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Association Between Baseline LDL-C Level and Total and Cardiovascular Mortality After LDL-C Lowering
A Systematic Review and Meta-analysis

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IMPORTANCE Effects on specific fatal and nonfatal end points appear to vary for low-density lipoprotein cholesterol (LDL-C)–lowering drug trials.

OBJECTIVE To evaluate whether baseline LDL-C level is associated with total and cardiovascular mortality risk reductions.

DATA SOURCESAND STUDY SELECTION Electronic databases (Cochrane, MEDLINE, EMBASE, TCTMD, ClinicalTrials.gov, major congress proceedings) were searched through February 2, 2018, to identify randomized clinical trials of statins, ezetimibe, and PCSK9-inhibiting monoclonal antibodies.

DATA EXTRACTION AND SYNTHESIS Two investigators abstracted data and appraised risks of bias. Intervention groups were categorized as "more intensive" (more potent pharmacologic intervention) or "less intensive" (less potent, placebo, or control group).

MAIN OUTCOMES AND MEASURES The coprimary end points were total mortality and cardiovascular mortality. Random-effects meta-regression and meta-analyses evaluated associations between baseline LDL-C level and reductions in mortality end points and secondary end points including major adverse cardiac events (MACE).

RESULTS In 34 trials, 136 299 patients received more intensive and 133 989 received less intensive LDL-C lowering. All-cause mortality was lower for more vs less intensive therapy (7.08% vs 7.70%; rate ratio [RR], 0.92 [95% CI, 0.88 to 0.96]), but varied by baseline LDL-C level. Meta-regression showed more intensive LDL-C lowering was associated with greater reductions in all-cause mortality with higher baseline LDL-C levels (change in RRs per 40-mg/dL increase in baseline LDL-C, 0.91 [95% CI, 0.86 to 0.96]; P = .001; absolute risk difference [ARD], −1.05 incident cases per 1000 person-years [95% CI, −1.59 to −0.51]), but only when baseline LDL-C levels were 100 mg/dL or greater (P < .001 for interaction) in a meta-analysis. Cardiovascular mortality was lower for more vs less intensive therapy (3.48% vs 4.07%; RR, 0.84 [95% CI, 0.79 to 0.89]) but varied by baseline LDL-C level. Meta-regression showed more intensive LDL-C lowering was associated with a greater reduction in cardiovascular mortality with higher baseline LDL-C levels (change in RRs per 40-mg/dL increase in baseline LDL-C, 0.86 [95% CI, 0.80 to 0.94]; P < .001; ARD, −1.0 incident cases per 1000 person-years [95% CI, −1.51 to −0.45]), but only when baseline LDL-C levels were 100 mg/dL or greater (P < .001 for interaction) in a meta-analysis. Trials with baseline LDL-C levels of 160 mg/dL or greater had the greatest reduction in all-cause mortality (RR, 0.72 [95% CI, 0.62 to 0.84]; P < .001; 4.3 fewer deaths per 1000 person-years) in a meta-analysis. More intensive LDL-C lowering was also associated with progressively greater risk reductions with higher baseline LDL-C level for myocardial infarction, revascularization, and MACE.

CONCLUSIONS AND RELEVANCE In these meta-analyses and meta-regressions, more intensive compared with less intensive LDL-C lowering was associated with a greater reduction in risk of total and cardiovascular mortality in trials of patients with higher baseline LDL-C levels. This association was not present when baseline LDL-C level was less than 100 mg/dL, suggesting that the greatest benefit from LDL-C–lowering therapy may occur for patients with higher baseline LDL-C levels.

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C onsistent evidence has shown that statins reduce total cardiovascular events, and that further lowering of low-density lipoprotein cholesterol (LDL-C) levels by intensifying statin therapy, adding ezetimibe, or adding a proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibiting monoclonal antibody provides incremental additional reduction in cardiovascular risk.[1-6] However, there is less consistency in the magnitude of the reductions in individual mortality and cardiovascular end points among the various trials. Total and cardiovascular mortality benefits were observed in several placebo-controlled statin cardiovascular outcomes trials as well as in meta-analyses of statin trials.[1,7-9] In contrast, no reduction in cardiovascular mortality was observed in 5-year trials of moderate- vs high-intensity statin therapy or in trials of ezetimibe or evolocumab added to background statin therapy.[2,3,10-12] Understanding differences in treatment effects across clinical trials may influence estimates of treatment benefit, have an important effect on guideline recommendations and clinical trial design, and has already had a significant influence on cost-effectiveness analyses and accessibility decisions.[13-15]

Over time, baseline mean or median LDL-C levels progressively decreased from 188 mg/dL (4.87 mmol/L) in the first statin cardiovascular outcomes trial[7] to 92 mg/dL (2.38 mmol/L) in a cardiovascular outcomes trial of evolocumab added to background statin therapy.[3] Differences in LDL-C–lowering efficacy also influenced the magnitude of LDL-C reductions occurring across this broad range of baseline LDL-C levels.[2,3,7] Therefore, the aim of this systematic review and meta-analysis was to determine whether baseline LDL-C level or the magnitude of LDL-C lowering with use of statins, ezetimibe, and PCSK9-inhibiting monoclonal antibodies were associated with reductions in fatal and nonfatal cardiovascular events.

Methods

Established methods recommended by the Cochrane Collaboration were used to conduct the meta-analysis.[16] The findings were reported according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement.[16,17] Methods are reported in full in eTable 1 in the Supplement. The following databases were searched: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, TCTMD (https://www.tctmd.com/), ClinicalTrials.gov, Clinical Trial Results (http://www.clinicaltrialresults.org), and major congress proceedings, from database inception date through February 2, 2018.

The main inclusion criteria were (1) randomized trials including at least 1000 patients receiving the allocated pharmacologic LDL-C–lowering strategy for a minimum of 48 weeks; (2) use of statin, nonstatin, or statin in combination with nonstatin therapies (either ezetimibe or a PCSK9-inhibiting monoclonal antibody); and (3) reported cardiovascular and mortality outcomes of interest. Trials performed in populations with heart failure or end-stage renal disease requiring hemodialy-

Key Points

Question Does the magnitude of reductions in total and cardiovascular mortality after low-density lipoprotein cholesterol (LDL-C) lowering depend on the baseline LDL-C level?

Findings In this meta-analysis of 34 randomized clinical trials that included 270 288 participants, more intensive LDL-C–lowering therapy was associated with a progressive reduction in total mortality with higher baseline LDL-C levels (rate ratio, 0.91 for each 40-mg/dL increase in baseline level); however, this relationship was not present with baseline LDL-C levels less than 100 mg/dL. There was a similar relationship for cardiovascular mortality.

Meaning The greatest benefit from LDL-C–lowering therapy may occur for patients with baseline LDL-C levels of 100 mg/dL or greater.

sis were excluded; additional exclusion criteria are listed in eTable 1 in the Supplement. Two investigators (M.K., M.K.) not involved in any of the selected trials independently abstracted the data using prespecified forms, appraised the accuracy of the abstractions, and resolved any discrepancies by consensus after discussion with a third investigator (E.P.N.). Two unblinded investigators (M.K., M.K.) independently appraised the potential risks of bias of the randomized clinical trials using the Cochrane Risk of Bias Tool.[16] Any divergences in the bias assessment were then reported and summarized as Cohen κ coefficients (eTable 2 in the Supplement).

More intensive therapy was defined as the more potent pharmacologic strategy, while less intensive therapy corresponded to the control group of the original trial. Mean or median baseline and final LDL-C values were abstracted for both treatment groups.

Outcomes

The coprimary end points were total mortality and cardiovascular mortality. Secondary end points included myocardial infarction, cerebrovascular events, revascularizations (coronary artery bypass graft surgery, coronary or other arterial percutaneous interventions), and major cardiovascular events (MACE) (eTables 3 and 4 in the Supplement). Event rates reported in the trial manuscript were abstracted if available; if not reported, then event rates from the 2010 Cholesterol Treatment Trialists' Collaboration (CTT) meta-analysis of statin trials were used.[1]

Statistical Analyses

Trial-level data were analyzed according to the original randomization group for which outcome data were available. To account for potential differences in study duration and drug exposure, rate ratios (RRs) with 95% confidence intervals derived from an analysis with adjusted models by person-years, a measure incorporating trial duration, were used as summary statistics. Absolute risk differences (ARDs) were expressed as incident events per 1000 person-years.

Random-effects meta-regression with baseline LDL-C level as a covariate was used for the main model, with additional

Figure 1. Search and Selection Process of Randomized Clinical Trials Evaluating the Effect of Low-Density Lipoprotein Cholesterol–Lowering Therapies on Cardiovascular Outcomes

LDL-C indicates low-density lipoprotein cholesterol.

a Comparison of different groups of drugs in monotherapy.
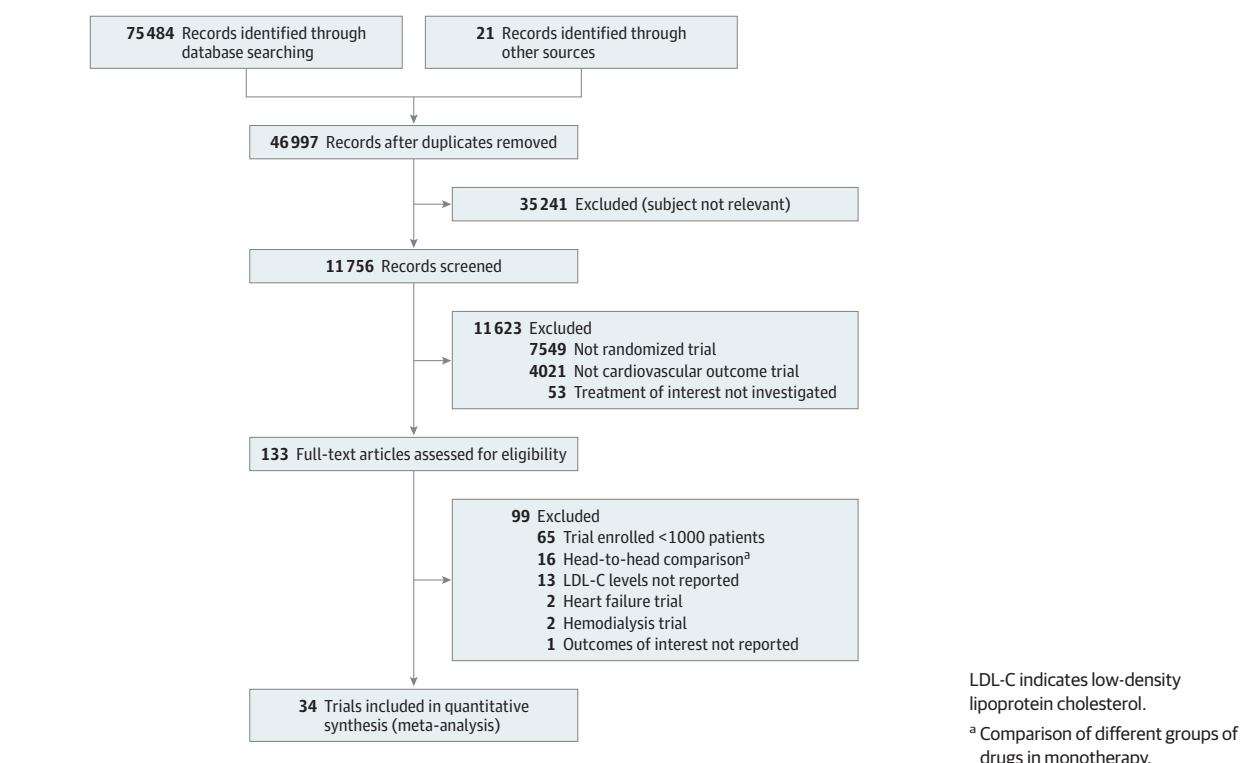
covariates added in the adjusted analyses. Statistical heterogeneity was assessed using the Cochran Q test and the I^2 statistic.[18] In the meta-analyses, pooled RRs were calculated using a random-effects model. Stratified analyses were prespecified. Potential publication bias was estimated both visually and by a linear regression approach.[19] Meta-regression was used to investigate the associations of baseline LDL-C levels on the trial RRs for all end points.[20]

Sensitivity analyses were performed to evaluate the robustness of the association between baseline LDL-C level and each outcome after adjustment for magnitude of LDL-C reduction, type of drug, trial population, age, and date of publication (Supplement).

For the summary treatment association estimate, $P < .05$ (2-tailed) was considered statistically significant. To compare treatment associations in subgroups, a χ^2 test of interaction was performed; the Bonferroni correction was applied for multiple comparisons.

Analyses were conducted using Review Manager version 5.3 (Cochrane Collaboration) and Comprehensive Meta-Analysis Software 2.0 (Biostat).

Results

Study Selection and Patient Population

The PRISMA flow diagram of the meta-analysis is shown in **Figure 1**. Of the 11 756 studies initially identified, 11 625 were

excluded based on title/abstract content; 99 studies did not meet explicit inclusion criteria. Two additional trials were identified by reviewing previous systematic reviews and meta-analyses. **Table 1** describes the characteristics of each included trial. Each event analysis included 34 trials[2-5,7-12,21-43] (N = 270 288) except the MACE analysis, which included 32 trials (N = 258 333). In 26 trials, the patients received statin monotherapy[7-12,21-40]; in 3 trials,[2,41,42] statin and ezetimibe; and in 5 trials,[3-5,43] statin and PCSK9-inhibiting monoclonal antibodies. Eight trials[9,24,32,35,37,40-42] were conducted in primary prevention, 16[2,3,7,8,10-12,22,23,25,27,29,33,34,38,39] in secondary prevention, and 10[4,5,21,26,28,30,31,36,43] in both primary and secondary prevention. The longest mean follow-up was 6.7 years,[39] and the mean weighted follow-up was 3.9 years. Baseline LDL-C levels ranged from 92 mg/dL to 192 mg/dL (weighted mean, 122 mg/dL). (To convert LDL-C values to mmol/L, multiply by 0.0259.)

Risk of Bias

Potential sources of bias are shown in eTable 2 in the Supplement. Publication bias ranging from none to moderate was suggested by visual inspection of the funnel plots or by the linear regression approach (eFigure 1 in the Supplement). The included trials were not significantly different with regard to risk of bias. All were multicenter and conducted according to the intention-to-treat principle. Blinding was applied to participants and personnel (28/34 trials), outcome assessment (32/34 trials), or both.

Table 1. Study and Patient Baseline Characteristics[a]

Source	No.	No. (%) Women	History Diabetes	Vascular Disease	CAD	Median Follow-up, y	More Intensive LDL-C Lowering Treatment	Baseline LDL-C, Mean (SD), mg/dL	LDL-C Reduction, %	Less Intensive LDL-C Lowering Treatment	Baseline LDL-C, Mean (SD), mg/dL	LDL-C Reduction, %
4S,[7] 1994	4444	827 (19)	202 (5)	4444 (100)	4444 (100)	5.4 (IQR, 4.9-6.3)	Simvastatin (20-40 mg) [n = 2221]	188.32 (25.52)	−35	Placebo [n = 2223]	188.32 (25.14)	1
WOSCOPS,[21] 1995	6595	0	76 (1)	531 (8)	338 (5)	4.9	Pravastatin (40 mg) [n = 3302]	192 (17)	−26	Placebo [n = 3293]	192 (17)	NA
CARE,[22] 1996	4159	576 (14)	586 (14)	4159 (100)	4159 (100)	5.0 (IQR, 4.0-6.2)	Pravastatin (40 mg) [n = 2081]	139 (15)	−32	Placebo [n = 2078]	139 (15)	−3
THE POST CABG Trial,[23] 1997	1351	105 (8)	118 (9)	1351 (100)	1351 (100)	4.3	Lovastatin (40-80 mg) [n = 676][a]	155.35 (1.11)	−40	Lovastatin (2.5-5 mg) [n = 675][b]	155.60 (1.09)	−13
AFCAPS-TexCAPS,[24] 1998	6605	997 (15)	155 (2)	<1	<1	5.2 (range, 0.2-7.2)	Lovastatin (20-40 mg) [n = 3304]	150 (17)	−23	Placebo [n = 3301]	150 (17)	4
LIPID,[8] 1998	9014	1516 (17)	782 (9)	9014 (100)	9014 (100)	6.1	Pravastatin (40 mg) [n = 4512]	150	>25	Placebo [n = 4502]	150	NA
GISSI-P,[25] 2000	4271	587 (14)	582 (14)	4271 (100)	4271 (100)	2	Pravastatin (20 mg) [n = 2138]	151.8 (25.8)	−15	Usual care [n = 2133]	151.5 (26.0)	−3
ALLHAT-LLT,[26] 2002	10355	5051 (49)	3638 (35)	NR	1475 (14)	4.8	Pravastatin (40 mg) [n = 5170]	145.6 (21.4)	−29	Usual care [n = 5185]	145.5 (21.3)	−17
GREACE,[27] 2002	1600	344 (22)	313 (20)	1600 (100)	1600 (100)	3	Atorvastatin (10-80 mg) [n = 800]	180 (27)	−46	Usual care [n = 800]	179 (28)	−5
HPS,[28] 2002	20536	5082 (25)	5963 (29)	17907 (87)	13 3386 (65)	5	Simvastatin (40 mg) [n = 10269]	131.47 (30.93)	−29	Placebo [n = 10267]	131.47 (30.931)	−9
LIPS,[29] 2002	1677	271 (16)	202 (12)	1677 (100)	1677 (100)	3.9	Fluvastatin (80 mg) [n = 844]	131 (29.0)	−27	Placebo [n = 833]	132 (30.5)	11
PROSPER,[30] 2002	5804	3000 (52)	623 (11)	2565 (44)	2335 (40)	3.2 (range, 2.8-4.0)	Pravastatin (40 mg) [n = 2891]	146.95 (30.94)	−34	Placebo [n = 2913]	146.95 (30.94)	0
ALERT,[31] 2003	2102	715 (34)	396 (19)	158 (8)	148 (7)	5.4 (IQR, 5.2-5.6)	Fluvastatin (40 mg) [n = 1050]	158.54 (38.67)	−32	Placebo [n = 1052]	158.54 (38.67)	−8
ASCOT-LLA,[32] 2003	10305	1942 (19)	2527 (25)	1515 (15)	<1	3.3	Atorvastatin (10 mg) [n = 5168]	133.02 (27.84)	−33	Placebo [n = 5137]	133.02 (27.84)	−5
A to Z,[33] 2004	4497	1100 (24)	1059 (24)	4497 (100)	4497 (100)	2	Simvastatin (80 mg) [n = 2265][c]	112	−41	Simvastatin (20 mg) [n = 2232][c]	111	−27
ALLIANCE,[34] 2004	2442	434 (18)	540 (22)	2442 (100)	2442 (100)	4.5	Atorvastatin (10-80 mg) [n = 1217]	147	−34	Usual care [n = 1225]	146	−23
CARDS,[35] 2004	2841	909 (32)	2838 (100)	<1	<1	3.9 (IQR, 3.0-4.7)	Atorvastatin (10 mg) [n = 1429]	117.56 (27.84)	−31	Placebo [n = 1412]	116.78 (27.07)	3
PROVE IT-TIMI,[12] 22 2004	4162	911 (22)	734 (18)	4162 (100)	4162 (100)	2	Atorvastatin (80 mg) [n = 2099]	106	−42	Pravastatin (40 mg) [n = 2063]	106	−10
TNT,[10] 2005	10001	1902 (19)	1501 (15)	10001 (100)	10001 (100)	4.9	Atorvastatin (80 mg) [n = 4995]	97 (18)	−21	Atorvastatin (10 mg) [n = 5006]	98 (18)	3
IDEAL,[11] 2005	8888	1702 (19)	1069 (12)	8888 (100)	8888 (100)	4.8 (range, 4.0-5.9)	Atorvastatin (80 mg) [n = 4439]	121.6 (0.5)	−34	Simvastatin (20 mg) [n = 4449]	121.4 (0.5)	−18
ASPEN,[36] 2006	2410	811 (34)	2410 (100)	1121 (47)	790 (33)	4	Atorvastatin (10 mg) [n = 1211]	113 (25)	−30	Placebo [n = 1199]	114 (26)	−1

(continued)

Table 1. Study and Patient Baseline Characteristics[a] (continued)

Source	No.	Women	Diabetes	Vascular Disease	CAD	Median Follow-up, y	More Intensive LDL-C Lowering Treatment	Baseline LDL-C, Mean (SD), mg/dL	LDL-C Reduction, %	Less Intensive LDL-C Lowering Treatment	Baseline LDL-C, Mean (SD), mg/dL	LDL-C Reduction, %
MEGA,[37] 2006	8214	5547 (68)	1686 (21)	<1	<1	5.3	Pravastatin (10-20 mg) [n=3866]	156.61 (17.79)	−22	Usual care [n=3966]	156.61 (17.40)	−9
SPARCL,[38] 2006	4731	1908 (40)	794 (17)	4731 (100)	0	4.9 (range, 4.0-6.6)	Atorvastatin (80 mg) [n=2365]	132.7 (0.5)	−45	Placebo [n=2366]	133.7 (0.5)	−4
JUPITER,[9] 2008	17802	6801 (30)	76 (<1)	0	0	1.9	Rosuvastatin (20 mg) [n=8901]	108	−49	Placebo [n=8901]	108	1
SEARCH,[39] 2010	12064	2052 (17)	1267 (11)	12064 (100)	12064 (100)	6.7	Simvastatin (80 mg) [n=6031]	96.67	>13	Simvastatin (20 mg) [n=6033]	96.67	NA
HOPE-3,[40] 2016	12705	5874 (46)	731 (6)	0	0	5.6	Rosuvastatin (10 mg) [n=6361]	127.8 (36.1)	−26	Placebo [n=6344]	127.9 (36.0)	−4
SEAS,[41] 2008	1873	723 (39)	0%	0	0	4.4	Simvastatin (40 mg) + ezetimibe (10 mg) [n=944]	140 (36)	−54	Placebo [n=929]	139 (35)	−4
SHARP,[42] 2011	9270	3470 (37)	2094 (23)	1393 (15)	0	4.9	Simvastatin (20 mg) + ezetimibe (10 mg) [n=4650][b]	107.12 (34.03)	−30	Placebo [n=4620]	107.50 (33.64)	−3
IMPROVE-IT,[2] 2015	18144	4416 (24)	4933 (27)	18144 (100)	18144 (100)	6	Simvastatin (40 mg) + ezetimibe (10 mg) [n=9067]	93.8	−43	Simvastatin (40 mg) [n=9077]	93.8	−26
ODYSSEY LONG TERM,[4] 2015	2341	884 (38)	809 (35)	2341 (100)[d]	1607 (69)	1.5	Alirocumab (150 mg every 2 wk) [n=1553]	122.7 (42.6)	−53	Placebo [n=788]	121.9 (41.4)	1
OSLER 1 & 2,[5] 2015	4465	2210 (49)	599 (13)	1303 (29)	896 (20)	0.9	Evolocumab (140 mg or 420 mg every mo) [n=2976]	120	−61	Usual care [n=1489]	121	NA
FOURIER,[3] 2017	27564	6769 (25)	10081 (37)	27564 (100)	22351 (81)	2.2 (IQR, 1.8-2.5)	Evolocumab (140 mg or 420 mg every mo) [n=13784]	92	−61	Placebo [n=13780]	92	0
SPIRE-1,[43] 2017	16817	4439 (26)	8047 (48)	14563 (87)	NA	0.6	Bococizumab (150 mg every 2 wk) [n=8408]	93.8	−45	Placebo [n=8409]	93.7	7
SPIRE-2,[43] 2017	10621	3675 (35)	4986 (47)	8635 (81)	NA	1	Bococizumab (150 mg every 2 wk) [n=5312]	133.9	−41	Placebo [n=5309]	133.4	3
All trials	270288[e]					3.9						

Abbreviations: CAD, coronary artery disease; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NA, not available.

SI conversion factor: To convert LDL-C values to mmol/L, multiply by 0.02586.

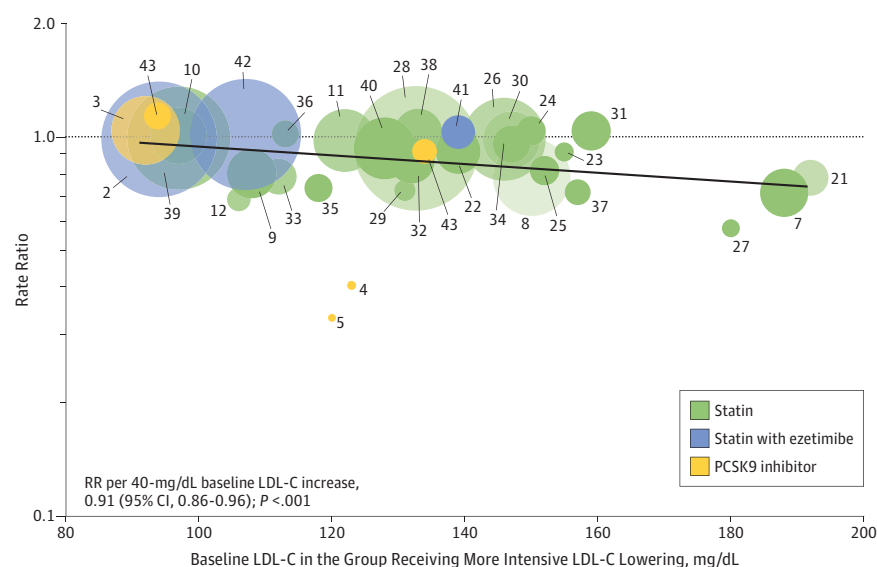[a] For expansions of study names, see eTable 3 in the Supplement.

[b] Cholestyramine (8 g/d) was added to the regimen if LDL-C level at 2 consecutive visits remained above 95 mg/dL in the more intensive treatment group or at or above 160 mg/dL in the less intensive group. Patients given cholestyramine continued to receive lovastatin (80 mg/d in the more intensive group and 5 mg/d in the less intensive group).

[c] Patients received 40 mg/d of simvastatin for 1 month followed by 80 mg/d in the more intensive treatment group, vs patients receiving placebo for 4 months followed by 20 mg/d of simvastatin in the less intensive group.

[d] Heterozygous familial hypercholesterolemia or a coronary heart disease risk equivalent defined as peripheral arterial disease, ischemic stroke, moderate chronic kidney disease (estimated glomerular filtration rate, 30 to <60 mL/min/1.73 m² of body surface area), or diabetes mellitus plus 2 or more additional risk factors (hypertension; ankle–brachial index ≤0.90; microalbuminuria, macroalbuminuria, or a urinary dipstick result of >2+ protein; preproliferative or proliferative retinopathy or laser treatment for retinopathy; or a family history of premature coronary heart disease).

[e] Total number of patients is not exact sum of the above values, as the analysis was performed according to intention-to-treat principle; the difference is driven by MEGA study, in which 382 patients were assigned and randomized to lipid-lowering regimens, but these data are missing in the final analysis.

Figure 2. Meta-regression Analysis of All-cause Mortality by Baseline LDL-C Level (34 RCTs)

Change in rate ratios (RRs) and 95% confidence intervals of more intensive vs less intensive low-density lipoprotein cholesterol (LDL-C)–lowering therapies plotted against baseline LDL-C level in the more intensive treatment group. Numbers indicate reference numbers of randomized clinical trials (RCTs). Size of the data markers is proportional to the weight in the meta-regression. Data marker colors represent the classes of lipid-lowering agents used in the active treatment group as per trial randomization design. Baseline levels are from the more intensive treatment group. The solid line represents the meta-regression slope of the change in rate ratio for treatment across increasing levels of baseline LDL-C. Results do not change when using baseline LDL-C values from the less intensive treatment group. To convert LDL-C values to mmol/L, multiply by 0.0259.

Table 2. Multivariable Meta-regression Models for the Association of Each 40-mg/dL (1-mmol/L) Reduction in LDL-C Level and Mortality and Other Cardiovascular Outcomes

| | No. | | RR (95%CI) | | Multivariable Models | |
Outcome	Studies	Patients	Baseline LDL-C	Magnitude of LDL-C Reduction	Baseline LDL-C Adjusted for Magnitude of LDL-C Reduction	Baseline LDL-C Adjusted for Magnitude of LDL-C Reduction, Baseline Risk Profile, Type of Agent, and Age[a]
All-cause mortality	34	270 288	0.91 (0.86-0.96)	0.96 (0.88-1.01)	0.90 (0.84-0.96)	0.91 (0.85-0.98)
Cardiovascular mortality	34	270 288	0.86 (0.80-0.94)	0.89 (0.73-1.01)	0.89 (0.81-0.95)	0.88 (0.80-0.97)
Myocardial infarction	34	270 288	0.90 (0.84-0.97)	0.85 (0.78-0.96)	0.90 (0.83-0.97)	0.91 (0.85-0.98)
Cerebrovascular events	34	270 288	1.02 (0.93-1.11)	0.99 (0.86-1.08)	1.04 (0.93-1.16)	1.07 (0.91-1.25)
Revascularization	34	270 288	0.91 (0.85-0.99)	0.89 (0.82-0.96)	0.92 (0.86-0.98)	0.90 (0.82-0.99)
Major cardiovascular events	32	258 333	0.90 (0.87-0.97)	0.96 (0.79-0.89)	0.89 (0.83-0.96)	0.91 (0.85-0.98)

Abbreviations: LDL-C, low-density lipoprotein cholesterol; RR, rate ratio.

[a] Type of agent refers to use of statins, ezetimibe, or proprotein convertase subtilisin/kexin type 9 inhibitor use in the active group and baseline risk profile to primary vs secondary prevention setting.

All-Cause Mortality

Overall, 9651 of 136 299 patients (7.08%) receiving the more intensive LDL-C–lowering strategy vs 10 311 of 133 989 (7.70%) receiving the less intensive strategy died during follow-up. In a meta-regression, for each 40-mg/dL higher baseline LDL-C level, more vs less intensive LDL-C lowering was associated with a change in RRs for all-cause mortality of 0.91 (95% CI, 0.86 to 0.96; $P = .001$; ARD, −1.05 incident cases per 1000 person-years [95% CI, −1.59 to −0.51]) (**Figure 2**), which remained unchanged after multivariable adjustment (**Table 2**). The risk reduction in all-cause mortality associated with more vs less intensive therapy across

all trials was 0.92 (95% CI, 0.88 to 0.96) but varied by the baseline LDL-C level in the trial (**Figure 3**). In a meta-analysis by subgroups of baseline LDL-C level, all-cause mortality risk was associated with a reduction only in the trials with baseline LDL-C levels of 100 mg/dL or greater ($P < .001$ for interaction) (Figure 3). The subgroup with baseline LDL-C levels of 160 mg/dL or greater yielded the highest reductions (RR, 0.72 [95% CI, 0.62 to 0.84]; $P < .001$; ARD, −4.37 incident cases per 1000 person-years [95% CI, −8.0 to −0.74]). Statistical heterogeneity was present in the trials with baseline LDL-C levels of 100 to 129 mg/dL, which appeared attributable to differences in the types of lipid-lowering agents

Figure 3. Meta-analysis of All-cause Mortality Stratified by Baseline LDL-C Level

Study and Subgroup	No. of Patients With Event/Total No. (%)		Rate Ratio (95% CI)	Favors More Intensive LDL-C Lowering / Favors Less Intensive LDL-C Lowering	Weight, %
	More Intensive LDL-C Lowering	Less Intensive LDL-C Lowering			
Baseline LDL-C <100 mg/dL					
FOURIER,[3] 2017	444/13784 (3.22)	426/13780 (3.09)	1.04 (0.91-1.19)		4.8
IMPROVE-IT,[2] 2015	1215/9067 (13.40)	1231/9077 (13.56)	0.99 (0.91-1.07)		6.6
SPIRE-1,[43] 2017	66/8408 (0.78)	58/8409 (0.69)	1.14 (0.80-1.62)		1.3
SEARCH,[39] 2010	964/6031 (15.98)	970/6033 (16.08)	0.99 (0.91-1.09)		6.3
TNT,[10] 2005	284/4995 (5.69)	282/5006 (5.63)	1.01 (0.86-1.19)		3.9
Subtotal	2973/42285 (7.03)	2967/42305 (7.01)	1.00 (0.95-1.06)		22.9
Heterogeneity: $\tau^2=0.00$; $\chi^2_4=0.99$ ($P=.91$); $I^2=0\%$					
Overall effect: $z=0.11$ ($P=.92$)					
Baseline LDL-C 100-129 mg/dL					
PROVE IT-TIMI 22,[12] 2004	46/2099 (2.19)	66/2063 (3.20)	0.69 (0.47-1.00)		1.2
SHARP,[42] 2011	1142/4650 (24.56)	1115/4620 (24.13)	1.02 (0.94-1.11)		6.5
JUPITER,[9] 2008	198/8901 (2.22)	247/8901 (2.77)	0.80 (0.66-0.97)		3.4
A to Z,[33] 2004	104/2265 (4.59)	130/2232 (5.82)	0.79 (0.61-1.02)		2.2
ASPEN,[36] 2006	70/1211 (5.78)	68/1199 (5.67)	1.02 (0.73-1.42)		1.5
CARDS,[35] 2004	61/1429 (4.27)	82/1412 (5.81)	0.74 (0.53-1.02)		1.5
OSLER 1 & 2,[5] 2015	4/2976 (0.13)	6/1489 (0.40)	0.33 (0.09-1.18)		0.1
IDEAL,[11] 2005	366/4439 (8.25)	374/4449 (8.41)	0.98 (0.85-1.13)		4.5
ODYSSEY LONG TERM,[4] 2015	8/1553 (0.52)	10/788 (1.27)	0.41 (0.16-1.03)		0.2
HOPE-3,[40] 2016	334/6361 (5.25)	357/6344 (5.63)	0.93 (0.80-1.08)		4.3
Subtotal	2333/35884 (6.50)	2455/33497 (7.33)	0.88 (0.79-0.98)		25.3
Heterogeneity: $\tau^2=0.01$; $\chi^2_9=19.23$ ($P=.02$); $I^2=53\%$					
Overall effect: $z=2.35$ ($P=.02$)					
Baseline LDL-C 130-159 mg/dL					
LIPS,[29] 2002	36/844 (4.27)	49/833 (5.88)	0.73 (0.47-1.11)		0.9
ASCOT-LLA,[32] 2003	185/5168 (3.58)	212/5137 (4.13)	0.87 (0.71-1.06)		3.2
HPS,[28] 2002	1328/10269 (12.93)	1507/10267 (14.68)	0.88 (0.82-0.95)		6.8
SPARCL,[38] 2006	216/2365 (9.13)	211/2366 (8.92)	1.02 (0.85-1.24)		3.3
SPIRE-2,[43] 2017	54/5312 (1.02)	59/5309 (1.11)	0.91 (0.63-1.32)		1.2
CARE,[22] 1996	180/2081 (8.65)	196/2078 (9.43)	0.92 (0.75-1.12)		3.1
SEAS,[41] 2008	105/944 (11.12)	100/929 (10.76)	1.03 (0.79-1.36)		2.0
ALLHAT-LLT,[26] 2002	631/5170 (12.21)	641/5185 (12.36)	0.99 (0.88-1.10)		5.5
ALLIANCE,[34] 2004	121/1217 (9.94)	127/1225 (10.37)	0.96 (0.75-1.23)		2.3
PROSPER,[30] 2002	298/2891 (10.31)	306/2913 (10.50)	0.98 (0.84-1.15)		4.0
AFCAPS-TexCAPS,[24] 1998	80/3304 (2.42)	77/3301 (2.33)	1.04 (0.76-1.42)		1.6
LIPID,[8] 1998	498/4512 (11.04)	633/4502 (14.06)	0.78 (0.70-0.88)		5.3
GISSI-P,[25] 2000	72/2138 (3.37)	88/2133 (4.13)	0.82 (0.60-1.11)		1.6
The Post CABG Trial,[23] 1997	32/676 (4.73)	35/675 (5.19)	0.91 (0.57-1.47)		0.8
MEGA,[37] 2006	55/3866 (1.42)	79/3966 (1.99)	0.71 (0.51-1.01)		1.4
ALERT,[31] 2003	143/1050 (13.62)	138/1052 (13.12)	1.04 (0.82-1.31)		2.5
Subtotal	4034/51807 (7.79)	4458/51871 (8.59)	0.91 (0.86-0.96)		45.6
Heterogeneity: $\tau^2=0.00$; $\chi^2_{15}=17.80$ ($P=.27$); $I^2=16\%$					
Overall effect: $z=3.57$ ($P<.001$)					
Baseline LDL-C ≥160 mg/dL					
GREACE,[27] 2002	23/800 (2.88)	40/800 (5.00)	0.57 (0.34-0.96)		0.7
4S,[7] 1994	182/2221 (8.19)	256/2223 (11.52)	0.71 (0.59-0.86)		3.3
WOSCOPS,[21] 1995	106/3302 (3.21)	135/3293 (4.10)	0.78 (0.61-1.01)		2.2
Subtotal	311/6323 (4.92)	431/6316 (6.82)	0.72 (0.62-0.84)		6.2
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=1.17$ ($P=.56$); $I^2=0\%$					
Overall effect: $z=4.38$ ($P<.001$)					
Total	9651/136299 (7.08)	10311/133989 (7.70)	0.92 (0.88-0.96)		100.0
Heterogeneity: $\tau^2=0.01$; $\chi^2_{33}=60.79$ ($P=.002$); $I^2=46\%$					
Overall effect: $z=3.80$ ($P<.001$)					
$P<.001$ for interaction (<100 mg/dL vs ≥100 mg/dL)					

0.2   1.0   2.0
Rate Ratio (95% CI)

Rate ratios (RRs) and 95% confidence intervals of more intensive vs less intensive low-density lipoprotein cholesterol (LDL-C)–lowering therapies. Size of study data markers is proportional to the weight in the meta-analysis. To convert LDL-C values to mmol/L, multiply by 0.0259.
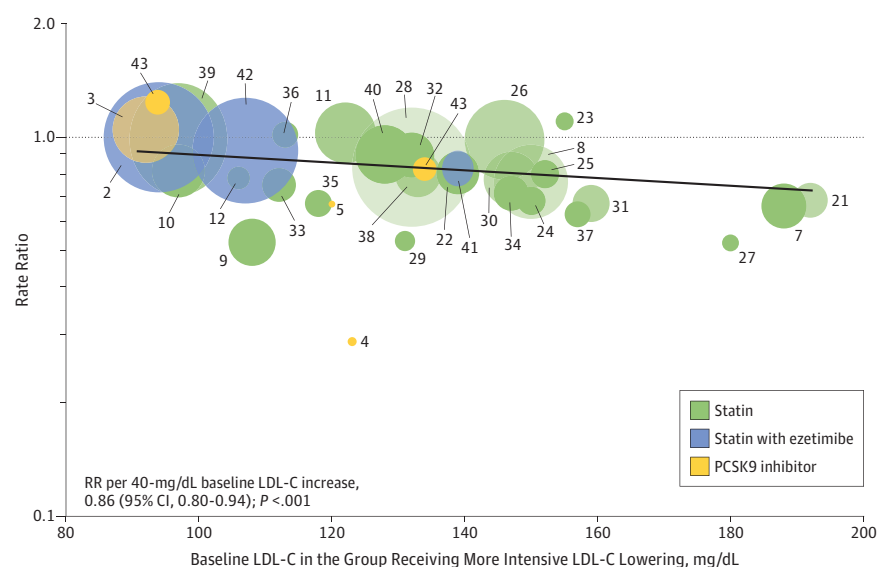
used: statins (7 trials; RR, 0.88 [95% CI, 0.80 to 0.96]) vs PCSK9-inhibiting monoclonal antibodies (2 trials [ODYSSEY LONG TERM[4] and OSLER[5]]; RR, 0.38 [95% CI, 0.18 to 0.80]) vs statin + ezetimibe (1 trial; RR, 1.02 [95% CI, 0.94 to 1.11]), $P=.02$ for interaction (eTable 5 in the Supplement).

Cardiovascular Mortality

Overall, 4738 of 136299 patients (3.48%) receiving the more intensive LDL-C-lowering strategy vs 5457 of 133989 (4.07%)

receiving the less intensive strategy died of cardiovascular causes during follow-up. In a meta-regression, for each 40-mg/dL higher baseline LDL-C level, more vs less intensive LDL-C lowering was associated with a change in RRs for cardiovascular mortality of 0.86 (95% CI, 0.80 to 0.94; $P<.001$; ARD, −1.0 incident cases per 1000 person-years [95% CI, −1.51 to −0.45]) (Figure 4), which remained unchanged after multivariable adjustment (Table 2). The overall risk reduction in cardiovascular mortality associated with more vs less

Figure 4. Meta-regression Analysis of Cardiovascular Mortality by Baseline LDL-C Level (34 RCTs)

Change in rate ratios (RRs) and 95% confidence intervals of more intensive vs less intensive low-density lipoprotein cholesterol (LDL-C)–lowering therapies plotted against baseline LDL-C level in the more intensive treatment group. Numbers indicate reference numbers of randomized clinical trials (RCTs). Size of the data markers is proportional to the weight in the meta-regression. Data marker colors represent the classes of lipid-lowering agents used in the active treatment group as per trial randomization design. Baseline levels are from the more intensive treatment group. The solid line represents the meta-regression slope of the change in rate ratio for treatment across increasing levels of baseline LDL-C. Results do not change when using baseline LDL-C values from the less intensive treatment group. To convert LDL-C values to mmol/L, multiply by 0.0259.

intensive therapy across all trials was 0.84 (95% CI, 0.79 to 0.89) but varied by baseline LDL-C of those in the trial (**Figure 5**). In a meta-analysis by subgroups of baseline LDL-C level, cardiovascular mortality was associated with a reduction in risk only in the trials with baseline LDL-C levels of 100 mg/dL or greater ($P < .001$ for interaction) (Figure 5). The subgroup with baseline LDL-C levels of 160 mg/dL or greater yielded the highest reductions (RR, 0.65 [95% CI, 0.54 to 0.77]; $P < .001$; ARD, −4.3 incident cases per 1000 person-years [95% CI, −8.30 to −0.38]; $P < .001$ for interaction). Statistical heterogeneity was present in the subgroup of trials with baseline LDL-C levels of 100 to 129 mg/dL, which did not appear to be attributable to agents used, trial population, level of risk, or age (eTable 5 in the Supplement).

In the more intensive groups, cardiovascular deaths comprised 51.0% of total deaths when baseline LDL-C level was less than 100 mg/dL, 42.8% when 100 to 129 mg/dL, 50.0% when 130 to 159 mg/dL, and 66.2% when 160 mg/dL or greater.
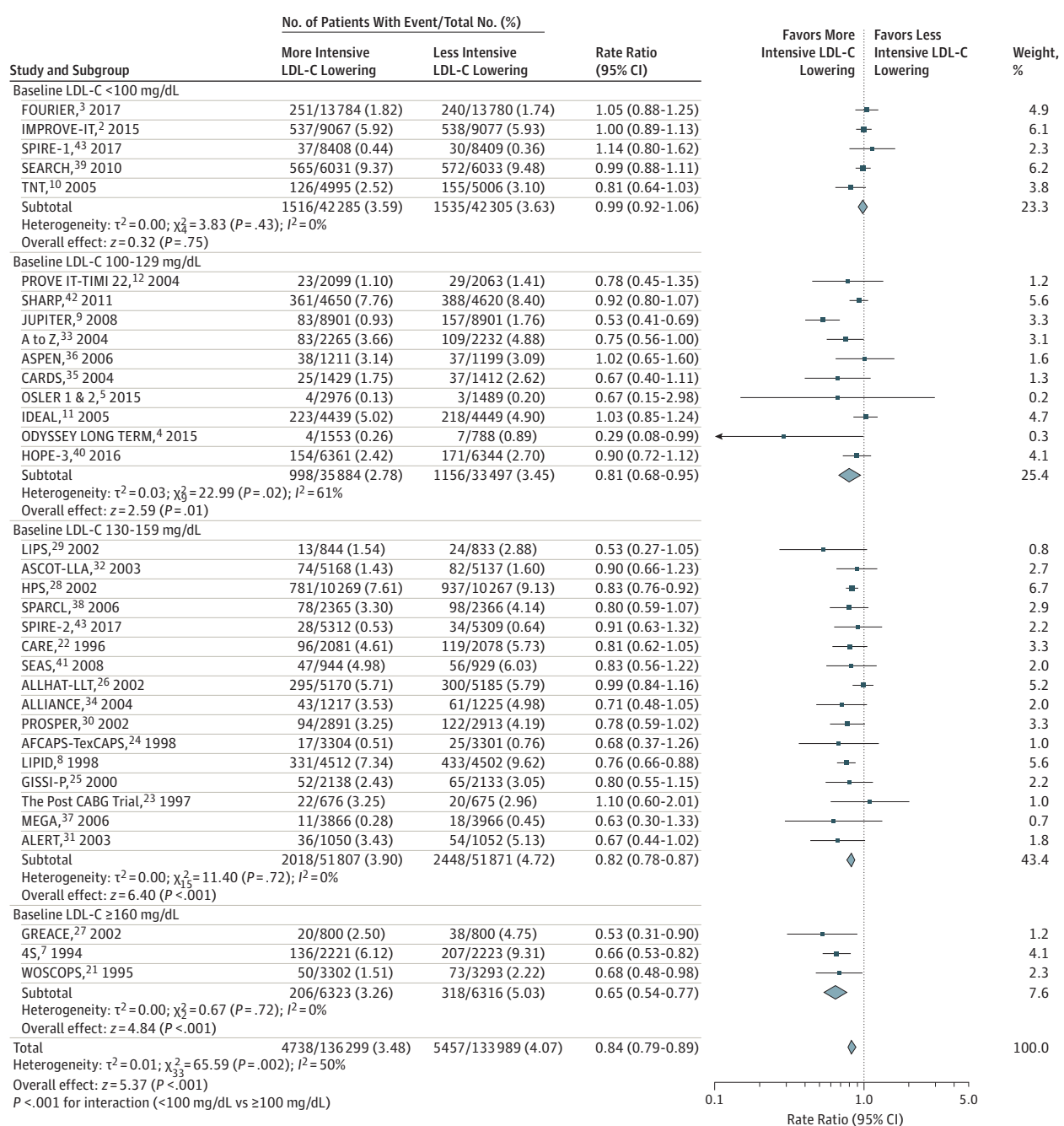
Myocardial Infarction
Overall, 6343 of 136 299 patients (4.65%) receiving the more intensive LDL-C–lowering strategy vs 8098 of 133 989 (6.04%) receiving the less intensive strategy experienced a myocardial infarction during follow-up. In a meta-regression, for each 40-mg/dL higher baseline LDL-C level, more vs less intensive LDL-C lowering was associated with a change in RRs for myocardial infarction of 0.90 (95% CI, 0.84 to 0.97; $P = .007$; ARD, −1.23 incident cases per 1000 person-years [95% CI, −2.24 to −0.21]) (**Figure 6**), which remained unchanged after multivariable adjustment (Table 2). The

overall risk reduction in myocardial infarction with more vs less intensive LDL-C therapy across all trials was 0.76 (95% CI, 0.72 to 0.80) (eFigure 2 in the Supplement) but varied by the baseline LDL-C levels of those in the trial. In a meta-analysis by subgroups of baseline LDL-C, risk of myocardial infarction was associated with a risk reduction in all subgroups of baseline LDL-C level, ranging from baseline levels less than 100 mg/dL (RR, 0.84 [95% CI, 0.76-0.92]; $P < .001$; ARD, −2.89 incident cases per 1000 person-years [95% CI, −4.40 to −1.38]) to baseline levels of 160 mg/dL or greater (RR, 0.64 [95% CI, 0.53 to 0.78]; $P < .001$; ARD, −8.82 incident cases per 1000 person-years [95% CI, −15.13 to −2.52]), with a nonsignificant P value for interaction in the subgroups with baseline LDL-C levels less than 100 mg/dL vs 100 mg/dL or greater (eFigure 2 in the Supplement). Statistical heterogeneity was present in the trials with baseline LDL-C levels less than 100 mg/dL and in those with baseline LDL-C levels of 100 to 129 mg/dL, which did not appear to be attributable to agents used, trial population, level of risk, or age (eTable 5 in the Supplement).

Cerebrovascular Events
Overall, 3271 of 136 299 patients (2.40%) receiving the more intensive LDL-C–lowering strategy vs 3970 of 133 989 (2.96%) receiving the less intensive strategy developed a cerebrovascular event during follow-up. In a meta-regression, cerebrovascular risk was not significantly different for each 40-mg/dL higher baseline LDL-C level and was associated with a change in RR of 1.02 (95% CI, 0.93 to 1.11; $P = .61$; ARD, −0.11 incident cases per 1000 person-years

Figure 5. Meta-analysis of Cardiovascular Mortality Stratified by Baseline LDL-C Level

Study and Subgroup	No. of Patients With Event/Total No. (%)		Rate Ratio (95% CI)	Favors More Intensive LDL-C Lowering / Favors Less Intensive LDL-C Lowering	Weight, %
	More Intensive LDL-C Lowering	Less Intensive LDL-C Lowering			
Baseline LDL-C <100 mg/dL					
FOURIER,[3] 2017	251/13784 (1.82)	240/13780 (1.74)	1.05 (0.88-1.25)		4.9
IMPROVE-IT,[2] 2015	537/9067 (5.92)	538/9077 (5.93)	1.00 (0.89-1.13)		6.1
SPIRE-1,[43] 2017	37/8408 (0.44)	30/8409 (0.36)	1.14 (0.80-1.62)		2.3
SEARCH,[39] 2010	565/6031 (9.37)	572/6033 (9.48)	0.99 (0.88-1.11)		6.2
TNT,[10] 2005	126/4995 (2.52)	155/5006 (3.10)	0.81 (0.64-1.03)		3.8
Subtotal	1516/42285 (3.59)	1535/42305 (3.63)	0.99 (0.92-1.06)		23.3
Heterogeneity: $\tau^2=0.00$; $\chi^2_4=3.83$ ($P=.43$); $I^2=0\%$					
Overall effect: $z=0.32$ ($P=.75$)					
Baseline LDL-C 100-129 mg/dL					
PROVE IT-TIMI 22,[12] 2004	23/2099 (1.10)	29/2063 (1.41)	0.78 (0.45-1.35)		1.2
SHARP,[42] 2011	361/4650 (7.76)	388/4620 (8.40)	0.92 (0.80-1.07)		5.6
JUPITER,[9] 2008	83/8901 (0.93)	157/8901 (1.76)	0.53 (0.41-0.69)		3.3
A to Z,[33] 2004	83/2265 (3.66)	109/2232 (4.88)	0.75 (0.56-1.00)		3.1
ASPEN,[36] 2006	38/1211 (3.14)	37/1199 (3.09)	1.02 (0.65-1.60)		1.6
CARDS,[35] 2004	25/1429 (1.75)	37/1412 (2.62)	0.67 (0.40-1.11)		1.3
OSLER 1 & 2,[5] 2015	4/2976 (0.13)	3/1489 (0.20)	0.67 (0.15-2.98)		0.2
IDEAL,[11] 2005	223/4439 (5.02)	218/4449 (4.90)	1.03 (0.85-1.24)		4.7
ODYSSEY LONG TERM,[4] 2015	4/1553 (0.26)	7/788 (0.89)	0.29 (0.09-0.99)		0.3
HOPE-3,[40] 2016	154/6361 (2.42)	171/6344 (2.70)	0.90 (0.72-1.12)		4.1
Subtotal	998/35884 (2.78)	1156/33497 (3.45)	0.81 (0.68-0.95)		25.4
Heterogeneity: $\tau^2=0.03$; $\chi^2_9=22.99$ ($P=.02$); $I^2=61\%$					
Overall effect: $z=2.59$ ($P=.01$)					
Baseline LDL-C 130-159 mg/dL					
LIPS,[29] 2002	13/844 (1.54)	24/833 (2.88)	0.53 (0.27-1.05)		0.8
ASCOT-LLA,[32] 2003	74/5168 (1.43)	82/5137 (1.60)	0.90 (0.66-1.23)		2.7
HPS,[28] 2002	781/10269 (7.61)	937/10267 (9.13)	0.83 (0.76-0.92)		6.7
SPARCL,[38] 2006	78/2365 (3.30)	98/2366 (4.14)	0.80 (0.59-1.07)		2.9
SPIRE-2,[43] 2017	28/5312 (0.53)	34/5309 (0.64)	0.91 (0.63-1.32)		2.2
CARE,[22] 1996	96/2081 (4.61)	119/2078 (5.73)	0.81 (0.62-1.05)		3.3
SEAS,[41] 2008	47/944 (4.98)	56/929 (6.03)	0.83 (0.56-1.22)		2.0
ALLHAT-LLT,[26] 2002	295/5170 (5.71)	300/5185 (5.79)	0.99 (0.84-1.16)		5.2
ALLIANCE,[34] 2004	43/1217 (3.53)	61/1225 (4.98)	0.71 (0.48-1.05)		2.0
PROSPER,[30] 2002	94/2891 (3.25)	122/2913 (4.19)	0.78 (0.59-1.02)		3.3
AFCAPS-TexCAPS,[24] 1998	17/3304 (0.51)	25/3301 (0.76)	0.68 (0.37-1.26)		1.0
LIPID,[8] 1998	331/4512 (7.34)	433/4502 (9.62)	0.76 (0.66-0.88)		5.6
GISSI-P,[25] 2000	52/2138 (2.43)	65/2133 (3.05)	0.80 (0.55-1.15)		2.2
The Post CABG Trial,[23] 1997	22/676 (3.25)	20/675 (2.96)	1.10 (0.60-2.01)		1.0
MEGA,[37] 2006	11/3866 (0.28)	18/3966 (0.45)	0.63 (0.30-1.33)		0.7
ALERT,[31] 2003	36/1050 (3.43)	54/1052 (5.13)	0.67 (0.44-1.02)		1.8
Subtotal	2018/51807 (3.90)	2448/51871 (4.72)	0.82 (0.78-0.87)		43.4
Heterogeneity: $\tau^2=0.00$; $\chi^2_{15}=11.40$ ($P=.72$); $I^2=0\%$					
Overall effect: $z=6.40$ ($P<.001$)					
Baseline LDL-C ≥160 mg/dL					
GREACE,[27] 2002	20/800 (2.50)	38/800 (4.75)	0.53 (0.31-0.90)		1.2
4S,[7] 1994	136/2221 (6.12)	207/2223 (9.31)	0.66 (0.53-0.82)		4.1
WOSCOPS,[21] 1995	50/3302 (1.51)	73/3293 (2.22)	0.68 (0.48-0.98)		2.3
Subtotal	206/6323 (3.26)	318/6316 (5.03)	0.65 (0.54-0.77)		7.6
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=0.67$ ($P=.72$); $I^2=0\%$					
Overall effect: $z=4.84$ ($P<.001$)					
Total	4738/136299 (3.48)	5457/133989 (4.07)	0.84 (0.79-0.89)		100.0
Heterogeneity: $\tau^2=0.01$; $\chi^2_{33}=65.59$ ($P=.002$); $I^2=50\%$					
Overall effect: $z=5.37$ ($P<.001$)					
$P<.001$ for interaction (<100 mg/dL vs ≥100 mg/dL)					

Rate ratios (RRs) and 95% confidence intervals of more intensive vs less intensive low-density lipoprotein cholesterol (LDL-C)–lowering therapies. Size of study data markers is proportional to the weight in the meta-analysis. To convert the values for LDL cholesterol to mmol/L, multiply by 0.0259.

[95% CI, −1.02 to 0.76]) (Figure 6). Cerebrovascular events were associated with an RR of 0.82 (95% CI, 0.78 to 0.87; $P < .001$; ARD, −0.11 incident cases per 1000 person-years [95% CI, −1.02 to 0.76]) across the range of baseline LDL-C levels (eFigure 3 in the Supplement) and magnitudes of LDL-C lowering, which remained unchanged after multivariable adjustment (Table 2).

An analysis of 24 trials reporting ischemic stroke rates found that baseline LDL-C level was not significantly different for each 40-mg/dL higher LDL-C level (RR, 1.00 [95% CI, 0.90 to 1.12]; $P = .96$) (eFigure 4 in the Supplement) and was associated with an RR of 0.79 (95% CI, 0.74 to 0.84) across levels of baseline LDL-C less than 100 mg/dL and 100 mg/dL or greater ($P = .72$ for interaction) (eFigure 5 in the Supplement).

Revascularization Procedures

Overall, 9012 of 136299 patients (6.61%) receiving the more intensive LDL-C-lowering strategy vs 10991 of 133989 (8.20%)

Figure 6. Meta-regression Analysis of (A) Myocardial Infarction; and (B) Cerebrovascular Events by Baseline LDL-C Level (34 RCTs)

Change in rate ratios (RRs) and 95% confidence intervals of more intensive vs less intensive low-density lipoprotein cholesterol (LDL-C)–lowering therapies plotted against baseline LDL-C level in the more intensive treatment group. Numbers indicate reference numbers of randomized clinical trials (RCTs). Size of the data markers is proportional to the weight in the meta-regression. Data marker colors represent the classes of lipid-lowering agents used in the active treatment group as per trial randomization design. Baseline levels are from the more intensive treatment group. The solid line represents the meta-regression slope of the change in rate ratio for treatment across increasing levels of baseline LDL-C. Results do not change when using baseline LDL-C values from the less intensive treatment group. To convert LDL-C values to mmol/L, multiply by 0.0259.

receiving the less intensive strategy underwent revascularization. In a meta-regression, for each 40-mg/dL higher baseline LDL-C level, more vs less intensive LDL-C lowering was associated with a change in RRs for revascularization risk of 0.91 (95% CI, 0.85 to 0.99; $P < .001$), which remained unchanged after multivariable adjustment (eFigure 6 in the Supplement). Additional results for revascularization analyses are presented in Table 2 and in eFigure 7 in the Supplement.

Major Cardiovascular Events

MACE rates were reported in 32 trials, which included 258 333 patients. Overall, 14 460 of 130 329 patients (11.09%) receiving the more intensive LDL-C–lowering strategy experi-

enced a MACE vs 17 091/128 004 (13.35%) for the less intensive strategy. In a meta-regression analysis, for each 40-mg/dL higher baseline LDL-C level, more vs less intensive LDL-C lowering was associated with a change in RRs for MACE of 0.90 (95% CI, 0.87 to 0.97; $P < .001$; ARD, −0.69 incident cases per 1000 person-years [95% CI, −1.30 to −0.11]), which remained unchanged after multivariable adjustment (Table 2; eFigure 8 in the Supplement). The overall risk reduction in MACE with more vs less intensive therapy across all trials was 0.81 (95% CI, 0.78 to 0.85) (eFigure 9 in the Supplement) but varied by the baseline LDL-C levels of those in the trial. In a meta-analysis by subgroup of baseline LDL-C level, in trials with baseline LDL-C levels less

than 100 mg/dL, MACE risk was associated with an RR of 0.90 (95% CI, 0.85 to 0.96; *P* = .002; ARD, −3.66 incident cases per 1000 person-years [95% CI, −5.72 to −0.81) (eFigure 9 in the Supplement); statistical heterogeneity was present but did not appear to be attributable to agents used, trial population, level of risk, or age (eTable 5 in the Supplement). There was a significant interaction *P* value (*P* < .001) in treatment associations across the subgroups with baseline LDL-C levels of 100 mg/dL or greater vs lower than 100 mg/dL (eFigure 9 in the Supplement). In the group of trials with baseline LDL-C levels of 100 to 129 mg/dL, MACE risk was associated with an RR of 0.78 (95% CI, 0.70 to 0.86; ARD, −5.51 incident cases per 1000 person-years [95% CI, −7.76 to −3.26]), with statistical heterogeneity that did not appear to be attributable to agents used, trial population, level of risk, or age (eTable 5 in the Supplement).

Additional Analyses

The associations with risk reduction for each individual clinical end point remained unchanged across different subgroups when CTT baseline LDL-C cutoffs[1] were applied (eFigures 10-15 in the Supplement), nor did they change by year of trial publication (eTable 6 in the Supplement), type of treatment in the control group (eTable 7 in the Supplement), type of agent used in the active treatment group (eTable 8 in the Supplement), or type of population (eTable 9 in the Supplement).

Meta-analysis of all-cause mortality found no association with achieved LDL-C level (eFigure 16 in the Supplement). The between-trials variance was largely attributable to baseline LDL-C level for rates of all-cause mortality (61%), cardiovascular mortality (61%), and MACE (62%) (eTable 10 in the Supplement). Baseline LDL-C level accounted for a substantial proportion of the variance for rates of myocardial infarction (45%) and had a more modest role in revascularization (28%). As a further sensitivity analysis, the influence of each trial was addressed, testing whether deleting each in turn would change significantly the pooled results of the meta-analysis. Deleting each trial in turn did not result in significant deviations from the original overall estimate, suggesting that the overall association is robust (eTable 11 in the Supplement). A further analysis restricted to studies at lower risk of bias with the blinding procedure applied during randomization confirmed the overall results (eTable 12 in the Supplement).

The association between all-cause mortality and absolute magnitude of LDL-C lowering was further investigated. All-cause mortality risk was minimally associated with 35-mg/dL or less reductions in LDL-C level (eFigure 17 in the Supplement). All-cause mortality was associated with an RR of 0.90 (95% CI, 0.85 to 0.96) in the trials with an LDL-C reduction of 35 to 65 mg/dL and an RR of 0.70 (95% CI, 0.52 to 0.95) in the trials with an LDL-C reduction greater than 65 mg/dL (*P* = .11 for interaction); however, statistical heterogeneity was present, and the 95% confidence intervals were wide.

Cardiovascular mortality risk was minimally associated with a reduction in the subgroup of trials with an LDL-C reduction less than 35 mg/dL (RR, 0.94 [95% CI, 0.89 to

1.00]) (eFigure 18 in the Supplement). Cardiovascular mortality was associated with an RR of 0.80 (95% CI, 0.73 to 0.88) in trials with an LDL-C reduction of 35 to 65 mg/dL and an RR of 0.66 (95% CI, 0.56 to 0.79) in trials with an LDL-C reduction greater than 65 mg/dL (*P* = .06 for interaction). Statistical heterogeneity was present in trials with LDL-C reductions of 35 to 65 mg/dL, with suggested differences in risk reduction across types of lipid-lowering agents used: statin (13 trials; RR, 0.76 [95% CI, 0.70 to 0.83]) vs PCSK9-inhibiting monoclonal antibody (3 trials; RR, 1.04 [95% CI, 0.89 to 1.22]; *P* < .001 for interaction) (eTable 5 in the Supplement). Myocardial infarction, stroke, and revascularization procedures were associated with a reduction across the range of magnitudes of LDL-C lowering (eFigures 19-21 in the Supplement). MACE risk was associated with reductions across the range of magnitudes of LDL-C lowering (eFigure 22 in the Supplement).

Discussion

In these meta-analyses and meta-regressions, more intensive compared with less intensive LDL-C lowering was associated with greater reduction in the risk of all-cause and cardiovascular mortality in trials of patients with higher baseline LDL-C levels. These associations were not present when baseline LDL-C levels were less than 100 mg/dL.

Statins, ezetimibe, and PCSK9-inhibiting monoclonal antibodies lower LDL-C level by a percentage of the baseline, so the magnitude of LDL-C lowering is a function of both baseline LDL-C level and drug efficacy. Although LDL-C reduction of 35 mg/dL or greater was also associated with progressively greater reductions in all-cause and cardiovascular mortality, the magnitude of LDL-C lowering did not alter the association between baseline LDL-C level and reductions in risk of all-cause or cardiovascular mortality.

Higher baseline LDL-C level was also associated with progressively greater relative risk reductions in myocardial infarction, revascularization procedures, and MACE, but no lower baseline LDL-C limit to this benefit was observed. Reduction in these events occurred across the range of LDL-C lowering, with progressively larger reductions in events as the baseline LDL-C level and the magnitude of LDL-C lowering increased. In contrast, the reduction in cerebrovascular events did not appear to be influenced by baseline LDL-C level or by the magnitude of LDL-C lowering. A similar lack of association with baseline LDL-C level and magnitude of LDL-C lowering was found for ischemic stroke.

These findings may provide an explanation for the lack of cardiovascular or all-cause mortality reductions that has been noted in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, despite a significant LDL-C reduction, as well as in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) and in the high- vs moderate-intensity statin trials with lesser magnitudes of LDL-C lowering.[2,3,10-12] However, additional LDL-C lowering

in these trials still provided additional reduction in myocardial infarctions, cerebrovascular events, revascularizations, and MACE.

Two smaller trials of the efficacy and safety of the PCSK9-inhibiting monoclonal antibodies alirocumab (ODYSSEY LONG TERM[4]) and evolocumab (OSLER[5]) support the role of higher baseline LDL-C level, along with greater magnitude of LDL-C lowering, for predicting a mortality benefit from LDL-C-lowering therapy. The ODYSSEY LONG TERM and OSLER trials had baseline LDL-C levels of approximately 120 mg/dL and LDL-C reductions of approximately 70 mg/dL. When pooled together in a previous meta-analysis, an association with all-cause and cardiovascular mortality benefit was found.[6] The SPIRE-2 trial, another trial of a PCSK9-inhibiting monoclonal antibody, bococizumab, with a higher baseline LDL-C level was terminated early at 1 year because of loss of LDL-C-lowering efficacy from neutralizing antibodies.[43]

The relatively short 2.2-year duration of the FOURIER trial has been implicated in the lack of a cardiovascular mortality benefit, and trial duration was accounted for in the rate ratios used in these analyses. The ongoing ODYSSEY OUTCOMES trial (NCT01663402) is planned to be of somewhat longer duration than the FOURIER trial.[44,45] Patients in the ODYSSEY OUTCOMES trial are within 1 year of an acute coronary event and have baseline LDL-C levels of 87 mg/dL; 80% are receiving a high-intensity statin.

These findings suggest that the CTT meta-analysis of statin trials finding that each 39-mg/dL (1-mmol/L) reduction in LDL-C level was associated with a hazard ratio of 0.78 (95% CI, 0.76 to 0.80) in the reduction in MACE may not be generalizable to populations with baseline LDL-C levels higher or lower than the mean LDL-C of 120 mg/dL in the meta-analysis or to composite end points other than MACE.[1]

In addition, in this analysis, stroke was reduced by a similar magnitude across the range of LDL-C lowering. It could be hypothesized that a greater reduction in risk of ischemic stroke might be counterbalanced by an increase in hemorrhagic stroke with increasing magnitude of LDL-C lowering. Although consistent reductions in ischemic stroke risk of 21% were found in a sensitivity analysis, too few trials reported hemorrhagic stroke rates for a definite conclusion (Supplement).

If additional LDL-C-lowering therapies are considered in statin-treated patients, nonstatin LDL-C-lowering therapies shown to reduce cardiovascular disease events are recommended.[13,15] This analysis further supports individualizing estimates of the potential for a cardiovascular risk reduction benefit from LDL-C-lowering therapy based on consideration of not only a patient's absolute risk and current LDL-C level but also an individualized estimate of the risk reduction based on current LDL-C level and the outcomes desired.[46]

Limitations

This study has several limitations. First, the analysis included only trial-level data. Only main trial results were considered. Subgroup analyses might have provided additional information on sources of heterogeneity of treatment associations. Second, end-of-trial LDL-C levels were used, which may have underestimated the full association of the magnitude of LDL-C lowering during a trial. Third, there was evidence of heterogeneity in some of the subgroup meta-analyses for mortality, coronary events, and MACE, although this may reflect the prespecified groupings used. No characteristic appeared to affect the meta-regression sensitivity analyses, in which the associations remained robust to all adjustments.

Conclusions

In these meta-analyses and meta-regressions, more intensive compared with less intensive LDL-C lowering was associated with a greater reduction in risk of total and cardiovascular mortality in trials of patients with higher baseline LDL-C levels. This association was not present when baseline LDL-C level was less than 100 mg/dL, suggesting that the greatest benefit from LDL-C-lowering therapy may occur for patients with higher baseline LDL-C levels.

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