

Association Between Baseline, Achieved, and Reduction of CRP and Cardiovascular Outcomes After LDL Cholesterol Lowering with Statins or Ezetimibe: A Systematic Review and Meta-Analysis

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Background—Several lipid-lowering therapies reduce CRP (C-reactive protein) independently of LDL-C (low-density lipoprotein cholesterol) reduction, but the association between CRP parameters and benefits from more-intensive LDL-C lowering is inconclusive. We aimed to determine whether the benefits of more- versus less-intensive LDL-C lowering on cardiovascular events related to baseline, achieved, or magnitude of reduction in CRP concentrations.

Methods and Results—PubMed, EMBASE, and Cochrane were searched through July 2, 2018. We included randomized controlled cardiovascular outcome trials of LDL-C lowering with statins or ezetimibe. Two reviewers independently extracted study data and rated study quality. Data were analyzed using meta-analysis and metaregression analysis. Rate ratios of mortality and cardiovascular outcomes associated with baseline, achieved, and magnitude reduction of CRP concentration were calculated. Twenty-four trials were included, with 171 250 patients randomly assigned to more- or less-intensive LDL-C- lowering treatments. Median follow-up duration was 4.2 years. More-intensive LDL-C lowering resulted in a significant reduction in incidences of all outcomes. Compared with less-intensive LDL-C lowering, more-intensive LDL-C lowering was associated with less reductions in myocardial infarction with a higher baseline CRP concentration (change in rate ratios per 1-mg/L increase in log-transformed CRP, 1.12 [95% CI, 1.04–1.22; *P*=0.007]), but not other outcomes. Similar risk reductions occurred for more- versus less-intensive LDL-C–lowering therapy regardless of the magnitude of CRP reduction or the achieved CRP level for all outcomes.

Conclusions—Baseline CRP concentrations might be associated with the benefits of LDL-C lowering on myocardial infarction, but no other outcomes, whereas the achieved and magnitude of reduction in CRP did not seem to have an important association. (*J Am Heart Assoc.* 2019;8:e012428. DOI: 10.1161/JAHA.119.012428.)

Key Words: cardiovascular outcomes • C-reactive protein • LDL-cholesterol • lipid lowering • meta-analysis • randomized controlled trials

L-C (Low-density lipoprotein cholesterol) and inflammation are important risk factors for cardiovascular disease. Lowering LDL-C with statins or ezetimibe and inhibiting inflammation with canakinumab significantly reduce major cardiovascular events.¹⁻⁴ hsCRP (high-sensitivity C-reactive protein) is a predictor of cardiovascular disease and cardiovascular mortality as well as total cholesterol and blood pressure.⁵ Several lipid-lowering therapies (ie, stains and ezetimibe) prove to reduce hsCRP independently of LDL-C reduction.⁶ However, it is inconclusive whether benefits from LDL-C lowering are associated with baseline CRP concentrations. Larger cardio-vascular benefits were observed after statin therapy among patients with elevated baseline CRP concentrations in some trials,⁷ but not others.^{8,9} Similarly, whether achieved and reduction of CRP concentrations would affect benefits from more-intensive LDL-C lowering is unknown. We sought to

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Accompanying Data S1, Tables S1 through S11, and Figure S1 through S27 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012428 *Dr Zhang and Dr Lan contributed equally to this work.

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Clinical Perspective

What Is New?

- Baseline CRP (C-reactive protein) concentrations might be associated with the benefits of LDL-C (low-density lipoprotein cholesterol) lowering on myocardial infarction, but no other outcomes.
- There appears to be similar risk reductions for more- versus less-intensive LDL-C-lowering therapy regardless of the magnitude of CRP reduction or the achieved CRP level for all outcomes, but with limited number of trials.

What Are the Clinical Implications?

- More-intensive LDL-C lowering appeared to reduce the risk of myocardial infarction (but not other outcomes) to a lesser extent when baseline CRP levels were higher.
- More-intensive LDL-C lowering was associated with similar risk reduction for mortality and other cardiovascular outcomes across baseline CRP concentrations.
- The achieved and magnitude of reduction in CRP did not seem to have an important association with the benefits of LDL-C lowering on all outcomes.

determine whether the benefits of LDL-C–lowering therapy on cardiovascular events related to baseline, achieved, or magnitude of reduction in CRP concentrations.

Methods

The data that support the findings of this study are available from Dr Xin-Lin Zhang upon reasonable request (xinlzhang0807@gmail.com). We conducted the meta-analysis in accord with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

Data Sources and Searches

We searched PubMed, EMBASE, and the Cochrane Library from their inception through July 2, 2018. The following keywords were used: lipid lowering, statin, ezetimibe, lowdensity lipoprotein cholesterol, randomized controlled trial, and individual drug names of statins. The search strategy is provided in Data S1. One reviewer (X.Z.) identified potential relevant citations from reference lists of the identified reports and relevant reviews.

Study Selection

Two reviewers (X.Z. and R.L.) independently evaluated the eligibility of studies. Discrepancies were resolved by discussion (W.X.). The main inclusion criteria were: (1) randomized

controlled cardiovascular outcome trials involving human subjects; (2) evaluated any comparison of the following strategies: statins, ezetimibe, or placebo (therapy to lower LDL-C versus no therapy or more- versus less-intensive intervention); and (3) included a minimum of 500 patients and 40 clinical events and reported outcomes of interest with at least 6 months of follow-up. We excluded trials investigating LDL-C-lowering drugs other than statins and ezetimibe. Trials with PCSk9 (proprotein convertase subtilisin/kexin type 9) monoclonal antibodies were excluded because they do not affect CRP concentrations. We did not impose limitations on language, sex, or age.

Outcomes of Interest

Outcomes of interest were all-cause and cardiovascular mortality, myocardial infarction, stroke, coronary revascularization, and major adverse cardiovascular events (MACEs).

Data Extraction and Assessment of Study Quality

Three investigators (X.Z., R.L., and W.X.) independently extracted data using a prespecified form. Median CRP and mean LDL-C values were abstracted from each trial. Two reviewers (X.Z and W.X.) independently assessed risk of bias of each trial by using the Cochrane Collaboration's tool,¹⁰ which assessing random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias. Consensus was achieved through referral to a third investigator (L.W.) in case of disagreement.

Data Synthesis and Statistical Analysis

To investigate the association between baseline CRP concentrations and risks of mortality and cardiovascular outcomes with more-intensive LDL-C lowering, random-effects metaregression analysis was performed, with log-transformed baseline CRP concentration as the covariate for the main model. Several other variables were added in the adjusted analyses, which included age, absolute magnitude of reduction in CRP concentrations (difference between achieved CRP concentrations in the more- and less-intensive study arms), baseline LDL-C, and absolute magnitude of reduction in LDL-C concentrations. Baseline CRP concentrations were logtransformed because their distributions were markedly skewed. Similar analyses were carried out for achieved and magnitude of reduction in CRP concentrations. Given that statins and ezetimibe differ in their effects on CRP concentrations, we performed sensitivity analyses restricted to statin trials. We also performed sensitivity analyses based on different study populations (primary or secondary prevention trials). To account for the variability in the length of follow-up for each of these trials, we used rate ratios (RRs) with their corresponding 95% CIs adjusted for patient-years as the statistic estimate.

Prespecified subgroup analyses were performed for all outcomes (see Data S1). A test for subgroup differences was performed across the examined subgroups with a χ^2 test of interaction. Heterogeneity was assessed by the Cochran Q test and the I² statistic. We examined potential publication bias by visually inspecting the asymmetry of the funnel plot and Begg's test. For the summary treatment effect estimate, a 2-tailed *P* value <0.05 was considered statistically significant. Analyses were conducted with Stata software (version 12.0; StataCorp LP, College Station, TX) and Review Manager (version 5.3; Cochrane Collaboration).

Results

Study Selection and Characteristics

The flow diagram of the study selection is shown in Figure S1. Twenty-four trials were included in the meta-analysis and metaregression analysis.^{3,11–33} Twelve trials that were otherwise eligible were not included because CRP concentrations were not reported. All trials except 1 were multicenter studies. Statin monotherapy was used in 20 trials and statin and ezetimibe in 4 trials. Overall, 171 250 patients were randomly assigned to more- or less-intensive LDL-C–lowering treatments. Median follow-up duration was 4.2 years (range, 1–11.5). Mean age of patients were 62.7 years, and 73.0% were men. The median baseline CRP concentration was 3.1 mg/L and ranged from 0.57 to 21.2 mg/L. Detailed characteristics of each trial are presented in Tables S1 through S3.

Risk of Bias in the Included Trials

Risk of bias for each trial is shown in Table S4. Most trials had blinded outcome adjudication and blinding of participants and personnel. Risk for attrition bias and reporting bias were generally low. Publication bias was detected for a number of outcomes, as revealed by visual inspection of the funnel plots and Begg's test (Figure S2).

All-Cause Mortality

There were 8355 deaths among 83 209 patients randomly assigned to receive more-intensive LDL-C–lowering treatment and 8989 deaths among 83 018 patients assigned to less-intensive LDL-C–lowering treatment. Metaregression analysis

showed that all-cause mortality risk was not significantly different for each 1-mg/L higher log-transformed baseline CRP concentration between more- versus less-intensive LDL-C-lowering treatments (RR, 0.98; 95% Cl, 0.91–1.05; P=0.512; Figure 1), with or without multivariable adjustment (Table). A similar observation was found for magnitude of reduction in CRP concentrations (RR, 0.98; 95% Cl, 0.91–1.06; P=0.590; Figure S3). The overall risk reduction in all-cause mortality with more- versus less-intensive therapy across all trials was 0.91 (95% Cl, 0.87–0.96) and were consistent across the range of baseline (Figure 2) and magnitude of reduction in CRP concentrations (Figure S4).

Cardiovascular Mortality

Metaregression analysis showed that cardiovascular mortality risk was not significantly different for each 1-mg/L higher logtransformed baseline CRP concentration between more- versus less-intensive LDL-C–lowering treatments (RR, 1.01; 95% Cl, 0.91-1.12; *P*=0.803; Figure 3), with or without multivariable adjustment (Table). A similar observation was found for magnitude of reduction in CRP concentrations (RR, 0.97; 95% Cl, 0.87-1.08; *P*=0.542; Figure S5). The overall risk reduction in cardiovascular mortality with more- versus less-intensive therapy across all trials was 0.84 (95% Cl, 0.79-0.90) and was consistent across the range of baseline (Figure 4) and magnitude of reduction in CRP concentrations (Figure S6).

Myocardial Infarction

Overall, 3745 of 85 723 patients receiving the more-intensive LDL-C-lowering strategy versus 4825 of 85 527 receiving the less-intensive strategy experienced myocardial infarction. Metaregression showed that more-versus less-intensive LDL-C lowering was associated with a significant change in RR for myocardial infarction (RR, 1.12; 95% Cl, 1.04–1.22; P=0.007) for each 1-mg/L higher log-transformed baseline CRP concentration (Figure 5), with or without multivariable adjustment (Table). The overall risk reduction in myocardial infarction associated with more- versus less-intensive therapy across all trials was 0.75 (95% Cl, 0.70-0.81), but varied by baseline CRP concentration (Figure 6). The RR was 0.79 (95% CI, 0.72-0.87) in trials with baseline CRP concentrations ≥2.7 mg/L (median) and 0.70 (95% Cl, 0.65–0.76) in trials with baseline CRP concentrations <2.7 mg/L (P=0.060 for interaction). Metaregression analysis did not show a significant correlation between magnitude of reduction in CRP concentrations and risk of myocardial infarction (RR, 0.93; 95% CI, 0.84–1.04; P=0.19; Figure S7). The overall risk reduction in myocardial infarction with more- versus lessintensive therapy was consistent across the range of magnitude of reduction in CRP concentrations (Figure S8).



Figure 1. Meta-regression analysis of all-cause mortality rate ratios plotted against log-transformed baseline CRP concentrations in the more-intensive group. The size of the data marker is proportional to the weight in the metaregression. CRP indicates C-reactive protein; RR, rate ratio.

Stroke

Metaregression analysis showed that stroke risk was not significantly different for each 1-mg/L higher log-transformed baseline CRP concentration between more- versus less-intensive LDL-C-lowering treatments (RR, 0.94; 95% Cl, 0.84–1.05; P=0.253; Figure S9), with or without multivariable

adjustment (Table). A similar observation was found for magnitude of reduction in CRP concentrations (RR, 0.90; 95% CI, 0.80-1.01; *P*=0.084; Figure S10). The overall risk reduction in stroke with more- versus less-intensive therapy across all trials was consistent across the range of baseline (Figure S11) and magnitude of reduction in CRP concentrations (Figure S12).

Table.Multivariable Metaregression Models for the Association of Each 1-mg/L Increase in log(Baseline CRP Concentration),Magnitude of Reduction in CRP Concentration, Achieved CRP, and Mortality and Cardiovascular Outcomes

| | | | Rate Ratio (95% CI) | | | |
|----------------------------|------------------|-------------------|--|---|----------------------------------|-------------------|
| Outcomes | No. of Trials | log(Baseline CRP) | log(Baseline CRP) Adjusted for Magnitude of Reduction in CRP | log(Baseline CRP) Adjusted for Magnitude of Reduction in CRP, Baseline LDL-C, Magnitude of Reduction in LDL-C and Age | Magnitude of Reduction in CRP | Achieved CRP |
| All-cause mortality | 22 | 0.98 (0.91, 1.05) | 1.00 (0.92, 1.10) | 1.01 (0.90, 1.13) | 0.98 (0.91, 1.06) | 1.00 (0.96, 1.03) |
| Cardiovascular mortality | 22 | 1.01 (0.91, 1.12) | 1.02 (0.89, 1.16) | 1.03 (0.89, 1.19) | 0.97 (0.87, 1.08) | 1.00 (0.94, 1.05) |
| Myocardial infarction | 24 | 1.12 (1.04, 1.22) | 1.16 (1.05, 1.27) | 1.16 (1.02, 1.33) | 0.93 (0.84, 1.04) | 0.98 (0.93, 1.04) |
| Stroke | 24 | 0.94 (0.84, 1.05) | 0.96 (0.84, 1.09) | 0.96 (0.81, 1.13) | 0.90 (0.80, 1.01) | 0.97 (0.91, 1.03) |
| Coronary revascularization | 22 | 1.06 (1.00, 1.13) | 1.07 (0.99, 1.15) | 1.05 (0.96, 1.14) | 0.94 (0.84, 1.04) | 0.99 (0.94, 1.04) |
| MACE | 24 | 1.04 (0.98, 1.11) | 1.05 (0.96, 1.15) | 1.08 (0.97, 1.19) | 0.96 (0.89, 1.03) | 0.99 (0.95, 1.03) |

CRP indicates C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event.

| | | No. of Patients Wi | ith Event/Total No. | |
|---|---------------------------|--------------------|---------------------|--------|
| | Rate Ratio | More Intensive | Less Intensive | Weight |
| Study and Subgroup | (95% CI) | LDL-C Lowering | LDL-C Lowering | % |
| Baseline CRP ≥ median | | | | |
| 4D (2005) ¹¹ | 0.95 (0.85, 1.06) | 559/636 | 573/619 | 7.02 |
| A to Z (2004) ¹² | 0.79 (0.61, 1.02) | 104/2265 | 130/2232 | 2.46 |
| AURORA (2009) ¹⁶ | 0.96 (0.87, 1.06) | 636/1389 | 660/1384 | 7.59 |
| CARDS (2004) ¹⁷ | 0.74 (0.53, 1.02) | 61/1429 | 82/1412 | 1.60 |
| CORONA (2007) ¹⁹ | 0.95 (0.87, 1.05) | 728/2514 | 759/2497 | 7.95 |
| HIJ-PROPER (2017) ²⁰ | 0.69 (0.47, 1.03) | 42/864 | 60/857 | 1.17 |
| HPS (2002) ²² | 0.88 (0.82, 0.95) | 1328/10269 | 1507/10267 | 9.43 |
| IMPROVE-IT (2015) ³ | 0.99 (0.91, 1.07) | 1215/9067 | 1231/9077 | 9.06 |
| JUPITER (2008) ²³ | 0.80 (0.67, 0.97) | 198/8901 | 247/8901 | 3.95 |
| Liu, et al (2016) ²⁵ | 0.62 (0.21, 1.88) | 5/400 | 8/398 | 0.16 |
| PROSPER (2002) ²⁷ | 0.98 (0.84, 1.15) | 298/2891 | 306/2913 | 4.91 |
| PROVE IT-TIMI 22 (2004) ²⁸ | 0.69 (0.47, 1.00) | 46/2099 | 66/2063 | 1.27 |
| SHARP (2011) ³¹ | 1.02 (0.94, 1.10) | 1142/4650 | 1115/4620 | 8.93 |
| Subtotal (I-squared = 43.6%, <i>P</i> = 0.046) | 0.93 (0.88, 0.98) | 6362/47374 | 6744/47240 | 65.51 |
| Subtotal effect: $z = 2.93$, $P = 0.003$ | | | | |
| Baseline CRP < median | | | | |
| AFCAPS_TEXCAPS (1998) ¹³ | 1.04 (0.76, 1.42) | 80/3304 | 77/3301 | 1.75 |
| ALERT (2003) ¹⁴ | 1.03 (0.84, 1.25) | 194/1050 | 189/1052 | 3.62 |
| ASCOT-LLA (2003) ¹⁵ | 0.87 (0.71, 1.06) | 185/5168 | 212/5137 | 3.66 |
| HOPE-3 (2016) ²¹ | 0.93 (0.80, 1.08) | 334/6361 | 357/6344 | 5.25 |
| LIPID (1998) ²⁴ | 0.78 (0.70, 0.88) | 498/4512 | 633/4502 | 6.78 |
| REAL-CAD (2018) ²⁹ | 0.80 (0.67, 0.96) | 207/6199 | 260/6214 | 4.07 |
| SEAS (2008) ³⁰ | 1.03 (0.79, 1.35) | 105/944 | 100/929 | 2.23 |
| TNT (2005) ³² | 1.01 (0.86, 1.19) | 284/4995 | 282/5006 | 4.66 |
| WOSCOPS (1995) ³³ | 0.78 (0.61, 1.01) | 106/3302 | 135/3293 | 2.48 |
| Subtotal (I-squared = 41.6%, <i>p</i> = 0.090) | 0.90 (0.83, 0.98) | 1993/35835 | 2245/35778 | 34.49 |
| Subtotal effect: $z = 2.53$, $P = 0.011$ | | | | |
| Overall (I-squared = 44.5%, <i>P</i> = 0.014) | 0.91 (0.87, 0.96) | 8355/83209 | 8989/83018 | 100.00 |
| Overall effect: z = 3.96, <i>P</i> < 0.001 | | | | |
| $P = 0.60$ for interaction (\geq median vs. < median) | | | | |
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Figure 2. Meta-analysis of all-cause mortality stratified by baseline CRP concentrations between more- and less-intensive lipid-lowering group. CRP indicates C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

Coronary Revascularization

For each 1-mg/L higher log-transformed baseline CRP concentration, more- versus less-intensive LDL-C lowering was associated with a modest change in RRs for coronary revascularization (RR, 1.06; 95% CI, 1.00–1.13; P=0.062; Figure S13), which became nonsignificant after multivariable adjustment (Table). Metaregression analysis did not show a significant correlation between magnitude of reduction in CRP concentrations and risk of revascularization (RR, 0.94; 95% CI, 0.84–1.04; P=0.181; Figure S14). The overall risk reduction in coronary revascularization with more- versus less-intensive therapy across all trials was consistent across the range of

baseline (Figure S15) and magnitude of reduction in CRP concentrations (Figure S16).

Major Adverse Cardiovascular Events

Metaregression analysis showed that MACE risk was not significantly different for each 1-mg/L higher log-transformed baseline CRP concentration between more- versus less-intensive LDL-C-lowering treatments (RR, 1.04; 95% Cl, 0.98–1.11; P=0.182; Figure S17), with or without multivariable adjustment (Table). A similar observation was found for magnitude of reduction in CRP concentrations (RR, 0.96; 95% Cl, 0.89–1.03; P=0.252; Figure S18). The overall risk



Figure 3. Meta-regression analysis of cardiovascular mortality rate ratios plotted against log-transformed baseline CRP concentrations in the more-intensive group. The size of the data marker is proportional to the weight in the metaregression. CRP indicates C-reactive protein; RR, rate ratio.

reduction in MACE with more- versus less-intensive therapy across all trials was consistent across the range of baseline (Figure S19) and magnitude of reduction in CRP concentrations (Figure S20).

primary prevention trials (Table S11). Metaregression and meta-analysis of mortality and cardiovascular outcomes found no association with achieved CRP concentrations (Table; Figures S22 through S27).

Additional Analyses

Analyses excluding trials with heart failure or chronic kidney disease requiring hemodialysis, trials with less than 1000 patients, or trials published before 2000 yielded similar results (Table S5), as were analyses stratified by types of intervention in the more-intensive LDL-C–lowering treatment (Table S6), types of treatment in the less-intensive LDL-C– lowering treatment (Table S7), and type of population (Table S8). Consistent with previous studies, a lack of significant reduction in all-cause and cardiovascular mortality was observed in statin with ezetimibe trials (Table S6).

Metaregression analysis restricted to statin trials confirmed that more- versus less-intensive LDL-C lowering was associated with a significant change in RRs for myocardial infarction, but no other outcomes of interest (Table S9). For each 1-mg/L higher log-transformed baseline CRP concentration, more- versus less-intensive LDL-C lowering was associated with a significant change in RRs for myocardial infarction (RR, 1.12; 95% Cl, 1.03–1.21; P=0.011) in secondary prevention trials (Table S10; Figure S21), but not in

Discussion

In this meta-analysis and metaregression analysis of 24 trials involving >170 000 patients and \approx 24 000 clinical events, more-intensive LDL-C lowering appeared to reduce the risk of myocardial infarction to a lesser extent when baseline CRP levels were higher, but was associated with similar risk reduction for mortality and other cardiovascular outcomes across baseline CRP concentrations. Similar risk reductions occurred for more- versus less-intensive LDL-C-lowering therapy regardless of the magnitude of CRP reduction or the achieved CRP level for all outcomes.

Plasma CRP concentrations is a predictor of cardiovascular risk independent of other risk factors.¹ Although a causal role of CRP for atherosclerosis and ischemic vascular disease is not supported by previous studies,³⁴ there is potential in using CRP concentration as a marker for benefit from LDL-C–lowering therapy. In the AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention) trial, patients with an elevated baseline CRP concentration benefited markedly from lovastatin, whereas those with a low baseline CRP level had no

| | | No. of Patients Wi | ith Event/Total No. | |
|--|-------------------------|--------------------|---------------------|--------|
| | Rate Ratio | More Intensive | Less Intensive | Weight |
| Study and Subgroup | (95% CI) | LDL-C Lowering | LDL-C Lowering | % |
| Baseline CRP ≥ median | | | | |
| 4D (2005) ¹¹ | 0.82 (0.68, 0.98) | 202/636 | 241/619 | 6.11 |
| A to Z (2004) ¹² | 0.75 (0.57, 1.00) | 83/2265 | 109/2232 | 3.66 |
| AURORA (2009) ¹⁶ | 1.00 (0.86, 1.16) | 324/1389 | 324/1384 | 7.35 |
| CARDS (2004) ¹⁷ | 0.67 (0.40, 1.11) | 25/1429 | 37/1412 | 1.44 |
| CARE (1996) ¹⁸ | 0.81 (0.62, 1.05) | 96/2081 | 119/2078 | 3.94 |
| CORONA (2007) ¹⁹ | 1.00 (0.88, 1.12) | 488/2514 | 487/2497 | 8.49 |
| HPS (2002) ²² | 0.83 (0.76, 0.92) | 781/10269 | 937/10267 | 9.62 |
| IMPROVE-IT (2015) ³ | 1.00 (0.89, 1.13) | 537/9067 | 538/9077 | 8.58 |
| JUPITER (2008) ²³ | 0.53 (0.41, 0.69) | 83/8901 | 157/8901 | 3.99 |
| PROSPER (2002) ²⁷ | 0.78 (0.59, 1.01) | 94/2891 | 122/2913 | 3.94 |
| PROVE IT-TIMI 22 (2004) ²⁸ | 0.78 (0.45, 1.35) | 23/2099 | 29/2063 | 1.26 |
| SHARP (2011) ³¹ | 0.92 (0.80, 1.07) | 361/4650 | 388/4620 | 7.63 |
| Subtotal (I-squared = 64.9%, <i>P</i> = 0.001) | 0.85 (0.78, 0.93) | 3097/48191 | 3488/48063 | 66.00 |
| Subtotal effect: z = 3.46, P = 0.001 | | | | |
| Baseline CRP < median | | | | |
| AFCAPS_TEXCAPS (1998) ¹³ | 0.68 (0.37, 1.26) | 17/3304 | 25/3301 | 1.01 |
| ALERT (2003) ¹⁴ | 0.94 (0.71, 1.25) | 93/1050 | 99/1052 | 3.68 |
| ASCOT-LLA (2003) ¹⁵ | 0.90 (0.66, 1.23) | 74/5168 | 82/5137 | 3.15 |
| HOPE-3 (2016) ²¹ | 0.90 (0.72, 1.12) | 154/6361 | 171/6344 | 5.11 |
| LIPID (1998) ²⁴ | 0.76 (0.66, 0.88) | 331/4512 | 433/4502 | 7.63 |
| PREVEND-IT (2004) ²⁶ | 1.00 (0.25, 3.97) | | 4/431 | 0.21 |
| REAL-CAD (2018) ²⁹ | 0.77 (0.58, 1.02) | 86/6199 | 112/6214 | 3.69 |
| SEAS (2008) 30 | 0.83 (0.56, 1.21) | | 56/929 | 2.28 |
| TNT (2005) ³² | 0.81 (0.64, 1.03) | 126/4995 | 155/5006 | 4.67 |
| WOSCOPS (1995) ³³ | 0.68 (0.48, 0.98) | 50/3302 | 73/3293 | 2.56 |
| Subtotal (I-squared = 0.0%, <i>P</i> = 0.879) | 0.81 (0.75, 0.88) | 982/36268 | 1210/36209 | 34.00 |
| Subtotal effect: $z = 4.91$, $P < 0.001$ | | | | |
| Overall (I-squared = 46.3%, <i>P</i> = 0.009) | 0.84 (0.79, 0.90) | 4079/84459 | 4698/84272 | 100.00 |
| Overall effect: z = 5.13, P < 0.001 | | | | |
| $P = 0.54$ for interaction (\geq median vs. < median) | | | | |
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Figure 4. Meta-analysis of cardiovascular mortality stratified by baseline CRP concentrations between more- and less-intensive lipid-lowering group. CRP indicates C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

cardiovascular benefit.⁷ However, others have not shown such an association both in primary and secondary prevention trials.⁸ Our present metaregression analyses demonstrated no association between baseline CRP concentrations with mortality outcomes following LDL-C lowering, which, to the best of our knowledge, has not been evaluated in randomized trials because of the rarity of mortality outcomes. It is worth noting that a significant association between baseline CRP concentrations and risks for myocardial infarction was evident, with a less-robust benefit for more-intensive LDL-C lowering in patients who had higher baseline CRP concentrations. In line with our finding, post-hoc analyses of the JUPITER (the JUPITER trial from the US Food and Drug Administration) trial from the US Food and Drug Administration revealed an inverse relationship between baseline hsCRP concentrations and clinical response to statin therapy.³⁵ Subjects with baseline hsCRP above the median cut point of 4.2 mg/L had lower relative risk reduction with statin therapy than those with hsCRP <4.2 mg/L (relative risk reduction, 29% versus 58%).³⁵ The very recently published St. Francis Heart Study also reported a trend toward less benefit in patients with higher baseline hsCRP.³⁶

Several trials suggest that achieving lower CRP concentrations might be associated with better outcomes for patients being treated with statins.^{37–41} In the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) trial, patients who achieved CRP concentrations of <2 mg/L after



Figure 5. Meta-regression analysis of myocardial infarction rate ratios plotted against log-transformed baseline CRP concentrations in the more-intensive group. The size of the data marker is proportional to the weight in the metaregression. CRP indicates C-reactive protein; RR, rate ratio.

statin therapy had a lower rate of cardiovascular events than those who did not.³⁸ A similarly negative association was detected in the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering),³⁹ A-to-Z (Aggrastat-to-Zocor),⁴⁰ and the JUPITER⁴¹ trials. Fueling this debate, trials including the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcome Trial– Lipid Lowering Arm),⁴² the CARDS (Collaborative Atorvastatin Diabetes Study),⁴³ and TNT (Treating New Targets)⁴⁴ studies showed no association between achieved hsCRP concentrations and magnitude of statin efficacy in the prevention of cardiovascular events. Our meta-analysis and metaregression analysis do not lend support to the hypotheses that the beneficial effects of LDL-C–lowering therapy are affected by achieved CRP concentrations, in contrast with those found with achieved LDL-C concentrations.^{45,46}

The REVERSAL trial demonstrates that magnitude of reduction in CRP concentrations is significantly correlated with rate of progression of atherosclerosis (determined with intravascular ultrasonography).³⁹ The JUPITER trial also shows an association with magnitude of cardiovascular benefit of statin therapy.⁴¹ However, evidence remains scare given that the vast majority of trials did not report these relationship data. Our metaregression analysis revealed no significant correlation between magnitude of reduction in CRP concentrations and benefit from LDL-C–lowering therapy,

which needs to be confirmed in large, prospective trials in the future.

Although previous LDL-C-lowering trials with stains or ezetimibe reduce CRP concentrations, the concomitant reduction of LDL-C makes it difficult to conclude a causal role of inflammation in atherothrombotic events. The recently published CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) trial, which enrolled 10 061 patients with previous myocardial infarction and an hsCRP level of ≥ 2 mg/L, is a proof-of-concept trial directly testing the inflammatory hypothesis of atherothrombosis.⁴ Canakinumab confers a significant 15% reduction in MACEs without altering the lipid profile, supporting that reducing inflammation per se could reduce vascular risk.⁴ Of note, a CRP concentration < 2 mg/dL after the first dose of cankinumab was associated with greater relative reduction in MACE risk.⁴⁷ Canakinumab's reduction in atherothrombotic events involves inhibition of interleukin-6, indicating that treatments targeting downstream from interleukin-1 β merit evaluation for cardiovascular benefits.⁴⁸ However, whether the cardiovascular benefits of canakinumab will translate to other targeted anti-inflammatory treatments that reduce CRP remains to be determined. If confirmed, whether these benefits relate to baseline, achieved, or reduction of CRP concentrations also requires investigation.

| | | No. of Patients Wi | th Event/Total No. | |
|--|--------------------|--------------------|--------------------|--------|
| | Rate Ratio | More Intensive | Less Intensive | Weight |
| Study and Subgroup | (95% CI) | LDL-C Lowering | LDL-C Lowering | % |
| Baseline CRP ≥ median | | | | |
| 4D (2005) ¹¹ | 0.84 (0.67, 1.07) | 124/636 | 143/619 | 4.71 |
| A to Z (2004) ¹² | 0.96 (0.77, 1.20) | 151/2265 | 155/2232 | 5.09 |
| AURORA (2009) ¹⁶ | 0.85 (0.64, 1.12) | 91/1389 | 107/1384 | 4.00 |
| CARDS (2004) ¹⁷ | 0.53 (0.35, 0.82) | 33/1429 | 61/1412 | 2.26 |
| CARE (1996) ¹⁸ | 0.76 (0.62, 0.93) | 157/2081 | 207/2078 | 5.41 |
| CORONA (2007) ¹⁹ | 0.81 (0.63, 1.03) | 115/2514 | 141/2497 | 4.60 |
| HIJ-PROPER (2017) ²⁰ → | 1.09 (0.46, 2.57) | 11/864 | 10/857 | 0.67 |
| HPS (2002) ²² | 0.62 (0.55, 0.71) | 357/10269 | 574/10267 | 7.29 |
| IMPROVE-IT (2015) ³ | 0.87 (0.80, 0.95) | 977/9067 | 1118/9077 | 8.47 |
| JUPITER (2008) 23 | 0.46 (0.30, 0.70) | 31/8901 | 68/8901 | 2.24 |
| Liu, et al (2016) ²⁵ | 0.70 (0.36, 1.36) | 14/400 | 20/398 | 1.05 |
| PROSPER (2002) 27 | 0.83 (0.71, 0.96) | 292/2891 | 356/2913 | 6.74 |
| PROVE IT-TIMI 22 (2004) ²⁸ | 0.89 (0.71, 1.12) | 139/2099 | 153/2063 | 4.97 |
| SHARP (2011) 31 | 0.92 (0.76, 1.11) | 213/4650 | 230/4620 | 5.89 |
| Subtotal (I-squared = 63.5% , $P = 0.001$) | 0.79 (0.72, 0.87) | 2705/49455 | 3343/49318 | 63.40 |
| Baseline CRP < median | | | | |
| AFCAPS TEXCAPS $(1998)^{13}$ | 0.60 (0.43, 0.83) | 57/3304 | 95/3301 | 3 24 |
| $AI ERT (2003)^{14}$ | 0.70 (0.48, 1.02) | 46/1050 | 66/1052 | 2.69 |
| ASCOT-LLA (2003) ¹⁵ | 0.65 (0.50, 0.83) | 100/5168 | 154/5137 | 4 47 |
| HOPE-3 (2016) 21 | 0.65 (0.45, 0.95) | 45/6361 | 69/6344 | 2 69 |
| LIPID (1998) ²⁴ | 0.72 (0.63, 0.83) | 336/4512 | 463/4502 | 7.08 |
| PREVEND-IT (2004) ²⁶ | 0.53 (0.23, 1.25) | 8/433 | 15/431 | 0.67 |
| REAL-CAD (2018) ²⁹ | 0.56 (0.38, 0.82) | 40/6199 | 72/6214 | 2.58 |
| SEAS (2008) ³⁰ | 0.60 (0.35, 1.02) | 22/944 | 36/929 | 1.57 |
| TNT (2005) ³² | 0.79 (0.67, 0.93) | 243/4995 | 308/5006 | 6.35 |
| WOSCOPS (1995) ³³ | 0.70 (0.57, 0.86) | 143/3302 | 204/3293 | 5.26 |
| Subtotal (I-squared = 0.0%, $P = 0.766$) | 0.70 (0.65, 0.76) | 1040/36268 | 1482/36209 | 36.60 |
| Subtotal effect: $z = 8.80$, $P < 0.001$ | | | | |
| Overall (I-squared = 54.3%, <i>P</i> = 0.001) | 0.75 (0.70, 0.81) | 3745/85723 | 4825/85527 | 100.00 |
| Overall effect: z = 7.75, P < 0.001 | | | | |
| P = 0.06 for interaction (≥ median vs. < median) | | | | |
| | , | | | |
| Favors More Intensive LDL-C Lowering Favors Le | ess Intensive LDL- | C Lowering | | |

Figure 6. Meta-analysis of myocardial infarction stratified by baseline CRP concentrations between more- and less-intensive lipid-lowering group. CRP indicates C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

Limitations

Our study has several limitations. First, our analysis was based on trial-level data rather than patient-level data. Metaregression analyses might be subject to risk of aggregation bias because they attempt to make inferences about individuals using study-level information.⁴⁹ Second, a number of LDL-C-lowering cardiovascular trials did not report CRP data (especially achieved CRP concentrations), which might contribute to the publication bias detected in several analyses. The inclusion of these trials, if CRP data are reported, might erase the publication bias and considerably improve the statistical power and improve strength of evidence of our

analysis. Third, considerable heterogeneity was detected in several analyses, which may be attributed to the differences in patient characteristics not evaluated in our study given that no characteristics tested appeared to affect the results. Fourth, the inclusion criteria in these trials varied; these differences in selection will play out in the baseline risk and the magnitude of absolute risk reduction achieved. Fifth, the definitions of some outcomes, such as MACE and myocardial infarction, were not completely consistent across trials, and a considerable part of trials did not report outcome definition; it is unclear whether this variation could affect our results. Finally, the study enrollment included in the analysis extended from 1995 to 2018, during which

background therapy and cardiovascular event rates have changed.

Conclusions

In this metaregression and meta-analysis, more-intensive LDL-C lowering might have reduced the risk of myocardial infarction to a lesser extent when baseline CRP levels were higher, but was associated with similar risk reduction for mortality and other cardiovascular outcomes across baseline CRP concentrations. Similar risk reductions occurred for more- versus less-intensive LDL-C-lowering therapy regardless of the magnitude of CRP reduction or the achieved CRP level for all outcomes.

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Disclosures

None.

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Supplemental Material

Supplemental Methods

We conducted the meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

Data Sources and Searches

We searched PubMed, EMBASE, and the Cochrane Library from their inception through July 2, 2018. The following search terms was used: (Statin OR "Hydroxymethylglutaryl-CoA Reductase Inhibitor" OR "Pravastatin" OR "Lovastatin" OR "Simvastatin" OR "Rosuvastatin" OR "Atorvastatin" OR "Pitavastatin" OR "Mevastatin" OR "Fluvastatin" OR ezetimibe OR "LDL-C lowering") AND Random* AND Trial. One reviewer (X.L.Z.) identified potential relevant citations from reference lists of the identified reports and relevant reviews.

Study Selection

Two reviewers (X.L.Z. and R.F.L.) independently evaluated the eligibility of studies. Discrepancies were resolved by discussion (W.X.). The main inclusion criteria were: (1) randomized controlled, cardiovascular outcome trials involving human subjects; (2) evaluated any comparison of the following strategies: statins, ezetimibe, or placebo (therapy to lower LDL-C vs. no therapy or more-intensive vs. less-intensive intervention); (3) included >500 patients and >40 clinical events and reported cardiovascular or mortality outcomes with at least 6 months of follow-up. We excluded trials investigating LDL-C lowering drugs other than statins and ezetimibe. Trials with proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies were not included because PCSK9 antibodies do not have an effect on CRP. We did not impose limitations on language, sex, or age.

Outcome Measures

The outcomes of interest were all-cause and cardiovascular mortality, myocardial infarction, stroke, coronary revascularization, and major adverse cardiovascular events (MACEs).

Data Extraction and Assessment of Study Quality

Three investigators (X.L.Z., R.F.L. and W.X.) independently extracted data using a prespecified form which included trial name, year of publication, number of patients, duration of follow-up, intervention and comparison treatments, baseline, achieved and the magnitude of reduction in CRP and LDL-C concentrations in each treatment group, and absolute event rates of mortality and cardiovascular outcomes in both treatment groups. Median CRP and mean LDL-C values were abstracted from each trial. Consensus was achieved through referral to a third investigator (L.W.) in case of disagreement. Two reviewers (X.L.Z and W.X.) independently assessed risk of bias of each trial by using the Cochrane Collaboration's tool.

Data Synthesis and Statistical Analysis

To investigate the association between baseline CRP concentrations and risks of mortality and cardiovascular outcomes with more-intensive LDL-C lowering, random-effects meta-regression analysis was performed, with log-transformed baseline CRP concentration as the covariate for the main model. Additional co-variates including age, absolute magnitude of reduction in CRP concentrations (difference between achieved CRP concentrations in the more intensive and less intensive study arms), baseline LDL-C and absolute magnitude of reduction in LDL-C concentrations were added in the adjusted analyses. Baseline CRP concentrations were log-transformed because their distributions were markedly skewed. The association between achieved and magnitude of reduction in CRP concentrations was also assessed by meta-regression analysis. Because

statins and ezetimibe differ in their effects on CRP concentrations, we performed sensitivity analyses in statin trials. We also performed sensitivity analyses according to study population (primary or secondary prevention trials). To account for the variability in the length of follow-up for each of these trials, we used rate ratios (RRs) with their corresponding 95% CIs adjusted for patient-years as the statistic estimate.

Prespecified subgroup analyses were performed for all outcomes of interest on a trial level by (1) baseline CRP concentrations (using the median value across trials as cut-point); (2) magnitude of reduction in CRP concentrations (using the median value across trials as cut-point); (3) type of intervention in the more intensive treatment (statin, statin with ezetimibe); and (4) treatment in the less intensive group (active vs placebo). In addition, trials were stratified by achieved CRP concentrations. Sensitivity analyses excluding trials with heart failure or chronic kidney disease requiring hemodialysis, trials with less than 1000 patients, and trials published before year 2000 were performed to evaluate the robustness of our findings. To compare treatment associations in subgroups, a χ 2 test of interaction was performed.

Heterogeneity was assessed by the Cochran Q test and the I2 statistic. A P value < 0.10 or an I2 statistic > 50% indicates substantial heterogeneity. We examined potential publication bias by visually inspecting the asymmetry of the funnel plot and Begg's test. For the summary treatment effect estimate, a 2-tailed P value less than 0.05 was considered statistically significant. Analyses were conducted with the Stata software, version 12.0 (STATA Corporation) and Review Manager, version 5.3 (Cochrane Collaboration).

PRISMA Checklist.

| Section/topic | # | Checklist item | Reported on page # |
|---------------------------|----|---|-----------------------|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2,3 |
| INTRODUCTION | - | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| METHODS | - | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | NA |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 5 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 5 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 6 |

| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 6 |
|------------------------------------|----|--|-----|
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 6 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 7 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis. | 6,7 |

| Section/topic | # | Checklist item | Reported on page # |
|-------------------------------|----|--|-----------------------|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 7 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 7 |
| RESULTS | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 8 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 8 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 8 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 8-12 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 8-12 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 8-12 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 12,13 |
| DISCUSSION | | | |

| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | | | | | |
|---------------------|----|--|----|--|--|--|--|
| Limitations | 25 | cuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of intified research, reporting bias). | | | | | |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 17 | | | | |
| FUNDING | | | | | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 3 | | | | |

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table S1. Study and Patient Baseline Characteristics.

| | | | | | | | | | | | | More intensive LDL-C lowering | | | | Less inten | sive LDL· | | | | |
|---------|-----|----------|-------|------|-----|---------|------|----|------|------|------|-------------------------------|-------|--------|---------|------------|-----------|--------|----------|-----------|-----------|
| Trial | Yea | Total | Age | Men | СН | Other | DM, | HB | Sm | BMI | Medi | Treatment | No. | Baseli | Baselin | Treatmen | No. of | Baseli | Baseline | Magnitud | Magnitude |
| | r | No. of | , yrs | , % | D, | vascula | % | Ρ, | oker | (kg/ | an | | of | ne | е | t | patien | ne | LDL-C | e of | of |
| | | patients | | | % | r | | % | , % | m2) | FU, | | patie | CRP | LDL-C | | ts | CRP | (mg/dL) | reduction | reduction |
| | | | | | | disease | | | | | ys | | nts | (mg/L | (mg/dL) | | | (mg/L | | in CRP | in LDL-C |
| | | | | | | , % | | | | | | | |) | | | |) | | (mg/L) | (mg/dL) |
| 4D | 200 | 1255 | 65.7 | 54 | 50 | 53 | 100 | NA | 41 | 27.5 | 11.5 | Atorvastati | 636 | 5 | 125 | Placebo | 619 | 5 | 127 | 1.6 | 40 |
| | 5 | | | | | | | | | | | n (20 mg) | | | | | | | | | |
| A to Z | 200 | 4497 | 61 | 76 | 100 | 11 | 24 | 50 | 41 | NA | 2 | Simvastatin | 2265 | 20.1 | 112 | Simvasta | 2232 | 20.4 | 111 | 0.3 | 15.7 |
| | 4 | | | | | | | | | | | (80 mg) | | | | tin (20 | | | | | |
| | | | | | | | | | | | | | | | | mg) | | | | | |
| AFCAPS | 199 | 6605 | 58 | 85 | <1 | <1 | 15 | 22 | 12 | NA | 5.2 | Lovastatin | 3304 | 1.6 | 150 | Placebo | 3301 | 1.5 | 153 | 0.3 | 40.5 |
| _TEXCA | 8 | | | | | | | | | | | (20-40 mg) | | | | | | | | | |
| PS | | | | | | | | | | | | | | | | | | | | | |
| ALERT | 200 | 2102 | 50 | 66 | 19 | 11 | 19 | 75 | 18.5 | 25.8 | 6.7 | Fluvastatin | 1050 | 1.62 | 159 | Placebo | 1052 | 1.6 | 159 | NA | 38.2 |
| | 3 | | | | | | | | | | | (40 mg) | | | | | | | | | |
| ASCOT-L | 200 | 10305 | 63.2 | 81 | <1 | 14 | 25 | NA | 32.7 | 28.7 | 3.3 | Atorvastati | 5168 | 2.72 | 133 | Placebo | 5137 | 2.7 | 133 | NA | 37.2 |
| LA | 3 | | | | | | | | | | | n (10 mg) | | | | | | | | | |
| AURORA | 200 | 2773 | 64.1 | 62 | 24 | 27 | 26.4 | NA | 15 | 25.4 | 3.8 | Rosuvastat | 1389 | 4.8 | 100 | Placebo | 1384 | 5.2 | 99 | 1.6 | 39 |
| | 9 | | | | | | | | | | | in (10 mg) | | | | | | | | | |
| CARDS | 200 | 2841 | 61.5 | 68 | <1 | 3 | 18 | NA | 46 | 28.7 | 3.9 | Atorvastati | 1429 | 12.6 | 117 | Placebo | 1412 | 14.5 | 117 | 5.3 | 39.8 |
| | 4 | | | | | | | | | | | n (10 mg) | | | | | | | | | |
| CARE | 199 | 4159 | 59 | 86 | 100 | 0 | 14 | 43 | 21 | 28 | 5 | Pravastatin | 2081 | 3.8 | 139 | Placebo | 2078 | 3.6 | 139 | 1.2 | 40.3 |
| | 6 | | | | | | | | | | | (40 mg) | | | | | | | | | |
| CORONA | 200 | 5011 | 73 | 76 | 73 | 13 | 30 | 63 | 9 | 27 | 2.7 | Rosuvastat | 2514 | 3.1 | 137 | Placebo | 2497 | 3 | 136 | 1.2 | 34 |
| | 7 | | | | | | | | | | | in (10 mg) | | | | | | | | | |
| HIJ-PRO | 201 | 1721 | 65.7 | 75.6 | 100 | 7 | 30 | 68 | 59 | 24.3 | 3.9 | Pitavastatin | 864 | 21.2 | 135 | Pitavasta | 857 | 21 | 135 | NA | 20 |
| PER | 7 | | | | | | | | | | | (1-4mg) + | | | | tin | | | | | |
| | | | | | | | | | | | | ezetimibe | | | | (1-4mg) | | | | | |
| | | | | | | | | | | | | (10 mg) | | | | | | | | | |

| HOPE-3 | 201 6 | 12705 | 65.8 | 53.7 | 0 | 0 | 6 | 38 | 28 | 27.1 | 5.6 | Rosuvastat | 6361 | 2 | 128 | Placebo | 6344 | 2 | 128 | 1.2 | 28.2 |
|------------|----------|-------|------|------|-----|-----|------|------|------|------|-----|--------------|------|------|-------|-----------|-----------|------|-----|------|------|
| НРС | 200 | 20536 | 64 | 75 | 65 | 13 | 20 | ΝΔ | ΝΔ | ΝΔ | 5 | Simvastatin | 1026 | 31 | 131.5 | Placebo | 1026 | 3.1 | 131 | 1.38 | 26.3 |
| 111 0 | 200 | 20000 | 04 | 15 | 00 | -10 | 23 | INA | INA | INA | 0 | (40 mg) | 9 | 0.1 | 101.0 | T IACEDO | 7 | 0.1 | 101 | 1.00 | 20.0 |
| IMPROV | 201 | 18144 | 63.6 | 75 7 | 100 | 55 | 27 | 61 5 | 33 | 28.3 | 6 | Simvastatin | 9067 | 9.6 | 94 | Simvasta | , 9077 | 95 | 94 | 0.3 | 16 |
| E-IT | 5 | | 00.0 | | | 010 | | 0110 | | 20.0 | Ū | (40 mg) + | | | - | tin (40 | | 0.0 | 0. | | |
| | • | | | | | | | | | | | ezetimibe | | | | ma) | | | | | |
| | | | | | | | | | | | | (10 mg) | | | | 5/ | | | | | |
| JUPITER | 200 | 17802 | 66 | 62 | 0 | 0 | <1 | NA | 16 | 28.3 | 1.9 | Rosuvastat | 8901 | 4.2 | 108 | Placebo | 8901 | 4.3 | 108 | 1.5 | 54 |
| | 8 | | | | | | | | | | | in (20 mg) | | | | | | | | | |
| LIPID | 199 | 9014 | 62 | 83 | 100 | 10 | 9 | 41 | 74 | NA | 6.1 | Pravastatin | 4512 | 2.5 | 150 | Placebo | 4502 | 2.4 | 150 | 0.4 | 39.8 |
| | 8 | | | | | | | | | | | (40 mg) | | | | | | | | | |
| Liu, et al | 201 | 798 | 62 | 72 | 100 | 0 | 32.5 | 64.6 | 20.6 | NA | 1 | Atorvastati | 400 | 4.3 | 131 | Atorvasta | 398 | 4.5 | 131 | NA | NA |
| | 6 | | | | | | | | | | | n (40-80 | | | | tin (20 | | | | | |
| | | | | | | | | | | | | mg) | | | | mg) | | | | | |
| PREVEN | 200 | 864 | 52 | 65 | <1 | 1.5 | NA | NA | 74 | 26 | 3.8 | Pravastatin | 433 | 1.3 | 158 | Placebo | 431 | 1.3 | 154 | 0.28 | 35 |
| D-IT | 4 | | | | | | | | | | | (40 mg) | | | | | | | | | |
| PROSPE | 200 | 5804 | 75 | 48 | 32 | 18 | 11 | NA | 27 | NA | 3.2 | Pravastatin | 2891 | 3.1 | 147 | Placebo | 2913 | 3.1 | 147 | NA | 50 |
| R | 2 | | | | | | | | | | | (40 mg) | | | | | | | | | |
| PROVE | 200 | 4162 | 58 | 78 | 100 | 8 | 18 | 50 | 36.8 | NA | 2 | Atorvastati | 2099 | 12.3 | 106 | Pravastat | 2063 | 12.3 | 106 | 0.8 | 34 |
| IT-TIMI | 4 | | | | | | | | | | | n (80 mg) | | | | in (40 | | | | | |
| 22 | | | | | | | | | | | | | | | | mg) | | | | | |
| REAL-CA | 201 | 12413 | 68 | 83 | 100 | 14 | 40 | 75.7 | 16.4 | 24.6 | 3.9 | Pitavastatin | 6199 | 0.57 | 88 | Pitavasta | 6214 | 0.59 | 88 | 0.1 | 14 |
| D | 8 | | | | | | | | | | | (4mg) | | | | tin (1mg) | | | | | |
| SEAS | 200 | 1873 | 68 | 71 | 0 | 0 | 0 | 51.5 | 55 | 27 | 4.4 | Simvastatin | 944 | 2.1 | 140 | Placebo | 929 | 2.2 | 139 | 0.6 | 70 |
| | 8 | | | | | | | | | | | (40 mg) + | | | | | | | | | |
| | | | | | | | | | | | | ezetimibe | | | | | | | | | |
| | | | | | | | | | | | | (10 mg) | | 0 | 407 | | | - | | 0.7 | 00 |
| SHARP | 201 | 9270 | 62 | 62 | 0 | 15 | 23 | | 13 | 27 | 4.9 | Simvastatin | 4650 | 3 | 107 | Placebo | 4620 | 3 | 107 | 0.7 | 29 |
| | 1 | | | | | | | | | | | (20 mg) + | | | | | | | | | |
| | | | | | | | | | | | | ezetimibe | | | | | | | | | |
| | | | | | | | | | | | | (10 mg) | | | | | | | | | |

| TNT | 200 | 10001 | 61 | 81 | 100 | 15 | 15 | 54 | 76 | 28.4 | 4.9 | Atorvastati | 4995 | 1.7 | 97 | Atorvasta | 5006 | 1.7 | 98 | NA | 23.3 |
|-------|-----|-------|----|-----|-----|----|----|----|----|------|-----|-------------|------|-----|-----|-----------|------|-----|-----|----|------|
| | 5 | | | | | | | | | | | n (80 mg) | | | | tin (10 | | | | | |
| | | | | | | | | | | | | | | | | mg) | | | | | |
| WOSCO | 199 | 6595 | 55 | 100 | 5 | 3 | 1 | 16 | 78 | | 4.9 | Pravastatin | 3302 | 2 | 192 | Placebo | 3293 | 2 | 192 | NA | 41.3 |
| PS | 5 | | | | | | | | | | | (40 mg) | | | | | | | | | |

BMI, body mass index; CRP, C-reactive protein; CHD, coronary heart disease; DM, diabetes mellitus; FU, follow-up; HBP, high blood pressure; LDL-C, low-density lipoprotein cholesterol; NA, not available

4D, German Diabetes Dialysis Study—Die Deutsche Diabetes Dialyse Studies; A to Z, Aggrastat to Zocor; AFCAPS-TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALERT, Assessment of LEscol in Renal Transplantation Study; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; AURORA, An Assessment of Survival and Cardiovascular Events; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol And Recurrent Events; CORON, the Controlled Rosuvastatin Multinational Trial in Heart Failure; HIJ-PROPER, the Heart Institute of Japan PRoper level of lipid IOwering with Pitavastatin and Ezetimibe in acute coRonary syndrome trial; HOPE-3, Heart Outcomes Prevention Evaluation; HPS, Heart Protection Study; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin study group; LIPID, Long–term Intervention with Pravastatin in Ischaemic Disease; PREVEND IT, the Prevention of REnal and Vascular ENdstage Disease Intervention Trial; PROSPER, PROspective Study of Pravastatin in the Elderly at Risk; PROVE IT-TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy; REAL-CAD, Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy With Pitavastatin in Coronary Artery Disease; SEAS, Simvastatin and Ezetimibe in Aortic Stenosis; SHARP, Study of Heart and Renal Protection; TNT, Treating to New Targets; WOSCOPS, West of Scotland Coronary Prevention Study.

| Trial | Year | Selected composite | Reported primary | Definition of myocardial infarction |
|----------|------|------------------------------|------------------------------|---|
| | | endpoint (major adverse | endpoint in original trial | |
| | | cardiovascular events) | | |
| 4D | 2005 | Cardiac death, nonfatal | Cardiac death, nonfatal | Two of the following three criteria |
| | | myocardial infarction, and | myocardial infarction, and | were met: typical symptoms; elevated |
| | | stroke | stroke | levels of cardiac enzymes (i.e., a |
| | | | | level of creatine kinase MB above 5 |
| | | | | percent of the total level of creatine |
| | | | | kinase, a level of lactic |
| | | | | dehydrogenase 1.5 times the upper |
| | | | | limit of normal, or a level of troponin T |
| | | | | greater than 2 ng per milliliter); or |
| | | | | diagnostic changes on the |
| | | | | electrocardiogram. |
| A to Z | 2004 | Cardiovascular death, | Cardiovascular death, | NA |
| | | myocardial infarction, | myocardial infarction, | |
| | | Stroke, or Hospitalization | Stroke, or Hospitalization | |
| | | for acute coronary | for acute coronary | |
| | | syndrome | syndrome | |
| AFCAPS_ | 1998 | Myocardial infarction, | Myocardial infarction, | NA |
| TEXCAPS | | unstable angina, or sudden | unstable angina, or sudden | |
| | | cardiac death | cardiac death | |
| ALERT | 2003 | Cardiac death, definite or | Cardiac death, definite or | An adjudicated MI was classified as |
| | | probable non-fatal | probable non-fatal | definite if a new Q-wave developed in |
| | | myocardial infarction, | myocardial infarction, | the presence of abnormal cardiac |
| | | coronary-artery bypass | coronary-artery bypass | markers or symptoms, or pathological |
| | | grafting, percutaneous | grafting, percutaneous | ST elevations and T-wave changes |
| | | coronary intervention | coronary intervention | developed in the presence of |
| | | | | abnormal cardiac markers plus |
| | | | | symptoms. An MI was classified as |
| | | | | probable if pathological ST elevations |
| | | | | and T-wave changes developed in |
| | | | | the presence of abnormal cardiac |
| | | | | markers or symptoms |
| ASCOT-LL | 2003 | Total cardiovascular events | Cardiovascular death and | NA |
| А | | and procedures | non-fatal myocardial | |
| | | | infarction | |
| AURORA | 2009 | Nonfatal myocardial | Nonfatal myocardial | NA |
| | | infarction, nonfatal stroke, | infarction, nonfatal stroke, | |
| | | or death from | or death from | |
| | | cardiovascular causes | cardiovascular causes | |
| CARDS | 2004 | Cardiovascular death, | Cardiovascular death, | NA |
| | | myocardial infarction, | myocardial infarction, | |
| | | stroke, unstable angina or | stroke, unstable angina or | |
| | | revascularization | revascularization | |

Table S2. Study Characteristics of the Included Randomized Trials.

| CARE | 1996 | Cardiovascular death or | Cardiovascular death or | NA |
|------------|------|--------------------------------|--------------------------------|--|
| | | myocardial infarction | myocardial infarction | |
| CORONA | 2007 | Cardiovascular death, | Cardiovascular death, | NA |
| | | nonfatal myocardial | nonfatal myocardial | |
| | | infarction, or nonfatal stroke | infarction, or nonfatal stroke | |
| HIJ-PROP | 2017 | All-cause death, non-fatal | All-cause death, non-fatal | NA |
| ER | | myocardial infarction, | myocardial infarction, | |
| | | non-fatal stroke, unstable | non-fatal stroke, unstable | |
| | | angina, or revascularization | angina, or revascularization | |
| HOPE-3 | 2016 | Cardiovascular death, | Cardiovascular death, | EITHER Cardiac Ischemic Symptoms |
| | | nonfatal myocardial | nonfatal myocardial | lasting > 20 minutes, determined by |
| | | infarction, or nonfatal stroke | infarction, or nonfatal stroke | the site investigator to be secondary |
| | | | | to ischemia OR ECG or changes |
| | | | | consistent with acute infarction or |
| | | | | ischemia MI AND Elevated cardiac |
| | | | | biomarkers (values according to each |
| | | | | hospital's laboratory): A rise and/or |
| | | | | fall in cardiac biomarker values |
| | | | | (preferably troponin, CKMB, AST, |
| | | | | LDH or myoglobin) with at least one |
| | | | | value above the 99th percentile of the |
| | | | | upper reference limit. |
| HPS | 2002 | Cardiovascular death, | Mortality and fatal or | NA |
| | | myocardial infarction, | non-fatal vascular events | |
| | | stroke, or revascularization | | |
| IMPROVE- | 2015 | Death from cardiovascular | Death from cardiovascular | The presence of either ECG evidence |
| IT | | causes, major coronary | causes, major coronary | or cardiac marker evidence |
| | | event, or nonfatal stroke | event, or nonfatal stroke | (post-CABG, both ECG and cardiac |
| | | | | marker evidence were required, if the |
| | | | | CK-MB was ≥5X ULN to <10X ULN). |
| JUPITER | 2008 | Cardiovascular death, | Cardiovascular death, | NA |
| | | myocardial infarction, | myocardial infarction, | |
| | | stroke, unstable angina, or | stroke, unstable angina, or | |
| | | revascularization | revascularization | |
| LIPID | 1998 | Cardiovascular death or | Cardiovascular death | The presence of at least two new |
| | | nonfatal myocardial | | pathologic Q waves on the |
| | | infarction | | electrocardiogram or two of the |
| | | | | following three criteria: at least 15 |
| | | | | minutes of ischemic chest pain, |
| | | | | evolutionary ST-T wave changes (as |
| | | | | previously defined), or elevation of |
| | | | | the serum level of creatine kinase or |
| | | | | its MB isoenzyme to at least twice the |
| | | | | upper limit of normal |
| Liu, et al | 2016 | Cardiovascular death, | Cardiovascular death, | A rise in cardiac biomarkers |
| | | spontaneous myocardial | spontaneous myocardial | (preferably troponin), with at least 1 |

| | | infarction, and unplanned | infarction, and unplanned | value above the 99th percentile of the |
|-------------|------|-------------------------------|-------------------------------|--|
| | | revascularization | revascularization | upper reference limit together with |
| | | | | evidence of myocardial ischemia with |
| | | | | at least 1 of the following: symptoms |
| | | | | of ischemia, electrocardiogram |
| | | | | changes indicative of new ischemia |
| | | | | (new specific ST-T changes or new |
| | | | | left-bundle branch block), |
| | | | | development of pathological Q waves |
| | | | | in the electrocardiogram, imaging |
| | | | | evidence of new loss of viable |
| | | | | mvocardium, or new regional wall |
| | | | | motion abnormality. |
| PREVEND 2 | 2004 | Cardiovascular death and | Cardiovascular death and | At least 2 of 4 of the following, which |
| -IT | | hospitalization for | hospitalization for | should include either new Q waves or |
| | | cardiovascular morbidity | cardiovascular morbidity | enzyme elevation: (1) presence or |
| | | · | | history of typical or atypical chest |
| | | | | pain of at least 15 minutes' duration; |
| | | | | (2) ECG detection of ST-segment |
| | | | | changes of at least 0.1 mV and/or |
| | | | | T-wave inversion in at least 2 of 12 |
| | | | | leads: (3) ECG detection of new |
| | | | | significant Q waves in at least 2 of 12 |
| | | | | leads: and (4) elevation of |
| | | | | measurements of total creatine |
| | | | | kinase (CK) and/or its isoenzyme |
| | | | | CK-MB in at least 2 samples drawn |
| | | | | within 48 hours of development of |
| | | | | chest pain |
| PROSPER 2 | 2002 | Coronary heart disease | Coronary heart disease | NA |
| | | death or non-fatal | death or non-fatal | |
| | | myocardial infarction or | myocardial infarction or | |
| | | fatal or non-fatal stroke | fatal or non-fatal stroke | |
| PROVE 20 | 2004 | Death from any cause. | Death from any cause. | The presence of symptoms |
| IT-TIMI 22 | | mvocardial infarction. | mvocardial infarction. | suggestive of ischemia or infarction. |
| | | documented unstable | documented unstable | with either electrocardiographic |
| | | angina requiring | angina reguiring | evidence (new Q waves in two or |
| | | rehospitalization. | rehospitalization. | more leads) or cardiac-marker |
| | | revascularization. and | revascularization. and | evidence of infarction, according to |
| | | stroke | stroke | the standard TIMI and American |
| | | | | College of Cardiology definition. |
| REAL-CAD 20 | 2018 | Cardiovascular death. | Cardiovascular death. | Spontaneous: troponin with at least |
| | | nonfatal myocardial | nonfatal myocardial | one value above the 99 th percentile of |
| | | infarction, nonfatal ischemic | infarction, nonfatal ischemic | the upper reference limit |
| | | | | |
| | | stroke, or unstable angina | stroke, or unstable angina | Periprocedural PCI: Troponin>3 |

| | | hospitalization. hospitalization. | | |
|--------|------|-----------------------------------|-------------------------------|----|
| | | | | |
| SEAS | 2008 | Cardiovascular death, aort | Cardiovascular death, | NA |
| | | ic-valve replacement, | aortic-valve replacement, | |
| | | nonfat al myocardial infarct | nonfat al myocardial infarct | |
| | | ion, hospitalization for | ion, hospitalization for | |
| | | unstable angina pectoris, | unstable angina pectoris, | |
| | | heart failure, | heart failure, | |
| | | coronary-artery bypass | coronary-artery bypass | |
| | | grafting, percutaneous | grafting, percutaneous | |
| | | coronary intervention, and | coronary intervention, and | |
| | | nonhemorrhagic stroke | nonhemorrhagic stroke | |
| SHARP | 2011 | Cardiovascular death, | Non-fatal myocardial | NA |
| | | myocardial infarction, | infarction or coronary death, | |
| | | stroke, or coronary | non-haemorrhagic stroke, | |
| | | revascularization | or any arterial | |
| | | | revascularisation procedure | |
| TNT | 2005 | Cardiovascular death, | Cardiovascular death, | NA |
| | | nonfatal non- | nonfatal non- | |
| | | procedure-related | procedure-related | |
| | | myocardial infarction, or | myocardial infarction, or | |
| | | resuscitation after cardiac | resuscitation after cardiac | |
| | | arrest | arrest | |
| WOSCOP | 1995 | Cardiovascular death or | Cardiovascular death or | NA |
| S | | nonfatal myocardial | nonfatal myocardial | |
| | | infarction | infarction | |

4D, German Diabetes Dialysis Study—Die Deutsche Diabetes Dialyse Studies; A to Z, Aggrastat to Zocor; AFCAPS-TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALERT, Assessment of LEscol in Renal Transplantation Study; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; AURORA, An Assessment of Survival and Cardiovascular Events; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol And Recurrent Events; CORON, the Controlled Rosuvastatin Multinational Trial in Heart Failure; HIJ-PROPER, the Heart Institute of Japan PRoper level of lipid IOwering with Pitavastatin and Ezetimibe in acute coRonary syndrome trial; HOPE-3, Heart Outcomes Prevention Evaluation; HPS, Heart Protection Study; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin study group; LIPID, Long–term Intervention with Pravastatin in Ischaemic Disease; PREVEND IT, the Prevention of REnal and Vascular ENdstage Disease Intervention Trial; PROSPER, PROspective Study of Pravastatin in the Elderly at Risk; PROVE IT-TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy; REAL-CAD, Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy With Pitavastatin in Coronary Artery Disease; SEAS, Simvastatin and Ezetimibe in Aortic Stenosis; SHARP, Study of Heart and Renal Protection; TNT, Treating to New Targets; WOSCOPS, West of Scotland Coronary Prevention Study.

| Trial | Year | Inclusion criteria | Exclusion criteria |
|---------|------|-------------------------------|--|
| 4D | 2005 | Subjects with type 2 | Levels of fasting serum low-density lipoprotein (LDL) |
| | | diabetes mellitus 18 to 80 | cholesterol of less than 80 mg per deciliter (2.1 mmol per liter) |
| | | years of age who had | or more than 190 mg per deciliter (4.9 mmol per liter), |
| | | been receiving | triglyceride levels greater than 1000 mg per deciliter (11.3 mmol |
| | | maintenance | per liter); liver function values more than three times the upper |
| | | hemodialysis for less than | limit of normal or equal to those in patients with symptomatic |
| | | two years. | hepatobiliary cholestatic disease; hematopoietic disease or |
| | | | systemic disease unrelated to end-stage renal disease; |
| | | | vascular intervention, congestive heart failure, or myocardial |
| | | | infarction within the three months preceding the period of |
| | | | enrollment; unsuccessful kidney transplantation; and |
| | | | hypertension resistant to therapy (i.e., systolic blood pressure |
| | | | continuously greater than 200 mm Hg or diastolic blood |
| | | | pressure greater than 110 mm Hg). |
| A to Z | 2004 | Patients between the | Patients receiving statin therapy at the time of randomization, if |
| | | ages of 21 and 80 years | coronary artery bypass graft surgery was planned, or if PCI was |
| | | with either non- | planned within the first 2 weeks after enrollment. Patients also |
| | | ST-elevation ACS or | were excluded for having an alanine aminotransferase (ALT) |
| | | ST-elevation MI were | level higher than 20% above the upper limit of normal (ULN); for |
| | | eligible for enrollment if | having an increased risk for myopathy due to renal impairment |
| | | they had a total | (serum creatinine level 2.0 mg/dL [176.8 μmol/L]) or |
| | | cholesterol level of 250 | concomitant therapy with agents known to enhance myopathy |
| | | mg/dL (6.48 mmol/L) or | risk, such as fibrates, cyclosporine, macrolide antibiotics, azole |
| | | lower. | antifungals, amiodarone, or verapamil; or for having a prior |
| | | | history of nonexerciserelated elevations in creatine kinase level |
| | | | or nontraumatic rhabdomyolysis. |
| AFCAPS_ | 1998 | Men aged 45 to 73 years | Individuals with uncontrolled hypertension, secondary |
| TEXCAPS | | and postmenopausal | hyperlipidemia, or type 1 or type 2 diabetes mellitus that was |
| | | women aged 55 to 73 | either managed with insulin or associated with a |
| | | years who met the lipid | glycohemoglobin level of at least 10% (20% above the upper |
| | | entrance criteria (TC, | limit of normal), had a body weight of more than 50% greater |
| | | 4.65-6.82 mmol/L | than the desirable limit for height |
| | | [180-264 mg/dL]; LDL-C, | |
| | | 3.36-4.91 mmol/L | |
| | | [130-190 mg/dL]; HDL-C, | |
| | | 1.16 mmol/L [45 mg/dL] | |
| | | for men or ≤1.22 mmol/L | |
| | | [47 mg/dL] for women; | |
| | | and triglycerides \leq 4.52 | |
| | | mmol/L [400 mg/dL]). | |

Table S3. Inclusion and Exclusion criteria of Included Randomized Controlled Trials.

| ALERT | 2003 | Men and women aged 30–75 years who had received renal or combined renal and pancreas transplants more than 6 months before randomisation and who had stable graft function. All patients were receiving immunosuppressive therapy with ciclosporin and had total serum cholesterol concentrations of 4.0–9.0 mmol/l | Patients who were already taking statins, who had familial hypercholesterolaemia, had experienced acute rejection episodes in the previous 3 months, or who had a predicted life expectancy of less than 1 year. |
|-----------|------|---|--|
| ASCOT-LLA | 2003 | Men and women aged between 40 and 79 years at randomisation, with either untreated hypertension. Patients had to have total cholesterol concentrations of 6.5 mmol/L or lower, and not currently be taking a statin or a fibrate. | Previous myocardial infarction, currently treated angina, a cerebrovascular event within the previous 3 months, fasting triglycerides higher than 4.5 mmol/L, heart failure, uncontrolled arrhythmias or any clinically important haematological or biochemical abnormality on routine screening. |
| AURORA | 2009 | Men and women 50 to 80 years of age who had end-stage renal disease and had been treated with regular hemodialysis or hemofiltration for at least 3 months were recruited from 280 centers in 25 countries. | Statin therapy within the previous 6 months, expected kidney transplantation within 1 year, and serious hematologic, neoplastic, gastrointestinal, infectious, or metabolic disease (excluding diabetes) that was predicted to limit life expectancy to less than 1 year, with a history of a malignant condition, active liver disease (indicated by an alanine aminotransferase level that was more than three times the upper limit of the normal range), uncontrolled hypothyroidism, and an unexplained elevation in the creatine kinase level to more than three times the upper limit of the normal range. |
| CARDS | 2004 | Men and women aged 40–75 years with type 2 diabetes mellitus and had at least one or more of the following: a history of hypertension,; retinopathy; or currently smoking (no minimum number of cigarettes per day was required). | Had any past history of myocardial infarction, angina, coronary vascular surgery, cerebrovascular accident, or severe peripheral vascular disease (defined as warranting surgery). We checked eligibility against the patient's clinical notes and their own recall and assessed lipid eligibility criteria by blood testing at one screening and four pretreatment visits over a 10-week period. |

| CARE | 1996 | Men and postmenopausal women had an acute myocardial infarction between 3 and 20 months before randomization, were 21 to 75 years of age, and had plasma total cholesterol levels of less than 240 mg per deciliter, LDL cholesterol levels of 115 to 174 mg per deciliter. | Patients with serious noncardiovascular disease likely to interfere with participation or to cause death before the trial is over, with contraindications to pravastatin. |
|------------|------|--|--|
| CORONA | 2007 | Patients who were at least 60 years of age and who had chronic New York Heart Association (NYHA) class II, III, or IV heart failure of ischemic cause (as reported by investigators) and an ejection fraction of no more than 40% (no more than 35% in patients in NYHA class II) | Previous statin-induced myopathy or hypersensitivity reaction; decompensated heart failure or a need for inotropic therapy; myocardial infarction within the past 6 months; unstable angina or stroke within the past 3 months; percutaneous coronary intervention (PCI), coronary-artery bypass grafting (CABG), or the implantation of a cardioverter–defibrillator or biventricular pacemaker within the past 3 months or a planned implantation of such a device; previous or planned heart transplantation; clinically significant, uncorrected primary valvular heart disease or a malfunctioning prosthetic valve; hypertrophic cardiomyopathy; acute endomyocarditis or myocarditis, pericardial disease, or systemic disease (e.g., amyloidosis); acute or chronic liver disease; levels of alanine aminotransferase or thyrotropin of more than 2 times the upper limit of the normal range; a serum creatinine level of more than 2.5 mg per deciliter (221 µmol per liter); chronic muscle disease or an unexplained creatine kinase level of more than 2.5 times the upper limit of the normal range; previous treatment with cyclosporine; any other condition that would substantially reduce life expectancy or limit compliance with the protocol; or the receipt of less than 80% of dispensed placebo tablets during the run-in period |
| HIJ-PROPER | 2017 | All participants had been hospitalized for ST-segment elevation myocardial infarction (STEMI) or for non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina (UA) within 72 h before randomization, with at least 20 years of age. | The occurrence within 24 hours before enrolment of (i) hemodynamic instabilities such as hypotension, pulmonary oedema, congestive heart failure, acute mitral regurgitation, or ventricular rupture; (ii) ischaemic events (stroke, recurrent symptoms of cardiac ischaemia, acute occlusion of target vessel); and (iii) arrhythmic events (ventricular fibrillation, sustained ventricular tachycardia, advanced heart block). |

| | | Low-density lipoprotein cholesterol was at least 100 mg/dL (2.6 mmol/L). | |
|------------|------|---|--|
| HOPE-3 | 2016 | Men 55 years of age or older and women 65 years of age or older who had at least one of cardiovascular risk factors | Participants with cardiovascular disease and those with an indication for or contraindication to statins, angiotensin-receptor blockers, angiotensin-converting–enzyme inhibitors, or thiazide diuretics |
| HPS | 2002 | Men and women aged about 40–80 years with non-fasting blood total cholesterol concentrations of at least 3.5 mmol/L (135 mg/dL) if they were considered to be at substantial 5-year risk of death from coronary heart disease. | Patients had: chronic liver disease (cirrhosis or hepatitis) or evidence of abnormal liver function (eg, alanine aminotransferase >67 IU/L [1.5 times the central laboratory upper limit of normal: ULN]); severe renal disease or evidence of impaired renal function (creatinine >200 mmol/L); inflammatory muscle disease (eg, dermatomyositis or polymyositis) or evidence of muscle problems (creatine kinase >750 IU/L [3 ULN]); concurrent treatment with ciclosporin, fibrates, or high-dose niacin; child-bearing potential (premenopausal woman not sterilised or using reliable contraception); severe heart failure; some lifethreatening condition other than vascular disease or diabetes (eg, severe chronic airways disease or any cancer other than non-melanoma skin cancer); or conditions that might limit long-term compliance (eg, severely disabling stroke, dementia, or psychiatric disorder). |
| IMPROVE-IT | 2015 | Men and women who were at least 50 years of age if they had been hospitalized within the preceding 10 days for an acute coronary syndroma. Patients were required to have an LDL cholesterol level of 50 mg per deciliter (1.3 mmol per liter) or higher. | Planned coronary-artery bypass grafting for the acute coronary syndrome event, creatinine clearance of less than 30 ml per minute, active liver disease, or use of statin therapy that had LDL cholesterol–lowering potency greater than 40 mg of simvastatin. |

| JUPITER | 2008 | Men 50 years of age or older and women 60 years of age or older if they did not have a history of cardiovascular disease and if, at the initial screening visit, they had an LDL cholesterol level of less than 130 mg per deciliter (3.4 mmol per liter) and a high-sensitivity C-reactive protein level of 2.0 mg per liter or more. | previous or current use of lipid-lowering therapy, current use of postmenopausal hormone-replacement therapy, evidence of hepatic dysfunction (an alanine aminotransferase level that was more than twice the upper limit of the normal range), a creatine kinase level that was more than three times the upper limit of the normal range, a creatinine level that was higher than 2.0 mg per deciliter (176.8 µmol per liter), diabetes, uncontrolled hypertension (systolic blood pressure >190 mm Hg or diastolic blood pressure >100 mm Hg), cancer within 5 years before enrollment (with the exception of basal-cell or squamous-cell carcinoma of the skin), uncontrolled hypothyroidism (a thyroid-stimulating hormone level that was more than 1.5 times the upper limit of the normal range), and a recent history of alcohol or drug abuse or another medical condition that might compromise safety or the successful completion of the study. Because a core scientific hypothesis of the trial concerned the role of underlying low-grade inflammation as evidenced by elevated high-sensitivity C-reactive protein levels, patients with inflammatory conditions such as severe arthritis, lupus, or inflammatory bowel disease were excluded, as were patients taking immunosuppressant agents such as cyclosporine, tacrolimus, azathioprine, or long-term oral duccocriticoids |
|------------|------|---|--|
| LIPID | 1998 | Patients had an acute myocardial infarction or had a hospital discharge diagnosis of unstable angina between 3 and 36 months before study entry, and the plasma total cholesterol level measured four weeks before randomization was required to be 155 to 271 mg per deciliter and the fasting triglyceride level less than 445 mg per deciliter (5.0 mmol per | A clinically significant medical or surgical event within three months before study entry, cardiac failure, renal or hepatic disease, and the current use of any cholesterol-lowering agents. |
| Liu, et al | 2016 | Itter). (1) Stable angina with inducible myocardial ischemia and indication for coronary angiography or (2) ACS requiring primary or elective PCI | Chronic atorvastatin use ≥20 mg/d (or equivalent dose of other statins) before PCI, abnormal liver enzymes (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] more than 40 U/L); blood creatinine >2 mg/dL, or muscle disease. |

| PREVEND-IT PROSPER | 2004 | Persistent microalbuminuria, a blood pressure 160/100 mm Hg and no use of antihypertensive medication, and a total cholesterol level <8.0 mmol/L, or <5.0 mmol/L | Any of the following: creatinine clearance< 60% of the normal age-adjusted value, serum potassium >5.5 mmol/L, history of chronic liver disease, lactate dehydrogenase, aspartate-amino transferase or alanine-amino transferase .3 times the upper limit of normal, use of angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, use of insulin, previously documented allergy or intolerance to study drugs, and pregnant or nursing women. |
|-----------------------|------|--|---|
| | 2004 | 70–82 years if they had either pre-existing vascular disease or raised risk of such disease. Their plasma total cholesterol was required to be 4.0– 9.0 mmol/L and their triglyceride concentrations less than 6.0 mmol/L. | examination score <24). |
| PROVE IT-TIMI 22 | 2004 | Men and women who were at least 18 years old if they had been hospitalized for an acute coronary syndrome or high-risk unstable angina. Patients had to have a total cholesterol level of 240 mg per deciliter (6.21 mmol per liter) or less. | Had a coexisting condition that shortened expected survival to less than two years, were receiving therapy with any statin at a dose of 80 mg per day at the time of their index event or lipid-lowering therapy with fibric acid derivatives or niacin that could not be discontinued before randomization, had received drugs that are strong inhibitors of cytochrome P-450 3A4 within the month before randomization or were likely to require such treatment during the study period (because atorvastatin is metabolized by this pathway), had undergone percutaneous coronary intervention within the previous six months (other than for the qualifying event) or coronary-artery bypass surgery within the previous two months or were scheduled to undergo bypass surgery in response to the index event, had factors that might prolong the QT interval, had obstructive hepatobiliary disease or other serious hepatic disease, had an unexplained elevation in the creatine kinase level that was more than three times the upper limit of normal and that was not related to myocardial infarction, or had a creatinine level of more than 2.0 mg per deciliter (176.8 µmol per liter). |
| REAL-CAD | 2018 | Men and women 20 to 80 years of age with stable CAD | Patients with LDL-C <100 mg/dL without statin therapy before enrollment because the label in the instructions for pitavastatin restricted use to patients with hypercholesterolemia. |
| SEAS | 2008 | Men and women between the ages of 45 and 85 years who had asymptomatic, mild-to-moderate aortic valve stenosis, as | Patients had received a diagnosis or had symptoms of coronary artery disease, peripheral arterial disease, cerebrovascular disease, or diabetes mellitus or if they had any other condition requiring lipid-lowering therapy. |

| | | assessed on | |
|---------|------|------------------------------|---|
| | | echocardiography, with a | |
| | | peak aortic-jet velocit y of | |
| | | 2.5 to 4 m per second. | |
| SHARP | 2011 | Patients aged 40 years | Definite history of MI or coronary revascularization procedure; |
| | | and older were eligible to | Functioning renal transplant or living donor renal ; transplant |
| | | participate if they had | planned; Less than 2 months since presentation as an acute |
| | | chronic kidney disease | uremic emergency; Definite history of chronic liver disease or |
| | | with more than one | abnormal liver function (ie, ALT N1.5× ULN or, if ALT not |
| | | previous measurement of | available, AST N1.5× ULN) (patients with a history of hepatitis |
| | | serum or plasma | are eligible if these limits are not exceeded); Evidence of active |
| | | creatinine of at least 150 | inflammatory muscle disease (eg, dermatomyositis, |
| | | µmol/L (1·7 mg/dL) in men | polymyositis) or CK N3× ULN; Definite previous adverse |
| | | or 130 µmol/L (1·5 mg/dL) | reaction to a statin or to ezetimibe; Concurrent treatment with a |
| | | in women, whether | contraindicated drug; Child-bearing potential (ie, |
| | | receiving dialysis or not. | premenopausal woman who is not using a reliable method of |
| | | | contraception); Known to be poorly compliant with clinic visits or |
| | | | prescribed medication; Medical history that might limit the |
| | | | individual's ability to take the trial treatments for the duration of |
| | | | the study (eg, severe respiratory disease, history of cancer |
| | | | other than nonmelanoma skin cancer or recent history of |
| | | | alcohol or substance misuse) |
| TNT | 2005 | Men and women 35 to 75 | Hypersensitivity to statins; active liver disease or hepatic |
| | | years of age who had | dysfunction defined as alanine aminotransferase or aspartate |
| | | clinically evident CHD, | aminotransferase >1.5 times the upper limit of normal; women |
| | | defined by one or more of | who are pregnant or breastfeeding; patients with nephrotic |
| | | the following: previous | syndrome; uncontrolled diabetes mellitus; uncontrolled |
| | | myocardial infarction, | hypothyroidism; uncontrolled hypertension (as defined by the |
| | | previous or current angina | investigator) at the screening visit; a MI, coronary |
| | | with objective evidence of | revascularization procedure or severe/unstable angina within 1 |
| | | atherosclerotic CHD, and | month of screening; any planned surgical procedure for the |
| | | a history of coronary | treatment of atherosclerosis; an ejection fraction <30%; |
| | | revascularization. | hemodynamically important valvular disease; gastrointestinal |
| | | | disease limiting drug absorption or partial ileal bypass; any |
| | | | nonskin malignancy, malignant melanoma or other |
| | | | survival-limiting disease; unexplained creatine phosphokinase |
| | | | levels >6 times the upper limit of normal; concurrent therapy |
| | | | with long-term immunosuppressants; concurrent therapy with |
| | | | lipid-regulating drugs not specified as study treatment in the |
| | | | protocol; history of alcohol abuse; and participation in another |
| | ļ | | clinical trial concurrently or within 30 days before screening. |
| WOSCOPS | 1995 | Males aged 45-64 yr who, | NA |
| | | at randomization, display | |
| | | at most minor overt | |
| | | evidence of CHD. (1) | |
| | | LDL > 4.0 mmol/l at both | |

| screening visits 2 and 3; |
|-----------------------------|
| (2) LDL > 4.5 mmol/l at |
| one or both of screening |
| visits 2 and 3; (3) LDL < |
| 6.0 mmol/l at one or both |
| of screening visits 2 and 3 |

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Table S4. Listing of Potential Sources of Bias.

| Study | Year | Random | Allocatio | Blinding of | Blinding of | Incomple | Selective | Other |
|------------|------|-----------|-----------|--------------|--------------|------------|-----------|-----------|
| | | sequenc | n | participants | outcome | te | reporting | bias |
| | | е | conceal | and | assessme | outcome | (reportin | |
| | | generatio | ment | personnel | nt | data | g bias) | |
| | | n | (selectio | (performanc | (detection | (attrition | | |
| | | (selectio | n bias) | e bias) | bias) | bias) | | |
| | | n bias) | | | | | | |
| 4D | 2005 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | High risk |
| A to Z | 2004 | Low risk | Unclear | Low risk | Low risk | Low risk | Low risk | High risk |
| | | | risk | | | | | |
| AFCAPS_T | 1998 | Low risk | Unclear | Low risk | Low risk | Low risk | Low risk | Low risk |
| EXCAPS | | | risk | | | | | |
| ALERT | 2003 | Low risk | Unclear | Low risk | Low risk | Low risk | Low risk | High risk |
| | | | risk | | | | | |
| ASCOT-LL | 2003 | Low risk | Unclear | Low risk | Low risk | Low risk | Low risk | High risk |
| А | | | risk | | | | | |
| AURORA | 2009 | Low risk | Unclear | Low risk | Low risk | Low risk | Low risk | High risk |
| | | | risk | | | | | |
| CARDS | 2004 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | High risk |
| CARE | 1996 | Low risk | Unclear | Low risk | Low risk | Low risk | Low risk | Unclear |
| | | | risk | | | | | risk |
| CORONA | 2007 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | High risk |
| HIJ-PROP | 2017 | Low risk | Unclear | High risk | Low risk | Low risk | Low risk | Low risk |
| ER | | | risk | | | | | |
| HOPE-3 | 2016 | Low risk | Unclear | Low risk | Low risk | Low risk | Low risk | High risk |
| | | | risk | | | | | |
| HPS | 2002 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | High risk |
| IMPROVE-I | 2015 | Low risk | Unclear | Low risk | Low risk | Low risk | Low risk | High risk |
| Т | | | risk | | | | | |
| JUPITER | 2008 | Unclear | Low risk | Low risk | Low risk | Low risk | Low risk | High risk |
| | | risk | | | | | | |
| LIPID | 1998 | Low risk | Unclear | Low risk | Low risk | Low risk | Low risk | High risk |
| | | | risk | | | | | |
| Liu, et al | 2016 | Low risk | Unclear | Unclear risk | Unclear risk | Low risk | Low risk | Low risk |
| | | | risk | | | | | |
| PREVEND- | 2004 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| | | | | | | | | |
| PROSPER | 2002 | Low risk | Low risk | Low risk | Low risk | Unclear | Low risk | Low risk |
| | 2004 | Unclear | Low risk | Low risk | Low risk | Low risk | Low risk | High risk |
| 11-11MI 22 | 0040 | risk | | | | | | 11 |
| REAL-CAD | 2018 | Low risk | Unclear | Unclear risk | Low risk | Low risk | Low risk | Unclear |
| | 0005 | | risk | | | | | risk |
| SEAS | 2008 | Low risk | Low risk | Unclear risk | Low risk | Unclear | Low risk | High risk |
| | 0041 | | | | | risk | | |
| SHARP | 2011 | Low risk | Low risk | LOW ISK | LOW risk | Low risk | Low risk | High risk |

| TNT | 2005 | Low risk | Low risk | Low risk | Unclear risk | Low risk | Low risk | Low risk |
|---------|------|----------|----------|----------|--------------|----------|----------|-----------|
| WOSCOPS | 1995 | Low risk | Unclear | Low risk | Low risk | Low risk | Low risk | High risk |
| | | | risk | | | | | |

4D, German Diabetes Dialysis Study—Die Deutsche Diabetes Dialyse Studies; A to Z, Aggrastat to Zocor; AFCAPS-TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALERT, Assessment of LEscol in Renal Transplantation Study; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; AURORA, An Assessment of Survival and Cardiovascular Events; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol And Recurrent Events; CORON, the Controlled Rosuvastatin Multinational Trial in Heart Failure; HIJ-PROPER, the Heart Institute of Japan PRoper level of lipid IOwering with Pitavastatin and Ezetimibe in acute coRonary syndrome trial; HOPE-3, Heart Outcomes Prevention Evaluation; HPS, Heart Protection Study; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin study group; LIPID, Long–term Intervention with Pravastatin in Ischaemic Disease; PREVEND IT, the Prevention of REnal and Vascular ENdstage Disease Intervention Trial; PROSPER, PROspective Study of Pravastatin in the Elderly at Risk; PROVE IT-TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy; REAL-CAD, Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy With Pitavastatin in Coronary Artery Disease; SEAS, Simvastatin and Ezetimibe in Aortic Stenosis; SHARP, Study of Heart and Renal Protection; TNT, Treating to New Targets; WOSCOPS, West of Scotland Coronary Prevention Study.

Table S5. Meta-analysis Excluding Trials with Potential Bias.

| | Ba | seline CRP ≥ me | edian | Bas | eline CRP < med | lian | | Overall | |
|--|--------|-----------------|---------|--------|-----------------|--------|--------|-------------|--------|
| | Trials | Rate Ratio | P value | Trials | Rate Ratio | Р | Trials | Rate Ratio | Р |
| | | (95% CI) | | | (95% CI) | value | | (95% CI) | value |
| All-cause mortality | | | | | | | | | |
| Trials with HF or requiring hemodialysis | 10 | 0.90 (0.83, | 0.007 | 10 | 0.92 (0.85, | 0.043 | 20 | 0.91 (0.86, | 0.001 |
| excluded | | 0.97) | | | 0.99) | | | 0.96) | |
| Trials with less than 1000 patients excluded | 12 | 0.93 (0.88, | 0.004 | 9 | 0.90 (0.83, | 0.011 | 21 | 0.91 (0.87, | <0.001 |
| | | 0.98) | | | 0.98_ | | | 0.96) | |
| Year before 2000 excluded | 13 | 0.93 (0.88, | 0.003 | 6 | 0.93 (0.86, | 0.099 | 19 | 0.93 (0.89, | 0.001 |
| | | 0.98) | | | 1.01) | | | 0.97) | |
| Cardiovascular mortality | | | | | | | | | |
| Trials with HF or requiring hemodialysis | 9 | 0.81 (0.72, | <0.001 | 11 | 0.85 (0.78, | <0.001 | 20 | 0.83 (0.78, | <0.001 |
| excluded | | 0.91) | | | 0.92) | | | 0.90) | |
| Trials with less than 1000 patients excluded | 12 | 0.85 (0.78, | 0.001 | 9 | 0.81 (0.74, | <0.001 | 21 | 0.84 (0.79, | <0.001 |
| | | 0.93) | | | 0.88) | | | 0.90) | |
| Year before 2000 excluded | 11 | 0.85 (0.77, | 0.001 | 7 | 0.86 (0.77, | 0.007 | 18 | 0.86 (0.80, | <0.001 |
| | | 0.94) | | | 0.96) | | | 0.92) | |
| Myocardial infarction | | | | | | | | | |
| Trials with HF or requiring hemodialysis | 11 | 0.80 (0.69, | <0.001 | 11 | 0.71 (0.67, | <0.001 | 22 | 0.74 (0.68, | <0.001 |
| excluded | | 0.88) | | | 0.76) | | | 0.80) | |
| Trials with less than 1000 patients excluded | 13 | 0.79 (0.72, | <0.001 | 9 | 0.70 (0.65, | <0.001 | 22 | 0.75 (0.70, | <0.001 |
| | | 0.88) | | | 0.76) | | | 0.81) | |
| Year before 2000 excluded | 13 | 0.80 (0.72, | <0.001 | 7 | 0.70 (0.63, | <0.001 | 20 | 0.76 (0.70, | <0.001 |
| | | 0.88) | | | 0.79) | | | 0.83) | |
| Stroke | | | | | | | | | |
| Trials with HF or requiring hemodialysis | 11 | 0.79 (0.71, | <0.001 | 11 | 0.85 (0.77, | 0.003 | 22 | 0.82 (0.77, | <0.001 |
| excluded | | 0.88) | | | 0.95) | | | 0.89) | |
| Trials with less than 1000 patients excluded | 13 | 0.84 (0.75, | 0.001 | 9 | 0.86 (0.77, | 0.017 | 22 | 0.85 (0.79, | <0.001 |
| | | 0.93) | | | 0.97) | | | 0.92) | |

| Year before 2000 excluded | | 0.84 (0.76, | 0.001 | 7 | 0.89 (0.75, | 0.188 | 20 | 0.86 (0.78, | 0.001 |
|--|----|-------------|--------|----|-------------|--------|----|-------------|--------|
| | | 0.94) | | | 1.06) | | | 0.94) | |
| Coronary revascularization | | | | | | | | | |
| Trials with HF or requiring hemodialysis | 11 | 0.80 (0.73, | <0.001 | 10 | 0.77 (0.72, | <0.001 | 21 | 0.78 (0.73, | <0.001 |
| excluded | | 0.88) | | | 0.81) | | | 0.83) | |
| Trials with less than 1000 patients excluded | 12 | 0.82 (0.75, | <0.001 | 9 | 0.75 (0.70, | <0.001 | 21 | 0.78 (0.73, | <0.001 |
| | | 0.89) | | | 0.81) | | | 0.84) | |
| Year before 2000 excluded | 12 | 0.82 (0.74, | <0.001 | 6 | 0.75 (0.68, | <0.001 | 18 | 0.79 (0.73, | <0.001 |
| | | 0.90) | | | 0.82) | | | 0.85) | |
| MACE | | | | | | | | | |
| Trials with HF or requiring hemodialysis | 11 | 0.80 (0.74, | <0.001 | 11 | 0.80 (0.76, | <0.001 | 22 | 0.81 (0.77, | <0.001 |
| excluded | | 0.87) | | | 0.85) | | | 0.85) | |
| Trials with less than 1000 patients excluded | 13 | 0.85 (0.79, | <0.001 | 9 | 0.79 (0.74, | <0.001 | 22 | 0.82 (0.78, | <0.001 |
| | | 0.90) | | | 0.83) | | | 0.86) | |
| Year before 2000 excluded | 13 | 0.85 (0.79, | <0.001 | 7 | 0.81 (0.77, | <0.001 | 20 | 0.84 (0.80, | <0.001 |
| | | 0.90) | | | 0.87) | | | 0.88) | |

CRP, C-reactive protein; MACE, major adverse cardiovascular event.
| | | | | Statin | • | | Statin + ezetimibe | |
|----------------------------|-------------------------------|----------|--------|---------------------|---------|--------|---------------------|---------|
| | | Subgroup | Trials | Rate Ratio (95% CI) | P value | Trials | Rate Ratio (95% CI) | P value |
| All-cause mortality | Baseline CRP | < median | 8 | 0.89 (0.82, 0.97) | 0.005 | 1 | 1.04 (0.80, 1.36) | 0.763 |
| | | ≥ median | 10 | 0.91 (0.86, 0.97) | <0.001 | 3 | 0.99 (0.90, 1.08) | 0.745 |
| | Magnitude of reduction in CRP | < median | 4 | 0.81 (0.74, 0.88) | <0.001 | 2 | 0.99 (0.92, 1.07) | 0.839 |
| | | ≥ median | 8 | 0.91 (0.87, 0.96) | <0.001 | 1 | 1.02 (0.94, 1.10) | 0.671 |
| | | Total | 19 | 0.90 (0.86, 0.94) | <0.001 | 4 | 1.00 (0.94, 1.05) | 0.91 |
| Cardiovascular mortality | Baseline CRP | < median | 9 | 0.81 (0.74, 0.88) | <0.001 | 1 | 0.85 (0.58, 1.24) | 0.385 |
| | | ≥ median | 10 | 0.82 (0.73, 0.91) | <0.001 | 2 | 0.97 (0.88, 1.06) | 0.481 |
| | Magnitude of reduction in CRP | < median | 5 | 0.76 (0.68, 0.85) | <0.001 | 2 | 0.98 (0.88, 1.10) | 0.786 |
| | | ≥ median | 9 | 0.84 (0.75, 0.94) | 0.002 | 1 | 0.92 (0.80, 1.07) | 0.278 |
| | | Total | 19 | 0.82 (0.77, 0.88) | <0.001 | 3 | 0.96 (0.88, 1.05) | 0.374 |
| Myocardial infarction | Baseline CRP | < median | 9 | 0.70 (0.65, 0.76) | <0.001 | 1 | 0.65 (0.39, 1.08) | 0.094 |
| | | ≥ median | 11 | 0.75 (0.67, 0.86) | <0.001 | 3 | 0.88 (0.82, 0.96) | 0.002 |
| | Magnitude of reduction in CRP | < median | 5 | 0.71 (0.58, 0.87) | 0.001 | 2 | 0.84 (0.70, 1.02) | 0.08 |
| | | ≥ median | 9 | 0.72 (0.64, 0.82) | <0.001 | 1 | 0.92 (0.76, 1.11) | 0.378 |
| | | Total | 21 | 0.73 (0.68, 0.78) | <0.001 | 4 | 0.88 (0.81, 0.95) | 0.001 |
| Stroke | Baseline CRP | < median | 9 | 0.86 (0.76, 0.97) | 0.011 | 1 | 1.12 (0.69, 1.82) | 0.659 |
| | | ≥ median | 11 | 0.81 (0.70, 0.93) | 0.003 | 3 | 0.85 (0.75, 0.96) | 0.008 |
| | Magnitude of reduction in CRP | < median | 5 | 0.93 (0.77, 1.12) | 0.443 | 2 | 0.88 (0.76, 1.02) | 0.089 |
| | | ≥ median | 9 | 0.79 (0.68, 0.91) | 0.001 | 1 | 0.83 (0.68, 1.01) | 0.065 |
| | | Total | 21 | 0.83 (0.76, 0.91) | <0.001 | 4 | 0.86 (0.77, 0.97) | 0.014 |
| Coronary Revascularization | Baseline CRP | < median | 8 | 0.76 (0.71, 0.82) | <0.001 | 1 | 0.68 (0.49, 0.94) | 0.018 |
| | | ≥ median | 10 | 0.78 (0.70, 0.86) | <0.001 | 3 | 0.89 (0.80, 0.98) | 0.022 |
| | Magnitude of reduction in CRP | < median | 4 | 0.83 (0.76, 0.90) | <0.001 | 2 | 0.83 (0.60, 1.14) | 0.253 |
| | | ≥ median | 8 | 0.76 (0.68, 0.84) | <0.001 | 1 | 0.80 (0.69, 0.94) | 0.005 |
| | | Total | 19 | 0.77 (0.72, 0.81) | < 0.001 | 4 | 0.85 (0.75, 0.96) | 0.010 |
| MACE | Baseline CRP | < median | 9 | 0.77 (0.73, 0.81) | < 0.001 | 1 | 0.93 (0.81, 1.07) | 0.332 |
| | | ≥ median | 11 | 0.81 (0.75, 0.88) | <0.001 | 3 | 0.91 (0.85, 0.97) | 0.004 |

Table S6. Sensitivity Analysis Stratified for Agent Used in the More-intensive Treatment Group.

| Magnitude of reduction in CRP | < median | 5 | 0.79 (0.72, 0.87) | <0.001 | 2 | 0.94 (0.89, 0.99) | 0.010 |
|-------------------------------|----------|----|-------------------|--------|---|-------------------|--------|
| | ≥ median | 9 | 0.81 (0.74, 0.88) | <0.001 | 1 | 0.84 (0.75, 0.95) | 0.004 |
| | Total | 21 | 0.80 (0.76, 0.84) | <0.001 | 4 | 0.92 (0.88, 0.96) | <0.001 |

CRP, C-reactive protein; MACE, major adverse cardiovascular event.

| | | | | Active | - | | Placebo | |
|----------------------------|-------------------------------|----------|--------|-------------------|---------|--------|-------------------|---------|
| | | Subgroup | Trials | Rate Ratio | P value | Trials | Rate Ratio | P value |
| | | | | (95% CI) | | | (95% CI) | |
| All-cause mortality | Baseline CRP | < median | 2 | 0.90 (0.72, 1.13) | 0.372 | 7 | 0.90 (0.82, 0.99) | 0.026 |
| | | ≥ median | 5 | 0.82 (0.67, 1.00) | 0.05 | 8 | 0.94 (0.89, 0.99) | 0.015 |
| | Magnitude of reduction in CRP | < median | 3 | 0.88 (0.74, 1.04) | 0.128 | 3 | 0.91 (0.74, 1.13) | 0.393 |
| | | ≥ median | 1 | 0.69 (0.47, 1.00) | 0.047 | 8 | 0.93 (0.88, 0.98) | 0.009 |
| | | Total | 7 | 0.87 (0.77, 0.98) | 0.024 | 15 | 0.92 (0.88, 0.97) | 0.001 |
| Cardiovascular mortality | Baseline CRP | < median | 2 | 0.80 (0.67, 0.95) | 0.013 | 8 | 0.81 (0.74, 0.90) | <0.001 |
| | | ≥ median | 3 | 0.89 (0.71, 1.10) | 0.268 | 9 | 0.84 (0.75, 0.93) | 0.001 |
| | Magnitude of reduction in CRP | < median | 3 | 0.86 (0.70, 1.06) | 0.162 | 4 | 0.77 (0.67, 0.87) | <0.001 |
| | | ≥ median | 1 | 0.78 (0.45, 1.35) | 0.371 | 9 | 0.85 (0.77, 0.94) | 0.003 |
| | | Total | 5 | 0.86 (0.74, 0.99) | 0.034 | 17 | 0.84 (0.78, 0.90) | <0.001 |
| Myocardial infarction | Baseline CRP | < median | 2 | 0.69 (0.50, 0.97) | 0.031 | 8 | 0.69 (0.63, 0.75) | <0.001 |
| | | ≥ median | 5 | 0.89 (0.82, 0.95) | 0.001 | 9 | 0.75 (0.66, 0.85) | <0.001 |
| | Magnitude of reduction in CRP | < median | 3 | 0.83 (0.67, 1.02) | 0.078 | 4 | 0.69 (0.61, 0.78) | <0.001 |
| | | ≥ median | 1 | 0.89 (0.71, 1.12) | 0.325 | 9 | 0.73 (0.63, 0.83) | <0.001 |
| | | Total | 7 | 0.85 (0.77, 0.93) | 0.001 | 17 | 0.72 (0.66, 0.78) | <0.001 |
| Stroke | Baseline CRP | < median | 2 | 0.92 (0.62, 1.36) | 0.680 | 8 | 0.84 (0.75, 0.95) | 0.004 |
| | | ≥ median | 5 | 0.85 (0.74, 0.97) | 0.017 | 9 | 0.83 (0.72, 0.95) | 0.009 |
| | Magnitude of reduction in CRP | < median | 3 | 0.93 (0.76, 1.14) | 0.496 | 4 | 0.87 (0.73, 1.05) | 0.141 |
| | | ≥ median | 1 | 0.98 (0.54, 1.80) | 0.955 | 9 | 0.79 (0.69, 0.90) | <0.001 |
| | | Total | 7 | 0.87 (0.77, 0.99) | 0.030 | 17 | 0.84 (0.76, 0.92) | <0.001 |
| Coronary Revascularization | Baseline CRP | < median | 2 | 0.79 (0.69, 0.90) | <0.001 | 7 | 0.72 (0.65, 0.80) | <0.001 |
| | | ≥ median | 5 | 0.92 (0.86, 0.97) | 0.005 | 8 | 0.76 (0.69, 0.83) | <0.001 |
| | Magnitude of reduction in CRP | < median | 3 | 0.91 (0.85, 0.98) | 0.015 | 3 | 0.74 (0.63, 0.87) | <0.001 |
| | | ≥ median | 1 | 0.87 (0.75, 0.99) | 0.043 | 8 | 0.75 (0.68, 0.82) | <0.001 |
| | | Total | 7 | 0.85 (0.78, 0.94) | 0.001 | 15 | 0.74 (0.70, 0.79) | <0.001 |
| MACE | Baseline CRP | < median | 2 | 0.80 (0.72, 0.88) | <0.001 | 8 | 0.78 (0.73, 0.84) | <0.001 |

Table S7. Sensitivity Analysis Stratified for the Type of Treatment in the Less-intensive Group.

| | ≥ median | 5 | 0.89 (0.83, 0.96) | 0.001 | 9 | 0.82 (0.75, 0.90) | <0.001 |
|-------------------------------|----------|---|-------------------|--------|----|-------------------|--------|
| Magnitude of reduction in CRP | < median | 3 | 0.89 (0.82, 0.98) | 0.016 | 4 | 0.79 (0.67, 0.93) | 0.004 |
| | ≥ median | 1 | 0.85 (0.76, 0.96) | 0.006 | 9 | 0.81 (0.74, 0.89) | <0.001 |
| | Total | 7 | 0.86 (0.80, 0.92) | <0.001 | 17 | 0.81 (0.76, 0.85) | <0.001 |

CRP, C-reactive protein; MACE, major adverse cardiovascular event.

| | | | | Primary Preventie | on | Secondary Prevention | | |
|----------------------------|-------------------------------|----------|--------|-------------------|---------|----------------------|-------------------|---------|
| | | Subgroup | Trials | Rate Ratio | P value | Trials | Rate Ratio | P value |
| | | | | (95% CI) | | | (95% CI) | |
| All-cause mortality | Baseline CRP | < median | 6 | 0.94 (0.86, 1.02) | 0.127 | 3 | 0.86 (0.73, 1.00) | 0.051 |
| | | ≥ median | 3 | 0.87 (0.71, 1.08) | 0.208 | 6 | 0.90 (0.81, 1.00) | 0.051 |
| | Magnitude of reduction in CRP | < median | 2 | 1.04 (0.84, 1.27) | 0.739 | 4 | 0.85 (0.73, 0.98) | 0.029 |
| | | ≥ median | 4 | 0.90 (0.79, 1.03) | 0.139 | 2 | 0.85 (0.63, 1.16) | 0.301 |
| | | Total | 9 | 0.93 (0.86, 1.01) | 0.065 | 9 | 0.87 (0.79, 0.96) | 0.004 |
| Cardiovascular mortality | Baseline CRP | < median | 7 | 0.86 (0.76, 0.98) | 0.019 | 3 | 0.78 (0.69, 0.87) | <0.001 |
| | | ≥ median | 3 | 0.70 (0.46, 1.06) | 0.091 | 5 | 0.93 (0.84, 1.04) | 0.184 |
| | Magnitude of reduction in CRP | < median | 3 | 0.79 (0.58, 1.09) | 0.150 | 4 | 0.83 (0.70, 0.99) | 0.036 |
| | | ≥ median | 4 | 0.76 (0.58, 0.99) | 0.042 | 3 | 0.93 (0.80, 1.08) | 0.327 |
| | | Total | 10 | 0.80 (0.69, 0.92) | 0.002 | 8 | 0.86 (0.77, 0.95) | 0.004 |
| Myocardial infarction | Baseline CRP | < median | 7 | 0.66 (0.58, 0.74) | <0.001 | 3 | 0.73 (0.64, 0.83) | <0.001 |
| | | ≥ median | 3 | 0.63 (0.39, 1.02) | 0.058 | 7 | 0.87 (0.81, 0.93) | <0.001 |
| | Magnitude of reduction in CRP | < median | 3 | 0.68 (0.59, 0.80) | <0.001 | 4 | 0.80 (0.68, 0.94) | 0.007 |
| | | ≥ median | 4 | 0.64 (0.45, 0.91) | 0.012 | 3 | 0.81 (0.72, 0.93) | 0.002 |
| | | Total | 10 | 0.66 (0.58, 0.76) | <0.001 | 10 | 0.81 (0.75, 0.88) | <0.001 |
| Stroke | Baseline CRP | < median | 7 | 0.86 (0.73, 1.00) | 0.053 | 3 | 0.88 (0.71, 1.11) | 0.001 |
| | | ≥ median | 3 | 0.64 (0.45, 0.92) | 0.016 | 7 | 0.83 (0.74, 0.93) | 0.279 |
| | Magnitude of reduction in CRP | < median | 3 | 1.07 (0.73, 1.57) | 0.741 | 4 | 0.90 (0.78, 1.03) | 0.121 |
| | | ≥ median | 4 | 0.68 (0.54, 0.85) | 0.001 | 3 | 0.80 (0.66, 0.99) | 0.037 |
| | | Total | 10 | 0.80 (0.68, 0.92) | 0.003 | 10 | 0.85 (0.78, 0.93) | <0.001 |
| Coronary Revascularization | Baseline CRP | < median | 6 | 0.66 (0.58, 0.75) | <0.001 | 3 | 0.80 (0.74, 0.87) | <0.001 |
| | | ≥ median | 3 | 0.71 (0.56, 0.89) | 0.003 | 6 | 0.87 (0.79, 0.95) | 0.003 |
| | Magnitude of reduction in CRP | < median | 2 | 0.65 (0.53, 0.79) | <0.001 | 4 | 0.89 (0.82, 0.96) | 0.002 |
| | | ≥ median | 4 | 0.71 (0.60, 0.84) | <0.001 | 2 | 0.81 (0.70, 0.93) | 0.003 |
| | | Total | 9 | 0.70 (0.64, 0.76) | <0.001 | 9 | 0.84 (0.78, 0.90) | <0.001 |
| MACE | Baseline CRP | < median | 7 | 0.78 (0.71, 0.86) | <0.001 | 3 | 0.79 (0.73, 0.85) | <0.001 |

Table S8. Sensitivity Analysis Stratified for the Type of Population.

| | ≥ median | 3 | 0.68 (0.52, 0.90) | 0.007 | 7 | 0.89 (0.84, 0.94) | <0.001 |
|-------------------------------|----------|----|-------------------|--------|----|-------------------|--------|
| Magnitude of reduction in CRP | < median | 3 | 0.79 (0.59, 1.06) | 0.118 | 4 | 0.86 (0.77, 0.95) | 0.004 |
| | ≥ median | 4 | 0.71 (0.59, 0.86) | <0.001 | 3 | 0.87 (0.78, 0.96) | 0.007 |
| | Total | 10 | 0.75 (0.68, 0.83) | <0.001 | 10 | 0.85 (0.80, 0.90) | <0.001 |

CRP, C-reactive protein; MACE, major adverse cardiovascular event.

Table S9. Multivariable Meta-regression Models for the Association of Each 1-mg/L Reduction in log(baseline CRP Concentration), Magnitude of Reduction in CRP Concentration, and Mortality and Cardiovascular Outcomes in Statin Trials.

| | | | Rate Ratio (95% CI) | | | | | | |
|--------------------------|--------|-------------------|---------------------|-------------------|-------------------|--------------------------------|--|--|--|
| Outcomes | No. of | log(Baseline CRP) | Magnitude of | Achieved CRP | log(Baseline CRP) | log(Baseline CRP) Adjusted for | | | |
| | Trials | | reduction in CRP | | Adjusted for | Magnitude of reduction in CRP, | | | |
| | | | | | Magnitude of | Baseline LDL-C, Magnitude of | | | |
| | | | | | reduction in CRP | reduction in LDL-C and Age | | | |
| All-cause mortality | 18 | 0.97 (0.90, 1.05) | 1.01 (0.93, 1.10) | 1.00 (0.96, 1.04) | 0.98 (0.88, 1.09) | 0.99 (0.86, 1.14) | | | |
| Cardiovascular mortality | 19 | 0.98 (0.87, 1.10) | 0.99 (0.88, 1.12) | 1.00 (0.94, 1.07) | 0.98 (0.83, 1.15) | 1.01 (0.84, 1.22) | | | |
| Myocardial infarction | 20 | 1.12 (1.01, 1.23) | 0.95 (0.84, 1.07) | 0.99 (0.93, 1.04) | 1.18 (1.06, 1.30) | 1.22 (1.06, 1.41) | | | |
| Stroke | 20 | 0.91 (0.79, 1.04) | 0.90 (0.78, 1.02) | 0.96 (0.90, 1.03) | 0.96 (0.80, 1.16) | 0.97 (0.76, 1.24) | | | |
| Revascularization | 18 | 1.04 (0.96, 1.12) | 0.94 (0.85, 1.05) | 0.99 (0.94, 1.05) | 1.04 (0.96, 1.15) | 1.04 (0.89, 1.22) | | | |
| MACE | 20 | 1.03 (0.95, 1.12) | 0.97 (0.89, 1.05) | 0.99 (0.95, 1.04) | 1.05 (0.94, 1.17) | 1.08 (0.95, 1.22) | | | |

CRP, C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event.

Table S10. Multivariable Meta-regression Models for the Association of Each 1-mg/LReduction in log(baseline CRP Concentration), Magnitude of Reduction in CRPConcentration, and Mortality and Cardiovascular Outcomes in Secondary Prevention Trials*.

| | | Rate Ratio (95% CI) | | | | | | |
|----------------------------|--------|---------------------|-------------------|------------------------|--|--|--|--|
| Outcomes | No. of | log(Baseline | Magnitude of | log(Baseline CRP) | | | | |
| | Trials | CRP) | Reduction in CRP | Adjusted for Magnitude | | | | |
| | | | | of Reduction in CRP | | | | |
| All-cause mortality | 9 | 0.98 (0.87, 1.10) | 1.09 (0.72, 1.65) | 1.01 (0.84, 1.22) | | | | |
| Cardiovascular mortality | 8 | 1.03 (0.90, 1.19) | 1.11 (0.76, 1.61) | 1.03 (0.86, 1.23) | | | | |
| Myocardial infarction | 10 | 1.12 (1.03, 1.21) | 1.00 (0.68, 1.48) | 1.15 (1.02, 1.29) | | | | |
| Stroke | 10 | 0.95 (0.85, 1.07) | 0.83 (0.59, 1.17) | 0.94 (0.82, 1.07) | | | | |
| Coronary revascularization | 9 | 1.04 (0.97, 1.11) | 0.87 (0.67, 1.14) | 1.06 (0.99, 1.13) | | | | |
| MACE | 10 | 1.04 (0.98, 1.10) | 1.02 (0.80, 1.29) | 1.04 (0.94, 1.14) | | | | |

*Meta-regression analyses were not adjusted for age, baseline LDL-C and magnitude reduction of LDL-C because of limited number of trials.

CRP, C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event.

Table S11. Multivariable Meta-regression Models for the Association of Each 1-mg/LReduction in log(baseline CRP Concentration), Magnitude of Reduction in CRPConcentration, and Mortality and Cardiovascular Outcomes in Primary Prevention Trials*.

| | | Rate Ratio (95% CI) | | | | | |
|----------------------------|--------|---------------------|-------------------|---------------------------|--|--|--|
| Outcomes | No. of | log(Baseline | Magnitude of | log(Baseline CRP) | | | |
| | Trials | CRP) | Reduction in | Adjusted for Magnitude of | | | |
| | | | CRP | Reduction in CRP | | | |
| All-cause mortality | 9 | 0.87 (0.71, 1.07) | 0.92 (0.83, 1.01) | 0.96 (0.55, 1.66) | | | |
| Cardiovascular mortality | 10 | 0.82 (0.59, 1.14) | 0.95 (0.78, 1.15) | 0.73 (0.22, 2.43) | | | |
| Myocardial infarction | 10 | 0.91 (0.67, 1.25) | 0.95 (0.79, 1.14) | 1.29 (0.35, 4.72) | | | |
| Stroke | 10 | 0.71 (0.53, 0.96) | 0.89 (0.74, 1.05) | 0.74 (0.22, 2.43) | | | |
| Coronary revascularization | 9 | 1.01 (0.76, 1.35) | 0.98 (0.83, 1.16) | 1.11 (0.44, 2.78) | | | |
| MACE | 10 | 0.90 (0.73, 1.12) | 0.96 (0.84, 1.08) | 0.89 (0.35, 2.27) | | | |

*Meta-regression analyses were not adjusted for age, baseline LDL-C and magnitude reduction of LDL-C because of limited number of trials.

CRP, C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event.

Figure S1. Identification and Selection of Randomized Clinical Trials Evaluating the Effect of Low-Density Lipoprotein Cholesterol Lowering Therapy on Cardiovascular Outcomes.



CRP, C-reactive protein.

Figure S2. Publication Bias. (A) All-cause mortality; (B) cardiovascular mortality; (C) myocardial infarction; (D) stroke; (E) Coronary revascularization; (F) MACE.



MACE, major adverse cardiovascular event.

Figure S3. Meta-regression Analysis of All-Cause Mortality Rate Ratio Plotted Against Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.



CRP, C-reactive protein; RR, rate ratio.

Figure S4. Meta-analysis of All-cause Mortality Stratified by Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.

| | | No. of Patients With Event/Total No | | | | | |
|---|---------------------|-------------------------------------|----------------|--------|--|--|--|
| | Rate Ratio | More Intensive | Less Intensive | Weight | | | |
| Study and Subgroup | (95% CI) | LDL-C Lowering | LDL-C Lowering | % | | | |
| CRP reduction ≥ median | | | | | | | |
| 4D (2005) | - 0.95 (0.85, 1.06) | 559/636 | 573/619 | 8.83 | | | |
| AURORA (2009) | - 0.96 (0.87, 1.06) | 636/1389 | 660/1384 | 9.48 | | | |
| CARDS (2004) | 0.74 (0.53, 1.02) | 61/1429 | 82/1412 | 2.14 | | | |
| CORONA (2007) | - 0.95 (0.87, 1.05) | 728/2514 | 759/2497 | 9.89 | | | |
| HOPE-3 (2016) | - 0.93 (0.80, 1.08) | 334/6361 | 357/6344 | 6.73 | | | |
| HPS (2002) 📥 | 0.88 (0.82, 0.95) | 1328/10269 | 1507/10267 | 11.54 | | | |
| JUPITER (2008) | 0.80 (0.67, 0.97) | 198/8901 | 247/8901 | 5.14 | | | |
| PROVE IT-TIMI 22 (2004) | 0.69 (0.47, 1.00) | 46/2099 | 66/2063 | 1.71 | | | |
| SHARP (2011) | 1.02 (0.94, 1.10) | 1142/4650 | 1115/4620 | 10.99 | | | |
| Subtotal (I-squared = 45.4%, p = 0.067) Subtotal effect: z = 2.75, p = 0.006 | 0.92 (0.87, 0.98) | 5032/38248 | 5366/38107 | 66.45 | | | |
| CRP reduction < median | | | | | | | |
| A to Z (2004) | 0.79 (0.61, 1.02) | 104/2265 | 130/2232 | 3.27 | | | |
| AFCAPS_TEXCAPS (1998) | 1.04 (0.76, 1.42) | 80/3304 | 77/3301 | 2.34 | | | |
| IMPROVE-IT (2015) | ₽ 0.99 (0.91, 1.07) | 1215/9067 | 1231/9077 | 11.14 | | | |
| LIPID (1998) | 0.78 (0.70, 0.88) | 498/4512 | 633/4502 | 8.55 | | | |
| REAL-CAD (2018) | 0.80 (0.67, 0.96) | 207/6199 | 260/6214 | 5.29 | | | |
| SEAS (2008) | 1.03 (0.79, 1.35) | 105/944 | 100/929 | 2.97 | | | |
| Subtotal (I-squared = 67.1%, p = 0.010) Subtotal effect: z = 1.93, p = 0.053 | 0.89 (0.79, 1.00) | 2209/26291 | 2431/26255 | 33.55 | | | |
| Overall (I-squared = 54.0%, p = 0.007) | 0.91 (0.86, 0.96) | 7241/64539 | 7797/64362 | 100.00 | | | |
| Overall effect: z = 3.57, p < 0.001 p = 0.58 for interaction (≥ median vs. < median) | | | | | | | |
| 0.2 | 1 2 | | | | | | |

Favors More Intensive LDL-C Lowering

Favors Less Intensive LDL-C Lowering

Figure S5. Meta-regression Analysis of Cardiovascular Mortality Rate Ratio Plotted Against Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.



CRP, C-reactive protein; RR, rate ratio.

Figure S6. Meta-analysis of Cardiovascular Mortality Stratified by Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.

| | No. of Patients With Event/Total No. | | | | |
|--|--------------------------------------|----------------|----------------|--------|--|
| | Rate Ratio | More Intensive | Less Intensive | Weight | |
| Study and Subgroup | (95% CI) | LDL-C Lowering | LDL-C Lowering | % | |
| CRP reduction ≥ median | | | | | |
| 4D (2005) | 0.82 (0.68, 0.98) | 202/636 | 241/619 | 7.50 | |
| AURORA (2009) | 1.00 (0.86, 1.16) | 324/1389 | 324/1384 | 8.82 | |
| CARDS (2004) | 0.67 (0.40, 1.11) | 25/1429 | 37/1412 | 1.95 | |
| CARE (1996) | 0.81 (0.62, 1.05) | 96/2081 | 119/2078 | 5.05 | |
| CORONA (2007) | 1.00 (0.88, 1.12) | 488/2514 | 487/2497 | 9.97 | |
| HOPE-3 (2016) | 0.90 (0.72, 1.12) | 154/6361 | 171/6344 | 6.41 | |
| HPS (2002) | 0.83 (0.76, 0.92) | 781/10269 | 937/10267 | 11.05 | |
| JUPITER (2008) | 0.53 (0.41, 0.69) | 83/8901 | 157/8901 | 5.11 | |
| PROVE IT-TIMI 22 (2004) | 0.78 (0.45, 1.35) | 23/2099 | 29/2063 | 1.71 | |
| SHARP (2011) | 0.92 (0.80, 1.07) | 361/4650 | 388/4620 | 9.10 | |
| Subtotal (I-squared = 64.0%, p = 0.003) | 0.85 (0.77, 0.94) | 2537/40329 | 2890/40185 | 66.66 | |
| Subtotal effect: z = 3.19, p = 0.001 | | | | | |
| CRP reduction < median | | | | | |
| A to Z (2004) | 0.75 (0.57, 1.00) | 83/2265 | 109/2232 | 4.72 | |
| AFCAPS_TEXCAPS (1998) | 0.68 (0.37, 1.26) | 17/3304 | 25/3301 | 1.38 | |
| IMPROVE-IT (2015) | 1.00 (0.89, 1.13) | 537/9067 | 538/9077 | 10.05 | |
| LIPID (1998) | 0.76 (0.66, 0.88) | 331/4512 | 433/4502 | 9.10 | |
| PREVEND-IT (2004) | → 1.00 (0.25, 3.97) | 4/433 | 4/431 | 0.30 | |
| REAL-CAD (2018) | 0.77 (0.58, 1.02) | 86/6199 | 112/6214 | 4.76 | |
| SEAS (2008) | 0.83 (0.56, 1.21) | 47/944 | 56/929 | 3.03 | |
| Subtotal (I-squared = 45.4%, p = 0.089) | 0.83 (0.72, 0.95) | 1105/26724 | 1277/26686 | 33.34 | |
| Subtotal effect: z = 2.71, p = 0.007 | | | | | |
| Overall (I-squared = 55.6%, p = 0.003) | 0.85 (0.78, 0.91) | 3642/67053 | 4167/66871 | 100.00 | |
| Overall effect: z = 4.30, p < 0.001 | | | | | |
| p = 0.79 for interaction (≥ median vs. < median) | | | | | |
| 0.2 1 | 2 | | | | |
| Favors More Intensive LDL-C Lowering Fa | avors Less Intensive LDL- | C Lowering | | | |

Figure S7. Meta-regression Analysis of Myocardial Infarction Rate Ratio Plotted Against Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.



CRP, C-reactive protein; RR, rate ratio.

Figure S8. Meta-analysis of Myocardial Infarction Stratified by Magnitude of Reduction in **CRP** Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.

| | | No. of Patients Wi | f Patients With Event/Total No. | |
|---|---------------------------------|--------------------|---------------------------------|--------|
| | Rate Ratio | More Intensive | Less Intensive | Weight |
| Study and Subgroup | (95% CI) | LDL-C Lowering | LDL-C Lowering | % |
| CRP reduction ≥ median | | | | |
| 4D (2005) | 0.84 (0.67, 1.07) | 124/636 | 143/619 | 6.59 |
| AURORA (2009) | 0.85 (0.64, 1.12) | 91/1389 | 107/1384 | 5.77 |
| CARDS (2004) | 0.53 (0.35, 0.82) | 33/1429 | 61/1412 | 3.52 |
| CARE (1996) | 0.76 (0.62, 0.93) | 157/2081 | 207/2078 | 7.36 |
| CORONA (2007) | 0.81 (0.63, 1.03) | 115/2514 | 141/2497 | 6.47 |
| HOPE-3 (2016) | 0.65 (0.45, 0.95) | 45/6361 | 69/6344 | 4.10 |
| HPS (2002) | 0.62 (0.55, 0.71) | 357/10269 | 574/10267 | 9.22 |
| JUPITER (2008) | 0.46 (0.30, 0.70) | 31/8901 | 68/8901 | 3.49 |
| PROVE IT-TIMI 22 (2004) | 0.89 (0.71, 1.12) | 139/2099 | 153/2063 | 6.89 |
| SHARP (2011) | 0.92 (0.76, 1.11) | 213/4650 | 230/4620 | 7.86 |
| Subtotal (I-squared = 64.1%, p = 0.003) Subtotal effect: z = 4.50, p < 0.001 | 0.74 (0.65, 0.85) | 1305/40329 | 1753/40185 | 61.27 |
| CRP reduction < median | | | | |
| A to Z (2004) | - 0.96 (0.77, 1.20) | 151/2265 | 155/2232 | 7.01 |
| AFCAPS_TEXCAPS (1998) | 0.60 (0.43, 0.83) | 57/3304 | 95/3301 | 4.83 |
| IMPROVE-IT (2015) | 0.87 (0.80, 0.95) | 977/9067 | 1118/9077 | 10.26 |
| LIPID (1998) | 0.72 (0.63, 0.83) | 336/4512 | 463/4502 | 9.02 |
| PREVEND-IT (2004) | - 0.53 (0.23, 1.25) | 8/433 | 15/431 | 1.12 |
| REAL-CAD (2018) | 0.56 (0.38, 0.82) | 40/6199 | 72/6214 | 3.96 |
| SEAS (2008) | 0.60 (0.35, 1.02) | 22/944 | 36/929 | 2.53 |
| Subtotal (I-squared = 64.5%, p = 0.010) | 0.75 (0.64, 0.87) | 1591/26724 | 1954/26686 | 38.73 |
| Overall (I-squared = 64.9%, p = 0.000) | 0.75 (0.68, 0.82) | 2896/67053 | 3707/66871 | 100.00 |
| $p = 0.97$ for interaction (\geq median vs. < median) | | | | |
| | 1 | | | |
| 0.2 1 Favors More Intensive LDL-C Lowering | 2 Favors Less Intensive LDL- | C Lowerina | | |

Favors Less Intensive LDL-C Lowering

Figure S9. Meta-regression Analysis of Stroke Rate Ratio Plotted Against log(baseline CRP Concentrations) in the More Intensive Group.



CRP, C-reactive protein; RR, rate ratio.

Figure S10. Meta-regression Analysis of Stroke Rate Ratio Plotted Against Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.



CRP, C-reactive protein; RR, rate ratio.

Figure S11. Meta-analysis of Stroke Stratified by Baseline CRP Concentrations.

| | | No. of Patients Wi | th Event/Total No. | |
|--|----------------------------|--------------------|--------------------|--------|
| | Rate Ratio | More Intensive | Less Intensive | Weight |
| Study and Subgroup | (95% CI) | LDL-C Lowering | LDL-C Lowering | % |
| Baseline CRP > median | | | | |
| 4D (2005) | | 84/636 | 76/619 | 4.33 |
| A to Z (2004) | - 0.79 (0.48, 1.29) | 28/2265 | 35/2232 | 2.05 |
| AURORA (2009) | 1.17 (0.79, 1.74) | 53/1389 | 45/1384 | 2.98 |
| CARDS (2004) | 0.53 (0.31, 0.90) | 21/1429 | 39/1412 | 1.83 |
| CARE (1996) | 0.69 (0.49, 0.98) | 54/2081 | 78/2078 | 3.67 |
| CORONA (2007) | 0.85 (0.64, 1.13) | 89/2514 | 104/2497 | 4.93 |
| HIJ-PROPER (2017) | 0.94 (0.48, 1.81) | 17/864 | 18/857 | 1.22 |
| HPS (2002) | 0.76 (0.67, 0.86) | 444/10269 | 585/10267 | 10.72 |
| IMPROVE-IT (2015) | 0.86 (0.74, 1.00) | 296/9067 | 345/9077 | 9.21 |
| JUPITER (2008) | 0.52 (0.34, 0.78) | 33/8901 | 64/8901 | 2.71 |
| Liu, et al (2016) | 0.65 (0.38, 1.11) | 21/400 | 32/398 | 1.80 |
| PROSPER (2002) | - 1.04 (0.82, 1.32) | 135/2891 | 131/2913 | 6.06 |
| PROVE IT-TIMI 22 (2004) | 0.98 (0.54, 1.80) | 21/2099 | 21/2063 | 1.45 |
| SHARP (2011) | 0.83 (0.68, 1.01) | 176/4650 | 211/4620 | 7.38 |
| Subtotal (I-squared = 38.8%, p = 0.068) | 0.83 (0.75, 0.92) | 1472/49455 | 1784/49318 | 60.34 |
| Subtotal effect: z = 3.56, p < 0.001 | | | | |
| Baseline CPR < median | | | | |
| AFCAPS_TEXCAPS (1998) | 0.82 (0.41, 1.67) | 14/3304 | 17/3301 | 1.08 |
| ALERT (2003) | — 1.02 (0.77, 1.36) | 93/1050 | 91/1052 | 4.79 |
| ASCOT-LLA (2003) | 0.73 (0.56, 0.96) | 89/5168 | 121/5137 | 5.12 |
| HOPE-3 (2016) | 0.71 (0.52, 0.96) | 70/6361 | 99/6344 | 4.39 |
| LIPID (1998) | 0.83 (0.67, 1.01) | 169/4512 | 204/4502 | 7.23 |
| PREVEND-IT (2004) | | 7/433 | 4/431 | 0.38 |
| REAL-CAD (2018) | — 1.13 (0.87, 1.45) | 127/6199 | 113/6214 | 5.65 |
| SEAS (2008) | 1.12 (0.68, 1.84) | 33/944 | 29/929 | 2.04 |
| TNT (2005) | 0.76 (0.60, 0.96) | 117/4995 | 155/5006 | 6.03 |
| WOSCOPS (1995) | - 0.90 (0.60, 1.34) | 46/3302 | 51/3293 | 2.95 |
| Subtotal (I-squared = 27.6%, p = 0.190) | 0.87 (0.77, 0.98) | 765/36268 | 884/36209 | 39.66 |
| Subtotal effect: z = 2.26, p = 0.024 | | | | |
| Overall (I-squared = 33.0%, p = 0.061) | 0.85 (0.78, 0.91) | 2237/85723 | 2668/85527 | 100.00 |
| Overall effect: z = 4.28, p < 0.001 | | | | |
| p = 0.56 for interaction (≥ median vs. < median) | | | | |
| 0.2 1 | 2 | | | |
| Favors More Intensive LDL-C Lowering | Favors Less Intensive LDL- | C Lowering | | |

Figure S12. Meta-analysis of Stroke Stratified by Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.

| | No. of Patients With Event/Total No. | | | |
|--|--------------------------------------|----------------|----------------|--------|
| | Rate Ratio | More Intensive | Less Intensive | Weight |
| Study and Subgroup | (95% CI) | LDL-C Lowering | LDL-C Lowering | % |
| CRP reduction ≥ median | | | | |
| 4D (2005) | 1.08 (0.79, 1.46) | 84/636 | 76/619 | 6.19 |
| AURORA (2009) | — 1.17 (0.79, 1.74) | 53/1389 | 45/1384 | 4.35 |
| CARDS (2004) | 0.53 (0.31, 0.90) | 21/1429 | 39/1412 | 2.72 |
| CARE (1996) | 0.69 (0.49, 0.98) | 54/2081 | 78/2078 | 5.30 |
| CORONA (2007) | 0.85 (0.64, 1.13) | 89/2514 | 104/2497 | 6.97 |
| HOPE-3 (2016) | 0.71 (0.52, 0.96) | 70/6361 | 99/6344 | 6.27 |
| HPS (2002) | 0.76 (0.67, 0.86) | 444/10269 | 585/10267 | 13.84 |
| JUPITER (2008) | 0.52 (0.34, 0.78) | 33/8901 | 64/8901 | 3.98 |
| PROVE IT-TIMI 22 (2004) | - 0.98 (0.54, 1.80) | 21/2099 | 21/2063 | 2.17 |
| SHARP (2011) | 0.83 (0.68, 1.01) | 176/4650 | 211/4620 | 10.03 |
| Subtotal (I-squared = 44.8%, p = 0.061) | 0.79 (0.70, 0.90) | 1045/40329 | 1322/40185 | 61.81 |
| Subtotal effect: z = 3.54, p < 0.001 | | | | |
| CRP reduction < median | | | | |
| A to Z (2004) | 0.79 (0.48, 1.29) | 28/2265 | 35/2232 | 3.04 |
| AFCAPS_TEXCAPS (1998) | - 0.82 (0.41, 1.67) | 14/3304 | 17/3301 | 1.63 |
| IMPROVE-IT (2015) | 0.86 (0.74, 1.00) | 296/9067 | 345/9077 | 12.17 |
| LIPID (1998) | 0.83 (0.67, 1.01) | 169/4512 | 204/4502 | 9.86 |
| PREVEND-IT (2004) | — =→ 1.74 (0.51, 5.94) | 7/433 | 4/431 | 0.58 |
| REAL-CAD (2018) | 1.13 (0.87, 1.45) | 127/6199 | 113/6214 | 7.89 |
| SEAS (2008) | 1.12 (0.68, 1.84) | 33/944 | 29/929 | 3.02 |
| Subtotal (I-squared = 4.0%, p = 0.396) Subtotal effect: z = 1.81, p < 0.070 | 0.90 (0.81, 1.01) | 674/26724 | 747/26686 | 38.19 |
| Overall (I-squared = 39.6%, p = 0.047) | 0.84 (0.76, 0.92) | 1719/67053 | 2069/66871 | 100.00 |
| p = 0.13 for interaction (≥ median vs. < median) | | | | |
| 0.2 1 | 2 | | | |

Favors More Intensive LDL-C Lowering Favors Less Intensive LDL-C Lowering





CRP, C-reactive protein; RR, rate ratio.

Figure S14. Meta-regression Analysis of Coronary Revascularization Rate Ratio Plotted Against Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.



CRP, C-reactive protein; RR, rate ratio.

Figure S15. Meta-analysis of Coronary Revascularization Stratified by Baseline CRP Concentrations.

| | No. of Patients With Event/Total No. | | | |
|--|--------------------------------------|----------------|----------------|--------|
| | Rate Ratio | More Intensive | Less Intensive | Weight |
| Study and Subgroup | (95% CI) | LDL-C Lowering | LDL-C Lowering | % |
| Baseline CRP ≥ median | | | | |
| 4D (2005) | 0.74 (0.52, 1.05) | 55/636 | 72/619 | 2.51 |
| A to Z (2004) | 0.95 (0.74, 1.21) | 119/2265 | 124/2232 | 3.96 |
| AURORA (2009) | 0.97 (0.78, 1.21) | 148/1389 | 152/1384 | 4.46 |
| CARDS (2004) | 0.70 (0.41, 1.17) | 24/1429 | 34/1412 | 1.32 |
| CARE (1996) | 0.75 (0.65, 0.87) | 294/2081 | 391/2078 | 6.34 |
| HIJ-PROPER (2017) | 0.87 (0.73, 1.03) | 225/864 | 257/857 | 5.69 |
| HPS (2002) | 0.71 (0.63, 0.79) | 513/10269 | 725/10267 | 7.42 |
| IMPROVE-IT (2015) | 0.94 (0.88, 1.01) | 1690/9067 | 1793/9077 | 8.72 |
| JUPITER (2008) | 0.58 (0.44, 0.77) | 76/8901 | 131/8901 | 3.39 |
| Liu, et al (2016) | 0.57 (0.31, 1.03) | 16/400 | 28/398 | 1.04 |
| PROSPER (2002) | 0.82 (0.54, 1.25) | 39/2891 | 48/2913 | 1.88 |
| PROVE IT-TIMI 22 (2004) | 0.87 (0.75, 1.00) | 342/2099 | 388/2063 | 6.63 |
| SHARP (2011) - | 0.80 (0.69, 0.94) | 284/4650 | 352/4620 | 6.16 |
| Subtotal (I-squared = 66.1%, p = 0.000) | 0.81 (0.74, 0.89) | 3825/46941 | 4495/46821 | 59.52 |
| Subtotal effect: z = 4.60, p < 0.001 | | | | |
| Baseline CPR < median | | | | |
| AFCAPS_TEXCAPS (1998) | 0.67 (0.53, 0.86) | 106/3304 | 157/3301 | 4.01 |
| ALERT (2003) | 0.67 (0.48, 0.93) | 59/1050 | 88/1052 | 2.75 |
| ASCOT-LLA (2003) | 0.63 (0.44, 0.89) | 51/5168 | 81/5137 | 2.51 |
| HOPE-3 (2016) | 0.68 (0.49, 0.96) | 56/6361 | 82/6344 | 2.62 |
| LIPID (1998) | 0.82 (0.74, 0.92) | 585/4512 | 708/4502 | 7.55 |
| REAL-CAD (2018) | 0.85 (0.76, 0.95) | 529/6199 | 626/6214 | 7.36 |
| SEAS (2008) | 0.65 (0.49, 0.86) | 77/944 | 117/929 | 3.35 |
| TNT (2005) 🚽 | 0.74 (0.67, 0.82) | 667/4995 | 904/5006 | 7.83 |
| WOSCOPS (1995) | 0.64 (0.45, 0.90) | 51/3302 | 80/3293 | 2.50 |
| Subtotal (I-squared = 27.6%, p = 0.199) Subtotal effect: $z = 7.51$, $p < 0.001$ | 0.75 (0.70, 0.81) | 2181/35835 | 2843/35778 | 40.48 |
| Overall (lequared = 61.6% $p = 0.000$) | 0 78 /0 73 0 83) | 6006/82776 | 7338/82599 | 100.00 |
| Overall effect: $z = 7.56$ n < 0.001 | 0.10 (0.10, 0.00) | 000002110 | 1000102000 | 100.00 |
| p = 0.24 for interaction (> median vs < median) | | | | |
| | | | | |
| 0.2 1 | 2 | . | | |

Favors More Intensive LDL-C Lowering

Favors Less Intensive LDL-C Lowering

Figure S16. Meta-analysis of Coronary Revascularization Stratified by Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.

| | No. of Patients With Event/Total No. | | | |
|--|--------------------------------------|----------------|----------------|--------|
| | Rate Ratio | More Intensive | Less Intensive | Weight |
| Study and Subgroup | (95% CI) | LDL-C Lowering | LDL-C Lowering | % |
| CRP reduction ≥ median | | | | |
| 4D (2005) | 0.74 (0.52, 1.05) | 55/636 | 72/619 | 3.40 |
| AURORA (2009) | 0.97 (0.78, 1.21) | 148/1389 | 152/1384 | 5.95 |
| CARDS (2004) | 0.70 (0.41, 1.17) | 24/1429 | 34/1412 | 1.80 |
| CARE (1996) | 0.75 (0.65, 0.87) | 294/2081 | 391/2078 | 8.34 |
| HOPE-3 (2016) | 0.68 (0.49, 0.96) | 56/6361 | 82/6344 | 3.54 |
| HPS (2002) | 0.71 (0.63, 0.79) | 513/10269 | 725/10267 | 9.69 |
| JUPITER (2008) | 0.58 (0.44, 0.77) | 76/8901 | 131/8901 | 4.55 |
| PROVE IT-TIMI 22 (2004) | 0.87 (0.75, 1.00) | 342/2099 | 388/2063 | 8.71 |
| SHARP (2011) | 0.80 (0.69, 0.94) | 284/4650 | 352/4620 | 8.11 |
| Subtotal (I-squared = 42.8%, p = 0.082) | 0.77 (0.70, 0.84) | 1792/37815 | 2327/37688 | 54.10 |
| Subtotal effect: z = 5.82, p < 0.001 | | | | |
| CRP reduction < median | | | | |
| A to Z (2004) | 0.95 (0.74, 1.21) | 119/2265 | 124/2232 | 5.30 |
| AFCAPS_TEXCAPS (1998) | 0.67 (0.53, 0.86) | 106/3304 | 157/3301 | 5.37 |
| IMPROVE-IT (2015) | 0.94 (0.88, 1.01) | 1690/9067 | 1793/9077 | 11.28 |
| LIPID (1998) | 0.82 (0.74, 0.92) | 585/4512 | 708/4502 | 9.84 |
| REAL-CAD (2018) | 0.85 (0.76, 0.95) | 529/6199 | 626/6214 | 9.61 |
| SEAS (2008) | 0.65 (0.49, 0.86) | 77/944 | 117/929 | 4.50 |
| Subtotal (I-squared = 67.7%, p = 0.008) | 0.83 (0.75, 0.92) | 3106/26291 | 3525/26255 | 45.90 |
| Subtotal effect: z = 3.41, p = 0.001 | | | | |
| Overall (I-squared = 66.5%, p = 0.000) | 0.79 (0.74, 0.86) | 4898/64106 | 5852/63943 | 100.00 |
| Overall effect: z = 5.95, p < 0.001 | | | | |
| p = 0.21 for interaction (≥ median vs. < median) | | | | |
| 0.2 | 2 | | | |

Favors More Intensive LDL-C Lowering

Favors Less Intensive LDL-C Lowering

Figure S17. Meta-regression Analysis of MACE Rate Ratio Plotted Against log(baseline CRP Concentrations) in the More Intensive Group.



CRP, C-reactive protein; RR, rate ratio.

Figure S18. Meta-regression Analysis of MACE Rate Ratio Plotted Against Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.



CRP, C-reactive protein; RR, rate ratio.

Figure S19. Meta-analysis of MACE Stratified by Baseline CRP Concentrations.

| | | No. of Patients Wi | th Event/Total No. | |
|--|-----------------------------------|--------------------|--------------------|--------|
| | Rate Ratio | More Intensive | Less Intensive | Weight |
| Study and Subgroup | (95% CI) | LDL-C Lowering | LDL-C Lowering | % |
| Baseline CRP ≥ median | | | | |
| 4D (2005) | 0.91 (0.78, 1.06) | 294/636 | 315/619 | 4.22 |
| A to Z (2004) | 0.89 (0.77, 1.03) | 309/2265 | 343/2232 | 4.39 |
| AURORA (2009) | 0.97 (0.85, 1.10) | 396/1389 | 408/1384 | 4.77 |
| CARDS (2004) | 0.65 (0.49, 0.85) | 83/1429 | 127/1412 | 2.22 |
| CARE (1996) | 0.77 (0.65, 0.92) | 212/2081 | 274/2078 | 3.74 |
| CORONA (2007) | 0.94 (0.85, 1.04) | 692/2514 | 732/2497 | 5.67 |
| HIJ-PROPER (2017) | 0.89 (0.76, 1.04) | 283/864 | 316/857 | 4.27 |
| HPS (2002) | 0.79 (0.74, 0.83) | 2033/10269 | 2585/10267 | 6.70 |
| IMPROVE-IT (2015) | 0.94 (0.89, 0.99) | 2572/9067 | 2742/9077 | 6.79 |
| JUPITER (2008) | 0.57 (0.46, 0.69) | 142/8901 | 251/8901 | 3.21 |
| Liu, et al (2016) | 0.62 (0.42, 0.93) | 35/400 | 56/398 | 1.25 |
| PROSPER (2002) | 0.87 (0.76, 0.99) | 408/2891 | 473/2913 | 4.86 |
| PROVE IT-TIMI 22 (2004) | 0.85 (0.76, 0.96) | 470/2099 | 543/2063 | 5.21 |
| SHARP (2011) | 0.84 (0.75, 0.95) | 526/4650 | 619/4620 | 5.24 |
| Subtotal (I-squared = 74.8%, p = 0.000) | 0.84 (0.79, 0.90) | 8455/49455 | 9784/49318 | 62.53 |
| Subtotal effect: z = 5.26, p < 0.001 | | | | |
| Baseline CPR < median | | | | |
| AFCAPS_TEXCAPS (1998) | 0.63 (0.50, 0.80) | 116/3304 | 183/3301 | 2.77 |
| ALERT (2003) | 0.79 (0.63, 0.98) | 137/1050 | 174/1052 | 2.93 |
| ASCOT-LLA (2003) | 0.80 (0.70, 0.91) | 389/5168 | 486/5137 | 4.80 |
| HOPE-3 (2016) | 0.77 (0.65, 0.91) | 235/6361 | 304/6344 | 3.90 |
| LIPID (1998) | 0.78 (0.70, 0.87) | 557/4512 | 715/4502 | 5.38 |
| PREVEND-IT (2004) | 0.87 (0.49, 1.56) | 21/433 | 24/431 | 0.64 |
| REAL-CAD (2018) | 0.80 (0.68, 0.94) | 266/6199 | 334/6214 | 4.11 |
| SEAS (2008) | 0.92 (0.80, 1.07) | 333/944 | 355/929 | 4.51 |
| TNT (2005) | 0.79 (0.70, 0.90) | 434/4995 | 548/5006 | 4.98 |
| WOSCOPS (1995) | 0.70 (0.58, 0.85) | 174/3302 | 248/3293 | 3.44 |
| Subtotal (I-squared = 8.9%, p = 0.360) | 0.79 (0.75, 0.83) | 2662/36268 | 3371/36209 | 37.47 |
| Subtotal effect: z = 8.74, p < 0.001 | | | | |
| Overall (I-squared = 67.5%, p = 0.000) | 0.82 (0.78, 0.86) | 11117/85723 | 13155/85527 | 100.00 |
| Overall effect: z = 8.00, p < 0.001 | | | | |
| p = 0.16 for interaction (≥ median vs. < median) | | | | |
| | | | | |
| Eavors More Intensive I DI -C Lowering | ∠ Favors Less Intensive I DI - | C Lowering | | |

Figure S20. Meta-analysis of MACE Stratified by Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.

| Study and Subgroup Rate Ratio More Intensive Less Intensive Weight 5tudy and Subgroup (95% CI) LDL-C Lowering % CRP reduction ≥ median 0.91 (0.78, 1.06) 294/636 315/619 5.82 AURORA (2009) 0.97 (0.85, 1.10) 396/1389 408/1384 6.50 CARDS (2004) 0.97 (0.65, 0.92) 212/2081 274/2078 5.23 CORONA (2007) 0.94 (0.85, 1.04) 692/2514 732/2497 7.56 HOPE-3 (2016) 0.77 (0.65, 0.92) 212/2081 274/2078 5.23 DYPITER (2008) 0.77 (0.66, 0.91) 235/6361 304/6344 5.43 DYPITER (2008) 0.57 (0.46, 0.69) 142/8901 251/8901 4.55 Subtotal (I-squared = 73.6%, p = 0.000) 0.82 (0.75, 0.88) 5083/40329 6158/40185 61.10 Subtotal effect: z = 5.04, p < 0.001 0.49 (0.89, 0.99) 2572/9067 274/2077 8.81 IMPROVE-IT (2015) 0.49 (0.89, 0.99) 2572/9067 274/2077 8.81 LIPID (1998) 0.49 (0.89, 0.99) | | No. of Patients With Event/Total No. | | | |
|--|--|--------------------------------------|----------------|----------------|--------|
| Study and Subgroup (95% Cl) LDL-C Lowering LDL-C Lowering % CRP reduction ≥ median 4D (2005) 0.91 (0.78, 1.06) 294/636 315/619 5.82 AURORA (2009) 0.91 (0.78, 1.06) 294/636 315/619 5.82 CARDS (2004) 0.97 (0.85, 1.10) 396/1389 408/1384 6.50 CARE (1996) 0.77 (0.65, 0.92) 212/2081 274/2078 5.23 CORONA (2007) 0.94 (0.85, 1.04) 692/2514 732/2497 7.56 HOPE-3 (2016) 0.77 (0.65, 0.91) 235/6361 304/6344 5.43 PROVE IT-TIMI 22 (2004) 0.78 (0.76, 0.96) 470/2099 543/2063 7.02 ShARP (2011) 0.85 (0.76, 0.96) 470/2099 543/2232 6.04 AFC APS_TEXCAPS (1998) 0.89 (0.77, 1.03) 309/2265 343/2232 6.04 AFC APS_TEXCAPS (1998) 0.44 0.89 (0.77, 1.03) 309/2265 343/2232 6.04 NFP OVE-IT (2015) 0.48 (0.76, 0.93) 116/3304 183/3301 3.98 0.94 (0.89, 0.99) 257/9067 <th></th> <th>Rate Ratio</th> <th>More Intensive</th> <th>Less Intensive</th> <th>Weight</th> | | Rate Ratio | More Intensive | Less Intensive | Weight |
| $ \begin{array}{c c c c c c c c c c c c c c c c c c c $ | Study and Subgroup | (95% CI) | LDL-C Lowering | LDL-C Lowering | % |
| 4D (2005) 0.91 (0.78, 1.06) 294/636 315/619 5.82 AURORA (2009) 0.97 (0.85, 1.10) 396/1389 408/1384 6.50 CARDS (2004) 0.65 (0.49, 0.85) 83/1429 127/1412 3.23 CORONA (2007) 0.94 (0.85, 0.92) 21/2081 274/2078 5.23 ORONA (2007) 0.94 (0.85, 0.92) 21/212081 274/2078 5.23 OROVE IT-TIMI 22 (2004) 0.97 (0.85, 0.91) 235/6381 304/6344 5.43 NPS (2011) 0.97 (0.85, 0.96) 470/2099 543/2063 7.02 Subtotal (I-squared = 73.6%, p = 0.000) 0.88 (0.77, 1.03) 309/2265 343/2232 6.04 AFCAPS_TEXCAPS (1998) 0.94 (0.89, 0.99) 572/9067 2742/9077 8.81 ILPID (1998) 0.94 (0.89, 0.99) 257/9067 2742/9077 8.81 NPROVE-IT (2015) 0.94 (0.89, 0.99) 257/9067 2742/9077 8.81 ILPID (1998) 0.94 (0.89, 0.99) 257/9067 2742/9077 8.81 Ox84 (0.76, 0.93) 4174/26724 4696/26686 38.90 Subtotal effect: z = 3.52, p < 0.001 | CRP reduction ≥ median | | | | |
| AURORA (2009) CARDS (2004) CARDS (2004) CORONA (2007) HOPE-3 (2016) HPS (2002) JUPITER (2008) PROVE IT-TIMI 22 (2004) Subtotal (I-squared = 73.6%, p = 0.000) Subtotal (I-squared = 70.3%, p = 0.001) PREVEND-IT (2015) LIPID (1998) MPROVE-IT (2015) LIPID (1998) MEAL-CAD (2018) Subtotal (I-squared = 70.3%, p = 0.003) Subtotal (I-squared = 70.3%, p = | 4D (2005) | 0.91 (0.78, 1.06) | 294/636 | 315/619 | 5.82 |
| $\begin{array}{c} \text{CARDS} (2004) \\ \text{CARE} (1996) \\ \text{CARE} (1996) \\ \text{CARE} (1996) \\ \text{CARE} (1996) \\ \text{CORONA} (2007) \\ \text{HOFE-3} (2016) \\ \text{HPS} (2002) \\ \text{JUPITER} (2008) \\ \text{PROVE} [1-TIMI 22 (2004) \\ \text{SHARP} (2011) \\ \text{Subtotal} (I-squared = 73.6\%, p = 0.000) \\ \text{Subtotal} (I-squared = 70.3\%, p = 0.003) \\ \text{MPROVE-IT} (2015) \\ \text{LIPID} (1998) \\ \text{REAL-CAD} (2018) \\ \text{Subtotal} (I-squared = 70.3\%, p = 0.003) \\ \text{Subtotal} (I-squared = 70.3\%, p = 0.003) \\ \text{Subtotal} (I-squared = 74.1\%, p = 0.000) \\ \text{Overall} (I-squared = 74.1\%, p = 0.000) \\ $ | AURORA (2009) | 0.97 (0.85, 1.10) | 396/1389 | 408/1384 | 6.50 |
| CARE (1996) CORONA (2007) HOPE-3 (2016) HOPE-3 (2016) JUPITER (2008) PROVE IT-TIMI 22 (2004) ShaRP (2011) Subtotal (I-squared = 73.6%, p = 0.000) Subtotal effect: $z = 5.04$, $p < 0.001$ CRP reduction < median A to Z (2004) AFCAPS_TEXCAPS (1998) IMPROVE-IT (2015) LIPID (1988) PREVEND-IT (2018) Subtotal (I-squared = 70.3%, p = 0.003) Subtotal effect: $z = 5.22$, $p < 0.001$ Overall (I-squared = 70.3%, p = 0.003) Subtotal effect: $z = 3.52$, $p < 0.001$ Overall (I-squared = 70.3%, p = 0.003) Subtotal effect: $z = 5.22$, $p < 0.001$ Overall (I-squared = 70.3%, p = 0.003) Subtotal effect: $z = 5.22$, $p < 0.001$ Overall (I-squared = 70.3%, p = 0.003) Subtotal effect: $z = 6.22$, $p < 0.001$ Overall (I-squared = 70.3%, p = 0.000) Overall effect: $z = 6.22$, $p < 0.001$ Dec 1 $\frac{1}{2}$ | CARDS (2004) | 0.65 (0.49, 0.85) | 83/1429 | 127/1412 | 3.23 |
| $\begin{array}{c c c c c c c c c c c c c c c c c c c $ | CARE (1996) | 0.77 (0.65, 0.92) | 212/2081 | 274/2078 | 5.23 |
| HOPE-3 (2016) 0.77 (0.65, 0.91) 235/6361 304/6344 5.43 HPS (2002) JUPITER (2008) 0.79 (0.74, 0.83) 2033/10269 2585/10267 8.71 JUPITER (2008) 0.57 (0.46, 0.69) 142/8901 251/8901 4.55 PROVE IT-TIMI 22 (2004) 0.85 (0.76, 0.96) 470/2099 543/2063 7.02 Subtotal (I-squared = 73.6%, p = 0.000) 0 0.84 (0.75, 0.95) 526/4650 619/4620 7.05 Subtotal effect: z = 5.04, p < 0.001 | CORONA (2007) | 0.94 (0.85, 1.04) | 692/2514 | 732/2497 | 7.56 |
| $\begin{array}{c c c c c c c c c c c c c c c c c c c $ | HOPE-3 (2016) | 0.77 (0.65, 0.91) | 235/6361 | 304/6344 | 5.43 |
| JUPITER (2008) 0.57 (0.46, 0.69) 142/8901 251/8901 4.55 PROVE IT-TIMI 22 (2004) 0.85 (0.76, 0.96) 470/2099 543/2063 7.02 SHARP (2011) 0.84 (0.75, 0.95) 526/4650 619/4620 7.05 Subtotal (I-squared = 73.6%, p = 0.000) 0.82 (0.75, 0.88) 5083/40329 6158/40185 61.10 Subtotal effect: z = 5.04, p < 0.001 | HPS (2002) | 0.79 (0.74, 0.83) | 2033/10269 | 2585/10267 | 8.71 |
| PROVE IT-TIMI 22 (2004) 0.85 (0.76, 0.96) 470/2099 543/2063 7.02 SHARP (2011) 0.85 (0.76, 0.96) 470/2099 543/2063 7.02 Subtotal (I-squared = 73.6%, p = 0.000) 0 0.84 (0.75, 0.95) 526/4650 619/4620 7.05 Subtotal effect: z = 5.04, p < 0.001 | JUPITER (2008) | 0.57 (0.46, 0.69) | 142/8901 | 251/8901 | 4.55 |
| SHARP (2011) 0.84 (0.75, 0.95) 526/4650 619/4620 7.05 Subtotal (I-squared = 73.6%, p = 0.000) 0 0 0.82 (0.75, 0.88) 5083/40329 6158/40185 61.10 Subtotal effect: $z = 5.04$, $p < 0.001$ 0 0.82 (0.75, 0.88) 5083/40329 6158/40185 61.10 CRP reduction < median | PROVE IT-TIMI 22 (2004) | 0.85 (0.76, 0.96) | 470/2099 | 543/2063 | 7.02 |
| Subtotal (I-squared = 73.6%, p = 0.000) \bigcirc Subtotal effect: z = 5.04, p < 0.001 | SHARP (2011) | 0.84 (0.75, 0.95) | 526/4650 | 619/4620 | 7.05 |
| Subtotal effect: $z = 5.04$, $p < 0.001$ CRP reduction < median A to Z (2004) AFCAPS_TEXCAPS (1998) IMPROVE-IT (2015) LIPID (1998) PREVEND-IT (2004) REAL-CAD (2018) Subtotal (I-squared = 70.3%, $p = 0.003$) Subtotal effect: $z = 3.52$, $p < 0.001$ Overall (I-squared = 74.1%, $p = 0.000$) Overall (I-squared = 74.1%, $p = 0.000$) Overall effect: $z = 6.22$, $p < 0.001$ Dverall (I-squared = 74.1%, $p = 0.000$) Overall effect: $z = 6.22$, $p < 0.001$ Dverall (I-squared = 74.1%, $p = 0.000$) Overall effect: $z = 6.22$, $p < 0.001$ Dverall (I-squared = 74.1%, $p = 0.000$) Overall effect: $z = 6.22$, $p < 0.001$ Dverall (I-squared = 74.1%, $p = 0.000$) Dverall of the squared in two. < median) Dverall of the squared in two. < median) | Subtotal (I-squared = 73.6%, p = 0.000) | 0.82 (0.75, 0.88) | 5083/40329 | 6158/40185 | 61.10 |
| CRP reduction < median | Subtotal effect: z = 5.04, p < 0.001 | | | | |
| A to Z (2004) 0.89 (0.77, 1.03) 309/2265 343/2232 6.04 AFCAPS_TEXCAPS (1998) 0.63 (0.50, 0.80) 116/3304 183/3301 3.98 IMPROVE-IT (2015) 0.94 (0.89, 0.99) 2572/9067 2742/9077 8.81 LIPID (1998) 0.87 (0.49, 1.56) 21/433 24/431 0.98 REAL-CAD (2018) 0.80 (0.68, 0.94) 266/6199 334/6214 5.70 SEAS (2008) 0.92 (0.80, 1.07) 333/944 355/929 6.19 Subtotal (I-squared = 70.3%, p = 0.003) 0.82 (0.78, 0.88) 9257/67053 10854/66871 100.00 Overall (I-squared = 74.1%, p = 0.000) 0.82 (0.78, 0.88) 9257/67053 10854/66871 100.00 Overall effect: z = 6.22, p < 0.001 | CRP reduction < median | | | | |
| AFCAPS_TEXCAPS (1998)0.63 (0.50, 0.80)116/3304183/33013.98IMPROVE-IT (2015)0.94 (0.89, 0.99)2572/90672742/90778.81LIPID (1998)0.78 (0.70, 0.87)557/4512715/45027.22PREVEND-IT (2004)0.87 (0.49, 1.56)21/43324/4310.98REAL-CAD (2018)0.80 (0.68, 0.94)266/6199334/62145.70SEAS (2008)0.92 (0.80, 1.07)333/944355/9296.19Subtotal (I-squared = 70.3%, p = 0.003)0.84 (0.76, 0.93)4174/267244696/2668638.90Overall (I-squared = 74.1%, p = 0.000)0.82 (0.78, 0.88)9257/6705310854/66871100.00Overall effect: z = 6.22, p < 0.001 | A to Z (2004) | 0.89 (0.77, 1.03) | 309/2265 | 343/2232 | 6.04 |
| IMPROVE-IT (2015) 0.94 (0.89, 0.99) 2572/9067 2742/9077 8.81 LIPID (1998) 0.78 (0.70, 0.87) 557/4512 715/4502 7.22 PREVEND-IT (2004) 0.87 (0.49, 1.56) 21/433 24/431 0.98 REAL-CAD (2018) 0.80 (0.68, 0.94) 266/6199 334/6214 5.70 SEAS (2008) 0.92 (0.80, 1.07) 333/944 355/929 6.19 Subtotal (I-squared = 70.3%, p = 0.003) 0.84 (0.76, 0.93) 4174/26724 4696/26686 38.90 Subtotal effect: z = 3.52, p < 0.001 | AFCAPS_TEXCAPS (1998) | 0.63 (0.50, 0.80) | 116/3304 | 183/3301 | 3.98 |
| LIPID (1998) 0.78 (0.70, 0.87) $557/4512$ $715/4502$ 7.22 PREVEND-IT (2004) 0.87 (0.49, 1.56) $21/433$ $24/431$ 0.98 REAL-CAD (2018) 0.80 (0.68, 0.94) $266/6199$ $334/6214$ 5.70 SEAS (2008) 0.92 (0.80, 1.07) $333/944$ $355/929$ 6.19 Subtotal (I-squared = 70.3%, p = 0.003) $4174/26724$ $4696/26686$ 38.90 Subtotal effect: $z = 3.52$, $p < 0.001$ $0.82 (0.78, 0.88)$ $9257/67053$ $10854/66871$ 100.00 Overall effect: $z = 6.22$, $p < 0.001$ 0.2 1 2 1 1 | IMPROVE-IT (2015) | 0.94 (0.89, 0.99) | 2572/9067 | 2742/9077 | 8.81 |
| PREVEND-IT (2004) 0.87 (0.49, 1.56) $21/433$ $24/431$ 0.98 REAL-CAD (2018) 0.80 (0.68, 0.94) $266/6199$ $334/6214$ 5.70 SEAS (2008) 0.92 (0.80, 1.07) $333/944$ $355/929$ 6.19 Subtotal (I-squared = 70.3%, p = 0.003) $4174/26724$ $4696/26686$ 38.90 Subtotal effect: z = 3.52, p < 0.001 | LIPID (1998) | 0.78 (0.70, 0.87) | 557/4512 | 715/4502 | 7.22 |
| REAL-CAD (2018) 0.80 (0.68, 0.94) 266/6199 334/6214 5.70 SEAS (2008) 0.92 (0.80, 1.07) 333/944 355/929 6.19 Subtotal (I-squared = 70.3%, p = 0.003) \bigcirc 0.84 (0.76, 0.93) 4174/26724 4696/26686 38.90 Subtotal effect: z = 3.52, p < 0.001 | PREVEND-IT (2004) | 0.87 (0.49, 1.56) | 21/433 | 24/431 | 0.98 |
| SEAS (2008) 0.92 (0.80, 1.07) 333/944 355/929 6.19 Subtotal (I-squared = 70.3%, p = 0.003) \bullet 0.84 (0.76, 0.93) 4174/26724 4696/26686 38.90 Subtotal effect: z = 3.52, p < 0.001 | REAL-CAD (2018) | 0.80 (0.68, 0.94) | 266/6199 | 334/6214 | 5.70 |
| Subtotal (I-squared = 70.3%, p = 0.003) Subtotal effect: $z = 3.52$, $p < 0.001$ 0.84 (0.76, 0.93) 4174/26724 4696/26686 38.90 Overall (I-squared = 74.1%, p = 0.000) Overall effect: $z = 6.22$, $p < 0.001$ 0.82 (0.78, 0.88) 9257/67053 10854/66871 100.00 $p = 0.63$ for interaction (\geq median vs. < median) | SEAS (2008) | 0.92 (0.80, 1.07) | 333/944 | 355/929 | 6.19 |
| Overall (I-squared = 74.1%, p = 0.000) Overall (I-squared = 74.1%, p = 0.000) Overall (0.82 (0.78, 0.88) 9257/67053 10854/66871 100.00) Overall effect: z = 6.22, p < 0.001 | Subtotal (I-squared = 70.3%, p = 0.003) Subtotal effect: z = 3.52, p < 0.001 | 0.84 (0.76, 0.93) | 4174/26724 | 4696/26686 | 38.90 |
| 0.2 1 2 | Overall (I-squared = 74.1%, p = 0.000) O Overall effect: z = 6.22, p < 0.001 | 0.82 (0.78, 0.88) | 9257/67053 | 10854/66871 | 100.00 |
| | 0.2 | 2 | | | |

Favors More Intensive LDL-C Lowering Favors Less Intensive LDL-C Lowering



Figure S21. Meta-regression Analysis of Myocardial Infarction Rate Ratio Plotted Against log(baseline CRP Concentrations) in the Secondary Prevention Trials.

CRP, C-reactive protein; RR, rate ratio.

Figure S22. Meta-analysis of All-Cause Mortality Stratified by the Achieved CRP Concentrations.

| | No. of Patients With Event/Total No. | | | |
|--|--------------------------------------|----------------|----------------|--------|
| | Rate Ratio | More Intensive | Less Intensive | Weight |
| Study and Subgroup | (95% CI) | LDL-C Lowering | LDL-C Lowering | % |
| Achieved CRP ≥ median | | | | |
| 4D (2005) | 0.95 (0.85, 1.06) | 559/636 | 573/619 | 10.65 |
| AURORA (2009) | 0.96 (0.87, 1.06) | 636/1389 | 660/1384 | 11.30 |
| CARDS (2004) | 0.74 (0.53, 1.02) | 61/1429 | 82/1412 | 2.93 |
| CORONA (2007) | 0.95 (0.87, 1.05) | 728/2514 | 759/2497 | 11.71 |
| JUPITER (2008) | 0.80 (0.67, 0.97) | 198/8901 | 247/8901 | 6.64 |
| LIPID (1998) | 0.78 (0.70, 0.88) | 498/4512 | 633/4502 | 10.37 |
| SHARP (2011) | 1.02 (0.94, 1.10) | 1142/4650 | 1115/4620 | 12.77 |
| Subtotal (I-squared = 66.9%, p = 0.006) | 0.91 (0.84, 0.98) | 3822/24031 | 4069/23935 | 66.36 |
| Subtotal effect: z = 2.35, p = 0.019 | | | | |
| Achieved CRP < median | | | | |
| A to Z (2004) | 0.79 (0.61, 1.02) | 104/2265 | 130/2232 | 4.37 |
| AFCAPS_TEXCAPS (1998) | 1.04 (0.76, 1.42) | 80/3304 | 77/3301 | 3.19 |
| IMPROVE-IT (2015) | 0.99 (0.91, 1.07) | 1215/9067 | 1231/9077 | 12.91 |
| PROVE IT-TIMI 22 (2004) | 0.69 (0.47, 1.00) | 46/2099 | 66/2063 | 2.37 |
| REAL-CAD (2018) | 0.80 (0.67, 0.96) | 207/6199 | 260/6214 | 6.81 |
| SEAS (2008) | 1.03 (0.79, 1.35) | 105/944 | 100/929 | 3.99 |
| Subtotal (I-squared = 50.6%, p = 0.072) | 0.90 (0.79, 1.02) | 1757/23878 | 1864/23816 | 33.64 |
| Subtotal effect: z = 1.71, p = 0.087 | | | | |
| Overall (I-squared = 57.6%, p = 0.005) | 0.91 (0.85, 0.97) | 5579/47909 | 5933/47751 | 100.00 |
| Overall effect: z = 3.03, p = 0.022 | | | | |
| p = 0.87 for interaction (≥ median vs. < median) | | | | |
| 0.2 | 2 | | | |
| Favors More Intensive LDL-C Lowering Fav | ors Less Intensive LDL- | C Lowering | | |

Figure S23. Meta-analysis of Cardiovascular Mortality Stratified by the Achieved CRP Concentrations.

| | | No. of Patients With Event/Total No. | | | |
|--|---------------------------|--------------------------------------|----------------|--------|--|
| | Rate Ratio | More Intensive | Less Intensive | Weight | |
| Study and Subgroup | (95% CI) | LDL-C Lowering | LDL-C Lowering | % | |
| Achieved CRP ≥ median | | | | | |
| 4D (2005) | 0.82 (0.68, 0.98) | 202/636 | 241/619 | 9.03 | |
| AURORA (2009) | 1.00 (0.86, 1.16) | 324/1389 | 324/1384 | 10.27 | |
| CARDS (2004) | 0.67 (0.40, 1.11) | 25/1429 | 37/1412 | 2.73 | |
| CARE (1996) | 0.81 (0.62, 1.05) | 96/2081 | 119/2078 | 6.49 | |
| CORONA (2007) | 1.00 (0.88, 1.12) | 488/2514 | 487/2497 | 11.29 | |
| JUPITER (2008) | 0.53 (0.41, 0.69) | 83/8901 | 157/8901 | 6.55 | |
| LIPID (1998) | 0.76 (0.66, 0.88) | 331/4512 | 433/4502 | 10.53 | |
| SHARP (2011) | 0.92 (0.80, 1.07) | 361/4650 | 388/4620 | 10.53 | |
| Subtotal (I-squared = 74.4%, p = 0.000) | 0.83 (0.73, 0.94) | 1910/26112 | 2186/26013 | 67.43 | |
| | | | | | |
| Achieved CRP < median | 0.75 (0.57, 4.00) | 92/2265 | 100/2222 | 0.44 | |
| | 0.75 (0.57, 1.00) | 03/2203 | 109/2232 | 6.11 | |
| AFCAPS_TEXCAPS (1998) | | 17/3304 | 25/3301 | 1.97 | |
| | 1.00 (0.89, 1.13) | 537/9067 | 538/9077 | 11.36 | |
| PREVEND-IT (2004) | → 1.00 (0.25, 3.97) | 4/433 | 4/431 | 0.44 | |
| PROVE IT-TIMI 22 (2004) | 0.78 (0.45, 1.35) | 23/2099 | 29/2063 | 2.41 | |
| REAL-CAD (2018) | 0.77 (0.58, 1.02) | 86/6199 | 112/6214 | 6.16 | |
| SEAS (2008) | - 0.83 (0.56, 1.21) | 47/944 | 56/929 | 4.12 | |
| Subtotal (I-squared = 13.9%, p = 0.324) | 0.88 (0.78, 0.99) | 797/24311 | 873/24247 | 32.57 | |
| Subtotal effect: z = 2.10, p = 0.036 | | | | | |
| Overall (I-squared = 59.9%, p = 0.002) | 0.84 (0.76, 0.92) | 2707/50423 | 3059/50260 | 100.00 | |
| Overall effect: z = 3.75, p < 0.001 | | | | | |
| p = 0.52 for interaction (≥ median vs. < median) | | | | | |
| | 2 | | | | |
| Favors More Intensive LDL-C Lowering | Favors Less Intensive LDL | -C Lowering | | | |

Figure S24. Meta-analysis of Myocardial Infarction Stratified by the Achieved CRP Concentrations.

| | | No. of Patients With Event/Total No. | | | |
|---|--------------------------------------|--------------------------------------|----------------|--------|--|
| | Rate Ratio | More Intensive | Less Intensive | Weight | |
| Study and Subgroup | (95% CI) | LDL-C Lowering | LDL-C Lowering | % | |
| Achieved CRP ≥ median | | | | | |
| 4D (2005) | 0.84 (0.67, 1.07) | 124/636 | 143/619 | 7.52 | |
| AURORA (2009) | - 0.85 (0.64, 1.12) | 91/1389 | 107/1384 | 6.41 | |
| CARDS (2004) | 0.53 (0.35, 0.82) | 33/1429 | 61/1412 | 3.65 | |
| CARE (1996) - | 0.76 (0.62, 0.93) | 157/2081 | 207/2078 | 8.61 | |
| CORONA (2007) | 0.81 (0.63, 1.03) | 115/2514 | 141/2497 | 7.34 | |
| JUPITER (2008) | 0.46 (0.30, 0.70) | 31/8901 | 68/8901 | 3.62 | |
| LIPID (1998) | 0.72 (0.63, 0.83) | 336/4512 | 463/4502 | 11.17 | |
| SHARP (2011) | - 0.92 (0.76, 1.11) | 213/4650 | 230/4620 | 9.35 | |
| Subtotal (I-squared = 50.9%, p = 0.047) | 0.76 (0.67, 0.86) | 1100/26112 | 1420/26013 | 57.67 | |
| Subtotal effect: z = 4.45, p < 0.001 | | | | | |
| Achieved CRP < median | | | | | |
| A to Z (2004) | - 0.96 (0.77, 1.20) | 151/2265 | 155/2232 | 8.11 | |
| AFCAPS_TEXCAPS (1998) | 0.60 (0.43, 0.83) | 57/3304 | 95/3301 | 5.21 | |
| IMPROVE-IT (2015) | 0.87 (0.80, 0.95) | 977/9067 | 1118/9077 | 13.28 | |
| PREVEND-IT (2004) | 0.53 (0.23, 1.25) | 8/433 | 15/431 | 1.09 | |
| PROVE IT-TIMI 22 (2004) | - 0.89 (0.71, 1.12) | 139/2099 | 153/2063 | 7.93 | |
| REAL-CAD (2018) | 0.56 (0.38, 0.82) | 40/6199 | 72/6214 | 4.16 | |
| SEAS (2008) | 0.60 (0.35, 1.02) | 22/944 | 36/929 | 2.55 | |
| Subtotal (I-squared = 55.8%, p = 0.035) | 0.78 (0.67, 0.91) | 1394/24311 | 1644/24247 | 42.33 | |
| Subtotal effect: z = 3.16, p = 0.002 | | | | | |
| Overall (I-squared = 54.6%, p = 0.006) Overall effect: z = 5.47, p < 0.001 | 0.77 (0.70, 0.85) | 2494/50423 | 3064/50260 | 100.00 | |
| p = 0.81 for interaction (≥ median vs. < median) | | | | | |
| 0.2 Favors More Intensive LDL-C Lowering | I 2 Favors Less Intensive LDL- | C Lowering | | | |

Figure S25. Meta-analysis of Stroke Stratified by the Achieved CRP Concentrations.

| | | No. of Patients With Event/Total No. | | | |
|--|------------|--------------------------------------|----------------|----------------|--------|
| | 1 | Rate Ratio | More Intensive | Less Intensive | Weight |
| Study and Subgroup | | (95% CI) | LDL-C Lowering | LDL-C Lowering | % |
| Achieved CRP ≥ median | | | | | |
| 4D (2005) | | 1.08 (0.79, 1.46) | 84/636 | 76/619 | 7.80 |
| AURORA (2009) | 1 | 1.17 (0.79, 1.74 | 53/1389 | 45/1384 | 5.55 |
| CARDS (2004) | | 0.53 (0.31, 0.90) | 21/1429 | 39/1412 | 3.51 |
| CARE (1996) | | 0.69 (0.49, 0.98 | 54/2081 | 78/2078 | 6.72 |
| CORONA (2007) | + (| 0.85 (0.64, 1.13 | 89/2514 | 104/2497 | 8.74 |
| JUPITER (2008) | | 0.52 (0.34, 0.78 | 33/8901 | 64/8901 | 5.08 |
| LIPID (1998) | | 0.83 (0.67, 1.01 | 169/4512 | 204/4502 | 12.14 |
| SHARP (2011) | | 0.83 (0.68, 1.01 | 176/4650 | 211/4620 | 12.35 |
| Subtotal (I-squared = 51.4%, p = 0.044) | (| 0.81 (0.69, 0.95 | 679/26112 | 821/26013 | 61.89 |
| Subtotal effect: z = 2.64, p = 0.008 | | | | | |
| Achieved CRP < median | | | | | |
| A to Z (2004) | - | 0.79 (0.48, 1.29 | 28/2265 | 35/2232 | 3.91 |
| AFCAPS_TEXCAPS (1998) | - | 0.82 (0.41, 1.67 | 14/3304 | 17/3301 | 2.12 |
| IMPROVE-IT (2015) | | 0.86 (0.74, 1.00 | 296/9067 | 345/9077 | 14.78 |
| PREVEND-IT (2004) | | 1.74 (0.51, 5.94 | 7/433 | 4/431 | 0.75 |
| PROVE IT-TIMI 22 (2004) | <u>μ</u> α | 0.98 (0.54, 1.80 | 21/2099 | 21/2063 | 2.81 |
| REAL-CAD (2018) | | 1.13 (0.87, 1.45 | 127/6199 | 113/6214 | 9.84 |
| SEAS (2008) | a 1 | 1.12 (0.68, 1.84 | 33/944 | 29/929 | 3.89 |
| Subtotal (I-squared = 0.0%, p = 0.501) | <u>ب</u> ا | 0.93 (0.83, 1.05 | 526/24311 | 564/24247 | 38.11 |
| Subtotal effect: z = 1.18, p = 0.239 | | | | | |
| Overall (I-squared = 36.7%, p = 0.077) | . (| 0.87 (0.78, 0.97 | 1205/50423 | 1385/50260 | 100.00 |
| Overall effect: z = 2.58, p = 0.010 | | | | | |
| p = 0.17 for interaction (≥ median vs. < median) | <u> </u> | | | | |
| 0.2 | 1 2 | | . | | |
| Favors More Intensive LDL-C Lowering | Favors Les | s Intensive LDL | -C Lowering | | |

Figure S26. Meta-analysis of Coronary Revascularization Stratified by the Achieved CRP Concentrations.

| | | No. of Patients With Event/Tota | | | |
|--|---------------------------|---------------------------------|----------------|--------|--|
| | Rate Ratio | More Intensive | Less Intensive | Weight | |
| Study and Subgroup | (95% CI) | LDL-C Lowering | LDL-C Lowering | % | |
| Achieved CRP ≥ median | | | | | |
| 4D (2005) | 0.74 (0.52, 1.05) | 55/636 | 72/619 | 3.59 | |
| AURORA (2009) | 0.97 (0.78, 1.21) | 148/1389 | 152/1384 | 6.60 | |
| CARDS (2004) | 0.70 (0.41, 1.17) | 24/1429 | 34/1412 | 1.85 | |
| CARE (1996) | 0.75 (0.65, 0.87) | 294/2081 | 391/2078 | 9.70 | |
| JUPITER (2008) | 0.58 (0.44, 0.77) | 76/8901 | 131/8901 | 4.91 | |
| LIPID (1998) | 0.82 (0.74, 0.92) | 585/4512 | 708/4502 | 11.80 | |
| SHARP (2011) | 0.80 (0.69, 0.94) | 284/4650 | 352/4620 | 9.39 | |
| Subtotal (I-squared = 35.2%, p = 0.160) | 0.79 (0.72, 0.86) | 1466/23598 | 1840/23516 | 47.84 | |
| Subtotal effect: z = 5.01, p < 0.001 | | | | | |
| Achieved CRP < median | | | | | |
| A to Z (2004) | 0.95 (0.74, 1.21) | 119/2265 | 124/2232 | 5.81 | |
| AFCAPS_TEXCAPS (1998) | 0.67 (0.53, 0.86) | 106/3304 | 157/3301 | 5.88 | |
| IMPROVE-IT (2015) | 0.94 (0.88, 1.01) | 1690/9067 | 1793/9077 | 13.94 | |
| PROVE IT-TIMI 22 (2004) | 0.87 (0.75, 1.00) | 342/2099 | 388/2063 | 10.20 | |
| REAL-CAD (2018) | 0.85 (0.76, 0.95) | 529/6199 | 626/6214 | 11.47 | |
| SEAS (2008) | 0.65 (0.49, 0.86) | 77/944 | 117/929 | 4.85 | |
| Subtotal (I-squared = 63.9%, p = 0.017) | 0.84 (0.76, 0.94) | 2863/23878 | 3205/23816 | 52.16 | |
| Subtotal effect: z = 3.23, p = 0.001 | | | | | |
| Overall (I-squared = 60.5%, p = 0.002) | 0.81 (0.75, 0.88) | 4329/47476 | 5045/47332 | 100.00 | |
| Overall effect: z = 5.36, p < 0.001 | | | | | |
| p = 0.33 for interaction (≥ median vs. < median) | | | | | |
| 1 | | | | | |
| Favors More Intensive LDL-C Lowering | Favors Less Intensive LDL | -C Lowering | | | |

Figure S27. Meta-analysis of MACE Stratified by the Achieved CRP Concentrations.

| | | No. of Patients With Event/Total No. | | | |
|---|---------------|--------------------------------------|----------------|----------------|--------|
| | | Rate Ratio | More Intensive | Less Intensive | Weight |
| Study and Subgroup | | (95% CI) | LDL-C Lowering | LDL-C Lowering | % |
| Achieved CRP ≥ median | | | | | |
| 4D (2005) | +=+ | 0.91 (0.78, 1.06) | 294/636 | 315/619 | 6.81 |
| AURORA (2009) | ; | 0.97 (0.85, 1.10) | 396/1389 | 408/1384 | 7.56 |
| CARDS (2004) - | | 0.65 (0.49, 0.85) | 83/1429 | 127/1412 | 3.85 |
| CARE (1996) | | 0.77 (0.65, 0.92) | 212/2081 | 274/2078 | 6.14 |
| CORONA (2007) | | 0.94 (0.85, 1.04) | 692/2514 | 732/2497 | 8.72 |
| JUPITER (2008) - | - | 0.57 (0.46, 0.69) | 142/8901 | 251/8901 | 5.37 |
| LIPID (1998) | - | 0.78 (0.70, 0.87) | 557/4512 | 715/4502 | 8.35 |
| SHARP (2011) | + | 0.84 (0.75, 0.95) | 526/4650 | 619/4620 | 8.17 |
| Subtotal (I-squared = 77.3%, p = 0.000) Subtotal effect: z = 3.89, p < 0.001 | \diamond | 0.81 (0.73, 0.90) | 2902/26112 | 3441/26013 | 54.97 |
| Achieved CRP < median | | | | | |
| A to Z (2004) | | 0.89 (0.77, 1.03) | 309/2265 | 343/2232 | 7.05 |
| AFCAPS_TEXCAPS (1998) - | | 0.63 (0.50, 0.80) | 116/3304 | 183/3301 | 4.71 |
| IMPROVE-IT (2015) | = | 0.94 (0.89, 0.99) | 2572/9067 | 2742/9077 | 10.07 |
| PREVEND-IT (2004) - | - | - 0.87 (0.49, 1.56) | 21/433 | 24/431 | 1.19 |
| PROVE IT-TIMI 22 (2004) | ÷ | 0.85 (0.76, 0.96) | 470/2099 | 543/2063 | 8.14 |
| REAL-CAD (2018) | | 0.80 (0.68, 0.94) | 266/6199 | 334/6214 | 6.67 |
| SEAS (2008) | | 0.92 (0.80, 1.07) | 333/944 | 355/929 | 7.21 |
| Subtotal (I-squared = 58.9%, p = 0.024) Subtotal effect: z = 3.55, p < 0.001 | \diamond | 0.86 (0.79, 0.93) | 4087/24311 | 4524/24247 | 45.03 |
| Overall (I-squared = 71.9%, p = 0.000) Overall effect: $z = 5.39$, $p < 0.001$ $p = 0.39$ for interaction (\geq median vs. < median | n) | 0.83 (0.78, 0.89) | 6989/50423 | 7965/50260 | 100.00 |
| I 0.2 Favors More Intensive LDL-C I | Lowering Fa | I 2 vors Less Intensive LDL- | C Lowering | | |