Drug Class Review

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

Final Report
Update 5

November 2009

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

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

Authors for Update 5:
M.E. Beth Smith, DO
Nancy J. Lee, PharmD, BCPS
Elizabeth Haney, MD
Susan Carson, MPH

Original authors:
Mark Helfand, MD, MPH
Cathy Kelley, PharmD

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director

Oregon Health & Science University

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

TABLE OF CONTENTS

INTRODUCTION **7**

Purpose and Limitations of Systematic Reviews 9
Scope and Key Questions 11
Inclusion Criteria 13

METHODS **14**

Literature Search 14
Study Selection 14
Data Abstraction 15
Validity Assessment 15
Data Synthesis 15
Peer Review and Public Comment 16

RESULTS **16**

Overview 16
Report Organization 18

ADULTS **18**

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? 18
Summary of findings 18
Key Question 1a. Are there doses for each statin or fixed-dose combination product containing a statin and another lipid-lowering drug that produce similar percent reduction in low-density lipoprotein cholesterol? 18
Statins 18
Fixed-dose combination products containing a statin and another lipid-lowering drug 27
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? 28
Statins 29
Fixed-dose combination products containing a statin and another lipid-lowering drug 30
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? 31
Summary of findings 31
Key Question 2a. Are there doses for each statin or fixed-dose combination product containing a statin and another lipid-lowering drug that produce similar percent increase in high-density lipoprotein cholesterol between statins? 32
Statins 32
Fixed-dose combination products containing a statin and another lipid-lowering drug 33
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? 34
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)? 35
Summary of findings 35
Detailed assessment 36
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)? 56
Summary of findings 56

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? ... 58
Summary of findings ... 58
Detailed assessment ... 58
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)? ... 63
Summary of findings ... 63
Detailed assessment ... 64

CHILDREN ... 72

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? ... 72
Summary of findings ... 72
Key Question 1a. Are there doses for each statin or fixed-dose combination product containing a statin and another lipid-lowering drug that produce similar percent reduction in low-density lipoprotein cholesterol? ... 72
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? ... 74
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? ... 74
Summary of findings ... 74
Key Question 2b. Are there doses for each statin or fixed-dose combination product containing a statin and another lipid lower drug that produce similar percent increase in high-density lipoprotein cholesterol between statins? ... 74
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)? ... 76
Summary of findings ... 76
Detailed assessment ... 76
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)? ... 76
Summary of findings ... 76
Detailed assessment ... 76
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?. 77
Summary of findings ... 77
Detailed assessment ... 77
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)? ... 78
Summary of findings ... 78
Detailed assessment ... 78

SUMMARY ... 78

TABLES

Table 1. Included statins ... 8
Table 2. Included fixed-dose combination products ... 9
Table 3. Percent reduction in low-density lipoprotein cholesterol with statins ... 20
Table 4. Doses of statins that result in similar percent reductions in low-density lipoprotein cholesterol[a] ... 21

Table 5. Trials comparing atorvastatin to rosuvastatin 22
Table 6. Percent reduction in low-density lipoprotein cholesterol with fixed-dose combination products 28
Table 7. Achieving target low-density lipoprotein cholesterol goals 29
Table 8. Achievement of National Cholesterol Education Program low-density lipoprotein cholesterol goals of fixed-dose combination products 31
Table 9. Outpatient and community-based placebo-controlled trials of statins with coronary heart disease endpoints 40
Table 10. Placebo-controlled trials in patients with diabetes 47
Table 11. Inpatient trials of acute myocardial infarction or unstable angina (statins compared with placebo or usual care) 50
Table 12. Studies of atherosclerotic progression that reported coronary heart disease outcomes 53
Table 13. Post-revascularization trials 54
Table 14. Miscellaneous trials reporting clinical outcomes 55
Table 15. Summary of the evidence by key question 78

FIGURES

Figure 1. Results of literature search 17
Figure 2. Low-density lipoprotein cholesterol lowering in placebo-controlled trials of statins in children with familial hypercholesterolemia 73
Figure 3. High-density lipoprotein cholesterol increases in placebo-controlled trials of statins in children with familial hypercholesterolemia 75

APPENDIXES

Appendix A. Glossary 105
Appendix B. Search strategy 115
Appendix C. Methods used to assess quality of studies 119
Appendix D. Excluded studies 123
Appendix E. Black box warnings for US Food and Drug Administration-approved drugs 128

EVIDENCE TABLES are available as a separate document

Shading indicates new information for Update 5

Acknowledgments
We thank Leah Williams, our publications editor, for putting this report into its present form for you to read. We also thank Trish Thieda, MA and Miranda Walker, MA for assistance with data abstraction and quality assessment of studies, and Theresa Nguyen for retrieval of articles and assistance with editing and formatting.

Suggested citation for this report
Smith MEB, Lee NJ, Haney E, Carson S. Drug class review: HMG-CoA reductase inhibitors (statins). Update 5.
http://www.ohsu.edu/drugeffectiveness/reports/final.cfm

Funding
The Drug Effectiveness Review Project, composed of 15 organizations including 14 state Medicaid agencies and the Canadian Agency for Drugs and Technology in Health, commissioned and funded for this report. These organizations selected the topic of the report and had input into its Key Questions. The content and conclusions of the report were entirely determined by the Evidence-based Practice Center researchers. The authors of this report have no financial interest in any company that makes or distributes the products reviewed in this report.

INTRODUCTION

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

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

The third report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) was released in September 2002[4] and updated in August 2004 to include evidence from more recent trials.[5] The report stressed that the intensity of treatment should be directed by the degree of cardiovascular risk. Target low-density lipoprotein cholesterol levels depend on the patient's risk of heart disease, medical history, and initial low-density lipoprotein cholesterol level. For most patients who are prescribed a statin, the target will be less than 130 mg/dL or less than 100 mg/dL. In the Adult Treatment Panel III, patients who have type 2 diabetes without coronary heart disease, peripheral or carotid vascular disease, and patients who have multiple risk factors and a 10-year risk of coronary heart disease of greater than 20% are said to have "coronary heart disease equivalents." This means that the criteria for using drug therapy and the low-density lipoprotein target (less than 100 mg/dL) is the same as for patients who have a history of coronary heart disease. A low-density lipoprotein cholesterol goal of less than 70 mg/dL for high-risk patients is a therapeutic option. Factors that place patients in the category of *very high risk* favor a decision to reduce low-density lipoprotein cholesterol levels to less than 70 mg/dL. These factors are the presence of established cardiovascular disease plus (1) multiple major risk factors (especially diabetes), (2) severe and poorly controlled risk factors (especially continued cigarette smoking), (3) multiple risk factors of the metabolic syndrome (triglycerides greater than 200 mg/dL plus non-high-density lipoprotein cholesterol greater than 130 mg/dL with low high-density lipoprotein cholesterol [less than 40 mg/dL]), and (4) patients with acute coronary syndromes. The optional goal of less than 70 mg/dL does not apply to individuals who are not high risk.

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

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

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

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

Table 1. Included statins

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

[a] Available in generic and trade form.

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

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

Table 2. Included fixed-dose combination products

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

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

Purpose and Limitations of Systematic Reviews

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

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

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

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

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

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

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

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

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

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

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

Scope and Key Questions

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

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

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

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

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

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

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

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

Inclusion Criteria

Populations

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

Interventions

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

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

Comparators

For effectiveness and harms of individual statins:

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

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

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

Outcomes

Intermediate outcomes

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

Health outcomes

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

Harms outcomes

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

Study designs

Based on the "hierarchy of evidence" approach, controlled clinical trials and systematic reviews were considered for assessment of effectiveness, whereas for the assessment of harms, controlled clinical trials, observational studies, and systematic reviews were considered. If higher-level evidence was not available and a gap existed then the authors considered other levels of evidence. However, studies that did not provide original data (editorials, letters), were shorter than 4 weeks in duration, did not have an English-language title or abstract, or were published only in abstract form, were excluded.

METHODS

Literature Search

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

Study Selection

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

Data Abstraction

We abstracted the following data from included trials: study design, setting, and population characteristics (including sex, age, ethnicity, and diagnosis); eligibility and exclusion criteria; interventions (dose and duration); comparisons; numbers screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome (nonfatal myocardial infarction), new coronary heart disease (new angina or unstable angina), coronary heart disease mortality, all-cause mortality, stroke or transient ischemic attack, need for revascularization, and percent change from baseline in low-density lipoprotein cholesterol and high-density lipoprotein cholesterol. Since several of the trials grouped some of these events and referred to them as major coronary events, we also included it as a category of cardiovascular health outcomes. We recorded intention-to-treat results if available.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix C. These criteria are based on those developed by the United States Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).[10, 11] For Key Question 3, we rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw in 1 or more categories were rated poor quality; trials meeting all criteria were rated good quality; the remainder were rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population and how similar patients were to the target population in whom the intervention will be applied. We also recorded the funding source and role of the funder.

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

Data Synthesis

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

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

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

Peer Review and Public Comment

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

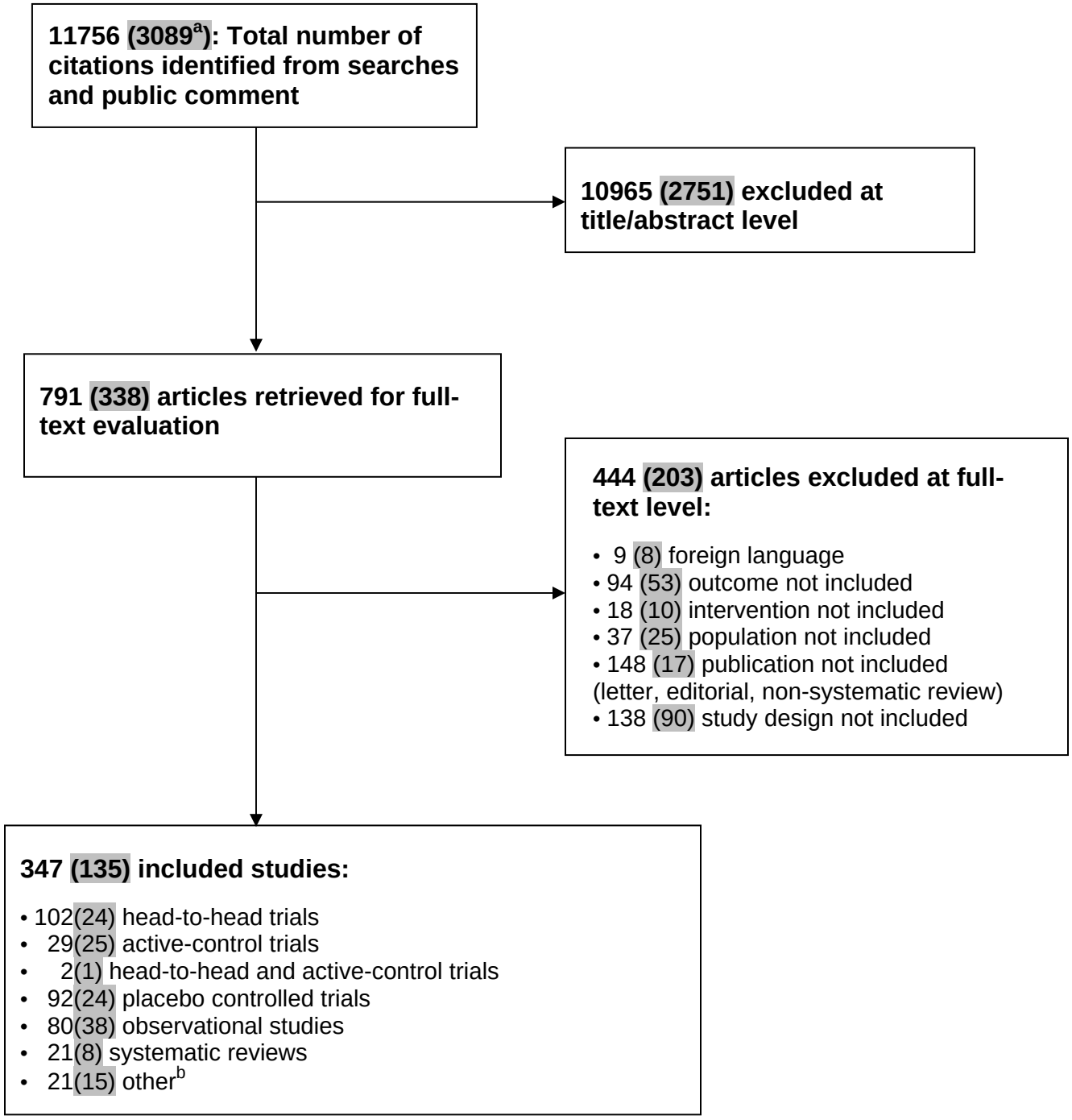
Peer reviewers have a maximum of 3 weeks for review and comment. They are asked to submit their comments in a standardized form in order to maintain consistent handling of comments across reports and to allow the Drug Effectiveness Review Project team to address all comments adequately. The Drug Effectiveness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

RESULTS

Overview

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

Figure 1. Results of literature search



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

Report Organization

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

ADULTS

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

Summary of findings

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

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

Statins

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Comparisons of high-potency and high-dose statins

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

Atorvastatin compared with simvastatin

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

Three studies directly compared atorvastatin 80 mg to simvastatin 80 mg daily.[52, 56, 58] In the first study, atorvastatin 80 mg reduced low-density lipoprotein cholesterol by 53.6% compared with 48.1% for simvastatin 80 mg ($P \leq 0.001$).[52] Compared with the simvastatin 80 mg groups, a greater number of patients in the atorvastatin 80 mg groups reported clinical adverse effects, primarily gastrointestinal diarrhea (23% compared with 11.9%; $P<0.001$). There was no significant difference between atorvastatin 80 mg and simvastatin 80 mg in withdrawal rates due to adverse effects. Withdrawal from the study due to adverse laboratory events occurred more often in the atorvastatin 80 mg compared with the simvastatin 80 mg daily group (4% compared with 0.8%; $P<0.05$). Clinically important alanine aminotransferase elevation (greater than 3 times the upper limit of normal) occurred statistically more often in the atorvastatin 80 mg compared with the simvastatin 80 mg group (17 compared with 2 cases, respectively, $P=0.002$) and was especially pronounced in women (there were statistically more women randomized to atorvastatin than simvastatin). Aminotransferase elevation generally occurred within 6 to 12 weeks after initiation of the 80 mg statin dose.

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

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

Atorvastatin compared with rosuvastatin

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

Table 5. Trials comparing atorvastatin to rosuvastatin

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 7. Achieving target low-density lipoprotein cholesterol goals

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

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

Statins

Fifty-one reports measured the percentage of patients meeting their National Cholesterol Education Program low-density lipoprotein cholesterol treatment goals.[15-17, 19-22, 29, 86, 87, 113, 114] Additionally, 1 study reported only on the European guidelines goal attainment,[113] 1 study reported on the Japanese goal attainment,[22] and 3 reported on attainment of both the Adult Treatment Panel III and the 2003 European goals.[17, 20, 29] Many of the studies compared the efficacy of the usual starting doses of the compared drugs rather than the efficacy and adverse events when the drugs were tailored over time.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Summary of findings

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

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

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

Statins

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

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

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

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

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

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

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

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

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

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

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

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

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

Summary of findings

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

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

Detailed assessment

Head-to-head trials

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

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

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

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

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

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

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

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

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

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

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[118, 121-134] and 7 studies in inpatients with acute myocardial infarction or unstable angina.[81, 117, 135-146] The primary endpoint in these trials was a reduction in cardiovascular health outcomes.

   a. *Outpatient studies*. Enrollment was in excess of 4000 patients with an average follow-up period of 5 years. All of the trials were good or fair quality and were considered the best evidence for demonstrating a reduction in cardiovascular health outcomes with statins.

   b. *Inpatient studies*. These included studies of patients hospitalized with acute myocardial infarction or unstable angina. There was 1 head-to-head trial of intensive atorvastatin therapy compared with a standard dose of pravastatin. Six other trials compared a statin to placebo or usual care. No study in this group was rated good quality.

(2) *Studies of the progression of atherosclerosis with secondary or incidental coronary heart disease endpoints* are placebo-controlled trials in which the primary endpoint was progression of atherosclerosis measured by angiography or B-mode ultrasonography.[147-158] In these trials, coronary heart disease events or cardiovascular morbidity and mortality was reported either as a secondary endpoint or incidentally (that is, even though it was not a predefined endpoint). In general, these studies had insufficient power to assess coronary heart disease events. Only 2[148, 155] of these trials

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

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

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

Studies with primary coronary heart disease endpoints

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

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

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

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

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

Abbreviations: CABG, Coronary artery bypass graft, CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; HTN, hypertension; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; PTCA, percutaneous transluminal coronary angioplasty.
[a] **Bolding** indicates statistically significant results.
[b] Not adjusted for length of trial or for baseline risk.

Studies in outpatients

Primary prevention

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

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

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

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

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

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

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

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

Studies enrolling mixed populations or subjects with coronary risk equivalents

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

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

Simvastatin reduced all-cause mortality from 14.7% to 12.9% (a 13% reduction). Simvastatin also reduced the risk of major coronary events (number needed to treat, 32 after 5 years) and of stroke.[177] In subgroups, simvastatin 40 mg was effective in primary prevention of coronary heart disease in patients with diabetes (number needed to treat, 24 to prevent a major event in 5 years)[178] and in patients who had a history of peripheral or carotid atherosclerosis but not coronary heart disease. Simvastatin 40 mg was also effective in patients who had a baseline low-density lipoprotein less than 116 mg/dL (both patients with and without diabetes).

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

The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-lowering Arm (ASCOT-LLA) was a randomized, double-blind, placebo-controlled, fair-to-good quality trial of atorvastatin 10 mg in 10 305 patients with well-controlled hypertension, total cholesterol concentrations less than 251 mg/dL, and an average of 3.7 cardiovascular disease risk factors.[171, 172] The trial was terminated after a median of 3.3 years of follow-up because a statistically significant benefit was shown on the primary endpoint, non-fatal myocardial infarction (including silent myocardial infarction) and fatal coronary heart disease. Treatment with atorvastatin 10 mg per day for 1 year

reduced low-density lipoprotein by 35%, from 133 mg/dL to 87 mg/dL. By the end of follow-up (about 3.3 years), low-density lipoprotein was 89 mg/dL in the patients still taking atorvastatin compared with 127 mg/dL in the control group.

There were 100 primary endpoint events in the atorvastatin group (100/5168, or 1.9%) and 150 events in the placebo group (3%). The event rate in the placebo group corresponded to a 10-year coronary event rate of 9.4%. Over 3.3 years, the number needed to treat to prevent 1 nonfatal myocardial infarction or death from coronary heart disease was 94 (P=0.005). Atorvastatin increased the chance of remaining free of myocardial infarction for 3.3 years from 95% to 97%.

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

In ALLHAT-LLC (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack—Lipid-lowering Arm), a fair-to-good quality, open-label randomized trial, 10 355 hypertensive patients, aged 55 and older, were randomized to pravastatin 40 mg or to usual care.[121] Nearly half the subjects were women, 35% had diabetes, 15% had a history of coronary heart disease, and about 35% were African-American. Pravastatin reduced low-density lipoprotein cholesterol from 145.6 mg/dL at baseline to 111 mg/dL after 2 years, a 24% reduction. However, because the control group was usual care instead of placebo, 10% of control patients were taking a lipid-lowering drug by year 2, and, by year 6, 28.5% of control subjects were taking a lipid-lowering drug. Thus the control group had a mean reduction in low-density lipoprotein cholesterol concentration of 11% over the course of the study.

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

The good-quality PROSPER trial was designed to examine the benefits of statin therapy in women and in the elderly.[133] High-risk men and women were randomized to pravastatin 40 mg or to placebo. Before treatment, the mean low-density lipoprotein was 147 mg/dL. Overall, pravastatin reduced the composite primary endpoint (coronary heart disease death, nonfatal myocardial infarction, and fatal/nonfatal stroke) from 16.2% in the placebo group to 14.1% (P=0.014; number needed to treat, 48). There was also a reduction in transient ischemic attacks, but not in strokes, in the pravastatin group. There was no effect on all-cause mortality, which was 10.5% in the placebo group compared with 10.3% in the pravastatin group (hazard ratio, 0.97; 95% CI, 0.83 to 1.14). The reduction in coronary heart disease deaths in the pravastatin group (4.2% compared with 3.3%; P=0.043) was balanced by an increase in cancer deaths (3.1% compared with 4%; P=0.082).

Pravastatin was more effective in men than in women. There were more women (n=3000) than men (n=2804) in the study. The baseline risk in men was higher. In the placebo group, almost 20% of men and 13% of women had an event (coronary heart disease death, nonfatal myocardial infarction, or stroke) over the 3 years of the study. For men, there was a statistically significant reduction in the primary endpoint (hazard ratio, 0.77; 95% CI, 0.65 to 0.92; number needed to treat, 26). For women, there was no apparent effect (hazard ratio, 0.96; 95% CI, 0.79

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

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

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

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

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

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

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

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

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

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

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

Table 10. Placebo-controlled trials in patients with diabetes

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

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

Abbreviations: BP, blood pressure; CABG, Coronary artery bypass graft, CAD, coronary artery disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; HF, heart failure; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.
[a] All-cause mortality was a secondary outcome.
[b] P=0.059.
[c] P=0.196.

Secondary prevention

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

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

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

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

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

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

Studies in inpatients with acute coronary syndrome

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Twelve studies of the effects of statins on progression of atherosclerosis also reported rates of coronary or cardiovascular events.[147-158] A head-to-head trial[187] of the effect of atorvastatin 80 mg compared with pravastatin 40 mg on progression of atherosclerosis did not meet inclusion criteria because it did not report health outcomes. However, this study did meet inclusion criteria for Key Question 1 (see Evidence Table 1). In these studies, the primary endpoint was progression of atherosclerosis, and all of the patients had known coronary heart disease. To answer the question of whether treatment with a statin is associated with a reduction in clinical cardiovascular outcomes in patients with coronary heart disease, these studies were considered fair or fair-to-poor quality. In 6 of the 12 trials clinical outcomes were not a preplanned endpoint (they were "spontaneously reported"), and sample sizes were relatively small.

Table 12 and Evidence Table 5 summarize the results of these studies. The number of trials and patients studied for each statin are as follows: fluvastatin (1 trial; N=429), lovastatin (3 trials; N=1520), pravastatin (5 trials; N=2220), and simvastatin (3 trials; N=1118). The information about fluvastatin was inconclusive and the other 3 statins were already known to be effective from better studies.

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

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

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

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

Revascularization studies with restenosis or clinical outcome endpoints

This group (Table 13 and Evidence Table 6) included placebo-controlled trials in revascularized patients (coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or coronary stent).[159-165, 167] The primary endpoint in 5 of the trials was the rate of restenosis. A reduction in clinical outcomes was the primary outcome in the 6th study (subgroup analysis of CARE).[161] Most of the studies were fair or fair-to-poor in quality for the question of whether treatment with a statin is associated with a reduction in clinical cardiovascular outcomes in patients with coronary heart disease. Sample sizes were relatively small and the studies were not powered to assess these types of events.

The number of studies and patients per statin were as follows: fluvastatin (2 trials; N=2086), lovastatin (3 trials; N=1981), pravastatin (3 trials; N=3017; Table 9 presented data on 2245 patients already included in CARE). In these trials, pravastatin and fluvastatin had statistically significant effects on prespecified coronary disease outcomes.

Table 13. Post-revascularization trials

Study Drug, patients	Clinical endpoint	Clinical events
FLARE[163] Fluvastatin 40 mg twice daily vs. placebo to reduce restenosis after successful single-lesion PTCA	Prespecified composite clinical endpoint of death, myocardial infarction, coronary artery bypass graft surgery, or re-intervention.	No effect on restenosis or on the preplanned composite clinical end-point at 40 weeks (22.4% vs. 23.3%; log rank *P*=0.74); incidence of total death and myocardial infarction was lower in the fluvastatin group (1.4% vs. 4.0%; log rank *P*=0.025)
Weintraub 1994[164] Lovastatin 40 mg twice daily vs. placebo to reduce restenosis after PTCA	Spontaneous report	No effect on restenosis; NS trend to more MIs in the lovastatin group; no difference in fatal or nonfatal events at 6 months
PCABG[159] Lovastatin 40 mg (aggressive) vs. lovastatin 2.5 mg titrated to target; before and after CABG	Pre-specified composite clinical endpoint of death from cardiovascular disease or unknown causes, nonfatal MI, stroke, CABG, or angioplasty	No difference in composite outcome (12.6% vs. 15.3%, *P*=0.12); no differences in individual components except a lower rate of repeat PTCA or CABG (6.5% vs. 9.2%; *P*=0.03; NS by study criteria for multiple comparisons)
CLAPT[162] Lovastatin plus diet vs. lovastatin, before and after PTCA.	Pre-specified endpoint of MI, revascularization, or death	No effect on restenosis; significant reduction in 2nd or 3rd re-PTCA (*P*=0.02)
PREDICT[160] Pravastatin 40 mg vs. placebo after PTCA	Secondary endpoint of death, myocardial infarction, target vessel revascularization	No effect on restenosis or on clinical endpoints.
CARE (subgroup)[161] Pravastatin vs. placebo in patients with CABG and/or PTCA	Primary endpoint coronary heart disease death or nonfatal MI	Reduction in primary endpoint (relative risk, 36; 95% CI, 17 to 51; *P*=0.001)
LIPS[167, 188] Fluvastatin vs. placebo in patients who had PCI and average cholesterol values	Primary endpoint cardiac death, nonfatal MI, CABG, or repeat PCI	For primary endpoint (relative risk, 0.78; 95% CI, 0.64 to 0.95; *P*=0.01)
Kayikcioglu 2002[165] Pravastatin 40 mg and thrombolytics vs. thrombolytics in patients who under went coronary balloon angioplasty during 1st month of acute MI (6 month study)	Major adverse cardiovascular events: fatal or nonfatal MI, cardiac death, angina	No difference in reducing cardiac deaths, rate of reinfarctions, or repeat revascularizations. Rate of angina was reduced with pravastatin (30%) compared with control (59.5%), *P*=0.018

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

In the Lescol Intervention Prevention Study (LIPS), patients who had undergone angioplasty or other percutaneous coronary intervention were randomized to fluvastatin 40 mg twice daily or placebo for 4 years.[167, 188] One hundred eighty-one (21.4%) of 844 patients in the fluvastatin group and 222 (26.7%) of 833 patients in the placebo group had at least 1 major adverse cardiac event, defined as cardiac death, nonfatal myocardial infarction, or a reintervention procedure. There was a 22% (*P*=0.0127) reduction in major coronary events (cardiac death, nonfatal myocardial infarction, coronary artery bypass graft or repeat percutaneous coronary intervention). The number needed to treat was 19 (21.4% in fluvastatin group compared with 26.7% in placebo group). Patients with diabetes and those with multi-vessel disease experienced a comparable or greater benefit with fluvastatin than other subjects.

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

Miscellaneous studies

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

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

Table 14. Miscellaneous trials reporting clinical outcomes

Study Drug Patients	Clinical endpoint	Clinical events
AVERT[166] Atorvastatin vs. percutaneous Transluminal coronary angioplasty in stable, low-risk coronary artery disease patients	Primary endpoint included cardiac events and revascularization procedures	No difference
Target Tangible[65] Atorvastatin vs. simvastatin Safety trial	Clinical endpoints reported in safety analysis	See text (above)
Pravastatin Multinational Study Group[190] Pravastatin 20 mg (dose could be increased) vs. placebo Subjects at high-risk for coronary artery disease	Reported in safety analysis after 6 months of treatment	13 serious cardiovascular events were reported in the placebo group vs. 1 for pravastatin ($P<0.001$; ARR 2.2/100 persons; number needed to treat, 44)

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

Summary of findings

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

Efficacy in demographic subgroups

Women and the elderly

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

One meta-analysis[191] evaluated the effect of statins on the risk of coronary disease from 5 large, long-term, primary and secondary prevention trials (see Evidence Table 2). Women accounted for an average of 17% of subjects and individuals age 65 and older accounted for an average of 29% of subjects with a range of 21% to 39% (WOSCOPS did not enroll women or anyone 65 years or older). The risk reduction in major coronary events was 29% (95% CI, 13 to 42) in women, 31% (95% CI, 26 to 35) for men, 32% (95% CI, 23 to 39) in those over age 65, and 31% (95% CI, 24 to 36) in those younger than age 65. Similarly, the Heart Protection Study[123, 178] found that simvastatin reduced cardiovascular events among women generally and particularly in women with diabetes, who benefited dramatically (number needed to treat, 23 to prevent 1 major vascular event).

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

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

African American, Hispanic, and other ethnic groups

African Americans had the greatest overall coronary heart disease mortality and the highest out-of-hospital coronary death rates of any other ethnic group in the United States.[4] Other ethnic and minority groups in the United States included Hispanics, Native Americans, Asian and Pacific Islanders, and South Asians. However, these groups are underrepresented in randomized clinical trials reporting reductions in clinical outcomes. As a result there was no evidence to answer whether or not statins differ in their ability to reduce clinical events in the African American, Hispanic, or other ethnic groups. Significant numbers of African American and Hispanic patients participated in AFCAPS/TexCAPS, but the investigators did not analyze events by racial group. In EXCEL, lovastatin 20 mg, 40 mg, and 80 mg daily reduced low-density lipoprotein cholesterol by similar percentages in blacks and in whites.[195]

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

Safety in demographic subgroups

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

In a large, observational study of lovastatin, men, women, and the elderly experienced similar rates of adverse effects.[197, 198] The Expanded Clinical Evaluation of Lovastatin (EXCEL) Study was a 4-year study of the tolerability of lovastatin 20 mg, 40 mg, or 80 mg daily in 8245 patients, including over 3000 women.[199-203] The rates of myopathy and liver enzyme elevations increased with increasing doses of lovastatin, but did not differ among men, women, and healthy elderly subjects. A meta-analysis of randomized trials of simvastatin 80 mg involving 2819 subjects (Worldwide Expanded Dose Simvastatin Study Group) had similar results.[197] These studies were important because they demonstrated that the maximum (80 mg) doses of simvastatin and lovastatin were well tolerated. Similar findings were observed in 3 additional publications.[18, 194, 204]

A subgroup analysis[195] from the EXCEL Study examined the efficacy and safety of lovastatin compared with placebo in 459 African-Americans. The endpoints in the trial were reduction in total cholesterol, low-density lipoprotein cholesterol, triglycerides, and an increase in high-density lipoprotein cholesterol. With regard to safety, there was a significantly higher incidence of creatine kinase elevation in African-Americans compared to white Americans in both placebo and lovastatin treatment groups. However, no cases of myopathy, defined as creatine kinase elevations greater than 10 times the upper limit of normal, occurred in African-Americans. There were no other safety differences between lovastatin and placebo in African-Americans or Caucasians.

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

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

Summary of findings

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

Detailed assessment

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

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

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

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

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

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

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

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

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

Myotoxicity

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

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

Magnitude of risk

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

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

Myotoxicity of different statins

All of the available statins (simvastatin, lovastatin, atorvastatin, fluvastatin, pravastatin, and rosuvastatin), when administered alone, have been associated with infrequent myotoxic adverse effects ranging from myalgia and myopathy to rhabdomyolysis.[206] Factors that may increase the risk for myopathy or rhabdomyolysis with statins are higher dosages, drug interactions, other myotoxic drugs (fibrates or niacin), increased age, hypothyroidism, surgery or trauma, heavy exercise, excessive alcohol intake, and renal or liver impairment.[217, 219, 223, 224]

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

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

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

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

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

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

Elevations of liver enzymes

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

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

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

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

In GREACE, there were 5 patients out of 25 who received atorvastatin 80 mg daily that experienced clinically significant increases in liver function tests. In all cases, the transaminase elevations were reversible upon discontinuation or reduction in dose of atorvastatin. There were no significant differences in transaminase elevation (greater than 3 times the upper limit of normal) with other statins compared with placebo or non-drug interventions. However, in the majority of studies reporting health outcomes involving fluvastatin, lovastatin, pravastatin, or simvastatin, the maximum daily dose was not used.

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

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

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

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

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

Proteinuria

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

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

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

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

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

Summary of findings

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

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

Detailed assessment

Myotoxicity and hepatic enzymes (special populations)

Patients with diabetes

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

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

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

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

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

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

Special populations and statin-drug interactions

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

the possibility for adverse effects and does not include all drugs capable of inhibiting metabolism via the CYP 3A4 isoenzyme system.

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

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

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

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

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

Potent inhibitors of CYP 3A4 are listed below:

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

Published reports of rhabdomyolysis exist in patients receiving concomitant statin with Clarithromycin, Erythromycin, Cyclosporine, Itraconazole, and Nefazodone.

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

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

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

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

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

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

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

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

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

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

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

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

Two groups of experts have made recommendations regarding the use of statins in HIV-infected individuals receiving protease inhibitors, including the Adult AIDS Clinical Trials Research Group (AACTG) Cardiovascular Disease Focus Group and the Centers for Disease Control and Prevention/Department of Health and Human Services/Henry J Kaiser Foundation. Both groups have recommended avoidance of simvastatin and lovastatin in patients receiving protease inhibitors largely based on pharmacokinetic studies and suggest using low-to mid-level doses of atorvastatin, fluvastatin, or pravastatin as alternatives (http://wwwhivatis.org and http://www.aactg.s-3.com/ann.htm).

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

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

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

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

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

In the systematic review by Shek and colleagues,[219] the majority of included studies used gemfibrozil (total daily dose of 1200 mg; n=20, 63% of patients). Ten studies used bezafibrate, 2 used fenofibrate, 1 used clofibrate, 1 used ciprofibrate, 1 used both bezafibrate and ciprofibrate, 1 used bezafibrate or fenofibrate, and 1 used gemfibrozil or ciprofibrate. No reports of rhabdomyolysis were observed in the 1674 patients receiving statin-fibrate combination. A total of 19 (1.14%) patients withdrew secondary to myalgia or creatine kinase elevation. Two patients (0.12%) developed myopathy (defined as myalgia with creatine kinase >10 times the upper limit of normal) and 33 (1.9%) patients experienced other muscle symptoms including myalgia, musculoskeletal pain or weakness, or myositis. There were 35 reports (2.1%) of subclinical elevation of creatine kinase (<10 times the upper limit of normal) in 16 of the included studies. All but 2 of these studies used gemfibrozil; the others used bezafibrate plus simvastatin 20 mg and fenofibrate plus pravastatin 20 mg or simvastatin 10 mg. Some of the studies did not report whether the creatine kinase elevation was symptomatic or if treatment was discontinued as a result. In 1 of the included studies, a patient tolerated the combination of pravastatin and gemfibrozil for 4 years, and then developed myopathy with clinically important elevation in creatine kinase after being switched to simvastatin.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CHILDREN

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

Summary of findings

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

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

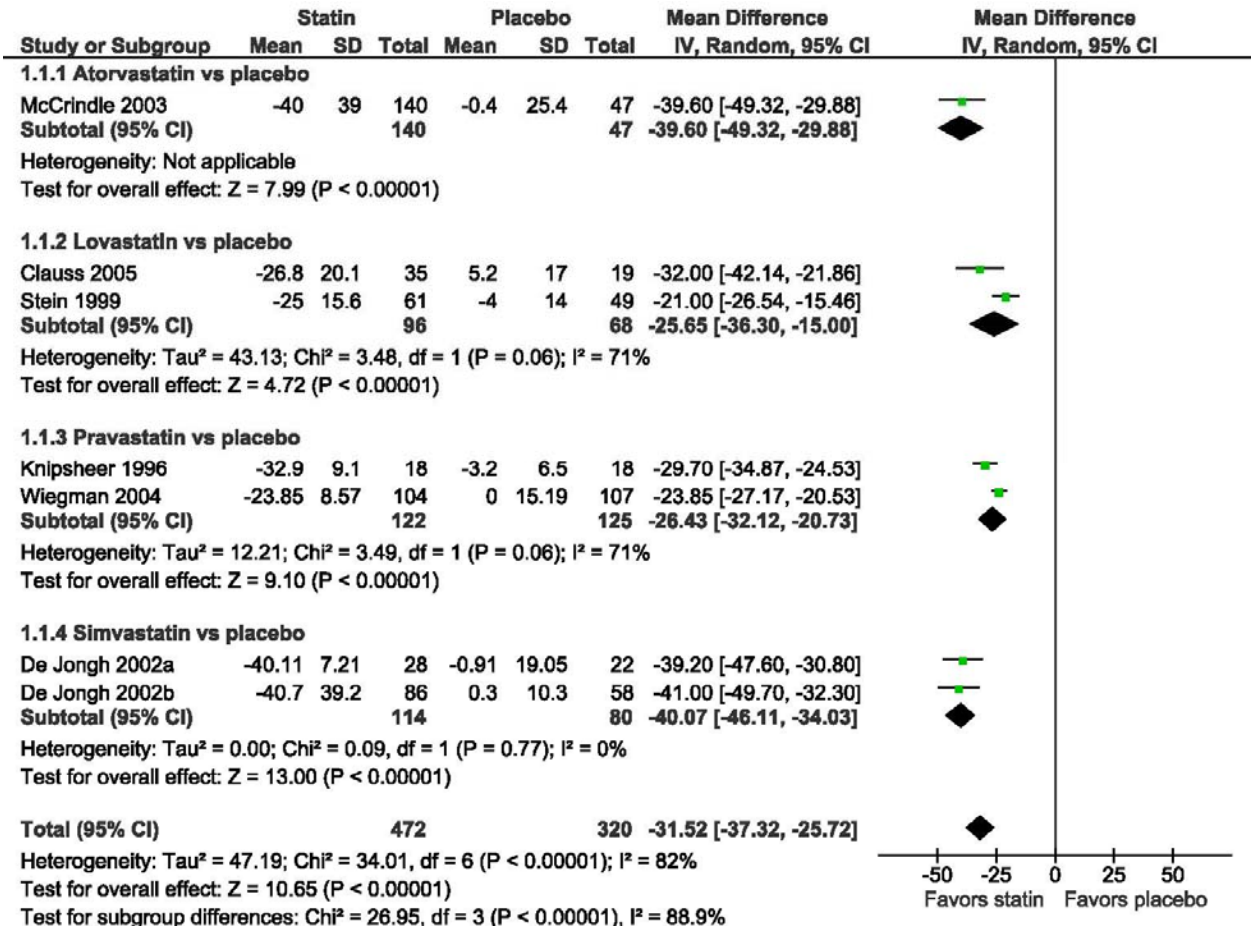
All the trials of statin drugs compared to placebo, including 1 trial of atorvastatin [285] 2 of lovastatin,[286, 287] 2 of pravastatin,[288, 289] and 3 of simvastatin,[290-292] demonstrated improvement in total cholesterol and low-density lipoprotein cholesterol among children and adolescents with familial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

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

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

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

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



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

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

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

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

Summary of findings

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

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

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

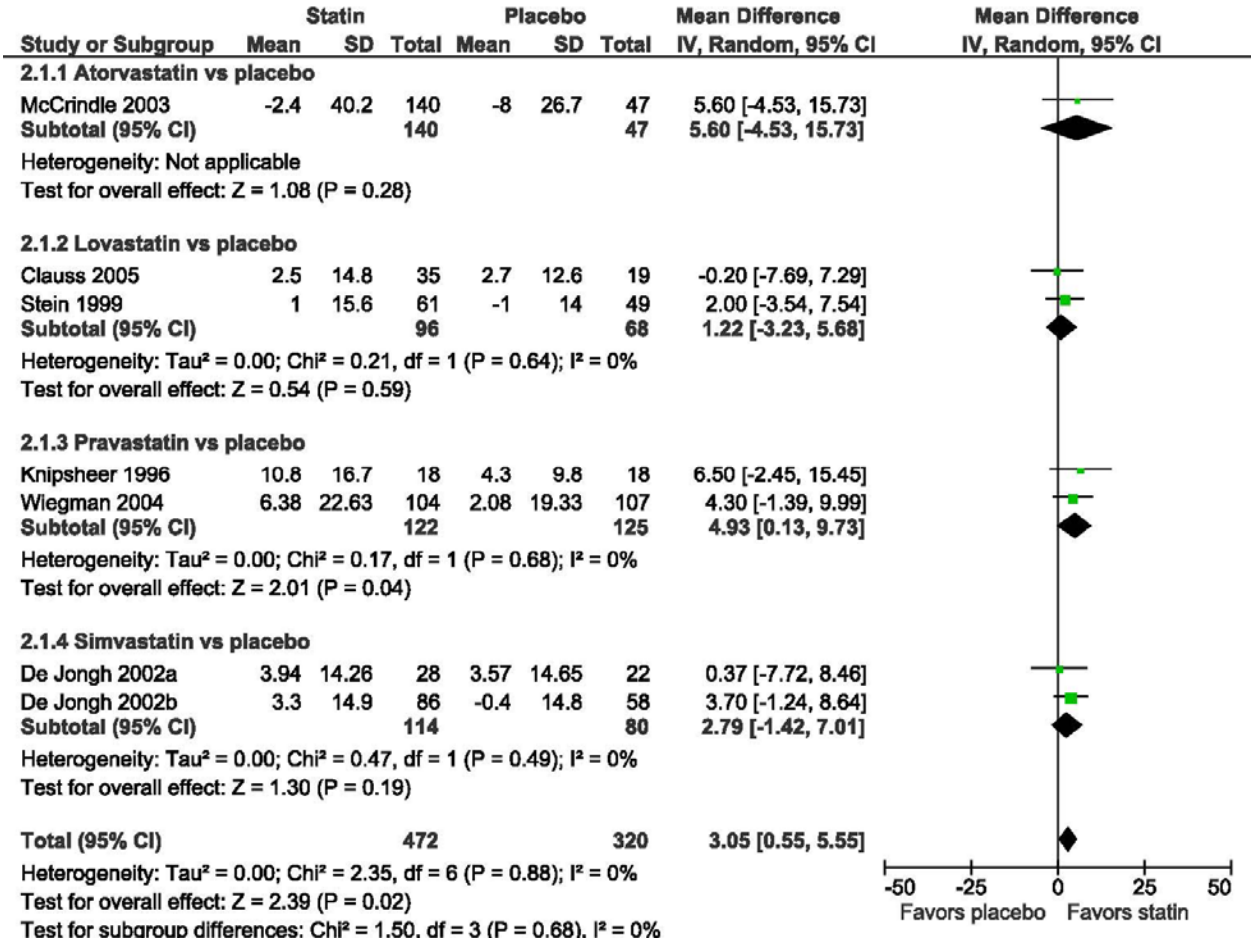
The trial of atorvastatin compared to rosuvastatin started with open-label dose titration of rosuvastatin for 18 weeks and then randomized patients to atorvastatin or rosuvastatin (both at 80 mg/day doses) in a crossover design for 6 weeks. Eight of 44 patients enrolled in the trial were under age 18;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

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

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

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

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



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

Summary of findings

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

Detailed assessment

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

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

Summary of findings

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

Detailed assessment

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

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

Summary of findings

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

Detailed assessment

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

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

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

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

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

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

Summary of findings

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

Detailed assessment

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

SUMMARY

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

Table 15. Summary of the evidence by key question

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

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

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

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

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

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

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

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Appendix A. Glossary

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

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

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

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

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

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

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

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

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

Applicability: see *External Validity*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Generalizability: See *External Validity.*

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

Harms: See *Adverse Event*

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

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

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

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

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

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

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

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

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

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

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

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

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

Masking: See *Blinding*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Appendix B. Search strategy

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

Database: Ovid MEDLINE(R) <1996 to January Week 4 2009>
Search Strategy:
----
1 lovastatin.mp. or exp Lovastatin/ (5022)
2 simvastatin.mp. or exp Simvastatin/ (3948)
3 pravastatin.mp. or exp Pravastatin/ (2578)
4 atorvastatin.mp. (3245)
5 fluvastatin.mp. (1073)
6 rosuvastatin.mp. (726)
7 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or statin$.mp. (18571)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (20058)
9 Comparative Study/ (686468)
10 drug evaluation studies.mp. or exp Drug Evaluation/ (4285)
11 9 or 10 (689769)
12 8 and 11 (2374)
13 limit 12 to humans (2036)
14 limit 13 to english language (1761)
15 limit 13 to abstracts (1812)
16 14 or 15 (1964)
17 exp clinical trials/ or clinical trial$.mp. (380571)
18 exp Cohort Studies/ (431690)
19 (cohort stud$ or longitudinal stud$ or prospective stud$).mp. (296276)
20 17 or 18 or 19 (762070)
21 8 and 20 (5991)
22 limit 21 to humans (5938)
23 limit 21 to abstracts (5335)
24 22 or 23 (5988)
25 16 or 24 (6831)
26 (2006$ not (200601$ or 200602$)).ed. (526925)
27 (2007$ or 2008$ or 2009$).ed. (1409839)
28 26 or 27 (1936764)
29 25 and 28 (2347)
30 from 29 keep 1-2347 (2347)

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Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <February 05, 2009>
Search Strategy:
----

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

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2008>
Search Strategy:
---
1 lovastatin.mp. or exp Lovastatin/ (1204)
2 simvastatin.mp. or exp Simvastatin/ (1167)
3 pravastatin.mp. or exp Pravastatin/ (949)
4 atorvastatin.mp. (941)
5 fluvastatin.mp. (368)
6 rosuvastatin.mp. (143)
7 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or statin$.mp. (2749)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (3802)
9 Comparative Study/ or comparative study.mp. (12886)
10 drug evaluation studies.mp. or exp Drug Evaluation/ (5646)
11 9 or 10 (18324)
12 8 and 11 (90)
13 meta analysis/ or meta analysis.mp. (1027)
14 multicenter study/ or multicenter study.mp. (6897)
15 exp clinical trials/ or clinical trial$.mp. (82715)
16 exp Cohort Studies/ (73025)
17 (cohort stud$ or longitudinal stud$ or prospective stud$).mp. (59519)
18 13 or 14 or 15 or 16 or 17 (152832)
19 12 or (8 and 18) (1240)
20 limit 19 to abstracts (1190)

21 from 20 keep 1-1190 (1190)

- -

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

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

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

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

Appendix C. Methods used to assess quality of studies

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

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

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

Systematic Reviews

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

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

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

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

3. Is the validity of included studies adequately assessed?

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

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

4. Is sufficient detail of the individual studies presented?

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

5. Are the primary studies summarized appropriately?

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

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

Controlled Trials

Assessment of Internal Validity

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

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
    - Inferior approaches to concealment of randomization:
        - Use of alternation, case record number, birth date, or day of week
        - Open random numbers lists
        - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

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

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to treatment allocation?

6. Was the care provider blinded?

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

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

9. Did the study maintain comparable groups?

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

11. Is there important differential loss to follow-up or overall high loss to follow-up? (Study should give number for each group.)

Nonrandomized studies

Assessment of Internal Validity

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

2. Was there important differential loss to follow-up or overall high loss to follow-up? (Numbers should be given for each group.)

3. Were the events investigated specified and defined?

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

5. Was there unbiased and accurate ascertainment of events (that is, by independent ascertainers using a validated ascertainment technique)?

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

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

References

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

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

Appendix D. Excluded studies

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

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

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

Excluded studies	Exclusion code
Barter PJ, O'Brien RC. Achievement of target plasma cholesterol levels in hypercholesterolaemic patients being treated in general practice. Atherosclerosis. 2000;149:199-205.	3
Ballantyne CM, McKenney J, Trippe BS. Efficacy and safety of an extended-release formulation of fluvastatin for once-daily treatment of primary hypercholesterolemia. American Journal of Cardiology. 2000;86(7):759-763.	6
Rosuvastatin shows superiority to atorvastatin in lowering cholesterol in type 2 diabetes. British Journal of Cardiology. 2004;11:188%N 183."	5
Active- control trials	
Bays H. Combination niacin and statin therapy compared with monotherapy. Cardiology Review. 2003;20(11):34-37.	3
Zeman M, Zak A, Vecka M, Romaniv S. Long-lasting combination treatment of mixed hyperlipoproteinaemias with statins and fibrates. Casopis Lekaru Ceskych. 2003;142(8):500-504.	1
Wiklung O, Angelin B, Fager G, et al. Treatment of familial hypercholesterolaemia: A controlled trial of the effects of pravastatin or cholestyramine therapy on lipoprotein and apoliprotein levels. J Intern Med. 1990;228(3):241-247.	4
Widimsky J, Hulinsky V, Balazovjech I, Lanska V. The long-term treatment of combined hyperlipidemia in CHD patients with a combination of fluvastatin and fenofibrate. Vnitrni Lekarstvi. 1999;45(4):210-216.	1
Stein E, Stender S, Mata P, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: Efficacy and safety of ezetimibe co-administered with atorvastatin. American Heart Journal. 2004;148(3):447-455.	3
Nagai R, Izumi T, Kurabayashi M, et al. Rationale and design of a study to examine lower targets for low-density lipoprotein-cholesterol and blood pressure in coronary artery disease patients. Circulation Journal. Apr 2008;72(4):515-520.	5
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Appendix E. Black box warnings for US Food and Drug Administration-approved drugs

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