



Effective Health Care

Comparative Effectiveness of Lipid-Modifying Agents *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.

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm



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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 co-administration 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 ¹	Simvastatin ¹	Rosuvastatin ¹	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

¹Dose 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 (4 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.

Full Report

This executive summary is part of the following document: Sharma M, Ansari MT, Soares-Weiser K, Abou-setta AM, Ooi TC, Sears M, Yazdi F, Tsertsvadze A, Moher D. Comparative Effectiveness of Lipid-Modifying Agents. Comparative Effectiveness Review No. 16. (Prepared by the University of Ottawa Evidence-based Practice Center under contract No. 290-02-0021.) Rockville, MD: Agency for Healthcare Research and Quality. September 2009. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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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 co-administration 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.
Serious¹ 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.

¹Because 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.