

Comparative Effectiveness of Lipid-Modifying Agents



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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see <http://effectivehealthcare.ahrq.gov/reference/purpose.cfm>.

AHRQ expects that Comparative Effectiveness Reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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Executive Summary

Background

Over 28 million Americans have some form of cardiovascular disease (CVD), which causes more deaths than cancer, diabetes, accidents, and chronic lung diseases combined. Estimated direct medical expenditures and lost productivity from CVD amounted to \$431.8 billion in the United States in 2007.

A large amount of observational data, as well as clinical trials, support a significant, modifiable role of blood lipids in the production of disease. Cholesterol is transported in the blood in the form of particles containing lipids and proteins, called lipoproteins. Levels of low-density lipoprotein cholesterol (LDL-c) correlate with the development of CVD, while levels of high-density lipoprotein cholesterol (HDL-c) are associated with a lower risk of disease.

Cholesterol is a normal part of cell membranes, hormones, and bile acids that are involved in the absorption of some vitamins. Levels of cholesterol are influenced by its production in the liver and the ingestion of dietary fats. Bile acids are released into the intestine, aid in digestion, and then are mostly reabsorbed.

Evidence suggests that lowering LDL-c reduces coronary heart disease (CHD) and ischemic stroke, making LDL-c a primary target of therapy. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) recommendations provide guidance on the initiation of treatment aimed at lowering lipid levels based on individual patient characteristics. Three levels of risk have been established, with the highest risk individuals being those with CHD, diabetes, clinical atherosclerotic disease in other vascular beds, or multiple risk factors, resulting in a 10-year risk of developing CHD of more than 20 percent. LDL-c levels are indications for the initiation of treatment and represent therapeutic targets, but these targets are achieved by only one-third of all patients, and even fewer of those with established CHD. LDL-c levels are the primary target of treatment, with HDL-c and triglyceride levels forming secondary goals in these guidelines. For individuals with elevated triglycerides, the primary goal remains achieving the appropriate LDL-c target. The ATP III recommendations do not specify a target for HDL-c increment due to insufficient evidence regarding the proper level.

Medications available for lipid-lowering therapy have various mechanisms of action and pharmacokinetic properties. The most widely prescribed are the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. Known as statins, these agents reduce the production of cholesterol in the liver by binding with the enzyme responsible for its production. In contrast, fibrates do not influence lipid synthesis but rather reduce the levels of fatty acids in the blood. Ezetimibe is an agent that inhibits intestinal absorption by acting on the sterol transporter NPC1L1. Niacin (nicotinic acid) reduces LDL-c and increases HDL-c via a mechanism yet to be fully elucidated, although it is suspected to be involved in the synthesis and metabolism of apolipoproteins. Bile acid sequestrants (BAS) bind bile acids in the bowel, thereby preventing reabsorption of bile from the intestine. Omega-3 fatty acids have been postulated to lower postprandial triglycerides and have antithrombotic and blood-pressure-reducing effects.

Statins are the most studied and prescribed group of lipid-lowering medications and may be used alone or in combination with a medication of another type. Treatment options for individuals requiring intensive lipid-modifying therapy include increasing the dose of a statin or using a statin in combination with a lipid-modifying agent of another class. It is unclear which of

these strategies is superior with respect to clinical outcomes or the attainment of treatment targets. Combining different types of medications may appear attractive but could result in more harms, be less tolerable, or be less effective than statin therapy alone. This systematic review compares the benefits and risks of these two options in terms of clinical events (e.g., myocardial infarction, stroke, or death), surrogate measures (e.g., levels of LDL-c), tolerability, and adherence.

This evidence report was commissioned by the Agency for Healthcare Research and Quality (AHRQ) to address the following key questions:

Key Question 1. For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits and rates of serious adverse events of coadministration of different lipid-modifying agents (i.e., a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

Key Question 2. Do these regimens differ in reaching LDL targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

Key Question 3. Compared with higher dose statins and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

Methods

Search Strategy

MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials were searched from inception to August 2008, and Scopus was searched for references citing eight expert-nominated articles. Additional searches included statistical and medical reviews of drug applications posted by the U.S. Food and Drug Administration (FDA), information packages submitted by the pharmaceutical companies marketing lipid-modifying drugs, and the Internet.

Study Selection

Studies employing therapeutic doses of drugs were included. Relevant nonstatin hypolipidemic drugs included ezetimibe, fibrates, niacin, BAS, and omega-3 fatty acids. Randomized controlled trials for all outcomes and nonrandomized comparative studies of 24 weeks or more in duration for clinical outcomes, serious adverse events (SAE), and cancer were eligible.

Screening and Data Extraction

One reviewer screened abstracts to include studies, and exclusions were verified by another reviewer. Two reviewers independently screened full-text reports, with conflicts resolved by consensus or third party adjudication. Data were extracted in standardized forms.

Evidence Synthesis

Primary outcomes were all-cause mortality and vascular death. Secondary outcomes were myocardial infarction (fatal, nonfatal, or unspecified MI), acute coronary syndrome, stroke (hemorrhagic, ischemic, or unspecified), transient ischemic attack, unspecified cerebrovascular

event, and revascularization procedures. Surrogate outcomes included attainment of NCEP ATP III LDL-c goals, LDL-c, HDL-c, total cholesterol (TC):HDL-c ratio, non-HDL-c and triglycerides in the subgroup with diabetes mellitus, and measures of carotid or coronary atherosclerosis. Harms were SAE, cancer, treatment adherence, withdrawal due to adverse events, participants with at least one adverse event, elevated serum aspartate transaminase (AST) and/or alanine transaminase (ALT) above 3 times the upper limit of normal and/or hepatitis, myalgia, creatinine phosphokinase (CPK) above 10 times the upper limit of normal, and rhabdomyolysis.

Populations requiring intensive therapy included participants with a 10-year CHD risk above 20 percent and/or mean baseline LDL-c of at least 190 mg/dL.

Statin plus another hypolipidemic drug combination therapy was compared with statin monotherapy. Synthesis of evidence was specific to combinations employing different nonstatin hypolipidemic drugs. Evidence from nonrandomized studies was synthesized qualitatively only. Anticipating a dearth of available evidence in answering the key questions, analyses were broadened to the following categories:

Dose and statin-specific analyses comparing lower dose of a specific statin plus any dose of a nonstatin lipid-lowering drug vs. higher dose of the same statin monotherapy in:

- All trial populations (or mixed populations).
- Population in need of intensive lipid lowering.
- Subgroups.

Analyses of various statins and doses comparing any dose and subtype of statin plus any dose of a nonstatin lipid-lowering drug vs. any dose and subtype of statin monotherapy in:

- All trial populations.
- Population in need of intensive lipid lowering.
- Subgroups.

Lower and higher doses of statins were defined as shown in Table A.

Table A. Types and doses of statins

Statin	Atorvastatin ^a	Simvastatin ^a	Rosuvastatin ^a	Pravastatin	Fluvastatin	Lovastatin
Lower dose (mg/day)	5 and/or 10 and/or 20	5 and/or 10 and/or 20	5 and/or 10	5 and/or 10 and/or 20 and/or 40	5 and/or 10 and/or 20 and/or 40	5 and/or 10 and/or 20 and/or 40
Higher dose (mg/day)	40 and/or 80	40 and/or 80	20 and/or 40 and/or 80	80	80	80

^aDose and statin specific analyses were restricted to these statins in meta-analyses of randomized controlled trials in all trial populations.

All-cause mortality, vascular death, and surrogate efficacy outcomes were examined for all trial populations, populations in need of intensive lipid-lowering, and subgroups. However, anticipating insufficient evidence pertaining to specific populations, syntheses of evidence on harms and clinical outcomes, other than the primary outcomes of all-cause mortality and vascular death, were undertaken irrespective of population characteristics (i.e., across all available trial populations) for each combination vs. monotherapy comparison.

Data were synthesized qualitatively when heterogeneity was substantial (I^2 greater than 50 percent). Trials of greater than 24 weeks duration were defined as long term, while those less than 24 weeks were considered short term. A systematic procedure was employed to avoid

double counting treatment group data when trials presented multiple unequal numbers of combination and monotherapy arms (unit-of-analysis error). Details of the procedure are provided in the full report.

The DerSimonian and Laird approach was used for all meta-analyses, except for rare events (less than 1 percent of participants), when fixed Peto Odds Ratios were calculated.

Methodological Quality Assessment

Study quality of RCTs was assessed with the Jadad scale, and of nonrandomized studies with the Downs and Black criteria. Reporting of adequacy of allocation concealment was also assessed and considered in the sensitivity analyses.

Rating the Quality of Evidence Synthesized

Using GRADE (Grading of Recommendations Assessment, Development and Evaluation), evidence was rated for the primary outcomes, ATP III goal attainment, and SAE. The GRADEpro software was used.

Conclusions

Table B is a summary table that presents the main conclusions of this report. Conclusions pertaining to the key questions, as well as additional analyses in mixed populations, are summarized below. Ninety-seven unique randomized controlled trials (RCTs) and four controlled clinical trials (CCTs) were included.

Key Question 1. Long-Term Benefits and Serious Adverse Events

There are several important limitations in the evidence regarding long-term clinical outcomes. Most of the evidence originates from short-term studies aimed at biochemical measures and therefore is insufficient for the clinical events of interest, including the occurrence of MI, stroke, or death. In trials of combination therapy, the monotherapy comparator arms rarely explored higher-dose statins or were not performed in individuals requiring intensive lipid lowering. Due to these limitations in the available data, we present first our results based on the available evidence for the group requiring intensive lipid lowering when combination treatment is compared to a higher dose of a statin, and then provide a broader perspective using available data in all risk groups comparing combination therapy to any monotherapy statin dose.

All-cause mortality. The quality of evidence was very low for all available comparisons of combinations and monotherapy reported below.

For individuals requiring intensive therapy, limited evidence was available for statin combinations with ezetimibe and fibrates compared to higher doses of statins. In the two statin-ezetimibe combination trials, no deaths occurred in either the combination or the statin monotherapy group, precluding a comparative analysis of mortality. A single trial with a statin-fibrate combination showed no difference in mortality compared with a higher dose statin.

Trials comparing combination therapy with statin monotherapy that were not limited to individuals requiring intensive lipid lowering and did not necessarily compare combination therapy with a higher dose of statin monotherapy were examined for an effect on mortality. No significant differences between treatments were observed across any combination, including

statin-omega-3 combination, which was studied in three trials, one of which was a large trial lasting 5 years of 18,645 Asians.

Vascular death. Treatments aimed at modifying lipids might be expected to lower the rates of death due to vascular diseases such as heart disease and stroke. However, no trials examined this outcome in a high-risk population and compared the combination to a higher statin dose. Across all available trial populations, two trials each of statin-ezetimibe and statin-niacin combinations did not demonstrate a difference in the occurrence of rare vascular deaths. The quality of evidence was very low for evidence pertaining to both combinations.

Other clinical outcomes. For the outcomes of reduction of MI or stroke or avoidance of revascularization procedures on the carotid or coronary vessels, no evidence comparing combination therapy with a higher dose of statin was available. Evidence comparing various doses of statin-ezetimibe, statin-fibrate, statin-niacin, and statin-BAS combinations with statin monotherapy was available from few trials registering rare events, and no significant difference was detected. One large statin-omega-3 trial of 18,645 Asians demonstrated no significant difference between treatments for the outcomes of nonfatal MI, hemorrhagic stroke, ischemic stroke, and all stroke over a period of 5 years.

Serious adverse events. The quality of evidence was very low for all available combination and monotherapy comparisons.

Evidence pertained to all available trial populations and not specifically those in need of intensive treatment. Evidence comparing a combination with a higher dose of statin monotherapy was available only for the statin-ezetimibe combination. Three trials with a maximum duration of 24 weeks demonstrated no difference in the rate of serious adverse events. Overall, 5 percent of participants had an event. When various doses and statin types in combinations were compared with statin monotherapy, no significant differences were noted across all combinations, including evidence that combined 27 statin-ezetimibe trials with over 13,000 participants. Absolute rates of serious adverse events varied between 2 and 4 percent. Even across all combinations, no differences were detected when analyses were restricted to the few long-term trials of 24 to 52 weeks duration.

Cancer. Evidence pertained to all available trial populations and not only those in need of intensive treatment. Some data were available for individuals at any risk level and statin dose. One 5-year omega-3 trial of 18,645 participants demonstrated no significant difference in the incidence of cancer, with an overall rate of 3 percent. With two 24-48-week statin-ezetimibe trials of 971 participants, the rate of incident cancer was 1 percent, with no significant difference between treatments. Cancer was too rare in a single small statin-niacin trial to permit any conclusion. No evidence was available for statin-fibrate and statin-BAS combinations. While the available data do not suggest an increased incidence of cancer with ezetimibe or omega-3 combinations, the power to detect small differences in the rates of conditions, such as cancer which may have a long latency prior to presentation, is limited given the current data.

Key Question 2. LDL-c Targets, Short-Term Side Effects, Tolerability, and Adherence

Surrogate markers are biological markers that are linked to the occurrence of disease and used as targets for therapy. The NCEP ATP report sets treatment goals for various risk categories. In this report, we examine the proportion of individuals attaining the LDL-c goals set by the ATP III panel, the effect on LDL-c and HDL-c levels, the total cholesterol:HDL-c ratio, and markers of atherosclerosis.

Participants attaining ATP III LDL-c goals. The available evidence is of very low quality for all comparisons of combination with monotherapy.

For individuals requiring intensive therapy, two trials employing fixed dose or titrations could be statistically combined. Compared with a higher dose statin alone, statin-ezetimibe combination demonstrated a greater probability of reaching treatment goals. A single trial using a statin-fibrate combination demonstrated no significant difference in the number of participants reaching goals compared to a higher dose statin. No evidence comparing higher dose statin monotherapy with any of the remaining combinations was available for participants requiring intensive treatment.

Substantially more information was available for statin-ezetimibe combination therapy in which the treatment comparison was not necessarily a higher dose of statin. In 88 percent of 18 trials conducted in a population in need of intensive treatment, combination therapy was more likely than statin monotherapy to help participants reach LDL-c targets. Likewise, 96 percent of 23 trials favored the statin-ezetimibe combination when all trial populations using various statins as the two treatments were included.

No evidence was available for the statin-omega-3 combination. Sparse evidence precluding meaningful conclusions was identified for statin-fibrate (two trials), statin-niacin (one trial), and statin-BAS (one trial) combinations across various doses and populations.

LDL-c. When comparing a specific statin in combination with a higher dose statin in populations requiring intensive treatment, evidence was either insufficient or absent for statin-fibrate, statin-niacin, statin-BAS, and statin-omega-3 combinations. Scant evidence from two statin-ezetimibe trials was not statistically combined because of heterogeneity, but both trials indicated significant additional reductions of 10 to 20 percent favoring statin-ezetimibe combination therapy over monotherapy.

More data were observed for individuals requiring intensive therapy when combinations were compared with any dose of statin. Substantial heterogeneity precluded statistical analysis of 18 statin-ezetimibe and 4 statin-BAS trials. However, all statin-ezetimibe trials favored combination treatment, with mean additional reductions of 4 to 27 percent. Inconsistent results were found for statin-BAS trials, while evidence was insufficient for statin-niacin, statin-BAS, and statin-omega-3 combinations.

Across all trial populations, when lower doses of statins in combination were compared with higher doses of the same statin monotherapy, significant additional LDL-c reductions of 3 to 20 percent were observed with statin-ezetimibe combinations (six trials); however, heterogeneity precluded a statistical estimate. Evidence was insufficient or absent for each of the remaining combinations.

Across various doses of statins in combination and as monotherapy in all trial populations, significant LDL-c reductions were found with statin-ezetimibe combination (35

trials, of which 94 percent showed 4 to 27 percent additional reduction in LDL-c) and statin-BAS (11 trials, of which 8 trials employing similar doses showed significant, 8 to 16 percent, additional reductions favoring combination). With two statin-omega-3 trials, monotherapy was superior. Indeterminate efficacy was noted for the few statin-fibrate and statin-niacin trials.

HDL-c. There is lack of evidence permitting meaningful conclusions from trials comparing a combination with higher dose of statin monotherapy in populations requiring intensive treatment.

In trials comparing various statins and doses in combination with various statin monotherapies in populations requiring intensive treatment, there was evidence of 1.5 percent increment in HDL-c favoring statin-ezetimibe (15 trials) and statin-fibrate combination therapy, and of no significant difference between monotherapy and statin-BAS combination (four trials). Insufficient evidence compared statin-niacin and statin-omega-3 combination with monotherapy in this population.

When trials were not restricted to populations in need of intensive treatment, no significant difference in change in HDL-c was noted for simvastatin in combination with ezetimibe vs. higher doses of simvastatin alone (five trials). Evidence from a single trial favored statin-niacin combination, and showed no difference between statin-fibrate and monotherapy.

No consistent effect was noted for the statin-ezetimibe combination across diverse trial populations employing various statins and doses. However, across various statins and doses in all populations, significant advantages of the statin-omega-3 and statin-fibrate combinations were noted for HDL-c increment when compared with monotherapy (three trials each), while no significant difference was noted for the statin-BAS combination (nine trials). Five of the six statin-niacin trials favored combination, the exception being the one trial that employed high-dose rosuvastatin in both treatments.

Total cholesterol:HDL-c ratio. When comparing a specific statin in combination with a higher dose statin in populations requiring intensive treatment, evidence was either absent or based on single-trial data, precluding robust conclusions across any combination therapy. A single ezetimibe trial compared lower dose simvastatin in combination vs. higher dose of simvastatin monotherapy in participants requiring intensive lipid-lowering therapy; results favored the combination therapy, demonstrating 14 percent additional reduction.

When comparing various statins and doses in combination with various statin monotherapies in populations requiring intensive treatment, additional data were available. Significant additional reductions of 3 to 20 percent favoring statin-ezetimibe combination therapy were noted in all 10 trials, with substantial heterogeneity precluding meta-analysis. Evidence was neutral for the statin-fibrate combination (two trials). For other combinations, evidence was either insufficient or absent.

Across all available populations, evidence comparing a lower statin dose in combination with a higher dose as monotherapy demonstrated no significant difference between statin-ezetimibe combination and monotherapy. Evidence was insufficient for statin-fibrate combination.

Across various statins and doses in all trial populations, 20 statin-ezetimibe trials were not meta-analyzed because of substantial heterogeneity; however, combination treatment was significantly favored in all but one trial. Evidence favored statin-omega combination, did not show a difference for statin-fibrate, was insufficient for statin-niacin, and was totally absent for statin-BAS.

Measures of atherosclerosis. Carotid intimal media thickness (IMT) can be measured by ultrasound and correlates with the presence of atherosclerotic plaque and vascular risk factors. Previous research has shown that statin treatment reduces the progression of this marker. Two trials were available that compared mean change from baseline in the IMT with combination therapy compared to statin monotherapy. One trial of 642 evaluable participants requiring intensive lipid lowering compared simvastatin plus ezetimibe with identical-dose simvastatin monotherapy and yielded indeterminate results. Another trial of 149 evaluable participants requiring intensive lipid-lowering therapy and using mixed statins with niacin and as monotherapy also demonstrated indeterminate results.

Adherence and harm. For the comparison of a specific statin in combination with a higher dose of its monotherapy across all trial populations, insufficient evidence was available for all combinations except statin-ezetimibe, which showed no significant differences between treatments for the outcomes of withdrawal due to adverse events and liver toxicity (defined as AST/ALT above three times the upper limit of normal). Most trials had a short duration of treatment and followup.

Conclusions summarized below pertain to the comparisons of various statins and doses in combination with various statin monotherapies in all trial populations.

Early withdrawal due to adverse events was more likely for the combination of statin plus niacin than for statin therapy alone (10 trials with an average duration of 24 weeks). No significant difference was noted for other combinations.

Compared with statin monotherapy, more participants developed at least one adverse event with statin-BAS combination (four trials). Inconsistent results were obtained when statin-niacin combination was compared with statin monotherapy. However, three of six trials showed significantly more participants experiencing adverse events with combination than with monotherapy.

Available evidence did not indicate significant differences between participants developing AST/ALT above 3 times the upper limit of normal and/or hepatitis, CPK above 10 times the upper limit of normal, or myalgia for a comparison of any combination with statin monotherapy. In addition, no participant developed rhabdomyolysis in any of the 27 RCTs investigating the five statin combination therapies, 85 percent of which were short term.

No significant difference in treatment adherence was noted for statin-ezetimibe and statin-niacin combinations compared to monotherapy. The statin-BAS trials could not be meta-analyzed due to inconsistent and unexplained direction and magnitude of effects on adherence across five trials.

Key Question 3. Benefits and Harms Within Subgroups of Patients

Evidence in subgroups.

Participants with diabetes mellitus. Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with a higher dose of statin monotherapy for any relevant outcomes.

Across various statin doses in combination and monotherapy, no evidence was available for statin-niacin, statin-BAS, and statin-omega-3 combinations. Compared with statin monotherapy, the statin-ezetimibe combination allowed more participants with diabetes to reach

ATP III LDL-c goals when monotherapy was of similar statin dose and potency to combination statin (very low quality of evidence) and allowed greater additional reductions in LDL-c, ranging from 4 to 26 percent; TC:HDL-c ratio, 3 to 17 percent; and non-HDL-c, 4 to 24 percent. There was inconsistent evidence for a change in HDL-c between combination and monotherapy treatments.

Meta-analysis of two statin-fibrate trials demonstrated no significant difference between treatments for LDL-c reduction, but a significant increase in HDL-c of 5 percent favored the combination. There was insufficient evidence on statin-fibrate combination for other outcomes in participants with diabetes mellitus, including one trial that examined mean percentage reduction in triglyceride in 164 participants, with additional mean reduction of 14 percent favoring combination therapy. Due to the rarity of events, evidence was indeterminate and of very low quality for a difference in all-cause mortality with six statin-ezetimibe and one statin-fibrate trial, and evidence for vascular death was absent across all combinations using various statin doses.

Participants with established vascular disease. Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with higher dose statin monotherapy for any relevant outcomes in individuals with pre-existing vascular disease.

Across various statin doses in combination and monotherapy, there was insufficient evidence examining the statin-fibrate, statin-niacin, statin-BAS, and statin-omega-3 combinations with respect to statin monotherapy. Compared with statin monotherapy, statin-ezetimibe combination therapy allowed more participants to reach ATP III LDL-c goals and to reach 9 to 27 percent additional reduction in LDL-c. No significant difference was noted for change in HDL-c for this combination, and evidence was insufficient for TC:HDL-c ratio.

Due to the rarity of events, evidence was indeterminate and of very low quality for a difference in all-cause mortality with six statin-ezetimibe and one statin-fibrate trial, and not estimable for vascular death from one short-term statin-niacin trial registering no event.

Participants with baseline LDL-c of 190 mg/dL or above. Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with higher dose statin monotherapy for any relevant outcomes.

Across various statin doses in combination and monotherapy, no evidence examined the statin-fibrate, statin-niacin, and statin-omega-3 combinations. Compared with statin monotherapy, the statin-ezetimibe combination allowed 17 percent additional reductions in LDL-c. Insufficient evidence for this combination was available for other outcomes.

No significant difference was noted for change in HDL-c with statin-BAS combination, and evidence was inconsistent for a reduction in LDL-c. Insufficient evidence for this combination was available for other outcomes.

Participants with cerebrovascular disease, females, participants of 80 years of age or older, participants of African descent, participants of Asian descent, and Hispanics. No evidence was available for participants with cerebrovascular disease and those age 80 years and over. Sparse evidence of very low quality, precluding meaningful conclusions, was available in subgroups of participants of different ethnic origins and females. However, one large 5-year trial investigating various statins in both treatments among 18,645 Asians resulted in low-quality evidence that there was no significant difference between statin-omega-3 combination and statin monotherapy for the outcome of all-cause mortality.

Applicability of the Body of Evidence

Available Evidence

Population. In general, studies excluded participants with statin-associated myopathy, deranged liver enzymes, high triglycerides, recent vascular events, uncontrolled hypertension, and diabetes mellitus and also excluded the frail elderly over 80 years of age. Most trials were in mixed CHD risk populations, employed a prerandomization run-in phase to minimize nonadherence, and conducted frequent laboratory monitoring for liver and muscle enzyme elevations to withdraw participants with deranged levels.

Intervention and comparators. Studies generally employed therapeutic doses of interventions, but few compared the addition of another nonstatin lipid-lowering drug to a statin with the alternative of statin dose escalation.

Outcomes. Clinical outcomes other than evident all-cause mortality were infrequently assessed. Nevertheless, all-cause mortality was a rare event across most trials.

Followup duration. Most trials were of less than 6 months duration.

Implications

There is a dearth of evidence directly examining the comparative effectiveness of treatments. Available evidence mostly compared statin combination therapy with similar or equipotent doses of statin monotherapy and examined relative efficacy using surrogate outcomes over a short-term period. Only one large statin-omega-3 trial can be considered an effectiveness trial; however, this trial examined various statins in various doses in combination and as monotherapy. Direct comparative evidence of clinical effectiveness was also lacking from long-term observational studies

Remaining Issues

This review has identified a number of areas requiring future research. Our recommendations address research methodologies in general and specific needs for research to address the key questions.

All trials must clearly report adequate allocation concealment and intention-to-treat analysis. Blinding and endpoint adjudication should be employed to minimize bias. Failure to comply with these standards has adversely affected the quality of trials in this therapeutic area.

Pragmatic trials are required in order to provide relevant guidance to practitioners and patients. In trials of this type, oversampling of populations of interest, including women, ethnic groups, elderly Americans, and persons with diabetes, would help define the relative applicability of the results. Ample evidence supports the role of LDL-c as a determinant of risk as well as a target for therapy. The current data would support investigation of statin-ezetimibe combinations in this regard. Statin-BAS combinations would also be of some interest, although the potential for BAS to interact with other medications by limiting absorption would limit the broad application of these findings. Further research is required to establish the relevance of therapy directed at triglycerides and HDL-c with respect to clinical outcomes. Trials of statin-niacin combination in individuals with low HDL-c in spite of statin therapy and in individuals on maximal statin therapy would serve to define the clinical relevance of these combinations and, at this time, seem more likely to produce relevant data than more broadly inclusive trials for this combination. Similarly, trials of statin-fibrate therapy in individuals with elevated triglycerides

are recommended. Omega-3 preparations are variable in content and source, with no clear accepted formulation for individuals requiring intensive lipid lowering. While a number of benefits have been suggested, it is unclear that statin-omega-3 combination preparations have any benefits over higher dose statins in this population based on the negative data to date. Further investigation of these combinations should focus on optimizing the formulations and establishing added clinical benefit when used in maximally treated populations. The following points apply to the proposed trials of combination therapy and serve to amplify these comments in the context of the key questions.

Key Question 1. Long-Term Benefits and Serious Adverse Events

- The comparator for trials of combination therapy in which LDL-c reduction or clinical events are a major outcome should be a higher dose statin. The bulk of the clinical evidence for this endpoint, as well as clinical endpoints, exists for statin monotherapy. Until a compelling case can be made for a particular combination therapy, comparisons with similar doses of statin monotherapy are unhelpful in resolving the issue.
- Studies of combination therapy should be conducted over longer time periods and be powered for clinical endpoints. Since the lipid-lowering treatment is usually required for life, both trial treatment and observation duration should be of longer duration. The current evidence base lacks trials of this type, significantly limiting the conclusions that can be drawn. The specific duration will be determined by the endpoints and the risk profile of the population studied but, in general, studies of less than 2 years are unlikely to add significantly to the evidence base on clinical outcomes.
- Harms should be prospectively collected and comprehensively reported. Short-duration trials are unlikely to accrue sufficient adverse events, particularly those with longer latency periods, such as cancer.
- As the possibility of harm cannot be excluded for some individuals with symptomatic cerebrovascular disease due to the unique risk for cerebral hemorrhage in these individuals, this population should be specifically studied in order to better define the parameters for those in whom intensive combination therapy is recommended.
- Concomitant and antecedent therapy should be explicitly stated, as both of these factors may influence outcomes. In studies employing a mixture of statin medications and/or doses, results should be reported by medication and dose in order to allow pooling across studies.
- Studies investigating HDL-c and non-HDL-c targets in a population with LDL-c at target are recommended. The absence of such evidence limits the ability to assess the role of combination therapies that raise HDL-c levels.

Key Question 2. LDL-c Targets, Short-Term Side Effects, Tolerability, and Adherence

- The comparator for trials of combination therapy, with LDL-c reduction as a primary outcome, should be a higher dose statin, as noted above.
- Studies to correlate LDL-c with carotid IMT and clinical outcomes should be conducted in different populations (e.g., participants with diabetes mellitus, CHD, and multiple risk factors as defined by ATP III), with reporting of antecedent therapy, as this may be a determinant of outcome. Such work would help further validate carotid IMT as a suitable surrogate marker for future trials.
- As medication adherence and persistence are important determinants of outcome and are correlated with the complexity of the treatment regimen, studies should be undertaken to compare combinations delivered as a single pill as opposed to two separate ones.
- Measures of adherence and persistence are affected by the duration of the study period, and thus longer term trials are required for combination therapies of lipid-modifying agents. Trial durations of greater than 6 months and preferably 1 year are recommended.

Key Question 3. Benefits and Harms Within Subgroups of Patients

- Trials should be conducted in, or oversample, specific subgroups in order to determine relative benefits and harms of a statin combination compared with statin monotherapy. These groups include women, older individuals more susceptible to harms of drug therapy, participants with diabetes mellitus and multiple risk factors, and those of African, Hispanic, and Asian descent.
- Trials including women and the groups identified above should report results in a manner amenable to extraction and pooling in order to permit the early identification of a differential effect in specific subgroups. Specifically, whenever possible, results should be reported by subgroups in trial publications.

Addendum

We updated the evidence report in May 2009 by rerunning the previous literature search strategy in the MEDLINE and EMBASE databases. In the initial search, the CENTRAL database identified only 7 percent of retrieved records, none of them unique to CENTRAL, and thus was excluded in the updated search. We searched Ovid MEDLINE[®] from August Week 1, 2008, to May Week 5, 2009, and EMBASE from Week 30, 2008, to Week 23, 2009. We restricted our focus to studies of 24 weeks or longer that reported clinical efficacy outcomes, the incidence of serious adverse events, and cancer.

Of a total of 1,271 newly identified records, 25 met the original inclusion criteria. (An updated search flow chart is shown in Appendix K of the full report.) Of these, 20 records were excluded, as they either did not report clinical outcomes or had durations shorter than 24 weeks.

Two more studies, one that employed a statin not marketed in the United States and another that failed to report relevant outcomes by treatment groups, were also excluded.

The remaining three studies were included in the evidence update (Appendix K of full report). All were randomized controlled trial reports, two of which were companion reports of previously included reports, contributing no new relevant data. Only one trial provided evidence on a clinical outcome of interest over a minimum period of 24 weeks. In this 56-week trial of 100 participants of mostly European descent with established carotid artery stenosis, one individual in the 80 mg/day simvastatin monotherapy group experienced an acute coronary event, as opposed to none in the 20 mg/day simvastatin monotherapy and 20 mg/day simvastatin plus 2 g/day niacin extended-release combination groups.

Overall, the update of this review did not add significant evidence on longer term clinical outcomes, serious adverse events, or cancer to the report. The conclusions were not altered based on updated evidence.

Finally, as this report was going to press, the U.S. Food and Drug Administration approved a statin drug, pitavastatin, which was excluded in this review as it was not marketed in the United States at the time of the initial evidence search or the update.

Table B. Summary of conclusions from evidence comparing use of a specific statin in combination with another lipid-modifying agent with use of a higher dose statin in populations requiring intensive treatment and subgroups

Outcome	Strength of Evidence (GRADE)	Summary/conclusions
<i>Key Question 1. For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits and rates of serious adverse events of coadministration of different lipid-modifying agents (i.e., a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?</i>		
All-cause mortality	Very low	Insufficient evidence was available regarding mortality. Based on small trials with few events, no difference in mortality was noted for any statin combination associated with ezetimibe or fibrates compared with higher dose statin monotherapy. No evidence was available for other combinations.
Vascular death	---	No evidence was available for any statin combination vs. higher dose statin monotherapy.
Serious^a adverse events	Very low	Up to a maximum followup of 24 weeks, no intervention was significantly safer when statin-ezetimibe combination was compared with higher dose statin monotherapy. No evidence was available for other combinations.
<i>Key Question 2. Do these regimens differ in reaching LDL targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?</i>		
Attainment of ATP III LDL-c goals	Very low	Ezetimibe plus simvastatin therapy is more likely to result in attainment of LDL-c target than higher dose simvastatin, based on 2 small trials. Results for statin-fibrate combination (1 trial) were indeterminate. No evidence was available for other combinations.
<i>Key Question 3. Compared with higher dose statins and to one another, do combination regimens differ in benefits and harms within subgroups of patients?</i>		
All-cause mortality, vascular death, and attainment of ATP III LDL-c goals	Very low	There is insufficient evidence to draw any meaningful conclusions in subgroups for any combination.
Serious adverse events	---	Since absent to scant subgroup evidence was anticipated, SAE was examined across all trial populations (see above).
Inter-combination, indirect comparison of syntheses		We are unable to confirm a difference in benefits or harms between combinations due to the lack of evidence.

^aBecause of scant evidence for those in need of intensive lipid lowering, SAE was examined across all trial populations
Abbreviations: ATP III=Adult Treatment Panel III (of the National Cholesterol Education Program); GRADE=Grading of Recommendations Assessment, Development and Evaluation; LDL-c=low-density lipoprotein cholesterol; SAE=serious adverse events.

Introduction

Background

Over 28 million Americans have some form of cardiovascular disease (CVD) and these conditions cause more deaths than cancer, diabetes, accidents and chronic lung diseases combined.¹ An American dies every 36 seconds as a result of CVD, amounting to 2,400 deaths per day.¹

CVD includes coronary heart disease (CHD), heart failure (HF) and stroke. The Framingham Heart Study, an ongoing longitudinal study of CVD and its risk factors, suggests that the lifetime risk of developing disease for those well at age 50 is 51.7 percent for men and 39.2 percent for women.⁸ Direct medical expenditures and lost productivity as a result of these conditions result in an estimated cost of \$431.8 billion in the United States in the year 2007.⁹

Experimental evidence linking cholesterol and vascular disease existed as early as the beginning of the 20th century. In 1913 Nikolai Anitschkow, a Russian experimental pathologist demonstrated that feeding rabbits a diet rich in cholesterol resulted in vascular lesions with the same pathology as those which were known to occur in human atherosclerosis.¹⁰

Ansel Keys, working at the University of Minnesota, performed one of the earliest epidemiologic studies correlating cholesterol levels with the risk of death from CHD in the Seven Countries study.¹¹⁻¹³ This ecologic correlation data analysis demonstrated a relationship between dietary cholesterol intake, serum cholesterol levels and the CHD death rate of seven populations chosen to represent a range of serum cholesterol.

The American Heart Association accepted that cholesterol was causally linked to CHD as early as 1961, and recommended that people at high risk be advised to modify their diets.¹⁰ The first large trial demonstrating a reduction in cardiac endpoints by lowering cholesterol levels was the Coronary Primary Prevention trial, funded by the National Institutes of Health (NIH) and published in 1984.¹⁴ Subsequently the National Cholesterol Education Program (NCEP) was established, with its first report published in 1988.¹⁵ The era of potent lipid lowering therapies was ushered in by the 4S Trial, which demonstrated a 42 percent reduction in CHD mortality and a reduction in all cause mortality following treatment with simvastatin. The NCEP guidelines have been updated, with the most recent full report published in 2002 as the Adult Treatment Panel III (ATP III).¹⁶

An understanding of the biology underlying vascular disease has paralleled the development of therapeutic options and guidelines. Atherosclerosis is a pathologic process involving injury to vessel walls with subsequent accumulation of lipids, proteins and inflammatory cells within the wall. Impairment of blood flow due to blockage of the vessel, and promotion of thrombosis or embolization of material into smaller blood vessels result in impaired function or death of tissues.

Cholesterol is transported in the blood as particles combining lipids and proteins called lipoproteins. Low density lipoprotein cholesterol (LDL-c) level in the serum is positively correlated with the development of atherosclerosis, while the levels of high density lipoprotein cholesterol (HDL-c) show an inverse relationship with the atherosclerotic process. The levels of HDL-c are affected by a number of other risk factors including diabetes, obesity and smoking. Guidelines have not identified a level of HDL-c as a goal for therapy, although ATP III does encourage therapies to elevate HDL-c as part of the management strategy.¹⁶ Additionally, elevated serum triglycerides are atherogenic and associated with increased risk for CHD.

Therefore, lifestyle modification is recommended for first line therapy in individuals with elevated triglycerides. The biologic processes and interactions between other lipid fractions and risk factors are complex and beyond the scope of this review.

Trial evidence suggests that lowering of LDL-c results in a reduction in CHD and, recently, rates of ischemic stroke.^{17,18} Due to the consistent and robust association of higher LDL-c levels with disease across experimental and epidemiologic studies, therapeutic strategies have focused on LDL-c reduction as the primary goal. The ATP III report established three risk strata for CHD, with upper LDL-c cut-off points for the initiation of treatment and therapeutic LDL-c targets. The highest risk individuals were defined as those with established CHD or CHD risk equivalents (i.e. diabetes, clinical atherosclerotic disease in other vascular beds, or multiple (2 or more) risk factors resulting in a CHD ten year risk of more than 20 percent). This stratification expanded the population for whom lipid lowering therapy was recommended.

Following the 2002 publication of the NCEP ATP III guidelines, five major trials were published, resulting in a revision in 2004.¹⁹ These additions to the evidence base led to the inclusion of diabetes as a CHD equivalent risk and reinforced the benefits of lowering LDL-c in older individuals. In addition, for very high risk individuals, more aggressive targets were felt to be a therapeutic option. The previous target of LDL-c below 100 mg/dL was supplemented with an optional goal of LDL-c below 70 mg/dL in very high risk populations who already have baseline LDL-c below 100 mg/dL. Very high risk individuals were defined as those with acute coronary syndromes, multiple major risk factors (especially diabetes and smoking), severe and poorly controlled risk factors, and multiple risk factors for metabolic syndrome.¹⁹ High risk patients continued to be defined as in the 2002 ATP III. While the optional target of LDL-c below 70 mg/dL was supported by two of the reviewed trials,^{20,21} further trial confirmation was sought prior to considering this to be definitive. Finally, ATP III suggests that individuals without established disease or multiple risk factors but with an LDL-c above 190 mg/dL should be treated to a target LDL-c of 160 mg/dL. This population may also be considered to be in need of intensive lipid lowering therapy if the initial LDL-c is very high.

Cholesterol is a structural component of cellular membranes, and is a precursor of steroid hormones and bile acids. Plasma cholesterol levels are influenced by production in the liver as well as absorption of ingested fats. Hepatic synthesis of cholesterol begins with 2-carbon acetyl-CoA moieties which are condensed to hydroxymethylglutaryl-CoA (HMG-CoA) by HMG-CoA synthase. The next step in this metabolic pathway, the conversion of HMG-CoA to mevalonate by HMG-CoA reductase, has been the chief pharmaceutical target. Dietary cholesterol reaches the liver after absorption in the intestine as chylomicrons containing triglycerides and cholesterol. The triglycerides are metabolized to fatty acids that are taken up by peripheral tissue, leaving the cholesterol rich particles to be absorbed by the liver. Bile acids, which are critical for absorption of dietary fat and fat soluble vitamins, are produced in the liver and excreted with free cholesterol into the intestine. Approximately 90 percent of the excreted bile salts are reabsorbed during digestion. Cholesterol is actively absorbed from the intestine by Niemann-Pick C1-Like 1 protein (NPC1L1), localized in jejunal enterocytes.

A number of medications are available for use as lipid lowering therapy (Table 1). These agents differ in mechanism of action and pharmacokinetic properties (Appendix C).

The most widely prescribed agents are the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors commonly known as statins. These agents are structural analogues of HMG-CoA, the rate limiting enzyme for cholesterol synthesis in the liver, and competitively bind to it. Statins also reduce plasma cholesterol by upregulating the LDL-c

receptor, that leads to increased uptake of LDL-c from the blood. A number of other actions have been noted experimentally including suppression of inflammatory molecules, stimulation of endothelial nitric oxide (eNOS), and inhibition of smooth muscle proliferation and reactive oxygen species. These mechanisms may have a role in the reduction of clinical events, though some debate remains. The older statins (mevastatin, lovastatin, pravastatin, and simvastatin) are fungal metabolites, whereas the newer ones are synthetic (fluvastatin, atorvastatin, and rosuvastatin).

In contrast with statins, fibrates do not influence lipid synthesis but rather reduce the levels of fatty acids in the blood by facilitating oxidation of these molecules. Fibrates are synthetic ligands for hormone activated nuclear receptors, chiefly peroxisome proliferator-activated receptor α (PPAR α).²² PPAR α binding results in alteration of the transcription rate of target genes related to lipid metabolism.²³ Fibrates reduce triglyceride levels by 30-50 percent and may have beneficial effects on HDL-c and LDL-c levels, depending on the baseline phenotype.²³ As statins do not have a significant impact on triglyceride levels, use of these agents has been an option in populations with hypertriglyceridemia or mixed dyslipidemia, in place of or in addition to statins.²⁴ Individuals with diabetes mellitus or metabolic syndrome form important high risk groups for whom fibrate therapy may be considered.²⁴ Two fibrates, gemfibrozil and fenofibrate, are available for use in the U.S.

Ezetimibe is an agent that inhibits intestinal absorption by acting on the sterol transporter NPC1L1.² Thus combination therapy using a statin plus ezetimibe has the potential to influence both the biosynthetic pathway for cholesterol synthesis and absorption, resulting in a greater reduction in LDL-c levels than with either agent alone. Ezetimibe monotherapy results in a LDL-c reduction of approximately 18 percent, along with a reduction in triglycerides and elevation in HDL-c.²⁵

Niacin (nicotinic acid) reduces LDL-c and increases HDL-c via a mechanism yet to be fully elucidated. Niacin is suspected to be involved in the metabolism of apolipoproteins, stimulating production of Apo A-I and Apo A-II, and possibly decreasing their turnover. It also decreases synthesis of LDL-c and VLDL-c, without affecting fecal excretion of fats and bile acids.^{26,27} Niacin was first introduced in 1954 and is available in immediate release, slow release and extended release forms. However the high prevalence of side effects, chiefly flushing and rash which may occur in up to 60 percent of individuals, has limited usage.²⁸

Bile acid sequestrants (BAS) bind bile acids in the bowel. The bound bile acids are subsequently excreted in the feces, thereby preventing reabsorption and depleting the intrahepatic pool of bile acids. BAS are not absorbed in the intestine and thus do not have systemic side effects. These agents have been available for over thirty years, with clinical benefit demonstrated in the Lipid Research Clinics Coronary Primary Prevention Trial.¹⁴ This trial demonstrated a reduction in CAD (coronary heart disease) of approximately 19 percent in dyslipidemic males with cholestyramine used as monotherapy. Drawbacks of these agents include gastrointestinal side effects, especially constipation, the need for frequent dosing, and the potential to interfere with absorption of other drugs and essential nutrients such as some vitamins.²⁹

Omega-3 fatty acids have been postulated to have a number of beneficial effects in individuals at risk for vascular disease, including antithrombotic and blood pressure lowering effects. They are considered to be lipid modifying agents due to a reduction in triglycerides, particularly postprandially.³⁰⁻³³ Omega-3 fatty acids come in two forms: the fish oil derived long chain fatty acids, eicosapentaenoic (EPA), docosapentaenoic (DPA) and docosahexaenoic

(DHA), and the plant oil derived alpha linolenic acid (ALA). Based on a review of the available epidemiologic and trial data the American Heart Association (AHA) nutrition committee has recommended an intake of one gram of EPA+DHA per day for individuals with documented CHD and two to four grams per day for those needing to lower triglycerides.³⁴

A large number of Americans fall into populations requiring lipid modifying therapy. The populations have been well defined by the ATP III guidelines and recent modifications have served to increase both the number of individuals falling into groups for whom therapy is recommended as well as increasing the intensity of treatment recommended to reach lower targets. For this systematic review, populations requiring intensive lipid lowering are considered to be those with a 10 year risk of CHD greater than 20 percent, or baseline LDL cholesterol of at least 190mg/dL. Lipid lowering in these populations is likely to require treatment modifications in order to achieve LDL-c targets and maximal clinical benefit. Therapeutic options for individuals requiring intensive lowering of cholesterol include an increased dose of a statin medication or the use of a statin in combination with a lipid modifying agent of another class. The purpose of this review is to compare the benefits and risks of these two options.

Table 1. Drugs included in the review

Drug	Trade name	Dosage Form
HMG-CoA reductase inhibitors (Statins) inhibit conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, an early step in the cholesterol biosynthetic pathway		
Atorvastatin Calcium	Lipitor [®]	10, 20, 40, 80 mg tablets
Fluvastatin sodium or Fluvastatin sodium Extended-Release	Lescol [®] or Lescol [®] XL	20, 40 mg Lescol [®] capsules and 80 mg Lescol [®] XL tablets
Lovastatin	ALTOCOR [™] Extended release	10, 20, 40, 60 mg tablets
Pravastatin sodium	PRAVACHOL [®]	10, 20, 40, 80 mg tablets
Rosuvastatin calcium	CRESTOR [®]	5, 10, 20, 40 mg tablets
Simvastatin	ZOCOR [®]	5, 10, 20, 40, 80 mg tablets
Ezetimibe selective inhibitor of intestinal cholesterol and related phytosterol absorption by the Niemann-Pick C1-Like 1 (NPC1L1) sterol transporter in the brush border of the small intestine		
Ezetimibe	Zetia [®]	10 mg tablets
Ezetimibe/ Simvastatin	Vytorin [™]	10/10, 10/20, 10/40, 10/80 mg ezetimibe / mg Simvastatin
Fibrates		
Fenofibrate	TRICOR [®]	54, 160 mg tablets
Micronized fenofibrate	Lofibra [®]	134, 200 mg tablets
Gemfibrozil	LOPID [®]	600 mg tablets
Niacin		
Niacin (NIR)	Niacor [®]	500 mg tablets
Niacin extended-release (NER)	NIASPAN [®]	500, 750, 1000 mg
Niacin extended-release/lovastatin	Advicor [®]	500/20, 750/20, 1000/20 mg niacin / mg Lovastatin
Bile acid sequestrants - Strong acid ion exchange resins that are not bioabsorbed, to remove bile acids from hepatic re-circulation		
Cholestyramine	Cholestyramine	9 g/dose (packet or scoop) mixed with liquid
Colestipol	Cholestid [®]	5 g/scoop granules or 1 g tablets
Colesevelam	Welchol [®]	625 mg tablets
Omega-3 fatty acids		
Omega-3-acid ethyl esters	OMACOR [®]	1 g capsules (900 mg ethyl esters of omega-3 fatty acids) ~ 465 mg EPA, ~ 375 mg DHA

Abbreviations: ~ = approximately, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, g = gram, mg = milligram

Scope and Key Questions

Normal LDL-c values range from 50 mg/dL to 70 mg/dL in native hunter-gatherers, newborn infants and wild primates, none of whom develop atherosclerosis.³⁵ Lowering of LDL-c has been shown to reduce major coronary and cerebrovascular events.^{17,18,36} Additionally, higher serum HDL-c levels have been associated with reduced CHD risk.^{37,38} Early arterial atherosclerotic changes have also been shown to be positively correlated with cardiovascular events.^{39,40}

Lipid modifying therapy with statins and other non-statin medications aims to reduce these major clinical events and associated mortality primarily by effecting favorable changes in LDL-c, HDL-c and TC:HDL-c ratio.

LDL-c reduction is the primary intermediate goal.^{41,42} The Executive Summary of the Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) indicates that LDL-c is the primary target of lipid modifying therapy.⁴³

Only one third of all patients achieve their LDL-c goals, and proportionally even fewer of those with established CHD.⁴⁴ Alternatives for patients who remain dyslipidemic despite ongoing statin therapy include dose titration, combination therapy or prescribing a more efficacious statin. Increasing statin dose or potency, potentially increases the frequency of important adverse events such as rhabdomyolysis and liver damage. Combining statin therapy with another lipid-modifying agent could be an alternative, relative safety and efficacy of which remain unclear.⁴⁵ As noted in the wording of the key questions below, this review does not address the addition of a second agent in populations not at target in spite of maximal statin therapy.

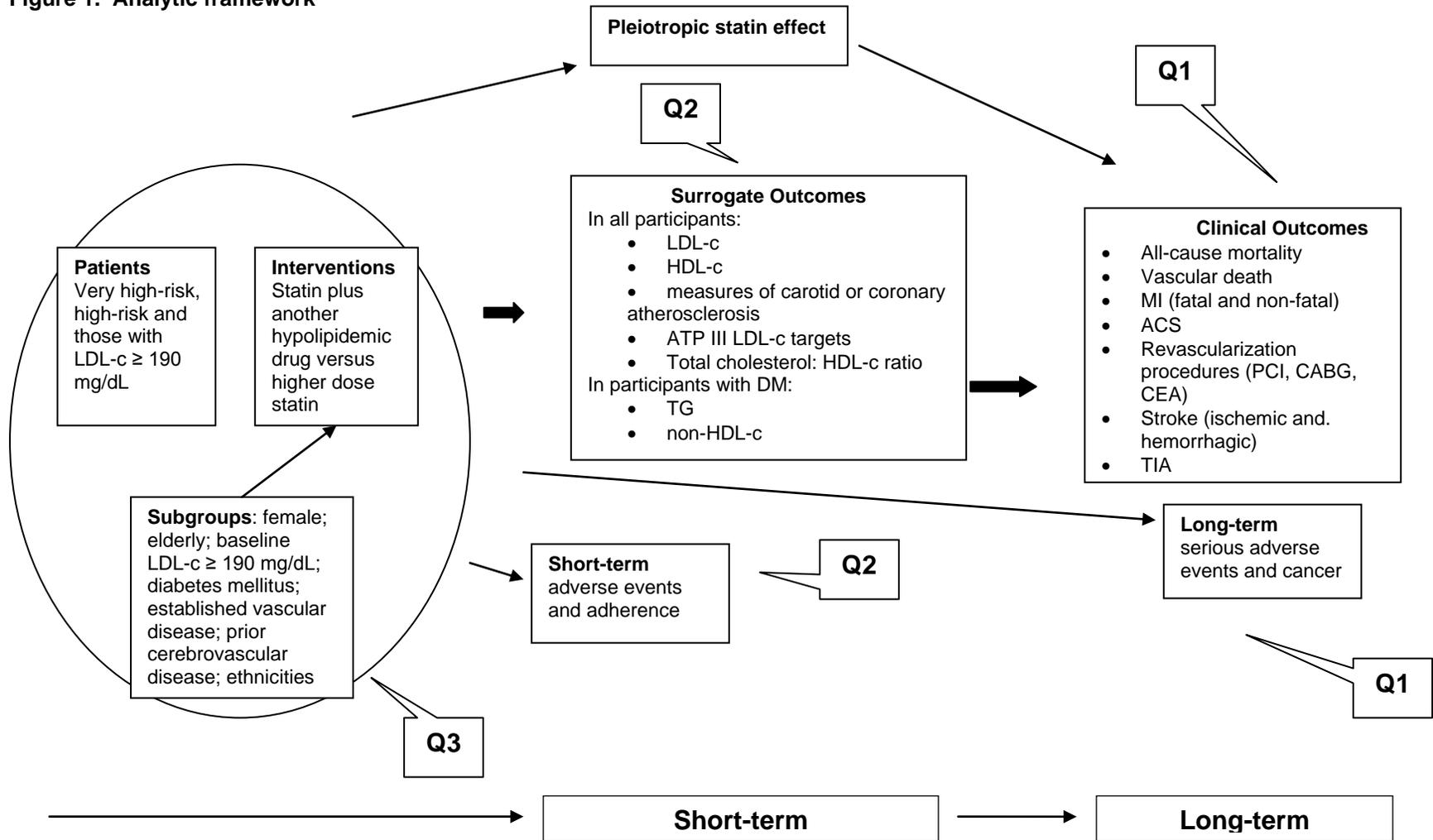
The analytic framework (Figure 1) depicts the approach taken to address the key questions, and the specifics we explored. The framework reflects the relative importance of outcomes queried in key questions and their linkages based on extant epidemiologic evidence.

Key Question 1. For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits, and rates of serious adverse events of coadministration of different lipid-modifying agents (i.e. a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

Key Question 2. Do these regimens differ in reaching LDL-targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

Key Question 3. Compared with higher-dose statins, and to one another, do combination regimens differ in benefits and harms within subgroups of patients

Figure 1. Analytic framework



Abbreviations: ACS = acute coronary syndrome, ATP III = Adult Treatment Panel III (of the NCEP), DM = diabetes mellitus, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, non-HDL-c = non-high density lipoprotein-c, Q = question, TG = triglycerides, TIA = transient ischemic attack

Methods

Topic Development

The topic for this evidence report was nominated in a public process. With input from technical experts, the Scientific Resource Center (SRC) for the AHRQ Effective Health Care Program selected and refined the questions to be addressed. Initial questions were posted on a website for public feedback. Investigators at the University of Ottawa Evidence-based Practice Center, including a lipidologist and clinical specialists in relevant fields, further refined the questions with the assistance of the SRC and AHRQ.

Search Strategy

Initial and updated searches for the review were conducted in MEDLINE (1966 to August Week 3 2008), EMBASE (1980 to 2008 Week 36) and CENTRAL (The Cochrane Library, 3rd Quarter 2008) using the Ovid interface, and limited to English language publications from 1980 or later. Searches were also conducted for subsequent publication of trials identified in U.S. Food and Drug Administration (FDA) reports, and to seek longer term followup. Citing reference searches were performed on expert nominated references using Scopus, to identify missed trials and longer-term follow-up.^{21,46-52} An updated and expanded search to capture observational studies (i.e. without an RCT filter and without date limits) was conducted in MEDLINE (1950 to August Week 3 2008). The search strategies for each database are presented in Appendix A.

Serious or rare harms were sought by searching for named harms – neoplasms, rhabdomyolysis, myocardial infarction, liver failure and stroke, by searching for harm related terms, and by searching for publications arising from administrative databases.^{53,54} Certain harms specified in the protocol (rhabdomyolysis, stroke, myocardial infarction, cancer, liver failure and death) were sought using the relevant search terms. In order to detect unexpected serious or rare harms, harm-related terms were assembled from research on information retrieval of etiology and harms⁵⁵⁻⁵⁷ and from previous AHRQ evidence reports.^{58,59} Administrative databases included prescription claims databases, health care utilization, hospital discharge and practice-based databases and regional, and national and international surveillance systems. The search for reports from administrative databases included database names nominated by the Scientific Resource Center (personal communication, Nancy Brown SRC Research Librarian, 8/22/2006), and derived from a systematic review of biotherapeutics surveillance,⁶⁰ a previous published report of harms with statin uses,⁶¹ as well as relevant subject headings.

Additional material from the SRC or obtained through a search of regulatory agency websites included:

- FDA-posted statistical and medical reviews of new and amended drug applications (ezetimibe, fenofibrate, colesevalam, atorvastatin, rosuvastatin, pravastatin, lovastatin, fluvastatin, simvastatin, advicor (niacin/lovastatin), and vytorin (ezetimibe/simvastatin))
- scientific information packages submitted by industry: Abbott (fenofibrate-statin and niacin-statin combinations); Merck (simvastatin, ezetimibe and vytorin); AstraZeneca (rosuvastatin in combination with other agents).
- grey literature reports from internet searches.

Authors of included reports were also contacted for data clarification and additional data as needed, within a pre-specified time frame. When authors passed our data requests to a third party, we included only data that was returned from the third party via one of the authors. This process of additional data acquisition was facilitated by the SRC.

Study Selection

Study selection was based on predefined eligibility criteria of interventions, patient populations, outcome measures, and study design (Table 2). The electronic literature search, hand search, and expert-nominated records, were uploaded to the software program SRS version 4.0 (Trialstat), along with screening questions developed by the review team. Titles and abstracts were screened by one reviewer for potential relevance, and exclusions at this level were verified by a second reviewer. If there was disagreement or uncertainty about relevance, the record was passed through to the next level for full-text review. Two reviewers reviewed full text reports independently, applying a priori eligibility criteria. Discrepancies were resolved through discussion and consensus or by third party adjudication if consensus could not be reached. Reviewers were not masked to the reports' authors, institution or journal. Studies that were available only as abstracts or conference proceedings and publications that reported study design or rationale only were excluded, as were letters and editorials.

Population and Health

Studies that enrolled adults (18 years of age and above) who were candidates for intensive lipid-modifying therapy were included. For the purposes of the review, an indication for intensive lipid-modifying therapy was defined on the basis of an estimated risk of greater than 20 percent for developing major cardiovascular events over 10 years, based on the Framingham global risk equations for major cardiovascular events, and according to the risk categories of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).⁶² Patients at high risk have either established coronary heart disease (CHD) (candidates for secondary prevention), multiple risk factors or CHD risk equivalents (candidates for primary prevention). Since individual participant risk assessments are not routinely reported, CHD risk equivalence was considered when one or more of the following criteria were met for all trial population or trial subgroups(s):

- report explicitly stated CHD risk equivalent status of trial population as per NCEP ATP III criteria
- participants were reported to have prior established coronary or carotid artery disease
- participants were reported to have prior established peripheral arterial disease
- participants were reported to have prior abdominal aortic aneurysm
- participants were reported to have diabetes mellitus

Adults with isolated hypercholesterolemia and a very high LDL-c (190 mg/dL and above), generally associated with genetic forms of hypercholesterolemia, were also considered to be candidates for intensive lipid-modifying treatment due to the magnitude of LDL-c reduction required to reach target goals, at least below 160 mg/dL.

Studies that enrolled patients with lower or mixed 10-year CHD risk levels were also included since we anticipated little evidence strictly in populations of interest, and also as we

aimed to explore incremental benefits of adding a non-statin drug to statin therapy with the totality of available evidence. However, we did not specifically examine the effect of adding a non-statin lipid lowering drug in participants already receiving maximally tolerated statin doses.

We identified those subgroups of the population in need of intensive lipid lowering that were likely to be reported as trial level covariates. Included were clinical populations that qualified as high-risk according to NCEP ATP III as explained above. Additionally, we considered those with severe hypercholesterolemia likely to require intensive lipid lowering, adult populations more vulnerable to treatment harms,⁶³ females, and distinct minority ethnic populations. Thus, the subgroups included:

- participants with baseline LDL-c above 190 mg/dL
- participants with diabetes mellitus (type 1 or type 2)
- participants with established vascular disease
- participants with cerebrovascular disease
- African, Asian and Hispanic racial/ethnic groups
- women
- the elderly, 80 years of age and above

Interventions and Comparators

The comparison of interest was statin plus another lipid-modifying therapy versus statin monotherapy (with or without a placebo). Studies that assessed the six current FDA-approved statins (atorvastatin, lovastatin, fluvastatin, simvastatin, rosuvastatin and pravastatin) were eligible.

Relevant combinations included one or more of the eligible statins mentioned above, combined with one of the following in any FDA approved dose:

- niacin (immediate, slow or extended release)
- peroxisome proliferator-activated receptor alpha (PPAR α) agonists; i.e. fibric acid derivatives (gemfibrozil, fenofibrate, micronized fenofibrate)
- a specific cholesterol absorption inhibitor (ezetimibe)
- bile acid sequestrants (colesevelam; colestipol; cholestyramine)
- omega-3 (ω -3) polyunsaturated fatty acids [e.g. eicosapentaenoic acid (EPA; 20:5 n-3), docosahexanoic acid (DHA; 22:6 n-3) and docosapentaenoic acid (DPA; 22:5 n-3)].

Omega-3 fatty acids studies were eligible if they administered Omacor,[®] or dietary supplements or fish oils in which the amount and type of omega-3 fatty acid was reported.

Fixed dose combinations administered as single oral medications were included, as well as combinations administered separately. Extended release forms of medications such as fluvastatin (lescol XL), lovastatin (altocor) and niacin (niaspan) were considered as well as immediate release forms. As the number of trials comparing lower statin doses in combination therapy with higher dose monotherapy was expected to be small, trials comparing similar doses of statins were included in the initial analyses.

Medications were excluded if they have been withdrawn from the market, were approved only outside of North America, or were investigational drugs or statin combinations (Table 2).

Since pharmacodynamic pleiotropy, variable lipohilicity and drug interactions are noted for statins,^{64,65} individual as well as statin class effects were investigated.

Outcomes of Interest

Predefined clinical and surrogate outcomes, and outcomes of harms considered for data extraction and syntheses are summarized in Table 2.

We considered all-cause mortality and vascular death to be the primary outcomes. We also considered the composite outcome of vascular death plus non-fatal MI plus non-fatal stroke, but our preliminary review of the included studies indicated that this outcome was reported infrequently. Further, since only summary trial data were available, it was not possible to ascertain whether the number of participants with events was equivalent to the reported number of events because one participant may have experienced multiple non-fatal events. Thus, summing a dichotomous composite outcome from individual outcome data may introduce a ‘unit of analysis’ error. The composite outcome, therefore, could not be estimated for trials.

Clinical outcomes, ATP-III LDL-c target attainment, and harms outcomes were considered as dichotomous instead of count data (i.e. time-to-event data). Therefore, the proportion of participants with at least one event, and not the number of events constituted the aforementioned dichotomous outcomes.

Continuous data can be analyzed either as post-treatment score, absolute difference (or change score) from baseline, or as percentage change from baseline.⁶⁶ Percentage change from baseline was considered to be the primary statistical data for synthesis because randomization may not eliminate baseline imbalance (this is particularly so in small trials). Change score was used only when percentage change data were not available.

Types of Studies

We anticipated that study populations in studies comparing combination therapy with statin monotherapy would likely include more participants with severe dyslipidemia, combined dyslipidemia, inadequate response to prior statin treatment, and/or previous intolerance to maximal statin doses, compared with populations in statin monotherapy studies. With this high probability of differences in study populations, we did not carry out indirect comparisons.

Thus the following study designs were included only if they permitted a direct, head to head comparison of combination versus statin monotherapy:

1. Parallel (including factorial) randomized controlled trials (RCTs)
2. Crossover trials
3. Non-randomized studies (NRS) that were quasi-experimental controlled clinical trials (CCT), and prospective or retrospective cohort studies, nested case-control and case-control studies, and cross-sectional studies.

For effects on lipid levels and short-term harm outcomes, we included head to head comparator RCTs of combination therapy versus statin monotherapy of any sample size, duration or followup, but more importance was given to longer duration, well-conducted trials that reported clinical effectiveness.

For all-cause mortality, vascular death, major cardiovascular outcomes, serious adverse events, and cancer we anticipated that the available RCT data would be of inadequate followup duration to capture these rare events and decided a priori to include evidence from eligible NRSs that were 24 weeks or longer in followup.

We did not define inclusion or exclusion criteria with regards to a diet requirement or a washout period for previous medications prior to initiation of the study.

Table 2. Inclusion and exclusion criteria

Population	Adults , including healthy participants
Interventions	<i>Included</i> <ul style="list-style-type: none"> • statin plus another hypolipidemic drug versus statin monotherapy with or without placebo (direct comparisons) • statins - atorvastatin, simvastatin, fluvastatin, pravastatin, lovastatin, simvastatin • nonstatin medications - ezetimibe, fibrates, niacin (IR, SR or ER), BAS or omega-3 fatty acids
	<i>Excluded</i> <ul style="list-style-type: none"> • cerivastatin, mevastatin, and pitavastatin • clofibrate, cirprofibrate and bezafibrate • colestimide • statin plus thiazolidinediones • statin plus cholesterol ester transferase inhibitor • statin plus plant stanols/sterol • any eligible drug in non-therapeutic or unapproved doses • any non-approved investigational agent of one of the above drug classes
Outcomes	<i>Clinical:</i> <ul style="list-style-type: none"> • all-cause mortality, vascular death, • fatal MI, non-fatal MI, any or unspecified MI, ACS (unstable angina or acute MI), • hemorrhagic stroke, ischemic stroke, any or unspecified stroke, TIA, any cerebrovascular event • CEA, PCI, CABG and any or unspecified revascularization procedure
	<i>Surrogate:</i> <ul style="list-style-type: none"> • NCEP ATP III LDL-c target attainment, LDL-c, HDL-c, TC:HDL-c ratio • non-HDL-c and triglycerides in subgroup with diabetes mellitus • measures of carotid or coronary atherosclerosis (arterial intima-media thickness, plaque area, plaque volume, arterial calcification and/or measure of stenosis)
	<i>Harms:</i> <ul style="list-style-type: none"> • treatment adherence (investigator defined), • participants experiencing at least one adverse event, serious adverse event (explicitly stated), withdrawal due to an adverse event, cancer, elevated serum AST and/or ALT ≥ 3 times ULN and/or hepatitis, myalgia, CPK ≥ 10 times ULN, and rhabdomyolysis (investigator defined)
Study design	<i>Included - Directly comparative studies</i> <ul style="list-style-type: none"> • RCT and • NRS if over 24 weeks duration, and investigating clinical outcomes, SAE or cancer
	<i>Excluded</i> <ul style="list-style-type: none"> • other observational designs • indirect comparisons • crossover trials with fewer than 4 weeks washout • crossover trials without paired observations, within-person differences, nor pre-crossover data.
Publication	<i>Exclude:</i> non-English publication, editorials, full text not presented or unavailable.

Abbreviations: ACS = acute coronary syndrome, ALT = alanine transaminase, AST = aspartate transaminase, BAS = bile acid sequestrants, CABG = coronary artery bypass graft, CEA = carotid endarterectomy, CPK = creatine phosphokinase, ER = extended release, HDL-c = high density lipoprotein cholesterol, IR = immediate release, LDL-c = low density lipoprotein cholesterol, MI = myocardial infarction, NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III, NRS = nonrandomized study, PCI = percutaneous coronary intervention, RCT = randomized controlled trial, SAE = serious adverse events, SR = slow release, TC = total cholesterol, TIA = transient ischemic attack , ULN = upper limit of normal

Data Extraction

Published data were extracted by members of the research team (KS, AA, MA). Extracted data were checked for gross inaccuracies by one reviewer (AA), and 30 percent of the data were randomly and independently verified by another member of the research team (MSe). FDA and scientific information package data were identified and extracted by one reviewer (MSe), and both were independently verified by another (FY). Minimal, data accuracy checks were additionally undertaken during the process of data syntheses.

Standardized and comprehensive online electronic data extraction forms were developed using SRS. Data extraction forms were piloted with three studies and identified issues were resolved. Descriptive data, outcomes, subgroup, and quality assessment data extracted included: general study characteristics (e.g. study design and duration); population characteristics (e.g. age, gender and race/ethnicity); interventions and dosing regimens including whether conditional titration was utilized; numbers of patients randomized into relevant treatment groups; outcomes measured, method of ascertainment and the results of each outcome, including measures of variability, by relevant intervention arm. Funding source was also noted.⁷

When there were multiple reports of the same study we referenced the primary or most relevant study in this report, and extracted only additional or extension phase data from companion reports. Corresponding authors were contacted for data clarification and missing data, but assumptions were not made for imputation. Furthermore, data were not imputed when they were only represented graphically. When relevant data for multiple followup/observation periods were reported, only the longest available followup data were extracted and used.

Complex data queries were conducted using the Structured English Query Language (SQL) functionality of the ACCESS program after a pilot test was refined.

Details of Data Extraction

Dichotomous data were extracted either as the number (n) of participants with events and the total number evaluable (N) or as summary between treatments (combination versus statin monotherapy) with 95 percent confidence interval (CI). Continuous outcomes were extracted as the mean (percentage change or change score) with the accompanying measure of dispersion for each treatment group, or as a mean difference between treatments.

Some trials reported a common range of numbers of evaluable participants for the outcomes in the table of results. In such cases, the lower bound of the range was extracted as N for all relevant outcomes.

When trials incorporated multiple relevant treatment arms, data from all were extracted. We noted whether extracted data belonged to a specific statin type and dose or was pooled across doses.

In order to standardize treatment followup from different trial reports, we considered one month to be equivalent to four weeks and recorded all followup periods in weeks. Only relevant trial data were extracted and synthesized. For example, if a trial randomized participants to placebo, niacin, statin plus niacin, and statin alone, only data pertaining to the last two treatments were extracted. Trials reported variable drug dosing regimens. We used the following guidance: *fixed* dosing was considered to occur when participants were assigned to a specific dose of drug treatment and continued throughout the trial duration. In *fixed titrated* dosing schedule, the drug dose was increased to a maximum in all participants. A *conditional titration* required only a select group not meeting pre-stated cholesterol or LDL-c criteria to be titrated to the next higher

drug dose. In trials that employed fixed or conditional titration, the maximum statin dose was extracted for treatment group identification and the type of dosing regimen was noted.

When reports did not explicitly state or allow clear inference of a dichotomous outcome, data was not assumed. For example, when all-cause mortality was not reported but it was stated that there were no serious adverse events, we recorded all-cause mortality as zero (i.e. no mortality). However, when neither all-cause mortality nor serious adverse events were reported, and it was not clear whether or not all participants completed the trial, all-cause mortality was not extracted. Adherence data were also extracted, if available, as a binary outcome (e.g. participants who were adherent) according to the definition provided in the respective trial reports.

Data Extraction of Crossover Trials

With respect to crossover trials, we regarded a minimally sufficient washout period to be four weeks. When carryover effects were analyzed and reported, the estimate had to be statistically nonsignificant. Further, crossover data were considered for extraction and syntheses only when standard deviation, standard error or confidence interval for the within-person differences were reported (or were obtained from authors) for continuous outcomes; or dichotomous data were based on paired observations from the same individual.⁶⁷ If relevant crossover data were not available, only pre-crossover data were extracted and synthesized. If neither, then the study was excluded because no data imputations were attempted.

Data Extraction of LDL-c

The broad-cut LDL-c fraction based on beta-quantification *reference method* recommended by NCEP as the evaluating standard has been epidemiologically linked to cardiovascular diseases.⁶⁸⁻⁷⁰ LDL-c (indirectly) calculated with the commonly employed Friedewald's formula agrees with β -quantification reference method up to triglyceride (TG) levels of 400 mg/dL. However, at higher TG levels (as in diabetes and non-fasting states) estimation of LDL-cholesterol by this method is not accurate.^{68,69,71} The NCEP recommended that laboratories employ LDL-c assays with a total analytical error < 12 percent, imprecision < 4 percent, and inaccuracy < 4 percent.⁷¹ New (third) generation of homogeneous assays directly measuring LDL-c offer the capability for fully automated measurement of LDL-c.⁷²

When studies reported both direct and indirectly measured LDL-c, we extracted indirectly measured LDL-c when TG < 400 mg/dL or patients were fasting. Otherwise direct LDL-c was extracted. Since it was ensured that extracted indirect LDL-c data pertained to adequately fasted blood samples, indirect LDL-c data were considered valid estimation of true LDL-c (adequate fasting). We, therefore, did not distinguish between direct and indirect LDL-c measurements in quantitative or qualitative syntheses and heterogeneity assessments.

Unit Conversion

Biochemical data reported in SI units (e.g. LDL-c in mmol/L) were converted to mg/dL. The conversion factor for LDL-c, HDL-c and non-HDL-c was 38.7 mg/dL per mmol/L. The conversion factor for triglycerides into mg/dL was 88.6 mg/dL per mmol/L.⁷³

Definition of Serious Adverse Event

We stipulated that only explicitly stated serious adverse events (SAE) be extracted. The U.S. FDA defines a serious adverse event (SAE) as any untoward medical occurrence that at any dose:

- results in death;
- is life threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- results in a congenital anomaly or birth defect.

Identification of Trial Data

Trials were identified by first author and year of publication. When the same first author published two different trials in the same year, trial data for a common outcome were differentiated as follows:

- author_year_a
- author_year_b

Quality Assessment

We used predefined criteria to evaluate the quality of included studies. Reports of RCTs were assessed using the Jadad scale, a 5 point scale that evaluates sequence generation (randomization), blinding, withdrawals and dropouts.⁷⁴ Studies scoring 3-5 on the Jadad scale are considered to be of higher quality than studies scoring 0-2. Adequacy of allocation concealment was assessed as adequate, inadequate or unclear.⁷⁵

The quality of non-randomized studies was assessed using the Downs and Black criteria.⁷⁶ The final question of the Downs and Black instrument was operationalized to a 0 or 1 score (from a 0-5) depending whether a power or sample size calculation was reported (1) or not (0). The total Downs and Black score ranged from 0-28 with higher scores indicative of less bias.

A trial was considered to have employed intention-to-treat (ITT) analysis when data were analyzed for all randomized participants in the treatment groups to which they were originally randomized.⁷⁷ If the number of participants associated with the outcome data were not clear, then authors' statement that ITT analysis was employed was considered to be sufficient evidence.

Applicability

The clinically important outcomes, study durations, setting, participant characteristics and country of origin are reported in the results.

Applicability of evidence distinguishes between *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer followup periods than most *efficacy* studies. The results of effectiveness studies are more applicable to the spectrum of patients in the community who will use combinations of lipid-modifying agents, than efficacy studies in highly selected populations.

Rating the Body of Evidence

The overall strength of evidence for outcomes was assessed using a method developed by the GRADE Working Group.⁷⁸ Rating the body of evidence incorporates the following key

elements: study design, study quality, consistency and directness, and also considers the presence of imprecise or sparse data, probability of publication bias, evidence of a dose gradient effect where applicable and magnitude of the effect. Quality of syntheses or the body of evidence are rated to indicate the level of confidence that can be placed on the summary findings:

- “high” means that further research is very unlikely to change our confidence in the estimate of effect
- “moderate” means that further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate
- “low” means that further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate.
- “very low” means that any estimate of effect is very uncertain.

A detailed explanation of the parameters used to grade the evidence and their operationalization are summarized in Appendix H.

The GRADEpro software was used on four select important outcomes of interest for the key questions.⁷⁹ The outcomes chosen for grading the strength of evidence were:

- all-cause mortality
- vascular death
- participants experiencing a serious adverse event
- participants attaining ATP III LDL-c goals

Evidence Synthesis

Quantitative syntheses were attempted to answer the key questions. In the case of substantial statistical heterogeneity (defined below), we did not proceed with the meta-analysis. Exploration of heterogeneity was undertaken qualitatively as per the following guidance:

- explore heterogeneity when I^2 was above 50 percent, and the number of studies was greater than five
- remove extreme outliers where applicable and re-run meta-analysis
- explore heterogeneity qualitatively based on a limited number of important and pre-defined covariates or effect modifiers

We defined effect modifiers that were considered important to explain heterogeneity. These included 10-year CHD risk (i.e. low/moderate/mixed risk trials versus high risk trials); sponsorship (nonindustry versus industry); statin dose (trials employing statin doses of similar strength or potencies in combination and monotherapy arms versus those employing lower statin doses in combination therapy and higher statin doses or potencies in monotherapy); trial duration (fewer than 24 weeks versus those of 24 weeks or longer duration); and allocation concealment (trials with adequate allocation concealment versus those with inadequate/unclear allocation concealment).

Planned Analyses

Data analyses were carried out to evaluate: (1) efficacy/effectiveness; and (2) adverse events and adherence. Each statin was considered separately in comparisons using each of the five possible non-statin medications (ezetimibe, niacin, fibrates, bile acid sequestrants and omega-3 fatty acids) in combination therapy.

Nonrandomized studies (NRSs) were synthesized qualitatively, as meta-analysis of them is controversial.⁸⁰⁻⁸² Furthermore, estimates from individual studies are often adjusted for

confounding, which may vary across studies. Diversity in study designs, patient characteristics and measurement of outcome variables in NRSs are further factors impeding quantitative summary estimation. Instead, we chose to appraise the quality of the evidence and to explore its strengths and limitations.

For Key Question 1, the primary outcomes of interest were long-term clinical outcomes, serious adverse events and cancer. Based on our preliminary review of the RCT literature, we considered long-term to be study duration of 24 weeks or longer. Evidence from both randomized and NRSs was considered. For Key Question 2, focusing on short-term intermediate measures of efficacy and harm, evidence syntheses were restricted to RCTs. For Key Question 3, both RCT and NRS evidence were considered.

Dichotomous summary estimates were reported as odds ratios with 95 percent confidence interval (CI), and continuous surrogate biochemical outcomes were pooled as differences in means of percentage change from baseline, and when not available, difference in mean change scores.

The key questions focused on the population in need of intensive lipid lowering therapy, and subgroups. Questions also entailed that the statin used in combination therapy be of a lower dose than statin monotherapy. We anticipated sparse evidence in these populations, especially investigations of lower dose combination statin versus higher dose statin monotherapy. As such we employed the following general approach in evidence syntheses (see Planned analyses, Appendix D):

- synthesize evidence related to *various statins and doses* across all available populations. (Does addition of another drug to statin therapy offer a common incremental benefit across various populations?)
- synthesize evidence pertaining to lower dose of a specific statin in combination with another lipid modifying drug, and higher dose of the same statin as monotherapy, across all available populations – atorvastatin, simvastatin and rosuvastatin were considered in this *dose and statin specific analysis*. (Is adding another lipid lowering drug better than increasing the statin dose across various populations?)
- synthesize evidence related to *various statins and doses* in participants requiring intensive lipid lowering and subgroups
- synthesize efficacy/effectiveness evidence pertaining to a lower dose of a specific statin in combination with another lipid modifying drug, compared with higher dose monotherapy using the same statin, in participants requiring intensive lipid lowering and in subgroup population – atorvastatin, simvastatin, rosuvastatin, pravastatin, lovastatin and fluvastatin were considered in this *dose and statin specific analysis*.

For each of these syntheses associated with clinical outcomes and serious adverse events, we conducted sensitivity analyses on trials of long-term duration, and trials with reports of adequate allocation concealment for the outcomes of all-cause mortality and vascular death.

Thus, all-cause mortality, vascular death and surrogate efficacy outcomes were examined for all trial populations, populations in need of intensive lipid lowering, and subgroups. However, anticipating availability of insufficient evidence pertaining to specific populations, synthesis of evidence on harms and clinical outcomes, other than the primary outcomes of all-cause mortality and vascular death, was undertaken irrespective of population characteristics (i.e. across all trials or mixed populations) for each combination versus monotherapy comparison.

Population in Need of Intensive Lipid Lowering and Subgroups

To synthesize evidence regarding those in need of intensive lipid lowering therapy, data were considered from trials restricted to, or providing subgroup data on, those with CHD, CHD risk equivalent disease (as per NCEP ATP III criteria), and/or baseline LDL-c equal to or above 190 mg/dL. Subgroup analyses focused on participants with/of:

- baseline LDL-c \geq 190 mg/dL
- diabetes mellitus
- established vascular disease – i.e. subgroup or full trial data on those with peripheral vascular disease, cerebrovascular disease, and/or established CAD
- cerebrovascular disease – i.e. subgroup or full trial data on those with ischemic stroke, hemorrhagic stroke, unspecified stroke and/or TIA
- African descent
- Asian descent
- Hispanic profile
- women
- participants \geq 80 years of age

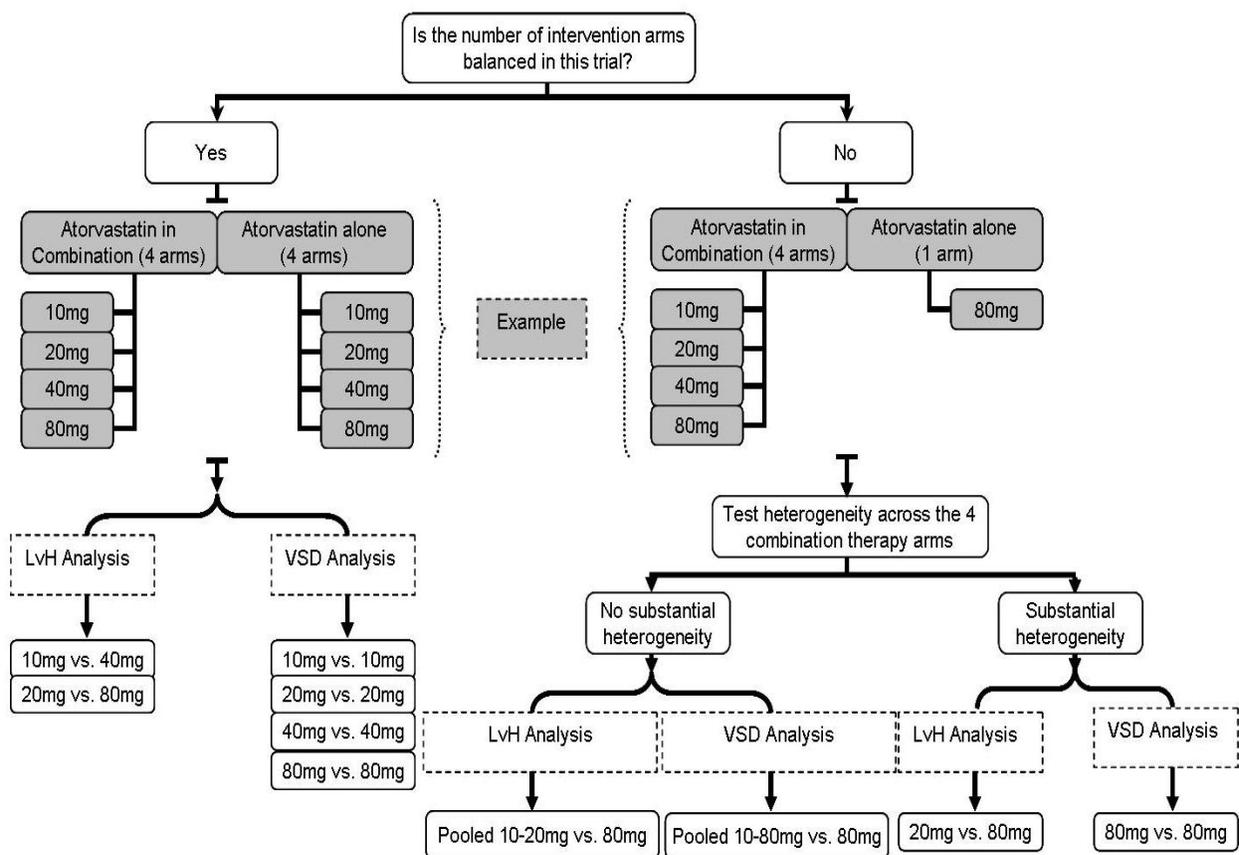
Operationalizing Lower Dose Statin in Combination with Another Hypolipidemic Drug Versus Higher Dose Statin Monotherapy

Given the absence of bioequivalence studies across different statins, comparison of lower dose statin in combination therapy with higher dose statin monotherapy was statin specific. In order to avoid multiple comparisons across numerous permutations of lower versus higher dose statins, lower and higher statin doses were defined a priori as follows:

Statin	Atorvastatin	Simvastatin	Rosuvastatin	Pravastatin	Fluvastatin	Lovastatin
Lower dose (mg/day)	5 and/or 10 and/or 20	5 and/or 10 and/or 20	5 and/or 10	5 and/or 10 and/or 20 and/or 40	5 and/or 10 and/or 20 and/or 40	5 and/or 10 and/or 20 and/or 40
Higher dose (mg/day)	40 and/or 80	40 and/or 80	20 and/or 40 and/or 80	80	80	80

Trials with Multiple Intervention Arms

More than a quarter (28%) of the trials compared different doses of statins in combination or alone incorporating multiple intervention arms. In the example below two categories of such trials with balanced or unbalanced intervention arms are presented.



LvH Analysis = lower dose statin in combination vs. higher dose statin monotherapy; VSD Analysis = various statins and doses in combination vs. various statin and doses as monotherapy

How data from treatment arms were included in the evidence synthesis is depicted above. When the number of treatment arms were unbalanced between combination and monotherapy groups within a trial, heterogeneity between arms (but within trial, within treatment group) was assessed using Fisher's Exact test or Chi-square test for dichotomous outcomes, and generic inverse variance methods for continuous outcomes. When between-arms heterogeneity was not significant or substantial (i.e. $p \geq 0.05$ for Fisher's Exact test or Chi-square test, and $I^2 \leq 50\%$), continuous data were pooled using generic inverse variance, and binary data were pooled by summing the numerators and the denominators of corresponding proportions. Pooled treatment group data from this trial were then used in the meta-analysis.

When pooling was not possible or not applicable (as in the case of a balanced trial), highest of the *lower statin* doses in combination arm was compared with the highest (e.g. atorvastatin 80 mg) of the available *higher doses* (in monotherapy arm) for the *dose and statin specific analysis*. The *lower* and *higher* doses of the statins were predefined as mentioned above. For the *various statins and doses* analysis, treatment arms with identical (or closer) doses were compared as shown for the balanced trial.

In the forest plot, multiple treatment arm data from the same trial were presented as separate comparative estimates, and identified as single trial evidence as per the following identification for the atorvastatin example:

- author 2008_1 A 10 combination therapy versus A10 monotherapy
- author 2008_2 A 20 combination therapy versus A 20 monotherapy
- author 2008_3 A 40 combination therapy versus A 40 monotherapy
- author 2008_4 A 80 combination therapy versus A 80 monotherapy

Meta-Analysis and Publication Bias

Data from crossover trials were combined with parallel design trials only when the appropriate paired or precrossover data were available. Heterogeneity across trials was tested using an I^2 statistic,⁸³ with an I^2 value greater than 50 percent considered to be substantial, thereby precluding quantitative pooling across studies.

Meta-analyses were based on the random effects model of DerSimonian and Laird,⁸⁴ except for those binary outcome meta-analyses in which the percentage of participants with an event was less than one percent, in which case Peto's odds ratio was calculated using a fixed effects model. The Comprehensive Meta-Analysis software version 2.2046 was used to complete all meta-analyses.

In addition to the sensitivity analyses focusing on long-term trials, additional analyses of the adequacy of allocation concealment for the main outcomes of all-cause mortality and vascular death were undertaken to estimate robustness of findings.⁸⁵

Dose and statin specific meta-analyses (i.e. lower dose of a specific statin in combination with another lipid lowering drug compared with higher dose monotherapy using the same statin) were considered both regardless of mode of dosing (fixed dose, fixed titrated, or conditionally titrated dosing) and those restricted to trials employing fixed dose or fixed titrated dosing regimens.

Dichotomous data with zero values (e.g. no participant experiencing myalgia) were not included in meta-analyses because summary trial results were not estimable, but such trials, with their evaluable sample, were reported in the particular synthesis.

For surrogate outcomes, some studies reported effect estimates as adjusted means (least square mean), usually from an ANCOVA model. The covariates adjusted for included variables such as gender, doses, study center, etc. However, the included variables differed across studies, and some trial reports did not report the adjusted covariates. It was therefore not possible to combine studies that all used a common analytic model.

Meta-analyses, or even qualitative syntheses, in the case of high heterogeneity, comparing lower dose (specific) statin plus another lipid modifying drug with higher dose of the same statin as monotherapy, were not conducted when the trial:

- employed two different statin types in combination and monotherapy;
- compared a lower dose of a particular statin in combination therapy with a higher dose of the same statin monotherapy, but both doses met our pre-stated lower or higher dose criteria (see above). For example, atorvastatin 40 mg/day in combination with another lipid lowering drug versus atorvastatin 80 mg/day monotherapy would not be considered in lower statin dose combination versus higher dose monotherapy syntheses, since both atorvastatin doses qualified as higher doses;
- reported only pooled data despite randomization of participants to appropriate lower and higher doses of statins;
- employed randomization to a non-statin lipid lowering drug or placebo as add-on to background statin therapy in which participants were already taking a variety of statins in various doses;

- employed an identical dose of statin in both combination and monotherapy arms; or
- employed a higher dose of statin in the combination arm(s) than monotherapy arm(s).

Potential publication bias was explored graphically through funnel plots for each comparison of interest for which meta-analyses were conducted. Although other explanations exist, an asymmetric funnel plot suggests the possibility of bias. In addition, the degree of funnel plot asymmetry was measured by the intercept from regression of standard normal deviates against precision – the Egger’s regression test.⁸⁵ A two-tailed p-value above 0.1 was considered to be significant for lateral asymmetry of the funnel plot.

We planned to:

- present *forest plots* for important outcomes regardless of heterogeneity as long as there were at least two trials contributing to the synthesis – namely, all-cause mortality, vascular death, participants attaining ATP-III LDL-c targets, LDL-c and serious adverse events;
- conduct meta-analysis and report pooled estimate only when I^2 was not greater than 50 percent;
- present *funnel plots* as long as there were at least six included studies in an analysis; and
- perform *Egger’s regression test* if there were more than 10 studies included in an analysis.

Results

Search Results

Searches identified 8451 bibliographic records from searches of MEDLINE (1966 to August Week 3 2008), EMBASE (1980 to 2008 Week 36) and CENTRAL (The Cochrane Library, Issue 3, 2008) using the Ovid interface, and limited to English language publications from 1980 or later. Scopus was searched to identify articles cited in eight reviewer nominated papers from earlier searches.^{21,46-52} An updated and expanded search to systematically capture observational studies (i.e. without an RCT filter and without date limits) was conducted in MEDLINE (1950 to August Week 3 2008). The search strategies for each database are presented in Appendix A. As well, 12 unique records were identified by hand searching reference lists of review papers, FDA data, and information provided by drug manufacturers to the Scientific Resource Center updated as of April 2008. One report was nominated by a reviewer.

Of the 8,464 unique records identified, 7,587 were excluded following initial screening, and 716 studies were excluded upon full-text screening, as detailed in Figure 2.

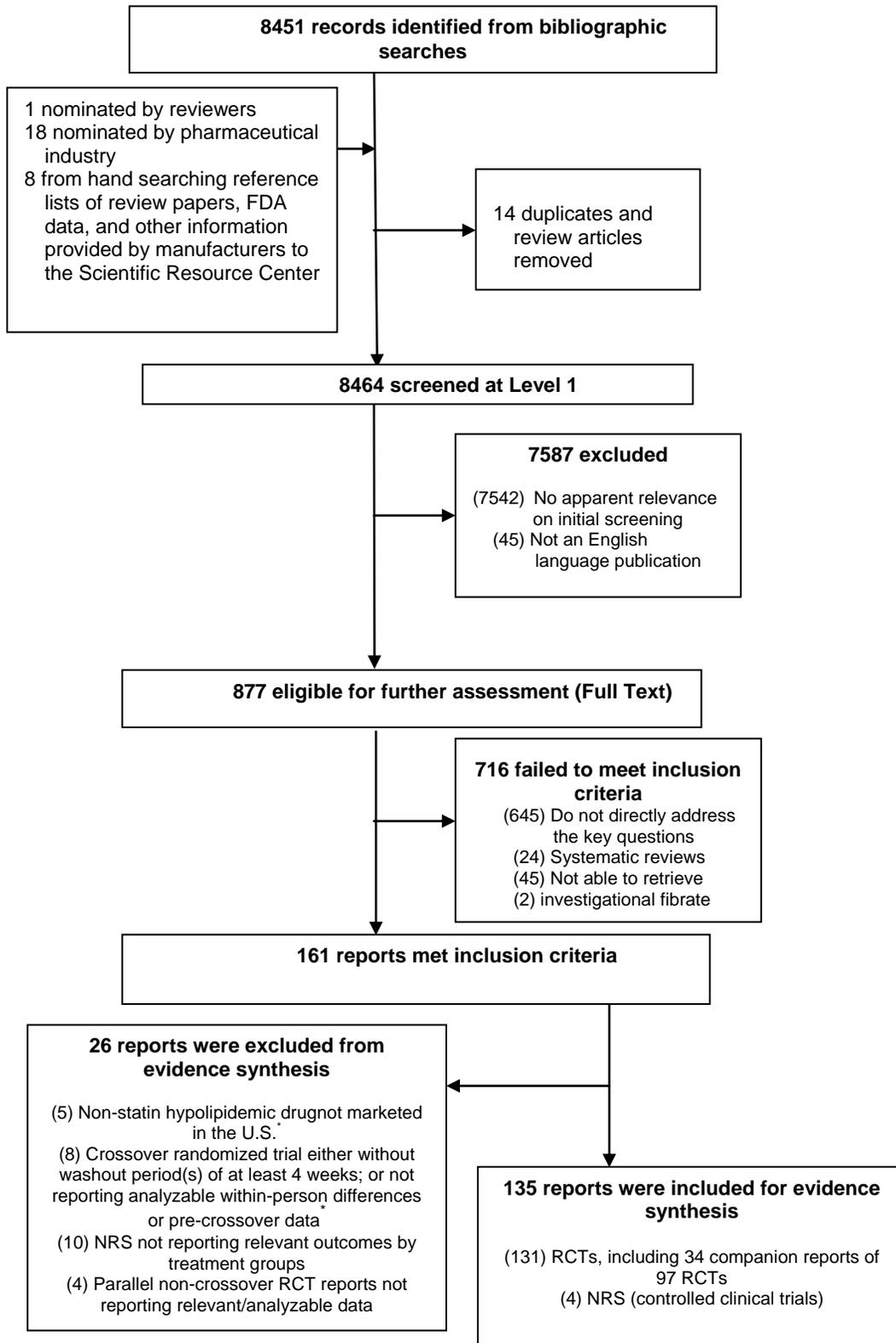
Overall, 131 reports of 101 trials were considered for quantitative or qualitative evidence syntheses to answer questions regarding comparisons of all statin plus non-statin hypolipidemic drug combinations of interest (Tables 4 and 5). Of these reports, 97 were randomized and four non-randomized controlled clinical trials.⁸⁶⁻⁸⁹ Thirty four additional companion reports of trials were included which occasionally contributed longer-term or additional data, but only the main trial report was used for trial identification (Table 6). No studies of observational design met inclusion criteria. Eight of ten randomized controlled crossover trials were excluded because reported data did not incorporate within-person differences for continuous outcomes and paired observations for dichotomous endpoints, while pre-crossover data were not reported.⁹⁰⁻⁹⁷ Excluded trials and reasons for exclusion are contained in Appendix B.

Eligible FDA reports were either companions of already published randomized trials contributing previously unpublished data,⁹⁸⁻¹⁰³ or unpublished trials (Tables 4 and 6).^{104,105}

There were no eligible studies exclusively in women or the elderly of 80 years of age or more. Five trials restricted recruitment to male gender.¹⁰⁶⁻¹¹⁰

Authors were contacted to request additional data or data clarification associated with 50 randomized controlled trial reports.^{42,47-50,91,107,111-153} Additional data or clarification from authors were obtained for 15 reports within the stipulated timeframe.^{47,48,107,114,122,124,125,130,139,142,144,145,149,152,154}

Figure 2. QUOROM flow chart



* One study report is common to both of these categories

Abbreviations: NRS = nonrandomized studies, RCT = randomized controlled trial

Table 3. Randomized controlled trials included in evidence syntheses

Trials are referenced according to the primary study
 Reports in ***bold italics*** provided analyzable crossover data

Statin	Drug in combination with statin				
	Ezetimibe	Fibrates	Niacin	Bile Acid Sequestrants	Omega-3 Fatty Acids
Rosuvastatin	Kosoglou (2004) ¹²⁴ Ballantyne (2007) ¹⁴²	Durrington (2004) ¹²⁵	Capuzzi (2003) ¹⁵⁵ McKenney (2007) ¹³⁹	Ballantyne (2004) ¹²²	X
Atorvastatin	Cruz-Fernandez (2005) ¹¹⁵ Stein (2004) ¹⁵⁶ Ballantyne (2003) ¹²⁶ Blagden (2007) ¹⁴⁰ Piorkowski (2007) ¹⁵⁷ Conrad (2008) ¹⁵⁸ Leiter (2008) ¹⁵⁹	Athyros (2005) ¹⁶⁰ Athyros (2002) ¹⁶¹	Moore (2007) ¹⁶²	Hunninghake (2001) ¹³³ Isaacsohn (1997) ¹⁶³ Heinonen (1996) ¹⁶⁴	Nordoy (2001) ¹⁶⁵ Chan (2002) ¹⁰⁷
Simvastatin	Rodney (2006) ¹¹¹ Landray (2006) ¹⁶⁶ Farnier (2005) ¹¹⁴ Brohet (2005) ¹¹⁶ Masana (2005) ¹⁶⁷ Gaudiani (2005) ¹²¹ Bays (2004) ¹⁵⁴ Feldman (2004) ⁴⁷ Goldberg (2004) ⁴⁸ Davidson (2002) ¹³⁰ Kosoglou (2002) ¹⁰⁶ Patel (2006) ¹⁴³ Berthold (2006) ¹⁰⁹ Chenot (2007) ¹⁴⁶ Shankar (2007) ¹⁶⁸ Kastelein (2008) ⁴² Roeters van Lennep (2008) ¹⁵¹ Gouni-Berthold (2008) ¹¹⁰ Dobs (2003) ¹⁶⁹	Grundy (2005) ¹²⁰ Muhlestein (2006) ¹⁴⁵	Stein (1996) ¹⁷⁰ Ballantyne (2008) ¹⁵⁰ Ballantyne (2008) ¹⁷¹	Knapp (2001) ¹⁷² Simons (1992) ¹⁷³ O'Brien (1990) ¹⁷⁴ Johansson (1995) ¹³⁷	Hong (2004) ¹⁷⁵ Durrington (2001) ¹⁷⁶ Nordoy (1998) ¹⁷⁷ Davidson (1997) ¹⁷⁸ Liu (2003) ¹⁷⁹ Davidson (2007) ¹⁸⁰

Statin	Drug in combination with statin				
	Ezetimibe	Fibrates	Niacin	Bile Acid Sequestrants	Omega-3 Fatty Acids
Lovastatin	Kosoglou (2004) ¹⁸¹ Kerzner (2003) ¹²⁹	X	Insull, Jr. (2004) ¹⁸² Hunninghake (2003) ¹²⁸ Gardner (1996) ¹⁸³ FDA Report (2008) ¹⁰⁴ FDA Report (2008) ¹⁰⁵ Vacek (1995) ¹⁸⁴	Davidson (2001) ¹⁸⁵ Schrott (1995) ¹⁸⁶	X
Pravastatin	Melani (2003) ¹²⁷ Dagli (2007) ¹⁸⁷	Wiklund (1993) ¹³⁴ Napoli (1997) ¹⁸⁸	O'Keefe, Jr. (1995) ¹⁸⁹	Eriksson (1998) ¹⁹⁰ Ito (1997) ¹⁰⁸ Pravastatin Multicenter Study Group II (1993) ¹⁹¹ Ismail (1990) ¹³⁵ Barbi (1992) ¹³⁶	X
Fluvastatin	Stein (2008) ¹⁴⁸	Derosa (2004) ¹²³ Smit (1995) ¹⁹²	X	Sprecher (1994) ⁵²	X
Mixed statins*	Barrios (2005) ¹¹² Pearson (2005) ¹¹⁷ Ballantyne (2005) ¹¹⁸ Ballantyne (2004) ⁴⁶ Gagne (2002) ¹³² Geiss (2005)¹¹⁹ McKenney (2007) ¹³⁹ Goldberg (2006) ¹⁴⁴ Catapano (2006) ¹⁹³ Constance (2007) ¹⁹⁴ Reckless (2008) ¹⁴⁹ Roeters van Lennep (2008) ¹⁵¹	Athyros (2002) ⁵⁰ Shah (2007) ¹⁹⁵	Taylor (2004) ¹⁹⁶ Bays (2003) ⁴⁹ McKenney (2007) ¹³⁹ Kuvin (2006) ¹⁹⁷	Simons (1998) ¹⁹⁸	Yokoyama (2007) ¹⁴¹ Meyer (2007) ¹⁹⁹
Total trials	44	11	16	17	10

* Either participants were on several different statins a priori and were randomized to add on non-statin treatment or placebo/no drug, or statins in combination and monotherapy within a trial were not identical in type.

Table 4. Non-randomized studies included in evidence syntheses

Statin	Drug in combination with statin				
	Ezetimibe	Fibrates	Niacin	Bile Acid Sequestrants	Omega-3 Fatty Acids
Simvastatin				Mol (1990) ⁸⁹	
Lovastatin	Türk (2008) ⁸⁶		X	Ojala (1990) ⁸⁸	X
Fluvastatin		van Dam (2001) ⁸⁷			

Table 5. Companion reports for primary studies included in evidence syntheses

Reports in *bold italics* provided analyzable crossover data

Main report	Companion reports	SIP/FDA reports	
<i>Geiss (2005)¹¹⁹</i>	<i>Geiss (2006)²⁰⁰</i>		
Pearson (2005) ¹¹⁷	Pearson (2005) ²⁰¹	Pearson (2006) ²⁰²	Denke (2006) ²⁰³
Capuzzi (2003) ¹⁵⁵	Capuzzi (2004) ²⁰⁴		
Masana (2005) ¹⁶⁷	Gagne (2002) ¹³¹	Simons (2004) ²⁰⁵	
Davidson (2002) ¹³⁰	Sager (2003) ²⁰⁶		FDA Extension Trial Report ⁹⁸
Nordoy (2001) ¹⁶⁵	Nordoy (2003) ²⁰⁷		
Chan (2002) ¹⁰⁷	Chan (2002) ²⁰⁸	Chan (2002) ²⁰⁹	Chan (2006) ²¹⁰
Nordoy (1998) ¹⁷⁷	Nordoy (2000) ²¹¹		
Simons (1998) ¹⁹⁸	Simons (1998) ²¹²		
Wiklund (1993) ¹³⁴	Vanhanen (1995) ²¹³	Wiklund (1996) ²¹⁴	
Insull (2004) ¹⁸²	Insull (2005) ²¹⁵		
Bays (2003) ⁴⁹	Bays (2003) ²¹⁶	Bays (2003) ²¹⁷	Bays (2005) ²¹⁸
Taylor (2004) ¹⁹⁶	Taylor (2007) ²¹⁹		
Athyros (2005) ¹⁶⁰	Athyros (2006) ²²⁰		
Ballantyne (2005) ¹¹⁸	Pearson (2007) ²²¹	Abate (2008) ²²²	
Ballantyne (2003) ¹²⁶	Ballantyne (2004) ²²³		
Bays (2004) ¹⁵⁴	Ose (2007) ¹⁴⁷		
Catapano (2006) ¹⁹³	Abate (2008) ²²²		
Goldberg (2006) ¹⁴⁴	Guyton (2008) ¹⁵³		
Yokoyama (2007) ¹⁴¹	Tanaka (2008) ²²⁴		
Goldberg (2004) ⁴⁸			FDA Extension Trial Report ⁹⁹
Knapp (2001) ¹⁷²			FDA Companion Report ¹⁰⁰
Gagne (2002) ¹³²			FDA Companion Report ¹⁰¹
Melani (2003) ¹²⁷			FDA Companion Report ¹⁰²
Kerzner (2003) ¹²⁹			FDA Companion Report ¹⁰³

Data Synthesis and Pooling

For randomized controlled trials with multiple unbalanced intervention arms for the two interventions of a statin plus other hypolipidaemic drug combination and statin monotherapy, within-trial within-intervention data pooling was undertaken if statistical heterogeneity was not substantial. This was undertaken to avoid a unit of analysis error arising from double counting an intervention arm. When heterogeneity was considered substantial, then one of the intervention arms was left out of data synthesis based on a priori methodology. A log of pooled trial intervention arms data, and arms that were selected for data syntheses when pooling could not be undertaken because of high or significant statistical heterogeneity, is presented in Appendix C.

Statin Plus Ezetimibe Combination Therapy Versus Statin Monotherapy

Overview of Included Studies

A total of 44 randomized controlled trials evaluated relative efficacy and/or harms of the combination of a statin plus ezetimibe 10 mg/day compared with statin monotherapy, in a total of 22489 randomized participants (Table 3). Additionally, one eligible controlled clinical trial provided data on mortality.⁸⁶ Thirteen randomized trials had more than one associated journal or FDA report (Table 5).^{48,117-119,126,127,129,130,132,144,154,167,193} The longest available data were analyzed, and one of the companion reports was considered for trial referencing.

Thirty-five trials were conducted in multiple centers and eight in a single center,^{106,109,110,124,146,157,181,187} while the number of participating center(s) was not reported in one trial.¹¹⁹

Partial or complete pharmaceutical industry sponsorship was reported for 36 of 44 trials,^{42,46-48,106,109-112,114-118,121,124,126,127,129,130,132,139,140,143,144,148,149,151,154,156,158,159,166-169,181,193,194} while funding was not reported or unclear for four trials.^{119,142,146,157}

Total Jadad scores for trials ranged from 1 to 5, with a mean of 3 (SD 1.02). Twenty trials reported an appropriate method of randomization,^{42,48,111,112,114-117,127,130,140,144,148,151,154,158,159,169,193,194} while 10 reported an appropriate method of double blinding.^{48,111,114-116,148,154,158,159,169} Allocation concealment was reported to be adequate in 16 trials.^{42,48,111,117,118,127,130,144,148,154,158,159,166,169,193,194}

Distribution of trials by geographical region was as follows:

- North America – 26 trials^{42,46-48,106,115,117,118,121,126,127,129,130,132,139,142,144,148,154,156,158,159,167,181,193,194}
- Europe - 25 trials^{42,48,109,110,112,114-116,124,126,132,140,142,143,146,148,149,151,156-158,166,167,187,194}
- Asia – four trials^{48,112,168,194}
- Australia & New Zealand – three trials^{48,149,194}
- Africa - four trials^{42,132,142,156}
- Central and South America – five trials^{48,132,149,156,194}
- Middle East – two trials^{114,194}
- Not reported – three trials^{111,119,169}

No trial reported power to assess clinical outcomes, or endpoint adjudication. Also, except for four trials,^{97,142,144,146} active clinical adverse event data collection was either not

reported or unclear. Sparse evidence in subgroups was found that directly answered Key Question 3, as summarized in Table 8.

Key Question 1: For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits, and rates of serious adverse events of coadministration of different lipid-modifying agents (i.e. a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

Study Design and Population Characteristics

Clinical outcomes, serious adverse events or cancer were reported in 31 randomized trials, none of crossover design, randomizing 19107 participants, comparing statin plus ezetimibe combination therapy with statin monotherapy.^{42,47,48,110-112,114-117,121,126,127,129,130,140,142-144,149,151,154,156,158,159,166-169,193,194}

No trial was exclusively in females, in participants of 80 years of age or over, or in participants of Asian or Hispanic descent. However, one trial was in those of African descent.¹¹¹ A number of trials reported the ethnic composition of the trial population as follows:

- 23 trials reported a mean of 84 percent participants of European descent (range 54 to 99 percent)
- 18 trials reported a mean of 12 percent of African descent (range <1 to 100 percent)
- Eight trials reported a mean of 5 percent of Asian descent (range <1 to 11.4 percent)
- 10 trials reported a mean of 8 percent Hispanics (range 2 to 26 percent)

Trial duration ranged from six to 96 weeks, with an average of 15 weeks. On average 43 percent of participants were women (range 0 to 76 percent). One trial recruited only males.¹¹⁰ The average of mean ages of participants was 58 years (range of mean age, 32 to 66 years). Twelve trials recruited solely from outpatient settings,^{42,47,48,117,126,127,129,130,151,156,167,194} while 18 trials did not report recruitment setting. Mean Jadad score was 3.4 (range, 1 to 5) and 15 trials had adequate allocation concealment.^{42,48,111,117,127,130,144,149,154,158,159,166,169,193,194}

Of these 31 trials, 15 were exclusively in participants requiring intensive lipid lowering treatment (i.e. participants with established vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL).^{42,47,112,114-116,121,140,142-144,149,151,159,194} These 15 trials randomized 7349 participants.

Across trials, participants were of diverse clinical characteristics, including those with familial hypercholesterolemia and LDL-c above 190 mg/dL,⁴² diabetes mellitus,^{121,144,194} established vascular disease and/or CHD risk equivalent,^{47,112,114-116,140,142,143} and impaired renal function,¹⁶⁶ ethnicity of African descent,¹¹¹ healthy males,¹¹⁰ and no prior statin exposure.¹⁴⁰ Twenty-three trials incorporated a placebo/statin lead-in period in addition to diet, with or without a prior lipid lowering drug washout period.^{42,47,48,111,112,114-116,121,126,127,129,130,144,151,156,158,159,166,167,169,193,194}

Most trials excluded participants with TG over 300-600 mg/dL, recent or unstable vascular disease, uncontrolled diabetes mellitus or hypertension, liver or muscle disease, high ALT, AST and CPK, or impaired renal function. Nine trials excluded participants with baseline LDL-c over 250

mg/dL,^{48,111,126,127,129,130,142,154,193} two trials excluded those with LDL-c over 160 mg/dL,^{159,167} and two excluded CHD or risk equivalent participants with LDL-c over 160 mg/dL.^{112,159} Seven trials provided ezetimibe plus statin as a combined single pill,^{112,144,149,151,154,193,194} 14 employed a placebo in addition to statin monotherapy,^{42,111,114-117,140,143,156,158,159,166,167,169} and one trial used a placebo only in the extension phase of the study.¹²⁶

Of non-randomized studies, only one controlled clinical trial directly compared statin combination therapy with the same statin monotherapy and reported only the outcome of mortality of all clinical outcomes and SAE of interest.⁸⁶

Table 6. Evidence addressing key question 1 for statin plus ezetimibe versus statin monotherapy comparison

Outcome	Evidence availability	Key points
All-cause mortality	Yes	No trial comparing statin plus ezetimibe combination therapy with a higher dose of statin monotherapy reported estimable mortality in a population requiring intensive lipid lowering therapy. Seven trials of 6 to 12 weeks duration compared statin plus ezetimibe combination therapy with statin monotherapy without specifically employing higher statin monotherapy doses. The pooled result did not demonstrate a difference between these treatments for mortality in participants requiring intensive lipid lowering therapy.
Vascular death	Yes	No trials compared lower dose statin combination therapy with higher dose monotherapy in participants requiring intensive lipid lowering therapy. The pooled results of two trials reporting vascular mortality (for all participant risk strata and statin doses) was neutral.
Fatal myocardial infarction (MI)	Yes	Sparse data in short-term trials yielded indeterminate results.
Non-fatal MI	No	
Any or unspecified MI	Yes	Result of a single short term trial was indeterminate.
Acute coronary syndrome (ACS) (encompassing unstable angina or acute MI)	No	
Any cerebrovascular event	No	
Hemorrhagic stroke	No	
Ischemic stroke	No	
Any or unspecified stroke	Yes	Result of a single trial with one event was indeterminate.
Transient ischemic attack (TIA)	No	
Carotid endarterectomy (CEA)	No	
Percutaneous coronary interventional procedure (PCI)	No	
Coronary artery bypass graft procedure (CABG)	No	
Any or unspecified revascularization procedure	No	
Serious adverse events	Yes	No consistent difference was noted between statin plus ezetimibe combination and statin monotherapy in the occurrence of serious adverse events across all participants. A trend in favor of monotherapy was noted in high risk populations, using similar statin doses in combination with ezetimibe versus statin monotherapy.
Cancer	Yes	No consistent difference was noted between statin plus ezetimibe combination and statin monotherapy in the occurrence of cancer across two trials of 24 and 48 weeks duration.

Abbreviations: ACS = acute coronary syndrome, CABG = coronary artery bypass graft, CEA = carotid endarterectomy, MI = myocardial infarction, PCI = percutaneous coronary intervention, SAE = serious adverse event

Long-Term Efficacy, Serious Adverse Events, and Cancer

Comparing statin plus ezetimibe versus statin monotherapy (lower dose vs. higher dose and various statin doses)

All-cause mortality. All-cause mortality was reported for 24 trials in 14407 evaluable participants (Table 9). Four trials, in 1428 evaluable participants, provided treatment and followup during 24 weeks or longer.^{48,121,126,166} Of the four long-term trials, one provided estimable mortality odds of 7.51 (95% CI 0.38, 147.37) based on three deaths.¹⁶⁶ This 24 weeks trial randomized 203 participants with chronic renal disease and no definitive indication for cholesterol lowering, to simvastatin 20 mg/day and ezetimibe or simvastatin 20 mg/day alone, with adequate allocation concealment. Across all 24 trials assessing all-cause mortality, eight trials on 4006 evaluable participants with a total of 15 deaths could be meta-analyzed (Appendix G, Figure G-1). These trials, of six to 24 weeks duration, did not exhibit lateral asymmetry in the funnel plot (Appendix G, Figure G-1). Sixteen of the 24 trials, including the shortest trial of two weeks duration in healthy males, did not register mortality. There was no significant difference in odds of all-cause mortality between statin plus ezetimibe therapy and statin monotherapy in this quantitative synthesis, which included trials with all statin types and doses, and trial participant 10 year CHD risk status (OR 0.95; 95% CI 0.37, 2.41). Meta-analysis restricted to thirteen trials in 11113 evaluable participants with adequate allocation concealment, five of which contributed evaluable data to meta-analysis,^{118,144,149,166,194} resulted in a pooled odds ratio for all-cause mortality of 1.07 (95% CI 0.38, 2.99) (Table 9), (Appendix G, Figure G-2).

Four trials, 24 weeks or less in follow up duration, investigated a lower dose of a specific statin in combination with ezetimibe 10 mg/day versus higher dose of the same statin monotherapy and reported the outcome of all-cause mortality. Statins were either simvastatin^{121,151,169} or atorvastatin.¹⁵⁸ (Table 9). None of the trials registered any mortality.

Fourteen trials with 6275 evaluable participants reported all-cause mortality in participants requiring intensive lipid lowering therapy.^{114-116,118,121,140,142-144,149,151,159,193,194} Across these trials, participants were those with CHD and/or CHD risk equivalent including DM. The longest followup trial was of 24 weeks duration, which reported zero deaths.¹²¹ Meta-analysis of seven of the 14 trials with estimable odds resulted in a pooled odds ratio of 0.61 (95% CI 0.22, 1.71), based on a total of 15 deaths (Appendix G, Figure G-3). The remaining trials did not register any death. Six of 14 trials reported adequate allocation concealment.^{118,144,149,159,193,194} A sensitivity analysis on the four trials with adequate allocation concealment and estimable data yielded an all-cause mortality odds ratio of 0.64 (95% CI 0.20, 2.04) (Appendix G, Figure G-3) (Table 9).^{118,144,149,194}

Two 24 and 12 weeks trials comparing lower dose statin plus ezetimibe with a higher dose of the same statin monotherapy in those requiring intensive lipid lowering observed zero deaths (Table 9).^{121,151}

One controlled clinical trial investigated high doses of fluvastatin, pravastatin or simvastatin in combination with ezetimibe 10mg/day versus highdoses of fluvastatin and pravastatin monotherapies in 84 renal transplant patients with hypercholesterolemia and mean baseline LDL-c of 129 mg/dL over a period of one year. No death was noted during the followup period (Table 10).

Vascular death. Four vascular deaths were reported in two trials with 1196 evaluable participants (Table 9).^{42,130} Both trials used simvastatin as combination and monotherapy, and had adequate allocation concealment. Followup duration was 96 weeks in the long-term trial that registered three vascular deaths in 720 participants requiring intensive lipid lowering—all with off treatment LDL-c above 210 mg/dL—yielding an odds ratio of 1.98 (95% CI 0.21, 19.14).⁴² For the two trials, the pooled odds ratio of vascular death was 2.70 (95% CI 0.38, 19.20) (Appendix G, Figure G-5).

One trial of 12-week duration employing adequately concealed treatment allocation, with 121 evaluable participants with mixed 10 year CHD risk, employing fixed dose treatment, permitted a comparison of a lower dose of a particular statin (simvastatin 20 mg/day) plus ezetimibe with a higher dose of the same statin as monotherapy (simvastatin 80 mg/day). This trial randomized an additional number of participants into other treatment arms that registered zero mortality data. Based on a single vascular death, the odds ratio was 8.05 (95% CI 0.16, 407.27).¹³⁰

There was no evidence for the comparative analysis of a specific lower dose statin in combination with ezetimibe versus higher dose of the same statin monotherapy in participants requiring intensive lipid lowering therapy.

Fatal myocardial infarction. Based on a total of 1460 evaluable participants, three trials of less than 24 weeks duration reported four participants developing fatal myocardial infarction (Table 9).^{142,149,156} One trial recruited participants with elevated lipid levels despite low dose atorvastatin,¹⁵⁶ while two exclusively included those with CHD or risk equivalent.^{142,149} Pooled odds were 2.71 (95% CI 0.38, 19.30). Comparative analysis of a specific lower dose statin in combination with ezetimibe versus higher dose of the same statin monotherapy could not be permitted because either higher doses of statins were employed^{142,156} or mixed statins were administered to one of the intervention arms.¹⁴⁹

Any or unspecified myocardial infarction. One 12-week trial in patients admitted to the hospital for a recent coronary event compared simvastatin 40 mg/day in combination with ezetimibe 10 mg/day, with twice the dose of prior statin therapy. Eleven of 424 patients developed myocardial infarction, yielding an odds ratio 1.19 (95% CI 0.36, 3.97).¹⁴⁹

Stroke. In a single trial on 200 evaluable participants with impaired renal function of 24 weeks duration, one participant developed stroke on simvastatin 20 mg/day plus ezetimibe as a combined pill.¹⁶⁶ Compared with simvastatin 20 mg/day plus placebo, the odds ratio was 7.70 (95% CI 0.15, 388.20).

Serious adverse events. Participants experiencing serious adverse events were reported for 27 trials in 13463 evaluable participants (Table 9). Six trials, including 1893 evaluable participants of whom 191 had serious adverse events, were of 24-56 weeks in duration.^{48,121,126,130,166,167} However, odds ratios could not be pooled because of substantial statistical heterogeneity ($I^2 = 56\%$) (Appendix G, Figure G-6). All six trials failed to show a significant difference in SAE with no homogenous trend across the predefined covariates of heterogeneity. There was no obvious indication of funnel plot asymmetry for these trials. Gaudiani et al.'s trial was exclusively in participants with diabetes mellitus,¹²¹ while Landray et al. focused on those with moderate to severe renal impairment.¹⁶⁶ Others recruited more

clinically diverse participants. Five of six trials compared identical statins in combination and monotherapy,^{48,126,130,166,167} and all but one¹²⁶ investigated simvastatin.

Considering all statins and doses over any duration, pooling results of 24 out of 27 trials produced an odds ratio of 1.08 (95% CI 0.88, 1.33). Three short-term trials, none in high CHD risk participants, reported no serious adverse event (Table 9; Appendix G, Figure G-7).^{110,158,168} All but one trial, for which funding was not clearly reported, were funded by pharmaceutical industry.¹⁴² There was no significant lateral asymmetry on the funnel plot, with an Egger's regression intercept of 0.51, and two tailed p-value > 0.1. Although each trial showed no significant difference in SAE, of trials showing a trend in favor of monotherapy, 71% were in high risk participants with most employing similar doses of statins across combination and monotherapies.^{47,112,114,116,121,142,143,149,151,159}

Four trials permitted analysis of a lower dose of a particular statin in combination with a higher dose of the same statin.^{47,121,158,169} Meta-analysis of the three simvastatin-ezetimibe combination and monotherapy (40 mg/day) trials in 927 participants (44 with serious adverse events) produced a nonsignificant odds ratio of 1.64 (95% CI 0.85, 3.19).^{47,121,169} Excluding one trial that used a conditional upward titration of simvastatin,⁴⁷ the odds ratio remained nonsignificant (Table 9).

One trial employing atorvastatin 20 mg/day plus ezetimibe versus atorvastatin in moderately high risk participants and lasting six weeks did not register a single SAE.¹⁵⁸

Cancer. Eleven of a total of 971 participants developed a malignancy while on similar doses of simvastatin in combination and as monotherapy, during two trials of 24 and 48 weeks duration.^{48,166} Pooling yielded a nonsignificant odds ratio of 3.99 (0.71, 22.28), (Table 9). Most trials did not report active surveillance for cancer detection nor how malignancies were defined or detected.

Key Question 2: Do these regimens differ in reaching LDL-targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

Study Design and Population Characteristics

Forty-four trials, one of crossover design,¹¹⁹ randomized 22,489 participants to compare statin plus ezetimibe combination with statin monotherapy, and recorded one or more surrogate efficacy or harms outcomes other than serious adverse events or cancer.^{42,46-48,106,109-112,114-119,121,124,126,127,129,130,132,139,140,142-144,146,148,149,151,154,156-159,166-169,181,187,193,194}

There was no trial exclusively in females, while three trials exclusively recruited healthy male participants.^{106,109,151} One trial restricted recruitment to participants of African descent¹¹¹ and three restricted recruitment exclusively to those of European descent.^{106,109,181}

A number of trials reported the ethnic composition of the trial population:

- Thirty-one trials reported a mean of 87 percent participants of European descent (range 54 to 100 percent)
- Twenty trials reported a mean of 11 percent participants of African descent (range <1 to 100 percent)
- Nine reported a mean of 4 percent participants of Asian descent (range <1 to 11 percent)

- Twelve trials reported a mean of 7 percent Hispanic population (range 2 to 26 percent). Mean trial duration was 14 weeks, ranging from 1-96 weeks. Across all trials, 42 percent of participants were women (range, 0 to 76 percent). The average of mean ages of participants was 56 years (range, 32 to 66 years). Sixteen trials recruited outpatients,^{42,46-48,117,126,127,129,130,139,151,156,167,181,187,194} while 25 did not report recruitment setting.^{106,109-112,114-116,118,119,121,132,140,142-144,148,154,157-159,166,168,169,193} The mean Jadad score was 3 (range, 1 to 5) and 17 trials had adequate allocation concealment.^{42,48,111,117,118,127,130,144,148,149,154,158,159,166,169,193,194}

Twenty trials, randomizing 7635 participants, were exclusively in participants requiring intensive lipid lowering treatment (i.e. participants with established vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL).^{42,47,112,114-116,119,121,132,140,142-144,146,149,151,157,159,187,194}

Across trials, participants were of diverse clinical characteristics, including exclusively severe hypercholesterolemia (etiology unspecified),¹¹⁹ homozygous familial hypercholesterolemia¹³² familial hypercholesterolemia excluding homozygotes,⁴² diabetes mellitus,^{121,144,194} established vascular disease and/or CHD risk equivalent,^{47,112,114-116,119,140,142,143,146,149,151,157,159,187} impaired renal function,¹⁶⁶ no prior statin exposure,¹⁴⁰ and ethnicity of African descent.¹¹¹ Five trials were exclusively in otherwise healthy hypercholesterolemic participants.^{106,109,110,124,181} Twenty-six trials incorporated a placebo/statin lead-in period in addition to diet, with or without a prior lipid lowering drug washout period.^{42,46-48,111,112,114-116,118,121,126,129,130,132,144,151,156,158,159,166,167,169,187,193,194} Most trials excluded participants with TG over 300-600 mg/dL, patients with recent or unstable vascular disease, uncontrolled diabetes mellitus and hypertension, liver and muscle disease or high ALT, AST, CPK and/or impaired renal function. Nine trials excluded participants with baseline LDL-c over 250 mg/dL,^{48,111,126,127,129,130,142,154,193} one trial excluded those with LDL-c over 160 mg/dL¹⁶⁷ and two excluded high-risk patients with LDL-c over 160 mg/dL.^{112,159} Seven trials used an ezetimibe-statin combination pill,^{112,118,144,149,151,154,193,194} twenty used a placebo added to statin monotherapy,^{42,46,106,111,114-117,119,124,140,143,148,156,158,159,166,167,169,181} and one trial used placebo only in the extension phase of the study.¹²⁶

Table 7. Evidence addressing key question 2 for statin plus ezetimibe versus statin monotherapy comparison

Outcomes	Evidence availability	Key points
Participants attaining ATP III LDL-c targets	Yes	Most trials comparing combinations with monotherapy favored combination therapy. Ezetimibe plus lower dose simvastatin combination therapy was superior to higher dose simvastatin monotherapy, significantly increasing the probability of reaching the LDL-c target in those in need of intensive lipid lowering, in a pooled estimate from 2 trials.
LDL-c	Yes	Two trials in populations requiring intensive lipid lowering (patients with diabetes mellitus) demonstrated a 10% to 20% greater percentage LDL-c reduction for combination therapy (simvastatin plus ezetimibe) compared with higher dose simvastatin monotherapy. Across all populations, lower dose statin in combination therapy caused greater LDL-c reductions than higher dose statin monotherapy.
HDL-c	Yes	A single trial in a group requiring intensive lipid lowering, comparing lower dose simvastatin plus ezetimibe combination therapy with higher dose simvastatin monotherapy, showed no significant difference. Combination therapy produced a significant 1% greater increase in HDL-c than monotherapy when generally similar statin doses (in combination and monotherapies) were compared in participants qualifying for intensive lipid lowering therapy.
TC:HDL-c ratio	Yes	A single trial in a group requiring intensive lipid lowering, comparing a lower dose simvastatin plus ezetimibe combination therapy with higher dose simvastatin monotherapy showed a significant difference favoring combination therapy. Combination therapy produced a greater reduction in TC:HDL ratio in participants requiring intensive lipid lowering therapy when similar or closer statin doses were used in combination and monotherapy.
Measure(s) of atherosclerosis		A single trial over two years showed no significant difference between simvastatin plus ezetimibe compared with same dose of statin monotherapy in change in carotid-intima media thickness
Treatment adherence	Yes	A single trial comparing lower dose simvastatin in combination therapy with higher doses of simvastatin monotherapy found no significant difference. Similarly, comparing similar doses of statins in combination and monotherapies, no differences were measured between the statin plus ezetimibe combination therapy and statin monotherapy.
Participants experiencing at least one adverse event	Yes	No significant difference was noted across statin plus ezetimibe combinations compared with statin monotherapy, including a single trial comparing lower dose simvastatin in combination therapy with a higher dose of simvastatin monotherapy.
Withdrawal due to adverse events	Yes	No significant difference was noted across statin plus ezetimibe combinations compared with statin monotherapy, including comparisons of lower dose statin combination therapy with higher doses of the same statin monotherapy.
Participants developing AST and/or ALT > 3 the upper limit of normal, and/or hepatitis	Yes	No significant difference was noted across statin plus ezetimibe combinations compared with statin monotherapy, including comparisons of lower dose simvastatin combination therapy with higher dose simvastatin monotherapy.
Participants with myalgia		No significant difference was noted across various doses of statin plus ezetimibe combinations compared with statin monotherapy

Participants with CPK above 10 times the upper limit of normal		No significant difference was noted across statin plus ezetimibe combinations compared with statin monotherapy, including comparisons of lower dose simvastatin combination therapy with higher dose simvastatin monotherapy.
Participants with rhabdomyolysis	Yes	No case of rhabdomyolysis was noted in 8125 trial participants across 19 trials.

Abbreviations: ALT = alanine transferase, AST = aspartate transferase, ATP III = Third Adult Treatment Panel of the National Cholesterol Education Program, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, TC = total cholesterol, CPK = creatinine phosphokinase

LDL-c Targets and Other Surrogate Markers

Comparing statin plus ezetimibe versus statin monotherapy (lower dose vs. higher dose and various statin doses)

Participants reaching ATP III LDL-c goals. During 23 trials on 15,944 evaluable participants, 11329 participants attained ATP III LDL-c targets (Table 11). The duration of trials ranged from six to 24 weeks with most trials of six- or 12-week duration. Except one, for which sponsorship was not clear, all were pharmaceutical industry sponsored.¹⁴² Substantial statistical heterogeneity ($I^2 = 93$ percent) across trials precluded meta-analysis (Appendix G, Figure G-8). However, in 96 percent of trials, odds significantly favored the statin plus ezetimibe combination. All five trials with point estimates of odds greater than 10 in favor of combination therapy unclearly reported allocation concealment and employed similar doses of statin in both intervention arms.^{114-116,140,167} There was no significant lateral asymmetry on the funnel plot, with an Egger's regression intercept of -0.6, and two tailed p-value > 0.1. One trial comparing combination simvastatin plus ezetimibe with atorvastatin monotherapy in participants with type 2 diabetes mellitus, hemoglobin A1c below 8.5 percent and LDL-c above 100 mg/dL, demonstrated nonsignificant odds ratios when simvastatin 40 mg/day plus ezetimibe was compared with atorvastatin 40 mg/day monotherapy.¹⁴⁴

Restricting the analysis to participants requiring intensive lipid lowering therapy, 18 trials evaluating 7731 participants also demonstrated significant statistical heterogeneity ($I^2 = 90$ percent), precluding pooling of odds ratios (Table 11; Appendix G, Figure G-9). There was no significant lateral asymmetry on the funnel plot, with an Egger's regression intercept of -0.6, and two tailed p-value above 0.1. Sixteen of 18 trials yielded significant odds ratios favoring concomitant statin plus ezetimibe. Trials not demonstrating significant results had more potent statins (atorvastatin and rosuvastatin) in the monotherapy arms.^{144,193}

Three trials, employing fixed dose and conditional statin titration, permitted comparison of a lower dose of a particular statin plus ezetimibe with a higher dose of the same drug as monotherapy. All were in CHD or risk equivalent participants (i.e. those requiring intensive lipid lowering therapy).^{47,121,151} Although all showed a significant advantage of combination therapy over a 12-24 week period, pooling was not possible because of substantial heterogeneity (Table 11; Appendix G, Figure G-10). When Feldman's trial employing conditional titration and demonstrating lower point estimate was excluded, heterogeneity was reduced and pooled odds were 7.21 (95% CI 4.20, 12.08) (Appendix G, Figure G-11).

LDL-c, percentage mean change from baseline. LDL-c data in the form of percentage mean change from baseline was reported for a total of 35 trials including 18,788 evaluable participants.^{42,46-48,109-112,114-118,121,124,126,127,129,130,132,139,140,142-144,154,156,158,159,166-169,193,194}

Followup duration ranged from two to 96 weeks (mean 12 weeks), and 65 percent of trials were six or 12 weeks in length (Table 12).

Across trials, participant characteristics were diverse and included those who were exclusively of African descent,¹¹¹ or of South Asian descent.¹⁶⁸ Participants' health status varied from otherwise healthy,^{109,110,124} to severe hypercholesterolemia,^{42,119,132} established CHD or risk equivalent,^{47,112,114-116,119,121,140,142-144,159,194} or established renal disease.¹⁶⁶

Meta-analysis was not possible given substantial statistical heterogeneity ($I^2 = 97$ percent). Percentage of LDL-c reduction did not show a consistent pattern across the pre-specified covariates of heterogeneity. However, 94 percent of trials demonstrated significant additional percentage reduction from baseline in favor of the statin plus ezetimibe combination ranging from 4 to 27 percent, compared with mostly similar doses of statin monotherapy (Appendix G, Figure G-12). Two trials did not reach statistical significance. One employed an identical low dose of simvastatin in combination as well as monotherapy in South Asians of mixed 10 year CHD risk,¹⁶⁸ while the other compared a titrated dose of simvastatin 40 mg/day plus ezetimibe with the same dose of more potent rosuvastatin monotherapy in a mixed 10 year CHD risk population, 86 percent of whom were of European descent.¹³⁹ There was no significant lateral asymmetry on the funnel plot, with an Egger's regression intercept of 1.6, and two tailed p-value greater than 0.1 (Appendix G, Figure G-12). Except for one trial for which funding was not clearly reported, all 34 were sponsored by the pharmaceutical industry.¹⁴²

Of the 35 trials across different populations, six permitted comparison of lower dose combination simvastatin with a higher dose of it over an average follow up of 14 weeks (range 4 to 26). These six trials demonstrated heterogeneous but significant additional percentage LDL-c reductions ranging from 3 to 20 percent in favor of combination therapy, with the exception of simvastatin 10 mg/day in combination therapy versus 80 mg/day monotherapy in the 12 week Davidson et al. trial (mean difference -0.53, 95% CI -5.39, 4.33).^{47,48,121,130,154,169} One trial that compared lower dose atorvastatin combination therapy with higher dose atorvastatin monotherapy showed a 20 percent significant additional reduction in favor of combination therapy (Table 12).¹⁵⁸ In this subgroup of trials, no lateral asymmetry was evident in the funnel plot (Appendix G, Figure G-13). A further sensitivity analysis without Feldman et al's trial employing conditional titration of simvastatin did not eliminate substantial heterogeneity.

In participants who might require intensive lipid lowering therapy (i.e. participants with CHD and/or risk equivalent disease and/or those with baseline LDL-c ≥ 190 mg/dL), 18 trials with 6601 evaluable participants contributed efficacy data for a statin plus ezetimibe in comparison with statin monotherapy, for all statin doses (Table 12; Appendix G, Figure G-14). Statistical heterogeneity ($I^2 = 94$ percent) precluded meta-analysis. All trials showed significant mean differences in LDL-c percentage change from baseline, in favor of combination therapy. Mean additional percentage reduction ranged from 4 to 27 percent. No significant lateral asymmetry was noted (intercept 0.85, two tailed p-value > 0.1). Heterogeneity was further explored across trials in intensive lipid lowering populations, employing lower dose simvastatin 20 mg/day in combination therapy, with higher dose simvastatin 40mg/day monotherapy. Two trials, one each of fixed¹²¹ and conditional statin titrations,⁴⁷ showed significant additional LDL-c reductions of 20 percent (95% CI -26.60, -14.40) and 10 percent (95% CI --13.19, -6.81) respectively, but heterogeneity remained substantial ($I^2 = 89$ percent), precluding pooling of the two trials (Appendix G, Figure G-15).

HDL-c, percentage mean change from baseline. HDL-c, percentage mean change from baseline was reported for 32 trials on 18143 participants (Table 13).^{42,46-48,109,110,112,114-118,121,124,126,127,129,130,139,140,142,144,154,156,158,159,166-169,193,194}

Participant characteristics were diverse across trials and mean trial duration was 13 weeks (range 2 to 96) with 63 percent trials of six or 12 week followup. No significant lateral asymmetry of the funnel plot was noted (intercept -0.28, two tailed p-value > 0.1) (Appendix G, Figure G-16). Substantial heterogeneity (I^2 -squared, 54 percent) precluded meta-analysis. Thirty one percent of trials demonstrated significant increases in percentage HDL-c ranging from 2-6 percent, in favor of combination therapy. The heterogeneity could not be explained by any of the prespecified covariates, but when the analysis was restricted to trials of lower simvastatin dose in combination therapy versus higher monotherapy simvastatin doses, in trials with fixed doses or fixed titrations, the heterogeneity was eliminated and the pooled mean difference was 0.31 (95% CI -0.89, 1.52). A single trial permitted comparison of atorvastatin 20 mg/day in combination therapy versus 40 mg/day of atorvastatin monotherapy, with a mean difference of 2.40 (95% CI 1.97, 2.83) (Table 13, Appendix G, Figure G-17).

Meta-analysis of the 15 trials in 7020 participants requiring intensive lipid lowering therapy demonstrated a significant increase over baseline of percentage HDL-c with combination therapy compared with monotherapy using a statin of mostly similar doses, mean difference 1.53 (95 percent CI 0.81, 2.24).^{42,47,112,114-116,118,121,140,142,144,159,167,193,194} The pooled estimate was not associated with significant evidence of lateral asymmetry (Eggers intercept -1.06, two tailed p > 0.1) (Appendix G, Figure G-18).

One trial by Gaudiani et al compared fixed doses of simvastatin 20 mg/day in combination therapy with 40 mg/day monotherapy in 210 participants with type 2 diabetes mellitus on stable thiazolidinedione doses, with a baseline LDL-c over 100 mg/dL, some of whom had previously completed a simvastatin trial. This trial provided the only evidence comparing lower dose of a particular statin in combination with ezetimibe against higher dose monotherapy using the same drug.¹²¹ The nonsignificant percentage mean difference was -0.10 (-3.42, 3.22).

Total cholesterol:HDL-c ratio, percentage mean change from baseline. Total cholesterol:HDL-c ratio, percentage mean change from baseline was reported in 20 trials, including 11942 evaluable participants (Table 14).^{48,112,115,118,121,126,127,129,130,139,142,144,154,156,158,159,167,169,193,194}

Followup duration ranged from four to 24 weeks with a mean of nine weeks. Trials included participants with CHD or risk equivalents,^{112,115,121,142,144,159,194} or a mixed risk group. Substantial statistical heterogeneity (I^2 = 96 percent) precluded pooling of data. However, all but the six week trial of Goldberg et al. in participants with diabetes mellitus demonstrated statistically significant additional reductions favoring combination therapy ranging from 3 to 20 percent. Qualitatively, heterogeneity could not be explained in terms of pre-specified covariates. Lateral funnel plot asymmetry was significant (Eggers intercept -5.4, two tailed p = 0.04) (Appendix G, Figure G-19). Restricting the analysis to a comparison of lower statin dose in combination therapy versus higher statin dose monotherapy did not reduce heterogeneity across five simvastatin trials with no consistent direction of mean difference (Appendix G, Figure G-20). One atorvastatin trial comparing 20 mg/day of the drug in combination therapy with higher dose monotherapy, in

moderately high risk participants, showed a significant difference favoring combination therapy (Table 14).

Ten randomized trials evaluating 4677 participants requiring intensive lipid lowering could not be pooled because of substantial statistical heterogeneity ($I^2 = 93$ percent).^{112,115,118,121,142,144,159,167,193,194} Eighty percent of trials were six weeks in duration and all but one¹⁴² reported pharmaceutical industry funding. However, across all trials, statistically significant and consistent additional reductions in percentage change from baseline favoring combination therapy ranged from 3 to 20 percent (Table 14). This heterogeneity could not be explained based on the covariates of allocation concealment, trial duration, or lower compared with higher dose statin in combination and monotherapy respectively versus trials employing similar statin doses across interventions. The funnel plot of this set of trials did not demonstrate lateral asymmetry (Eggers intercept -8.2, two tailed $p > 0.1$) (Appendix G, Figure G-21).

One trial by Gaudiani et al compared fixed doses of simvastatin 20 mg/day plus ezetimibe with simvastatin 40mg/day, in 210 participants with type 2 diabetes mellitus on stable thiazolidinedione doses. These participants had baseline LDL-c above 100 mg/dL, and some had previously completed a simvastatin trial. The percentage mean difference favored combination therapy (-13.50 percent (95% CI -18.22, -8.78) (Table 14).¹²¹

Measure of atherosclerosis. A single placebo-controlled trial of two years duration in 642 evaluable participants with familial hypercholesterolemia and previously untreated LDL-c above 210 mg/dL compared change score from baseline in mean carotid intima-media thickness measured at the common carotid arteries, carotid bulbs, and internal carotid arteries.⁴² Compared with simvastatin 80 mg/day monotherapy, simvastatin 80 mg/day in combination with ezetimibe did not significantly change the arterial wall thickness. The combination therapy group experienced a mean increase of 11.1 μm , in contrast with 5.8 μm in the monotherapy group. The mean difference in change score in carotid intima-media thickness was 0.01 mm (95% CI -0.01, 0.02) (Table 15).

Harms and Treatment Adherence

Comparing statin plus ezetimibe versus statin monotherapy (lower dose vs. higher dose and various statin doses)

Participants adherent to treatment. In twelve trials with a total of 5,625 evaluable participants, 5020 individuals were considered to have adhered to trial medications per investigators' criteria.^{42,46,48,115,127,130,139,142,143,149,156,166} Trial populations were clinically diverse and followup ranged from six to 96 weeks. Five trials did not add a placebo to statin monotherapy and therefore were not blinded,^{48,127,130,139,142} and one trial used a single pill for the combination treatment.¹⁴⁹ The pooled odds ratio, for all types and doses of statins, was 0.97 (95% CI 0.74, 1.27), and the Egger's regression intercept was not significant for lateral asymmetry (0.39, two tailed $p > 0.1$) (Table 16; Appendix G, Figure G-22). Restricting analysis to the three trials of 24 weeks or more in duration, significant odds favoring combination therapy were found for the longest trial of two years duration.^{42,46,166} This trial was blinded and employed a placebo but compared an identical dose of simvastatin in both combination and monotherapy interventions.⁴²

Treatment adherence for 268 evaluable participants with hypercholesterolemia was estimated from a single trial of 12 weeks duration employing lower dose statin plus ezetimibe,

compared with higher dose statin monotherapy without a placebo. No significant differences were noted in treatment adherence with simvastatin 10 to 20 mg/day plus ezetimibe compared with simvastatin 40 to 80 mg/day [OR 0.53 (95% CI 0.21, 1.30)].¹³⁰

Participants with at least one adverse event. Adverse events such as myalgia, hepatitis and elevated CPK, AST or ALT were reported for 21 trials.⁴⁶⁻

^{48,111,112,119,124,126,127,129,130,142,144,154,156,167,168} With 4912 out of 10023 participants experiencing events, the pooled odds ratio was 0.99 (95% CI 0.90, 1.08). Trial populations were clinically diverse and followup ranged from two to 52 weeks. There was no evidence of significant funnel plot asymmetry (Egger's intercept 0.30, two tailed $p > 0.1$) (Table 16; Appendix G, Figure G-23). Trials that were 24 weeks or more in duration likewise failed to detect any difference.^{46,48,126,167,187}

One trial of 23 weeks duration allowed comparison of a lower dose of simvastatin (conditionally titrated) plus ezetimibe with a higher dose of simvastatin monotherapy, in 362 evaluable participants with CHD or risk equivalent disease.⁴⁷ The odds of an individual experiencing any adverse event with combination therapy compared with monotherapy was 1.07 (0.66, 1.73).

Participants withdrawing due to adverse events. In 32 trials with a total of 13667 evaluable participants, 490 individuals withdrew due to adverse events.^{42,46-}

^{48,106,111,112,115,116,118,121,126,127,129,130,132,140,142-144,148,151,154,156,158,159,167-169,187,193,194} Trial populations were clinically diverse and followup ranged from two to 96 weeks with a mean duration of 15 weeks. Two trials of 12 and 24 weeks duration employing simvastatin and pravastatin as combination and monotherapy interventions reported zero withdrawals.^{168,187} The pooled odds ratio for all statin types and doses was 1.20 (95% CI 0.98, 1.46), but the Egger's regression intercept was significant for lateral funnel plot asymmetry (Egger's intercept 0.74, two tailed p value = 0.04) (Table 16; Appendix G, Figure G-24).

The odds ratio for withdrawal from treatment with a lower dose of a statin plus ezetimibe compared with higher dose of the same statin monotherapy was not significant for the atorvastatin and simvastatin trials (Table 16).

Participants with AST and/or ALT above three times the upper limit of normal, and/or hepatitis. In 27 trials reporting this composite outcome, of a total of 15730 evaluable participants, 125 developed laboratory and/or clinical evidence of hepatic dysfunction.⁴⁶⁻

^{48,106,111,115,116,118,119,121,126,127,129,130,132,140,142,144,148,149,154,156,159,167,169,193,194} Trial populations were clinically diverse and followup ranged from two to 52 weeks with an average of 14 weeks. Five trials did not provide estimable odds as no participant had any elements of this composite outcome.^{106,111,116,119,140} The pooled odds ratio, for all statins and doses, was 1.35 (95% CI 0.94, 1.94), while the Egger's regression intercept was 0.7 and not significant for lateral asymmetry (two tailed $p > 0.1$) (Table 16; Appendix G, Figure G-25).

Odds of developing one of the composite outcomes with a lower dose of a particular statin plus ezetimibe compared with the same statin monotherapy could be estimated from five trials employing fixed dose or conditional titration in 1573 evaluable participants with hypercholesterolemia, nine of whom developed laboratory and/or clinical evidence of hepatic dysfunction.^{47,48,121,130,169} Simvastatin 10 mg/day to 20 mg/day in combination therapy compared with simvastatin 40 to 80 mg/day monotherapy yielded an odds ratio of 1.51 (95%

CI 0.40, 5.75). Restricting the meta-analysis to the four trials employing fixed statin dosing yielded an odds ratio of 1.28 (95% CI 0.31, 5.30) (Table 16; Appendix G, Figure G-26 and G-27).^{48,121,130}

Participants with myalgia. Among 15 trials, 125 (2.4 percent) of 5050 evaluable participants reported symptoms of myalgia.^{48,106,109,112,114,124,126,130,140,142,146,154,156,167,181} Trial populations were clinically diverse and followup ranged from one to 52 weeks. In two trials no participants developed myalgia.^{109,146} The pooled odds ratio, for all types and doses of statins, was 0.92 (95% CI 0.64, 1.33), while Egger's regression intercept of 0.25 was not significant for lateral asymmetry (two tailed $p > 0.1$) (Appendix G, Figure G-28).

No trial provided evaluable data comparing a lower dose of a particular statin plus ezetimibe with a higher dose of the same statin monotherapy.

Participants with CPK above 10 times the upper limit of normal. In 32 trials reporting CPK, 39 of a total of 20220 evaluable participants developed elevations in CPK more than 10 times upper limit of normal.^{42,46-48,106,111,112,114-119,121,126,127,129,130,139,140,142,144,148,149,154,156,159,166-169,193} Trial populations were clinically diverse and followup ranged from two to 96 weeks with an average of 14 weeks followup. Seventeen trials did not provide estimable odds as no participant developed CPK elevations to this extent.^{106,112,115-}

^{117,119,129,139,140,142,144,148,149,159,166,167,169} This included a 12 week trial in 133 evaluable participants with previously documented statin associated muscle-related side effects, treated with fluvastatin 80 mg/day in combination and monotherapy.¹⁴⁸ Pooling of 15 trials yielded an odds ratio of 0.78 (95% CI 0.41, 1.49). The Egger's regression intercept of -0.07 was not significant for lateral asymmetry (two tailed $p > 0.1$) (Appendix G, Figure G-29).

Three trials, one with zero participants with elevated CPK,¹⁶⁹ compared lower dose simvastatin plus ezetimibe with higher dose of the same statin monotherapy.^{47,121} Substantial heterogeneity precluded pooling, but in both trials elevated CPK was a rare event. Of the two trials with fixed rather than conditional dose assignment,^{121,169} one yielded an odds ratio of 7.91 (95% CI 0.16, 399.42).¹²¹

Participants with rhabdomyolysis. Nineteen trials reported zero incidence of rhabdomyolysis,^{46-48,111,112,114-116,129,132,142,146,148,154,156,159,167-169} including a 12 week trial in 133 evaluable participants with previously documented statin associated muscle related side effects, treated with Fluvastatin 80 mg/day in both combination and monotherapy.¹⁴⁸ Trial populations were clinically diverse and followup ranged from one to 48 weeks, with an average of 14 weeks. Five trials employed low dose statins in both combination and monotherapies.^{112,114-116,168} Rosuvastatin was investigated in only one trial.¹⁴² Two trials compared lower dose simvastatin plus ezetimibe with higher dose simvastatin monotherapy.^{47,169}

Key Question 3: Compared with higher dose statins, and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

Study Design and Population Characteristics

The availability of trials addressing aspects of question 3 are depicted in Table 8.

Table 8. Availability of evidence addressing key question 3 for statin plus ezetimibe versus statin monotherapy comparison

Condition	All-cause mortality	Vascular Death	Participants reaching ATP III LDL-c targets	LDL-c	HDL-c	TC:HDL-c ratio	Non-HDL-c	TG
LDL-c \geq 190 mg/dL	No available evidence	√	No available evidence	√	√	No available evidence	Not applicable	
Diabetes mellitus	√	No available evidence	√	√	√	√	√	No available evidence
Established vascular disease	√	No available evidence	√	√	√	√	Not applicable	
Cerebro-vascular disease	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence		
African descent	√	No available evidence	√	√	√	No available evidence		
Asian descent	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence		
Hispanic descent	No available evidence	No available evidence	√	√	√	No available evidence		
Females	√	No available evidence	√	√	No available evidence	No available evidence		
Age 80 years or more	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence		

Abbreviations: HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, TC = total cholesterol, TG = triglycerides

Clinical Outcomes

Comparing statin plus ezetimibe versus statin monotherapy (lower dose vs. higher dose and various statin doses)

All-cause mortality.

Participants with diabetes mellitus. Six deaths were reported among six trials, in 3016 evaluable participants with diabetes mellitus. Two trials reported no deaths, including a trial of 24 weeks duration comparing fixed lower dose simvastatin plus ezetimibe with higher dose monotherapy.^{121,193} The pooled odds ratio for the four adequately concealed trials with estimable odds and followup ranging from six to 12 weeks was 0.40 (95% CI 0.08, 2.09) (Table 9; Appendix G, Figure G-30).^{118,144,149,194} Odds were not estimable for a specific lower dose statin plus ezetimibe compared with higher dose statin monotherapy in this subgroup.

Participants with established vascular disease. Ten deaths were reported among six trials in a total of 1963 evaluable participants, all with six to 12 week followup.^{114-116,140,143,149} Three trials reported zero deaths.^{114,116,140} Odds of all-cause mortality were nonsignificant 0.66 (95% CI 0.19, 2.31) for combination therapy versus monotherapy (Appendix G, Figure G-31). Only

one trial reported adequate allocation concealment, for which odds were nonsignificant (Table 9).¹⁴⁹ There was no evidence comparing a specific lower dose combination statin with higher dose monotherapy.

Participants of African descent. No mortality was noted over the six month trial by Rodney et al, using simvastatin 20 mg/day with placebo or ezetimibe in 247 individuals of African descent.¹¹¹ There was no evidence comparing a lower dose statin in combination therapy with higher dose statin monotherapy using the same statin in this subgroup.

Female participants. One of two trials reporting mortality registered two deaths over a 12 week period in a subgroup of 128 females, odds 0.95 (95% CI 0.06, 15.75) (Table 9). There was no evidence providing estimable odds comparing a lower dose statin in combination therapy with higher dose monotherapy using the same statin in this subgroup.

Vascular death.

Participants with baseline LDL-c \geq 190 mg/dL. Three deaths from cardiovascular causes were reported for Kastelein et al's two year trial in 720 randomized participants with familial hypercholesterolemia, with baseline LDL-c above 210 mg/dL. Fixed dose simvastatin 80 mg/day was employed both in combination and monotherapy. The odds ratio of vascular death was 1.98 (95% CI 0.21, 19.14) for the combination therapy, compared with monotherapy.⁴²

LDL-c Targets and Other Surrogate Markers

Comparing statin plus ezetimibe versus statin monotherapy (lower dose vs. higher dose and various statin doses)

Participants reaching ATP III LDL-c goals.

Participants with diabetes mellitus. Nine trials in a total 4340 evaluable participants, with an average of seven weeks followup, reported that 2720 (63 percent) reached ATP III LDL-c goals.^{115,117,118,121,144,149,167,193,194} Most trials employed atorvastatin and simvastatin, in various doses. Significant statistical heterogeneity ($I^2 = 90$ percent) precluded meta-analysis. Six trials demonstrated significant odds in favor of combination treatment ranging from two to 24 (Appendix G, Figure G-32). Trials not demonstrating significant differences employed either more potent statins in the monotherapy arms or several different statins.^{144,149,193} Larger effect sizes favoring combination therapy were associated with similar doses of statins in combination and monotherapy arms.

Gaudiani et al's trial in 70 evaluable participants compared a lower dose of a statin plus ezetimibe with higher dose monotherapy using the same statin. The odds ratio of 4.79 (95% CI 1.72, 13.35) favored the lower dose simvastatin plus ezetimibe combination.

Participants with established vascular disease. Six trials, with 1131 of 1922 evaluable participants achieving ATP III LDL-c goals, could not be pooled due to substantial statistical heterogeneity ($I^2 = 90$ percent) (Appendix G, Figure G-33).^{114-116,140,149,168} However, all six trials showed significant odds ratios in favor of combination treatment, with point estimates ranging from two to 19. Heterogeneity could not be explained across the covariates of allocation

concealment, trial duration, drug dose and funding. There was no evidence comparing any specific lower dose statin plus ezetimibe with higher dose monotherapy.

Participants of African descent. Pearson et al reported subgroup data on participants of African descent on stable statin treatment, who had not previously met ATP III target LDL-c.¹¹⁷ ATP III LDL-c goals were achieved by 109 of 208 evaluable participants of African descent with odds in favor of combination therapy [OR 3.47 (95% CI 1.90, 6.33)]. There was no evidence comparing lower dose statin plus ezetimibe therapy with higher dose statin monotherapy using the same statin.

Participants of Hispanic descent. Pearson et al reported subgroup data on participants of Hispanic descent on stable statin treatment, who had not previously met ATP III target LDL-c.¹¹⁷ ATP III LDL-c goals were achieved by 54 of 113 participants with odds favoring combination treatment, with and odds ratio of 7.82 (95% CI 3.14, 19.45). There was no evidence comparing a specific lower dose statin plus ezetimibe with higher dose statin monotherapy.

Female participants. Two trials in female participants with CHD, of six and 12 weeks followup, using various statin and ezetimibe comparisons, demonstrated 104 of 189 participants reaching ATP III goals. Farnier et al's trial compared low dose simvastatin plus ezetimibe combination with identical doses of simvastatin monotherapy, with a highly significant odds ratio of 17.64 (95% CI 6.86, 45.36). The trial by Reckless et al. detected no significant difference, comparing simvastatin 40 mg/day plus ezetimibe 10 mg/day with twice the dose of previous statin therapy in 76 participants (Table 11; Appendix G, Figure G-34).

LDL-c, percentage mean change from baseline.

Participants with LDL-c above 190 mg/dL. Meta-analysis of two trials in 754 evaluable participants with homozygous and non-homozygous familial hypercholesterolemia yielded a difference in percentage mean change from baseline of -16.50 (95% CI -16.63, -16.37) in favor of combination treatment (Table 12; Appendix G, Figure G-35).^{42,132} Trials lasted 12 and 96 weeks respectively. There was no evidence comparing a specific lower dose statin combination with higher dose monotherapy of the same statin in this subgroup.

Participants with diabetes mellitus. Each of the seven trials with a total of 2627 evaluable participants providing evidence for this subgroup analysis showed significant differences in mean percentage change from baseline favoring combination treatment, with additional percentage LDL-c reduction ranging from 4 to 26 percent (Table 12; Appendix G, Figure G-36).^{118,121,144,154,167,193,194} Substantial heterogeneity ($I^2 = 93$ percent) precluded meta-analysis. Covariates of allocation concealment, trial duration, and statin dose could not explain this heterogeneity. All trials were sponsored by pharmaceutical industry. Lateral asymmetry of the funnel was apparent.

Gaudiani et al's trial provided data evaluable for lower dose statin plus ezetimibe compared with higher doses of the same statin.¹²¹ It compared fixed doses of simvastatin 20 mg/day in combination therapy with simvastatin 40mg/day monotherapy, in 210 participants with type 2 diabetes mellitus and baseline LDL-c over 100 mg/dL, on stable thiazolidinedione

doses, some of whom had previously completed a simvastatin trial. The percentage mean difference favoring combination therapy was -20.50 percent (95% CI -26.60 %, -14.40 %).

Participants with established vascular disease. Across six trials with relevant data, 1503 participants with CHD demonstrated significant differences in mean percentage change from baseline favoring combination treatment, with point estimates in the range of -26.90 to -9.40 (Table 12; Appendix G, Figure G-37).^{114-116,140,143,154} However, trial mean differences data could not be pooled because of heterogeneity ($I^2 = 93$ percent). Covariates of allocation concealment, trial duration, and statin dose could not explain this heterogeneity. All trials were sponsored by pharmaceutical industry. There was no evidence comparing a specific lower dose combination statin with higher dose monotherapy in this subgroup.

Participants of African descent. Meta-analysis of available data from two trials with 515 evaluable participants of African descent were considered for quantitative synthesis, but substantial statistical heterogeneity precluded pooling ($I^2 = 72$ percent). Trials employed different statins in combination and monotherapy arms. However, both trials were associated with significant differences in mean percentage change from baseline favoring combination treatment; -17.20 percent (95% CI -21.13 %, -13.27 %) and -23.00 percent (95% CI -27.55 %, -18.45) over a 12 and six week period respectively (Table 12; Appendix G, Figure G-38).^{111,117} There was no evidence comparing a specific lower dose statin plus ezetimibe with higher dose monotherapy using the same statin in either subgroup. Farnier et al.'s trial that evaluated one patient in each of the low dose simvastatin plus ezetimibe combination and simvastatin monotherapy treatment arms could not be considered for pooling because there was no measure of dispersion. Their trial reported 65 percent reduction from baseline in mean LDL-c with combination therapy and 0.67 percent increase with monotherapy over six weeks in the two patients with CHD.¹¹⁴

Participants of Hispanic descent. Pearson et al. reported subgroup data on participants of Hispanic descent on stable statin treatment who had not previous met ATP III target LDL-c.¹¹⁷ Over a six week followup, 147 Hispanic participants on ongoing statin therapy were randomized to add-on ezetimibe and placebo. The difference in mean percentage change from baseline was -21.10 (-27.16, -15.04) in favor of combination therapy. There was no evidence comparing a specific lower dose statin plus ezetimibe with higher dose statin monotherapy.

Female participants. Three trials in this subgroup compared simvastatin-ezetimibe combination therapy with simvastatin monotherapy over 4 to 12 weeks. The trial population was mixed^{130,169} or high risk,¹¹⁴ with the greatest significant additional reduction (up to 24 percent) in percentage LDL-c evident in females with prior CHD using combination therapy, compared with similar statin dose monotherapy. Mean percentage reductions varied from 13 to 24 percent and all significantly favored combination treatment. Substantial heterogeneity precluded meta-analysis. Heterogeneity persisted when the two trials permitting lower combination simvastatin comparison with higher dose simvastatin monotherapy in mixed risk population were analyzed separately ($I^2 = 63$ percent) – trials were inconsistent in the direction of effect estimate (Table 12; Appendix G, Figures G-39 and G-40).^{130,169}

HDL-c, percentage mean change from baseline.

Participants with LDL-c above 190 mg/dL. Kastelein et al's two year trial in 720 randomized participants with familial hypercholesterolemia yielded a nonsignificant difference in percentage mean increase of 2.40 percent (95% CI -0.23 percent, 5.03 percent) (Table 13). Fixed dose simvastatin 80 mg was compared in combination and monotherapy.⁴²

Participants with diabetes mellitus. Six trials in 2790 participants with diabetes could not be pooled, given substantial statistical heterogeneity ($I^2 = 55$ percent).^{118,121,144,167,193,194} Followup duration ranged from six to 24 weeks (mean 10 weeks). Heterogeneity could not be explained on the basis of statin dose, sponsorship, adequacy of allocation concealment or trial duration. Differences in mean ranged from -0.8 to 4 percent, with varying statistical significance. There was no obvious evidence of lateral asymmetry of the funnel plot ((Table 13; Appendix G, Figure G-41). Gaudiani et al's trial provided data comparing lower dose statin plus ezetimibe with higher doses of the same statin.¹²¹ It compared fixed doses of simvastatin 20 mg/day plus ezetimibe with simvastatin 40mg/day in 210 participants with type 2 diabetes mellitus on stable thiazolidinedione doses, and baseline LDL-c over 100 mg/dL, some of whom had previously completed a simvastatin trial. The percentage mean difference was -0.10 percent (95% CI -3.42, 3.22).

Participants with established vascular disease. A total of 924 evaluable participants with established CHD were analyzed in three randomized trials of less than 12 weeks duration, sponsored by the pharmaceutical industry and with unclear reporting of allocation concealment (Table 13).^{114,116,140} The pooled difference in means was nonsignificant, 0.04 (95% CI -1.63, 1.72). Similar statin doses were employed in both combination and monotherapy. There was no evidence comparing a specific lower dose statin in combination therapy with higher dose monotherapy in this subgroup.

Participants of African and Hispanic descent. Pearson et al. reported subgroup data on participants of African and Hispanic descent (Table 13). Participants on ongoing statin therapy were randomised to add-on ezetimibe or placebo. The mean differences in percentage change in HDL-c were 3.30 percent (95% CI 0.35, 6.25) in participants of African descent, and 0.30 percent (95% CI -3.64, 4.24) in those of Hispanic descent.¹¹⁷ There was no evidence comparing a specific lower dose combination statin with higher dose monotherapy in both subgroups.

Total cholesterol:HDL-c ratio, percentage mean change from baseline.

Participants with diabetes mellitus. Six pharmaceutical industry sponsored trials of a mean of eight week followup (range 6 to 24 weeks) with 2790 evaluable participants yielded this ratio. Statistical heterogeneity between trials precluded meta-analysis ($I^2 = 90$ percent). The individual mean differences in percentage change from baseline consistently and significantly favored combination therapy, with point estimates in the range of -17.30 to -3.4. The heterogeneity could not be explained based on duration, statin type and dosage, and adequacy of allocation concealment (Table 14). With this small number of trials, the funnel plot was suggestive of lateral asymmetry (Fig G-42). Gaudiani et al's trial provided data comparing lower dose statin plus ezetimibe with higher doses of the same statin.¹²¹ It compared fixed

doses of simvastatin 20 mg/day plus ezetimibe with simvastatin 40mg/day in 210 participants with type 2 diabetes mellitus on stable thiazolidinedione doses, and baseline LDL-c over 100 mg/dL, some of whom had previously completed a simvastatin trial. The percentage mean difference was -13.50 percent (95% CI -18.22, -8.78).

Participants with established vascular disease. A single six week trial by Cruz-Fernandez et al randomized participants with established CHD on prior low dose atorvastatin therapy to ezetimibe or placebo (Table 14). A significant mean difference in percentage change from baseline of -19.90 percent (95% CI -22.31, -17.49) was noted in favor of combination treatment.¹¹⁵

Non-HDL-c, percentage mean change from baseline.

Participants with diabetes mellitus. Six pharmaceutical industry sponsored trials of a mean of eight week followup (range 6 to 24 weeks) with 2790 evaluable participants yielded this outcome (Table 17). Statistical heterogeneity between trials precluded meta-analysis ($I^2 = 94$ percent). The individual mean differences in percentage change from baseline consistently and significantly favored combination therapy, with additional non-HDL-c reductions of 4 to 24 percent. Compared with trials reporting adequate allocation concealment and employing relatively more potent statins for monotherapy, there was a trend of higher point estimates associated with trials with allocation poorly concealed or reported, or less potent statin monotherapy.^{118,121,167,194} With this small number of trials, the funnel plot was suggestive of lateral asymmetry (Appendix G, Figure G-43). There was no analyzable evidence comparing a specific lower dose statin in combination therapy with higher dose monotherapy.

Strength of Evidence

The strength of the available evidence was assessed as GRADE (Grading of Recommendations Assessment, Development and Evaluation)²²⁵ for the key outcomes all-cause mortality, vascular death, serious adverse events and achieving ATP-III target LDL-c. Results generated using the GRADEpro software are presented in Tables H-1 to H-11 (Appendix H) can be summarized as follow:

1. Based on studies in participants requiring intensive lipid lowering therapy and comparing the combination of lower dose simvastatin plus ezetimibe to higher dose simvastatin, GRADE was “very low” for all cause mortality (2 trials) and participants reaching ATP III LDL-c goals (3 trials) (Appendix H, Table H-1).
2. Based on studies in participants requiring intensive lipid lowering therapy and comparing the combination of any dose statin plus ezetimibe to any dose statin, GRADE was “very low” for all cause mortality (14 trials), vascular death (1 trial) and participants reaching ATP III LDL-c goals (18 trials) (Appendix H, Table H-2).
3. Based on a single study in participants with baseline LDL-c above 190 mg/dL, GRADE was “very low” for vascular death for the combination of any dose statin plus ezetimibe compared to any dose statin (Appendix H, Table H-3).
4. Based on studies in participants with diabetes mellitus and comparing the combination of any dose statin plus ezetimibe to any dose statin,, GRADE was “very low” for all

- cause mortality (6 trials) and participants reaching ATP III LDL-c goals (9 trials) (Appendix H, Table H-4).
5. Based on six studies in participants with established vascular disease, GRADE was “very low” for all cause mortality and participants reaching ATP III LDL-c goals for the combination of any dose statin plus ezetimibe compared to any dose statin (Appendix H, Table H-5).
 6. Based on a single study in participants of African descent, GRADE was “very low” for all cause mortality and participants reaching ATP III LDL-c goals for the combination of any dose statin plus ezetimibe compared to any dose statin (Appendix H, Table H-6).
 7. Based on a single study in participants of Hispanic descent, GRADE was “very low” for participants reaching ATP III LDL-c goals for the combination of any dose statin plus ezetimibe compared to any dose statin (Appendix H, Table H-7).
 8. Based on two studies in female participants, GRADE was “very low” for all cause mortality and participants reaching ATP III LDL-c goals for the combination of any dose statin plus ezetimibe compared to any dose statin (Appendix H, Table H-8).
 9. Based on studies in participants regardless of baseline risk and comparing the combination of lower dose simvastatin plus ezetimibe to higher dose simvastatin, GRADE was “very low” for all cause mortality (3 trials), vascular death (1 trial), serious adverse events (3 trials) and participants reaching ATP III LDL-c goals (3 trials) (Appendix H, Table H-9).
 10. Based on studies in participants followed up for more than 24 weeks and comparing the combination of any dose statin plus ezetimibe to any dose statin, GRADE was “very low” for all cause mortality (4 trials), vascular death (1 trial), and serious adverse events (6 trials) (Appendix H, Table H-10).
 11. Based on studies in participants regardless of baseline risk and comparing the combination of any dose statin plus ezetimibe to any dose statin, GRADE was “very low” for all cause mortality (24 trials), vascular death (2 trials), serious adverse events (27 trials) and participants reaching ATP III LDL-c goals (23 trials) (Appendix H, Table H-11).

Evidence Summary Tables: Statin Plus Ezetimibe Combination Therapy Versus Statin Monotherapy

Table 9. Quantitative syntheses of long-term outcomes (clinical, serious adverse events and cancer) for ezetimibe plus statin combination therapy compared with statin monotherapy

Ezetimibe long-term outcomes	Number of trials reporting outcome	Number in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
All-cause mortality						
All trials, ≥ 24 weeks followup ^{48,121,126,166}	4	1428	3 (analyzable data from a single trial)	7.51	0.38	147.37
All trials ^{48,110,111,114-118,121,126,127,129,140,142-144,149,151,158,159,166,169,193,194}	24	14407	18	0.95	0.37	2.41
All trials with adequate allocation concealment ^{48,111,117,118,127,144,149,158,159,166,169,193,194}	13	11113	15	1.07	0.38	2.99
All trials investigating lower dose of statin in combination versus higher dose of the same as monotherapy <i>Simvastatin</i> ^{121,151,169}	3	539	0	-	-	-
All trials investigating lower dose of statin in combination versus higher dose of the same as monotherapy <i>Atorvastatin</i> ¹⁵⁸	1	194	0	-	-	-
Participants requiring intensive lipid lowering therapy ^{114-116,118,121,140,142-144,149,151,159,193,194}	14	6275	15	0.61	0.22	1.71
Participants requiring intensive lipid lowering therapy - Adequate allocation concealment ^{118,144,149,159,193,194}	6	3687	12	0.64	0.20	2.04
Participants requiring intensive lipid lowering therapy - lower dose of statin in combination versus higher dose of the same as monotherapy <i>Simvastatin</i> ^{121,151}	2	439	0	-	-	-
Participants with diabetes mellitus ^{118,121,144,149,193,194}	6	3016	6	0.40	0.08	2.09
Participants with diabetes mellitus, trials with adequate allocation concealment ^{118,144,149,193,194}	5	2802	6	0.40	0.08	2.09
Participants with established vascular disease ^{114-116,140,143,149}	6	1963	10	0.66	0.19	2.31
Participants with established vascular disease, adequate allocation concealment ¹⁴⁹	1	424	8	0.99	0.24	4.01
Participants of African descent ¹¹¹	1	247	0			
Female participants only	2	128	2	0.95	0.06	15.75

Ezetimibe long-term outcomes	Number of trials reporting outcome	Number in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Vascular death						
All trials \geq 24 weeks followup ⁴²	1	720	3	1.98	0.21	19.14
All trials ^{42,130}	2	1196	4	2.70	0.38	19.20
All trials with adequate allocation concealment ^{42,130}	2	1196	4	2.70	0.38	19.20
<i>Simvastatin</i> - lower dose (20mg/day) combination therapy versus higher dose (80 mg/day) monotherapy ¹³⁰	1	121	1	8.05	0.16	407.27
Participants requiring intensive lipid lowering therapy, with LDL-c \geq 190 mg/dL ⁴²	1	720	3	1.98	0.21	19.14
Fatal Myocardial Infarction						
All trials ^{142,149,156}	3	1460	4	2.71	0.38	19.30
Unspecified Myocardial Infarction						
All trials ¹⁴⁹	1	424	11	1.19	0.36	3.97
Stroke (ischemic and/or hemorrhagic)						
Stroke ¹⁶⁶	1	200	1	7.70	0.15	388.20
Serious Adverse Event(s)						
All trials, \geq 24 weeks followup ^{48,121,126,130,166,167}	6	1893	191	-	-	-
All trials ^{47,48,110-112,114-116,118,121,126,130,140,142-144,149,151,154,156,158,159,166-169,193}	27	13463	489	1.08	0.88	1.33
<i>Simvastatin</i> Lower dose statin in combination therapy versus higher dose monotherapy Fixed dose only ^{121,169}	2	314	9	4.85	0.84	28.00
<i>Simvastatin</i> Lower dose statin in combination therapy versus higher dose monotherapy Fixed and/or conditional titration ^{47,121,169}	3	927	44	1.64	0.85	3.19
<i>Atorvastatin</i> Lower dose statin in combination therapy versus higher dose monotherapy Fixed dose only ¹⁵⁸	1	194	0	-	-	-
Cancer						
All trials ^{48,166}	2	971	11	3.99	0.71	22.28

Abbreviations: CI = 95% confidence interval, LDL-c = low density lipoprotein-c

Table 10. Summary of non-randomized evidence on ezetimibe plus statin combination therapy compared with statin monotherapy

Trial	Design Duration Downs and Black score	Patients (LDL-c mg/dL)	Monotherapy	Combination Therapy	Results	Limitations	Applicability	Conclusion
Türk (2008) ⁸⁶ Trial country NR Sponsor NR	CCT 1 year 19/28	84 renal transplant patients with hypercholesterolemia on high dose statins Mean baseline LDL-c = 129 mg/dL	High doses of fluvastatin or pravastatin n = 28	High doses of fluvastatin or pravastatin or simvastatin plus ezetimibe 10 mg/day n = 56	No death Other clinical outcomes of interest, SAE and cancer not reported	Excluded participants likely to experience liver or muscle related AEs Study was not powered for the outcome of mortality	Applicability restricted to renal transplant patients	Results are inconclusive

Abbreviations: AEs = adverse events, CCT = controlled clinical trial, LDL-c = low density lipoprotein-c, n = number in treatment arm, NR = not reported, SAE = serious adverse event

Table 11. Quantitative syntheses of incidence of participants attaining ATP III LDL-c targets, for ezetimibe plus statin combination therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Relative probability of attaining ATP III LDL-c goal						
All trials ^{47,112,114-118,121,126,127,129,130,140,142,144,148,149,151,156,167,168,193,194}	23	15944	11329	-	-	-
Participants requiring intensive lipid lowering therapy ^{47,112,114-118,121,140,142,144,148,149,151,167,168,193,194}	18	7731	5342	-	-	-
<i>Simvastatin</i> Lower dose statin in combination versus higher dose monotherapy Participants requiring intensive lipid lowering therapy ^{47,121,151}	3	652	386	-	-	-
<i>Simvastatin</i> Lower dose statin in combination versus higher dose monotherapy fixed dose and/or fixed titration only Participants requiring intensive lipid lowering therapy ^{121,151}	2	295	149	7.21	4.30	12.08
Participants with diabetes mellitus ^{115,117,118,121,144,149,167,193,194}	9	4340	2720	-	-	-
<i>Simvastatin</i> Lower dose statin in combination versus higher dose monotherapy Participants with diabetes mellitus ¹²¹	1	70	41	4.79	1.72	13.35
Participants with established vascular disease ^{114-116,140,149,168}	6	1922	1131	-	-	-
Participants of Hispanic descent ¹¹⁷	1	113	54	7.82	3.14	19.45
Participants of African descent ¹¹⁷	1	208	109	3.47	1.90	6.33
Female participants only	2	189	104	-	-	-

Abbreviations: ATP III = Third Adult Treatment Panel of the National Cholesterol Education Program, CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

Table 12. Quantitative syntheses of LDL-c data, for ezetimibe plus statin combination therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant treatment groups	Point Estimate	Lower CI	Upper CI
Difference in mean LDL-c percentage change from baseline (%)					
All trials ^{42,46-48,109-112,114-118,121,124,126,127,129,130,132,139,140,142-144,154,156,158,159,166-169,193,194}	35	18788	-	-	-
<i>Simvastatin</i>					
Lower dose statin in combination therapy versus higher dose monotherapy across all populations ^{47,48,121,130,154,169}	6	1942	-	-	-
<i>Atorvastatin</i>					
Lower dose statin in combination therapy versus higher dose monotherapy across all populations ¹⁵⁸	1	184	-19.90	-25.17	-14.63
Participants requiring intensive lipid lowering therapy ^{42,47,112,114-116,118,121,132,140,142-144,154,159,167,193,194}	18	6601	-	-	-
<i>Simvastatin</i>					
Lower dose statin in combination therapy versus higher dose monotherapy Participants requiring intensive lipid lowering therapy ^{47,121}	2	567	-	-	-
Participants with baseline LDL-c>190 mg/dL ^{42,132}	2	754	-16.50	-16.63	-16.37
Participants with diabetes mellitus ^{118,121,144,154,167,193,194}	7	2627	-	-	-
Participants with diabetes mellitus <i>Simvastatin</i>					
Lower dose statin in combination versus higher dose monotherapy ¹²¹	1	210	-20.50	-26.60	-14.40
Participants with vascular disease ^{114-116,140,143,154}	6	1503	-	-	-
All participants of African descent ^{111,114,117}	3	517	-	-	-
All participants of Hispanic descent ¹¹⁷	1	147	-21.10	-27.16	-15.04
Female participants only ^{114,130,169}	3	456	-	-	-
Female participants only <i>Simvastatin</i>					
Lower dose statin in combination versus higher dose monotherapy ^{130,169}	2	186	-	-	-

Abbreviations: CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

Table 13. Quantitative syntheses of HDL-c data, for ezetimibe plus statin combination therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant treatment groups	Point estimate	Lower CI	Upper CI
Difference in mean HDL-c percentage change from baseline (%)					
All trials ^{42,46-48,109,110,112,114-118,121,124,126,127,129,130,139,140,142,144,154,156,158,159,166-169,193,194}	32	18143	-	-	-
<i>Simvastatin</i>					
Lower dose statin in combination therapy versus higher dose monotherapy – all participants ^{48,121,130,154,169}	5	1585	0.31	-0.89	1.52
<i>Atorvastatin</i>					
Lower dose statin in combination therapy versus higher dose monotherapy – moderately high risk ¹⁵⁸	1	184	2.40	1.97	2.83
Participants requiring intensive lipid lowering therapy ^{42,47,112,114-116,118,121,140,142,144,159,167,193,194}	15	7020	1.53	0.81	2.24
<i>Simvastatin</i>					
Lower dose statin in combination therapy versus higher dose monotherapy Participants requiring intensive lipid lowering therapy (diabetes mellitus) ¹²¹	1	210	-0.10	-3.42	3.22
Participants with LDL-c>190 mg/dL ⁴²	1	720	2.40	-0.23	5.03
Participants with diabetes mellitus ^{118,121,144,167,193,194}	6	2790	-	-	-
Participants with vascular disease ^{114,116,140}	3	924	0.04	-1.63	1.72
All participants of African origin ¹¹⁷	1	267	3.30	0.35	6.25
All participants of Hispanic origin ¹¹⁷	1	147	0.30	-3.64	4.24

Abbreviations: CI = 95% confidence interval, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol

Table 14. Quantitative syntheses of TC:HDL-c ratio data, for ezetimibe plus statin combination therapy compared with statin monotherapy

	Number of trials	Number of participants in relevant intervention groups	Point estimate	Lower CI	Upper CI
Difference in mean TC:HDL-c ratio percentage change from baseline					
All trials ^{48,112,115,118,121,126,127,129,130,139,142,144,154,156,158,159,167,169,193,194}	20	11942	-	-	-
Lower dose simvastatin in combination therapy versus higher dose simvastatin monotherapy ^{48,121,130,154,169}	5	1585	-	-	-
Lower dose atorvastatin in combination therapy versus higher dose atorvastatin monotherapy ¹⁵⁸	1	184	-13.00	-17.61	-8.39
Participants in need of intensive lipid lowering therapy ^{112,115,118,121,142,144,159,167,193,194}	10	4677	-	-	-
<i>Simvastatin</i>					
Lower dose simvastatin in combination therapy versus higher dose simvastatin monotherapy Fixed dosing Participants with diabetes mellitus ¹²¹	1	210	-13.50	-18.22	-8.78
All participants with diabetes mellitus ^{118,121,144,167,193,194}	6	2790	-	-	-
Participants with vascular disease ¹¹⁵	1	444	-19.90	-22.31	-17.49

Abbreviations: CI = 95% confidence interval, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, TC = total cholesterol

Table 15. Quantitative synthesis of carotid intima-media thickness data, for ezetimibe plus statin combination therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant treatment groups	Point estimate	Lower CI	Upper CI
Mean difference in CIMT change score (mm)					
All trials ⁴²	1	680	0.01	-0.01	0.02

Abbreviations: CI = 95% confidence interval, CIMT = carotid intima-media thickness

Table 16. Quantitative syntheses of short-term harms and adherence to treatment, for ezetimibe plus statin combination therapy compared with statin monotherapy

Ezetimibe short-term harms and adherence	Number of trials reporting outcome	Number of participants in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Adherence to treatment						
All trials 42,46,48,115,127,130,139,142,143,149,156,166	12	5625	5020	0.97	0.74	1.27
<i>Simvastatin</i>						
Lower dose statin in combination therapy versus higher dose monotherapy ¹³⁰	1	268	242	0.53	0.21	1.30
Participants experiencing at least one adverse event						
All trials ⁴⁶⁻ 48,111,112,119,124,126,127,129,130,142,144,149,151,154,156,159,167,168,187	21	10023	4912	0.99	0.90	1.08
<i>Simvastatin</i>						
Lower dose statin in combination therapy versus higher dose monotherapy Conditionally titrated dose (Fixed or conditional titration) ⁴⁷	1	362	242	1.07	0.66	1.73
Withdrawal due to an adverse event						
All trials ^{42,46-} 48,106,111,112,115,116,118,121,126,127,129,130,132,140,142-144,148,151,154,156,158,159,167-169,187,193,194	32	13667	490	1.20	0.98	1.46
<i>Simvastatin</i>						
Lower dose statin in combination therapy versus higher dose monotherapy Fixed dose ^{121,130,169}	3	582	27	1.43	0.49	4.23
<i>Simvastatin</i>						
Lower dose statin in combination therapy versus higher dose monotherapy Fixed dose or conditionally titrated ^{47,121,130,169}	4	1195	59	1.13	0.57	2.25
<i>Atorvastatin</i>						
Lower dose statin in combination therapy versus higher dose monotherapy Fixed dose ^{121,130,169}	1	194	2	0.20	0.01	4.22
AST and/or ALT ≥ 3 times the upper limit of normal, and/or hepatitis						
All trials ⁴⁶⁻ 48,106,111,115,116,118,119,121,126,127,129,130,132,140,142,144,148,149,154,156,159,167,169,193,194	27	15730	125	1.35	0.94	1.94
<i>Simvastatin</i>						
Lower dose statin in combination therapy versus higher dose monotherapy – fixed dose or fixed titration ^{48,121,130,169}	4	971	8	1.28	0.31	5.30

Ezetimibe short-term harms and adherence	Number of trials reporting outcome	Number of participants in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
<i>Simvastatin</i> Lower dose statin in combination therapy versus higher dose monotherapy – conditional or fixed titrations or fixed dose ^{47,48,121,130,169}	5	1573	9	1.51	0.40	5.75
Myalgia						
All trials ^{48,106,109,112,114,124,126,130,140,142,146,154,156,167,181}	15	5050	125	0.92	0.64	1.33
CPK ≥ 10 times the ULN						
All trials ^{42,46-48,106,111,112,114-119,121,126,127,129,130,139,140,142,144,148,149,154,156,159,166-169,193}	32	20220	39	0.78	0.41	1.47
<i>Simvastatin</i> Lower dose statin in combination therapy versus higher dose monotherapy—fixed dose or fixed titration ^{47,169}	2	313	1	7.91	0.16	399.42
<i>Simvastatin</i> Lower dose statin in combination therapy versus higher dose monotherapy ^{47,121,169}	3	915	3	-	-	-
Rhabdomyolysis (investigator defined)						
All trials ^{46-48,111,112,114-116,129,132,142,146,148,154,156,159,167-169}	19	8125	0	-	-	-
<i>Atorvastatin</i> Lower dose statin in combination therapy versus higher dose monotherapy ¹⁵⁹	1	564	0	-	-	-
<i>Simvastatin</i> Lower dose statin in combination therapy versus higher dose monotherapy ^{47,169}	2	713	0	-	-	-

Abbreviations: ALT = alanine transaminase, AST = aspartate transaminase, CI = 95% confidence interval, CPK = creatinine phosphokinase, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, TC = total cholesterol, ULN = upper limit of normal

Table 17. Quantitative syntheses of non-HDL-c, for ezetimibe plus statin combination therapy compared with statin monotherapy

	Number of trials	Number of participants in relevant intervention groups	Point estimate	Lower CI	Upper CI
Difference in mean non-HDL-c percentage change from baseline					
All trials ^{118,121,144,167,193,194}	6	2790	-	-	-

Abbreviations: CI = 95% confidence interval, HDL-c = high density lipoprotein cholesterol

Statin Plus Fibrate Combination Therapy Versus Statin Monotherapy

Overview of Included Studies

A total of 11 randomized controlled trials evaluated the relative efficacy and/or harms of the combination of statins plus fibrates (fenofibrate 200mg/day, gemfibrozil 1200 mg/day) versus statin monotherapy in a total of 1991 participants (Table 3; Appendix F, Tables F-9 to F-16).^{50,120,123,125,134,145,160,161,188,192,195} One included non-randomized study addressed this particular comparison (Table 4).⁸⁷ Two randomized trials had one or more companion reports of the same trial (Table 5).^{160,220} Data from the report with the longest available duration were used for analysis, and one of the companion reports was considered for trial referencing.

Three trials were conducted in multiple centers,^{120,125,134} and five in a single center,^{50,145,188,192,195} while this information was not reported for three trials.^{123,160,161} Three of 11 trials were partially or completely sponsored by the pharmaceutical industry,^{125,134,145} one study explicitly reported being conducted independently of industry funding,¹⁶⁰ and reports of seven trials did not disclose funding sources.^{50,120,123,161,188,192,195} Mean Jadad score was 2 (range 1 to 3). Two trials were reported to be appropriately randomized,^{50,160} while five used an appropriate method for double blinding.^{120,123,134,145,192} Allocation concealment was adequate in two trials^{50,160} and five trials used intention-to-treat analysis.^{123,145,160,161,192}

Trials were distributed by geographical region as follows:

- North America - two trials^{120,145}
- Europe - eight trials^{50,123,125,134,160,161,188,192}
- Asia - one trial¹⁹⁵

Reporting of participants' ethnicity was provided in three trials as follows:

- European descent (97 to 100 percent)^{120,123,125}
- Hispanic descent (6.5 percent)¹²⁰
- African descent (2.8 percent)¹²⁰

Power analyses regarding the primary outcome measures were reported for no trials, and except for three trials,^{134,188,192} active clinical adverse event data collection was either not reported or unclear.

Key Question 1: For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits, and rates of serious adverse events of coadministration of different lipid-modifying agents (i.e. a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

Study Design and Population Characteristics

One or more clinical outcomes or serious adverse events were reported for five trials, none using crossover design, that randomized 990 participants to compare a fibrate-statin combination with statin monotherapy (Table 21; Appendix F, Table F-9).^{120,123,125,134,188}

Three trials provided information on participants' descent, with a mean of 90 to 100 percent of participants of European descent,^{120,123,125} 2.8 percent of African descent,¹²⁰ and 6.5 percent of Hispanic descent.¹²⁰

No trial was conducted exclusively in a single gender. On average, 45 percent of participants were female (range 33 to 50 percent). The average of mean ages of participants was 55 years (range of mean ages, 49 to 60 years). Three trials recruited outpatients,^{125,134,188} while two trials did not report recruitment setting. The mean Jadad score was 2 (range 1 to 3) and one trial had adequate allocation concealment.¹²⁰ Two trials were exclusively in participants requiring intensive lipid lowering treatment (i.e. participants with established vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL).^{125,134} These two trials randomized 297 participants.

Participants in these five trials were of heterogeneous characteristics, including those with familial combined hypercholesterolemia,^{120,188} diabetes mellitus,¹²⁵ established vascular disease and/or CHD risk equivalent and/or diabetes mellitus,¹²³ and prior statin exposure.^{120,123} Most trials excluded participants with triglycerides above 300 to 600 mg/dL, patients with recent or unstable vascular disease, uncontrolled diabetes mellitus and hypertension, liver or muscle disease or high ALT, AST or CPK, or impaired renal function. No trial reported employing a fibrate-statin combination as a combined pill.

Table 18. Evidence addressing key question 1 for statin plus fibrate versus statin monotherapy comparison

Outcomes	Extractable data availability	Key points of evidence synthesis
All-cause mortality	Yes	Three trials used the same statins in combination therapy and monotherapy, one with higher dose monotherapy. A significant difference was not observed among participants with mixed risk factors. These trials reported 3 deaths in 339 evaluable participants.
Vascular death	No	
Fatal myocardial infarction (MI)	Yes	Two trials used the same statin and same dose in combination therapy and monotherapy. A significant difference was not observed among participants with mixed risk factors. These trials reported 1 fatal MI in 194 evaluable participants.
Non-fatal MI	Yes	One trial compared combination therapy with same statin and same dose monotherapy in participants with diabetes mellitus. No events were reported. This trial reported no events in 48 evaluable participants.
Any or unspecified MI	Yes	One trial compared combination therapy with the same statin and same dose monotherapy in participants with diabetes mellitus. No events were reported. This trial reported no events in 48 evaluable participants.
Acute coronary syndrome (ACS) (encompassing unstable angina or acute MI)	Yes	One trial compared combination therapy with same statin and same dose monotherapy in participants with diabetes mellitus. No events were reported. This trial reported no events in 48 evaluable participants.
Any cerebrovascular event	No	
Hemorrhagic stroke	No	
Ischemic stroke	No	
Any or unspecified stroke	No	
Transient ischemic attack (TIA)	No	
Carotid endarterectomy (CEA)	No	
Percutaneous coronary interventional procedure (PCI)	No	
Coronary artery bypass graft procedure (CABG)	No	
Any or unspecified revascularization procedure	No	
Serious adverse events (SAEs)	Yes	Two trials compared combination therapy with the same statin and same dose monotherapy. SAEs were reported in a single trial and a significant difference was not observed. These trials reported 17 SAEs in 652 evaluable participants.
Cancer	No	

Abbreviations: ACS = acute coronary syndrome, CABG = coronary artery bypass graft, CEA = carotid endarterectomy, MI = myocardial infarction, PCI = percutaneous coronary intervention, SAE = serious adverse event

Longer Term Efficacy, Serious Adverse Events, and Cancer

Comparing statin plus fibrate versus statin monotherapy (lower dose vs. higher dose and various statin doses)

All-cause mortality. All-cause mortality was reported for three trials in 339 evaluable participants.^{125,134,188} One long-term trial, in 27 participants, compared pravastatin 40 mg/day plus gemfibrozil 1200 mg/day with pravastatin 40 mg/day in participants with familial type II-b hyperlipoproteinemia or familial combined hyperlipidemia¹⁸⁸ No deaths were reported

throughout followup of 48 to 92 weeks. Across these three trials of 12 to 92 weeks duration, two trials on 297 evaluable participants had a total of three deaths (Table 21; Appendix F, Table F-9). These could be meta-analyzed without asymmetry evident (Appendix G, Figure G-44).^{125,134} A nonsignificant odds ratio of 0.28 (95% CI 0.03, 2.97) was observed. Neither trial report included a procedure to guarantee allocation concealment, and sensitivity analyses were not conducted.

Only one trial of 18 weeks duration permitted a comparison of lower dose rosuvastatin 5 to 10 mg/day in combination with fenofibrate 200mg/day with higher dose rosuvastatin 40 mg/day monotherapy in 166 evaluable participants (Table 21; Appendix F, Table F-9).¹²⁵ All participants on this trial had diabetes mellitus at baseline and required intensive lipid lowering therapy.¹²⁵ In this study, participants on combination therapy received fixed doses of medications and participants on monotherapy had their medication dose increased every six weeks if LDL-c cholesterol remained above 50 mg/dL. The estimable odds ratio (fibrate plus statin combination compared with monotherapy) for this trial, based upon two deaths, was 0.46 (95% CI 0.03, 7.57).

One multicenter, non-randomized, controlled, 36 week trial compared fluvastatin 80mg/day plus gemfibrozil 1200 mg/day with fluvastatin 20, 40 or 80 mg/day in a conditional dose titration. Eleven deaths were reported in 1077 evaluable participants with or without CHD, with triglycerides above 400 mg/dL and baseline mean LDL-c of 186 mg/dL.⁸⁷ A single death was reported among 162 participants receiving combination therapy, while for monotherapy the deaths were 1/77 participants receiving fluvastatin 20mg/day, 4/237 receiving fluvastatin 40 mg/day, and 5/601 receiving fluvastatin 80 mg/day. No other outcome of interest was reported (Table 22).

Fatal myocardial infarction. Two trials in 194 evaluable participants reported one fatal MI. One 52 week trial, in 48 participants, compared fluvastatin 80 mg/day and fenofibrate 200 mg/day with fluvastatin 80 mg/day monotherapy in participants with combined hyperlipidemia, type II diabetes mellitus and coronary heart disease. No fatal myocardial infarction was reported.¹²³ Another 12 week trial in 146 evaluable participants reported one fatal myocardial infarction in a participant receiving statin monotherapy therapy, yielding an nonsignificant odds ratio for fatal myocardial infarction of 0.31 (95% CI 0.01, 7.77).¹³⁴ None of the trials comparing lower dose fibrate plus statin combination therapy with a higher dose of the same statin monotherapy reported fatal myocardial infarction (Table 21; Appendix F, Table F-9).

Myocardial infarction and acute coronary syndrome. A single trial with a followup of 52 weeks on 48 evaluable participants comparing fluvastatin 80 mg/day plus fenofibrate 200 mg/day with fluvastatin 80 mg/day monotherapy in participants with combined hyperlipidemia, type II diabetes mellitus and coronary heart disease reported no occurrence of myocardial infarction (including non-fatal myocardial infarction) or acute coronary syndrome (Table 21; Appendix F, Table F-9).¹²³

Serious Adverse Events. Two trials in 652 evaluable participants reported the proportion of participants experiencing serious adverse events (Table 21; Appendix F, Table F-9).^{120,123} In the 52 week trial described above Derosa et al reported no serious adverse events in 48 participants requiring intensive lipid lowering therapy.¹²³ Another trial of 12 weeks duration, comparing simvastatin (20 mg/day) and fenofibrate (200 mg/day) with simvastatin (20 mg/day)

monotherapy in 604 participants reported 17 serious adverse events and a nonsignificant odds ratio (combination therapy versus monotherapy) of 1.2 (95% CI 0.42, 3.46) (Table 21).¹²⁰

Cancer. There was no evidence for the outcome of cancer.

Key Question 2: Do these regimens differ in reaching LDL-c targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

Overview of Included Studies

Eleven trials, none of crossover design, randomizing 1991 participants compared statin plus fibrate-statin combinations with statin monotherapy and reported one or more surrogate efficacy or harms outcomes other than serious adverse events and cancer [Table 3; Appendix F, Table F-10 to F-16].^{50,120,123,125,134,145,160,161,188,192,195} Three trials provided information on participants' descent,^{120,123,125} with 90 to 100 percent of participants of European descent, 2.8 percent of African descent, and 6.5 percent of Hispanic descent. Trial duration ranged from six to 104 weeks, with an average of 32 weeks. No trial was conducted exclusively in a particular gender, and on average 40 percent of participants were female (range 11 to 58 percent). The average of mean ages of participants was 57 years (range of mean age 49 to 60 years). Five trials recruited outpatients,^{50,125,134,188,192} one trial recruited inpatients,¹⁹⁵ and five trials did not report recruitment setting. The mean Jadad score was 2 (range 1 to 3) and two trials had adequate allocation concealment.^{120,160} Five trials recruited participants requiring intensive lipid lowering treatment, because of established vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL.^{123,125,145,161,195} These five trials randomized 598 participants.

Across trials, participants were of heterogeneous characteristics including those with familial combined hypercholesterolemia,^{50,120,161,188,192} diabetes mellitus,^{125,145,161} established vascular disease and/or CHD risk equivalent and/or diabetes mellitus,¹²³ and prior statin exposure.^{120,123,145} There was one trial exclusively in participants with metabolic syndrome.¹⁶⁰ Most trials excluded participants with triglycerides above 300 to 600 mg/dL, patients with recent or unstable vascular disease, uncontrolled diabetes mellitus and hypertension, liver and muscle disease or high ALT, AST and CPK, and impaired renal function. No trial reported employing a fibrate-statin combined pill.

Table 19. Evidence addressing key question 2 for statin plus fibrate versus statin monotherapy comparison

Outcomes	Extractable data availability	Key points of evidence synthesis
Participants attaining ATP III LDL-c targets	Yes	One trial using a higher dose statin monotherapy in participants with diabetes mellitus showed no significant results. Another study comparing the same statin and same dose in combination therapy and monotherapy favored combination therapy.
LDL-c	Yes	Two trials using the same statin in combination and monotherapy, one of them with higher statin dose monotherapy, in participants with diabetes mellitus showed no significant results.
HDL-c		Three trials using the same statin, one of them with higher statin dose monotherapy, showed a significant difference favoring the fibrate plus statin combination.
TC:HDL ratio		One trial used higher dose statin monotherapy in participants with diabetes mellitus. No significant difference was observed.
Measure(s) of atherosclerosis	No	
Treatment Adherence	No	
Participants experiencing at least one adverse event	Yes	Three trials using the same statin, one of them with higher dose statin monotherapy reported 90 adverse events in 362 evaluable participants. Data was heterogeneous and not pooled.
Withdrawal due to adverse events	Yes	Five trials, one comparing different statins, and one using higher dose statin monotherapy, reported 41 withdrawals due to AEs in 1269 evaluable participants. Data was heterogeneous and not pooled.
Elevated AST and/or ALT > 3 times ULN and/or hepatitis	Yes	Four trials, one comparing various statins, and two comparing with higher dose statin monotherapy, reported 11 episodes of myalgia in 841 evaluable participants. No significant difference was observed.
Myalgia	Yes	No significant difference was noted across statin plus fibrate combination compared with statin monotherapy, including comparisons of lower dose statin combination with higher doses of the same statin monotherapy in six trials
CPK > 10 times ULN	Yes	Five 12 to 24 week trials in 1199 evaluable participants reported one event. No significant difference was observed.
Rhabdomyolysis (investigator defined)	Yes	Three 12 week trials in 951 evaluable participants reported no events.

Abbreviations: ALT = alanine transferase, AST = aspartate transferase, ATP III = Third Adult Treatment Panel of the National Cholesterol Education Program, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, TC = total cholesterol

LDL-c Targets and Other Surrogate Markers

Comparing statin plus fibrate versus statin monotherapy (lower dose vs. higher dose and various statin doses)

Participants reaching LDL-c ATPIII goals. Two trials in 240 evaluable participants reported 197 (82 percent) participants reaching the ATP III LDL-c targets. Both trials were conducted in participants requiring intensive lipid lowering therapy, with followup durations of 18 and 24 weeks (Table 23; Appendix F, Table F-10). No consistent trend was observed and significant heterogeneity prevented data being pooled ($I^2 = 84$ percent) (Appendix G, Figure G-45). The 24 week trial, in 80 participants compared atorvastatin 20 mg/day and fenofibrate 200 mg/day with atorvastatin 20 mg/day in participants with combined hyperlipidemia and type II diabetes mellitus, and had a significant odds ratio of 9.75 (95% CI 1.16, 82.11) favoring combination therapy.¹⁶¹ In contrast, the 18 week trial comparing rosuvastatin 5 to 10 mg/day plus fenofibrate

200mg/day with rosuvastatin 40 mg/day monotherapy in 163 evaluable participants with diabetes mellitus, showed a nonsignificant odds ratio of 0.49 (95% CI 0.20, 1.22).¹²⁵ Only the latter trial permitted a comparison of lower dose statin plus fenofibrate with higher dose monotherapy using the same statin, or provided data for this comparison in those requiring intensive lipid lowering therapy.¹²⁵ In this study participants on combination therapy received fixed doses of medications and participants receiving monotherapy had their medication dose increased every six weeks if LDL-c cholesterol remained above 50 mg/dL. All participants had diabetes mellitus at baseline (Appendix G, Figure G-45).

LDL-c, percentage mean change from baseline. Three trials of 12 to 18 weeks duration randomizing 904 evaluable participants yielded relevant data but because of substantial statistical heterogeneity ($I^2 = 82$ percent) data were not pooled (Table 24; Appendix G, Figure G-46).^{120,125,145} One trial in a North America population, 90 percent of European descent, with prior use of statins showed a statistically significant difference in means of -5.4 percent (95% CI -8.39, -2.41) in favor of the statin plus fenofibrate combination.¹²⁰ Results were similar, but not statistically significant, in two trials exclusively in participants requiring intensive lowering therapy because of diabetes mellitus, with a pooled mean difference of 4.82 percent (95% CI -0.35, 9.99) (Appendix G, Figure G-47).^{125,145} Across the three trials, only one permitted comparison of lower dose rosuvastatin (10 mg/day) plus fenofibrate (200mg/day) with higher dose rosuvastatin (40 mg/day) monotherapy in 104 evaluable participants.¹²⁵ A nonsignificant mean difference of 4.5 percent (95% CI -4.1, 13.1) was observed (Table 24; Appendix F, Table F-11).

HDL-c, percentage mean change from baseline. Three trials with followup duration of 12 to 18 weeks in 964 evaluable participants yielded a statistically significant mean difference of 7.44 percent (95% CI 4.95, 9.92) (Table 25; Appendix F, Table F-12) favoring the statin plus fenofibrate combination.^{120,125,145} Two trials were exclusively in participants with diabetes mellitus,^{125,145} and two were in participants with prior use of statins.^{120,145} All three trials compared identical statins in combination and monotherapy, and all but one¹²⁵ investigated simvastatin 20 mg/day. Doses of fenofibrate were 200 mg/day. Pooled mean differences for the two trials conducted in participants requiring intensive lipid lowering therapy were 5.18 percent (95% CI 1.23, 9.11) (Table 19).^{125,145} One trial permitted comparison of lower dose statin in combination therapy with higher dose monotherapy using the same statin.¹²⁵ In the trials in participants with diabetes mellitus, fixed dose treatment with rosuvastatin 10 mg/day plus fenofibrate 200 mg/day was compared with conditionally dosed rosuvastatin up to 40 mg/day, over 18 weeks. LDL-c mean percentage difference between treatments was 4.81 percent (95% CI -0.56, 10.18) (Table 25).

TC:HDL-c ratio, percentage mean change from baseline. A single trial in participants requiring intensive lipid lowering therapy because of diabetes mellitus compared fixed lower dose rosuvastatin 10 mg/day in combination with fenofibrate (200mg/day) with conditionally dosed rosuvastatin up to 40 mg/day monotherapy, in 104 evaluable participants. The nonsignificant mean difference was -2.7 percent (95% CI -10.46, 5.06) (Table 26; Appendix F, Table F-13).¹²⁵

Harms and Treatment Adherence

Comparing statin plus fibrate versus statin monotherapy (lower dose vs. higher dose and various statin doses)

Participants with at least one adverse event. Three trials of 12 to 52 weeks duration in 362 evaluable participants reported 90 adverse events, but because of substantial statistical heterogeneity ($I^2 = 60$ percent) data were not pooled (Table 27). No consistent trend was observed. One 52 week trial compared fluvastatin 80 mg/day plus fenofibrate 200 mg/day with fluvastatin 80 mg/day in 48 evaluable participants of European descent with established coronary artery diseases and prior use of statins. The authors reported a nonsignificant odds ratio of 1.43 (95% CI 0.22, 9.44) favoring monotherapy based on 5 events.¹²³ A second trial in 168 participants with followup duration of 18 weeks, comparing rosuvastatin 5 to 10 mg/day plus fenofibrate 200mg/day with rosuvastatin 40 mg/day monotherapy in participants with diabetes mellitus, yielded a nonsignificant odds ratio of 0.73 (95% CI 0.34, 1.57) favoring monotherapy based on 38 events.¹²⁵ A third 12 week trial comparing pravastatin 40 mg/day plus gemfibrozil 1200 mg/day with pravastatin 40 mg/day in 146 evaluable participants yielded a significant odds ratio of 2.42 (95% CI 1.18, 4.99) favoring monotherapy based on 47 events (Appendix F, Table F-16).¹³⁴ As described here, only one of the described trials compared lower dose statin plus fenofibrate with higher dose monotherapy.¹²⁵

Participants withdrawing due to adverse events. Five trials of 12 to 52 weeks duration in 1269 evaluable participants reported 41 withdrawals due to adverse events, but because of substantial statistical heterogeneity ($I^2 = 56$ percent) data were not pooled (Table 27). With low event rates across trials, no trial showed a significant difference in odds between groups. Point estimates for odds ranged from 0.29 to 7.22. One trial, with the smallest sample size, did not register any event over 24 weeks of followup. Although no significant trend in results was observed across most of the prestated heterogeneity covariates, Durrington et al.'s¹²⁵ was the only trial demonstrating a nonsignificantly higher proportion of participants withdrawing due to adverse events in a monotherapy arm that employed rosuvastatin 40 mg/day (Appendix F, Table F-16).

Participants with AST and/or ALT above 3 times the upper limit of normal, and/or hepatitis. In four trials of 18 to 54 weeks, in 841 evaluable participants, 11 cases of elevated AST/ALT above three times the upper limit were reported (Table 27; Appendix F, Table F-16).^{50,125,160,161} One trial, in 80 participants, compared atorvastatin 20 mg/day plus fenofibrate 200 mg/day with atorvastatin 20 mg/day in participants with combined hyperlipidemia and diabetes mellitus. No participants had any element of the composite outcome during 24 weeks of followup.¹⁶¹ Three trials of 18 to 54 weeks duration, in 761 evaluable participants, could be meta-analyzed and yielded a nonsignificant pooled odds ratio of 2.38 (95% CI 0.41, 14.0) favoring monotherapy based on 11 events (Table 27).^{50,125,160} In a single trial in 168 evaluable participants comparing rosuvastatin plus fibrate with higher dose rosuvastatin monotherapy, six participants in the combination therapy experienced AST/ALT above three times the upper limit of normal, yielding a nonsignificant estimable odds ratio of 6.35 (95% CI 0.35, 114.85) favoring monotherapy (Table 27).

Participants with myalgia. In six trials of 12 to 104 weeks, 32 cases of myalgia were reported in 1439 evaluable participants (Table 27; Appendix F, Table F-16). One trial comparing

atorvastatin 20 mg/day plus fenofibrate 200 mg/day with atorvastatin 10 mg/day in two of its four arms, reported no cases of myalgia among participants during 12 weeks followup.¹⁹⁵ Data on 1389 evaluable participants could be meta-analyzed without evident heterogeneity (Table 27).^{50,120,125,134,188,195} A nonsignificant odds ratio of 1.17 (95% CI 0.52, 2.62) was observed, and asymmetry was not evident on the funnel plot (Appendix G, Figure G-49). Two trials using different statins permitted a comparison of lower dose statin plus fenofibrate with higher dose monotherapy using the same statin.^{125,195} One trial compared fixed dosed rosuvastatin 5 to 10 mg/day plus fenofibrate 200mg/day with a conditionally titrated dose of rosuvastatin 40 mg/day monotherapy in 168 evaluable participants with diabetes mellitus, yielding an estimable nonsignificant odds ratio of 1.39 (95% CI 0.14, 13.71) based on four cases of myalgia (Table 27).¹²⁵ Another trial compared lower dose simvastatin 20 mg/day plus fenofibrate (200 mg/day) with higher dose simvastatin (40 mg/day) monotherapy in 50 evaluable participants of South Asian descent, yielding a nonsignificant estimable odds ratio of 0.18 (95% CI 0.01, 4.04) based on two cases of myalgia (Table 27).¹⁹⁵

Participants with CPK above 10 times the upper limit of normal. Five trials in 1,199 evaluable participants reported one event of CPK above 10 times the upper limit of normal (Table 27; Appendix F, Table F-16). Four trials reported no events in participants during 12 to 24 weeks followup.^{125,134,145,161} One trial of 12 weeks duration in 605 evaluable participants reported one event of elevated CPK and a nonsignificant estimable odds ratio of 1.51 (95% CI 0.06, 37.22) (Table 27).¹²⁰ Lower dose rosuvastatin plus fibrate was compared with higher dose monotherapy in one trial with no events.¹²⁵

Participants with rhabdomyolysis. Three trials in 951 evaluable participants reported no events of rhabdomyolysis during a followup of 12 weeks (Table 27; Appendix F, Table F-16).^{120,134,145}

Key Question 3: Compared with higher-dose statins, and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

Table 20. Availability of evidence addressing key question 3 for statin plus fibrate versus statin monotherapy comparison

Condition	All-cause mortality	Vascular Death	Participants reaching ATP III LDL-c targets	LDL-c	HDL-c	TC:HDL-c ratio	Non-HDL-c	TG
LDL-c \geq 190 mg/dL	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
Diabetes mellitus	√	No available evidence	√	√	√	√	√	√
Established vascular disease	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
Cerebrovascular disease	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
African descent	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
Asian descent	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
Hispanic descent	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
Females	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
Age 80 years or more	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	

Abbreviations: HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, TC = total cholesterol, TG = triglycerides

Clinical Outcomes

Comparing statin plus fibrate versus statin monotherapy (lower dose vs. higher dose and various statin doses)

All-cause mortality.

Participants with diabetes mellitus. One trial with estimable data on all-cause mortality permitted the comparison of lower dose rosuvastatin 5 to 10 mg/day plus fenofibrate 200 mg/day with higher dose rosuvastatin 40 mg/day monotherapy in 166 evaluable participants with diabetes mellitus.¹²⁵ Those on combination therapy received fixed doses of medications, while participants on monotherapy had their medication dose increased every six weeks if LDL-c cholesterol remained above 50 mg/dL. A nonsignificant odds ratio of 0.46 (95% CI 0.03, 7.57)

was observed (Table 21; Appendix F, Table F-9). No studies reported data on vascular death for participants with diabetes mellitus.

LDL-c Targets and Other Surrogate Markers

Comparing statin plus fibrate versus statin monotherapy (lower dose vs. higher dose and various statin doses)

Participants attaining ATP III LDL-c goals.

Participants with diabetes mellitus. In two trials of 18 to 24 weeks duration, in 240 evaluable participants, 197 participants reaching ATP III LDL-c targets (Table 23; Appendix F, Table F-10). No consistent trend was observed and significant heterogeneity prevented data being pooled ($I^2 = 84$ percent) (Appendix G; Figure G-45). The 24-week trial in 80 participants compared atorvastatin 20 mg/day plus fenofibrate 200 mg/day with atorvastatin 20 mg/day in participants with combined hyperlipidemia and type II diabetes mellitus, yielding a significant estimable odds ratio of 9.75 (95% CI 1.16, 82.11) favoring combination therapy.¹⁶¹ In contrast, a 18-week trial comparing rosuvastatin 5 to 10 mg/day plus fenofibrate 200mg/day with rosuvastatin 40 mg/day monotherapy in 163 evaluable participants with diabetes mellitus, showed a nonsignificant odds ratio of 0.50 (95% CI 0.20, 1.24) (forest plot).¹²⁵ The latter trial compared lower dose rosuvastatin plus fenofibrate with higher dose rosuvastatin monotherapy (Table 23).¹²⁵

LDL-c, percentage mean change from baseline.

Participants with diabetes mellitus. Two trials of 12 to 18 weeks duration, in 304 evaluable participants, yielded a pooled mean difference of 4.82 percent (95% CI -0.35, 9.99) (Table 24; Appendix F, Table F-11; Appendix G, Figure G-48).^{125,145} One trial compared lower dose rosuvastatin plus fenofibrate with higher dose rosuvastatin monotherapy, yielding a nonsignificant mean difference of 4.5 percent (95% CI -4.10, 13.10) (Figure G-48, Table 24).¹²⁵

HDL-c, percentage mean change from baseline.

Participants with diabetes mellitus. Two trials of 12 to 18 weeks in 364 evaluable participants yielded a significant pooled mean difference of 5.17 percent (95% CI 1.23, 9.11) (Table 25; Appendix F, Table F-12).^{125,145} One trial compared lower dose rosuvastatin plus fenofibrate with higher dose rosuvastatin monotherapy, yielding a nonsignificant mean difference of 4.81 percent (95% CI -0.56, 10.18) (Table 25).¹²⁵

TC:HDL-c ratio, percentage mean change from baseline.

Participants with diabetes mellitus. One trial comparing lower dose rosuvastatin 10 mg/day plus fenofibrate 200mg/day with higher dose rosuvastatin 40 mg/day monotherapy in 104 evaluable participants yielded a nonsignificant mean difference of -2.7 (95% CI -10.46, 5.06) (Table 26; Appendix F, Table F-12).¹²⁵

Non-HDL-c, percentage mean change from baseline.

Participants with diabetes mellitus. One trial comparing the simvastatin 20 mg/day plus fenofibrate 160mg/day with simvastatin 20 mg/day monotherapy in 200 evaluable participants yielded a nonsignificant mean difference of 1.80 (95% CI -3.01, 6.61) (Appendix F, Table F-14).¹⁴⁵

Triglycerides, percentage mean change from baseline.

Participants with diabetes mellitus. One trial comparing lower dose rosuvastatin 10 mg/day plus fenofibrate 200mg/day with higher dose rosuvastatin 40 mg/day monotherapy in 154 evaluable participants yielded a significant mean difference of -13.57 (95% CI -24.16, -2.98) favoring fibrate-statin combination therapy.¹²⁵

Strength of Evidence

The strength of the available evidence was assessed as GRADE (Grading of Recommendations Assessment, Development and Evaluation)²²⁵ for the key outcomes all-cause mortality, vascular death, serious adverse events and achieving ATP-III target LDL-c. Results generated using the GRADEpro software presented in Tables H-12 to H-16 (Appendix H) are summarized as follows:

1. Based on a single study in participants requiring intensive lipid lowering therapy, GRADE was “very low” for all cause mortality and participants reaching ATP III LDL-c goals for the combination of lower dose statin plus fenofibrate compared to higher dose statin (Appendix H, Table H-12).
2. Based on studies in participants requiring intensive lipid lowering therapy and comparing the combination of any dose statin plus fibrate to any dose statin, GRADE was “very low” for all cause mortality (1 trial), serious adverse events (1 trial) and participants reaching ATP III LDL-c goals (2 trials) (Appendix H, Table H-13).
3. Based on studies in participants with diabetes mellitus and comparing the combination of any dose statin plus fibrate to any dose statin,, GRADE was “very low” for all cause mortality (1 trial) and participants reaching ATP III LDL-c goals (2 trials) (Appendix H, Table H-14).
4. Based on a one study in participants followed up for more than 24 weeks, GRADE was “very low” for all cause mortality, serious adverse events and participants reaching ATP III LDL-c goals for the combination of any dose statin plus fibrate compared to any dose statin (Appendix H, Table H-15).
5. Based on studies in participants regardless of baseline risk and comparing the combination of any dose statin plus fibrate to any dose statin, GRADE was “very low” for all cause mortality (3 trials), serious adverse events (2 trials) and participants attaining ATP III LDL-c goals (2 trials) (Appendix H, Table H-16).

Evidence Summary Tables: Statin Plus Fibrate Combination Therapy versus Statin Monotherapy

Table 21. Quantitative syntheses of longer-term outcomes data (clinical, serious adverse events and cancer) for fibrate-statin combination therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant intervention groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
All-cause mortality						
All trials ^{125,134,188}	3	339	3	0.28*	0.03	2.97
<i>Rosuvastatin</i>						
Lower dose statin in combination therapy versus higher dose monotherapy ¹²⁵	1	166	2	0.46	0.03	7.57
Participants requiring intensive lipid lowering therapy, due to diabetes mellitus ¹²⁵						
Fatal Myocardial Infarction						
All trials ^{123,134}	2	194	1	0.31	0.01	7.77
Myocardial Infarction						
Non-fatal myocardial infarction ¹²³	1	48	0			
Any myocardial infarction ¹²³	1	48	0			
Acute coronary syndrome						
All trials ¹²³	1	48	0			
Serious Adverse Event(s)						
All trials ^{120,123}	2	652	17	1.20	0.42	3.46

* Peto Odds Ratio; **Abbreviation:** CI = 95% confidence interval

Table 22. Summary of non-randomized evidence on fluvastatin plus gemfibrozil combination therapy versus gemfibrozil monotherapy

Trial	Design Duration Downs and Black score	Patients (LDL-c mg/dL)	Monotherapy Dose (mg/day)	Combination Therapy Dose (mg/day)	Results	Limitations	Applicability	Conclusion
van Dam (2001) ⁸⁷ Multicenter/ Europe Pharmaceutical Industry	CCT Conditional dose titration and fibrate addition to statin therapy over 9 months Stable doses for 1 year 15/28	1501 (N evaluabe = 1077) outpatients with or without CHD TG < 400 mg/dL Mean baseline LDL-c = 186 mg/dL	Fluvastatin (20, 40 and 80 mg)	Fluvastatin plus (80); Gemfibrozil (1200)	All-cause mortality: F20 = 1/77 F40 = 4/237 F80 = 5/601 F80+G1200 = 1/162 Other clinical outcomes of interest, SAE and cancer not reported	Unlike statin monotherapy groups, patients on combination therapy had combined hyperlipidemia (additional hypertriglyceridemia). Those on statin monotherapies differed in LDL-c target goals and degree of dyslipidemia. Study was not powered for the outcome of mortality	Narrow eligibility criteria, lack of reporting of important clinical outcomes, 1 year stable dose followup, and low event rates are suggestive of low applicability	Results are inconclusive given low event rate and lack of statistical significance

Abbreviations: CCT = controlled clinical trial, F = fluvastatin, G = gemfibrozil, LDL-c = low density lipoprotein cholesterol, N = number, SAE = serious adverse events, TG = triglycerides

Table 23. Quantitative syntheses of participants attaining ATP III LDL-c targets data, for fibrate-statin combination therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Relative probability of attaining ATPIII LDL-c goal						
All trials						
All participants with diabetes mellitus Participants requiring intensive lipid lowering therapy ^{125,161} <i>Rosuvastatin</i>	2	240	197	-	-	-
Lower dose statin in combination therapy versus higher dose monotherapy ¹²⁵	1	163	126	0.49	0.20	1.22

Abbreviations: ATP III = Third Adult Treatment Panel of the National Cholesterol Education Program, CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

Table 24. Quantitative syntheses of LDL-c data for fibrate-statin combination therapy compared with statin monotherapy

	Number of trials	Number of participants in relevant treatment groups	Point Estimate	Lower CI	Upper CI
Difference in mean LDL-c percentage change from baseline (%)					
All trials ^{120,125,145}	3	904	-	-	-
Lower dose statin in combination versus higher dose monotherapy ¹²⁵	1	104	4.50	-4.10	13.10
Participants in need of intensive lipid lowering therapy, all with diabetes mellitus ^{125,145}	2	304	4.82	-0.35	9.99

Abbreviations: CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

Table 25. Quantitative syntheses of HDL-c data, for fibrate-statin combination therapy compared with statin monotherapy

	Number of trials	Number of participants in relevant treatment groups	Point Estimate	Lower CI	Upper CI
Difference in mean HDL-c percentage change from baseline (%)					
All trials 120,125,145 Rosuvastatin Lower dose statin in combination therapy versus higher dose monotherapy	3	964	7.44	4.95	9.92
Participants requiring intensive lipid lowering therapy, all with diabetes mellitus 125	1	164	4.81	-0.56	10.18
Participants in need of intensive lipid lowering therapy, all with diabetes mellitus 125,145	2	364	5.18	1.23	9.12

Abbreviations: CI = 95% confidence interval, HDL-c = high density lipoprotein cholesterol

Table 26. Quantitative syntheses of total cholesterol:HDL-c ratio data, for fibrate-statin combination therapy compared with statin monotherapy

	Number of trials	Number of participants in relevant treatment groups	Point Estimate	Lower CI	Upper CI
Difference in mean TC:HDL-c percentage change from baseline (%)					
All trials <i>Rosuvastatin</i> Lower dose statin in combination therapy versus higher dose monotherapy ¹²⁵	1	104	-2.70	-10.46	5.06
All participants with diabetes mellitus Participants in need of intensive lipid lowering therapy ¹²⁵					

Abbreviations: CI = 95% confidence interval, HDL-c = high density lipoprotein cholesterol, TC = total cholesterol

Table 27. Quantitative syntheses of short-term harms and treatment adherence data for fibrate-statin combination therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Participants with adverse events						
All trials ^{123,125,134}	3	362	90	-	-	-
<i>Rosuvastatin</i>						
Lower dose statin in combination therapy versus higher dose monotherapy ¹²⁵	1	168	38	0.73	0.34	1.57
Withdrawals due to adverse events						
All trials ^{50,120,125,134,161}	5	1269	41	-	-	-
<i>Rosuvastatin</i>						
Lower dose statin in combination therapy versus higher dose monotherapy ¹²⁵	1	168	5	0.29	0.05	1.82
AST and/or ALT ≥ 3 times the upper limit of normal, and/or hepatitis						
All trials ^{50,125,160,161}	4	841	11	2.38	0.41	14.00
<i>Rosuvastatin</i>						
Lower dose statin in combination therapy versus higher dose monotherapy ¹²⁵	1	168	6	6.35	0.35	114.85
Myalgia						
All trials ^{50,120,125,134,188,195}	6	1439	31	1.17	0.52	2.62
<i>Rosuvastatin</i>						
Lower dose statin in combination therapy versus higher dose monotherapy ¹²⁵	1	168	4	1.39	0.14	13.71
<i>Simvastatin</i>						
Lower dose statin in combination therapy versus higher dose monotherapy ¹⁹⁵	1	50	2	0.18	0.01	4.04
CPK ≥ 10 times the upper limit of normal						
All trials ^{120,125,134,145,161}	5	1199	1	4.49	0.07	286.36
<i>Rosuvastatin</i>						
Lower dose statin in combination therapy versus higher dose monotherapy ¹²⁵	1	168	0	-	-	-
Rhabdomyolysis (investigator defined)						
All trials ^{120,134,145}	3	951	0	-	-	-

Abbreviations: ALT = alanine transaminase, AST = aspartate transaminase, CI = 95% confidence interval, CPK = creatinine phosphokinase

Statin Plus Niacin Combination Therapy Versus Statin Monotherapy

Overview of Included Studies

A total of 16 randomized controlled trials evaluated relative efficacy and/or harms of the combination of niacin plus a statin compared with statin monotherapy, in a total of 2,731 participants (Table 3; Appendix F, Table F-17 to F-23). None of the included non-randomized studies addressed this particular comparison. Nine of the 16 randomized trials had more than one associated journal published or FDA report (Table 5). Data reported in the two FDA reports^{104,105} are similar to data presented in two published manuscripts.^{128,182} The similarities included the inclusion/exclusion criteria, number of patients randomized and outcomes. However, since no direct connection could be found in the reports to confirm that they are the same trial, they were included as separate trial reports.

Ten trials were conducted in multiple centers,^{49,104,105,128,139,150,155,170,171,182} and six in a single center.^{162,183,184,189,196,197} There were no trials exclusively in females, or participants of Asian, Hispanic, and/or African descent.

Reporting of participants' ethnic background was as follows:

- 10 trials reported a mean of 85 percent of participants of European descent (range 75 to 94 percent)
- Three trials reported a mean of 3 percent of participants of Asian descent (range 2 to 4 percent)
- Six trials reported a mean of 8 percent of participants of Hispanic descent (range 0 to 22 percent)
- Four trials reported a mean of 9 percent of participants of African descent (range 5 to 15 percent)

Trial duration ranged from six to 52 weeks, with an average of 23 weeks. On average 35 percent of participants were women (range 7 to 50 percent). The average of mean ages of participants was 58 years (range of mean age 51 to 67 years). Nine trials recruited solely from outpatient settings,^{49,104,105,128,139,155,183,196,197} while seven did not report recruitment setting.

Of these sixteen trials, only three were exclusively in participants requiring intensive lipid lowering therapy (i.e. participants with established vascular disease and/or cerebro-vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL).^{162,196,197}

Additionally, one trial provided data on the subgroup for participants with established vascular disease.⁴⁹

The mean Jadad score was 2.6 (range, 1 to 5). Five trial reports described an appropriate method of randomization,^{104,105,171,183,196} while seven reported an appropriate method of double blinding.^{104,105,128,150,171,182,196} Two of these trials with an appropriate method of double blinding added immediate release Niacin 50mg/ day in the monotherapy arms to protect the blinding.^{150,171} Allocation concealment was reported to be adequate in four trials.^{104,105,171,196}

Twelve of sixteen trials were partially or completely sponsored by the pharmaceutical industry,^{49,128,139,150,155,162,170,171,182-184,197} while this was not reported or unclear for three trials.^{104,105,189}

All trials were conducted in North America.

Key Question 1: For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits, and rates of serious adverse events of coadministration of different lipid-modifying agents (i.e. a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

Table 28. Evidence addressing key question 1 for statin plus niacin versus statin monotherapy comparison

Outcomes	Evidence availability	Key points of evidence synthesis
All-cause mortality	Yes	No significant difference was observed for the outcome in trials in mixed populations (OR 1.08; 95% CI 0.17, 6.72) or in participants requiring intensive lipid lowering therapy (OR 1.84; CI 0.16, 20.76)
Vascular death	Yes	No significant difference was observed for the outcome in trials in mixed populations (OR 0.53; 95% CI 0.03, 8.64) or in participants requiring intensive lipid lowering therapy (no deaths occurred in either group)
Fatal myocardial infarction (MI)	Yes	No significant difference was observed for the outcome (OR 4.64; 95% CI 0.08, 283.78)
Non-fatal MI	No	
Any or unspecified MI	No	
Acute coronary syndrome (ACS) (encompassing unstable angina or acute MI)	Yes	No significant difference was observed for the outcome in (OR 0.91; 95% CI 0.12, 6.62)
Any cerebrovascular event	No	
Hemorrhagic stroke	No	
Ischemic stroke	No	
Any or unspecified stroke	Yes	No significant difference was observed for the outcome in one trial (OR 0.12; 95% CI 0.00, 6.21)
Transient ischemic attack (TIA)	No	
Carotid endarterectomy (CEA)	No	
Percutaneous coronary interventional procedure (PCI)	Yes	No significant difference was observed for the outcome in one trial (OR 3.78; 95% CI 0.41, 34.68)
Coronary artery bypass graft procedure (CABG)	No	
Any or unspecified revascularization procedure	No	
Serious adverse events	Yes	No significant difference was observed for the outcome (OR 1.29; 95% CI 0.44, 3.80)
Cancer	Yes	No significant difference was observed for the outcome (OR 0.10; 95% CI 0.00, 2.20)

Abbreviations: ACS = acute coronary syndrome, CABG = coronary artery bypass graft, CEA = carotid endarterectomy, MI = myocardial infarction, PCI = percutaneous coronary intervention, SAE = serious adverse event

Study Design and Population Characteristics

A total of eight trials, one of crossover design, randomizing 1481 participants compared niacin plus a statin with statin monotherapy and reported one or more of clinical outcomes, serious adverse events and cancer (Table 31; Appendix F, Table F-17).^{104,105,128,150,170,171,196,197}

There were no trials exclusively in females or participants of Asian, Hispanic, or African descent.

Reporting of participants' ethnic background was as follows:

- Six trials reported a mean of 84 percent of participants of European descent (range 75 to 90 percent)
- Three trials reported a mean of 3 percent of participants of Asian descent (range 2 to 4 percent)
- Five trials reported a mean of 9 percent of participants of Hispanic descent (range 1 to 22 percent)
- Three trials reported a mean of 8 percent of participants of African descent (range 5 to 13 percent)

Trial duration ranged from 12 to 52 weeks with an average of 28 weeks. Although no trial totally excluded females, on average 33 percent of participants were women (range 7 to 49 percent). The average of mean ages of participants was 59 years (range of mean age 53 to 67 years). Five trials recruited outpatients,^{104,105,128,196,197} while three trials did not report recruitment setting. The mean Jadad score was 3.4 (range, 1 to 5) and four trials had adequate allocation concealment.^{104,105,171,196}

Of these eight trials, only three were exclusively in participants requiring intensive lipid lowering therapy (i.e. participants with established vascular disease and/or cerebro-vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL).^{162,196,197} Additionally, one trial provided data on the subgroup for participants with established vascular disease.⁴⁹

Long-Term Efficacy, Serious Adverse Events, and Cancer

Comparing statin plus niacin versus statin monotherapy (lower dose vs. higher dose and various statin doses)

All-cause mortality. Incidence of all cause mortality for participants requiring intensive lipid-modifying therapy (participants with established vascular disease), using various statins and doses, was reported for one trial with a 52-week followup period, with adequate allocation concealment (Table 31).¹⁹⁶ There were no statistically significant differences between the incidence in the two groups, with an odds ratio of 1.84 (95% CI 0.16, 20.76).

For all trials, using various statins and doses, all-cause mortality was reported for six trials,^{104,105,150,170,171,196} four of which were 24 weeks or longer in duration.^{105,150,171,196} Of these four trials, two provided analyzable data (Table 31; Appendix G, Figure G-50).^{105,196} Data from the other trials were not analyzable because no deaths were recorded during the followup period.^{104,150,170,171}

In addition, four trials were considered to have adequate allocation concealment,^{104,105,171,196} three of which were 24 weeks or longer in duration.^{105,171,196} Two provided analyzable data.^{105,196} Pooling of these two trials demonstrated no significant

differences in mortality between the two groups, with an odds ratio of 1.08 (95% CI 0.17, 6.72) based on five events.

There was no evidence for the comparative analysis of a specific lower dose statin in combination with niacin versus higher dose of the same statin monotherapy in all trial populations.

Vascular death. The incidence of vascular death was reported for one trial, for participants requiring intensive lipid-modifying therapy (Table 31) with an unclear form of allocation concealment and a followup duration of 12 weeks.¹⁹⁷ Participants had established vascular disease and were receiving various statins and doses. No deaths were recorded during the followup period and so the outcome was not analyzable.

For all trials, using various statins and doses, vascular death was reported for two trials,^{128,197} one of which had a followup duration of 24 weeks or more (Table 31).¹²⁸ Both trials had an unclear form of allocation concealment. One study had no analyzable data (no events in both groups),¹⁹⁷ while the other demonstrated no statistically significant difference in the incidence between the two groups, with an odds ratio of 0.53 (95% CI 0.03, 8.64) based on two events.¹²⁸

There was no evidence for the comparative analysis of a specific lower dose statin in combination with niacin versus higher dose of the same statin monotherapy in all trial populations.

Fatal myocardial infarction. In all trial populations, fatal myocardial infarction was reported for two trials,^{105,197} using various statins and doses; one of which had a followup duration of 28 weeks.¹⁰⁵ Analyzable data was only provided for one trial,¹⁰⁵ which demonstrated no statistically significant difference in the incidence between the two groups, with an odds ratio of 4.64 (95% CI 0.08, 283.78), based upon one event in both groups (Table 31).

There was no evidence for the comparative analysis of a specific lower dose statin in combination with niacin versus higher dose of the same statin monotherapy in all trial populations.

Any or unspecified stroke. Stroke was reported for only one trial with a followup duration of 52 weeks in participants using various statins and doses (Table 31).¹⁹⁶ The study demonstrated no statistically significant difference in the incidence between the two groups, with an odds ratio of 0.12 (95% CI 0.00, 6.21) based upon one event in both groups.

There was no evidence for the comparative analysis of a specific lower dose statin in combination with niacin versus higher dose of the same statin monotherapy in all trial populations.

Acute coronary syndrome. In all trial populations, acute coronary syndrome was reported for one trial with a followup duration of 52 weeks in participants using various statins and doses (Table 31).¹⁹⁶ The study demonstrated no statistically significant difference in the incidence between the two groups, with an odds ratio of 0.91 (95% CI 0.12, 6.62) based on four events in both groups.

There was no evidence for the comparative analysis of a specific lower dose statin in combination with niacin versus higher dose of the same statin monotherapy in all trial populations.

Percutaneous coronary intervention. Percutaneous coronary intervention was reported for one trial with a followup duration of 52 weeks in participants using various statins and doses (Table 31).¹⁹⁶ The study demonstrated no statistically significant difference in the incidence between the two groups, with an odds ratio of 3.78 (95% CI 0.41, 34.68) based upon five events.

There was no evidence for the comparative analysis of a specific lower dose statin in combination with niacin versus higher dose of the same statin monotherapy in all trial populations.

Serious adverse events. In all trial populations, serious adverse events were reported for five trials,^{104,105,150,170,171} three of which had a followup duration of 28 weeks or more^{105,150,171} (Table 31; Appendix G, Figure G-51). Pooling of the trial data demonstrated no statistically significant difference in the incidence between the two groups based upon sixteen events (OR 1.29; 95% CI 0.44, 3.80). Furthermore, in the long-term trials,^{105,150,171} there was no statistically significant difference in the incidence of participants with a serious adverse event between the two groups, with an odds ratio of 1.00 (95% CI 0.26, 3.86) based on seven events.

There was no evidence for the comparative analysis of a specific lower dose statin in combination with niacin versus higher dose of the same statin monotherapy in all trial populations.

Cancer. In all trial populations, cancer was reported for one trial (Table 31).¹⁰⁵ The study followed up 175 participants for 28 weeks. The data demonstrated no statistically significant difference in the incidence between the two groups, with an odds ratio of 0.10 (95% CI 0.00, 2.20) based upon two events.

There was no evidence for the comparative analysis of a specific lower dose statin in combination with niacin versus higher dose of the same statin monotherapy in all trial populations.

Key Question 2: Do these regimens differ in reaching LDL-c targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

Table 29. Evidence addressing key question 2 for statin plus niacin versus statin monotherapy comparison

Outcomes	Evidence availability	Key points of evidence synthesis
Patients attaining ATP III LDL-c targets	Yes	No significant difference was observed in trials in participants requiring intensive lipid lowering therapy (OR 1.51; 95% CI 0.56, 4.08). Results for participants from mixed populations were not pooled due to substantial heterogeneity.
LDL-c	Yes	Compared with monotherapy, no significant difference was observed for the outcome in trials in participants requiring intensive lipid lowering therapy (MD 0.00 %; 95% CI -6.51, 6.51). Results for participants from mixed populations were not pooled due to substantial heterogeneity.
HDL-c	Yes	A significant difference was observed for the outcome in trials comprising of participants requiring intensive lipid lowering therapy favoring combination therapy (MD 13.00 %; 95% CI 6.01 , 20.00). Results for participants from mixed populations were not pooled due to substantial heterogeneity.
TC:HDL ratio	Yes	Data from one trial demonstrated significantly greater reduction favoring niacin plus statin combination therapy (MD -6.00 %; 95% CI -9.60, -2.40) in a mixed population.
Measure(s) of atherosclerosis	Yes	Niacin plus statin combination therapy was not significantly different from monotherapy in reducing carotid-intima media thickness
Treatment adherence	Yes	In one trial comparing niacin plus 10 mg rosuvastatin versus 40 mg rosuvastatin there was more favorable adherence to the combination medication (OR 0.40; 95% CI 0.19, 0.84). No significant difference in the incidence was observed in reports of treatment adherence with various statins and doses (OR 0.79; 95% CI 0.50, 1.27).
Total adverse events	Yes	In one trial comparing niacin plus rosuvastatin 10 mg/day versus rosuvastatin 40 mg/day there was better adherence to the combination medication (OR 1.94; 95% CI 0.79, 4.78). Results from trials with various statins and doses were not pooled due to substantial heterogeneity.
Withdrawal due to adverse events	Yes	The odds of withdrawal due to adverse events was significantly higher following niacin plus statin combination therapy than statin monotherapy (OR 2.38; 95% CI 1.63, 3.47).
Elevated serum AST and/or ALT > 3 times ULN and/or hepatitis	Yes	The incidence of these outcomes was similar (OR 1.39; 95% CI 0.36, 5.36).
Myalgia	Yes	Compared with monotherapy, in mixed populations the incidence of these outcomes was similar following niacin plus statin combination therapy than statin monotherapy (OR 0.45; 0.19, 1.07).
CPK > 10 times ULN	Yes	There was no reported incidence
Rhabdomyolysis	Yes	There was no reported incidence

Abbreviations: ALT = alanine transferase, AST = aspartate transferase, ATP III = Third Adult Treatment Panel of the National Cholesterol Education Program, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, TC = total cholesterol

Study Design and Population Characteristics

A total of fifteen trials, none of crossover design, randomizing 2677 participants compared niacin plus statin therapy with statin monotherapy and reported one or more of the following outcomes: participants reaching LDL-targets and/or other surrogate markers, short-term side effects, tolerability, and/or adherence to treatment (Table 32 to 37; Appendix F, Table F-18 to F-23).^{49,104,105,128,139,150,155,162,170,171,182-184,189,196} There were no trials exclusively in females, or participants of Asian, Hispanic, and/or African descent.

Reporting of participants' ethnic background was as follows:

- Ten trials reported a mean of 85 percent of participants of European descent (range 75 to 94 percent)
- Three trials reported a mean of 3 percent of participants of Asian descent (range 2 to 4 percent)
- Five trials reported a mean of 9 percent of participants of Hispanic descent (range 1 to 22 percent)
- Four trials reported a mean of 9 percent of participants of African descent (range 5 to 15 percent)

Trial duration ranged from six to 52 weeks, with an average of 23 weeks. Although no trial totally excluded the female gender, on average 37 percent of participants were women (range, 9 to 50 percent). The average of mean ages of participants was 57 years (range of mean age 51 to 67 years). Eight trials recruited outpatients,^{49,104,105,128,139,155,183,196} while seven trials did not report recruitment setting. The mean Jadad score was 2.7 (range 1 to 5) and four trials had adequate allocation concealment.^{104,105,171,196}

Of these fifteen trials, two trials were exclusively in participants requiring intensive lipid lowering treatment (i.e. participants with established vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL).^{49,162}

LDL-c Targets and Other Surrogate Markers

Comparing statin plus niacin versus statin monotherapy (lower dose vs. higher dose and various statin doses)

Participants reaching ATP III LDL-c goals. The incidence of participants reaching their ATP-III targets was reported for one trial in participants not in particular need of intensive lipid lowering (Table 32).⁴⁹ This trial compared a fixed dose combination of lovastatin plus extended release niacin with atorvastatin or simvastatin monotherapy. Data was available for a subgroup of participating requiring intensive lipid lowering therapy and demonstrated nonsignificant results. In addition, two balanced pairs of treatment groups for the whole trial were analyzed. Neither of the comparisons yielded any statistically significance between the two groups, but the two comparisons were not pooled because of substantial heterogeneity ($I^2 = 63$ percent).

LDL-c, percentage mean change from baseline. LDL-c percent change from baseline was reported for one trial in participants requiring intensive lipid lowering using various doses of atorvastatin in combination and monotherapy arms (Table 33).¹⁶² No statistically significant difference was noted between the two groups, with a mean difference of 0.00 (95% CI -6.51,

6.51). No trial data was available that compared niacin plus a lower dose statin versus higher dose statin monotherapy in participants requiring intensive lipid lowering.

One study presented data for niacin plus a lower dose statin versus higher dose statin monotherapy in participants not in particular need for intensive lipid lowering comparing extended release niacin 2 g/day plus rosuvastatin 10 mg/day with rosuvastatin 40 mg/day monotherapy (Tables 33).¹⁵⁵ Combination therapy had a significantly higher percent change in LDL-c, with a mean difference of 12.00 percent (95% CI 2.26, 21.74) and therefore favoring monotherapy.

In all trial populations, using various statins and doses, LDL-c percent change from baseline was reported for seven trials (Table 33; Appendix G, Figure G-53).^{104,105,139,155,162,182,184} Pooling of studies was not possible due to substantial heterogeneity ($I^2 = 85$ percent), that may be explained due to the use of various statins and doses. Trials that used similar statins and doses in monotherapy and combination arms demonstrated a significant reductions in percentage LDL-c compared with trials that employed higher dose or potency of statin monotherapy showing no significant difference (Figure 50).^{104,105,182,184}

HDL-c, percentage mean change from baseline. HDL-c percent change from baseline was reported for one trial in participants requiring intensive lipid lowering therapy (Table 34).¹⁶² There was a significant increase in HDL-c in the Niacin plus statin group compared with the statin monotherapy group, with a mean difference of 13.00 percent (95% CI 6.01, 20.00). No trial data was available that compared niacin plus a lower dose statin versus higher dose statin monotherapy in participants requiring intensive lipid lowering.

In all trial populations, one study presented data for niacin plus a lower dose statin versus higher dose statin monotherapy in participants not in particular need for intensive lipid lowering comparing extended release niacin 2 g/day plus rosuvastatin 10 mg/day with rosuvastatin 40 mg/day monotherapy (Tables 34).¹⁵⁵ Combination therapy significantly increased the HDL-c percentage from baseline compared with monotherapy with a mean difference of 13.00 percent (95% CI 6.10, 19.90).

In all trial populations comparing various statins and doses in combination and monotherapy, HDL-c percent change from baseline was available for six trials (Table 34).^{104,105,139,155,162,182} Pooling of the studies was not possible due to substantial heterogeneity ($I^2 = 76$ percent). Trials that used similar statins and doses of lovastatin in monotherapy and combination arms demonstrated a greater percentage increase in HDL-c from baseline with combination therapy,^{104,105,182} compared to trials that used more potent statins in combination and monotherapy. With high doses of rosuvastatin in both treatment arms, no significant change was noted for this outcome.

Total cholesterol:HDL-c ratio, percentage mean change from baseline. No trial data was available for participants requiring intensive lipid lowering. In all trial populations, the TC:HDL-c ratio percent change from baseline was reported for one trial (Table 35).¹³⁹ The TC:HDL-c ratio was significantly lower following niacin plus statin than with statin monotherapy, with a mean difference of -6.00 percent (95% CI -9.60, -2.40).

Measures of atherosclerosis. Carotid intima-media thickness (CIMT) was reported for only one trial, as mean change from baseline in a participant requiring intensive lipid lowering therapy (Table 36).¹⁹⁶ Niacin plus statin combination therapy was marginally more effective than statin

monotherapy in reducing the rate of increase in CIMT over 52 weeks, with a mean difference of -0.03 mm (95% CI -0.06, 0.00).

Harms and Treatment Adherence

Comparing statin plus ezetimibe versus statin monotherapy (lower dose vs. higher dose and various statin doses)

Participants adherent to treatment. In all trial populations, one study presented data for niacin plus a lower dose statin versus higher dose statin monotherapy in participants not in particular need for intensive lipid lowering comparing extended release niacin 2 g/day plus rosuvastatin 10 mg/day with rosuvastatin 40 mg/day monotherapy.¹⁵⁵ Treatment adherence was significantly lower with niacin plus statin than with statin monotherapy, with an odds ratio of 0.40 (95% CI 0.19, 0.84).

In all trials, using various statins and doses, treatment adherence was reported for five trials (Table 37).^{49,139,155,182,196} Pooling of the studies demonstrated no significant difference in the incidence between the groups treated with niacin plus statin compared with statin monotherapy, with an odds ratio of 0.79 (95% CI 0.50, 1.27). Two of the trials had long-term followup of 24 to 52 weeks duration.^{155,196} Pooling of the studies was not possible due to substantial heterogeneity ($I^2 = 59$ percent).

Participants with at least one adverse event. In all trial populations, one study presented data for niacin plus a lower dose statin versus higher dose statin monotherapy in participants not in particular need for intensive lipid lowering comparing extended release niacin 2 g/day plus rosuvastatin 10 mg/day with rosuvastatin 40 mg/day monotherapy.¹⁵⁵ There was no significant difference in the incidence of participants experiencing an adverse event between the combination and monotherapy arms, with an odds ratio of 1.94 (95% CI 0.79, 4.78).

In all trials, using various statins and doses, total participants with adverse events were reported for six trials (Table 37),^{104,105,150,155,171,182} which were not pooled due to substantial heterogeneity ($I^2 = 57$ percent). This heterogeneity could not be explained, however, three of six trials showed significantly more participants experiencing adverse events with statin-niacin combination when compared with monotherapy.

Participants withdrawing due to adverse events. In all trials using various statins and doses, withdrawals due to adverse events was reported for ten trials (Table 37; Appendix G, Figure G-56).^{49,104,105,128,150,170,171,182,189,196} Pooling of the studies demonstrated a significantly higher incidence of withdrawals in the combination group with an odds ratio of 2.38 (95% CI 1.63, 3.47). No trial data was available that compared niacin plus a lower dose statin versus higher dose statin monotherapy.

Participants with AST and/or ALT above three times the upper limit of normal, and/or hepatitis. In all trial populations, one study presented data for niacin plus a lower dose statin versus higher dose statin monotherapy in participants not in particular need for intensive lipid lowering comparing extended release niacin 2 g/day plus rosuvastatin 10 mg/day with rosuvastatin 40 mg/day monotherapy.¹⁵⁵ There were no instances of elevated serum AST and/or ALT above 3 times the upper limit of normal and/or hepatitis recorded.

In all trials, using various statins and doses, elevated serum AST and/or ALT above 3 times the upper limit of normal and/or hepatitis was reported for ten trials,^{49,104,128,150,155,162,170,171,182,196} five of which reported events and therefore provided analyzable data (Table 37).^{104,128,162,170,182} Pooling of the studies demonstrated no significant difference in the incidence between the two groups with an odds ratio of 1.39 (95% CI 0.36, 5.36), based upon 12 events in 1,942 participants.

Participants with myalgia. In all trials, using various statins and doses, incidence of myalgia was reported for three trials.^{49,105,128} Pooling of the studies demonstrated a nonsignificant difference in the incidence of myalgia in both groups with an odds ratio of 0.45 (95% CI 0.19, 1.07), based upon 22 events in 665 participants. No trial data was available that compared niacin plus a lower dose statin versus higher dose statin monotherapy.

Participants with CPK above 10 times the upper limit of normal. In all trial populations, one study presented data for niacin plus a lower dose statin versus higher dose statin monotherapy in participants not in particular need for intensive lipid lowering comparing extended release niacin 2 g/day plus rosuvastatin 10 mg/day with rosuvastatin 40 mg/day monotherapy.¹⁵⁵ There were no instances of CPK above 10 times the upper limit of normal (Table 37).

In all trials, using various statins and doses, the incidence of CPK above 10 times the upper limit of normal was reported in nine trials, with one event identified for 1690 participants for the trials' respective followup durations with a nonsignificant odds ratio of 16.70 (95% CI 0.28, 1002.74) (Table 37).^{49,104,105,139,155,162,170,171,182}

Participants with rhabdomyolysis. In all trial populations, using various statins and doses, rhabdomyolysis was reported not to have occurred in four trials in 944 participants (Table 37).^{104,105,150,171}

Key Question 3: Compared with higher-dose statins, and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

Table 30. Availability of evidence addressing niacin key question 3 for statin plus niacin versus statin monotherapy comparison

Condition	All-cause mortality	Vascular Death	Participants reaching ATP III LDL-c targets	LDL-c	HDL-c	TC:HDL-c ratio	Non-HDL-c	TG
LDL-c \geq 190 mg/dL	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
Diabetes mellitus	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence
Established vascular disease	√	√	√	√	√	No available evidence	Not applicable	
Cerebrovascular disease	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence		
African descent	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence		
Asian descent	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence		
Hispanic descent	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence		
Females	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence		
Age 80 years or more	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence		

Abbreviations: ATP III = the third Adult Treatment Panel III Adult Treatment Panel of the National Cholesterol Education Program, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, TC = total cholesterol

Clinical Outcomes

Comparing statin plus niacin versus statin monotherapy (lower dose vs. higher dose and various statin doses)

All-cause mortality.

Participants with established vascular disease. Incidence of all cause mortality was reported for one trial, for the subgroup of participants with vascular disease (Table 31).¹⁹⁶ There was no statistically significant difference between the two treatment groups, with an odds ratio of 1.84 (95% CI 0.16, 20.76) for both subgroups.

Vascular death.

Participants with established vascular disease. The incidence of vascular death was reported for one trial, for participants with established vascular disease (Table 31).¹⁹⁷ No events were recorded.

LDL-c Targets and Other Surrogate Markers

Comparing statin plus niacin versus statin monotherapy (lower dose vs. higher dose and various statin doses)

Participants reaching ATP III LDL-c goals.

Participants with established vascular disease. The surrogate outcome incidence of participants reaching their ATP-III targets was reported for one trial with established vascular disease (Table 33).⁴⁹ No statistically significant difference was noted between the two groups (OR 1.51, 95% CI 0.56, 4.08).

LDL-c, percentage mean change from baseline.

Participants with established vascular disease. The surrogate outcome LDL-c percent change from baseline for participants with established vascular disease was reported for one trial (Table 33).¹⁶² No statistically significant difference was noted between the two groups (MD 0.00, 95% CI -6.51, 6.51).

HDL-c, percentage mean change from baseline.

Participants with established vascular disease. HDL-c percent change from baseline was reported for one trial (Table 34).¹⁶² There a significant increase in HDL-c in the combination group compared with monotherapy (MD 13.00 percent, 95% CI 6.01, 20.00).

Strength of Evidence

The strength of the available evidence was assessed as GRADE (Grading of Recommendations Assessment, Development and Evaluation)²²⁵ for the key outcomes all-cause mortality, vascular death, serious adverse events and achieving ATP-III target LDL-c. Results

generated using the GRADEpro software are presented in Tables H-17 to H-20 (Appendix H) can be summarized as follow:

1. Based on a single study in participants requiring intensive lipid lowering therapy, GRADE was “very low” for all cause mortality, vascular death and participants reaching ATP III LDL-c goals for the combination of any dose statin plus niacin compared to any dose statin (Appendix H, Table H-17).
2. Based on a single study in participants with established vascular disease, GRADE was “very low” for all cause mortality, vascular death and participants reaching ATP III LDL-c goals for the combination of any dose statin plus niacin compared to any dose statin (Appendix H, Table H-18).
3. Based on studies in participants followed up for more than 24 weeks and comparing the combination of any dose statin plus niacin to any dose statin, GRADE was “very low” for all cause mortality (4 trials), vascular death (1 trial) and serious adverse events (3 trials) (Appendix H, Table H-19).
4. Based on studies in participants regardless of baseline risk and comparing the combination of any dose statin plus niacin to any dose statin, GRADE was “very low” for all cause mortality (6 trials), vascular death (2 trials), serious adverse events (5 trials) and participants reaching ATP III LDL-c goals (1 trial) (Appendix H, Table H-20).

Evidence Summary Tables: Statin Plus Niacin Combination Therapy Versus Statin Monotherapy

Table 31. Quantitative syntheses of longer term outcomes (clinical, serious adverse events and cancer) for niacin plus a statin therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant treatment groups	Number of Events	Odds ratio	Lower CI	Upper CI
All-cause mortality						
Participants requiring intensive lipid lowering therapy – All trials ¹⁹⁶						
Participants requiring intensive lipid lowering therapy – All trials 24 weeks or more followup ¹⁹⁶	1	149	3	1.84	0.16	20.76
Participants requiring intensive lipid lowering therapy – Trials with adequate allocation concealment ¹⁹⁶						
Participants with vascular disease ¹⁹⁶						
All trials ^{104,105,150,170,171,196}	6	1213	5	1.08	0.17	6.72
All trials 24 weeks or more followup ^{105,150,171,196}	4	960	5	1.08	0.17	6.72
Trials with adequate allocation concealment ^{104,105,171,196}	3	792	5	1.08	0.17	6.72
Vascular death						
Participants requiring intensive lipid lowering therapy ¹⁹⁷	1	54	0	-	-	-
Participants with vascular disease ¹⁹⁷						
All trials ^{128,197}	2	229	2	0.53	0.03	8.64
All trials 24 weeks or more followup ¹²⁸	1	175	2	0.53	0.03	8.64
Fatal myocardial infarction						
All trials ^{105,197}	2	229	1	4.64	0.08	283.78
All trials 24 weeks or more followup ¹⁰⁵	1	175	1	4.64	0.08	283.78
Participants requiring intensive lipid lowering therapy ¹⁹⁷	1	54	0	-	-	-
Any unspecified stroke						
All trials ¹⁹⁶						
All trials 24 weeks or more followup ¹⁹⁶	1	149	1	0.12	0.00	6.21
Participants requiring intensive lipid lowering therapy ¹⁹⁶						

Acute coronary syndrome							
All trials ¹⁹⁶	1	149	4	0.91	0.12	6.62	
Percutaneous coronary intervention							
All trials ¹⁹⁶							
Participants requiring intensive lipid lowering therapy ¹⁹⁶	1	149	5	3.78	0.41	34.68	
All trials 24 weeks or more followup ¹⁹⁶							
Serious adverse events							
All trials ^{104,105,150,170,171}	5	1064	16	1.29	0.44	3.80	
All trials 24 weeks or more followup ^{105,150,171}	3	811	9	1.00	0.26	3.86	
Cancer							
All trials ¹⁰⁵	1	175	2	0.10	0.00	2.20	

Abbreviations: CI = 95% confidence interval

Table 32. Quantitative syntheses of the incidence of participants achieving ATP-III LDL-c targets, for niacin plus a statin therapy compared with statin monotherapy

	Number of trials	Dose Niacin (mg/day)	Number of participants in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Relative probability of attaining ATPIII target							
Participants requiring intensive lipid lowering therapy ⁴⁹	1	2000	66	40	1.51	0.56	4.08
Participants with vascular disease ⁴⁹							
All trials ⁴⁹	1	2000	222	166	-	-	-

Abbreviations: ATP III = the third Adult Treatment Panel III Adult Treatment Panel of the National Cholesterol Education Program, CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

Table 33. Quantitative syntheses of LDL-c data, for niacin plus a statin combination therapy compared with statin monotherapy

	Number of trials	Number of participants in relevant treatment groups	Point Estimate	Lower CI	Upper CI
Difference in mean percentage change from baseline (%)					
Participants requiring intensive lipid lowering therapy ¹⁶²	1	83	0.00	-6.51	6.51
Participants with vascular disease ¹⁶²					
All trials ^{104,105,139,155,162,182,184}	7	673	-	-	-
Rosuvastatin - Lower dose statin in combination versus higher dose monotherapy ¹⁵⁵	1	124	12.00	2.26	21.74

Abbreviations: CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

Table 34. Quantitative syntheses of HDL-c data, for niacin plus a statin combination therapy compared with statin monotherapy

Population	Number of trials	Number of participants in relevant treatment groups	Point Estimate	Lower CI	Upper CI
Difference in mean percentage change from baseline					
Participants requiring intensive lipid lowering therapy ¹⁶²	1	83	13.00	6.01	20.00
Participants with vascular disease ¹⁶²					
All trials ^{104,105,139,155,162,182}	6	732	-	-	-
<i>Rosuvastatin</i> Lower dose statin in combination compared with higher dose monotherapy ¹⁵⁵	1	67	13.00	6.10	19.90

Abbreviations: CI = 95% confidence interval, HDL-c = high density lipoprotein cholesterol

Table 35. Quantitative syntheses of total cholesterol:HDL-c ratios, for niacin plus a statin combination therapy compared with statin monotherapy

Population	Number of trials	Number of participants in relevant treatment groups	Max dose niacin (mg/d)	Point estimate	Lower CI	Upper CI
Difference in mean percentage change in TC: HDL-c ratio (%)						
All trials ¹³⁹	1	198	2000	-6.00	-9.60	-2.40

Abbreviations: CI = 95% confidence interval, HDL-c = high density lipoprotein cholesterol, TC = total cholesterol

Table 36. Quantitative synthesis of CIMT data, for niacin plus a statin combination therapy compared with statin monotherapy

	Number of trials	Number of participants in relevant treatment groups	Max dose niacin (mg/d)	Point estimate	Lower CI	Upper CI
Difference in mean CIMT						
All trials ¹⁹⁶						
Participants requiring intensive lipid lowering therapy ¹⁹⁶	1	149	1000	-0.03	-0.06	0.003

Abbreviations: CI = 95% confidence interval, CIMT = carotid intima-medial thickness

Table 37. Quantitative syntheses of short term harms and adherence to treatment, for niacin plus a statin combination therapy compared with statin monotherapy

Population	Number of trials	Niacin Dose (mg/d)	Number of participants in relevant treatment groups	Number of events	Odds ratio	Lower CI	Upper CI
Relative probability of participants adhering to treatment							
All trials ^{49,139,155,182,196}	5	1000 - 2500	1011	851	0.79	0.50	1.27
Trials 24-weeks or longer followup ^{155,196}	2	1000 - 2000	365	251	-	-	-
<i>Rosuvastatin</i>							
Lower dose statin in combination versus higher dose monotherapy ¹⁵⁵	1	2000	126	67	0.40	0.19	0.84
Relative probability of participants experiencing an adverse event							
All trials ^{104,105,150,155,171,182}	6	2000 - 2500	1275	681	-	-	-
Trials 24 weeks or longer followup ^{105,150,155,171}	4	1000 - 2000	1009	499	-	-	-
<i>Rosuvastatin</i>							
Lower dose statin in combination versus higher dose monotherapy ¹⁵⁵	1	2000	124	100	1.94	0.79	4.78
Relative probability of participants withdrawing from treatment due to an adverse event							
All trials ^{49,104,105,128,150,170,171,182,189,196}	10	1000 - 3000	1900	223	2.38	1.63	3.47
Relative probability of participants experiencing rhabdomyolysis							
All trials ^{104,105,150,171}	4	2000 - 2500	944	0	-	-	-
Relative probability of participants experiencing elevated serum AST and/or ALT greater than 3 times the upper limit of normal, and/or hepatitis							
All trials ^{49,104,128,150,155,162,170,171,182,196}	10	1000 - 2500	1942	12	1.39	0.36	5.36
<i>Rosuvastatin</i>							
Lower dose statin in combination versus higher dose monotherapy ¹⁵⁵	1	2000	126	0	-	-	-
Relative probability of participants experiencing myalgia							
All trials ^{49,105,128}	3	2000	665	22	0.45	0.19	1.07
Relative probability of participants experiencing CPK greater than 10 times the upper limit of normal							
All trials ^{49,49,104,105,139,155,170,182}	10	2000 - 2500	1690	1	16.70	0.28	1002.74
<i>Rosuvastatin</i>							
Lower dose statin in combination versus higher dose monotherapy ¹⁵⁵	1	2000	126	0	-	-	-

Abbreviations: ALT = alanine transaminase, AST = aspartate transaminase, CI = 95% confidence interval, CPK = creatinine phosphokinase

Statin Plus Bile Acid Sequestrant Combination Therapy Versus Statin Monotherapy

Overview of Included Studies

A total of 17 RCTs evaluated the relative efficacy and/or harm of the combination of statin plus bile acid sequestrant (BAS) (cholestyramine 1.6 to 24 g/day, colestipol 1.65 to 20 g/day) therapy compared with statin monotherapy, in a total of 2,930 participants (Table 3; Appendix F, Table F-24 to F-28). In addition, two non-randomized studies addressed this comparison (Table 4).^{88,89} Two trials included companion reports (Table 6); one in the published literature,¹⁹⁸ and one a Federal Drug Agency report of an extension of treatment and followup for a longer period of time.¹⁷² The longest available data for any given trial were analyzed. One companion report was considered for trial referencing.²¹²

Twelve trials were conducted in multiple centers^{52,122,133,137,164,172,174,185,186,190,191,198}, and three in single centers.^{136,163,173} Information regarding site was not reported for two trials.^{108,135} Fifteen of the 17 trials were partially or completely sponsored by the pharmaceutical industry,^{52,108,122,133,135-137,172,174,185,186,190,191,198} while funding was not disclosed for two trials.^{163,164} Total Jadad scores ranged from one to five with an average score of 2. An appropriate method of randomization was reported for three trials,^{172,173,190} and appropriate methods of double blinding were reported for four trials.^{133,172,173,185} Allocation concealment was deemed adequate for three trials^{122,172,173} and the results of two trials were based on intention-to-treat analyses.^{133,135}

Most trials (12) were carried out in North America,^{52,108,122,133,135,136,163,172,185,186,191} with three trials in Europe^{137,173,190} and two trials in Australia.^{174,198}

Reporting of participants' ethnicity was provided in five trials as follow

- European descent (89 to 96 percent)^{52,122,172,185,191}
- Hispanic descent (1.3 to 1.5 percent)^{172,185}
- African descent (3 to 8 percent)^{52,122,172,185}
- Asian descent (3 percent)¹⁸⁵

Neither power analyses regarding the primary outcome measures nor adjudication of outcomes were reported. Also, except for two trials,^{52,191} active clinical adverse event data collection was either not reported or unclear.

Key Question 1: For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits, and rates of serious adverse events of coadministration of different lipid-modifying agents (i.e. a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

Study Design and Population Characteristics

A total of four parallel group RCTs including 511 participants compared statin plus BAS combinations and statin monotherapy, and reported one or more clinical outcomes or serious adverse events (Table 41; Appendix F, Table F-24).^{52,172,185,198} Three trials provided information on participants' ethnic descent.^{52,172,185} In included arms of those trials, 89 to 95 percent of

participants were of European descent, 3 to 7 percent of African descent, 1.5 percent of Hispanic descent and 2.6 percent of Asian descent. No trial was conducted exclusively in one gender. On average, 51 percent of participants were female (range 43 to 60 percent). The average of mean ages of participants was 54 years (range 49 to 59 years). Two trials recruited outpatients,^{172,198} while two trials did not report recruitment setting.^{52,185} Mean Jadad score was 3 (range 1 to 5) and one trial had adequate allocation concealment.¹⁷² No trials were exclusively in participants requiring intensive lipid lowering therapy.

The participants in these four trials were relatively homogenous, as none of the trials were performed in high risk participants, and none reported prior statin exposure. Most trials excluded participants with triglycerides above 300 to 600 mg/dL, patients with recent or unstable vascular disease, uncontrolled diabetes mellitus and hypertension, liver and muscle disease or high ALT, AST and/or CPK, and/or impaired renal function. No trial employed a statin plus BAS combined pill.

Table 38. Evidence addressing key question 1 for statin plus BAS versus statin monotherapy comparison

Outcomes	Extractable data availability	Key points of evidence synthesis
All-cause mortality	Yes	Three trials compared BAS-statin combination therapy with the same statin and same dose monotherapy. A significant difference was not observed in participants with mixed risk factors. These trials reported 2 deaths in 373 evaluable participants.
Vascular death	No	
Fatal myocardial infarction (MI)	Yes	One trial compared BAS-statin combination with the same statin and same dose monotherapy. A significant difference was not observed in participants with mixed risk factors. This trial reported 1 fatal MI in 150 evaluable participants.
Non-fatal MI	No	
Any or unspecified MI	No	
Acute coronary syndrome (ACS) (encompassing unstable angina or acute MI)	No	
Any cerebrovascular event	No	
Hemorrhagic stroke	No	
Ischemic stroke	No	
Any or unspecified stroke	No	
Transient ischemic attack (TIA)	No	
Carotid endarterectomy (CEA)	No	
Percutaneous coronary interventional procedure (PCI)	No	
Coronary artery bypass graft procedure (CABG)	No	
Any or unspecified revascularization procedure	No	
Serious adverse events	Yes	Two trials compared BAS-statin combination therapy with the same statin and same dose monotherapy. A significant difference was not observed in participants with mixed risk factors. These trials reported 7 SAEs in 278 evaluable participants.
Cancer	No	

Abbreviations: ACS = acute coronary syndrome, CABG = coronary artery bypass graft, CEA = carotid endarterectomy, MI = myocardial infarction, PCI = percutaneous coronary intervention, SAE = serious adverse event

Long-Term Efficacy, Serious Adverse Events, and Cancer

Comparing statin plus BAS versus statin monotherapy (lower dose vs. higher dose and various statin doses)

All-cause mortality. Three trials in 373 evaluable participants reported two deaths during a follow up of four to 24 weeks duration (Table 41).^{52,172,185} Only one of these trials, in 150 participants, was based on treatment and follow up of 24 weeks.⁵² This study compared fluvastatin 10-20 mg/day and cholestyramine 16 g/day plus fluvastatin 10 to 20 mg/day, and reported one death.⁵² Across these three trials of four to 24 weeks duration, two trials with 151 evaluable participants and a total of two deaths could be meta-analyzed (Appendix G, Figure G-57).^{52,172} A nonsignificant odds ratio of 1.07 (95% CI 0.11, 10.51) was observed (Table 41). A report of one trial with adequate allocation concealment had a nonsignificant estimable odds ratio of 3.25 (95% CI 0.13, 82.24) (Appendix F, Table F-24).¹⁷² No report permitted comparison of lower dose statin plus BAS with higher dose statin monotherapy, and none of the trials was performed specifically in participants requiring intensive lipid lowering therapy.

Fatal myocardial infarction. One trial in 150 evaluable participants compared fluvastatin (10-20 mg/day) and cholestyramine (16 g/day) with fluvastatin (10-20 mg/day), and reported one fatal myocardial infarction on monotherapy. A nonsignificant odds ratio of 0.35 (95% CI 0.01, 8.91) was observed (Table 41).⁵²

Serious adverse events. Seven participants experienced serious adverse events during two trials on 278 evaluable participants, during a followup of six to 30 weeks (Table 41).^{172,198} Simons et al compared simvastatin (40 mg/day) plus cholestyramine (4 g/day) with atorvastatin (80 mg/day) monotherapy in 136 participants, with six serious adverse events during a followup of 30 weeks.¹⁹⁸ Knapp et al compared simvastatin (10 to 20 mg/day) plus colestivelam (2.3 to 3.8 g/day) with simvastatin (10 to 20 mg/day) monotherapy in 142 participants, with one serious adverse event during a six week trial (Appendix F, Table F-24).¹⁷² The pooled nonsignificant odds ratio was 0.39 (95% CI 0.06, 2.36) (Appendix G, Figure G58).

Non-RCT evidence. Two non-randomized controlled trials compared statin plus BAS therapy with statin monotherapy (Table 42). Ojala et al⁸⁸ added colestipol (dose range from 5 to 20 g/day) to treatment of patients with primary hypercholesterolemia, some of whom had CHD. LDL-c was above 120 mg/dL in CHD patients or above 140 mg/dL for those without CHD, despite the use of lovastatin 80 mg/day. The only reported outcome of interest was the absence of serious adverse events in either treatment group during the three year follow up.⁸⁸ Mol et al compared simvastatin 40mg/day plus cholestyramine 4 g/day or colestipol 5g/day, with simvastatin 40 mg/day in 26 patients with severe familial hypercholesterolemia, for two years.⁸⁹ In the combination group, one participant experienced a myocardial infarction and one experienced unstable angina, but there were no cases of coronary arterial bypass graft.⁸⁹ No other outcome of interest was reported (Table 42).

Key Question 2: Do these regimens differ in reaching LDL-targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

Study Design and Population Characteristics

Records of seventeen trials comparing a statin plus BAS combination with statin monotherapy reported one or more surrogate efficacy or harm outcomes, other than serious adverse events and cancer (Table 39; Appendix F, Table F-25 to F-28).^{52,108,122,133,135-137,163,164,172-174,185,186,190,191,198} These trials included 2,930 randomized participants. No trials were of crossover design. Six records provided information on participants' descent,^{52,122,164,172,185,191} with reports of 87 to 96 percent of participants of European descent, 3 to 8 percent of African descent, 1.5 percent of Hispanic descent and 2.6 percent of Asian descent. Trial duration ranged from four to 192 weeks with an average of 32 weeks. One trial was conducted exclusively in males.¹⁰⁸ In the remaining 16 trials, on average 38 percent of participants were females (range, 5 to 60 percent). The average of mean ages of participants was 54 years (range of mean age, 45 to 62 years). Five trials recruited outpatients,^{133,172,190,191,198} while 12 trials did not report recruitment setting. Mean Jadad score was 2 (range 1 to 5) and four trials had adequate allocation concealment.^{122,172,173,190} Five of these trials included 426 participants requiring intensive lipid lowering treatment and/or participants with baseline LDL-c above 190 mg/dL.^{108,122,163,174,198}

Three trials included only participants with familial combined hypercholesterolemia,^{136,163,164} three included participants all with LDL-c above 190mg/dL,^{122,163,198} two reported past history of coronary artery diseases in most or all participants,^{108,174} and one reported that all participants had prior statin exposure.¹²² The other seven trials were relatively homogenous regarding participants' characteristics. Most trials excluded participants with TG above 300 to 600 mg/dL, recent or unstable vascular disease, uncontrolled diabetes mellitus or hypertension, liver and muscle disease, high ALT, AST and CPK, or impaired renal function. No trial employed a BAS plus statin combined pill.

Table 39. Evidence addressing key question 2 for statin plus BAS versus statin monotherapy comparison

Relevant outcomes	Extractable data availability	Key points of evidence synthesis
Participants attaining ATP III LDL-c targets	Yes	One trial comparing lower dose statin in combination with higher dose monotherapy in participants with history of cardiovascular diseases favored combination therapy.
LDL-c	Yes	Compared with same statin monotherapy (one trial with higher statin dose) in participants with heterogeneous risk factors, nine of 11 trials favored BAS-statin combination, but results could not be pooled.
HDL-c	Yes	Nine trials compared combination therapy with the same statin monotherapy (one trial with higher statin dose) in participants with heterogeneous risk factors. A significant difference was not observed.
TC:HDL ratio	No	
Carotid artery	No	
Coronary artery	No	
Treatment Adherence	Yes	Five trials compared combination therapy with the same statin monotherapy (two trials with higher statin dose monotherapy) in participants with heterogeneous risk factors. All trials favored monotherapy, but results could not be pooled.
All participants with adverse events	Yes	Four trials compared combination therapy with the same statin monotherapy (one trial with higher statin dose monotherapy) in participants with heterogeneous risk factors. All trials favored monotherapy, but results could not be pooled.
Withdrawal due to adverse events	Yes	Eight trials compared combination therapy with the same statin monotherapy (four with higher statin dose monotherapy) in participants with heterogeneous risk factors, with 31 withdrawals due to AEs in 966 evaluable participants. No significant difference was observed.
Elevated AST and/or ALT > 3 times ULN and/or hepatitis	Yes	Two 4 to 30 week trials in 212 evaluable participants reported no events.
Myalgia	Yes	Four trials comparing combination therapy with the same statin monotherapy (one with higher statin dose) in participants with heterogeneous risk factors, reported 11 episodes of myalgia in 343 evaluable participants. No significant difference was observed.
CPK > 10 times ULN	Yes	Two 6 to 30 week trials in 283 evaluable participants reported no events.
Rhabdomyolysis (investigator defined)	No	

Abbreviations: ALT = alanine transferase, AST = aspartate transferase, ATP III = Third Adult Treatment Panel of the National Cholesterol Education Program, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, TC = total cholesterol

LDL-c Targets and Other Surrogate Markers

Comparing statin plus BAS versus statin monotherapy (lower dose vs. higher dose and various statin doses)

Participants reaching ATP III LDL-c goals. One record of a 12 week trial on 59 evaluable participants reported attainment of ATP III LDL-c targets (Table 43).¹⁰⁸ This trial compared pravastatin 20 mg/day plus cholestyramine 10 g/day with pravastatin 40 mg/day in 59 male

North American participants. All had moderate hypercholesterolemia, history of coronary artery diseases and prior use of statins. Eighteen participants reached ATP III LDL-c target levels, yielding a nonsignificant odds ratio of 4.51 (1.34, 15.14) favoring combination therapy (Table 43; Appendix F, Table F-25).¹⁰⁸

LDL-c, percentage mean change from baseline. A total of 11 trials provided data on 15 pairs of analyzable arms on 1010 evaluable participants.^{52,122,133,163,164,172-174,185,191,198} Followup duration ranged from four to 40 weeks, with the majority of trials less than 24 weeks in duration. Across trials, participant characteristics were relatively heterogeneous, with four trials including participants with moderate to severe familial hypercholesterolemia requiring intensive lipid lowering therapy,^{122,163,174,198} and/or LDL-c above 190 mg/dL at baseline.^{122,163,198}

Meta-analysis was not possible due to substantial statistical heterogeneity ($I^2 = 88$ percent). However, most trials demonstrated significant percentage reductions from baseline in favor of statin plus BAS combination therapy compared with statin monotherapy, ranging from 4 to 16 percent (Table 44; Appendix G, Figure G-59). In contrast, two trials showed a difference in means favoring monotherapy. One 30 week trial in 136 participants comparing simvastatin 40 mg/day plus colestyramine 4 g/day, with atorvastatin 80 mg/day monotherapy in participants with no prior exposure to statins, showed a significant difference in means of 11 percent (95% CI 6.45, 15.55) in favor of monotherapy.¹⁹⁸ Another 32 week trial in 37 participants, comparing mixed statins plus colestipol 20 g/day with atorvastatin 80 mg/day monotherapy in participants heterogeneous familial and polygenic hypercholesterolemia, showed a nonsignificant difference in means of 5.43 percent (95% CI -1.84, 12.7) in favor of monotherapy.¹⁶³ When the analyses were rerun after removing these two outliers a significant percentage reductions from baseline in favor of statin plus BAS combination of -10.6 percent (95% CI -12.56, -8.65) was demonstrated, without significant heterogeneity ($I^2 = 17.7$ percent). There was no significant lateral asymmetry on the funnel plot, with an Egger's regression intercept of -1.7, and two tailed p-value > 0.647.

Four trials contributed efficacy data comparing statin plus BAS therapy with statin monotherapy, regardless of statin dose, in those who require intensive lipid lowering therapy (i.e. participants with baseline LDL-c above 190 mg/dL, or history of coronary artery disease).^{122,163,174,198} Persistent statistical heterogeneity prevented meta-analysis ($I^2 = 89$ percent). Results of individual trials were inconsistent, with one trial showing a mean percentage change of -10 percent in favor of combination (95% CI -19.92, -0.28)¹⁷⁴, one trial showing significant results favoring monotherapy (MD 11; 95% CI 6.45, 15.55)¹⁹⁸ and two trials yielding nonsignificant mean differences in percentage change from baseline LDL-c ranging from -4.1 to 5.4 percent (Table 44; Appendix G, Figure G-60).^{122,163} Hunninghake et al provided data comparing lower dose atorvastatin 10 mg/day plus colesevalam 3.8 g/day with higher dose atorvastatin 80 mg/day monotherapy.¹³³ This study investigated 38 participants without any particular risk factor and reported a percentage mean difference of 5.00 percent (95% CI -3.34, 13.34) (Table 44).

HDL-c, percentage mean change from baseline. A total of nine trials provided 10 pairs of meta-analyzable data on 911 evaluable participants.^{52,122,163,164,173,174,185,191,198} Followup duration ranged from four to 40 weeks, and five trials were more than 24 weeks in length. Across trials, participants presented with moderate to severe familial hypercholesterolemia and/or LDL-c above 190 mg/dL at baseline.^{122,163,174,198} Pooled results yielded an estimable mean percentage

difference of 0.33 percent (95% CI -1.86, 2.52) and no significant heterogeneity ($I^2 = 29$ percent) (Table 45). Asymmetry was not evident on the funnel plot.

Four trials contributed efficacy data comparing statin plus BAS with statin monotherapy, for all statin doses, in those requiring intensive lipid lowering therapy.^{122,163,174,198} Pooled results showed an estimable mean percentage difference of 2.25 percent (95% CI -0.56 mg/dL, 5.06 mg/dL) and no significant heterogeneity ($I^2 = 3$ percent) (Table 45; Appendix F, Table F-27). None of the trials provided evaluable data comparing combination therapy using lower dose statin with higher dose statin monotherapy.

Harms and Treatment Adherence

Comparing statin plus BAS versus statin monotherapy (lower dose vs. higher dose and various statin doses)

Participants adherent to treatment. Five trials of four to 96 weeks duration provided analyzable data in 1420 evaluable participants.^{122,133,137,164,190} Data could not be pooled because of significant heterogeneity ($I^2 = 53$ percent) (Table 46; Appendix F, Table F-28). Asymmetry was not evident on the funnel plot (Appendix G, Figure G-62). One long-term trial (96 weeks) compared pravastatin 20 mg/day plus cholestyramine 8 g/day with pravastatin 20 to 40 mg/day monotherapy, in 1073 evaluable participants, and yielded a significant odds ratio of 0.41 (95% CI 0.26, 0.7) in favor of monotherapy.¹⁹⁰ Four trials with less than 24 months followup yielded odds ratios ranging from 0.1 to 0.97.^{122,133,137,164} Potential factors contributing to the heterogeneity among these studies included:

- One study was conducted in participants requiring intensive lipid lowering therapy because of baseline LDL-c levels above 190 mg/dL.¹²² Participants in the remaining four studies presented with moderate hypercholesterolemia.
- Four studies were sponsored by the pharmaceutical industry,^{122,133,137,190} and this information was not reported in one study.¹⁶⁴
- All trials employed a similar statin in combination and monotherapy arms. Two trials compared lower dose statin plus BAS with higher dose statin monotherapy,^{133,137} one four to 12 week trial compared simvastatin 20 mg/day plus colestipol 5 to 10 g/day with higher dose simvastatin 40 mg/day monotherapy in 81 evaluable healthy participants, and yielded a nonsignificant odds ratio of 0.33 (95% CI 0.09, 1.27).¹³⁷ A second trial compared atorvastatin 10 mg/day plus colesvelam 3.8 g/day with higher dose atorvastatin 80 mg/day monotherapy in 39 evaluable participants, and showed a nonsignificant odds ratio of 0.94 (95% CI 0.12, 7.48) (Table 46).¹³³
- A procedure to guarantee adequate allocation concealment was reported in only two of the five studies.^{122,190}

Participants with at least one adverse event. Four 4 to 24 week trials provided six pairs of analyzable arms including 522 evaluable participants, reporting 301 adverse events.^{52,122,137,172} One long-term trial (24 weeks) compared in its four arms fluvastatin 10 and 20 mg/day plus cholestyramine 8 to 16 g/day, with fluvastatin 10 and 20 mg/day monotherapy in 150 evaluable participants, and showed a pooled significant odds ratio of 5.14 (2.39, 11.07) in favor of monotherapy.⁵² (Table 46). Asymmetry was not evident on the funnel plot (Appendix G, Figure G-63). It is worth noting that doses of BAS varied among trials. In particular, cholestyramine was employed in combination with statins in doses varying from 1.6 g/day¹²² to 16 g/day.⁵² Only

one four to 12 week trial compared simvastatin 20 mg/day plus colestipol 5 to 10 g/day with higher dose simvastatin 40 mg/day monotherapy, in 83 evaluable healthy participants, and yielded a nonsignificant odds ratio of 1.19 (95% CI 0.47, 3.02) (Table 46).¹³⁷

Participants withdrawing due to adverse event. Eight trials of four to 24 week duration provided nine pairs of analyzable arms in 966 evaluable participants, with 31 withdrawals due to adverse events.^{52,122,133,164,172,185,191,198} Pooled results showed a nonsignificant odds ratio of 1.80 (95% CI 0.68, 4.76) and no significant heterogeneity ($I^2 = 19$ percent) (Table 46; Appendix F, Table F-28). Asymmetry was not evident on the funnel plot (Appendix G, Figure G-64). Doses of BAS varied widely among trials. Cholestyramine was administered in four trials in doses from 1.6 to 24 g/day,^{52,122,191,198} colestipol was administered in three trials in doses from 2.3 to 3.8 g/day,^{133,172,185} and colestipol was administered in one trial at 1.65 g/day.¹⁶⁴

One 4 week trial compared atorvastatin 10 mg/day plus colestipol 3.8 g/day with atorvastatin 80 mg/day monotherapy in 39 evaluable participants. There were two withdrawals due to adverse events, with a nonsignificant odds ratio of 1.06 (95% CI 0.06, 18.17)¹³⁷ (Table 46).

Participants with AST and/or ALT above 3 times the upper limit of normal, and/or hepatitis. Two 4- to 30-week trials in 212 evaluable participants reported no cases of elevated AST/ALT above three times the upper limit of normal (Table 46; Appendix F, Table F-28).^{185,198}

Participants with myalgia. Four 4 to 12 week trials reported 11 cases of myalgia among 343 evaluable participants (Table 46; Appendix F, Table F-28).^{108,122,173,185} A nonsignificant odds ratio of 0.43 (95% CI 0.12, 1.54), without evidence of significant heterogeneity ($I^2 = 0$ percent) was observed. No trials with estimable data enabled comparison of lower dose statin plus BAS with a higher dose of the same statin monotherapy.

Participants with CPK above 10 times the upper limit of normal. Two 6- to 30-week trials in 283 evaluable participants reported no cases of elevated CPK above 10 times the upper limit (Table 46; Appendix F, Table F-28).^{122,198}

Key Question 3: Compared with higher-dose statins, and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

Table 40. Availability of evidence addressing key question 3 for statin plus BAS versus statin monotherapy comparison

Condition	All-cause mortality	Vascular Death	Participants reaching ATP III LDL-c targets	LDL-c	HDL-c	TC:HDL-c ratio	Non-HDL-c	TG
LDL-c \geq 190 mg/dL	No available evidence	No available evidence	No available evidence	√	√	No available evidence	Not applicable	
Diabetes mellitus	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence
Established vascular disease	No available evidence	No available evidence	√	No available evidence	No available evidence	No available evidence	Not applicable	
Cerebrovascular disease	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
African descent	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
Asian descent	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
Hispanic descent	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
Females	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
Age 80 years or more	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	

Abbreviations: HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, TC = total cholesterol, TG = triglycerides

LDL-c Targets and Other Surrogate Markers

Comparing statin plus BAS versus statin monotherapy (lower dose vs. higher dose and various statin doses)

Participants reaching ATP III LDL-c goals.

Participants with established vascular diseases. A single 12-week trial in 59 evaluable participants reported attainment of ATP III LDL-c targets (Table 43).¹⁰⁸ This trial compared pravastatin (20 mg/day) and cholestyramine (10 g/day) with pravastatin (40 mg/day) in 59 male North American participants, all with moderate hypercholesterolemia, a history of coronary artery disease and prior use of statins. Eighteen participants reached ATP III LDL-c target

levels, yielding a significant odds ratio of 4.51 (1.34, 15.14) favoring combination therapy (Table 43; Appendix F, Table F-25).¹⁰⁸

LDL-c and HDL-c, percentage mean change from baseline.

Participants with baseline LDL-c above 190 mg/dL. Three trials contributed efficacy data for statin plus BAS combination therapy in comparison with statin monotherapy, for any statin dose, in participants with baseline LDL-c above 190 mg/dL.^{122,163,198} Statistical heterogeneity precluded meta-analysis ($I^2 = 78$ percent). All trials showed nonsignificant mean differences in percentage change from baseline in LDL-c (Appendix G, Figure G-61). One six week trial in 144 evaluable participants employing identical high dose rosuvastatin in combination and monotherapy had a mean percentage reduction of -4.1 percent (95% CI, -9.1, 0.9).¹²² One 48 week trial in 37 evaluable participants compared 40 mg/day of atorvastatin or simvastatin plus 20 g/day of colestipol with 80 mg/day of atorvastatin monotherapy and had a mean percentage reduction of 5.4 percent (95% CI -1.84, 12.67).¹⁶³ Finally, a 30 week trial in 136 evaluable participants compared simvastatin 40 mg/day plus cholestyramine 4 g/day with atorvastatin 80 mg/day monotherapy, and had a mean percentage reduction of 11 percent favoring monotherapy (95% CI 6.45, 15.55).¹⁹⁸

HDL-c, percentage mean change from baseline in participants with baseline LDL-c above 190 mg/dL. The same three trials described above for percentage changes in LDL-c also provided data on mean percentage change in HDL-c.^{122,163,198} Pooled results showed an estimable mean percentage difference of 2.37 percent (95% CI -1.18, 5.93) and no significant heterogeneity ($I^2 = 2$ percent)(Table 45).

Strength of Evidence

The strength of the available evidence was assessed as GRADE (Grading of Recommendations Assessment, Development and Evaluation)²²⁵ for the key outcomes all-cause mortality, vascular death, serious adverse events and achieving ATP-III target LDL-c. Results generated using the GRADEpro software are presented in Tables H-21 to H-23 (Appendix H) and can be summarized as follows:

1. Based on a single study in participants requiring intensive lipid lowering therapy, GRADE was “very low” for participants reaching ATP III LDL-c goals for the combination of any dose statin plus BAS compared to any dose statin (Appendix H, Table H-21).
2. Based on a single study in participants followed up for more than 24 weeks, GRADE was “very low” for all cause mortality and participants reaching ATP III LDL-c goals for the combination of any dose statin plus BAS compared to any dose statin (Appendix H, Table H-22).
3. Based on studies in participants regardless of baseline risk and comparing the combination of any dose statin plus BAS to any dose statin, GRADE was “very low” for all cause mortality (3 trials), serious adverse events (2 trials) and participants reaching ATP III LDL-c goals (1 trial) (Appendix H, Table H-23).

Evidence Summary Tables: Statin Plus Bile Acid Sequestrant Combination Therapy Compared With Statin Monotherapy

Table 41. Quantitative syntheses of longer term outcomes data (clinical, serious adverse events and cancer) for BAS plus statin therapy compared with statin monotherapy

Outcome	Number of trials reporting outcome	Number of participants in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
All-cause mortality						
All trials ^{52,172,185}	3	373	2	1.07	0.11	10.51
All trials 24 weeks or more followup ⁵²	1	77	1	0.35	0.01	8.9
Trials with adequate allocation concealment ¹⁷²	1	147	1	3.25	0.13	82.24
Fatal Myocardial Infarction						
All trials Trial 24 weeks ⁵²	1	150	1	0.35	0.01	8.91
Serious Adverse Event(s)						
All trials ^{172,198}	2	278	7	0.39	0.06	2.36

Abbreviations: BAS = bile acid sequestrant, CI = 95% confidence interval

Table 42. Non-randomized controlled trial evidence regarding BAS plus statin therapy compared with statin monotherapy

Trial	Design Duration Downs and Black score	Patients (LDL-c mg/dL)	Monotherapy Dose (mg/d)	Combination Therapy Dose (mg/d)	Results	Limitations	Applicability	Conclusion
Ojala (1990) ⁸⁸	CCT 3 years 16/28	54 men and postmenopausal women less than 70 years with 1° HC, with or without CHD, and without marked hypertriglyceridemia who had previously participated in a lovastatin-probuco RCT Baseline LDL-c (SD) combination 395 (66)mg/dL mono 240 (39)mg/dL	Lovastatin (max 80mg/d) Titrated in CHD if LDL-c ≥ 120 mg/dL Titrated in others if LDL-c ≥ 140 mg/dL	In patients with LDL-c still above target, colestipol was added and titrated to maximal tolerated dose – lovastatin (80, average dose 74), colestipol (maximum dose 2000, average dose 1200)	Mortality and other clinical outcomes of interest, cancer and cognitive decline NR SAE: Zero patients with in both treatment groups	Groups were not comparable based on type of hypercholesterolemia: non-familial hypercholesterolemia mono, familial hypercholesterolemia combination	Low event rate and lack of reporting of other important long-term outcomes, unknown setting, and patient population are suggestive of low applicability	No comparative analysis can be made given different patient subtypes in the two arms
Mol (1990) ⁸⁹	CCT	26 patients with severe familial hypercholesterolemia	Simvastatin 40	S 40 plus C-amine 4000 or colestipol 5000	Mortality and other clinical outcomes of interest, SAE, cancer and cognitive decline NR Myocardial infarction: S40 = 0/12; S40 + BAS = 1/14 Unstable angina: MI: S40 = 0/12; S40 + BAS = 1/14 CABG/MI: S40 = 0/12; S40 + BAS = 2/14	No comparison of baseline characteristics was reported	Low event rate, lack of reporting of other important long-term outcomes, unknown setting, and absence of reporting of exclusion criteria are suggestive of low applicability	Results inconclusive given low event rate and lack of statistical significance

Abbreviations: BAS = bile acid sequestrant, CABG = coronary arterial bypass graft, C-amine = colestyramine, CCT = clinical controlled trial, CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol, N = number, S = simvastatin, SAE = serious adverse events, TG = triglycerides

Table 43. Quantitative syntheses of participants attaining ATP III LDL-c targets, for BAS plus statin therapy compared with statin monotherapy

Outcome	Number of trials reporting outcome	Number of participants in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Relative probability of attaining ATP III LDL-c goal						
All trials						
Participants requiring intensive lipid lowering therapy	1	59	18	4.51	1.34	15.14
All participants with established vascular diseases ¹⁰⁸						

Abbreviations: ATP III = Third Adult Treatment Panel of the National Cholesterol Education Program, BAS = bile acid sequestrant, CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

Table 44. Quantitative syntheses of LDL-c data, for BAS plus statin therapy compared with statin monotherapy

Quantitative syntheses	Number of trials reporting outcome	Number in relevant treatment groups	Point Estimate	Lower CI	Upper CI
Difference in mean LDL-c percentage change from baseline					
All trials ^{52,52,122,133,163,164,172,172-174,185,191,198}	11	1010			
<i>Atorvastatin</i> Lower dose statin in combination versus higher dose monotherapy ¹³³	1	38	5	-3.34	13.34
Participants in need of intensive lipid lowering therapy ^{122,163,174,198}	4	367			
Participants with LDL-c > 190 ^{122,163,198}	3	317			

Abbreviations: BAS = bile acid sequestrant, CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

Table 45. Quantitative syntheses of HDL-c data, for BAS plus statin therapy compared with statin monotherapy

Quantitative syntheses	Number of trials reporting outcome	Number in relevant treatment groups	Point Estimate	Lower CI	Upper CI
Difference in mean HDL-c percentage change from baseline (%)					
All trials ^{52,122,163,164,173,174,185,191,198}	9	911	0.33	-1.86	2.52
Participants in need of intensive lipid lowering therapy ^{122,163,174,198}	4	367	2.25	-0.56	5.06
Participants with LDL > 190 ^{122,163,198}	3	317	2.37	-1.18	5.93

Abbreviations: BAS = bile acid sequestrant, CI = 95% confidence interval, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol

Table 46. Quantitative syntheses of short term harms and adherence data, for BAS plus statin therapy compared with statin monotherapy

	Number of trials reporting outcome	Number in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Treatment adherence						
All trials ^{122,133,137,164,190}	5	1420	1262			
<i>Simvastatin</i>						
Lower dose statin in combination versus higher dose monotherapy ¹³⁷	1	81	64	0.33	0.09	1.27
<i>Atorvastatin</i>						
Lower dose statin in combination versus higher dose monotherapy ¹³³	1	39	35	0.94	0.12	7.48
At least one adverse event						
All trials ^{52,122,137,172}	4	522	301	2.19	1.28	3.75
All trials 24 weeks or more followup ⁵²	1	150	99	5.14	2.39	11.07
<i>Simvastatin</i>						
Lower dose statin in combination versus higher dose monotherapy ¹³⁷	1	83	44	1.19	0.47	3.02
Withdrawal due to adverse event						
All trials ^{52,122,133,164,172,185,191,198}	8	966	31	1.80	0.68	4.76
<i>Atorvastatin</i>						
Lower dose statin in combination versus higher dose monotherapy ¹³³	1	39	2	1.06	0.06	18.17
AST and/or ALT ≥ 3 times ULN, and/or hepatitis						
All trials ^{185,198}	2	212	0			
Myalgia						
All trials ^{108,122,173,185}	4	343	11	0.43	0.12	1.54
CPK ≥ 10 times the ULN						
All trials ^{122,198}	2	156	0			

Abbreviations: ALT = alanine transaminase, AST = aspartate transaminase, BAS = bile acid sequestrant, CI = 95% confidence interval, CPK = creatinine phosphokinase

Statin Plus Omega-3 Fatty Acid Versus Statin Monotherapy

Overview of Included Studies

A total of 10 randomized controlled trials trial reports evaluated relative efficacy and/or harms of omega-3 plus statin combination therapy compared with statin monotherapy, in a total of 19212 participants (Table 3; Appendix F, Table F-29 to F-33). It should be noted that the majority of participants was from one study.¹⁴¹ None of the included non-randomized studies addressed this particular comparison. Four randomized trials had more than one associated journal published or FDA report (Table 5). None of the trials had any companion or extension report of longer treatment or followup period.

Two trials were conducted in multiple centers,^{141,180} and eight trials in single centers (Table 50; Appendix F, Table F-29).^{107,165,175-179,199} There were no trials exclusively in females, or participants of Hispanic, or African descent.

Reporting of participants' ethnic background was as follows:

- One trial reported a mean of 96 percent of participants of European descent
- Two trials reported a mean of 51 percent of participants of Asian descent (range 1 to 100 percent)
- One trial reported a mean of 2 percent of participants of Hispanic descent
- One trial reported a mean of 1 percent of participants of African descent

Trial duration ranged from five to 240 weeks, with an average of 34 weeks. On average 39 percent of participants were women (range 0 to 78 percent). The average of mean ages of participants was 56 years (range of mean age 47 to 61 years). All trials recruited solely from outpatient settings, with the exception of three in which the recruitment setting was not reported.^{141,178,179}

Of the ten trials, only two trials were exclusively in participants requiring intensive lipid lowering treatment (i.e. participants with established vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL).^{175,176}

The mean Jadad score for trial reports was 3 (range 1 to 4). Four trials involved an appropriate method of randomization,^{141,175,180,199} while six had an appropriate method of double blinding.^{107,165,175-177,180} Allocation concealment was reported as adequate in four trials.^{141,175,180,199}

Five of the 10 trials were partially or completely sponsored by the pharmaceutical industry,^{107,141,176,177,180} while funding was not reported or unclear in five reports.^{165,175,178,179,199}

Distribution of trials by geographical region as follows:

- North America - 2 trials^{178,180}
- Europe - 4 trials^{165,176,177,179}
- Asia - 2 trials^{141,175}
- Australia - 2 trials^{107,199}

Key Question 1: For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits, and rates of serious adverse events of coadministration of different lipid-modifying agents (i.e. a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

Table 47. Evidence addressing key question 1 for statin plus omega-3 fatty acids versus statin monotherapy comparison

Outcomes	Evidence availability	Key points of evidence synthesis
All-cause mortality	Yes	No significant difference was observed for the outcome in trials in mixed populations (OR 1.08; 95% CI 0.91, 1.28)
Vascular death	No	
Fatal myocardial infarction (MI)	Yes	No significant difference was observed for the outcome in trials in mixed populations (OR 0.73; 95% CI 0.34, 1.58) or in participants requiring intensive lipid lowering therapy (OR 0.29; 95% CI 0.01, 7.39)
Non-fatal MI	Yes	No significant difference was observed for the outcome in one 240 week trial comprising of a mixed population (OR 0.75; 95% CI 0.54, 1.03)
Any or unspecified MI	Yes	No significant difference was observed for the outcome in one 240 week trial comprising of a mixed population (OR 0.76; 95% CI 0.56, 1.04)
Acute coronary syndrome (ACS) (encompassing unstable angina or acute MI)	No	
Any cerebrovascular event	No	
Hemorrhagic stroke	Yes	No significant difference was observed for the outcome in one 240 week trial comprising of a mixed population (OR 1.26; 95% CI 0.83, 1.91)
Ischemic stroke	Yes	No significant difference was observed for the outcome in one 240 week trial comprising of a mixed population (OR 0.93; 95% CI 0.72, 1.21).
Any or unspecified stroke	Yes	No significant difference was observed for the outcome in one 240 week trial comprising of a mixed population (OR 0.42; 95% CI 0.10, 1.87).
Transient ischemic attack (TIA)	No	
Carotid endarterectomy (CEA)	No	
Percutaneous coronary interventional procedure (PCI)	No	
Coronary artery bypass graft procedure (CABG)	No	
Any or unspecified revascularization procedure	No	
Serious adverse events	Yes	No significant difference was observed for the outcome in one 8 week trial in a mixed population (OR 4.44; 0.49, 40.29)
Cancer	Yes	No significant difference was observed for the outcome in one 240 week trial in a mixed population (OR 1.11; 0.92, 1.34).

Abbreviations: ACS = acute coronary syndrome, CABG = coronary artery bypass graft, CEA = carotid endarterectomy, MI = myocardial infarction, PCI = percutaneous coronary intervention, SAE = serious adverse event

Four trials, randomizing 19002 participants, compared omega-3 fatty acid plus statin combination therapy with statin monotherapy, and reported one or more of the clinical outcomes, serious adverse events or cancer (Table 50).^{141,176,177,180} There were no trials exclusively in females.

Reporting of participants' ethnic background was as follows:

- One trial reported a mean of 96 percent of participants of European descent
- Two trials reported a mean of 51 percent of participants of Asian descent (range 1 to 100 percent)
- One trial reported a mean of 2 percent of participants of Hispanic descent
- One trial reported a mean of 1 percent of participants of African descent

Trial duration ranged from five to 240 weeks with an average of 69 weeks. Although no trial totally excluded the female gender, on average 42 percent of participants were women (range 27 to 69 percent).

The average of mean ages of participants was 56 years (range 47 to 61 years).

All trials recruited outpatients with the exception of one trial in which recruitment was not reported.¹⁴¹

The mean Jadad score for trial reports was 3 (range 2 to 4), and two trials reports reported an adequate method of allocation concealment.^{141,180}

Of the four trials, only one trial was exclusively in participants requiring intensive lipid lowering treatment (i.e. participants with established vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL).¹⁷⁶

Long-Term Efficacy, Serious Adverse Events, and Cancer

Comparing statin plus omega-3 fatty acids versus statin monotherapy (lower dose vs. higher dose and various statin doses)

All-cause mortality. All-cause mortality data was reported for three trials,^{141,177,180} all of which were in populations not in particular need of intensive lipid lowering and using various statins and doses. Two of these trials presented an adequate form of allocation concealment,^{141,180} and one trial which had a long-term followup of 240 weeks (Table 50).¹⁴¹ Of the trials, only one yielded analyzable data.¹⁴¹ This trial report demonstrated no statistically significant difference in the incidence of mortality between omega-3 plus statin combination therapy and statin monotherapy, with an odds ratio of 1.08 (95% CI 0.91, 1.28), based 551 events.

Myocardial infarction. Incidence of myocardial infarction as well as non-fatal myocardial infarction was reported for one trial,¹⁴¹ which had a followup duration of 240 weeks (Table 50). Fatal myocardial infarction was reported for two trials, which had long-term followup durations of 24 weeks and 240 weeks.^{141,176}

Incidence of myocardial infarction was available for one trial which demonstrated no significant difference between omega-3 plus statin combination therapy and statin monotherapy, with an odds ratio of 0.76 (95% CI 0.56, 1.04) based upon 164 events.¹⁴¹ Non-fatal myocardial infarction data from the same trial demonstrated no statistically significant difference in the incidence of non-fatal myocardial infarction, with an odds ratio of 0.75 (95% CI 0.54, 1.03), based upon 145 events.¹⁴¹

Pooling of fatal myocardial infarction data from two trials demonstrated no statistically significant difference in the incidence of fatal myocardial infarction between omega-3 plus statin combination therapy and statin monotherapy, with an odds ratio of 0.73 (95% CI 0.34, 1.58), based upon 25 deaths.^{141,176}

Stroke. Stroke, hemorrhagic stroke and ischemic stroke, were reported for one trial, which had a followup duration of 240 weeks (Table 50).¹⁴¹ There was no significant difference in the incidence of participants with stroke (hemorrhagic or ischemic) between the omega-3 plus statin combination therapy and statin monotherapy, with an odds ratio of 0.42 (95% CI 0.10, 1.87), based upon 328 participants experiencing stroke. This incidence was similar for participants with hemorrhagic stroke (OR 1.26, 95% CI 0.83, 1.91) and ischemic stroke (OR 0.93, 95% CI 0.72, 1.21).

Serious adverse events. Data on the incidence of serious adverse events was reported for one trial (Table 50).¹⁸⁰ Data from this trial demonstrated that there was no significant difference in the incidence of patients developing a serious adverse event, with an odds ratio of 4.44 (95% CI 0.49, 40.29), based upon five cases.

Cancer. Data on the incidence of cancer was reported for one trial (Table 50).¹⁴¹ There was no significant difference in the incidence of patients developing cancer, with an odds ratio of 1.11 (95% CI 0.92, 1.34), based upon 460 cases.

Key Question 2: Do these regimens differ in reaching LDL-targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

Table 48. Evidence addressing key question 2 for statin plus omega-3 fatty acids versus statin monotherapy comparison

Outcomes	Evidence availability	Key points of evidence synthesis
Patients attaining ATP III LDL-c targets	No	
LDL-c	Yes	In one trial in a population requiring intensive lipid lowering therapy, no significant difference was noticeable (MD -4.60, 95% CI -16.32, 7.12). Compared with monotherapy, in mixed populations, significantly smaller reduction in LDL-c concentrations with omega-3 plus statin combination than statin monotherapy, (MD 5.26 %; 1.79 %, 8.74 %).
HDL-c	Yes	In one trial in a population requiring intensive lipid lowering therapy, no significant difference were noticeable (MD 1.80; 95% CI -5.61, 9.21). Compared with monotherapy, in mixed populations, significantly greater increase in HDL-c concentrations with omega-3 plus statin combination than statin monotherapy, (MD 5.31 %; 95% CI 3.16, 7.45).
TC:HDL ratio	Yes	In one trial in a population requiring intensive lipid lowering therapy, no significant difference were noticeable (MD -0.41; 95% CI -1.43, 0.61). Compared with monotherapy, in mixed populations, significantly smaller reduction in LDL-c concentrations with omega-3 plus statin combination than statin monotherapy, (MD -7.77 %; 95% CI -10.27, -5.27).
CIMT	No	
Treatment Adherence	No	
Total adverse events	Yes	Compared with monotherapy, no significant difference was observed for the outcome in mixed populations (OR 1.11; 95% CI 0.82, 1.51). Long-term trials favored monotherapy over combination (OR 1.22; 1.14, 1.31)
Withdrawal due to adverse events	Yes	Compared with monotherapy, no significant difference was observed for the outcome (OR 1.09; 95% CI 0.22, 5.52).
Elevated serum AST and/or ALT > 3 times ULN and/or hepatitis	Yes	No significant difference in the incidence observed for the outcome as there was no reported incidence in either group
Myalgia	No	
CPK > 10 times ULN	Yes	No reported incidence in either group
Rhabdomyolysis	Yes	No reported incidence in either group

Abbreviations: ALT = alanine transferase, AST = aspartate transferase, ATP III = Third Adult Treatment Panel of the National Cholesterol Education Program, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, TC = total cholesterol

Study Design and Population Characteristics

Ten trials yielded data on participants reaching LDL-c targets and/or other surrogate markers of efficacy, short-term side effects, tolerability, and/or treatment adherence (Table 51 to 54; Appendix F, Table F-230 to F-33).^{107,141,165,175-180,199}

Two trials included participants of Asian descent,^{141,180} with one trial exclusively in participants of Asian descent.¹⁴¹ One trial included participants of Hispanic descent,¹⁸⁰ and one trial included participants of African descent.¹⁸⁰

There were no trials exclusively in females, or participants of Hispanic, and/or African descent.

Reporting of participants' ethnic background was as follows:

- One trial reported a mean of 96 percent of participants of European descent
- Two trials reported a mean of 51 percent of participants of Asian descent (range 1 to 100 percent)
- One trial reported a mean of 2 percent of participants of Hispanic descent
- One trial reported a mean of 1 percent of participants of African descent

Trial duration ranged from 5 to 240 weeks with an average of 34 weeks. Only one trial totally excluded the female gender, and on average 39 percent of participants were women (range 0 to 78 percent). The average of mean ages of participants was 56 years (range 47 to 61 years). Seven of the trials recruited outpatients,^{107,165,175-177,180,199} while three trials did not report recruitment setting.^{141,178,179} The mean Jadad score was 3 (range 2 to 4) and four trials had adequate allocation concealment.^{141,175,180,199}

Of these 10 trials, only two were exclusively in participants requiring intensive lipid lowering treatment (i.e. participants with established vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL).^{175,176}

LDL-c Targets and Other Surrogate Markers

Comparing statin plus omega-3 fatty acids versus statin monotherapy (lower dose vs. higher dose and various statin doses)

LDL-c, change score from baseline. In participants requiring intensive lipid lowering therapy LDL-c mean change from baseline (change score) was reported for one trial employing similar doses of simvastatin in the two treatment groups (Table 51).¹⁷⁵ There was no significant difference in LDL-c reduction in participants on omega-3 plus statin combination therapy compared with statin monotherapy with a mean difference of -4.60 (95% CI -16.32, 7.12).

LDL-c, percentage mean change from baseline. The surrogate outcome LDL-c percentage change from baseline was reported for 278 participants in two trials employing identical doses of statins in combination and monotherapy treatment groups (Table 51).^{107,180} Pooling demonstrated a significantly smaller reduction in LDL-c concentrations with omega-3 plus statin combination than statin monotherapy, with a mean difference of 5.26 (95% CI 1.79, 8.74) favoring statin monotherapy (Figure 63).

HDL-c, change score from baseline. In participants requiring intensive lipid lowering therapy HDL-c mean change from baseline (change score) was reported for one trial (Table 52).¹⁷⁵ There was no significant difference in changes in HDL-c concentrations between omega-3 plus statin combination therapy and statin monotherapy, with a mean difference of 1.80 (95% CI -5.61, 9.21).

HDL-c, percentage mean change from baseline. The surrogate outcome HDL-c percentage change from baseline was reported for three trials (Table 52).^{107,178,180} Pooling demonstrated a significantly greater HDL-c increase with omega-3 plus statin combination therapy than with statin monotherapy, with a mean difference of 5.31 percent (95% CI 3.16, 7.45).

TC:HDL-c ratio, change score from baseline. TC:HDL-c ratio in participants requiring intensive lipid lowering therapy. TC:HDL-c mean change ratio from baseline was reported for one trial (Table 53).¹⁷⁵ There was no statistically significant difference between omega-3 plus statin combination therapy and statin monotherapy, with a mean difference of -0.41 (95% CI -1.43, 0.61).

TC:HDL-c ratio, percentage mean change from baseline. TC:HDL-c. Two reports presented data for TC:HDL-c ratio percentage change from baseline (Table 53).^{178,180} Pooling demonstrated a significantly greater decrease in TC:HDL-c concentrations following omega-3 plus statin combination therapy than with statin monotherapy, with a mean difference of -7.77 percent (95% CI -10.27, -5.27).

Harms and Treatment Adherence

Comparing statin plus omega-3 fatty acids versus statin monotherapy (lower dose vs. higher dose and various statin doses)

Participants with at least one adverse event. The incidence of participants experiencing an adverse event was reported for six trials,^{141,165,176,177,179,180} three of which presented analyzable data (Table 54).^{141,176,180} Meta-analysis demonstrated no significant difference in the incidence of patients with adverse events following omega-3 plus statin combination therapy compared with statin monotherapy, with an odds ratio of 1.11 (95% CI = 0.82, 1.51). Two trials had a followup duration of 24 weeks or more (range 24 to 240 weeks).^{141,176} Pooling of the data from these trials demonstrated a significantly higher incidence with omega-3 plus statin combination therapy than with statin monotherapy, with an odds ratio of 1.22 (95% CI = 1.44, 1.31) based upon 4377 participants with events.

Rhabdomyolysis. The number of participants with rhabdomyolysis was reported for one trial, with no events in either arm (Table 54).¹⁸⁰

CPK above 10 times the upper limit of normal. The number of participants with CPK above 10 times the upper limit of normal was reported for three trials, with no events in any treatment arm (Table 54).^{165,177,180}

Elevated serum AST and/or ALT above 3 times the upper limit of normal and/or hepatitis. The number of participants with elevated serum AST and/or ALT above 3 times the upper limit of normal and/or hepatitis was reported for three trials, with no events in any treatment arm (Table 54).^{165,177,180}

Key Question 3: Compared with higher-dose statins, and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

Table 49. Availability of evidence addressing key question 3 for statin plus omega-3 fatty acids versus statin monotherapy comparison

Condition	All-cause mortality	Vascular Death	Participants reaching ATP III LDL-c targets	LDL-c	HDL-c	TC:HDL-c ratio	Non-HDL-c	TG
LDL-c \geq 190 mg/dL	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
Diabetes mellitus	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence
Established vascular disease	No available evidence	No available evidence	No available evidence	√	√	√	Not applicable	
Cerebrovascular disease	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
African descent	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
Asian descent	√	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
Hispanic descent	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
Females	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	
Age 80 years or more	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	Not applicable	

Abbreviations: Abbreviations: ATP III = the third Adult Treatment Panel III Adult Treatment Panel of the National Cholesterol Education Program, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, TC = total cholesterol

Clinical Outcomes

Comparing statin plus omega-3 fatty acids versus statin monotherapy (lower dose vs. higher dose and various statin doses)

All-cause mortality.

Participants of Asian descent. One trial presented data regarding all-cause mortality within a subgroup of persons of Asian descent.¹⁴¹ The trial utilized an adequate form of allocation concealment and had a followup of 240 weeks. There was no statistically significant difference in the incidence of mortality between the participants on omega-3 plus statin combination therapy compared with statin monotherapy, with an odds ratio of 1.08 (95% CI 0.91, 1.28) based 551 deaths.

LDL-c Targets and Other Surrogate Markers

Comparing statin plus omega-3 fatty acids versus statin monotherapy (lower dose vs. higher dose and various statin doses)

Participants with established vascular disease. Evidence was available only for this subgroup.

LDL-c mean change from baseline was reported in one trial.¹⁷⁵ There was no significant differences in LDL-c concentrations between omega-3 plus statin combination therapy and statin monotherapy, with a mean difference of -4.60 (95% CI -16.32, 7.12).

HDL-c mean change from baseline was reported in one trial.¹⁷⁵ There was no significant difference in HDL-c concentrations between omega-3 plus statin combination therapy and statin monotherapy, with a mean difference of 1.80 (95% CI -5.61, 9.21).

TC:HDL-c ratio mean change ratio from baseline was reported for one trial.¹⁷⁵ There was no statistically significant difference between omega-3 plus statin combination therapy and statin monotherapy, with a mean difference of -0.41 (95% CI -1.43, 0.61).

Strength of Evidence

The strength of the available evidence was assessed as GRADE (Grading of Recommendations Assessment, Development and Evaluation)²²⁵ for the key outcomes all-cause mortality, vascular death, serious adverse events and achieving ATP-III target LDL-c. Results generated using the GRADEpro software are presented in Tables H-12 to H-16 (Appendix H) can be summarized as follow:

1. Based on studies in participants regardless of baseline risk and comparing the combination of any dose statin plus omega-3 to any dose statin, GRADE was “very low” for all cause mortality (3 trials), and serious adverse events (1 trial) (Appendix H, Table H-24).
2. Based on a single study in participants followed up for more than 24 weeks, GRADE was “very low” for all cause mortality for the combination of any dose statin plus omega-3 compared to any dose statin (Appendix H, Table H-25).
3. Based on a single study in participants with of Asian descent, GRADE was “very low” for all cause mortality for the combination of any dose statin plus omega-3 compared to any dose statin (Appendix H, Table H-25).

Evidence Summary Tables: Statin Plus Omega-3 Fatty Acid Combination Therapy Versus Statin Monotherapy

Table 50. Quantitative syntheses of longer term outcomes data (clinical, serious adverse events and cancer) for omega-3 fatty acid plus statin therapy compared with statin monotherapy

Population	Number of trials reporting outcome	Number of participants in relevant intervention groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
All-cause mortality						
All trials ^{141,177,180}	3	18940	551	1.08	0.91	1.28
All trials 24 weeks or more followup ¹⁴¹	1	18645	551	1.08	0.91	1.28
Adequate allocation concealment ^{141,180}	2	18899	551	1.08	0.91	1.28
Participants of Asian descent ¹⁴¹	1	18645	551	1.08	0.91	1.28
Fatal myocardial infarction						
Participants requiring intensive lipid lowering therapy ¹⁷⁶						
Participants with vascular disease – All trials ¹⁷⁶	1	254	1	0.29	0.01	7.39
Participants with vascular disease – All trials 24 weeks or more followup ¹⁷⁶						
All trials ^{141,176}	2	18700	26	0.73	0.34	1.58
All trials 24 weeks or more followup ^{141,176}						
Non-fatal myocardial infarction						
All trials ¹⁴¹						
All trials 24 weeks or more followup ¹⁴¹	1	18645	145	0.75	0.54	1.03
Unspecified myocardial infarction						
All trials ¹⁴¹	1	18645	164	0.76	0.56	1.04
All trials 24 weeks or more followup ¹⁴¹						
Hemorrhagic stroke						
All trials ¹⁴¹						
All trials 24 weeks or more followup ¹⁴¹	1	18645	88	1.26	0.83	1.91
Ischemic stroke						
All trials ¹⁴¹						
All trials 24 weeks or more followup ¹⁴¹	1	18645	238	0.93	0.72	1.21
Unspecified stroke						
All trials ¹⁴¹						
All trials 24 weeks or more followup ¹⁴¹	1	18645	328	0.42	0.10	1.87
Serious adverse events						
All trials ¹⁸⁰	1	254	5	4.44	0.49	40.29
Cancer						
Cancer ¹⁴¹	1	18645	460	1.11	0.92	1.34

Abbreviations: CI 95% confidence interval

Table 51. Quantitative syntheses of LDL-c data for omega-3 fatty acid plus statin therapy compared with statin monotherapy

Population	Number of trials reporting outcome	Number of participants in relevant intervention groups	Point Estimate	Lower CI	Upper CI
Difference in mean change from baseline					
Participants requiring intensive lipid lowering therapy ¹⁷⁵	1	40	-4.60	-16.32	7.12
Participants with vascular diseases ¹⁷⁵					
Difference in mean percentage change from baseline (%)					
All trials ^{107,180}	2	278	5.26	1.79	8.74

Abbreviations: CI = 95% confidence interval, HDL-c = high density lipoprotein cholesterol

Table 52. Quantitative syntheses of HDL-c data for omega-3 fatty acid plus statin therapy compared with statin monotherapy

Population	Number of trials reporting outcome	Number of participants in relevant intervention groups	Point Estimate	Lower CI	Upper CI
Difference in mean change from baseline					
Participants requiring intensive lipid lowering therapy ¹⁷⁵	1	40	1.80	-5.61	9.21
Participants with vascular diseases ¹⁷⁵					
Difference in mean percentage change from baseline (%)					
All trials ^{107,178,180}	3	297	5.31	3.16	7.45

Abbreviations: CI = 95% confidence interval, HDL-c = high density lipoprotein cholesterol

Table 53. Quantitative syntheses of total cholesterol : HDL-c ratios, for omega-3 fatty acid plus statin therapy compared with statin monotherapy

Population	Number of trials reporting outcome	Number of participants in relevant intervention groups	Point Estimate	Lower CI	Upper CI
Difference in mean change from baseline					
Participants requiring intensive lipid lowering ¹⁷⁵	1	40	-0.41	-1.43	0.61
Participants with established vascular diseases ¹⁷⁵					
Difference in changes in mean percentage change from baseline TC:HDL-c					
All trials ^{178,180}	2	273	-7.77	-10.27	-5.27

Abbreviations: CI = 95% confidence interval, TC = total cholesterol, HDL-c = high density lipoprotein cholesterol

Table 54. Quantitative syntheses of short term harms and adherence, for omega-3 fatty acid plus statin therapy compared with statin monotherapy

Population	Number of trials reporting outcome	Max dose omega-3	Number of participants in relevant intervention groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Relative probability of an adverse event							
All trials ^{141,165,176,177,179,180}	6	1800 – 9200	19074	4491	1.11	0.82	1.51
Trials 24 weeks or longer ^{141,176}	2	1800 – 4000	18700	4377	1.22	1.14	1.31
Relative probability of participants withdrawing from treatment due to an adverse event							
All trials ¹⁸⁰	1	4000	255	6	1.09	0.22	5.52
Relative probability of participants experiencing elevated serum AST and/or ALT > 3 times the upper limit of normal and/or hepatitis							
All trials ^{165,177,180}	3	2000 – 4000	337	0			
Relative probability of participants experiencing CPK greater than 10 times the upper limit of normal							
All trials ^{165,177,180}	3	2000 – 4000	337	0			
Relative probability of participants experiencing rhabdomyolysis (investigator defined)							
All trials ¹⁸⁰	1	4000	254	0			

Abbreviations: ALT = alanine transaminase, AST = aspartate transaminase, CI = 95% confidence interval, CPK = creatinine phosphokinase

Applicability of the Body of Evidence for All Comparisons

	Available evidence	Implications
Population	In general studies excluded participants with statin associated myopathy, deranged liver enzymes, high triglycerides, recent vascular events, uncontrolled hypertension, diabetes mellitus and frail elderly over 80 years. Most trials were in mixed CHD risk populations, employed pre-randomization run-in phase to minimize non-adherence, and conducted frequent laboratory monitoring for liver and muscle enzyme elevations to withdraw participants with deranged levels	There is dearth of evidence directly examining comparative effectiveness of treatments. Available evidence mostly compared statin combination therapy with similar or equipotent doses of statin monotherapy and examined relative efficacy using surrogate outcomes over a short-term period. Only one large statin-omega-3 trial can be considered an effectiveness trial, however, this trial examined various statins in various doses in combination and as monotherapy. Direct comparative evidence of clinical effectiveness was also lacking from long-term observational studies
Intervention and comparators	Studies generally employed therapeutic doses of interventions, but few compared addition of another non-statin lipid lowering drug to a statin with the alternative of statin dose escalation	
Outcomes	Clinical outcomes except for evident all-cause mortality were infrequently assessed. Nevertheless, all-cause mortality was a rare event across most trials	
Followup duration	Most trials were of less than 6 months duration	

Summary and Discussion

This report addresses the effectiveness and safety of adding lipid modifying agents to statin therapy. Few long term studies were available reporting on major clinical endpoints such as incidence of myocardial infarction, mortality, adverse events and adherence. Most of the available evidence focused on short term studies of surrogate markers linked to vascular disease. The largest number of trials was found for the ezetimibe plus statin combination, with fewer studies for other combinations.

In treated individuals whose lipid profile is suboptimal the clinician must decide whether to increase the dose of statin and continue monotherapy or to add another medication. However, the comparator for most trials was not a higher, but rather the same dose of statin monotherapy. Indeed, a number of publications specifically stated that the comparator was the starting dose of the particular ongoing statin. Of note, a recent meta-analysis comparing more intensive statin treatment with less intensive treatment demonstrated a significant reduction in LDL-c levels in high risk patients with more intensive therapy. No statistical difference was observed in discontinuation rates attributable to drug related harms.²²⁶ Further, as discussed below, multiple medications may decrease adherence to treatment, a critical factor in determining the outcomes of individuals on long term preventive therapies.

The choice of nonstatin medication to be added to therapy was more difficult to address. A single included study compared statin combination therapies using niacin or ezetimibe, with statin monotherapy.¹³⁹ All treatments examined resulted in similar reductions in LDL-c, while the niacin combination therapy resulted in significantly greater increases in HDL-c. No other direct comparisons of various combinations were identified, so the effect of these strategies can only be compared indirectly.

Clinical Outcomes

All cause mortality and vascular death in individuals requiring intensive lipid lowering therapy was not specifically examined in trials of combination therapy and higher dose statin monotherapy, for any of the combinations studied.

We therefore examined all trials providing evaluable data on these mortality endpoints, for all statin doses, and found a neutral odds ratio for all-cause mortality with ezetimibe, bile acid sequestrants, fibrate, niacin, or omega-3 fatty acids in combination with statins, compared with statin monotherapy. It should be noted that there were few deaths in the included trials, which is likely a function of the relatively short periods of followup. Thus the statistical power to observe such differences was low. This finding is in keeping with that of Josan et al, who noted a neutral impact on all-cause mortality with intensive statin therapy compared with lower dose statin therapy, in a quantitative systematic review of seven trials.²²⁶ Similar findings were noted for vascular mortality. Among all reports of this outcome there were few participants with fatal myocardial infarctions, with no observed differences between combination and monotherapy treatments. A previous meta-analysis of mortality comparing classes of lipid modifying therapy to placebo suggested benefits from all therapies considered in the present review with the exception of fibrates, which were associated with an excess of noncardiovascular mortality.²²⁷ A subsequent report suggested that this association disappears if trials employing clofibrate are excluded from statistical pooling.²²⁸ Clofibrate is not approved for use in the United States.

No significant difference was noted in the occurrence of non-fatal myocardial infarction or acute coronary syndrome. Indeed, there was no evidence of additional benefit from

combination therapy when compared to higher dose statin monotherapy for any clinical outcomes. Several caveats are important to note regarding clinical outcomes. First, as noted above, most of the evidence to date has focused on short duration studies aimed at intermediate outcomes and there is insufficient data for most outcomes of clinical importance. Second, the comparator arms rarely explored higher statin doses which may have advantages in terms of medication adherence and, for some medications, cost. While some data exists for the benefit of niacin and sequestrants alone or in combination with a statin in coronary heart disease, it remains unclear if the marginal benefit of adding these agents to a lower dose of a statin is a better strategy than increasing statin dose, particularly for individuals managed to ATP III targets.⁴³

Stroke was a very rare event in this group of trials and no conclusions can be drawn regarding the differential impact of these interventions on its occurrence. While stroke is commonly considered to be an indication for lipid modification, note should be made that the NCEP ATP III guidelines specify symptomatic carotid disease as a coronary heart disease risk equivalent. This therefore excludes cardioembolic stroke, stroke due to small vessel disease and intracerebral hemorrhage as guideline supported indications for therapy. Ample evidence supports the beneficial effects of statins on stroke incidence in individuals with cardiac disease, but there is only a single trial demonstrating benefit from statin therapy in individuals treated after stroke.^{18,229} In addition, lower cholesterol levels are associated epidemiologically with higher rates of intracranial hemorrhage, and statin treatment may increase the likelihood of its occurrence.^{230,231} Thus the therapeutic window, balancing potential risks and benefits, for treatment following stroke may be narrower than for coronary heart disease. Further work is required to identify the characteristics of individuals with stroke whose potential for benefit with intensive lipid lowering exceeds any potential for harm. Specifically, trials are required with significant recruitment from secondary prevention stroke populations.

Serious Adverse Events

Our review of serious adverse events and cancer was not constrained to specific statin dose comparisons but rather included all trials comparing combination therapy with statin monotherapy. The ezetimibe combination had the largest number of trials reporting this outcome, but the majority of these were less than 24 weeks duration, with a small minority reporting up to 52 weeks. In these longer duration studies the serious adverse events rate was approximately 10 percent in the combination and monotherapy groups, with no significant difference in proportions of participants experiencing serious adverse events between groups. One large trial of omega-3 fatty acids added to statin therapy in a Japanese population did not demonstrate any increase in cancer compared with monotherapy.¹⁴¹ Data for the other interventions was sparse or had significant limitations.

Surrogate Outcomes

Ample evidence supports the selection of LDL-c as the primary target for lipid modifying therapy. A number of studies have established the correlation of LDL-c cholesterol and incident coronary heart disease or recurrent myocardial infarction in men and women.²³²⁻²³⁷ Law et al, in a review of 164 trials of statins noted that these interventions reduce LDL-c by an average of 70 mg/dL, with a range from 70 to 108 mg/dL. For each reduction of 40 mg/dL cardiac events were reduced by 11 percent in the first year, 24 percent in the second and over 30 percent subsequently.²³⁸ A lower incidence of major cardiovascular events is associated with more intensive statin therapy than with less intensive treatment.²²⁶

When compared to a higher dose of statin, no significant difference was found in LDL-c reduction for fibrate in combination with statins compared with statin monotherapy in populations requiring intensive lipid lowering therapy. However, in two trials, 10 to 20 percent significant additional mean percentage reductions in LDL-c were demonstrated in high CHD risk participants, in favor of lower dose simvastatin plus ezetimibe combination therapy compared with higher dose monotherapy. There were no trials with this comparison for niacin, bile acid sequestrants or omega-3 combinations with statins.

Overall, there was at best scant evidence to support a greater lowering of LDL-c with any of the five combinations reviewed than with higher dose statin therapy in participants requiring intensive lipid lowering therapy. However, when combinations were compared with similar doses of statin monotherapy in this population, statin-ezetimibe combinations caused additional reductions in LDL-c compared with statin monotherapy. In populations requiring intensive lipid lowering therapy, all 18 trials exceeding 6 weeks in duration of statin-ezetimibe combination therapy were associated with a greater reduction in LDL-c ranging from 4 to 27 percent. This compares to indeterminate or inconsistent results for Fibrates, BAS, Niacin and Omega-3, possibly due to small sample sizes, differences in statin dosages, or few to absent trial data in populations requiring intensive lipid lowering therapy. Both BAS and ezetimibe interfere with absorption from the intestines and would be expected to have an impact on LDL-c levels. When used as monotherapy, BAS have been shown to decrease LDL-c by 15 to 30 percent^{43,239} and ezetimibe by 18 percent,²⁴⁰ while the LDL-c reduction by fibrate has been considered to be marginal.²⁴¹

Evidence was reviewed for the outcome of attainment of ATP III LDL-c goals for combination therapy compared with a higher dose statin. Ezetimibe in combination with lower dose simvastatin compared with higher dose simvastatin monotherapy was associated with a significantly greater odds of attaining the LDL-c target, with an odds ratio of 7.21 (95% CI 4.30, 12.08), on the basis of two pooled trials. No difference was noted for fibrate on the basis of a single small trial, and no evidence was available for niacin, BAS or omega-3 combinations. As treatment to a target LDL-c is both the major goal of therapy as well as a justification for using combinations, this represents an important issue to be addressed in future work.

HDL-c is identified in the ATP III report as inversely correlated with coronary heart disease risk, and while the relationship is continuous, a level below 40 mg/dL has been identified as low.⁴³ A target for therapeutic intervention has not been set by these guidelines and it remains unclear whether raising HDL-c has an impact on coronary heart disease that is independent of LDL-c levels. For the direct comparison of combination therapy versus higher dose statin monotherapy, a single trial suggested no difference for combinations with ezetimibe or fibrate in participants requiring intensive lipid lowering therapy. In another trial, a significant increase in mean percentage change was noted for the combination of rosuvastatin 10 mg/day plus niacin 2 g/day compared with rosuvastatin 40 mg/day monotherapy in participants with combined dyslipidemia and low HDL-c (below 45 mg/dL), who were not necessarily in need of intensive lipid lowering therapy. Niacin has an effect on HDL-c levels at low doses, while higher doses are required to reduce LDL-c.⁴³ Thus these findings are consistent with previous work with this agent.¹⁹⁶

Some evidence suggests that treatment with niacin plus a statin may affect the progression of intermediate markers of atherosclerosis. Taylor et al examined the progression of CIMT in individuals with CAD and HDL-c below 45 mg/dL, treated with niacin or placebo added to ongoing statin therapy. Over a one year period combination therapy was associated with

a nonsignificantly lower rate of progression than the comparator monotherapy group. The majority of the comparator group was on a statin, usually simvastatin, but the diversity of statin treatments in this group makes interpretation somewhat difficult.¹⁹⁶ While the accumulated evidence suggests that raising HDL-c levels may be helpful in high risk populations, the target levels and optimal strategies remain unknown.

Two trials investigated this outcome measure in participants in need of intensive lipid lowering therapy. One compared niacin-statin combination with background statin monotherapy (ARBITER-2) while the other investigated simvastatin 80 mg/day plus ezetimibe 10 mg/day, compared with simvastatin 80 mg/day monotherapy (ENHANCE trial). No significant differences were found between the treatments. No evidence was found pertaining to the question of lower dose statin in combination therapy versus higher dose monotherapy for CIMT. The ENHANCE trial was similar in design to the two year ASAP trial that showed significant regression in CIMT with atorvastatin 80 mg/day compared with simvastatin 40 mg/day.²⁴² Important differences can be recognized between the ASAP and ENHANCE trials, including a higher baseline CIMT and inclusion of statin naïve participants in ASAP. Further, as pointed out by Brown and Taylor, none of the intervention studies on CIMT of two years or less duration have demonstrated an effect.⁴¹ The questions surrounding the findings of the ENHANCE trial will require further long term studies focused on clinical outcomes.

Adherence and Harms

Scant evidence exists, comparing short term harms and treatment adherence for lower dose statin in combination therapy with higher dose monotherapy across all populations. No significant treatment differences were noted.

A common adverse event with niacin is flushing, reported by as many as 88 percent of individuals initiating slow release niacin.²⁴³ Of note however, the absolute rates of withdrawal in niacin plus statin treatment groups in four trials were not more than 10 percent, even with significant odds in favor of monotherapy (2.38, 95% CI 1.63, 3.47). On average 5 percent withdrew from statin plus BAS combination therapy in contrast to 2 percent from statin monotherapy, but the pooled odds from nine trials was not significant (OR 1.80; 95% CI 0.68, 4.76).

No participant developed rhabdomyolysis across all 87 RCTs investigating five statin combination therapies. These results are recognized in and consistent with extant literature.²⁴⁴ However, this lack of evidence fails to shed light upon the relative safety of lower dose statin in combinations, compared with higher dose monotherapy.

Comparing statin combination therapies with monotherapy using similar statin doses in single trials, significantly fewer participants adhered to pravastatin plus cholestyramine combination therapy (OR 0.41, 95% CI 0.26, 0.65), rosuvastatin plus cholestyramine (OR 0.10, 95% CI 0.04, 0.25), and rosuvastatin plus niacin combination treatments (OR 0.42, 95% CI 0.21, 0.85).

Medication adherence is a significant issue in determining population benefit. In a population based cohort study, Sokol demonstrated an association between medication adherence and lower medical costs and reduced hospitalization rates in individuals with hypercholesterolemia.²⁴⁵ In general, medication nonadherence rates range from 20 to 50 percent.^{246,247} Chronic conditions and preventive therapies are associated with poorer adherence rates than acute conditions.²⁴⁷ The complexity of medication regimen and the number of medications may play a role in adherence.^{248,249} Thus there may be benefit from less complex

regimens employing fewer separate agents. Medication adherence and persistence are related but distinct concepts. Adherence is defined as the extent to which an individual acts in accordance with the prescribed interval and dose of a dose regimen while persistence is the accumulation of time from initiation to discontinuation of therapy.²⁵⁰ The previous literature uses the terms interchangeably. While this report refers to adherence, this outcome was rarely reported and for most reports we could only extract data regarding the proportion of participants withdrawing from treatment.

Subgroups

There is dearth of evidence regarding lower dose statin in combination therapy versus higher dose monotherapy in subgroups. Absence of evidence or at best scant trial evidence precluded definitive conclusions regarding short term and longer term efficacy.

Seven trials were included which reported on surrogate outcomes in participants with diabetes mellitus, comparing ezetimibe combination therapy with statin monotherapy. Considerable heterogeneity precluded a summary point estimate, but the results favored combination therapy in all trials with the mean percentage change in LDL-c from baseline ranging from 4 to 26 percent. Only one trial compared higher dose monotherapy with combination therapy. Asymmetry of the funnel plot was noted in this group of trials. While such asymmetry may be the consequence of publication bias it can be observed for other reasons including heterogeneity. The small number of studies and the presence of heterogeneity in this group of trials makes it difficult to ascribe the observed lateralization to publication bias.²⁵¹

There was no analyzable evidence comparing lower dose statin combination therapy with higher dose statin monotherapy for the mean percentage change from baseline or changes scores in participants with diabetes mellitus. Reductions in triglyceride levels and elevations in HDL-c are considered to be desirable, albeit with a lower level of evidence. Both non-HDL-c cholesterol and apolipoprotein b (Apo-B) correlate with cardiovascular risk. The ATP III guidelines recommend non-HDL-c as a secondary target in individuals with hypertriglyceridemia. A single trial compared combination therapy with fibrates versus a higher dose statin in individuals with diabetes. The combination was favored with a mean percentage change from baseline of -13.57 mg/dL (95% CI -24.16 mg/dL, -2.98 mg/dL).¹²⁵ Evidence was available for non-HDL-c in diabetics for the comparison of combination therapy with ezetimibe or fibrates, with similar dose statin monotherapy. In six trials an additional reduction of 4 to 27 percent was seen with the addition of ezetimibe to statin. A single trial with fibrate combination therapy resulted in no significant benefit.

While current treatment guidelines in diabetes continue to support the primacy of statin therapy and LDL-c reduction in managing vascular risk,²⁵² a consensus panel assembled by the American Diabetes Association and the American College of Cardiology Foundation recommended targets for both non HDL-c and Apo-B in individuals with diabetes, established cardiac disease or combinations of risk factors.²⁵³ The panel acknowledged that further data was needed regarding these therapeutic targets and that there was a lack of robust data on the effects of combination therapies on outcomes. The optimal management of individuals with diabetes as well as the role of targets other than LDL-c will continue to evolve as the results of ongoing trials of niacin and fibrates in combination with statins become available.

With few exceptions, included trials were mixed with respect to gender, but limited subgroup data in women did not show a definitive difference in LDL-c reduction between lower dose statin plus ezetimibe combination therapy versus higher dose statin monotherapy. This

finding may be the result of the small number of participants available for analysis. Most trials were comprised of a majority white population of European descent. Goff et al in a multicenter cohort study reported that the prevalence of dyslipidemia was similar in populations of African and Hispanic descent in the US, but that they were less likely to be treated or controlled.²⁵⁴ Mexican Americans are significantly less likely than non-Hispanic whites to be aware of and treated for dyslipidemia, despite having only slightly lower prevalence of the condition. While access and socioeconomic issues impact treatment and control, members of both populations fall into groups who require lipid modifying treatment and trials of these therapies should reflect that reality.

Demographic trends suggest that the elderly will grow more sharply than other segments of the population, with those over 65 increasing from 37 million in 2005 to 81 million in 2050.²⁵⁵ The average age of participants in included trials was in the fifties, limiting generalizability to older populations. Deedwania et al compared moderate statin therapy (pravastatin 40 mg/day) with intensive therapy (atorvastatin 80 mg/day) in individuals aged 65 to 85 years, with coronary artery disease. The atorvastatin group had fewer deaths and major cardiac events, though there was an increase in the proportion with elevated hepatic enzymes.²⁵⁶ Robinson et al²⁵⁷ examined 16 trials of ezetimibe plus statin or placebo combination therapy and statin monotherapy. All included trials were performed by Merck/Schering Plough and published by December 2006. A four week single blind placebo run in was followed by a treatment period of six to 12 weeks. The analysis was not by intention to treat. Of the over 13,000 individuals randomized, approximately 4,400 were over 65 years, of whom 1,147 were over 75 years of age. Neither the treatment effect for surrogate outcomes nor the incidence of adverse events varied significantly by age group. Limitations, including trial selection and short durations, limit the applicability of this review. Further it must be acknowledged that individuals over the age of 65 are heterogeneous with respect to the probability of benefit as well as susceptibility to adverse events. Trials of combination therapy need to involve the larger population of Americans at older ages who require therapy, to confirm efficacy and tolerability.

Long-term nonrandomized studies directly investigating clinical effectiveness, serious adverse events and cancer were also lacking. Sparse event data in the three included studies could not guide any definitive conclusions.

C-reactive protein is an inflammatory biomarker which predicts vascular risk and may improve risk stratification beyond that afforded by LDL-c.²⁵⁸ Ridker et al examined the impact of rosuvastatin monotherapy in a group of apparently healthy individuals with LDL-c levels below current levels for drug therapy, but elevated levels of C-reactive protein.²⁵⁹ Significant reductions in the occurrence of cardiac events, stroke and vascular death were observed in the treated group, suggesting that this biomarker may identify a subgroup for treatment. The role of combination therapy in this population has not been studied to date.

Limitations

Our review does not examine specifically the addition of a combination medication to maximal statin therapy. There are instances, such as familial dyslipidemia, in which maximal statin therapy may be insufficient, so combinations may be required to achieve primary or secondary treatment goals in some individuals.

The assessments of clinical outcomes, harms and treatment adherence were limited by the paucity of long term studies with a sufficient number of events to offer meaningful results. The search for specific harms was limited to prespecified important events rather than all potential

adverse experiences. Thus studies investigating specific minor adverse experiences were not captured unless adverse events lead to nonadherence or withdrawal from treatment. Composite outcomes were rarely reported in the included trials and imputation was not attempted as the possibility of double counting could not be avoided. We used a conservative approach to pooling with a strict limit to allowable heterogeneity which precluded pooling of results in a number of instances.

A number of caveats apply to the evaluation of surrogate outcomes. First, the absolute benefit in measures of LDL-c and HDL-c may depend on the baseline status, including intensity of prior statin therapy and comorbidities. In conducting our review we used percentage change from baseline as that was most commonly reported, as well as change scores if data permitted. Percentage change from baseline has lower statistical power and may fail to protect against bias in the case of baseline imbalances.³ Triglyceride levels may be reported as medians rather than means when the distribution is skewed, but there are no widely accepted methods to pool data reported as medians. For this reason we specifically extracted means because there are techniques to pool these values. However, due to this methodological limitation the impact of therapies on triglyceride levels may be underestimated.

Indirect comparisons are hazardous given the potential differences in trial populations and design. Indirect comparisons may inflate estimates of differences and were not attempted.⁴

A large number of studies were funded by pharmaceutical companies. Evidence suggests that industry sponsorship of research is associated with a greater likelihood of results favoring the sponsored product.⁵⁻⁷ We did not detect many instances of possible publication bias based upon funnel plots in this review, but the power to detect was limited.

A number of concerns regarding trial quality were identified. Only 26 of 87 (30%) included randomized controlled trials reported allocation concealment and 21 (24 percent) reported an intention to treat analysis. Clinical end points were rarely adjudicated and blinding was not consistently reported.

Conclusion

Statin therapy has been an invaluable tool in the prevention of vascular disease, with robust evidence to support benefit for important clinical outcomes. The trend toward more stringent targets and identification of coronary heart disease risk equivalents is increasing the number of Americans being identified as potentially benefitting from lipid modifying therapies, and combination therapy is likely to increase in order to achieve targets expanded populations of high risk individuals.

In summary, the available clinical trial evidence supporting the use of combination therapies over higher dose statin therapy is insufficient to guide clinical decisions. The long term clinical benefits and risks of combination therapies have yet to be demonstrated. There are some instances, such as failure to reach targets in spite of maximal statin therapy, and populations with elevated triglycerides who need to achieve secondary goals, in which clinicians may choose combinations pending definitive evidence.

It is improbable that a single therapeutic strategy will be optimal for all individuals, so future research should be targeted to specific clinical and lipid profiles. A number of questions remain as to the optimal strategies for addressing efficacy, safety and adherence for lipid modification in those requiring intensive therapy. Long term trials examining clinical outcomes are required to resolve these issues.

Remaining Issues

This review has identified a number of areas requiring future research. Our recommendations address research methodologies in general, and specific needs for research to address the key questions.

All trials must clearly report adequate allocation concealment and intention to treat analysis. Blinding and end point adjudication should be employed to minimize bias. Failure to comply with these standards has adversely affected the quality of trials in this therapeutic area.

Pragmatic trials are required in order to provide relevant guidance to practitioners and patients. In trials of this type oversampling of populations of interest including women, ethnic groups, elderly Americans as well as diabetics would help define the relative applicability of the results. Ample evidence supports the role of LDL-c as a determinant of risk as well as a target for therapy. The current data would support investigation of statin-ezetimibe combinations in this regard. Statin-BAS combinations would also be of some interest though the potential for BAS to interact with other medications by limiting absorption would limit the broad application of these findings. Further research is required to establish the relevance of therapy directed at triglycerides and HDL-c with respect to clinical outcomes. Trials of statin-niacin combination in individuals with low HDL-c in spite of statin therapy and in individuals on maximal statin therapy would serve to define the clinical relevance of these combinations and, at this time, seem more likely to produce relevant data than more broadly inclusive trials for this combination. Similarly, trials of statin-fibrate therapy in individuals with elevated triglycerides are recommended. Omega-3 preparations are variable in content and source with no clear accepted formulation for individuals requiring intensive lipid lowering. While a number of benefits have been suggested, it is unclear that statin-omega 3 combination preparations have any benefits over higher dose statins in this population based on the negative data to date. Further investigation of these combinations should focus on optimizing the formulations and establishing added clinical benefit when used in maximally treated populations. The following points apply to the proposed trials of combination therapy and serve to amplify these comments in the context of the Key Questions.

Key Question 1: For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits, and rates of serious adverse events of coadministration of different lipid-modifying agents (i.e. a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

1. The comparator for trials of combination therapy in which LDL-c reduction or clinical events are a major outcome should be a higher dose statin. The bulk of the clinical evidence for this endpoint as well as clinical endpoints exists for statin monotherapy. Until a compelling case can be made for a particular combination therapy, comparisons with similar doses of statin monotherapy are unhelpful in resolving the issue.
2. Studies of combination therapy should be conducted over longer time periods and be powered for clinical endpoints. Since the lipid lowering treatment is usually required for

life, both trial treatment and observation duration should be of longer duration. The current evidence base lacks trials of this type, significantly limiting the conclusions which can be drawn. The specific duration will be determined by the endpoints and the risk profile of the population studied but, in general, studies of less than 2 years are unlikely to add significantly to the evidence base on clinical outcomes.

3. Harms should be prospectively collected and comprehensively reported. Short duration trials are unlikely to accrue sufficient adverse events, particularly those with longer latency periods such as cancer.
4. As the possibility of harm cannot be excluded for some individuals with symptomatic cerebrovascular disease due to the unique risk for cerebral hemorrhage in these individuals, this population should be specifically studied in order to better define the parameters for those in whom intensive combination therapy is recommended.
5. Concomitant and antecedent therapy should be explicitly stated as both of these factors may influence outcomes. In studies employing a mixture of statin medications and/or doses, results should be reported by medication and dose in order to allow pooling across studies.
6. Studies investigating HDL-c and non-HDL-c targets in a population with LDL-c at target are recommended. The absence of such evidence limits the ability to assess the role of combination therapies which raise HDL-c levels.

Key Question 2: Do these regimens differ in reaching LDL-targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

1. The comparator for trials of combination therapy, with LDL-c reduction as a primary outcome, should be a higher dose statin as noted above.
2. Studies to correlate LDL-c with CIMT and clinical outcomes should be conducted in different populations (e.g. participants with diabetes mellitus, CHD, and multiple risk factors as defined by ATP III), with reporting of antecedent therapy as this may be a determinant of outcome. Such work would help further validate CIMT as a suitable surrogate marker for future trials.
3. As medication adherence and persistence are important determinants of outcome and are correlated with the complexity of the treatment regimen, studies should be undertaken to compare combinations delivered as a single pill as opposed to two separate ones.
4. Measures of adherence and persistence are affected by the duration of the study period and thus longer term trials are required for combination therapies of lipid modifying agents. Trial durations of greater than six months and preferably one year are recommended.

Key Question 3: Compared with higher dose statins, and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

1. Trials should be conducted in, or over sample, specific subgroups in order to determine relative benefits and harms of a statin combination compared with statin monotherapy. These groups include women, older individuals more susceptible to harms of drug therapy, participants with diabetes mellitus and multiple risk factors, and those of African, Hispanic and Asian descent.
2. Trials including women and the groups identified above should report results in a manner amenable to extraction and pooling in order to permit the early identification of a differential effect in specific subgroups. Specifically, whenever possible, results should be reported by subgroups in trial publications.

Abbreviations

AAC	adequate allocation concealment	GRADE	Grading of Recommendations Assessment, Development and Evaluation
ACS	acute coronary syndrome		
ALT	alanine transaminase	h	hour
Apo	apolipoprotein	HC	hypercholesterolemia
ApoA-I	apolipoprotein A-I	HDL-c	high density lipoprotein cholesterol
ApoA-II	apolipoprotein A-II		
AST	aspartate transaminase	HDL ₂	subfraction 2 of HDL-c
ATP III	Adult Treatment Panel III (of the NCEP)	HDL ₃	subfraction 3 of HDL-c
Ator	atorvastatin	HF	heart failure
AUC	area under the curve	hsCRP	high sensitivity C-reactive protein
BAS	bile acid sequestrant	HeFH	heterozygous familial hypercholesterolemia
bid	twice daily		
c	calculated	HMG CoA	hydroxymethylglutaryl coenzyme A
CABG	coronary artery bypass graft	HoFH	homozygous familial hypercholesterolemia
C-amine	cholestyramine	HoFS	homozygous familial sitosterolemia
CCT	controlled clinical trial		
CEA	carotid endarterectomy	hsCRP	high sensitivity C-reactive protein
C-lam	colesevelam	IMT	intima-media thickness
CHD	coronary heart disease	ITTA	intention to treat analysis
CIMT	carotid intima-media thickness	LDL-c	low density lipoprotein cholesterol
Cmax	maximum plasma concentration	Lov	lovastatin
CPK	creatine phosphokinase	Lp(a)	lipoprotein A
C-pol	colestipol	max	maximum
CT	conditional titration	MD	mean difference
CVD	cardiovascular disease	MetS	metabolic syndrome
DHA	docosahexaenoic acid	mFF	micronized fenofibrate
dir	direct	MI	myocardial infarction
DM	diabetes mellitus	NIH	National Institutes of Health
eNOS	endothelial nitric oxide	NCEP	National Cholesterol Education Program
EPA	eicosapentaenoic acid		
ER	extended release (for niacin)	NIH	National Institutes of Health
Ez	ezetimibe	non-HDL-c	non-HDL cholesterol
FF	fenofibrate	NPC1L1	Niemann-Pick C1-Like 1 sterol transporter
FH	familial hypercholesterolemia		
FT	fixed titration	NR	not reported
Fluv	fluvastatin	NSAID	non-steroidal anti-inflammatory drug
GF	gemfibrozil		
GI	gastrointestinal		

od	once daily	t½	half-life (time for concentration to decrease to half the initial level)
OL	open label		
Om3	omega-3-acid ethyl esters		
OR	odds ratio	T1DM	type 1 diabetes mellitus
PCI	percutaneous coronary intervention	T2DM	type 2 diabetes mellitus
		TG	triglycerides
Pl	placebo	TIA	transient ischemic attack
Prav	pravastatin	tid	three times daily
q	every	VLDL	very low density lipoprotein
RLP	remnant-like particle	vs	versus
Ros	rosuvastatin	wk	week(s)
SB	single blind	y	year(s)
Sim	simvastatin		