



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

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Produced by:

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Health Resources Commission

The State of Oregon’s Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative and two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

In 2007 the Oregon Health Resources Commission (HRC) appointed a pharmaceutical subcommittee to perform evidence-based reviews of pharmaceutical agents. Members of the subcommittee for this review consisted of three Physicians, a Nurse Practitioner, and two pharmacists. All meetings were held in public with appropriate notice provided. The HRC director worked with the Center for Evidence-based Policy (Center) and the Oregon

Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The EPC's report, "*HMG-CoA Reductase Inhibitors (Statins) and Fixed-dose Combination Products Containing a Statin*", November, 2009 was circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately twice per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. This report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a subcommittee.

The full OHSU Evidence-based Practice Center's draft report is available via the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website:

www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: <http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml>

You may request more information including copies of the draft report from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

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There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

Critical Policy

Senate Bill 819

– “The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”

Health Resources Commission

– “Clinical outcomes are the most important indicators of comparative effectiveness”

– “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

Clinical Overview

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 5⁵ 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 pleiotropic² 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 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

Quality of the Evidence

For quality of evidence the EPC and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

- 1) Methods used for randomization
- 2) Allocation concealment and blinding
- 3) Similarity of compared groups at baseline and maintenance of comparable groups
- 4) Adequate reporting of dropouts, attrition, and crossover
- 5) Loss to follow-up
- 6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

- 1) Adequate description of the study population
- 2) Similarity of patients to other populations to whom the intervention would be applied
- 3) Control group receiving comparable treatment
- 4) Funding source that might affect publication bias.

Weighing the Evidence

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the body of evidence relevant to that question.

The subcommittee's task was to evaluate

Scope and Key Questions

To identify articles relevant to each key question, the EPC 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.

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. 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 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.

The participating organizations approved the following key questions to guide this review:

Key Questions:

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

Table 1. Included Statins				
Drug:generic name (trade name)	Strength	Dose range	Usual starting dose	Black Box Warning?
Single Agent Statins				
Atorvastatin (Lipitor®)	10 mg, 20 mg, 40 mg, 80mg	10-80 mg once daily	20 mg	No
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	No
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	No
Pravastatin _a (Pravachol®)	10 mg, 20 mg, 40 mg, 80 mg (also 30 mg in generic only)	10-80 mg once daily	40 mg	No
Rosuvastatin (Crestor®)	5 mg, 10 mg, 20 mg, 40 mg	5-40 mg once daily	10 mg	No
Simvastatin _a (Zocor®)	5 mg, 10 mg, 20 mg, 40 mg, 80 mg	5-80 mg once daily	40 mg	No
Fixed Dose Combination agents				
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	No
Simvastatin/Niacin-ER (Simcor®)	20/500 mg 20/750 mg 20/1000 mg	10/500 – 40/2000 mg	20/500 mg if niacin naive	No
Simvastatin/Ezetimibe (Vytorin®)	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)	No

Conclusions:

Limitations of the Evidence:

1. No study met the ideal design of 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.
2. The majority of trials that evaluated harms of the fixed dose combination products were not longer than 12 weeks in duration.
3. In trials including children, reporting of adverse events was poor.

Conclusions:

Adults

1. Evidence supports the ability of atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin to improve coronary heart disease clinical outcomes.

2. Atorvastatin, pravastatin and simvastatin have been shown to reduce strokes.
3. While these drugs improve clinical outcomes the absolute risk reduction is small.
4. Fair to good strength evidence demonstrates that when statins are provided in doses that are approximately equipotent, a similar percent reduction in low-density lipoprotein cholesterol can be achieved, along with comparable increases in high-density lipoprotein cholesterol.
5. In adult 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) for health outcomes.
6. There are no clinical outcome studies for fixed dose combination products containing a statin and another lipid lowering agent.
7. No evidence supports differences between Statins in adverse effects in sub-populations by race and ethnicity, age, gender or comorbidity.
8. Niacin containing fixed dose combination products have a higher rate of discontinuation due to flushing.
9. Studies in patients with diabetes did not have higher rates of adverse events
10. Potential for interactions with CYP 3A4 inhibitors (atorvastatin, lovastatin, and simvastatin)
11. Potential for interaction with CYP 2C9 inhibitors (fluvastatin)
12. Statin-fibrate combination increases risk of musculoskeletal-related adverse events compared with monotherapy

Children

1. Trials of statins (simvastatin, atorvastatin, lovastatin, pravastatin, and rosuvastatin) have been conducted primarily in children with familial hypercholesterolemia and other familial dyslipidemias in trials of less than one year duration.
2. The comparison of the fixed dose combination product ezetimibe/simvastatin vs. simvastatin demonstrated a 54% reduction in low-density lipoprotein for the combination vs. 38% for simvastatin alone.
3. Studies of statins in children have not been conducted with long enough follow-up to assess for outcomes related to cardiovascular mortality and morbidity.
4. No trials have evaluated statins in children with diabetes or obesity.
5. There is insufficient data to determine rates of adverse events or harms in children taking statin medications.

Supporting Evidence:

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?

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:

The EPC 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. 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.

The EPC evaluated 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.

From the trials evaluated the EPC determined the following approximate equivalent daily doses for statins with respect to their low-density lipoprotein cholesterol-lowering abilities (Table 2)

Table 2. 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

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. 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. 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 ($P<0.001$).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 trial⁵⁶ 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 and 3 meta-analyses have compared rosuvastatin to atorvastatin. Nine trials concerned patients who had moderate to no risk factors for coronary artery disease and 19 trials enrolled patients at high risk for cardiovascular disease. All studies comparing rosuvastatin to atorvastatin that reported low-density lipoprotein cholesterol reductions at 12 weeks 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 weeks²⁴ 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. 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 ($P = \text{NS}$).

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-blinded⁹¹ 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. 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 simvastatin¹¹⁰ 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 data 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.

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 trial¹⁰² which obtained 42% reduction with niacin ER/lovastatin 1000/40 mg compared to simvastatin 20 mg (34%, $P < 0.001$).

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. 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.

Statins

Fifty-one reports measured the percentage of patients meeting their National Cholesterol Education Program low-density lipoprotein cholesterol treatment goals. 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. 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 atorvastatin⁶⁹ 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 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.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

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?

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%. 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, but in 14 others, there was no significant difference between the 2 on this measure. 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. Five studies reported greater increases in high-density lipoprotein cholesterol with rosuvastatin 5 or 10 mg than with atorvastatin 10 mg. 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 trial⁷⁹ 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)?

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-IT¹¹⁷ 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 trial¹¹⁹ 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 suggests that the included population in PROVE-IT had relatively higher risk for events than patients in IDEAL.

(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 and 7 studies in inpatients with acute myocardial infarction or unstable angina. 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. 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).

(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 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.

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 trial¹⁴³ 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. 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 trial¹²⁴ 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 study¹⁴⁴ 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 evaluating long-term effectiveness of atorvastatin 10-20 mg, simvastatin 40 mg, and fluvastatin 80 mg in patients with diabetes.

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. 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. 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. 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. All-cause mortality reported in 1145 trial was not significant. The 4D trial¹³⁴ enrolled patients with type 2 diabetes who had end-stage renal disease and were receiving maintenance hemodialysis. 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 publication¹⁴⁶ was rated poor quality due to unclear randomization, allocation concealment, intention-to-treat analysis, and inadequate blinding.

Secondary prevention

Four placebo-controlled trials recruited patients with documented coronary heart disease while 1141 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. 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. 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.

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 study¹³⁷ 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. PACT¹⁴⁰ 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.

FLORIDA¹³⁶ 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 trial¹³⁸ 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 (creatinine 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. A head-to-head trial¹⁸⁷ 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. 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.

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, the EPC did not conduct a meta-analysis to pool the results of these studies.

Revascularization studies with restenosis or clinical outcome endpoints

This group 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). In these trials, pravastatin and fluvastatin had statistically significant effects on prespecified coronary disease outcomes.

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 diabetes¹⁸³ (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.^{65, 166, 190}

The Target Tangible study⁶⁵ 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.

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)?

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-analyses¹⁹¹⁻¹⁹⁴ suggesting that statins are equally efficacious in men, women, and the elderly.

One meta-analysis¹⁹¹ 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 colleagues¹⁹¹ that reported morbidity results, a meta-analysis by Walsh and colleagues¹⁹² 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 16,486 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 hierarchical bayesian meta-analysis¹⁹³ 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. 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 Hispanic,²³ South Asian,¹⁹⁶ and African American⁷⁴ 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 analysis¹⁹⁵ 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?

Six reviews evaluated the safety profiles of statins. 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 (creatinine 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 to 1.55). 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. 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 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 colleagues²²² 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.

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 daily⁵² 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 AVERT¹⁶⁶ 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 data (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)?

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 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 study²⁶¹ 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, 7²⁶⁴⁻²⁷⁰ studied primarily pravastatin while 1²⁵ 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 study²⁶⁵ 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://www.hivatis.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 reporting harms with statin-fibrate combination. Of these, reported information on rhabdomyolysis, 3 on myopathy, and 4 studies 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 review²¹⁹ 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 colleagues²¹⁹ 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 to 104) 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 study²⁷⁶ 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 study²⁸² 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?

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 atorvastatin²⁸⁵ 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

The EPC conducted a meta-analysis of the percent change from baseline in low-density lipoprotein levels in placebo-controlled trials. 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.

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 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?

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 atorvastatin²⁸⁵ 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

The EPC 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. Seven trials contributed data to the meta-analysis,^{285-289, 291, 292} representing 472 patients taking a statin and 320 taking a placebo. 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.

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)?

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)?

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?

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)?

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.

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