Supplementary Online Content

Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA*. doi:10.1001/jama.2016.13985

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Database Search Strategy

A Pubmed MEDLINE search was conducted in July 2016. The term 'LDL lowering' yielded 8,972 articles. The term 'clinical outcomes' yielded 253,860 articles. The combination of 'LDL lowering' and 'clinical outcomes' yielded 405 articles. The limitation 'randomized controlled trial' resulted in 91 articles. The limitation 'humans' did not change this number.

A search of EMBASE was also conducted in July of 2016. The term 'LDL lowering' yielded 12,284 articles. The term 'clinical outcomes' yielded 595,988 articles. The combination of 'LDL lowering' and 'clinical outcomes' yielded 811 articles. The limitation 'randomized controlled trial' resulted in 138 articles. The limitation 'humans' decreased the search result to 137 articles. Of the 228 articles identified, there were 56 duplicates, resulting in 172 articles from the database search that were evaluated for possible study eligibility (Figure 1).

Lipid levels

For the absolute achieved LDL-C difference between treatment arms, if available, the mean difference averaged over the course of follow up was used. When this information was not reported, the mean achieved LDL-C at the time point closest to 50% of the median follow up was used (usually 1-2 years). Some earlier trials did not report LDL-C, therefore baseline LDL-C values were estimated using the following regression equation derived from 24 trials that had baseline measurements of both LDL-C and total cholesterol (TC): baseline LDL-C = (baseline TC)*[(baseline TC)*0.0012 + 0.3793].

The achieved LDL-C difference was estimated using a specific ratio for each class of intervention based on data from other trials in the same intervention class that had both measurements. For niacin (used for Coronary Drug Project), the percent reduction in TC was multiplied by 1.73 to estimate the percent reduction in LDL-C [1]. For fibrates (used for Coronary Drug Project, WHO CO-OP), the percent reduction in TC was multiplied by 1.05 to estimate the percent reduction in LDL-C [2-4]. For all the diet trials, the percent reduction in TC was multiplied by 1.14 to estimate the percent reduction in LDL-C [5]. For bile acid sequestrants (used for the Upjohn trial), the absolute reduction in TC was multiplied by 1.1 to estimate the absolute reduction in LDL-C [6].

For the LDL-C reductions with CETP inhibitors, a sensitivity analysis was performed in which the LDL-C reductions were adjusted for potential inaccuracies stemming from use of the Friedewald equation. The difference in achieved LDL-C was estimated by applying a correction factor based on previously published LDL-C data from treatment with anacetrapib in which the absolute LDL-C reduction as measured by beta-quantification was 74% the amount when estimated using the Friedewald equation [7].

Outcomes

When actual hazard or risk ratios were not available, we calculated risk ratios and 95% CIs based on reported event rates using Stata version 12 (StataCorp, College Station, TX, USA). For the analysis of achieved LDL-C and the rates of major coronary events, rates were obtained from trials approximately contemporary to the statin era and for which achieved levels of LDL-C in each arm were provided or could be calculated.

Estimated 5 year event rates were extrapolated as needed based on the duration of follow-up of the trial.

Sensitivity analyses

The following sensitivity analyses were done:

- Restricting analyses to trials with reported LDL-C (ie, excluding estimated LDL-C)
- Testing whether baseline LDL-C was a significant predictor of the relative risk reduction in major vascular events
- Performing the meta-regression in trials subdivided into those with baseline LDL-C above or below the median
- Testing whether a quadratic term for absolute LDL-C was significant

Assessment of study quality, consistency, and publication bias

The Cochrane Collaboration's tool [8] was used to assess the risk of bias within a study. A sensitivity analysis was performed examining only double-blind trials of statins or established non-statin therapies that work primarily via upregulation of LDL receptor expression. For consistency of results within a group of trials, the hazard or risk ratio from each trial was normalized to the degree of LDL-C lowering and the results were combined using inverse variance-weighted fixed effects meta-analysis. The Q test of heterogeneity and its corresponding P value and the I^2 metric were calculated. Egger's test of the intercept was used to examine for publication bias and Duval and Tweedie's

trim and fill method (only looking for unpublished studies with lesser effects) was used to calculate adjusted effect estimates.

eResults

Sensitivity analyses

Several sensitivity analyses were performed in the meta-regression of statin trials and trials of established non-statin therapies that work primarily via upregulation of LDL receptor expression. When excluding trials (n=5 of 33) in which LDL-C was not reported, the results were identical: relative risk 0.77 for major vascular events per 1 mmol/L reduction in LDL-C. When baseline LDL-C was added to the model, the term was not significant (P=0.98). In analyses stratified according to baseline LDL-C level (above or below the median baseline LDL-C level [3.8 mmol/L]) for the trials, there was no difference in the relative risk of major vascular events per mmol/L LDL-C reduction (below median baseline LDL-C = 0.77 [95%CI 0.74-0.80] vs above median baseline LDL-C = 0.77 [95%CI 0.73-0.80]). In a model in which a quadratic term (LDL-C absolute difference squared) was added, it was not significant (p=0.99). When excluding trials that were not double-blind (n=11 of 33), the slope was the same: 0.77 relative risk of major vascular events per 1 mmol/L reduction in LDL-C.

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eTable 1. Statin trials

Trial	Year published	Primary or Secondary Prevention	Intervention		Average* follow-up (years)	Between-group Difference* in Achieved LDL-C (mmol/L)	Selected Composite Endpoint
			Experimental Group	Control Group			
4S[9]	1994	Secondary	Simvastatin 20–40 mg	Placebo	5.4	1.75	CHD death, MI, or Resuscitated arrest
WOSCOPS[10]	1995	Primary	Pravastatin 40 mg	Placebo	4.9	0.98	CHD death or MI
CARE[11]	1996	Secondary	Pravastatin 40 mg	Placebo	5	0.98	CHD death or MI
Post-CABG[12]	1997	Secondary	Lovastatin 40–80 mg	Lovastatin 2.5–5 mg	4.3	1.11	ACM, MI, Stroke, or Revascularization
AFCAPS/TexCAPS[13]	1998	Primary	Lovastatin 20–40 mg	Placebo	5.2	1.08	CHD death, MI or UA
LIPID[14]	1998	Secondary	Pravastatin 40 mg	Placebo	6.1	0.97	CHD death or MI
GISSI Prevention[15]	2000	Secondary	Pravastatin 20 mg	Usual care	2	0.35	ACM, MI, or Stroke
LIPS[16]	2002	Secondary	Fluvastatin 80 mg	Placebo	3.9	1.06	CHD Death, MI, or Revascularization
HPS[17]	2002	Both	Simvastatin 40 mg	Placebo	5	1.00	CHD death, MI, Stroke, or Revascularization
GREACE[18]	2002	Secondary	Atorvastatin 10–80 mg	Usual care	3	1.86	CHD Death or non-fatal MI

Trial	Year published	Primary or Secondary Prevention	Intervention		Average* follow-up (years)	Between-group Difference* in Achieved LDL-C (mmol/L)	Selected Composite Endpoint
			Experimental Group	Control Group			
PROSPER[19]	2002	Both	Pravastatin 40 mg	Placebo	3.2	1.03	CHD death, MI, or Stroke
ALLHAT-LLT[20]	2002	Both	Pravastatin 40 mg	Usual care	4.8	0.62	CHD death or MI
ASCOT-LLA[21]	2003	Primary	Atorvastatin 10 mg	Placebo	3.3	1.20	CHD death or MI
PROVE-IT[22]	2004	Secondary	Atorvastatin 80 mg	Pravastatin 40 mg	2	0.85	ACM, MI, Stroke, UA hospitalization, or Revascularization
CARDS[23]	2004	Primary	Atorvastatin 10 mg	Placebo	3.9	1.20	CHD death, MI, Stroke, UA, or Revascularization
A to Z[24]	2004	Secondary	Simvastatin 40–80 mg	Placebo titrated to simvastatin 20mg	2	0.36	CV death, MI, Stroke, or Hospitalization for ACS
ALLIANCE[25]	2004	Secondary	Atorvastatin 10–80 mg	Usual care	4.5	0.39	CHD death, MI, UA, Resuscitated arrest, or Revascularization
TNT[26]	2005	Secondary	Atorvastatin 80 mg	Atorvastatin 10 mg	4.9	0.62	CHD death, MI, Stroke, or Resuscitated arrest
IDEAL[27]	2005	Secondary	Atorvastatin	Simvastatin	4.8	0.56	CHD death, MI, Stroke, or

Trial	Year published	Primary or Secondary Prevention	Intervention		Average* follow-up (years)	Between-group Difference* in Achieved LDL-C (mmol/L)	Selected Composite Endpoint
			Experimental Group	Control Group			
			40–80 mg	20–40 mg			Resuscitated arrest
ASPEN[28]	2006	Both	Atorvastatin 10 mg	Placebo	4	0.88	CV death, MI, Stroke, UA, Resuscitated arrest, or Revascularization
SPARCL[29]	2006	Secondary	Atorvastatin 80 mg	Placebo	4.9	1.43	CHD Death, MI, Stroke, or Cardiac arrest
MEGA[30]	2006	Primary	Pravastatin 10–20 mg	Usual care	5.3	0.59	CHD death, MI, Stroke, UA, or Revascularization
JUPITER[31]	2008	Primary	Rosuvastatin 20 mg	Placebo	1.9	1.42	CV death, MI, Stroke, UA, or Revascularization
SEARCH[32]	2010	Secondary	Simvastatin 80 mg	Simvastatin 20 mg	6.7	0.35	CHD death, MI, Stroke, or Revascularization
HOPE-3[33]	2016	Primary	Rosuvastatin 10 mg	Placebo	5.6	0.89	CV death, MI, or Stroke

*Mean or median depending on what was reported in the trial.

ACM = all-cause mortality; ACS = acute coronary syndrome; CHD = coronary heart disease; CV = cardiovascular; MI = myocardial infarction; UA = unstable angina

eTable 2. Diet trials

Trial	Year published	Primary or Secondary Prevention	Intervention		Average* follow-up (years)	Between-group Difference* in Achieved LDL-C (mmol/L)	Selected Composite Endpoint
			Experimental Group	Control Group			
Research Committee[34]	1965	Secondary	Low-fat diet	Usual diet	3	0.47	Death or MI
Oslo[35]	1966	Secondary	Low saturated fat and high polyunsaturated fat diet	Usual diet	5	0.88	CHD death or MI
MRC Soya-Bean[36]	1968	Secondary	Low saturated fat plus Soya-bean oil	Usual diet	3.4	0.85	Death or MI
LA Veteran's Study[37]	1969	Both	Low saturated fat and high polyunsaturated fat diet	Usual diet	5	0.62	CHD death or MI

*Mean or median depending on what was reported in the trial.
CHD = coronary heart disease; MI = myocardial infarction

eTable 3. Bile acid sequestrant trials

Trial	Year published	Primary or Secondary Prevention	Intervention		Average* follow-up (years)	Between-group Difference* in Achieved LDL-C (mmol/L)	Selected Composite Endpoint
			Experimental Group	Control Group			
Upjohn[38]	1978	Both	Colestipol 15g/day	Placebo	2	0.67	CHD death, MI, UA, or HF
Lipid Research Clinics[6]	1984	Primary	Cholestyramine resin 24g/day	Placebo	7.4	1.02	CHD death or MI

*Mean or median depending on what was reported in the trial.

CHD = coronary heart disease; HF = heart failure; MI = myocardial infarction; UA = unstable angina

eTable 4. Ileal bypass surgery trial

Trial	Year published	Primary or Secondary Prevention	Intervention		Average* follow-up (years)	Between-group Difference* in Achieved LDL-C (mmol/L)	Selected Composite Endpoint
			Experimental Group	Control Group			
POSCH[39]	1990	Secondary	Ileal bypass surgery	No surgery	9.7	1.62	CHD death or MI

*Mean or median depending on what was reported in the trial
CHD = coronary heart disease; MI = myocardial infarction

eTable 5. Ezetimibe trial

Trial	Year published	Primary or Secondary Prevention	Intervention		Average* follow-up (years)	Between-group Difference* in Achieved LDL-C (mmol/L)	Selected Composite Endpoint
			Experimental Group	Control Group			
IMPROVE-IT[40]	2015	Secondary	Simvastatin 40 mg plus Ezetimibe 10 mg	Simvastatin 40 mg plus Placebo	6	0.33	CV death, MI, Stroke, UA hospitalization, or revascularization

*Mean or median depending on what was reported in the trial
CV = cardiovascular; MI = myocardial infarction; UA = unstable angina

eTable 6. Fibrate trials

Trial	Year published	Primary or Secondary prevention	Intervention		Average* follow-up (years)	Between-group Difference* in Achieved LDL-C (mmol/L)	Selected Composite Endpoint
			Experimental Group	Control Group			
Coronary Drug Project[41]	1975	Secondary	Clofibrate 1.8g	Placebo	5	0.31	CHD death or MI
WHO CO-OP[42]	1978	Primary	Clofibrate 1.6g	Placebo	5.3	0.41	CHD death or MI
HHS[2]	1987	Primary	Gembibrozil 1.2g	Placebo	5	0.54	CHD death or MI
VA-HIT [43]	1999	Secondary	Gemfibrozil 1.2g	Placebo	5.1	0	CHD death or MI
BIP[44]	2000	Secondary	Bezafibrate 400mg	Placebo	6.2	0.16	CHD death or MI
DAIS[45]	2001	Both	Fenofibrate 200mg	Placebo	3.3	0.27	ACM, MI, UA, or Revascularization
LEADER[3]	2002	Primary	Bezafibrate 400mg	Placebo	4.6	0.31	CHD death, MI, or Stroke
FIELD[4]	2005	Both	Fenofibrate 200mg	Placebo	5	0.36	CV death, MI, Stroke, or Revascularization
ACCORD[46]	2010	Both	Simvastatin plus Fenofibrate 160mg	Simvastatin plus Placebo	4.7	0	CV death, MI, or Stroke

*Mean or median depending on what was reported in the trial;
ACM = all-cause mortality; CHD = coronary heart disease; CV = cardiovascular; MI = myocardial infarction; UA = unstable angina

eTable 7. Niacin trials

Trial	Year published	Primary or Secondary prevention	Intervention		Average* follow-up (years)	Between-group Difference* in Achieved LDL-C (mmol/L)	Selected Composite Endpoint
			Experimental Group	Control Group			
Coronary Drug Project[41]	1975	Secondary	Niacin 3g	Placebo	5	0.78	CHD death or MI
AIM-HIGH[47]	2011	Secondary	Simvastatin ± ezetimibe plus niacin 1.5-2g	Simvastatin ± ezetimibe plus placebo (niacin 50 mg)	3	0.16	CHD death, MI, Stroke, UA, or Revascularization
HPS2-Thrive[48]	2014	Secondary	Simvastatin ± ezetimibe plus niacin 2g/laropiprant 40mg	Simvastatin ± ezetimibe plus placebo	3.9	0.26	CHD death, MI, Stroke, or Revascularization

*Mean or median depending on what was reported in the trial
CHD = coronary heart disease; MI = myocardial infarction; UA = unstable angina

eTable 8. CETP inhibitor trials

Trial	Year published	Primary or Secondary prevention	Intervention		Average* follow-up (years)	Between-group Difference* in Achieved LDL-C (mmol/L)	Selected Composite Endpoint
			Experimental Group	Control Group			
DEFINE[49]	2010	Both	Anacetrapib 100mg	Placebo	1.5	0.83	CV death, MI, Stroke, or UA
dal-OUTCOME[50]	2012	Secondary	Dalcetrapib 600mg	Placebo	2.6	0	CHD death, MI, Stroke, UA, or Resuscitated arrest
ACCELERATE[51]	2016	Secondary	Evacetrapib 130mg	Placebo	2.1	0.75	CV death, MI, Stroke, UA, or Revascularization

*Mean or median depending on what was reported in the trial

CHD = coronary heart disease; CV = cardiovascular; MI = myocardial infarction; UA = unstable angina

eTable 9. PCSK9 inhibitor trials

Trial	Year published	Primary or Secondary prevention	Intervention		Average* follow-up (years)	Between-group Difference* in Achieved LDL-C (mmol/L)	Selected Composite Endpoint
			Experimental Group	Control Group			
ODYSSEY Long Term[52]	2015	Both	Alirocumab 150mg subcutaneously every 2 weeks	Placebo	1.6	1.83	CHD death, MI, Stroke, or UA
OSLER[53]	2015	Both	Evolocumab 140mg subcutaneously every 2 weeks or 420mg every month plus standard of care	Standard of care alone	0.9	1.89	ACM, MI, Stroke, TIA, UA, or Revascularization

*Mean or median depending on what was reported in the trial

ACM = all-cause mortality; CHD = coronary heart disease; MI = myocardial infarction; TIA = transient ischemic attack; UA = unstable angina

eTable 10. Estimated 5-year rates of coronary death or MI

Trial	Primary or Secondary Prevention	Intervention		Achieved LDL-C (mmol/L)*		Estimated 5-year Rate of Coronary Death or MI	
		Experimental Group	Control Group	Experimental Group	Control Group	Experimental Group (%)	Control Group (%)
4S[9]	Secondary	Simvastatin 20–40 mg	Placebo	3.17	4.92	17.6	25.9
WOSCOPS[10]	Primary	Pravastatin 40 mg	Placebo	3.85	4.84	5.6	8.1
CARE[11]	Secondary	Pravastatin 40 mg	Placebo	2.52	3.50	10.2	13.2
Post-CABG[12]	Secondary	Lovastatin 40–80 mg	Lovastatin 2.5–5 mg	2.40	3.52	6.0	6.9
AFCAPS/TexCAPS[13]	Primary	Lovastatin 20–40 mg	Placebo	2.96	4.04	1.7	2.8
LIPID[14]	Secondary	Pravastatin 40 mg	Placebo	2.91	3.88	10.1	13.0
LIPS[16]	Secondary	Fluvastatin 80 mg	Placebo	2.51	3.57	6.4	9.2
HPS[17]	Both	Simvastatin 40 mg	Placebo	2.30	3.30	8.7	11.8
GREACE[18]	Secondary	Atorvastatin 10–80 mg	Usual care	2.51	4.37	4.3	10.7
PROSPER[19]	Both	Pravastatin 40 mg	Placebo	2.77	3.80	15.8	19.1
ALLHAT-LLT[20]	Both	Pravastatin 40 mg	Usual care	2.87	3.49	7.8	8.7
ASCOT-LLA[21]	Primary	Atorvastatin 10 mg	Placebo	2.25	3.45	3.0	4.7
CARDS[23]	Primary	Atorvastatin 10 mg	Placebo	1.94	3.04	2.9	5.5
ALLIANCE[25]	Secondary	Atorvastatin 10–80 mg	Usual care	2.46	2.84	4.8	8.6
TNT[26]	Secondary	Atorvastatin 80 mg	Atorvastatin 10 mg	1.99	2.61	6.8	8.5
IDEAL[27]	Secondary	Atorvastatin 40–80	Simvastatin	2.12	2.69	9.7	10.8

Trial	Primary or Secondary Prevention	Intervention		Achieved LDL-C (mmol/L)*		Estimated 5-year Rate of Coronary Death or MI	
		Experimental Group	Control Group	Experimental Group	Control Group	Experimental Group (%)	Control Group (%)
		mg	20–40 mg				
ASPEN[28]	Both	Atorvastatin 10 mg	Placebo	2.04	2.92	5.0	6.9
SPARCL[29]	Secondary	Atorvastatin 80 mg	Placebo	1.89	3.34	3.5	5.2
MEGA[30]	Primary	Pravastatin 10–20 mg	Usual care	3.31	3.90	0.5	0.8
JUPITER[31]	Primary	Rosuvastatin 20 mg	Placebo	1.42	2.84	0.9	1.9
SEARCH[32]	Secondary	Simvastatin 80 mg	Simvastatin 20 mg	2.15	2.50	4.9	5.7
HOPE-3[33]	Primary	Rosuvastatin 10 mg	Placebo	2.34	3.24	0.6	1.0
Lipid Research Clinics[6]	Primary	Cholestyramine resin 24g/day	Placebo	4.12	5.14	5.5	6.7
POSCH[39]	Secondary	Ileal bypass surgery	No surgery	2.68	4.30	10.0	15.5

*Mean or median depending on what was reported in the trial. MI, myocardial infarction.

eTable 11. Risk-of-bias assessments for statin trials

Trial	Random sequence generation	Allocation concealment	Blinding	Outcome assessment	Withdrawal consent No. (%)	Lost to follow up No. (%)	Outcomes reported
4S[9]	NR	NR	Double-blind	Central	NR	0%	Prespecified
WOSCOPS[10]	NR	NR	Double-blind	Central	NR	0%	Prespecified
CARE[11]	NR	Central rando	Double-blind	Central	NR	1 (0.02%)	Prespecified
Post-CABG[12]	NR	Central rando	NR	NR	NR	3 (0.2%)	Prespecified
AFCAPS/TexCAPS[13]	NR	NR	Double-blind	Central	NR	4 (0.06)	Prespecified
LIPID[14]	NR	NR	Double-blind	Central	NR	1 (0.01%)	Prespecified
GISSI Prevention[15]	NR	NR	Open label	NR	NR	NR	Prespecified
LIPS[16]	NR	NR	Double-blind	Central	NR	17 (1.01%)	Prespecified
HPS[17]	Minimization algorithm	Central rando	Double-blind	Central	NR	67 (0.3%)	Prespecified
GREACE[18]	NR	NR	Open label	Central	NR	0 (0%)	Prespecified
PROSPER[19]	Computer	Central rando	Double-blind	Central	12 (0.21%)	NR	Prespecified
ALLHAT-LLT[20]	Computer	Central rando	Open label	Central	46 (0.44%)	208 (1.99%)	Prespecified
ASCOT-LLA[21]	Computer	NR	Double-blind	Central	14 (0.14%)	17 (0.16%)	Prespecified
PROVE IT-TIMI 22[22]	Computer	Central rando	Double-blind	Central	NR	8 (0.2%)	Prespecified
CARDS[23]	Computer	Central rando	Double-blind	Central	NR	24 (0.84%)	Prespecified
A to Z[24]	NR	NR	Double-blind	Central	NR	44 (0.98%)	Prespecified
ALLIANCE[25]	NR	NR	Open label	Central	217 (8.89%)	165 (6.76%)	Prespecified
TNT[26]	NR	NR	Double-blind	Central	11 (0.11%)	73 (0.73%)	Prespecified
IDEAL[27]	NR	Central Rando	Open label	Central	48 (0.54%)	6 (0.07%)	Prespecified
ASPEN[28]	NR	NR	Double-blind	Central	287 (11.90%)	56 (2.32%)	Prespecified

Trial	Random sequence generation	Allocation concealment	Blinding	Outcome assessment	Withdrawal consent No. (%)	Lost to follow up No. (%)	Outcomes reported
SPARCL[29]	NR	NR	Double-blind	Central	181 (3.83%)	25 (0.53%)	Prespecified
MEGA[30]	Computer	NR	Open label	Central	94 (1.14%)	102 (1.24%)	Prespecified
JUPITER[31]	NR	Central Rando	Double-blind	Central	NR	NR	Prespecified
SEARCH[32]	Minimization algorithm	Central Rando	Double-blind	Central	NR	119 (0.99)	Prespecified
HOPE-3[33]	NR	Central Rando	Double-blind	Central	23 (0.18%)	90 (0.71%)	Prespecified

NR, not reported; rando, randomization

eTable 12. Risk-of-bias assessments for diet trials

Trial	Random Sequence generation	Allocation concealment	Blinding	Outcome assessment	Withdrawal of consent No. (%)	Lost to follow up No. (%)	Outcomes reported
Research Committee[34]	NR	NR	Open label	Central	NR	NR	Prespecified
Oslo[35]	NR	NR	Open label	Central	NR	0 (0%)	Prespecified
MRC Soya-Bean[36]	NR	NR	Open label	Central	NR	8 (2%)	Prespecified
LA Veteran's Study[37]	NR	NR	Double-blind	Central	NR	No. not provided (< 1%)	Prespecified

NR, not reported; rando, randomization

eTable 13. Risk-of-bias assessments for bile acid sequestrant trials

Trial	Random Sequence generation	Allocation concealment	Blinding	Outcome assessment	Withdrawal of consent No. (%)	Lost to follow up No. (%)	Outcomes reported
Upjohn[38]	NR	Central Rando	Single-blind	Central	NR	No. not provided (3.0%)	Prespecified
Lipid Research Clinics[6]	NR	NR	Double-blind	Central	NR	0 (0%)	Prespecified

NR, not reported; rando, randomization

eTable 14. Risk-of-bias assessments for ileal bypass surgery trial

Trial	Random Sequence generation	Allocation concealment	Blinding	Outcome assessment	Withdrawal of consent No. (%)	Lost to follow up No. (%)	Outcomes reported
POSCH[39]	NR	Central Rando	Open label	Central	NR	0 (0%)	Prespecified

NR, not reported; rando, randomization

eTable 15. Risk-of-bias assessments for ezetimibe trial

Trial	Random Sequence generation	Allocation concealment	Blinding	Outcome assessment	Withdrawal of consent No. (%)	Lost to follow up No. (%)	Outcomes reported
IMPROVE-IT[40]	Computer	Central Rando	Double-blind	Central	1603 (8.83%)	93 (0.51%)	Prespecified

NR, not reported; rando, randomization

eTable 16. Risk-of-bias assessments for fibrate trials

Trial	Random Sequence generation	Allocation concealment	Blinding	Outcome assessment	Withdrawal of consent No. (%)	Lost to follow up No. (%)	Outcomes reported
Coronary Drug Project[41]	NR	Central Rando	Double-blind	Central	NR	1 (0.03%)	Prespecified
WHO CO-OP[42]	NR	NR	Double-blind	Central	NR	NR	Prespecified
HHS[2]	NR	NR	Double-blind	Central	NR	0 (0%)	Prespecified
VA-HIT [43]	NR	Central Rando	Double-blind	Central	NR	3 (0.12%)	Prespecified
BIP[44]	NR	NR	Double-blind	Central	NR	1 (0.03%)	Prespecified
DAIS[45]	Computer	Central Rando	Double-blind	Central	NR	NR	Not prespecified
LEADER[3]	NR	Central Rando	Double-blind	Central	NR	21 (1.3%)	Prespecified
FIELD[4]	Computer	Central Rando	Double-blind	Central	9 (0.09%)	22 (0.22%)	Prespecified
ACCORD[46]	Computer	Central Rando	Double-blind	Central	NR	56 (1.01%)	Prespecified

NR, not reported; rando, randomization

eTable 17. Risk-of-bias assessments for niacin trials

Trial	Random Sequence generation	Allocation concealment	Blinding	Outcome assessment	Withdrawal of consent No. (%)	Lost to follow up No. (%)	Outcomes reported
Coronary Drug Project[41]	NR	Central Rando	Double-blind	Central	NR	4 (0.10%)	Prespecified
AIM-HIGH[47]	Computer	Central Rando	Double-blind	Central	27 (0.79%)	25 (0.73%)	Prespecified
HPS2-Thrive[48]	NR	NR	Double-blind	Central	NR	203 (0.79%)	Prespecified

NR, not reported; rando, randomization

eTable 18. Risk-of-bias assessments for cetp inhibitor trials

Trial	Random Sequence generation	Allocation concealment	Blinding	Outcome assessment	Withdrawal of consent No. (%)	Lost to follow up No. (%)	Outcomes reported
DEFINE[49]	NR	NR	Double-blind	Central	NR	14 (0.86%)	Prespecified
dal-OUTCOME[50]	NR	NR	Double-blind	Central	342* (2.15%)	230* (1.45%)	Prespecified
ACCELERATE[51]	NR	Central Rando	Double-blind	Central	NR	NR	Prespecified

NR, not reported; rando, randomization

* Numbers are estimated as only percentages were reported

eTable 19. Risk-of-bias assessments for PCSK9 inhibitor trials

Trial	Random Sequence generation	Allocation concealment	Blinding	Outcome assessment	Withdrawal of consent No. (%)	Lost to follow up No. (%)	Outcomes reported
ODYSSEY Long Term[52]	Computer	Central Rando	Double-blind	Central	NR	NR	Post hoc
OSLER[53]	Computer	Central Rando	Open label	Central	NR	NR	Prespecified

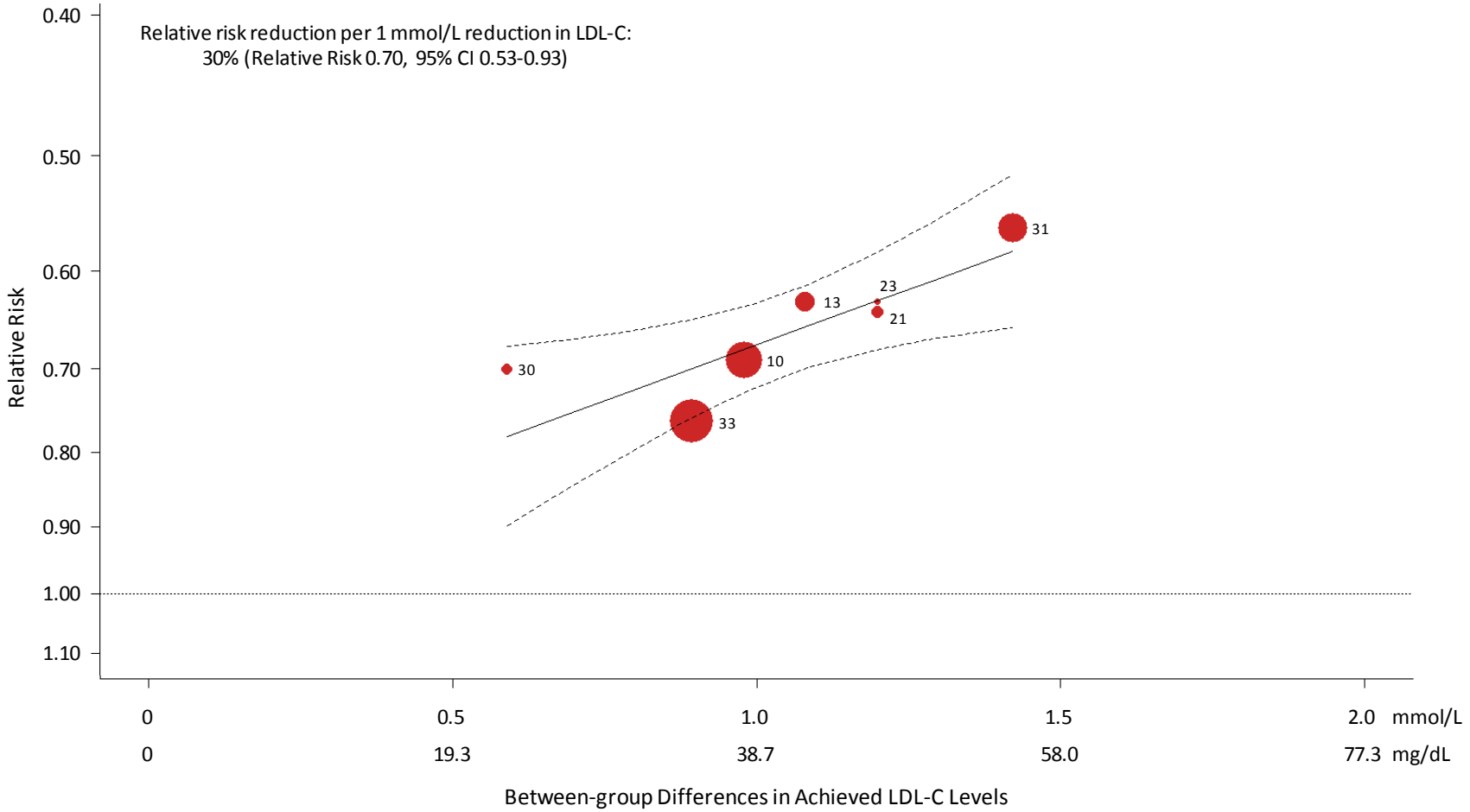
NR, not reported; rando, randomization

eTable 20. Assessment for heterogeneity and publication bias

Type of Intervention	Tests for Heterogeneity			Tests for Publication Bias		
	Q (df)	P value	I^2	Egger's P value	Observed RR (95% CI)	Duval and Tweedie's Trim & Fill RR (95% CI)
Statins	29.5 (24)	0.20	18.7%	0.068	0.77 (0.75-0.79)	0.78 (0.76-0.81)
Diet, Bile Acid Sequestrants, Ileal Bypass, Ezetimibe	2.4 (7)	0.94	0.0%	0.18	0.79 (0.72-0.86)	0.79 (0.73-0.87)
Fibrates	4.0 (6)	0.68	0.0%	0.10	0.68 (0.57-0.82)	0.72 (0.60-0.86)
Niacin	0.5 (2)	0.79	0.0%	0.03	0.83 (0.73-0.94)	0.83 (0.73-0.94)
CETP inhibitors	3.7 (1)	0.056	72.6%	n/a	n/a	n/a
PCSK9 inhibitors	0.04 (1)	0.84	0.0%	n/a	n/a	n/a

Analyses included trials with a non-zero change in LDL-C. Tests for publication bias could only be performed if there were at least 3 trials. RR, risk ratio.

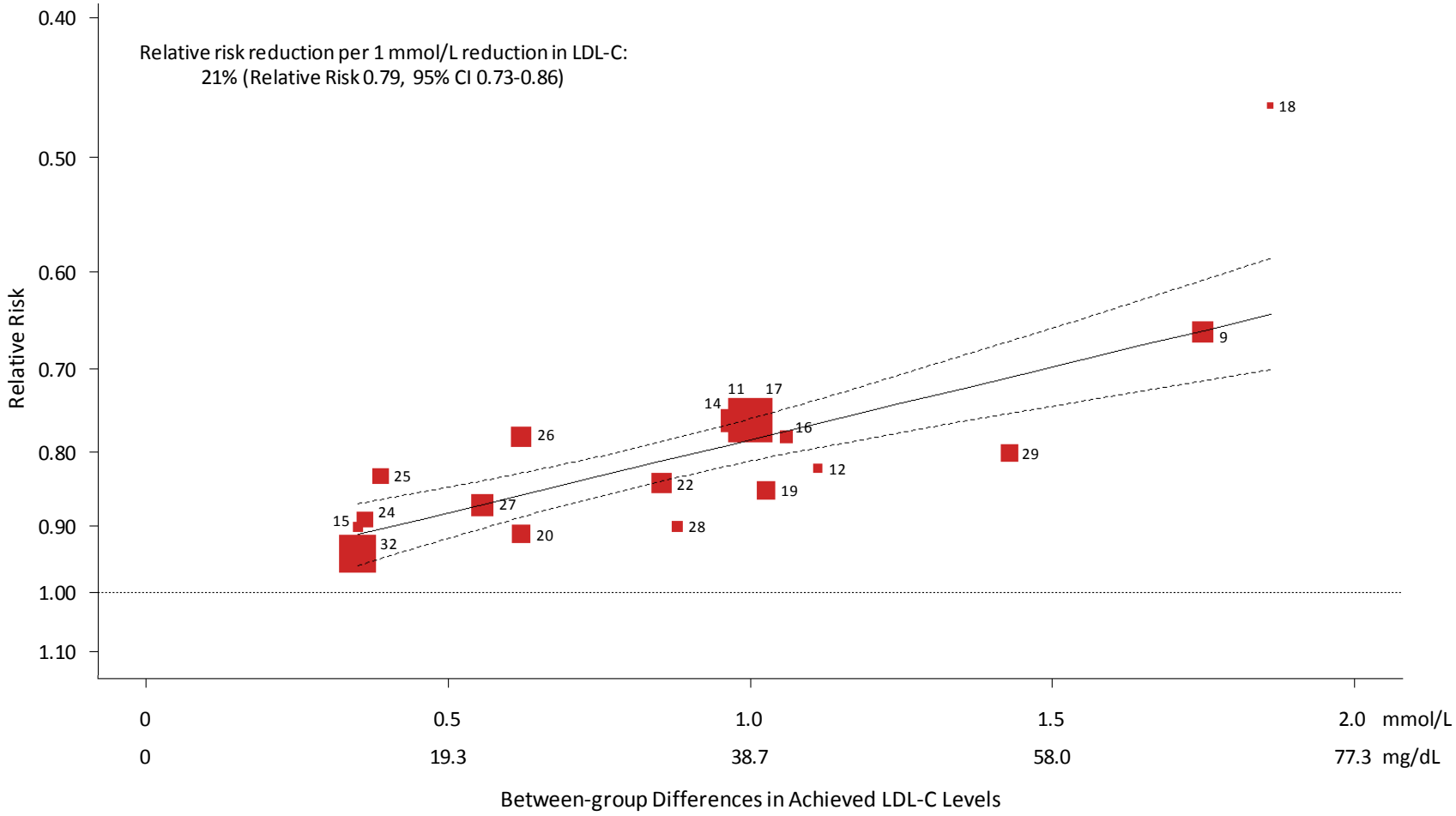
eFigure 1. Major vascular event relative risk per mmol/L decrease in LDL-C in primary prevention population statin trials



Relationship between absolute LDL-C reduction and the relative risk of major vascular events (cardiovascular death, acute myocardial infarction or other acute coronary syndrome, coronary revascularization, or stroke, when available) in 7 statin trials in a primary

prevention population. Each trial is represented by 1 circle, the size of which is proportional to the weight in the meta-regression. The number by each symbol is the reference number for that trial in the Supplement. The meta-regression slope (predicted relative risk for degree of LDL-C reduction) is represented by the solid line and the 95% confidence intervals by the dashed lines.

eFigure 2. Major vascular event relative risk per mmol/L decrease in LDL-C in secondary prevention population statin trials

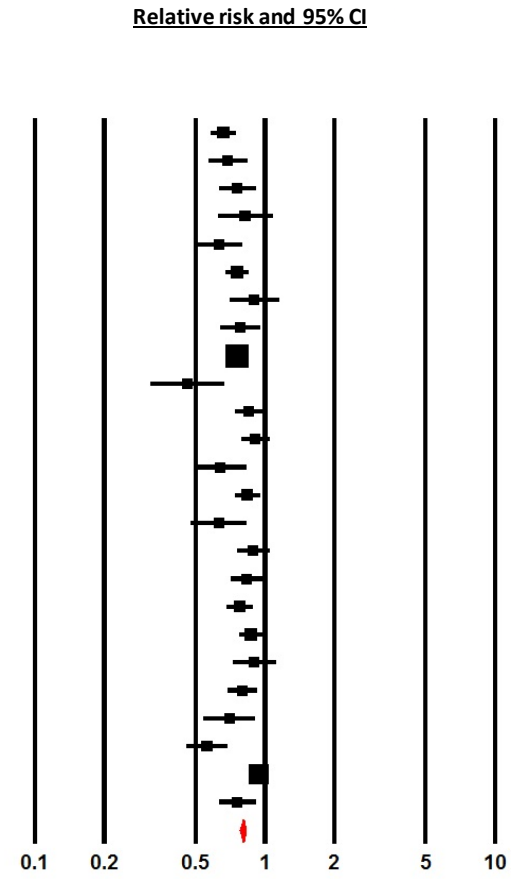


Relationship between absolute LDL-C reduction and the relative risk of major vascular events (cardiovascular death, acute myocardial infarction or other acute coronary syndrome, coronary revascularization, or stroke, when available) in 18 statin trials in a secondary prevention population. Each trial is represented by 1 circle, the size of which is proportional to the weight in the meta-regression. The

number by each symbol is the reference number for that trial in the Supplement. The meta-regression slope (predicted relative risk for degree of LDL-C reduction) is represented by the solid line and the 95% confidence intervals by the dashed lines.

eFigure 3. Statin trials meta-analysis

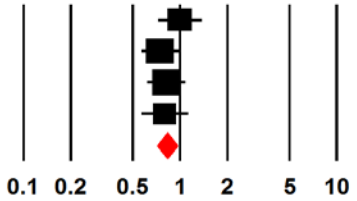
Study Name	Year Published	Participants: Experimental Group	Participants: Control Group	Major Vascular Events: Experimental Group	Major Vascular Events: Control Group	Statistics for each study: Relative Risk	Lower Limit	Upper Limit	p-Value
4S[9]	1994	2221	2223	431	622	0.660	0.585	0.744	0.000
WOSCOPS[10]	1995	3302	3293	174	248	0.690	0.572	0.833	0.000
CARE[11]	1996	2081	2078	212	274	0.760	0.637	0.906	0.002
Post-CABG[12]	1997	676	675	85	103	0.820	0.626	1.074	0.149
AFCAPS/TexCAPS[13]	1998	3304	3301	116	183	0.630	0.501	0.792	0.000
LIPID[14]	1998	4512	4502	557	715	0.760	0.680	0.850	0.000
GISSI - P[15]	2000	2138	2133	120	136	0.900	0.707	1.145	0.392
LIPS[16]	2002	844	833	181	222	0.780	0.640	0.950	0.014
HPS[17]	2002	10,269	10,267	2033	2585	0.760	0.717	0.806	0.000
GREACE[18]	2002	800	800	41	89	0.460	0.320	0.661	0.000
PROSPER[19]	2002	2891	2913	408	473	0.850	0.742	0.973	0.019
ALLHAT-LLT[20]	2002	5170	5185	380	421	0.910	0.793	1.044	0.179
ASCOT-LLA[21]	2003	5168	5137	100	154	0.640	0.497	0.825	0.001
PROVE-IT[22]	2004	2099	2063	464	537	0.840	0.741	0.952	0.006
CARDS[23]	2004	1428	1410	83	127	0.630	0.479	0.828	0.001
A to Z[24]	2004	2265	2232	309	343	0.890	0.761	1.041	0.145
ALLIANCE[25]	2004	1217	1225	289	333	0.830	0.710	0.970	0.019
TNT[26]	2005	4995	5006	434	548	0.780	0.687	0.886	0.000
IDEAL[27]	2005	4439	4449	533	608	0.870	0.776	0.975	0.017
ASPEN[28]	2006	1211	1199	166	180	0.900	0.727	1.115	0.335
SPARCL[29]	2006	2365	2366	334	407	0.800	0.693	0.924	0.002
MEGA[30]	2006	3866	3966	98	144	0.700	0.542	0.904	0.006
JUPITER[31]	2008	8901	8901	142	251	0.560	0.457	0.686	0.000
SEARCH[32]	2010	6031	6033	1477	1553	0.940	0.877	1.007	0.078
HOPE-3[33]	2016	6361	6344	235	304	0.760	0.637	0.906	0.002
Total		88554	88534	9402	11560	0.798	0.776	0.820	0.000



Meta-analysis of the effects of the lipid intervention on the relative risk (hazard ratio or risk ratio) for major vascular events (MVE: cardiovascular death, acute myocardial infarction or other acute coronary syndrome, coronary revascularization, or stroke, when available). The red diamond indicates the summary effect.

eFigure 4. Diet trials meta-analysis

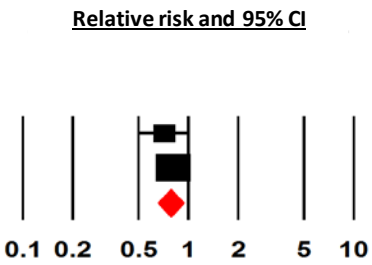
Study Name	Year Published	Participants: Experimental Group	Participants: Control Group	Major Vascular Events: Experimental Group	Major Vascular Events: Control Group	Statistics for each study: Relative Risk	Lower Limit	Upper Limit	p-Value
Research Committee[34]	1965	123	129	46	48	1.000	0.727	1.375	1.000
Oslo[35]	1966	206	206	61	81	0.750	0.569	0.988	0.041
MRC Soya-Bean[36]	1968	199	194	62	74	0.820	0.624	1.077	0.154
LA Veteran's Study[37]	1969	424	422	52	65	0.800	0.571	1.121	0.195
Total		952	951	221	268	0.830	0.716	0.964	0.014



Meta-analysis of the effects of the lipid intervention on the relative risk (hazard ratio or risk ratio) for major vascular events (MVE: cardiovascular death, acute myocardial infarction or other acute coronary syndrome, coronary revascularization, or stroke, when available). The red diamond indicates the summary effect.

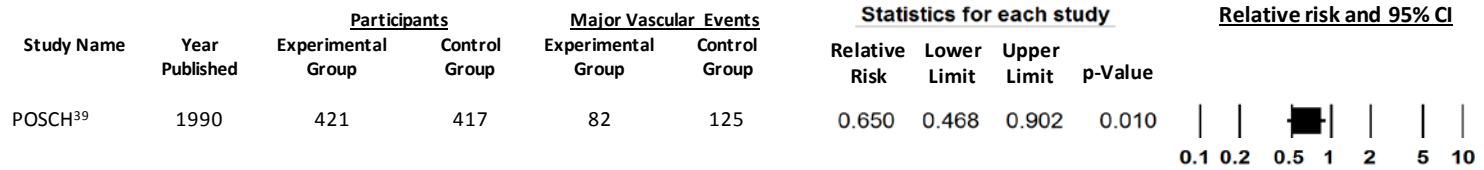
eFigure 5. Bile acid sequestrant trials meta-analysis

Study Name	Year Published	Participants: Experimental Group	Participants: Control Group	Major Vascular Events: Experimental Group	Major Vascular Events: Control Group	Statistics for each study: Relative Risk	Lower Limit	Upper Limit	p-Value
Upjohn[38]	1978	1149	1129	54	74	0.720	0.512	1.013	0.059
Lipid Clinics[6]	1984	1906	1900	155	187	0.810	0.656	1.001	0.051
Total		3055	3029	209	261	0.784	0.655	0.938	0.008



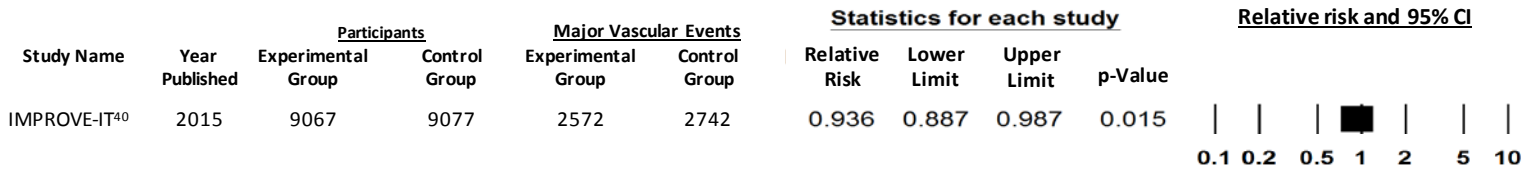
Meta-analysis of the effects of the lipid intervention on the relative risk (hazard ratio or risk ratio) for major vascular events (MVE: cardiovascular death, acute myocardial infarction or other acute coronary syndrome, coronary revascularization, or stroke, when available). The red diamond indicates the summary effect.

eFigure 6. Ileal bypass trial



Effect of the lipid intervention on the relative risk (risk ratio) for major vascular events (MVE: cardiovascular death, acute myocardial infarction or other acute coronary syndrome, coronary revascularization, or stroke, when available).

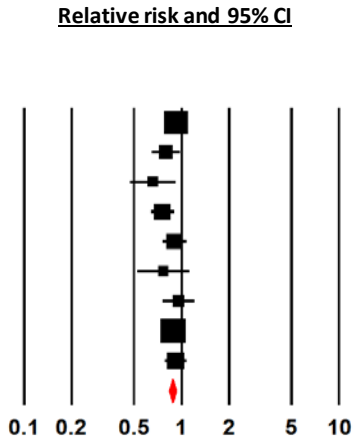
eFigure 7. Ezetimibe trial



Effect of the lipid intervention on the relative risk (hazard ratio) for major vascular events (MVE: cardiovascular death, acute myocardial infarction or other acute coronary syndrome, coronary revascularization, or stroke, when available).

eFigure 8. Fibrate trials meta-analysis

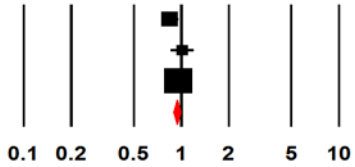
Study Name	Year Published	Participants: Experimental Group	Participants: Control Group	Major Vascular Events: Experimental Group	Major Vascular Events: Control Group	Statistics for each study: Relative Risk	Lower Limit	Upper Limit	p-Value
Coronary Drug Project[41]	1975	1103	2789	309	839	0.930	0.831	1.041	0.207
WHO CO-OP[42]	1978	5331	5296	167	208	0.800	0.655	0.977	0.029
HHS[2]	1987	2051	2030	56	84	0.660	0.474	0.918	0.014
VA-HIT[43]	1999	1264	1267	219	275	0.760	0.644	0.896	0.001
BIP[44]	2000	1548	1542	211	232	0.906	0.762	1.077	0.263
Dais[45]	2001	207	211	38	50	0.770	0.527	1.124	0.176
LEADER[3]	2002	783	785	150	160	0.960	0.761	1.211	0.731
FIELD[4]	2005	4895	4900	612	683	0.890	0.800	0.990	0.032
ACCORD[46]	2010	2765	2753	291	310	0.920	0.787	1.076	0.296
Total		19947	21573	2053	2841	0.876	0.829	0.925	0.000



Meta-analysis of the effects of the lipid intervention on the relative risk (hazard ratio or risk ratio) for major vascular events (MVE: cardiovascular death, acute myocardial infarction or other acute coronary syndrome, coronary revascularization, or stroke, when available). The red diamond indicates the summary effect.

eFigure 9. Niacin trials meta-analysis

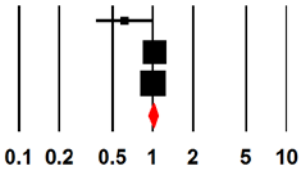
Study Name	Year Published	Participants: Experimental Group	Participants: Control Group	Major Vascular Events: Experimental Group	Major Vascular Events: Control Group	Statistics for each study: Relative Risk	Lower Limit	Upper Limit	p-Value
Coronary Drug Project[41]	1975	1119	2789	287	839	0.850	0.756	0.955	0.006
AIM-HIGH[47]	2011	1718	1696	282	274	1.020	0.865	1.203	0.814
HPS2-Thrive[48]	2014	12,838	12,835	1696	1758	0.960	0.897	1.027	0.236
Total		15,675	17,320	2265	2871	0.941	0.890	0.994	0.030



Meta-analysis of the effects of the lipid intervention on the relative risk (hazard ratio or risk ratio) for major vascular events (MVE: cardiovascular death, acute myocardial infarction or other acute coronary syndrome, coronary revascularization, or stroke, when available). The red diamond indicates the summary effect.

eFigure 10. CETP inhibitor trials meta-analysis

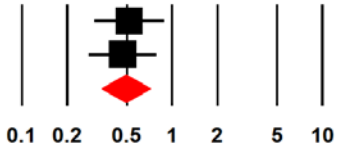
Study Name	Year Published	Participants: Experimental Group	Participants: Control Group	Major Vascular Events: Experimental Group	Major Vascular Events: Control Group	Statistics for each study: Relative Risk	Lower Limit	Upper Limit	p-Value
DEFINE[49]	2010	811	812	27	43	0.620	0.380	1.011	0.055
dal-OUTCOME[50]	2012	7938	7933	656	633	1.040	0.931	1.162	0.487
ACCELERATE[51]	2016	6038	6054	774	768	1.010	0.910	1.120	0.851
Total		14787	14799	1457	1444	1.012	0.939	1.091	0.754



Meta-analysis of the effects of the lipid intervention on the relative risk (hazard ratio) for major vascular events (MVE: cardiovascular death, acute myocardial infarction or other acute coronary syndrome, coronary revascularization, or stroke, when available). The red diamond indicates the summary effect.

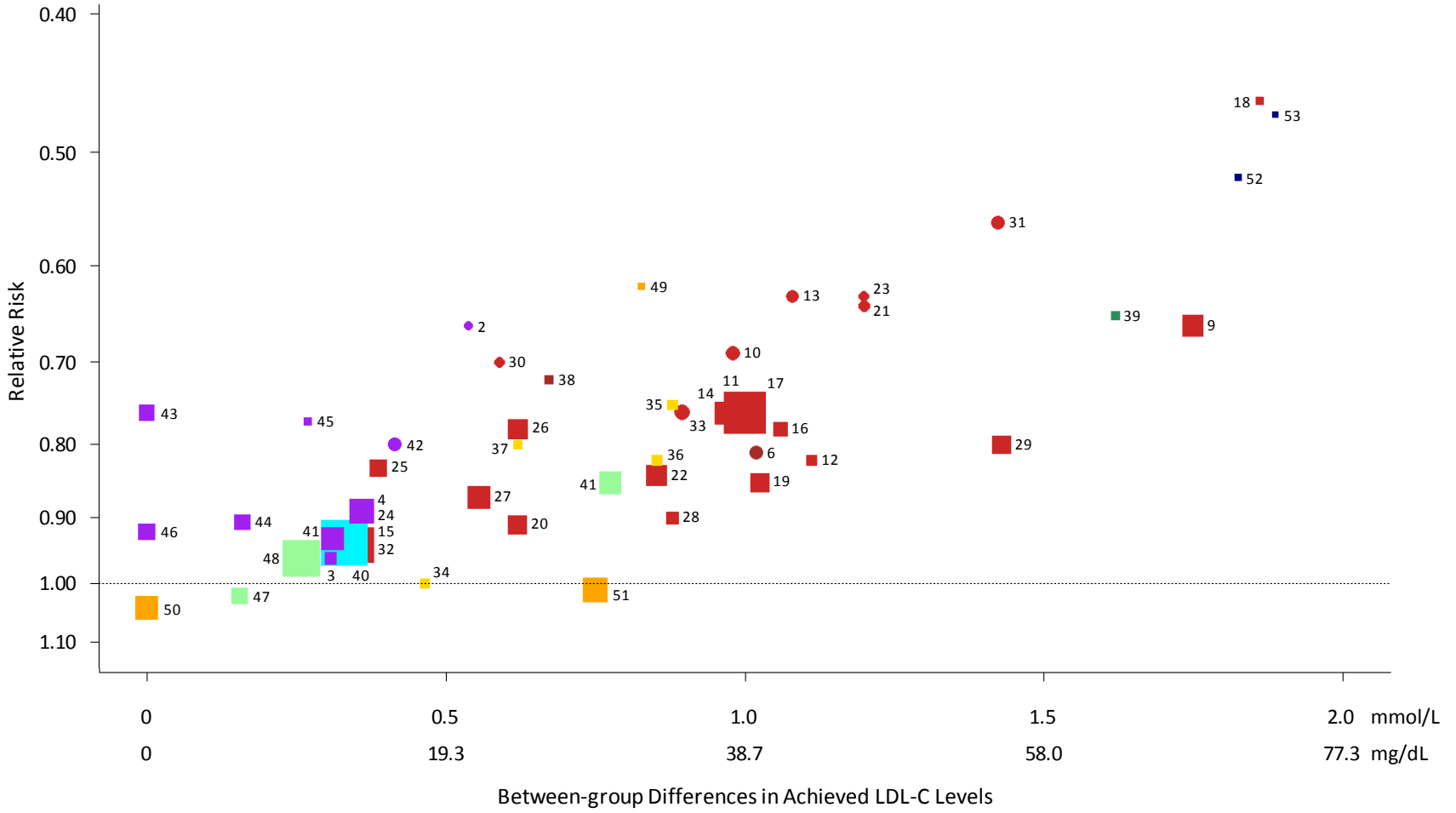
eFigure 11. PCSK9 inhibitor trials meta-analysis

Study Name	Year Published	Participants: Experimental Group	Participants: Control Group	Major Vascular Events: Experimental Group	Major Vascular Events: Control Group	Statistics for each study: Relative Risk	Lower Limit	Upper Limit	p-Value
ODYSSEY Long Term[52]	2015	1553	788	27	26	0.520	0.305	0.886	0.016
OSLER[53]	2015	2976	1489	28	30	0.470	0.282	0.784	0.004
Total		4529	2277	55	56	0.493	0.341	0.714	0.000



Meta-analysis of the effects of the lipid intervention on the relative risk (hazard ratio) for major vascular events (MVE: cardiovascular death, acute myocardial infarction or other acute coronary syndrome, coronary revascularization, or stroke, when available). The red diamond indicates the summary effect.

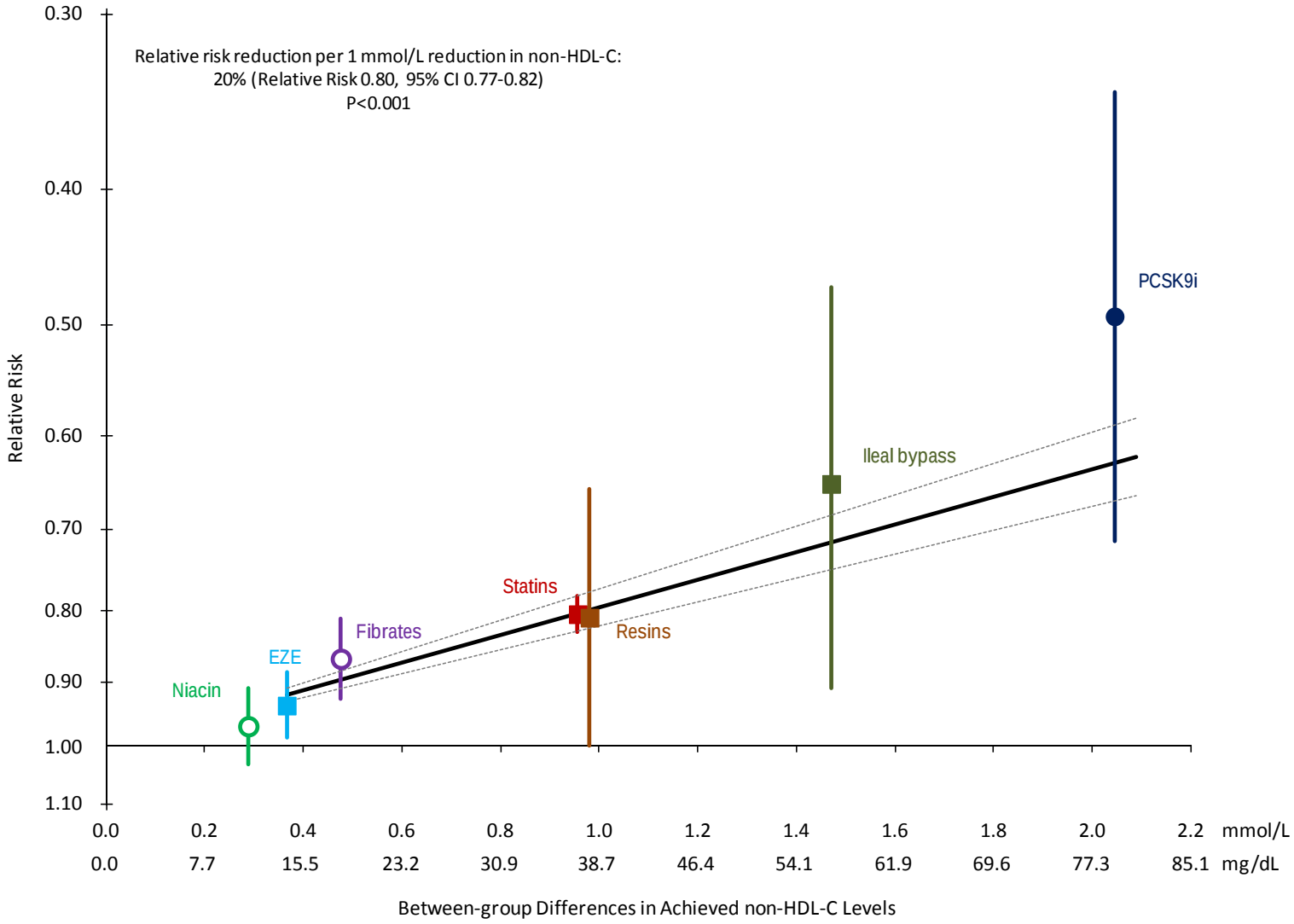
eFigure 12. Scatterplot of all trials



Scatterplot of absolute LDL-C reduction (X-axis) and major vascular event (MVE) relative risk (Y-axis) for each trial. Statin trials are in red, diet trials in gold, bile acid sequestrant trials in brown, ileal bypass trial in dark green, ezetimibe trial in light blue, fibrate trials in purple, niacin trials in light green, CETP inhibitor trials in orange and PCSK9 inhibitor trials in dark blue. Secondary prevention

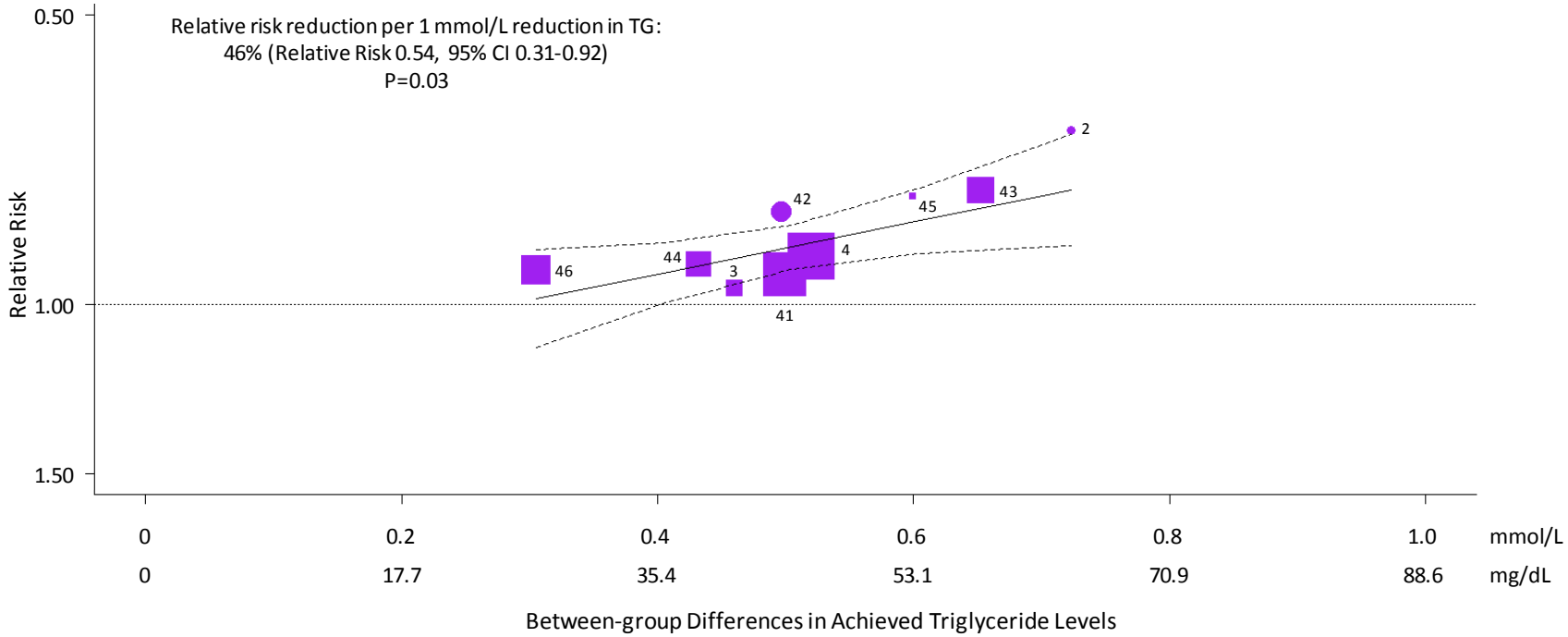
trials are squares, primary prevention trials are circles. The size of the marker is proportional to the inverse variance of the trial. The number by each symbol is the reference number for that trial in the Supplement.

eFigure 13. Absolute non-HDL-C reduction and major vascular event relative risk for each class of intervention



Absolute non-HDL-C reduction and major vascular event (MVE) relative risk for each class of intervention. The meta-regression slope (predicted relative risk for degree of non-HDL-C reduction) is represented by the solid black line and the 95% confidence intervals by the dotted gray lines, both of which are derived from a trial-level analysis of interventions depicted by filled squares. Symbols as per legend for Figure 3 in main manuscript.

eFigure 14. Major vascular event relative risk per mmol/l decrease in triglycerides in fibrate trials



Relationship between absolute triglyceride (TG) reduction and the relative risk of major vascular events (cardiovascular death, acute myocardial infarction or other acute coronary syndrome, coronary revascularization, or stroke, when available) in 9 fibrate trials (squares represent secondary prevention populations and circles primary prevention populations). The size of the symbol is proportional to the weight in the meta-regression. The number by each symbol is the reference number for that trial in the Supplement. The meta-regression slope (predicted relative risk for degree of triglyceride reduction) is represented by the solid line and the 95% confidence intervals by the dashed lines. 1 mmol/L of triglycerides = 88.6 mg/dL of triglycerides.