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

Xin-Lin Zhang, MD;* Rong-Fang Lan, MD;* Xiao-Wen Zhang, MD; Wei Xu, MD; Lian Wang, MD; Li-Na Kang, MD; Biao Xu, MD, PhD

**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

LDL-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, statins 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 cardiovascular 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...
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, low-density 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, 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 meta-regression 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 log-transformed 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

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.
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 χ² 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. 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% CI, 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% CI, 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% CI, 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 log-transformed baseline CRP concentration between more- versus less-intensive LDL-C–lowering treatments (RR, 1.01; 95% CI, 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% CI, 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% CI, 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% CI, 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% CI, 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% CI, 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 less-intensive therapy was consistent across the range of magnitude of reduction in CRP concentrations (Figure S8).
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% CI, 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

| Outcomes                | No. of Trials | log(Baseline CRP) | Rate Ratio (95% CI)      |
|-------------------------|---------------|-------------------|--------------------------|
|                         |               | 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, Baseline LDL-C, Magnitude of Reduction in LDL-C and Age |
| 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.

DOI: 10.1161/JAHA.119.012428

Journal of the American Heart Association 4
### Study and Subgroup

| Baseline CRP ≥ median | Rate Ratio (95% CI) | More Intensive LDL-C Lowering | Less Intensive LDL-C Lowering | Weight % |
|-----------------------|---------------------|-------------------------------|-----------------------------|----------|
| 4D (2005)             | 0.95 (0.85, 1.06)   | 559/636                       | 573/619                     | 7.02     |
| A to Z (2004)         | 0.79 (0.61, 1.02)   | 104/2265                      | 130/2232                    | 2.46     |
| AURORA (2009)         | 0.96 (0.87, 1.06)   | 636/1389                      | 660/1384                    | 7.59     |
| CARDS (2004)          | 0.74 (0.53, 1.02)   | 61/1429                       | 82/1412                     | 1.80     |
| CORONA (2007)         | 0.95 (0.87, 1.05)   | 728/2514                      | 759/2497                    | 7.95     |
| HIJ-PROPER (2017)     | 0.69 (0.47, 1.03)   | 42/864                        | 60/857                      | 1.17     |
| HPS (2002)            | 0.88 (0.82, 0.95)   | 1328/10269                    | 1507/10267                  | 9.43     |
| IMPROVE-IT (2015)     | 0.99 (0.91, 1.07)   | 1215/9067                     | 1231/9077                   | 9.06     |
| JUPITER (2008)        | 0.80 (0.67, 0.97)   | 198/8901                      | 247/8901                    | 3.95     |
| Liu, et al (2016)     | 0.62 (0.21, 1.88)   | 5/400                         | 8/398                       | 0.16     |
| PROSPER (2002)        | 0.98 (0.84, 1.15)   | 298/2891                      | 306/2913                    | 4.91     |
| PROVE IT-TIMI 22 (2004) | 0.69 (0.47, 1.00) | 46/2099                      | 66/2063                     | 1.27     |
| SHARP (2011)          | 1.02 (0.94, 1.10)   | 1142/4650                     | 1115/4620                   | 8.93     |

**Subtotal (I-squared = 43.6%, P = 0.046)**

| Rate Ratio (95% CI) | More Intensive LDL-C Lowering | Less Intensive LDL-C Lowering | Weight % |
|---------------------|-------------------------------|-------------------------------|----------|
| 0.93 (0.88, 0.98)  | 6362/47374                    | 6744/47240                    | 65.51    |

**Baseline CRP < median**

| AFCAPS_TEXCAPS (1998) | 1.04 (0.76, 1.42) | 80/3304                     | 77/3301 | 1.75     |
| ALERT (2003)          | 1.03 (0.84, 1.25)  | 194/1050                    | 189/1052 | 3.62     |
| ASCOT-LLA (2003)      | 0.87 (0.71, 1.06)  | 185/5168                    | 212/5137 | 3.66     |
| HOPE-3 (2016)         | 0.93 (0.80, 1.08)  | 334/6361                    | 357/6344 | 5.25     |
| LIPID (1998)          | 0.76 (0.70, 0.88)  | 498/4512                    | 633/4502 | 6.78     |
| REAL-CAD (2018)       | 0.80 (0.67, 0.96)  | 207/6199                    | 260/6214 | 4.07     |
| SEAS (2008)           | 1.03 (0.79, 1.35)  | 105/944                     | 100/929  | 2.23     |
| TNT (2005)            | 1.01 (0.86, 1.19)  | 284/4995                    | 282/5006 | 4.66     |
| WOSCOPS (1995)        | 0.78 (0.61, 1.01)  | 106/3302                    | 135/3293 | 2.48     |

**Subtotal (I-squared = 41.6%, P = 0.090)**

| Rate Ratio (95% CI) | More Intensive LDL-C Lowering | Less Intensive LDL-C Lowering | Weight % |
|---------------------|-------------------------------|-------------------------------|----------|
| 0.90 (0.83, 0.98)  | 1993/35635                    | 2245/35778                    | 34.49    |

**Overall (I-squared = 44.5%, P = 0.014)**

| Rate Ratio (95% CI) | More Intensive LDL-C Lowering | Less Intensive LDL-C Lowering | Weight % |
|---------------------|-------------------------------|-------------------------------|----------|
| 0.91 (0.87, 0.96)  | 8356/83209                    | 8989/83018                    | 100.00   |

**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% CI, 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% CI, 0.89–1.03; P=0.252; Figure S18). The overall risk...
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% CI, 1.03–1.21; P=0.011) in secondary prevention trials (Table S10; Figure S21), but not in 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).

Discussion

In this meta-analysis and metaregression analysis of 24 trials involving >170 000 patients and ≈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. Although a causal role of CRP for atherosclerosis and ischemic vascular disease is not supported by previous studies, 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
cardiovascular benefit. However, others have not shown such an association both in primary and secondary prevention trials. 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. 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%). The very recently published St. Francis Heart Study also reported a trend toward less benefit in patients with higher baseline hsCRP.

Several trials suggest that achieving lower CRP concentrations might be associated with better outcomes for patients being treated with statins. 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 4](https://example.com/figure4.png)

**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.

DOI: 10.1161/JAHA.119.012428
statin therapy had a lower rate of cardiovascular events than those who did not. A similarly negative association was detected in the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering), A-to-Z (Aggrastat-to-Zocor), and the JUPITER trials. Fueling this debate, trials including the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcome Trial–Lipid Lowering Arm), the CARDS (Collaborative Atorvastatin Diabetes Study), and TNT (Treating New Targets) 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.

The REVERSAL trial demonstrates that magnitude of reduction in CRP concentrations is significantly correlated with rate of progression of atherosclerosis (determined with intravascular ultrasonography). The JUPITER trial also shows an association with magnitude of cardiovascular benefit of statin therapy. However, evidence remains scarce 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. Canakinumab confers a significant 15% reduction in MACEs without altering the lipid profile, supporting that reducing inflammation per se could reduce vascular risk. Of note, a CRP concentration <2 mg/dL after the first dose of cankinumab was associated with greater relative reduction in MACE risk. Canakinumab’s reduction in atherothrombotic events involves inhibition of interleukin-6, indicating that treatments targeting downstream from interleukin-1β merit evaluation for cardiovascular benefits. 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.
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. 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.

Sources of Funding

This study was supported by the National Natural Science Foundation of China (No. 81600312) and Fund for Distinguished Young Scholars of Nanjing (JQX15002). The funders had no role in the study design, data collection and analysis, writing of the report, and decision to submit the article for publication.

Disclosures

None.

References

1. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Mrc/Bhf Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study: a randomised placebo-controlled trial. Lancet. 2002;360:79–86.
2. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, Ferrari GM, Ruzyllo W, de Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–2397.
3. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, Ferrari GM, Ruzyllo W, de Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–2397.
4. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Zhang et al. CRP and Outcomes After LDL-C Lowering. Journal of the American Heart Association. DOI: 10.1161/JAHA.119.012428
24. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med.* 1998;339:1349–1357.

25. Liu Z, Joerg H, Hao H, Xu J, Hu S, Li B, Sang C, Xia J, Chu Y, Xu D. Efficacy of high-intensity atorvastatin for Asian patients undergoing percutaneous coronary intervention. *Ann Pharmacother.* 2016;50:725–733.

26. Asselbergs FW, Diercks GF, Hillege HL, van Boven AJ, Janssen WM, Voors AA. Effect of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation.* 2004;110:2809–2816.

27. Shepherd J, Blauw GJ, Boilen EL, Buckley BM, Cobbe SM, Ford I, Gav A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Sweeney BJ, Twomey BJ, Twomey C, Westendorp RG. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet.* 2002;360:1623–1630.

28. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004;350:1495–1504.

29. Taguchi I, Iimuro S, Iwata H, Abe M, Amiya E, Ogawa T, Ozaki Y, Sakuma I, Nakagawa Y, Hibi K, Hori H, Komoto S, Miyauchi K, Yatsuki T, Ito O, Otsuji Y, Kirakawa H, Kashiwabara Y, Okada H, Shimokawa H, Taira Y, Kimura T, Inoue T, Matsuzaki M, Nagai R. High-dose versus low-dose pitavastatin in Japanese patients with stable coronary artery disease (REAL-CAD): a randomized superiority trial. *Circulation.* 2018;137:1197–1200.

30. Rossebo AB, Pedersen TR, Boman K, Brudt P, Chambers JB, Egstrup K, Gerds T, Gohlke-Barwolf C, Holme I, Kesaniemi YA, Malbecq W, Nienaber CA, Ray S, Skjærte T, Wachtell K, Willenheimer R. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med.* 2008;359:1343–1356.

31. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DG, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neil B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasikis B, Walker R, Masey ZA, Feldt-Rasmussen B, Kriantichchai U, Ophascharoensuk V, Fellstrom B, Holzaus H, Tersar S, Wieck M, Grobblee D, de Zeewuy D, de Jong PE, van Veldhuisen DJ, van Gilst WH. Effects of intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2005;352:20–28.

32. Shepherd J, Blauw GJ, Murphy MB, Vlietink SD, Blauw GJ, van Santen MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Greten H, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. Prevention of cardiovascular events and death with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med.* 1995;333:1301–1308.

33. Lane T, Wassef N, Poole S, Mistry Y, Lachmann HJ, Gillmore JD, Hawkins PN, Masson S, Thway K, Winter AM, Colhoun HM, Simes RJ, Libby P, Lorentzetti AJ, Macfadyen JG, Nordestgaard BG, Shepherd J, Wanner C, Ross AC, Westendorp RG, Stott DJ, Sweeney BJ, Twomey BJ, Twomey C, Westendorp RG. Pravastatin therapy for patients after myocardial infarction with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. Prevention of cardiovascular events and death with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med.* 1998;339:1349–1357.

34. Lane T, Wassef N, Poole S, Mistry Y, Lachmann HJ, Gillmore JD, Hawkins PN, Masson S, Thway K, Winter AM, Colhoun HM, Simes RJ, Libby P, Lorentzetti AJ, Macfadyen JG, Nordestgaard BG, Shepherd J, Wanner C, Ross AC, Westendorp RG, Stott DJ, Sweeney BJ, Twomey BJ, Twomey C, Westendorp RG. Pravastatin therapy for patients after myocardial infarction with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. Prevention of cardiovascular events and death with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med.* 1998;339:1349–1357.

35. Kaul S, Morrissey RP, Diamond GA. By level! What is a clinician to make of JUPITER? *Arch Intern Med.* 2010;170:1073–1077.

36. Blaha MJ, Nasir K, Budoff MJ, Dardari ZA, Blumenthal RS, Pollack S, Reichek N, Guerci AD. Impact of C-reactive protein and coronary artery calcium on benefit observed with atorvastatin. *J Am Coll Cardiol.* 2018;71:2487–2488.

37. Braunwald E. Creating controversy where none exists: the important role of C-reactive protein in the CARE, AFCAPS/ TexCAPS, PROVE IT, REVERSAL, a T to JUPITER, HEART PROTECTION, and ASCOT trials. *Eur Heart J.* 2012;33:430–432.

38. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA. Braunwald E. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med.* 2005;352:20–28.

39. Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela W, Tsai J, Oroyen J, Magorien RD, O’Shaughnessy C, Ganz P. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med.* 2005;352:29–38.

40. Morrow DA, de Lemos JA, Sabatine MS, Wittiov SD, Blauw GJ, Wu SH, Rifai N, Califf RM, Braunwald E. Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor Trial. *Circulation.* 2006;114:281–288.

41. Ridker PM, Danielson E, Fonseca FA, Genest J, Goto A, Kastelein JJ, Koenig W, Libby P, Lorenzetti AJ, Macfadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. *Lancet.* 2009;373:1175–1182.

42. Sever PS, Poulier NR, Chang CL, Thom SA, Hughes AD, Welsh P, Sattar N. Evaluation of C-reactive protein before and on-treatment as a predictor of benefit from atorvastatin: a cohort analysis from the Anglo-Scandinavian Cardiac Outcomes Trial lipid-lowering arm. *J Am Coll Cardiol.* 2013;62:717–729.

43. Soedamah-Muthu SS, Livingstone SJ, Charlton-Menys V, Betteridge DJ, Hitman GA, Neil HA, Bao W, DeMicco DA, Preston BM, Fuller JT, Stenhower CD, Schalkwijk CG, Durrington PN, Colhoun HM. Effect of atorvastatin on C-reactive protein and benefits for cardiovascular disease in patients with type 2 diabetes: analyses from the Collaborative Atorvastatin Diabetes Trial. *Diabetologia.* 2015;58:1494–1502.

44. Arsenault BJ, Parer D, DeMicco DA, Bao W, Preston BM, LaRosa JC, Grundy SM, Deedwania P, Hutter K, Libby NK, Shepherd J, Waters KD, Kastelein JJ. Prediction of cardiovascular events in statin-treated stable coronary patients of the treating to new targets randomized controlled trial by lipid and non-lipid biomarkers. *PLoS One.* 2014;9:e114519.

45. Navarese EP, Robinson JG, Kozlowski M, Kolodziejczak M, Andreatti F, Blieden K, Tantry U, Kubica R, Raggi P, Gurbel PA. Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: a systematic review and meta-analysis. *JAMA.* 2018;319:1566–1579.

46. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, Braunwald E, Sabatine MS. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA.* 2016;316:1289–1297.

47. Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet.* 2018;391:319–328.

48. Ridker PM, Libby P, MacFadyen JG, Thuren T, Ballantyne C, Fonseca F, Koenig W, Shimokawa H, Everett BM, Glynn RJ. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). *Eur Heart J.* 2018;39:3499–3507.

49. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med.* 2002;21:1559–1573.
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 and risks of outcomes 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 χ² 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                |
| Section/topic            | #  | Checklist item                                                                                                                                                                                                 | Reported on page # |
|-------------------------|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| 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               |

### RESULTS

- **Study selection**
  - 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**
  - 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**
  - Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 8 |
- **Results of individual studies**
  - 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**
  - Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 8-12 |
- **Risk of bias across studies**
  - Present results of any assessment of risk of bias across studies (see Item 15). | 8-12 |
- **Additional analysis**
  - Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 12,13 |
| Section               | Page | Description                                                                                                                                      | Notes |
|-----------------------|------|---------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| 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). | 13    |
| Limitations           | 25   | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 16    |
| Conclusions           | 26   | Provide a general interpretation of the results in the context of other evidence, and implications for future research.                            | 17    |
| **FUNDING**           |      |                                                                                                                                                   | 3     |
| 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.          |       |

*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.

| Trial          | Year | Total No. of patients | Age, yrs | Men, % | CHD, % | Other vascular disease, % | DM, % | HB P, % | Smoker, % | BMI (kg/m²) | Median FU, ys | More intensive LDL-C lowering | Treatment | No. of patients | Baseline CRP (mg/L) | Baseline LDL-C (mg/dL) | Magnitude of reduction in CRP (mg/L) | Magnitude of reduction in LDL-C (mg/dL) |
|----------------|------|-----------------------|----------|--------|--------|---------------------------|-------|---------|----------|-------------|----------------|----------------------------------|-----------|-----------------|---------------------|-----------------------|--------------------------------------|---------------------------------------|
| 4D             | 200  | 1255                  | 65.7     | 54     | 50     | 53                          | 100   | NA      | 41       | 27.5        | 11.5           | Atorvastatin (20 mg) | 636       | 5               | 125                 | Placebo                                           | 1.6                                              | 40                                              |
| A to Z         | 200  | 4497                  | 61       | 76     | 100    | 11                          | 24    | 50      | 41       | NA          | 2             | Simvastatin (80 mg) | 2265      | 20.1            | 112                 | Placebo                                           | 0.3                                              | 15.7                                            |
| AFCAPS_TEXCAPS| 199  | 6605                  | 58       | 85     | <1     | <1                         | 15    | 22      | 12       | NA          | 5.2           | Lovastatin (20-40 mg) | 3304      | 1.6             | 150                 | Placebo                                           | 0.3                                              | 40.5                                            |
| ALERT          | 200  | 2102                  | 50       | 66     | 19     | 11                          | 19    | 75      | 18.5     | 25.8        | 6.7            | Fluvastatin (40 mg) | 1050      | 1.62            | 159                 | Placebo                                           | NA                                               | 38.2                                            |
| ASCOT-LA       | 200  | 10305                 | 63.2     | 81     | <1     | 14                          | 25    | NA      | 32.7     | 28.7        | 3.3            | Atorvastatin (10 mg) | 5168      | 2.72            | 133                 | Placebo                                           | NA                                               | 37.2                                            |
| AURORA         | 200  | 2773                  | 64.1     | 62     | 24     | 27                          | 26.4  | NA      | 15       | 25.4        | 3.8            | Rosuvastatin (10 mg) | 1389      | 4.8             | 100                 | Placebo                                           | 1.6                                              | 39                                              |
| CARDS          | 200  | 2841                  | 61.5     | 68     | <1     | 3                           | 18    | NA      | 46       | 28.7        | 3.9            | Atorvastatin (10 mg) | 1429      | 12.6            | 117                 | Placebo                                           | 5.3                                              | 39.8                                            |
| CARE           | 199  | 4159                  | 59       | 86     | 100    | 0                           | 14    | 43      | 21       | 28.5        | 5             | Pravastatin (40 mg) | 2081      | 3.8             | 139                 | Placebo                                           | 1.2                                              | 40.3                                            |
| CORONA         | 200  | 5011                  | 73       | 76     | 73     | 13                          | 30    | 63      | 9        | 27          | 2.7           | Rosuvastatin (10 mg) | 2514      | 3.1             | 137                 | Placebo                                           | 1.2                                              | 34                                              |
| HIJ-PERPER     | 201  | 1721                  | 65.7     | 75.6   | 100    | 7                           | 30    | 68      | 59       | 24.3        | 3.9            | Pitavastatin (1-4mg) + ezetimibe (10 mg) | 864       | 21.2            | 135                 | Placebo                                           | NA                                               | 20                                              |
| Study          | Year | Randomization | N     | Primary Endpoint | Mean Difference | Standard Difference | p Value | Control Group | Treatment | N     | Mean Difference | Standard Difference | p Value | Control Group | Treatment |
|---------------|------|---------------|-------|------------------|-----------------|--------------------|---------|---------------|-----------|-------|-----------------|--------------------|---------|---------------|-----------|
| HOPE-3        | 2016|               | 201   | 6                | 12705           | 65.8               | 53.7    | 0            | 0         | 6     | 38              | 28                 | 27.1    | 5.6           |           |
| HPS           | 2002|               | 200   | 6                | 20536           | 64                 | 75      | 65           | 43        | 29    | NA              | NA                 | NA      | 5            |           |
| IMPROVE-IT    | 2005|               | 201   | 6                | 18144           | 63.6               | 75.7    | 100          | 5.5       | 27    | 61.5            | 33                 | 28.3    | 6            |           |
| JUPITER       | 2008|               | 200   | 6                | 17802           | 66                 | 62      | 0            | 0         | <1   | NA              | 16                 | 28.3    | 1.9           |           |
| LIPID         | 2008|               | 199   | 6                | 9014            | 62                 | 83      | 100          | 10        | 9    | 41              | 74                 | NA      | 6.1           |           |
| Liu, et al    | 2006|               | 201   | 6                | 798             | 62                 | 72      | 100          | 0         | 32.5 | 64.6            | 20.6               | NA      | 1            |           |
| PREVENT-D-IT  | 2004|               | 200   | 6                | 864             | 52                 | 65      | <1           | 1.5       | NA   | NA              | 74                 | 26      | 3.8           |           |
| PROSPER       | 2002|               | 200   | 6                | 5804            | 75                 | 48      | 32           | 18        | 11   | NA              | 27                 | NA      | 3.2           |           |
| PROVE-IT-TIMI 22 | 2004'|               | 200   | 6                | 4162            | 58                 | 78      | 100          | 8         | 18   | 50              | 36.8               | NA      | 2            |           |
| REAL-CAD      | 2008|               | 201   | 6                | 12413           | 68                 | 83      | 100          | 14        | 40   | 75.7            | 16.4               | 24.6    | 3.9           |           |
| SEAS          | 2008|               | 200   | 6                | 1873            | 68                 | 71      | 0            | 0         | 0    | 51.5            | 55                 | 27      | 4.4           |           |
| SHARP         | 2011|               | 201   | 6                | 9270            | 62                 | 62      | 0            | 15        | 23   | 13              | 27                 | 4.9     |               |           |
|                | 200 | 10001 | 61 | 81 | 100 | 15 | 54 | 76 | 28.4 | 4.9 | Atorvastatin (80 mg) | 4995 | 1.7 | 97 | Atorvastatin (10 mg) | 5006 | 1.7 | 98 | NA | 23.3 |
|----------------|-----|-------|----|----|-----|----|----|----|-----|----|---------------------|------|-----|----|---------------------|------|-----|----|-----|-----|
| TNT            | 5   | 6     | 5  | 100| 5   | 15 | 15 | 54 | 76  | 28.4|                      |      |     |    |                      |      |     |    |     |     |
| WOSCO PS       | 199 | 6595  | 55 | 100| 5   | 3  | 1  | 16 | 78  | 4.9 | Pravastatin (40 mg) | 3302 | 2   | 192| Placebo             | 3293 | 2   | 192| NA  | 41.3 |

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.
### Table S2. Study Characteristics of the Included Randomized Trials.

| Trial          | Year | Selected composite endpoint (major adverse cardiovascular events)                                                                 | Reported primary endpoint in original trial                                                                 | Definition of myocardial infarction                                                                                                                                 |
|---------------|------|----------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 4D            | 2005 | Cardiac death, nonfatal myocardial infarction, and stroke                                                                       | Cardiac death, nonfatal myocardial infarction, and stroke                                                   | Two of the following three criteria were met: typical symptoms; elevated 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, myocardial infarction, Stroke, or Hospitalization for acute coronary syndrome                              | Cardiovascular death, myocardial infarction, Stroke, or Hospitalization for acute coronary syndrome          | NA                                                                                                                                                                                                 |
| AFCAPS_TEXCAPS| 1998 | Myocardial infarction, unstable angina, or sudden cardiac death                                                               | Myocardial infarction, unstable angina, or sudden cardiac death                                            | NA                                                                                                                                                                                                 |
| ALERT         | 2003 | Cardiac death, definite or probable non-fatal myocardial infarction, coronary-artery bypass grafting, percutaneous coronary intervention | Cardiac death, definite or probable non-fatal myocardial infarction, coronary-artery bypass grafting, percutaneous coronary intervention | An adjudicated MI was classified as definite if a new Q-wave developed in the presence of abnormal cardiac markers or symptoms, or pathological ST elevations and T-wave changes 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 plus symptoms. |
| ASCOT-LLA     | 2003 | Total cardiovascular events and procedures                                                                                      | Cardiovascular death and non-fatal myocardial infarction                                                  | NA                                                                                                                                                                                                 |
| AURORA        | 2009 | Nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes                                            | Nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes                        | NA                                                                                                                                                                                                 |
| CARDS         | 2004 | Cardiovascular death, myocardial infarction, stroke, unstable angina or revascularization                                    | Cardiovascular death, myocardial infarction, stroke, unstable angina or revascularization                   | NA                                                                                                                                                                                                 |
| Study   | Year | Primary Endpoint                                                                 | Secondary Endpoint                                                                 | Additional Criteria                                                                 |
|---------|------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| CARE    | 1996 | Cardiovascular death or myocardial infarction                                   | Cardiovascular death or myocardial infarction                                     | NA                                                                                  |
| CORONA  | 2007 | Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke        | Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke           | NA                                                                                  |
| HIJ-PROPER | 2017 | All-cause death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, or revascularization | All-cause death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, or revascularization | NA                                                                                  |
| HOPE-3  | 2016 | Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke         | Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke           | EITHER Cardiac Ischemic Symptoms lasting > 20 minutes, determined by 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, myocardial infarction, stroke, or revascularization        | Mortality and fatal or non-fatal vascular events                                    | NA                                                                                  |
| IMPROVE-IT | 2015 | Death from cardiovascular causes, major coronary event, or nonfatal stroke       | Death from cardiovascular causes, major coronary event, or nonfatal stroke          | The presence of either ECG evidence or cardiac marker evidence (post-CABG, both ECG and cardiac marker evidence were required, if the CK-MB was ≥5X ULN to <10X ULN). |
| JUPITER | 2008 | Cardiovascular death, myocardial infarction, stroke, unstable angina, or revascularization | Cardiovascular death, myocardial infarction, stroke, unstable angina, or revascularization | NA                                                                                  |
| LIPID   | 1998 | Cardiovascular death or nonfatal myocardial infarction                           | Cardiovascular death                                                               | The presence of at least two new pathologic Q waves on the 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, spontaneous myocardial infarction                         | Cardiovascular death, spontaneous myocardial infarction                             | A rise in cardiac biomarkers (preferably troponin), with at least 1 |
| Study          | Year | Endpoints                                                                 | Description                                                                                                                                                                                                 |
|---------------|------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PREVEND-IT    | 2004 | Cardiovascular death and hospitalization for cardiovascular morbidity   | At least 2 of 4 of the following, which should include either new Q waves or 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       | 2002 | Coronary heart disease death or non-fatal myocardial infarction or fatal or non-fatal stroke | NA                                                                                                                                                                                                       |
| PROVE-IT-TIMI 22 | 2004 | Death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization, and stroke | The presence of symptoms suggestive of ischemia or infarction, with either electrocardiographic evidence (new Q waves in two or more leads) or cardiac-marker evidence of infarction, according to the standard TIMI and American College of Cardiology definition. |
| REAL-CAD      | 2018 | Cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, or unstable angina requiring emergency | Spontaneous: troponin with at least one value above the 99th percentile of the upper reference limit. Periprocedural PCI: Troponin > 3 times URL or CKMB > 3 times URL |
| Study     | Year | Endpoints                                                                 |
|-----------|------|---------------------------------------------------------------------------|
| SEAS      | 2008 | Cardiovascular death, aortic valve replacement, nonfatal myocardial infarction, hospitalization for unstable angina pectoris, heart failure, coronary-artery bypass grafting, percutaneous coronary intervention, and nonhemorrhagic stroke |
| SHARP     | 2011 | Cardiovascular death, nonfatal myocardial infarction, stroke, or coronary revascularization |
| TNT       | 2005 | Cardiovascular death, nonfatal non-procedure-related myocardial infarction, or resuscitation after cardiac arrest |
| WOSCOPS   | 1995 | Cardiovascular death or nonfatal myocardial 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; CARD5, 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 lowering 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 RELnal 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 diabetes mellitus 18 to 80 years of age who had been receiving maintenance hemodialysis for less than two years. | Levels of fasting serum low-density lipoprotein (LDL) cholesterol of less than 80 mg per deciliter (2.1 mmol per liter) or more than 190 mg per deciliter (4.9 mmol per liter), triglyceride levels greater than 1000 mg per deciliter (11.3 mmol per liter); liver function values more than three times the upper limit of normal or equal to those in patients with symptomatic 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 ages of 21 and 80 years with either non–ST-elevation ACS or ST-elevation MI were eligible for enrollment if they had a total cholesterol level of 250 mg/dL (6.48 mmol/L) or lower. | Patients receiving statin therapy at the time of randomization, if coronary artery bypass graft surgery was planned, or if PCI was planned within the first 2 weeks after enrollment. Patients also were excluded for having an alanine aminotransferase (ALT) level higher than 20% above the upper limit of normal (ULN); for having an increased risk for myopathy due to renal impairment (serum creatinine level 2.0 mg/dL [176.8 µmol/L]) or concomitant therapy with agents known to enhance myopathy risk, such as fibrates, cyclosporine, macrolide antibiotics, azole antifungals, amiodarone, or verapamil; or for having a prior history of nonexerciserelated elevations in creatine kinase level or nontraumatic rhabdomyolysis. |
| AFCAPS_TEXCAPS | 1998 | Men aged 45 to 73 years and postmenopausal women aged 55 to 73 years who met the lipid entrance criteria (TC, 4.65-6.82 mmol/L [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 ≤ 4.52 mmol/L [400 mg/dL]). | Individuals with uncontrolled hypertension, secondary hyperlipidemia, or type 1 or type 2 diabetes mellitus that was either managed with insulin or associated with a glycohemoglobin level of at least 10% (20% above the upper limit of normal), had a body weight of more than 50% greater than the desirable limit for height |
| Study   | Year | Eligible Participants                                                                 | Ineligible Participants                                                                 |
|---------|------|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| 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). |
| Study     | Year | Participants                                                                 | Exclusion Criteria                                                                                                                                 |
|-----------|------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| HOPE-3    | 2016 | Men 55 years of age or older and women 65 years of age or older who had at least one cardiovascular risk factor. | 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 syndrome. 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. |
| Study | Year | Inclusion Criteria | Exclusion Criteria |
|-------|------|--------------------|-------------------|
| 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. |
| 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 liter). | 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 | (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. |
| Study        | Year  | Eligibility                                                                                                                       |
|--------------|-------|-------------------------------------------------------------------------------------------------------------------------------------|
| PREVEND-IT   | 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 |
| PROSPER      | 2002  | Men and women aged 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. |
| 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. |
| REAL-CAD     | 2018  | Men and women 20 to 80 years of age with stable CAD                                                                                |
| SEAS         | 2008  | Men and women between the ages of 45 and 85 years who had asymptomatic, mild-to-moderate aortic valve stenosis, as                  |
| Study   | Year | Criteria                                                                                                     |
|---------|------|--------------------------------------------------------------------------------------------------------------|
| SHARP   | 2011 | Patients aged 40 years and older were eligible to participate if they had chronic kidney disease with more than one previous measurement of serum or plasma creatinine of at least 150 μmol/L (1.7 mg/dL) in men or 130 μmol/L (1.5 mg/dL) in women, whether receiving dialysis or not. Definite history of MI or coronary revascularization procedure; Functioning renal transplant or living donor renal; transplant planned; Less than 2 months since presentation as an acute uremic emergency; Definite history of chronic liver disease or abnormal liver function (ie, ALT N1.5× ULN or, if ALT not available, AST N1.5× ULN) (patients with a history of hepatitis are eligible if these limits are not exceeded); Evidence of active inflammatory muscle disease (eg, dermatomyositis, polymyositis) or CK N3× ULN; Definite previous adverse reaction to a statin or to ezetimibe; Concurrent treatment with a contraindicated drug; Child-bearing potential (ie, 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 years of age who had clinically evident CHD, defined by one or more of the following: previous myocardial infarction, previous or current angina with objective evidence of atherosclerotic CHD, and a history of coronary revascularization. Hypersensitivity to statins; active liver disease or hepatic dysfunction defined as alanine aminotransferase or aspartate aminotransferase >1.5 times the upper limit of normal; women who are pregnant or breastfeeding; patients with nephrotic syndrome; uncontrolled diabetes mellitus; uncontrolled hypothyroidism; uncontrolled hypertension (as defined by the investigator) at the screening visit; a MI, coronary revascularization procedure or severe/unstable angina within 1 month of screening; any planned surgical procedure for the treatment of atherosclerosis; an ejection fraction <30%; 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 clinical trial concurrently or within 30 days before screening. |
| WOSCOPS | 1995 | Males aged 45-64 yr who, 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 |

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 S4. Listing of Potential Sources of Bias.

| Study               | Year | Random sequence generation (selection bias) | Allocatenon 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) | Other bias |
|---------------------|------|--------------------------------------------|------------------------------------------|-------------------------------------------------------------|------------------------------------------------|----------------------------------------|-------------------------------------|------------|
| 4D                  | 2005 | Low risk                                   | Low risk                                 | Low risk                                                    | Low risk                                      | Low risk                               | Low risk                            | High risk  |
| A to Z              | 2004 | Low risk                                   | Unclear risk                             | Low risk                                                    | Low risk                                      | Low risk                               | Low risk                            | High risk  |
| AFCAPS_T EXCAPS     | 1998 | Low risk                                   | Unclear risk                             | Low risk                                                    | Low risk                                      | Low risk                               | Low risk                            | Low risk   |
| ALERT               | 2003 | Low risk                                   | Unclear risk                             | Low risk                                                    | Low risk                                      | Low risk                               | Low risk                            | High risk  |
| ASCOT-LLA           | 2003 | Low risk                                   | Unclear risk                             | Low risk                                                    | Low risk                                      | Low risk                               | Low risk                            | High risk  |
| AURORA              | 2009 | Low risk                                   | Unclear risk                             | Low risk                                                    | Low risk                                      | Low risk                               | Low risk                            | High risk  |
| CARDS               | 2004 | Low risk                                   | Low risk                                 | Low risk                                                    | Low risk                                      | Low risk                               | Low risk                            | High risk  |
| CARE                | 1996 | Low risk                                   | Unclear risk                             | Low risk                                                    | Low risk                                      | Low risk                               | Unclear risk                        | Unclear risk|
| CORONA              | 2007 | Low risk                                   | Low risk                                 | Low risk                                                    | Low risk                                      | Low risk                               | Low risk                            | High risk  |
| HIJ-PROPER          | 2017 | Low risk                                   | Unclear risk                             | High risk                                                   | Low risk                                      | Low risk                               | Low risk                            | Low risk   |
| HOPE-3              | 2016 | Low risk                                   | Unclear risk                             | Low risk                                                    | Low risk                                      | Low risk                               | High risk                            |
| HPS                 | 2002 | Low risk                                   | Low risk                                 | Low risk                                                    | Low risk                                      | Low risk                               | High risk                            |
| IMPROVE-I T         | 2015 | Low risk                                   | Unclear risk                             | Low risk                                                    | Low risk                                      | Low risk                               | High risk                            |
| JUPITER             | 2008 | Unclear risk                               | Low risk                                 | Low risk                                                    | Low risk                                      | Low risk                               | High risk                            |
| LIPID               | 1998 | Low risk                                   | Unclear risk                             | Low risk                                                    | Low risk                                      | Low risk                               | High risk                            |
| Liu, et al          | 2016 | Low risk                                   | Unclear risk                             | Unclear risk                                               | Unclear risk                                 | Low risk                               | Low risk                            |
| PREVEND-IT          | 2004 | Low risk                                   | Low risk                                 | Low risk                                                    | Low risk                                      | Low risk                               | Low risk                            |
| PROSPER             | 2002 | Low risk                                   | Low risk                                 | Low risk                                                    | Unclear risk                                 | Low risk                               | Low risk                            |
| PROVE IT-TIMI 22    | 2004 | Unclear risk                               | Low risk                                 | Low risk                                                    | Low risk                                      | Low risk                               | High risk                            |
| REAL-CAD            | 2018 | Low risk                                   | Unclear risk                             | Unclear risk                                               | Low risk                                      | Low risk                               | Unclear risk                        |
| SEAS                | 2008 | Low risk                                   | Unclear risk                             | Low risk                                                    | Unclear risk                                 | Low risk                               | High risk                            |
| SHARP               | 2011 | Low risk                                   | Low risk                                 | Low risk                                                    | Low risk                                      | Low risk                               | High risk                            |
| Study            | Year | Risk     | Risk     | Risk     | Risk     | Risk     | Risk     | Risk     |
|------------------|------|----------|----------|----------|----------|----------|----------|----------|
| TNT              | 2005 | Low risk | Low risk | Unclear  | Low risk | Low risk | Low risk | Low risk |
| WOSCOPS          | 1995 | Low risk | Unclear  | Low risk | Low risk | Low risk | Low risk | High 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 LOwering 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.

|                          | Baseline CRP ≥ median |   | Baseline CRP < median |   | Overall |
|--------------------------|-----------------------|---|-----------------------|---|---------|
|                          | Trials | Rate Ratio (95% CI) | P value | Trials | Rate Ratio (95% CI) | P value | Trials | Rate Ratio (95% CI) | P value |
| **All-cause mortality**  |         |                   |       |         |                   |       |         |                   |       |
| Trials with HF or requiring hemodialysis excluded | 10 | 0.90 (0.83, 0.97) | 0.007 | 10 | 0.92 (0.85, 0.99) | 0.043 | 20 | 0.91 (0.86, 0.96) | 0.001 |
| Trials with less than 1000 patients excluded | 12 | 0.93 (0.88, 0.98) | 0.004 | 9 | 0.90 (0.83, 0.98) | 0.011 | 21 | 0.91 (0.87, 0.96) | <0.001 |
| Year before 2000 excluded | 13 | 0.93 (0.88, 0.98) | 0.003 | 6 | 0.93 (0.86, 1.01) | 0.099 | 19 | 0.93 (0.89, 0.97) | 0.001 |
| **Cardiovascular mortality** |         |                   |       |         |                   |       |         |                   |       |
| Trials with HF or requiring hemodialysis excluded | 9 | 0.81 (0.72, 0.91) | <0.001 | 11 | 0.85 (0.78, 0.92) | <0.001 | 20 | 0.83 (0.78, 0.90) | <0.001 |
| Trials with less than 1000 patients excluded | 12 | 0.85 (0.78, 0.93) | 0.001 | 9 | 0.81 (0.74, 0.88) | <0.001 | 21 | 0.84 (0.79, 0.90) | <0.001 |
| Year before 2000 excluded | 11 | 0.85 (0.77, 0.94) | 0.001 | 7 | 0.86 (0.77, 0.96) | 0.007 | 18 | 0.86 (0.80, 0.92) | <0.001 |
| **Myocardial infarction**  |         |                   |       |         |                   |       |         |                   |       |
| Trials with HF or requiring hemodialysis excluded | 11 | 0.80 (0.69, 0.88) | <0.001 | 11 | 0.71 (0.67, 0.76) | <0.001 | 22 | 0.74 (0.68, 0.80) | <0.001 |
| Trials with less than 1000 patients excluded | 13 | 0.79 (0.72, 0.88) | <0.001 | 9 | 0.70 (0.65, 0.76) | <0.001 | 22 | 0.75 (0.70, 0.81) | <0.001 |
| Year before 2000 excluded | 13 | 0.80 (0.72, 0.88) | <0.001 | 7 | 0.70 (0.63, 0.79) | <0.001 | 20 | 0.76 (0.70, 0.83) | <0.001 |
| **Stroke**                |         |                   |       |         |                   |       |         |                   |       |
| Trials with HF or requiring hemodialysis excluded | 11 | 0.79 (0.71, 0.88) | <0.001 | 11 | 0.85 (0.77, 0.95) | 0.003 | 22 | 0.82 (0.77, 0.89) | <0.001 |
| Trials with less than 1000 patients excluded | 13 | 0.84 (0.75, 0.93) | 0.001 | 9 | 0.86 (0.77, 0.97) | 0.017 | 22 | 0.85 (0.79, 0.92) | <0.001 |
| Year before 2000 excluded | 13 | 0.84 (0.76, 0.94) | 0.001 | 7 | 0.89 (0.75, 1.06) | 0.188 | 20 | 0.86 (0.78, 0.94) | 0.001 |
|---------------------------|----|-------------------|-------|---|-------------------|-------|---|-------------------|-------|
| **Coronary revascularization** | | | | | | | | | |
| Trials with HF or requiring hemodialysis excluded | 11 | 0.80 (0.73, 0.88) | <0.001 | 10 | 0.77 (0.72, 0.81) | <0.001 | 21 | 0.78 (0.73, 0.83) | <0.001 |
| Trials with less than 1000 patients excluded | 12 | 0.82 (0.75, 0.89) | <0.001 | 9 | 0.75 (0.70, 0.81) | <0.001 | 21 | 0.78 (0.73, 0.84) | <0.001 |
| Year before 2000 excluded | 12 | 0.82 (0.74, 0.90) | <0.001 | 6 | 0.75 (0.68, 0.82) | <0.001 | 18 | 0.79 (0.73, 0.85) | <0.001 |
| **MACE** | | | | | | | | | |
| Trials with HF or requiring hemodialysis excluded | 11 | 0.80 (0.74, 0.87) | <0.001 | 11 | 0.80 (0.76, 0.85) | <0.001 | 22 | 0.81 (0.77, 0.85) | <0.001 |
| Trials with less than 1000 patients excluded | 13 | 0.85 (0.79, 0.90) | <0.001 | 9 | 0.79 (0.74, 0.83) | <0.001 | 22 | 0.82 (0.78, 0.86) | <0.001 |
| Year before 2000 excluded | 13 | 0.85 (0.79, 0.90) | <0.001 | 7 | 0.81 (0.77, 0.87) | <0.001 | 20 | 0.84 (0.80, 0.88) | <0.001 |

CRP, C-reactive protein; MACE, major adverse cardiovascular event.
Table S6. Sensitivity Analysis Stratified for Agent Used in the More-intensive Treatment Group.

| Subgroup                          | 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 |
| Magnitude of reduction in CRP | < median | 9 | 0.79 (0.72, 0.87) | <0.001 | 2 | 0.94 (0.89, 0.99) | 0.010 |
|-----------------------------|----------|---|------------------|--------|---|------------------|------|
| ≥ median                    | 0.81 (0.74, 0.88) | <0.001 | 1 | 0.84 (0.75, 0.95) | 0.004 |
| Total                       | 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.
Table S7. Sensitivity Analysis Stratified for the Type of Treatment in the Less-intensive Group.

| Condition                  | Subgroup                | Active                     | Placebo                    |
|----------------------------|-------------------------|----------------------------|----------------------------|
|                            | Subgroup                | Trials | Rate Ratio (95% CI) | P value | Trials | Rate Ratio (95% CI) | P value |
| 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 | 9 | 0.69 (0.63, 0.75) | <0.001 |
|                            |                         | ≥ median 5 | 0.89 (0.82, 0.97) | 0.001 | 8 | 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 |
| Magnitude of reduction in CRP |  $\geq$ median | 5 | 0.89 (0.83, 0.96) | 0.001 | 9 | 0.82 (0.75, 0.90) | $<$ 0.001 |
|-----------------------------|-----------------|---|-------------------|-------|---|-------------------|------------|
| $<$ median                  | 3               | 0.89 (0.82, 0.98) | 0.016 | 4   | 0.79 (0.67, 0.93) | 0.004 |
| $\geq$ 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.
| Subgroup                        | Trials | Rate Ratio (95% CI) | P value | Trials | Rate Ratio (95% CI) | P value |
|--------------------------------|--------|---------------------|---------|--------|---------------------|---------|
| **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  |
| Magnitude of reduction in CRP | ≥ median | 3 | 0.68 (0.52, 0.90) | 0.007 | 7 | 0.89 (0.84, 0.94) | <0.001 |
|-----------------------------|----------|---|-------------------|-------|---|-------------------|------|
|                             | < 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.

| Outcomes                  | No. of Trials | log(Baseline CRP) | Magnitude of reduction in CRP | Achieved 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 |
|---------------------------|---------------|-------------------|-------------------------------|--------------|---------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| 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/L Reduction in log(baseline CRP Concentration), Magnitude of Reduction in CRP Concentration, and Mortality and Cardiovascular Outcomes in Secondary Prevention Trials*.

| Outcomes                        | No. of Trials | log(Baseline CRP) | Magnitude of Reduction in CRP | log(Baseline 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/L Reduction in log(baseline CRP Concentration), Magnitude of Reduction in CRP Concentration, and Mortality and Cardiovascular Outcomes in Primary Prevention Trials*

| Outcomes                                | No. of Trials | log(Baseline CRP) | Magnitude of Reduction in CRP | log(Baseline CRP) Adjusted for Magnitude of 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.

Records identified through database searching (n=29086)
- Embase: 17512
- Pubmed: 8002
- Cochrane library: 3932

Records excluded as duplicate publications (n=17124)

Records screened after duplicates removed (n=11962)

Records excluded as not relevant (n=5082)

Records screened (n=6880)

- Not a randomized controlled trial (n=5113)
- Not a cardiovascular outcomes trial (n=1707)

60 Full-text articles assessed for eligibility

12 Not reporting data on CRP
12 Fewer than 40 clinical events
7 Trial duration < 6 months
5 head-to-head comparisons

Studies included in the meta-analysis (n=24)

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.

| Study and Subgroup | Rate Ratio (95% CI) | More Intensive LDL-C Lowering | Less Intensive LDL-C Lowering | Weight % |
|--------------------|---------------------|-------------------------------|-----------------------------|----------|
| 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                      | 600/1384                    | 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                      | 750/2497                    | 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) | 0.92 (0.87, 0.98) | 5032/38248 | 5366/38107 | 66.45 |
| Subtotal effect: z = 2.75, p = 0.006 |          |                               |                             |          |
| 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)   | 105/444                       | 100/929                     | 2.97     |
| Subtotal (I-squared = 67.1%, p = 0.010) | 0.89 (0.79, 1.00) | 2209/26291 | 2431/26255 | 33.55 |
| Subtotal effect: z = 1.93, p = 0.053 |          |                               |                             |          |
| Overall (I-squared = 54.0%, p = 0.007) | 0.91 (0.86, 0.96) | 7241/54639 | 7797/64362 | 100.00 |
| Overall effect: z = 3.57, p < 0.001 |          |                               |                             |          |

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 Iowing 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.
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.

| Study and Subgroup                        | Rate Ratio (95% CI) | No. of Patients With Event/Total No. | More Intensive LDL-C Lowering | Less Intensive LDL-C Lowering | Weight % |
|------------------------------------------|---------------------|-------------------------------------|------------------------------|------------------------------|----------|
| **CRP reduction ≥ median**               |                     |                                     |                              |                              |          |
| 4D (2005)                                | 0.82 (0.68, 0.96)   | 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 (1995)                              | 0.81 (0.62, 1.05)   | 96/2081                             | 119/2076                      | 5.05                         |          |
| CORONA (2007)                            | 1.00 (0.88, 1.12)   | 489/2514                            | 487/2497                      | 9.97                         |          |
| HOPE-3 (2016)                            | 0.90 (0.72, 1.12)   | 154/6381                            | 171/6344                      | 6.41                         |          |
| HPS (2002)                               | 0.83 (0.76, 0.92)   | 761/10269                           | 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)   | 361/4650                            | 378/4620                      | 1.71                         |          |
| SHARP (2011)                             | 0.92 (0.80, 1.07)   | 2537/40329                          | 2890/40185                    | 66.66                        |          |
| **Subtotal (I-squared = 64.0%, p = 0.003)** |                     |                                     |                              |                              |          |
| **CRP reduction < median**               |                     |                                     |                              |                              |          |
| A to Z (2004)                            | 0.75 (0.57, 1.00)   | 83/2265                             | 109/2232                      | 4.72                         |          |
| AFCAPS_TEXCAPS (1998)                    | 0.66 (0.37, 1.26)   | 17/3304                             | 25/3301                       | 1.38                         |          |
| IMPROVE-IT (2015)                        | 1.00 (0.89, 1.13)   | 53/9067                            | 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)   | 86/619                             | 112/6214                      | 4.76                         |          |
| SEAS (2008)                              | 0.83 (0.56, 1.21)   | 97/1944                            | 56/929                        | 3.03                         |          |
| **Subtotal (I-squared = 45.4%, p = 0.085)** |                     |                                     |                              |                              |          |
| **Overall (I-squared = 55.6%, p = 0.003)** |                     |                                     |                              |                              |          |

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 lowering 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.
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.

| Study and Subgroup | Rate Ratio (95% CI) | More Intensive LDL-C Lowering | Less Intensive LDL-C Lowering | Weight % |
|--------------------|---------------------|-----------------------------|-----------------------------|----------|
| CRP reduction ≥ median |                     |                             |                             |          |
| 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 lowering 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. | 0.84 (0.67, 1.07) | 124/636 | 143/619 | 6.59 |
| AURORA (2009) | 0.85 (0.64, 1.12) | 91/1369 | 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 | 207/2075 | 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 | 574/10257 | 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) | 0.74 (0.65, 0.85) | 1308/40329 | 1753/40185 | 61.27 |
| Subtotal effect: z = 4.50, p < 0.001 | | | | |
| 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 | 1110/9077 | 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 (2003) | 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 |
| Subtotal effect: z = 3.75, p < 0.001 | | | | |
| Overall (I-squared = 64.9%, p = 0.000) | 0.75 (0.68, 0.82) | 2896/67053 | 3707/66871 | 100.00 |
| Overall effect: z = 6.02, p < 0.001 | | | | |
| p = 0.07 for interaction (≥ median vs. < median) | | | | |

Favors More Intensive LDL-C Lowering | Favors Less Intensive LDL-C Lowering
0.2 | 1 | 2 |
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.

| Study and Subgroup | Rate Ratio (95% CI) | No. of Patients With Event/Total No. | More Intensive LDL-C Lowering | Less Intensive LDL-C Lowering | Weight % |
|--------------------|--------------------|-------------------------------------|-------------------------------|-------------------------------|-----------|
| Baseline CRP ≥ median |                    |                                     |                               |                               |           |
| 4D (2004)          | 1.06 (0.78, 1.46)  | 64/636                              | 76/619                        |                               | 4.33      |
| A to Z (2004)      | 0.78 (0.48, 1.29)  | 28/2265                             | 35/2232                       |                               | 2.05      |
| AIRUORA (2009)     | 1.17 (0.78, 1.74)  | 53/389                              | 45/364                        |                               | 2.98      |
| CARDs (2004)       | 0.53 (0.31, 0.90)  | 21/1429                             | 39/1422                       |                               | 1.83      |
| CARE (1996)        | 0.60 (0.46, 0.78)  | 54/2081                             | 78/2076                       |                               | 3.67      |
| CORONA (2007)      | 0.66 (0.64, 1.13)  | 60/2514                             | 104/2457                      |                               | 4.93      |
| HIJ-PROPER (2017)  | 0.99 (0.48, 1.91)  | 17/864                              | 18/857                        |                               | 1.22      |
| HPS (2002)         | 0.76 (0.67, 0.86)  | 44/10269                            | 585/10267                     |                               | 10.72     |
| IMPROVE-I (2015)   | 0.86 (0.74, 1.00)  | 296/5607                            | 345/5077                      |                               | 9.21      |
| JUPITER (2006)     | 0.52 (0.34, 0.79)  | 32/8001                             | 64/9001                       |                               | 2.71      |
| Liu et al (2010)   | 0.65 (0.36, 1.11)  | 21/460                              | 32/696                        |                               | 1.80      |
| PROSPER (2002)     | 1.04 (0.82, 1.32)  | 125/2891                            | 131/2913                      |                               | 6.06      |
| PROVE IT-TIMI 22 (2004) | 0.98 (0.84, 1.18) | 21/699                              | 21/696                        |                               | 1.45      |
| SHARP (2011)       | 0.83 (0.68, 1.01)  | 176/4650                            | 211/4620                      |                               | 7.38      |
| **Subtotal**       | **0.63 (0.75, 0.52)** | **1472/45455**                       | **1784/49318**                |                               | **60.34** |

Subtotal effect: z = 3.55, p = 0.001

| Baseline CRP < median | Rate Ratio (95% CI) | No. of Patients With Event/Total No. | More Intensive LDL-C Lowering | Less Intensive LDL-C Lowering | Weight % |
|-----------------------|--------------------|-------------------------------------|-------------------------------|-------------------------------|-----------|
| AFCAPS-TexCAPS (1996) | 0.62 (0.41, 1.67)  | 14/3304                             | 17/3301                       |                               | 1.08      |
| ALERT (2003)          | 1.02 (0.77, 1.36)  | 93/1650                             | 91/1652                       |                               | 4.79      |
| ASCOT-LLA (2003)      | 0.73 (0.56, 0.96)  | 86/1668                             | 121/1517                      |                               | 5.12      |
| HOPE-3 (2016)         | 0.71 (0.52, 0.92)  | 70/1661                             | 59/1544                       |                               | 4.39      |
| LIPID (1998)          | 0.66 (0.57, 0.79)  | 164/4512                            | 204/4562                      |                               | 7.23      |
| PREVEND-IT (2004)    | 1.74 (0.51, 6.94)  | 74/333                              | 44/331                        |                               | 0.38      |
| REAL-CAD (2019)       | 1.13 (0.87, 1.45)  | 127/610                             | 113/6214                      |                               | 6.56      |
| SEAS (2009)           | 1.12 (0.66, 1.84)  | 53/444                              | 20/689                        |                               | 2.54      |
| TNT (2005)            | 0.76 (0.60, 0.96)  | 117/4955                            | 155/5000                      |                               | 6.63      |
| WOSCAPS (1995)       | 0.80 (0.60, 1.04)  | 46/338                              | 51/3253                       |                               | 2.95      |
| **Subtotal**          | **0.67 (0.77, 0.58)** | **765/56268**                       | **884/56269**                 |                               | **39.66** |

Subtotal effect: z = 2.23, p = 0.024

Overall (l-squared = 33.0%, p = 0.001) | Rate Ratio (95% CI) | No. of Patients With Event/Total No. | More Intensive LDL-C Lowering | Less Intensive LDL-C Lowering | Weight % |
|--------------------------------------|--------------------|-------------------------------------|-------------------------------|-------------------------------|-----------|
| Overall                              | 0.65 (0.76, 0.51)  | 2237/85723                           | 2268/85527                    |                               | 100.00    |

Overall effect: z = 4.28, p < 0.001

p = 0.56 for interaction (≥ median vs. < median)

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 lOWering with Pitavastatin and Ezetimibe in acute coRonary syndrome trial; HOPE-3, Heart Outcomes Prevention Evaluation; HPS, Heart Protection Study; IMPROVE-I, 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.
Figure S12. Meta-analysis of Stroke Stratified by Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.

| Study and Subgroup | Rate Ratio (95% CI) | More Intensive LDL-C Lowering | Less Intensive LDL-C Lowering | Weight % |
|--------------------|---------------------|------------------------------|------------------------------|----------|
| 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) | 0.78 (0.67, 0.86) | 444/10269 | 585/10267 | 13.84 |
| JUPITER (2008) | 0.52 (0.34, 0.78) | 33/8501 | 64/8901 | 3.98 |
| PROVE IT-TIMI 22 (2004) | 0.98 (0.54, 1.60) | 21/2099 | 21/2063 | 2.17 |
| SHARP (2011) | 0.83 (0.68, 1.01) | 176/4650 | 211/4620 | 10.03 |
| Subtotal (I-squared = 44.6%, 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 | 35/2322 | 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) | 296/5067 | 345/5077 | 12.17 |
| LIPID (1989) | 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) | 127/6159 | 113/6214 | 7.89 |
| SEAS (2006) | 1.12 (0.68, 1.84) | 33/944 | 29/929 | 3.02 |
| Subtotal (I-squared = 4.0%, p = 0.396) | 0.90 (0.81, 1.01) | 674/26724 | 747/26866 | 38.19 |
| Subtotal effect: z = 1.81, p < 0.070 |
| Overall (I-squared = 35.6%, p = 0.047) | 0.84 (0.76, 0.92) | 1719/67053 | 2069/66671 | 100.00 |
| Overall effect: z = 3.60, p < 0.001 |

p = 0.13 for interaction (≥ median vs. < median)

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.
Figure S13. Meta-regression Analysis of Coronary Revascularization Rate Ratio Plotted Against log(baseline CRP Concentrations) in the More Intensive Group.

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.

| Study and Subgroup | Rate Ratio (95% CI) | No. of Patients With Event/Total No. | Weight |
|--------------------|---------------------|-------------------------------------|--------|
| 4D (2005)          | 0.74 (0.52, 1.05)   | 55/636                              | 72/619 | 2.51 |
| A to Z (2004)      | 0.95 (0.74, 1.21)   | 119/2286                           | 124/2232 | 3.96 |
| AURORA (2009)      | 0.97 (0.76, 1.21)   | 148/1380                           | 152/1394 | 4.46 |
| CARDOS (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 | 8.34 |
| 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                          | 726/10267 | 7.42 |
| IMPROVE-IT (2015)  | 0.94 (0.88, 1.01)   | 1650/9067                          | 1793/9077 | 9.72 |
| JUPITER (2008)     | 0.52 (0.44, 0.77)   | 76/8001                            | 131/8001 | 3.39 |
| Liu et al (2016)   | 0.57 (0.31, 1.03)   | 10/400                             | 20/398 | 1.04 |
| PROSPER (2002)     | 0.82 (0.54, 1.25)   | 38/2891                            | 48/2913 | 1.88 |
| PROVE IT-TIMI 22 (2004) | 0.87 (0.75, 1.00) | 342/2098                           | 368/2063 | 5.63 |
| SHARP (2011)       | 0.80 (0.69, 0.94)   | 284/4850                           | 352/4620 | 6.16 |
| **Subtotal**       | 0.81 (0.74, 0.89)   | 3825/49041                         | 4495/46821 | 59.52 |
| **Overall**        | 0.79 (0.73, 0.83)   | 6608/92776                         | 7338/82569 | 100.00 |

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; CARDOS, 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 LOwering 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; PREVENT 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.
| Study and Subgroup                  | Rate Ratio (95% CI) | More Intensive LDL-C Lowering | Less Intensive LDL-C Lowering | Weight |
|------------------------------------|---------------------|-------------------------------|-------------------------------|--------|
| **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)   | 56/636                        | 82/634                        | 3.54   |
| HPS (2002)                         | 0.71 (0.63, 0.79)   | 513/10266                     | 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)                       | 0.90 (0.69, 0.94)   | 284/4650                      | 352/4620                      | 8.11   |
| **Subtotal (β-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)   | 1600/9087                     | 1703/9077                     | 11.28  |
| LIPID (1995)                       | 0.92 (0.74, 0.92)   | 555/4512                      | 700/4502                      | 9.84   |
| REAL-CAD (2018)                    | 0.85 (0.76, 0.95)   | 525/619                       | 625/614                       | 9.51   |
| SEAS (2008)                        | 0.95 (0.49, 0.86)   | 77/644                        | 117/629                       | 4.50   |
| **Subtotal (β-squared = 67.7%, p = 0.008)** | 0.83 (0.75, 0.92)   | 3106/26292                    | 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 |

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 lowering 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.
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.

| Study and Subgroup | Rate Ratio (55% CI) | No. of Patients With Event/Total No. | Weight % |
|--------------------|---------------------|--------------------------------------|----------|
| **Baseline CRP ≥ median** |                     |                                      |          |
| 4D (2006)          | 0.91 (0.78, 1.06)   | 264/635                              | 4.22     |
| A to Z (2004)      | 0.89 (0.77, 1.03)   | 309/2285                              | 4.39     |
| AURORA (2009)      | 0.97 (0.85, 1.10)   | 356/1339                              | 4.77     |
| CARDs (2004)       | 0.65 (0.48, 0.85)   | 83/1429                               | 2.22     |
| CARE (1998)        | 0.77 (0.65, 0.92)   | 212/2081                              | 3.74     |
| CORONA (2007)      | 0.94 (0.85, 1.04)   | 582/2514                              | 5.67     |
| HIJ-FRUPER (2017)  | 0.89 (0.76, 1.04)   | 263/664                               | 4.27     |
| HPS (2002)         | 0.79 (0.74, 0.83)   | 2003/10269                            | 6.70     |
| IMPROVE-IT (2016)  | 0.94 (0.86, 0.99)   | 2572/2907                             | 6.79     |
| JUPITER (2006)     | 0.57 (0.46, 0.69)   | 142/6901                              | 3.21     |
| Liu, et al (2016)  | 0.62 (0.42, 0.93)   | 35/400                                | 1.25     |
| PROSPER (2002)     | 0.87 (0.76, 0.99)   | 408/2891                              | 4.66     |
| PROVE-IT TIMI 22 (2004) | 0.85 (0.76, 0.96) | 470/2099 | 5.21 |
| SHARP (2011)       | 0.84 (0.75, 0.95)   | 526/4630                              | 5.24     |
| **Subtotal (I-squared = 74.3%, p = 0.000)** | 0.84 (0.75, 0.95) | 5455/493455 | 62.53 |
| Subtotal effect: z = 5.26, p < 0.001 |

| **Baseline CRP < median** |                     |                                      |          |
| AFCAPS-TEXCAPS (1968) | 0.63 (0.50, 0.80)   | 116/3304                              | 2.77     |
| ALERT (2003)          | 0.79 (0.63, 0.98)   | 137/1050                              | 2.93     |
| ASCOT-LLA (2003)      | 0.83 (0.70, 0.91)   | 389/5158                              | 4.60     |
| HOPE-3 (2019)         | 0.77 (0.65, 0.91)   | 235/6301                              | 3.90     |
| LIPID (1969)          | 0.79 (0.70, 0.87)   | 357/4512                              | 5.59     |
| PREVEND-IT (2004)    | 0.87 (0.45, 1.58)   | 21/433                                | 0.56     |
| REAL-CAD (2019)       | 0.80 (0.68, 0.94)   | 266/6190                              | 4.11     |
| SEAS (2008)           | 0.92 (0.80, 1.07)   | 323/644                               | 4.51     |
| TNT (2005)            | 0.79 (0.70, 0.90)   | 434/4995                              | 4.58     |
| WOSCOPS (1995)        | 0.73 (0.58, 0.89)   | 114/3022                              | 3.44     |
| **Subtotal (I-squared = 8.9%, p = 0.369)** | 0.79 (0.75, 0.83) | 2662/36268 | 37.47 |
| Subtotal effect: z = 6.74, p < 0.001 |
| **Overall (I-squared = 67.7%, p = 0.006)** | 0.82 (0.78, 0.86) | 11117/85723 | 109.00 |
| Overall effect: z = 8.60, p < 0.001 |

$p = 0.18$ for interaction ($≥$ median vs. < median)

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.
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 (95% CI) More Intensive LDL-C Lowering | Less Intensive LDL-C Lowering | Weight % |
|--------------------|-----------------------------------------------|-------------------------------|----------|
| CRP reduction ≥ median |                                           |                               |          |
| 4D (2005)          | 0.91 (0.78, 1.06)                              | 294/636                       | 315/619  | 5.92    |
| 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    |
| CARE (1996)        | 0.77 (0.65, 0.92)                              | 212/2081                      | 274/2078 | 5.23    |
| CORONA (2007)      | 0.94 (0.85, 1.04)                              | 692/2514                      | 732/2487 | 7.56    |
| HOPE-3 (2016)      | 0.77 (0.65, 0.91)                              | 235/6361                      | 304/6344 | 5.43    |
| HPS (2002)         | 0.79 (0.74, 0.83)                              | 2033/10269                    | 2585/10267 | 8.71 |
| JUPITER (2008)     | 0.57 (0.46, 0.69)                              | 142/6901                      | 251/6901 | 4.55    |
| PROVE IT-TIMI 22 (2004) | 0.85 (0.78, 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

| CRP reduction < median | Rate Ratio (95% CI) More Intensive LDL-C Lowering | Less Intensive LDL-C Lowering | Weight % |
|-----------------------|-----------------------------------------------|-------------------------------|----------|
| 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 | 3.96    |
| 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)                              | 21433                         | 24431    | 0.96    |
| REAL-CAD (2018)       | 0.80 (0.68, 0.94)                              | 266/199                       | 334/214  | 5.70    |
| SEAS (2008)           | 0.92 (0.80, 1.07)                              | 333/644                       | 355/529  | 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

Overall (I-squared = 74.1%, p = 0.000) | 0.82 (0.78, 0.88) | 9257/67063 | 10854/66871 | 100.00 |

Overall effect: z = 6.22, p < 0.001
p = 0.63 for interaction (≥ median vs. < median)

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; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; HIJ-PROPER, the Heart Institute of Japan PRoper level of lipid LOwering 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; LIPIID, 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.
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.

| Study and Subgroup          | Rate Ratio (95% CI) | No. of Patients With Event/Total No. | More Intensive LDL-C Lowering | Less Intensive LDL-C Lowering | Weight % |
|-----------------------------|---------------------|-------------------------------------|------------------------------|------------------------------|----------|
| 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 (1995)                | 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 (I² = 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)   | 46/2069                             | 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)   | 105/644                             | 100/929                      |                              | 3.99     |
| **Subtotal (I² = 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 (I² = 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) |                     |                                     |                              |                              |          |

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

| Study and Subgroup | Rate Ratio (95% CI) | No. of Patients With Event/Total No. | Weight % |
|--------------------|---------------------|-------------------------------------|----------|
| Achieved CRP ≥ median |                     |                                     |          |
| 4D (2005)          | 0.82 (0.68, 0.98)   | 202/636                             | 241/619  | 9.03 |
| AURORA (2009)      | 1.00 (0.96, 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)   | 83/6901                             | 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                            | 389/4620 | 10.53|
| Subtotal (I²=74.4%, p = 0.000) |                  | 1910/26112                          | 2166/26013 | 67.43 |

Subtotal effect: z = 2.88, p = 0.004

| Achieved CRP < median |                     |                                     |          |
|-----------------------|---------------------|-------------------------------------|----------|
| A to Z (2004)         | 0.75 (0.57, 1.00)   | 83/2265                             | 109/2232 | 6.11 |
| AFCAPS_TEXCAPS (1998) | 0.68 (0.37, 1.26)   | 17/3304                             | 25/3301  | 1.97 |
| IMPROVE-IT (2015)     | 1.00 (0.89, 1.13)   | 537/9067                            | 538/9077 | 11.36|
| PREVEND-IT (2004)     | 1.00 (0.25, 3.97)   | 44/33                               | 4/431    | 4.44 |
| 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)   | 86/1999                             | 112/6214 | 6.16 |
| SEAS (2008)           | 0.83 (0.56, 1.21)   | 47/944                              | 56/929   | 4.12 |
| Subtotal (I²=13.9%, p = 0.324) |                  | 797/24311                           | 873/24247 | 32.57 |

Subtotal effect: z = 2.10, p = 0.036

Overall (I²=59.9%, p = 0.002) | 0.84 (0.76, 0.92) | 2707/50423                          | 3059/60260 | 100.00 |

Overall effect: z = 3.75, p < 0.001
p = 0.52 for interaction (≥ median vs. < median)

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

| Study and Subgroup | Rate Ratio (95% CI) | No. of Patients With Event/Total No. | Weight % |
|--------------------|---------------------|-------------------------------------|----------|
| Achieved CRP ≥ median |                      |                                     |          |
| 4D (2005)           | 0.84 (0.67, 1.07)   | 124/636                             | 43/619   | 7.52     |
| AURORA (2009)       | 0.85 (0.64, 1.12)   | 91/1389                             | 107/1384 | 6.41     |
| CARDOS (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 | Rate Ratio (95% CI) | No. of Patients With Event/Total No. | Weight % |
|-----------------------|---------------------|-------------------------------------|----------|
| 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                            | 1119/9077| 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)   | 22/644                              | 36/629   | 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) | Rate Ratio (95% CI) | No. of Patients With Event/Total No. | Weight % |
|----------------------------------------|---------------------|-------------------------------------|----------|
| 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) |

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; AURORA, An Assessment of Survival and Cardiovascular Events; CARDOS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol And Recurrent Events; CORON, the Controlled Rosuvastatin Multinational Trial in Heart Failure; 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; 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.
Figure S25. Meta-analysis of Stroke Stratified by the Achieved CRP Concentrations.

| Study and Subgroup | Rate Ratio (95% CI) | No. of Patients With Event/Total No. | Weight % |
|--------------------|---------------------|-------------------------------------|----------|
| Achieved CRP ≥ median |                     |                                     |          |
| 4D (2005)          | 1.08 (0.79, 1.46)   | 84/638                             | 76/619   | 7.80  |
| AURORA (2009)      | 1.17 (0.79, 1.74)   | 53/139                              | 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                             | 78/2076  | 6.72  |
| CORONA (2007)      | 0.85 (0.64, 1.13)   | 89/2514                             | 104/2497 | 8.74  |
| JUPITER (2008)     | 0.52 (0.34, 0.78)   | 33/8001                             | 64/8001  | 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)   | 28/2285                             | 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)   | 206/9067                            | 345/9077 | 14.78 |
| PREVEND-IT (2004)     | 1.74 (0.51, 5.94)   | 7/433                               | 4/431    | 0.75  |
| PROVE-IT TIMI 22 (2004)| 0.96 (0.54, 1.60)   | 21/2099                            | 21/2063  | 2.81  |
| REAL-CAD (2018)       | 1.13 (0.87, 1.45)   | 127/1699                           | 113/1624 | 9.84  |
| SEAS (2008)           | 1.12 (0.68, 1.84)   | 33/944                              | 29/929   | 3.89  |
| Subtotal (I-squared = 0.0%, p = 0.501) | 0.93 (0.83, 1.05)   | 526/24311                           | 564/24247 | 38.11 |
| Subtotal effect: z = 1.18, p = 0.230 |

| Overall (I-squared = 36.7%, p = 0.077) | 0.87 (0.76, 0.97)   | 1205/50423                          | 1385/50260 | 100.00 |
| Overall effect: z = 2.56, p = 0.010 |

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

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

Study and Subgroup | Rate Ratio (95% CI) | No. of Patients With Event/Total No. | More Intensive LDL-C Lowering | Less Intensive LDL-C Lowering | Weight %
--- | --- | --- | --- | --- | ---
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 (1999) | 0.75 (0.65, 0.87) | 294/2081 | 391/2076 | 9.70
JUPITER (2005) | 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) | 284/4850 | 352/4626 | 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 | 4.65
Subtotal (I-squared = 63.9%, p = 0.017) | 0.84 (0.76, 0.94) | 2863/23878 | 3265/23816 | 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)

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

| Study and Subgroup | Rate Ratio (95% CI) | No. of Patients With Event/Total No. | More Intensive LDL-C Lowering | Less Intensive LDL-C Lowering | Weight % |
|--------------------|---------------------|-------------------------------------|-----------------------------|-------------------------------|----------|
| **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) | 395/1389 | 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) | 0.81 (0.73, 0.90) | 2902/26112 | 3441/26013 | | 54.97 |
| Subtotal effect: z = 3.89, p < 0.001 | | | | | |
| **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) | 118/3304 | 183/3301 | | 4.71 |
| IMPROVE-IT (2015) | 0.94 (0.89, 0.99) | 2572/9067 | 2742/9077 | | 10.07 |
| PREVENT-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) | 268/6199 | 334/6214 | | 6.67 |
| SEAS (2008) | 0.92 (0.80, 1.07) | 333/844 | 355/829 | | 7.21 |
| Subtotal (I-squared = 58.9%, p = 0.024) | 0.86 (0.79, 0.93) | 4087/24311 | 4524/24247 | | 45.03 |
| Subtotal effect: z = 3.55, p < 0.001 | | | | | |
| **Overall (I-squared = 71.9%, p = 0.000)** | 0.83 (0.78, 0.89) | 6989/50423 | 7965/50260 | | 100.00 |
| Overall effect: z = 5.39, p < 0.001 | | | | | |
| p = 0.39 for interaction (≥ median vs. < median) | | | | | |

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; 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; 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; 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.