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 6 for obtaining and confirming data from investigators.				

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., I²) 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.					
Study characteristics	18	18 For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.				
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	across studies 22 Present results of any assessment of risk of bias across studies (see Item 15).					
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	scuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of entified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

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

Table S1. Study and Patient Baseline Characteristics.

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

HOPE-3	201 6	12705	65.8	53.7	0	0	6	38	28	27.1	5.6	Rosuvastat in (10 mg)	6361	2	128	Placebo	6344	2	128	1.2	28.2
HPS	200 2	20536	64	75	65	43	29	NA	NA	NA	5	Simvastatin (40 mg)	1026 9	3.1	131.5	Placebo	1026 7	3.1	131	1.38	26.3
IMPROV E-IT	201 5	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	Simvasta tin (40 mg)	9077	9.5	94	0.3	16
JUPITER	200 8	17802	66	62	0	0	<1	NA	16	28.3	1.9	Rosuvastat in (20 mg)	8901	4.2	108	Placebo	8901	4.3	108	1.5	54
LIPID	199 8	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	201 6	798	62	72	100	0	32.5	64.6	20.6	NA	1	Atorvastati n (40-80 mg)	400	4.3	131	Atorvasta tin (20 mg)	398	4.5	131	NA	NA
PREVEN D-IT	200 4	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
PROSPE R	200 2	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	200 4	4162	58	78	100	8	18	50	36.8	NA	2	Atorvastati n (80 mg)	2099	12.3	106	Pravastat in (40 mg)	2063	12.3	106	0.8	34
REAL-CA D	201 8	12413	68	83	100	14	40	75.7	16.4	24.6	3.9	Pitavastatin (4mg)	6199	0.57	88	Pitavasta tin (1mg)	6214	0.59	88	0.1	14
SEAS	200 8	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	201	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	200 5	10001	61	81	100	15	15	54	76	28.4	4.9	Atorvastati n (80 mg)	4995	1.7	97	Atorvasta tin (10	5006	1.7	98	NA	23.3
WOSCO PS	199 5	6595	55	100	5	3	1	16	78		4.9	Pravastatin (40 mg)	3302	2	192	mg) Placebo	3293	2	192	NA	41.3

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

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

Table S2. Study Characteristics of the Included Randomized Trials.

Trial	Year	Selected composite	Reported primary	Definition of myocardial infarction
		endpoint (major adverse	endpoint in original trial	-
		cardiovascular events)		
4D	2005	Cardiac death, nonfatal	Cardiac death, nonfatal	Two of the following three criteria
		myocardial infarction, and	myocardial infarction, and	were met: typical symptoms; elevated
		stroke	stroke	levels of cardiac enzymes (i.e., a
				level of creatine kinase MB above 5
				percent of the total level of creatine
				kinase, a level of lactic
				dehydrogenase 1.5 times the upper
				limit of normal, or a level of troponin T
				greater than 2 ng per milliliter); or
				diagnostic changes on the
A 1 . 7	0004	On the second section	On Property land	electrocardiogram.
A to Z	2004	Cardiovascular death,	Cardiovascular death,	NA
		myocardial infarction,	myocardial infarction,	
		Stroke, or Hospitalization for acute coronary	Stroke, or Hospitalization for acute coronary	
		syndrome	syndrome	
AFCAPS_	1998	Myocardial infarction,	Myocardial infarction,	NA
TEXCAPS	1550	unstable angina, or sudden	unstable angina, or sudden	
/ (0 / 1 0		cardiac death	cardiac death	
ALERT	2003	Cardiac death, definite or	Cardiac death, definite or	An adjudicated MI was classified as
		probable non-fatal	probable non-fatal	definite if a new Q-wave developed in
		myocardial infarction,	myocardial infarction,	the presence of abnormal cardiac
		coronary-artery bypass	coronary-artery bypass	markers or symptoms, or pathological
		grafting, percutaneous	grafting, percutaneous	ST elevations and T-wave changes
		coronary intervention	coronary intervention	developed in the presence of
				abnormal cardiac markers plus
				symptoms. An MI was classified as
				probable if pathological ST elevations
				and T-wave changes developed in
				the presence of abnormal cardiac
ASCOT-LL	2003	Total cardiovascular events	Cardiovascular death and	markers or symptoms NA
ASCOT-LL A	2003	and procedures	non-fatal myocardial	IVA
		ana procedures	infarction	
AURORA	2009	Nonfatal myocardial	Nonfatal myocardial	NA
		infarction, nonfatal stroke,	infarction, nonfatal stroke,	
		or death from	or death from	
		cardiovascular causes	cardiovascular causes	
CARDS	2004	Cardiovascular death,	Cardiovascular death,	NA
		myocardial infarction,	myocardial infarction,	
		stroke, unstable angina or	stroke, unstable angina or	
		revascularization	revascularization	

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

		infarction, and unplanned 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.
-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.	
0540	0000	O . F I . I I I	O . P I I II	ALA
SEAS	2008	Cardiovascular death, aort	Cardiovascular death,	NA
		ic-valve replacement,	aortic-valve replacement,	
		nonfat al myocardial infarct	nonfat al myocardial infarct	
		ion, hospitalization for	ion, hospitalization for	
		unstable angina pectoris,	unstable angina pectoris,	
		heart failure,	heart failure,	
		coronary-artery bypass	coronary-artery bypass	
		grafting, percutaneous	grafting, percutaneous	
		coronary intervention, and	coronary intervention, and	
		nonhemorrhagic stroke	nonhemorrhagic stroke	
SHARP	2011	Cardiovascular death,	Non-fatal myocardial	NA
		myocardial infarction,	infarction or coronary death,	
		stroke, or coronary	non-haemorrhagic stroke,	
		revascularization	or any arterial	
			revascularisation procedure	
TNT	2005	Cardiovascular death,	Cardiovascular death,	NA
		nonfatal non-	nonfatal non-	
		procedure-related	procedure-related	
		myocardial infarction, or	myocardial infarction, or	
		resuscitation after cardiac	resuscitation after cardiac	
		arrest	arrest	
WOSCOP	1995	Cardiovascular death or	Cardiovascular death or	NA
S		nonfatal myocardial	nonfatal myocardial	
		infarction	infarction	

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

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

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

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

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

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

Table S4. Listing of Potential Sources of Bias.

Study	Year	Random	Allocatio	Blinding of	Blinding of	Incomple	Selective	Other
		sequenc	n	participants	outcome	te	reporting	bias
		е	conceal	and	assessme	outcome	(reportin	, siac
		generatio	ment	personnel	nt	data	g bias)	
		n	(selectio	(performanc	(detection	(attrition	g Diac,	
		(selectio	n bias)	e bias)	bias)	bias)		
		n bias)	ii biao,	o blac,	blue,	Diac,		
4D	2005	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
A to Z	2004	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	High risk
71.02	200.	2011 11011	risk	20W Hok	20W Hok	20W Hok	20W Hork	I ngi nok
AFCAPS_T	1998	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
EXCAPS			risk					
ALERT	2003	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	High risk
			risk					3
ASCOT-LL	2003	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	High risk
Α			risk					
AURORA	2009	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	High risk
			risk					
CARDS	2004	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
CARE	1996	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear
			risk					risk
CORONA	2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
HIJ-PROP	2017	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	Low risk
ER			risk					
HOPE-3	2016	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	High risk
			risk					
HPS	2002	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
IMPROVE-I	2015	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	High risk
Т			risk					
JUPITER	2008	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
		risk						
LIPID	1998	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	High risk
			risk					
Liu, et al	2016	Low risk	Unclear	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
			risk					
PREVEND-	2004	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
IT								
PROSPER	2002	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk
PROVE	2004	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
IT-TIMI 22	2042	risk	l lacter:	l la alees del	l au sial	I amendal	I approvided	Lineles
REAL-CAD	2018	Low risk	Unclear	Unclear risk	Low risk	Low risk	Low risk	Unclear
CE A C	2000	I averaled	risk	llaster (1)	l au sial	l la al a a :	I approvided	risk
SEAS	2008	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	High risk
SHARP	2011	Low riok	Low rick	Lowrick	Low risk		Low rick	High rick
SHARP	2011	Low risk	Low risk	Low risk	LOW HSK	Low risk	Low risk	High risk

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

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

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

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

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

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

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		

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

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

	≥ 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.

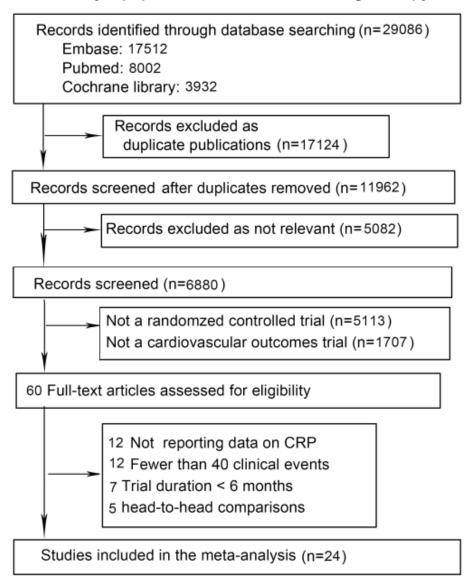
Table S11. Multivariable Meta-regression Models for the Association of Each 1-mg/L Reduction in log(baseline CRP Concentration), Magnitude of Reduction in CRP Concentration, and Mortality and Cardiovascular Outcomes in Primary Prevention Trials*.

		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.

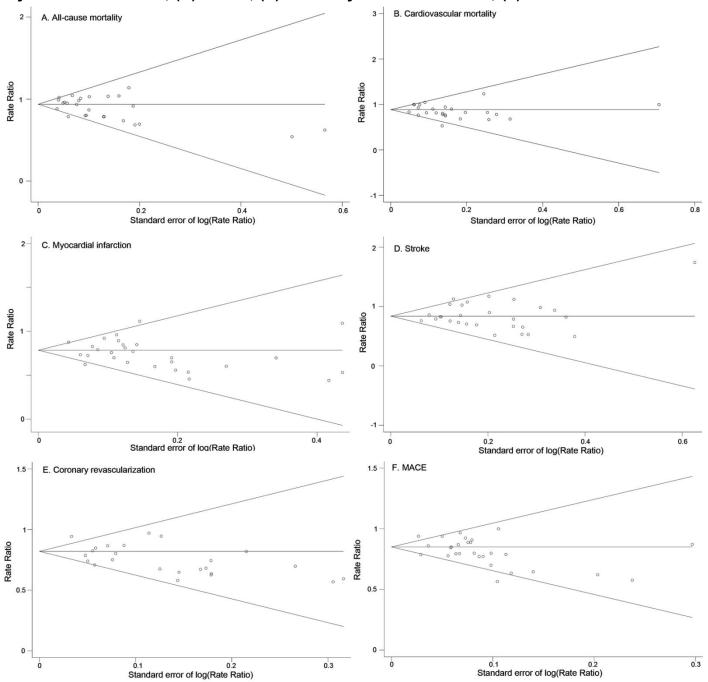
CRP, C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event.

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.

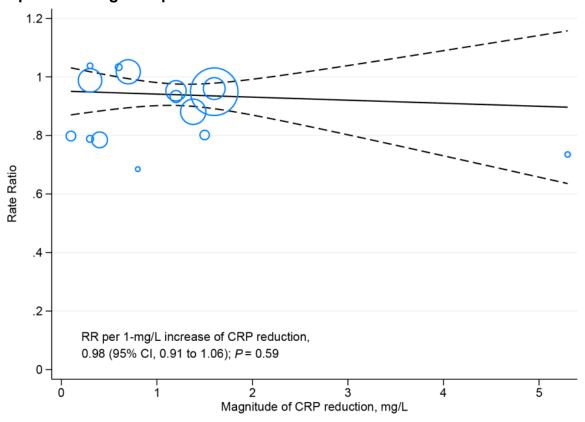


Figure S4. Meta-analysis of All-cause Mortality Stratified by Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.

	No. of Patients With Event/Total No.			
	Rate Ratio	More Intensive	Less Intensive	Weight
Study and Subgroup	(95% CI)	LDL-C Lowering	LDL-C Lowering	%
CRP reduction ≥ median				
4D (2005)	0.95 (0.85, 1.06)	559/636	573/619	8.83
AURORA (2009)	0.96 (0.87, 1.06)	636/1389	660/1384	9.48
CARDS (2004)	0.74 (0.53, 1.02)	61/1429	82/1412	2.14
CORONA (2007)	0.95 (0.87, 1.05)	728/2514	759/2497	9.89
HOPE-3 (2016)	0.93 (0.80, 1.08)	334/6361	357/6344	6.73
HPS (2002)	0.88 (0.82, 0.95)	1328/10269	1507/10267	11.54
JUPITER (2008) — <u>■ †</u>	0.80 (0.67, 0.97)	198/8901	247/8901	5.14
PROVE IT-TIMI 22 (2004)	0.69 (0.47, 1.00)	46/2099	66/2063	1.71
SHARP (2011)	1.02 (0.94, 1.10)	1142/4650	1115/4620	10.99
Subtotal (I-squared = 45.4%, p = 0.067) Subtotal effect: z = 2.75, p = 0.006	0.92 (0.87, 0.98)	5032/38248	5366/38107	66.45
CRP reduction < median				
A to Z (2004)	0.79 (0.61, 1.02)	104/2265	130/2232	3.27
AFCAPS_TEXCAPS (1998)	1.04 (0.76, 1.42)	80/3304	77/3301	2.34
IMPROVE-IT (2015)	0.99 (0.91, 1.07)	1215/9067	1231/9077	11.14
LIPID (1998)	0.78 (0.70, 0.88)	498/4512	633/4502	8.55
REAL-CAD (2018)	0.80 (0.67, 0.96)	207/6199	260/6214	5.29
SEAS (2008)	1.03 (0.79, 1.35)	105/944	100/929	2.97
Subtotal (I-squared = 67.1%, p = 0.010) Subtotal effect: z = 1.93, p = 0.053	0.89 (0.79, 1.00)	2209/26291	2431/26255	33.55
Overall (I-squared = 54.0%, p = 0.007) Overall effect: z = 3.57, p < 0.001 p = 0.58 for interaction (≥ median vs. < median)	0.91 (0.86, 0.96)	7241/64539	7797/64362	100.00
02 1	1			
Favors More Intensive LDL-C Lowering	Favors Less Intensive LDL	-C Lowering		

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

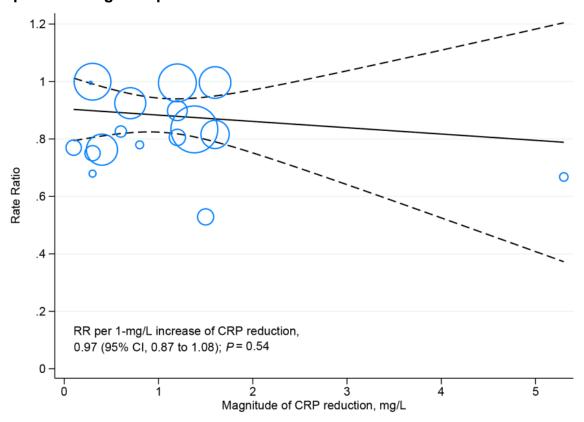


Figure S6. Meta-analysis of Cardiovascular Mortality Stratified by Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.

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

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

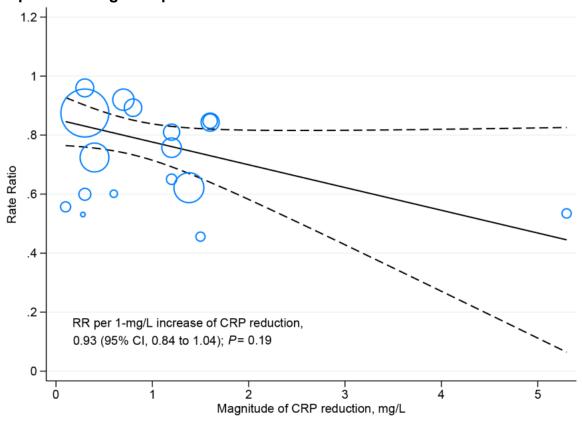


Figure S8. Meta-analysis of Myocardial Infarction Stratified by Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.

	No. of Patients With Event/Total No.			
	Rate Ratio	More Intensive	Less Intensive	Weight
Study and Subgroup	(95% CI)	LDL-C Lowering	LDL-C Lowering	%
CRP reduction ≥ median				
4D (2005)	0.84 (0.67, 1.07)	124/636	143/619	6.59
AURORA (2009)	0.85 (0.64, 1.12)	91/1389	107/1384	5.77
CARDS (2004)	0.53 (0.35, 0.82)	33/1429	61/1412	3.52
CARE (1996)	0.76 (0.62, 0.93)	157/2081	207/2078	7.36
CORONA (2007)	0.81 (0.63, 1.03)	115/2514	141/2497	6.47
HOPE-3 (2016)	0.65 (0.45, 0.95)	45/6361	69/6344	4.10
HPS (2002)	0.62 (0.55, 0.71)	357/10269	574/10267	9.22
JUPITER (2008) — ■	0.46 (0.30, 0.70)	31/8901	68/8901	3.49
PROVE IT-TIMI 22 (2004)	0.89 (0.71, 1.12)	139/2099	153/2063	6.89
SHARP (2011)	0.92 (0.76, 1.11)	213/4650	230/4620	7.86
Subtotal (I-squared = 64.1%, p = 0.003)	0.74 (0.65, 0.85)	1305/40329	1753/40185	61.27
Subtotal effect: z = 4.50, p < 0.001				
CRP reduction < median				
A to Z (2004)	0.96 (0.77, 1.20)	151/2265	155/2232	7.01
AFCAPS_TEXCAPS (1998)	0.60 (0.43, 0.83)	57/3304	95/3301	4.83
IMPROVE-IT (2015)	0.87 (0.80, 0.95)	977/9067	1118/9077	10.26
LIPID (1998)	0.72 (0.63, 0.83)	336/4512	463/4502	9.02
PREVEND-IT (2004)	0.53 (0.23, 1.25)	8/433	15/431	1.12
REAL-CAD (2018)	0.56 (0.38, 0.82)	40/6199	72/6214	3.96
SEAS (2008)	0.60 (0.35, 1.02)	22/944	36/929	2.53
Subtotal (I-squared = 64.5%, p = 0.010) Subtotal effect: z = 3.75, p < 0.001	0.75 (0.64, 0.87)	1591/26724	1954/26686	38.73
Overall (I-squared = 64.9%, p = 0.000) Overall effect: z = 6.02, p < 0.001 p = 0.97 for interaction (≥ median vs. < median)	0.75 (0.68, 0.82)	2896/67053	3707/66871	100.00
0.2	1			
	vors Less Intensive LDL-	C Lowering		

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

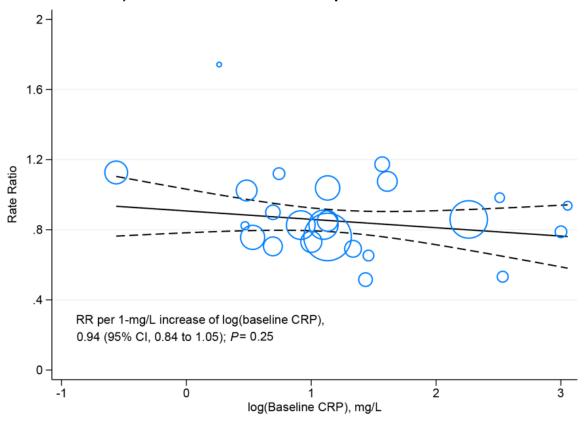


Figure S10. Meta-regression Analysis of Stroke Rate Ratio Plotted Against Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.

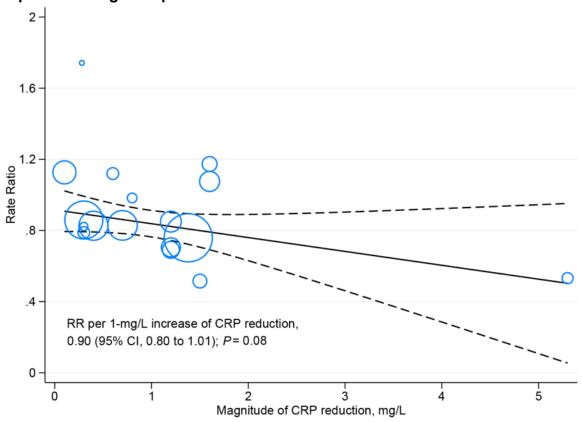


Figure S11. Meta-analysis of Stroke Stratified by Baseline CRP Concentrations.

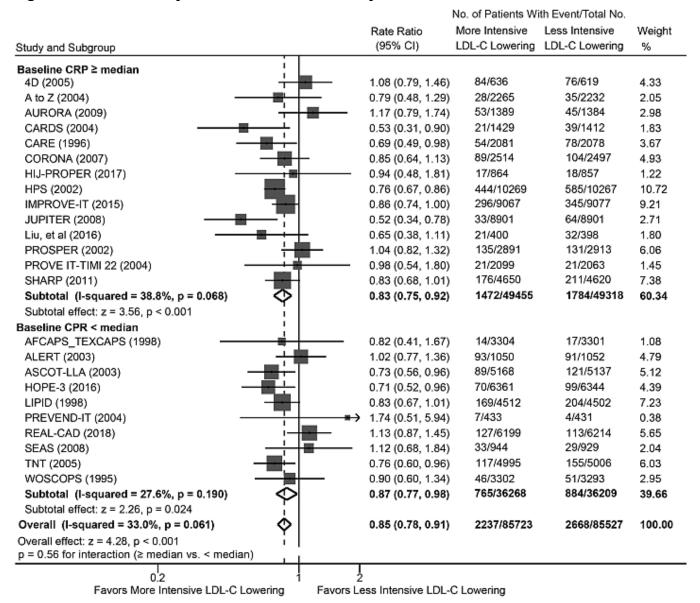


Figure S12. Meta-analysis of Stroke Stratified by Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.

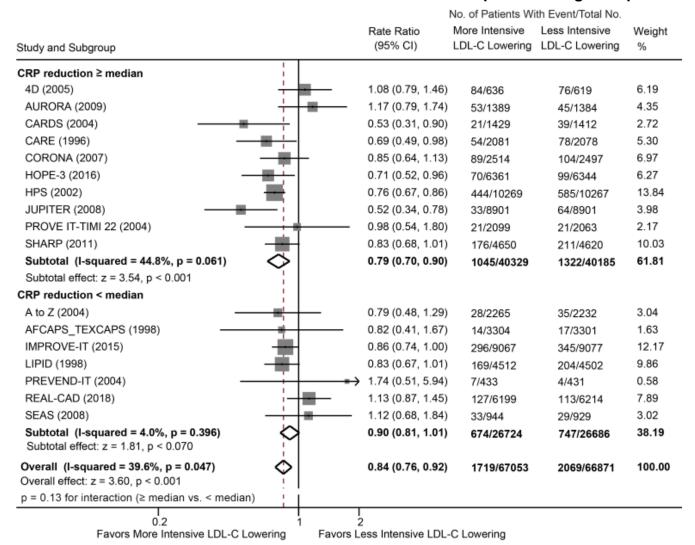


Figure S13. Meta-regression Analysis of Coronary Revascularization Rate Ratio Plotted Against log(baseline CRP Concentrations) in the More Intensive Group.

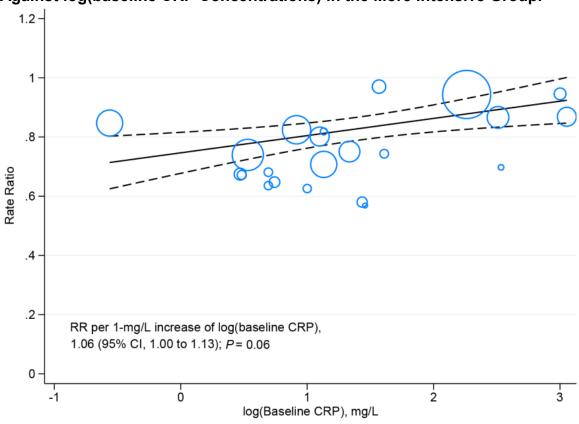


Figure S14. Meta-regression Analysis of Coronary Revascularization Rate Ratio Plotted Against Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.

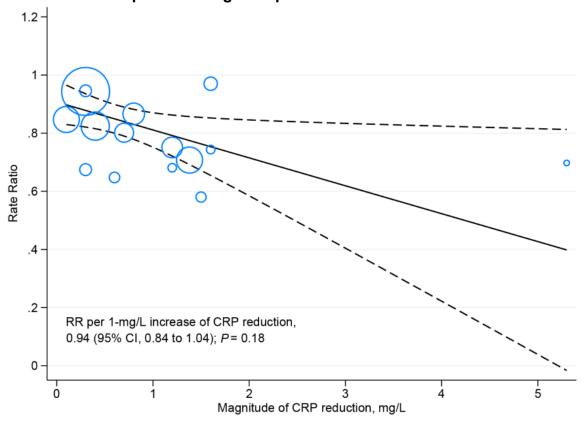


Figure S15. Meta-analysis of Coronary Revascularization Stratified by Baseline CRP Concentrations.

		No. of Patients With Event/Total No.			
	Rate Ratio	More Intensive	Less Intensive	Weight	
Study and Subgroup	(95% CI)	LDL-C Lowering	LDL-C Lowering	%	
Baseline CRP ≥ median					
4D (2005)	0.74 (0.52, 1.05)	55/636	72/619	2.51	
A to Z (2004)	— 0.95 (0.74, 1.21)	119/2265	124/2232	3.96	
AURORA (2009)	— 0.97 (0.78, 1.21)	148/1389	152/1384	4.46	
CARDS (2004)	— 0.70 (0.41, 1.17)	24/1429	34/1412	1.32	
CARE (1996)	0.75 (0.65, 0.87)	294/2081	391/2078	6.34	
HIJ-PROPER (2017)	0.87 (0.73, 1.03)	225/864	257/857	5.69	
HPS (2002)	0.71 (0.63, 0.79)	513/10269	725/10267	7.42	
IMPROVE-IT (2015)	0.94 (0.88, 1.01)	1690/9067	1793/9077	8.72	
JUPITER (2008) —■	0.58 (0.44, 0.77)	76/8901	131/8901	3.39	
Liu, et al (2016)	0.57 (0.31, 1.03)	16/400	28/398	1.04	
PROSPER (2002)	— 0.82 (0.54, 1.25)	39/2891	48/2913	1.88	
PROVE IT-TIMI 22 (2004) +	0.87 (0.75, 1.00)	342/2099	388/2063	6.63	
SHARP (2011)	0.80 (0.69, 0.94)	284/4650	352/4620	6.16	
Subtotal (I-squared = 66.1%, p = 0.000)	0.81 (0.74, 0.89)	3825/46941	4495/46821	59.52	
Subtotal effect: z = 4.60, p < 0.001	, , ,				
Baseline CPR < median					
AFCAPS_TEXCAPS (1998)	0.67 (0.53, 0.86)	106/3304	157/3301	4.01	
ALERT (2003)	0.67 (0.48, 0.93)		88/1052	2.75	
ASCOT-LLA (2003)	0.63 (0.44, 0.89)		81/5137	2.51	
HOPE-3 (2016)	0.68 (0.49, 0.96)		82/6344	2.62	
LIPID (1998)	0.82 (0.74, 0.92)		708/4502	7.55	
REAL-CAD (2018)	0.85 (0.76, 0.95)		626/6214	7.36	
SEAS (2008)	0.65 (0.49, 0.86)		117/929	3.35	
TNT (2005)	0.74 (0.67, 0.82)		904/5006	7.83	
WOSCOPS (1995)	0.64 (0.45, 0.90)		80/3293	2.50	
Subtotal (I-squared = 27.6%, p = 0.199)	0.75 (0.70, 0.81)		2843/35778	40.48	
Subtotal effect: z = 7.51, p < 0.001	()				
Overall (I-squared = 61.6%, p = 0.000)	0.78 (0.73, 0.83)	6006/82776	7338/82599	100.00	
Overall effect: z = 7.56, p < 0.001	55 (56) 6166)				
p = 0.24 for interaction (≥ median vs. < median)					
·					
0.2	2				
Favors More Intensive LDL-C Lowering	Favors Less Intensive LDL	-C Lowering			

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

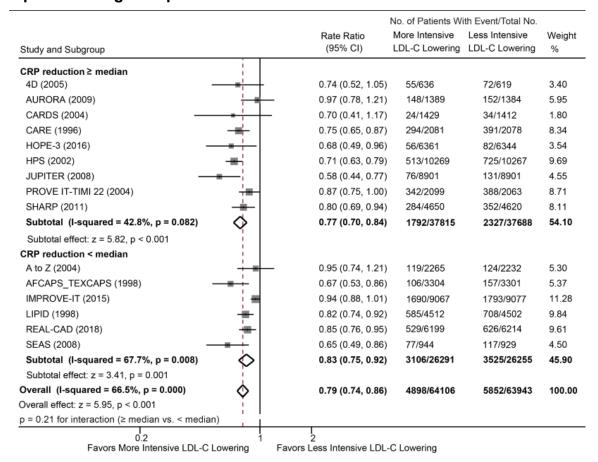


Figure S17. Meta-regression Analysis of MACE Rate Ratio Plotted Against log(baseline CRP Concentrations) in the More Intensive Group.

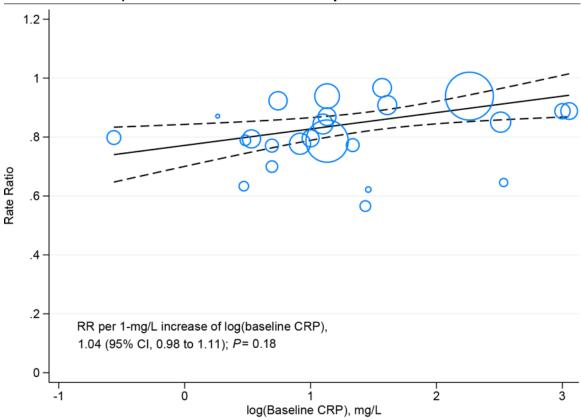


Figure S18. Meta-regression Analysis of MACE Rate Ratio Plotted Against Magnitude of Reduction in CRP Concentrations Between More-intensive and Less-Intensive Lipid-Lowering Group.

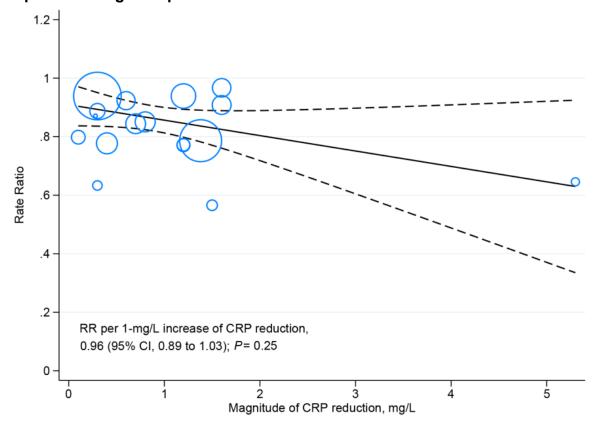


Figure S19. Meta-analysis of MACE Stratified by Baseline CRP Concentrations.

	No. of Patients With Event/Total No.			
	Rate Ratio	More Intensive	Less Intensive	Weight
Study and Subgroup	(95% CI)	LDL-C Lowering	LDL-C Lowering	%
Baseline CRP ≥ median				
4D (2005)	0.91 (0.78, 1.06)	294/636	315/619	4.22
A to Z (2004)	0.89 (0.77, 1.03)	309/2265	343/2232	4.39
AURORA (2009)	0.97 (0.85, 1.10)	396/1389	408/1384	4.77
CARDS (2004)	0.65 (0.49, 0.85)	83/1429	127/1412	2.22
CARE (1996)	0.77 (0.65, 0.92)	212/2081	274/2078	3.74
CORONA (2007)	0.94 (0.85, 1.04)	692/2514	732/2497	5.67
HIJ-PROPER (2017)	0.89 (0.76, 1.04)	283/864	316/857	4.27
HPS (2002)	0.79 (0.74, 0.83)	2033/10269	2585/10267	6.70
IMPROVE-IT (2015)	0.94 (0.89, 0.99)	2572/9067	2742/9077	6.79
JUPITER (2008)	0.57 (0.46, 0.69)	142/8901	251/8901	3.21
Liu, et al (2016)	0.62 (0.42, 0.93)	35/400	56/398	1.25
PROSPER (2002)	0.87 (0.76, 0.99)	408/2891	473/2913	4.86
PROVE IT-TIMI 22 (2004)	0.85 (0.76, 0.96)	470/2099	543/2063	5.21
SHARP (2011)	0.84 (0.75, 0.95)	526/4650	619/4620	5.24
Subtotal (I-squared = 74.8%, p = 0.000)	0.84 (0.79, 0.90)	8455/49455	9784/49318	62.53
Subtotal effect: z = 5.26, p < 0.001				
Baseline CPR < median				
AFCAPS_TEXCAPS (1998)	0.63 (0.50, 0.80)	116/3304	183/3301	2.77
ALERT (2003)	0.79 (0.63, 0.98)	137/1050	174/1052	2.93
ASCOT-LLA (2003)	0.80 (0.70, 0.91)	389/5168	486/5137	4.80
HOPE-3 (2016)	0.77 (0.65, 0.91)	235/6361	304/6344	3.90
LIPID (1998)	0.78 (0.70, 0.87)	557/4512	715/4502	5.38
PREVEND-IT (2004)	0.87 (0.49, 1.56)	21/433	24/431	0.64
REAL-CAD (2018)	0.80 (0.68, 0.94)	266/6199	334/6214	4.11
SEAS (2008)	0.92 (0.80, 1.07)	333/944	355/929	4.51
TNT (2005)	0.79 (0.70, 0.90)	434/4995	548/5006	4.98
WOSCOPS (1995)	0.70 (0.58, 0.85)	174/3302	248/3293	3.44
Subtotal (I-squared = 8.9%, p = 0.360)	0.79 (0.75, 0.83)	2662/36268	3371/36209	37.47
Subtotal effect: z = 8.74, p < 0.001				
Overall (I-squared = 67.5%, p = 0.000)	0.82 (0.78, 0.86)	11117/85723	13155/85527	100.00
Overall effect: z = 8.00, p < 0.001				
p = 0.16 for interaction (≥ median vs. < median)				
	Ţ			
0.2 1 Favors More Intensive LDL-C Lowering	Equare Lace Intensive LDL	CLowering		
ravois more intensive LDL-C Lowering	Favors Less Intensive LDL-	C Lowering		

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

		No. of Patients With Event/Total No.			
	Rate Ratio	More Intensive	Less Intensive	Weight	
Study and Subgroup	(95% CI)	LDL-C Lowering	LDL-C Lowering	%	
CRP reduction ≥ median					
4D (2005)	0.91 (0.78, 1.06)	294/636	315/619	5.82	
AURORA (2009)	0.97 (0.85, 1.10)	396/1389	408/1384	6.50	
CARDS (2004)	0.65 (0.49, 0.85)	83/1429	127/1412	3.23	
CARE (1996)	0.77 (0.65, 0.92)	212/2081	274/2078	5.23	
CORONA (2007)	0.94 (0.85, 1.04)	692/2514	732/2497	7.56	
HOPE-3 (2016)	0.77 (0.65, 0.91)	235/6361	304/6344	5.43	
HPS (2002)	0.79 (0.74, 0.83)	2033/10269	2585/10267	8.71	
JUPITER (2008)	0.57 (0.46, 0.69)	142/8901	251/8901	4.55	
PROVE IT-TIMI 22 (2004)	0.85 (0.76, 0.96)	470/2099	543/2063	7.02	
SHARP (2011)	0.84 (0.75, 0.95)	526/4650	619/4620	7.05	
Subtotal (I-squared = 73.6%, p = 0.000)	0.82 (0.75, 0.88)	5083/40329	6158/40185	61.10	
Subtotal effect: z = 5.04, p < 0.001					
CRP reduction < median					
A to Z (2004)	0.89 (0.77, 1.03)	309/2265	343/2232	6.04	
AFCAPS_TEXCAPS (1998) —■	0.63 (0.50, 0.80)	116/3304	183/3301	3.98	
IMPROVE-IT (2015)	0.94 (0.89, 0.99)	2572/9067	2742/9077	8.81	
LIPID (1998)	0.78 (0.70, 0.87)	557/4512	715/4502	7.22	
PREVEND-IT (2004)	0.87 (0.49, 1.56)	21/433	24/431	0.98	
REAL-CAD (2018)	0.80 (0.68, 0.94)	266/6199	334/6214	5.70	
SEAS (2008)	0.92 (0.80, 1.07)	333/944	355/929	6.19	
Subtotal (I-squared = 70.3%, p = 0.003) Subtotal effect: z = 3.52, p < 0.001	0.84 (0.76, 0.93)	4174/26724	4696/26686	38.90	
Overall (I-squared = 74.1%, p = 0.000) Overall effect: z = 6.22, p < 0.001	0.82 (0.78, 0.88)	9257/67053	10854/66871	100.00	
p = 0.63 for interaction (≥ median vs. < median)					
0.2	2				
Favors More Intensive LDL-C Lowering	Favors Less Intensive LDL-	C Lowering			

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

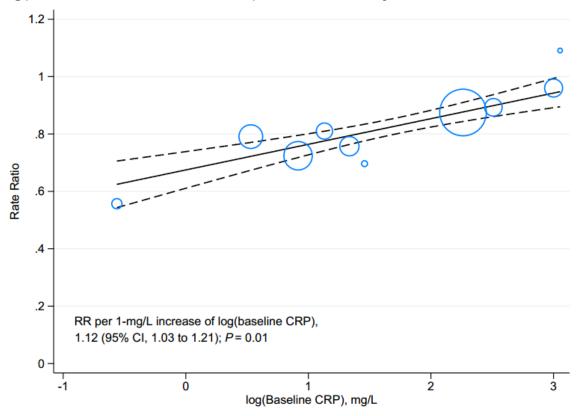


Figure S22. Meta-analysis of All-Cause Mortality Stratified by the Achieved CRP Concentrations.

		No. of Patients With Event/Total N			
Children and Culturary	Rate Ratio (95% CI)	More Intensive	Less Intensive LDL-C Lowering	Weight %	
Study and Subgroup	(95 % OI)	LDL-C Lowering	LDL-C Lowelling	70	
Achieved CRP ≥ median					
4D (2005)	0.95 (0.85, 1.06)	559/636	573/619	10.65	
AURORA (2009)	0.96 (0.87, 1.06)	636/1389	660/1384	11.30	
CARDS (2004)	0.74 (0.53, 1.02)	61/1429	82/1412	2.93	
CORONA (2007)	0.95 (0.87, 1.05)	728/2514	759/2497	11.71	
JUPITER (2008)	0.80 (0.67, 0.97)	198/8901	247/8901	6.64	
LIPID (1998)	0.78 (0.70, 0.88)	498/4512	633/4502	10.37	
SHARP (2011)	1.02 (0.94, 1.10)	1142/4650	1115/4620	12.77	
Subtotal (I-squared = 66.9%, p = 0.006) Subtotal effect: z = 2.35, p = 0.019	0.91 (0.84, 0.98)	3822/24031	4069/23935	66.36	
Achieved CRP < median					
A to Z (2004)	0.79 (0.61, 1.02)	104/2265	130/2232	4.37	
AFCAPS_TEXCAPS (1998)	1.04 (0.76, 1.42)	80/3304	77/3301	3.19	
IMPROVE-IT (2015)	0.99 (0.91, 1.07)	1215/9067	1231/9077	12.91	
PROVE IT-TIMI 22 (2004)	0.69 (0.47, 1.00)	46/2099	66/2063	2.37	
REAL-CAD (2018)	0.80 (0.67, 0.96)	207/6199	260/6214	6.81	
SEAS (2008)	1.03 (0.79, 1.35)	105/944	100/929	3.99	
Subtotal (I-squared = 50.6%, p = 0.072)	0.90 (0.79, 1.02)	1757/23878	1864/23816	33.64	
Subtotal effect: z = 1.71, p = 0.087					
Overall (I-squared = 57.6%, p = 0.005) Overall effect: z = 3.03, p = 0.022 p = 0.87 for interaction (≥ median vs. < median)	0.91 (0.85, 0.97)	5579/47909	5933/47751	100.00	
I 0.2 Favors More Intensive LDL-C Lowering	1 1 2 Favors Less Intensive LDL	-C Lowering			

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

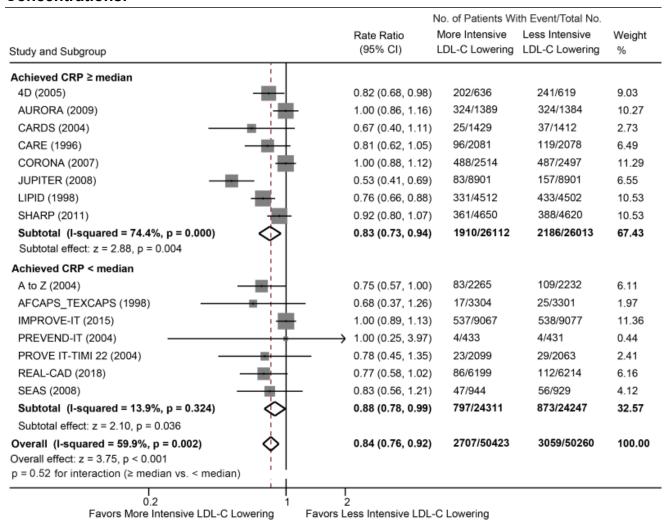


Figure S24. Meta-analysis of Myocardial Infarction Stratified by the Achieved CRP Concentrations.

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

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

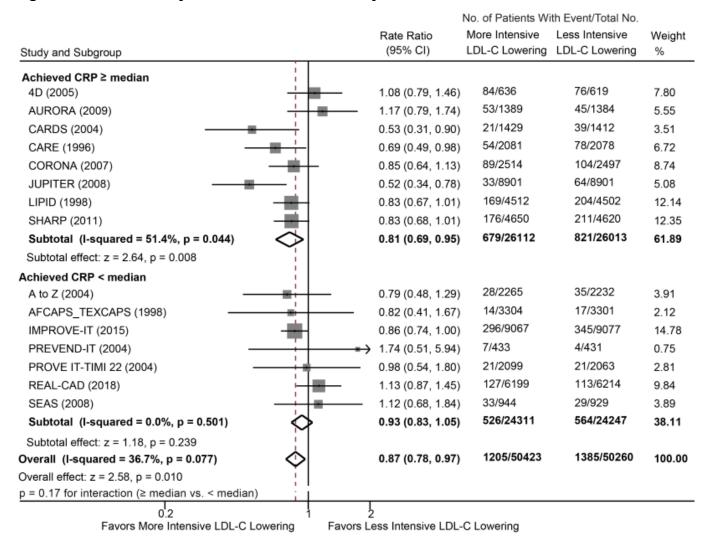


Figure S26. Meta-analysis of Coronary Revascularization Stratified by the Achieved CRP Concentrations.

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

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

	No. of Patients With Event/Total No.			
	Rate Ratio	More Intensive	Less Intensive	Weight
Study and Subgroup	(95% CI)	LDL-C Lowering	LDL-C Lowering	%
Achieved CRP ≥ median				
4D (2005)	0.91 (0.78, 1.06)	294/636	315/619	6.81
AURORA (2009)	0.97 (0.85, 1.10)	396/1389	408/1384	7.56
CARDS (2004)	0.65 (0.49, 0.85)	83/1429	127/1412	3.85
CARE (1996)	0.77 (0.65, 0.92)	212/2081	274/2078	6.14
CORONA (2007)	0.94 (0.85, 1.04)	692/2514	732/2497	8.72
JUPITER (2008)	0.57 (0.46, 0.69)	142/8901	251/8901	5.37
LIPID (1998)	0.78 (0.70, 0.87)	557/4512	715/4502	8.35
SHARP (2011)	0.84 (0.75, 0.95)	526/4650	619/4620	8.17
Subtotal (I-squared = 77.3%, p = 0.000) Subtotal effect: z = 3.89, p < 0.001	0.81 (0.73, 0.90)	2902/26112	3441/26013	54.97
Achieved CRP < median				
A to Z (2004)	0.89 (0.77, 1.03)	309/2265	343/2232	7.05
AFCAPS_TEXCAPS (1998) — ■	0.63 (0.50, 0.80)	116/3304	183/3301	4.71
IMPROVE-IT (2015)	0.94 (0.89, 0.99)	2572/9067	2742/9077	10.07
PREVEND-IT (2004)	0.87 (0.49, 1.56)	21/433	24/431	1.19
PROVE IT-TIMI 22 (2004)	0.85 (0.76, 0.96)	470/2099	543/2063	8.14
REAL-CAD (2018)	0.80 (0.68, 0.94)	266/6199	334/6214	6.67
SEAS (2008)	0.92 (0.80, 1.07)	333/944	355/929	7.21
Subtotal (I-squared = 58.9%, p = 0.024) Subtotal effect: z = 3.55, p < 0.001	0.86 (0.79, 0.93)	4087/24311	4524/24247	45.03
Overall (I-squared = 71.9%, p = 0.000) Overall effect: z = 5.39, p < 0.001 p = 0.39 for interaction (≥ median vs. < median)	0.83 (0.78, 0.89)	6989/50423	7965/50260	100.00
0.2 1 Favors More Intensive LDL-C Lowering	I 2 Favors Less Intensive LDL-	Cloworing		