# Effectiveness of Combination Therapy With Statin and Another Lipid-Modifying Agent Compared With Intensified Statin Monotherapy

## A Systematic Review

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**Background:** Some patients do not tolerate or respond to high-intensity statin monotherapy. Lower-intensity statin combined with nonstatin medication may be an alternative, but the benefits and risks compared with those of higher-intensity statin monotherapy are unclear.

**Purpose:** To compare the clinical benefits, adherence, and harms of lower-intensity statin combination therapy with those of higher-intensity statin monotherapy among adults at high risk for atherosclerotic cardiovascular disease (ASCVD).

**Data Sources:** MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from inception to July 2013, with an updated MEDLINE search through November 2013.

**Study Selection:** Randomized, controlled trials published in English.

**Data Extraction:** Two reviewers extracted information on study design, population characteristics, interventions, and outcomes (deaths, ASCVD events, low-density lipoprotein [LDL] cholesterol level, adherence, and adverse events). Two independent reviewers assessed risk of bias.

**Data Synthesis:** A total of 36 trials were included. Low-intensity statin plus bile acid sequestrant decreased LDL cholesterol level 0% to 14% more than mid-intensity monotherapy among high-risk hyperlipidemic patients. Mid-intensity statin plus ezetimibe decreased LDL cholesterol level 5% to 15% and 3% to 21% more than high-intensity monotherapy among patients with ASCVD and diabetes mellitus, respectively. Evidence was insufficient to evaluate LDL cholesterol for fibrates, niacin, and $\omega$-3 fatty acids. Evidence was insufficient for long-term clinical outcomes, adherence, and harms for all regimens.

**Limitation:** Many trials had short durations and high attrition rates, lacked blinding, and did not assess long-term clinical benefits or harms.

**Conclusion:** Clinicians could consider using lower-intensity statin combined with bile acid sequestrant or ezetimibe among high-risk patients intolerant of or unresponsive to statins; however, this strategy should be used with caution given the lack of evidence on long-term clinical benefits and harms.

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Atherosclerotic cardiovascular disease (ASCVD) affects more than 15 million Americans (1) and is the leading cause of death for both men and women in the United States (2). Trials have demonstrated reductions in low-density lipoprotein (LDL) cholesterol levels (3) and decreased ASCVD risk with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) monotherapy (4). Over the past decade, statins have often been used in combination with other lipid-modifying agents. Recently, several high-profile randomized, controlled trials (RCTs) have evaluated "add-on" therapy (5–7), wherein statin monotherapy is compared with the combination of the same statin dose and another lipid-modifying agent. Add-on combination therapy can lead to superior lipid outcomes, but studies have not shown decreased rates of cardiovascular death, myocardial infarction, revascularization, or stroke (5–7). Therefore, the 2013 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines recommend moderate- or high-intensity statin monotherapy as the first-line strategy for ASCVD risk reduction among patients with LDL cholesterol levels of 4.91 mmol/L or greater (≥190 mg/dL), preexisting ASCVD, diabetes mellitus (DM), or estimated 10-year ASCVD risk of 7.5% or greater (8).

Clinicians may find applying these new guidelines in clinical practice challenging, especially among patients who cannot tolerate the recommended intensity of statin because of adverse effects or those who have limited LDL cholesterol response. Adverse effects are more common with higher-intensity statin regimens (9), and musculoskeletal adverse events occur frequently among patients with the C variant in the *SLCO1B1* gene (10). Pharmacogenetic variability may also decrease statin efficacy (11). Consequently, higher-intensity statin monotherapy may not be appropriate for all patients. The 2013 ACC/AHA guidelines suggest that clinicians consider "moderated" combination therapy with a lower-intensity statin and another lipid-modifying medication among high-risk patients (LDL cholesterol level ≥4.91 mmol/L [≥190 mg/dL], preexisting ASCVD, or DM) who are intolerant of or unresponsive to statins (evidence grade E: expert opinion) (8).

*See also:*

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Yet, it is unclear whether this strategy results in similar ASCVD risk reductions and fewer adverse effects compared with higher-intensity statin monotherapy. A 2009 systematic review that examined these questions found insufficient evidence to weigh benefits and risks of moderated combination therapy (12).

We aimed to compare the effectiveness, safety, and tolerability of moderated combination therapy of statin with another lipid-modifying medication (bile acid sequestrant, ezetimibe, fibrate, niacin, or ω-3 fatty acid) with those of higher-intensity statin monotherapy among high-risk patients. We sought to compare the long-term clinical benefits and short-term lipid effects of moderated combination therapy with those of higher-intensity statin monotherapy, as well as to determine whether these regimens differ in rates of adherence and harms.

## METHODS

We developed and publicly posted a protocol to conduct this review (http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1496), and the search strategies and detailed evidence tables are available online (13). Given the recent release of the 2013 ACC/AHA guidelines (8), we narrowed the scope of this manuscript to focus on evidence most relevant to high-risk populations for whom combination therapy might be considered.

### Data Sources and Searches

We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials for primary studies published from May 2008 through July 2013. To update our review, we searched MEDLINE through November 2013. We screened all articles included in the prior review (12). We also reviewed the reference lists of each included article, relevant review articles, relevant studies identified on ClinicalTrials.gov, and scientific information packets provided by pharmaceutical manufacturers.

### Study Selection

Two study team members independently screened each identified article against prespecified eligibility criteria (**Table 1** of the **Supplement**, available at www.annals.org). We included RCTs in adults with high ASCVD risk (LDL cholesterol level ≥4.91 mmol/L [≥190 mg/dL], preexisting ASCVD, or DM) (8) that compared a moderated combination regimen with higher-intensity statin monotherapy. We excluded studies not reported in English. We also considered nonrandomized extensions of clinical trials of more than 24 weeks' duration and U.S. Food and Drug Administration reports for evaluation of long-term benefits, serious adverse events, and harms. We anticipated that few trials of only statin-intolerant or statin-unresponsive patients would exist and therefore included studies of statin-tolerant and statin-responsive patients.

### Data Extraction and Quality Assessment

Two team members extracted data on study design, setting, population characteristics, and intervention characteristics. Our long-term clinical outcomes included mortality, acute coronary events, cerebrovascular events, and revascularization procedures. Our lipid outcome was LDL cholesterol level. Investigator-defined outcomes included adherence, serious adverse events, withdrawals due to adverse events, and occurrence of any adverse event. Secondary harms outcomes included elevations in liver aminotransferase levels, elevated measures of muscle-related harm (for example, elevated creatine phosphokinase level or myalgia), acute kidney injury, or incident DM.

We rated the strength of evidence (SOE) by evaluating the risk of bias, consistency of results, directness, and precision. We assessed risk of bias using the Cochrane Collaboration's tool (14) for studies identified in the new search and the Jadad score (15) for studies identified during the prior review. Two reviewers independently assessed the risk of bias for each included study. We labeled results as consistent if most of the interventions' point estimates favored statin monotherapy or combination therapy. Most outcomes were directly measured, except for LDL cholesterol level, which we considered to be indirect because the Friedewald equation may underestimate it among high-risk patients (16). We assessed precision on the basis of the studies' variance estimates and sufficiency of the sample size by comparing them to the optimal information size. To be rated as high-strength, the body of evidence would need to be rated as having low risk of bias and as being consistent, direct, and precise. We rated the SOE as moderate if 1 of these elements was downgraded. We rated the SOE as low if 2 or more of these elements were downgraded.

### Data Synthesis and Analysis

The evidence base contained different statins and different statin doses both within and across studies, which limited our ability to make statin-specific comparisons. Prior studies have suggested schemes to group statins on the basis of their reported LDL cholesterol reduction (17, 18), which are similar to the strategy used by the ACC/AHA committee (8). We used the strategy proposed by Weng and colleagues (18) to group statins when synthesizing data (**Table 2** of the **Supplement**). We compared moderated combination therapy with higher-intensity statin monotherapy among high-risk patients with LDL cholesterol levels of 4.91 mmol/L or greater (≥190 mg/dL), preexisting ASCVD, or DM.

For all comparisons, we report the qualitative synthesis of data by calculating and displaying the individual mean differences with 95% CIs (if calculable) for individual studies grouped by combination therapy agent, statin intensity, and high-risk population. For studies with 2 monotherapy groups of the same intensity, we used only 1 group as the comparator to the combination groups ac-

*Table.* **Population Characteristics and Study Quality of Included Trials, by Combination Therapy Agent and Potency Comparison**

| Statin Monotherapy Potency | Combination Therapy Potency | RCTs by Population, *n* (*N* eligible) | Range of Study Duration, *wk* | Overall Baseline Population Characteristics | | | | Risk of Bias | RCTs That Received Pharmaceutical Company Support, % |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Mean Age Range, *y* | Range of Women, % | Range of White Patients, % | Mean LDL Cholesterol Range, *mg/dL** | | |
| **Bile acid sequestrants** | | | | | | | | | |
| High-intensity | Low-intensity | 0 | – | – | – | – | – | – | – |
| High-intensity | Mid-intensity | 1 HLD (83) | 12 | 51–53 | 14–38 | NR | 218–224 | Low | 100 |
| Mid-intensity | Low-intensity | 4 HLD (288) | 6–24 | 52–61 | 29–42† | 95–98† | 180–236 | Moderate | 100 |
| **Ezetimibe** | | | | | | | | | |
| High-intensity | Low-intensity | 1 HLD (23) | 4 | NR | NR | NR | 200–206 | Moderate | 0 |
| | | 1 ASCVD (112) | 6 | 56 | 43–46 | NR | 126–128 | Low | 100 |
| | | 1 DM (21) | 8 | 56–65 | 55–60 | NR | 145–147 | Low | 100 |
| High-intensity | Mid-intensity | 1 HLD (145) | 8 | 57–59 | 47–48 | 84–87 | 198–202 | Low | 100 |
| | | 12 ASCVD (2590) | 4–12 | 59–72† | 17–51† | 73–93† | 84–151† | Low | 50 |
| | | 11 DM (>3448) | 6–24 | 58–66† | 38–56† | 0–96† | 91–147† | Low | 100 |
| Mid-intensity | Low-intensity | 1 DM (24) | 10 | 64–65 | 50–58 | NR | 154–164 | Moderate | NR |
| **Fibrates** | | | | | | | | | |
| High-intensity | Low-intensity | 1 HLD (396) | 52 | 50–52 | 27–33 | NR | 203–208 | Low | NR |
| High-intensity | Mid-intensity | 1 HLD (389) | 52 | 50–52 | 26–30 | NR | 196–203 | Low | NR |
| | | 1 ASCVD (102) | 13 | 56–58 | 4–20 | NR | 92–102 | High | NR |
| Mid-intensity | Low-intensity | 1 DM (291) | 12 | 56–57 | 49–55 | NR | 127–128 | Low | 100 |
| **Niacin** | | | | | | | | | |
| High-intensity | Low-intensity | 0 | – | – | – | – | – | – | – |
| High-intensity | Mid-intensity | 1 HLD (315) | 16 | 52–54 | 25–31 | 84–89 | 189–196 | Low | 100 |
| Mid-intensity | Low-intensity | 2 HLD (219) | 20–28 | 58–61 | 36–50 | 74–88 | 186–200 | Moderate | 100 |
| **ω-3 Fatty acids** | | | | | | | | | |
| High-intensity | Low-intensity | 0 | – | – | – | – | – | – | – |
| High-intensity | Mid-intensity | 0 | – | – | – | – | – | – | – |
| Mid-intensity | Low-intensity | 0 | – | – | – | – | – | – | – |

ASCVD = subgroup with preexisting atherosclerotic cardiovascular disease; DM = subgroup with diabetes mellitus; HLD = subgroup with LDL cholesterol level ≥190 mg/dL (≥4.91 mmol/L); LDL = low-density lipoprotein; NR = not reported; RCT = randomized, controlled trial.
* Wide range of values may be reported because some studies evaluated baseline LDL cholesterol level while participants were receiving lipid-modifying therapy. To convert values to mmol/L, multiply by 0.026.
† Only a subset of trials reported this characteristic, so range reflects that of those studies reporting.

cording to a priori criteria. If the groups involved the same statin, we used the group with the higher dose. If the groups involved different statins, we selected the group according to prioritized statin agent (rosuvastatin, atorvastatin, simvastatin, lovastatin, pravastatin, and fluvastatin; no studies used pitavastatin). We performed no meta-analyses given the small number of heterogeneous trials.

### Role of the Funding Source

Funding was provided by the Agency for Healthcare Research and Quality. The funding source had no role in study selection, quality assessment, or data synthesis or in the decision to submit the manuscript for publication.

## RESULTS

The **Appendix Figure** (available at www.annals.org) summarizes the search results, and **Table 3** of the **Supplement** lists all included studies. The literature search identified 4369 unique citations. We included 36 studies reported in 43 articles. The **Table** summarizes the study and population characteristics of included studies by combination agent and by population. All trials were RCTs. No nonrandomized extensions of clinical trials greater than 24 weeks' duration and U.S. Food and Drug Administration reports met our inclusion criteria. Most study populations included men in their 50s or 60s.

### Long-Term Clinical Outcomes

We found insufficient evidence to compare long-term clinical outcomes (mortality, acute coronary events, cerebrovascular events, and revascularization procedures) for all combination therapy and statin intensity comparisons. **Figure 1** presents an evidence map of studies that evaluated these outcomes (19–27). Most studies that reported events lasted less than 20 weeks; event rates were very low or no events occurred.

### LDL Cholesterol, Treatment Adherence, and Harms Outcomes

#### *Combination Therapy With Bile Acid Sequestrants by Intensity Comparison*

**Figure 2** shows the differences in change in LDL cholesterol level among high-risk groups by nonstatin agent (28–61). Five RCTs compared statin monotherapy to

combination therapy with bile acid sequestrant (371 participants) among hyperlipidemic patients (28–33). We identified no studies that reported results within the ASCVD and DM groups.

Four trials compared low-intensity statin in combination with bile acid sequestrants to mid-intensity statin monotherapy (288 participants) (29–33). Low-intensity statin in combination with bile acid sequestrant decreased LDL cholesterol level 0% to 14% more than mid-intensity statin monotherapy (moderate SOE). One study reported adherence, which was 97% among monotherapy recipients and 93% to 95% among combination therapy recipients (33). One study reported on withdrawals due to adverse events at 6 weeks, which did not statistically significantly differ between groups (0 participants receiving monotherapy vs. 3% of participants receiving combination therapy; $P = 0.28$) (29). Evidence was insufficient to evaluate LDL cholesterol outcomes for other intensity comparisons and to compare adherence and harms, regardless of statin intensity.

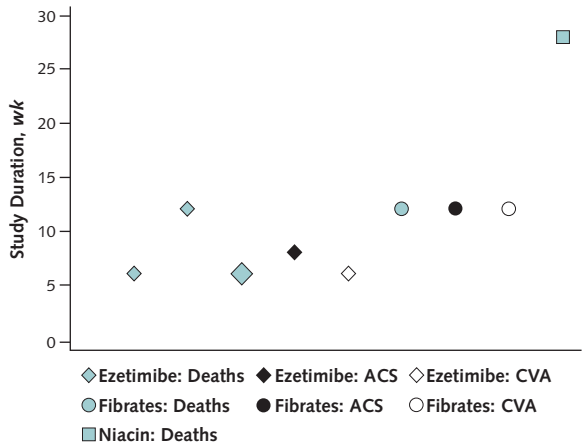
### *Combination Therapy With Ezetimibe by Intensity Comparison*

Two RCTs compared statin monotherapy and combination therapy with ezetimibe (168 participants) among hyperlipidemic patients (34, 36). We identified 12 RCTs and 1 RCT subgroup analysis among patients with preexisting ASCVD (2702 participants). We identified 9 RCTs and 4 RCT subgroups analyses among patients with DM (>3493 participants). Results of all trials are displayed in **Figure 2**. There was insufficient evidence to evaluate LDL cholesterol, adherence, and harms for other intensity comparisons among patient groups other than those reported below.

Eleven RCTs and 1 RCT subgroup analysis compared mid-intensity statin combined with ezetimibe to high-intensity statin monotherapy (2590 participants) among patients with preexisting ASCVD (19–21, 38–48). Mid-intensity statin combined with ezetimibe decreased LDL cholesterol level 5% to 15% more than high-intensity statin monotherapy (moderate SOE). Two trials reported adherence, which was greater than 95% in all groups (38, 40). Three studies reported serious adverse events, which were similar between groups (0% to 2% of monotherapy recipients vs. 0% to 2% of combination therapy recipients) (19, 38, 39), and 5 reported withdrawals due to adverse events, which occurred among more monotherapy recipients (difference, 1% to 18%) (19, 20, 38, 39, 43, 44). Secondary harms, including elevated liver aminotransferase levels and muscle-related events, when reported, occurred infrequently (**Table 4** of the **Supplement**).

Seven RCTs and 4 RCT subgroup analyses compared mid-intensity statin combined with ezetimibe to high-intensity statin monotherapy (>3448 participants) among patients with DM (22–25, 38, 39, 47–56). Mid-intensity statin combined with ezetimibe decreased LDL cholesterol level 3% to 21% more than high-intensity statin monotherapy (moderate SOE). One trial reported high treatment adherence in both groups (99% and 98% for monotherapy and combination therapy, respectively) (22). Five studies reported on serious adverse events, which were similar between groups (0% to 3% of monotherapy recipients vs. 0% to 5% of combination therapy recipients) (22–25, 38, 54, 56). Four reported on withdrawals due to adverse events, which occurred in 1% to 5% of monotherapy recipients and 2% to 4% of combination therapy recipients (22–25, 38, 56). Secondary harms, including elevated liver aminotransferase levels and muscle-related events, when reported, occurred infrequently (**Table 4** of the **Supplement**).

*Figure 1.* **Evidence map for studies reporting long-term clinical outcomes, by combination agent and outcome.**




The figure includes the clinical outcomes of death (green), ACS (black), and CVA (white). No studies reported on revascularization procedures. The different combination therapy agents are represented by the different symbols (diamond = ezetimibe [27, 34, 38, 43, 51]; circle = fibrates [58]; square = niacin [60]). No trials with bile acid sequestrants or $\omega$-3 fatty acids reported on any clinical outcomes. Each marker represents a different trial, where the sample size is represented by the size of the marker and the *y*-axis reflects the study duration. Differences in populations, potency comparisons, or event rates are not represented. Most event rates were very low or no events occurred, which limited our ability to make any inferences. ACS = acute coronary syndrome; CVA = cerebrovascular event.

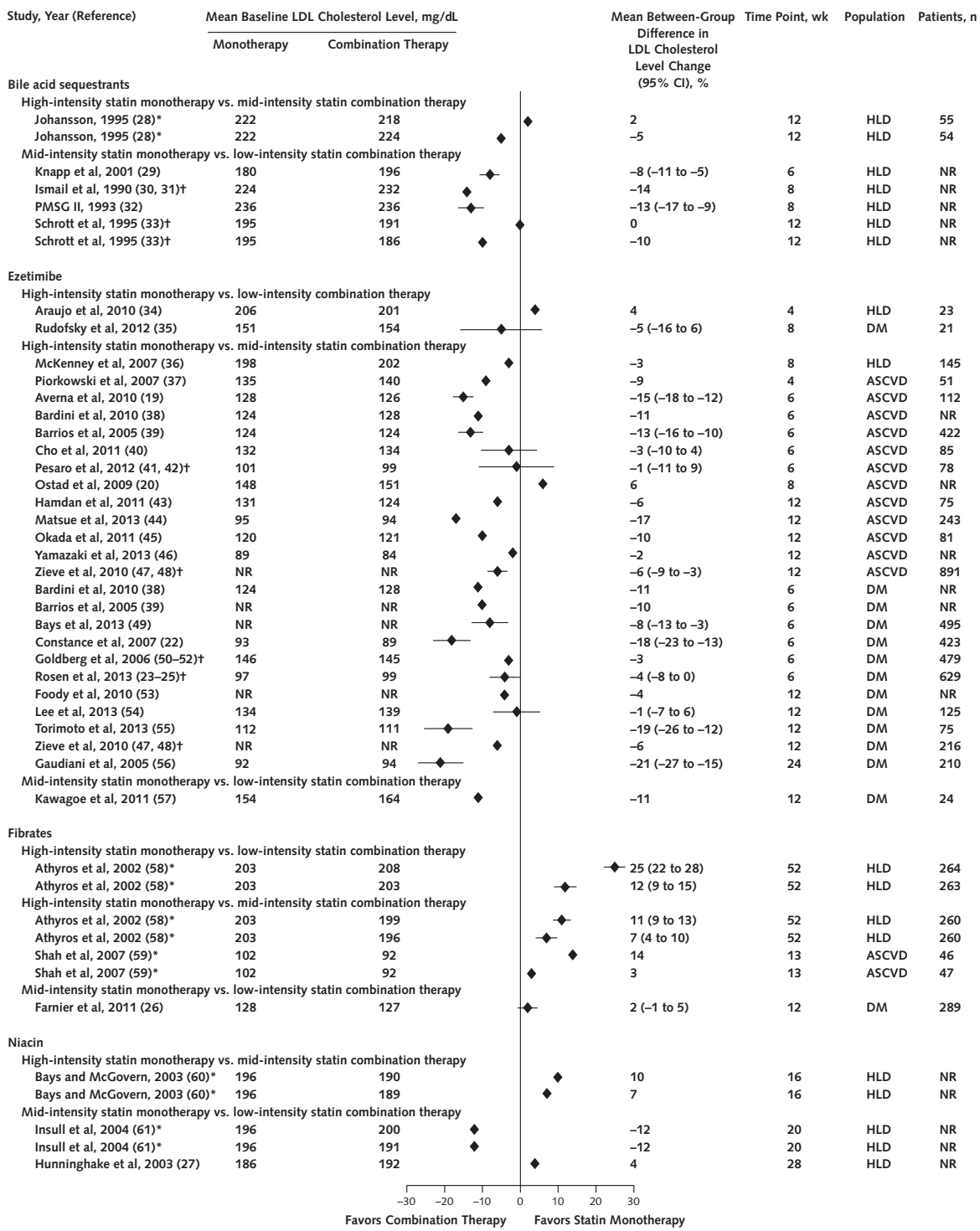
### *Combination Therapy With Fibrate by Intensity Comparison*

We identified 1 RCT in each high-risk population (hyperlipidemia, 654 participants; ASCVD, 102 participants; DM, 291 participants) (**Figure 2**) (26, 58, 59). We found insufficient evidence to compare LDL cholesterol level, adherence, and harms regardless of statin intensity and population. Secondary harms, when reported, occurred infrequently (**Table 4** of the **Supplement**).

### *Combination Therapy With Niacin by Intensity Comparison*

Three RCTs (534 participants) were identified among hyperlipidemic patients (**Figure 2**) (27, 60, 61). We iden-

*Figure 2.* **Difference in mean percentage of change in LDL cholesterol level among high-risk groups, by nonstatin agent, between higher-intensity statin monotherapy and lower-intensity statin combination therapy.**




| Study, Year (Reference) | Mean Baseline LDL Cholesterol Level, mg/dL | | Mean Between-Group Difference in LDL Cholesterol Level Change (95% CI), % | Time Point, wk | Population | Patients, n |
|---|---|---|---|---|---|---|
| | Monotherapy | Combination Therapy | | | | |
| **Bile acid sequestrants** | | | | | | |
| High-intensity statin monotherapy vs. mid-intensity statin combination therapy | | | | | | |
| Johansson, 1995 (28)* | 222 | 218 | 2 | 12 | HLD | 55 |
| Johansson, 1995 (28)* | 222 | 224 | −5 | 12 | HLD | 54 |
| Mid-intensity statin monotherapy vs. low-intensity statin combination therapy | | | | | | |
| Knapp et al, 2001 (29) | 180 | 196 | −8 (−11 to −5) | 6 | HLD | NR |
| Ismail et al, 1990 (30, 31)† | 224 | 232 | −14 | 8 | HLD | NR |
| PMSG II, 1993 (32) | 236 | 236 | −13 (−17 to −9) | 8 | HLD | NR |
| Schrott et al, 1995 (33)† | 195 | 191 | 0 | 12 | HLD | NR |
| Schrott et al, 1995 (33)† | 195 | 186 | −10 | 12 | HLD | NR |
| **Ezetimibe** | | | | | | |
| High-intensity statin monotherapy vs. low-intensity combination therapy | | | | | | |
| Araujo et al, 2010 (34) | 206 | 201 | 4 | 4 | HLD | 23 |
| Rudofsky et al, 2012 (35) | 151 | 154 | −5 (−16 to 6) | 8 | DM | 21 |
| High-intensity statin monotherapy vs. mid-intensity statin combination therapy | | | | | | |
| McKenney et al, 2007 (36) | 198 | 202 | −3 | 8 | HLD | 145 |
| Piorkowski et al, 2007 (37) | 135 | 140 | −9 | 4 | ASCVD | 51 |
| Averna et al, 2010 (19) | 128 | 126 | −15 (−18 to −12) | 6 | ASCVD | 112 |
| Bardini et al, 2010 (38) | 124 | 128 | −11 | 6 | ASCVD | NR |
| Barrios et al, 2005 (39) | 124 | 124 | −13 (−16 to −10) | 6 | ASCVD | 422 |
| Cho et al, 2011 (40) | 132 | 134 | −3 (−10 to 4) | 6 | ASCVD | 85 |
| Pesaro et al, 2012 (41, 42)† | 101 | 99 | −1 (−11 to 9) | 6 | ASCVD | 78 |
| Ostad et al, 2009 (20) | 148 | 151 | 6 | 8 | ASCVD | NR |
| Hamdan et al, 2011 (43) | 131 | 124 | −6 | 12 | ASCVD | 75 |
| Matsue et al, 2013 (44) | 95 | 94 | −17 | 12 | ASCVD | 243 |
| Okada et al, 2011 (45) | 120 | 121 | −10 | 12 | ASCVD | 81 |
| Yamazaki et al, 2013 (46) | 89 | 84 | −2 | 12 | ASCVD | NR |
| Zieve et al, 2010 (47, 48)† | NR | NR | −6 (−9 to −3) | 12 | ASCVD | 891 |
| Bardini et al, 2010 (38) | 124 | 128 | −11 | 6 | DM | NR |
| Barrios et al, 2005 (39) | NR | NR | −10 | 6 | DM | NR |
| Bays et al, 2013 (49) | NR | NR | −8 (−13 to −3) | 6 | DM | 495 |
| Constance et al, 2007 (22) | 93 | 89 | −18 (−23 to −13) | 6 | DM | 423 |
| Goldberg et al, 2006 (50–52)† | 146 | 145 | −3 | 6 | DM | 479 |
| Rosen et al, 2013 (23–25)† | 97 | 99 | −4 (−8 to 0) | 6 | DM | 629 |
| Foody et al, 2010 (53) | NR | NR | −4 | 12 | DM | NR |
| Lee et al, 2013 (54) | 134 | 139 | −1 (−7 to 6) | 12 | DM | 125 |
| Torimoto et al, 2013 (55) | 112 | 111 | −19 (−26 to −12) | 12 | DM | 75 |
| Zieve et al, 2010 (47, 48)† | NR | NR | −6 | 12 | DM | 216 |
| Gaudiani et al, 2005 (56) | 92 | 94 | −21 (−27 to −15) | 24 | DM | 210 |
| Mid-intensity statin monotherapy vs. low-intensity statin combination therapy | | | | | | |
| Kawagoe et al, 2011 (57) | 154 | 164 | −11 | 12 | DM | 24 |
| **Fibrates** | | | | | | |
| High-intensity statin monotherapy vs. low-intensity statin combination therapy | | | | | | |
| Athyros et al, 2002 (58)* | 203 | 208 | 25 (22 to 28) | 52 | HLD | 264 |
| Athyros et al, 2002 (58)* | 203 | 203 | 12 (9 to 15) | 52 | HLD | 263 |
| High-intensity statin monotherapy vs. mid-intensity statin combination therapy | | | | | | |
| Athyros et al, 2002 (58)* | 203 | 199 | 11 (9 to 13) | 52 | HLD | 260 |
| Athyros et al, 2002 (58)* | 203 | 196 | 7 (4 to 10) | 52 | HLD | 260 |
| Shah et al, 2007 (59)* | 102 | 92 | 14 | 13 | ASCVD | 46 |
| Shah et al, 2007 (59)* | 102 | 92 | 3 | 13 | ASCVD | 47 |
| Mid-intensity statin monotherapy vs. low-intensity statin combination therapy | | | | | | |
| Farnier et al, 2011 (26) | 128 | 127 | 2 (−1 to 5) | 12 | DM | 289 |
| **Niacin** | | | | | | |
| High-intensity statin monotherapy vs. mid-intensity statin combination therapy | | | | | | |
| Bays and McGovern, 2003 (60)* | 196 | 190 | 10 | 16 | HLD | NR |
| Bays and McGovern, 2003 (60)* | 196 | 189 | 7 | 16 | HLD | NR |
| Mid-intensity statin monotherapy vs. low-intensity statin combination therapy | | | | | | |
| Insull et al, 2004 (61)* | 196 | 200 | −12 | 20 | HLD | NR |
| Insull et al, 2004 (61)* | 196 | 191 | −12 | 20 | HLD | NR |
| Hunninghake et al, 2003 (27) | 186 | 192 | 4 | 28 | HLD | NR |

To convert LDL cholesterol values to mmol/L, multiply by 0.026. ASCVD = subgroup with preexisting atherosclerotic cardiovascular disease; DM = subgroup with diabetes mellitus; HLD = subgroup with LDL cholesterol level ≥4.91 mmol/L (≥190 mg/dL); LDL = low-density lipoprotein; NR = not reported; PMSG = Pravastatin Multicenter Study Group.

* Two eligible combination therapy groups were available at this time point. We report the comparison between monotherapy and combination therapy with the lower-dose nonstatin agent on the first line and the higher-dose nonstatin agent on the second.

† These study results were reported in multiple articles, which are listed in **Table 3** of the **Supplement** (available at www.annals.org).

tified no studies that reported results within the ASCVD and DM groups.

Two trials compared low-intensity statin combined with niacin to mid-intensity statin monotherapy (219 participants) (27, 61). We found inconsistent effects on LDL cholesterol level for this comparison (insufficient SOE). One trial reported on adherence, which was 96% in each group (61). One trial reported withdrawals due to adverse events, which did not statistically significantly differ between groups (19% of monotherapy recipients vs. 10% of combination therapy recipients; $P = 0.06$) (27). Secondary harms occurred infrequently (**Table 4** of the **Supplement**).

#### *Combination Therapy With ω-3 Fatty Acid by Intensity Comparison*

We identified no relevant studies of ω-3 fatty acids.

## DISCUSSION

Prior National Cholesterol Education Program Adult Treatment Panel III guidelines emphasized achieving certain LDL cholesterol targets (62, 63); however, the new ACC/AHA guidelines have departed from this strategy given the lack of evidence supporting this approach (8). These new guidelines recommend prescribing at least a moderate-intensity statin to all patients with moderate or greater ASCVD risk regardless of LDL cholesterol value. Statins may reduce ASCVD by reducing LDL cholesterol level and inflammation (64). Although this strategy offers evidence-based risk reduction for many patients, it creates a clinical conundrum for high-risk patients who cannot tolerate higher-intensity statins because of adverse effects or who have limited LDL cholesterol response to statins.

Higher-intensity statin regimens have been linked to a statistically significant increased risk for adverse events and discontinuation of therapy due to adverse events (65). Statin users have a 50% greater adjusted odds of reporting musculoskeletal pain than nonusers (66), and such symptoms may lead to medication nonadherence. Individual LDL cholesterol responses to statins vary widely. One study found that 4% of patients do not respond and that another 10% have inadequate LDL cholesterol reduction (67). The ACC/AHA guidelines suggest the addition of a nonstatin lipid-modifying agent to maximally tolerated statin among high-risk statin-intolerant or statin-unresponsive patients (8). This recommendation was based on expert opinion, and the authors did not offer recommendations with respect to which nonstatin agent or agents should be used, other than recommending that clinicians weigh potential ASCVD risk-reduction benefits against risk for adverse events. Given that statin intolerance and unresponsiveness are relatively common, many clinicians will probably care for these patients at some point; our review may address, in part, this evidence gap.

Our results suggest that moderated statin combination therapy with bile acid sequestrants decreases LDL cholesterol level to a similar or greater extent compared with higher-intensity statin monotherapy among patients at high risk for ASCVD. Unfortunately, we could not determine whether the LDL cholesterol benefits of these regimens translate into decreased risk for death, ASCVD events, or revascularization procedures. We suspect that the short duration of most trials included in this review contributed to their failure to capture changes in these clinical outcomes, which typically require follow-up over several years. A 7-year RCT of hypercholesterolemic men found that bile acid sequestrant monotherapy conferred a 24% reduction in risk for coronary heart disease deaths and a 19% reduction in risk for nonfatal myocardial infarction compared with placebo (68). Few trials included in this review reported on harms or adherence. Prior reviews have found that adverse effects of bile acid sequestrant monotherapy include constipation and bloating; increased plasma triglyceride levels; and decreased absorption of anionic medications, including statins (68, 69). Reported rates of gastrointestinal adverse effects and drug interactions differ by agent, with colesevelam typically producing fewer effects (69, 70). When considering combination therapy with a lower-intensity statin and bile acid sequestrant, patients may benefit from counseling on separating drug administration to ensure maximal effect of each medication.

We also found that the combination of ezetimibe and lower-intensity statin would offer LDL cholesterol–lowering benefits similar to or better than those of higher-intensity statin monotherapy among patients at high ASCVD risk while producing similar rates of short-term adverse events. Previous reviews link ezetimibe use with diarrhea, and the incidence of elevated liver aminotransferase levels may increase with coadministration of ezetimibe and statin (69, 70). No trials in this review had statistically significant between-group differences in liver aminotransferase elevations, although event rates were low and all trials lasted 24 weeks or less. We again could not determine whether the LDL cholesterol benefits of lower-intensity statin and ezetimibe translate into decreased risk for death, ASCVD events, or revascularization procedures, which we suspect is related to the short duration of included trials. Although clinicians could consider a combination of lower-intensity statin and ezetimibe to decrease LDL cholesterol level among high-risk patients who are intolerant or unresponsive to statins, clinicians should counsel patients that this regimen may not result in reduced ASCVD risk.

We found insufficient evidence regarding LDL cholesterol reduction when comparing moderated combination therapy with fibrates, niacin, or ω-3 fatty acids to higher-intensity statin monotherapy. The role of niacin or ω-3 fatty acids combined with a statin as alternative strategies remains unclear; the niacin trials demonstrated inconsistent results for LDL cholesterol, only 1 reported on long-term clinical outcomes, and we identified no ω-3 trials. We

found only 3 trials of moderated combination therapy with statin and fibrate among populations at high ASCVD risk, but all favored statin monotherapy with respect to decreasing LDL cholesterol level. We could not compare the benefits of these regimens with respect to risk for death and ASCVD events. A recent meta-analysis found that fibrate monotherapy conferred a 13% decreased risk for coronary heart events but had no effect on stroke compared with placebo (71). However, a recent RCT found that the addition of fenofibrate to simvastatin did not reduce the rates of cardiovascular deaths, myocardial infarction, or stroke more than same-dose simvastatin monotherapy among patients with DM (5). No included trials reported statistically significant differences in adverse events between combined lower-intensity statin and fibrate and higher-intensity statin monotherapy. A previous review noted that fibrate therapy has been associated with increased creatinine and homocysteine levels and increased risk for myopathy, cholelithiasis, and venous thrombosis (72). Overall, the combination of lower-intensity statin and fibrates may hold less promise for ASCVD risk reduction, despite its consideration as a strategy in the ACC/AHA guidelines (8).

Our review has several limitations. Moderated statin combination therapy may be of greatest utility among patients who cannot tolerate high-intensity statin monotherapy. Unfortunately, we found no trials among patients with statin intolerance; in fact, many trials excluded participants with this history. We must cautiously extrapolate the potential benefits and harms seen among these patients to those with statin intolerance. Most trials we identified were of relatively short duration, even though these medications are used in clinical practice as long-term medications (73). Although our findings may suggest that one therapeutic option provides LDL cholesterol benefit over another, we cannot comment on the long-term clinical benefits of, tolerability of, or persistence with the regimen given the lack of data and short trial duration. Future trials should consider longer durations (>12 months) to reflect how these medications are currently used in clinical practice and to evaluate long-term clinical outcomes and medication persistence. We standardized the intensity of different doses of various statins according to a recent meta-analysis (18), which differed from that in the ACC/AHA guidelines (8) given that this report was released after the completion of our data collection.

We also identified several methodological limitations within the evidence base. Trials were frequently downgraded during risk-of-bias assessment because they lacked blinding of participants and study personnel (performance bias), did not report the blinding of outcome assessors (detection bias), or did not account for losses to follow-up or handling of incomplete data (attrition bias). Many trials did not provide all data elements needed to conduct meta-analyses; when we did attempt meta-analyses, substantial clinical and statistical heterogeneity precluded the presentation of summary estimates.

In conclusion, lower-intensity statin combined with bile acid sequestrant or ezetimibe may be alternatives to higher-intensity statin monotherapy among high-risk patients who are statin-intolerant or who have a less-than-anticipated LDL cholesterol response. These regimens decreased LDL cholesterol level to an extent similar to or better than that of higher-intensity statin monotherapy (0% to 14% more for both). However, clinicians should use these strategies with caution and counsel their patients, given the lack of evidence on ASCVD risk reduction benefits and limited data on adverse events. Future studies should evaluate long-term clinical outcomes and harms among statin-intolerant and statin-unresponsive patients, which would provide important information for clinical decision making, patient choice, and clinical practice guidelines.

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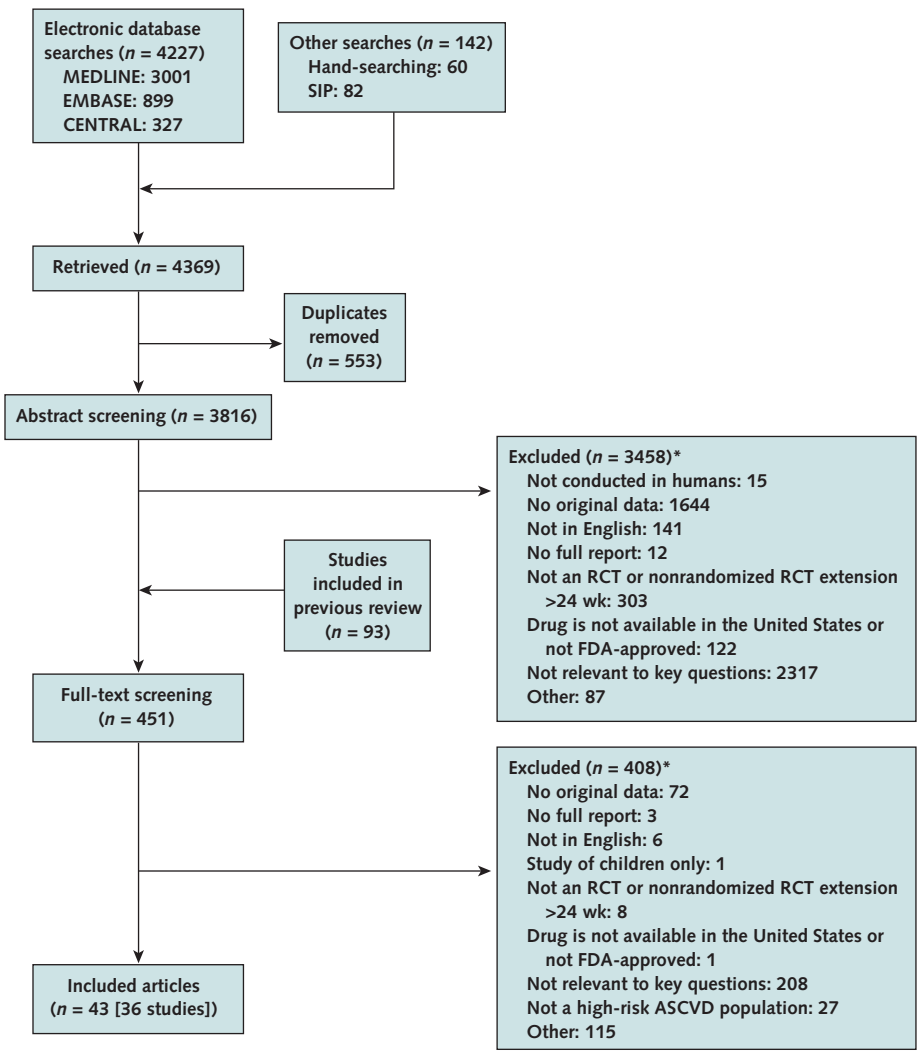
*Appendix Figure.* **Summary of evidence search and selection.**




ASCVD = atherosclerotic cardiovascular disease; CENTRAL = Cochrane Central Register of Controlled Trials; FDA = U.S. Food and Drug Administration; RCT = randomized, controlled trial; SIP = scientific information packet.

* Citations could be excluded for >1 reason; therefore, the sum of excluded studies listed from each category may exceed the actual number of citations excluded.