Systematic Review: Comparative Effectiveness and Harms of Combination Therapy and Monotherapy for Dyslipidemia

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Background: Statin therapy effectively prevents vascular disease, but treatment targets are often not achieved.

Purpose: To compare the benefits and harms of high-dose statin monotherapy with those of combination therapy in adults at high risk for coronary disease.

Data Sources: English-language records from MEDLINE (1966 to 2009), EMBASE (1980 to 2009), and the Cochrane Library (third quarter of 2008).

Study Selection: A reviewer screened records, and a second reviewer verified selection of randomized, controlled trials in adult patients that compared combinations of statins and bile-acid sequestrants, fibrates, ezetimibe, niacin, or ω-3 fatty acids with statin monotherapy, as well as nonrandomized comparative studies that were longer than 24 weeks and reported clinical and harms outcomes.

Data Extraction: Data were abstracted for studies by using standardized forms, and study quality was rated with a standardized scale and strength of evidence by using the Grading of Recommendations Assessment, Development, and Evaluation approach.

Data Synthesis: 102 studies met eligibility criteria. The main analysis compared combination therapy with high-dose statin monotherapy in high-risk patients. Very-low-strength evidence showed that statin–ezetimibe (2 trials; $n = 439$) and statin–fibrate (1 trial; $n = 166$) combinations did not reduce mortality more than high-dose statin monotherapy. No trials compared the effect of combination therapy versus high-dose statin monotherapy on the incidence of myocardial infarction, stroke, or revascularization procedures. Two statin–ezetimibe trials ($n = 295$) demonstrated higher low-density lipoprotein cholesterol goal attainment with combination therapy (odds ratio, 7.21 [95% CI, 4.30 to 12.08]). Trials in lower-risk patients did not show a difference in mortality.

Limitations: Studies were generally short, focused on surrogate outcomes, and were heterogeneous in the sample's risk for coronary disease. Few studies examined treatment combinations other than statin–ezetimibe.

Conclusion: Limited evidence suggests that combinations of lipid-lowering agents do not improve clinical outcomes more than high-dose statin monotherapy. Very-low-quality evidence favors statin–ezetimibe treatment for attainment of low-density lipoprotein cholesterol goals.

Primary Funding Source: Agency for Healthcare Research and Quality.

Ann Intern Med. 2009;151:622-630. www.annals.org
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This article was published at www.annals.org on 1 September 2009.

More than 28 million Americans have some form of cardiovascular disease (1). Resulting medical expenditures and lost productivity cost an estimated $431.8 billion in the United States in 2007 (2). Lowering low-density lipoprotein (LDL) cholesterol levels reduces rates of coronary heart disease (CHD) and ischemic stroke (3, 4). Successive versions of guidelines have established treatment thresholds and recommend aggressive treatment for high-risk persons (5). However, only one third of all patients, and proportionally fewer patients with established CHD, achieve guideline targets (6). Effective strategies in persons requiring intensive lipid-lowering therapy are critically needed.

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After dietary and lifestyle recommendations, statins are first-line medications for lipid-lowering. These agents are used alone or in combination with other lipid-lowering medications. Options for patients requiring intensive lowering of cholesterol levels include an increased dose of a statin alone or use of a statin in combination with a lipid-modifying agent of another class. Ezetimibe, niacin, bile-acid sequestrants, fibrates, and ω-3 fatty acids are available options for combination with statins (7–13). The Agency for Healthcare Research and Quality (AHRQ) commissioned a comparative effectiveness review to evaluate which of these strategies is superior with respect to clinical outcomes. We compare the benefits and risks of high-dose statin monotherapy and combination therapy for clinical events, surrogate measures, tolerability, and adherence in persons requiring intensive lipid-lowering therapy.

METHODS

We address the following 2 key questions:

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 (that is, a statin plus another

lipid-modifying agent) compared with those of higher-dose statin monotherapy?

2. Do these regimens differ in achievement of LDL cholesterol targets (or other surrogate markers), short-term side effects, tolerability, or adherence?

We followed a standard protocol for this review. The full technical report (14) contains a detailed description of the methods and results, including search strategies and additional evidence tables. We expected that few reports would directly address high-risk patients and compare combination therapy with high-dose statin monotherapy. In discussion with AHRQ, we expanded the scope of patient risk and comparator dose to include studies that enrolled mixed-risk patients and used various statin doses.

Data Sources and Searches

We searched MEDLINE from 1966 to May 2009, EMBASE from 1980 to May 2009, and the Cochrane Library to the third quarter of 2008. We searched Scopus for references that cited 8 expert-nominated articles, the U.S. Food and Drug Administration statistical and medical reviews of drug applications, and the Internet. Information on published and unpublished studies of drugs was requested from Abbott, AstraZeneca, and Merck/Schering-Plough Pharmaceuticals by the Oregon Evidence-based Practice Center's Scientific Resource Center. We contacted corresponding authors of included studies for additional unpublished data relevant to the key questions.

Study Selection

We included English-language studies in adult patients that compared combinations of statins plus bile-acid sequestrants, fibrates, ezetimibe, niacin, or ω-3 fatty acids with statin monotherapy. We included randomized, controlled trials that reported mortality rates, vascular events, and lipid levels. Because we expected few long-term randomized trials, we also included long-term (≥24 weeks) nonrandomized comparative studies that reported clinical outcomes, serious adverse events, and cancer incidence. We excluded abstracts and reports on investigational agents.

Data Extraction and Quality Assessment

One reviewer screened record titles or abstracts to include studies; a second reviewer independently verified exclusions. Two reviewers independently screened full-text reports and resolved conflicts by consensus. Data for the longest study follow-up were extracted in standardized forms. We assessed study quality as good, fair, or poor by predefined criteria. We also evaluated the strength of the body of evidence for all-cause mortality, vascular death, Adult Treatment Panel III (ATP III) goal attainment, and serious adverse events by using the Grading of Recommendations, Assessment, Development, and Evaluation approach (15).

Data Synthesis and Analysis

All-cause mortality and vascular death were the main outcomes of interest. Other clinical outcomes were myocardial infarction (MI), the acute coronary syndrome, stroke, transient ischemic attack, and revascularization procedures. We considered the following surrogate outcomes: attainment of ATP III LDL cholesterol goals, LDL cholesterol and high-density lipoprotein (HDL) cholesterol levels, and measures of carotid or coronary atherosclerosis. Harms outcomes were serious adverse events, cancer, withdrawals because of adverse events, incidence of at least 1 adverse event, elevated serum aminotransferase levels, hepatitis, myalgia, creatine kinase levels greater than 10 times the upper limit of normal, and rhabdomyolysis. Treatment adherence was also investigated.

The main analyses were conducted in patients who required intensive lipid-lowering therapy, in which the statin in combination therapy was compared with a high dose of the same statin as monotherapy (**Appendix Table 1**, available at www.annals.org). Patients requiring intensive lipid-lowering therapy included those with a 10-year CHD risk greater than 20%, mean baseline LDL cholesterol levels of at least 5.0 mmol/L (≥190 mg/dL), or both. We expected few reports addressing this specific dose comparison, so we conducted additional analyses unrestricted by patient risk and statin type and dose.

We used the DerSimonian and Laird approach, or Peto odds ratio (OR) for rare events, for meta-analysis. We used Comprehensive Meta-Analysis software, version 2.2046 (Biostat, Englewood, New Jersey). We performed a meta-analysis when the set of trials did not have substantial heterogeneity. We avoided double counting for trials with multiple unequal numbers of treatment groups (14). We examined all-cause mortality, vascular death, and surrogate efficacy outcomes for patients who needed intensive lipid-lowering therapy, as well as for all patients. Evidence syntheses of harms and clinical outcomes other than

Context

Although they are frequently used, whether combinations of lipid-lowering agents improve outcomes more than high-dose statin monotherapy in adults with dyslipidemia is not known.

Contribution

This review of 102 studies found 2 trials that suggested lower target lipid levels were more often achieved with statin–ezetimibe combination therapy than with high-dose statin monotherapy. No firm trial evidence showed that combining a statin with another agent (bile-acid sequestrant, fibrate, ezetimibe, niacin, or ω-3 fatty acids) improved clinical outcomes (myocardial infarction, stroke, or mortality) more often than high-dose statin monotherapy.

Caution

Most trials were of short duration, focused on surrogate outcomes, and used similar doses of statins in the combination and monotherapy groups.

—The Editors

all-cause mortality and vascular death were done regardless of patient risk. We defined long-term trials as those lasting longer than 24 weeks.

Role of the Funding Source

The review was funded by AHRQ. Staff from AHRQ participated in the formulation of the research questions and reviewed the methods and the draft report but were not involved in study selection, data abstraction, and synthesis of results or approval of the manuscript for publication.

RESULTS

We screened 9735 records and reviewed 923 full-text articles. The initial search was performed in August 2008 and updated in May 2009. When updating the evidence, we restricted inclusion to clinical efficacy outcomes, serious adverse events, and cancer incidence from studies of at least 24 weeks' duration. We included 98 unique randomized, controlled trials (RCTs) (16–113) and 4 nonrandomized studies (114–117) (**Appendix Figure** and **Appendix Table 2**, available at www.annals.org).

Characteristics of Included Studies

Few studies compared combination therapy with high-dose statin monotherapy particularly in patients requiring intensive lipid-lowering therapy. Most studies were of fair quality, used strict eligibility criteria, excluded very sick patients, and compared similar doses of statins in combination and monotherapy, focusing on surrogate outcomes over a short-term period. Few clinical events were reported in the nonrandomized studies. Results are presented by outcome, the 10-year CHD risk stratum of the trial sample, and the statin dose in the monotherapy group. The **Table** summarizes the overall strength of evidence for the important outcomes.

Mortality

Three fair- to poor-quality RCTs comparing statin–ezetimibe (19, 108) and statin–fibrate (24) with high-dose statin monotherapy reported all-cause mortality in high-risk patients, but none specified vascular death. Death was rare, and no difference between treatments was noted.

Meta-analysis of 14 short-term fair-quality trials ($n = 6275$) that used various doses and types of statins in combination with ezetimibe compared with statin monotherapy in high-risk patients showed no statistically significant difference (but a wide confidence bound) in mortality (OR, 0.61 [95% CI, 0.22 to 1.71]) (19, 30–32, 34, 81, 83, 84, 86, 88, 95, 106, 108, 112). In an analysis unrestricted by patient risk and dose, we meta-analyzed 3 fair-quality trials with more than 18 000 participants for the statin–ω-3 fatty acids combination and found no statistically significant difference in mortality (OR, 1.08 [CI, 0.91 to 1.28]) (63, 82, 90).

Other Clinical Outcomes

No trials comparing combination therapy with high-dose statin monotherapy reported the occurrence of MI, stroke, transient ischemic attacks, or revascularization procedures in patients requiring intensive lipid-lowering therapy. Rare events in the few trials of statin–ezetimibe, statin–fibrate, statin–niacin, and statin–bile-acid sequestrant combinations lasting 12 to 52 weeks precluded meaningful conclusions for other clinical outcomes. One fair-quality, large statin–ω-3 fatty acids trial that used various statins and doses in mixed-risk patients reported no statistically significant difference between treatments for nonfatal MI and stroke over 5 years (82). Our meta-analysis of 2 statin–ω-3 fatty acids trials demonstrated no statistically significant difference (but a wide confidence bound) between treatments for fatal MI (OR, 0.73 [CI, 0.34 to 1.58]) (59, 82).

Table. **Strength of Evidence for Statin Combination Therapy Versus Monotherapy in Patients Requiring Intensive Treatment**

Outcome	Strength of Evidence*	Conclusion
All-cause mortality	Very low	No difference in all-cause mortality was noted for any statin combination with ezetimibe or fibrates. No evidence was available for other combinations.
Vascular death	–	No evidence was available for any statin combination.
Serious adverse events†	Very low	No difference was found for statin–ezetimibe. No evidence was available for other combinations.
Attainment of ATP III LDL cholesterol goals	Very low	Statin–ezetimibe is more likely to result in attainment of LDL cholesterol target. Evidence is insufficient for statin–fibrates, and no evidence was available for other combinations.

ATP III = Adult Treatment Panel III; LDL = low-density lipoprotein.
* Rated by using the Grading of Recommendations, Assessment, Development, and Evaluation approach.
† Because evidence in patients who needed intensive lipid-lowering therapy was scant, we examined serious adverse events across all trial populations.

Serious Adverse Events

In 3 short-term fair-quality trials ($n = 927$) of statin–ezetimibe compared with high-dose statin monotherapy in diverse samples, few (5%) participants had a serious adverse event (OR for difference between treatments, 1.64 [CI, 0.85 to 3.19]) (16, 19, 21). Meta-analysis of 27 fair-quality trials, unrestricted by statin dose, showed no statistically significant difference in the rate of adverse events (OR, 1.08 [CI, 0.88 to 1.33]) (16–22, 26–28, 30–32, 34, 36, 41, 48, 81, 83, 84, 86, 88, 93, 106, 108, 109, 112). For statin–fibrate (37, 39), statin–niacin (100, 103, 104, 107, 111), statin–bile-acid sequestrant (60, 61), and statin–ω-3 fatty acid combinations (90), the evidence was restricted to few trials with mixed-risk patient samples that used similar statin doses in both groups, with absolute rates of serious adverse events of 2% to 3%.

Cancer Incidence

Evidence was limited to trials in mixed-risk patients with various statins and doses. A fair-quality, 5-year, statin–ω-3 fatty acids trial, with 3% incidence of cancer, reported no statistically significant difference between treatments (82). Two 24- to 48-week statin–ezetimibe trials ($n = 971$), with 1% incidence of cancer, demonstrated no statistically significant difference between treatments (18, 28). Events were rare in a small statin–niacin trial (104).

Attainment of ATP III LDL Cholesterol Goals

Meta-analysis of 2 fair-quality trials that compared statin–ezetimibe with high-dose statin monotherapy in patients requiring intensive lipid-lowering therapy demonstrated a greater probability of goal attainment with combination therapy (OR, 7.21 [CI, 4.30 to 12.08]) (19, 108). Twenty-three fair-quality trials of statin–ezetimibe combinations, unrestricted by statin dose, in diverse samples reported attainment of guideline LDL cholesterol goals (16, 17, 19, 27, 30–34, 36, 41, 48, 49, 51, 81, 83, 86, 88, 93, 95, 101, 106, 108). All but 1 of these trials reported that a higher proportion of participants attained goals with statin–ezetimibe.

LDL Cholesterol Levels

Two fair-quality statin–ezetimibe trials assessed reductions in LDL cholesterol levels in patients requiring intensive lipid-lowering therapy. Both showed additional reductions of 10% to 20% with combination therapy (16, 19). Eighteen fair-quality statin–ezetimibe trials (16, 19, 20, 27, 30–32, 34, 36, 55, 81, 83, 84, 86, 88, 95, 99, 112) and 4 poor-quality statin–bile-acid sequestrant trials (38, 61, 76, 97) in high-risk patients used various statin doses in the monotherapy groups. All statin–ezetimibe trials favored combination treatment with mean additional LDL cholesterol reductions of 4% to 27%. Inconsistent results were found in the statin–bile-acid sequestrant trials.

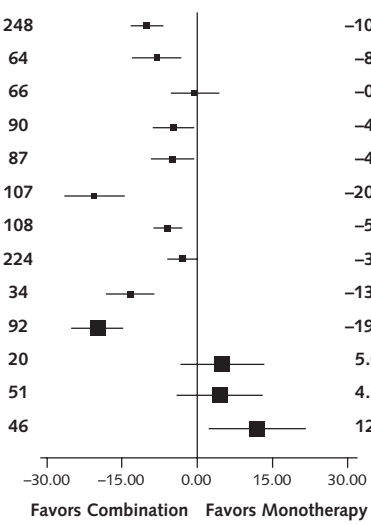
When lower statin doses in combination therapies were compared with high doses of the same statin monotherapies across a wide spectrum of patient samples, additional LDL cholesterol reductions of 3% to 20% were demonstrated in 6 fair-quality statin–ezetimibe trials (**Figure**) (16–21). Most of the 35 fair-quality statin–ezetimibe trials unrestricted by patient risk and statin dose showed 4% to 27% additional reductions in LDL cholesterol levels with combination therapy (16–22, 26–28, 30–34, 36, 41, 42, 45, 48, 49, 51, 55, 80, 81, 83, 84, 86–88, 93, 95, 99, 109, 112). Eleven, mostly poor-quality, statin–bile-acid sequestrant trials could not be pooled because of heterogeneity. These trials were unrestricted by patient risk or statin dose and favored combination therapy (23, 38, 57, 60, 61, 71, 72, 74, 76, 97, 102). In 2 fair-quality statin–ω-3 fatty acids trials that were unrestricted by dose and patient risk, statin monotherapy was superior (mean difference in LDL cholesterol reduction, 5.26% [CI, 1.79% to 8.74%]) (54, 90). The few statin–fibrate (24, 37, 89) and statin–niacin (25, 46, 68, 80, 103, 104, 110) trials had inconsistent results.

HDL Cholesterol Levels

Meta-analysis of 5 fair-quality randomized trials in diverse samples showed no statistically significant difference in percentage change in HDL cholesterol levels for statin–ezetimibe versus high doses of statin alone (mean difference,

Figure. **Percentage of change in low-density lipoprotein cholesterol levels from baseline after low-dose statin combination therapy versus high-dose statin monotherapy in diverse populations.**

Combination Therapy	Study, Year (Reference)	Follow-up, wk	Sample Size, n		Mean Difference (95% CI)	Mean Difference (95% CI)
			Combination	Monotherapy		
Simvastatin–ezetimibe	Feldman et al, 2004 (16)	23	109	248		–10.00 (–13.19 to –6.81)
Simvastatin–ezetimibe	Davidson et al, 2002 (17)	12	67	64		–8.12 (–13.03 to –3.21)
Simvastatin–ezetimibe	Davidson et al, 2002 (17)	12	68	66		–0.53 (–5.39 to 4.33)
Simvastatin–ezetimibe	Goldberg et al, 2004 (18)	12	87	90		–4.70 (–8.91 to –0.49)
Simvastatin–ezetimibe	Goldberg et al, 2004 (18)	12	86	87		–4.90 (–9.12 to –0.59)
Simvastatin–ezetimibe	Gaudiani et al, 2005 (19)	6–24	103	107		–20.50 (–26.60 to –14.40)
Simvastatin–ezetimibe	Bays et al, 2004 (20)	6–26	222	108		–5.90 (–8.80 to –3.00)
Simvastatin–ezetimibe	Bays et al, 2004 (20)	6–26	106	224		–3.00 (–5.93 to –0.07)
Simvastatin–ezetimibe	Dobs et al, 2003 (21)	4	66	34		–13.36 (–18.31 to –8.41)
Atorvastatin–ezetimibe	Conard et al, 2008 (22)	6	92	92		–19.90 (–25.17 to –14.63)
Atorvastatin–BAS	Hunninghake et al, 2001 (23)	4	18	20		5.00 (–3.34 to 13.34)
Rosuvastatin–fibrates	Durrington et al, 2004 (24)	18	53	51		4.50 (–4.10 to 13.10)
Rosuvastatin–niacin	Capuzzi et al, 2003 (25)	24	78	46		12.00 (2.26 to 21.74)



BAS = bile-acid sequestrant.

0.31% [CI, −0.89% to 1.52%]) (17–21). Evidence for statin–fibrate and statin–niacin combinations for this comparison was insufficient.

Measures of Atherosclerosis

One trial of 642 evaluable participants compared simvastatin–ezetimibe with identical-dose simvastatin monotherapy in participants requiring intensive lipid-lowering therapy. The mean between-group difference of change in mean carotid intima–media thickness was 0.01 mm (CI, −0.01 to 0.02 mm) (99). Another trial in 149 evaluable participants requiring intensive lipid-lowering therapy and using various statins in combination with niacin reported no statistically significant difference in intima–media thickness (mean difference, −0.03 mm [CI, −0.06 to 0.003 mm]) (40).

Treatment Adherence and Harm

Evidence comparing combination therapy with high-dose statin monotherapy was available only for statin–ezetimibe in 5 short-term trials (16–19, 21), which showed no statistically significant differences between treatments in withdrawal because of adverse events and aminotransferase levels greater than 3 times the upper limit of normal.

Meta-analysis of 10 trials evaluating various statins and doses in diverse samples showed that rates of early withdrawal because of adverse events were higher for statin–niacin than for statin monotherapy (OR, 2.38 [CI, 1.63 to 3.47]) (40, 46, 47, 50, 67, 100, 103, 104, 107, 111). More participants developed at least 1 adverse event with the statin–bile-acid sequestrant combination (OR, 2.19 [CI, 1.28 to 3.75]) (38, 60, 71, 79). Rates of aminotransferase level elevations, hepatitis, increased creatine kinase levels, or myalgia did not differ between any combination therapy and statin monotherapy (14). In addition, no participant developed rhabdomyolysis across 27 trials, 85% of which were short-term and investigated all 5 combination therapies.

No statistical difference in treatment adherence was observed for statin–ezetimibe (17, 18, 28, 31, 41, 45, 49, 80, 83, 84, 99, 106) and statin–niacin (25, 40, 46, 47, 80), whereas 5 trials of statin–bile-acid sequestrant showed inconsistent effects precluding meta-analysis (23, 38, 62, 79, 102).

DISCUSSION

We found no benefit of combination therapy over high-dose statin monotherapy in terms of mortality, MI, stroke, and revascularization procedures in patients requiring intensive lipid-lowering therapy. Most studies were short and focused on surrogate markers, which limited their ability to detect potential differences in important clinical outcomes. Assessment of these outcomes requires large long-term trials in high-risk patients. Data are insufficient to comment on effects in racial or ethnic subgroups, women, and frail elderly persons. Future trials should include people from those and other specific populations of interest.

The statin dose in most trials was similar in the combination and monotherapy groups. More intensive statin therapy is associated with a greater reduction in LDL cholesterol levels and vascular events without increasing discontinuation because of drug-related harms (118). Therefore, the appropriate comparator for combination therapies may be high-dose statin therapy.

Very few studies examined combinations other than statin–ezetimibe. Overall, limited evidence demonstrated a greater reduction in LDL cholesterol levels with any of the 5 combinations than with high-dose statin monotherapy in participants requiring intensive lipid-lowering therapy. In 2 trials, 10% to 20% additional reductions in LDL cholesterol were demonstrated in high-risk participants receiving low-dose simvastatin–ezetimibe compared with high-dose statin monotherapy. In studies of statin–ω-3 fatty acid therapy, participants in the monotherapy groups achieved greater reductions in LDL cholesterol levels. ω-3 Fatty acids are primarily used to improve the lipid profile by decreasing triglyceride levels; elevated LDL cholesterol levels with ω-3 fatty acid therapy are consistent with our results (13).

The absence of an effect on carotid intima–media thickness despite reductions in LDL cholesterol levels was the unexpected outcome of 2 trials. Many explanations have been suggested, but this finding may be the result of the relatively short study period, because no intervention studies with a 2-year duration or less have demonstrated an effect on carotid intima–media thickness (119).

Adverse events were not reported systematically, and many trial protocols did not specify standard methods for ascertainment of harms. The follow-up periods for most studies were too short to discern events with long latency, such as cancer.

Medication adherence is important in determining population benefit. Less complex regimens with fewer separate agents may be preferable (120). Adherence was rarely reported, and most reports mentioned only data on the proportion of participants who discontinued treatment. Absolute rates of withdrawal in statin–niacin therapy in 4 trials were less than 10%, favoring statin monotherapy. In single trials, significantly fewer participants adhered to statin–bile-acid sequestrant and statin–niacin therapy. Both treatments have well-known short-term side effects, which are the probable cause of these findings (10).

Our review has limitations. We did not examine all possible medication combinations, doses, or patient populations. Some combinations may prove to be useful for selected lipid profiles or in patients who do not reach targets despite maximal therapy. Assessments of clinical outcomes, harms, and treatment adherence were limited by the shortage of long-term studies, with relatively few studies for combination therapies other than statin–ezetimibe and, for surrogate outcomes, by the statistical limitations of the outcome measures. The extent to which short-term surrogate measures correlate with outcome is well demonstrated for statin monotherapy but remains unclear for

combination therapies. We did not attempt imputation, because the possibility of double counting could not be ruled out, limiting inclusion of composite outcomes. Our statistically conservative approach to meta-analyses precluded analyses in many instances. We rated the strength of the evidence as very low for the main outcomes (**Table**) because reports directly addressing the specified patient samples and comparators are lacking. The available evidence supporting the use of combination therapies over high-dose statin monotherapy, including long-term clinical benefits and reduced risks, is insufficient to guide many clinical decisions. The effectiveness of statins in reducing vascular events suggests that the benefits of additional therapies need to be clearly defined along with attendant risks and costs before widespread use of combination treatments can be advocated.

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Acknowledgment: The authors thank Margaret Sampson, Chantelle Garritty, Heather Clark, Robert Côté, Nick Barrowman, Raymond Daniel, and Sophia Tsouros for their collective efforts.

Grant Support: By AHRQ, U.S. Department of Health and Human Services (contract 290-02-0021).

Potential Conflicts of Interest: *Honoraria:* M. Sharma (Merck & Co., Schering-Plough), T.C. Ooi (Oryx Pharmaceuticals, Fournier Pharma, AstraZeneca, Merck Frosst, Solvay Pharma, Schering-Plough).

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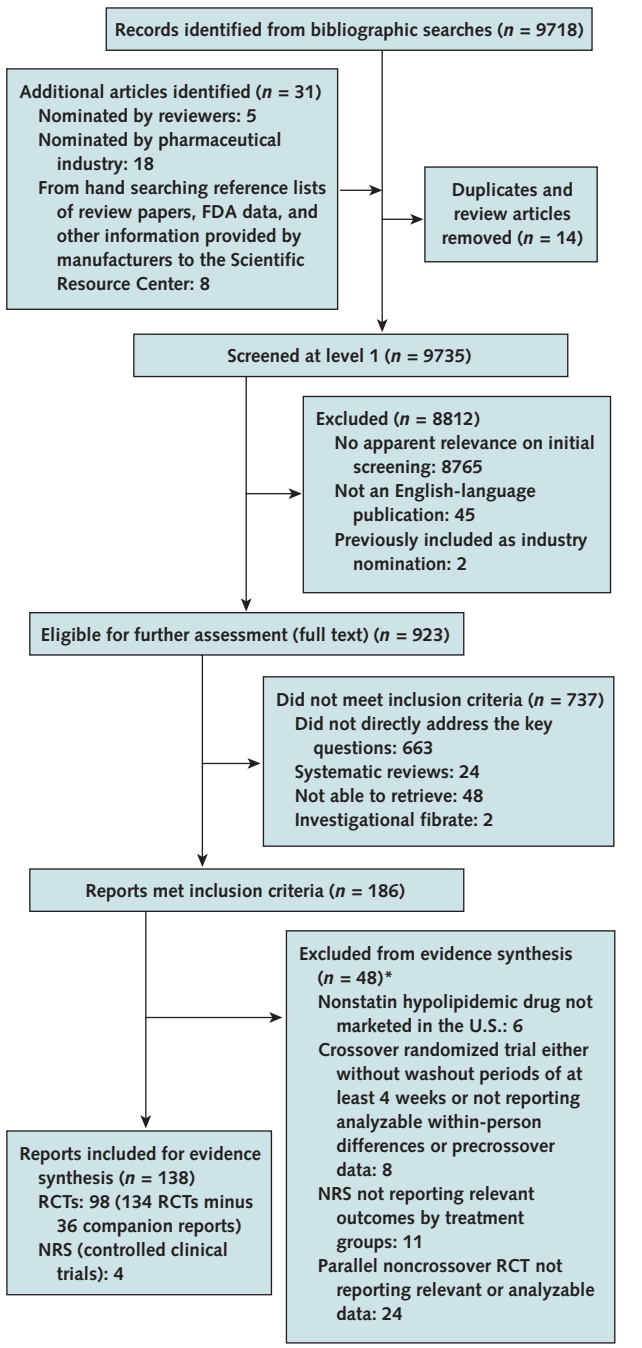
Appendix Figure. **Literature search and selection.**



FDA = U.S. Food and Drug Administration; NRS = nonrandomized study; RCT = randomized, controlled trial.
* Total does not sum to 48 because 1 study was excluded in 2 categories.

Appendix Table 1. **Definitions of Low and High Doses of Statins**

Dose	Low Dose, *mg/d*	High Dose, *mg/d*
Atorvastatin	5, 10, and/or 20	40 and/or 80
Simvastatin	5, 10, and/or 20	40 and/or 80
Rosuvastatin	5 and/or 10	20, 40, and/or 80
Pravastatin	5, 10, 20, and/or 40	80
Fluvastatin	5, 10, 20, and/or 40	80
Lovastatin	5, 10, 20, and/or 40	80

Appendix Table 2. Therapies Evaluated in Included Studies

Drug	Study, Year (Reference)				
	Ezetimibe	**Fibrates**	**Niacin**	**Bile-Acid Sequestrants**	**ω-3 Fatty Acids**
Rosuvastatin	Kosoglou et al, 2004 (42) Ballantyne et al, 2007 (83)	Durrington et al, 2004 (24)	Capuzzi et al, 2003 (25) McKenney et al, 2007 (80)	Ballantyne et al, 2004 (38)	None
Atorvastatin	Cruz-Fernández et al, 2005 (31) Stein et al, 2004 (41) Ballantyne et al, 2003 (48) Blagden et al, 2007 (81) Piorkowski et al, 2007 (85) Conard et al, 2008 (22) Leiter et al, 2008 (112)	Athyros et al, 2005 (29) Athyros et al, 2002 (53)	Moore et al, 2007 (110)	Hunninghake et al, 2001 (23) Isaacsohn et al, 1997 (97) Heinonen et al, 1996 (102)	Nordøy et al, 2001 (58) Chan et al, 2002 (54)
Simvastatin	Rodney et al, 2006 (26) Landray et al, 2006 (28) Farnier et al, 2005 (30) Brohet et al, 2005 (32) Masana et al, 2005 (36) Gaudiani et al, 2005 (19) Bays et al, 2004 (20) Feldman et al, 2004 (16) Goldberg et al, 2004 (18) Davidson et al, 2002 (17) Kosoglou et al, 2002 (52) Patel and Hughes, 2006 (84) Berthold et al, 2006 (87) Chenot et al, 2007 (91) Shankar et al, 2007 (93) Kastelein et al, 2008 (99) Roeters van Lennep et al, 2008 (108) Gouni-Berthold et al, 2008 (109) Dobs et al, 2003 (21)	Grundy et al, 2005 (37) Muhlestein et al, 2006 (89)	Stein et al, 1996 (100) Ballantyne et al, 2008 (107) Ballantyne et al, 2008 (111) Airan-Javia et al, 2009 (113)	Knapp et al, 2001 (60) Simons et al, 1992 (74) O'Brien et al, 1990 (76) Johansson, 1995 (79) Mol et al, 1990 (116)*	Hong et al, 2004 (43) Durrington et al, 2001 (59) Nordøy et al, 1998 (63) Davidson et al, 1997 (65) Liu et al, 2003 (77) Davidson et al, 2007 (90)
Lovastatin	Kosoglou et al, 2004 (44) Kerzner et al, 2003 (51)	None	Insull et al, 2004 (46) Hunninghake et al, 2003 (50) Gardner et al, 1996 (66) FDA report, 2008 (103) FDA report, 2008 (104) Vacek et al, 1995 (68)†	Davidson et al, 2001 (57) Schrott et al, 1995 (70) Ojala et al, 1990 (115)*	None
Pravastatin	Melani et al, 2003 (49) Dagli et al, 2007 (105)	Wiklund et al, 1993 (73) Napoli et al, 1997 (98)	O'Keefe et al, 1995 (67)	Eriksson et al, 1998 (62) Ito and Shabetai, 1997 (64) Pravastatin Multicenter Study Group II, 1993 (72) Ismail et al, 1990 (75) Barbi et al, 1992 (78)	None
Fluvastatin	Stein et al, 2008 (101)	Derosa et al, 2004 (39) Smit et al, 1995 (69) van Dam and Kastelein, 2001 (114)*	None	Sprecher et al, 1994 (71)	None
Mixed statins‡	Barrios et al, 2005 (27) Pearson et al, 2005 (33) Ballantyne et al, 2005 (34) Ballantyne et al, 2004 (45) Gagné et al, 2002 (55) Geiss et al, 2005 (35)† McKenney et al, 2007 (80) Goldberg et al, 2006 (86) Catapano et al, 2006 (88) Constance et al, 2007 (95) Reckless et al, 2008 (106) Roeters van Lennep et al, 2008 (108) Türk et al, 2008 (117)*	Athyros et al, 2002 (56) Shah et al, 2007 (94)	Taylor et al, 2004 (40) Bays et al, 2003 (47) McKenney et al, 2007 (80) Kuvin et al, 2006 (96)	Simons, 1998 (61)	Yokoyama et al, 2007 (82) Meyer et al, 2007 (92)
Total trials, *n*	45	12	17	19	10

FDA = U.S. Food and Drug Administration.
* Nonrandomized studies were included in evidence syntheses.
† Reports provided analyzable crossover data.
‡ Participants were receiving several different statins a priori and were randomly assigned to add-on nonstatin treatment, or statins in combination and monotherapy within a trial were not identical subtypes.