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.
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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, stains and ezetimibe) prove to reduce hsCRP independently of LDL-C reduction.[6] However, it is inconclusive whether benefits from LDL-C lowering are associated with baseline CRP concentrations. Larger 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

From the Department of Cardiology, Affiliated Drum Tower Hospital, Nanjing University School of Medicine, Nanjing, China (X.-L.Z., R.-F.L., W.X., L.W., L.-N.K., B.X.); Department of Endocrinology, Affiliated Drum Tower Hospital, Nanjing University School of Medicine, Nanjing, China (X.-W.Z.).

Accompanying Data S1, Tables S1 through S11, and Figure S1 through S27 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012428

*Dr Zhang and Dr Lan contributed equally to this work.

Correspondence to: Biao Xu and Wei Xu, Department of Cardiology, Affiliated Drum Tower Hospital, Nanjing University School of Medicine, 321 Zhongshan Rd, 210008 Nanjing, China. E-mails: xubiao62@nju.edu.cn, 13390900868@163.com

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Clinical Perspective

What Is New?

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

What Are the Clinical Implications?

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

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

Methods

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

Data Sources and Searches

We searched PubMed, EMBASE, and the Cochrane Library from their inception through July 2, 2018. The following keywords were used: lipid lowering, statin, ezetimibe, 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,[10] which assessing random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias. Consensus was achieved through referral to a third investigator (L.W.) in case of disagreement.

Data Synthesis and Statistical Analysis

To investigate the association between baseline CRP concentrations and risks of mortality and cardiovascular outcomes with more-intensive LDL-C lowering, random-effects 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

trials. We also performed sensitivity analyses based on different study populations (primary or secondary prevention trials). To account for the variability in the length of follow-up for each of these trials, we used rate ratios (RRs) with their corresponding 95% CIs adjusted for patient-years as the statistic estimate.

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

Results

Study Selection and Characteristics

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

Risk of Bias in the Included Trials

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

All-Cause Mortality

There were 8355 deaths among 83 209 patients randomly assigned to receive more-intensive LDL-C–lowering treatment and 8989 deaths among 83 018 patients assigned to less-intensive LDL-C–lowering treatment. Metaregression analysis showed that all-cause mortality risk was not significantly different for each 1-mg/L higher log-transformed baseline CRP concentration between more- versus less-intensive LDL-C–lowering treatments (RR, 0.98; 95% 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).

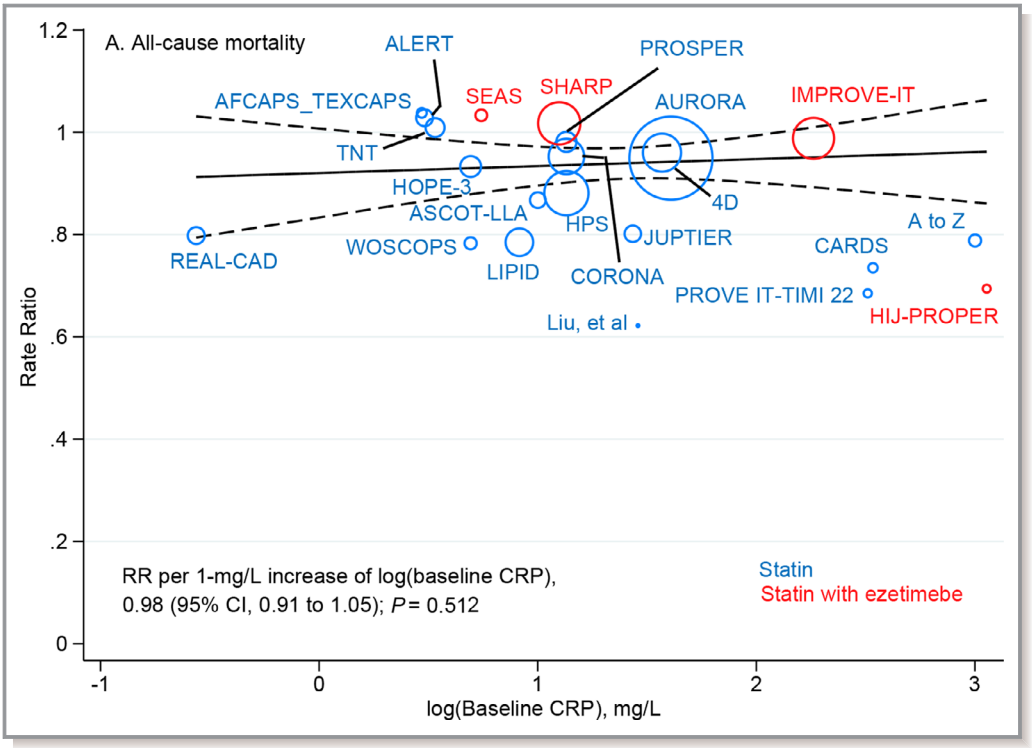

Figure 1. Meta-regression analysis of all-cause mortality rate ratios plotted against log-transformed baseline CRP concentrations in the more-intensive group. The size of the data marker is proportional to the weight in the metaregression. CRP indicates C-reactive protein; RR, rate ratio.

Stroke

Metaregression analysis showed that stroke risk was not significantly different for each 1-mg/L higher log-transformed baseline CRP concentration between more- versus less-intensive LDL-C–lowering treatments (RR, 0.94; 95% 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)			
			log(Baseline CRP) Adjusted for Magnitude of Reduction in CRP	log(Baseline CRP) Adjusted for Magnitude of Reduction in CRP, Baseline LDL-C, Magnitude of Reduction in LDL-C and Age	Magnitude of Reduction in CRP	Achieved CRP
All-cause mortality	22	0.98 (0.91, 1.05)	1.00 (0.92, 1.10)	1.01 (0.90, 1.13)	0.98 (0.91, 1.06)	1.00 (0.96, 1.03)
Cardiovascular mortality	22	1.01 (0.91, 1.12)	1.02 (0.89, 1.16)	1.03 (0.89, 1.19)	0.97 (0.87, 1.08)	1.00 (0.94, 1.05)
Myocardial infarction	24	1.12 (1.04, 1.22)	1.16 (1.05, 1.27)	1.16 (1.02, 1.33)	0.93 (0.84, 1.04)	0.98 (0.93, 1.04)
Stroke	24	0.94 (0.84, 1.05)	0.96 (0.84, 1.09)	0.96 (0.81, 1.13)	0.90 (0.80, 1.01)	0.97 (0.91, 1.03)
Coronary revascularization	22	1.06 (1.00, 1.13)	1.07 (0.99, 1.15)	1.05 (0.96, 1.14)	0.94 (0.84, 1.04)	0.99 (0.94, 1.04)
MACE	24	1.04 (0.98, 1.11)	1.05 (0.96, 1.15)	1.08 (0.97, 1.19)	0.96 (0.89, 1.03)	0.99 (0.95, 1.03)

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

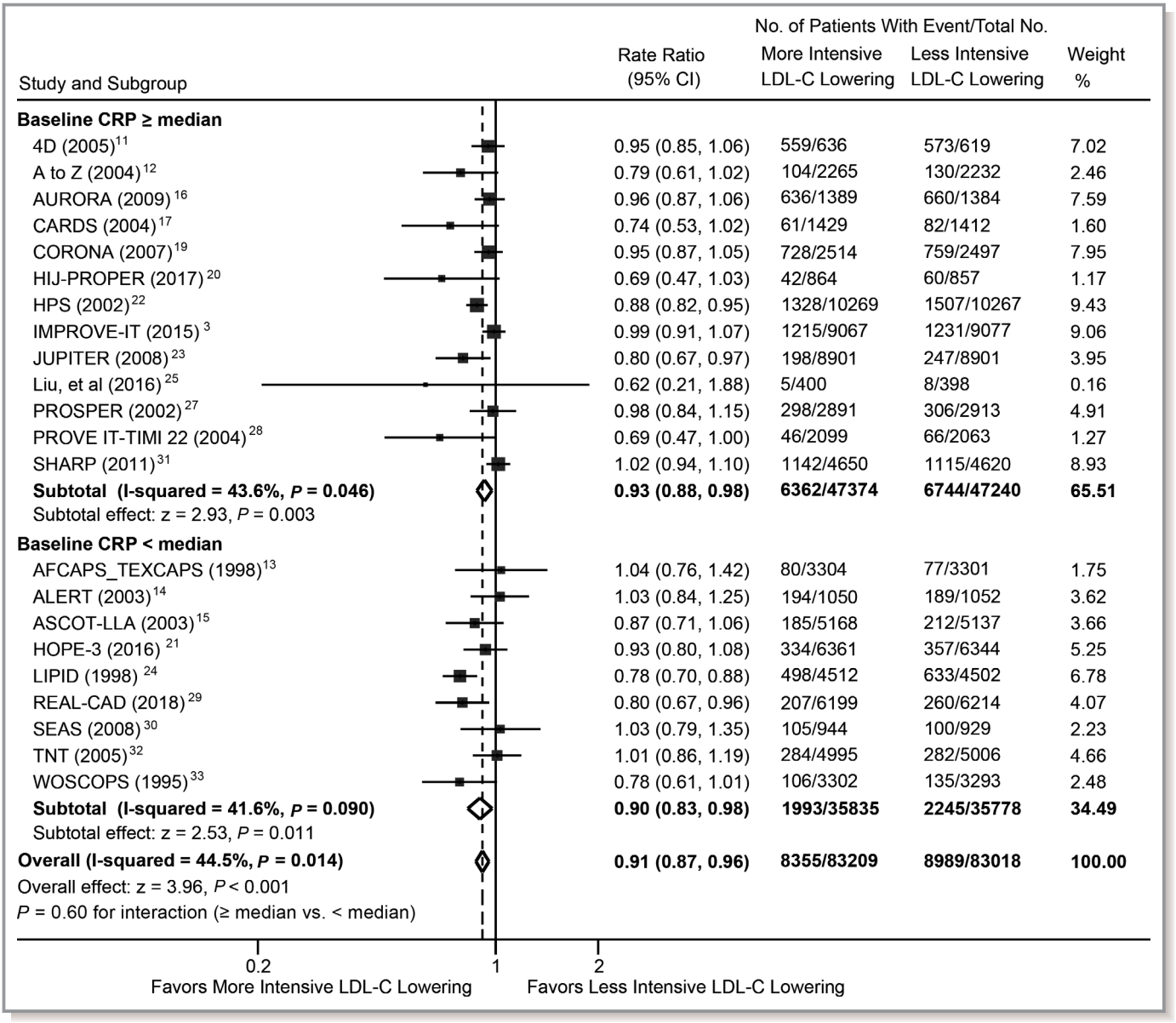

Figure 2. Meta-analysis of all-cause mortality stratified by baseline CRP concentrations between more- and less-intensive lipid-lowering group. CRP indicates C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

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

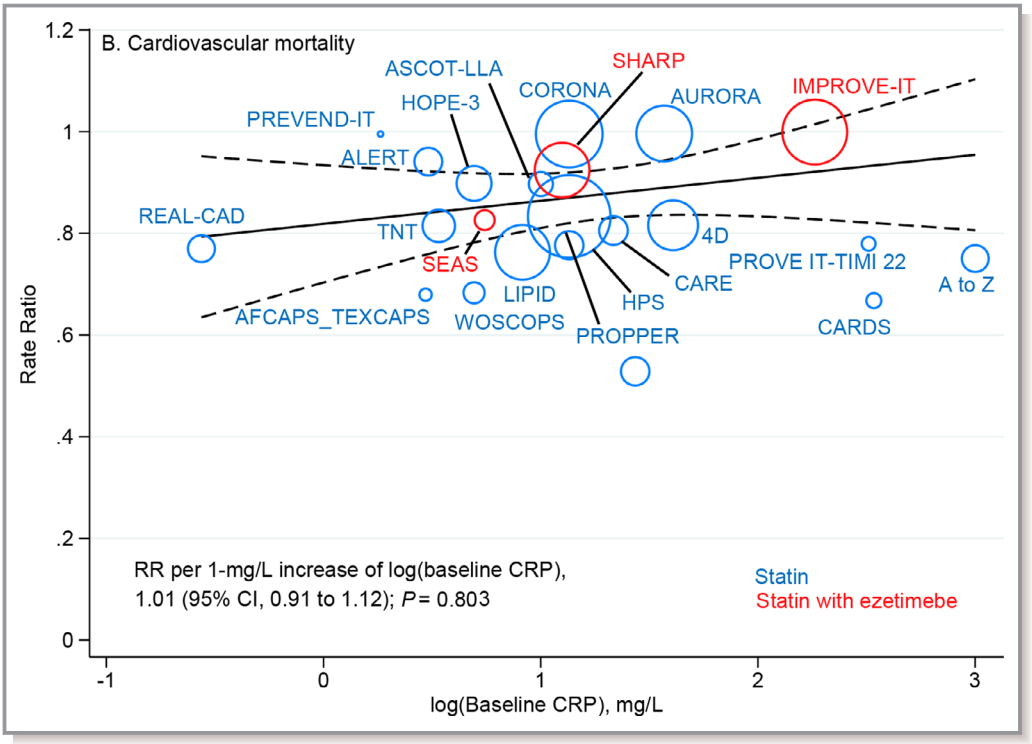

Figure 3. Meta-regression analysis of cardiovascular mortality rate ratios plotted against log-transformed baseline CRP concentrations in the more-intensive group. The size of the data marker is proportional to the weight in the metaregression. CRP indicates C-reactive protein; RR, rate ratio.

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

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

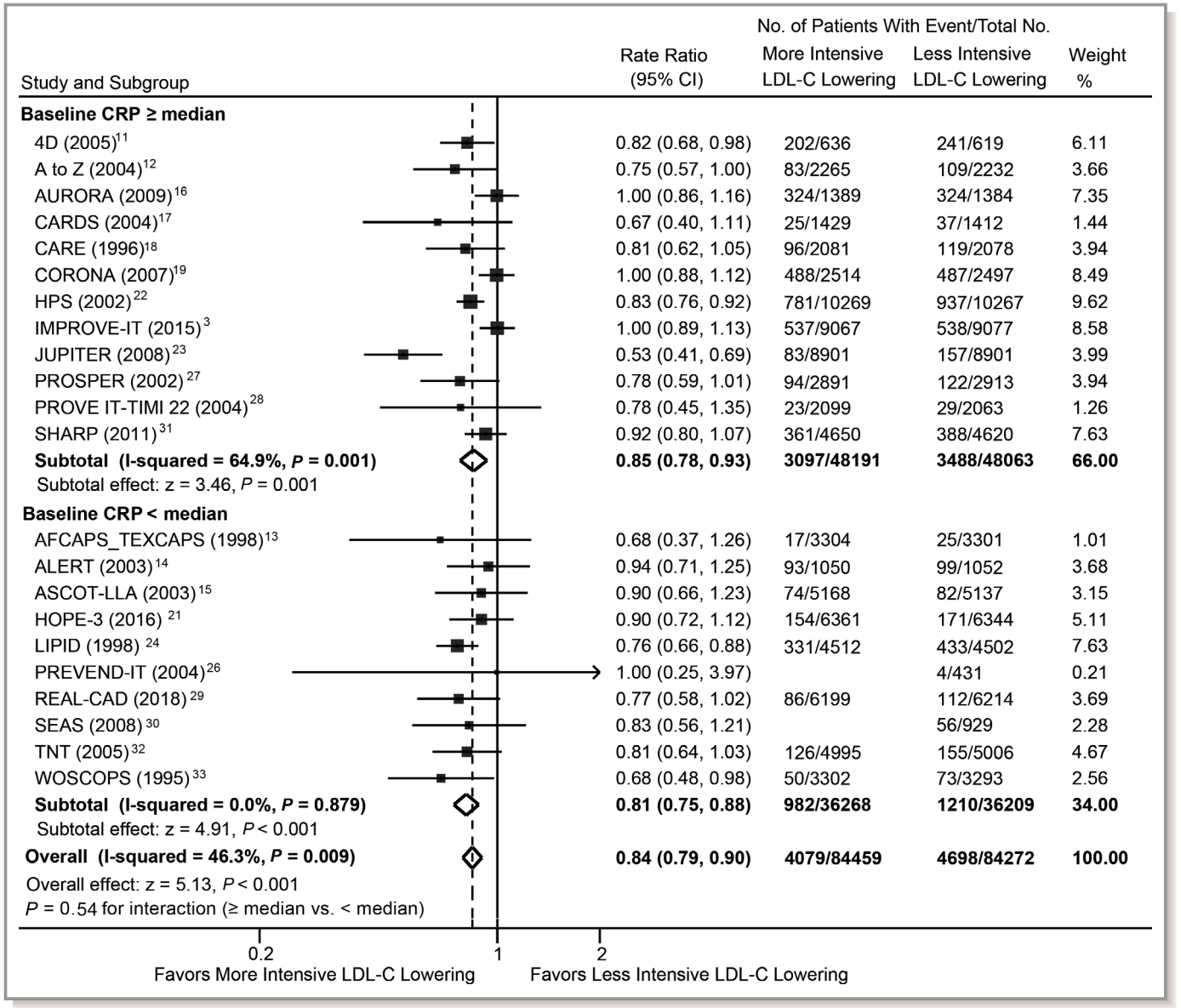

Figure 4. Meta-analysis of cardiovascular mortality stratified by baseline CRP concentrations between more- and less-intensive lipid-lowering group. CRP indicates C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

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

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

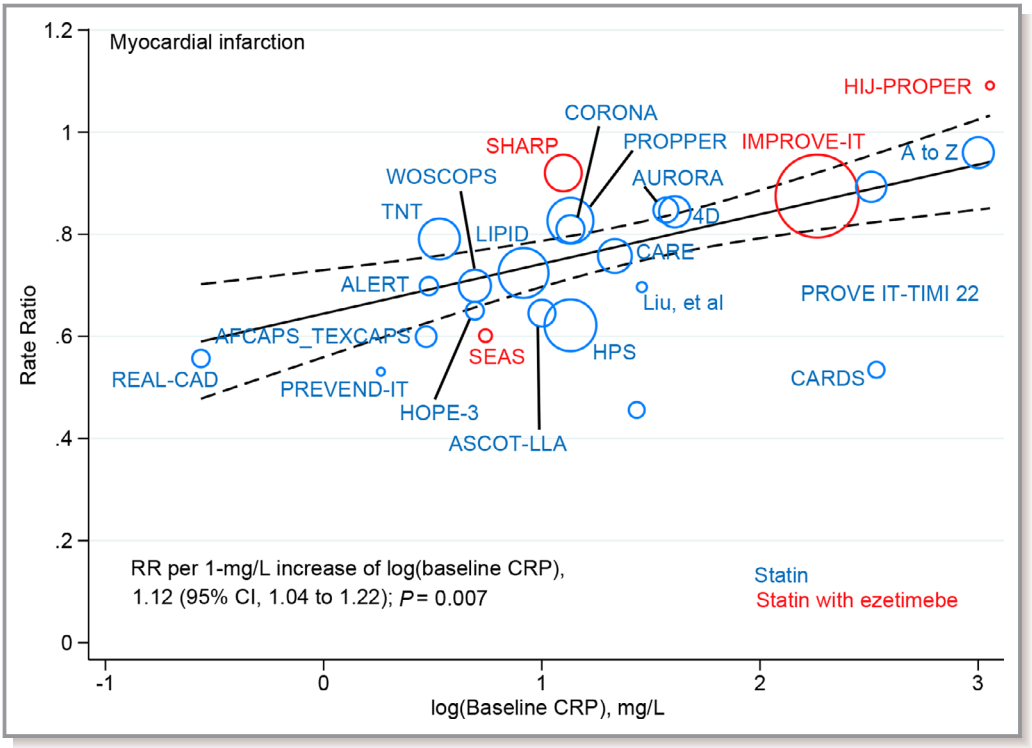

Figure 5. Meta-regression analysis of myocardial infarction rate ratios plotted against log-transformed baseline CRP concentrations in the more-intensive group. The size of the data marker is proportional to the weight in the metaregression. CRP indicates C-reactive protein; RR, rate ratio.

statin therapy had a lower rate of cardiovascular events than those who did not.[38] A similarly negative association was detected in the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering),[39] A-to-Z (Aggrastat-to-Zocor),[40] and the JUPITER[41] trials. Fueling this debate, trials including the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcome Trial–Lipid Lowering Arm),[42] the CARDS (Collaborative Atorvastatin Diabetes Study),[43] and TNT (Treating New Targets)[44] studies showed no association between achieved hsCRP concentrations and magnitude of statin efficacy in the prevention of cardiovascular events. Our meta-analysis and metaregression analysis do not lend support to the hypotheses that the beneficial effects of LDL-C–lowering therapy are affected by achieved CRP concentrations, in contrast with those found with achieved LDL-C concentrations.[45,46]

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

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

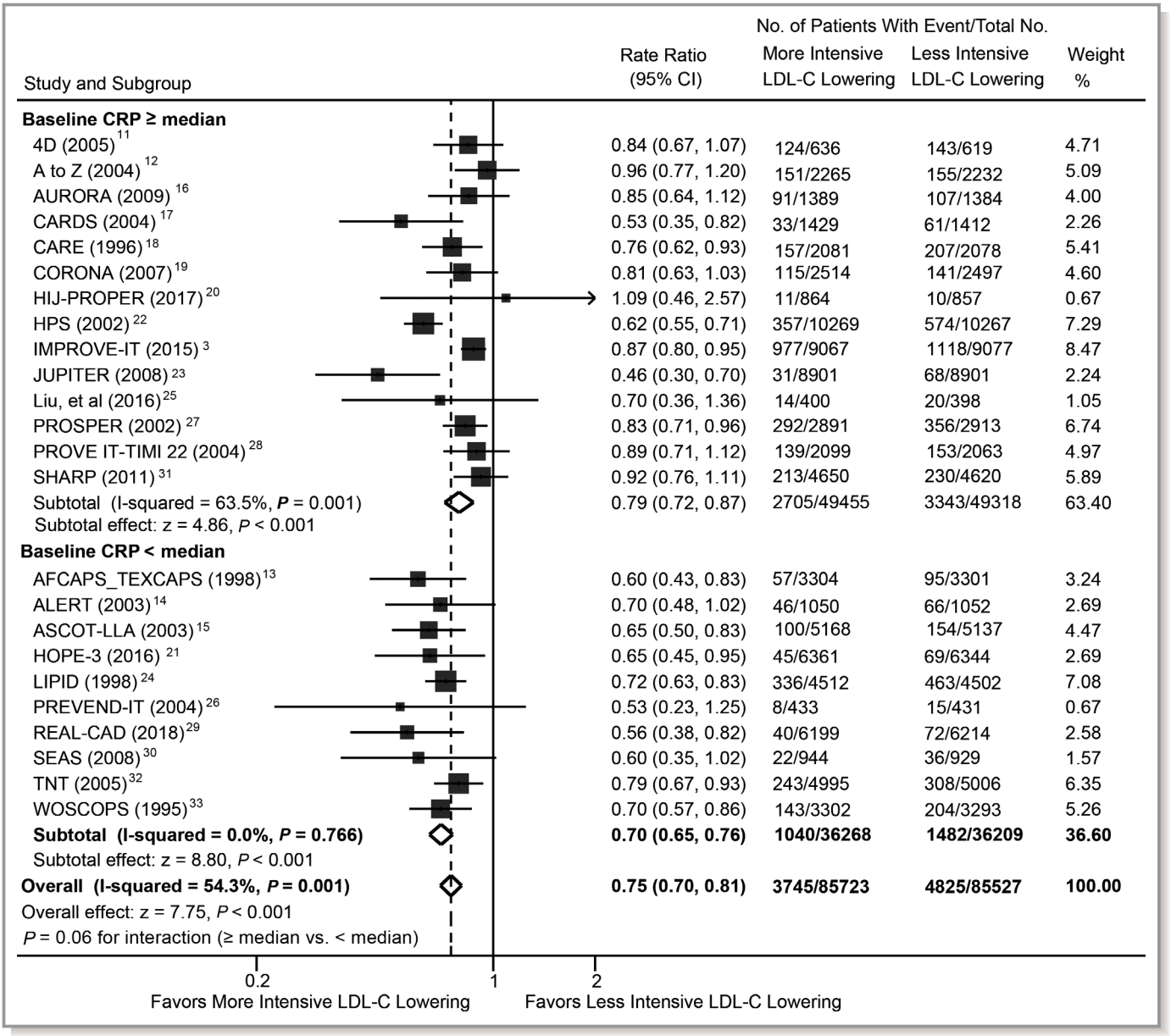

Figure 6. Meta-analysis of myocardial infarction stratified by baseline CRP concentrations between more- and less-intensive lipid-lowering group. CRP indicates C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

Limitations

Our study has several limitations. First, our analysis was based on trial-level data rather than patient-level data. Metaregression analyses might be subject to risk of aggregation bias because they attempt to make inferences about individuals using study-level information.[49] Second, a number of LDL-C–lowering cardiovascular trials did not report CRP data (especially achieved CRP concentrations), which might contribute to the publication bias detected in several analyses. The inclusion of these trials, if CRP data are reported, might erase the publication bias and considerably improve the statistical power and improve strength of evidence of our analysis. Third, considerable heterogeneity was detected in several analyses, which may be attributed to the differences in patient characteristics not evaluated in our study given that no characteristics tested appeared to affect the results. Fourth, the inclusion criteria in these trials varied; these differences in selection will play out in the baseline risk and the magnitude of absolute risk reduction achieved. Fifth, the definitions of some outcomes, such as MACE and myocardial infarction, were not completely consistent across trials, and a considerable part of trials did not report outcome definition; it is unclear whether this variation could affect our results. Finally, the study enrollment included in the analysis extended from 1995 to 2018, during which

background therapy and cardiovascular event rates have changed.

Conclusions

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

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Disclosures

None.

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Supplemental Material

Data S1.

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 $\chi 2$ test of interaction was performed.

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

PRISMA Checklist.

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

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

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

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	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			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

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

Table S1. Study and Patient Baseline Characteristics.

												More intensive LDL-C lowering			Less intensive LDL-C lowering				
Trial	Year	Total No. of patients	Age, yrs	Men, %	CHD, %	Other vascular disease, %	DM, %	HBP, %	Smoker, %	BMI (kg/m2)	Median FU, ys	Treatment	No. of patients	Baseline CRP (mg/L)	Baseline LDL-C (mg/dL)	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	2005	1255	65.7	54	50	53	100	NA	41	27.5	11.5	Atorvastatin (20 mg)	636	5	125	Placebo	619	5	127	1.6	40
A to Z	2004	4497	61	76	100	11	24	50	41	NA	2	Simvastatin (80 mg)	2265	20.1	112	Simvastatin (20 mg)	2232	20.4	111	0.3	15.7
AFCAPS_TEXCAPS	1998	6605	58	85	<1	<1	15	22	12	NA	5.2	Lovastatin (20-40 mg)	3304	1.6	150	Placebo	3301	1.5	153	0.3	40.5
ALERT	2003	2102	50	66	19	11	19	75	18.5	25.8	6.7	Fluvastatin (40 mg)	1050	1.62	159	Placebo	1052	1.6	159	NA	38.2
ASCOT-LLA	2003	10305	63.2	81	<1	14	25	NA	32.7	28.7	3.3	Atorvastatin (10 mg)	5168	2.72	133	Placebo	5137	2.7	133	NA	37.2
AURORA	2009	2773	64.1	62	24	27	26.4	NA	15	25.4	3.8	Rosuvastatin (10 mg)	1389	4.8	100	Placebo	1384	5.2	99	1.6	39
CARDS	2004	2841	61.5	68	<1	3	18	NA	46	28.7	3.9	Atorvastatin (10 mg)	1429	12.6	117	Placebo	1412	14.5	117	5.3	39.8
CARE	1996	4159	59	86	100	0	14	43	21	28	5	Pravastatin (40 mg)	2081	3.8	139	Placebo	2078	3.6	139	1.2	40.3
CORONA	2007	5011	73	76	73	13	30	63	9	27	2.7	Rosuvastatin (10 mg)	2514	3.1	137	Placebo	2497	3	136	1.2	34
HIJ-PROPER	2017	1721	65.7	75.6	100	7	30	68	59	24.3	3.9	Pitavastatin (1-4mg) + ezetimibe (10 mg)	864	21.2	135	Pitavastatin (1-4mg)	857	21	135	NA	20

HOPE-3	2016	12705	65.8	53.7	0	0	6	38	28	27.1	5.6	Rosuvastatin (10 mg)	6361	2	128	Placebo	6344	2	128	1.2	28.2
HPS	2002	20536	64	75	65	43	29	NA	NA	NA	5	Simvastatin (40 mg)	10269	3.1	131.5	Placebo	10267	3.1	131	1.38	26.3
IMPROVE-IT	2015	18144	63.6	75.7	100	5.5	27	61.5	33	28.3	6	Simvastatin (40 mg) + ezetimibe (10 mg)	9067	9.6	94	Simvastatin (40 mg)	9077	9.5	94	0.3	16
JUPITER	2008	17802	66	62	0	0	<1	NA	16	28.3	1.9	Rosuvastatin (20 mg)	8901	4.2	108	Placebo	8901	4.3	108	1.5	54
LIPID	1998	9014	62	83	100	10	9	41	74	NA	6.1	Pravastatin (40 mg)	4512	2.5	150	Placebo	4502	2.4	150	0.4	39.8
Liu, et al	2016	798	62	72	100	0	32.5	64.6	20.6	NA	1	Atorvastatin (40-80 mg)	400	4.3	131	Atorvastatin (20 mg)	398	4.5	131	NA	NA
PREVEND-IT	2004	864	52	65	<1	1.5	NA	NA	74	26	3.8	Pravastatin (40 mg)	433	1.3	158	Placebo	431	1.3	154	0.28	35
PROSPER	2002	5804	75	48	32	18	11	NA	27	NA	3.2	Pravastatin (40 mg)	2891	3.1	147	Placebo	2913	3.1	147	NA	50
PROVE IT-TIMI 22	2004	4162	58	78	100	8	18	50	36.8	NA	2	Atorvastatin (80 mg)	2099	12.3	106	Pravastatin (40 mg)	2063	12.3	106	0.8	34
REAL-CAD	2018	12413	68	83	100	14	40	75.7	16.4	24.6	3.9	Pitavastatin (4mg)	6199	0.57	88	Pitavastatin (1mg)	6214	0.59	88	0.1	14
SEAS	2008	1873	68	71	0	0	0	51.5	55	27	4.4	Simvastatin (40 mg) + ezetimibe (10 mg)	944	2.1	140	Placebo	929	2.2	139	0.6	70
SHARP	2011	9270	62	62	0	15	23		13	27	4.9	Simvastatin (20 mg) + ezetimibe (10 mg)	4650	3	107	Placebo	4620	3	107	0.7	29

TNT	2005	10001	61	81	100	15	15	54	76	28.4	4.9	Atorvastatin (80 mg)	4995	1.7	97	Atorvastatin (10 mg)	5006	1.7	98	NA	23.3
WOSCOPS	1995	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 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 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 or 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

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	Cardiovascular death, spontaneous myocardial	A rise in cardiac biomarkers (preferably troponin), with at least 1

		infarction, and unplanned revascularization	infarction, and unplanned revascularization	value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least 1 of the following: symptoms of ischemia, electrocardiogram changes indicative of new ischemia (new specific ST-T changes or new left-bundle branch block), development of pathological Q waves in the electrocardiogram, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.
PREVEND -IT	2004	Cardiovascular death and hospitalization for cardiovascular morbidity	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	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	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	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

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

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

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

ALERT	2003	Men and women aged 30–75 years who had received renal or combined renal and pancreas transplants more than 6 months before randomisation and who had stable graft function. All patients were receiving immunosuppressive therapy with ciclosporin and had total serum cholesterol concentrations of 4·0–9·0 mmol/L	Patients who were already taking statins, who had familial hypercholesterolaemia, had experienced acute rejection episodes in the previous 3 months, or who had a predicted life expectancy of less than 1 year.
ASCOT-LLA	2003	Men and women aged between 40 and 79 years at randomisation, with either untreated hypertension. Patients had to have total cholesterol concentrations of 6·5 mmol/L or lower, and not currently be taking a statin or a fibrate.	Previous myocardial infarction, currently treated angina, a cerebrovascular event within the previous 3 months, fasting triglycerides higher than 4·5 mmol/L, heart failure, uncontrolled arrhythmias or any clinically important haematological or biochemical abnormality on routine screening.
AURORA	2009	Men and women 50 to 80 years of age who had end-stage renal disease and had been treated with regular hemodialysis or hemofiltration for at least 3 months were recruited from 280 centers in 25 countries.	Statin therapy within the previous 6 months, expected kidney transplantation within 1 year, and serious hematologic, neoplastic, gastrointestinal, infectious, or metabolic disease (excluding diabetes) that was predicted to limit life expectancy to less than 1 year, with a history of a malignant condition, active liver disease (indicated by an alanine aminotransferase level that was more than three times the upper limit of the normal range), uncontrolled hypothyroidism, and an unexplained elevation in the creatine kinase level to more than three times the upper limit of the normal range.
CARDS	2004	Men and women aged 40–75 years with type 2 diabetes mellitus and had at least one or more of the following: a history of hypertension,; retinopathy; or currently smoking (no minimum number of cigarettes per day was required).	Had any past history of myocardial infarction, angina, coronary vascular surgery, cerebrovascular accident, or severe peripheral vascular disease (defined as warranting surgery). We checked eligibility against the patient's clinical notes and their own recall and assessed lipid eligibility criteria by blood testing at one screening and four pretreatment visits over a 10-week period.

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

		Low-density lipoprotein cholesterol was at least 100 mg/dL (2.6 mmol/L).	
HOPE-3	2016	Men 55 years of age or older and women 65 years of age or older who had at least one of cardiovascular risk factors	Participants with cardiovascular disease and those with an indication for or contraindication to statins, angiotensin-receptor blockers, angiotensin-converting–enzyme inhibitors, or thiazide diuretics
HPS	2002	Men and women aged about 40–80 years with non-fasting blood total cholesterol concentrations of at least 3·5 mmol/L (135 mg/dL) if they were considered to be at substantial 5-year risk of death from coronary heart disease.	Patients had: chronic liver disease (cirrhosis or hepatitis) or evidence of abnormal liver function (eg, alanine aminotransferase >67 IU/L [1·5 times the central laboratory upper limit of normal: ULN]); severe renal disease or evidence of impaired renal function (creatinine >200 mmol/L); inflammatory muscle disease (eg, dermatomyositis or polymyositis) or evidence of muscle problems (creatine kinase >750 IU/L [3 ULN]); concurrent treatment with ciclosporin, fibrates, or high-dose niacin; child-bearing potential (premenopausal woman not sterilised or using reliable contraception); severe heart failure; some lifethreatening condition other than vascular disease or diabetes (eg, severe chronic airways disease or any cancer other than non-melanoma skin cancer); or conditions that might limit long-term compliance (eg, severely disabling stroke, dementia, or psychiatric disorder).
IMPROVE-IT	2015	Men and women who were at least 50 years of age if they had been hospitalized within the preceding 10 days for an acute coronary syndroma. Patients were required to have an LDL cholesterol level of 50 mg per deciliter (1.3 mmol per liter) or higher.	Planned coronary-artery bypass grafting for the acute coronary syndrome event, creatinine clearance of less than 30 ml per minute, active liver disease, or use of statin therapy that had LDL cholesterol–lowering potency greater than 40 mg of simvastatin.

JUPITER	2008	Men 50 years of age or older and women 60 years of age or older if they did not have a history of cardiovascular disease and if, at the initial screening visit, they had an LDL cholesterol level of less than 130 mg per deciliter (3.4 mmol per liter) and a high-sensitivity C-reactive protein level of 2.0 mg per liter or more.	previous or current use of lipid-lowering therapy, current use of postmenopausal hormone-replacement therapy, evidence of hepatic dysfunction (an alanine aminotransferase level that was more than twice the upper limit of the normal range), a creatine kinase level that was more than three times the upper limit of the normal range, a creatinine level that was higher than 2.0 mg per deciliter (176.8 μmol per liter), diabetes, uncontrolled hypertension (systolic blood pressure >190 mm Hg or diastolic blood pressure >100 mm Hg), cancer within 5 years before enrollment (with the exception of basal-cell or squamous-cell carcinoma of the skin), uncontrolled hypothyroidism (a thyroid-stimulating hormone level that was more than 1.5 times the upper limit of the normal range), and a recent history of alcohol or drug abuse or another medical condition that might compromise safety or the successful completion of the study. Because a core scientific hypothesis of the trial concerned the role of underlying low-grade inflammation as evidenced by elevated high-sensitivity C-reactive protein levels, patients with inflammatory conditions such as severe arthritis, lupus, or inflammatory bowel disease were excluded, as were patients taking immunosuppressant agents such as cyclosporine, tacrolimus, azathioprine, or long-term oral glucocorticoids.
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.

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	Any of the following: creatinine clearance< 60% of the normal age-adjusted value, serum potassium >5.5 mmol/L, history of chronic liver disease, lactate dehydrogenase, aspartate-amino transferase or alanine-amino transferase .3 times the upper limit of normal, use of angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, use of insulin, previously documented allergy or intolerance to study drugs, and pregnant or nursing women.
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.	Individuals with poor cognitive function (mini mental state examination score <24).
PROVE IT-TIMI 22	2004	Men and women who were at least 18 years old if they had been hospitalized for an acute coronary syndrome or high-risk unstable angina. Patients had to have a total cholesterol level of 240 mg per deciliter (6.21 mmol per liter) or less.	Had a coexisting condition that shortened expected survival to less than two years, were receiving therapy with any statin at a dose of 80 mg per day at the time of their index event or lipid-lowering therapy with fibric acid derivatives or niacin that could not be discontinued before randomization, had received drugs that are strong inhibitors of cytochrome P-450 3A4 within the month before randomization or were likely to require such treatment during the study period (because atorvastatin is metabolized by this pathway), had undergone percutaneous coronary intervention within the previous six months (other than for the qualifying event) or coronary-artery bypass surgery within the previous two months or were scheduled to undergo bypass surgery in response to the index event, had factors that might prolong the QT interval, had obstructive hepatobiliary disease or other serious hepatic disease, had an unexplained elevation in the creatine kinase level that was more than three times the upper limit of normal and that was not related to myocardial infarction, or had a creatinine level of more than 2.0 mg per deciliter (176.8 µmol per liter).
REAL-CAD	2018	Men and women 20 to 80 years of age with stable CAD	Patients with LDL-C <100 mg/dL without statin therapy before enrollment because the label in the instructions for pitavastatin restricted use to patients with hypercholesterolemia.
SEAS	2008	Men and women between the ages of 45 and 85 years who had asymptomatic, mild-to-moderate aortic valve stenosis, as	Patients had received a diagnosis or had symptoms of coronary artery disease, peripheral arterial disease, cerebrovascular disease, or diabetes mellitus or if they had any other condition requiring lipid-lowering therapy.

		assessed on echocardiography, with a peak aortic-jet velocit y of 2.5 to 4 m per second.	
SHARP	2011	Patients aged 40 years 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	NA

		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 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 S4. Listing of Potential Sources of Bias.

Study	Year	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)	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_TEXCAPS	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	Low 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	Low risk	High risk
HPS	2002	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
IMPROVE-IT	2015	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	High risk
JUPITER	2008	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
LIPID	1998	Low risk	Unclear risk	Low 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	Low risk
PREVEND-IT	2004	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
PROSPER	2002	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk
PROVE IT-TIMI 22	2004	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
REAL-CAD	2018	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk
SEAS	2008	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	High risk
SHARP	2011	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk

TNT	2005	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
WOSCOPS	1995	Low risk	Unclear risk	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.

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

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

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

			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	8	0.69 (0.63, 0.75)	<0.001
		≥ median	5	0.89 (0.82, 0.95)	0.001	9	0.75 (0.66, 0.85)	<0.001
	Magnitude of reduction in CRP	< median	3	0.83 (0.67, 1.02)	0.078	4	0.69 (0.61, 0.78)	<0.001
		≥ median	1	0.89 (0.71, 1.12)	0.325	9	0.73 (0.63, 0.83)	<0.001
		Total	7	0.85 (0.77, 0.93)	0.001	17	0.72 (0.66, 0.78)	<0.001
Stroke	Baseline CRP	< median	2	0.92 (0.62, 1.36)	0.680	8	0.84 (0.75, 0.95)	0.004
		≥ median	5	0.85 (0.74, 0.97)	0.017	9	0.83 (0.72, 0.95)	0.009
	Magnitude of reduction in CRP	< median	3	0.93 (0.76, 1.14)	0.496	4	0.87 (0.73, 1.05)	0.141
		≥ median	1	0.98 (0.54, 1.80)	0.955	9	0.79 (0.69, 0.90)	<0.001
		Total	7	0.87 (0.77, 0.99)	0.030	17	0.84 (0.76, 0.92)	<0.001
Coronary Revascularization	Baseline CRP	< median	2	0.79 (0.69, 0.90)	<0.001	7	0.72 (0.65, 0.80)	<0.001
		≥ median	5	0.92 (0.86, 0.97)	0.005	8	0.76 (0.69, 0.83)	<0.001
	Magnitude of reduction in CRP	< median	3	0.91 (0.85, 0.98)	0.015	3	0.74 (0.63, 0.87)	<0.001
		≥ median	1	0.87 (0.75, 0.99)	0.043	8	0.75 (0.68, 0.82)	<0.001
		Total	7	0.85 (0.78, 0.94)	0.001	15	0.74 (0.70, 0.79)	<0.001
MACE	Baseline CRP	< median	2	0.80 (0.72, 0.88)	<0.001	8	0.78 (0.73, 0.84)	<0.001

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

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

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

			Primary Prevention			Secondary Prevention		
		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

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

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

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

		Rate Ratio (95% CI)				
Outcomes	**No. of 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*.

		Rate Ratio (95% CI)		
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.

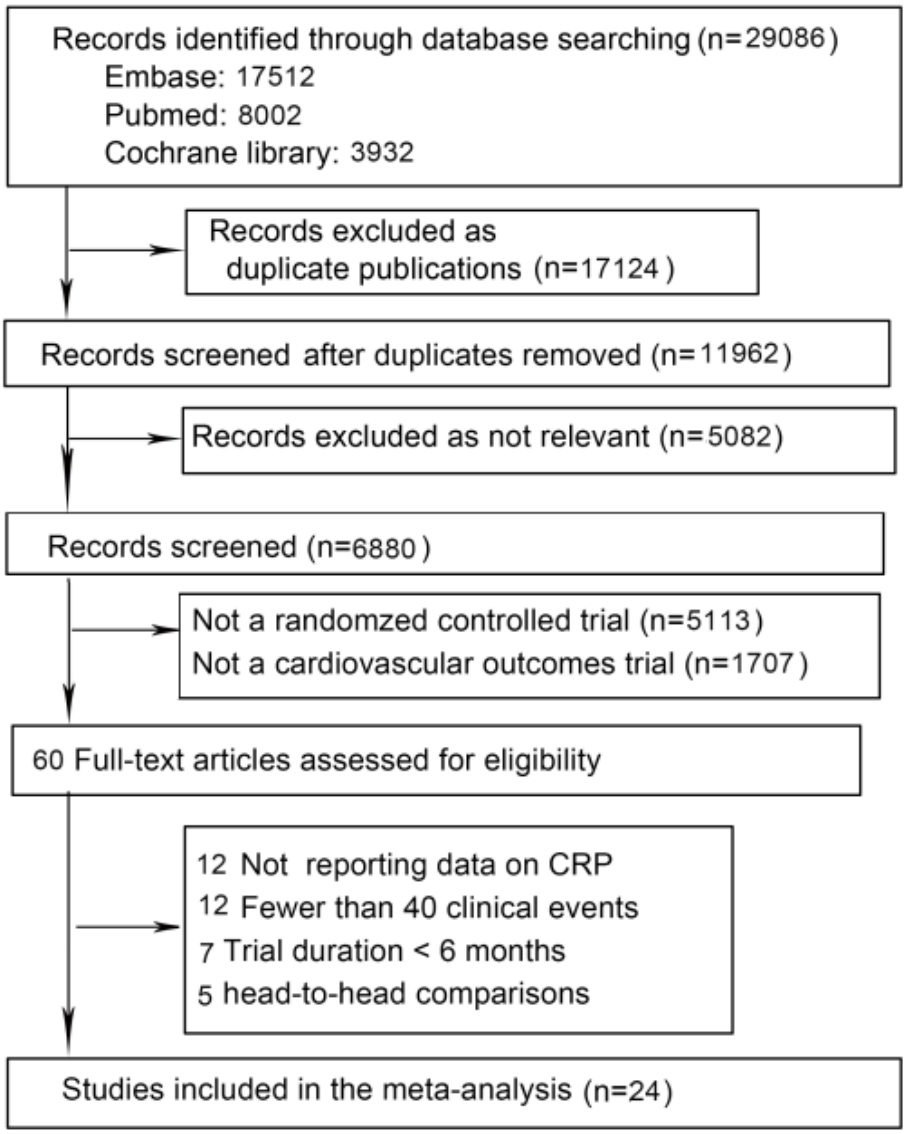
Table S11. Multivariable Meta-regression Models for the Association of Each 1-mg/L Reduction in log(baseline CRP Concentration), Magnitude of Reduction in CRP Concentration, and Mortality and Cardiovascular Outcomes in Primary Prevention Trials*.

		Rate Ratio (95% CI)		
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.

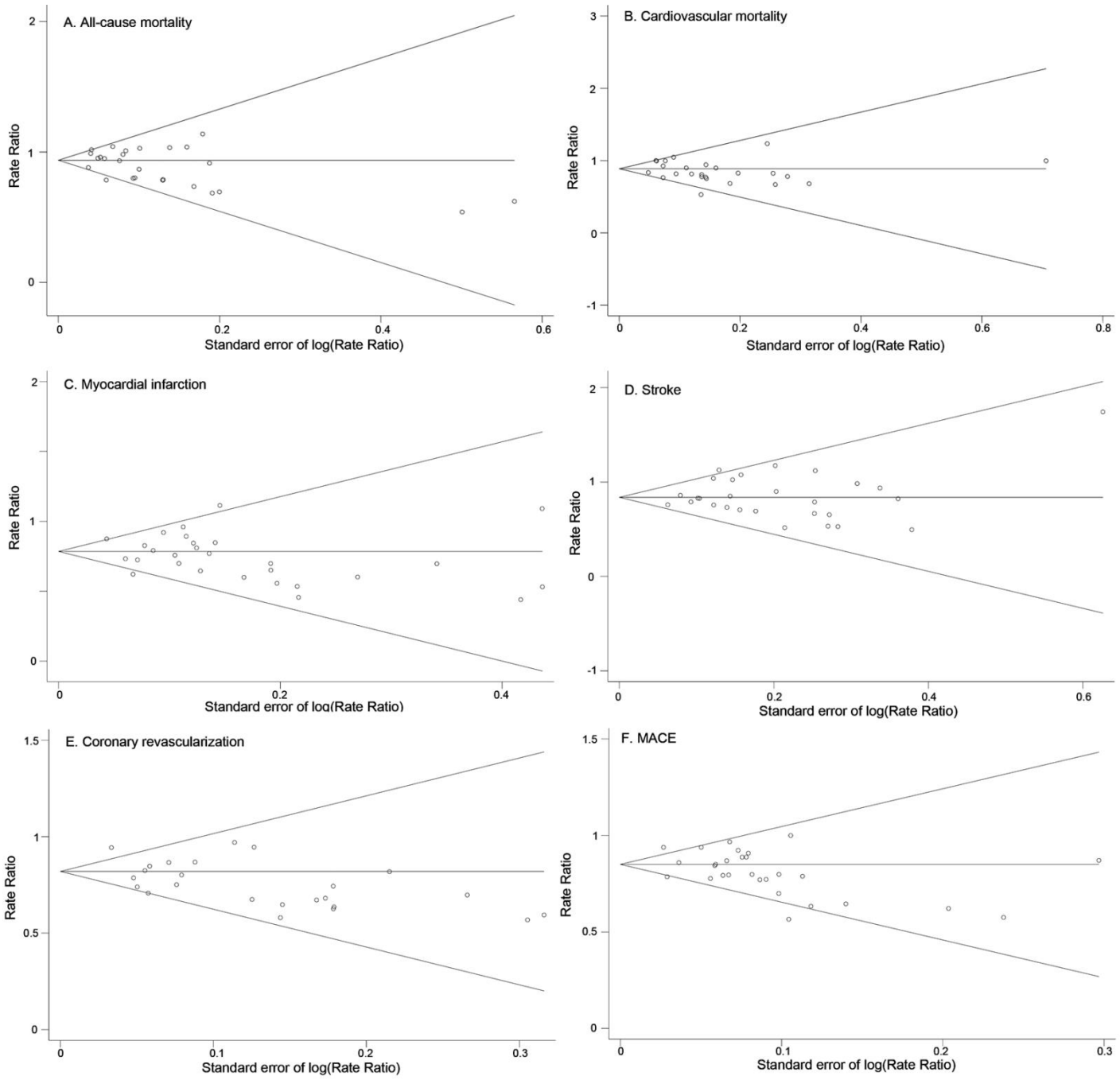
CRP, C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event.

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



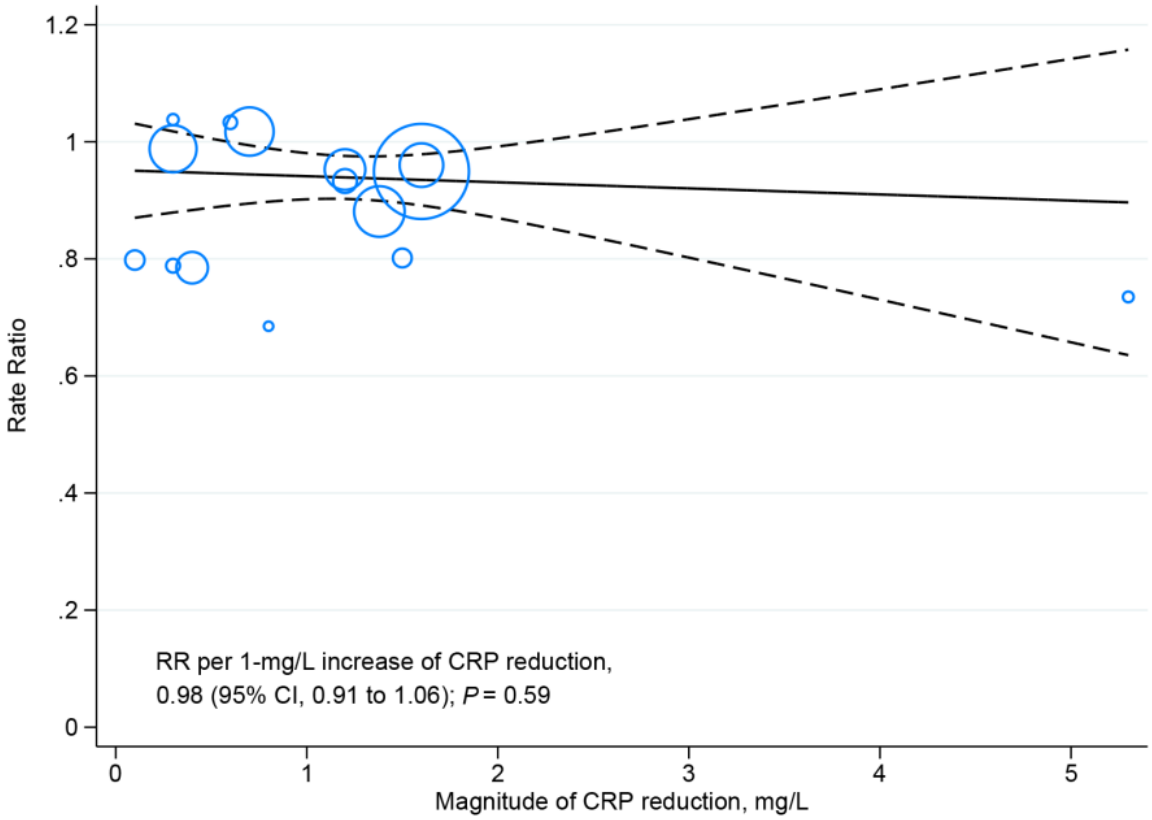
CRP, C-reactive protein.

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.

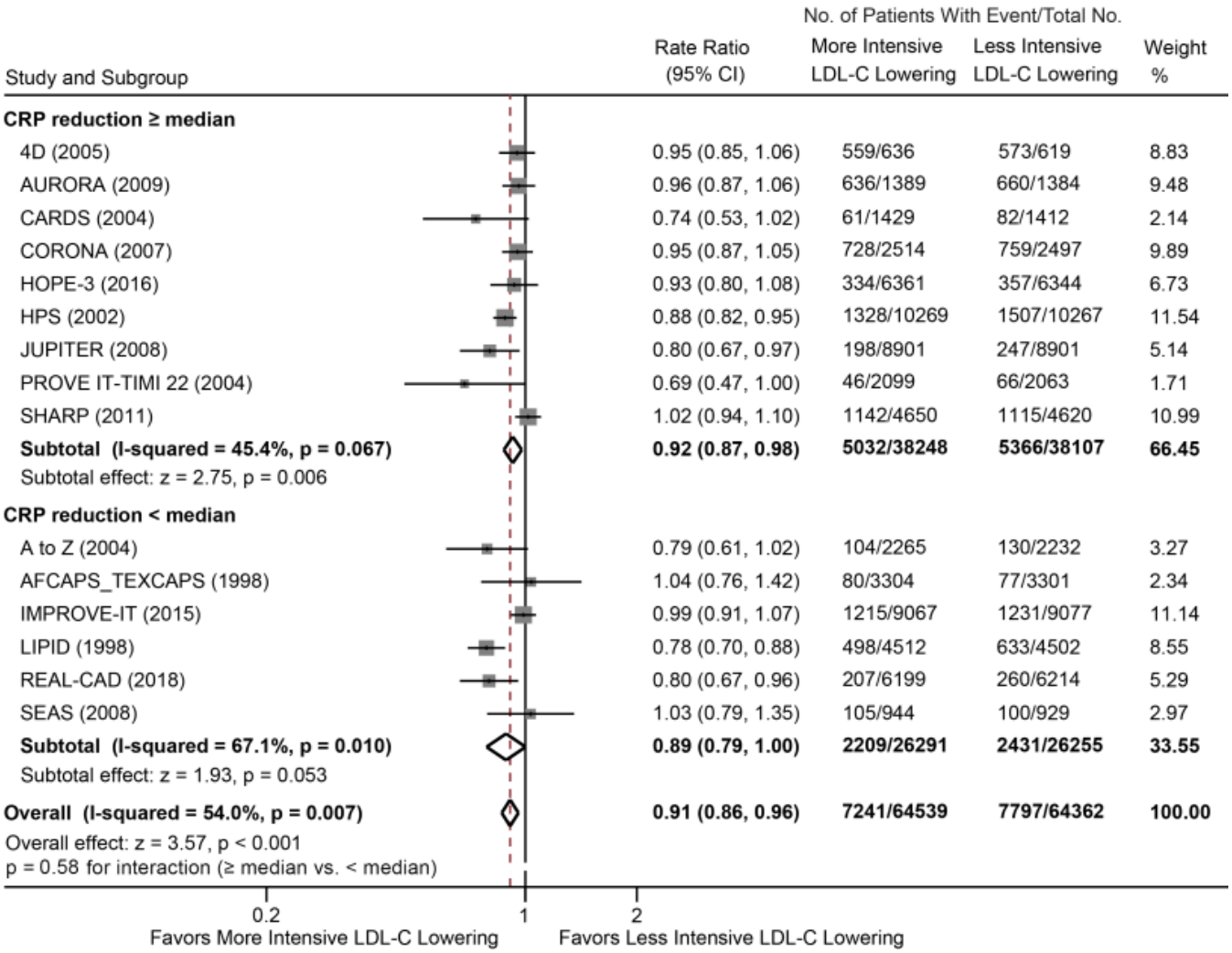


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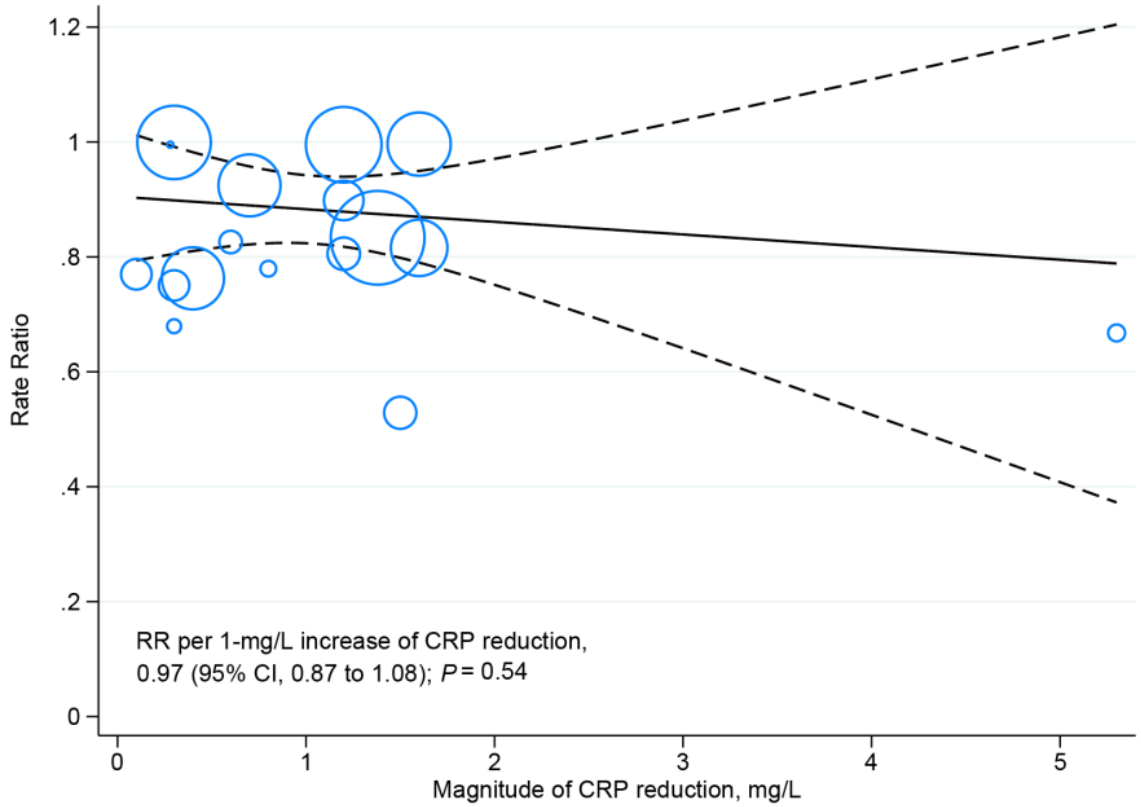
Figure S5. Meta-regression Analysis of Cardiovascular Mortality Rate Ratio Plotted Against Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.



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.

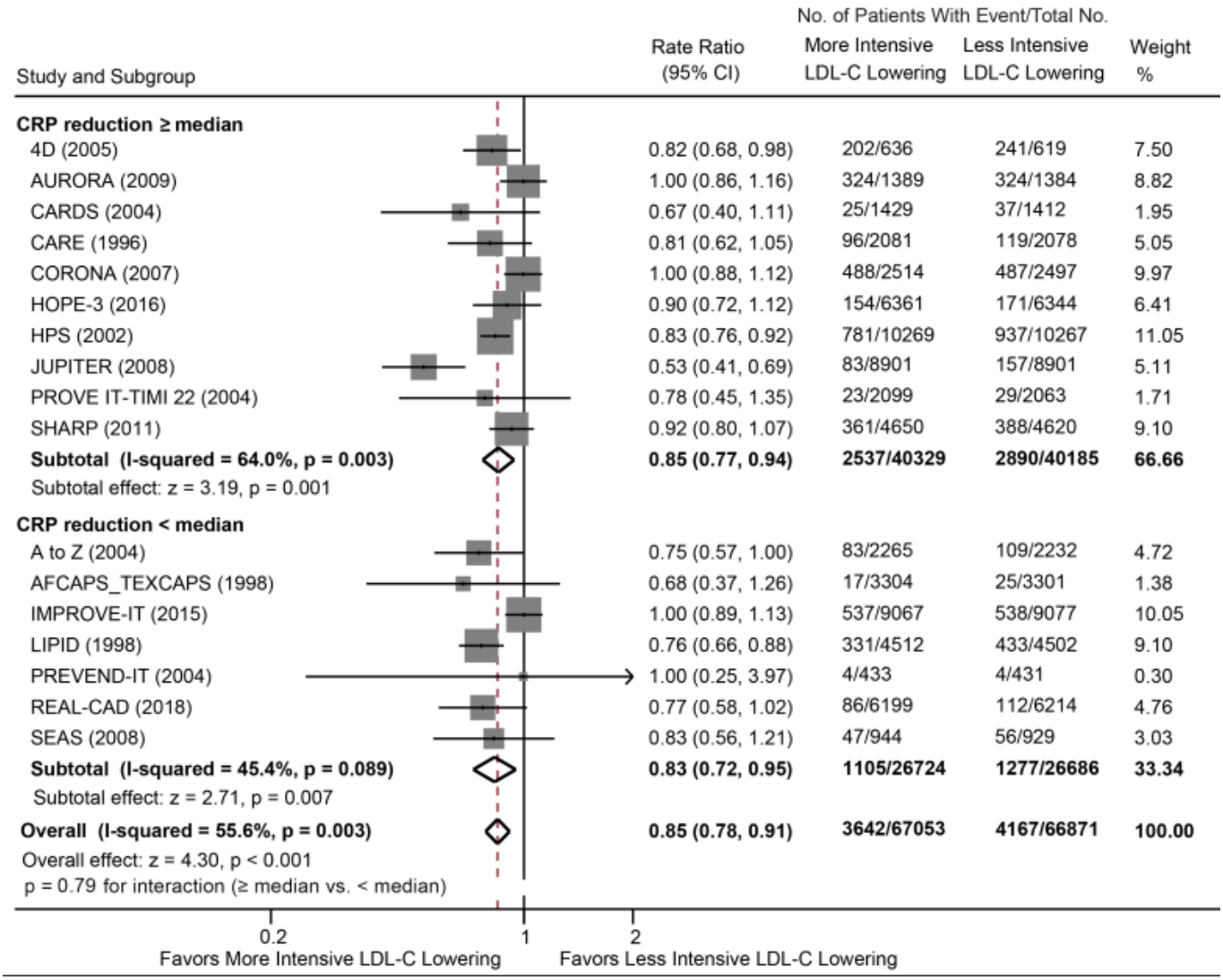


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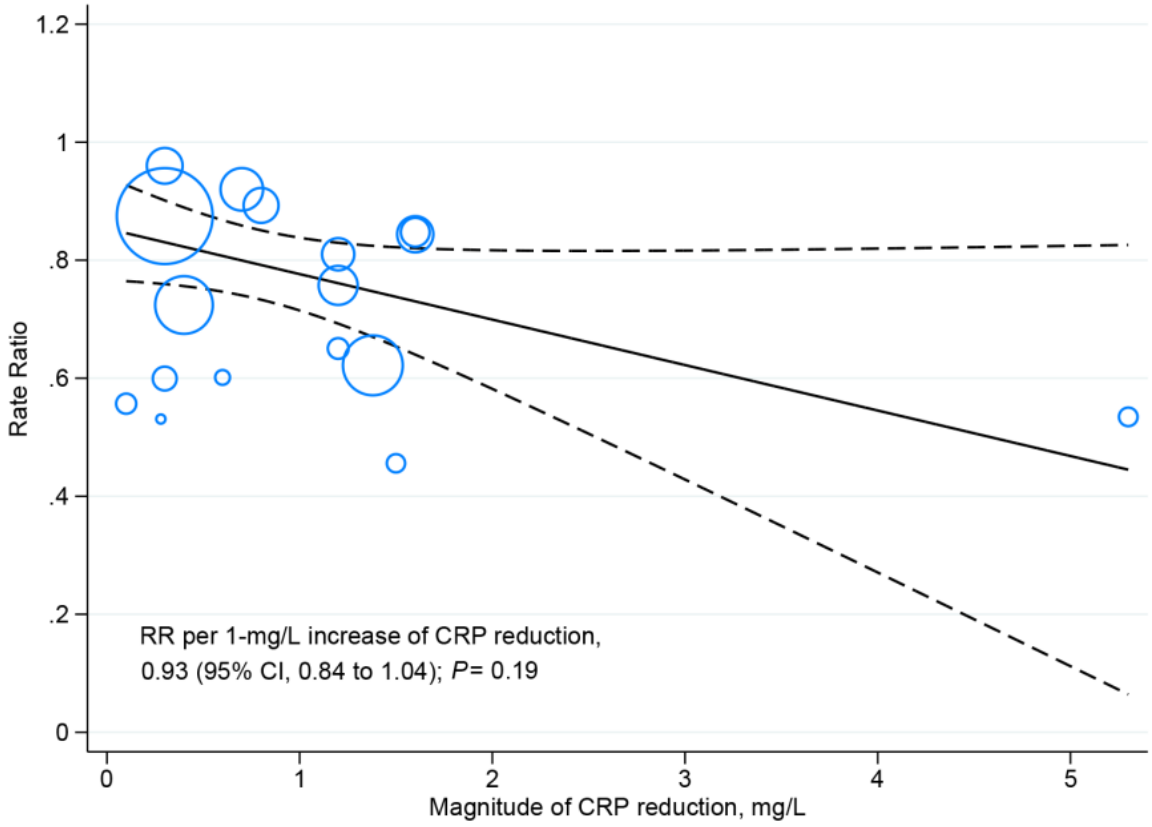
Figure S7. Meta-regression Analysis of Myocardial Infarction Rate Ratio Plotted Against Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.



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.

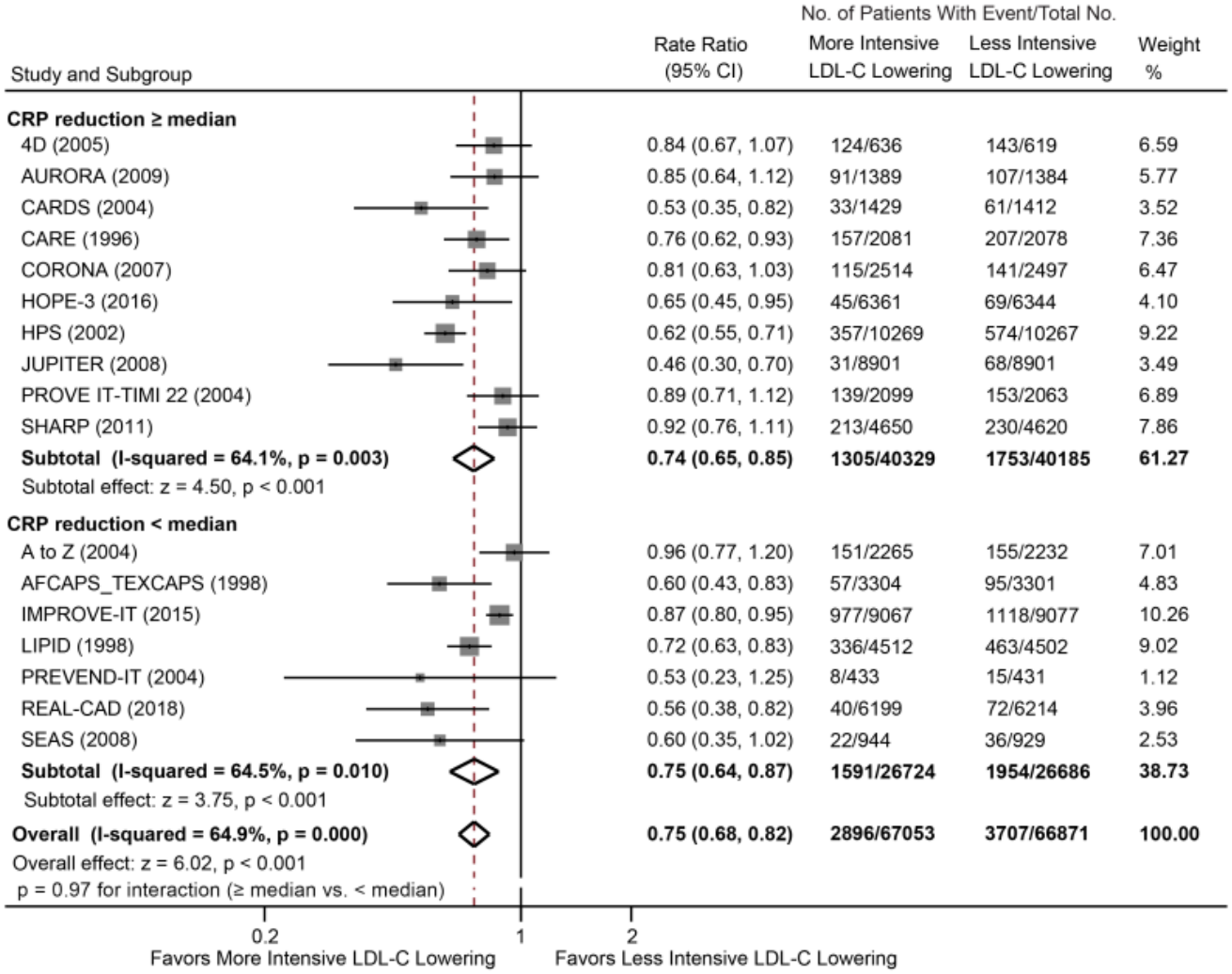


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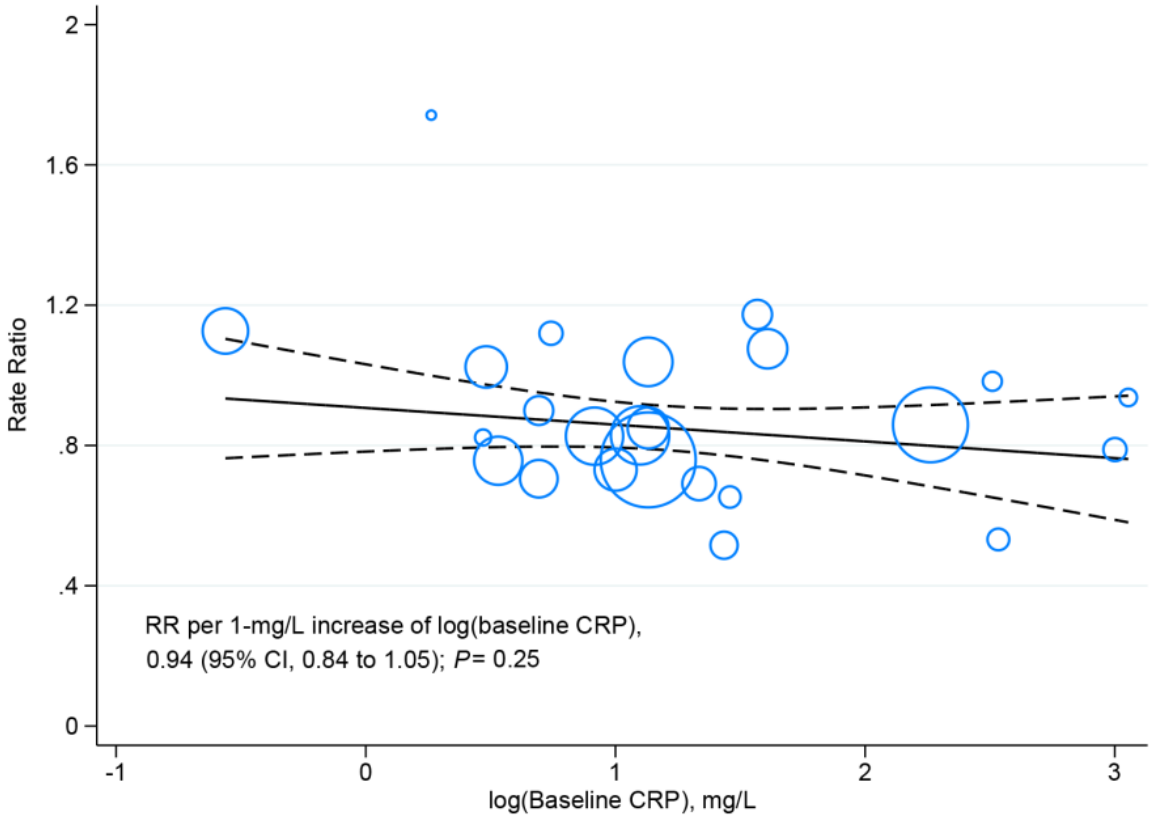
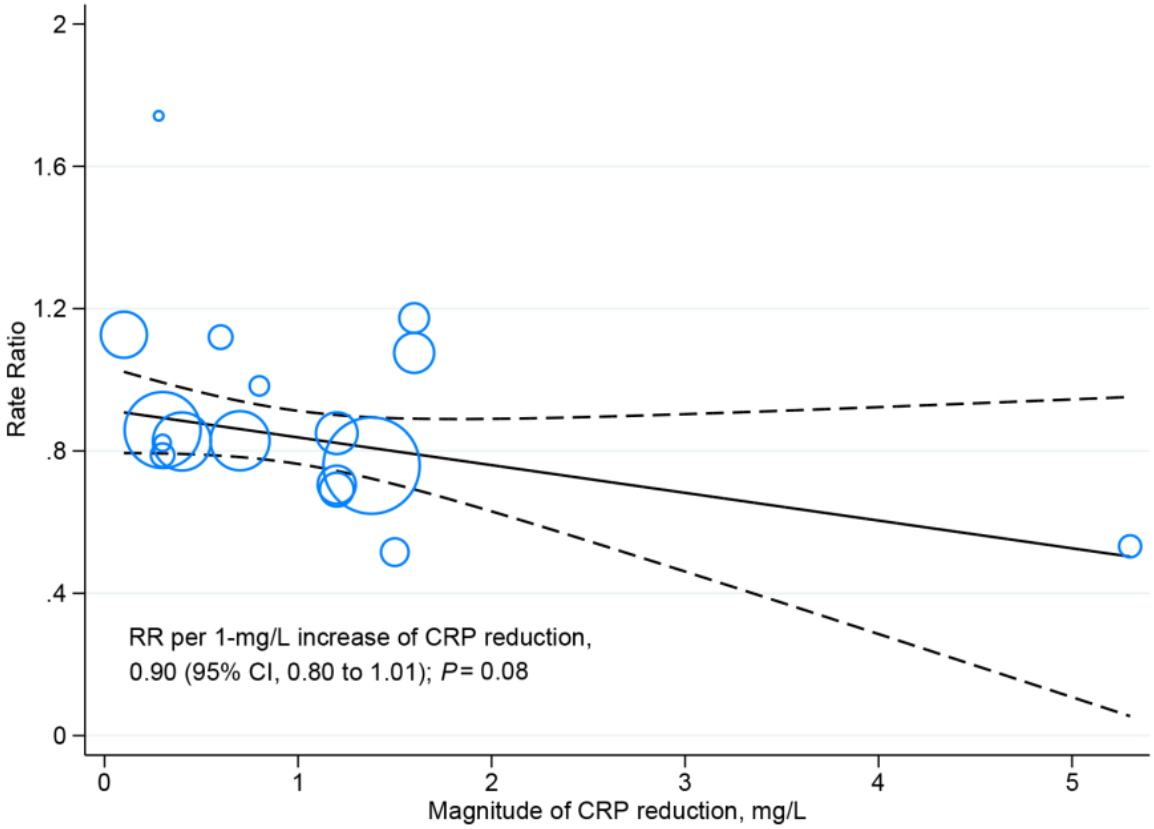
Figure S9. Meta-regression Analysis of Stroke Rate Ratio Plotted Against log(baseline CRP Concentrations) in the More Intensive Group.



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.

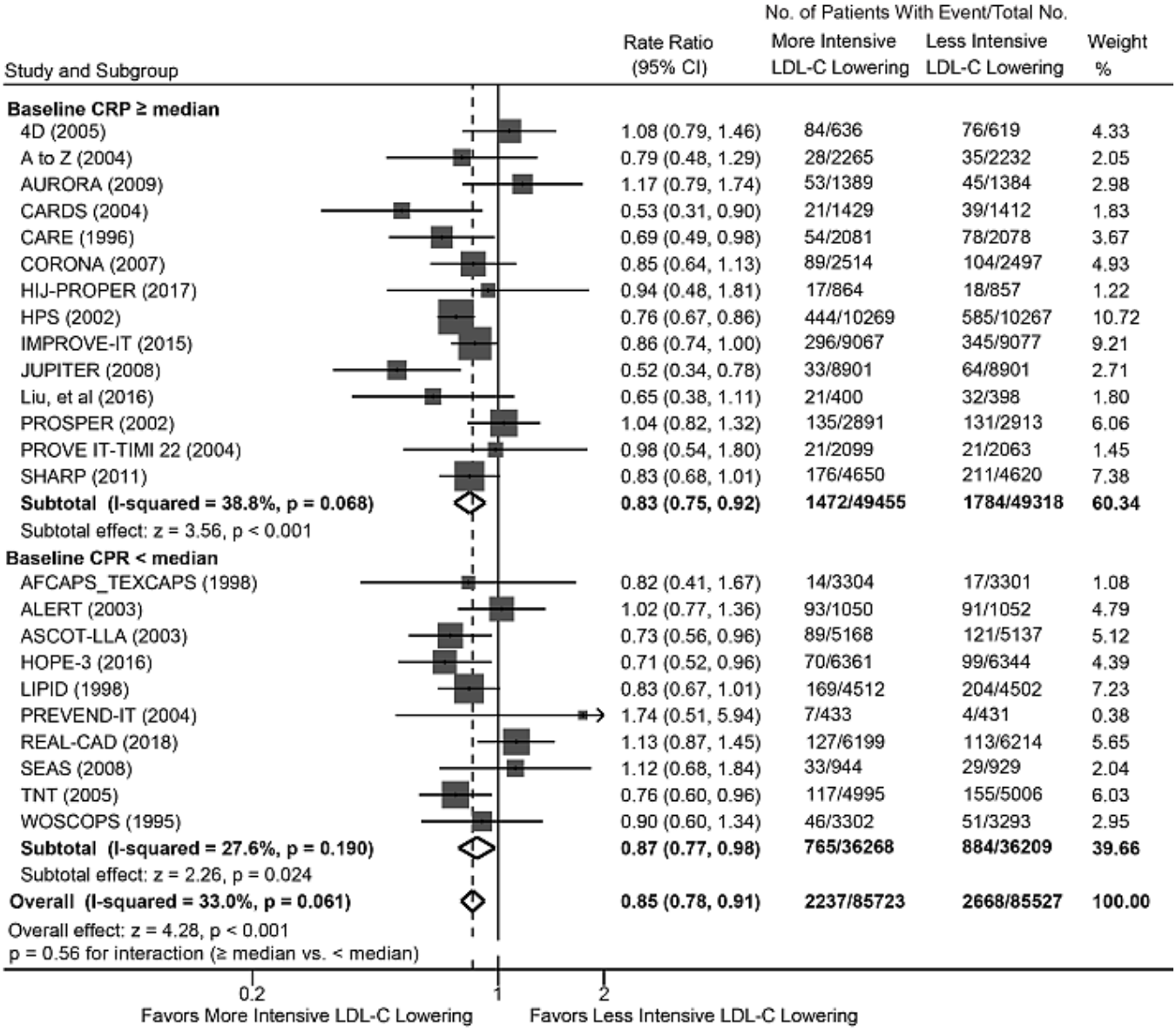


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Figure S12. Meta-analysis of Stroke Stratified by Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.

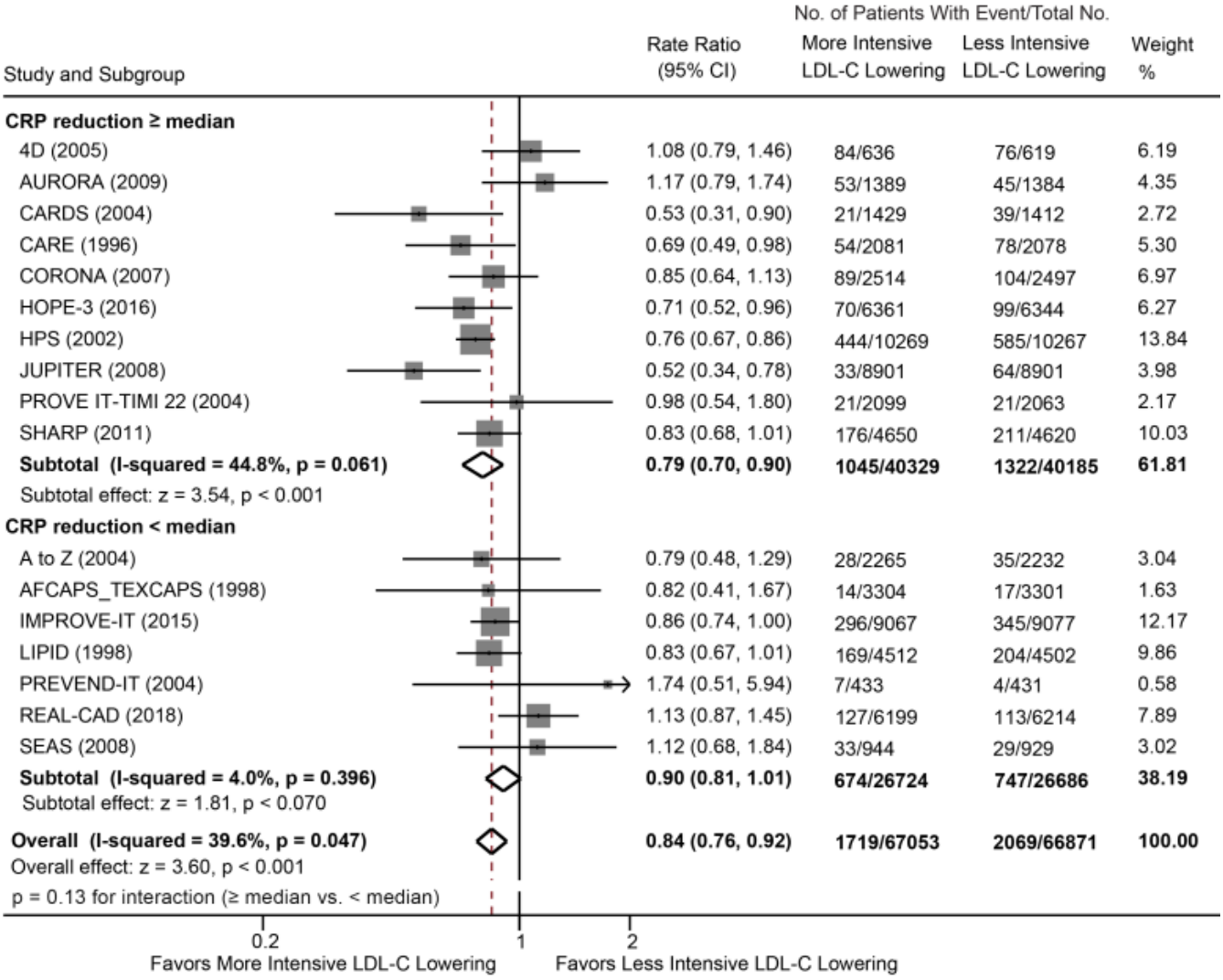

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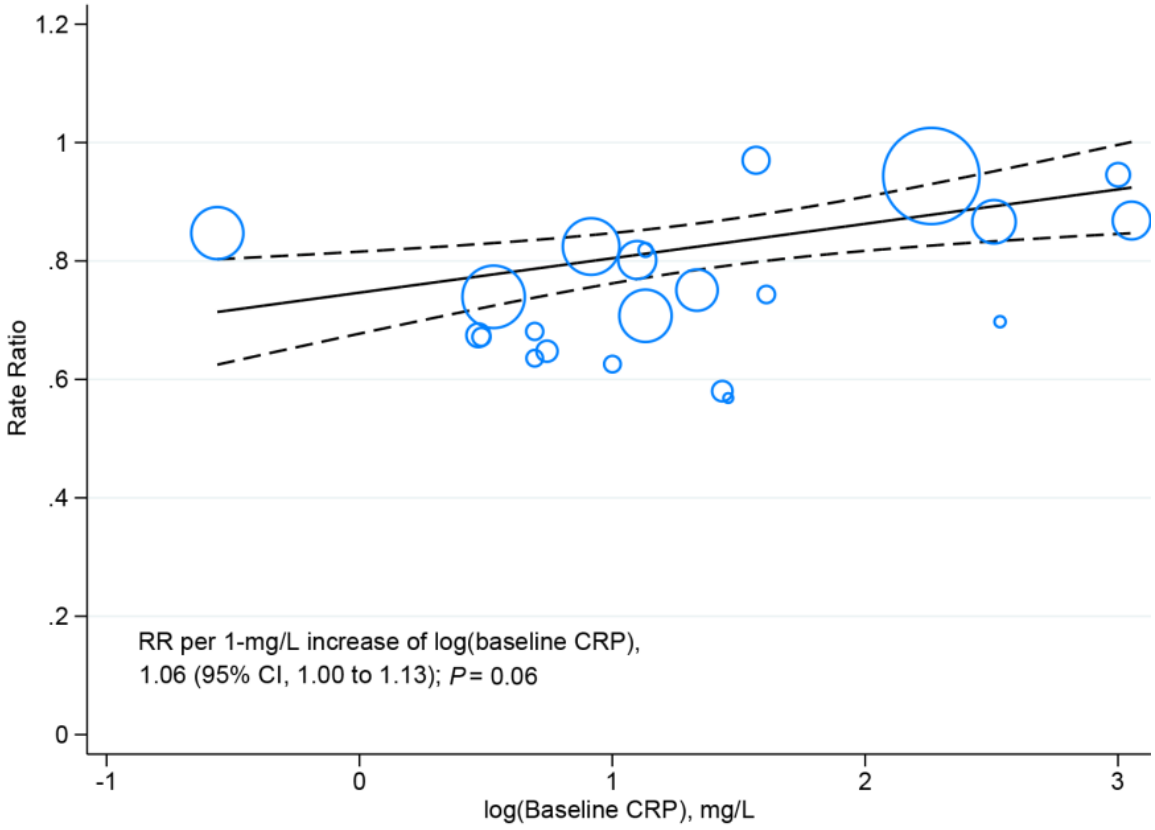
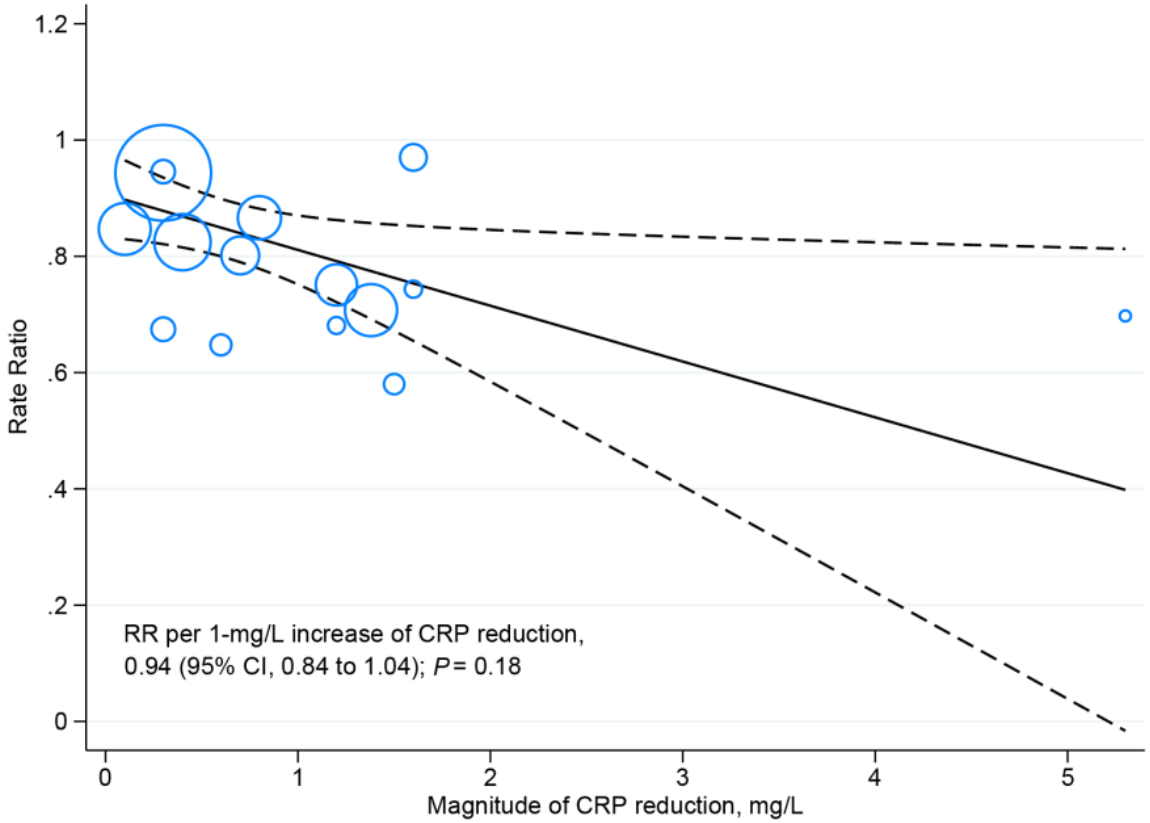
Figure S13. Meta-regression Analysis of Coronary Revascularization Rate Ratio Plotted Against log(baseline CRP Concentrations) in the More Intensive Group.



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.

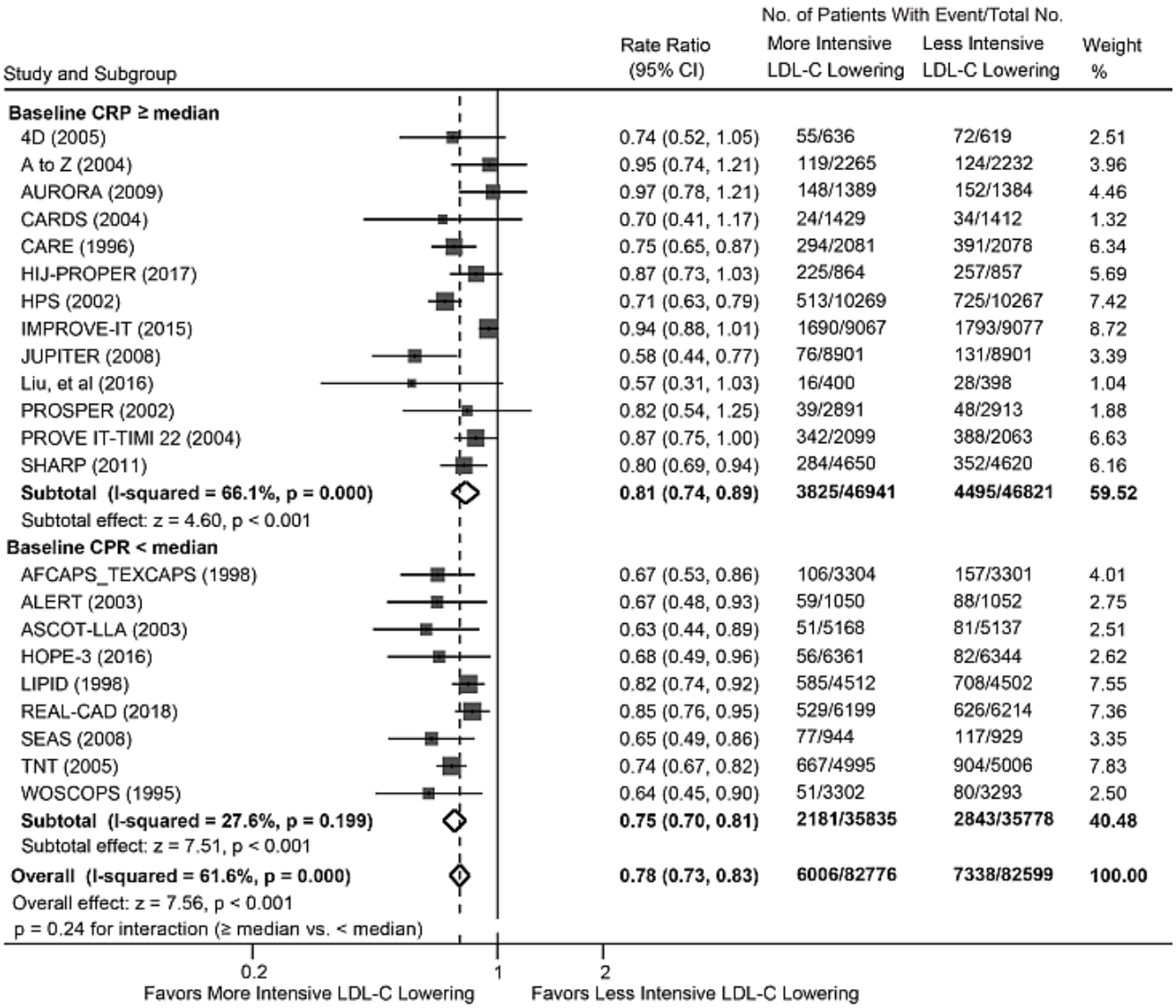


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Figure S16. Meta-analysis of Coronary Revascularization Stratified by Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.

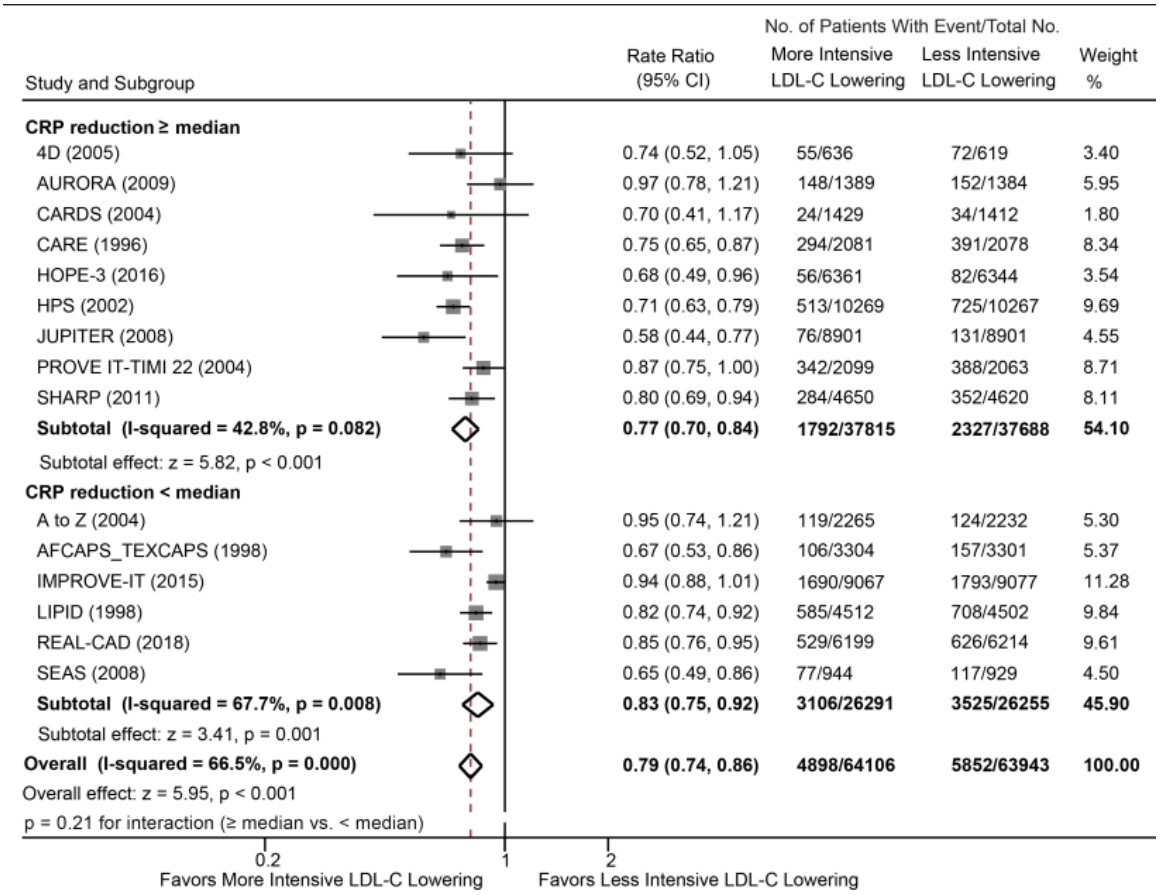

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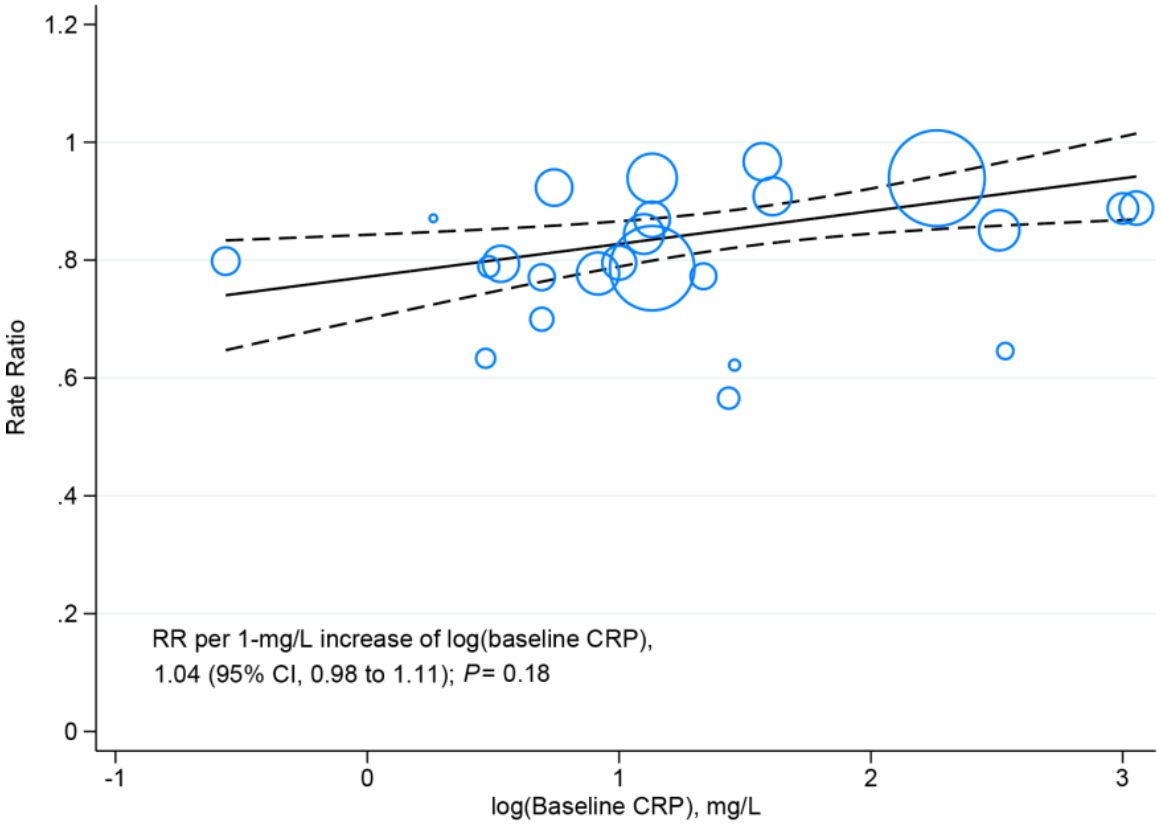
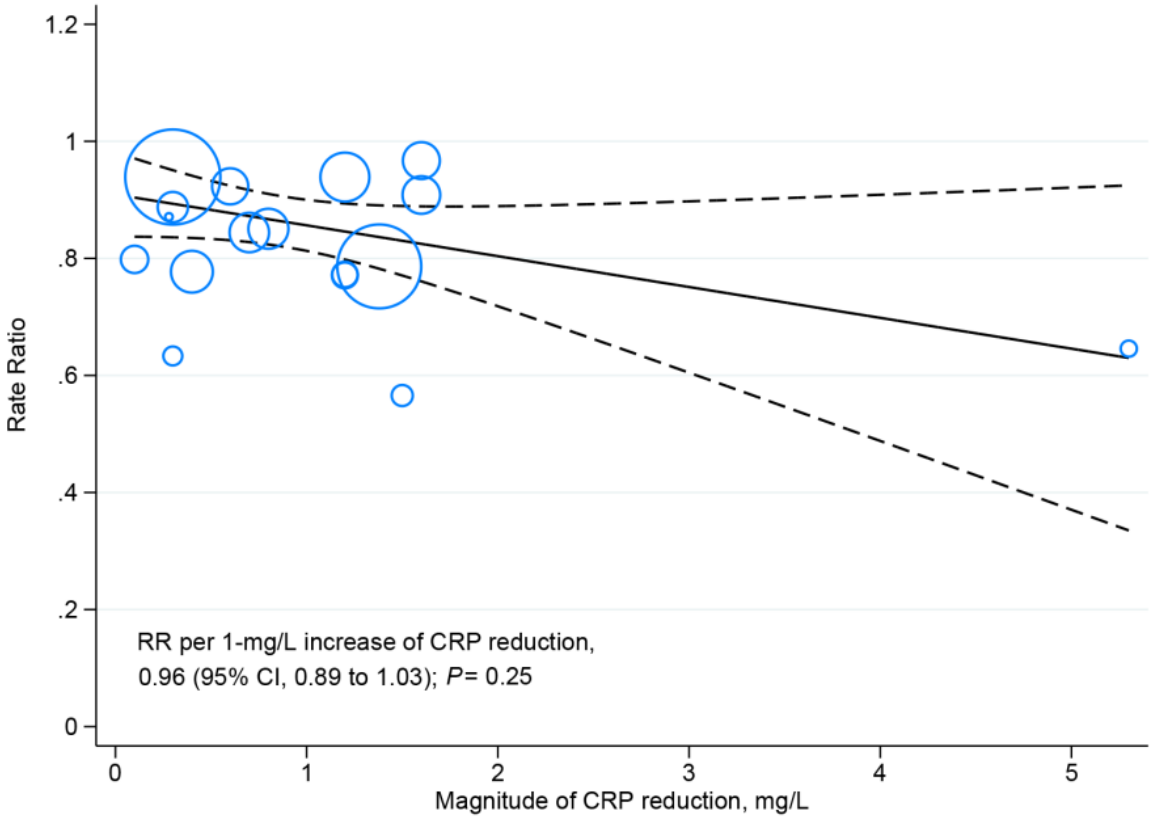
Figure S17. Meta-regression Analysis of MACE Rate Ratio Plotted Against log(baseline CRP Concentrations) in the More Intensive Group.



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.

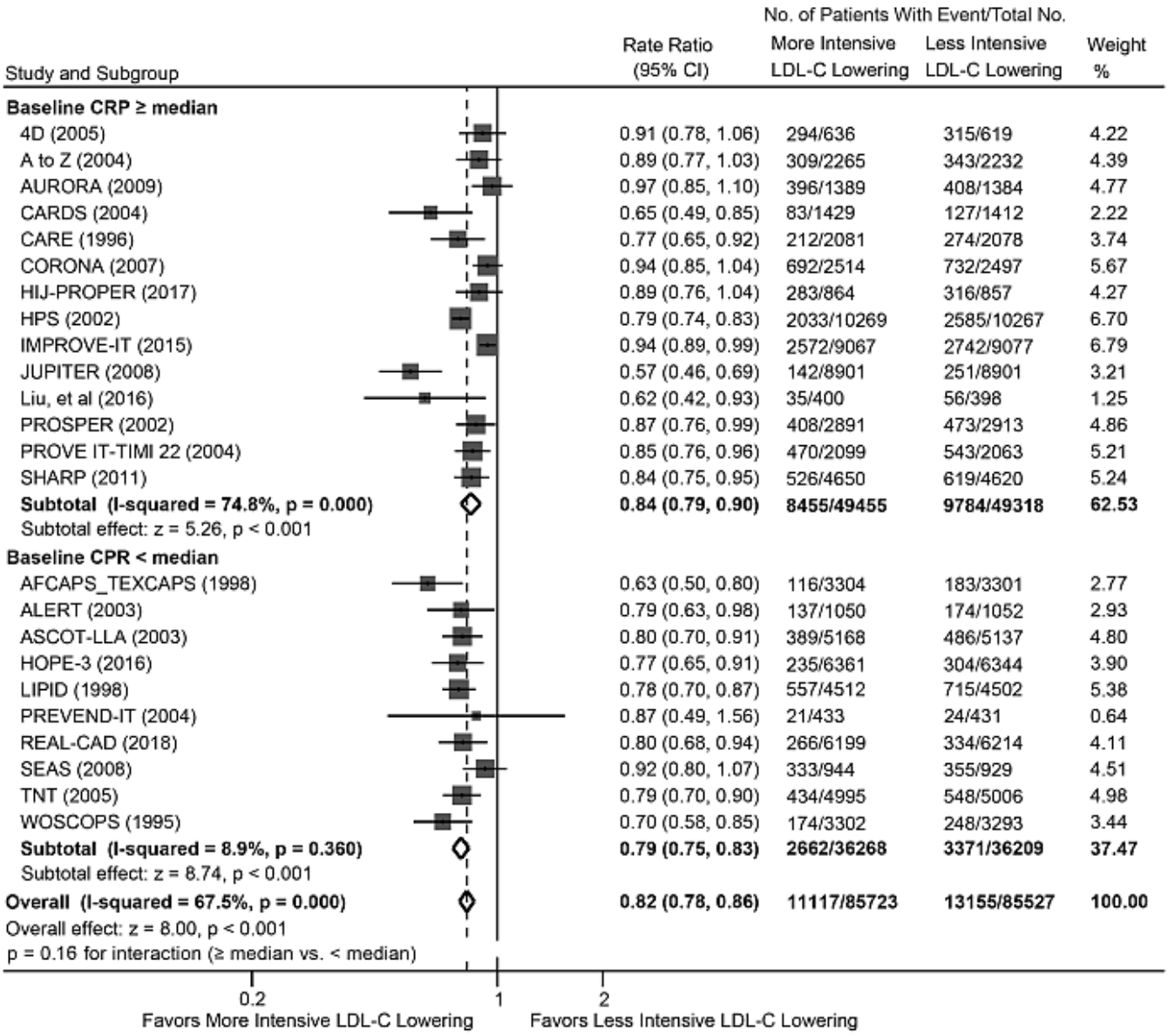


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Figure S20. Meta-analysis of MACE Stratified by Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.

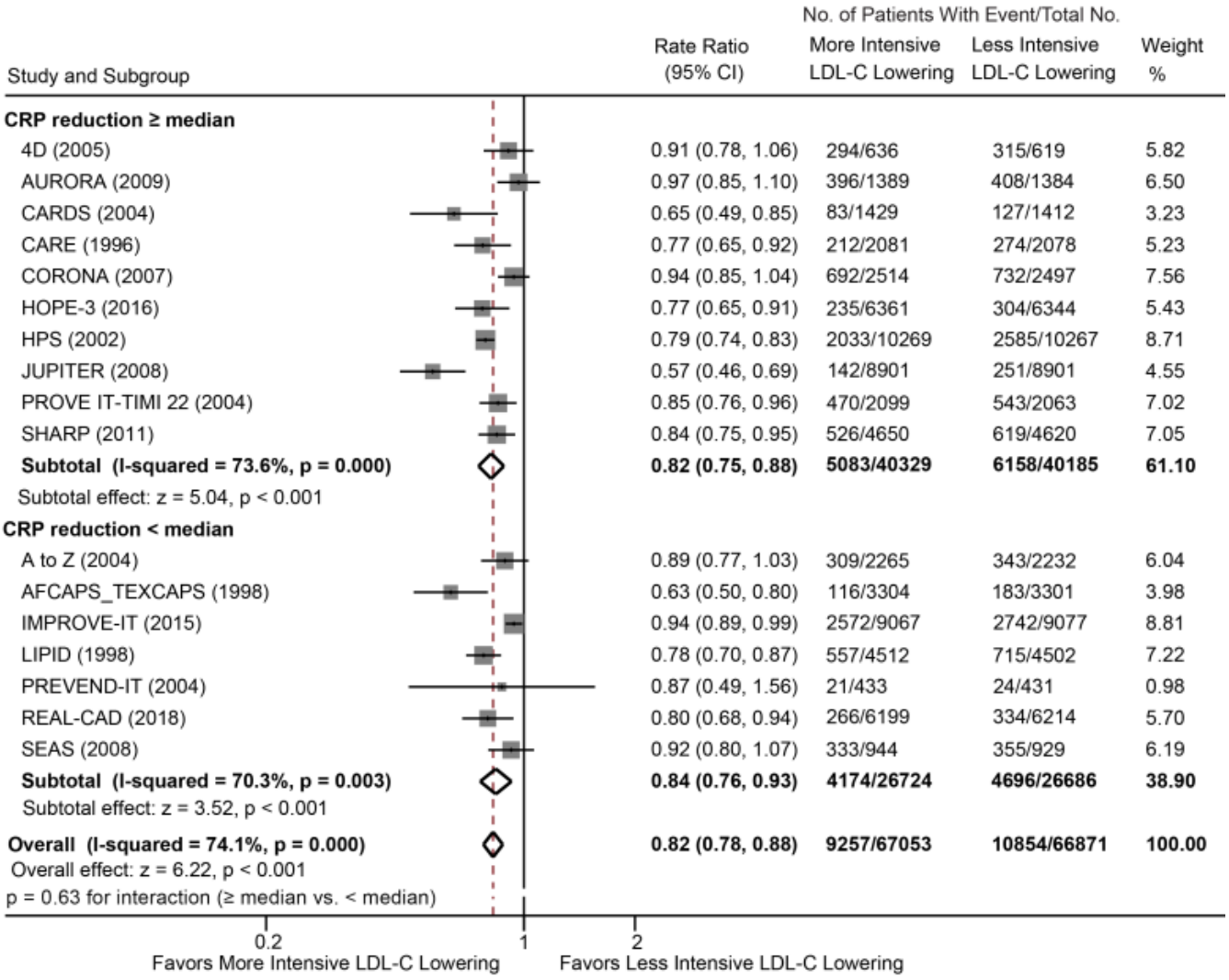

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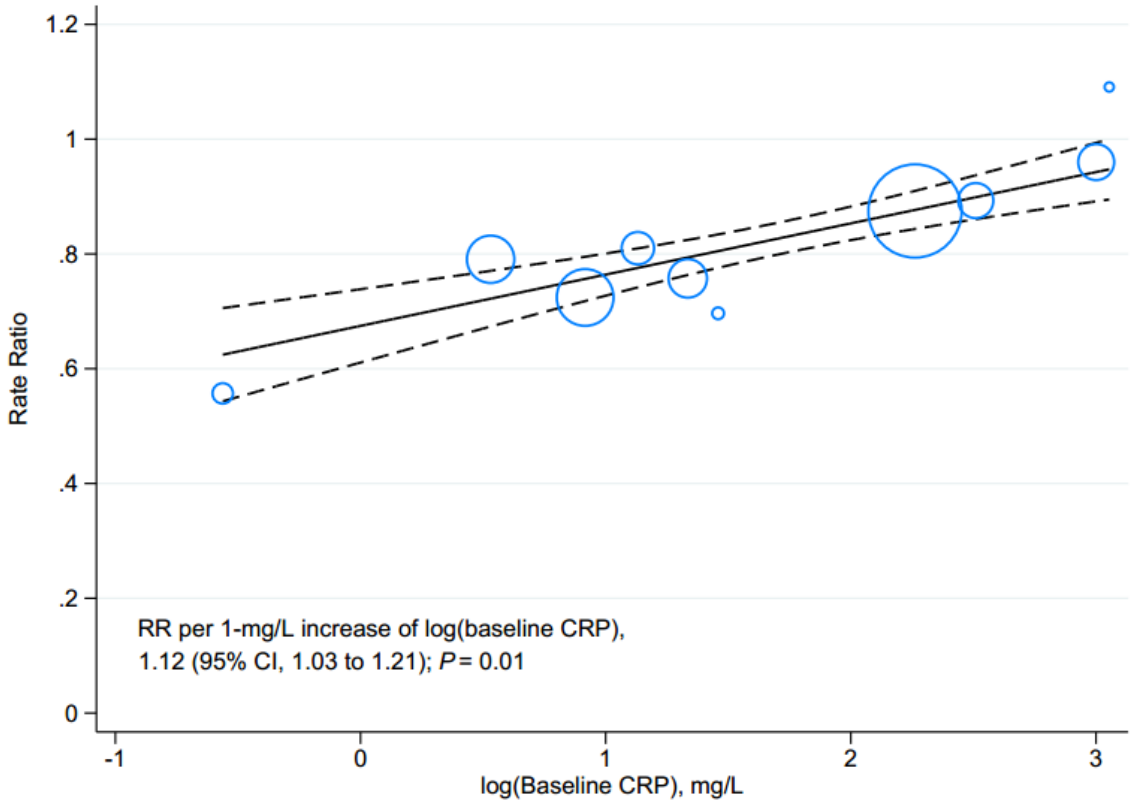
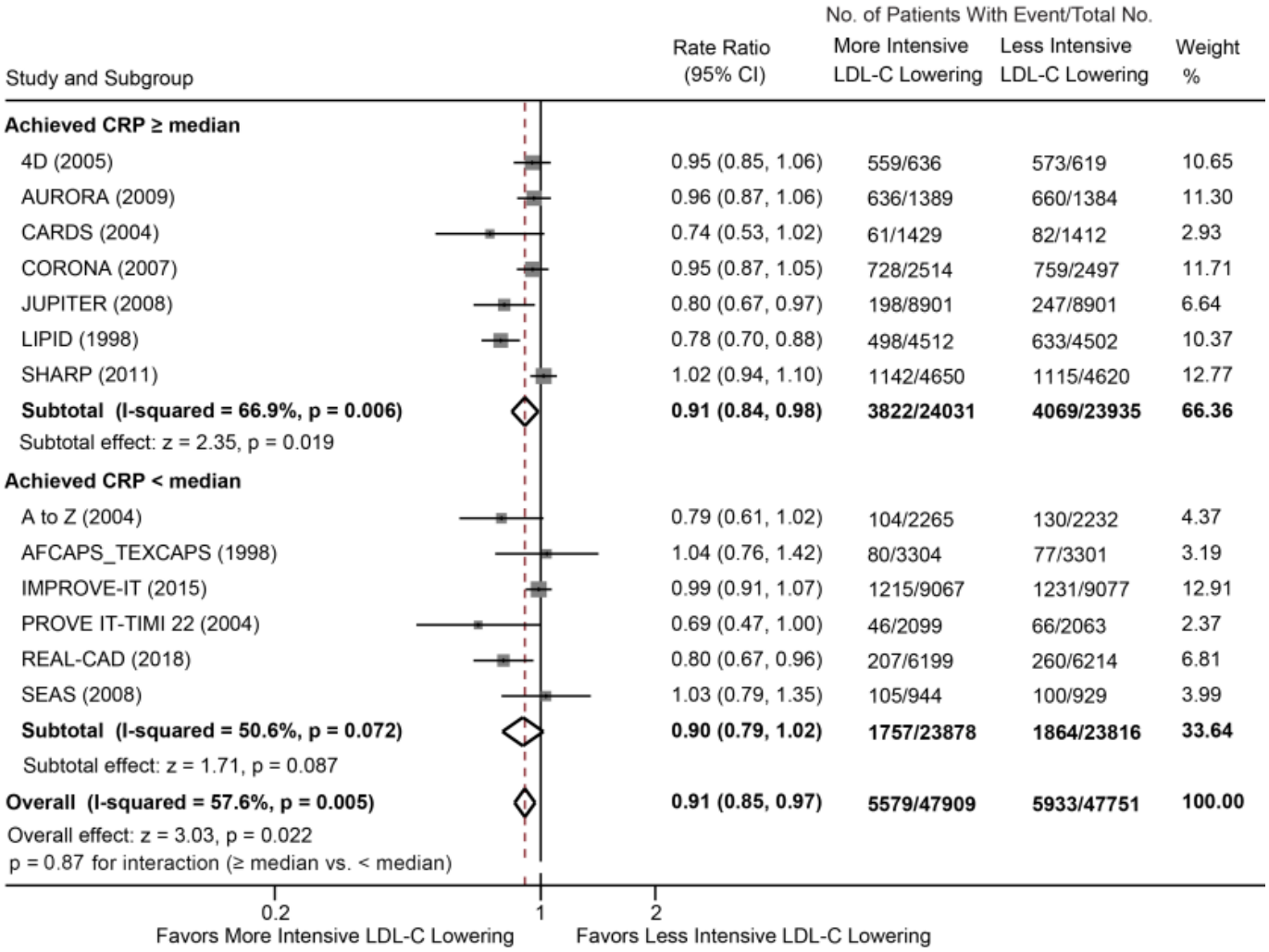
Figure S21. Meta-regression Analysis of Myocardial Infarction Rate Ratio Plotted Against log(baseline CRP Concentrations) in the Secondary Prevention Trials.



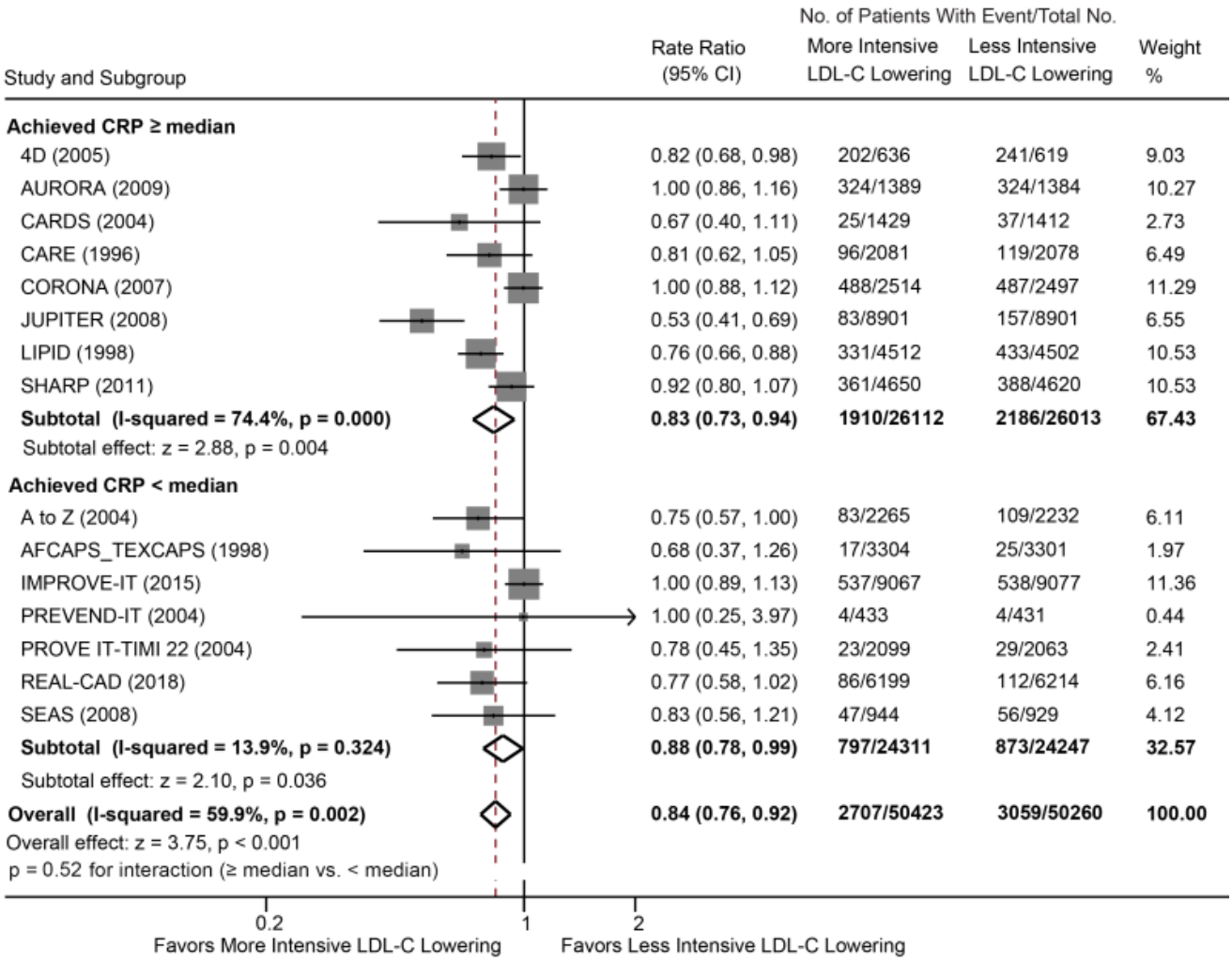
CRP, C-reactive protein; RR, rate ratio.

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



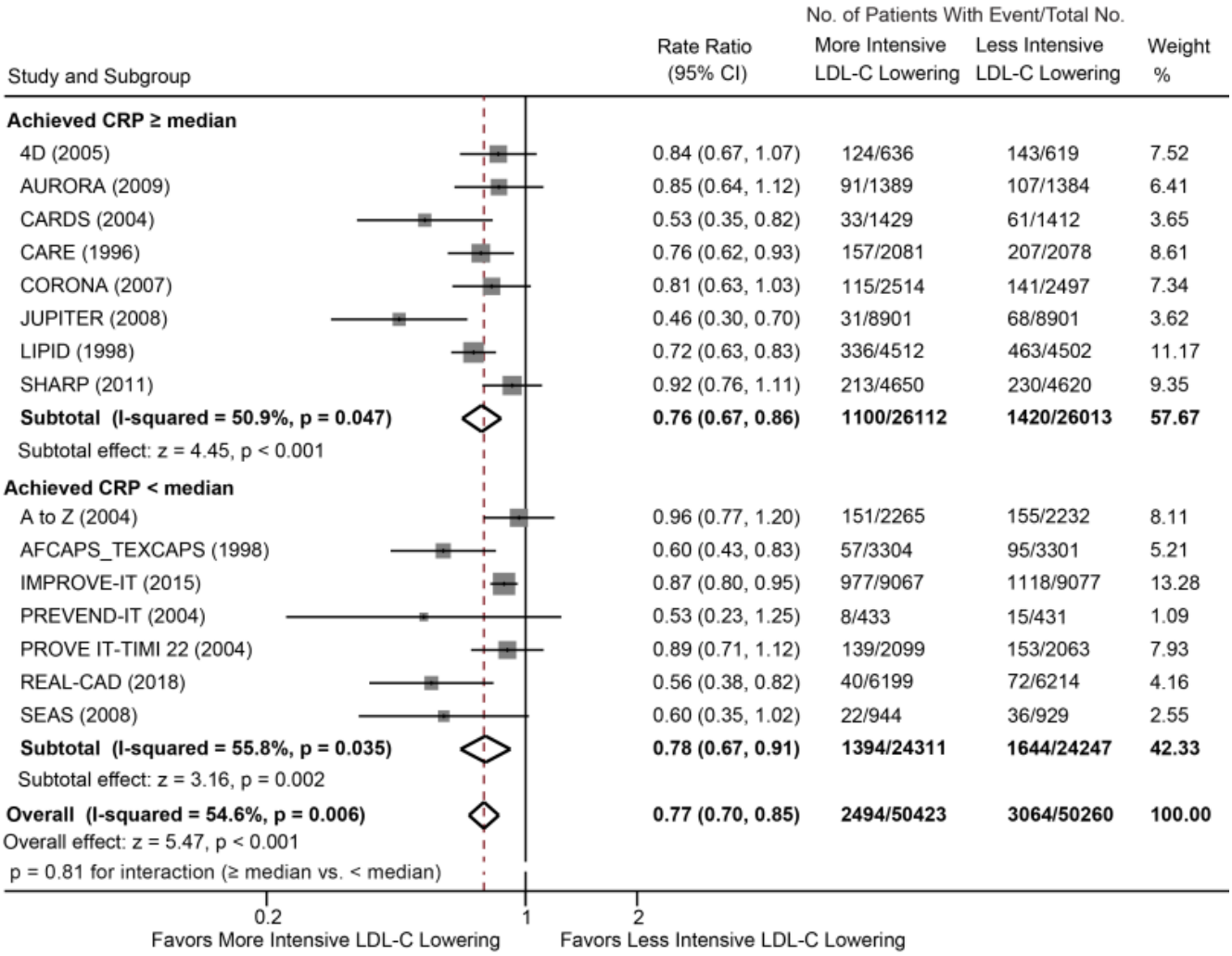
4D, German Diabetes Dialysis Study—Die Deutsche Diabetes Dialyse Studies; A to Z, Aggrastat to Zocor; AFCAPS-TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; AURORA, An Assessment of Survival and Cardiovascular Events; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol 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.



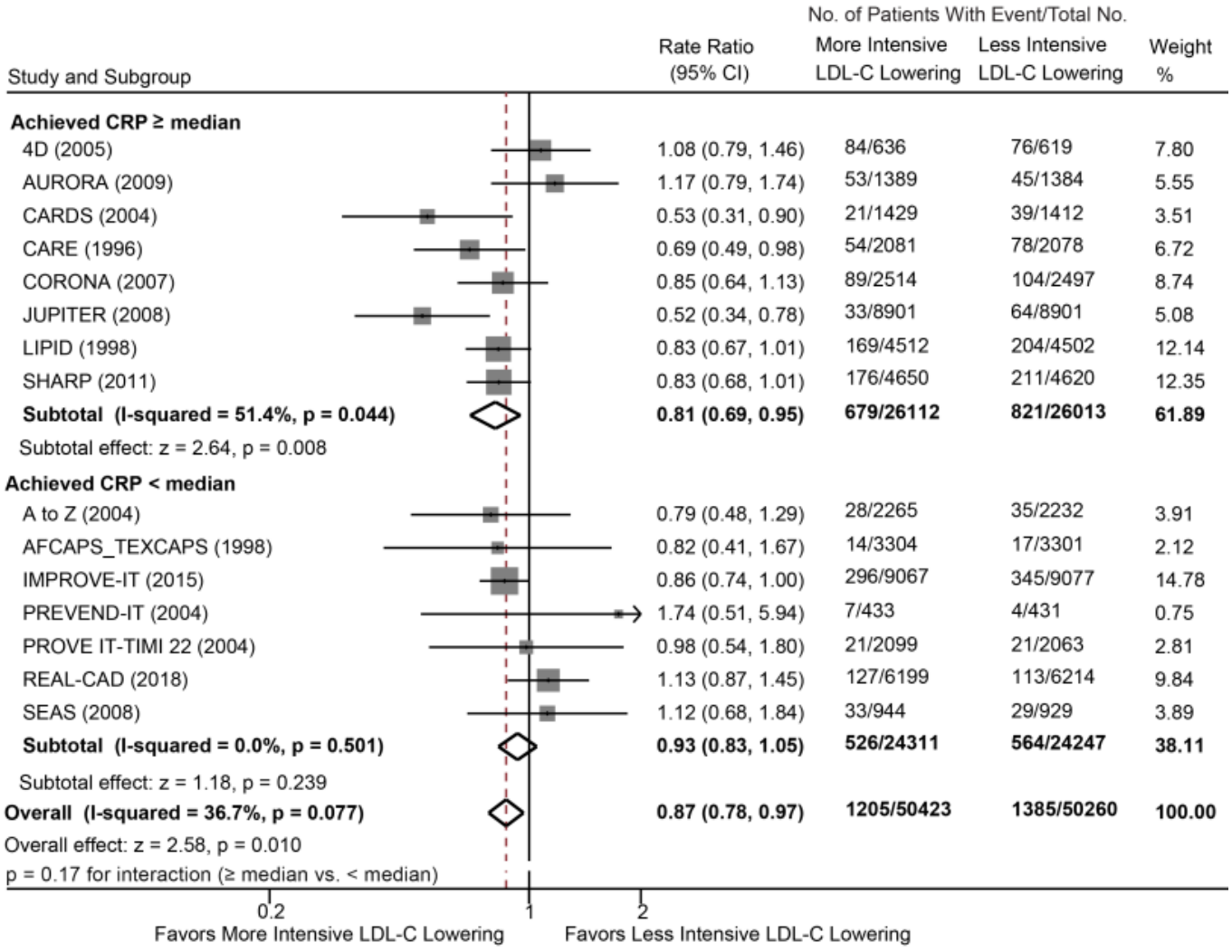
4D, German Diabetes Dialysis Study—Die Deutsche Diabetes Dialyse Studies; A to Z, Aggrastat to Zocor; AFCAPS-TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; AURORA, An Assessment of Survival and Cardiovascular Events; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol 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.



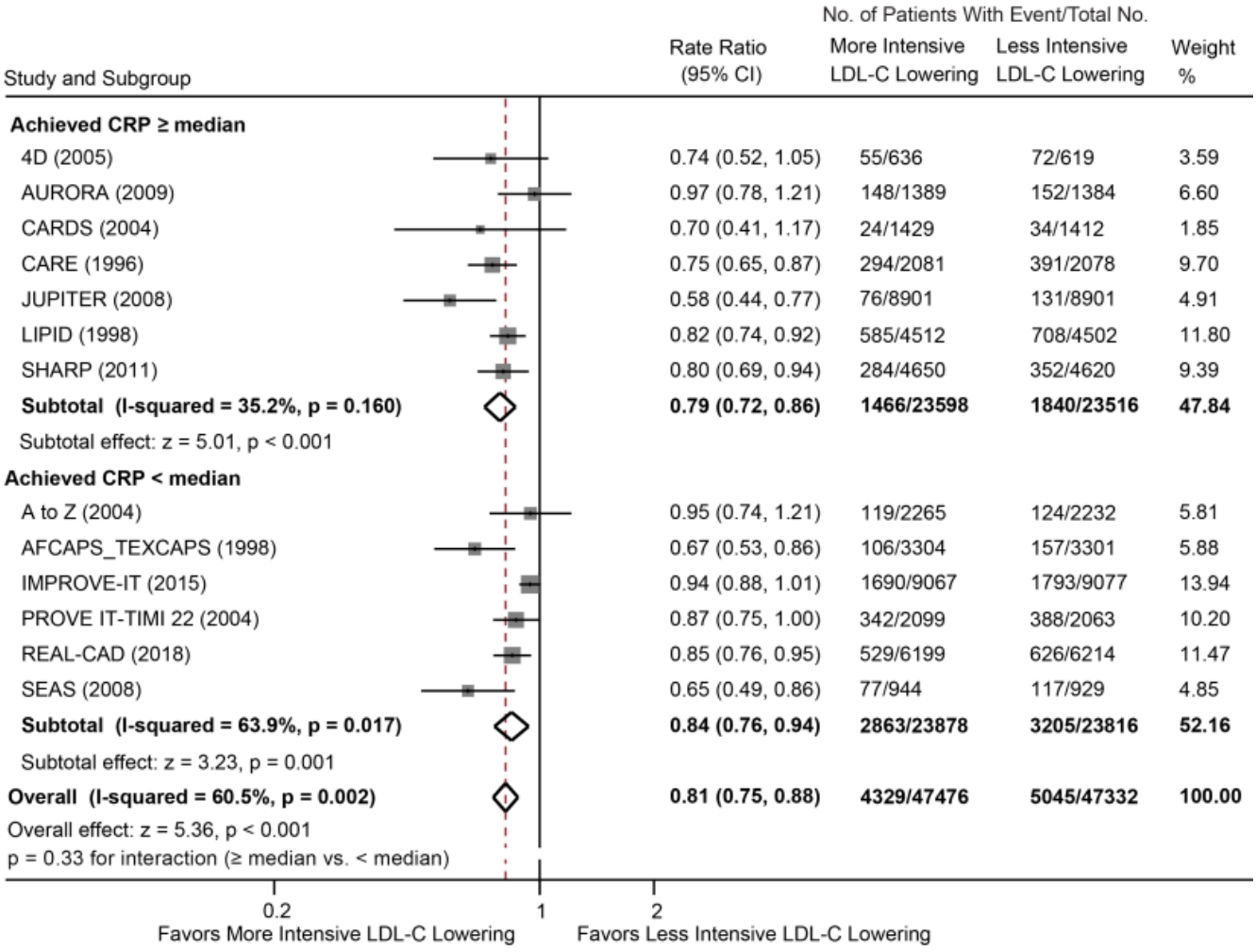
4D, German Diabetes Dialysis Study—Die Deutsche Diabetes Dialyse Studies; A to Z, Aggrastat to Zocor; AFCAPS-TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; AURORA, An Assessment of Survival and Cardiovascular Events; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol 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 S25. Meta-analysis of Stroke Stratified by the Achieved CRP Concentrations.



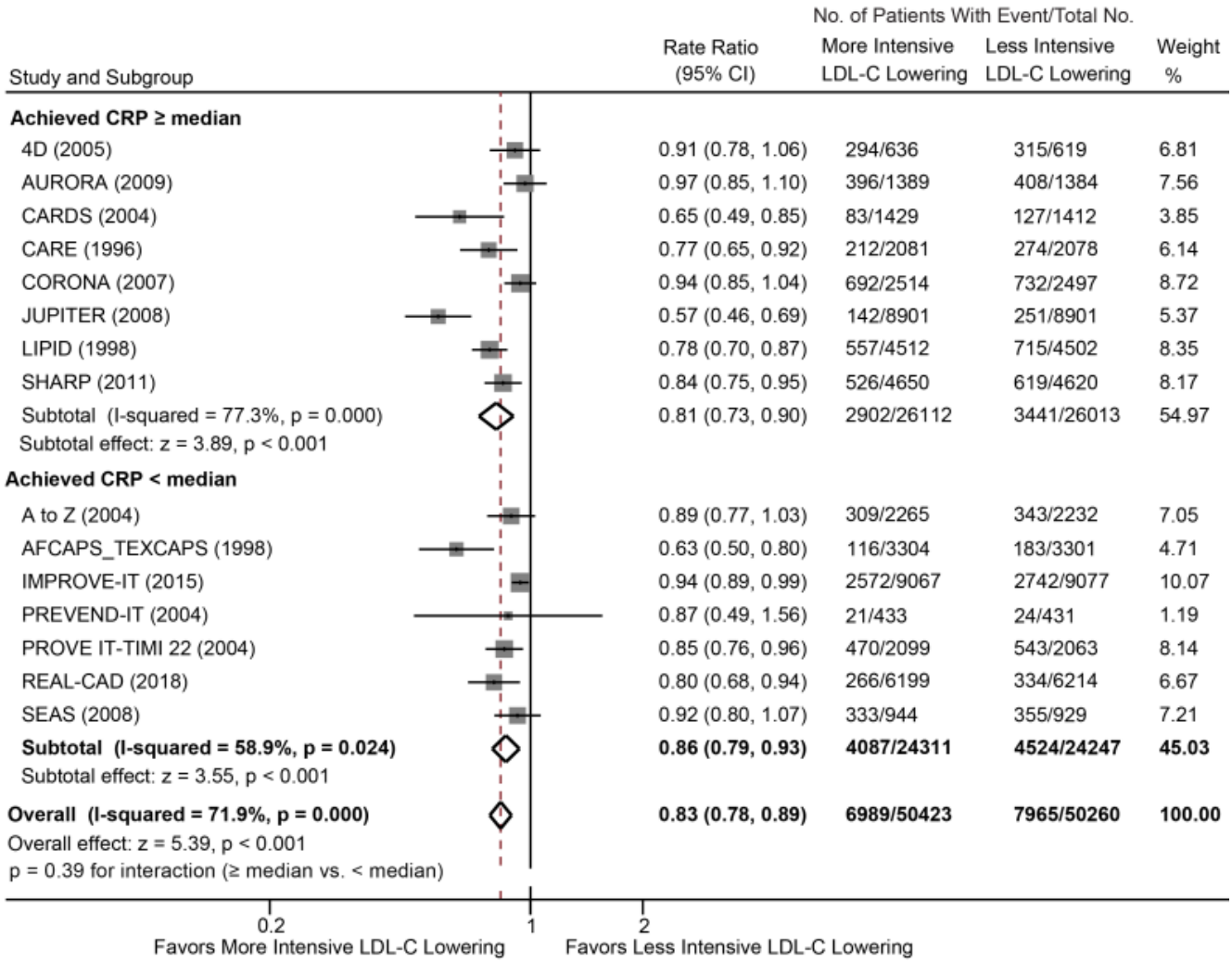
4D, German Diabetes Dialysis Study—Die Deutsche Diabetes Dialyse Studies; A to Z, Aggrastat to Zocor; AFCAPS-TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; AURORA, An Assessment of Survival and Cardiovascular Events; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol 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.



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.



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.