

# Effectiveness of Statin Therapy in Adults With Coronary Heart Disease

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**Background:** We conducted a meta-analysis of patients with coronary heart disease (CHD) to determine the effectiveness of statin therapy; whether effectiveness varied according to patient characteristics, outcomes, or pretreatment low-density lipoprotein cholesterol (LDL-C) levels; and the optimal LDL-C goal and the level at which to initiate statin therapy.

**Methods:** Randomized trials or systematic reviews for secondary prevention of CHD with statin therapy published between January 1966 and December 2002 were identified through MEDLINE and the Cochrane Library. Studies were included if they randomly assigned adults with CHD to statin therapy or control, enrolled at least 100 individuals per arm, reported clinical outcomes and LDL-C levels, and were published as full studies in English. Two reviewers abstracted data using a prospectively designed protocol.

**Results:** Twenty-five studies enrolling 69 511 individuals were included. Participants in 19 placebo-controlled

trials had a mean age of 63 years and a mean pretreatment LDL-C level of 149 mg/dL (3.85 mmol/L); 23% were women. Statin therapy reduced CHD mortality or nonfatal myocardial infarction 25% (relative risk [RR], 0.75; 95% confidence interval [CI], 0.71-0.79), all-cause mortality 16% (RR, 0.84; 95% CI, 0.79-0.89), and CHD mortality 23% (RR, 0.77; 95% CI, 0.71-0.83). Beneficial effects were seen in women and the elderly. There were no data to determine whether lowering the LDL-C level to less than 100 mg/dL (<2.59 mmol/L) was superior to lowering it to 100 to 130 mg/dL (2.59-3.36 mmol/L). Meta-regression analyses revealed risk reductions for CHD mortality or nonfatal myocardial infarction and major vascular events across available pretreatment LDL-C levels.

**Conclusion:** Statin therapy reduces mortality and morbidity in adults with CHD, even at pretreatment LDL-C levels as low as 100 mg/dL (2.59 mmol/L).

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**C**ORONARY HEART DISEASE (CHD) is the leading cause of death in the United States among men and women, accounting for more than 681 000 deaths in 2000, or 1 of every 5 deaths in the United States.<sup>1</sup> A history of CHD increases the relative risk (RR) of subsequent cardiovascular morbidity and mortality by 5 to 7 times. Randomized controlled trials (RCTs)<sup>2-6</sup> demonstrate that lowering high levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) reduces cardiovascular events and mortality and is cost-effective.

Effective secondary prevention with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) requires long-term medication adherence. However, 1 study<sup>7</sup> found that only 40% of elderly individuals who had a recent acute coronary syndrome were still adherent 2 years

after receiving an initial prescription for statins. Adherence was 36% for chronic CHD and 25% for primary prevention. These percentages are much lower than reported from long-term secondary prevention RCTs and may be partly due to uncertainty regarding the benefits of statins, especially across different LDL-C subgroups, patient populations, and outcomes.

Previous systematic reviews have included results from primary prevention trials and nonrandomized studies or were published before completion of the largest secondary prevention RCTs that included individuals with low pretreatment LDL-C levels. We conducted a systematic review and meta-analysis of RCTs to evaluate the efficacy of statin therapy in adults with CHD. We evaluated whether statins reduced fatal and nonfatal CHD, all-cause mortality, vascular events, and revascularization proce-

dures. This systematic review sought to determine the magnitude of the effectiveness of statin therapy, the optimal LDL-C level at which to initiate statin therapy, whether aggressive LDL-C reduction was superior to moderate LDL-C reduction, and whether effectiveness varied according to patient characteristics, statin type or dose, pretreatment LDL-C level, or magnitude of LDL-C reduction.

## METHODS

### SYSTEMATIC REVIEW PROTOCOL AND TRIAL SELECTION

The protocol for the systematic review was prospectively designed.<sup>8</sup> Randomized or controlled clinical trials of secondary prevention of cardiovascular disease with statin therapy published between January 1966 and January 2003 were identified through MEDLINE and the Cochrane Library using the following Medical Subject Heading terms and key words: "cardiovascular diseases," "myocardial ischemia," "coronary disease," "lipoproteins," "LDL cholesterol," "hypercholesterolemia," "anticholesteremic agents," "hydroxymethylglutaryl-CoA reductase inhibitors," "atorvastatin," "cerivastatin," "fluvastatin," "lovastatin," "pravastatin," and "simvastatin."<sup>9</sup> Reference lists from identified trials, cross-references from original articles, and reviews were searched for additional trials.

Studies were included if they enrolled adults with CHD, included at least 100 individuals per arm, reported clinical outcomes, randomly assigned participants to statin use or control (placebo, active control, or usual care), and were published as full studies in English. Two reviewers (R.M. and I.R.) identified the inclusion criteria, determined whether trials met the inclusion criteria, and abstracted the data. Study quality was evaluated according to a scale developed by Schulz et al.<sup>10</sup>

### DATA ANALYSIS

The primary outcome measure was CHD death plus nonfatal myocardial infarction (MI). For categorical outcomes, weighted RRs and their 95% confidence intervals (CIs) were calculated using a software program (Cochrane Review Manager Version 4.1 for Windows; The Cochrane Collaboration, Oxford, England). A fixed-effects model was used if there was no evidence of heterogeneity among the studies, based on the  $\chi^2$  test for heterogeneity and scatterplots.<sup>11</sup> Results of placebo-controlled trials were pooled and reported separately from those of trials involving usual care or active control groups. Two placebo-controlled trials<sup>12,13</sup> included individuals at high risk of CHD (vascular disease, diabetes mellitus, and hypertension) without overt CHD in addition to those with established CHD. To maintain consistency with our inclusion criteria, individuals without overt CHD were excluded from the analyses. If the actual number of events for the statin and placebo arms of CHD were not provided, the number of events was estimated using the event rates for the investigated outcomes for all participants. Sensitivity analyses were conducted to evaluate the variability in the estimated effects of statin therapy on outcomes related to (1) study duration, (2) inclusion of patients without overt CHD, (3) whether trials had CHD death or MI as a primary end point, (4) limited enrollment to patients undergoing percutaneous coronary intervention (PCI), or (5) patients with acute coronary syndromes. Prespecified subgroup analyses examined the effects of statin therapy by statin type, sex, race, age, occurrence of a PCI, and the presence of acute coronary syndromes. We examined associations between outcomes and statin dose, absolute and percentage reductions in

LDL-C levels, and use of concomitant cardiovascular medications.

Analysis of the relationship between baseline LDL-C levels and CHD outcomes used meta-regression analyses. Analyses were limited to placebo-controlled trials of at least 1-year duration that reported the relevant outcome measure. The first analysis used a weighted regression to model the log of the observed RR for each study as a function of study duration and average baseline or initial LDL-C level using the inverse of the estimated variances for the log RRs as weights. A similar weighted regression analysis was used to model the differences in the observed risks. Analyses used LDL-C subgroup data reported for 4 trials.<sup>2,4,12,14</sup>

Average baseline LDL-C levels were not reported for some of these subgroups, so the analysis used the midrange or an estimate of the midrange of the LDL-C levels for these subgroups in the meta-regression models. In the analyses that examined CHD death, 2 trials reported no CHD mortality in 1 of the treatment arms. A value of 0.5 was added to the number of events for these study arms to include these trials in the meta-regression. We examined possible transformations of baseline LDL-C values to assess the sensitivity of the results to the functional form used for baseline LDL-C values in the previous analyses and to examine whether a more optimal model could be identified. These investigations did not substantively alter the results and did not identify better-fitting models. Similar meta-regression analyses added the absolute change or the percentage change in LDL-C level to the regression models to examine the association between the change in LDL-C concentration and the outcome when controlling for the baseline LDL-C level.

## RESULTS

The literature search identified 2169 articles. After further evaluation, 104 articles representing 25 unique trials involving 69 511 participants met the inclusion criteria. Nineteen trials were placebo controlled: pravastatin sodium (7 trials and 22 177 participants [18 938 with CHD]),<sup>3,4,15-19</sup> simvastatin (5 trials and 26 075 participants [18 925 with CHD]),<sup>2,12,20-22</sup> lovastatin (3 trials and 1005 participants),<sup>23-25</sup> and fluvastatin sodium (4 trials and 3525 participants).<sup>14,26-28</sup> Of the remaining trials, 3 compared statin therapy with usual care (12 181 participants),<sup>29-31</sup> 1 compared an "aggressive dose" vs a "moderate dose" of lovastatin,<sup>32</sup> 1 compared simvastatin use with atorvastatin calcium use,<sup>33</sup> and 1 compared atorvastatin therapy with angioplasty.<sup>34</sup> Four placebo-controlled studies<sup>14,15,24,27</sup> limited enrollment to patients undergoing PCI. Three studies enrolled individuals at high risk of CHD even if overt CHD was not present (Heart Protection Study [HPS],<sup>12</sup> 35% of enrolled patients; PROSPER [Prospective Study of Pravastatin in the Elderly at Risk],<sup>13</sup> 56%; and ALLHAT [Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial],<sup>30</sup> 86%). One trial<sup>35</sup> evaluated atorvastatin and was limited to patients (n = 3076) with acute coronary syndromes and is addressed separately. Although all included studies reported that treatment assignment was randomized, treatment allocation concealment was judged to be adequate in only 6 trials.<sup>2,3,12,13,20,30</sup>

The mean or median follow-up ranged from 0.3 to 6.1 years, with 15 studies lasting at least 1 year. Nine trials used escalating doses of medication to achieve a specific LDL-C goal. The average dose ranged from 27 to 34 mg/d

**Baseline Characteristics of 52 782 Participants Enrolled in 19 Placebo-Controlled Statin Trials**

Characteristic	Statin Group (n = 26 407)	Placebo Group (n = 26 375)	Studies Reporting, No.* (n = 19 Studies)
Age, mean, y	63	63	18
Women, mean (range), %	23 (0-52)	23 (0-52)	18†
White, mean (range), %	94 (88-100)	93 (88-100)	3
Baseline lipid levels, mean (range), mg/dL			
LDL cholesterol	148 (130-198)	150 (126-193)	19‡
Total cholesterol	227 (200-289)	228 (199-284)	19‡
Previous CHD, %	80	80	19
No previous CHD, mean, %	20	20	2§
Previous MI, mean (range), %	48 (13-99)	48 (14-99)	17
Previous PTCA or CABG, mean (range), %	24 (1-100)	23 (2-100)	13
History of diabetes mellitus, mean (range), %	17 (0-29)	17 (0-29)	18¶
Concomitant medication use (patients with overt CHD only), mean (range), %			
Aspirin	75 (37-100)	75 (37-100)	13
β-Blocker	43 (23-73)	43 (19-74)	12
Calcium channel blocker	38 (12-67)	38 (17-63)	11
ACE inhibitor	18 (5-38)	18 (5-38)	10
Nitrates	38 (31-66)	38 (33-63)	9

Abbreviations: ACE, angiotension-converting enzyme; CABG, coronary artery bypass graft; CHD, coronary heart disease; LDL, low-density lipoprotein; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.02586.

\*According to treatment group.

†Two trials included no women.

‡Included participants with overt CHD only (n = 42 173).

§Trials that enrolled high-risk patients without overt CHD included the Heart Protection Study (HPS) (n = 7150, 35%) and Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) (n = 3239, 56%). Among these patients, 3982 were diabetic, 2701 had peripheral vascular disease, and 1820 had cerebrovascular disease (with some having >1 of these conditions).

||If "any" previous revascularization procedure was not provided, the procedure with the highest frequency was used.

¶Four studies excluded individuals with diabetes mellitus, usually requiring treatment.

for trials using simvastatin,<sup>2,20,21</sup> 33 to 76 mg/d for trials using lovastatin,<sup>23,25,29,32</sup> 49 mg/d in the study using fluvastatin,<sup>26</sup> and 24 mg/d in the study using atorvastatin.<sup>31</sup> One study<sup>32</sup> compared "aggressive" with "moderate" doses of statins, evaluating lovastatin in doses up to 80 mg with doses up to 5 mg. The trial<sup>33</sup> comparing simvastatin and atorvastatin used doses up to 40 mg/d each. The remainder of the studies used a fixed statin dose (generally 40 mg/d with pravastatin, 20 or 40 mg/d with simvastatin, and 40 or 80 mg/d with lovastatin, fluvastatin, or atorvastatin). Seven trials<sup>2,4,12,13,19,20,28</sup> used a prerandomization placebo run-in period, and 2 trials<sup>12,26</sup> included a treatment (statin) run-in phase.

## PLACEBO-CONTROLLED TRIALS

### Baseline Characteristics

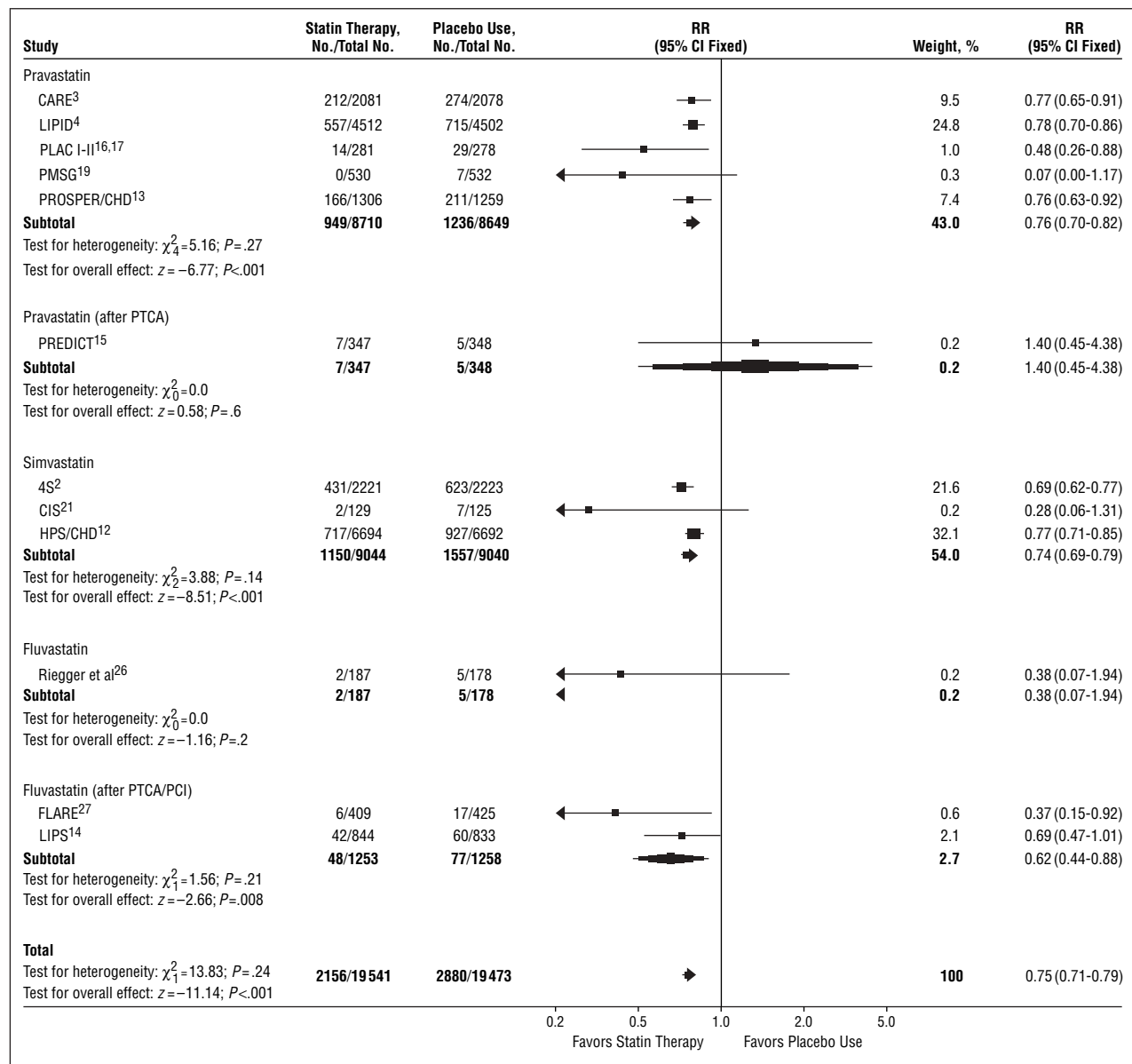
A total of 52 782 individuals with chronic CHD or at high risk of CHD were enrolled in 19 placebo-controlled, double-masked trials (**Table**). On average, participants were 63 years old and had a weighted mean baseline LDL-C level of 149 mg/dL (3.85 mmol/L) (range, 126-198 mg/dL [3.26-5.12 mmol/L]); 23% were women. Twenty percent of enrollees did not have overt CHD but were at high risk owing to the presence of concomitant conditions such as diabetes mellitus, peripheral or cerebrovascular disease, hypertension, or smoking. Participants treated with simvastatin or pravastatin composed greater than 90% of the participants.

## Outcomes

### What Is the Magnitude of the Effectiveness of Statins?

**Total Cholesterol and LDL-C Levels.** The mean on-study total cholesterol level for participants randomized to receive statins ranged from 156 to 240 mg/dL (4.03-6.21 mmol/L) compared with a range of 205 to 270 mg/dL (5.30-6.98 mmol/L) for participants receiving placebo. The mean on-study LDL-C level ranged from 88 to 145 mg/dL (2.28-3.75 mmol/L) for participants randomized to receive statins and from 128 to 191 mg/dL (3.31-4.94 mmol/L) for participants randomized to receive placebo. The percentage change in LDL-C level from baseline for participants receiving statins ranged from -22% to -38%. The LDL-C reduction compared with the placebo group ranged from 19% to 37%. The achieved LDL-C concentration in patients assigned to receive statins was less than 100 mg/dL (<2.59 mmol/L) in 7 studies.<sup>3,12-14,20,24,25</sup> In all but 2 trials<sup>20,24</sup> the achieved LDL-C in the control group was greater than 130 mg/dL (>3.36 mmol/L).

**CHD Mortality or Nonfatal MIs.** Twelve studies (n=39 014) reported on the combined outcome of CHD mortality or nonfatal MI (**Figure 1**). Six studies demonstrated a statistically significant reduction. The HPS<sup>12</sup> noted a significant reduction among participants with and without overt CHD. In pooled analyses, statin therapy reduced CHD mortality or nonfatal MI by 25% (RR, 0.75; 95% CI, 0.71-0.79), with an absolute risk reduction (ARR) of 3.8%.



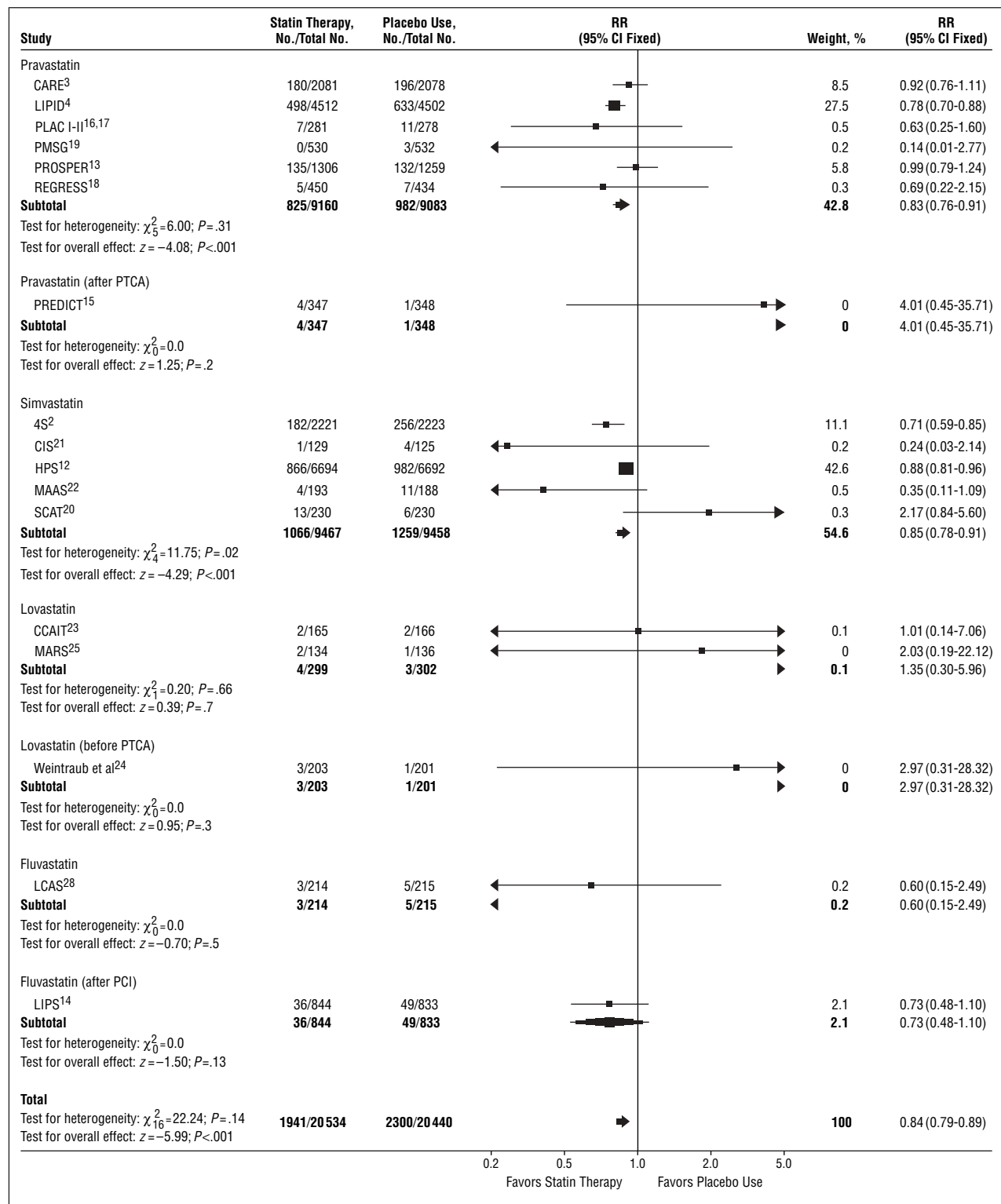
**Figure 1.** Statin therapy vs placebo use: relative risk for coronary heart disease mortality or nonfatal myocardial infarction. RR indicates relative risk; CI, confidence interval; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty. For expansions of trial names, see the reference list.

**All-Cause Mortality.** Seventeen trials ( $n = 40974$ ) provided data sufficient for pooling (**Figure 2**). Three trials were limited to patients undergoing PCI. Three studies demonstrated a statistically significant risk reduction, and 8 favored statin therapy but were not statistically significant. Overall, statin therapy reduced all-cause mortality by 16% (RR, 0.84; 95% CI, 0.79-0.89; ARR, 1.8%). A statistically significant reduction of similar magnitude was observed for studies involving either pravastatin or simvastatin.

**CHD Mortality.** Of 19 trials ( $n = 42173$ ) that reported CHD mortality, 4 were limited to patients undergoing PCI. Three trials<sup>2,4,12</sup> demonstrated a statistically significant reduction in CHD mortality. Statin therapy reduced CHD mortality by 23% (RR, 0.77; 95% CI, 0.71-0.83; ARR, 1.4%). This reduction was statistically significant in trials using all statins except lovastatin.

**Sensitivity Analyses.** Results changed little when the following sensitivity analyses were performed: inclusion of patients with acute coronary syndromes, minimum study duration of 1 or 2 years, inclusion of studies only if their primary outcome was CHD mortality or MI, exclusion of patients without overt CHD or trials that limited enrollment to individuals undergoing PCI, fixed vs random effects models, and high vs low utilization of concomitant cardiovascular medications. Similar benefits were seen in revascularizations, cerebrovascular events, and major coronary or vascular events.

**Does Effectiveness Vary According to Sex, Age, Race, or Revascularization Status?** Women were enrolled in 17 of 19 placebo-controlled trials. Six trials provided primary outcome data separately for women ( $n = 7920$ ).<sup>2-4,12,13,16</sup> Coronary heart disease mortality or nonfatal MI was re-

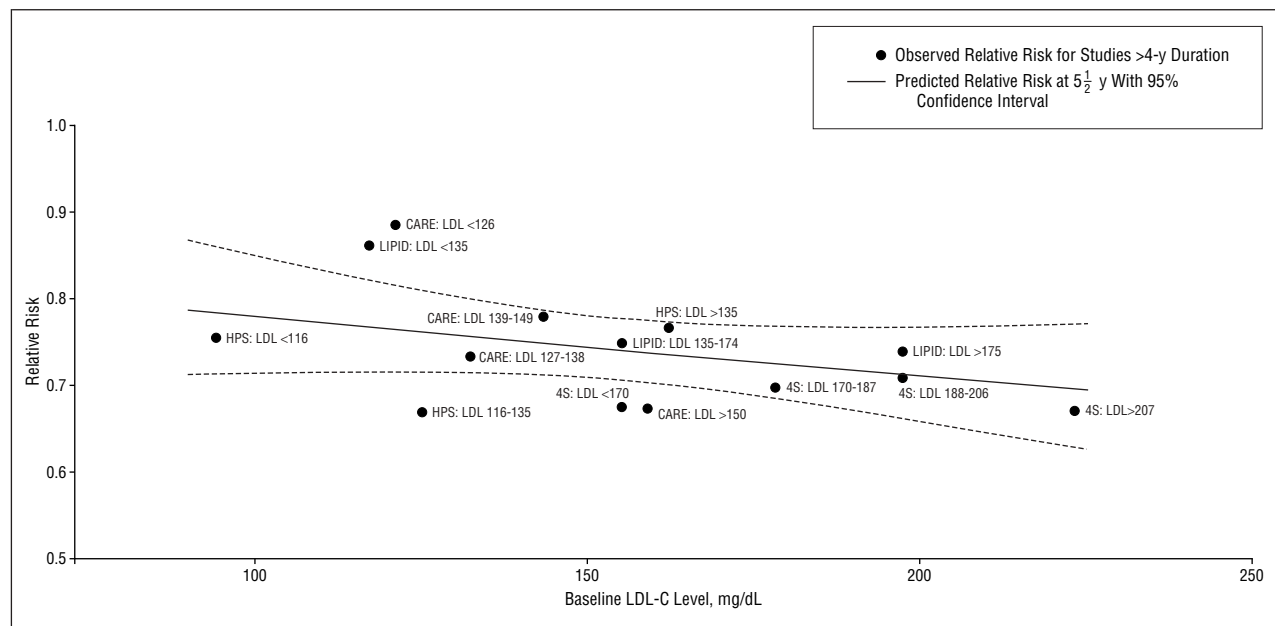


**Figure 2.** Statin therapy vs placebo use: relative risk for all-cause mortality. RR indicates relative risk; CI, confidence interval; PTCA, percutaneous transluminal coronary angioplasty. For expansions of trial names, see the reference list.

duced by 25% (RR, 0.75; 95% CI, 0.65-0.86; ARR, 2.8%), a relative benefit due to statin therapy similar to that observed in all participants. Only 2 trials reported all-cause<sup>2,16</sup> and CHD mortality<sup>2,3</sup> data, and no significant differences were evident in both outcomes.

Six trials<sup>2-4,12,13,17</sup> provided event data specifically for “older patients,” and the definition of older patients varied among studies. Some studies provided data on adults older than 60 years, others<sup>2-4,17</sup> reported results for adults 65 years and older, and 1 study<sup>12</sup> provided information





**Figure 3.** Relative risk from the meta-regression model for coronary heart disease mortality or myocardial infarction. Analyses were limited to placebo-controlled statin trials of at least 1-year duration that reported the respective outcome measures. The analyses used low-density lipoprotein cholesterol (LDL-C) subgroup data from the trials that reported that information. The models provide outcome estimates for statin therapy vs placebo use for a 5½-year period (midrange of trial follow-up for most included study groups) across a range of values for the typical or average baseline LDL-C level. To convert LDL-C from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.02586. For expansions of trial names, see the reference list.

for adults 70 years and older and 75 to 80 years. Pravastatin or simvastatin reduced CHD death plus nonfatal MI by 24% in older patients (RR, 0.76; 95% CI, 0.71-0.81; ARR, 4.2%; n=16785), all-cause death 15% (RR, 0.85; 95% CI, 0.73-0.99; ARR, 1.8%; n=4941), and CHD death 35% (RR, 0.65; 95% CI, 0.49-0.86; ARR, 2.1%; n=3942). The HPS<sup>12</sup> found a statistically significant ARR of 3.1% for major vascular events (28.7% vs 23.6%) in patients 70 years and older. This study reported an even larger reduction (32.3% vs 23.1%;  $P<.001$ ) among 1263 individuals aged 75 to 80 years at study entry.

Only 2 placebo-controlled trials<sup>28,35</sup> described the number of black participants enrolled (n=110), and 1 involved patients with acute coronary syndromes. No placebo-controlled trials provided data on other nonwhite groups.

The percentage of enrollees with previous revascularization procedures (coronary artery bypass graft or PCI) was reported in 13 placebo-controlled trials. Enrollment was limited in 4 studies<sup>14,15,24,27</sup> to individuals scheduled for, or recently undergoing, PCI. Baseline LDL-C levels ranged from 130 to 181 mg/dL (3.36-4.68 mmol/L). The mean duration of 3 trials was less than 1 year. Statin therapy reduced CHD mortality or nonfatal MI 33% in patients undergoing PCI (RR, 0.67; 95% CI, 0.48-0.93; ARR, 1.7%; n=3206). There were nonsignificant reductions in all-cause death (RR, 0.83) and CHD mortality (RR, 0.66). Studies using fluvastatin showed a beneficial effect, and pooled estimates were statistically significant for CHD mortality or nonfatal MI (RR, 0.62) and CHD mortality (RR, 0.51).<sup>14,27</sup>

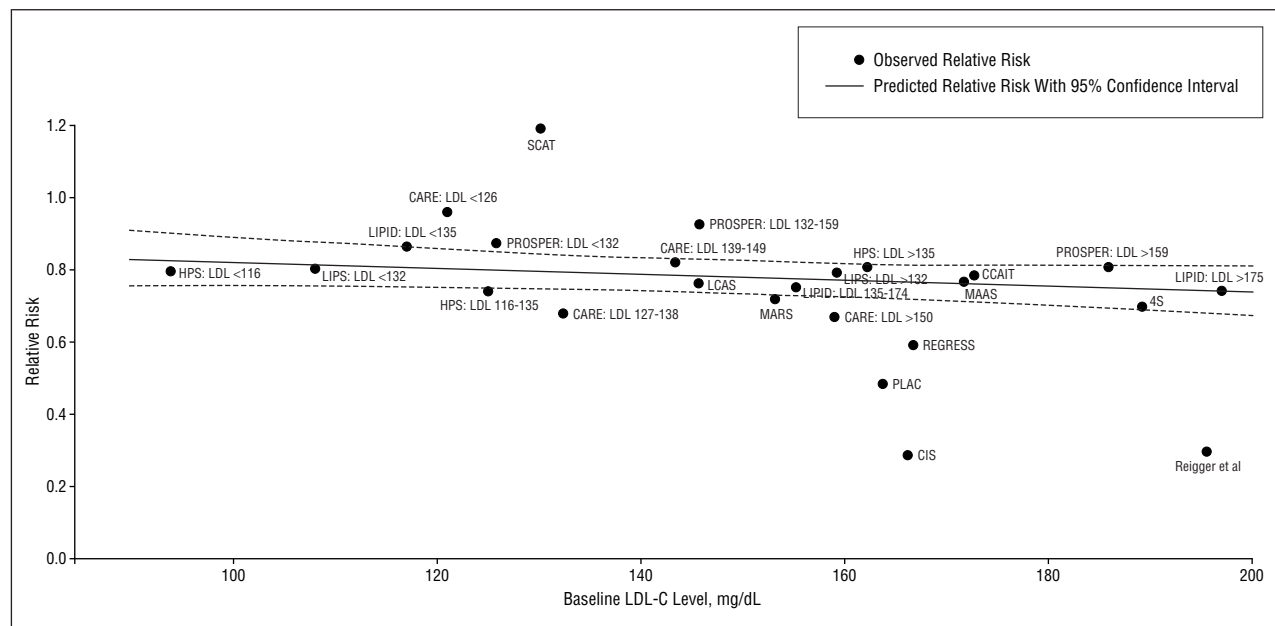
**Does Effectiveness Vary According to Pretreatment LDL-C Level?** To assess the relationship between pretreatment LDL-C level and outcomes, we conducted a se-

ries of meta-regression analyses for the risks of CHD mortality or nonfatal MI, all-cause mortality, and major clinical and vascular events.

For CHD mortality or MI, the pretreatment LDL-C value ranged from 94 to 223 mg/dL (2.43-5.77 mmol/L). The RR decreased by a factor of 0.99 (95% CI, 0.98-1.00) for every 10-mg/dL (0.26-mmol/L) increase in pretreatment LDL-C concentration. The model-estimated RR reduction for a 5½-year period (midrange of trial follow-up for most included study groups) ranged from 22% for an LDL-C value of 120 mg/dL (3.10 mmol/L) (RR, 0.78; 95% CI, 0.72-0.85) to 30% for an LDL-C value of 220 mg/dL (5.69 mmol/L) (RR, 0.70; 95% CI, 0.63-0.77) (**Figure 3**). The ARR ranged from 2.6% (95% CI, 1.5%-3.6%) at an LDL-C level of 100 mg/dL (2.59 mmol/L) to 6.0% (95% CI, 4.1%-7.8%) at an LDL-C level of 220 mg/dL (5.69 mmol/L), a 0.28% increase for every 10-mg/dL (0.26-mmol/L) increase in baseline LDL-C concentration (Figure 3).

For all-cause mortality, the range of LDL-C levels available was 130 to 189 mg/dL (3.36-4.89 mmol/L). The RR decreased by a factor of 0.97 for every 10-mg/dL (0.26-mmol/L) increase in pretreatment LDL-C level ( $P=.05$ ). The model-estimated RR reduction ranged from 3.4% at a baseline LDL-C level of 130 mg/dL (3.36 mmol/L) (RR, 0.97, 95% CI, 0.88-1.01) to 22% at an LDL-C level of 190 mg/dL (4.91 mmol/L) (RR, 0.78; 95% CI, 0.65-0.94). The ARR ranged from 0.4% (95% CI, -0.4%-1.1%) at an LDL-C value of 130 mg/dL (3.36 mmol/L) to 2.3% (95% CI, 1.2%-3.4%) at an LDL-C value of 190 mg/dL (4.91 mmol/L), a 0.31% increase for every 10-mg/dL (0.26-mmol/L) increase in the baseline LDL-C value. Similar results were observed for CHD mortality.

For major clinical and vascular events, the range of LDL-C levels available was 94 to 200 mg/dL (2.43-5.17



**Figure 4.** Relative risk from meta-regression model for major cardiac events. Analyses were limited to placebo-controlled statin trials of at least 1-year duration that reported the respective outcome measures. The analyses used low-density lipoprotein cholesterol (LDL-C) subgroup data from the trials that reported that information. The models provide outcome estimates for statin therapy vs placebo use for a 5½-year period (midrange of trial follow-up for most included study groups) across a range of values for the typical or average baseline LDL-C level. To convert LDL-C from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.02586. For expansions of trial names, see the reference list.

mmol/L) (**Figure 4**). The reduction in risk was not associated with pretreatment LDL-C concentration ( $P=.13$ ), and a statistically significant risk reduction was observed at all pretreatment LDL-C levels. The RR reduction ranged from 18% (RR, 0.82; 95% CI, 0.75-0.89) at an LDL-C level of 100 mg/dL (2.59 mmol/L) to 26% (RR, 0.74; 95% CI, 0.67-0.81) at an LDL-C level of 220 mg/dL (5.69 mmol/L). Similarly, the ARR ranged from 4.0% (95% CI, 2.3%-5.6%) at an LDL-C level of 100 mg/dL (2.59 mmol/L) to 6.1% (95% CI, 4.1%-8.0%) at an LDL-C level of 200 mg/dL (5.17 mmol/L) (Figure 4).

We conducted meta-regression analyses to evaluate the association between percentage or absolute LDL-C reduction and all-cause mortality and CHD mortality. Analyses were not feasible for the combined outcome of CHD or nonfatal MI because too few trials provided data regarding this outcome and percentage or absolute LDL-C reduction. For the meta-regression models evaluating LDL-C reduction, the absolute LDL-C reduction was highly correlated with baseline LDL-C concentration ( $r>0.7$ ). When controlling for baseline LDL-C concentration, the absolute LDL-C reduction was not significantly associated with CHD mortality and was associated with an increase in all-cause mortality. The unanticipated direction of the estimated association between the change in LDL-C concentration and mortality seems to be a consequence of the large correlation between the change in the LDL-C level and the baseline LDL-C concentration. The percentage reduction in LDL-C concentration showed low correlation with baseline LDL-C concentration, but the range across studies in the percentage reduction was small. This small range in the percentage reduction limited our ability to examine an association between percentage reduction and risk reduction, and, hence, in the available data we could not

find an association between percentage reduction in LDL concentration and reduction in risk of outcomes.

**Is Aggressive LDL-C Reduction Superior to More Moderate LDL-C Lowering?** In no placebo-controlled trials was the goal LDL-C concentration less than 100 mg/dL (<2.59 mmol/L) compared with a goal of 100 to 130 mg/dL (2.59-3.36 mmol/L). Results with on-trial LDL-C levels less than 100 mg/dL (<2.59 mmol/L) do not clearly demonstrate that achieving LDL-C levels less than 100 mg/dL (<2.59 mmol/L) reduces mortality, nonfatal CHD events, or procedure utilization compared with less intensive lipid reduction (eg, 100-130 mg/dL [2.59-3.36 mmol/L]). The Post Coronary Artery Bypass Graft Study<sup>36</sup> compared “aggressive LDL-C reduction” with lovastatin (average dose, 76 mg/d) and, if necessary, cholestyramine resin (target LDL-C level, 60-85 mg/dL [1.55-2.20 mmol/L]) with “moderate LDL-C reduction” (target LDL-C level, 130-140 mg/dL [3.36-3.62 mmol/L]) with lovastatin doses titrated up to 5 mg/d. Treatment with high-dose lovastatin reduced the risk of repeated revascularization at 4 years (6.5% with aggressive treatment vs 9.2% with moderate treatment; on-trial LDL-C, 93 vs 136 mg/dL [2.40 vs 3.52 mmol/L]). There were no differences in all-cause or CHD mortality or the composite end point of major coronary events. The mean dose of lovastatin in the moderate treatment group was very low (4 mg/d), and the on-trial LDL-C level in this group was 136 mg/dL (3.52 mmol/L). This study does not address whether reducing LDL-C levels to less than 100 mg/dL (<2.59 mmol/L) is superior to reducing LDL-C levels to less than 130 mg/dL (<3.36 mmol/L).

**Statin Therapy in Individuals With LDL-C Levels Already Less Than 100 mg/dL (<2.59 mmol/L).** The HPS<sup>12</sup> provided the only information on individuals with LDL-C

levels already less than 100 mg/dL (<2.59 mmol/L) or with total cholesterol levels less than 200 mg/dL (<5.17 mmol/L). Statin therapy reduced the risk of major vascular events by 4.6% (16.4% vs 21.0%;  $P<.001$ ) in a subgroup of 3421 individuals with LDL-C levels less than 100 mg/dL (<2.59 mmol/L). There were significant risk reductions among 4072 participants with pretreatment total cholesterol levels less than 193 mg/dL (<4.99 mmol/L) (17.7% vs 23.1%;  $P<.001$ ).

**Does Effectiveness Vary According to Dose or Type of Statin?** There is little information to assess whether effectiveness varies according to dose or type of statin. All placebo-controlled studies used moderate-high doses of statins (20-80 mg), and most used a fixed statin dose. Although the Post Coronary Artery Bypass Graft Study evaluated the relative effectiveness of different doses of statins, the results do not adequately address the question of whether relatively low doses of statins (eg, 10-20 mg of simvastatin) or reducing LDL-C with statin therapy to levels less than 100 mg/dL (<2.59 mmol/L) is superior to higher doses or to reducing LDL-C levels to less than 130 mg/dL (<3.36 mmol/L).

Studies involving pravastatin and simvastatin enrolled nearly 90% of all participants. TARGET TANGIBLE<sup>33</sup> was the only trial comparing 2 different types of statins (atorvastatin vs simvastatin). Mean follow-up was only 4 months, which is inadequate to evaluate the relative effectiveness of these 2 statins. Although there was no statistical heterogeneity in our meta-analysis, the second largest trial (ALLHAT-LLT<sup>30</sup>), in which only 14% of participants had CHD, did not demonstrate a benefit with pravastatin.<sup>30</sup> It is plausible that these results are due to the relatively modest differential in total cholesterol (9.6%) and LDL-C (16.7%) levels achieved between the pravastatin group and the usual care controls. Fluvastatin was effective in studies that primarily enrolled patients undergoing PCI. Reduction in death, CHD events, or revascularizations was not consistently seen with lovastatin therapy, perhaps owing to relatively few individuals being enrolled. A primary prevention trial<sup>36</sup> reported a reduction in first major acute coronary event with lovastatin use (20-40 mg) in adults with a mean baseline LDL-C level of 150 mg/dL (3.88 mmol/L). There were no trials evaluating atorvastatin therapy in long-term CHD. The MIRACL (Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering) trial<sup>35</sup> showed a short-term benefit with atorvastatin use in patients with acute coronary syndromes.

#### STUDIES COMPARING STATIN THERAPY WITH USUAL CARE

Three trials ( $n=12081$ ) used a usual care control group. The pooled results from 3301 patients with overt CHD demonstrated a 31% reduction in CHD mortality (RR, 0.69; 95% CI, 0.47-1.01).<sup>29-31</sup> There were no significant reductions in CHD mortality and nonfatal MI (1 trial,  $n=1475$ )<sup>30</sup> or all-cause mortality (2 trials,  $n=3075$ ).<sup>30,31</sup>

The ALLHAT-LLT evaluated older, moderately hypercholesterolemic (mean baseline LDL level, 146 mg/dL [3.78 mmol/L]), hypertensive individuals with CHD

(14%) or at least 1 other CHD risk factor.<sup>30</sup> It is the only trial that enrolled a large number of ethnic minorities and specifically limited entry LDL-C concentration in patients with CHD to less than 130 mg/dL (<3.36 mmol/L). Compared with usual care, open-label pravastatin use (40 mg/d) did not reduce all-cause mortality or CHD mortality plus nonfatal MI in patients with ( $n=1475$ ) or without ( $n=8880$ ) CHD. There was no reduction in all-cause mortality for any predefined subgroups, including those 65 years and older, women, blacks, diabetic patients, or high-risk individuals without CHD regardless of whether pretreatment LDL-C levels were greater or less than 130 mg/dL (3.36 mmol/L). The relative reduction in LDL-C concentration from baseline with pravastatin use (27.7%) vs the usual care control group (11.0%) (difference, 16.7%) was smaller than that reported in other randomized trials.

The GREACE (Greek Atorvastatin and Coronary-Heart-Disease Evaluation) trial<sup>31</sup> randomized 1600 men and women with CHD younger than 75 years to receive atorvastatin (titrated to 80 mg/d) or usual care that included lifestyle changes. The treatment goal in the group assigned to atorvastatin therapy was to achieve an LDL-C level less than 100 mg/dL (<2.59 mmol/L) (mean atorvastatin dose, 27 mg/d; mean on-trial LDL-C level in the atorvastatin and usual care groups, 97 and 179 mg/dL [2.51 and 4.63 mmol/L], respectively). Patients assigned to receive atorvastatin had a significant reduction in total mortality (5.0% vs 2.9%; RR, 0.57), CHD mortality (4.8% vs 2.5%), revascularization procedures (5.6% vs 2.7%), and stroke (2.1% vs 1.1%). Benefits were observed in women, individuals aged 60 to 75 years, patients undergoing revascularization procedures, and those with a history of congestive heart failure or diabetes mellitus. These results support the beneficial effect of atorvastatin in adults with CHD and high pretreatment LDL-C levels.

#### COMMENT

The results of this systematic review and meta-analysis indicate that use of statins, in moderate doses, lowered LDL-C levels 20% to 40% and reduced CHD mortality or nonfatal MI 25%, all-cause mortality 16%, and CHD mortality 23%. Similar reductions in strokes, major coronary and vascular events, and revascularization procedures were also observed. Reductions in cardiovascular events occurred within 2 years of initiation of statin therapy and across a wide range of baseline LDL-C levels. Beneficial results were observed in patients undergoing PCI, women, the elderly, and individuals with acute coronary syndromes. There were no data for blacks. Results changed little with multiple sensitivity analyses.

Meta-regression analyses from placebo-controlled trials revealed statistically significant risk reductions due to statin therapy for CHD mortality or nonfatal MI and major vascular events across all available pretreatment LDL-C levels. The absolute and relative reductions in all-cause mortality due to statin therapy were associated with pretreatment LDL-C levels. Reductions were statistically significant at LDL-C levels greater than 130 mg/dL (>3.36 mmol/L).



There were no data to determine whether lowering LDL-C levels to less than 100 mg/dL (<2.59 mmol/L) compared with 100 to 130 mg/dL (2.59-3.36 mmol/L) reduces all-cause death, fatal and nonfatal CHD events, or stroke. In addition, the preferred starting dose of statins is not known, although most trials used moderate fixed doses. The achieved LDL-C level was less than 100 mg/dL (<2.59 mmol/L) in 7 studies.<sup>3,12-14,20,24,25</sup> However, in all but 2 studies<sup>20,24</sup> the achieved LDL-C level was greater than 130 mg/dL (>3.36 mmol/L) in the control group. The results of these studies indicate that achieving an LDL-C concentration less than 100 mg/dL (<2.59 mmol/L) may decrease utilization of coronary revascularization procedures. The HPS<sup>12</sup> indicated that a 39-mg/dL (1.00-mmol/L) reduction in LDL-C concentration reduced the risk of major vascular events approximately 25% regardless of whether the pretreatment LDL level was 116 or 77 mg/dL (3.00 or 2.00 mmol/L). This suggests that even larger and longer reductions in LDL-C levels with statin therapy may result in greater effectiveness.<sup>12</sup>

One pooled analysis<sup>30</sup> of 9 large primary and secondary prevention trials (n=64 736) indicated a reduction in total cholesterol level, mortality, and CHD events (pooled percentage change in total cholesterol, 18.5%; all-cause mortality odds ratio, 0.86; CHD events odds ratio, 0.73).<sup>30</sup> The magnitude of benefit was inversely related to the magnitude of total cholesterol reduction. An additional meta-analysis<sup>37</sup> of 58 primary and secondary randomized trials of cholesterol lowering by any means indicated that for an LDL-C reduction of 39 mg/dL (1.0 mmol/L), the risk of ischemic heart disease events was reduced by 11% in the first year of treatment, 24% in the second year, 33% in years 3 to 5, and 36% thereafter.<sup>37</sup> These authors estimated that the incidence of ischemic heart disease was inversely associated with the magnitude of LDL-C reduction. They suggested that a moderate dose of a statin would lower the LDL-C level by 70 mg/dL (1.8 mmol/L) and reduce ischemic heart disease events in individuals aged 60 years by approximately 61%.

Our meta-regression analysis found that absolute LDL-C reduction was highly correlated with baseline LDL-C levels. The percentage reduction in LDL-C concentration showed low correlation with baseline LDL-C levels, but the range across studies in the percentage reduction was small. This small range limited our ability to examine an association between percentage reduction and risk reduction, and, hence, in the available data we could not find an association between percentage reduction in LDL concentration and reduction in risk of outcomes. Therefore, it is difficult to determine whether higher statin doses or larger reductions in LDL-C concentration (independent of pretreatment LDL-C level) will result in greater clinical benefits.

The reduction in mortality, vascular events, and revascularization procedures was observed within 2 years of initiation of statin therapy. The magnitude and relatively early benefits of statin therapy should be emphasized, especially to groups known to have poor adherence, such as elderly individuals with chronic CHD. Early initiation of statins in adults with acute coronary syndromes also decreased short-term coronary events. Our

results indicate that completion of ongoing RCTs is required to determine whether achieving a goal LDL-C level of less than 100 mg/dL (<2.59 mmol/L) is more effective than an LDL-C level of 100 to 130 mg/dL (2.59-3.36 mmol/L), to evaluate the relative effectiveness of different statins, to assess statin therapy in blacks and other minorities, and to identify methods to improve adherence to statin therapy.

In conclusion, using moderate doses of statins decreases mortality, CHD or cerebrovascular events, and cardiovascular procedures in adults with CHD by 16% to 24%. The benefits occur within 2 years of initiation of statin therapy, at pretreatment LDL-C levels less than 100 mg/dL (<2.59 mmol/L), in women, in the elderly, and independent of concomitant CHD medication use. The preferred dose of statins is not known, although most trials used moderate fixed doses. There is no conclusive evidence that lowering LDL-C levels to less than 100 mg/dL (<2.59 mmol/L) with statin therapy is superior to lowering levels to 100 to 130 mg/dL (2.59-3.36 mmol/L). However, results from 2 other meta-analyses suggest that risk reduction is related to the reduction in cholesterol levels.

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