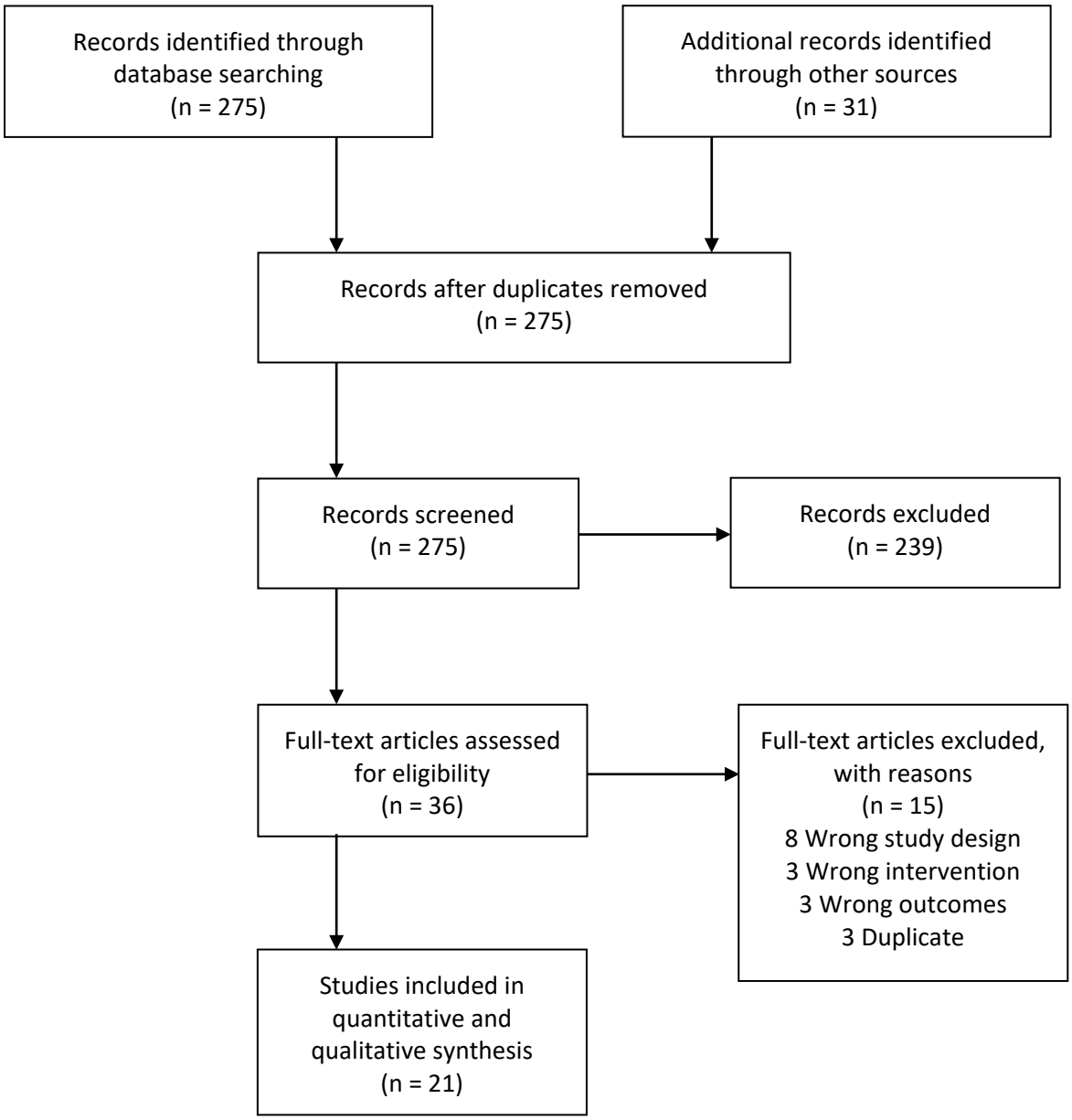
Supplemental Online Content

Byrne P, Demasi M, Jones M, Smith SM, O'Brien KK, DuBroff R. Evaluating the association between low-density lipoprotein cholesterol reduction and relative and absolute effects of statin treatment: a systematic review and meta-analysis. *JAMA Intern Med*. Published online March 14, 2022. doi:10.1001/jamainternmed.2022.0134

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

Supplementary Figure e1 PRISMA Flow diagram



Supplementary Figure e2 PICOTTS (Patients, Interventions, Comparators, Outcomes, Timing, Setting and Study Design) Format

Patients

- Adults ≥18 years of age

Interventions

- Statins (HMG-CoA reductase inhibitors)

Comparators

- Placebo
- No treatment
- Usual care

Primary outcomes

- All-cause mortality

Secondary outcomes

- Myocardial infarction (MI)
- Stroke

Timing

- Studies whose intended duration is greater than two years

Setting and Study Design

- Systematic reviews of randomised controlled trials
- Systematic reviews of individual patient data

Table e1: Included trials & references

Trial Year	Duration of follow-up (years)*	Treatment	Control	Participants	Primary or secondary prevention	Primary endpoint	Achieved LDL-C difference (mmol/L)		Control group event rate (100 patient-years)	
								All cause mortality	MI	Stroke
4S 1994	5.4	Simvastatin 10-40 mg/d	Placebo	4,444 angina or s/p MI	Secondary	All cause mortality	1.75	2.13	4.4	0.53
WOSCOPS 1995	4.9	Pravastatin 40 mg/d	Placebo	6,595 men hypercholesterolemia	Primary	CHD death or nonfatal MI	0.98	0.84	1.83	0.32
CARE 1996	5	Pravastatin 40 mg/d	Placebo	4,159 s/p MI	Secondary	CHD death or nonfatal MI	0.96	1.89	2.59	0.75
LIPID 1998	6.1	Pravastatin 40 mg/d	Placebo	9,014 history CHD	Secondary	CHD death	9.97	2.3	1.69	0.74
AFCAPS/TexCAPS 1998	5.2**	Lovastatin 20-40 mg/d	Placebo	6,605 average cholesterol	Primary	First acute coronary event	1.08	NR	0.55	1.49
LIPS 2002	3.9	Fluvastatin 80 mg/d	Placebo	1,677 s/p PCI	Secondary	Cardiac death, nonfatal MI or reintervention procedure	1.08	1.51	NR	NR
HPS 2002	5	Simvastatin 40 mg/d	Placebo	20,536 high risk	Both	All cause mortality	1	2.94	2.36	1.14
PROSPER 2002	3.2	Pravastatin 40 mg/d	Placebo	5,804 elderly	Both	CHD death, nonfatal MI or any stroke	1.03	6.79	7.9	3
ALLHAT-LLT 2002	4.8	Pravastatin 40 mg/d	Usual care	10,355 moderate hypercholesterolemia HBP	Primary	All cause mortality	0.44	2.58	1.69	0.93
ASCOT-LLA 2003	3.3**	Atorvastatin 10 mg/d	Placebo	10,305 HBP average cholesterol	Primary	CHD death or nonfatal MI	1.2	1.28	0.94	0.74
ALERT 2003	5.1	Fluvastatin 40 mg/d	Placebo	2,104 renal transplant recipients	Both	Cardiac death, nonfatal MI or coronary intervention procedure	1	2.57	1.96	1.17
CARDS 2004	3.9**	Atorvastatin 10 mg/d	Placebo	2,838 T2DM	Primary	Acute coronary event, coronary revascularization or stroke	1.2	1.49	1.11	0.71
4D 2005	4	Atorvastatin 10-20 ng/d	Placebo	1,255 T2DM haemodialysis	Both	Cardiac death, nonfatal MI or stroke	1.08	12.58	4.4	2.32
ASPEN 2006	4	Atorvastatin 10 mg/d	placebo	2,410 T2DM	Both		0.79	1.43	1.38	0.79
MEGA 2006	5.3	Pravastatin 10-20 mg/d	Usual care	7,832 hypercholesterolemic	Primary	CV death, nonfatal MI, nonfatal stroke, recanalization, CABG, resuscitated cardiac arrest or angina requiring hospitalization	0.61	0.38	0.16	0.29
SPARCL 2006	4.9	Atorvastatin 80 mg/d	Placebo	4,731 s/p stroke or TIA	Secondary	Fatal or nonfatal stroke	1.4	1.82	1.04	2.68
CORONA 2007	2.7	Rosuvastatin 10 mg/d	Placebo	5,011 systolic HF	Secondary	CV death, nonfatal MI or nonfatal stroke	1.56	11.26	2.28	2.05
JUPITER 2008	1.9**	Rosuvastatin 20 mg/d	Placebo	17,802 elevated hs CRP	Primary	CV death, MI, stroke, arterial revascularization angina requiring hospitalization	1.43	1.46	0.4	0.38
GISSI-HF 2008	3.9	Rosuvastatin 10 mg/d	Placebo	4,574 chronic heart failure	Both	All cause mortality	0.75	7.21	0.78	0.74
AURORA 2009	3.8	Rosuvastatin 10 mg/d	Placebo	2,776 hemodialysis	Both	CV death, nonfatal MI or nonfatal stroke	0.73	12.55	6.01	1.54
HOPE-3 2016	5.6	Rosuvastatin 10 mg/d	Placebo	12,705 intermediate risk	Primary	CV death, nonfatal MI or nonfatal stroke or CV death, nonfatal MI,nonfatal stroke, revascularization, heart failure or resuscitated cardiac arrest	0.89	1	0.19	0.28

Note: All included trials were commercially funded by pharmaceutical companies.
*mean or median
** premature termination

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Table e2: Excluded trials & reasons for exclusion

Short title	Title	Author	Year of publication	Journal	DOI	Exclusion reason
GISSI-P[a]	Dietary supplementation with n-3 polyunsaturated fatty acids vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico,	1999	The Lancet	10.1016/S0140-6736(99)07072-5	Wrong study design
WOSCOPS[b] (follow-up analysis)	Low-Density Lipoprotein Cholesterol Lowering for the Primary Prevention of Cardiovascular Disease Among Men With Primary Elevations of Low-Density Lipoprotein Cholesterol Levels of 190 mg/dL or Above: Analyses From the WOSCOPS	Vallejo-Vaz AJ; Robertson M; Catapano AL; Watts GF; Kastelein JJ; Packard CJ; Ford I; Ray KK	2017	Circulation	10.1161/CIRCULATIONAHA.117.027966	Wrong study design
ALLIANCE[c]	Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the alliance study.	Koren MJ; Hunninghake DB	2004	J Am Coll Cardiol	10.1016/j.jacc.2004.07.053	Wrong study design
TNT[d]	Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study	Shepherd, James; Kastelein, John JP; Bittner, Vera; Deedwania, Prakash; Breazna, Andrei; Dobson, Stephen; Wilson, Daniel J; Zuckerman, Andrea; Wenger, Nanette K; TNT Investigators	2008	Journal of the American College of Cardiology	10.1016/j.jacc.2007.11.072	Wrong study design
Na	The effect of fluvastatin on cardiac events in patients with symptomatic coronary artery disease during one year of treatment.	Riegger G; Abletshauser C; Ludwig M; Schwandt P; Widimsky J; Weidinger G; Welzel D	1999[e]	Atherosclerosis	10.1016/s0021-9150(99)00062-3	Wrong study design
AFCAPS/TexCAPS[f]	Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS	Downs JR; Clearfield M; Tyroler HA; Whitney	2001	Am J Cardiol	10.1016/s0002-9149(01)01464-3	Wrong study design

	): additional perspectives on tolerability of long-term treatment with lovastatin.	EJ; Kruyer W; Langendorfer A; Zagrebelsky V; Weis S; Shapiro DR; Beere PA; Gotto AM				
SEARCH[g]	Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH): characteristics of a randomized trial among 12 064 myocardial infarction survivors	SEARCH Study Collaborative Group,	2007	American Heart Journal	10.1016/j.ahj.2007.06.034	Wrong intervention
MARS[h]	The Monitored Atherosclerosis Regression Study (MARS). Design, methods and baseline results.	Cashin-Hemphill L; Kramsch DM; Azen SP; DeMets D; DeBoer LW; Hwang I; Vailas L; Hirsch LJ; Mack WJ; DeBoer L; et al.	1992	Online J Curr Clin Trials	na	Wrong outcomes
TECOS[i]	Low-density lipoprotein cholesterol treatment and outcomes in patients with type 2 diabetes and established cardiovascular disease: Insights from TECOS.	De Ferrari GM; Stevens SR; Ambrosio G; Leonardi S; Armstrong PW; Green JB; Wamil M; Holman RR; Peterson ED	2020	Am Heart J	10.1016/j.ahj.2019.11.005	Wrong intervention
na	Efficacy and safety of cerivastatin 0.8 mg in patients with hypercholesterolaemia: the pivotal placebo-controlled clinical trial. Cerivastatin Study Group.	Insull W Jr; Isaacsohn J; Kwiterovich P; Ra P; Brazg R; Dujovne C; Shan M; Shugrue-Crowley E; Ripa S; Tota R	2000[j]	J Int Med Res	10.1177/147323000002800201	Wrong outcomes
CHORUS[k]	The CHORUS (Cerivastatin in Heart Outcomes in Renal Disease: Understanding Survival) protocol: a double-blind, placebo-controlled trial in patients with esrd.	Keane WF; Brenner BM; Mazzu A; Agro A	2001	Am J Kidney Dis	10.1053/ajkd.2001.20739	Wrong study design
na	Efficacy and safety of pravastatin in the long-term treatment of elderly patients with hypercholesterolemia.	Santinga JT; Rosman HS; Rubenfire M; Maciejko JJ; Kobylak	1994[l]	Am J Med	10.1016/0002-9343(94)90090-6	Wrong outcomes

		L; McGovern ME; Behounek BD				
St Francis[m]	Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial	Arad, Yadon; Spadaro, Louise A; Roth, Marguerite; Newstein, David; Guerci, Alan D	2005	Journal of the American College of Cardiology	10.1016/j.jacc.2005.02.089	Wrong interventio n
na	Pitavastatin demonstrates long-term efficacy, safety and tolerability in elderly patients with primary hypercholesterolaemi a or combined (mixed) dyslipidaemia.	Stender S; Budinski D; Hounslow N	2013[n]	Eur J Prev Cardiol	10.1177/2047487312437326	Wrong study design

na – not available

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Supplementary Figure e3 - Risk of bias of included studies for all outcomes

Study ID	Trial ID	Outcome	D1	D2	D3	D4	D5	Overall
1	4D	All cause mortality	+	+	+	+	+	+
1	4D	Cardiac mortality	+	+	+	+	+	+
1	4D	Non-fatal MI	+	+	+	+	+	+
1	4D	Fatal Stroke	+	+	+	+	!	!
2	CARDS	All cause mortality	+	!	+	+	+	!
2	CARDS	Stroke	+	!	+	+	+	!
3	WOSCOPS	All cause mortality	+	+	+	+	+	+
3	WOSCOPS	Death from all CV causes	+	+	+	+	+	+
3	WOSCOPS	Definate non-fatal MI	+	+	+	+	+	+
3	WOSCOPS	Fatal or non fatal stroke	+	+	+	+	+	+
4	GISS-HF	All cause mortality	+	+	+	+	+	+
4	GISS-HF	Cardiac mortality	+	+	+	+	+	+
4	GISS-HF	Fatal and non-fatal MI	+	+	+	+	+	+
4	GISS-HF	Fatal and non-fatal stroke	+	+	+	+	+	+
5	ASCOT-LL/	All Cause mortaility	+	!	+	+	+	!
5	ASCOT-LL/	CV mortality	+	!	+	+	+	!
5	ASCOT-LL/	Fatal and non fatal stroke	+	!	+	+	+	!
6	ASPEN	All cause mortality	+	+	+	+	!	!
6	ASPEN	CV mortality	+	+	+	+	!	!
6	ASPEN	Fatal and non-fatal MI	+	+	+	+	!	!
6	ASPEN	fatal and non-fatal stroke	+	+	+	+	!	!
7	LIPID	All cause mortality	+	+	+	+	+	+
7	LIPID	CVD mortality	+	+	+	+	+	+
7	LIPID	Any MI	+	+	+	+	+	+
7	LIPID	Any stroke	+	+	+	+	+	+
8	JUPITER	All cause mortality	+	!	+	+	+	!
8	JUPITER	Any MI	+	!	+	+	+	!
8	JUPITER	Any stroke	+	!	+	+	+	!
9	AFCAPS/T	Fatal CV events	+	!	+	+	+	!
9	AFCAPS/T	Fatal and non-fatal MI	+	!	+	+	+	!
10	CARE	Death from CHD	+	+	+	+	+	+
10	CARE	Fatal MI	+	+	+	+	+	+
11	ALERT	All cause Mortality	+	+	+	+	+	+
11	ALERT	Cardiac mortality	+	+	+	+	+	!
11	ALERT	Defininate non-fatal MI	+	+	+	+	+	+
12	MEGA	All cause mortality	+	+	+	+	+	+
12	MEGA	CVD death	+	+	+	+	+	+
12	MEGA	MI	+	+	+	+	+	+
12	MEGA	Stroke	+	+	+	+	+	+
13	LIPS	All cause mortality	+	+	+	+	+	+
13	LIPS	Cardiac mortality	+	+	+	+	+	+
14	AURORA	All cause mortality	+	+	+	+	+	+
14	AURORA	CV mortality	+	+	+	+	+	+
14	AURORA	Non-fatal MI	+	+	+	+	+	+
14	AURORA	Non-fatal stroke	+	+	+	+	+	+
15	ALLHAT-LL	All cause mortality	+	+	+	+	+	+
15	ALLHAT-LL	CV mortality	+	+	+	+	+	+
15	ALLHAT-LL	Any stroke	+	+	+	+	+	+
16	HPS	All cause mortality	+	+	+	+	+	+
16	HPS	cardiovascular mortality	+	+	+	+	+	+
16	HPS	Non-fatal MI	+	+	+	+	+	+
16	HPS	Any stroke	+	+	+	+	+	+
17	SPARCL	All cause mortality	+	+	+	+	+	+
17	SPARCL	Cardiovascular mortality	+	+	+	+	+	+
17	SPARCL	Non-fatal MI	+	+	+	+	+	+
17	SPARCL	Any stroke	+	+	+	+	+	+
18	4S	All cause mortality	+	+	+	+	+	+
18	4S	Cardiovascular mortality	+	+	+	+	+	+
18	4S	Any major coronary event	+	+	+	+	+	+
19	CORONA	All cause mortality	+	+	+	+	+	+
19	CORONA	Cardiovascular mortality	+	+	+	+	+	+
19	CORONA	Non-Fatal MI	+	+	+	+	+	+
19	CORONA	Any stroke	+	+	+	+	+	+
20	HOPE	All cause mortality	+	+	+	+	+	+
20	HOPE	Cardiovascular mortality	+	+	+	+	+	+
20	HOPE	Non-fatal MI	+	+	+	+	+	+
20	HOPE	Any stroke	+	+	+	+	+	+
21	PROSPER	All cause mortality	+	+	+	+	+	+
21	PROSPER	Non-fatal MI	+	+	+	+	+	+
21	PROSPER	Any stroke	+	+	+	+	+	+

Low risk

Some concerns

High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

Note: All trials were funded partly or wholly by the pharmaceutical industry.

Table e3: GRADE Table

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	statin induced reductions in LDL-C	placebo or usual care	Relative (95% CI)		
All cause mortality - primary prevention trials											
6	randomised trials	serious[a]	not serious	not serious	serious[b]	none	29,028	29,099	RR 0.87 (0.78 to 0.97)	⨁⨁⨁◯ Moderate	CRITICAL
All cause mortality - secondary prevention trials											
5	randomised trials	not serious	serious[c]	not serious	serious[d]	none	12,227	12,209	RR 0.86 (0.73 to 1.02)	⨁⨁◯◯ Low	CRITICAL
All cause mortality -All trials											
19	randomised trials	serious[e]	serious[f]	not serious	serious[g]	none	56,331	56,375	RR 0.91 (0.86 to 0.95)	⨁⨁⨁◯ Low/Moderate	CRITICAL
Myocardial Infarction - primary prevention trials											
6	randomised trials	serious[h]	not serious	not serious	not serious	none	27,162	27,215	RR 0.62 (0.54 to 0.71)	⨁⨁⨁⨁ Moderate/High	CRITICAL
Myocardial Infarction - secondary prevention trials											
5	randomised trials	not serious	not serious	not serious	not serious	none	13,464	13,457	RR 0.73 (0.65 to 0.82)	⨁⨁⨁⨁ High	CRITICAL
Myocardial infarction - All trials											
18	randomised trials	serious[i]	not serious	not serious	serious[j]	none	31,989	32,040	RR 0.71 (0.66 to 0.78)	⨁⨁⨁◯ Moderate	CRITICAL
Stroke - primary prevention trials											
6	randomised trials	serious[k]	serious[l]	not serious	serious[m]	none	29,028	29,099	RR 0.76 (0.63 to 0.91)	⨁⨁⨁◯ Low/Moderate	CRITICAL
Stroke - secondary prevention trials											
4	randomised trials	not serious	serious[n]	not serious	serious[o]	none	11,383	11,376	RR 0.93 (0.80 to 1.08)	⨁⨁⨁◯ Low/Moderate	CRITICAL
Stroke - All trials											
18	randomised trials	serious[p]	serious[q]	not serious	serious[r]	none	61,656	61,594	RR 0.86 (0.78 to 0.95)	⨁⨁⨁◯ Low/Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio

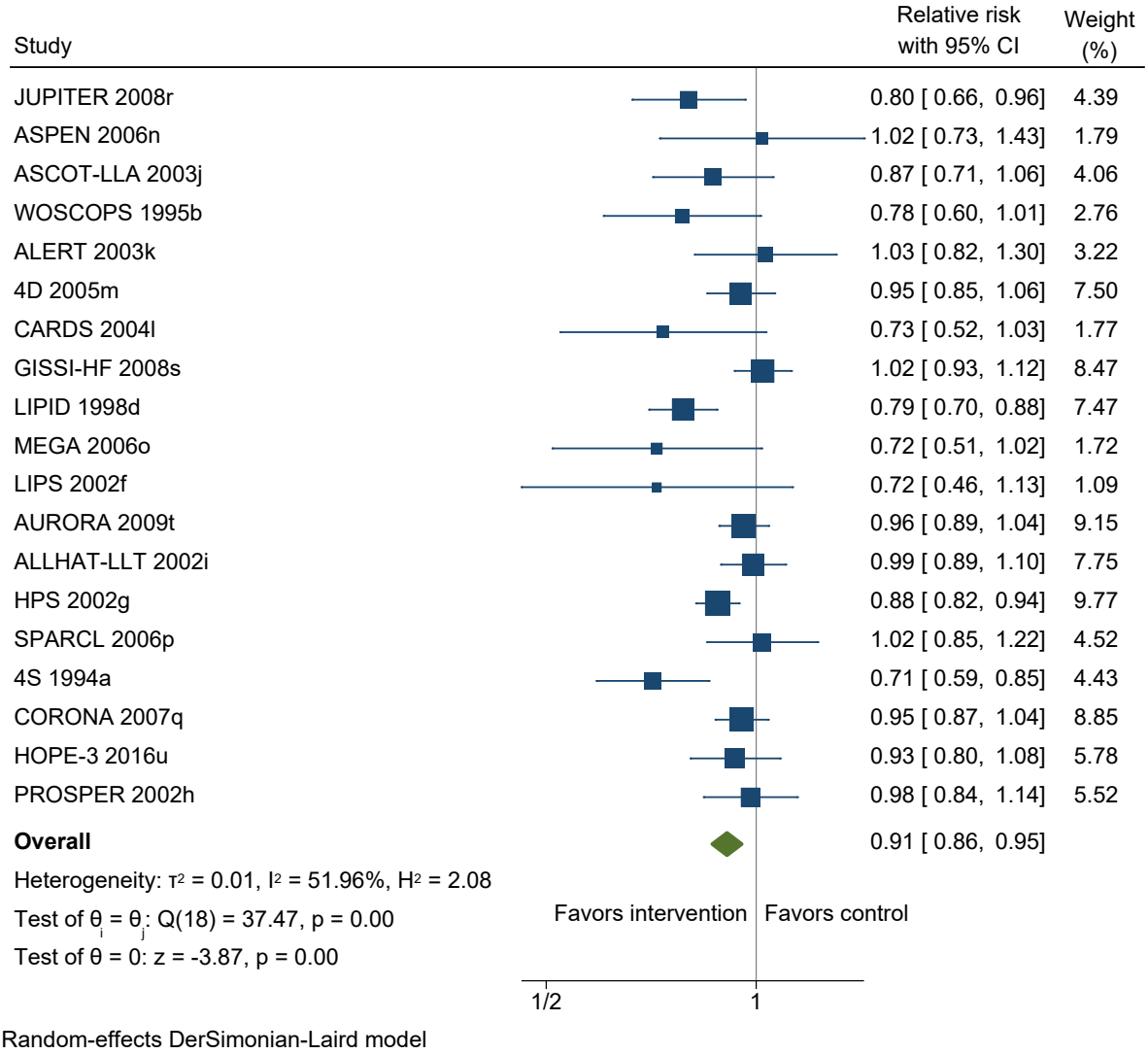
Explanations

Note: We have marked some items down by 0.5 points when we considered that the issue was but not worthy of a 1-point reduction. This method is suggested by Dr Paul Glasziou (Pers. Comm. Glasziou, P.)

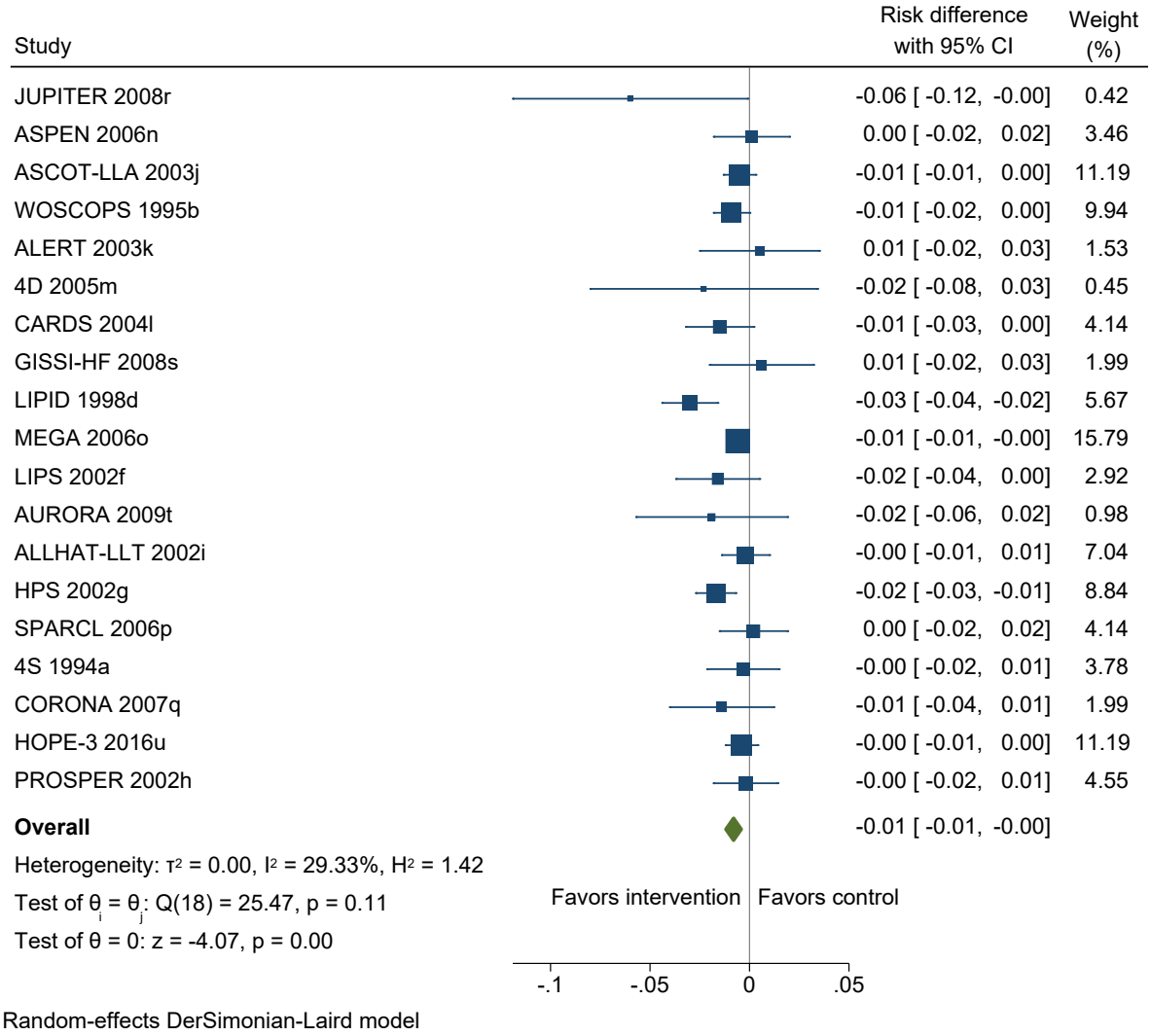
a. Marked down by 0.5 points as 2 out of 6 trials were stopped early (CARDS and JUPITER)
b. Marked down by 0.5 points. For 5 out of 6 trials the CIs cross 1 (more than half the trials), however for the pooled estimate the CI does not cross 1.
c. Marked down by 1 point because estimates range from 0.71 to 1.02 and the I squared value is 81.75%
d. Marked down by 1 point because for 3 out of 5 trials (more than half the trials) and for the pooled estimate the CIs crosses 1
e. Marked down by 0.5 points as 3 out of 19 trials were stopped early (JUPITER, CARDS and ASCOT). There were some concerns with ROB2 for ASPEN trial.
f. Marked down by 0.5 points as the point estimates range from 0.72 to 1.02. and the I squared value 51.96%
g. Marked down by 0.5 points as in 15 out of 19 trials the CIs cross 1 (more than half the trials), however, for the pooled estimate the CI does not cross 1.
h. Marked down by 0.5 points as 3 of the trials were stopped early (JUPITER, CARDS, AFCAPS/TexCAPS)
i. Marked down by 0.5 points as 3 out of 18 trials were stopped early (JUPITER, CARDS and ASCOT). There were some concerns with ROB2 for ASPEN trial
j. Marked down by 0.5 points as 8 out of 18 trials (almost half the trials) the CIs cross 1, however, the pooled estimate CI is quite tight and does not cross 1.
k. Marked down by 0.5 points as 2 of the 6 trials were stopped early
l. Marked down by 0.5 points as the point estimates range from 0.52 to 0.91, however, I^2 is 41%.
m. Marked down by 0.5 as in 3 out of 6 trials (half the trials) the CIs cross 1, however, the CI of the pooled estimate does not cross 1.
n. Marked down 0.5 points as the point estimates range from 0.64 to 1.24 and the I^2 is 57.5%
o. Marked down by 1 point because in 3 out of 4 trials (three quarters of the trials) the CIs cross 1, as does the pooled estimate.
p. Marked down by 0.5 points as three of the trials were stopped early and there were 'some concerns' regarding two trials on ROB2 (4D and ASPEN).

q. Marked down by 0.5 points as the point estimates for the trials ranged from 0.52 to 1.17 and the I^2 is 49.1%.
r. Marked down by 0.5 points as in 12 out of 18 trials (two thirds of the trials) the confidence intervals cross 1, however, the CI of the pooled estimate does not cross 1.

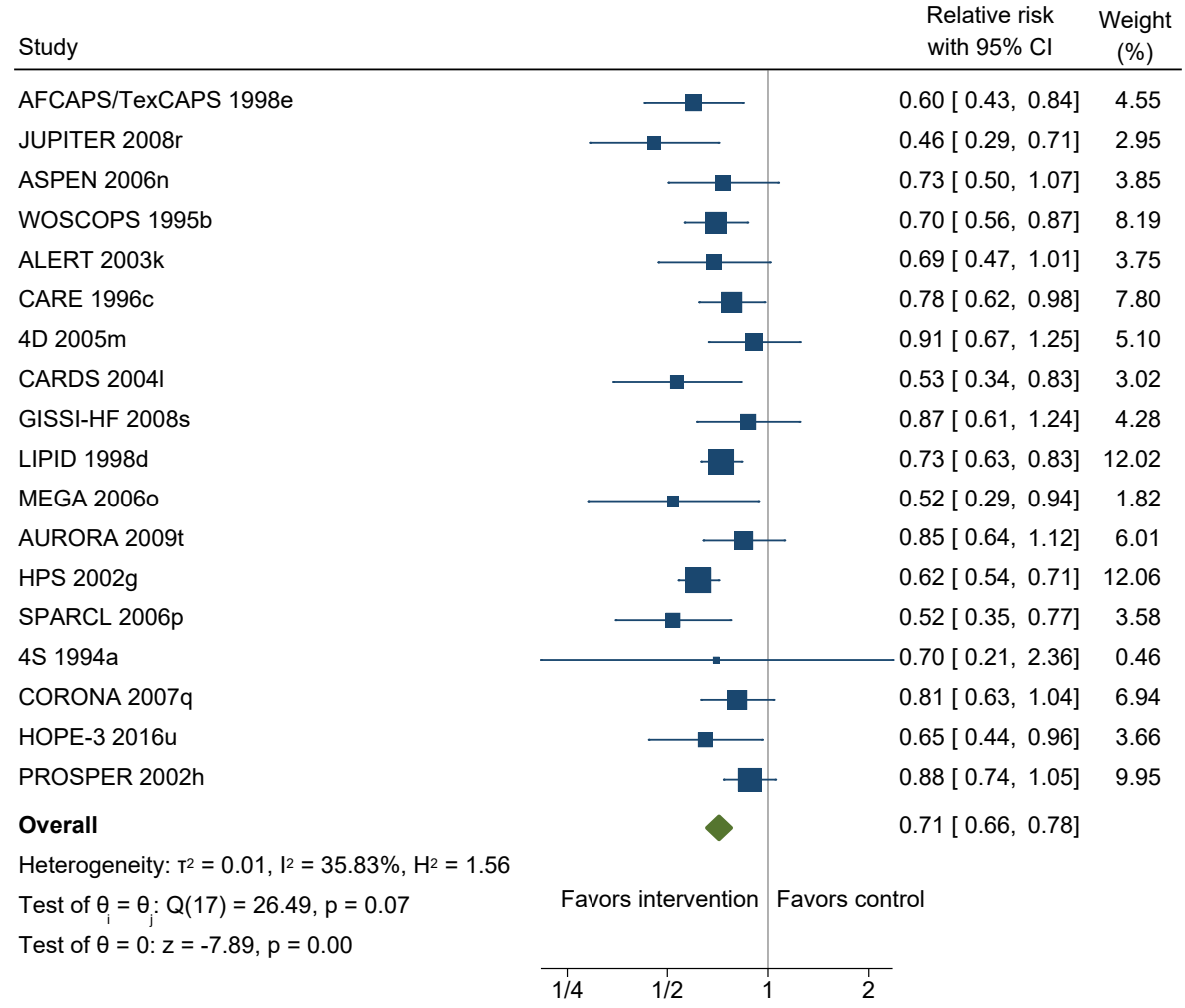
Supplementary Figure e4: Meta-analysis of relative effects of treatment on all-cause mortality, all trials



Supplementary Figure e5: Meta-analysis of absolute effects of treatment on all-cause mortality, all trials

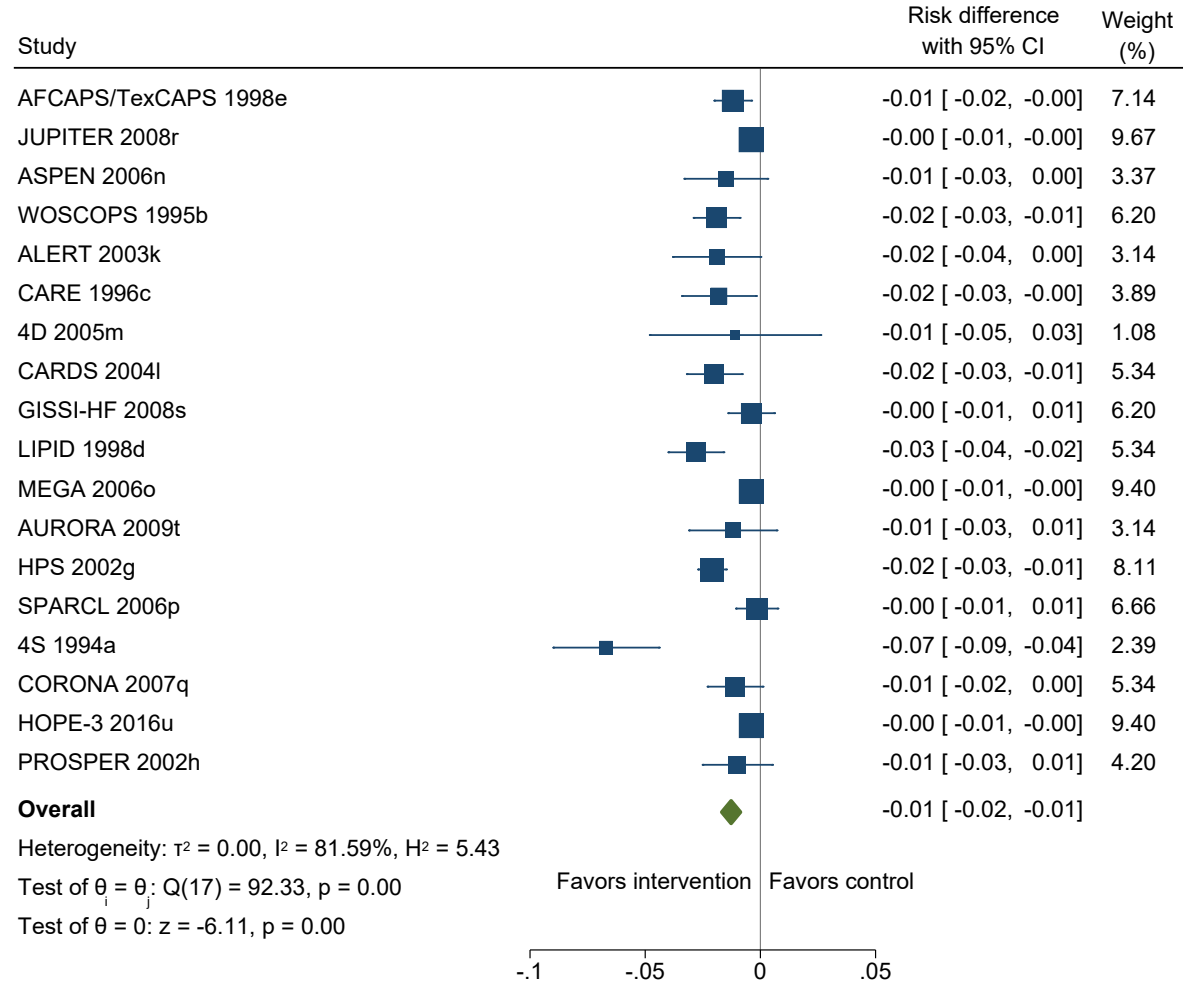


Supplementary Figure e6: Meta-analysis of relative effects of treatment on myocardial infarction, all trials

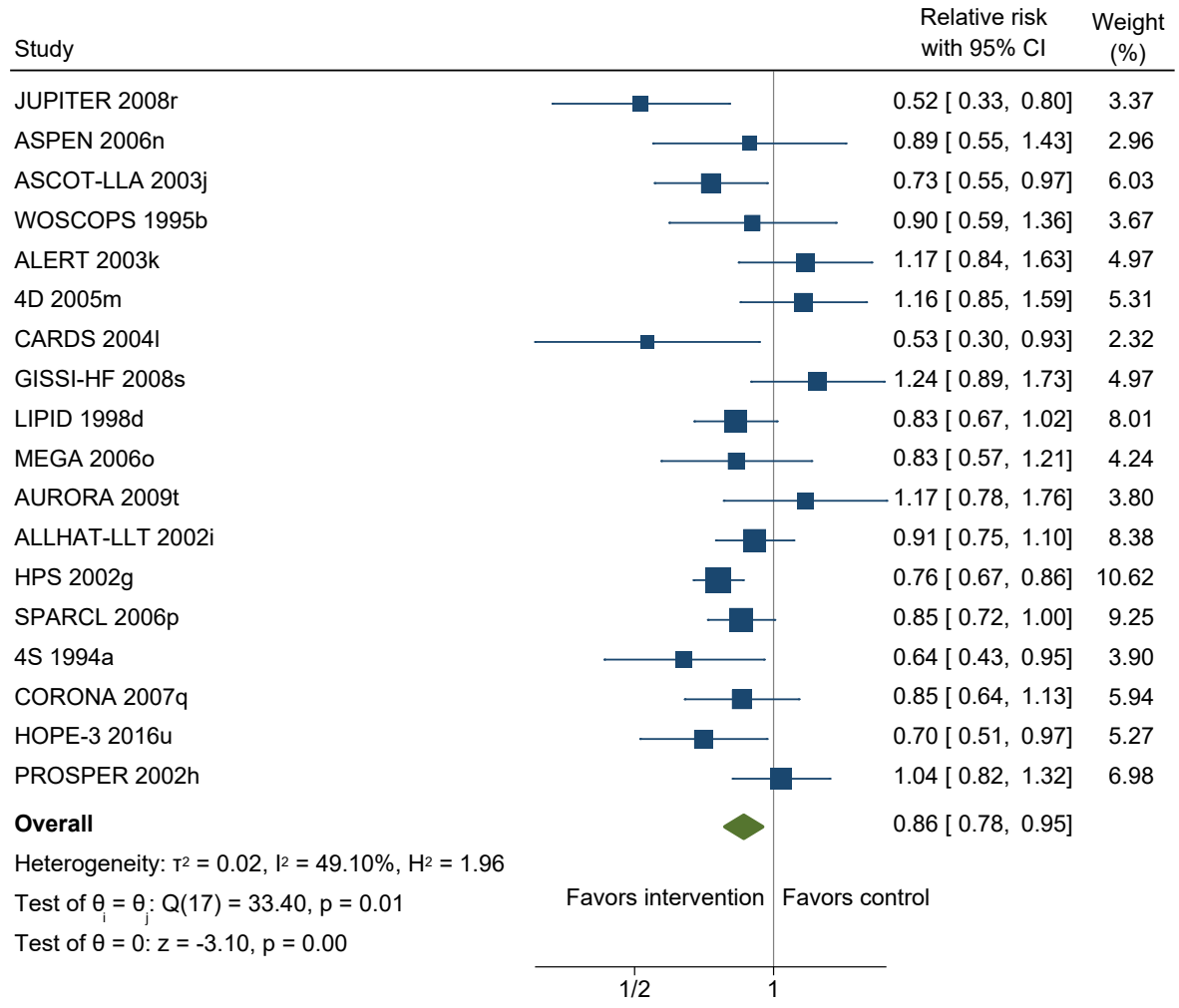


Random-effects DerSimonian-Laird model

Supplementary Figure e7: Meta-analysis of absolute effects of treatment on myocardial infarction, all trials

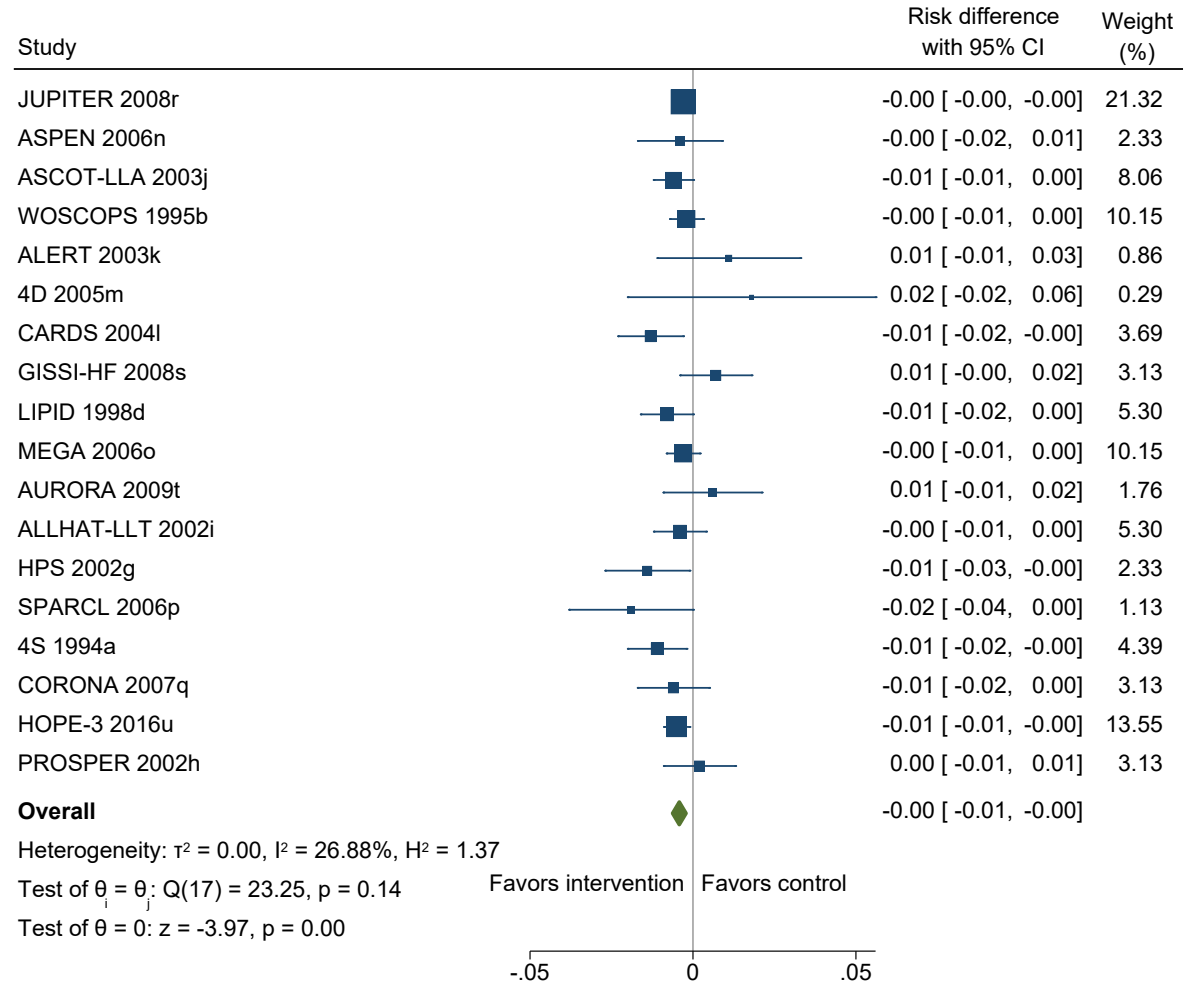


Supplementary Figure e8: Meta-analysis of relative effects of treatment on stroke, all trials



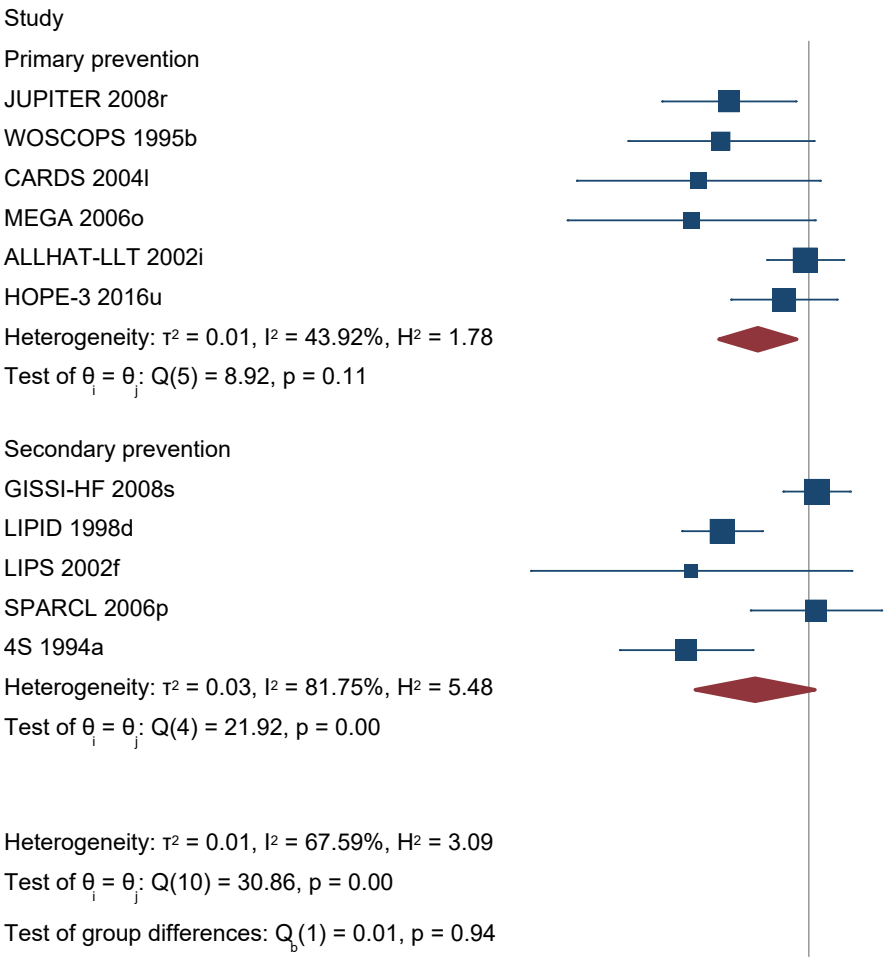
Random-effects DerSimonian-Laird model

Supplementary Figure e9: Meta-analysis of absolute effects of treatment on stroke, all trials

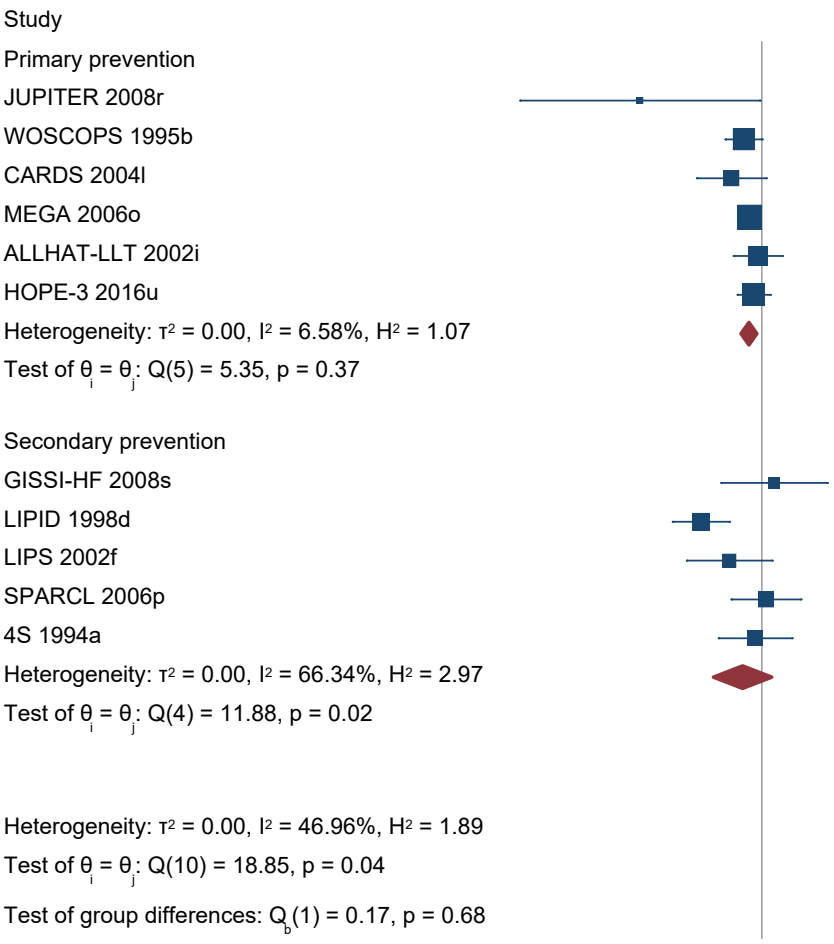


Random-effects DerSimonian-Laird model

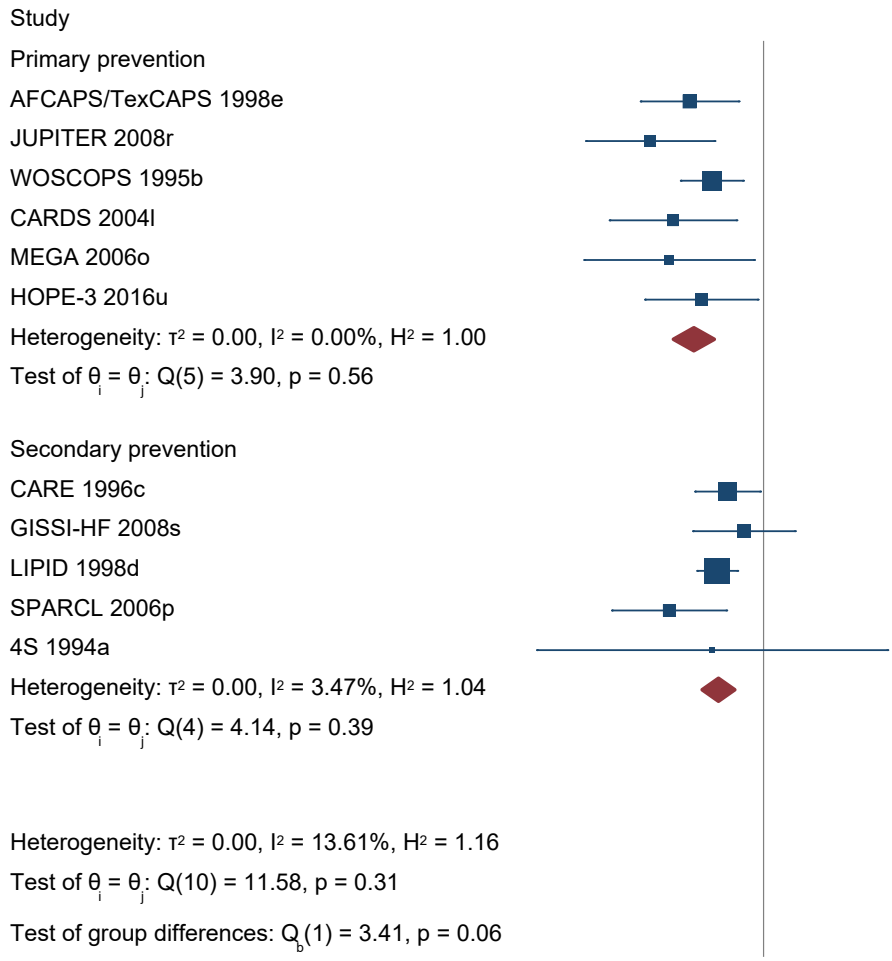
Supplementary Figure e10: Meta-analysis of relative effects of treatment on all-cause mortality in primary and secondary prevention trials



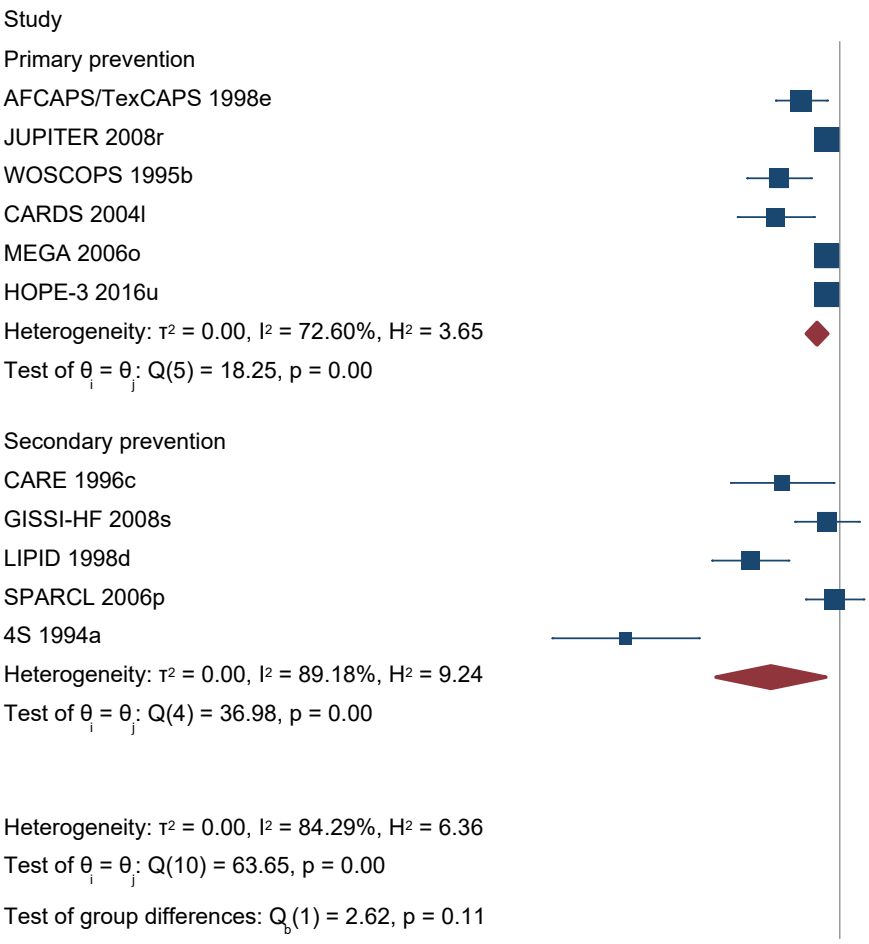
Supplementary Figure e11: Meta-analysis of absolute effects of treatment on all-cause mortality in primary and secondary prevention trials



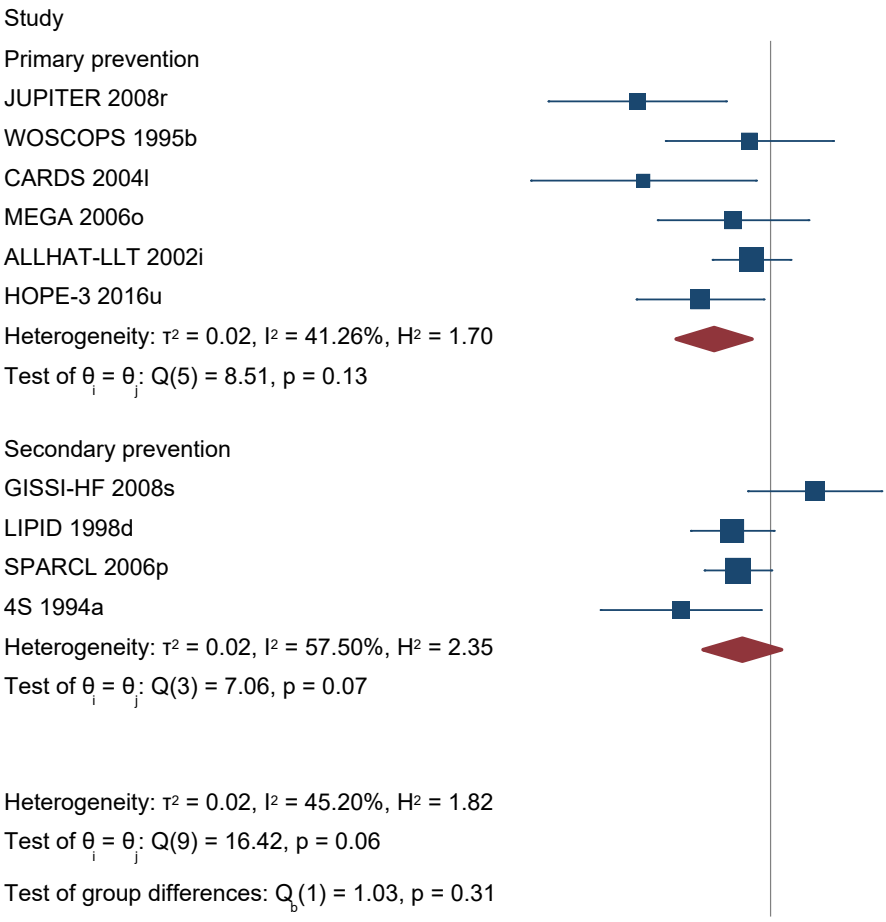
Supplementary Figure e12: Meta-analysis of relative effects of treatment on myocardial infarction in primary and secondary prevention trials



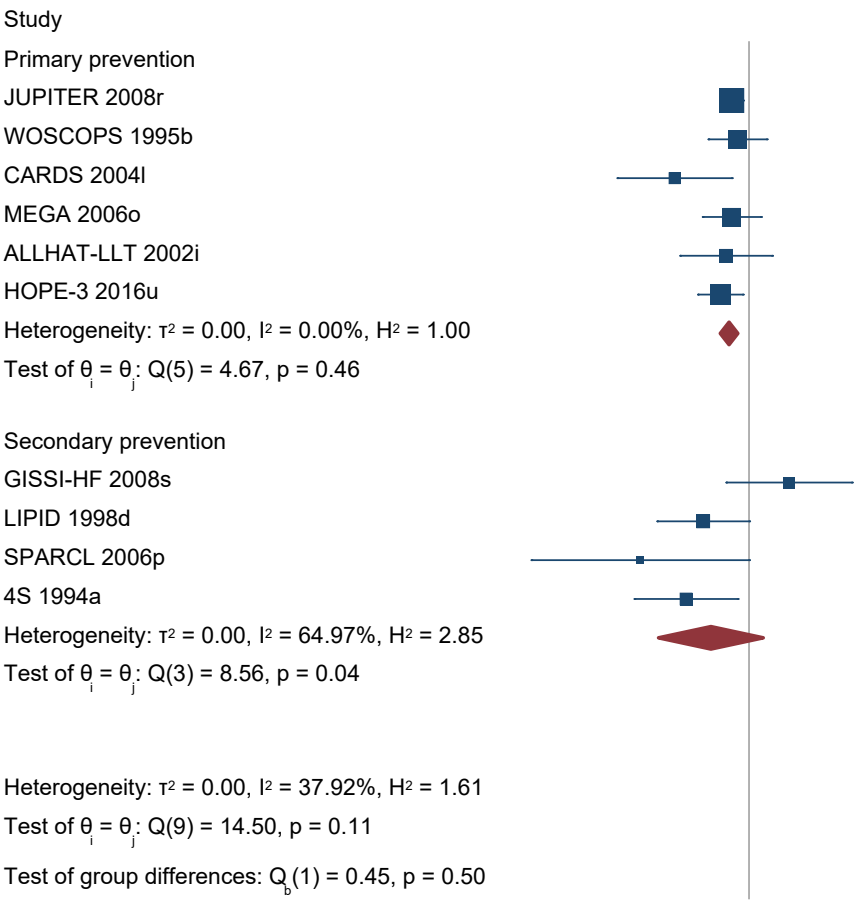
Supplementary Figure e13: Meta-analysis of absolute effects of treatment on myocardial infarction in primary and secondary prevention trials



Supplementary Figure e14: Meta-analysis of relative effects of treatment on stroke from primary and secondary prevention trials



Supplementary Figure e15: Meta-analysis of absolute effects of treatment on stroke in primary and secondary prevention trials



Supplementary Table e4: Meta-regression results of outcomes by mean difference in LDL-C (unadjusted)

Outcome	Number of trials	Coefficient	95% CI	p-value	R^2
All death logRR	19	-0.12	-0.28, 0.03	0.11	14%
All death ARD	19	-0.004	-0.019, 0.01	0.54	0%
MI logRR	18	-0.19	-0.61, 0.23	0.35	0%
MI ARD	18	-0.014	-0.036, 0.008	0.19	0%
Stroke logRR	18	-0.26	-0.58, 0.05	0.098	4%
Stroke ARD	18	-0.004	-0.011, 0.003	0.24	0%

logRR = log relative risk; ARD = absolute risk difference; coefficient = estimate of slope in meta-regression model; R^2 = proportion of between-study variance explained by mean difference in LDL-C; R^2 values of zero imply that the mediator variable explains none of the observed heterogeneity