parva analyzed) 26 weeks	3-6 months after **LDL-c** aorta 124 (48.6) vs.. parva 113 (17.7) (p =0.0186) **HDL-c** aorta 54.7 (14.6) vs. parva 51.5 (14.8) (p = ns)	None reported
Nissen et al, 2004 R, DB, MC, PC 657 patients randomized 18 months	Efficacy analysis on 502 patients. LDL-c reduction from baseline at 18 months: Atorva 80 mg: 46.3% (p<0.001) Prava 40 mg: 25.2% HDL-c increase from baseline at 18 months: Atorva 80 mg: 2.9% Prava 40 mg: 5.6% (p=0.06) Trigs reduction from baseline at 18 months: Atorva 80 mg: 20.0% (p<0.001) Prava 40 mg: 6.8%	6.7% of parva and 6.4% of aorta group discontinued drug for adverse events. Most common reason was musculoskeletal complaints (3.4% parva, 2.8% aorta). Equivalent doses not compared

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

Clinical Trial	Funding Source
Murakami T, et al 2006 RCT, DB, MC, not ITT 41 patients randomized (n= 11 aorta, 18 parva analyzed) 26 weeks	NR
Nissen et al, 2004 R, DB, MC, PC 657 patients randomized 18 months	Funded by Pfizer

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Saklamaz et al, 2005 R, single center, blinding not reported 21 patients randomized 8 weeks treatment	Men and women (mean age 51.7±9.1 years) with type IIa and IIb hyperlipidemia. Mean baseline LDL-c pravastatin: 186±36 mg/dL atorvastatin: 174±10 mg/dL	Patients with endocrine, liver, hepatic, thyroid, and renal disorders, BMI of less than 30, and alcohol abuse.	pravastatin 20 mg or atorvastatin 10 mg or fenofibrate 250 mg

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Saklamaz et al, 2005 R, single center, blinding not reported 21 patients randomized 8 weeks treatment	**% LDL-c reduction from baseline at 12 weeks:** pravastatin 20: 24.2% atorvastatin 10: 40.2% **% HDL-c increase from baseline at 12 weeks:** pravastatin 20: 3.4% atorvastatin 10: 9.8% **% trig reduction from baseline at 12 weeks:** pravastatin 20: 24.3% atorvastatin 10: 20.1%	Adverse events not reported.

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

Clinical Trial	Funding Source
Saklamaz et al, 2005 R, single center, blinding not reported 21 patients randomized 8 weeks treatment	Funding not reported

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
	Atorvastatin vs. Simvastatin		
Ballantyne et al, 2003 R, DB, MC 917 patients randomized(n=464 aorta, 453 simva) 24 weeks	Men and women 21-75 with LDL-c >130 mg/dL in CHD patients, >160 mg/dL in patients without CHD and with 2 or more risk factors, and >190 mg/dL in patients without CHD and with <2 risk factors; patients with diabetes were considered CHD equivalents; eligible LDL-c was >130 mg/dL in patients with HDL-c <40 mg/dL (men) and <50 mg/dL (women) plus 2 risk factors. All had triglyceride levels <400 mg/dL. Mean baseline LDL-c aorta: 187.5 mg/dL simva:190.3 mg/dL	use of systematic immunosuppressive drugs or drugs known to interfere with simvastatin or atorvastatin metabolism. renal insufficiency or significant proteinuria; secondary causes of hypercholesterolemia; type I diabetes; type 2 diabetes with hemoglobin A1C 10%; hepatic transaminase levels 30% above upper limit of normal (ULN); known active liver disease; and creatine kinase (CK)levels 50% above ULN	Atorva 80 mg qd or simva 80 mg qd for 24 weeks.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Ballantyne et al, 2003 R, DB, MC 917 patients randomized(n=464 aorta, 453 simva) 24 weeks	**Increase in HDL-c from baseline, average of weeks 18 and 24** **Patients with baseline HDL-c <40mg/dL (n=267):** **aorta: 2.1%** **simva: 5.4% (NS)** **Patients with baseline HDL-c >40mg/dL (n=650):** **aorta: 2.1%** **simva: 5.43% (NS)** **Patients without metabolic syndrome (n=437):** **aorta: 2.8%** **simva: 5.6% (NS)**	No difference between groups in number of drug-related clinical gastrointestinal adverse events. Most common GI adverse events were diarrhea (simva 1.3%; aorta 3.0%), constipation (simva 1.3%; aorta 1.5%), and nausea (simva 1.8%; aorta 0.9%). Most common drug-related muscular AEs resulting in discontinuation were myalgia, arthralgia, muscular weakness, muscular cramp, musculoskeletal stiffness, and body ache. Patients treated with aorta more likely to have elevations in ALT >3 times the upper limit of normal (difference -2.4%; 95% CI -4.3 to -0.7; p=0.007) Equivalent doses not compared

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

Clinical Trial	Funding Source
Ballantyne et al, 2003 R, DB, MC 917 patients randomized(n=464 aorta, 453 simva) 24 weeks	Supported by a grant from Merck

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Bays et al., 2005 R, Open-label, multicenter 315 patients randomized (n=82 atorvastatin, 76 simvastatin, 157 niacin ER plus lovastatin) 16 weeks treatment	Men and women with elevated LDL-c (>=160mg/dL, or, if coronary heart disease was present, >=130 mg/dL) and low HDL-c (<45 mg/dL for men and <50 mg/dL for women). Mean baseline LDL-c 194 mg/dL	Known prior allergy or intolerability to any of the study drugs, H/O substance abuse or dependence within 12 months of screening, consumption of >14 alcoholic drinks per week, uncontrolled psychiatric disease, participation in another investigational study within 30 days of screening, or probucol administration within the previous year. H/O: active gallbladder disease; uncontrolled hypertension; renal insufficiency (serum creatinine ≥1.5 mg/dl); hepatic dysfunction (aspartate aminotransferase or alanine aminotransferase >1.3 times the upper limit of normal); fasting glucose ≥115 mg/dl; New York Heart Association class III/IV congestive heart failure; active gout symptoms or uric acid >1.3 times the upper limit of normal; active peptic ulcer disease; type 1 or 2 diabetes; fibromyalgia; cancer within the previous 5 years (except for basal cell carcinoma); unstable angina, myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or stroke within prior 6 months; or any condition or laboratory abnormality which, in the opinion of the investigator, might be adversely affected by the study procedures or medications.	6-week screening phase during which lipid modifying drugs were discontinued, then treatment for the first 8 weeks: atorvastatin 10 mg or simvastatin 10 mg At week 8, dose increased for 4 weeks: atorvastatin 20 mg or simvastatin 20 mg At week 12, dose increased for 4 weeks: atorvastatin 40 mg or simvastatin 40 mg
Branchi et al. 2001 R, OL, not ITT 200 patients randomized (n= 100 aorta, 100 simva) Up to 6 months	Men or women with hypercholesterolemia not controlled with diet. Mean baseline LDL-c Atorva 228.2 mg/dl Simva 235.1 mg/dl	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.	8-week dietary run-in, then randomization to: aorta 10 mg or simva 20 mg qd.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Bays et al., 2005 R, Open-label, multicenter 315 patients randomized (n=82 atorvastatin, 76 simvastatin, 157 niacin ER plus lovastatin) 16 weeks treatment	% LDL-c reduction from baseline at 8, 12, and 16 weeks (p vs aorta): aorta 10/20/40: 38% (p<0.05)/45% (p<0.05)/49% (p<0.05) simva 10/20/40: 28%/35%/39% % HDL-c increase from baseline at 8, 12, and 16 weeks (p vs aorta): aorta 10/20/40: 3% (p<0.05)/4% (p<0.05)/6% (p<0.05) simva 10/20/40: 7%/8%/7% % trig reduction from baseline at 8, 12, and 16 weeks (p vs aorta): aorta 10/20/40: 20%/30% (p<0.05)/31% (p<0.05) simva 10/20/40: 18%/15%/19%	Adverse events not reported.
Branchi et al. 2001 R, OL, not ITT 200 patients randomized (n= 100 aorta, 100 simva) Up to 6 months	Efficacy analysis for 199 patients. LDL-c reduction from baseline at 2 months: aorta: 148.7 mg/dl (34.8%) simva: 158.4 mg/dl (32.6%)(NS) HDL increase from baseline at 2 months (n=235, adjusted for baseline values): aorta: 4.3% simva: 9.0% (p<0.05) Trigs reduction from baseline at 2 months: aorta: 27.4% simva: 24.8% (NS)	Significant number withdrew from treatment after 2 months. 46 required an increase in dose (20 aorta vs. 26 simva); 10 refused to continue; 8 stopped treatment during a recent illness. No differences in ADEs noted. 55 aorta 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. aorta group. Dose equivalence Atorvastatin 10 mg qd ≈ simvastatin 20 mg qd

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

Clinical Trial	Funding Source
Bays et al., 2005 R, Open-label, multicenter 315 patients randomized (n=82 atorvastatin, 76 simvastatin, 157 niacin ER plus lovastatin) 16 weeks treatment	Funded by Kos Pharmaceuticals
Branchi et al. 2001 R, OL, not ITT 200 patients randomized (n= 100 aorta, 100 simva) Up to 6 months	Role and source of funding not reported.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Chan, et al, 2004 R, Blinded, SC 10 week dietary run-in; 18 weeks of treatment. 120 patients (n=60 simva; n=60 aorta)	Men and women 20-75 with Type 2 diabetes with mixed hyperlipidemia (serum trig 203.7-398.6 mg/dL and LDL-c >=131.5 mg/dL) Mean baseline LDL -c: aorta: 171.3 mg/dL simva: 160.5 mg/dL	Not reported	10 week NIH NCEP Step 1 dietary run-in and patients on lipid-lowering drugs did a 4 week wash-out before starting. aorta: 10 mg/d for 9 weeks then increased to 20 mg/d for 9 weeks simva: 20 mg/d for 9 weeks and then increased to 40 mg/d for 9 weeks.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Chan, et al, 2004	**% patients reaching the LDL-c target (<100 mg/dL)**	No adverse events discussed in detail.
	aorta: 74.1%	
R, Blinded, SC	**simva: 75.4%**	Atorva: 5 patients withdrew (8.3%)
	% patients reaching the TG target (151 mg/dL):	Simva: 7 patients withdrew (11.7%)
10 week dietary run-in;	**aorta: 27.8%**	reason stated for both groups withdrawals: "mainly because of non-
18 weeks of treatment.	**simva: 35.1%**	compliance"
	% patients reaching both targets:	
120 patients (n=60	**aorta: 22.2%**	Overall drug compliance was 91.5%.
simva;	**simva: 29.8%**	
n=60 aorta)		No subject developed a significant rise in liver enzymes or in CPK during
	LDL-c Change from baseline (approx. from table):	study.
	aorta 10 mg:-37%	
	aorta 20mg:-28%	
	simva 20mg:-42%	
	simva 40 mg:-40%	
	HDL-c Change from baseline (approx. from table):	
	aorta 10 mg:+4%	
	aorta 20mg:<=+1.0%	
	simva 20mg:+4%	
	simva 40 mg:+4.5%	
	Trig change from baseline (approx. from table):	
	aorta 10 mg:-20%	
	aorta 20mg:-25%	
	simva 20mg:-20%	
	simva 40 mg:-25%	
	no p-values given	

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

Clinical Trial	Funding Source
Chan, et al, 2004 R, Blinded, SC 10 week dietary run-in; 18 weeks of treatment. 120 patients (n=60 simva; n=60 aorta)	No industry support mentioned

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Crouse et al. 1999 R, OL, MC, not ITT 846 patients randomized 12 weeks	Men or women Mean baseline LDL-c 212.7 mg/dl	Not reported	4-week dietary run-in phase, then: aorta 20 mg qd (n=210) or aorta 40 mg qd (n=215) or simva 40 mg qd (n=202) or simva 80 mg qd (n=215)

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Crouse et al. 1999 R, OL, MC, not ITT 846 patients randomized 12 weeks	*Efficacy analysis for 842 patients.* *LDL-c reduction from baseline at 12 weeks:* *aorta 20 mg: 45% ** *aorta 40 mg: 51.1%* *simva 40 mg: 42.7%* *simva 80 mg: 49.2%* *(*p<0.05 aorta 20 vs. simva 40)* *HDL-c increase from baseline at 12 weeks:* *aorta 20 mg: 4%* *aorta 40 mg: 3%* *simva 40 mg: 6.7% ** *simva 80 mg: 6.6% ** *(*p<0.01 aorta vs. simva)* *Trig reduction from baseline at 12 weeks:* *aorta 20 mg: 23.3%* *aorta 40 mg: 29.6% ** *simva 40 mg: 23%* *simva 80 mg: 25.2%* *(*p<0.01 aorta 40 vs. simva 80)*	No safety data or details on patient population provided in this trial. Primary endpoint in this study was effects of aorta or simva on HDL and Apolipoprotein A-1. Dose equivalence Atorva 20 mg > or ≈ Simva 40 mg. Atorva 40 mg = Simva 80 mg

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

Clinical Trial	Funding Source
Crouse et al. 1999 R, OL, MC, not ITT 846 patients randomized 12 weeks	Merck supported and participated in study.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Dart A et al. 1997 R (3:1), DB, MC, not ITT 177 patients randomized (n= 132 atorvastatin, 45 simvastatin) 1 year	Men or women 18-80 years with an LDL-c 160-300 mg/dl during the dietary phase. Mean baseline LDL-c 208-214 mg/dl	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	6-week dietary and placebo phase. NCEP step 1 diet and atorvastatin 10 mg qd or simvastatin 10 mg qd. Doses were doubled at week 16 if LDL-c was not ≤ 130 mg/dl.
Farnier et al. 2000 **R (2:1:2), OL, MC, ITT** 272 patients randomized (n= 109 atorvastatin, 163 simvastatin) 12 weeks	Men or women 18-70 years with elevated LDL-c. Mean baseline LDL-c Atorvastatin 10 mg: 247 ± 45 mg/dl Simvastatin 10 mg: 242 ± 47 mg/dl Simvastatin 20 mg: 237 ± 39 mg/dl.	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.	6-week placebo-dietary run-in phase then randomized to: Atorvastatin 10 mg, simvastatin 10 mg or simvastatin 20 mg qd for 6 weeks.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Dart A et al. 1997 R (3:1), DB, MC, not ITT 177 patients randomized (n= 132 atorvastatin, 45 simvastatin) 1 year	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<0.05) HDL at week 16: Atorvastatin increased 7% Simvastatin increased 7% (p NS) HDL at week 52: Atorvastatin increased 7% Simvastatin increased 7% (p NS) Trigs: Atorvastatin reduction 21% Simvastatin reduction 12% (p<0.05) Achieved LDL-c goal: aorta 46% vs. simva 27%	No clinically significant changes in ALT, AST or CK in either group. No differences in percentages of reported ADE between groups. None of the serious ADEs in either group thought to be due to the statin. Most common ADE with atorvastatin was myalgia (3%). Most common ADE with simvastatin was arthralgia (7%) and chest pain (4%). 2 patients in each group withdrawn as a result of ADEs. Details only provided for 1 patient on atorvastatin who reported excessive sweating possibly related to treatment. No other details on ADEs provided. Equivalent doses not compared.
Farnier et al. 2000 **R (2:1:2), OL, MC, ITT** 272 patients randomized (n= 109 atorvastatin, 163 simvastatin) 12 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 aorta 10 mg vs. simva 20 mg) HDL: (NS Atorva 10 mg vs. simva 20 mg) aorta 10 mg increased 5.7% simva 10 mg increased 2.2% simvastatin 20 mg increased 3% Trigs: (NS aorta 10 vs. simva 20) aorta 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 (aorta 10 mg = 11.9% vs. simva 10 mg =5.5% vs. simva 20 mg = 3.7%). Few details provided. One patient in aorta group had an increase in ALT >3x ULN. No elevation in CK reported. Dose equivalence atorvastatin 10 mg qd ≈ simva 20 mg qd

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

Clinical Trial	Funding Source
Dart A et al. 1997 R (3:1), DB, MC, not ITT 177 patients randomized (n= 132 atorvastatin, 45 simvastatin) 1 year	Support and contribution by Parke-Davis Pharmaceutical Research Division
Farnier et al. 2000 **R (2:1:2), OL, MC, ITT** 272 patients randomized (n= 109 atorvastatin, 163 simvastatin) 12 weeks	Supported by grant from Parke-Davis.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Illingworth et al. 2001 **R, DB, MC, not ITT** **826 patients randomized** **(n= 408 aorta, 405 simva)** **36 weeks**	Men or women 21-70 years with elevated cholesterol. <u>Mean baseline LDL-c</u> Atorva 206 mg/dl Simva 209 mg/dl	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.	4-week dietary run-in phase followed by randomization to 6 weeks of: aorta 20 mg or simva 40 mg qd, then 6 weeks of aorta 40 mg or simva 80 mg qd. If CK < 5x ULN, patients were eligible for 24 weeks of aorta or simva 80 mg qd.
Insull et al. 2001 R, OL, MC, not ITT 1,424 patients randomized (n= 730 aorta, 694 simva) First 6 weeks of planned 54 weeks	Men or women 18-80 years with or without CHD and with or without Type 2 DM with elevated LDL. <u>Mean baseline LDL-c</u> Atorva 181.2 mg/dl Simva 181.9 mg/dl	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.	8-week dietary run-in with NCEP step 1 or 2 diet. Eligible patients randomized to: aorta 10 mg qd or simva 10 mg qd.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Illingworth et al. 2001 **R, DB, MC, not ITT** **826 patients randomized (n= 408 aorta, 405 simva)** **36 weeks**	Efficacy analysis for 813 patients. LDL-c reduction from baseline at 6 weeks: aorta 20 mg= 46.1% vs. simva 40 mg= 42.4% LDL-c reduction from baseline at 2nd 6 weeks: aorta 40 mg= 51.3% vs. simva 80 mg= 48.8% LDL-c reduction from baseline at 36 weeks: aorta 80 mg= 53.6% vs. simva 80mg= 48.1% (p< 0.001 for all 3 comparisons) HDL increased: Week 6: aorta 20 mg= 7.3% vs. simva 40 mg= 8.5% (NS) Week 12: aorta 40 mg= 6.4% vs. simva 80 mg= 9.7% (p<0.001) Week 18-36: aorta 80 mg= 3% vs. simva 80 mg= 7.5% (p<0.001) Trigs reduction: aorta 20 mg= 23.6% vs. simva 40 mg= 22.4% aorta 40 mg= 31.6% vs. simva 80 mg= 25.9% aorta 80 mg= 31.3% vs. simva 80 mg= 23.6% (p< 0.05 for all 3 comparisons)	HDL elevation was primary endpoint. ADEs similar during first 12 weeks of study. At end of 24-week period, 23.4% of aorta 80 mg vs. 11.9% of simva 80 mg experienced an ADE. (p<0.001). Difference due primarily to GI ADE (diarrhea). More in aorta 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 aorta 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 aorta 80 mg vs. simva 80 mg group. ALT elevations especially prominent in women in aorta group. No myopathy reported in any group. A significantly higher number of women randomized to the aorta group.
Insull et al. 2001 R, OL, MC, not ITT 1,424 patients randomized (n= 730 aorta, 694 simva) First 6 weeks of planned 54 weeks	Efficacy analysis for 1,378 patients. LDL-c reduction from baseline at 6 weeks: aorta 10 mg: 37.2% simva 10 mg: 29.6% (p<0.0001) Reaching NCEP goal at 6 weeks: aorta 10 mg: 55.6% simva 10 mg: 38.4% (p<0.0001) HDL increased: Atorva: 7.4% Simva: 6.9% (NS) Trigs reduction: Atorva: 27.6% Simva: 21.5% (p<0.0001)	No differences in treatment-related ADEs: aorta 5.8% vs. simva 2.9%. No reports of myopathy. 2 aorta patients had elevated ALT or AST >3x ULN. Equivalent doses not compared.

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

Clinical Trial	Funding Source
Illingworth et al. 2001 **R, DB, MC, not ITT** **826 patients randomized** **(n= 408 aorta, 405 simva)** **36 weeks**	5 authors employed by Merck. Merck assisted in preparation of manuscript.
Insull et al. 2001 R, OL, MC, not ITT 1,424 patients randomized (n= 730 aorta, 694 simva) First 6 weeks of planned 54 weeks	Supported by grant from Parke-Davis.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Kadikoylu et al, 2003 R, DB 61 patients randomized (n=35 aorta, 26 simva) 24 weeks	Men and women with at least 2 coronary risk factors and LDL-c levels >130 mg/dL. Mean baseline LDL-c aorta: 168.5 mg/dL simva: 172.1 mg/dL	Patients with pregnancy, lactation, malignancy, CHD, type 1 or uncontrolled type 2 diabetes mellitus (glycosylated hemoglobin >6%), TG concentrations >500 mg/dL, body mass index >35 kg/m2, prolonged prothrombin time (PT) and partial thromboplastin time (PTT), hypo/hyperfibrinogenemia, elevated serum creatine phosphokinase (CK) and liver enzyme levels at the upper limit of normal, thrombocytopenia (<100 × 103/mm3) or thrombocytosis (>400 × 103/mm3), history of hemorrhagic diathesis, acute or chronic hepatitis, chronic renal failure, alcohol abuse, secondary hypercholesterolemia due to hypothyroidism, obstructive liver disease, and nephrotic syndrome were excluded. Patients with hypersensitivities to statins, taking lipid-lowering drugs within 8 weeks, and employing concomitant use of drugs such as erythromycin, oral contraceptives, hormone replacement, systemic steroids, heparin, low-molecular weight heparin, oral anticoagulants, or immunosuppressive agents were not enrolled in the study.	Atorva 10 mg qd or simva 10 mg qd . When target level of LDL-c was not reached at 12 weeks according to ATP-III, dosage was increased to 20 mg qd.
Karalis et al. 2002 R, OL, MC, not ITT 1,732 patients randomized 6 weeks	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	Body mass index 32 kg/m2; known hypersensitivity to statins; uncontrolled hypothyroidism, nephrotic syndrome, or renal dysfunction; diabetes mellitus type 1 or uncontrolled diabetes mellitus type 2 (hemoglobin A1c 10%); hepatic dysfunction; creatine phosphokinase levels 3 times the upper limit of normal; myocardial infarction, revascularization procedures, or severe or unstable angina within 3 months before screening; significant medical or psychological abnormalities that could compromise the patient's safety in the study; use of any drugs known to affect lipid levels; immunosuppressive agents; or drugs associated with rhabdomyolysis in combination with statins.	4-week dietary run-in followed by randomization to: aorta 10 mg qd (n=650) or aorta 80 mg qd (n=216) or simva 20 mg qd (n=650) or simva 80 mg qd (n=216)

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Kadikoylu et al, 2003 R, DB 61 patients randomized (n=35 aorta, 26 simva) 24 weeks	**LDL-c goal reached at 24 weeks (all patients):** **aorta: 85.7%** **simva: 84.6% (NS)** **Diabetics only (n=23):** **aorta: 64.3%** **simva: 55.6% (NS)** **LDL-c reduction from baseline at 24 weeks:** **aorta: 38.6%** **simva: 33.6% (NS)** **HDL-c increase from baseline at 24 weeks:** **aorta: 12.6%** **simva: -0.6% (NS)** **Trigs change from baseline at 24 weeks:** **aorta: -15.8%** **simva:+2.0% (NS)**	Adverse effects seen in 5 patients (14.2%) aorta and 3 patients (11.5%) in simva group (headache, diarrhea, constipation, myalgia). Elevations in ALT>3 times the upper limit of normal and in CK >5 times the upper limit of normal did not occur. No discontinuations due to adverse effects; no significant differences between groups in adverse effects, adverse effects not dose-related. Equivalent doses not compared
Karalis et al. 2002 R, OL, MC, not ITT 1,732 patients randomized 6 weeks	Efficacy analysis for 1694 patients. LDL-c decrease from baseline at 6 weeks: aorta 10 mg= 37% vs. simva 20 mg = 35% (p<0.025) aorta 80 mg= 53% vs. simva 80 mg= 47% (p<0.0001) HDL increase from baseline: aorta 10 mg= 5% vs. simva 20 mg= 6% aorta 80 mg= 2% vs. simva 80 mg= 6% (p<0.0001) Trigs reduction from baseline: aorta 10 mg= 18% vs. simva 20 mg= 14% (p<0.025) aorta 80 mg= 28% vs. simva 80 mg= 23% (p<0.025)	Patients in aorta 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.

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

Clinical Trial	Funding Source
Kadikoylu et al, 2003 R, DB 61 patients randomized (n=35 aorta, 26 simva) 24 weeks	Funding not reported
Karalis et al. 2002 R, OL, MC, not ITT 1,732 patients randomized 6 weeks	Pfizer supported and participated in the trial.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Kastelein et al, 2000 R, DB, PC 826 patients (n=406 aorta, 405 simva) 36 weeks	Men and women with LDL-c >160 mg/dL and triglycerides <350 mg/d Mean baseline LDL-c simva: 208.7 mg/dL aorta: 205.8 mg/dL	NR	Atorva 20 mg qd for 6 weeks, then 40 mg qd or simva 40 mg qd for 6 weeks then 80 mg qd.
Marz et al. 1999 **R (2:1) OL, MC, not ITT** 2,856 patients randomized (n= 1897 aorta, 959 simva) 14 weeks	Men or women 35-75 years with CHD and LDL-c ≥130 mg/dl after the diet phase. Mean baseline LDL-c 186-188 mg/dl	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	6-week diet phase then aorta 10 mg qd or simva 10 mg qd. Doses were doubled at weeks 5 and/or 10 if LDL-c was > 100 mg/dl.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Kastelein et al, 2000 R, DB, PC 826 patients (n=406 aorta, 405 simva) 36 weeks	**Increase in HDL-c (average of results from weeks 6 and 12):** **simva 9.1% vs** **aorta 6.8% (p<0.001)** **simvastatin 80mg: 9.7%** **atorvastatin 40mg: 6.4% (p<0.001)** **simva 40mg vs aorta 20mg (NS, percent change not reported)**	No difference between the 2 drugs in tolerability profile after 12 weeks of treatment. Dose equivalence simva 80mg >aorta 40mg simva 40mg ≈ aorta 20mg
Marz et al. 1999 **R (2:1) OL, MC, not ITT** 2,856 patients randomized (n= 1897 aorta, 959 simva) 14 weeks	Number of patients in efficacy analysis not specified. LDL-c reduction from baseline at week 14: aorta 10 mg: 37.6% simva 10 mg: 31.9% (p<0.001) Overall LDL-c reduction: 188-105 mg/dl in aorta vs. 186-112 mg/dl in simva group. (p<0.001) 38% aorta vs. 54% simva users increased to 40 mg qd.	ADEs were similar between groups occurring in 36.3% in the aorta vs. 35.7% in the simva group. Withdrawal due to ADE were similar between groups. Serious ADEs occurred in 2% aorta vs. 3% simva (NS). No differences in elevation in ALT or AST or CK during the trial between groups. Dose equivalence Atorvastatin 20 mg qd ≈ simvastatin 40 mg qd.

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

Clinical Trial	Funding Source
Kastelein et al, 2000 R, DB, PC 826 patients (n=406 aorta, 405 simva) 36 weeks	Supported by a grant from Merck Research Laboratories
Marz et al. 1999 **R (2:1) OL, MC, not ITT** 2,856 patients randomized (n= 1897 aorta, 959 simva) 14 weeks	Sponsored by Parke-Davis and Pfizer

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Mulder D, et al 2007 **R(1:1), DB, MC, completers analysis** **235 patients randomized (n= 116 aorta, 119 simva)** **16 weeks**	Men or women 30-75 years with elevated LDL-c >2.6. Mean baseline LDL-c Atorva10: 3.70 (0.83) Simva10 : 3.59 (0.79)	all forms of secondary dyslipidemia; diabetes mellitus; dysfunction of the thyroid gland, unless adequately treated; acute CVD, surgical procedures or inflammatory disease; all conditions affecting plasma levels of cellular adhesion molecules; active liver disease or hepatic dysfunction; known allergic reaction to statins; clinically manifest heart failure or severe cardiac arrhythmias; uncontrolled hypertension, as defined by a systolic blood pressure >160 mmHg and/or a diastolic blood pressure >95 mmHg; severe or unstable angina pectoris; excessive alcohol consumption (over 4 units per day) or a history of drug abuse; use of systemic steroids or androgens; impaired renal function with plasma creatinine >150 µmol/l; a history of partial ileal bypass surgery; inadequate contraceptive measures, pregnancy or lactation in premenopausal women; baseline creatinine phosphokinase values >150% upper limit of normal.	4 week run in, simva 40, then 16-week treatment phase starting on atorvastatin 40 mg or continuing with simvastatin 40 mg. After 8 weeks of treatment the dosage of atorvastatin was increased to 80 mg, whereas the dosage of simvastatin remained stable at 40 mg.
Olsson et al. 2003 **R(1:1), DB, MC, ITT** 1087 patients randomized (n= 552 aorta, 535 simva) 52 weeks	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)	Patients with fasting serum TG _>4.0 mmol/L or total cholesterol _>10.0 retool/L, secondary hypercholesterolemia, unstable angina, heterozygous and homozygous familial hypercholesterolemia, planned coronary artery surgery or angioplasty, and acute MI in patients already on lipid-lowering agents; currently treated with lipid-lowering or antiarrhythmic drugs or treated for congestive heart failure, presence of hemodynamically important valvular heart disease, active liver disease or hepatic dysfunction (defined as S-aspartate aminotransferase [S-AST] or S-alanine aminotransferase [S-ALT] _>2 times the upper limit of normal [ULN]), partial ileal bypass, creatine kinase [CK] _>10 times ULN, or other serious disease.	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.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Mulder D, et al 2007 **R(1:1), DB, MC, completers analysis** **235 patients randomized (n= 116 aorta, 119 simva)** **16 weeks**	**Efficacy analysis for 1087 patients.** **Total cholesterol change at 16 weeks:** **aorta -15.9% vs. simva 2.8% (p < 0.001)** **LDL-c change at 16 weeks:** **aorta: -20.8% vs. simva: 3.7% (p < 0.001)** **HDL change at 16 weeks:** **aorta: 4.4% vs. simva: 1.8% (p = 0.67)** **(*p<.001 vs. simva)** **Trigs change eat 16 weeks:** **aorta: 15% vs. Simva -0.8 (p < 0.002)**	155 adverse events occurred simva: 52 mild; 17 moderate; 6 severe; aorta: 52 mild; 24 moderate; 4 severe). No difference between treatment groups (p = 0.49).
Olsson et al. 2003 **R(1:1), DB, MC, ITT** 1087 patients randomized (n= 552 aorta, 535 simva) 52 weeks	Efficacy analysis for 1087 patients. LDL-c reduction at 8 (and 52) weeks: aorta: 46%* (49%*) simva: 40% (44%) (*p<.001 vs. simva) HDL increase at 8 (and 52) weeks: aorta: -0.1%* (6.3%) simva: 3.3% (8.3%) (*p<.001 vs. simva) Trigs reduction at 8 (and 52) weeks: aorta: 23%* (24%*) simva: 14% (16%) (*p<.001 vs. simva) Achieved NECP LDL-c goal at 8 (and 52) weeks: aorta: 45%* (61%*) simva: 24% (41%) (*p<.001 vs. simva) 45% aorta vs. 24% simva patients remained at 20 mg	ADE comparable between groups. 12 (2.2%) aorta 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%) aorta vs. 14/537 (2.6%) simva. 6 withdrawals serious, with aorta heart failure, cerebral infarction and 2 malignancies; and simva acute MI and chest pain. No significant changes in either group for S-ALT, S-AST or CK. 1 patient in each group withdrawn due to elevated liver aminotransferase.

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

Clinical Trial	Funding Source
Mulder D, et al 2007 **R(1:1), DB, MC, completers analysis** **235 patients randomized (n= 116 aorta, 119 simva)** **16 weeks**	Parke-Davis Pharmaceutical Research.
Olsson et al. 2003 **R(1:1), DB, MC, ITT** 1087 patients randomized (n= 552 aorta, 535 simva) 52 weeks	Supported by Pfizer.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Praagh et al, 2004 R, OL, crossover, ITT not stated 49 patients randomized (50% to simvastatin and 50% to atorvastatin) 10 months (3 mos./drug)	Men or women 25-70 years with Frederickson IIa and IIb hyperlipoproteinemia with LDL-c >158 ml/dL and trigs <398 mg/dL. **Mean baseline LDL-c:** Simvastatin 20 mg: 182 mg/dL Atorvastatin 10 mg: 174 mg/dL	Patients with diabetes mellitus, previous myocardial infarction, coronary heart disease, liver disease, renal dysfunction (serum creatinine >130 micromole/L) alcoholism, smoking habit, drug addiction, pregnancy, lactation, malignant disease, or had previously received lipid reducing therapy.	8-week NCEP Step 1 dietary run-in then randomized to simva 20 mg/d or atorv 10 mg/d for 3 months. Followed by 8-week washout period, then switched to alternate drug in corresponding dose for 3 months.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Praagh et al, 2004 R, OL, crossover, ITT not stated 49 patients randomized (50% to simvastatin and 50% to atorvastatin) 10 months (3 mos./drug)	**% LDL-c reduced from baseline after 3 months:** **Simva 20 mg: -18.5%** **Atorva 10 mg: -28.9%** **(p<0.001 for baseline vs. 3 month levels; p<0.001 for simva vs. aorta)** **% HDL-c increased from baseline after 3 months:** **Simva 20 mg/d: +3.8%** **Atorva 10 mg/d: + 9.2%** **(p=not significant(n.s.) for baseline vs. 3 month levels; p=n.s. for simva vs. Atorva)** **% Trig level decreased from baseline after 3 months:** **Simva 20 mg/d: -15.2 %** **Atorva 10 mg/d: -29.5%** **(p<0.01 for baseline vs. 3 month levels; p=n.s. for simva vs. aorta)** **% patients reaching target LDL-c levels:** **Simva 20 mg/d: 28%** **Atorva 10 mg/d: 44%** **(no p-values given)**	No serious adverse events reported nor discussed in detail. No changes in physical examination findings or laboratory values occurred.

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

Clinical Trial	Funding Source
Praagh et al, 2004 R, OL, crossover, ITT not stated 49 patients randomized (50% to simvastatin and 50% to atorvastatin) 10 months (3 mos./drug)	Industry role, if any, not specified

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Recto et al. 2000 **R, OL, MC, crossover, not ITT** **258 (?) patients (n= 125 aorta, 126 simva)** **12 weeks**	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	Secondary hyperlipoproteinemia; types I, 111, IV, or V hyperlipidemia; myocardial infarction, coronary angioplasty or coronary bypass surgery within 3 months of trial entry; acute coronary insufficiency; active liver disease; renal insufficiency; partial ileal bypass; obesity (body weight > 50% of ideal); uncontrolled or insulin-dependent diabetes mellitus; uncontrolled hypertension; and excessive alcohol consumption (> 10 drink/week).	4-week dietary and placebo run-in phase, then randomized to: aorta 10 mg or simva 20 mg qd or to a higher dose aorta 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.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Recto et al. 2000	Efficacy analysis for 251 patients.	No differences in ADEs reported between groups.
R, OL, MC, crossover,	LDL-c reduction from baseline at 6 weeks:	
not ITT	aorta 10 mg: 36.7% + 13.3	1 patient in simva 20 mg group withdrawn due to ADE vs. 2 in aorta 10 mg and
	simva 20 mg: 34.8% + 14	3 in aorta 20 mg group.
258 (?) patients	aorta 20 mg: 42.1% + 15.6	
(n= 125 aorta, 126	simva 40 mg: 41% + 15.9	2 serious ADEs in aorta 20 mg group. Myalgia occurred in 1 simva 20 mg vs. 2
simva)	(p>0.05 for aorta 10 mg vs. simva 20 mg, and aorta 20 mg vs. simva 40 mg)	aorta 10 mg patients.
12 weeks	HDL: (p>0.05)	
	Atorva 10 mg increased 8.1 %	One patient in simva 40 mg group experienced elevation in ALT >3x ULN.
	Atorva 20 mg increased 8.5%	
	Simva 20 mg increased 8.7 %	Dose equivalence
	Simva 40 mg increased 9.3 %	Atorva 10 mg qd ≈ simva 20 mg qd.
	Trigs: (p>0.05)	Atorva 20 mg ≈ simva 40 mg qd.
	Atorva 10 mg reduction 22%	
	Atorva 20 mg reduction 25%	
	Simva 20 mg reduction 21.5%	
	Simva 40 mg reduction 21.4%	

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

Clinical Trial	Funding Source
Recto et al. 2000 **R, OL, MC, crossover, not ITT** **258 (?) patients (n= 125 aorta, 126 simva)** **12 weeks**	Study supported by grant from Merck.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Van Dam et al. 2000 R, SB, MC, not ITT 378 patients randomized (n= 185 atorvastatin, 193 simvastatin) 8 weeks	Men or women 18-80 years currently treated with simvastatin 20 or 40 mg qd and LDL-c levels > 100 mg/dl. Mean baseline LDL-c Simvastatin 20 mg: 138 mg/dl Simvastatin 40 mg: 145 mg/dl	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.	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
Wu S, et al 2005 Cross-over 66 patients 8 months	Men and women, cholesterol level ≥ 240mg/dl	Pregnant or lactating females, secondary hypertension of any etiology, history of malignant hypertension, sitting systolic blood pressure 210mmHg, history of myocardial infarction or angina pectoris, clinically important cardiac arrhythmia, history of unexplained syncope within 2 years, symptomatic heart failure, presence of hemodynamically significant obstructive valvular disease or cardiomyopathy, history of coronary angioplasty or coronary artery bypass surgery within the previous 6 months, clinically important malabsorption syndrome or gastric resection, cirrhosis of the liver, patient with only a single functioning kidney, unstable noninsulin-dependent diabetes mellitus (HbA1C 8%), elevated creatine kinase level, abnormal thyroid function, nephrotic syndrome, alcoholism, or medication known to be associated with rhabdomyolysis or other concurrent severe diseases	Cross over aorta vs. simva phase one 3 months then stopped for two months then phase two for three months

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Van Dam et al. 2000 R, SB, MC, not ITT 378 patients randomized (n= 185 atorvastatin, 193 simvastatin) 8 weeks	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% aorta vs. 13% simva	Total 71 ADEs for 54 of 185 aorta 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 aorta 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 aorta vs. increased 1.3% in simva group (p=0.04). Triglycerides reduced by 7.5% in aorta vs. increased 5.6% in simva group (p=0.005). Equivalent doses not compared.
Wu S, et al 2005 Cross-over 66 patients 8 months	**Phase one** **LDL-c change at 12 weeks** **aorta -35% vs. simva -25.5% (p <0.001)** **HDL-c change at 12 weeks** **aorta 18.5% vs. simva 13.0%** **Phase two** **LDL-c change at 12 weeks** **aorta -34.1% vs. simva -25.9% (p < 0.01)** **HDL-c change at 12 weeks** **aorta 11.7% vs. simva 6.1%**	Flatulence simva 1 patient aorta 1 patient Diarrhea simva 1 patient aorta 1 patient Abdominal pain simva 0 patient aorta 1 patient

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

Clinical Trial	Funding Source
Van Dam et al. 2000 R, SB, MC, not ITT 378 patients randomized (n= 185 atorvastatin, 193 simvastatin) 8 weeks	Supported by Parke-Davis and Pfizer Pharmaceuticals. One author employed by Parke-Davis.
Wu S, et al 2005 Cross-over 66 patients 8 months	Supported by Kaohsiung Veterans General Hospital, Gran No. VGHKS 91-41 and Veterans General Hospital, Tsin-Hua, Yang-Ming Research Program, Grant no. VTY92-G3-03

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
	Atorvastatin vs. Multiple Statins		
Andrews et al. 2001 R (4:1:1:1:1), OL, MC, not ITT 3,916 patients randomized 54 weeks	Men and women 18-80 years with elevated cholesterol, with or without CHD. Mean baseline LDL-c 176-179 mg/dl	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.	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.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Andrews et al. 2001 R (4:1:1:1:1), OL, MC, not ITT 3,916 patients randomized 54 weeks	**Efficacy analysis for 3,757 patients (mean dose).** **LDL-c reduction from baseline at 54 weeks:** **aorta (24 mg) 42% (p<0.01 vs. other statins)** **fulva (62 mg) 29%** **lova (52 mg) 36%** **parva (31 mg) 28%** **simva (23 mg) 36%** **HDL increase from baseline at 54 weeks (NS):** **aorta 5%** **fulva 6%** **lova 5%** **parva 6%** **simva 6%** **Trigs reduction from baseline at 54 weeks:** **aorta 19% (p<0.01 vs other statins)** **fulva 7%** **lova 12%** **parva 9%** **simva 13%** **Achieved LDL-c goal at 54 weeks (p not reported):** **aorta 76%** **fulva 37%** **lova 49%** **parva 34%** **simva 58%**	ALT elevation >3x ULN occurred in 10 (0.5%) aorta patients vs. 1 patient each (0.2%) in fulva, parva and simva groups. None in lova. Withdrawal due to ADEs occurred in 7% aorta vs. 13% fulva vs. 8% lova vs. 4% parva vs. 8% simva patients. Myalgia occurred similarly in all groups. Serious treatment related ADEs occurred in 2 aorta patients (elevated CK , muscle cramps and rash) and 1 patient in simva (gastroenteritis). No details on dose for withdrawals or serious ADEs. Questionable why doses were not doubled for more patients to reach NCEP goals. Equivalent doses not compared.

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

Clinical Trial	Funding Source
Andrews et al. 2001 R (4:1:1:1:1), OL, MC, not ITT 3,916 patients randomized 54 weeks	Supported by grant from Pfizer. One Pfizer employee acknowledged for analysis and interpretation of data.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Brown et al. 1998 **R, OL, MC, not ITT** **318 patients randomized (n= 80 aorta, 80 fulva, 81 lova, 77 simva)** **54 weeks**	Men and women 18-80 years with documented CHD and LDL-c 130-250 mg/dl. Mean baseline LDL-c 173 mg/dl	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.	Optional 8-week dietary phase, 4-week dietary run-in, then randomization to: aorta 10 mg, fulva 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 (aorta 80 mg, fulva 40 mg, lova 80 mg, or simva 40 mg qd). If goal not reached with statin, colestipol added (aorta 8%, fulva 76%, lova 15%, simva 33%).
Calza L, et al 2008 **RCT (1:1:1), OL, SC, not ITT** **94 patients randomized (n=28 rosuva, 34 parva, 32 aorta) 85 analyzed** **1 year**	Stable PI-based antiretroviral therapy at least 12 months, and presenting hypercholesterolemia (total cholesterol level >250 mg/dL) of at least 3-month duration and unresponsive to a hypolipidemic diet and physical exercise **LDL-C at baseline mg/dL** Rosuva 177 parva 173 aorta 180	Drug or alcohol abuse; genetic hyperlipidemia, diabetes, hypothyroidism, Cushings, acute or chronic myopathy, kidney disease, acute hepatitis, liver cirrhosis, treatment with corticosteroids, androgens, estrogens, growth hormones, thiazide diuretics, beta-blockers, thyroid preparations or other hypolipidemic drugs	rosuvastatin (10 mg once daily), pravastatin (20 mg once daily) or atorvastatin (10 mg once daily)

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Brown et al. 1998	Efficacy analysis for 308 patients (median dose/day).	ADEs similar across treatment groups at 54 weeks, except fluvastatin where
R, OL, MC, not ITT	LDL reduction from baseline at 54 weeks:	patients also receiving colestipol experienced a 2-fold increase in GI ADEs.
	aorta 20 mg: 41%	
318 patients	fulva 80 mg +colestipol 20 g: 30%*	Withdrawal for ADEs similar among groups, included 3 aorta, 4 fulva, and 2
randomized	lova 80 mg: 41%	each for lova and simva. 1 lova patient experienced pancreatitis. Two fulva
(n= 80 aorta, 80 fulva,	simva 40 mg: 37%	patients had elevations in either ALT or AST >3x ULN. No myopathy observed.
81 lova, 77 simva)	HDL increase at 54 weeks:	
54 weeks	aorta: 7%	No details on ADEs and statin dose.
	fulva: 7%	
	lova: 12%	Equivalent doses not compared; treat to target.
	simva: 11%	
	Trigs reduction at 54 weeks:	
	aorta: 19% vs. fulva: 2%,* lova: 14%, simva: 15%	
	Achieved LDL-c goal at 54 weeks:	
	aorta 83% vs. fulva 50%*, lova 81%, simva 75%	
	(*p<0.05 vs. aorta)	
Calza L, et al 2008	**LDL-c change from baseline at 12 months:**	Rosuva vs. parva vs. aorta %
	rosuva -26.3%	Nausea 7.7 vs. 3.2 vs. 0
RCT (1:1:1), OL, SC,	**parva -18.1% (vs. rosuva p=0.04)**	Dyspepsia 11.5 vs. 9.7 vs. 7.1
not ITT	**aorta -20.3% (vs. rosuva p=0.02)**	Diarrhea 3.8 vs. 0 vs. 3.6
	HDL-c change from baseline at 12 months:	Meteorism 7.7 vs. 3.2 vs. 3.6
94 patients randomized	**rosuva 18.2%**	
(n=28 rosuva, 34 parva,	**parva 17.2% (vs. rosuva p=ns)**	
32 aorta) 85 analyzed	**aorta 16% (vs. rosuva p=ns)**	
1 year		

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

Clinical Trial	Funding Source
Brown et al. 1998 **R, OL, MC, not ITT** **318 patients randomized** **(n= 80 aorta, 80 fulva, 81 lova, 77 simva)** **54 weeks**	Study funded by Parke-Davis. One author employed by Parke-Davis.
Calza L, et al 2008 **RCT (1:1:1), OL, SC, not ITT** **94 patients randomized (n=28 rosuva, 34 parva, 32 aorta) 85 analyzed** **1 year**	NR

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Gentile et al. 2000 R, OL, MC, not ITT 412 patients randomized 24 weeks	Men and women 50-65 years with type 2 diabetes mellitus and LDL-c >160 mg/dl <u>Mean baseline LDL-c</u> 199-218 mg/dl	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.	6-week dietary run-in phase followed by randomization to: aorta 10 mg qd lova 20 mg qd parva 20 mg qd simva 10 mg qd or placebo for 24 weeks.
Hadjibabaie M, et al 2006 **RCT (1:1:1), OL, SC, not ITT** **60 patients randomized (53 analyzed)(n=19 aorta, 18 simva, 16 lova)** **12 weeks**	Men and women 18-70 years old with T2DM and a LDL-c 100 mg/dl or more Baseline LDL-c levels mg/dl aorta 151 simva 155 lova 144 Baseline HDL-c levels mg/dl aorta 45 simva 45 lova 44	Hepatic or renal dysfunction, uncontrolled hypothyroidism, type 1 DM, pregnancy, current use of lipid lowering drugs, hormone replacement therapy, uncontrolled hypertension.	atorvastatin 10 mg, simvastatin 20 mg, lovastatin 20 mg once daily for 12 weeks

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Gentile et al. 2000 R, OL, MC, not ITT 412 patients randomized 24 weeks	Efficacy analysis for 409 patients LDL-c reduction from baseline: aorta 37% (*p<0.05 vs. other statins) lova 21% parva 23% simva 26% placebo 1% HDL increase from baseline: aorta 7.4% lova 7.2% parva 3.2% (p<0.05 vs. other statins) simva 7.1% placebo 0.5% Trigs reduction from baseline: aorta 24% (p<0.05 vs. other statins) lova 11% parva 12% simva 14% placebo 1%	ADEs similar for all groups. Withdrawal for ADEs: 1 aorta, 1 lova and 1 parva patient. No clinically important elevation in ALT, AST or CK observed in any group. Equivalent doses not compared.
Hadjibabaie M, et al 2006 **RCT (1:1:1), OL, SC, not ITT** **60 patients randomized (53 analyzed)(n=19 aorta, 18 simva, 16 lova)** **12 weeks**	**LDL-c change from baseline at 12 weeks:** aorta -37% (vs. simva or lova p < 0.05) simva -19% lova -22% **HDL-c (% change) at 12 weeks:** aorta 48 (6.6%) simva 49 (8.8%) lova 47 (6.8%)	Adverse events were similar between groups. No data reported

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

Clinical Trial	Funding Source
Gentile et al. 2000 R, OL, MC, not ITT 412 patients randomized 24 weeks	Supported in part (60%) by MURST, Italy.
Hadjibabaie M, et al 2006 **RCT (1:1:1), OL, SC, not ITT** **60 patients randomized (53 analyzed)(n=19 aorta, 18 simva, 16 lova)** **12 weeks**	NR

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Hunninghake et al. 1998 **R, OL, MC, not ITT** **344 patients randomized** **(n= 85 aorta, 82 fulva, 83 lova, 87 simva)** **54 weeks**	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	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.	8-week optional dietary phase, 4-week dietary run-in followed by randomization to aorta 10 mg, fulva 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 (aorta 80 mg, fulva 40 mg , lova 80 mg, simva 40 mg qd). If goal not reached with statin, colestipol added. Colestipol added = aorta 2%, fulva 67%, lova 24%, simva 24%.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Hunninghake et al. 1998 **R, OL, MC, not ITT** **344 patients randomized (n= 85 aorta, 82 fulva, 83 lova, 87 simva)** **54 weeks**	Efficacy analysis for 337 patients (median dose/day). LDL reduction from baseline at 54 weeks : aorta 10 mg: 36% fulva 40 mg: 22%* lova 40 mg: 28%* simva 20 mg: 33% HDL increase at 54 weeks: aorta 9 % fulva 6 % lova 10% simva 11% TRIGS reduction at 54 weeks: aorta 20% fulva +2%* lova 16% simva 11% Achieved LDL-c goal at 54 weeks: aorta 95% vs. fulva 60%,* lova 77%,* simva 83%.* (*p<0.05 vs. aorta).	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 fulva and lova groups than in the aorta or simva groups primarily GI in nature. Withdrawal for ADEs were 3% aorta, 4% fulva, 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 fulva experienced acute pancreatitis. No myopathy observed. No details on ADE and statin dose. Equivalent doses not compared; treat to target.

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

Clinical Trial	Funding Source
Hunninghake et al. 1998 **R, OL, MC, not ITT** **344 patients randomized (n= 85 aorta, 82 fulva, 83 lova, 87 simva)** **54 weeks**	Funded by Parke-Davis. One author employed by Parke-Davis.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Insull W, et al 2007 (SOLAR) **RCT (1:1:1), OL, MC, ITT** **1632 patients randomized (n = 542 rosuva, 544 aorta, 546 simva)** **12 weeks**	18 years or older, enrolled in a managed care health plan, and classified as high risk by NCEP ATP III; LDL 130-250 and TG <400 after dietary 6-week dietary run-in	Active vascular disease , uncontrolled hypertension, a fasting serum glucose level of 180 mg/dL or higher or a hemoglobin A1c level of 9% or higher, active liver disease or dysfunction (alanine aminotransferase [ALT], aspartate aminotransferase, or bilirubin levels of ≥2 times the upper limit of normal [ULN]), unexplained serum creatine kinase (CK) elevation of more than 3 times the ULN, and a serum creatinine level of more than 2.0 mg/dL.	6 week dietary lead-in, randomized to rosuvastatin at 10 mg/d, atorvastatin at 10 mg/d, or simvastatin at 20 mg/d, for 6 weeks. Patients not reaching the NCEP ATP III high-risk LDL-C goal of less than 100 mg/dL after 6 weeks had doses doubled to rosuvastatin at 20 mg, atorvastatin at 20 mg, or simvastatin at 40 mg for an additional 6 weeks .

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Insull W, et al 2007 (SOLAR) **RCT (1:1:1), OL, MC, ITT** **1632 patients randomized (n = 542 rosuva, 544 aorta, 546 simva)** **12 weeks**	**proportion of patients who achieved NCEP ATP III high-risk LDL-C goal (<100 mg/dL) at week 6** **rosuva 65%** **aorta 41% (p < 0.001 vs rosuva)** **simva 39% (p < 0.001 vs rosuva)** **proportion of patients who achieved NCEP ATP III high-risk LDL-C goal (<100 mg/dL) at week 12 observed cases** **rosuva (n=501) 76%** **aorta (n=489) 58% (p < 0.001 vs rosuva)** **simva (n=493) 53% (p < 0.001 vs rosuva)** **LDL-c change at 6 weeks** **rosuva -45%** **aorta -36% (p < 0.001 vs rosuva)** **simva -34% (p < 0.001 vs rosuva)** **HDL-c change at 6 weeks** **rosuva 7%** **aorta 6%** **simva 6%** **LDL-c change at 12 weeks (observed cases)** **rosuva (n=501) -48%** **aorta (n=489) -41% (p < 0.001 vs rosuva)** **simva (n=493) -40% (p < 0.001 vs rosuva)** **HDL-c change at 12 weeks (observed cases)** **rosuva (n=501) 10%** **aorta (n=489) 6% (p < 0.001 vs rosuva)** **simva (n=493) 7% (p < 0.001 vs rosuva)**	rosuva vs aorta vs. simva n(%) Adverse events 662 vs. 579 vs. 618 Adverse events leading to death 0 (0.0) vs.3 (0.6) vs. 0 (0.0) Adverse events leading to withdrawal 15 (3) vs. 20 (4) vs. 19 (3) Serious adverse events not leading to death 18 (3) vs. 11 (2) vs. 13 (2) Alanine aminotransferase >3 times the ULN at any visit 2 (0.4) vs. 1 (0.2) vs. 1 (0.2) Creatine kinase >10 times the ULN at any visit 1 (0.2) vs.0 (0.0) vs. 0 (0.0) Creatinine increase >100% 0 for all

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

Clinical Trial	Funding Source
Insull W, et al 2007 (SOLAR) **RCT (1:1:1), OL, MC, ITT** **1632 patients randomized (n = 542 rosuva, 544 aorta, 546 simva)** **12 weeks**	AstraZeneca Pharmaceuticals LP

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Jones et al. 1998 **Jones et al. 2004** R, OL, MC, not ITT 534 patients randomized 8 weeks	Men or women 18-80 years with LDL > 160 mg/dl. Mean baseline LDL-c Range 192-244 mg/dl	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.	6-week dietary run-in phase, then randomization to one of 15 treatment groups: aorta 10, 20, 40, 80 mg fulva 20 or 40 mg lova 20, 40, or 80 mg parva 10, 20 or 40 mg simva 10, 20 or 40 mg qd.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Jones et al. 1998 **Jones et al. 2004** R, OL, MC, not ITT 534 patients randomized 8 weeks	Efficacy analysis for 522 patients. LDL reduction from baseline at 8 weeks: aorta 10 mg: 38% (n=73) / aorta 20 mg: 46% (n=51) aorta 40 mg: 51% (n=61) / aorta 80 mg: 54% (n=10) fulva 20 mg: 17% (n=12) / fulva 40 mg: 23% (n=12) lova 20 mg: 29% (n=16) / lova 40 mg: 31% (n=16) lova 80 mg: 48% (n=11) parva 10 mg: 19% (n=14) / parva 20 mg: 24% (n=41) parva 40 mg: 34% (n=25) simva 10 mg: 28% (n=70) / simva 20 mg: 35% (n=49) simva 40 mg: 41% (n=61) HDL increase: All similar (ranging from 3% ot 9%), except aorta 80 mg and fulva 40 mg, with reduction in HDL. Simva 40 mg increase significantly greater than aorta. Trigs reduction: All similar, except aorta 40 mg produced a greater reduction.	ADEs similar across treatment groups. 1 patient on aorta 20 mg developed myalgia judged unrelated to treatment. No clinically important elevations in liver transaminase or CK. <u>Dose equivalence</u> Atorvastatin 10 mg ≈ lovastatin 40 mg ≈ pravastatin 40 mg ≈ simvastatin 20 mg qd. Atorvastatin 20 mg ≈ lovastatin 80 mg ≈ simvastatin 40 mg qd.

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

Clinical Trial	Funding Source
Jones et al. 1998 **Jones et al. 2004** R, OL, MC, not ITT 534 patients randomized 8 weeks	Study funded by Parke-Davis. Parke-Davis Research played role in some portion of the study.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Schaefer et al. 2004 R, OL, MC, ITT crossover design 196 patients studied: 99 patients randomized and 97 controls 36 weeks	Men and women with a mean age of 61.4 years with CHD and with LDL-c >130 mg/dl while off lipid-lowering drugs for 6 weeks. Mean baseline LDL-c :Not reported	Evidence of renal impairment, hyperthyroidism, or liver dysfunction based on clinical chemistry testing, or had previous adverse reactions to statins.	4 week dietary run-in, then randomization to a dosing schedule that increased every 4 weeks (12 weeks total): fulva: 20 mg/d; 40 mg/d; 80 mg/d parva: 20 mg/d; 40 mg/d (8 weeks at this max dose) lova: 20 mg/d; 40 mg/d; 80 mg/d simva: 20 mg/d; 40 mg/d (8 weeks at this max dose) aorta: 20 mg/d; 40 mg/d; 80 mg/d for all 97 controls After the 12th week, an 8 week placebo period occurred. Then the patients were crossed over between atorv and another statin for 12 weeks (dosage increased every 4 weeks as before). 36 weeks total

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Schaefer et al. 2004 R, OL, MC, ITT crossover design 196 patients studied: 99 patients randomized and 97 controls 36 weeks	*% change in lipoproteins data includes pre- and post-crossover data combined.* *Mean % change in fasting lipoproteins after treatment (p-values are for paired comparisons between same doses of statins):* *fulva 20/40/80 vs aorta 20/40/80:* *LDL-c: -8%,-17%,-22% vs -34%,-45%,-51% (all have p<0.0001)* *HDL-c: +3%,+3%,+3% vs +2%,+6%,+1% (p not stated)* *trigs: -5%,-1%, 0% vs -20% (p<0.05), -25% (p<0.001), -33% (p<0.0001)* *lova 20/40/80 vs aorta 20/40/80:* *LDL-c: -20%,-28%,-31% vs -38%,-45%,-53% (all have p<0.0001)* *HDL-c: +4%,+3%,+9% vs +8% (p<0.01),+3% (p not stated),+1% (p not stated)* *trigs: -10%,-17%,-19% vs -27%,-32%,-32% (all have p<0.01)* *parva 20/40/40 vs aorta 20/40/80:* *LDL-c: -22%,-24%,-26% vs -39%,-46%,-50% (all have p<0.0001)* *HDL-c: +9%,+10%,+11% vs +8%,+5%,+6% (p not stated for any)* *trigs: -4%,-2%,-5% vs -9% (p not stated),-18% (p<0.05), -21% (p<0.05)* *simva 20/40/40 vs aorta 20/40/80:* *LDL-c: -28%,-39%,-39% vs -40% (p<0.001), -47% (p<0.01), -51%(p<0.001)* *HDL-c: +9%,+7%,+10% vs +5%,+5%,+4% (p not stated for any)* *trigs: -5%,-17%,-15% vs -27%(p<0.0001), -25%(p not stated), -32% (p<0.001)*	No safety data (adverse events and withdrawals) reported or discussed.

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

Clinical Trial	Funding Source
Schaefer et al. 2004 R, OL, MC, ITT crossover design 196 patients studied: 99 patients randomized and 97 controls 36 weeks	Supported by investigator-initiated research contracts from Parke-Davis/Pfeixer, and Otsuka America Pharmaceuticals, Inc.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Wolffenbuttel et al. 1998 R, OL, MC. cross-over, ITT 78 patients 4 weeks on each treatment	Men and women 18-70 years with LDL-c 160-240 mg/dl. Mean baseline LDL-c 215 mg/dl	Patients not eligible when they used lipid-lowering drugs after visit 1, or had a history of serious or hypersensitivity reactions to statins; active cardiovascular disease (uncontrolled hypertension >200/>95 mmHg), heart failure NYHA class IV, recent unstable angina, MI, transient ischemic attack, cerebrovascular accident, coronary artery bypass surgery or angioplasty within the previous 2 months, or likely to undergo coronary artery intervention within 6 months after randomization; women who were pregnant or lactating or those not using an effective form of birth control; metabolic abnormalities, such as kidney insufficiency, uncontrolled hypothyroidism, homozygous familial hypercholesterolemia, or familial dysbetalipoproteinemia, active liver disease or liver enzyme [alanine aminotransferase (ALT), aspartate transaminase (AST)] elevations >1.5 ULN and unexplained CK elevations >3 ULN.	4-week dietary run-in then randomized to: aorta 5 mg or aorta 20 mg or simva 10 mg or parva 20 mg qd for 4 weeks. After washout, patients were switched to alternate treatment.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Wolffenbuttel et al. 1998 R, OL, MC. cross-over, ITT 78 patients 4 weeks on each treatment	Efficacy analysis for 78 or 76 patients. LDL-c reduction from baseline: aorta 5 mg: 27% aorta 20 mg 44% (p<0.05 vs. simva and parva) parva 20 mg 24% simva 10 mg 28% HDL increase from baseline: aorta 5 mg 2% aorta 20 mg 8% parva 20 mg 3% simva 10 mg 1% (NS) Trigs reduction from baseline: aorta 5 mg 16% aorta 20 mg 23% (p<0.05 vs. simva and parva) parva 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. <u>Dose equivalence</u> Atorvastatin 5 mg = pravastatin 20 mg = simvastatin 10 mg qd

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

Clinical Trial	Funding Source
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.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
	Fluvastatin vs. Lovastatin		
Berger et al. 1996 R, OL, MC, ITT 270 patients randomized 6 weeks	Age ≥20 years, 45% male, with serum triglyceride levels <400 mg/dl, not following cholesterol-reducing diet, and (a) LDL-c ≥190 mg/dl and ≤2 CHD risk factors, or (b) ≥160 mg/dl and ≥2 CHD risk factors, or (c) ≥130 mg/dl and definite CHD. Mean baseline LDL-c 187 mg/dl	Concurrent use of immunosuppressants	5-week diet-only run-in phase, then randomization to: fulva 20 mg qd or lova 20 mg qd
Davidson et al, 2003 R, DB, MC, PC, 838 patients randomized (n=337 fulva, 501 lova) 6 weeks	Men and women >20 years with TG level ≤ 4.5 mmol/L and one of the following LDL-c levels after 6-week run-in on NCEP Step I diet: (1) > 3.4 mmol/L with evidence of CHD or other atherosclerotic disease; (2) >4.1 mmol/L with >2 other CHD risk factors but no CHD or other atherosclerotic disease; 30 >4.9 mmol/L without CHD or other atherosclerotic disease and <2 other CHD risk factors. Mean baseline LDL-c fulva 20 mg: 181.7 mg/dL fulva 40 mg: 189.5 mg/dL lova 10 mg: 189.5 mg/dL lova 20 mg: 189.5 mg/dL lova 40 mg: 185.6 mg/dL	Patients with myocardial infarction, coronary bypass surgery, or angioplasty in the prior 3 months; current coronary insufficiency; or clinically significant ventricular arrhythmias, pregnant or lactating women.	Fluva 20 or 40 mg qd or lova 10, 20, or 40 mg qd for 6 weeks.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Berger et al. 1996 R, OL, MC, ITT 270 patients randomized 6 weeks	Efficacy analysis for 270 patients. **LDL-c reduction from baseline:** fulva: 18% lova: 28% (p≤0.001) **HDL-c increase from baseline:** fulva and lova: ~8% (NS) **Trigs reduction from baseline:** fulva: 9% lova: 10% (NS) **Achieved NCEP LDL-c goal:** fulva: 24% lova: 37% (p=0.02)	Withdrawals due to AEs: 8 fulva vs. 3 lova. Serious AEs (not considered drug related): 3 fulva vs. 5 lova. Total AEs: 54% fulva vs. 47% lova.
Davidson et al, 2003 R, DB, MC, PC, 838 patients randomized (n=337 fulva, 501 lova) 6 weeks	**LDL-c reduction from baseline at 6 weeks:** fulva 20 mg: 18.8% fulva 40 mg: 22.6% lova 10 mg: 21.6% (p<0.05 vs fulva 20 mg) lova 20 mg: 27.3% (p<0.001 vs fulva 20 mg, p<0.05 vs fulva 40 mg) lova 40 mg: 31.8% (p <0.001 vs fulva 40 mg) **HDL-c increase from baseline at 6 weeks** (NS): fulva 20 mg: 3.5% fulva 40 mg: 4.3% lova 10 mg: 4.9% lova 20 mg: 5.7% lova 40 mg: 6.1% **Trigs reduction from baseline at 6 weeks** (NS): fulva 20 mg: 3.3% fulva 40 mg: 11.4% lova 10 mg: 6.4% lova 20 mg: 5.7% lova 40 mg: 11.3%	No significant differences between treatments in any AE reported. Most common were GI disturbances, flatulence in 16 (3.2%) lova and 19 (5.6%) fulva patients 21 (4.2%) lova and 22 (6.5%) fulva patients withdrew due to adverse effects. 4 lova and 4 fulva patients reported serious adverse effects; only one (fecal occult blood/gastric ulcer in 1 patient treated with fulva 20mg considered treatment related. Dose equivalence lova 20 mg > fulva 40 mg

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

Clinical Trial	Funding Source
Berger et al. 1996 R, OL, MC, ITT 270 patients randomized 6 weeks	Sponsored by Merck and Co.
Davidson et al, 2003 R, DB, MC, PC, 838 patients randomized (n=337 fulva, 501 lova) 6 weeks	3 authors from Merck

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Nash 1996 R, OL, MC, ITT 137 patients randomized 8 weeks	Men or women previously controlled on lovastatin 20 mg qd (LDL-c <150 mg/dl). After dietary washout phase, LDL-c required >160 mg/dl, trigs <350 mg/dl. <u>Mean baseline LDL-c</u> Not reported	363 patients screened, 137 patients randomized. (Were large numbers of patients not randomized because their LDL-c upon washout was <160 mg/dl?) Homozygous familial hypercholesterolemia, MI, unstable angina, major surgery or PTCA 6 months prior to study, secondary causes of hyperlipidemia (alcoholism, DM, thyroid disease), pregnant or lactating women and those women who were unwilling to use alternate forms of birth control other than the pill.	6-week dietary/placebo washout period then randomization to: fulva 20 mg qd or lova 20 mg qd. After 4 weeks, fulva was increased to 40 mg qd.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Nash 1996 R, OL, MC, ITT 137 patients randomized 8 weeks	Efficacy analysis for 137 patients. **LDL-c reduction from baseline at 8 weeks:** fulva: men and women 26% lova: men 29%, women 26% (NS) **HDL-c increase from baseline at 8 weeks (NS):** fulva: men: 7 %, women 8% lova: men 7%, women 4% **Trigs reduction from baseline at 8 weeks:** fulva: men 14%, women 10% lova: men 12%, women 20% **Achieved LDL-c goal (<160 mg/dl) at 4 weeks:** fulva: 85% lova: 91% (NS) **Achieved LDL-c goal (<160 mg/dl) at 8 weeks:** fulva: 89% lova: 91% (NS)	Myalgia occurred in 1 fulva vs. 2 lova patients. Musculoskeletal abnormalities existed significantly more often as a background medical condition in the lova group. 5 fulva and 1 lova patient experienced an increase in ALT or AST >3x ULN. No details on what dose of fulva patients experienced these ADEs.

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

Clinical Trial	Funding Source
Nash 1996 R, OL, MC, ITT 137 patients randomized 8 weeks	Funded by Sandoz Pharmaceuticals.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
	Fluvastatin vs. Pravastatin		
Jacotot et al. 1995 R, DB, MC, both ITT and on treatment analysis 134 patients randomized 16 weeks	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	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.	6-week dietary/placebo run-in phase then, randomization to: fulva 40 mg qd or parva 20 mg qd for 4 weeks. Doses doubled at 4 weeks and study continued another 12 weeks.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Jacotot et al. 1995 R, DB, MC, both ITT and on treatment analysis 134 patients randomized 16 weeks	Efficacy analysis for 134 patients. **LDL-c reduction from baseline at 16 weeks:** fulva 40 mg bid: 29.6% parva 40 mg qd: 26.1% (NS) **HDL-c increase from baseline at 16 weeks:** fulva 40 mg bid: 7.5% parva 40 mg qd: 9% (p<0.001) **Trigs reduction from baseline at 16 weeks:** fulva 40 mg bid: 14.9% parva 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 fulva group. No patient experienced clinically significant elevation in ALT, AST or CK. Dose equivalence Fluvastatin 40 mg ≈ pravastatin 20 mg qd. Fluvastatin 40 mg bid ≈ pravastatin 40 mg qd.

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

Clinical Trial	Funding Source
Jacotot et al. 1995 R, DB, MC, both ITT and on treatment analysis 134 patients randomized 16 weeks	Funding and participation by Sandoz Pharmaceuticals.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
	Fluvastatin vs. Simvastatin		
Bevilacqua M, et al 2005 **RCT, OL, SC, ITT** **94 patients randomized (n = fulva 48, simva 46)** **8 weeks**	Men and women with T2DM, triglycerides > 2.3, HDL < 1.3 and elevated sdLDL	Surgery, myocardial infarction, angioplasty in last 6 months, poorly controlled hypertension, liver disease, chronic renal failure, myopathy, alcohol/drug abuse, hypersensitivity to statins, pregnancy or lactation, lipid lowering therapy in last 8 weeks, use of oral contraceptives	4 week dietary run-in; fluvastatin extended-release (XL) 80 mg and simvastatin 20 mg for 8 weeks
Ose et al. 1995 R, DB, MC, ITT 432 patients randomized 6 weeks	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	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.	4-week dietary/placebo run-in, then randomized to: fulva 20 or 40 mg qd, or simva 5 or 10 mg qd for 6 weeks.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Bevilacqua M, et al 2005 **RCT, OL, SC, ITT** **94 patients randomized (n = fulva 48, simva 46)** **8 weeks**	LDL-c change from baseline at 8 weeks: fulva -51% vs. simva -55.1 (p = ns) HDL-c change from baseline at 8 weeks: fulva 14.3 vs. simva 0 (p < 0.01)	No severe AEs reported, Data = NR
Ose et al. 1995 R, DB, MC, ITT 432 patients randomized 6 weeks	Efficacy analysis for 432 patients. LDL-c reduction from baseline at 6 weeks: fulva 20 mg: 21.8% fulva 40 mg: 25.9% simva 5 mg: 25.7% (p<0.01 vs fulva 20 mg) simva 10 mg: 29.9% (p<0.01 vs fulva 20 mg, p<0.05 vs fulva 40 mg) HDL-c increase from baseline at 6 weeks: fulva 20 mg: 6.3% fulva 40 mg: 13% simva 5 mg: 10.1% simva 10 mg: 12.2% (p<0.01 vs fulva 20 mg) Trigs reduction from baseline at 6 weeks: fulva 20 mg: 10% fulva 40 mg: 12.8% simva 5 mg: 11.5% simva 10 mg: 14.5% Achieved NCEP LDL-c goal: fulva 20 mg: 12% fulva 40 mg: 21% simva 5 mg: 24% (p<0.05 vs fulva 20 mg) simva 10 mg: 25% (p<0.01 vs fulva 20 mg)	Number of patients reporting ADEs similar across all groups. GI ADEs were more frequent in fulva vs. simva groups, especially at 40 mg qd dose. One fulva 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.

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

Clinical Trial	Funding Source
Bevilacqua M, et al 2005 **RCT, OL, SC, ITT** **94 patients randomized (n = fulva 48, simva 46)** **8 weeks**	NR
Ose et al. 1995 R, DB, MC, ITT 432 patients randomized 6 weeks	Funded by Merck.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Schulte et al. 1996 R, DB 120 patients randomized 10 weeks	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	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.	4-week dietary run-in phase and randomized to: fulva 40 mg qd or simva 20 mg qd for 4 weeks. After 4 weeks, dose was doubled and continued for 6 more weeks.
Sigurdsson et al. 1998 R, DB, MC, not ITT 113 patients randomized 16 weeks	Men or women with CHD. <u>Mean baseline LDL-c</u> 185-187 mg/dl	Patients with concomitant conditions such as myocardial infarction or CVA within the past 6 months, planned angioplasty or coronary bypass surgery during the previous 6 months, unstable angina, cardiac or renal failure, hepatic disease, uncontrolled hypertension, partial ileal bypass, secondary hypercholesterolemia, or hypersensitivity to HMG-CoA reductase inhibitors, history of alcohol or drug abuse, and concomitant treatment with lipid lowering agents within 6 weeks.	8-week dietary and 2 week-placebo run-in phase, then randomized to: fulva 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.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Schulte et al. 1996 R, DB 120 patients randomized 10 weeks	Unclear if all patients included in efficacy analysis: LDL-c reduction from baseline at 4 and 10 weeks: fulva 40 mg: 23.8% simva 20: 23.6% fulva 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: fulva 40 mg: 7.1% simva 20 mg: 8% fulva 80 mg: 13.1% simva 40 mg: 12.3% (NS at 4 or 10 weeks) Trigs reduction from baseline at 4 and 10 weeks: fulva 40 mg: 2.1% simva 20 mg: +1% fulva 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 randomized 16 weeks	Efficacy analysis for 110 patients. LDL-c reduction from baseline at 16 weeks: fulva: 25.3% simva: 39.9% (p<0.001) HDL-c increase from baseline at 16 weeks: fulva: 8.8% simva: 11.1% (NS) Trigs reduction from baseline at 16 weeks: fulva: 23.1% simva: 22.5% (NS) Achieved LDL-c <200 mg/dl: 49.1% fulva vs. 87.3% simva (p<0.001) 63% fulva 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 fulva vs. simva group (8 vs. 4). The difference was not significant. No clinically important elevations in ALT, AST, or CK. Nonequivalent doses compared, treat to target.

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

Clinical Trial	Funding Source
Schulte et al. 1996 R, DB 120 patients randomized 10 weeks	Funded by Astra.
Sigurdsson et al. 1998 R, DB, MC, not ITT 113 patients randomized 16 weeks	Funded by grant from Merck. One author employed by Merck. Merck also supplied lovastatin and placebo.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
	Lovastatin Extended Release vs. Lovastatin Immediate Release		
Lukacsko et al, 2004 179 patients randomized (n= 90 lova ER, 89 lova IR) 12 weeks; crossover	Men and women ages 21 to 70 with a TG level less than 350 mg/dL and plasma LDL-c within the following parameters: >100 mg/dl for patients with a history of CHD, peripheral vascular disease (PVD), or cerebrovascular disease (CVD); 130 mg/dl or higher for patients without a history of CHD, PVD, or CVD, but with 2 or more risk factors for heart disease; or 160 mg/dl or higher for patients without a history of CHD, PVD, or CVD, but with less than 2 risk factors for heart disease. Mean baseline LDL-c 182.5 mg/dl lova ER; 174.7 mg/dl lova IR	History of underlying hepatic disease or elevation of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above 1.5 times the upper limit of normal (ULN) or clinically significant renal, gastrointestinal, metabolic, neurological, pulmonary, endocrine or psychiatric disorders, pregnant or became pregnant and failed to maintain 85% compliance with dosing	Lovastatin 20mg ER once daily vs lovastatin 20 mg IR once daily

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Lukacsko et al, 2004 179 patients randomized (n= 90 lova ER, 89 lova IR) 12 weeks; crossover	Efficacy analysis for 179 patients. **LDL-c reduction from baseline at week 12 (from baseline to endpoint for treatment periods 2 and 4 combined, results for separate treatment periods not reported):** Lova ER: 26.4% Lova IR: 23.1% (difference -3.3%; p=0.0028; 95% CI -5.43% to -1.15%) **HDL-c increase from baseline to endpoint for treatment periods 2 and 4 combined (12 week treatment periods, results for separate treatment periods not reported):** Lova ER: 4.1% Lova IR: 4.3% (difference -0.2%; p=0.8584)	No apparent trends by treatment in the incidence of treatment emergent signs and symptoms. Serious adverse events reported by 5 patients receiving ER lova (6 events: cholecystitis, accidental injury, cerebral ischemia, angina pectoris, enlarged uterine fibroids, and back pain), and 2 patients receiving IR lova (increased knee pain due to degenerative joint disease, and MI). Dose equivalence: lova ER > lova IR

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

Clinical Trial	Funding Source
Lukacsko et al, 2004 179 patients randomized (n= 90 lova ER, 89 lova IR) 12 weeks; crossover	Funded by Andrx Laboratories, and all authors employed by same.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
	Lovastatin vs. Pravastatin		
McPherson et al. 1992 R, DB, MC, not ITT 217 patients randomized 8 weeks	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	Hypersensitivity to HMG-CoA reductase inhibitors, plasma triglycerides> 4.0 mmol/L; impaired hepatic function or recent hepatitis; secondary hypercholesterolemia due to endocrine disease; insulin dependant or non insulin dependant diabetes with poor control; unstable angina or vaso spastic angina, myocardial infarction or coronary bypass surgery within previous 2 months; treatment with probucol within the last 6 months, history of drug/alcohol abuse, concurrent treatment with other investigational/immunosuppressive and lipid lowering agents	6-week dietary/placebo and washout phase followed by randomization to: lova 20 mg qd (n=73) or parva 10 mg qd (n=74) or parva 20 mg qd (n=70)

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
McPherson et al. 1992 R, DB, MC, not ITT 217 patients randomized 8 weeks	Efficacy analysis for 201 patients. **LDL-c reduction from baseline at 8 weeks:** lova 20 mg: 28% parva 10 mg: 24.5% parva 20 mg: 28.4% (all NS) **HDL-c increase from baseline at 8 weeks (p not reported):** lova 20 mg: 8.7% parva 10 mg: 10.8% parva 20 mg: 5.4% **Trigs reduction from baseline at 8 weeks:** lova 20 mg: 6.8% parva 10 mg: 0.9% parva 20 mg: 4.9% **High risk meeting NCEP goal:** lova: 29%, parva 10 mg: 25%, parva 20 mg: 26% (NS) **Moderate risk meeting NCEP goal:** lova 74%, parva 10 mg: 53%, parva 20 mg: 68% (NS)	Adverse effects not different between groups. Difference in LDL-c lowering greater at 4 weeks in lova vs. parva 10 mg groups, however was not different at 8 weeks. LDL-c lowering in lova vs. parva 20 mg groups not different at any time. Dose equivalence lova 20 mg = parva 20 mg ≈ parva 10 mg.

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

Clinical Trial	Funding Source
McPherson et al. 1992 R, DB, MC, not ITT 217 patients randomized 8 weeks	Merck funded the study.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Strauss et al. 1999 R, SB, Crossover, not ITT 31 patients randomized 12 weeks	Men and women with hypercholesterolemia Mean baseline LDL-c 185 mg/dl	Prior intolerance to HMG CoA reductase inhibitors, baseline creatine kinase (CK) or liver function tests >2 times the upper limit of normal, and fasting triglyceride levels >400 mg/dL.	4-week dietary run-in followed by randomization to: lova 10 mg qd or parva 10 mg qd for 4 weeks. Then a 4 week washout period followed by crossover to alternate statin for 4 weeks.
The Lovastatin Pravastatin Study Group 1993 R, DB, MC, not ITT 672 patients randomized 18 weeks	Men and women 25-75 years with hypercholesterolemia Mean baseline LDL-c 194-196 mg/dl	Patients aged <25 or >75 yrs, secondary hypercholesterolemia, triglyceride level >300mg/dl, women who could not conceive and DM,	7-week dietary/placebo run-in phase followed by randomization to: lova 20 mg qd (n=339) or parva 10 mg qd (n=333) for 6 weeks. Then doses doubled to lova 40 mg qd or parva 20 mg qd for 6 weeks, then doubled to lova 80 mg (40 mg bid) qd or parva 40 mg qd for the remaining 6 weeks.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Strauss et al. 1999 R, SB, Crossover, not ITT 31 patients randomized 12 weeks	Efficacy analysis for 30 patients. **LDL-c reduction from baseline at 4 weeks:** lova: 24% parva: 19% (NS) **HDL-c increase from baseline at 4 weeks:** lova: 0.9% parva: 1.6% (NS) **Trigs reduction from baseline at 4 weeks:** lova: 15.3% parva: 19.4% (NS)	There were no differences in ADEs between groups. No cases of myopathy or clinical significant elevation in ALT or AST observed. Dose equivalence Lova 10 mg = parva 10 mg qd.
The Lovastatin Pravastatin Study Group 1993 R, DB, MC, not ITT 672 patients randomized 18 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. parva 10 mg: 19% lova 40 mg: 33% vs. parva 20 mg: 25% lova 80 mg: 39% vs. parva 40 mg: 27% (p<0.01 all comparisons) **HDL-c increase from baseline at 18 weeks:** lova 80 mg: 19% parva 40 mg: 16% (NS) **Trigs reduction from baseline at 18 weeks:** lova 80 mg: 22% parva 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 parva patients. Equivalent doses not compared.

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

Clinical Trial	Funding Source
Strauss et al. 1999 R, SB, Crossover, not ITT 31 patients randomized 12 weeks	Merck and Bristol Myers Squibb provided active drug only.
The Lovastatin Pravastatin Study Group 1993 R, DB, MC, not ITT 672 patients randomized 18 weeks	Merck supported and participated in trial.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Weir et al. 1996 R, DB, MC, not ITT 426 patients randomized 12 weeks	Men and women 20-65 years with hypercholesterolemia <u>Mean baseline LDL-c</u> Lova 195 mg/dl Prava 202 mg/dl	Patients with impaired hepatic or renal function, history of myocardial infarction or coronary artery bypass surgery within 6 months, history of cerebrovascular accident associated with permanent sequelae, or peripheral vascular disease interfering with normal daily function, treatment with any investigational drug or any lipid-lowering medication during the previous 6 weeks (6 months for probucol), history of depression, anxiety, or other psychiatric disorder, a sleep disorder, an irregular or changing work-shift schedule, or use of any psychotropic drugs or other centrally acting agents.	6-week dietary/placebo run-in followed by randomization to: lova 40 mg qd (n=211) or parva 40 mg qd (n=215).

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Weir et al. 1996 R, DB, MC, not ITT 426 patients randomized 12 weeks	Efficacy analysis for 423 patients. **LDL-c reduction from baseline at 12 weeks:** lova: 27.9% parva: 23.6% (NS) **HDL-c increase from baseline at 12 weeks:** lova: 8.5% parva: 8.2% (NS) **Trigs reduction from baseline at 12 weeks:** lova: 6% parva: 8.6% (NS) **Achieved NECP LDL-c goal:** lova 45% vs. parva 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 = parva 40 mg qd.

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

Clinical Trial	Funding Source
Weir et al. 1996 R, DB, MC, not ITT 426 patients randomized 12 weeks	Merck participated in study.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
	Lovastatin vs. Simvastatin		
Farmer et al. 1992 R, DB, MC, not ITT 544 patients randomized 24 weeks	Men and women 30-85 years with hypercholesterolemia <u>Mean baseline LDL-c</u> 191.4-193.4 mg/dl	Patients with history of drug, alcohol abuse, poor mental function, impaired hepatic function, unstable coronary insufficiency, serum creatinine >2mg/dl, concomitant use of hypolipidemic or immunosuppressant drugs, or history of allergic response to lovastatin or simvastatin, premenopausal women, patient with secondary hypercholesterolemia, nephrotic syndrome, chronic use of corticosteroids, untreated hypothyroidism or any other condition interfering with interpretation of results.	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.
Frohlich et al. 1993 R, DB, MC, not ITT 298 patients randomized 18 weeks	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	Secondary hypercholesterolemias and hypercholesterolemia with a ratio of total cholesterol: high density lipoprotein cholesterol less than 4, insulin dependant or unstable non insulin dependant diabetes patients, impaired hepatic function, impaired history of hepatitis, biliary disease, partial ileal bypass, unstable angina or intermediate syndrome, myocardial infarction, coronary bypass surgery within the previous 2 months, vasospastic angina or other serious vasospastic cardiovascular disease. Current treatment with other investigational drug, hypersensitivity to HMG-CoA reductase inhibitors, concurrent use of cimetidine, use of antacids or immunosuppressive agents, drug or alcohol abuse, overweight and with poor mental function.	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 >200 mg/dl

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Farmer et al. 1992 R, DB, MC, not ITT 544 patients randomized 24 weeks	Efficacy analysis for 540 patients. LDL-c reduction from baseline at 24 weeks: lova 20 mg: 25.4% lova 40 mg: 31.2% simva 10 mg: 27.5% (NS) simva 20 mg: 34.7% (p<0.05) HDL-c increase from baseline at 24 weeks: lova 20 mg: 4.2% lova 40 mg: 7.4% simva 10 mg: 4.6% (NS) simva 20 mg: 4.6 (NS) Trigs reduction from baseline at 24 weeks: lova 20 mg: 10.5% lova 40 mg: 10.3% simva 10 mg: 3.9% (no significance reported) simva 20 mg: 10.3% (NS) Achieved NCEP LDL-c goal (p not reported): lova 20 mg: 33% lova 40 mg: 51% simva 10 mg: 41% simva 20 mg: 61%	No difference in ADEs between groups. Withdrawal for clinical or laboratory ADEs not different between groups. 1 patient in lova 40 mg group had ALT 3x ULN. Dose equivalence lova 20 mg = simva 10 mg qd lova 40 mg < or ≈ simva 20 mg qd.
Frohlich et al. 1993 R, DB, MC, not ITT 298 patients randomized 18 weeks	Efficacy analysis for 296 patients. LDL-c reduction from baseline at 18 weeks: Stratum 1 (mean dose): lova 50 mg qd: 34.3% simva 26.4 mg qd 34.6% (NS) Stratum 2 (mean dose): lova 71.7 mg qd: 37.2% simva 36.9 mg qd.: 37.1% (NS) HDL-c increase from baseline at 18 weeks: Stratum 1 (mean dose): lova 50 mg qd: 2.7% simva 26.4 mg qd 7.0% (NS) Stratum 2 (mean dose): lova 71.7 mg qd: 8.8% simva 36.9 mg qd: 5.3% (NS)	Patients in Stratum 2 experienced more laboratory ADEs in lova group vs. simva group (8.3% vs 0% , p<0.05). There were said to be minor and well within normal ranges. No other safety differences between groups. 1 major laboratory ADE occurred in lova group in Stratum 2, thought not to be drug-related. Dose equivalence lova 20 mg = simva 10 mg lova 80 mg = simva 40 mg qd

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

Clinical Trial	Funding Source
Farmer et al. 1992 R, DB, MC, not ITT 544 patients randomized 24 weeks	3 primary authors employed by Merck.
Frohlich et al. 1993 R, DB, MC, not ITT 298 patients randomized 18 weeks	Merck funded the study. Merck coordinated data and biostatistics groups.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
	Pravastatin vs. Simvastatin		
Douste-Blazy et al. 1993 R, DB, MC, not ITT 273 patients randomized 6 weeks	Men and women 22-75 years with an LDL-c ≥160 mg/dl Mean baseline LDL-c Prava 222 mg/dl Simva 224 mg/dl	Patients with plasma triglyceride levels >4.0mmol/L, total cholesterol: HDL cholesterol ratio of ≤4.0 or an LDL cholesterol<3.4 mmol/L, concomitant conditions such as myocardial infarction or coronary bypass surgery within the previous 2 months, unstable or prinzmetal's angina; ventricular ectopic beats> 5 per minute, coupling or the R on T phenomenon; impaired hepatic function or liver transaminase levels>20% above the normal range, recent history if hepatitis, complete biliary obstruction, CPK elevations >50% above normal range, diabetes mellitus or fasting blood glucose >7.8mmol/L or partial ileal bypass, poor mental function, hypersensitivity to HMG CoA reductase inhibitors, history or drug or alcohol abuse, and concurrent use of immunosuppressants or an investigational drug	4-week placebo/dietary run-in phase followed by randomization to: parva 20 mg qd (n=136) or simva 10 mg qd (n=137) for 6 weeks.
Lambrecht et al. 1993 R, DB, MC, not ITT 210 patients randomized 6 weeks	Men or women 18-70 years with total cholesterol ≥250 mg/dl Mean baseline LDL-c Prava 214 mg/dl Simva 219 mg/dl	Patients in whom hypercholesterolemia was secondary to conditions such as hypothyroidism, patients whose cholesterol to HDL ratio was ≤4, LDL cholesterol was <3.4 mmol/L, triglyceride concentrations were >4.0 mmol/L or those with combined hyperlipidemias in whom hypercholesterolemia was not a primary concern	4-week dietary-placebo run-in phase, then randomized to: parva 20 mg qd (n=105) or simva 20 mg qd (n=105) for 6 weeks.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Douste-Blazy et al. 1993 R, DB, MC, not ITT 273 patients randomized 6 weeks	Efficacy analysis for 268 patients. LDL-c reduction from baseline at 6 weeks: parva: 25% simva: 28.3% (p<0.01) HDL-c increase from baseline at 6 weeks: parva: 6.1% simva: 6.3% (NS) Trigs reduction from baseline at 6 weeks: parva: 12.9% simva: 13.8% (NS) Achieved LDL-c <130 mg/dl: 16% parva vs. 22% simva Achieved LDL-c <160 mg/dl: 53% parva vs. 60% simva	Reported ADEs were similar between groups. Two patients in each group stopped the statin due to ADEs and were not serious. No patient withdrew due to a laboratory ADE. Dose equivalence parva 20 mg ≈ or < simva 10 mg qd.
Lambrecht et al. 1993 R, DB, MC, not ITT 210 patients randomized 6 weeks	Efficacy analysis for 200 patients. LDL-c reduction from baseline at 6 weeks: parva: 29% simva: 38% (p<0.01) HDL-c increase from baseline at 6 weeks: parva: 7.3% simva: 6.7% (NS) Trigs reduction from baseline at 6 weeks: parva: 10.9% simva: 14.3% (NS) Achieved LDL-c <160 mg/dl: 78% simva vs. 64% parva (p=0.06) Achieved LDL-c <130 mg/dl: 46% simva vs. 19% parva (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 parva group. 3 patients withdrawn due to ADEs: 1 in simva (malaise) and 2 in parva (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.

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

Clinical Trial	Funding Source
Douste-Blazy et al. 1993 R, DB, MC, not ITT 273 patients randomized 6 weeks	Study supported by Merck.
Lambrecht et al. 1993 R, DB, MC, not ITT 210 patients randomized 6 weeks	Industry support not reported.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Lefebvre et al. 1992 R, DB, MC, not ITT 291 patients randomized 6 weeks	Men and women 18-79 years with total cholesterol ≥240 mg/dl Mean baseline LDL-c Prava 219 mg/dl Simva 223 mg/dl	Patients with plasma triglyceride levels >4.00 mmoL/L or a total cholesterol: HDL cholesterol ratio of <4.0, concomitant conditions such as myocardial infarction or coronary bypass surgery within the previous 2 months, or with other serious cardiovascular disease, established diabetes mellitus, hepatic or biliary disease or partial ileal bypass were excluded, poor mental function, history of drug or alcohol abuse or concurrent use of cimetidine, regular use of antacids, immunosuppressants such as cyclosporin or any investigational drug.	4-week dietary-placebo run-in phase, then randomized to: parva 10 mg qd (n=141) or simva 10 mg qd (n=142)
Lintott et al. 1993 R, DB, MC, not ITT 48 patients randomized 24 weeks	Men or women with hypercholesterolemia Mean baseline LDL-c Prava 243 mg/dl Simva 250 mg/dl	combined hyperlipidemia or primary hypertriglyceridemia, patients with hepatic or renal function outside the normal range, secondary hyperlipidemia or a coronary event within the previous 3 months.	6-week dietary-placebo phase then, randomization to: parva 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.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Lefebvre et al. 1992 R, DB, MC, not ITT 291 patients randomized 6 weeks	Efficacy analysis for 283 patients. LDL-c reduction from baseline at 6 weeks: parva: 22% simva:32% (p<0.01) HDL-c increase from baseline at 6 weeks: parva: 5% simva: 7% (p=0.06) Trigs reduction from baseline at 6 weeks: parva: 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 parva groups. Details not provided for all incidents. Equivalent doses not compared.
Lintott et al. 1993 R, DB, MC, not ITT 48 patients randomized 24 weeks	Efficacy analysis for 47 patients. LDL-c reduction from baseline at 6 weeks: parva: 17% simva: 29% (no p-value provided) LDL-c reduction from baseline at 18 weeks: parva: 27% simva: 38% (p=0.001) HDL-c increase from baseline at 18 weeks: parva: 7% simva: 11% (NS) Trigs reduction from baseline at 18 weeks: parva: unchanged at 18 weeks simva: 11.8% 18/24 simva vs. 22/23 parva 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 parva patient developed a rash and was withdrawn. Titrate to target, nonequivalent doses compared.

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

Clinical Trial	Funding Source
Lefebvre et al. 1992 R, DB, MC, not ITT 291 patients randomized 6 weeks	Study supported by Merck.
Lintott et al. 1993 R, DB, MC, not ITT 48 patients randomized 24 weeks	Study supported by Merck.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Malini et al. 1991 R, OL, ITT 100 patients randomized 6 weeks	Men and women 18-70 years with total cholesterol >240 mg/dl Mean baseline LDL-c Prava 205 mg/dl Simva 209 mg/dl	Patients with plasma triglyceride levels >4.00 mmoL/L or a total cholesterol: HDL cholesterol ratio of <4.0, concomitant conditions such as myocardial infarction or coronary bypass surgery within the previous 2 months, or with other serious cardiovascular, established DM, liver or biliary disease, or partial ileal bypass, poor mental function, history of drug or alcohol abuse, concurrent use of cimetidine, regular use of antacids, immunosuppressants or other investigational drugs,	4-week dietary-placebo run in phase then randomized to: parva 10 mg qd (n=50) or simva 10 mg qd (n=50)
Sasaki et al. 1997 R, OL, C, not ITT 74 patients randomized 16 weeks	Men or women with total cholesterol >220 mg/dl. Mean baseline LDL-c 177.7 mg/dl	patients with hypersensitivity to drugs; pregnant or lactating women and those suspected of being pregnant or a combination of these; patients with acute myocardial infarction or stroke; with severe liver dysfunction; hyperlipidemia associated with hypothyroidism, obstructive gallbladder, biliary diseases, pancreatitis, or immunologic abnormalities such as collagen diseases, or a combination of these; alcoholics or heavy alcohol drinkers; patients with hyperlipidemia induced by steroid hormones or other drugs; and patients who were considered inappropriate for the study by the attending physician for any other reason.	Observation period (duration not stated), then randomization to: parva 10 mg qd or simva 5 mg qd for 8 weeks - then switched to alternate statin for another 8 weeks.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Malini et al. 1991 R, OL, ITT 100 patients randomized 6 weeks	Efficacy analysis for 100 patients. LDL-c reduction from baseline at 6 weeks: parva: 21.8% simva 10 mg: 33.1% (p<0.01) HDL-c increase from baseline at 6 weeks: parva: 7% simva: 10% (p<0.05) Trigs reduction from baseline at 6 weeks: parva: 5.8% simva: 12.3% (p<0.01)	ADEs were reported in 4 parva patients vs. 2 simva patients. No patient withdrew from the study due to ADEs. Dose equivalence Equivalent doses not compared.
Sasaki et al. 1997 R, OL, C, not ITT 74 patients randomized 16 weeks	Efficacy analysis for 72 patients. LDL-c reduction from baseline at 8 weeks: parva: 23.1% simva: 31.1% (p<0.05) HDL-c increase from baseline at 8 weeks: parva: 6.6% simva: 7.9% (NS) Trigs reduction from baseline at 8 weeks: parva: 5.8% simva: 13% (NS) Achieved LDL-c goal: parva: 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 > parva 10 mg qd

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

Clinical Trial	Funding Source
Malini et al. 1991 R, OL, ITT 100 patients randomized 6 weeks	Industry support not reported.
Sasaki et al. 1997 R, OL, C, not ITT 74 patients randomized 16 weeks	Funding not reported.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Stalenhoef et al. 1993 R, DB, MC, not ITT 48 patients randomized 18 weeks	Men and women with primary hypercholesterolemia LDL-c >180 mg/dl <u>Mean baseline LDL-c</u> 316 mg/dl	Diabetes; use of lipid-lowering agents within the past 6 months, TG >=500 mg/dL, LDL-c >=250 mg/dL, documented history of CHD or other atherosclerotic disease, history of serious or hypersensitivity reactions to other statins; uncontrolled hypothyroidism; uncontrolled hypertension; acute liver disease or hepatic dysfunction; unexplained serum creatine kinase >3 x ULN; use of prohibited concomitant medications.	6-week dietary/placebo run-in period followed by randomization to: parva 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.
Steinhagen-Thiessen 1994 R, DB, MC, not ITT 281 patients randomized 12 weeks	Men or women 21-71 years with total cholesterol 220-280 mg/dl. <u>Mean baseline LDL-c</u> 174-176 mg/dl	Patients with diabetes [fasting glucose >6.94 mmol/L (125 mg/dL)] ;use of lipid lowering agents within the past 6 months; TG 5.65 mmol/L (500 mg/dL); LDL-C ≥ 6.48 mmol/L (250 mg/dL); documented history of CHD or other atherosclerotic disease; a history of known familial hypercholesterolemia; a history of serious or hypersensitivity reactions to other statins; uncontrolled hypothyroidism; uncontrolled hypertension; acute liver disease or hepatic dysfunction [hepatic transaminases or bilirubin ≥ 1.5 the upper limit of normal (ULN)]; unexplained serum creatine kinase (CK) >3 xULN; and use of prohibited concomitant medications.	4-week dietary/placebo run-in period followed by randomization to: parva 10 mg qd (n=138) or simva 5 mg qd (n=143) for 6 weeks. At 6 weeks, simva increased to 10 mg qd.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Stalenhoef et al. 1993 R, DB, MC, not ITT 48 patients randomized 18 weeks	Efficacy analysis for 46 patients. LDL-c reduction from baseline at 18 weeks: parva 40 mg: 33% (mean doses) simva 40 mg: 43% (p<0.01) HDL-c increase from baseline at 18 weeks: parva: 6% simva: 8% (NS) Trigs reduction from baseline at 18 weeks: parva: 13% simva: 15% (NS)	Two patients withdrew due to ADEs. No details provided. No clinically significant increases in ALT/AST or CK. Nonequivalent doses compared.
Steinhagen-Thiessen 1994 R, DB, MC, not ITT 281 patients randomized 12 weeks	Efficacy analysis for 273 patients. LDL-c reduction from baseline at 6 weeks: parva 10 mg: 17.7% simva 5 mg: 23.3% (p<0.01) LDL-c reduction from baseline at 12 weeks: parva 10 mg: 16.5% simva 10 mg: 26.8% (p<0.01) HDL-c increase from baseline at 12 weeks: parva 10 mg: 8.3% simva 10 mg: 8.1% (NS) Trigs reduction from baseline at 12 weeks: parva 10 mg: 4.2% simva 10 mg: 9.5% (NS) Achieved LDL-c <130 mg/dl: parva 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 parva 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 parva patient with CK elevation >10x ULN. No further details provided. Dose equivalence Simvastatin 5 and 10 mg > parva 10 mg qd

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

Clinical Trial	Funding Source
Stalenhoef et al. 1993 R, DB, MC, not ITT 48 patients randomized 18 weeks	Industry involvement not reported.
Steinhagen-Thiessen 1994 R, DB, MC, not ITT 281 patients randomized 12 weeks	Study supported by Merck.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Sweany et al., 1993 R, DB, MC, not ITT 550 patients 18 weeks	Men and women 18-71 years with LDL-c ≥160 mg/dl Mean baseline LDL-c Prava 212 mg/dl Simva 207 mg/dl	Presence of myocardial infarction, coronary bypass surgery and angioplasty, within the previous 3 months, unstable angina, cardiac or renal failure, hepatic disease, diabetes mellitus, secondary hypercholesterolemia, and hyperlipidemia type III, treatment with lipid lowering agents within 6 weeks or with probucol within 6 months before baseline and treatment with immunosuppressive drugs.	6-week dietary/placebo run-in phase, then randomized to: parva 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.
	Pravastatin vs. Misc		
Gratsianskii N, et al 2007 RCT status unknown, unknown, SC, not ITT Series 1 n=40 (n= 20 control, 20 parva) Series 2 n=90 (n=30 aorta, 29 aorta, 31 parva)	Men and postmenopausal women receiving no hormone-replacement therapy with ACS without stable ST elevation on day 1 after the development of anginal attack, which was the cause of hospitalization	Recent ACS, receiving statins, and patients with evident systemic inflammation.	Series 1- control vs. parva up to 60 mg for 14 days Series 2- atorva10, atorva40 or prava40 for 14 days

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Sweany et al., 1993 R, DB, MC, not ITT 550 patients 18 weeks	Efficacy analysis number of patients not reported. LDL-c reduction from baseline at 6 weeks: parva: 19% simva: 30% (p<0.01) LDL-c reduction from baseline at 18 weeks: (mean dose) parva 32 mg/d: 26% simva 27 mg/d: 38% (p<0.01) HDL-c increase from baseline at 18 weeks: parva 12% simva 15% (p<0.05) Trigs reduction from baseline at 18 weeks: parva 14% simva 18% (p<0.05) Achieved LDL-c <130 mg/dl 65% simva vs. 39% parva	5 patients in each group withdrew due to ADEs. Reasons in parva 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 parva users. 1 parva patient stopped due to myalgia and muscle cramps with CK 3-10x ULN. CK elevation in other myalgia reports not clinically significant. 2 simva patients had CK elevation > 10x ULN, attributed to exercise (simva continued without further problems). No clinically significant elevations in AST or ALT. Nonequivalent doses compared. Treat to target.
Gratsianskii N, et al 2007 RCT status unknown, unknown, SC, not ITT Series 1 n=40 (n= 20 control, 20 parva) Series 2 n=90 (n=30 aorta, 29 aorta, 31 parva)	LDL-c change at 14 days Series 1- control (n=13) NR vs.. Prava (n=10) -34% (p < 0.05) Series 2- atorva10 (n=23) -33% vs. atorva40 (n=23) -41% vs. Prava40 (n=25) -23% (atorva10 and prava40 vs. atorva40 p < 0.05)	NR

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

Clinical Trial	Funding Source
Sweany et al., 1993 R, DB, MC, not ITT 550 patients 18 weeks	Merck funded and participated in study.
Gratsianskii N, et al 2007 RCT status unknown, unknown, SC, not ITT Series 1 n=40 (n= 20 control, 20 parva) Series 2 n=90 (n=30 aorta, 29 aorta, 31 parva)	NR

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
	Rosuvastatin vs Atorvastatin		
Ballantyne C, et al 2006 (MERCURY II) RCT, OL, MC, AC, 1993 patients randomized (first 8 weeks rosuva20 = 392, atorva10 = 403, atorva20 = 395, simva20 = 402, simva40 = 401, second 8 weeks rosuva20 = 367, atorva10 = 185, atorva10 to rosuva10 191, atorva20 = 186, atorva20 to rosuva20 = 186, simva20 = 190, simva20 to rosuva10 = 183, simva40 = 191 simva 40 to rosuva20 = 189)	Men and women aged z18 years; high risk of CHD events; fasting LDL-C ≥130 yo<250 mg/dL; fasting TG <400 mg/dL **Baseline LDL-c** rosuva20 167.1 atorva10 169.0 atorva20 168.1 simva20 169.4 simva40 168.8	Pregnancy or lactation; history of homozygous familial percholesterolemia or known hyperlipoproteinemia types I, III, IV, or V; unstable arterial disease within 3 months of trial entry; uncontrolled hypertension; fasting serum glucose of >180 mg/dL; active liver disease or hepatic dysfunction; serum creatinine of >2.0 mg/dL; or unexplained serum creatine kinase (CK) levels >3 times ULN.	6 week dietary lead in, then randomized to rosuvastatin 20 mg, atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, or simvastatin 40 mg for 8 weeks. Patients either remained on starting treatment or switched to lower or milligram-equivalent doses of rosuvastatin for 8 more weeks.
Berne et al, 2005 **URANUS** R, DB, MC, not ITT 469 patients randomized 16 weeks	Men or women with a history of type 2 diabetes for at least 3 months, being treated with diet, oral antidiabetic medication, insulin, or a combination of these treatments, and fasting LDL-C of >=3.3 mmol/L and triglycerides <6.0 mmol/L at enrollment.	Type 1 diabetes, uncontrolled type 2 diabetes, uncontrolled hypothyroidism or hypertension, nephrotic syndrome or severe renal failure, active liver disease or hepatic dysfunction active arterial disease serum creatine kinase levels >3 X ULN, BMI >35, and known hypersensitivity to statins.	6-week dietary run-in, then randomization to: rosuva 10 mg or aorta 10 mg for 4 weeks, then 12-week period of dose titration if patient had not reached European guideline goal (LDL-c <117 mg/dL): rosuva 20 mg or aorta 20 mg for 4 weeks. Further dose titrations up to rosuva 40 mg or aorta 40 mg or 80 mg were performed at weeks 8 and 12 if patients were still not at goal.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Ballantyne C, et al 2006 (MERCURY II) RCT, OL, MC, AC, 1993 patients randomized (first 8 weeks rosuva20 = 392, atorva10 = 403, atorva20 = 395, simva20 = 402, simva40 = 401, second 8 weeks rosuva20 = 367, atorva10 = 185, atorva10 to rosuva10 191, atorva20 = 186, atorva20 to rosuva20 = 186, simva20 = 190, simva20 to rosuva10 = 183, simva40 = 191 simva 40 to rosuva20 = 189)	LDL-c change at 8 weeks rosuva20 -52.1% atorva10 -37.1%* atorva20 -43.3%* simva20 -34.2%* simva40 -41.2%* HDL-c change at 8 weeks rosuva20 6.9% atorva10 5.3% atorva20 3.7%* simva20 5.4% simva40 5.9% * p < 0 .0001 compared with rosuvastatin 20 mg. LDL-c change at 16 weeks rosuva20 -51.6% atorva10 -36.2% atorva10 to rosuva10 -46.6%* atorva20 -43.4% atorva20 to rosuva20 -50.8%* simva20 -32.1% simva20 to rosuva10 -45.1% * simva40 -39.6% simva 40 to rosuva20 -53.7%* *p < 0.001 for comparisons within treatment arms. HDL-c change at 16 weeks rosuva20 7.2% atorva10 -6.1% atorva10 to rosuva10 7.5% atorva20 4.0% atorva20 to rosuva20 5.3% simva20 4.3% simva20 to rosuva10 6.3% simva40 6.9% simva 40 to rosuva20 7.6%	**First 8 weeks n (%) rosuva20 vs. atorva10 vs. atorva20 vs. simva20 vs. simva40** Any adverse event, 150 (38.4%) vs.144 (36.0%) vs.126 (32.1%) 126 (31.5%) vs.152 (38.0%) Leading to death, 1 (0.3%) vs. 0 vs. 0 vs. 0 vs. 0 Leading to withdrawal, 15 (3.8%) vs. 12 (3.0%) vs. 7 (1.8%) vs. 16 (4.0%) vs. 9 (2.3%) Serious adverse events, 6 (1.5%) vs. 11 (2.8%) vs. 8 (2.0%) vs. 8 (2.0%) vs. 4 (1.0%) **Second 8 weeks n (%) rosuva10 vs. rosuva20 vs. atorva10 vs. atorva20 vs. simva20 vs. simva40** Any adverse event, 130 (34.9%) vs. 278 (37.6%) vs. 60 (32.4%) 72 (38.9%) vs. 58 (30.9%) vs. 51 (27.1%) Leading to death, 1 (0.3%) vs. 0 vs. 0 vs. 0 1 (0.5%) vs. 0 Leading to withdrawal, 9 (2.4%) vs. 7 (0.9%) vs. 1 (0.5%) vs. 4 (2.2%) vs. 1 (0.5%) vs. 1 (0.5%) Serious adverse events, 5 (1.3%) vs. 12 (1.6%) vs. 4 (2.2%) vs. 3 (1.6%) vs. 5 (2.7%) vs. 3 (1.6%)
Berne et al, 2005 **URANUS** R, DB, MC, not ITT 469 patients randomized 16 weeks	Efficacy analysis for 441 patients (least squares mean percentage change): LDL-c reduction from baseline to 16 weeks: rosuva 10 to 40 mg: ─52.3% aorta 10 to 80 mg: ─45.5% Difference: ─6.7% (95% CI ─8.8%, ─4.7%; p<0.0001) HDL-c increase from baseline to 16 weeks: rosuva 10 to 40 mg: 5.3% aorta 10 to 80 mg: 4.0% Difference: 1.3% (95% CI ─1.3%, 3.8%; p NS) Trig reduction from baseline to 16 weeks: rosuva 10 to 40 mg: ─21.2% aorta 10 to 80 mg: ─21.1% Difference: ─0.1% (95% CI ─5.6%, 5.3%; p NS)	**Overall adverse events:** **rosuva: 51%** **aorta: 53%** **Serious adverse events:** **rosuva: 0.86%** **aorta: 3.4%** **Withdrawals due to adverse events:** **rosuva: 1.3%** **aorta: 3.0%** **No cases of myopathy; myalgia in 3.4% of patients overall; no clinically important elevations in CK.**

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

Clinical Trial	Funding Source
Ballantyne C, et al 2006 (MERCURY II) RCT, OL, MC, AC, 1993 patients randomized (first 8 weeks rosuva20 = 392, atorva10 = 403, atorva20 = 395, simva20 = 402, simva40 = 401, second 8 weeks rosuva20 = 367, atorva10 = 185, atorva10 to rosuva10 191, atorva20 = 186, atorva20 to rosuva20 = 186, simva20 = 190, simva20 to rosuva10 = 183, simva40 = 191 simva 40 to rosuva20 = 189)	1 author from AstraZeneca
Berne et al, 2005 URANUS R, DB, MC, not ITT 469 patients randomized 16 weeks	Supported by AstraZeneca

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Betterridge D, et al 2007 (ANDROMEDA) RCT, DB, MC, AC, 509 patients randomized (mITT) (n=254(248) rosuva, 255(246) aorta) 16 weeks	Men and non-pregnant women aged at least 18 years who fulfilled WHO criteria for a diagnosis ofT2DM	Type 1 diabetes; HbA 1c > 9.0%; a history of CVD or familial hypercholesterolemia; an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥ 1.5 × upper limit of normal (ULN); resting diastolic or systolic blood pressure of > 95 mmHg or > 200 mmHg, respectively; an unexplained serum creatine kinase (CK) level > 3 × ULN.	4 week wash out, then rosuvastatin 10 mg or atorvastatin 10 mg for 8 weeks, after which doses were increased to 20 mg once daily for a second 8-week period.
Binbrek A, et al 2006 (DISCOVERY-Alpha) RCT, (2:1) OL, MC, ITT 1506 patients randomized (n= rosuvastatin, 1002 patients; atorvastatin, 504 patients)) 12 weeks	Male and female patients aged at least 18 years with primary hypercholesterolemia (LDL-C > 135 mg/dL] if LLT-naive or 120 mg/dL if switching; and triglycerides 400 mg/dL)and a 10-year coronary heart disease (CHD) risk >20% or a history of CHD or other established atherosclerotic disease	Familial hypercholesterolemia or dysbetalipoproteinemia; secondary dyslipidemia; hypersensitivity to statins; uncontrolled diabetes mellitus (DM) or hypertension; unstable CVD (including unstable angina); active hepatic disease or hepatic dysfunction ; unexplained serum creatine kinase (CK) >3 x ULN; women of childbearing age not using contraception, or pregnant or breastfeeding; and current treatment with medications not allowed during the study (lipid-modifying agents [e.g., fibrates, niacin/nicotinic acid, bile acid sequestrants, other statins, probucol, fish oils, lipid-modifying dietary supplements, food additives] or agents known to interact with statins and increase the risk for muscular adverse events [AEs] [e.g., cyclosporine, clarithromycin, erythromycin, fluconazole, ketoconazole, itraconazole]).	Naive had 4 week dietary run- in, switched did not, rosuvastatin 10 mg or atorvastatin 10 mg for 12 weeks.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Betterridge D, et al 2007 (ANDROMEDA) RCT, DB, MC, AC, 509 patients randomized (mITT) (n=254(248) rosuva, 255(246) aorta) 16 weeks	LDL-c change from baseline at 8 weeks: rosuva -51.8% vs.. aorta -40.3% (p = 0.001) HDL-c change from baseline at 8 weeks: rosuva 2.0% vs.. 3.6% aorta (p=0.170) LDL-C < 2.5 mmol/l at 8 weeks rosuva 94.1% vs.. atorva78.8% (p <0.001) LDL-c change from baseline at 16 weeks: rosuva -57.4% vs.. aorta -46.0% (p = 0.001) HDL-c change from baseline at 16 weeks: rosuva 1.9% vs.. 2.2 aorta (p=0.794) LDL-C < 2.5 mmol/l at 16 weeks rosuva 95.6% vs.. aorta 87.3% (p = 0.002)	Overall adverse events: rosuva 48.4%, atorva 53.7% Withdrawals due to adverse events: rosuva 5.9% , atorva 5.1% Most frequent adverse events: nasopharyngitis, lower respiratory tract infections, constipation, arthralgia, and diarrhea. Myopathy or rhabdomyolysis rosuva 0%, Atorva 0%
Binbrek A, et al 2006 (DISCOVERY-Alpha) RCT, (2:1) OL, MC, ITT 1506 patients randomized (n= rosuvastatin, 1002 patients; atorvastatin, 504 patients)) 12 weeks	LDL-c change from baseline at 12 weeks: LLT-naïve rosuva -44.7% vs.. aorta -33.9% (p < 0.001) Switched rosuva -32.0% vs.. aorta -26.5% (p = 0.006) HDL-c change from baseline at 12 weeks: LLT-naïve rosuva 4.7%% vs.. 1.7% aorta (p=0.109) Switched rosuva 2.6% vs.. aorta 1.3% (p = 0.524)	**Rosuva vs. aorta n(%)** Any AE 95 (9.5) vs. 52 (10.4) Led to treatment discontinuation 23 (2.3) vs. 14 (2.8) Serious t 12 (I .2) vs. 7 (I .4)[1 patient in each treatment group, the onset of the serious AE reported occurred before the commencement of study treatment] Led to death I (0.1) vs. 2 (0.4) Most frequent adverse events Headache 9 (0.9) vs 7 (1.4) Myalgia 6 (0.6) vs. 4 (0.8) Nausea 6 (0.6) vs. 4 (0.8) Dizziness 5 (0.5) vs. 4 (0.8) Diarrhea 4 (0.4) vs. 4 (0.8)

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

Clinical Trial	Funding Source
Betterridge D, et al 2007 (ANDROMEDA) RCT, DB, MC, AC, 509 patients randomized (mITT) (n=254(248) rosuva, 255(246) aorta) 16 weeks	AstraZeneca
Binbrek A, et al 2006 (DISCOVERY-Alpha) RCT, (2:1) OL, MC, ITT 1506 patients randomized (n= rosuvastatin, 1002 patients; atorvastatin, 504 patients)) 12 weeks	AstraZeneca,

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Blasetto et al, 2003; Shepherd et al, 2003 R, DB, MC 5 trials prospectively designed to allow pooling 2153 patients randomized (n=394 rosuva 5 mg, 392 rosuva 10 mg, 396 aorta 10 mg, 240 rosuva 5mg, 226 rosuva 10 mg, 250 simva 20 mg, 255 prava 20 mg) 12 weeks	Men and women age 18 or older with LDL-c ≥ 160 mg/dL and <250 mg/dL and triglyceride levels < 400 mg/dL Mean baseline LDL-c 3 pooled trials of rosuva vs aorta: rosuva 5mg: 188 mg/dL rosuva 10mg: 185 mg/dL aorta 10mg: 187 mg/dL 2 pooled trials of rosuva vs parva and simva: rosuva 5mg: 189 mg/dL rosuva 10mg: 187 mg/dL simva 20mg: 188 mg/dL parva 20mg: 189 mg/dL	Patients were excluded if they had disorders or were taking other medications known to affect lipid values or to present a potential safety concern	Rosuva 5 mg or 10 mg; aorta 10 mg; simva 20 mg; parva 20 mg

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Blasetto et al, 2003; Shepherd et al, 2003 R, DB, MC 5 trials prospectively designed to allow pooling 2153 patients randomized (n=394 rosuva 5 mg, 392 rosuva 10 mg, 396 aorta 10 mg, 240 rosuva 5mg, 226 rosuva 10 mg, 250 simva 20 mg, 255 prava 20 mg) 12 weeks	3 pooled trials of rosuva vs aorta: LDL-C reduction from baseline at week 12: rosuva 5mg: 41.9% (p<0.001 vs aorta); rosuva 10mg: 46.7% (p<0.001 vs aorta); aorta 10mg: 36.4% HDL-c increase from baseline at week 12: rosuva 5mg: 8.2% (p<0.01 vs aorta); rosuva 10mg: 8.9% (p<0.001 vs aorta); aorta 10mg: 5.5% Trigs decrease from baseline at week 12: rosuva 5mg: 16.4%; rosuva 10mg: 19.2%; aorta 10mg: 17.6% (NS) Achieved ATP-III LDL-c goal at week 12: rosuva 10 mg: 76% aorta 10 mg: 53% (p<0.001) 2 pooled trials of rosuva vs parva and simva: LDL-C reduction from baseline at week 12: rosuva 5mg: 40.6% (p<0.001 vs simva and parva); rosuva 10mg: 48.1% (p<0.001 vs simva and parva); parva 20mg 27.1%; simva 20mg 35.7% HDL-c increase from baseline at week 12: rosuva 5mg: 6.9%; rosuva 10mg: 9.1% (p<0.05 vs simva and parva); parva 20mg 6.2%; simva 20mg 6.2% Trigs decrease from baseline at week 12: rosuva 5mg: 14.9%; rosuva 10mg: 20.2% (p<0.01 vs simva and parva); parva 20mg 12.2%; simva 20mg 12.4%	No information on adverse events. Equivalent doses not compared

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

Clinical Trial	Funding Source
Blasetto et al, 2003; Shepherd et al, 2003 R, DB, MC 5 trials prospectively designed to allow pooling 2153 patients randomized (n=394 rosuva 5 mg, 392 rosuva 10 mg, 396 aorta 10 mg, 240 rosuva 5mg, 226 rosuva 10 mg, 250 simva 20 mg, 255 prava 20 mg) 12 weeks	Supported by AstraZeneca

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Bots A, et al, 2005 (Dutch DISCOVERY) RCT (3:1:1:1), DB, MC, AC, 1215 patients randomized (n=621 rosuva10, 189 atorva10, 194 simva20, 211 prava40) 16 weeks	Aged 18 years with type IIa or type IIb hypercholesterolemia and a 10-year cardiovascular risk of >20% or a history of CHD or other established atherosclerotic disease, fasting LDL-C of >3.5 mmol/l if untreated (not receiving lipid-lowering therapy in the 4 weeks before enrolment) or fasting LDL-C of >3.1 mmol/l if currently being treated with a start dose of other lipid-lowering therapy. Mean baseline LDL-C (SD) rosuva 4.46 (0.75) aorta 4.35 (0.73) simva 4.43 (0.70) parva 4.42 (0.75)	Familial hypercholesterolemia or type III hyperlipoproteinemia, secondary dyslipidemia (except diabetic dyslipidemia for patients with controlled diabetes), uncontrolled diabetes or hypertension, active liver disease or hepatic dysfunction, unstable CVD (including unstable angina), history of hypersensitivity to other statins, unexplained serum creatine kinase (CK) >3 times ULN and use of prohibited medications.	12- week treatment with rosuvastatin 10 mg, atorvastatin 10 mg, simvastatin 20 mg or pravastatin 40 mg.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Bots A, et al, 2005 (Dutch DISCOVERY) RCT (3:1:1:1), DB, MC, AC, 1215 patients randomized (n=621 rosuva10, 189 atorva10, 194 simva20, 211 prava40) 16 weeks	LDL-c change at 12 weeks: Naïve rosuva-45.6 atorva-37.6** simva -37.0** parva -32.9** Treated previously rosuva-22.6 atorva-11.3** simva --12.4* parva -6.9** *p < 0.01 vs. rosuva; **p < 0.001 vs. rosuva; HDL-c change at 12 weeks: Naïve rosuva 6.3 aorta 5.1 simva 3.7* parva 2.4** Treated previously rosuva 0.7 atorva-0.8 simva 1.1 parva -0.7 *p < 0.05 vs. rosuva. **p < 0.01 vs. rosuva	Rosuva vs. atorva vs. simva vs. prava n(%) Myalgia 22 (3.5) vs. 3 (1.6) vs. 3 (1.5) vs 5 (2.4) Headache 8 (1.3) vs. 8 (4.2) vs. 3 (1.5) vs. 3 (1.4) Cough 12 (1.9) vs. 1 (0.5) vs. 2 (1.0) vs. 6 (2.8) Fatigue 9 (1.4) vs. 1 (0.5) vs. 4 (2.1) vs. 5 (2.4) Eczema 8 (1.3) vs. 4 (2.1) vs. 2 (1.0) vs. 2 (0.9) Arthralgia 4 (0.6) vs. 2 (1.1) vs. 5 (2.6) vs. 4 (1.9) Back pain 6 (1.0) vs. 2 (1.1) vs. 3 (1.5) vs. 4 (1.9) Nausea 10 (1.6) vs. 1 (0.5) vs. 1 (0.5) vs. 2 (0.9) Constipation 6 (1.0) vs. 1 (0.5) vs. 4 (2.1) vs. 4 (1.9) Bronchitis (NOS) 6 (1.0) vs. 2 (1.1) vs. 1 (0.5) vs. 3 (1.4) Diarrhea (NOS) 5 (0.8) vs. 2 (1.1) vs. 3 (1.5) vs. 2 (0.9) Upper abdominal pain 5 (0.8) vs. 1 (0.5) vs. 2 (1.0) vs. 3 (1.4) Chest pain 7 (1.1) vs. 1 (0.5) vs. 2 (1.0) vs. 2 (0.9) Cystitis (NOS) 5 (0.8) vs. 3 (1.6) vs. 0 (0) vs.1 (0.5) Hypertension (aggravated) 3 (0.5) vs. 2 (1.1) vs. 5 (2.6) vs. 1 (0.5) Urinary tract infection (NOS) 5 (0.8) vs. 2 (1.1) vs. 1 (0.5) vs. 2 (0.9) Dyspepsia 4 (0.6) 0 (0) 3 (1.5) 1 (0.5) Influenza 2 (0.3) vs. 1 (0.5) vs. 2 (1.0) vs. 1 (0.5) Nasopharyngitis 4 (0.6) vs. 0 (0) vs. 1 (0.5) vs. 2 (0.9) NOS=not otherwise specified.

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

Clinical Trial	Funding Source
Bots A, et al, 2005 (Dutch DISCOVERY) RCT (3:1:1:1), DB, MC, AC, 1215 patients randomized (n=621 rosuva10, 189 atorva10, 194 simva20, 211 prava40) 16 weeks	AstraZeneca

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Brown et al, 2002 **R, DB, MC, not ITT** 477 patients randomized (n= 239 rosuva, 118 parva vs. 120 simva) 52 weeks	Men and women ≥18 years with LDL-c ≥160 and <250 mg/dl, and triglyceride levels ≤400 mg/dL Mean baseline LDL-c rosuva 5mg: 187.3 mg/dL rosuva 10mg: 187.0 mg/dL parva: 188.5 mg/dL simva: 188.0 mg/dL	Active hepatic disease or dysfunction, active arterial disease within 3 months, <10-year history of malignancy (unless basal or squamous cell skin carcinoma), uncontrolled hypertension, history of ketoacidosis within 5 years, uncontrolled hypothyroidism, serum creatine kinase (CK) concentration>3 times the upper limit of normal (ULN), familial hypercholesterolemia, serum creatinine concentration> 220 mol/L, fasting serum glucose >180 mg/dL or HbA1c >9%, alcohol or drug abuse, use of concomitant medications known to affect lipid values or present a potential safety concern, and known hypersensitivity to statins. Women of childbearing potential not using a reliable form of contraception or who were pregnant or lactating were also excluded.	6-week dietary run-in with NCEP Step 1 diet, then: rosuva 5 mg or rosuva 10 mg or parva 20 mg or simva 20 mg for 12 weeks. Then 40-week titration period to reach NCEP (ATP 2) targets or maximum dose of rosuva 80 mg, parva 40 mg or simva 80 mg.
Clearfield M, et al 2006 (PULSAR) RCT (1:1), OL, MC, ITT 996 patients randomized (n= 504 to rosuvastatin 10 mg, 492 to atorvastatin 20 mg) 6 weeks	Men and women, 18 years or more, hypercholesterolemia and either a history of CHD, clinical evidence of atherosclerosis or a CHD-risk equivalent , diabetes mellitus or ≥ 2 risk factors that confer a 10-year CHD-risk score > 20% Baseline LDL-C rosuva 165.1 aorta 164.9	History of statin-induced myopathy or a serious hypersensitivity to statins; patients considered to be unstable after a myocardial infarction (MI), unstable angina, myocardial revascularization or a transient ischemic attack or stroke; patients awaiting a planned myocardial revascularization; severe congestive heart failure; history of malignancy; history of known homozygous familial hypercholesterolemia; current active liver disease; uncontrolled hypothyroidism ; alcohol or drug abuse within the last 5 years, and initiation of hormone-replacement therapy or oral contraceptives within 3 months , women who were pregnant, breast-feeding or of child-bearing potential and not using a reliable form of contraception.	6 week dietary lead in then 6 weeks of RCT rosuva vs.. aorta

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Brown et al, 2002 **R, DB, MC, not ITT** 477 patients randomized (n= 239 rosuva, 118 parva vs. 120 simva) 52 weeks	Efficacy analysis for 472 patients. LDL-c reduction at 12 weeks: rosuva 5 mg: 39% (p<0.001 vs parva 20 mg; p<0.05 vs simva 20mg) rosuva 10 mg: 47% (p <0.001 vs parva 20 mg, ≤0.001 vs simva 20 mg) parva 20 mg: 27% simva 20 mg: 35% HDL increase at 12 weeks: rosuva 5 mg: 8.2% rosuva 10 mg: 11.9% (p<0.05 vs parva 20 mg) parva 20 mg: 8% simva 20 mg: 9% Trigs reduction at 12 weeks: rosuva 5 mg: 17.6% (p<0.05 vs simva 20 mg) rosuva 10 mg: 21.5% (p<0.01 vs parva 20 mg, p≤0.001 vs simva 20 mg) parva 20 mg: 11% simva 20 mg: 10% Achieved ATP III LDL-c goal at 12 weeks: rosuva 5 mg: 78% rosuva 10 mg: 88% parva 20 mg: 51% simva 20 mg: 63% (p-values not reported)	Withdrawals due to treatment-related adverse events:7 rosuva 5 mg, 7 rosuva 10 mg, 6 parva, 7 simva. 1 serious AE identified with treatment: simva patient with asthenia and chest pain, resolved with no change in treatment. Transient elevations in ALT >3x ULN without symptoms: 2 rosuva 5 mg, 0 rosuva 10 mg, 5 parva, 2 simva Equivalent doses not compared
Clearfield M, et al 2006 (PULSAR) RCT (1:1), OL, MC, ITT 996 patients randomized (n= 504 to rosuvastatin 10 mg, 492 to atorvastatin 20 mg) 6 weeks	LDL-c change from baseline at week 6: rosuva -44.6% vs. aorta -42.7% (p < 0.05) HDL-c change from baseline at week 6: rosuva 6.4% vs. atorva3.1% (p < 0.001) NCEP ATP III nonHDL-C goal of < 130 mg/dL rosuva 69.7% vs. aorta 65.0% (p = ns)	**Rosuvastatin 10 mg vs. Atorvastatin 20 mg n(%)** Any adverse event 139 (27.5) vs. 128 (26.1) Myalgia 24 (4.8) vs. 13 (2.6) Urinary tract infection 13 (2.6) vs. 16 (3.3) Headache 8 (1.6) vs. 7 (1.4) Nausea 4 (0.8) vs. 9 (1.8) Bone pain 8 (1.6) vs. 3 (0.6) Muscle cramp 5 (1.0) vs. 3 (0.6) Peripheral edema 3 (0.6) vs. 5 (1.0)

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

Clinical Trial	Funding Source
Brown et al, 2002 **R, DB, MC, not ITT** 477 patients randomized (n= 239 rosuva, 118 parva vs. 120 simva) 52 weeks	3 authors employed by AstraZeneca
Clearfield M, et al 2006 (PULSAR) RCT (1:1), OL, MC, ITT 996 patients randomized (n= 504 to rosuvastatin 10 mg, 492 to atorvastatin 20 mg) 6 weeks	AstraZeneca

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Davidson et al, 2002 **R, DB, MC, PC.** **519 patients randomized (n=132 placebo, 129 rosuva 5mg, 130 rosuva 10mg, 128 aorta 10mg)** **12 weeks**	Men and women age 18 and older with fasting LDL-c > 160 mg/dL and <250 mg/dL and fasting triglycerides < 400 mg/dL, and a score of 28 or less on section 1 of the Eating Pattern Assessment Tool (indicating compliance with NCEP step I diet). Mean baseline LDL-c rosuva 5mg: 188 mg/dL rosuva 10mg: 185 mg/dL aorta 10mg: 186 mg/dL	Active arterial disease within 3 months of trial entry, familial hypercholesterolemia, uncontrolled hypertension, active liver disease or hepatic dysfunction indicated by aspartate aminotransferase or alanine aminotransferase ≥1.5 times the upper limit of normal, serum creatine kinase >3 times the upper limit of normal, serum creatinine >220 mol/L (2.5 mg/dl), fasting serum glucose > 9.99 mmol/L (180 mg/dl), or glycated hemoglobin > 9%.	6-week dietary run-in with NCEP Step 1 diet 12 week trial with NCEP Step 1 diet and rosuvastatin 5 or 10 mg, atorvastatin 10 mg, or placebo once a day
Discovery-UK group, 2006 RCT (2:2:1), OL, MC, AC. **1874** patients randomized (1770 ITT) (n= 712 rosuva10, 709 aorta 10mg, 349 simva20) 12 weeks	18 years or more; with type Iia and IIb hypercholesterolemia, no previous statin treatment; LDL-C ≥ 3.5 mmol/L; fasting TG ≤ 4.52 mmol/L; a 10-year coronary heart disease (CHD) risk > 20%; or a history of CHD or other established atherosclerotic disease. **Baseline LDL-c mmol/L** rosuva10 4.5 atorva10 4.5 simva20 4.5	Active liver disease or hepatic dysfunction, known uncontrolled diabetes, uncontrolled hypertension and unexplained serum creatine kinase (CK) 3 x the upper limit of normal (ULN).	Rosuvastatin 10 mg, atorvastatin 10 mg or simvastatin 20 mg once daily for 12 weeks.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Davidson et al, 2002 **R, DB, MC, PC.** **519 patients randomized** **(n=132 placebo, 129 rosuva 5mg, 130 rosuva 10mg, 128 aorta 10mg)** **12 weeks**	LDL-c reduction from baseline at week 12: rosuva 5 mg: 40% (p< 0.01 vs aorta) rosuva 10 mg: 43% (p<0.001 vs aorta) aorta 10 mg: 35% HDL-c increase from baseline at week 12: rosuva 5 mg: 13% (p< 0.01 vs aorta) rosuva 10 mg: 12% (p< 0.05 vs aorta) aorta 10 mg: 8% Triglycerides reduction from baseline at week 12: rosuva 5 mg: 17% rosuva 10 mg: 19% aorta 10 mg: 19%	Withdrawals due to adverse events: 4 (3.1%) aorta, 6 (4.7%) rosuva 5mg, 4 (3.1%) rosuva 10mg. No clinically significant elevations in CK or ALT/AST. Types and incidences of adverse events similar across all treatment groups. Adverse events related to study treatment: 18 rosuva 5mg (14.1%), 17 rosuva 10mg (13.2%), 25 aorta (19.7%). Most frequently reported were constipation, flatulence, nausea, and myalgia. Serious adverse events in 5 (3.9%) aorta patients (angina, coronary vascular disorder, tooth disorder, pathologic fracture, hypertension, cholelithiasis, ileus, and pneumonia); 3 (2.3%) rosuva 5mg patients (angina, heart failure, meningitis, bone disorder, infection), 0 in rosuva 10mg group. No serious adverse event was considered by the investigators to be related to study drug. Equivalent doses not compared
Discovery-UK group, 2006 RCT (2:2:1), OL, MC, AC. **1874** patients randomized (1770 ITT) (n= 712 rosuva10, 709 aorta 10mg, 349 simva20) 12 weeks	LDL-c change at 12 weeks: rosuva10 -50% atorva10 -42% (vs. rosuva p < 0.0001) simva20 -40% (vs. rosuva p < 0.0001) 1998 European LDL-C goals were achieved rosuva10 89% atorva10 78% (vs. rosuva p < 0.0001) simva20 72% (vs. rosuva p < 0.0001) NCEP ATP III LDL-C goals rosuva10 76% atorva10 55% (vs. rosuva p < 0.0001) simva20 50% (vs. rosuva p < 0.0001)	**rosuva10 vs. atorva10 vs. simva20** **patients who reported adverse events** 47.7% vs. 46.5% vs. 46.4%. Discontinued treatment as a result of an AE 4.8% vs. 3.7% vs. 4.1% Lower respiratory tract infection 23 (3.1) vs. 24 (3.2) vs. 17 (4.7) Headache 20 (2.7) vs. 12 (1.6) vs. 13 (3.6) Constipation 23 (3.1) vs. 13 (1.7) vs. 5 (1.4) Upper respiratory tract infection 11 (1.5) vs. 18 (2.4) vs. 11 (3.0) Arthralgia 20 (2.7) vs. 11 (1.5) vs. 8 (2.2) Cough 16 (2.1) vs. 12 (1.6) vs. 10 (2.7) Pain in limb 21 (2.8) vs. 10 (1.3) vs. 5 (1.4) Myalgia 12 (1.6) vs. 13 (1.7) vs. 8 (2.2) Diarrhea 14 (1.9) vs. 13 (1.7) vs. 5 (1.4) Nausea 13 (1.7) vs. 9 (1.2) vs. 7 (1.9)

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

Clinical Trial	Funding Source
Davidson et al, 2002 **R, DB, MC, PC.** **519 patients randomized (n=132 placebo, 129 rosuva 5mg, 130 rosuva 10mg, 128 aorta 10mg)** **12 weeks**	Supported by a grant from AstraZeneca
Discovery-UK group, 2006 RCT (2:2:1), OL, MC, AC. **1874** patients randomized (1770 ITT) (n= 712 rosuva10, 709 aorta 10mg, 349 simva20) 12 weeks	AstraZeneca.

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Faergeman O, et al 2008 (ECLIPSE) RCT (1;1), OL, MC, AC. 1,036 patients were randomized (n (itt) = rosuva 522 (505), aorta 514(510).) 24 weeks	≥ 18 years with hypercholesterolemia and a history of CHD, LDL-C ≥160 to < 400 mg/dL, clinical evidence of atherosclerosis or a 10-year CHD risk score > 20% Mean baseline LDL-c rosuva 189.2 (21.0) aorta 188.3 (20.4)	History of statin-induced myopathy or a serious hypersensitivity reaction to statins, clinical instability after a cardiovascular event, homozygous familial hypercholesterolemia, uncontrolled hypothyroidism, severe hepatic impairment, and women who were pregnant or breastfeeding or of childbearing potential but not using contraception, unexplained CK ≥3x ULN and SCr >2.0 mg/dL.	6-week dietary lead-in period, randomized to daily treatment with rosuvastatin 10 mg or atorvastatin 10 mg for 6 weeks. Doses were increased incrementally (10–20– 40 mg rosuvastatin and 10–20–40–80 mg atorvastatin) every 6 weeks until the maximum doses were achieved (rosuvastatin 40 mg or atorvastatin 80 mg.
Ferdinand et al, 2006 R, Open, MC 774 patients randomized (rosuva 391, atorva 383) 6 week treatment period	African-American men and women aged 18 or older who were diagnosed with type IIa or IIb hypercholesterolemia. After dietary lead-in, patients were eligible for randomization if they had fasting LDL-C >=160 mg/dl and <=300 mg/dl and triglycerides <400 mg/dl. Mean baseline LDL-c: mean(SD) mg/dL Rosuva 10 mg: 191.8 (27.2), 20 mg: 189.6 (23.4) Atorva 10 mg: 189.1(29.0), 20 mg 191.9 (26.6)	History of homozygous familial hypercholesterolemia or known type I, III, or V hyperlipoproteinemia; active arterial disease (e.g., unstable angina, MI, TIA, CVA, CABG or angioplasty within 3 months of trial entry); uncontrolled hypertension; poorly controlled diabetes; active liver disease or dysfunction; unexplained serum creatine kinase levels >3 times ULN, and serum creatinine 2.0 mg/dL.	After a 6 week dietary lead-in, treatment for 6weeks: rosuva 10 or 20 mg or aorta 10 or 20 mg

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Faergeman O, et al 2008 (ECLIPSE) RCT (1;1), OL, MC, AC. 1,036 patients were randomized (n (itt) = rosuva 522 (505), aorta 514(510).) 24 weeks	NCEP ATP III LDL-C goal of < 100 mg/dl at 24 weeks rosuva 83.6% vs. aorta 74.6% p < 0.001 LDL-c change at 24 weeks rosuva –57.3 vs. aorta -52.2 p < 0.001 HDL-c change at 24 weeks rosuva 8.4 vs. atorva1.8 p < 0.001	Rosuva vs. aorta n(%) Any AE 282 (53.7) vs. 270 (52.5) Mild AE 153 (29.1) vs. 169 (32.9) Moderate AE 120 (22.9) vs. 94 (18.3) Treatment-related AE 66 (12.6) vs. 74 (14.4) Any SAE 33 (6.3) vs. 30 (5.8) Treatment-related SAE 0 (0) vs. 2 (0.4) AE leading to death 4 (0.8) vs.1 (0.2) Treatment-related AE leading to death 0 (0) vs. 0 (0) AE leading to premature discontinuation 39 (7.4) vs. 35 (6.8) Treatment-related AE leading to discontinuation 25 (4.8) vs. 31 (6.0)
Ferdinand et al, 2006 R, Open, MC 774 patients randomized (rosuva 391, atorva 383) 6 week treatment period	**% LDL-c reduction from baseline at 6 weeks:** **rosuva 10: ─37.1% (p<0.017 vs aorta 10)** **rosuva 20: ─45.7% (p<0.017 vs aorta 20)** **aorta 10: ─31.8%** **aorta 20: ─38.5%** **% HDL-c increase from baseline at 6 weeks:** **rosuva 10: +7.0% (p<0.017 vs aorta 20)** **rosuva 20: +6.5%** **aorta 10: +5.6%** **aorta 20: +3.7%** **% trig reduction from baseline at 6 weeks:** **rosuva 10: ─16.0%** **rosuva 20: ─20.9%** **aorta 10: ─17.1%** **aorta 20: ─19.6%** **% of patients meeting ATP III goal at 6 weeks:** **rosuva 10: ─66.1%** **rosuva 20: ─78.8%** **aorta 10: ─58.1%** **aorta 20: ─61.8%** **(no statistical comparisons)**	**Any adverse event:** **rosuva 10/20: 34.4%** **aorta 10/20: 33.6%** **Myalgia:** **rosuva 10: 2.6%** **rosuva 20: 3.6%** **aorta 10: 2.6%** **aorta 20: 1.0%** **Withdrawals due to AEs:** **rosuva 10/20: n=13 (3.3%)** **aorta 10/20: n=5 (1.3%)** **No deaths, myopathy, or rhabdomyolysis**

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

Clinical Trial	Funding Source
Faergeman O, et al 2008 (ECLIPSE) RCT (1;1), OL, MC, AC. 1,036 patients were randomized (n (itt) = rosuva 522 (505), aorta 514(510).) 24 weeks	AstraZeneca.
Ferdinand et al, 2006 R, Open, MC 774 patients randomized (rosuva 391, atorva 383) 6 week treatment period	Supported by AstraZeneca

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Fonseca et al, 2005 R, Open, MC 1124 patients randomized (rosuva 561, atorva 563) 12 week treatment period	Patients age 18 and older with primary hypercholesterolemia, with fasting LDL-C =>5 mg/dL above their NCEP ATP III goal by risk category. Mean baseline LDL-c: Statin-naïve: rosuva 171 mg/dL, atorva 174 mg/dL Switched: rosuva 165 mg/dL, atorva 161 mg/dL	Familial hypercholesterolemia, fasting TG levels >400 mg/dL, aspartate aminotransferase or alanine aminotransferase >1.5 times ULN, unstable angina, serum creatine kinase >3 times ULN, serum creatinine >2.5 mg/dL, uncontrolled hypertension, uncontrolled diabetes, history of hypersensitivity to other statins, history of alcohol or drug abuse and the use of other hypolipidemic drugs or disallowed medication, such as those with known interactions with statins (e.g., cyclosporine); women of childbearing potential and not using a reliable form of contraception, or who were pregnant or lactating.	Statin-naïve patients completed a 6-week dietary counseling period before entering the study, while switched patients entered the study directly with no dietary run-in. Treatment for 12 weeks: rosuva 10 mg (n=561) or aorta 10 mg (n=563)

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Fonseca et al, 2005 R, Open, MC 1124 patients randomized (rosuva 561, atorva 563) 12 week treatment period	**% LDL-c reduction from baseline at 12 weeks (statin-naïve patients):** **rosuva 10 (n=358): −40.9%** **aorta 10 (n=383): −34.8%** **(p<0.001)** **% LDL-c reduction from baseline at 12 weeks (switched patients):** **rosuva 10 (n=173): −35.3%** **aorta 10 (n=161): −27.5%** **(p<0.01)** **% HDL-c increase from baseline at 12 weeks (statin-naïve patients):** **rosuva 10 (n=358): 3.9%** **aorta 10 (n=383): 0.9%** **(p<0.05)** **% HDL-c increase from baseline at 12 weeks (switched patients):** **rosuva 10 (n=173): 2.5%** **aorta 10 (n=161): 0.0%** **(NS)** **% of patients achieving NCEP ATP III goal at 12 weeks:** **rosuva 10 (n not reported): 71.2%** **aorta 10 (n not reported): 61.4%** **(p<0.001)**	**Treatment-emergent adverse events:** **rosuva 10: 25.7%** **aorta 10: 21.2%** **Serious adverse events:** **rosuva 10: 1.2%** **aorta 10: 2.0%** **Discontinuations due to adverse events:** **rosuva 10: 4.8%** **aorta 10: 1.8%** **No cases of rhabdomyolysis, myopathy or renal insufficiency were observed.**

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

Clinical Trial	Funding Source
Fonseca et al, 2005 R, Open, MC 1124 patients randomized (rosuva 561, atorva 563) 12 week treatment period	Supported by AstraZeneca

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Herregods M, et al 2008 (Discovery-Belux) RCT (1;1), OL, MC, AC. 938 patients were randomized (n = rosuva 478, aorta 460) 24 weeks but primary outcome at 12 weeks	Patients (> or = 18 years) with primary hypercholesterolemia, with a low-density lipoprotein (LDL-C) level > 120 mg/dl (on treatment) or > 135 mg/dl (naive subjects), and with a statin Baseline LDL-c Naïve rosuva 166.5 Switched rosuva 159.9 Naïve aorta 169.4 Switched aorta 149.9	History of major adverse event with another HMG-CoA reductase inhibitor, active liver disease, unsuitable cardiovascular disease, severe renal or hepatic impairment, treatment with cyclosporin or any disallowed drug.	4 weeks of diet then randomized to rosuva 10 mg/day or aorta 10 mg/day for 12 weeks. Patients not at European LDL-C goal after 12 weeks and receiving ATV 10 were further switched to rosuva 10 mg for another 12 weeks. Patients not at goal with rosuva 10 mg were further titrated to rosuva 20 mg.
Jones et al, 2003 (STELLAR) R, OL, MC 2431 patients randomized (n=643 rosuva, 641 aorta, 655 simva, 492 parva) 6 weeks	Men and nonpregnant women age 18 or older with LDL-c >=160 and <250 mg/dL. Triglyceride levels <400 mg/dL. Mean baseline LDL-c (mg/dL) rosuva: 10mg 188; 20mg 187; 40mg 194 aorta: 10mg 189; 20mg 190; 40mg 189; 80mg 190 simva: 10mg 189; 20mg 189; 40mg 187; 80mg 190 parva: 10mg 189; 20mg 187; 40mg 190	History of sensitivity to statins; serious or unstable medical or psychological conditions; a history of heterozygous or homozygous familial hypercholesterolemia or familial dysbetalipoproteinemia; use of concomitant medications known to affect the lipid profile; a history of drug or alcohol abuse; unexplained increases in creatine kinase to > 3 times the upper limit of normal during the dietary lead-in period; alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin values ≥ 1.5 times the upper limit of normal during the dietary lead-in period; and participation in another investigational drug trial within 4 weeks of trial enrollment.	Rosuvastatin 10, 20, 40, or 80 mg; atorvastatin 10, 20, 40, or 80 mg; simvastatin 10, 20, 40, or 80 mg; pravastatin 10, 20, or 40 mg all once daily for 6 weeks.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Herregods M, et al 2008 (Discovery-Belux) RCT (1;1), OL, MC, AC. 938 patients were randomized (n = rosuva 478, aorta 460) 24 weeks but primary outcome at 12 weeks	LDL-c change from baseline at week 12: Naïve rosuva -47.4% (vs. naive aorta p < 0.001) Switched rosuva --32.0% (vs. switched aorta p = 0.08) Naïve aorta -38.1% Switched aorta -26.3% HDL-c change from baseline at week 12: Naïve rosuva 4.8% Switched rosuva 0.1% Naïve aorta 4.1% Switched aorta -0.2% Patients that achieved 2003 European goal (LDL-c<100 mg/dl) rosuva 72% aorta 46%	**rosuva vs. aorta** **myalgia 2.7% vs. 2.8%** **diarrhea 1.3% vs. 1.1%** **fatigue 1.3% vs.. 1.4%** **Nausea 1.3% vs. 0.4%** **muscle cramp 0.4% vs. 1.1%** **angina pectoris 0.8% vs. 0.4%** **upper abdominal pain 0.6% vs. 0.4%** **dizziness 0.8% vs. 0.2%**
Jones et al, 2003 (STELLAR) R, OL, MC 2431 patients randomized (n=643 rosuva, 641 aorta, 655 simva, 492 parva) 6 weeks	**LDL-c reduction from baseline at week 6:** **rosuva: 10mg 45.8%; 20mg 52.4%; 40mg 55%** **aorta: 10mg 36.8%; 20mg 42.6^; 40mg 47.8%; 80mg 51.1%** **simva: 10mg 28.3%; 20mg 35.0%; 40mg 38.8%; 80mg 45.8%** **parva: 10mg 20.1%; 20mg 24.4%; 40mg 29.7%** **equivalent doses:** **rosuva 10mg > aorta 20mg (p=0.026) and simva 40mg (p<0.001)** **rosuva 20mg > aorta 40mg (p<0.002) and simva 80mg (p<0.001)** **rosuva 40mg >aorta 80mg (p=0.006)** **HDL-c increase from baseline at week 6:** **rosuva: 10mg 7.7%; 20mg 9.5%; 40mg 9.6%** **aorta: 10mg 5.7%; 20mg 4.8%; 40mg 4.4% 80mg 2.1%** **simva: 10mg 5.3%; 20mg 6.0%; 40mg 5.2%; 80mg 6.8%** **parva: 10mg 3.2%; 20mg 4.4%; 40mg 5.6%** **equivalent doses:** **rosuva 10 mg = aorta 20 mg** **rosuva 10mg = simva 40 mg** **rosuva 20 mg > aorta 40mg (p<0.002)** **rosuva 20 mg = simva 80 mg** **Trigs reduction from baseline at week 6:** **rosuva: 10mg 19.8%; 20mg 23.7%; 40mg 26.1%** **aorta: 10mg 20.0%; 20mg 22.6%; 40mg 26.8%; 80mg 28.2%** **simva: 10mg 11.9%; 20mg 17.6%; 40mg 14.8%; 80mg 18.2%** **parva: 10mg 8.2%; 20mg 7.7%; 40mg 13.2%**	Withdrawals due to adverse events: 23/643 rosuva (3.6%), 25/641 aorta (3.9%), 19/655 simva (2.9%), 11/492 parva (2.2%); 46% of all patients reported adverse events, 29 patients had serious adverse events. 2 rosuva 80mg patients developed acute renal failure of uncertain etiology. Most common adverse events pain, pharyngitis, myalgia, headache. Dose equivalence (LDL-c lowering) rosuva 10mg > aorta 20mg and simva 40mg rosuva 20mg > aorta 40mg and simva 80mg rosuva 40mg >aorta 80mg

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

Clinical Trial	Funding Source
Herregods M, et al 2008 (Discovery-Belux) RCT (1;1), OL, MC, AC. 938 patients were randomized (n = rosuva 478, aorta 460) 24 weeks but primary outcome at 12 weeks	NR but 2 of authors work for AstraZeneca
Jones et al, 2003 (STELLAR) R, OL, MC 2431 patients randomized (n=643 rosuva, 641 aorta, 655 simva, 492 parva) 6 weeks	Supported by AstraZeneca

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Jukema et al, 2005 R, open-label, multicenter 461 patients randomized 18 week treatment period	Men and women aged 40 to 80 years with established cardiovascular disease, fasting HDL-c <40 mg/dL at visit 1 and baseline, and triglycerides <=400 mg/dL at visit 1. Mean baseline LDL-c: rosuva 139 mg/dL, atorva 143 mg/dL	Use of lipid-lowering drugs (including nicotinic acid), dietary supplements or food additives after enrollment, history of hypersensitivity to statins; pregnancy, lactations or childbearing potential without reliable contraceptive use; active arterial disease (unstable angina, MI, TIA, CVA, CABG or angioplasty) within 2 months of entry into the dietary lead-in phase; likely requirement for therapeutic coronary artery intervention within 6 months of randomization; uncontrolled hypertension; glycated hemoglobin >8% at enrollment, history of malignancy; uncontrolled hypothyroidism; homozygous familial hypercholesterolemia or type III hyperlipoproteinemia; history of alcohol and/or drug abuse; active liver disease; serum creatinine >180 µmol/L at enrollment; unexplained creatine kinase >3 times ULN at enrollment; received an investigational drug within 4 weeks before enrollment; serious or unstable medical or psychological conditions that could, in the opinion of the investigator, compromise the subject's safety or successful participation in the trial.	After a 6 week dietary lead-in, treatment for the first 6 weeks: rosuva 10 mg (n=230) or aorta 20 mg (n=231) At week 6, dosages increased for 6 weeks: rosuva 20 mg or aorta 40 mg At week 12, dosages increased for 6 weeks: rosuva 40 mg or aorta 80 mg
Kurabayashi, 2008 Open label, multicenter	Patients with hypercholesterolemia who had received atorvastatin (10 mg) once daily for at least 4 weeks. Aged 20 years or more and classified as being at high risk (JAS2002GL category B3, B4, or C). Mean baseline LDL-C: mean (SD) mg/dl rosuva 102.9(25.1) atorva 109.3(30.6)	Severe hypertension, type I diabetes, familial hypercholesterolemia, occurrence of cerebrovascular disease or myocardial infarction within the last 3 months, active hepatic disease, renal dysfunction, serum creatine kinase >1000 IU/L, hypothyroidism, pregnant women, women hoping to become pregnant.	Atorvastatin 10 mg (continued treatment) vs rosuvastatin 5 mg (switched treatment) for 8 weeks

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Jukema et al, 2005 R, open-label, multicenter 461 patients randomized 18 week treatment period	**% LDL-c reduction from baseline at 6, 12, and 18 weeks (p vs aorta):** **rosuva 10/20/40: –44.0% (p<0.05)/–50.4% (p<0.01)/–55.3% (p<0.0001)** **aorta 20/40/80: –38.4%/–45.1%/–48.1%** **% HDL-c increase from baseline at 6, 12, and 18 weeks:** **rosuva 10/20/40: 3.9%/5.5%/4.7%** **aorta 20/40/80: 4.1%/3.1%/2.7%** **All NS** **% trig reduction from baseline at 6, 12, and 18 weeks (p vs aorta):** **rosuva 10/20/40: –29.2% (p<0.05)/–32.2%/–35.4%** **aorta 20/40/80: –23.9%/–27.3%/–31.6%**	Occurrence of deaths, serious adverse events and withdrawals due to adverse events was low, with no differences noted between treatment groups (data not reported). 1 death in rosuva group (sudden death), 1 in aorta (liver metastasis), neither considered related to study treatment. 2 treatment related serious adverse events in aorta group (both high creatine kinase activities) Myalgia rosuva 7%, atorva 8%
Kurabayashi, 2008 Open label, multicenter	Percent change (SD) from baseline, atorvastatin vs rosuvastatin: LDL-C: -1.2% (14.7) vs -6.0% (17.0); p<0.01 HDL-C: -1.7% (11.7) vs 0.1 (12.2); NS Triglycerides: 5.2% (43.5) vs 12.9% (48.2); NS	atorvastatin vs rosuvastatin: Overall withdrawals: 3.3% vs 7.0% Withdrawals due to AE: 0 vs 3.8% Incidence of adverse events: 15.0% vs 15.8% Increased creatine kinase: 3.4% vs 2.4% 1 serious AE (rosuvastatin, tibial fracture, not related to study drug)

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

Clinical Trial	Funding Source
Jukema et al, 2005 R, open-label, multicenter 461 patients randomized 18 week treatment period	Supported by AstraZeneca
Kurabayashi, 2008 Open label, multicenter	Japan Heart Foundation

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Lloret R, et al 2006 (STARSHIP trial) RCT (1:1:1:1), OL, MC, AC. 696 (663 itt) patients were randomized (n = rosuva10 184, rosuva20 173, atorva10 168, atorva20 171) 6 weeks	Hispanic patients with low-density lipoprotein (LDL) cholesterol levels ≥130 and ≤300 mg/dl and triglyceride levels <400 mg/dl at medium or high risk of coronary heart disease Mean b**aseline LDL-c** rosuva 10mg: 165mg/dL rosuva 20mg: 160 mg/dL atorva 10mg: 165mg/dL atorva 20 mg:165mg/dL	history of homozygous familial hypercholesterolemia or known type I, III, or V hyperlipoproteinemia; active arterial disease (e.g., unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, coronary artery bypass grafting, or angioplasty within 3 months of entry); uncontrolled hypertension; poorly controlled diabetes; active liver disease or dysfunction indicated by hepatic transaminases or bilirubin levels ≥ 2 times the upper limit of normal; unexplained serum creatine kinase level > 3 times the upper limit of normal; and serum creatinine level > 2.0 mg/dl	6-week dietary lead-in phase, during which all lipid-lowering treatments were discontinued, eligible patients were randomized to receive 10 or 20 mg of rosuvastatin or 10 or 20 mg of atorvastatin for 6 weeks
Mazza F, et al, 2008 RCT, open-label, single center 106 patients randomized (n=52 rosuva, 54 aorta) 48 week treatment period	Male and female patients aged 18–65 years with primary hypercholesterolemia (LDL-C level >200 mg/dL) and at high risk for CHD Baselines LDL-c rosuva 217.74 ± 60.5 aorta 232.57 ± 65.17 NS Baseline HDL-c rosuva 56.55 ± 13.94 aorta 54 ± 15.40 NS	Myocardial infarction, unstable angina, stroke, transient ischemic attack, or uncontrolled hypertension within 3 months of enrollment; diabetes mellitus and or/other endocrine disorders; active liver disease or persistent elevations in liver function tests; significant abnormalities in creatine phosphokinase (CK); renal disease and acute or . chronic renal failure; hypersensitivity to statins; concomitant use of corticosteroids, ; use of immunosuppressants, macrolide antibacterials, azole antifungal agents and/or other lipid-lowering agents; diuretic or β-adrenoceptor blocker treatment for hypertension within 1 month of enrollment; drug or alcohol abuse; GI disorders; pregnancy and breast-feeding; ophthalmic abnormalities; night-shift work.	randomized to rosuvastatin 10 mg or atorvastatin 20 mg plus diet (American Heart Association Step II diet)
Milionis H, et al 2006 (ATOROS study) RCT, open-label, single center 120 patients randomized (n=60 rosuva, 60 aorta) 24 week treatment period	Men and women with dyslipidemia, totla cholesterol>240mg/dL at week 4 and 2 and triglycerides <350mg/dL Baseline LDL-c rosuva 205 (42) aorta 204 (40) Baseline HDL-c rosuva 48 (6) aorta 48 (8)	Abnormal liver function tests; Impaired renal function;) Diabetes mellitus; Raised thyroid-stimulating hormone (TSH) levels; any medical conditions that might preclude successful completion of the study.	6−week dietary lead-in period, randomized to rosuvastatin 10 mg/day or atorvastatin 20 mg/day . After 6 weeks on treatment the dose of the statin was increased for 18 weeks if the treatment goal was not achieved. Mean doses rosuva 12.5 mg and aorta 27.5 mg.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Lloret R, et al 2006 (STARSHIP trial) RCT (1:1:1:1), OL, MC, AC. 696 (663 itt) patients were randomized (n = rosuva10 184, rosuva20 173, atorva10 168, atorva20 171) 6 weeks	**LDL-c change at 6 weeks** rosuva10 -45% vs. atorva10 -36% (p < 0.0001) rosuva20 -50% vs. atorva20 -42% (p < 0.0001) **HDL-c change at 6 weeks** rosuva10 5.5% vs. atorva10 3.5% (p=ns) rosuva20 5.7% vs. atorva20 4.3% (p=ns) **achieving NCEP ATP III LDL cholesterol goals** rosuva10 78% vs. atorva10 60% (p=nr) rosuva20 88% vs. atorva20 73% (p=nr)	rosuva10 vs. rosuva20 vs. atorva10 vs. atorva20 n (%) Any adverse event 54 (30%) vs. 51 (30%) vs. 53 (32%) vs. 53 (31%) Leading to death 0 (0%) vs. 0 (0%) vs. 0 (0%) vs. 0 (0%) Leading to study discontinuation 4 (2.2%) vs. 7 (4.1%) vs. 3 (1.8%) vs. 2 (1.2%) Serious adverse events 2 (1.1%) vs. 1 (0.6%) vs. 4 (2.4%) vs. 2 (1.2%)
Mazza F, et al, 2008 RCT, open-label, single center 106 patients randomized (n=52 rosuva, 54 aorta) 48 week treatment period	LDL-c change from baseline at 48 weeks: rosuva –44.32% vs.. aorta –30% (p < 0.005) HDL-c change from baseline at 48 weeks: rosuva 4.52% vs.. aorta -2.04 (p=ns)	% mean change in lab values from baseline at 48 weeks: ALT (U/L ± SD) rosuva 24.64 (<0.005) aorta 4.33 (NS) No other adverse events were reported as occurring.
Milionis H, et al 2006 (ATOROS study) RCT, open-label, single center 120 patients randomized (n=60 rosuva, 60 aorta) 24 week treatment period	LDL-c change from baseline at 6 weeks: rosuva -43.9% aorta: -41.6% HDL-c change from baseline at 6 weeks: rosuva: 3.3% aorta: -1.6% Percentage of patients achieving LDL-c goal at 6weeks: rosuva 5 mg: 75% aorta 10 mg: 71.7% LDL-c at 24 weeks: rosuva 105 (21) vs. aorta 113(49)	rosuva vs. aorta Myalgia 5% vs. 5% Nausea 0 vs. 2%

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

Clinical Trial	Funding Source
Lloret R, et al 2006 (STARSHIP trial) RCT (1:1:1:1), OL, MC, AC. 696 (663 itt) patients were randomized (n = rosuva10 184, rosuva20 173, atorva10 168, atorva20 171) 6 weeks	AstraZeneca
Mazza F, et al, 2008 RCT, open-label, single center 106 patients randomized (n=52 rosuva, 54 aorta) 48 week treatment period	No sources of funding were used to assist in the preparation of this study
Milionis H, et al 2006 (ATOROS study) RCT, open-label, single center 120 patients randomized (n=60 rosuva, 60 aorta) 24 week treatment period	no company or institution supported it financially

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Olsson et al, 2002 **R, DB, MC** **412 patients randomized (n=138 rosuva 5mg, 134 rosuva 10mg, 140 aorta 10mg)** **52 weeks**	Men and women age 18 and older with LDL-c level between 160 and <250 mg/dL and an EPAT score 28 or less. Mean baseline LDL-c rosuva 5mg: 188.0 mg/dL rosuva 10mg:185.9 mg/dL aorta 10mg: 188.1mg/dL	Conventional exclusion criteria for lipid-modifying drugs under development were applied	5 or 10 mg rosuva or 10 mg aorta for 12 weeks, then titrated up to 80 mg if NCEP ATP-II LDL-c goal not met, for a total of 52 weeks.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Olsson et al, 2002 **R, DB, MC** **412 patients randomized (n=138 rosuva 5mg, 134 rosuva 10mg, 140 aorta 10mg)** **52 weeks**	**LDL-c reduction from baseline at 12 weeks:** **rosuva 5 mg: 46% (p<0.001 vs aorta)** **rosuva 10 mg: 50% (p<0.001 vs aorta)** **aorta 10 mg: 39%** **Percentage of patients achieving NCEP ATP-II LDL-c goal at 12 weeks:** **rosuva 5 mg: 86%** **rosuva 10 mg: 89%** **aorta 10 mg: 73%** **(NS)** **Percentage of patients achieving NCEP ATP-II LDL-c goal at 52 weeks:** **rosuva 5 mg: 88%** **rosuva 10 mg: 98%** **aorta 10 mg: 87%** **(NS)** **HDL-c increase from baseline at 12 weeks:** **rosuva 5 mg: 6% (NS vs aorta)** **rosuva 10 mg: 8% (NS vs aorta)** **aorta 10 mg: 6%** **Trigs reduction from baseline at 12 weeks:** **rosuva 5 mg: 15% (NS vs aorta)** **rosuva 10 mg: 19% (NS vs aorta)** **aorta 10 mg: 16%**	Adverse events considered to be treatment related occurred in 29% of rosuva 5mg, 27% rosuva 10mg, and 35% aorta 10mg patients. Most frequently reported were myalgia and GI complaints. Serious adverse events leading to withdrawal: rectal hemorrhage (rosuva 10mg(, serum creatinine elevation (rosuva 10mg), ALT/AST elevations (aorta 10mg). Total 28 withdrawals due to adverse events. Of these 5 rosuva 5mg, 5 rosuva 10mg, and 8 aorta 10mg had adverse events considered treatment-related. Equivalent doses not compared

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

Clinical Trial	Funding Source
Olsson et al, 2002 **R, DB, MC** **412 patients randomized (n=138 rosuva 5mg, 134 rosuva 10mg, 140 aorta 10mg)** **52 weeks**	Supported by a grant from AstraZeneca

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Paoletti et al., 2001 R, DB, MC, ITT 502 patients randomized 12 weeks	Men and women age≥18 years with hypercholesterolemia, fasting LDL-c ≥160 and <250 mg/dl, fasting trig ≤400 mg/dl Mean baseline LDL-c 189 mg/dl	Active arterial disease within 3 months of trial entry; familial hypercholesterolemia; uncontrolled hypertension; active liver disease or hepatic dysfunction indicated by AST, ALT, or bilirubin of ≥ 1.5 times the upper limit of normal; CK> 3 times the upper limit of normal; serum creatinine > 220 mol/l ; fasting serum glucose >9.99 mmol/ L or glycated hemoglobin >9%; history of alcohol or drug abuse; and use of cyclic hormonal therapy.	Screening phase, then randomization to: rosuva 5 or 10 mg parva 20 mg or simva 20 mg or for 12 weeks
Qu, 2009 Single center, double-blind	Outpatients with primary hypercholesterolemia. Mean baseline LDL-C: 150.4 (SD 25.7) mg/dl N=69	Liver disease or transaminase levels >1.5 times ULN, creatine kinase >1.5 times ULN, atrioventricular block and sinus bradycardia, acute or chronic renal failure, electrolyte disturbances, acute cerebrovascular disease or myocardial infarction within the preceding 3 months, or evidence of alcohol abuse.	Atorvastatin 10 mg vs rosuvastatin 10 mg for 12 weeks

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Paoletti et al., 2001 R, DB, MC, ITT 502 patients randomized 12 weeks	Efficacy analysis for 495 patients. LDL-c reduction from baseline at 12 weeks: rosuva 5 mg: 42% (p<0.001 vs parva, p<0.005 vs simva) rosuva 10mg: 49% (p<0.001 vs parva, p<0.001 vs simva) parva: 28% simva: 37% HDL-c increase from baseline at 12 weeks: rosuva 5 mg: 6% rosuva 10mg: 7% parva: 4% simva: 4% (NS) Trigs reduction from baseline at 12 weeks: rosuva 5 mg: 12% rosuva 10mg: 18% parva: 13% simva: 14% (NS) Achieved NCEP ATP II LDL-c goal: rosuva 5 mg: 71% rosuva 10mg: 87% parva: 53% simva: 64% (NS)	Serious AEs in 4 (3.5%) rosuva 10 mg patients (life-threatening cerebral hemorrhage, life threatening myocardial infarction, syncope, and cholecystitis plus cholelithiasis). No serious AEs considered by the investigator to be related to study treatment. Withdrawal due to AEs: rosuva 5 mg: 2 (1.6%) chest pain and infection, migraine rosuva 10 mg: 6 (5.2%) cerebral hemorrhage, diarrhea, CK increase and myalgia, headache and edema, urticaria) parva: 3 (2.2%) vasodilation and abdominal pain, dyspepsia, conjunctivitis) simva: 1 (0.8%) abdominal pain. ADEs: parva 19/136 (14%) vs simva 23/129 (18%). Most common ADEs: constipation (3 vs. 2), diarrhea ((1 vs. 1),, dyspepsia (2 vs. 3), pruritus (1 vs. 4), abdominal pain (2 vs. 4). ALT elevation in 2 simva, 3 rosuva 5 mg, and 1 rosuva 1 mg patients. No clinically significant ALT or CK elevations. Equivalent doses not compared
Qu, 2009 Single center, double-blind	Percent change from baseline, atorvastatin vs rosuvastatin: LDL-C: -36.1% vs -47.5%; p<0.05 HDL-C: 6.6% vs 9.1%; NS Triglycerides: 18.6% vs 20.5%; NS	No withdrawals reported. "No side effects related to the two agents were observed."

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

Clinical Trial	Funding Source
Paoletti et al., 2001 R, DB, MC, ITT 502 patients randomized 12 weeks	Sponsored by and one author employed by AstraZeneca
Qu, 2009 Single center, double-blind	National Basic Research Program and HI-TECH Technique and Development Program of China

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Rawlings, 2009 Multicenter (2 cardiology clinics), double-blind	Men with stale atherosclerosis and fasting LDL-C levels >=100 mg/dL off statin therapy. Presence of atherosclerosis determined by >=50% stenosis in at least one coronary artery at cardiac catheterization, history of previous myocardial infarction, previous angioplasty, previous coronary artery bypass graft, previous ischemic stroke, or documented peripheral arterial disease. Mean baseline LDL-C: 141 (SD 6) mg/dl N=30	Unstable angina or revascularization within 3 months of study enrollment, malignancy, chronic inflammatory disease, acute infection, history of myositis/myopathy, liver transaminases >2 times ULN, creatine phosphokinase greater than the ULN, and reluctance to discontinue statin therapy.	Atorvastatin 40 mg vs rosuvastatin 10 mg for 4 weeks
Schneck et al, 2003 **R, DB, MC** 374 patients randomized (n=165 aorta, 209 rosuva) 6 weeks	Men and women age 18 and older with hypercholesterolemia and without active arterial disease within 3 months of study entry or uncontrolled hypertension; LDL-c > 160 mg/dL but <250 mg/dL, triglycerides <400 mg/dL, and Eating Pattern Assessment Tool (to assess adherence to NCEP Step I diet) score of 28 or less. Mean baseline LDL-c aorta: 10mg 38.2%; 20mg:43.3%; 40mg 48.4%; 80 mg 53.5% rosuva: 5mg 41.5%; 10mg 46.6%; 20mg 51.7%; 40mg 56.8%; 80mg 61.9%	Pregnant or lactating women or women of childbearing potential not using a reliable form of contraception, as well as patients with a history of heterozygous or homozygous familial hypercholesterolemia or known type III hyperlipoproteinemia	Atorva 10, 20, 40, or 80 mg qd or rosuvastatin 5, 10, 20, 40, or 80 mg qd for 6 weeks.

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Rawlings, 2009 Multicenter (2 cardiology clinics), double-blind	Percent change from baseline, atorvastatin vs rosuvastatin: LDL-C: -45.2% vs -42.5%; p=0.28 HDL-C: 3.1% vs 1.6%; p=0.85 Triglycerides: -6.0% vs -40.2%; p=0.06	Not reported
Schneck et al, 2003 **R, DB, MC** 374 patients randomized (n=165 aorta, 209 rosuva) 6 weeks	**Reduction in LDL-c from baseline at 6 weeks:** **aorta: 10mg 38.2%; 20mg:43.3%; 40mg 48.4%; 80 mg 53.5%** **rosuva: 5mg 41.5%; 10mg 46.6%; 20mg 51.7%; 40mg 56.8%; 80mg 61.9%** **(p<0.001 difference vs aorta across dose range)** **Increase in HDL-c from baseline at 6 weeks:** **aorta: 10mg 5.0%; 20mg 7.6%; 40mg 4.1%; 80mg 2.1%** **rosuva: 5mg 7.4%; 10mg 6.0%; 20mg 9.1%; 40mg: 12.3%; 80mg 9.6%** **(NS)** **Reduction in trigs from baseline at 6 weeks:** **aorta: 10mg: 17.5%; 20mg 25.6%; 40mg 27.2%; 80mg 34.5%** **rosuva: 5mg 23.1%; 10mg 22.1%; 20mg 18.4%; 40mg 25.7%; 80mg 19.7%** **(NS)**	Any adverse event: 51.2% rosuva vs 47.9% aorta (NS); no consistent relation in occurrence of individual treatment-emergent adverse events to doses of either drug. Withdrawals due to adverse events infrequent (1 patient each in rosuva 10 mg, 20 mg, 80 mg groups, aorta 10 mg 40 mg, and 80 mg groups). Most common adverse events pharyngitis, headache, and pain. Dose equivalence (LDL-c lowering) rosuva 5mg > aorta 20mg rosuva 10mg > aorta 20mg rosuva 20mg > aorta 40mg rosuva 40mg > aorta 80mg

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

Clinical Trial	Funding Source
Rawlings, 2009 Multicenter (2 cardiology clinics), double-blind	NIH and Foundations
Schneck et al, 2003 **R, DB, MC** 374 patients randomized (n=165 aorta, 209 rosuva) 6 weeks	Supported by AstraZeneca Pharmaceuticals

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention

Schuster et al. 2004
R,OL,MC,ITT
 	
5-arm trial that included statin switching (to rosuvastatin) at 8 weeks
 	
3140 patients randomized
16 weeks of treatment
	Patients aged >=18 years, with CHD or other atherosclerotic disease, type 2 diabetes, a CHD risk >20% over 10 years, with LDL-c levels>=115 mg/dL and trig <400 mg/dL; LDL-c measurements had to be within 15% of each other during the lead-in period.
	
	Baseline LDL-c levels:
	Rosuv 10 mg: 164.9 mg/dL
	Atorva 10 mg: 162.2 mg/dL
	Atorva 20 mg: 167.5 mg/dL
	Simva 20 mg: 165.5 mg/dL
	Prava 40 mg: 163.8 mg/dL
		Pregnant and lactating women, women not using reliable contraception, patients with a history of homozygous familial hypercholesterolemia or known type III hyperlipoproteinemia, with active arterial disease (e.g., unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, or coronary revascularization procedure within 2 months of screening), uncontrolled hypertension, active liver disease or hepatic dysfunction (hepatic transaminases or bilirubin levels >=1.5 times upper limit of normal [ULN]), unexplained serum creatine kinase elevation >3 times ULN, and serum creatinine >220 micromol/L.	6 week dietary lead-in phase, then randomization to 5 arm trial system (drug a for 8 weeks then drug b or c for eight additional weeks):
			rosuv 10 mg (n=538), to rosuv 10 mg (n=521);
			
			aorta 10 mg (n=529), to rosuv 10 mg (n=276) or aorta 10 mg (n=240);
			
			aorta 20 mg (n=925), to rosuv 10 mg (n=293), rosuv 20 mg (n=305), or aorta 20 mg (n=299);
			
			simva 20 mg (n=543), to rosuv 10 mg (n=277) or simva 20 mg (n=250);
			
			parva 40 mg (n=521), to rosuv 10 mg (n=253) or parva 40 mg (n=253).

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Schuster et al.	% LDL-c reduction from baseline to 8 weeks:	"Occurrence of deaths, serious adverse events (SAE's), and withdrawals due
2004	Rosuv 10 mg (n=521): -47.0%	to adverse events (AE's) were low, with no differences noted among the
R,OL,MC,ITT	Atorva 10 mg (n=240): -37.2%	treatment groups." 8 patients died during the trial, but those deaths occurred
	Atorva 20 mg (n=299): -43.7%	from "causes that would be expected in such a patient population (i.e.,
5-arm trial that included	Simva 20 mg (n=250): -35.4%	cardiovascular events=4, malignancy=2, pneumonia=1, and subdural
statin switching (to	Prava 40 mg (n=253): -31.0%	hematoma=1". No treatment-related AE's leading to death nor any treatment-
rosuvastatin) at 8 weeks	(p<0.0001 for all comparisons vs rosuva 10 mg)	related SAE's are reported. SAE's or AE's are not always categorized by drug
	% HDL-c increase from baseline to 8 weeks:	type.
3140 patients	Rosuv 10 mg (n=521): +9.2%	
randomized	Atorva 10 mg (n=240): +6.8% (p<0.01 vs rosuva 10 mg)	Myalgia - reported in 1.9% of patients in period 1 and 0.9% of patients in
16 weeks of treatment	Atorva 20 mg (n=299): +5.7% (p<0.0001 vs rosuva 10 mg)	period 2.
	Simva 20 mg (n=250): +8.0% (NS vs rosuva 10 mg)	No cases of myopathy were reported (creatine kinase >10 times ULN and
	Prava 40 mg (n=253): +7.6% (NS vs rosuva 10 mg)	muscle symptoms).
	% trig reduction from baseline to 8 weeks:	Atorva 20 mg and rosuv 10 mg each had 1 case of asymptomatic increase in
	Rosuv 10 mg (n=521): -18.9% (p<0.01 vs rosuva 10 mg)	creatine kinase >10 times ULN; both resolved during continued study
	Atorva 10 mg (n=240): -15.9% (NS vs rosuva 10 mg)	treatment.
	Atorva 20 mg (n=299): -18.3% (NS vs rosuva 10 mg)	No patients had increases in hepatic transaminases >3 times ULN and >=
	Simva 20 mg (n=250): -13.5% (p<0.01 vs rosuva 10 mg)	consecutive measurements.
	Prava 40 mg (n=253): -10.5% (p<0.0001 vs rosuva 10 mg)	
	Proportion of patients achieving the ATP III LDL-c goals at week 8:	
	Rosuv 10mg (n=538): 80%	
	Atorva 10 mg (n=529): 63% (p<0.0001 vs rosuva 10 mg)	
	Atorva 20 mg (n=925): 74% (p<0.01 vs rosuva 10 mg)	
	Simva 20 mg (n=543): 54% (p<0.0001 vs rosuva 10 mg)	
	Prava 40 mg (n=521): 45% (p<0.0001 vs rosuva 10 mg)	

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

Clinical Trial	Funding Source
Schuster et al. 2004 R,OL,MC,ITT 5-arm trial that included statin switching (to rosuvastatin) at 8 weeks 3140 patients randomized 16 weeks of treatment	Sponsored by Astra Zeneca

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Schwartz et al, 2004 R, DB, MC 382 patients randomized 24 week treatment period	Patients aged >18 years, with LDL-C levels >=160 and< 250 mg/dL, and trig levels <=400 mg/dL, and documented atherosclerosis, Type 2 diabetes, or both, assessed. Patients with score of <=28 on Eating Pattern Assessment Tool, fasting LDL-C levels >160mg/dL and trig levels <400 mg/dL at 2 consecutive measurements were randomized. <u>Mean baseline LDL-c levels:</u> Rosuv 5/20/80: 188 mg/dL Rosuv 10/40/80: 186 mg/dL Atorv 10/40/80: 188 mg/dL	Pregnant women, patients currently taking concomitant drugs known to affect the lipid profile or to present a potential safety concern, a history of active arterial disease (e.g., unstable angina, myocardial infarction, transient ischemic attack, or cerebrovascular accident) or coronary revascularization procedure within 3 months of trial entry, heterozygous or homozygous familial hypercholesterolemia, uncontrolled hypertension, uncontrolled hyperthyroidism, history of malignancy, active liver disease or dysfunction indicated by AST or ALT of >= 1.5 times the upper limit of normal (ULN), serum creatine kinase >3 times ULN, serum creatinine >2.5mg/dL, or uncontrolled diabetes (fasting serum glucose >9.99 mmol/L or hemoglobin A1c>9% recorded during the lead-in period).	<u>After a 6 week dietary lead-in, treatment for the first 12 weeks:</u> rosuv 5 mg (n=127) once daily or rosuv 10 mg (n=128) once daily or atorv 10 mg (n=128) once daily <u>If LDL-c remained >50 mg/dl, then the doses were uptitrated at weeks 12 and 18 to:</u> rosuv 5 mg became 20 mg and then 80 mg (rosuv 5/20/80) rosuv 10 mg became 40 mg and then 80 mg (rosuv 10/40/80) atorv 10 mg became 40 mg and then 80 mg (atorv 10/40/80)

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Schwartz et al, 2004 R, DB, MC 382 patients randomized 24 week treatment period	Efficacy analysis for 382 patients: **% LDL-C change from baseline** 12 weeks : Rosuva 5 mg: -39.81 (P=<0.1); Rosuva 10mg: -47.1 (P=<.001); Atorva 10 mg: .35.0; 18 weeks Rosuva 5/20mg:-51.6 (P=<0.1); Rosuva 10/40mg: -58.8 (P=<0.001); Atovra 10/40: -47.2 24 weeks Rosuva 5/20/80mg: -59.61 (P=<.001); Atorva 10/40/80 and 5/20/80:mg:-52.0 **% HDL-C increase from baseline** 12 weeks Rosuva 5: 6.6 (P=<.01); Rosuva 10mg: 7.7 (P=<.001); Atorva 10mg: 2.7 18 weeks Rosuva 5/20: 8.3 (P=<.001); Rosuva 10/40mg:10 (<.001); Atorva 10/40: 1.4 24 weeks Atorva 10/40/80: 0.9; Rosuva combined 5/20/80 & 10/40/80: 8 (P=<.001) **% Trig reduction from baseline** 12 weeks Rosuva 5mg: -17.4; Rosuva 10 mg: -19.8; Atorva 10 mg: -17.8 18 weeks Rosuva 5/20mg: -20.7; Rosuva 10/40mg: -22.9; Atorva 10/40mg: -22.1 24 weeks Rosuva combined 5/20/80 & 10/40/80: -24.61; Atorva 10/40/80: -27	"Although adverse events were frequently reported in these high-risk patients, they were generally mild and not attributed to trial medication." Most common AEs pharyngitis, pain, myalgia **Any adverse event (AE):** rosuv 5/20/80: n=116 (91%) rosuv 10/40/80: n=113 (88%) atorv 10/40/80: n=101 (80%) **AEs considered treatment-related:** rosuv 5/20/80: n=36 (28%) rosuv 10/40/80: n=38 (30%) atorv 10/40/80: n=35 (28%) **Serious AEs:** rosuv 5/20/80: n=12 (9%) rosuv 10/40/80: n=8 (6%) atorv 10/40/80: n=7 (6%) **Withdrawals due to AEs:** rosuv 5/20/80: n=5 (4%) rosuv 10/40/80: n=7 (6%) atorv 10/40/80: n=6 (5%)

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

Clinical Trial	Funding Source
Schwartz et al, 2004 R, DB, MC 382 patients randomized 24 week treatment period	Sponsored by Astra Zeneca

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Stalenhoef et al. 2005 R, DB, MC, PC, not ITT (COMETS) 401 patients randomized 12 weeks	Men and women >=18 years with the metabolic syndrome, defined by presence of at least 3 of the following: abdominal obesity, TG >=150 mg/dL, HDL-c <40mg/dL for men and <50mg/dL for women, blood pressure >=130/85 or receiving antihypertensive treatment, and fasting blood glucose >=110 mg/dL. Also required to have LDL-c >=130 mg/dL and additional multiple risk factors conferring a 10-year CHD risk score of >10%. Patients with diabetes excluded.	Patients with diabetes [fasting glucose >6.94 mmol/L (125 mg/dL)] were excluded, use of lipid lowering agents within the past 6 months; TG ≥ 5.65 mmol/L (500 mg/dL); LDL-C ≥ 6.48 mmol/L (250 mg/dL); documented history of CHD or other atherosclerotic disease; a history of known familial hypercholesterolemia; a history of serious or hypersensitivity reactions to other statins; uncontrolled hypothyroidism; uncontrolled hypertension; acute liver disease or hepatic dysfunction [hepatic transaminases or bilirubin ≥1.5X the upper limit of normal (ULN)]; unexplained serum creatine kinase (CK) >3X ULN; and use of prohibited concomitant medications.	After 4-week dietary lead-in rosuva 10 mg or aorta 10 mg or placebo for 6 weeks, then aorta rosuva 10 mg or aorta 20 mg for 6 weeks (placebo group also switched to rosuva 20 mg)

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Stalenhoef et al. 2005	Efficacy analysis for 397 patients:	**Overall adverse events:**
R, DB, MC, PC, not ITT	LDL-c reduction from baseline to 6 weeks:	**rosuva (weeks 1-6) 25.2%; (weeks 6-12) 22.2%**
(COMETS)	rosuva 10 mg: ─42.7% (p<0.001 vs aorta)	**aorta: (weeks 1-6) 25.3%; (weeks 6-12) 20.7%**
	aorta 10 mg: ─36.6%	
401 patients randomized	placebo: ─0.3%	**Serious adverse events:**
12 weeks	LDL-c reduction from baseline to 12 weeks:	**rosuva: (weeks 1-6) 0%; (weeks 6-12) 0.6%**
	rosuva 10 mg: ─48.9% (p<0.001 vs aorta)	**aorta: (weeks 1-6) 1.9%; (weeks 6-12) 0.7%**
	aorta 10 mg: ─42.5%	
	HDL-c increase from baseline to 6 weeks:	**Withdrawals due to adverse events:**
	rosuva 10 mg: 9.5% (p<0.01 vs aorta)	**rosuva: (weeks 1-6) 1.2%; (weeks 6-12) 1.3%**
	aorta 10 mg: 5.1%	**aorta: (weeks 1-6) 1.9%; (weeks 6-12) 0.7%**
	placebo: 1.1%	
	HDL-c increase from baseline to 12 weeks:	
	rosuva 10 mg: 10.4% (p<0.01 vs aorta)	
	aorta 10 mg: 5.8%	
	Trig reduction from baseline to 6 weeks:	
	rosuva 10 mg: ─19.1% (NS)	
	aorta 10 mg: ─20.9%	
	placebo: ─2.8%	
	Trig reduction from baseline to 12 weeks:	
	rosuva 10 mg: ─22.9% (NS)	
	aorta 10 mg: ─25.2%	
	Patients meeting NCEP ATP III goal at 6 weeks:	
	rosuva 10 mg: ─83% (p<0.05 vs aorta)	
	aorta 10 mg: ─72%	
	placebo: ─10%	
	Patients meeting NCEP ATP III goal at 12 weeks:	
	rosuva 10 mg: ─91% (p<0.001 vs aorta)	
	aorta 10 mg: ─79%	

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

Clinical Trial	Funding Source
Stalenhoef et al. 2005 **R, DB, MC, PC, not ITT** **(COMETS)** 401 patients randomized 12 weeks	Supported by AstraZeneca

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Strandberg et al, 2004 **R (2:1), OL, MC, 2-arm study, ITT** 1024 patients randomized (n=686 to rosuv 10 mg/d, n=338 to atorv 10 mg/d) 12 weeks	Men and women >=18 years with LDL-c level >135 mg/dL for statin-naïve patients or >120 mg/dL in patients using the starting dose of another lipid-lowering drug. They had to be at high risk for CHD and have primary hypercholesterolemia. Mean baseline LDL-c rosuva 10mg: 174 mg/dL aorta 10mg: 170 mg/dL	A history of serious adverse events or hypersensitivity to an hMG-CoA reductase inhibitor other than the study drugs; active hepatic disease; homozygous or heterozygous familial hypercholesterolemia (FH); unstable angina; elevated serum creatinine concentration (>220 micromol/L [2.5 mg/dL]) or treatment with a disallowed drug, such as those with known interactions with statins (i.e., cyclosporine).	rosuv 10 mg/d atorv 10 mg PO OD optional extension period for rosuv pts who did not have access to drug commercially, and for atorv pts who did not achieve the 1998 JTF goal for LDL-c after 12 weeks. Rosuv could be up-titrated at 12 wk intervals to 20 mg/d and then to 40 mg/d to achieve the 1998 JTF LDL-c goal (1998 target of <116 mg/dL; JTF 2003 target of <97 mg/dL).

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Strandberg et al, 2004 **R (2:1), OL, MC, 2-arm study, ITT** 1024 patients randomized (n=686 to rosuv 10 mg/d, n=338 to atorv 10 mg/d) 12 weeks	Efficacy analysis for 911 patients (rosuv 10mg/d, n= 627; atorv 10mg/d, n= 284) **LDL-c levels at 12 weeks:** rosuv 10 mg: 89 mg/dL atorv 10 mg: 104 mg/dL % **LDL-c reduction from baseline at 12 weeks:** rosuv 10 mg: -46.92 % change (p< 0.05 vs. atorv) atorv 10 mg: -38.07 % change from baseline % **HDL-c increase 12 weeks after baseline:** rosuv 10 mg: 4.00 % increase (p<0.05 vs. atorv) atorv 10 mg: 1.88 increase **% decrease in trig levels at 12 weeks:** rosuv 10 mg: -14.55% (p<0.05 vs. atorv) atorv 10 mg: -13.98% **% patients reaching JTF LDL-c targets after 12 weeks:** (1998 target of <116 mg/dL; 2003 target of <97 mg/dL) rosuv: 83.4%; ~73% (p<0.001 vs. atorv) atorv: 68.3%; ~51.1%	**Patients experiencing any AE (estimated from graph)**: Rosuv ~38% (n=261) Atorv ~37% (n=125). Rosuv: 1 patient had melena (later diagnosed as duodenal ulcer); 1 patient having a history of peptic ulcer disease and receiving concomitant treatment with a NSAID (diclofenac) had vomiting; 1 patient had myopathy accompanied by increased creatine levels Atorv: 1 patient had proteinuria found to be non-treatment related **AE's in rosuv vs. atorv:** *n=AE incidence (%)/ n=led to discontinuation (%)* muscle pain/myalgia: 18(2.6%)/ 13(1.9%) vs. 4(1.2%)/ 3(0.9%) nausea: 12(1.7%)/ 7(1.0%) vs.5(1.5%)/ 3(0.9%) increased ALT: 11(1.6%)/ 2(0.3%) vs. 1(0.3%)/ 0(0%) increased AST: 8(1.2%)/ 0(0%) vs. 3(0.9%)/ 0(0%) increased creatine kinase (CK): 6(0.9%)/ 0(0%) vs. 6(1.8%)/ 1(0.3%) headache: 6(0.9%)/ 2(0.3%) vs. 4(1.2%)/ 3(0.9%) **Total withdrawals due to AEs (some patients experienced >1 adverse event):** Rosuv: n=24 (3.5%) Atorv: n=10 (3.0%)

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

Clinical Trial	Funding Source
Strandberg et al, 2004 **R (2:1), OL, MC, 2-arm study, ITT** 1024 patients randomized (n=686 to rosuv 10 mg/d, n=338 to atorv 10 mg/d) 12 weeks	Supported by a grant from AstraZeneca

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
Wolffenbuttel et al. 2005 R, Open-label, MC 263 patients randomized (N=263) 18 week treatment period	Men and women with type 2 diabetes who had received treatment for diabetes for at least 3 months, older than 18 years, with fasting LDL-c concentrations of >=130 mg/dL in statin-naïve patients or >115 to <=193 in patients who had been taking a statin within the previous 4 weeks. Normal to moderately elevated trig levels, and in acceptable metabolic control. Mean baseline LDL-c: rosuva: 163.3 aorta: 171.0	use of lipid-lowering drugs after visit 1, or a history of serious or hypersensitivity reactions to statins. presence of active cardiovascular disease (uncontrolled hypertension >200/>95 mmHg), heart failure NYHA class IV, recent unstable AP, myocardial infarction, transient Ischaemic attack, cerebrovascular accident, coronary artery bypass surgery or angioplasty within the previous 2 months, or likely to undergo coronary artery intervention within 6 months after randomization, pregnant or lactating women not using sufficient contraception, subjects with metabolic abnormalities, such as kidney insufficiency (serum creatinine >220 lmol L)1), uncontrolled hypothyroidism [serum thyroid-stimulating hormone (TSH) >1.5 upper limit of normal (ULN)],homozygous familial hypercholesterolemia or familial dysbetalipoproteinemia, active liver disease or liver enzyme (ALT,AST) elevations >1.5 ULN and unexplained CK elevations >3 ULN. Concomitant treatment with erythromycin, clarithromycin, azole antifungal agents, cyclosporin, antiviral agents, phenytoin, carbamazepine, phenobarbital, or nefazodone.	After a 6-week dietary lead-in, treatment for the first 6 weeks: rosuva 10 mg or aorta 20 mg At week 6, dose increased for 6 weeks: rosuva 20 mg or aorta 40 mg At week 12, dose increased for 6 weeks: rosuva 40 mg or aorta 80 mg

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Wolffenbuttel et al. 2005 R, Open-label, MC 263 patients randomized (N=263) 18 week treatment period	**% LDL-c reduction from baseline at 6, 12, and 18 weeks (p vs aorta):** **rosuva 10/20/40: 45.9% (p<0.05)/50.6% (p<0.05)/53.6% (p<0.01)** **aorta 20/40/80: 41.3%/45.6%/47.8%** **% HDL-c increase from baseline at 6, 12, and 18 weeks (p vs aorta):** **rosuva 10/20/40: 0.7%/0.1%/─1.1%** **aorta 20/40/80: ─1.2%/─2.3%/─2.8%** **All NS** **% trig reduction from baseline at 6, 12, and 18 weeks:** **rosuva 10/20/40: 18.8%/23.7%/22.7%** **aorta 20/40/80: 16.3%/17.6%/23.7%** **All NS** **% of patients achieving LDL-c goals at 6, 12, and 18 weeks (p vs aorta):** **Patients reaching LDL-c <100.5 (ADA guideline)** **rosuva 10/20/40: 81.5%/83.8%/91.5% (p<0.05)** **aorta 20/40/80:73.5%/78.8%/81.1%** **Patients reaching LDL-c <96.8 (new EAS guideline)** **rosuva 10/20/40: 77.7%/83.1%/90.0% (p<0.05)** **aorta 20/40/80:70.5%/76.5%/78.0%**	**Overall adverse events:** **rosuva: 47%** **aorta: 50%** **Serious adverse events:** **rosuva: 5%** **aorta: 2%** **Withdrawals due to adverse events:** **rosuva: 7%** **aorta: 8%** **Myalgia was the most frequently reported adverse event (5% rosuva, 11% aorta). No myopathy. One aorta patient developed abnormality in ALT (>3X ULN)**

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

Clinical Trial	Funding Source
Wolffenbuttel et al. 2005 R, Open-label, MC 263 patients randomized (N=263) 18 week treatment period	Supported by AstraZeneca

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
	Rosuvastatin vs Simvastatin		
Laks, 2008 Open-label, multicenter	Men and women aged 18 or older with primary hypercholesterolemia and a 10-year CV risk >20% or a history of CHD or other established atherosclerotic disease and fasting triglycrides <=4.52 mmol/L at visit 2 (week 0). All were statin-naïve (not received a statin in the past 6 months) or subjects on a start dose or other lipid lowering therapy, which was ineffective (i.e., had not reached their LDL-C goal at that dose). Mean baseline LDL-C: 182.1 mg/dl N=504	Familial hypercholesterolemia, secondary dysliidemia of any cause, history of serious adverse effect or hypersensitivity to othe statins, pregnancy, breastfeeding, and women of childbearing potential not using contraception, malignancy, use of disallowed concomitant medications, history of alcohol or drug dependence, active liver disease or hepatic dysfunction, renal impairment, uncontrolled diabetes, unstable angina, uncontrolled hypertension, unexplained serum creatine kinase >3 times ULN, serious or unstable medical or psychological conditin that compromises safety or participation in the trial.	Rosuvastatin 10 mg vs simvastatin 20 mg for 12 weeks

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Laks, 2008 Open-label, multicenter	Least squares mean percent change (SE) from baseline, rosuvastatin vs simvastatin: LDL-C: -38.79% (1.27) vs -32.03% (1.37); p<0.001 HDL-C: 0.66% (1.14) vs 2.26% (1.47); NS Triglycerides: -14.47% (1.86) vs -14.43% (2.45); NS	rosuvastatin vs simvastatin: Overall withdrawals: 9.0% vs 8.2% Withdrawals due to AE: 7.2% vs 4.1% Incidence of adverse events: 20.0% vs 21.8% Serious AE: 1.2% vs 2.9% Death: 0.3% vs 0% (acute MI, judged not related to study treatment) Myalgia: 3.0% vs 0.6% Increased creatine kinase: 3.4% vs 2.4% 1 serious AE (rosuvastatin, tibial fracture)

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

Clinical Trial	Funding Source
Laks, 2008 Open-label, multicenter	AstraZeneca

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

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria	Intervention
	Switching statins		
Kai T et al, 2008 Open-label, single-center 27 patients 6 month treatment period	Men and women aged 41–87 years with mild hypertension and dyslipidemia who had already been treated with simvastatin 10 mg/day for six months or more (mean 7.1 ± 1.9 months).	Familial hypercholesterolemia, severe liver dysfunction (transaminase > 100 IU/l), severe renal failure (creatinine > 2.0 mg/dl), and a history of any contraindication to the use of statins.	Switching from simvastatin 10mg/day to pravastatin 20mg/day

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

Clinical Trial	Results (mean changes in lipoprotein levels)	Harms/Comments
Kai T et al, 2008 Open-label, single-center 27 patients 6 month treatment period	**Change in mean levels (baseline vs 6 months of treatment)** Total cholesterol (mg/dl): 194 vs 193 (P=0.851) Triglyceride (mg/dl): 102 vs 101 (P=0.693) HDL-C (mg/dl): 72 vs 70 (P=0.988) LDL-C (mg/dl): 103 vs 104 (P=0.782) VLDL-C (mg/dl): 16 vs 17 (P=0.572) LPa (mg/dl): 15 vs 16 (P=0.380) LDL/HDL: 1.7 vs 1.6 (P=0.459) Log TG/HDL: 0.14 vs 0.15 (P=0.939) SBP (mmHg): 133 vs 132 (P=0.337) DBP (mmHg): 70 vs 69 (P=0.578) Adiponectin (μg/ml): 11.9 vs 13.1 (P=0.009) CRP (mg/dl): 0.078 vs 0.062 (P=0.040) FBS (mg/dl): 111 vs 108 (P=0.738) CPK (IU/l): 99 vs 92 (P=0.142) GOT (IU/l): 25 vs 24 (P=0.174) GPT (IU/l) 22 vs 20 (P=0.059) BUN (mg/dl): 17 vs 17 (P=0.659) Creatinine (mg/dl): 0.76 vs 0.72 (P=0.019) eGFR (ml/min/1.73m^2): 68.6 vs 72.5 (P=0.016)	NR

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

Clinical Trial	Funding Source
Kai T et al, 2008 Open-label, single-center 27 patients 6 month treatment period	None

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c
Studies in outpatients					
ALLHAT Officers and Coordinators 2002 Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)	Randomized, open-label vs. usual care, intention-to-treat analysis	10,355 people age 55+ with stage 1 or 2 hypertension and 1+ CHD risk factor; for those with no known CHD: LDL-C 120-189 mg/dL; for those with known CHD: LDL-C 100-129 mg/dL; triglyceride lower than 350 mg/dL.	Pravastatin 40 mg/day or usual care	4.8 years (max=7.8)	145.55 mg/dL (calculated = 3.73 mmol/L)
Asselbergs et al 2004 Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT)	Randomized, active and placebo-controlled, double-blind, single center	864 residents of one city in the Netherlands, ages 28-75 with persistent microalbuminuria, blood pressure <160/100 mm Hg, and no use of antihypertensive medication, and a total cholesterol level <309 mg/dL, or <193 mg/dL in case of previous myocardial infarction, and no use of lipid-lowering medication.	Pravastatin 40 mg or matching placebo and fosinopril 20 mg or matching placebo.	46 $\pm$ 7 months	174 $\pm$ 37

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Percent LDL-c Reduction from Baseline	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death
Studies in outpatients				
ALLHAT Officers and Coordinators 2002 Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)	**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)	**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
Asselbergs et al 2004 Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT)	pravastatin vs placebo 3 months: 30% vs % 1 year: 25% vs 3% 2 years: 25% vs 3% 3 years: 25% vs 0% 4 years: 25% vs 3%	1.8% vs 3.5% (NS)	Not reported	0.9% vs 0.9% (NS)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	All Cause Mortality	Major Coronary Events	Stroke
Studies in outpatients			
ALLHAT Officers and Coordinators 2002 Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)	**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	**6-Year Rate** **Fatal & nonfatal** RRR= 9% ARR= 0.5 events/ 100 ppl p= .31 95% CI = -9-25% NNT= 200
Asselbergs et al 2004 Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT)	Not reported	Not reported	1.6% vs 0.9% (NS)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Studies in outpatients		
ALLHAT Officers and Coordinators 2002 Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)	NR	
Asselbergs et al 2004 Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT)	Not reported	

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Funding Source
Studies in outpatients	
ALLHAT Officers and Coordinators 2002 Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)	National Heart, Lung, and Blood Institute; Pfizer; AstraZeneca; Bristol-Myers Squibb
Asselbergs et al 2004 Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT)	Dutch Kidney Foundation, Netherlands Heart Foundation, and Bristol-Myers Squibb

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c
Colhoun 2004 Collaborative Atorvastatin Diabetes Study (CARDS)	Randomized, double-blind, placebo-controlled, multicenter	2838 men and women with no history of cardiovascular disease, LDL of 4.14 or lower, fasting triglyceride of 6.78 or less, and at least one of the following: retinopathy, albuminuria, current smoking, or hypertension.	Atorvastatin 10 mg/day or placebo	median 3.9 years	117 +32 mg/dl
Downs JR, et al.. 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 $\pm$17 mg/dl (3.88 mmol/l)
Heart Protection Study Collaborative Group 2002, 2004 Heart Protection Study (HPS)	Randomized, double-blind, placebo-controlled, intention to treat analysis	20,536 Men or women 40-80 years with a total cholesterol of >135 mg/dl and a substantial 5 year risk for death from coronary heart disease based on their past medical history.	Simvastatin 40 mg qd or placebo qd.	5 years	131 mg/dl (3.4 mmol/L)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Percent LDL-c Reduction from Baseline	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death
Colhoun 2004 Collaborative Atorvastatin Diabetes Study (CARDS)	36% (95% CI 37% to 35%)	**Any acute cardiovascular disease event:** 9.4% atorva vs 13.4% placebo. Hazard ratio=0.68 (95% CI 0.55, 0.85)	Not reported	Not reported
Downs JR, et al.. 1998 Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)	25% (at 1 year)	**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.
Heart Protection Study Collaborative Group 2002, 2004 Heart Protection Study (HPS)	29.5% (calculated)	**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

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	All Cause Mortality	Major Coronary Events	Stroke
Colhoun 2004 Collaborative Atorvastatin Diabetes Study (CARDS)	4.3% atorva vs 5.8% placebo. Hazard ratio=0.73 (95% CI 0.52, 1.01)	**Primary endpoint (acute coronary event, coronary revascularization, stroke):** 5.8% atorva vs 9.0% placebo. Hazard ratio=0.63 (95% CI 0.48, 0.83) **Acute coronary events:** 3.6% atorva vs 5.5% placebo. Hazard ratio=0.64 (95% CI 0.45, 0.91)	1.5% atorva vs 2.8% placebo. Hazard ratio=0.52 (95% CI 0.31, 0.89)
Downs JR, et al.. 1998 Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)	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	Not reported
Heart Protection Study Collaborative Group 2002, 2004 Heart Protection Study (HPS)	**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	RRR=25%, ARR=1.37/100 ppl, p<0.0001, 95% CI 15-34, NNT=72 (Ischemic stroke accounted for this difference).

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Colhoun 2004 Collaborative Atorvastatin Diabetes Study (CARDS)	1.7% atorva vs 2.4% placebo. Hazard ratio=0.69 (95% CI 0.41, 1.16)	
Downs JR, et al.. 1998 Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)	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.
Heart Protection Study Collaborative Group 2002, 2004 Heart Protection Study (HPS)	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.

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Funding Source
Colhoun 2004 Collaborative Atorvastatin Diabetes Study (CARDS)	Partly funded by Pfizer
Downs JR, et al.. 1998 Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)	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.
Heart Protection Study Collaborative Group 2002, 2004 Heart Protection Study (HPS)	UK Medical Research Council; British Heart Foundation; Merck & Co; Roche

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c
Holdaas et al. 2003 (ALERT)	Randomized, double-blind, intention-to-treat analysis for all randomized	2100 patients of renal or renal/pancreas transplant 6+ months prior w/ stable graft function, total serum cholesterol 4.0-9.0 mmol/L (calculated 154-347 mg/dl). Exclude those using a statin, with familial hypercholesterolemia, life expectancy <1 year, and acute rejection episode in previous 3 months.	Fluvastatin 40 mg daily vs. placebo; dose doubled after 2+ years.	5.1 years	4.1 mmol/L (calculated 158 mg/dl)
Pederson TR et al. 2005 Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL)	Randomized, open-label with blinded end-point classification, multicenter	8888 men and women aged 80 or younger with a history of a definite MI who qualified for statin therapy according to national guidelines at the time of recruitment.	Simvastatin 20 mg or atorvastatin 80 mg . Dose of simvastatin could be increased I to 40 mg if, at 24 weeks, TC was higher than 190 mg/dL. The dose of atorvastatin could be decreased to 40 mg for adverse events.	Median 4.8 years	122±0.5 mg/dL
Riegger G. et al.. 1999	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)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Percent LDL-c Reduction from Baseline	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death
Holdaas et al. 2003 (ALERT)	32% in 5.1 years mean follow-up	Total events RRR = 17%, p=.139 NS Definite nonfatal MI RRR= 32%, p= .05 ARR= 1.9 events/100 ppl 95% CI= 0-60% NNT= 47	NR	**Cardiac death** RRR= 38%, p= .031 ARR= 1.7 events/100 ppl 95% CI= 4-60% NTT= 41
Pederson TR et al. 2005 Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL)	33% simvastatin, 49% atorvastatin at 12 weeks	**Nonfatal MI:** 7.2% simva vs 6.0% atorva (p=0.02) Hazard ratio=0.83 (0.71, 0.98)	**Hospitalization for unstable angina:** 5.3% simva vs 4.4% atorva (p=0.06) Hazard ratio=0.83 (0.69, 1.01)	**CHD death:** 4.0% simva vs 3.9% atorva (p=0.90) Hazard ratio=0.99 (0.80, 1.22) **Cardiovascular death:** 4.9% simva vs 5.0% atorva (p=0.78) Hazard ratio=1.03 (0.85, 1.24)
Riegger G. et al.. 1999	26.90%	3 cardiac events occurred in the fluvastatin vs. 10 in the placebo group (p<0.05, ARR=4/100 persons, NNT=25).	**Unstable angina** 1 (0.53%) fluva vs 5 (2.8%) placebo	**Cardiac Death** 2 (1.07%) fluva vs 4 (2.25%) placebo

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	All Cause Mortality	Major Coronary Events	Stroke
Holdaas et al. 2003 (ALERT)	All cause death 143 (13.6%) Fluva vs 138 (13.11) placebo	NR	Fatal or non-fatal cerebrovascular events 74 (7.05%) fluva vs 63 (5.99%) placebo
Pederson TR et al. 2005 Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL)	**All-cause mortality:** 8.4% simva vs 8.2% atorva (p=0.81) Hazard ratio=0.98 (0.85, 1.13)	**Primary endpoint (CHD death, nonfatal MI, cardiac arrest with resuscitation):** 10.4% simva vs 9.3% atorva (p=0.07) Hazard ratio=0.89 (0.78, 1.01)	**Fatal or nonfatal stroke:** 3.9% simva vs 3.4% atorva (p=0.20) Hazard ratio=0.87 (0.70, 1.08)
Riegger G. et al.. 1999	NR	NR	NR

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Holdaas et al. 2003 (ALERT)	CABG or PCI RRR= 11%, p= NS	Rate of total adverse events similar for fluvastatin 40 mg, 80 mg, and placebo groups. Over study period, 14% of placebo group admitted to other lipid-lowering treatments, mostly statins, along with 7% of fluvastatin group. Other concurrent medications similar in both groups: ciclosporin (all), steroids (81%), beta blockers and calcium antagonists (95%), and aspirin (34%)
Pederson TR et al. 2005 Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL)	16.7% simva vs 13.0% atorva (p<0.001) Hazard ratio=0.77 (0.69, 0.86)	
Riegger G. et al.. 1999	NR	Fluvastatin resulted in a significant reduction in cardiac events compared to placebo in patients with CHD and elevated LDL-c. Just over 20% of patients withdrew because of noncompliance or lack of cooperation with similar distribution in each group. Fair in quality for assessment of differences in clinical events between groups.

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Funding Source
Holdaas et al. 2003 (ALERT)	Novartis Pharma AG
Pederson TR et al. 2005 Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL)	Pfizer
Riegger G. et al.. 1999	Not reported

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c
Sacks FM., et al. 1996 Cholesterol and Recurrent Events Trial (CARE)	Randomized, double-blind, placebo-controlled, intention to treat analysis	4159 men and postmenopausal women 21-75 years with an acute MI 3-20 months prior to randomization.	Pravastatin 40 mg qpm or placebo qpm.	5 years (median)	139 mg/dl (3.4 mmol/l)
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)
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)
Shepherd J., et al. 1995 West of Scotland Coronary Prevention Study Group (WOSCOPS)	Randomized, double-blind, placebo-controlled, intention to treat analysis	6595 Scottish men (45-64 years) with no history of MI and elevated cholesterol.	Pravastatin 40 mg qpm or placebo qpm.	4.9 years	192 $\pm$ 17 mg/dl (5 mmol/l)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Percent LDL-c Reduction from Baseline	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death
Sacks FM., et al. 1996 Cholesterol and Recurrent Events Trial (CARE)	32% (28% vs. placebo)	**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
Scandinavian Simvastatin Survival Study Group 1994 Scandinavian Simvastatin Survival Study (4S)	35%	Not reported separately	Not reported	**Death due to CHD:** RRR=42% ARR=3.5/100 ppl 95% CI 27-54% NNT=28
Sever, 2003 Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm (ASCOT-LLA) UK, Sweden, Norway, Denmark, Finland, Ireland	**6 months** - base = 35.8% - placebo = 35.9% **Year 2** - base = 34.9% - placebo = 33.5% **Year 3** - base = 33.7% - placebo = 30.9%	**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
Shepherd J., et al. 1995 West of Scotland Coronary Prevention Study Group (WOSCOPS)	26% in the on-treatment group, 16% in the intent to treat population.	**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

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	All Cause Mortality	Major Coronary Events	Stroke
Sacks FM., et al. 1996 Cholesterol and Recurrent Events Trial (CARE)	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	RRR=31%, ARR=1.1/100 ppl, p=0.03, 95% CI 3-52, NNT=86
Scandinavian Simvastatin Survival Study Group 1994 Scandinavian Simvastatin Survival Study (4S)	**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	**Post-hoc analysis: fatal and nonfatal cerebrovascular events:** RRR=30% ARR=1.2/100 ppl p=0.024 95% CI 4-48% NNT=80
Sever, 2003 Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm (ASCOT-LLA) UK, Sweden, Norway, Denmark, Finland, Ireland	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	**Fatal & nonfatal** RRR= 27% ARR= 0.7 events/ 100 ppl p= .0236 95% CI = 4-44% NNT= 142
Shepherd J., et al. 1995 West of Scotland Coronary Prevention Study Group (WOSCOPS)	RRR=22% ARR 0.9/100 ppl p=0.051 95% CI 0-40 NNT=112	**Primary endpoint: nonfatal MI or death:** RRR=31% ARR=2.2/100 ppl p<0.001 95% CI 17-43% NNT=44	46 in pravastatin vs. 51 in placebo (NS)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Sacks FM., et al. 1996 Cholesterol and Recurrent Events Trial (CARE)	RRR=27% ARR=4.7/100 ppl p<0.001 95% CI 15-37% NNT=41	Pravastatin reduced the incidence of the combined primary endpoint of nonfatal MI and death due to CHD. Stroke and need for revascularization was also reduced in the pravastatin compared to placebo group. Overall mortality and mortality from noncardiovascular causes was not reduced. The reduction in coronary events was greater in women and those with higher baseline LDL-c.
Scandinavian Simvastatin Survival Study Group 1994 Scandinavian Simvastatin Survival Study (4S)	RRR=37% ARR=5.9/100 ppl p<0.00001 95% CI 26-46% NNT=17	Simvastatin reduced the incidence of the primary endpoint of total mortality of which CHD death accounted for a reduction of 42% vs. placebo. Simvastatin also reduced the incidence of major coronary events, as defined in this trial, need for revascularization and combined fatal and nonfatal stroke. The risk for these events was reduced in women and in those over 60 years.
Sever, 2003 Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm (ASCOT-LLA) UK, Sweden, Norway, Denmark, Finland, Ireland	**Total CV events & procedures** RRR= 21% ARR= 2.0 events/ 100 ppl p= .0005 95% CI =10-31% NNT= 50	
Shepherd J., et al. 1995 West of Scotland Coronary Prevention Study Group (WOSCOPS)	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.

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Funding Source
Sacks FM., et al. 1996 Cholesterol and Recurrent Events Trial (CARE)	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.
Scandinavian Simvastatin Survival Study Group 1994 Scandinavian Simvastatin Survival Study (4S)	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.
Sever, 2003 Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm (ASCOT-LLA) UK, Sweden, Norway, Denmark, Finland, Ireland	Pfizer, New York, NY, USA; Servier Research Group; Leo Laboratories
Shepherd J., et al. 1995 West of Scotland Coronary Prevention Study Group (WOSCOPS)	Role unknown. Supported by a research grant from Bristol-Myers Squibb.

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c
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 ≤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)
Stone PH et al., 2005 The Vascular Basis for the Treatment of Myocardial Ischemia Study	Randomized, double-blind, multicenter	199 (excluding atorvastatin plus vitamins C and E arm) men and women age <85 years, with fasting TC 180 to 250 mg/dL, objective evidence of coronary disease, exercise-induced ST-segment depression >=1.0 mm, and >=1 episode of reversible ST depression of >=1.0 mm during 48-hour ambulatory ECG monitoring of routine activities.	Atorva titrated to achieve an LDL of <80 mg/dL or a maximum dose of 80 mg, or control group of diet plus low-dose lovastatin, if necessary, to achieve an LDL of <130 mg/dL. 91% of control patients required lovastatin (median dose 5 mg). (Also included an intensive atorva plus vitamins C and E arm).	12 months	atorva: 149±33 control (lova): 151±27
The Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group 1998 Colquhoun, 2004 Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)	Randomized, double-blind, placebo-controlled, intention to treat analysis	9014 men & women 31-75 years with a history of either MI or hospitalization for unstable angina.	Pravastatin 40 mg qpm or placebo qpm.	6.1 years	150 mg/dl 3.88 (mmol/l) (median)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Percent LDL-c Reduction from Baseline	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death
Shepherd 2002, 1999 Prospective Study of Pravastatin in the Elderly (PROSPER) Scotland, Ireland, The Netherlands	34% from baseline and placebo at 3 months (2.5 /3.8 mmol/L).	**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
Stone PH et al., 2005 The Vascular Basis for the Treatment of Myocardial Ischemia Study	42.9% atorva vs 18.5% control (lova)	1% atorva vs 0% control (p=0.32)	**Unstable angina:** 2% atorva vs 2% control (p=0.54)	Not reported
The Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group 1998 Colquhoun, 2004 Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)	25% vs. placebo	**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

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	All Cause Mortality	Major Coronary Events	Stroke
Shepherd 2002, 1999 Prospective Study of Pravastatin in the Elderly (PROSPER) Scotland, Ireland, The Netherlands	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	**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
Stone PH et al., 2005 The Vascular Basis for the Treatment of Myocardial Ischemia Study	1% atorva vs 0% control (p=0.32)	**Combined death, MI, unstable angina, stroke, revascularization):** 1% atorva vs 1% control (p=0.77) 3% atorva vs 1% control (p=0.62)	
The Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group 1998 Colquhoun, 2004 Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)	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	RRR=19% ARR=0.8/100 ppl p=0.48 95% CI 0-34% NNT=127

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Shepherd 2002, 1999 Prospective Study of Pravastatin in the Elderly (PROSPER) Scotland, Ireland, The Netherlands	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.
Stone PH et al., 2005 The Vascular Basis for the Treatment of Myocardial Ischemia Study	3% atorva vs 1% control (p=0.41)	Primary outcome was ischemia by ambulatory ECG.
The Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group 1998 Colquhoun, 2004 Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)	RRR=20% ARR=3/100 ppl p<0.001 95% CI 10-28% NNT=34	Pravastatin reduced the incidence of death from CHD, overall mortality, fatal and nonfatal MI and need for revascularization compared to placebo.

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Funding Source
Shepherd 2002, 1999 Prospective Study of Pravastatin in the Elderly (PROSPER) Scotland, Ireland, The Netherlands	Bristol-Myers Squibb, USA
Stone PH et al., 2005 The Vascular Basis for the Treatment of Myocardial Ischemia Study	NIH and Pfizer
The Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group 1998 Colquhoun, 2004 Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)	Bristol-Myers Squibb provided study medication but was not involved with the study design, management of the study or analyzing the data.

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c
Wanner C et al., 2005 4D Study	Randomized, double-blind, multicenter	1255 men and women with type 2 diabetes, ages 18 to 80 years, who had been receiving maintenance hemodialysis for less than 2 years.	Atorva 20 mg or placebo. If LDL-C levels fell below 50 mg/dL, the dose of atorva ws reduced to 10 mg.	Median 4 years	126 ± 30 mg/dL

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Percent LDL-c Reduction from Baseline	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death
Wanner C et al., 2005 4D Study	42.0% atorva vs 1.3% placebo	**Nonfatal MI:** 11% atorva vs 12% placebo (p=0.08) Relative risk=0.81 (0.64, 1.03) **Fatal MI:** 4% atorva vs 5% placebo (p NR)	Not reported	**Death from cardiac causes:** 20% atorva vs 23% placebo (p=0.42) Relative risk=0.88 (0.64, 1.21)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	All Cause Mortality	Major Coronary Events	Stroke
Wanner C et al., 2005 4D Study	48% atorva vs 50% placebo (p=0.33) Relative risk=0.93 (0.79, 1.08)	**All cardiac events combined (death from cardiac causes, nonfatal MI, PTCA, CABG, other interventions to treat coronary heart disease):** 33% atorva vs 39% placebo (p=0.03) Relative risk=0.82 (0.68, 0.99)	**Stroke:** 10% atorva vs 7% placebo (p=0.15) Relative risk=1.33 (0.90, 1.97) **TIAA or prolonged reversible ischemic neurologic deficit:** 4% atorva vs 5% placebo **All cerebrovascular events combined:** 13% atorva vs 11% placebo (p=0.49) Relative risk=1.12 (0.81, 1.55)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Wanner C et al., 2005 4D Study	**PTCA:** 7% atorva vs 7% placebo **CABG:** 4% atorva vs 5% placebo	

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Funding Source
Wanner C et al., 2005 4D Study	Pfizer

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c
Studies in inpatients with unstable angina or acute coronary syndrome					
Arntz et.al 2000 L-CAD	Randomized, double-blind, vs standard care, intention-to-treat	126 men and women with total cholesterol >200 to <400 mg/dl and LDL cholesterol >130 to <300 mg/dl with an acute MI and/or who underwent emergency PTCA due to severe or unstable angina pectoris.	Pravastatin 20 to 40 mg vs usual care; started on average 6 days after MI or PTCA	2 years	prava vs usual care 176 mg/dL (131-240) vs 172 mg/dL (132-239)
Cannon et al 2004 PROVE-IT	Randomized, head-to-head, double-blind	4162 men and women age 18 or older who had been hospitalized for an acute coronary syndrome (MI or high-risk angina) in the preceding 10 days, but stable. Total cholesterol level 240 mg/dL or less. If receiving long-term lipid-lowering therapy, total cholesterol level 200 mg/dL or less.	Pravastatin 40 mg vs atorvastatin 80 mg.	2 years (range 18 to 36 months)	Median (interquartile range): prava 106 (87-127) mg/dL; atorva 106 (89-128) mg/dL
de Lemos 2004 A to Z Trial (Phase Z)	Randomized, double-blind, placebo-controlled, multicenter	4497 men and women ages 21-80 with either non-ST-elevation acute coronary syndrome or ST elevation MI with a total cholesterol level of 250 mg or lower.	Early intensive statin treatment (simvastatin 40 mg for 30 days and then simvastatin 80 mg there after) vs less aggressive strategy (placebo for 4 months and then simvastatin 20 mg thereafter)	Median 721 days (range 6 months to 24 months)	Median 112 (25th-75th percentiles 94-131)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Percent LDL-c Reduction from Baseline	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death
Studies in inpatients with unstable angina or acute coronary syndrome				
Arntz et.al 2000 L-CAD	prava vs usual care 28% vs no change	1 in usual care group.	NR	NR
Cannon et al 2004 PROVE-IT	2985 patients who had not previously received statin therapy: 22% prava vs 51% atorva at 30 days (p<0.001)	death or MI: 18% reduction (p=0.06)	recurrent unstable angina: 29% reduction in atorva group (p=0.02)	prava vs atorva 22.3% vs 19.7% (p=0.029)
de Lemos 2004 A to Z Trial (Phase Z)	simvastatin first vs placebo first 1 month: 39% vs +10% (p<0.001) 4 months: 45% vs +12% (p<0.001) 8 months: 44% vs 31% (p<0.001) 24 months: 41% vs 27% (p<0.001)	Hazard ratio 0.96 (95% CI 0.61, 1.02)	Not reported	Hazard ratio 0.75 (95% CI 0.57, 1.00)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	All Cause Mortality	Major Coronary Events	Stroke
Studies in inpatients with unstable angina or acute coronary syndrome			
Arntz et.al 2000 L-CAD	2 deaths in each group.	1 ischemic stroke in each group; Group A: 12 coronary interventions vs Group B with 24 coronary interventions.	11/70 prava vs 24/56 usual care (15.7% vs 42.9%)
Cannon et al 2004 PROVE-IT	28% reduction in atorva group (p=0.07)	Infrequent, but rates did not differ significantly between groups	14% reduction in atorva group (p=0.04)
de Lemos 2004 A to Z Trial (Phase Z)	Hazard ratio 0.79 (0.61, 1.02)	**Primary end point (cardiovascular death, myocardial infarction, readmission for acute coronary syndrome, or stroke):** Hazard ratio 0.89 (95% CI 0.76, 1.04; p=0.14)	Hazard ratio 0.79 (95% CI 0.48, 1.30)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Studies in inpatients with unstable angina or acute coronary syndrome		
Arntz et.al 2000 L-CAD	NR	
Cannon et al 2004 PROVE-IT	High-dose atorva had 14% reduction in need for revascularization vs std dose Prava.	
de Lemos 2004 A to Z Trial (Phase Z)	Hazard ratio 0.93 (95% CI 0.73, 1.20)	

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Funding Source
Studies in inpatients with unstable angina or acute coronary syndrome	
Arntz et.al 2000 L-CAD	Supported in part by a grant from Bristol-Myers Squibb.
Cannon et al 2004 PROVE-IT	Supported by Bristol-Myers Squibb and Sankyo
de Lemos 2004 A to Z Trial (Phase Z)	Funded by Merck

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c
Den Hartog et al. 2001 (Pilot Study)	Pilot study; randomized, double-blind, placebo controlled.	99 men and women with acute MI or unstable angina who were hospitalized for less than 48 hours.	Pravastatin 40 mg	3 months	4.51 mmol/dL
Liem et al 2002 FLORIDA	Randomized, double-blind, placebo-controlled,	540 men and women with an MI and total cholesterol taken at admission or within 24 hours after onset of symptoms was 6.5mmol/L or higher; eligibility also required one of the following: new or markedly increased chest pain lasting longer than 30 minutes, or a new pathological Q wave.	Fluvastatin 80 mg	1 year	135 mg/dl vs 139 mg/dl
Schwartz et al. 2001 MIRACL	Randomized, double-blind, placebo-controlled	Men and women age 18 or older with unstable anginal or non-Q-wave MI.	Atorvastatin 80 mg	16 weeks	124 mg/dL
Thompson et al 2004 PACT	Randomized, double-blind, placebo-controlled, multicenter	3408 men and women age 18 to 85 within 24 hours of onset of acute MI or unstable angina.	Pravastatin 40 mg (20 mg for those subjects enrolled in the early stages of the study) for 4 weeks.	4 weeks	Not reported. Mean total cholesterol 219

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Percent LDL-c Reduction from Baseline	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death
Den Hartog et al. 2001 (Pilot Study)	25%	2/50 vs 1/49 (NS)	24/50 vs 21/49 (NS)	2(4%) Prava vs 2(4%) placebo
Liem et al 2002 FLORIDA	fluva vs placebo: 21% decrease vs 9% increase.	NR	NR	Cardiovascular death 6 (2.26%) Fluva vs 11 (4%) placebo Fatal MI 0 Fluva vs 3 (1.09%) placebo
Schwartz et al. 2001 MIRACL	atorva vs placebo: 40% decrease vs 12% increase (adjusted mean)	No significant differences	NR	Nonfatal MI 101(6.6%) Atorva vs 113(7.3%) Placebo
Thompson et al 2004 PACT	Not reported	nonfatal only: 0.8% vs 0.9% (NS) fatal and nonfatal: 3.8% vs 3.7% (NS)	New unstable angina: 2.4% vs 2.2% (NS) recurrent unstable angina: 4.7% vs 5.2% (NS)	Fatal MI: 0.8% vs 0.9% (NS) Death excluding fatal MI: 0.6% vs 1.3% (NS)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	All Cause Mortality	Major Coronary Events	Stroke
Den Hartog et al. 2001 (Pilot Study)	No significant differences	NR	11/50 vs 9/49 (NS)
Liem et al 2002 FLORIDA	2.6% vs 4.0% (p not reported)	62 (23.39%) Fluva vs 68(24.7%) placebo	Fatal Stroke 2 (0.75%) Fluva vs 1 (0.36%) placebo
Schwartz et al. 2001 MIRACL	No significant differences	NR	Fatal stroke 3(0.19%) Atorva vs 2(0.06%) placebo Nonfatal stroke 9 (0.6%) Atorva vs 22(1.4%) placebo
Thompson et al 2004 PACT	1.4% vs 2.2% (NS)	11.6% vs 12.4% (NS)	NR

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Den Hartog et al. 2001 (Pilot Study)	PTCA 7 (14%) Prava vs 4(8%) placebo CABG 4(8%) Prava vs 5(10%) placebo	
Liem et al 2002 FLORIDA	CABG 12 (4.53%) Fluva vs 19(6.9%) placebo PTCA 34(12.8%) Fluva vs 32(11.6%) placebo	
Schwartz et al. 2001 MIRACL	Coronary revascularization: 254 (16.5%) Atorva vs 143(9.2%) placebo	
Thompson et al 2004 PACT	NR	

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Funding Source
Den Hartog et al. 2001 (Pilot Study)	Not reported
Liem et al 2002 FLORIDA	Study financed by an unrestricted grant from AstraZeneca.
Schwartz et al. 2001 MIRACL	Supported by a grant from Pfizer Inc. Pfizer provided the atorvastatin and matching placebo used.
Thompson et al 2004 PACT	Supported by Bristol-Myers Squibb

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c
New studies added in Update 5					
Hogue J, 2008	Randomized, double-blind	40 men and women with type 2 diabetes mellitus and hypertriglyceridemia.	Atorvastatin 20mg/day micronized fenofibrate 200mg/day	6 weeks	Atorvastatin: 2.70 mmol/L Fenofibrate: 2.83 mmol/L
Nakamura H, 2006 (MEGA study)	Randomized, open-label, blinded-endpoint	8,214 men and postmenopausal women aged 40-70 years with a bodyweight of ≥40kg and hypercholesterolaemia	Pravastatin + diet, started at 10mg/day, dose could be adjusted with uptitration to 20mg/day or diet alone.	5.3 years	Pravastatin: 4.05 mmol/L Diet only: 4.05 mmol/L
Patti G, 2007 (ARMYDA-ACS)	Randomized, double-blind, placebo-controlled, multicenter	191 men and women with the presence of a non-ST-segment elevation acute coronary syndrome sent to early coronary angiopraphy.	Atorvastatin 80mg loading dose given a mean of 12 hours before coronary angiography, with a further 40mg dose approximately 2 hours before the procesdure.	30 days	NR
Ridker P, 2008 (JUPITER)	Randomized, double-blind, placeb-controlled, multicenter	17,802 men 50 years of age or older and women 60 years of age or older were eligible for the trial if they did not have a history of cardiovascular disease and if, at the initial screening visity, they had an LDL of <130mg/dl and a high-sensitivity C-reactive protein level of 2.0mg/l or more.	Rosuvastatin 20mg/day or placebo	60 months	Median LDL-c 108 mg/dl

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Percent LDL-c Reduction from Baseline	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death
New studies added in Update 5				
Hogue J, 2008	Atorvastatin: -43% Fenofibrate: +15.9% P=0.0004	NR	NR	NR
Nakamura H, 2006 (MEGA study)	NR	Nonfatal: 16 vs 30 (NS) Fatal: 2 vs 3 (NS)	Coronary heart disease: 66 vs 101 P=0.01 Coronary heart disease plus cerebral infarction: 98 vs 144 P=0.005 Angina: 46 vs 57 P=0.35	Cardiac sudden death: 5 vs 10 P=0.21 Cardiovascular death: 11 vs 18 P=0.22
Patti G, 2007 (ARMYDA-ACS)	NR	4 (5%) vs 13 (15%): P=0.04	NR	None
Ridker P, 2008 (JUPITER)	Rosuvastatin compared with placebo group had a 50% lower median LDL cholesterol level at the 12-month visit.	Non-fatal MI: 22 vs 62 P<0.00001 Any MI: 31 vs 68 P=0.0002	Hospitalization for unstable angina: 16 vs 27 P=0.09	NR

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	All Cause Mortality	Major Coronary Events	Stroke
New studies added in Update 5			
Hogue J, 2008	NR	NR	NR
Nakamura H, 2006 (MEGA study)	Total mortality: 55 vs 79 P=0.055	All cardiovascular events: 125 vs 172 P=0.01	Stroke: 50 vs 62 P=0.33 Cerebral infarction: 34 vs 46 P=0.22 Intracranial haemorrhage: 16 vs 14 P=0.65 Not classifiable: 0 vs 2 (NS)
Patti G, 2007 (ARMYDA-ACS)	None	Major adverse coronary events 4 (5%) vs 14 (17%): P=0.01	NR
Ridker P, 2008 (JUPITER)	Any death 198 vs 247 P=0.02	NR	Non-fatal stroke: 30 vs 58 P=0.003 Any stroke: 33 vs 64 P=0.002

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
New studies added in Update 5		
Hogue J, 2008	NR	
Nakamura H, 2006 (MEGA study)	Coronary revascularisation: 39 vs 66 P=0.01	
Patti G, 2007 (ARMYDA-ACS)	Target vessel revascularization 0 vs 1 (2%): P=1	
Ridker P, 2008 (JUPITER)	Arterial revascularization: 71 vs 131 P<0.0001	

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Funding Source
New studies added in Update 5	
Hogue J, 2008	Pfizer
Nakamura H, 2006 (MEGA study)	Japanese Ministry of Health, Labor and Welfare and Sankyo Co Ltd, Tokyo
Patti G, 2007 (ARMYDA-ACS)	NR (only stated that "the trial was not supported by any external source of funding")
Ridker P, 2008 (JUPITER)	AstraZeneca

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c
Sakamoto T, 2006	Randomized, open-label, multicenter	486 consecutive patients with AMI who were admitted to 54 medical centers in Japan were enrolled.	Pravastatin, atorvastatin, fluvastatin, simvastatin, or pitavastatin. Or no statin	24 months	Statin group: 134 mg/dl No statin group: 133 mg/dl
Xu K, 2007	Randomized, placebo-controlled, single center	648 consecutive patients with both diabetes and CAD who had undergone successful PCI.	Atorvastatin 20mg taken every night.	Median follow-up: 21 months	Atorvastatin: 3.21 (mmol/L) Placebo: 3.29 (mmol/L)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Percent LDL-c Reduction from Baseline	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death
Sakamoto T, 2006	Statin group: 24% at 6 months; 27% at 12 months; 25% at 24 months Nonstatin group: 4% at 6 months; 6% at 12 months; 8% at 24 months P<0.05	Nonfatal AMI: 3 vs 0	Symptomatic myocardial ischemia requiring emergency rehospitalization: 6 vs 17	2 vs 1
Xu K, 2007	NR	20 (6.4%) vs 39 (12.3%) P=0.013	NR	NR

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	All Cause Mortality	Major Coronary Events	Stroke
Sakamoto T, 2006	NR	Heart failure requiring emergency rehospitalization: 1 vs 9	3 vs 2
Xu K, 2007	All cause death 16 (5.1%) vs 25 (7.9%) P=0.196	NR	NR

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Sakamoto T, 2006	CABG: 2 vs 5 PCI for new lesions: 9 vs 9 Repeat PCI for infarct-related lesions: 7 vs 5 Repeat PCI for noninfacrt-related lesions: 0 vs 5	
Xu K, 2007	Revascularization: 60 (19.2%) vs 84 (26.6%) P=0.029	

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Funding Source
Sakamoto T, 2006	Research Grant for Cardiovascular Disease (14C-$) from the Ministryof Health, Labor and Welfare, Tokyo, Japan and by a grant from the Japan Heart Foundation, Tokyo, Japan
Xu K, 2007	NR

Evidence Table 3. Placebo-controlled trials of patients with atherosclerosis

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction from baseline
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%
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%
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%

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

Evidence Table 3. Placebo-controlled trials of patients with atherosclerosis

Author Year Study Name	Primary Endpoint	Primary Endpoint Results (clinical health outcome only)	Clinical Outcomes Measured	Clinical Outcome Results
Bestehorn et al. 1997 Multicenter Coronary Intervention Study (CIS)	Global change score and the per-patient mean change in MLD as assessed by coronary angiography.	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.
Blankenhorn et al. 1993 The Monitored Atherosclerosis Regression Study (MARS)	Per-patient change in percent diameter stenosis between groups as determined by quantitative coronary angiography.	N/A	Cardiac and noncardiac events, mortality and coronary revascularization 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.
Crouse et al. 1995 Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II)	Change in the mean of the maximal IMT measurement across time determined by B-mode ultrasonography.	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

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

Evidence Table 3. Placebo-controlled trials of patients with atherosclerosis

Author Year Study Name	Comments/Conclusions
Bestehorn et al. 1997 Multicenter Coronary Intervention Study (CIS)	There were no statistical differences in clinical events in the simvastatin 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.
Blankenhorn et al. 1993 The Monitored Atherosclerosis Regression Study (MARS)	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.
Crouse et al. 1995 Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II)	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 significantly reduced with pravastatin. Fair-poor 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 3. Placebo-controlled trials of patients with atherosclerosis

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction from baseline
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%
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)
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%

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

Evidence Table 3. Placebo-controlled trials of patients with atherosclerosis

Author Year Study Name	Primary Endpoint	Primary Endpoint Results (clinical health outcome only)	Clinical Outcomes Measured	Clinical Outcome Results
Furberg et al. 1994 Asymptomatic Carotid Artery Progression Study (ACAPS)	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.	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.
Herd et al. 1997 Lipoprotein and Coronary Atherosclerosis Study (LCAS)	Within patient per-lesion change in MLD of qualifying lesion as assessed by coronary angiography.	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.
Jukema et al. 1995 The Regression Growth Evaluation Statin Study (REGRESS)	Change in average mean segment diameter per patient and change in average minimum obstruction diameter per patient determined by coronary arteriography.	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 groups (p=0.004, RRR=57%, ARR 5.8/100 persons, NNT=17).

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

Evidence Table 3. Placebo-controlled trials of patients with atherosclerosis

Author Year Study Name	Comments/Conclusions
Furberg et al. 1994 Asymptomatic Carotid Artery Progression Study (ACAPS)	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 determine differences in clinical events.
Herd et al. 1997 Lipoprotein and Coronary Atherosclerosis Study (LCAS)	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.
Jukema et al. 1995 The Regression Growth Evaluation Statin Study (REGRESS)	REGRESS prespecified analysis of clinical events. The only significant difference in individual events was the reduced need for unscheduled PTCA in the pravastatin vs. placebo groups. This significant 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.

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

Evidence Table 3. Placebo-controlled trials of patients with atherosclerosis

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction from baseline
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%
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%
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)

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

Evidence Table 3. Placebo-controlled trials of patients with atherosclerosis

Author Year Study Name	Primary Endpoint	Primary Endpoint Results (clinical health outcome only)	Clinical Outcomes Measured	Clinical Outcome Results
Pitt et al. 1995 Pravastatin Limitation of Atherosclerosis in Coronary Arteries (PLAC- I)	Change in average MLD and change in percent diameter stenosis as determined by coronary arteriography.	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).
Salonen et al. 1995 Kuopio Atherosclerosis Prevention Study (KAPS)	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.	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.
Sato et al. 2001	Mean segment diameter and minimum obstruction diameter were used to evaluate progression as assessed by coronary angiography.	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)

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

Evidence Table 3. Placebo-controlled trials of patients with atherosclerosis

Author Year Study Name	Comments/Conclusions
Pitt et al. 1995 Pravastatin Limitation of Atherosclerosis in Coronary Arteries (PLAC- I)	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.
Salonen et al. 1995 Kuopio Atherosclerosis Prevention Study (KAPS)	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	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 3. Placebo-controlled trials of patients with atherosclerosis

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction from baseline
Simoons 1994 Multicentre Anti-Atheroma Study	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events.	404 men and women 30-67 years with 2 or > coronary artery segments occluded and hyper-cholesterolemia.	Simvastatin 20 mg qpm or placebo qpm.	4 years	169 mg/dl (4.38 mmol/L)	31%
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%
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%

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

Evidence Table 3. Placebo-controlled trials of patients with atherosclerosis

Author Year Study Name	Primary Endpoint	Primary Endpoint Results (clinical health outcome only)	Clinical Outcomes Measured	Clinical Outcome Results
Simoons 1994 Multicentre Anti-Atheroma Study	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.	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).
Teo et al. 2000 The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT)	Changes in absolute mean segment lumen diameter, absolute minimum segment lumen diameter, and maximum percent lumen diameter stenosis.	N/A	Prespecified clinical events: death, MI, stroke, hospitalization for angina, revascularization and cancer.	The only significant 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).
Waters et al. 1994 The Canadian Coronary Atherosclerosis Intervention Trial (CCAIT)	Comparison between groups for coronary change score (per-patient mean of the MLD for all lesions measured as determined by coronary angiography.	N/A	Cardiac and noncardiac events, mortality and revascularization were reported in the safety analysis.	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).

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

Evidence Table 3. Placebo-controlled trials of patients with atherosclerosis

Author Year Study Name	Comments/Conclusions
Simoons 1994 Multicentre Anti-Atheroma Study	There were no statistical differences in clinical events in the simvastatin 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)	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 differences in clinical events since clinical events were prespecified.
Waters et al. 1994 The Canadian Coronary Atherosclerosis Intervention Trial (CCAIT)	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 4. 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
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%
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%

*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 4. Post-revascularization and miscellaneous trials

Author Year Study Name	Primary Endpoint	Primary Endpoint Results (provided only if it is a clinical health outcome)	Other Clinical Outcomes Measured	Other Clinical Outcome Results
Bertrand ME. et al.,1997 Prevention of Restenosis by Elisor after Transluminal Coronary Angioplasty (PREDICT)	Minimum lumen diameter as assessed by coronary angiography.	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).
Flaker GC. et al., 1999 Subgroup of CARE	Reduction in clinical cardiovascular events (CHD death or nonfatal MI, fatal and nonfatal MI, revascularizations and stroke).	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.

*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 4. Post-revascularization and miscellaneous trials

Author Year Study Name	Comments/Conclusions
Bertrand ME. et al.,1997 Prevention of Restenosis by Elisor after Transluminal Coronary Angioplasty (PREDICT)	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 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 4. 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
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%
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%

*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 4. Post-revascularization and miscellaneous trials

Author Year Study Name	Primary Endpoint	Primary Endpoint Results (provided only if it is a clinical health outcome)	Other Clinical Outcomes Measured	Other Clinical Outcome Results
Kleeman A. et al., 1999 The Cholesterol Lowering Atherosclerosis Trial (CLAPT)	Angiographic progression and restenosis. Change in mean segment diameter (diffuse coronary atherosclerosis) of nondilated and dilated segments and MLD (focal coronary atherosclerosis) of dilated lesions at 2 years as assessed by angiography.	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).
Marz W. et al. 1999 The Target Tangible Trial (TT)*	Safety (adverse events and laboratory events) and efficacy (LDL-c reduction).	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

*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 4. Post-revascularization and miscellaneous trials

Author Year Study Name	Comments/Conclusions
Kleeman A. et al., 1999 The Cholesterol Lowering Atherosclerosis Trial (CLAPT)	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).
Marz W. et al. 1999 The Target Tangible Trial (TT)*	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 4. 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
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).
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%

*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 4. Post-revascularization and miscellaneous trials

Author Year Study Name	Primary Endpoint	Primary Endpoint Results (provided only if it is a clinical health outcome)	Other Clinical Outcomes Measured	Other Clinical Outcome Results
Pitt B. et al. 1999 The Atorvastatin vs. Revascularization Treatment (AVERT)*	Reduction in ischemic events: death from cardiac causes, resuscitation after cardiac arrest, nonfatal MI, CVA, CABG, PTCA, or hospitalization for angina.	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%)
Pravastatin Multinational Study Group 1993*	Change in serum lipids (TC, LDL-c, HDL-c, triglycerides)	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)

*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 4. Post-revascularization and miscellaneous trials

Author Year Study Name	Comments/Conclusions
Pitt B. et al. 1999 The Atorvastatin vs. Revascularization Treatment (AVERT)*	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.
Pravastatin Multinational Study Group 1993*	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 4. 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
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 ischemia 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%
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)

*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 4. Post-revascularization and miscellaneous trials

Author Year Study Name	Primary Endpoint	Primary Endpoint Results (provided only if it is a clinical health outcome)	Other Clinical Outcomes Measured	Other Clinical Outcome Results
Serruys PW. et al, 1999 Fluvastatin Angiographic Restenosis Trial (FLARE)	Angiographic restenosis as assessed by quantitative coronary angiography as the loss of MLD during followup.	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)
Serruys PW. et al., 2002 Lescol Intervention Prevention Study (LIPS)	Survival time free of major coronary events (any death, nonfatal MI, repeat revascularization). Divergence seen at 1.5 years.	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)

*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 4. Post-revascularization and miscellaneous trials

Author Year Study Name	Comments/Conclusions
Serruys PW. et al, 1999 Fluvastatin Angiographic Restenosis Trial (FLARE)	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).
Serruys PW. et al., 2002 Lescol Intervention Prevention Study (LIPS)	Time to major coronary events was significantly prolonged in the fluvastatin vs. placebo group. Adverse effects were not statistically different between groups. Fair-good in quality for assessment of differences in clinical events between groups (Number of diabetics was not equal between groups).

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

Evidence Table 4. 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
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
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%

*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 4. Post-revascularization and miscellaneous trials

Author Year Study Name	Primary Endpoint	Primary Endpoint Results (provided only if it is a clinical health outcome)	Other Clinical Outcomes Measured	Other Clinical Outcome Results
The Post Coronary Artery Bypass Graft Trial 1997 Post Coronary Artery Bypass Graft Trial (PCABG)	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	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).
Weintraub WS. et al., 1994 The Lovastatin Restenosis Trial	Extent of restenosis of the index lesion as assessed by angiography.	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).

*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 4. Post-revascularization and miscellaneous trials

Author Year Study Name	Comments/Conclusions
The Post Coronary Artery Bypass Graft Trial 1997 Post Coronary Artery Bypass Graft Trial (PCABG)	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.
Weintraub WS. et al., 1994 The Lovastatin Restenosis Trial	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 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria
Ballantyne C, et al, 2005 (Vyva study) R (1:1), DB, MC, AC, modified ITT 1,902 patients randomized (n= 951 atorva, 951 ez/simva) 6 weeks	Men and women, 18 to 79 years, LDL-C level at or above drug treatment thresholds established by NCEP ATP III; established CHD or CHD risk equivalent with an LDL-C ≥130 mg/dL; no established CHD or CHD risk equivalent, with ≥2 risk factors conferring a 10-year risk for CHD ≥10% and ≤20% with an LDL-C >130 mg/dL; no established CHD or CHD risk equivalent, with >2 risk factors conferring a 10-year risk for CHD <10% with an LDL-C ≥160 mg/dL; and no established CHD or CHD risk equivalent, with <2 risk factors, and with LDL-C z190 mg/dL; Fasting serum triglyceride (TG) level ≤350 mg/dL, alanine aminotransferase (ALT), aspartate aminotransferase (AST), or creatine kinase (CK) level ≤1.5 times the upper limit of normal, serum creatinine level V1.5 mg/dL, and hemoglobin A1C <9.0% in patients with diabetes.	See inclusion criteria
Barrios V, et al 2005 R (1:1), DB, MC, AC, modified ITT 435 patients randomized (EZE/SIMVA 10/20 mg (n = 221 eze/simva 10/20, 214 atv 20).	Men and women 18 years with documented hypercholesterolemia and atherosclerotic or CHD; serum LDL-C between 2.5 and 4.2 mmol/l (100 to 160 mg/dl) and triglycerides (TG) <4.0 mmol/l (350 mg/dl) while on a stable dose of ATV 10 mg for 6 weeks.	Congestive heart failure; MI, coronary artery bypass surgery or angioplasty within the past 3 months; poorly controlled or newly diagnosed (within 3 months) Type I or II diabetes; uncontrolled hypertension (systolic >160 mmHg or diastolic >100 mmHg); uncontrolled endocrine or metabolic disease known to influence serum lipids; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels >1.5 times the upper limit of normal (ULN) and creatine kinase (CK) levels >1.5 ULN.

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Intervention	Results (mean changes in lipoprotein levels)
Ballantyne C, et al, 2005 (Vyva study) R (1:1), DB, MC, AC, modified ITT 1,902 patients randomized (n= 951 atorva, 951 ez/simva) 6 weeks	10 weeks, with 4-week placebo/diet run-in period followed by 6 weeks of active treatment (ezetimibe/simvastatin (10/10, 10/20, 10/40, and 10/80 mg) and atorvastatin (10, 20, 40, and 80 mg).)	Efficacy analysis for 1850 patients. **LDL-c reduction % from baseline at week 6:** atorva 10 mg: 36.1 atorva 20 mg 43.7 atorva 40 mg 48.3 atorva 80 mg 52.9 All doses 45.3 ez/simva 10 mg 47.1 ez/simva 20 mg 50.6 ez/simva 40 mg 57.4 ez/simva 80 mg 58.6 All doses 53.4 Between differences at same dose and all p < 0.001 **HDL-c increase % from baseline at week 6:** atorva 10 mg: 6.9 atorva 20 mg 5.1 atorva 40 mg 3.8 atorva 80 mg 1.4 All doses 4.3 ez/simva 10 mg 7.7 ez/simva 20 mg 7.2 ez/simva 40 mg 9.0 ez/simva 80 mg 7.6 All doses 7.9 Between differences at same dose for 40 and 80 mg levels and all p < 0.001, others were NS
Barrios V, et al 2005 R (1:1), DB, MC, AC, modified ITT 435 patients randomized (EZE/SIMVA 10/20 mg (n = 221 eze/simva 10/20, 214 atv 20).	eze/simva 10/20 mg or atv 20 mg once daily for 6 weeks.	**LDL-c reduction % from baseline at week 6:** eze/simva -33 atv -20 (p < 0.001) **Non HDL-c reduction % from baseline at week 6:** eze/simva -28 atv -17 (p < 0.001) **HDL-c change % from baseline at week 6:** eze/simva +2 atv < -1 (p < 0.05)

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Safety/Comments	Funding Source
Ballantyne C, et al, 2005 (Vyva study) R (1:1), DB, MC, AC, modified ITT 1,902 patients randomized (n= 951 atorva, 951 ez/simva) 6 weeks	ALT ≥3 ULN, presumed consecutive all atorva 10 (1.1) vs.. All ez/simva 0 (0.0) p = 0.002 AST ≥3 ULN, presumed consecutive all atorva 7 (0.7) vs.. All ez/simva 1 (0.1) p = 0.070 No other AEs reported.	Merck/Schering Plough Pharmaceuticals
Barrios V, et al 2005 R (1:1), DB, MC, AC, modified ITT 435 patients randomized (EZE/SIMVA 10/20 mg (n = 221 eze/simva 10/20, 214 atv 20).	One or more clinical AEs [44 (19.9%) EZE/SIMVA vs. 51 (23.8%) ATV] Serious clinical AEs [5 (2.3%) EZE/SIMVA vs.2 (0.9%) ATV] myalgia [6 (2.7%) EZE/SIMVA vs. 5 (2.3%) ATV] headache [3 (1.4%) EZE/SIMVA vs. 8 (3.7%) ATV].	Merck/Schering-Plough Pharmaceuticals

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria
Constance C, et al 2007 R (1:1:1), DB, MC, AC, modified ITT 661 patients randomized (n= 220 eze/simva 10/20, 222 eze/simva 10/40, 219 atv) 6 weeks	Men and women ≥18 years of age, diagnosed with T2D, HBA1C < 10%, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels 1.5 times the upper limit of normal (ULN), and creatine kinase (CK) levels 1.5 times ULN, on ATV 10 mg for >6 weeks prior and complete a 4-week, open-label ATV 10 mg/day run-in.	Congestive heart failure defined by NYA class III or IV; myocardial infarction, coronary artery bypass surgery or angioplasty within 3 months; uncontrolled hypertension (systolic >160 mm Hg or diastolic >100 mm Hg); uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins; impaired renal function (creatinine 177 mmol/l) or nephrotic syndrome; alcohol consumption >14 drinks per week and treatment with excluded concomitant medications, pregnancy
Goldberg R, 2006 (Vital study) R (1:1:1:1:1), DB, MC, AC, mITT 1229 patients randomized (n= 245 atv 10, 247 eze/simva 10/20, 245 atv 20, 247 eze/simva 10/40, 245 atv 40) 6 weeks	type 2 diabetes (aged 18-80 years) with hemoglobin A1c levels of 8.5% or less	NR

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Intervention	Results (mean changes in lipoprotein levels)
Constance C, et al 2007 R (1:1:1), DB, MC, AC, modified ITT 661 patients randomized (n= 220 eze/simva 10/20, 222 eze/simva 10/40, 219 atv) 6 weeks	4-week baseline period while continuing to receive open label ATV 10 mg and counseling for a low cholesterol diet. EZE/SIMVA 10/20 mg, EZE/SIMVA 10/40 mg or ATV 20 mg once-daily for 6 weeks.	**LDL-C % change from baseline** eze/simva 10/20 -26.15 vs. atv -8.49 p < 0.001 eze/simva 10/20 -30.13 vs. atv -8.49 p < 0.001 **HDL-C % change from baseline** eze/simva 10/20 2.37 vs. atv 1.25 p = 0.569 eze/simva 10/20 1.29 vs. atv 1.25 p = 0.795
Goldberg R, 2006 (Vital study) R (1:1:1:1:1), DB, MC, AC, mITT 1229 patients randomized (n= 245 atv 10, 247 eze/simva 10/20, 245 atv 20, 247 eze/simva 10/40, 245 atv 40) 6 weeks	ezetimibe/simvastatin, 10/20 mg/d, vs atorvastatin, 10 or 20 mg/d) or next highest (ezetimibe/simvastatin, 10/40 mg/d, vs atorvastatin, 40 mg/d	Efficacy analysis for 1198 patients. **LDL-c reduction % from baseline at week 6:** eze/simva 10/20 -53.6 vs. atv 10 -38.3 p < 0.001 atv 20 -44.6 vs. eze/simva 10/20 -53.6 p < 0.001 eze/simva 10/40 -57.6 vs. atv 40 -50.9 p < 0.001 **HDL-c reduction % from baseline at week 6:** eze/simva 10/20 8.0 vs. atv 10 4.3 p < 0.001 atv 20 4.5 vs. eze/simva 10/20 8.0 p = 0.001 eze/simva 10/40 6.3 vs. atv 40 2.3 p < 0.001

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Safety/Comments	Funding Source
Constance C, et al 2007 R (1:1:1), DB, MC, AC, modified ITT 661 patients randomized (n= 220 eze/simva 10/20, 222 eze/simva 10/40, 219 atv) 6 weeks	Eze/simva 10/20 vs. eze/simva 10/40 vs. atv 20 Clinical AE 51 (23.2) vs.50 (22.5) vs. 42 (19.2) Treatment-related clinical AE 13 (5.9) vs. 9 (4.1) vs. 11 (5.0) Serious clinical AE 1 (0.5) vs.1 (0.5) vs.5 (2.3) Discontinuations due to AE 3 (1.4) vs. 7 (3.2) vs. 2 (0.9) Discontinuations due to treatment-related AE 3 (1.4) vs.4 (1.8) vs. 0 Allergic reaction/rash AE 4 (1.8) vs.0 vs. 3 (1.4) Gallbladder-related AE 0 vs. 1 (0.5) vs. 1 (0.5) Gastrointestinal-related AE 9 (4.1) vs. 10 (4.5) vs. 5 (2.3) Laboratory AE 10 (4.5) vs.10 (4.5) vs.8 (3.7) Treatment-related laboratory AE 5 (2.3) vs.4 (1.8) vs. 3 (1.4)	Merck/ Schering-Plough Pharmaceuticals
Goldberg R, 2006 (Vital study) R (1:1:1:1:1), DB, MC, AC, mITT 1229 patients randomized (n= 245 atv 10, 247 eze/simva 10/20, 245 atv 20, 247 eze/simva 10/40, 245 atv 40) 6 weeks	Atv vs. eze/simva CAEs ≥1 166 (22.7) 98 (19.8) p= 0.26 Drug related‡ 30 (4.1) 20 (4.0) p >.99 Serious 10 (1.4) vs.3 (0.6) p= 0.26 Serious drug related‡ 0 vs 0 Discontinuations 11 (1.5) vs. 4 (0.8) p= 0.43 Gastrointestinal 32 (4.4) 19 (3.8) 0.5 (–1.9 to 2.7) p= 0.77 Gallbladder related 0 (0.0) vs. 0 (0.0) Allergic reaction or rash 5 (0.7) vs. 1 (0.2) p= 0.41 Hepatitis related 0 (0.0) vs. 0 (0.0) ALT ≥3 times the ULN, consecutive 2 (0.3) vs. 0 (0.0) p=0.52 AST ≥3 times the ULN, consecutive 3 (0.4) vs. 0 (0.0) p=0.28 ALT and/or AST >3 times the ULN, consecutive 3 (0.4) vs. 0 (0.0) p=0.28	Merck/Schering-Plough Pharmaceuticals

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria
	Ezetimibe/Simvastatin (Vytorin) vs. Simvastatin	
Bays H, et al 2004 R(1:1:1:1:1:1:1:1::1:1) , DB, MC, PC, ITT 1,528 patients randomized (n= 148 placebo, 149 eze, 622 pooled simva, 609 pooled eze/simva) 12 weeks	men and women aged 18 to 80 years; primary hypercholesterolemia defined as LDL-C concentrations ≥145 mg/dL but ≤150 mg/dL and triglycerides (TG) ≤350 mg/dL at visit 2; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations ≤1.5 times the upper limit of normal (ULN) with no active liver disease and creatine kinase (CK) concentrations ≥ 1.5 times ULN at visit 2.	<50% of ideal body weight according to the 1983 Metropolitan Height and Weight tables (or body weight <100 lb), hypersensitivity to statins, or alcohol consumption >14 drinks per week; pregnant or lactating females.
Ose L, et al 2007 R(1:1:1:1:1:1) , DB, MC, AC, ITT 2959 patients randomized-2855 MITT (n= 1427 eze/simva and 1428 rosuvastatin) 14 weeks	See Bays 2004	See Bays 2004
Shankar, et al 2007 R(1:1) , DB, MC, AC, ITT 230 patients randomized (n= 116 simva, 609 114 eze/simva) 12 weeks	Male and female 18 years or more; LDL-C > 135 for naïve and >120 otherwise.	Unstable angina w/in 3 months; uncontrolled diabetes; hypertension, active hepatitis or hepatic dysfunction, renal failure, hypothyroidism, hypersensitivity to statins, pregnant or lactating.
	Ezetimibe/Simvastatin (Vytorin) vs. Rosuvastatin	

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Intervention	Results (mean changes in lipoprotein levels)
Bays H, et al 2004 R(1:1:1:1:1:1:1:1::1:1) , DB, MC, PC, ITT 1,528 patients randomized (n= 148 placebo, 149 eze, 622 pooled simva, 609 pooled eze/simva) 12 weeks	6- to 8 week washout period; 4-week, single-blind, placebo run in, randomized equally to 1 of 10 daily treatments for 12 weeks: EZE/SIMVA 10/10, 10/20, 10/40, or 10/80 rag; SIMVA 10, 20, 40, or 80 nag; EZE 10 rag; or placebo.	**LDL-c reduction % from baseline at week 12:** eze/simva 10/10 44.8* ** eze/simva10/20 51.9* ** eze/simva10/40 55.2* ** eze/simva10/80 60.2* ** pooled eze/simva 53.0 simva 10 32.7 simva 20 34.3 simva 40 40.6 simva 80 48.5 pooled simva 39.0 eze 18.9 placebo 2.2 *P < 0001 EZE/SIMVA versus same dose of SIMVA monotherapy **P < 0001 EZE/SIMVA versus next highest dose of SIMVA monotherapy.
Ose L, et al 2007 R(1:1:1:1:1:1) , DB, MC, AC, ITT 2959 patients randomized-2855 MITT (n= 1427 eze/simva and 1428 rosuvastatin) 14 weeks	Protocol-compliant patients who completed the 12-week base study were eligible to enter a randomized, double-blind, 14-week extension study and were administered 1 of 8 daily treatments: EZE/SIMVA 10/10-, 10/20-, 10/40- or 10/80-mg, or SIMVA 10-, 20-, 40- or 80-mg.	**LDL-c reduction % from baseline at week 14:** simva 10 31.4 vs. eze/simva 10/10 47.2 (p< 0.001) simva 20 34.3 vs. eze/simva10/20 51.3 (p< 0.001) simva 40 41.3 vs. eze/simva10/40 55.5 (p< 0.001) simva 80 48.5 vs. eze/simva10/80 60.8 (p< 0.001) pooled simva 38.8 vs. pooled eze/simva 53.3 (p< 0.001) **HDL-c increase % from baseline at week 14:** simva 10 4.0 vs. eze/simva 10/10 6.0 simva 20 6.1 vs. eze/simva10/20 6.1 simva 40 6.6 vs. eze/simva10/40 7.9 simva 80 5.6 vs. eze/simva10/80 4.8 pooled simva 5.6 vs. pooled eze/simva 6.4 (p= 0.30)
Shankar, et al 2007 R(1:1) , DB, MC, AC, ITT 230 patients randomized (n= 116 simva, 609 114 eze/simva) 12 weeks	4 week diet run in, eze/simva or simva for 12 weeks.	**LDL-c reduction % from baseline at week 12:** simva -26.3 vs.. Eze/simva -33.7 (p < 0.05) **HDL-c increase % from baseline at week 12:** simva 3.3 vs.. Eze/simva 6.0 (p=ns)

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Safety/Comments	Funding Source
Bays H, et al 2004 R(1:1:1:1:1:1:1:1::1:1) , DB, MC, PC, ITT 1,528 patients randomized (n= 148 placebo, 149 eze, 622 pooled simva, 609 pooled eze/simva) 12 weeks	placebo vs. eze vs. pooled simva vs. pooled eze/simva Treatment related AEs 54.1 vs.. 53 vs.. 53.4 vs. 57.5 Serious AEs 1.4 vs. 1.3 vs. 1.8 vs. 1.5 Serious treatment related AEs 0 vs. 0 vs. 0.2 vs. 0	Merck Research Laboratories,
Ose L, et al 2007 R(1:1:1:1:1:1) , DB, MC, AC, ITT 2959 patients randomized-2855 MITT (n= 1427 eze/simva and 1428 rosuvastatin) 14 weeks	Pooled simva vs. pooled eze/simva Number of patients with AEs 34.5% (193) vs. 34.9% (190) Drug-related AEs 5.5% (31) vs. 7.4% (40) Serious AEs 2.3% (13) vs. 2.0% (11) Discontinuations because of AEs 2.1% (12) vs. 2.0% (11) Discontinuations because of drug-related AEs 1.3% (7) vs. 0.9% (5) Discontinuations because of serious AEs 0.2% (1) vs.0.2% (1) Consecutive ALT and/or AST elevations $\geq$ 3 x ULN 1.3% (7/559) vs. 1.5% (8/540) CK elevations $\geq$ 10 x ULN 0.2% (1/559) vs. 0.2% (1/540)	Merck/ Schering-Plough Pharmaceuticals
Shankar, et al 2007 R(1:1) , DB, MC, AC, ITT 230 patients randomized (n= 116 simva, 609 114 eze/simva) 12 weeks	Simva vs. eze/simva Adverse events 34% vs. 35% Drug related AEs 26% vs. 29% GI complaints 16% vs. 18%	HeteroDrugs Unlimited

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria
Catapano A, et al 2006 R(1:1:1:1:1:1) , DB, MC, AC, ITT 2959 patients randomized-2855 MITT (n= 1427 eze/simva and 1428 rosuvastatin) 6 weeks	Men and women 18–81 years with LDL-C ≥ 145 mg/dL (3.7 mmol/L) and ≤ 250 mg/dL (6.5 mmol/L), fasting serum triglyceride (TG) level ≤ 350 mg/dL (4.0 mmol/L), alanine aminotransferase (ALT), aspartate aminotransferase (AST), or creatine kinase (CK) level ≤ 1.5 times the upper limit of normal (ULN), serum creatinine level ≤ 1.5 mg/dL (133 mmol/L), and HBA1c < 9.0% in patients with diabetes.	None reported

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Intervention	Results (mean changes in lipoprotein levels)
Catapano A, et al 2006 R(1:1:1:1:1:1) , DB, MC, AC, ITT 2959 patients randomized-2855 MITT (n= 1427 eze/simva and 1428 rosuvastatin) 6 weeks	10 weeks, 4 weeks placebo/diet run-in followed by 6 weeks active treatment of eve/simva vs. ros.	**LDL-C % change from baseline** ros 10 -45.8 vs. eze/simva 20 -51.5*** ros 20 -52.3 vs. eze/simva 40 -54.8** ros 40 -56.7 vs. eze/simva 80 -61.0*** all ros -51.6 vs all eze/simva -55.8*** ** p=0.001 *** p < 0.001 **HDL-C % change from baseline** ros 10 6.9 vs. eze/simva 20 7.0 ros 20 8.1 vs. eze/simva 40 8.3 ros 40 8.1 vs. eze/simva 80 7.6 all ros 7.6 vs. all eze/simva 7.6 P=NS ** p=0.001 *** p < 0.001

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Safety/Comments	Funding Source
Catapano A, et al 2006 R(1:1:1:1:1:1) , DB, MC, AC, ITT 2959 patients randomized-2855 MITT (n= 1427 eze/simva and 1428 rosuvastatin) 6 weeks	Pooled eze/simva vs., pooled ros One or clinical adverse events 29.2% vs. 31.1 Drug related adverse events 8.1% vs. 7.4% Serious adverse events 1.2% vs. 1.1%	Merck-Scering Plough Pharmaceuticals

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria
	Ezetimibe/Simvastatin (Vytorin) vs. Doubling of Statin dose	
Reckless J, 2008 (INFORCE) R(1:1) , open label, blinded endpoint, MC, AC, ITT 424 patients randomized (n= 213 eze/simva and 211 doubling of statin) 12 weeks	Men and women (≥18 years) hospitalized for investigation of a coronary event and taking a stable daily dose of one of the following statin medications for > 6 weeks prior, atorvastatin ; fluvastatin ; lovastatin; pravastatin; rosuvastatin or Simva	Congestive heart failure defined by NYA Class III or IV; poorly controlled (HBA1c > 9.0%) or newly diagnosed (within 3 months) type I or II diabetes; uncontrolled hypertension (systolic > 160 mmHg or diastolic > 100 mmHg); uncontrolled endocrine or metabolic disease known to influence serum lipids and lipoproteins; impaired renal function (creatinine ≥ 177 mmol/l) or nephrotic syndrome; alcohol consumption > 14 drinks per week; cancer diagnosis within the past 5 years (except for clinically cured cases with normal life expectancy); any medical condition that the investigator determined could limit a patient's evaluation or participation in the study; and treatment with excluded concomitant medications.
Roeters van Lennep H, 2008 (EASEGO) R(1:1) , open-label, MC, AC, ITT 367 patients randomized (n= 178 eze/simva and 189 doubling statin) 12 weeks	Men and women > 18 years of age with controlled stable DM2 (> 3 months) and/or established CHD. stable medical condition; stable daily statin dose of either atorvastatin 10 mg or simvastatin 20 mg for at least 4 weeks. LDL−C ≥ 2.5 mmol/L and < 5.0 mmol/L, TG ≤ 4.0 mmol/L and TC ≤ 7.0 mmol/L.	Cholesterol-lowering medication regime changed in the previous 4 weeks; any other investigational drug within 3 months; pregnant or lactating and any condition or situation which, might pose a risk to the patient or interfere with participation in the study; congestive heart failure NYHA class III or IV, uncontrolled hypertension with systolic blood pressure > 160 mmHg or diastolic > 100 mmHg; poorly controlled diabetes mellitus (HbA1c > 10.0%) or newly diagnosed diabetes mellitus (within 3 months) or a change in antidiabetic pharmacotherapy within 3 months; uncontrolled endocrine or metabolic disease ; impaired renal function (creatinine ≥ 177 µmol/L) or nephrotic syndrome; disorders of the hematologic, digestive or central nervous system, including CVD and degenerative disease that would limit study evaluation or participation; history of mental instability and/or drug/alcohol abuse within the past 5 years.
	Ezetimibe/Simvastatin (Vytorin) vs. Misc	
Farnier M, et al 2007 R (3:3:3:1), DB, MC, P/AC, ITT 611 patients randomized (Placebo (n = 60) eze/simva (n = 184) feno (n = 184) eze/simva + feno (n = 183)) 12 weeks	Men and women 18 through 79 years of age with mixed hyperlipidemia and no coronary heart disease (CHD) or CHD-risk equivalent disease (except for type 2 diabetes), or 10-year CHD risk >20%	homozygous familial hypercholesterolemia; type I or V hyperlipidemia; treatment with LDL apheresis; congestive heart failure ; uncontrolled cardiac arrhythmia; unstable hypertension; pancreatitis; inadequately controlled diabetes (HbA1c >8.5% or newly diagnosed within 3 months of screening); gallbladder, renal (serum creatinine N1.5 mg/dL), or active liver disease; uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins; pregnancy or lactation; contraindicated medications

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Intervention	Results (mean changes in lipoprotein levels)
Reckless J, 2008 (INFORCE) R(1:1) , open label, blinded endpoint, MC, AC, ITT 424 patients randomized (n= 213 eze/simva and 211 doubling of statin) 12 weeks	Doubling of the statin dose (n = 211) or Eze／Simva 10／40 mg (n = 213) for 12 weeks	LDL-c reduction % from baseline at week 12: eze/simva 27% vs.. doubling 4.2% (p < 0.001)
Roeters van Lennep H, 2008 (EASEGO) R(1:1) , open-label, MC, AC, ITT 367 patients randomized (n= 178 eze/simva and 189 doubling statin) 12 weeks	(1) doubling the statin dose or (2) switching to the ezetimibe/simvastatin 10/20 mg tablet in CHD/DM2 patients on the recommended starting doses of simvastatin 20 mg or atorvastatin 10 mg	**LDL-c reduction % from baseline at week 12:** eze/simva 29.1 vs. doubling 11.5 (p< 0.001) **HDL-c increase % from baseline at week 12:** eze/simva -2.6 vs. doubling 1.0 (p< 0.001)
Farnier M, et al 2007 R (3:3:3:1), DB, MC, P/AC, ITT 611 patients randomized (Placebo (n = 60) eze/simva (n = 184) feno (n = 184) eze/simva + feno (n = 183)) 12 weeks	Wash out, run in and one of 4 daily treatments for 12 weeks: EZE/SIMVA 10/20 mg + FENO 160 mg (EZE/SIMVA + FENO), FENO 160 mg, EZE/SIMVA 10/20 mg, or placebo.	**LDL-c reduction % from baseline at week 12:** Placebo 3.5 eze/simva 47.1 feno 15.7 eze/simva + feno 45.8 **HDL-c increase % from baseline at week 12:** Placebo 1.1 eze/simva 9.3 feno 18.2 eze/simva + feno 18.7

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Safety/Comments	Funding Source
Reckless J, 2008 (INFORCE) R(1:1) , open label, blinded endpoint, MC, AC, ITT 424 patients randomized (n= 213 eze/simva and 211 doubling of statin) 12 weeks	Eze/simva vs. doubling One or more clinical AEs 89.2% vs. 85.3% One or more lab AEs 4.9% vs. 6.4% Allergic reaction 6.6% vs. 6.6% Gallbladder related 0 vs. 0 Gastrointestinal AEs 7.0% vs. 11.8%	Merck／Schering-Plough Pharmaceuticals
Roeters van Lennep H, 2008 (EASEGO) R(1:1) , open-label, MC, AC, ITT 367 patients randomized (n= 178 eze/simva and 189 doubling statin) 12 weeks	Doubling vs. eze/simva All adverse events 66 (35%) vs. 64 (36%) Serious adverse events 7 (4%) vs. 9 (5%) Treatment-related adverse events 19 (10%) vs. 24 (13%) Gastrointestinal adverse events 10 (5%) vs. 10 (6%) Musculoskeletal adverse events 13 (7%) vs. 17 (10%) Laboratory adverse event 1 (1%) vs. 2 (1%)	Merck Sharp and Dohme and Schering Plough
Farnier M, et al 2007 R (3:3:3:1), DB, MC, P/AC, ITT 611 patients randomized (Placebo (n = 60) eze/simva (n = 184) feno (n = 184) eze/simva + feno (n = 183)) 12 weeks	Placebo vs eze/simva vs. feno vs. eze/simva + feno Number (%) of patients with- One or more AEs 18 (30.0) vs. 65 (35.3) vs. 87 (47.3) vs. 72 (39.3) Drug-related AEs 4 (6.7) vs. 13 (7.1) vs. 23 (12.5) vs. 16 (8.7) SAEs 2 (3.3) vs. 1 (0.5) vs. 3 (1.6) vs. 0 Drug-related SAEs 0 vs. 0 vs. 1 (0.5) vs. 0 ALT and/or AST $\geq$3 ULN (consecutive), 0 vs. 0 vs. 6 (3.3) vs. 5 (2.8) CK z10 ULN, 0 vs. 0 vs. 2 (1.1) vs. 0 Myopathy 0 vs. 0 vs. 0 vs. 0	Merck/Schering-Plough Pharmaceuticals

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria
Guyton J, et al 2008 R(2:2:5) , DB, MC, AC, ITT 1220 patients randomized-1112 MITT (n= 272 niacin, 272 eze/simva and 676 eze/simva+niacin) 24 weeks	Men and women aged 18 years to 79 years with LDL-C levels (130 to 190 mg/dl), triglyceride levels (500 mg/dl), and metabolic and clinical stability.	NR
	Lovastatin/Niacin-ER (Advicor) vs. Statin	
Bays H, et al 2003 R (1:1:1:1), Open label, MC, AC, modified ITT 315 patients randomized (niacin extended-release/lovastatin fixed-dose combination (1000/40 or 2000/40) (n=79 and 78) vs. atorvastatin (n=82) or simvastatin (n=76))	Women and men, 18 to 70 years old, with 2 consecutive baseline low-density lipoprotein (LDL) cholesterol blood levels ≥160 mg/dl without coronary artery disease, or ≥130 mg/dl if coronary artery disease was present. Other lipid inclusion criteria included triglycerides <300 mg/dl and high-density lipoprotein (HDL) cholesterol <45 mg/dl in men and <50 mg/dl in women.	Known prior allergy or intolerability to any of the study drugs, history of substance abuse or dependence within 12 months, >14 alcoholic drinks/week, uncontrolled psychiatric disease, participation in another investigational study within 30 days , or probucol administration within the previous year history of; active gallbladder disease; uncontrolled hypertension; renal insufficiency (serum creatinine 1.5 mg/dl); hepatic dysfunction ; fasting glucose 115 mg/dl; New York Heart Association class III/IV congestive heart failure; active gout symptoms or uric acid 1.3 times the upper limit of normal; active peptic ulcer disease; type 1 or 2 diabetes; fibromyalgia; cancer within the previous 5 years (except for basal cell carcinoma); unstable angina, myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or stroke within prior 6 months; or any condition or laboratory abnormality.

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Intervention	Results (mean changes in lipoprotein levels)
Guyton J, et al 2008 R(2:2:5) , DB, MC, AC, ITT 1220 patients randomized-1112 MITT (n= 272 niacin, 272 eze/simva and 676 eze/simva+niacin) 24 weeks	eze/simva (10/20 mg) or niacin (titrated to 2 g), eze/simva (10/20 mg) + niacin (titrated to 2 g) for 24 weeks	**LDL-c reduction % from baseline at week 24:** eze/simva -53.2 niacin -17.0 eze/simva+niacin -56.8 vs.. niacin (p< 0.001) vs. eze/simva (p=0.007) **HDL-c increase % from baseline at week 24:** eze/simva 7.3 niacin 22.6 eze/simva+niacin 25.1 vs.. niacin (p> 0.05) vs. eze/simva (p<0.001) From on-line appendix
Bays H, et al 2003 R (1:1:1:1), Open label, MC, AC, modified ITT 315 patients randomized (niacin extended-release/lovastatin fixed-dose combination (1000/40 or 2000/40) (n=79 and 78) vs. atorvastatin (n=82) or simvastatin (n=76))	Niacin extended-release/lovastatin fixed-dose combination(1000/40 or 2000/40) vs. Atorvastatin (10-40) or simvastatin (10-40) .	**LDL-c reduction % from baseline at week 16:** Niacin ER/Lovastatin 1000/40 39 Niacin ER/Lovastatin 2000/40 42 atorvastatin 49 simvastatin 39 niacin ER/lovastatin 2,000/40 mg vs. simvastatin (p =ns) or atorvastatin (p<0.001). **HDL-c increase % from baseline at week 16:** Niacin ER/Lovastatin 1000/40 17 Niacin ER/Lovastatin 2000/40 32 atorvastatin 6 simvastatin 7 Niacin ER/lovastatin vs. Atorvastatin or simvastatin at all compared doses (p <0.001)

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Safety/Comments	Funding Source
Guyton J, et al 2008 R(2:2:5) , DB, MC, AC, ITT 1220 patients randomized-1112 MITT (n= 272 niacin, 272 eze/simva and 676 eze/simva+niacin) 24 weeks	Eze/simva vs. niacin vs eze/simva + niacin One or more AE 62.9% vs.. 82.4% vs. 75.2% Drug related AE 18.4% vs. 59.9% vs. 54.2% Serious AE 2.6% vs. 2.6% vs. 2.1% Serious drug related AE 0.4 vs. 0 vs. 0 Death 0.4% vs. 0 vs. 0 Discontinuations 25% vs. 9.6% vs. 23.3% New onset diabetes 0.9% vs. 2.2% vs 4.4% Eze/simva+niacin vs eze/simva (p = 0.009) Lab AEs 7.4% vs. 7.0% vs. 5.1%	Merck/Schering-Plough Pharmaceuticals
Bays H, et al 2003 R (1:1:1:1), Open label, MC, AC, modified ITT 315 patients randomized (niacin extended-release/lovastatin fixed-dose combination (1000/40 or 2000/40) (n=79 and 78) vs. atorvastatin (n=82) or simvastatin (n=76))	One study subject receiving atorvastatin withdrew due to myalgias. Otherwise, no significant differences were seen in the incidence of rash, hyperglycemia, hyperuricemia, or gastrointestinal complaints between treatment groups.	Kos Pharmaceuticals

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria
Lin, et al 2006 R (1:1), DB, SC (Taiwan), AC, modified ITT 70 patients randomized (modified ITT 61) (niacin extended-release/lovastatin fixed-dose combination (n=36 (31)) vs. or simvastatin (n=34(30)))	≥ 20 years of age; failure to control LDL-C level under the 4-week therapeutic lifestyle changes (TLC); hyperlipidemia, CHD and CHD risk equivalents, receiving concomitant treatment other than lipid-control treatment that was known to affect lipid level and dose maintained unchanged throughout the study; male/female subject with reproductive potential is under appropriate contraception; compliance and geographic proximity to the study site and willing to participate.	TG > 500 mg/dL; breast feeding in female subject; pregnancy or not exercising appropriate birth control during course of study; type I diabetes; uncontrolled type II diabetes requiring insulin treatment; uncontrolled hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg); uncontrolled hypothyroidism; acute myocardial infarction within the proceeding 3 months; insufficient renal function (serum creatinine > 2.0 mg/dL); insufficient liver function (aspartate aminotransferase, AST/alanine aminotransferase, ALT > 2 times normal); severe peptic ulcer disease; not able to stop concomitant lipid-control treatment during the study; history of hypersensitivity to product being investigated; drug or alcohol abuse.

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Intervention	Results (mean changes in lipoprotein levels)
Lin, et al 2006 R (1:1), DB, SC (Taiwan), AC, modified ITT 70 patients randomized (modified ITT 61) (niacin extended-release/lovastatin fixed-dose combination (n=36 (31)) vs. or simvastatin (n=34(30)))	5-week wash out, 16-week drug treatment, and 4-week follow-up period	**LDL-c reduction % from baseline at week 16:** Niacin ER/Lovastatin 30.5 vs. simvastatin 36 (p=0.159) **HDL-c increase % from baseline at week 16:** Niacin ER/Lovastatin 10.4 vs. simvastatin 2.2 (p=0.029)

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Safety/Comments	Funding Source
Lin, et al 2006 R (1:1), DB, SC (Taiwan), AC, modified ITT 70 patients randomized (modified ITT 61) (niacin extended-release/lovastatin fixed-dose combination (n=36 (31)) vs. or simvastatin (n=34(30)))	Niacin ER/Lovastatin 30 vs. simvastatin Arrhythmia 3 (8.6%) vs. 1 (3.0%) Arteriosclerosis 4 (11.4%) 2 (6.1%) Cardiovascular disorder 9 (25.7%) vs 12 (36.4%) Myocardial ischemia 3 (8.6%) vs. 2 (6.1%) Palpitation 6 (17.1%) vs. 2 (6.1%) Pericardial effusion 1 (2.9%) vs. 3 (9.1%) Vascular disorder 5 (14.3%) vs. 1 (3.0%) Dyspepsia 2 (5.7%) vs. 5 (15.2%) Flatulence 2 (5.7%) vs. 3 (9.1%) Nausea 1 (2.9%) vs.3 (9.1%) Edema/cramp/pain 8 (22.9%) vs.2 (6.1%) Dizziness 8 (22.9%) vs 11 (33.3%) Insomnia 4 (11.4%) vs. 2 (6.1%) Cough and sputum 3 (8.6%) vs. 8 (24.2%) Pharyngitis 3 (8.6%) vs. 4 (12.1%) Pruritus or rash 2 (5.7%) vs. 4 (12.1%)	Lotus pharmaceutical

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Inclusion Criteria/ Patient Population	Exclusion criteria
	Simvastatin/Niacin-ER (Simcor) vs. Statin	
Ballantyne C, et a l 2008 (SEACOAST I study) R (2:2:1), DB, MC, AC, modified ITT (completers analysis) 319 patients randomized Simvastatin (20 mg/d) (n =121) vs.. NER/S (1,000/20 mg/d) (n = 127) vs.NER/S (2,000/20 mg/d) (n = 66) 6 weeks	Increased ATP III risk-adjusted non–HDL cholesterol at screening; men and women aged 21 years; Women could not be pregnant or breast-feeding or planning to conceive or breast-feed during the study. Patients had to comply reasonably with a standard cholesterol-lowering diet for at least 4 weeks and be willing to comply with this diet for the duration of the study.	Aspartate aminotransferase or alanine aminotransferase ≥1.3 times the upper limit of normal, calculated creatinine clearance < 30 ml/min, creatine kinase ≥ 3 times the upper limit of normal, hemoglobin A1c ≥ 9%, and active gout symptoms and/or uric acid level > 1.3 times the upper limit of normal.

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Intervention	Results (mean changes in lipoprotein levels)
Ballantyne C, et a l 2008 (SEACOAST I study) R (2:2:1), DB, MC, AC, modified ITT (completers analysis) 319 patients randomized Simvastatin (20 mg/d) (n =121) vs.. NER/S (1,000/20 mg/d) (n = 127) vs.NER/S (2,000/20 mg/d) (n = 66) 6 weeks	A screening phase, an open-label simvastatin run-in phase, a lipid qualification phase, and a double-blind treatment phase of 6 weeks.	Median % change in Non-HDL Cholesterol Simvastatin -7.4 NER/S (1000/20) -13.9 p < 0.01 compared with simvastatin 20 mg/day NER/S (2000/20) -22.5 p < 0.001 compared with simvastatin Median % change in LDL Cholesterol Simvastatin -7.1 NER/S (1000/20) -13.1 NER/S (2000/20) -14.2 Median % change in HDL Cholesterol Simvastatin 6.7 NER/S (1000/20) 18.3 p < 0.001 compared with simvastatin NER/S (2000/20) 24.9 p < 0.001 compared with simvastatin

Evidence Table 5. Trials comparing LDL-c lowering and HDL-c raising abilities of fixed-dose combination products

Clinical Trial	Safety/Comments	Funding Source
Ballantyne C, et a l 2008 (SEACOAST I study) R (2:2:1), DB, MC, AC, modified ITT (completers analysis) 319 patients randomized Simvastatin (20 mg/d) (n =121) vs.. NER/S (1,000/20 mg/d) (n = 127) vs.NER/S (2,000/20 mg/d) (n = 66) 6 weeks	Simvastatin (20 mg/d) vs.. NER/S (1,000/20 mg/d) vs.NER/S (2,000/20 mg/d) Any adverse events 20 (17.5%) vs.31 (25.2%) vs. 23 (35.9%) P < 0.05 vs. Sim Serious adverse events 0 (0.0%) vs.1 (0.8%) vs. 0 (0.0%) Discontinuation due to adverse events† 6 (5.3%) vs.15 (12.2%) vs.10 (15.6%) Discontinuation due to flushing 0 (0.0%) vs.8 (6.5%) vs. 6 (9.4%) Deaths 0 (0.0%) vs. 0 (0.0%) vs. 0 (0.0%) Flushing‡ 0 (0.0%) vs.9 (7.3%) P < 0.05 vs. Sim vs.7 (10.9%) P < 0.05 vs. Sim Headache 1 (0.9%) vs. 3 (2.4%) vs.3 (4.7%) Hyperglycemia 0 (0.0%) 2 (1.6%) 2 (3.1%) Vomiting 1 (0.9%) vs. 0 (0.0%) vs. 2 (3.1%) P < 0.05 vs.. NER/S (1,000/20 mg/d) Gastritis 2 (1.8%) vs.0 (0.0%) vs. 2 (3.1%) Hypertension 3 (2.6%) vs. 0 (0.0%) 1 (1.6%) Abdominal pain (upper) 3 (2.6%) vs.1 (0.8%) vs. 0 (0.0%) Nausea 1 (0.9%) vs. 3 (2.4%) vs. 1 (1.6%)	Abbott

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Studies from Evidence Table 1 (H2H)						
Andrews, 2001	Yes	Not reported	Yes	Yes	No	No
Assman, 1999	Yes	Not reported	Yes	Yes	No details given	No details given
Ballantyne C, 2006 (MERCURY II)	Method NR	NA	Yes	Yes	No	No
Bays, 2005	Method not reported	Not reported	Yes	Yes	No- open label	No- open label
Berger, 1996	Method not reported	Not reported	Yes	Yes	No	No
Berne, 2005	Method not reported	Not reported	Yes	Yes	Yes	Not reported

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
Studies from Evidence Table 1 (H2H)					
Andrews, 2001	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.
Assman, 1999	No details given	No	Yes	Attrition: yes, but no details on reasons for withdrawal, crossovers-no, adherence-yes, contamination-no	No
Ballantyne C, 2006 (MERCURY II)	NA- open label	Yes	Yes	Attrition-208 (10.4%), crossovers-no, adherence-no, contamination-no	No
Bays, 2005	No- open label	Unable to determine. States used intention to treat, but not defined.	Unable to determine.	No.	Not reported
Berger, 1996	No	Yes	Yes	No	Not clear
Berne, 2005	Described as "double-blind", but no details	No (465/469 analyzed)	Yes	Attrition yes, others no.	No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
Studies from Evidence Table 1 (H2H)	
Andrews, 2001	Poor-high early withdrawal rate, no reasons noted. LDL-c for Simva not as great as atorva and % meeting LDL-c also lower, possible that doses of simva not titrated properly? For safety - unknown what doses for serious adverse effects.
Assman, 1999	Fair-poor-LDL no details on blinding, Poor-safety no details on dose related adverse effects.
Ballantyne C, 2006 (MERCURY II)	Fair
Bays, 2005	Fair-Poor
Berger, 1996	Fair
Berne, 2005	Fair

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Bertolini, 1997	Yes	Not reported	Yes, not much detail	Yes	Yes	Yes
Betterridge D, 2007 (ANDROMEDA)	Yes	NR	Yes	Yes	NR	NR
Bevilacqua M, 2005	Method NR	Not reported	Yes	Yes	Yes	No
Binbrek A, 2006 (DISCOVERY-Alpha)	Yes	Yes	Yes	Yes	No	No
Bots A, 2005 (Dutch DISCOVERY)	Method NR	NR	Yes	Yes	Method NR	Method NR
Branchi, 2001	Yes	Not reported	Not enough detail given	Yes	Not reported	Not reported
Brown, 1998	Yes	Not reported	Yes	Yes	No	No
Calza L, 2008	Method NR	NR	Yes	Yes	NR	NR

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
Bertolini, 1997	Yes	No	Yes	Attrition-reported but no details on reasons for withdrawal. Crossovers-no, adherence to treatment-yes, contamination-no	No
Betterridge D, 2007 (ANDROMEDA)	Yes but method not reported	Yes mITT	Yes	Attrition-52 (10.2%); crossovers-no; adherence-no; contamination-no	No
Bevilacqua M, 2005	No	Yes	Yes	Attrition-5 (5.3%), crossovers-no, adherence-no, contamination-no	No
Binbrek A, 2006 (DISCOVERY-Alpha)	Yes	Yes	Yes	Attrition-114 (7.6%), crossovers-no, adherence-no, contamination-no	No
Bots A, 2005 (Dutch DISCOVERY)	Yes but method not reported	Yes	Yes	Attrition-34 (2.8%), crossovers-no, adherence-no, contamination-no	No
Branchi, 2001	Not reported	No	Not enough detail provided-age, etc.	Attrition-yes, crossovers-no, adherence-no, contamination-yes	No
Brown, 1998	No	No	Yes	Attrition-only reported for adverse effects, crossovers-no, adherence-yes-contamination-no	No
Calza L, 2008	NR	No	NR	Attrition-9 (9.6%), crossovers-no, adherence-yes, contamination-no	No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
Bertolini, 1997	Fair-LDL lowering Poor-safety (no details on serious adverse effects and dropouts).
Betterridge D, 2007 (ANDROMEDA)	Fair-LDL lowering Poor-safety (no details on serious adverse effects and dropouts).
Bevilacqua M, 2005	Fair-LDL lowering Poor-safety (no details on serious adverse effects and dropouts).
Binbrek A, 2006 (DISCOVERY-Alpha)	Fair
Bots A, 2005 (Dutch DISCOVERY)	Fair
Branchi, 2001	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.
Brown, 1998	Fair-LDL lowering equivalent doses not compared, treat to target. Safety-poor no details on reasons for withdrawal due to adverse effects or doses.
Calza L, 2008	Poor to fair

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Chan, 2004	Study states "blindly randomized," but no details given.	Study states "blindly randomized," but no details given.	Yes	Yes	Study states "blindly randomized," but no details given.	Study states "blindly randomized," but no details given.
Clearfield M, 2006 (PULSAR)	Yes	NR	Yes	Yes	NR	NR
Dart, 1997	Yes	Not reported	Yes	Yes	Yes	Yes
Davidson, 1997	Yes	Not reported	Yes	Yes	Yes	Yes
Deedwania P, 2007	Method NR	NR	Yes	Yes	NR	NR
Discovery-UK group, 2006	Method NR	NA	Yes	Yes	No	No
Faergeman O, 2008 (ECLIPSE)	Method NR	NA	Yes	Yes	No	No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
Chan, 2004	Study states "blindly randomized," but no details given.	Not clear	Not reported	Attrition - yes, crossovers - no, adherence - yes, contamination - no.	No (atorv: 5 withdrawals (8.3%) and simva 7 withdrawals (11.7%))
Clearfield M, 2006 (PULSAR)	No - open label	Yes	Yes	Attrition-42 (4.2%), crossovers-no, adherence-no contamination-no	No
Dart, 1997	Yes	No	Yes	Attrition-reported but no details on reasons for withdrawal. Crossovers-no, adherence to treatment-no, contamination-no.	No
Davidson, 1997	Yes	Unsure	Yes	Attrition-yes, crossovers-no, adherence-yes, contamination-no	No
Deedwania P, 2007	Yes	Modified ITT	Yes	Attrition-142 (15.9%, crossovers-no, adherence-yes, contamination-no	No
Discovery-UK group, 2006	No - open label	Modified ITT	Yes	Attrition-114 (6.1%), crossovers-no, adherence-no, contamination-no	No
Faergeman O, 2008 (ECLIPSE)	No - open label	Yes with LOCF (97.9%)	Yes	Attrition-117 (11.3%), crossovers-no, adherence-no, contamination-no	No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
Chan, 2004	Poor to fair
Clearfield M, 2006 (PULSAR)	Fair
Dart, 1997	Fair-LDL lowering Poor-safety (no details on serious adverse effects, dose and dropouts).
Davidson, 1997	Fair-LDL lowering Poor-safety (no details on serious adverse effects and dropouts).
Deedwania P, 2007	Fair
Discovery-UK group, 2006	Fair
Faergeman O, 2008 (ECLIPSE)	Fair

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Farnier, 2000	Yes	Not reported	Yes	Yes	Yes	No
Ferdinand, 2006	Method not reported	Not reported	Yes	Yes	No- open label	No- open label
Fonseca, 2005	Method not reported	Not reported	Yes	Yes	No- open label	No- open label
Gentile, 2000	Yes	Not reported	Yes	Yes	No	No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
Farnier, 2000	No	Yes	Yes	Attrition reported for adverse effects but no details for other reasons for withdrawal. crossovers-no, adherence-yes, contamination-no	No
Ferdinand, 2006	No- open label	No- analyzed patients with at least one dose of study medication and 1 baseline and 1 post-baseline lipid evaluation; used LOCF for dropouts.	Yes	Attrition yes, others no	No (2% rosuva, 1.3% atorva)
Fonseca, 2005	No- open label	No- analyzed patients who had a baseline measurement and received at least one dose of study medication; used LOCF for those who withdrew before 12 weeks. 94.7% of rosuva, 96.6% atorva included in ITT analysis.	Unable to determine	Attrition yes, others no	rosuva 8.2%, 4.8% atorva
Gentile, 2000	No	No	Yes	Attrition-yes, crossovers-no, adherence-no, contamination-yes	No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
Farnier, 2000	Fair-poor-LDL lowering, open-label, no details on withdrawal. Poor-safety-minimal details provided on adverse effects for each group.
Ferdinand, 2006	Fair
Fonseca, 2005	Fair
Gentile, 2000	Fair-poor LDL lowering. Nonequivalent doses compared. Fair-safety.

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Gratsianskii N, 2007	NR	NR	Yes except in series one placebo group older	Yes but not clearly	NR	NR
Hadjibabaie M, 2006	NR	NA	Yes	Yes	No	No
Herregod M, 2008 (Discovery-Bleux)	Method NR	NR	Yes	Yes	No	No
Hunninghake, 1998	Yes	Not reported	Yes	Yes	No	No
Illingworth, 2001	Yes	Not reported	More women in the atorva group	Yes	Yes	Yes
Insull W, 2007 (SOLAR)	Method NR	NA	Yes	Yes	No - open label	No - open label
Insull, 2001	Yes	Not reported	Yes	Yes	No	No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
Gratsianskii N, 2007	NR	Unable to determine, NR	Yes	None is reported	NR
Hadjibabaie M, 2006	No - open label	No - completers analysis	Yes	Attrition 7 (12%), others no	No
Herregod M, 2008 (Discovery-Bleux)	No - open label	Yes	Yes	Attrition-106 (11.3%), crossovers-no, adherence-no, contamination-no	No
Hunninghake, 1998	No	No	Yes	Attrition-not reported, crossovers-no, adherence-yes, contamination-no	No
Illingworth, 2001	Yes	No	More women in the atorva group	Attrition-only reported for adverse effects; Crossovers-no; Adherence-no; Contamination-no	Do not know
Insull W, 2007 (SOLAR)	No - open label	Yes at 6 weeks but at 12 weeks used observed cases	Yes	Attrition-138 (8.5%), crossovers-no, adherence-yes, contamination-no	No
Insull, 2001	No	No	Yes	Attrition-no, crossovers-no, adherence-no, contamination-no	Do not know

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
Gratsianskii N, 2007	Poor
Hadjibabaie M, 2006	Poor
Herregod M, 2008 (Discovery-Bleux)	Fair
Hunninghake, 1998	Fair-LDL lowering equivalent doses not compared, treat to target. Safety-poor no details on reasons for withdrawal due to adverse effects or doses.
Illingworth, 2001	Fair-LDL-lowering, Fair-good-safety
Insull W, 2007 (SOLAR)	Fair
Insull, 2001	Poor-equivalent doses not compared. Fair-safety although short-term study.

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Jacotot, 1995	Yes	Not reported	Yes, for height, weight, BMI	Yes	Yes	Yes
Jones,1998	Yes	Not reported	Yes-not much detail. LDL-c slightly lower for 3 of 4 atorva groups.	Yes	No	No
Jukema, 2005	Method not reported	Not reported	Yes	Yes	No-open label	No- open label
Kai T, 2008	Not randomized	Open-Label	Before and After, so Yes	Yes	No-open label	No-open label
Karalis, 2002	Method not reported	Not reported	Some differences- more men in atorva 10mg than simva 20mg, and BP higher in simva vs atorva group.	Yes	Yes	Not reported
Lloret R, 2006 (STARSHIP trial)	Method NR	NA	Yes	Yes	No - open label	No - open label

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
Jacotot, 1995	Yes	Yes and on treatment analysis too.	Yes	Attrition-yes, crossovers-no, adherence-no, contamination-no	No
Jones,1998	No	No	Yes, but LDL-c lower for 3 of 4 atorva groups	Attrition-yes, crossovers-no, adherence-no, contamination-no	No
Jukema, 2005	No- open label	Yes (used LOCF)	Yes	Attrition yes, others no.	No
Kai T, 2008	No-open label	Yes	Yes	No	Not reported
Karalis, 2002	No	No	Not enough detail provided	No	Not reported
Lloret R, 2006 (STARSHIP trial)	No - open label	Yes	Yes	Attrition-56 (8.4%), crossovers-no, adherence-no, contamination-no	No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
Jacotot, 1995	Fair-LDL lowering. Fair-safety although no doses provided at which adverse effects occurred.
Jones,1998	Fair-poor LDL lowering. Small sample size in certain groups and LDL-c was lower for 3 out of 4 atorva groups. Fair-poor-safety. Eight patients lost to follow up.
Jukema, 2005	Fair
Kai T, 2008	Fair-poor Small sample size. The patients were compared against their own baseline scores while on simvastatin, no real comparison group.
Karalis, 2002	Poor- differences at baseline, randomization and allocation methods not reported, not ITT, withdrawals not clear.
Lloret R, 2006 (STARSHIP trial)	Fair

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Marz,1999	Yes	Not reported	Yes	Yes	Yes-serious adverse effects	No
Mazza F, 2008	Method NR	NA	Yes	Yes	NA - open label	NA - open label
Milionis H, 2006 (ATOROS study)	Method NR	NA	Yes	Yes	NR	NR
Mulder D, 2007	Method NR	NR	NO BMI was sig more in atorva	Yes	NR	NR
Murakami T, 2006	NR	NR	Yes-minimal	Yes-minimal	NR	NR
Nash,1996	Yes	Not reported	No-higher rate of musculo-skeletal conditions in lova group.	Yes	No	No
Olsson, 2003	Method not reported	Not reported	Yes	Yes	Yes	Yes
Ose, 1995	Yes	Not reported	Yes	Yes	Yes	Yes

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
Marz,1999	No	Do not know	Yes	Attrition-reported, crossovers-no, adherence-no, contamination-no	No
Mazza F, 2008	NA - open label	Yes	Yes	Attrition-no, crossovers-no, adherence-no, contamination-no	No
Milionis H, 2006 (ATOROS study)	NA	Yes	Yes	Attrition-yes, crossovers-no, adherence-no, contamination-no	No
Mulder D, 2007	NR	No	Yes	Attrition-yes, crossovers-no, adherence-yes, contamination-no	16 dropped and 44 others excluded (total 26%)
Murakami T, 2006	Yes	No	NR	Attrition-yes, crossovers-no, adherence-yes, contamination-no	Not reported
Nash,1996	No	Yes	No-higher musculoskeletal conditions in lova.	Attrition-yes, crossovers-no, adherence-yes, contamination-no	No
Olsson, 2003	Yes	No	Yes	Attrition and adherence yes, others no	No
Ose, 1995	Yes	No	Yes	Attrition-yes, crossovers-no, adherence-yes, contamination-no	No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
Marz,1999	Fair-LDL-lowering, Fair-safety although no details on dose at which adverse effects occurred.
Mazza F, 2008	Fair
Milionis H, 2006 (ATOROS study)	Fair
Mulder D, 2007	Poor- lack of ITT and high loss to follow up.
Murakami T, 2006	Poor
Nash,1996	Fair-LDL lowering. Poor-safety since higher rate of musculo-skeletal conditions in lova group. Also no doses at which adverse effects in fluva group occurred.
Olsson, 2003	Fair
Ose, 1995	Fair-LDL lowering. Fair-safety.

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Paragh, 2004	Yes, though method not reported	Not reported	Not reported	Yes	No - open label	Not reported - open label
Recto, 2000	Yes	Not reported	Yes	Yes	No	No
Saklamaz, 2005	Method not reported	Not reported	Yes	Yes	Not reported	Not reported
Schaefer, 2003	Method not reported	Not reported - open label	Yes	Yes	No - open label	Not reported - open label
Schulte, 1996	Yes	Not reported	Yes	Yes	Yes	Yes
Schuster, 2004	Yes	Not reported	Yes	Yes	No - open label	Not reported - open label
Schwartz, 2004	Yes	Not reported	Yes	Yes	Yes	Not reported
Sigurdsson, 1998	Method not reported	Not reported	Simva group slightly older (61.4 years vs 59.3 years, p=0.059)	Yes	Yes	Not reported

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
Paragh, 2004	No - open label	Not clear	N/A - it was a crossover study.	Attrition - no, crossovers - no, adherence - no, contamination - no.	Not reported
Recto, 2000	No	No	Yes	Attrition-yes, crossovers-yes, adherence-not reported, contamination-N/A	No
Saklamaz, 2005	Not reported	Yes	Yes	No	No loss to followup
Schaefer, 2003	No - open label	Yes	Not reported	Attrition - no; crossovers - no; adherence - no; contamination - no.	Not reported
Schulte, 1996	Yes	Unable to determine	Yes	Attrition-no, crossovers-no, adherence-yes, contamination-no	Unable to determine the number completing study
Schuster, 2004	No - open label	Yes	Not reported	Attrition -yes, crossovers - no, adherence - yes, contamination - no.	No
Schwartz, 2004	Yes	Yes	Not reported	Attrition -yes, crossovers - yes, adherence - no, contamination - no.	No
Sigurdsson, 1998	Yes	Yes	Yes	Attrition yes, others no.	No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
Paragh, 2004	Poor to fair. Poor - safety. No specific details about adverse events or withdrawals given.
Recto, 2000	Fair-LDL lowering. Fair-safety included details on withdrawal and adverse effects.
Saklamaz, 2005	Fair
Schaefer, 2003	Fair/poor-LDL lowering: No drop-out data nor loss to follow-up data given. Poor - safety: no data given on any adverse effects nor on withdrawals due to adverse effects.
Schulte, 1996	Fair-poor-LDL lowering: Drop outs and loss to follow up not given. Fair-poor safety: not sure how many actually dropped out due to adverse effects.(?2)
Schuster, 2004	Fair
Schwartz, 2004	Fair - This study was designed to look at paraoxonase activity. Poor - safety. No specific details about adverse events or withdrawals given.
Sigurdsson, 1998	Fair

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Stalenhoef	Method not reported	Not reported	Yes	Yes	Yes	Not reported
Strandberg, 2004	Yes	Not reported	Yes	Yes	No - open label	Not reported - open label
Van Dam, 2000	Yes-computer lists (adequate)	Not reported	No-patient risk factors Yes-lipoprotein levels	Yes	Yes	Yes
Wolffenbuttel, 1998	Yes	Not reported	N/A cross-over trial	Yes	No	No
Wolffenbuttel, 2005	Method not reported	Not reported	Yes	Yes	No- open label	No- open label
Wu S, 2005	NA	NR	N/A cross-over trial	Yes	No	No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
Stalenhoef	Described as "double-blind", but no details	No (397/401 analyzed)	Yes	Attrition yes, others no	No
Strandberg, 2004	No - open label	Yes	Not reported	Attrition - yes, crossovers - no, dherence - no, contamination - no.	No.
Van Dam, 2000	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
Wolffenbuttel, 1998	No	No	N/A-cross-over	Attrition-yes, crossovers-yes, adherence-no, contamination-no	No
Wolffenbuttel, 2005	No- open label	Yes (used LOCF)	Yes	Attrition due to AEs only reported.	No
Wu S, 2005	NR	No	N/A-cross-over	Attrition-yes, crossovers-yes, adherence-no, contamination-no	No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
Stalenhoef	Fair
Strandberg, 2004	Fair
Van Dam, 2000	Fair-poor-LDL single-blinded, not intent to treat, 14% loss to follow up, Poor-safety no details on dose related adverse effects or withdrawals.
Wolffenbuttel, 1998	Fair-LDL lowering, Fair-poor safety. Short-term trial using relatively low statin doses.
Wolffenbuttel, 2005	Fair
Wu S, 2005	Fair

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Studies from Evidence Table 2 (CHD)						
4S 1994	Yes	Yes	Yes	Yes	Yes	Yes
A to Z de Lemos, 2004	Yes	Yes	More simvastatin patients had prior MI (18% vs 16%, p=0.05), otherwise similar	Yes	Yes	No details given
AFCAPS 1998	Yes	Not reported	Yes	Yes	Yes	Yes
ALLHAT-LLC *(open trial)*	Adequate; computer-generated scheme	adequate; centralized	Yes	Yes	No	No
Patti et al, 2007 (ARMYDA-ACS)	Yes, computer generated	Not reported	Yes	Yes	Yes	Yes

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
Studies from Evidence Table 2 (CHD)					
4S 1994	Yes	Yes	Yes	Attrition-yes, crossovers-no, adherence-reported as good with no details provided, and contamination-no.	No
A to Z de Lemos, 2004	Yes	Yes	Yes	Attrition yes,	No
AFCAPS 1998	Yes	Yes	Yes	Attrition-yes, crossovers-no actual numbers provided, adherence-yes and contamination-no actual numbers provided.	No
ALLHAT-LLC *(open trial)*	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
Patti et al, 2007 (ARMYDA-ACS)	Yes	Unclear, 191 patients randomized, but 171 patients were analyzed because 20 patients (10 from each group) did not receive angioplasty	Yes	Attrition-yes, others-no	No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
Studies from Evidence Table 2 (CHD)	
4S 1994	Good
A to Z de Lemos, 2004	Fair
AFCAPS 1998	Good
ALLHAT-LLC *(open trial)*	Fair-Good
Patti et al, 2007 (ARMYDA-ACS)	Fair

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Arntz et al, 2000 (L-CAD)	Method not reported	Not reported	Yes	Yes	Yes	Yes
ASCOT	NR	NR	Yes	Yes	Yes	Yes
Cannon et al, 2004 (PROVE-IT)	Method not reported	Not reported	History of peripheral arterial disease more common in prava group, uneven treatment group sizes.	Yes	Yes	Not reported
Colhoun, 2004 (CARDS)	Yes	Yes	Yes	Yes	Yes	Yes
CARE 1996	Yes	Yes	Yes	Yes	Yes	Yes
Den Hartog (Pilot Study)	Yes	Not reported	Some differences	Yes	Yes	Not reported

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
Arntz et al, 2000 (L-CAD)	Yes	Yes- able to calculate	Yes	Attrition yes, others no	Yes: 9 patients in control group withdrew consent after learning treatment assignment.
ASCOT	Yes	Yes	NR	Attrition unclear; others NR	No
Cannon et al, 2004 (PROVE-IT)	Yes	Not clear	Yes	Attrition yes, others no	No.
Colhoun, 2004 (CARDS)	Yes	4 patients not included, but able to calculate	Yes	attrition, adherence yes, others no.	No
CARE 1996	Yes	Yes	Yes	Attrition: yes, crossovers-no, adherence-no, and contamination-yes	No
Den Hartog (Pilot Study)	Yes	Yes	No	Attrition yes, others no	No, 2 placebo vs 0 prava lost to followup. High discontinuation rate (22%) and more placebo patients discontinued overall (26.5% vs 16%)

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
Arntz et al, 2000 (L-CAD)	Fair
ASCOT	Fair-Good
Cannon et al, 2004 (PROVE-IT)	Fair
Colhoun, 2004 (CARDS)	Good
CARE 1996	Good
Den Hartog (Pilot Study)	Poor

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Heljic B, 2009	Method not reported	Not reported	Yes	Yes	NR	NR
Hogue J, 2008	Method not reported	Not reported	Yes	Yes	NR	NR
Holdaas	NR	Adequate; serially-numbered identical medication packs	Yes	Yes	Yes	Yes
HPS	NR	Adequate; centralized	Unclear; "good balance" indicated; data NR	Yes	Yes	Yes
Pederson, 2005 (IDEAL)	NR	NR	Yes	Yes	Yes	No- open label, blinded endpoint classification

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
Heljic B, 2009	NR	Unclear--not reported	Unclear	NR NR NR NR	NR
Hogue J, 2008	NR	Unclear--not reported (5% in atorva arm vs 1.5% in placebo arm were lost to f/u)	Unclear	Yes NR NR NR	No No
Holdaas	Yes	Yes	NR	Attrition=314 (14.9%); others NR	No
HPS	Yes	Yes	NR	Attrition=13.9%; Crossovers NR; Adherence (>/= 80%)=82%; Contamination=4002(19.5%) taking non-study statin	No
Pederson, 2005 (IDEAL)	No- open label, blinded endpoint classification	Yes	Yes	Attrition and adherence reported.	No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
Heljic B, 2009	Poor
Hogue J, 2008	Fair-Poor
Holdaas	Good
HPS	Good
Pederson, 2005 (IDEAL)	Fair

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Ridker P, 2008 JUPITER	Yes	Yes	Yes	Yes	Stated "double-blind" but no details	Stated "double-blind" but no details
Liem et al, 2002 (FLORIDA)	Method not reported	Not reported	Yes	Yes	States "double blind," but no details.	Not reported
LIPID 1998	Yes	Not reported	Yes	Yes	Yes	Yes
Nakamura et al, 2006 MEGA	Yes, computer-generated list	Not reported	Yes	Yes	Yes, endpoint assessors were blinded and were reviewed by the endpoint committee.	Open-label
Schwartz et al, 2001 (MIRACL)	Method not reported	Not reported	Yes	Yes	Yes	Yes
Thompson, 2004 (PACT)	Method not reported	Not reported	Higher total cholesterol in placebo group, more placebo patients on HRT, and more prava patients on anticoagulants.	Yes	Yes	Yes
Asselbergs, 2004 (PREVEND IT)	Yes	Not reported	Appear similar	Yes	Yes	No details given

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
Ridker P, 2008 JUPITER	Yes	Yes	Yes	Attrition-yes, others-no	No
Liem et al, 2002 (FLORIDA)	States "double blind," but no details.	Yes	Yes	Attrition and adherence yes, crossover and contamination no	No
LIPID 1998	Yes	Yes	Yes	Attrition: yes, crossovers-no, adherence-no, and contamination-yes	No
Nakamura et al, 2006 MEGA	Open-label	Yes (95.3%)	Yes	Yes NR Yes NR	No No
Schwartz et al, 2001 (MIRACL)	Yes	Yes	Yes	Attrition yes, others no	No
Thompson, 2004 (PACT)	Yes	2.5% lost to followup not included in analysis, but possible to calculate ITT results.	Unable to assess	Attrition, adherence yes, others no.	No, 2.5% overall, 45 in each group.
Asselbergs, 2004 (PREVEND IT)	Yes	Yes	Yes	Yes	No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
Ridker P, 2008 JUPITER	Good
Liem et al, 2002 (FLORIDA)	Fair
LIPID 1998	Good
Nakamura et al, 2006 MEGA	Fair
Schwartz et al, 2001 (MIRACL)	Fair
Thompson, 2004 (PACT)	Fair-Poor
Asselbergs, 2004 (PREVEND IT)	Fair

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
PROSPER	Adequate; computer-generated scheme	Adequate; centralized	Yes	Yes	Yes	Yes
Sakamoto T, 2006	Randomized stated, but methods NR	NR	Yes	Yes	Unclear-members of data and safety monitoring committee were blinded but not sure if these members were 'outcome assessors' for this trial.	No-open-label
Stone et al, 2005	NR	NR	atorva group higher weight (198 lbs vs 188 lbs control), otherwise similar.	Yes	Yes	Not specified
Wanner et al, 2005	Yes	NR	Yes	Yes	Yes	Not specified (but described as double-blind)

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
PROSPER	Yes	Yes	NR	Attrition=1449(24.9%); Adherence (average)=94%; others NR	NR
Sakamoto T, 2006	No-open-label	NR	NR	Attrition yes, others-no	No
Stone et al, 2005	Yes	Not clear. 85% completed, numbers and reasons for withdrawal are given.	Unable to determine-numbers withdrawing NR by group.	Attrition and adherence reported.	No
Wanner et al, 2005	Not specified (but described as double-blind)	Yes	Yes	Attrition and adherence reported.	No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
PROSPER	Good
Sakamoto T, 2006	Fair-Poor
Stone et al, 2005	Fair
Wanner et al, 2005	Fair

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
WOSCOPS, 1995	Yes	Yes	Yes	Yes	Yes	Yes
Xu K, 2007	NR	NR	Yes	Yes	NR	NR
Studies from Evidence Table 4: Post-revascularization						
LIPS	NR	Adequate; serially-numbered identical medication packs.	No, more fluva patients with diabetes mellitus (14.2% vs 9.8%; p<0.05)	Yes	Yes	Yes
Studies from Evidence Table 5: Fixed-dose combination products						
Ballantyne et al, 2005 (Vyva study)	NR	NR	Yes	Yes	NR	NR
Ballantyne et al, 2008 (SEACOAST I)	NR	NR	Yes	Yes	NR	NR

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
WOSCOPS, 1995	Yes	Both intention to treat and on treatment analysis.	Yes	Attrition-yes, crossovers-no, adherence-no details and contamination-no	No
Xu K, 2007	NR	NR	Unclear	Attrition-yes, others-no	No/No
Studies from Evidence Table 4: Post-revascularization					
LIPS	Yes	Yes	NR	Attrition= 124(7.4%); others NR	No
Studies from Evidence Table 5: Fixed-dose combination products					
Ballantyne et al, 2005 (Vyva study)	Yes but method not reported	Modified ITT	NR	Attrition-55 (2.9%), crossovers-no, adherence-no details and contamination-no	No
Ballantyne et al, 2008 (SEACOAST I)	Yes but method not reported	No	NR	Attrition-86 (27%), crossovers-no, adherence-no details and contamination-no	No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
WOSCOPS, 1995	Good
Xu K, 2007	Fair-Poor
Studies from Evidence Table 4: Post-revascularization	
LIPS	Fair
Studies from Evidence Table 5: Fixed-dose combination products	
Ballantyne et al, 2005 (Vyva study)	Fair
Ballantyne et al, 2008 (SEACOAST I)	Poor

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Barrios et al, 2005	Yes	NR	Yes	Yes	NR	NR
Bays et al, 2003	Method NR	NR	Yes	Yes	NR	NR
Bays et al, 2004	Method NR	NR	Yes	Yes	NR	NR
Catapano et al, 2006	Yes	Yes	Yes	Yes	NR	NR
Constance et al, 2007	Yes	NR	Yes	Yes	NR	NR
Farnier et al, 2007	Yes	NR	Yes	Yes	NR	NR
Goldberg et al, 2006 (Vytal study)	Yes	NR	Yes	Yes	NR	NR
Guyton et al, 2008	Method NR	Yes	Yes	Yes	NR	Yes both methods NR
Lin et al, 2006	Method NR	NR	Yes	Yes	NR	NR
Ose et al, 2007	Yes	Yes	Yes	Yes	Yes	Yes
Reckless et al, 2008	Yes	NA	Yes	Yes	NR	NR
Roeters van Lennep et al, 2008	Yes	NA	Yes	Yes	NR	NR
Shankar et al, 2007	NR	NR	Yes	Yes	NR	NR
Other controlled clinical trials						
Bays H, 2003						

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
Barrios et al, 2005	Yes but method not reported	Yes	Yes	Attrition-16 (4%), crossovers-no, adherence-no details and contamination-no	No
Bays et al, 2003	No open label	Yes	Yes	NR	NR
Bays et al, 2004	Yes	Modified ITT	Yes	Attrition-33 (8.7%), crossovers-no, adherence-no details and contamination-no	No
Catapano et al, 2006	Yes	Modified ITT	Yes	Attrition-136 (5%), crossovers-no, adherence-no details and contamination-no	No
Constance et al, 2007	NR	Yes	Yes	Attrition-13 (2%), crossovers-no, adherence-no details, and contamination-no	No
Farnier et al, 2007	Yes	Yes	Yes	Attrition-47 (4%), crossovers-no, adherence-no details, and contamination-no	No
Goldberg et al, 2006 (Vytal study)	NR	Modified ITT	Yes	Attrition-44 (3.6%), crossovers-no, adherence-no details, and contamination-no	No
Guyton et al, 2008	Yes	mITT	Yes	Attrition-72 (6%), crossovers-no, adherence-no details, and contamination-no	No
Lin et al, 2006	Yes	Modified ITT	Yes	Attrition-9 (13%), crossovers-no, adherence-no details, and contamination-no	No
Ose et al, 2007	No - open label	Yes	Yes	Attrition-67 (6%), crossovers-no, adherence-no details, and contamination-no	No
Reckless et al, 2008	No - open label	Yes	Yes	Attrition-54 (13%), crossovers-no, adherence-no details, and contamination-no	No
Roeters van Lennep et al, 2008	No - open label	Yes	Yes	Attrition-66 (10%), crossovers-no, adherence-no details, and contamination-no	No
Shankar et al, 2007	Yes	mITT	Yes	Attrition-6 (3%), crossovers-no, adherence-no details, and contamination-no	No
Other controlled clinical trials					
Bays H, 2003					

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
Barrios et al, 2005	Fair
Bays et al, 2003	Poor
Bays et al, 2004	Fair
Catapano et al, 2006	Fair
Constance et al, 2007	Fair
Farnier et al, 2007	Fair
Goldberg et al, 2006 (Vytal study)	Fair
Guyton et al, 2008	Fair
Lin et al, 2006	Fair
Ose et al, 2007	Fair
Reckless et al, 2008	Fair
Roeters van Lennep et al, 2008	Fair
Shankar et al, 2007	Fair
Other controlled clinical trials	
Bays H, 2003	

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Bonnet F, 2007	Yes, centrally following a computer-generated random number list	Not reported	No, there were differences in number of males in each group, and protease inhibitor exposure was >2x longer for those in the placebo group (52 mos) than pravastatin group (21 mos).	Yes	Study states "double-blinded" but no details given	Study states "double-blinded" but no details given
Brown B, 2001	Method not reported	Not reported	Yes	Yes	Yes	Study states "double-blinded" but no details given
Fellstrom B, 2006 (companion to ALERT)	Yes	Not reported (see original trial)	Yes	Yes	Not reported (see original trial)	Not reported (see original trial)
Franceschini G, 2007	Randomization stated, but methods NR	NR	Yes	Minimal	Unclear, "double-blind", but methods NR	Unclear, "double-blind", but methods NR
Hanefeld M, 2007 (PIOSTAT)						
Hogue J, 2008	Randomization stated, but methods NR	Yes	Yes	Yes	Yes	Yes
Insull W, 2004	Method not reported	Not reported	Yes	Yes	Study states "double-blinded" but no details given.	Study states "double-blinded" but no details given.
Iwata A, 2006						
Kayikcioglu M, 2002 (PTT)	Method not reported	Not reported	Yes	Yes	Not reported (possibly open-label)	Not reported (possibly open-label)

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
Bonnet F, 2007	Study states "double-blinded" but no details given	Yes	Yes	Yes NR NR NR	No No
Brown B, 2001	Yes	Yes	Yes	Yes NR Yes NR	Unable to determine-differential No-overall
Fellstrom B, 2006 (companion to ALERT)	Not reported (see original trial)	Not reported (see original trial)	Yes	Yes NR NR NR	Not reported (see original trial)
Franceschini G, 2007	Yes	Unclear	NR	NR	Unable to assess
Hanefeld M, 2007 (PIOSTAT)					
Hogue J, 2008	Yes	NR	NR	NR	Unable to assess
Insull W, 2004	Study states "double-blinded" but no details given.	Not reported	Yes	Yes NR Yes NR	Yes-differential No-overall
Iwata A, 2006					
Kayikcioglu M, 2002 (PTT)	Not reported (possibly open-label)	Yes	Yes	Yes NR NR NR	No No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
Bonnet F, 2007	Fair-Poor
Brown B, 2001	Fair
Fellstrom B, 2006 (companion to ALERT)	See rating for original trial (Holdaas 2001)
Franceschini G, 2007	Poor
Hanefeld M, 2007 (PIOSTAT)	
Hogue J, 2008	Fair
Insull W, 2004	Fair
Iwata A, 2006	
Kayikcioglu M, 2002 (PTT)	Fair

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
The Kyushu Lipid Intervention Study Group	No (randomization failed)	Not reported; sealed envelopes were sent to centers and unknown whether there was someone to allocate randomization assignment.	No; pravastatin group tended to have patients with more severe disease.	Yes	No-study became open-label	No-open-label
Koh K, 2005	Method not reported	Not reported	Cross-over population	Yes	Study states "double-blinded" but no details given	Study states "double-blinded" but no details given
McKenney J, 2007 (COMPELL)	Method not reported	Not reported	Yes	Yes	No-open-label	No-open-label
Calza L, 2003	Yes, computer-generated list	Not reported	Unable to determine but authors report that they were comparable (data not shown)	Yes	No-open-label	No-open-label
Mohiuddin S, 2009 **Moura L, 2007**	Method not reported Randomization ratio was 2:2:2:2:2:1	Not reported	Yes	Yes	Study states "double-blinded" but no details given	Study states "double-blinded" but no details given.

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
The Kyushu Lipid Intervention Study Group	Unclear	No (patients with TC>300 mg/dL were excluded as well as those who were contaminated).	Unlikely	Unclear NR Yes Yes	Unable to determine
Koh K, 2005	Study states "double-blinded" but no details given	Not reported	Cross-over population	Yes NR NR NR	No No
McKenney J, 2007 (COMPELL)	No-open-label	Efficacy- No (92.2%) Harms- Yes (99.7%)	Yes	Yes NR Yes NR	Yes-more patients in statin/niacin groups WD than simva/ezet and rosuva Yes-up to 20-25% in statin/niacin groups
Calza L, 2003	No-open-label	No-7 patients were excluded from analysis (93.3%)	Unable to determine	Unclear NR Yes NR	No
Mohiuddin S, 2009	Study states "double-blinded" but no details given.	Efficacy- Yes (94.5%) with LOCF Harms- Yes (98.9%)	Yes	Yes NR NR NR	No No
Moura L, 2007					

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
The Kyushu Lipid Intervention Study Group	Poor
Koh K, 2005	Fair
McKenney J, 2007 (COMPELL)	Fair-Poor
Calza L, 2003	Poor to fair
Mohiuddin S, 2009	Fair
Moura L, 2007	

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Shah H, 2007	Method not reported	Not reported	Differing proportions of patients with 1-3 vessels involved (PCTA/ACS) More diabetics in Simva/fenofibrate group (48%) than other groups (24-36%) More HTNsive in Simva group (52%) than other groups (28-40%)	Yes	No-open-label	No-open-label
Verri V, 2004	Randomization stated, but methods NR	NR	Yes	Yes	"Double-blind" stated	"Double-blind" stated
Mallon P, 2006	Yes, study statistician prepared randomization schedule and central pharmacy executed the randomization.	Likely, central pharmacy (not involved in direct care) were used	Yes	Yes	Study states "double-blinded" but no details given	Study states "double-blinded" but no details given

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	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/withdrawal?
Shah H, 2007	No-open-label	No-89.2%	Yes	Yes NR NR NR	No No
Verri V, 2004	"Double-blind" stated	NR	NR	Attrition-yes, others-no	No
Mallon P, 2006	Study states "double-blinded" but no details given	No- 94%	Yes	Yes NR NR NR	No No

Evidence Table 6. Internal validity of controlled clinical trials

Study or Author Year	Score (good/ fair/ poor)
Shah H, 2007	Poor
Verri V, 2004	Fair-Poor
Mallon P, 2006	Fair-Poor

Evidence Table 7. Studies on harms

Author, year	Setting	Study design	Duration	Eligibility criteria
Bonnet F, et al 2007	Not reported	Randomized, placebo-controlled, double-blind trial	3 months	Adults with positive anti-HIV antibodies; had been receiving stable antiretroviral therapy including at least one PI for ≥3 months; had a plasma HIV RNA level of <50 copies/mL for ≥3 months before randomization; a TC ≥5.5 mmol/L with LDL-C ≥ 3.4 mmol/L on fasting status after at least 12 hours and after 3 months of standardized dietary advice; and were able to provide written informed consent.
Calza L, et al 2008	Single-center, university hospital; outpatient setting	Open-label, randomized, prospective, single-center	12 months	Adults on stable PI-based antiretroviral therapy since at least 12 months, with HIV viral load <50 copies/mL for at least 6 months and presenting hypercholesterolemia ± hypertriglyceridemia and lipodystrophy of at least 3 months and unresponsive to diet/exercise

Evidence Table 7. Studies on harms

Author, year	Exclusion criteria	Interventions	Number screened Eligible Enrolled	Total withdrawals Withdrawals due to AE Number analyzed
Bonnet F, et al 2007	Had current AIDS event or infectious disease; tumoral, inflammatory, or muscle diseases; kidney or hepatic failure; psychiatric conditions; biological elevated muscular enzymes; chronic alcohol consumption; or if pregnant or displayed no evidence of use of effective contraception.	Pravastatin 40 mg QHS Placebo	31 21 20	1 1 20
Calza L, et al 2008	Drug or alcohol abuse; history of genetic hyperlipidemia; diabetes; hypothyroidism; Cushing's syndrome; acute or chronic myopathy; acute or chronic kidney disease; acute hepatitis; liver cirrhosis; undergoing treatment with corticosteroids, androgens, estrogens, growth hormone, thiazide diuretics, beta-blockers, thyroid preparations, or other lipid lowering drugs.	Rosuvastatin 10 mg daily Pravastatin 20 mg daily Atorvastatin 10 mg daily	NR NR 94	9 5 85 (90%)

Evidence Table 7. Studies on harms

Author, year	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	How adverse events assessed
Bonnet F, et al 2007	42 yrs 78-92% Male NR	All patients using at least 1 protease inhibitor HIV stage C: 67-71% CD4 count: 465-484 cells/mm3 IVDU: 58-37% Baseline lipids (median) TC 239 mg/dL LDL 154 mg/dL HDL 39 mg/dL	Specific adverse events were graded in severity 1-4 and lab measurements were taken.
Calza L, et al 2008	37 yrs 56-74% Males NR	AIDS: 3% Mean CD4 count: 383 cells/mm3 All patients were using PI, ~88% were using regimens that included ritonavir Baseline lipid panel (mean) TC 282 mg/dL TG 274 mg/dL LDL 177 mg/dL HDL 51 mg/dL	Specifics on how adverse events were assessed were not reported, however, authors did report that adverse events were carefully checked on monthly outpatient visits in addition to lab measurements.

Evidence Table 7. Studies on harms

Author, year	Adverse events reported	Comments	Funding source
Bonnet F, et al 2007	There were a total of 12 adverse events Prava: 7 Placebo: 5 Grade 2 myalgias: Prava, 3 (1 patient had a 2x increase of CPK); Placebo, 1 Digestive symptoms: Prava, 4; Placebo, 3 Depressive symptoms: Prava, 1; Placebo, 0 Headache: Prava, 1; Placebo, 0 2-fold increase in CPK at week 4: Prava, 2; Placebo, 1 (CPK levels were normal at week 8) Others: Prava, 3; Placebo, 1 1 patient in the Prava group prematurely discontinued the study because of seizure and hospitalization not related to study treatment and another patient in the Prava group temporarily stopped treatment because of diarrhea between week 4-12. There was no significant change of AST, ALT, Bili, glucose, CPK, and myoglobin in both groups.		Center Hospital of Bordeaux; Roche labs
Calza L, et al 2008	No reports of myalgia or myositis across all groups No significant increases in CPK (>250) or ALT (>200) across all groups For Rosuva, Prava, Atorva Nausea: 7.7%, 3.2%, 0% Dyspepsia: 11.5%, 9.7%, 7.1% Diarrhea: 3.8%, 0%, 3.6% Meteorism: 7.7%, 3.2%, 3.6%		Not reported

Evidence Table 7. Studies on harms

Author, year	Setting	Study design	Duration	Eligibility criteria
Franceschini G, 2007	University hospital in Italy	Randomized, double-blind trial, parallel	8 weeks	Italian and French patients with low HDL-C (<40 mg/dl) and moderate elevations of both LDL-C (<160 mg/dl) and triglycerides (150–500 mg/dl)
Mallon P, et al 2006	Single-center, university hospital (Sydney, Australia); outpatient setting	Randomized, placebo-controlled, double-blind trial	3 months	HIV-infected men on stable PI therapy (min 12 weeks before screening and minimal changes to ART regimen during the study)

Evidence Table 7. Studies on harms

Author, year	Exclusion criteria	Interventions	Number screened Eligible Enrolled	Total withdrawals Withdrawals due to AE Number analyzed
Franceschini G, 2007	NR	Fenofibrate 160 mg/day Simvastatin 40 mg/day	NR/NR/52	NR/NR/52
Mallon P, et al 2006	HTN, congestive cardiac failure, malabsorption or other serious illness, active AIDS illness, serum lactate >2.2 mmol/L, or concurrent therapy with other lipid lowering agents, oral hypoglycemics, anabolic steroids, or insulin.	Pravastatin 40 mg QHS Placebo	34 33 33	2 0 31

Evidence Table 7. Studies on harms

Author, year	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	How adverse events assessed
Franceschini G, 2007	Mean age Fenofibrate: 56 years; Simvastatin: 53.9 years 78.8% male Ethnicity: NR	Fenofibrate vs Simvastatin Height (cm): 171.8 vs 169.6 Weight (kg): 81.1 vs 80.9 BMI (kg/m^2): 27.4 vs 28.1 Waist (cm): 96.9 vs 97.7 Hip (cm): 100.1 vs 103.4 SBP (mmHg): 130.7 vs 132.2 DBP (mmHg): 80.0 vs 78.6 Total cholesterol (mg/dl): 203.3 vs 196.5 Triglycerides (mg/dl): 286.5 vs 281.3 LDL cholesterol (mg/dl): 113.9 vs 108.0 HDL cholesterol (mg/dl): 32.2 vs 32.2 Apo A-I (mg/dl): 94.7 vs 91.0 Apo A-II (mg/dl): 31.5 vs 32.0 Apo B (mg/dl): 127.0 vs 124.4 Apo C-III (mg/dl): 12.7 vs 13.2	Laboratory tests and self report
Mallon P, et al 2006	47 yrs 100% Male 88-100% White	Mean CD4 count 442-502 cells/mm3 100% of patients are on PI (>81% of patients were using ritonavir)	Not reported

Evidence Table 7. Studies on harms

Author, year	Adverse events reported	Comments	Funding source
Franceschini G, 2007	NR		Fournier Pharma Spa
Mallon P, et al 2006	There were no significant changes in Scr, Bili, ALT, AST in either treatment group. Safety data were not shown in the publication.		Partial funding provided by BMS

Evidence Table 7. Studies on harms

Author, year	Setting	Study design	Duration	Eligibility criteria
Milazzol L, et al 2007 (exploratory) special group-co-infection group	Outpatient setting	Retrospective chart review	Not reported	Adults with HIV/HCV co-infection using statins at least 6 months after diagnosis of hepatitis C and patients who were HIV-positive but HCV/Hep B negative using statins
Rahman A, 2008	Single-center, VA North Texas Health Care System	Retrospective chart review	Minimum 6 months	Adults with HIV infection who received efavirenz-based HAART and simvastatin 20 mg/day. Patients had to be receiving stable HAART regimen (no changes to NRTI backbone or any other concurrent antiretroviral) for a minimum of 4 weeks before and after starting simvastatin. Lipid profiles w/in a 6 month period before simvastatin were required. Adults without HIV infection who received 20 mg/day were randomly selected as controls. These patients had to have been simvastatin naive for 6 months before starting treatment.

Evidence Table 7. Studies on harms

Author, year	Exclusion criteria	Interventions	Number screened Eligible Enrolled	Total withdrawals Withdrawals due to AE Number analyzed
Milazzol L, et al 2007 (exploratory) special group-co-infection group	Alcohol abuse; concomitant hepatotoxic medications other than antiretrovirals and patients on anti-HCV treatment	Statins in HCV+ versus Statins in HCV/Hep B-negative patients Most frequently prescribed statins: Atorvastatin 64% Pravastatin 29% Rosuvastatin 5% Simvastatin 2.5%	NR NR 80	NA NA 80
Rahman A, 2008	Receiving stavudine or had any additions or changes in the dosages of other lipid-lowering agents while receiving simvastatin; had significant changes in DM control; new diagnosis of thyroid disorder; uncontrolled thyroid disorder; had additions or dosage modifications of progestins, glucosteroids, isotretinoin, estrogens, azole antifungals, anabolic steroids, sevelamer, red yeast rice, and TZDs; any evidence of significant changes in dietary/exercise patterns.	Efavirenz-based HAART + simvastatin 20 mg/day vs. simvastatin 20 mg/day	302 NR 32	NA NA 32

Evidence Table 7. Studies on harms

Author, year	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	How adverse events assessed
Milazzol L, et al 2007 (exploratory) special group-co-infection group	45.5 yrs 76% Male NR	Mean CD4 count: 556 cells/mm3 Patients with HIV/HCV co-infection tended to be younger in age, a larger proportion were male, and had higher baseline LFTs (ALT 95 vs. 27; GGT 72 vs. 40) 45% of patients were taking Pis in their regimens	Assuming self-report (chart review); labs were measured
Rahman A, 2008	56-64 yrs NR (assuming all males, VA) NR	Mean CD4 count: 384 cells/mm3 DM 8-26% Hyperlipidemia 54-63% HTN 23-47% Other lipid lowering drugs 23%	Assuming self-report (chart review); labs were measured

Evidence Table 7. Studies on harms

Author, year	Adverse events reported	Comments	Funding source
Milazzol L, et al 2007 (exploratory) special group-co-infection group	There was no significant difference in the fold change of LFTs in both groups. There was no significant difference in the percentage of patients with increased AST, ALT, or GGT ≥1.5x baseline level between groups. The higher increase in GGT was observed in 2 HIV/HCV+ patients who were both taking simvastatin. None of the patients discontinued statins because of liver toxicity or modified theory antiretroviral regimens because of drug interactions. No patient had ≥3x ULN in LFTs About 37.5-42.5% of patients experienced a reduction in their LFTs after statin introduction. There was no significant difference between groups and no correlation with cholesterol reduction. Overall, 7.9% of coinfected patients experienced an increase in ALT ≥1.5x the baseline values (which was lower in the HCV-negative group).	There were statistically significant differences between treatment groups in baseline age, sex, and LFTs. Patients with HIV/HCV were younger in age and a larger proportion were male.	Not reported
Rahman A, 2008	No adverse events including myopathy were documented and no changes were noted in CK, AST, or ALT levels		Not reported

Evidence Table 7. Studies on harms

Author, year	Setting	Study design	Duration	Eligibility criteria
Verri V, 2004	2 centers, Brazilian National Institute of Cardiology and the Antonio Pedro University Hospital	Prospective, randomized, double-blind, placebo-controlled	6 months	Adults with coronary artery disease, serum total cholesterol levels of >200 mg/dl and/or LDL-C of >100 mg/dl, taking cardiovascular medication and with more than 2 risk factors for MI.

Evidence Table 7. Studies on harms

Author, year	Exclusion criteria	Interventions	Number screened Eligible Enrolled	Total withdrawals Withdrawals due to AE Number analyzed
Verri V, 2004	Patients who presented any of the following factors: 1) history of MI in the previous 3 months; 2) symptoms of unstable angina or heart failure; 3) EKG alterations that would hinder analysis of changes in the tracing; 4) patients taking lipid-lowering medication; and 5) those with chronic debilitating diseases, such as cancer, renal or liver failure, or hypo- or hyperthyroidism.	Simvastatin + AHA Step 1 diet, begun at 10mg/day, increased to a max of 20mg/day Placebo + AHA Step 1 diet	844 charts reviewed 28 25	2 deaths; 1 from non-cardiac cause and 1 from sudden death

Evidence Table 7. Studies on harms

Author, year	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	How adverse events assessed
Verri V, 2004	58.7 years (35-73) 56% male 84% white	**Obesity** Sim: 15.3% vs Placebo: 16.6% **Family history** Sim: 69.2% vs Placebo: 66.6% **Dyslipidemia** Sim: 100% vs Placebo: 100% **SHT** Sim: 76.9% vs Placebo: 75% **Diabetes** Sim: 23.% vs Placebo: 35% **Smoking** Sim: 30.7% vs Placebo: 8.3%	NR

Evidence Table 7. Studies on harms

Author, year	Adverse events reported	Comments	Funding source
Verri V, 2004	Sim vs Placebo Deaths: 1 (non-cardiac cause) vs 1 (cardiac arrest in ventricular fibrillation) Hospitalizations: 1 (gall bladder cancer) vs 2 (cardiac complications)		NR

Evidence Table 8. Systematic reviews

Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
Afilalo J et al 2007	To determine the effect of intensive statin therapy on all-cause mortality compared with moderate statin therapy in patients with recent ACS and in patients with stable CHD. Secondarily, we examined the effects of intensive statin therapy on MACE, admissions to hospital for heart failure, and adverse hepatic and muscular events.	MEDLINE (1966-March 2006) EMBASE (1980-March 2006) The Cochrane Central Register of Controlled Trials and Database of Abstracts of Reviews of Effects (inception to first quarter 2006) The ACP Journal Club (1991 to January/February 2006) The internet (http://www.clinicaltrials.gov, http://www.clinicaltrialresults.org, http://www.cardiosource.com, http://www.medscape.com, http://www.theheart.org, http://www.lipidsonline.org, all accessed 8 February 2007) Abstracts from major cardiology conferences in North America and Europe.	(a) randomized controlled trials (RCTs); (b) >6 months of follow-up; (c) documented recent ACS or stable CHD at the time of randomization; (d) intervention group given intensive statin therapy, defined as simvastatin 80 mg/day, atorvastatin 80 mg/ day, or rosuvastatin 20–40 mg/day; (e) control group given moderate statin therapy, defined as pravastatin (40 mg/day, lovastatin (40 mg/day, fluvastatin (40 mg/day, simvastatin (20 mg/day, atorvastatin (10 mg/day, rosuvastatin (5 mg/day; these definitions were derived from the National Cholesterol Education Program Adult Treatment Panel III Guidelines' table of currently available statins required to reduce LDL-C by 30–40% (''standard doses'').	6/28,505

Evidence Table 8. Systematic reviews

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Afilalo J et al 2007	RCTs	Mean age ranged from 56-64 years Proportion of men was 74% to 86% Proportion with diabetes ranged from 12% to 24% Proportion with prior MI ranged from 17% to 100%	Atorvastatin 10 or 80mg/day Simvastatin 20 or 80mg/day Pravastatin 40mg/day Lovastatin 5mg/day

Evidence Table 8. Systematic reviews

Author Year	Main efficacy outcome	Main efficacy results
Afilalo J et al 2007	Major coronary events	Patients with recent ACS, intensive statin therapy reduced all-cause mortality from 4.6% to 3.5% (OR=0.75; 95% CI 0.61 to 0.93), number needed to treat was 90 Patients with stable CHD, intensive statin therapy did not reduce all-cause mortality (OR=0.99, 95% CI 0.89 to 1.11) MACE were comparably reduced in patients with recent ACS (OR=0.86, 95% CI 0.73 to 1.01) and stable CHD (OR=0.82, 95% CI 0.75 to 0.91) Admissions to hospital for heart failure were reduced in patients with recent ACS (OR=0.63, 95% CI 0.46 to 0.86) and stable CHD (OR=0.77, 95% CI 0.64 to 0.92). Overall, the numbers needed to treat to prevent one MACE and one admission to hospital for heart failure were 46 and 112, respectively

Evidence Table 8. Systematic reviews

Author Year	Harms results	Quality assessment method
Afilalo J et al 2007	Intensive statin therapy was associated with a threefold increase in adverse hepatic events from 0.4% to 1.4% (OR=3.73, 95% CI 2.11 to 6.58) and a trend towards increased adverse muscular events from 0.05% to 0.11% (OR=1.96, 95% CI 0.50 to 7.63). As a result, the number needed to harm to cause one adverse hepatic event was 96. The odds ratios for adverse hepatic events demonstrated significant heterogeneity (I2=63%).	Described method of assessment, but did not cite a specific tool. All qualifying studies were assessed for blinding, concealment of randomized assignment, completeness of follow-up, and intention to treat analysis. We recorded whether patients in the intervention group and control group were similar at the start of the study and treated equally except for the designated treatment. Table 1 presents the validity parameters.

Evidence Table 8. Systematic reviews

Author Year	Limitations of primary studies	Data synthesis methods	Comments
Afilalo J et al 2007	External validity and generalizability to other statins is limited Some classified revascularization and resuscitated cardiac arrest as MACE Most did not report measurements of left ventricular function after statin therapy	Random-effects model	

Evidence Table 8. Systematic reviews

Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
Afilalo J, 2008	To determine whether statins reduce all-cause mortality in elderly patients with CHD and to quantify the magnitude of the treatment effect. To determine whether statins reduce CHD mortality, nonfatal MI, need for revascularization, and stroke.	MEDLINE (1966 to December 2007) EMBASE (1980 to December 2007) Cochrane Central Register of Controlled Trials and Database of Abstracts of Reviews of Effects (from inception to the fourth quarter of 2007) ACP Journal Club (1991 to November/December 2007)	The inclusion criteria for our meta-analysis were: 1) randomized allocation to statin or placebo; 2) documented CHD at the time of randomization; 3) $\geq$ 50 elderly patients included in the study (defined as age 65 years); 4) $\geq$ 6 months of follow-up; and 5) all-cause mortality, CHD mortality, nonfatal MI, need for revascularization, or stroke reported as an outcome measure.	9/19,569
Henyan N, 2007	To elucidate the effect of statin therapy on all cerebrovascular events (CVEs), ischemic stroke, and hemorrhagic stroke.	MEDLINE EMBASE Cumulative Index to Nursing & Allied Health Literature Web of Science June 1975-September 2006	(1) controlled clinical trials versus placebo, (2) well-described protocol, and (3) data reported on incidence of all CVEs, ischemic stroke, or hemorrhagic stroke.	27/100,683

Evidence Table 8. Systematic reviews

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Afilalo J, 2008	RCTs 1995-2002	Mean Age range: 66.8-75.6 years Proportion of men ranged from 58%-82% Proportion with diabetes ranged from 0%-29% Proportion with HTN ranged from 27%-57% Proportion with a prior MI ranged from 26%-100% Mean baseline total cholesterol ranged from 5.1-6.7 mmol/L Mean baseline LDL-C ranged from 3.4-4.9 mmol/L Mean baseline HDL-C ranged from 0.9-1.2 mmol/L Mean baseline triglycerides ranged from 1.5-2.1 mmol/L	Pravastatin 40mg/day used in 5 studies Fluvastatin 80mg/day used in 2 studies Simvastatin 20-40mg/day used in 1 study Simvastatin 40mg/day used in 1 study
Henyan N, 2007	Randomized trials	Mean age ranged from 50-75 years Proportion of men ranged from 31% to 100% Follow-up ranged from 0.3 to 6.1 years	Atorvastatin 10, 20, or 80mg/day Simvastatin 10-40mg/day Lovastatin 20-80mg/day Fluvastatin 40-80mg/day Pravastatin 10-40mg/day

Evidence Table 8. Systematic reviews

Author Year	Main efficacy outcome	Main efficacy results
Afilalo J, 2008	Mean change in lipid levels Major adverse cardiac events	Relative risk reduction of 22% for all-cause mortality (RR 0.78; 95% CI 0.65 to 0.89), posterior median estimate of the number needed to treat to save 1 life was 28 (95% CI 15 to 56). Coronary heart disease mortality was reduced by 30% (RR 0.70; 95% CI 0.53 to 0.83), with a number needed to treat of 34 (95% CI 18 to 69). Nonfatal MI was reduced by 26% (RR 0.74; 95% CI 0.60 to 0.89), with a number needed to treat of 38 (95% CI 16 to 118). Need for revascularization was reduced by 30% (RR 0.70; 95% CI 0.53 to 0.83), with a number needed to treat of 24 (95% CI 12 to 59). Stroke was reduced by 25% (RR 0.75; 95% CI 0.56 to 0.94), with a number needed to treat of 58 (95% CI 27 to 177).
Henyan N, 2007	Cerebrovascular events	Statin therapy significantly reduced the risk of all CVEs (RR 0.83; 95% CI 0.76 to 0.9). Statin therapy was shown to significantly reduce the risk of ischemic stroke (RR 0.79; 95% CI 0.63 to 0.99). Statin therapy was shown to nonsignificantly increase the risk of hemorrhagic stroke (RR 1.11; 95% CI 0.77 to 1.60).

Evidence Table 8. Systematic reviews

Author Year	Harms results	Quality assessment method
Afilalo J, 2008	NR	Described method of assessment, but did not cite a specific tool. All qualifying studies were assessed for concealment of randomized assignment, completeness of follow-up, and intention-to-treat analysis. We recorded whether patients in the intervention and control groups were similar at the start of the study and treated equally except for the designated treatment. We also recorded whether patients in the control group were taking lipid lowering drugs during the study.
Henyan N, 2007	NR	Described method of assessment, but did not cite a specific tool. Randomization, concealment, masking of treatment allocation, and withdrawals

Evidence Table 8. Systematic reviews

Author Year	Limitations of primary studies	Data synthesis methods	Comments
Afilalo J, 2008	No placebo controlled studies of secondary prevention for newer statins. 7 of the studies did not have elderly data.	Bayesian meta-analysis	
Henyan N, 2007	Several studies reported data on all CVEs, but fewer than half reported the incidence of hemorrhagic or ischemic stroke. The definition of stroke, fatal stroke, and CVE was not uniform across all studies	Egger weighted regression method	

Evidence Table 8. Systematic reviews

Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
Rogers S, 2007	To provide current evidence for the comparative potency of atorvastatin and simvastatin in altering levels of serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C).	MEDLINE (1966-Week 1, August 2004) EMBASE (1980-Week 31, 2004) Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, the UK National Health Service (NHS) Centre for Reviews and Dissemination database, the NHS Economic Evaluation Database, and the Database of Abstracts of Reviews of Effects	For inclusion in the meta-analyses, studies had to be randomized, head-to-head trials comparing atorvastatin at doses of 10, 20, 40, and/or 80 mg with simvastatin at doses of 10, 20, 40, and/or 80 mg. Participants in the trials had to be aged _>18 years with elevated levels of serum TC and LDL-C. Studies were excluded if they involved animals; if they had a crossover, dose-titration, or forced dose-titration design; or if they did not include a washout period of previous statin or other lipid-lowering therapy before commencement of the trial.	18/8,420
Thavendiranathan et al 2006	To clarify the role of statins for the primary prevention of cardiovascular events.	MEDLINE (1966 to June 2005) EMBASE (1980 to June 2005) Cochrane Collaboration (CENTRAL, DARE, AND CDSR) American College of Physicians Journal Club	Randomized trials of statins compared with controls (placebo, active control, or usual care) with the following characteristics: a mean follow-up ≥ 1 year; ≥ 100 reported cardiovascular disease outcomes (e.g., major coronary events, strokes, all-cause mortality); no intervention difference between the treatment and control groups other than the use of statin; ≥ 80% of participants not known to have cardiovascular disease (i.e., coronary artery disease, cerebrovascular disease, and peripheral vascular disease); and ≥ 1 of our primary outcomes for the primary prevention subgroup reported.	7/42,848

Evidence Table 8. Systematic reviews

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Rogers S, 2007	RCTs 1 unpublished	Mean age: 58.9 years (range: 48.2 to 65.2 years) Proportion of men ranged from 23.3% to 66.7% Proportion with pre-existing coronary heart disease ranged from 20%-100% Proportion with type 2 diabetes ranged from 10%-100% (though this was not well reported) Duration of treatment ranged from 4 to 24 weeks	Atorvastatin 10-80mg/day Simvastatin 10-80mg/day
Thavendiranathan et al 2006	Randomized trials	Mean age of the enrolled patients ranged from 55.1 to 75.4 years Proportion of men ranged from 42% to 100% Mean (range) pretreatment LDL-C level was 147 (117-192) mg/dl (3.82 [3.04-4.97] mmol/L)	Pravastatin 40mg/day used in 2 studies Lovastatin 20-40mg/day used in 1 study Pravastatin 20-40mg/day used in 1 study Atorvastatin 10mg/day used in 2 studies Simvastatin 40mg/day used in 1 study

Evidence Table 8. Systematic reviews

Author Year	Main efficacy outcome	Main efficacy results
Rogers S, 2007	Change in lipids	**Total Cholesterol** Reductions favored atorvastatin over simvastatin in all but one dose-pair comparison (simvastatin 80mg/day over atorvastatin 10mg/day (P<0.001)) **LDL-C** Reductions favored atorvastatin over simvastatin in all dose-pair comparisons except as follows: simvastatin 40mg vs atorvastatin 10mg (P=0.01); simvastatin 80mg vs atorvastatin 10mg (P<0.001); simvastatin 80mg vs atorvastatin 20mg (P<0.001) **Triglycerides** Reductions favored atorvastatin over simvastatin in all dose-pair comparisons except as follows: simvastatin 40mg vs atorvastatin 10mg; simvastatin 80mg vs atorvastatin 10mg; simvastatin 40mg vs atorvastatin 20mg; simvastatin 80mg vs atorvastatin 20mg (all NS) **HDL-C** Increases favored simvastatin over atorvastatin as follows: atorvastatin 20 mg and simvastatin 40 mg (P = 0.03), atorvastatin 20 mg and simvastatin 80 mg (P = 0.006), atorvastatin 40 mg and simvastatin 40 mg (P = 0.01), atorvastatin 40 mg and simvastatin 80 mg (P < 0.001), atorvastatin 80 mg and simvastatin 10 mg (P < 0.02), atorvastatin 80 mg and simvastatin 20 mg (P < 0.001), and atorvastatin 80 mg and simvastatin 80 mg (P < 0.001)
Thavendiranathan et al 2006	Change in total cholesterol, LDL-C, HDL-C and triglycerides levels from baseline	**Mean (range) reductions** Total cholesterol: 17.8% (9.5%-21.8%) LDL-C: 26.1% (16.7%-33.9%) Triglycerides: 10.6% (0.0%-15.9%) **Mean (range) increases** HDL-C: 3.2% (0.9%-5.0%) **Major coronary events** 924 in statin groups vs 1219 in control groups 29.2% reduction in the RR (95% CI, 16.7%-39.8%) of a major coronary event from statin therapy (P<0.001) **Major cerebrovascular events** 440 in statin groups vs 517 in control groups 14.4% reduction in the RR (95% CI, 2.8%-24.6%) of a major cerebrovascular event from statin therapy (P=0.02)

Evidence Table 8. Systematic reviews

Author Year	Harms results	Quality assessment method
Rogers S, 2007	Reported by 12 of 18 studies, with majority reporting on an aggregate basis (i.e., across treatment arms as a whole, rather than by individual dose) Most common AEs were gastrointestinal complaints and myalgia	Adapted from Jadad
Thavendiranathan et al 2006	NR	Jadad scale

Evidence Table 8. Systematic reviews

Author Year	Limitations of primary studies	Data synthesis methods	Comments
Rogers S, 2007	All limitations reported are regarding the meta-analysis not the primary studies Only mention of limitations of primary studies is in regard to low quality, but nothing specific is stated	Der Simonian and Laird random-effects model in Review Manager version 4.2 (Update Software, Oxford, United Kingdom)	
Thavendiranathan et al 2006	3 of the included trials had a small proportion of secondary prevention patients, authors were unable to exclude these patients from the analysis. The authors combined primary prevention studies consisting of patients at different risk levels. The authors combined data from studies that used different statins.	Meta-regression assessing the relationship between study outcomes and the following study characteristics: (1) the proportion of primary prevention patients, (2) baseline LDL-C levels, (3) absolute changes in LDL-C levels at 1 year and percentage changes at the latest time period reported by the trial, (4) baseline risk for coronary artery disease outcomes in each study (estimated by calculating the yearly incidence of major coronary events in the placebo group27), (5) the percentage of men, and (6) the percentage of patients with diabetes.	

Evidence Table 8. Systematic reviews

Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
Brugts et al 2009	To investigate whether statins reduce all cause mortality and major coronary and cerebrovascular events in people without established cardiovascular disease but with cardiovascular risk factors, and whether these effects are similar in men and women, in young and older (>65 years) people, and in people with diabetes mellitus.	Cochrane Central Register of Controlled Trials, Medline (1990-November 2008), Embase (1980-November 2008), DARE, the ACP Journal Club, and the reference lists and related links of retrieved articles.	Randomised trials of statins compared with controls (placebo, active control, or usual care), had a mean follow-up of at least one year, reported on mortality or cardiovascular disease events as primary outcomes, and included at least 80% of people without established cardiovascular disease or reported data separately on a sole primary prevention group and provided specific numbers for patients and events in that group.	10/70,388

Evidence Table 8. Systematic reviews

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Brugts et al 2009	Randomized trials	Mean age 63 years (range 55.3-75.0); mean follow-up 4.1 years (range 1.9-5.3); 34% women; 23% had diabetes; mean baseline LDL 141.6 mg/dL; mean reduction in TC 17%, LDL 25.6%, TG 9.3%	Pravastatin 40 mg/day used in 3 studies Pravastatin 10-20 mg/day used in 2 studies Lovastatin 20-40 mg/day used in 1 study Atorvastatin 10 mg/day used in 3 studies Simvastatin 40 mg/day used in 1 study Rosuvastatin 20 mg/day used in 1 study

Evidence Table 8. Systematic reviews

Author Year	Main efficacy outcome	Main efficacy results
Brugts et al 2009	Primary endpoint was all -cause mortality Secondary endpoint were: composite major coronary events (death from coronary heart disease and nonfatal MI), composite of major cerebrovascular events (fatal and nonfatal stroke), death from coronary heart disease, nonfatal MI, revascularozations (PCI or CABG), and cancer (fatal and nonfatal).	All-cause mortality: pooled OR 0.88 (95% CI, 0.81-0.96) Sensitivity analyses excluding JUPITER trial remained statistically significant as well as when 3 trials that included 2ndary prevention patients were removed. Major coronary events: pooled OR 0.70 (95% CI, 0.61-0.81) Mjor cerebrovascular events: pooled OR 0.81 (95% CI, 0.71-0.93) Cancer: pooled OR 0.97 (95% CI, 0.89-1.05) There was also NSD in treatment effect for men/women, age, or diabetes status.

Evidence Table 8. Systematic reviews

Author Year	Harms results	Quality assessment method
Brugts et al 2009	Withdrawal rates and specific harms were not reported. Only incidence of cancer was reported (see OR in main results box)	Jadad scale

Evidence Table 8. Systematic reviews

Author Year	Limitations of primary studies	Data synthesis methods	Comments
Brugts et al 2009	Authors were unable to exclude a small proportion of secondary prevention patients from the West of Scotland Coronary Prevention Study, ALLHAT, and the Anglo-Scandinavian Cardiac Outcomes Trial lipid lowering arm, and these therefore constitute about 6% of the study population. Sensitivity analyses were performed.	Summary odds ratio using fixed and random effects model.	

Evidence Table 9. Internal validity of systematic reviews

Study	Searches through	1. Search methods reported?	2. Comprehensive search?	3. Inclusion criteria reported?	4. Selection bias avoided?
Afilalo J, et al, 2007	March 2006	Yes	Yes	Yes	Yes
Afilalo J, 2008	December 2007	Yes	Yes	Yes	Yes
Henyan N, et al, 2007	2006	Yes	Yes	Yes	Minimal
Rogers S, 2007	August 2004	Yes	Yes	Yes	Yes
Thavendiranathan, et al, 2006	June 2005	Yes	Yes	Yes	Yes
Brugts JJ, 2009	November 2009	Yes	Yes	Yes	Yes

Evidence Table 9. Internal validity of systematic reviews

Study	5. Validity criteria reported?	6. Validity assessed appropriately?	7. Methods used to combine studies reported?	8. Findings combined appropriately?	9. Conclusions supported by data?
Afilalo J, et al, 2007	Described, but standarardized method NR	Unclear	Minimally	Yes	Yes
Afilalo J, 2008	Described, but standarardized method NR	No	Yes	Yes	Yes
Henyan N, et al, 2007	Described, but standarardized method NR	Unclear	Yes	Yes	Yes
Rogers S, 2007	Yes	Yes	Yes	Unclear	Yes
Thavendiranathan, et al, 2006	Yes	Yes	Yes	Yes	Yes
Brugts JJ, 2009	Yes	Yes	Yes	Yes	Yes

Evidence Table 9. Internal validity of systematic reviews

Study	10. Overall scientific quality (score 1-7)
Afilalo J, et al, 2007	5
Afilalo J, 2008	6
Henyan N, et al, 2007	5 to 6
Rogers S, 2007	6
Thavendiranathan, et al, 2006	7
Brugts JJ, 2009	7

Evidence Table 10. Trials comparing efficacy and safety of statins in children

Author, year	Interventions	Duration	Number screened Eligible Enrolled	Total withdrawals Withdrawals due to AE Number analyzed
Clauss, 2005	Lovastatin 40 mg placebo	24 weeks	81 64 54	3 0 54
deJongh, 2002 ('Efficacy and safety…')	Simvastatin 40 mg placebo	48 weeks	223 NR 175	10 1 173
deJongh, 2002 ('Early statin therapy…')	Simvastatin 40 mg placebo (also had control group of healthy, non-FH siblings)	28 weeks	NR NR 50	NR
Knipscheer, 1996	Pravastatin 5, 10, or 20 mg placebo	12 weeks	NR NR 72	0 0 72

Evidence Table 10. Trials comparing efficacy and safety of statins in children

Author, year	Baseline lipid levels (mg/dl) Mean (SD)	Results (lipid levels)	Comments
Clauss, 2005	LDL-C: 211.3 (45.8) HDL-C: 47.6 (10.9)	Lovastatin 40 mg vs placebo: least squares mean percent change from baseline (SE) LDL-C at week 24: -26.8% (3.4) vs 5.2% (3.9); p<0.001 HDL-C at week 24: 2.5% (2.5) vs 2.7% (2.9); (NS)	
deJongh, 2002 ('Efficacy and safety…')	LDL-C: 207.3 (44.5) HDL-C: 47.6 (10.1)	Simvastatin 40 mg vs placebo: mean percent change from baseline (SD) LDL-C at week 48: -40.7% (39.2) vs 0.3% (10.3); p<0.001 HDL-C at week 48: 3.3% (14.9) vs -0.4% (14.8); NS	
deJongh, 2002 ('Early statin therapy…')	LDL-C: 144.6 (33.6) HDL-C: 52.2 (10.4)	Simvastatin 40 mg vs placebo: mean absolute change from baseline (SD) LDL-C at week 28: -38.3 mg/dl (17.8) vs - 0.9 mg/dl (19.1); p=0.0001 HDL-C at week 28: 0.9 mg/dl (3.06) vs -0.9 mg/dl (4.0); p=0.080	
Knipscheer, 1996	LDL-C: 245.6 (range 139-460) HDL-C: 44.5 (range 23.2-69.6)	Pravastatin 5 mg vs 10 mg vs 20 mg vs placebo: mean percent change from baseline (95% CI) LDL-C at week 12: -23.3% (-27.9 to -18.4) vs -23.8% (-28.5 to -18.8) vs -32.9% (-37.0 to -28.6) vs -3.2% (-9.0 to 3.0) All doses p<0.001 compared to baseline; p<0.05 compared to placebo HDL-C at week 12: 3.8% (-27.9 to 11.2) vs 5.5% (-1.7 to 13.2) vs 10.8% (3.4 to 18.8) vs 4.3% (-2.7to 11.8) All doses NS compared to baseline and placebo	

Evidence Table 10. Trials comparing efficacy and safety of statins in children

Author, year	Interventions	Duration	Number screened Eligible Enrolled	Total withdrawals Withdrawals due to AE Number analyzed
Marais, 2008	Atorvastatin 80 mg rosuvastatin 80 mg	6 weeks (after 18-week forced titration period with rosuvastatin 20, 40, and 80 mg)	NR NR 44	4 0 40
McCrindle, 2003	Atorvastatin 10 mg to 20 mg placebo	26 weeks, plus 26 weeks open-label extension with atorvastatin 10 mg	NR NR 187	4 1 187
Stein, 1999	Lovastatin 40 mg placebo	24-week titration, then 24 weeks stable dose	NR NR 132	22 3 110
van der Graaf, 2008	Ezetimibe/simvastatin 10 mg/40 mg placebo/simvastatin 40 mg	26 weeks after 6 weeks titration period	342 268 248	20 5 246
Wiegman, 2004	Pravastatin 20 mg (under age 14) or 40 mg (14 or older) placebo	2 years	274 258 214	10 0 211

Evidence Table 10. Trials comparing efficacy and safety of statins in children

Author, year	Baseline lipid levels (mg/dl) Mean (SD)	Results (lipid levels)	Comments
Marais, 2008	LDL-C: 514.3 (116.0) HDL-C: 36.0 (10.4)	Atorvastatin 80 mg vs rosuvastatin 80 mg: least squares mean percent change from baseline (SE) LDL-C at week 6: -18.0% (1.9) vs -19.1% (1.9); p=0.67 HDL-C at week 6: -4.9% (4.6) vs 2.5% (4.6); p=0.24	Included both adults and children; homozygous FH
McCrindle, 2003	LDL-C: 221.5 (4.4) HDL-C: 45.9 (1.0)	Atorvastatin 10-20 mg vs placebo: least squares mean percent change from baseline (SEM) LDL-C at week 26: -40.0% (3.3); p<0.001 vs -0.4% (3.7); NS HDL-C at week 26: -2.4% (3.4); p=0.02 vs -8.0% (3.9); NS	
Stein, 1999	LDL-C: 250.5 (6.5) HDL-C: 44.5 (1.0)	Lovastatin 40 mg vs placebo: mean percent change from baseline (SE) LDL-C at week 48: -25% (2) vs -4% (2); p<0.001 HDL-C at week 48: 1% (2) vs -1% (2); NS	
van der Graaf, 2008	LDL-C: 222.0 (42.9) HDL-C: 21% below 40, 48% 40-49, 24% 50-59, 7% 60 or higher	Ezetimibe/simvastatin 10 mg/40 mg vs placebo/simvastatin 40 mg: mean percent change from baseline (SD) LDL-C at week 33: -54.0% (1.4) vs -38.14% (1.4); p<0.01 HDL-C at week 33: 4.7% (1.3) vs 3.7% (1.3); p=0.58	
Wiegman, 2004	LDL-C: 238.0 (49.5) HDL-C: 47.5 (10.5)	Pravastatin 20-40 mg vs placebo: mean absolute change from baseline (SD) LDL-C at year 2: -57 mg/dl (40) vs 0 mg/dl (36); p<0.001 HDL-C at year 2: 3 mg/dl (10) vs 1 mg/dl (9); p=0.09	

Evidence Table 11. Studies on harms of statins in children

Author, year	How adverse events assessed	Adverse events reported
Clauss, 2005	Clinical review	Lovastatin vs placebo (no significant differences): Any clinical AE: 66% vs 68% Treatment-related clinical AE: 9% vs 5% No serious clinical AE, treatment related AE, discontinuations due to AE, CK greater than 10 times ULN, or ALT and/or AST greater than 3 times ULN
deJongh, 2002 ('Efficacy and safety…')	Laboratory tests, otherwise not specified. Prespecified adverse experiences were compared between treatment groups.	Simvastatin vs placebo at 48 weeks (no significant differences): Drug-related clinical AE: 4.7% vs 3.4% Drug-related laboratory AE: 1.2% vs 1.7% No serious AE
deJongh, 2002 ('Early statin therapy…')	Safety measurements including ALT, AST, and CK were measured during each visit.	No significant differences with regard to safety measurements between simvastatin and placebo groups and no adverse events were reported.
Knipscheer, 1996	Adverse events and vital signs recorded by physicians unaware of treatment allocation; laboratory safety parameters (routine hematology, biochemistry, and urinalysis).	Adverse events equally distributed among treatment groups. No changes in laboratory safety measurement, including plasma TSH, ACTH, cortisol, creatine phosphokinasae, and liver enzyme levels, in any group from baseline to end of treatment period.
Marais, 2008	Review of all safety parameters, including adverse events, clinical laboratory evaluations including regular assessments of liver transaminases and serum creatine kinase, vital signs, EKG, and physical examinations.	Atorvastatin vs rosuvastatin (crossover comparison): All AE: 15.8% vs 39.5% Serious AE: 0 vs 5.3% Treatment-related AE: 2.6% vs 0 No elevations of CK >10 times ULN During first 18 weeks (rosuvastatin 20/40/80 mg): All AE: 65.9% Serious AE: 9.1% Treatment-related AE: 18.2%

Evidence Table 11. Studies on harms of statins in children

Author, year	How adverse events assessed	Adverse events reported
McCrindle, 2003	AE reported by the subject or investigator were recorded at each study visit and for up Safety laboratories including AST, ALT, and CPK, were performed at weeks 4, 8, 18, and 39. Blood pressure and pulse measured at each study visit, and a full physical exam at screening and weeks 12, 16, and 52.	Atorvastatin vs placebo: AE: 62.9% vs 61.7% Treatment-related Aes: 7% vs 4% (p=0.70) Laboratory abnormalities: 29% vs 34% One discontinuation in atorva group due to increased depression. No clinically relevant changes in vital signs noted in either group.
Stein, 1999	Laboratory measurements including ALT, AST, and CK. Sexual maturation evaluated by Tanner staging.	Lovastatin had no significant effect on growth parameters at 24 and 48 weeks. More advanced Tanner staging and lager testicular volumes in lovastatin group, but not significantly different from placebo (p=0.85 and 0.33 for 24 and 48 weeks). Increase from baseline in ALT in both groups, no significant difference between groups (p=0.20). No consistent changes in AST or CK. No clinically significant increase in transaminaes levels (>3 times ULN) or CK level (>10 times ULN). No differences between groups in clinical adverse events.
van der Graaf, 2008	Physical examination, EKG, assessment of sexual maturation and growth, monitoring of menstrual periods fo female subjects, adverse event reports, and laboratory assessments.	Treatment-emergent AE at 33 weeks, ezetimibe + simva vs simva: Any AE: 83% vs 84% ALT increased: 5% vs 2% CPK elevation >10 times ULN: 1.6% vs 0 Myalgia: 6% vs 1% No clinically significant adverse effects on growth, sexual maturation, or steroid hormones.

Evidence Table 11. Studies on harms of statins in children

Author, year	How adverse events assessed	Adverse events reported
Wiegman, 2004	Measured levels of sex steroids, gonadotopins, and variables of the pituitary-adrenal axis at baseline and at 1 and 2 years. Measurements of height, weight, body surface area, Tanner staging, and menarche or testicular volume. BMI, school records for education level and yearly progress, ALT, AST, adn CPK assessed at same time as lipids.	No significant differences between pravastatin and placebo in change from baseline in physical characteristics, liver and muscle enzymes, or hormones; no effect of pravastatin on academic performance.

Evidence Table 12. Internal validity of trials evaluating statins in children

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Clauss et al, 2005	Yes	Yes	Drug estradiol 61 vs 95 for placebo Drug LDL 218 vs 199 Drug ApoB 187 vs 168	Yes	Yes	Not reported
deJongh, 2002A Early Statin Therapy Restores…	Method not described	NR	FH groups were similar	Yes	NR	NR
deJongh, 2002b "Efficacy and safety of statin therapy…"	Yes	NR	Yes	Yes	Described as "double blind"	NR
Knipscheer, 1996	Method not described	NR	Yes	Yes	Yes	NR (n/a)
McCrindle, 2003	Method not described	NR	Yes	Yes	Yes	NR (n/a)

Evidence Table 12. Internal validity of trials evaluating statins in children

Study or Author Year	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/withdrawal?
Clauss et al, 2005	Yes	Yes	Yes	Attrition reported. No contamination reported.	No differential loss or high overall loss. 33/35 (94%) drug and 18/19 (95%) placebo completed
deJongh, 2002A Early Statin Therapy Restores…	NR but "placebo"	NR	NR	NR	NR
deJongh, 2002b "Efficacy and safety of statin therapy…"	Yes	Yes	Yes	Attrition reported, no contamination evident	78% of those randomized to drug completed to week 48, and 81% of placebo completed to week 48
Knipscheer, 1996	Unclear, reported as double-blind	Yes	Yes	Attrition reported (none), no contamination evident	No loss- all completed
McCrindle, 2003	Unclear, reported as double-blind	NR Very low attrition	Yes	Attrition reported. No contamination reported.	No differential loss. 98% completed double-blind period

Evidence Table 12. Internal validity of trials evaluating statins in children

Study or Author Year	Comments	Score (good/ fair/ poor)
Clauss et al, 2005		Good
deJongh, 2002A Early Statin Therapy Restores…		Poor
deJongh, 2002b "Efficacy and safety of statin therapy…"		Good-Fair
Knipscheer, 1996		Fair
McCrindle, 2003		Fair

Evidence Table 12. Internal validity of trials evaluating statins in children

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Stein, 1999	Method not described	NR	Yes	Yes	Yes, "double blind"	NR
van der Graaf A, et al 2008	Not described	NR	More mutiracial participants in SIM monotherapy groups (pooled): 13 (10%) for EZE plus SIM groups vs. 19 (15%); also more cigarette use in previous month for SIM monotherapy groups (pooled): 1(1%) for EZE plus SIM groups. Vs 12 (10%) for SIM monotherapy groups.	Yes	Yes "double blind" for steps 1 and 2	NR
Wiegman, 2004	Yes	Not reported	Yes	Yes	Unclear, reported as double-blind	NR (n/a)

Evidence Table 12. Internal validity of trials evaluating statins in children

Study or Author Year	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/withdrawal?
Stein, 1999	Yes, "double blind"	For safety; for efficacy, those who > one 8-week phase of the study were included	Unclear	Attrition reported No contamination reported	110/132 (83%) completed Period 2. Drug: 61/67 (91%) completed Period 2. Placebo: 49/65 (75%) completed Period 2.
van der Graaf A, et al 2008	Yes for steps 1 and 2	Not stated, but they appear to have analyzed 246 people total, out of 248 randomized.	Yes	Attrition reported. No contamination reported. Adherence NR. Contamination NR.	No.
Wiegman, 2004	Yes, other than they knew whether they got 1/2 or whole tablet (dose 20mg or 40mg).	NR Low attrition	Yes	Attrition reported.	No differential loss. Treatment: 101/106 (95%)completed Placebo: 103/108 completed (95%)

Evidence Table 12. Internal validity of trials evaluating statins in children

Study or Author Year	Comments	Score (good/ fair/ poor)
Stein, 1999		Fair
van der Graaf A, et al 2008	Randomzied to 6 arms of varied doses for two treatment options (SIM alone vs EZE plus SIM), but analyzed in only two groups (lumped all doses together)	Fair
Wiegman, 2004		Good-Fair