Eligible criteria

The lists of source that was processed to manual search

Figure S8. Surface under the cumulative ranking probabilities of statins, ezetimibe, PCSK9 inhibitors for (A) new-onset diabetes, (B) alanine aminotransferase, and (C) creatine kinase. PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease.

Figure S7. Comparison-adjusted funnel plot for the network of (A) cardiovascular events, (B) all-cause mortality, and (C) cardiovascular mortality. Pla = placebo, Sta = Statins, Eze = Ezetimibe, P9 = proprotein convertase subtilisin-kexin type 9 serine protease.

eReferences

Eligible criteria:

1) Participants were 18 years or older with hypercholesterolemia;

2) Lipid-lowering therapy with ezetimibe, statin, or PCSK9 inhibitor monotherapy.

3) One lipid-lowering agent compared with another lipid-lowering agent or placebo.

4) The trials should report one of the predefined outcomes, including low-density lipoprotein cholesterol, high density lipoprotein cholesterol, and total cholesterol, cardiovascular events, all-cause mortality, cardiovascular mortality, serious adverse events, neurocognitive event, new-onset diabetes, and elevation of serum creatine kinase (three to ten folds increase) and alanine aminotransferase level (three to ten folds increase).

5) Study was randomized controlled trial, and not included crossover randomized controlled trials or quasi-randomized.

The lists of source that was processed to manual search

Meta-analyses	1. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials 2. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials 3. Effect of statin and non-statin LDL-lowering medications on cardiovascular outcomes in secondary prevention: a meta-analysis of randomized trials 4. Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: a systematic review and meta-analysis
Reviews	1. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel 2. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-Cholesterol lowering in the management of atherosclerotic cardiovascular disease risk 3. 2016 European guidelines on cardiovascular disease prevention in clinical practice
Major cardiovascular conferences	1. European Society of Cardiology Congress held in the past two years. 2. American College of Cardiology Congress held in the past two years.

Table S1: PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	3-4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any*	4-5

		have been clustered or merged into the same node (with justification).	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	5-6
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	6
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	6-7
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	6-7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication	6-7

		bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	7
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	9-11
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	9-11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	9-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	9-11
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency	11

		and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	11
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	11-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	NA

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Table S2: Electronic search strategies

Embase (between January 1, 2000 and April 1, 2017)	**PubMed** (between January 1, 2000 and April 1, 2017)	**Cochrane Central Register of Controlled Trials** (Publication Year from 2000 to 2017, in Trials)
#1 'hydroxymethylglutaryl-coa reductase inhibitors'/exp	**#1** "hydroxymethylglutaryl-coa reductase inhibitors"[mesh]	**#1** MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees
#2 'statin'/exp OR 'statin':ab,ti	**#2** "ezetimibe"[mesh]	**#2** MeSH descriptor: [Ezetimibe] explode all trees
#3 'atorvastatin':ab,ti	**#3** "AMG 145"[supplementary concept]	**#3** AMG 145:ti,ab,kw
#4 'fluvastatin':ab,ti	**#4** "alirocumab"[supplementary concept]	**#4** alirocumab:ti,ab,kw
#5 'lovastatin':ab,ti	**#5** "statin"[tiab]	**#5** statin:ti,ab,kw
#6 'pitavastatin':ab,ti	**#6** "atorvastatin"[tiab]	**#6** atorvastatin:ti,ab,kw
#7 'pravastatin':ab,ti	**#7** "fluvastatin"[tiab]	**#7** fluvastatin:ti,ab,kw
#8 'rosuvastatin':ab,ti	**#8** "lovastatin"[tiab]	**#8** lovastatin:ti,ab,kw
#9 'simvastatin':ab,ti	**#9** "pitavastatin"[tiab]	**#9** pitavastatin:ti,ab,kw
#10 'ezetimibe':ab,ti	**#10** "pravastatin"[tiab]	**#10** pravastatin:ti,ab,kw
#11 'ezetimib':ab,ti	**#11** "rosuvastatin"[tiab]	**#11** rosuvastatin:ti,ab,kw
#12 'ezetrol':ab,ti	**#12** "simvastatin"[tiab]	**#12** simvastatin:ti,ab,kw
#13 'zetia':ab,ti	**#13** "ezetimibe"[tiab]	**#13** ezetimibe:ti,ab,kw
#14 'pcsk9':ab,ti	**#14** "ezetimib"[tiab]	**#14** ezetimib:ti,ab,kw
#15 'evolocumab':ab,ti	**#15** "ezetrol"[tiab]	**#15** ezetrol:ti,ab,kw
#16 'amg 145':ab,ti	**#16** "zetia"[tiab]	**#16** zetia:ti,ab,kw
#17 'alirocumab':ab,ti	**#17** "PCSK9"[tiab]	**#17** PCSK9:ti,ab,kw
#18 'regn727':ab,ti	**#18** "evolocumab"[tiab]	**#18** evolocumab:ti,ab,kw
#19 'sar236553':ab,ti	**#19** "AMG 145"[tiab]	**#19** AMG 145:ti,ab,kw
#20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #116 OR #17 OR #18 OR #19	**#20** "alirocumab"[tiab]	**#20** alirocumab:ti,ab,kw
#21 'hypercholesterolemia'/exp	**#21** "REGN727"[tiab]	**#21** REGN727:ti,ab,kw
#22 'hypercholesterolemia':ab,ti	**#22** "SAR236553"[tiab]	**#22** SAR236553:ti,ab,kw
	#23 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	**#23** #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR

#23 'hypercholesterolaemia':ab,ti **#24** 'hypercholesteremia':ab,ti **#25** 'hyperlipidaemia':ab,ti **#26** 'dyslipidaemia':ab,ti **#27** 'elevated cholesterol':ab,ti **#28** #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 **#29** 'randomized controlled trial'/exp **#30** 'randomized controlled trial (topic)'/exp **#31** 'controlled clinical trial (topic)'/exp **#32** 'randomized controlled trial':ab,ti **#33** 'random':ab,ti OR 'randomized':ab,ti **#34** 'double blind method':ab,ti OR 'triple blind method':ab,ti **#35** 'placebo':ab,ti OR 'placebos':ab,ti OR 'control':ab,ti OR 'controlled':ab,ti **#36** #33 AND #34 AND #35 **#37** #29 OR #30 OR #31 OR #32 OR #36 **#38** #20 AND #28 AND #37 AND [humans]/lim NOT [1-4-2017]/sd AND [2000-2017]/py	OR #18 OR #19 OR #20 OR #21 OR #22 **#24** "hypercholesterolemia"[mesh] **#25** "hypercholesterolemia"[tiab] **#26** "hypercholesterolaemia"[tiab] **#27** "hypercholesteremia"[tiab] **#28** "hyperlipidaemia"[tiab] **#29** "dyslipidaemia"[tiab] **#30** "elevated cholesterol"[tiab] **#31** #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 **#31** "randomized controlled trial"[publication type] **#32** "randomized controlled trials as topic"[mesh] **#33** "controlled clinical trial"[publication type] **#34** "randomized"[tiab] OR "random$"[tiab] **#35** "double blind method"[tiab] OR "single blind method"[tiab] OR "triple blind method"[tiab] **#36** "placebo"[tiab] OR "placebos"[tiab] OR "control"[tiab] OR "controlled"[tiab] **#37** #34 AND #35 AND #36 **#38** #31 OR #32 OR #33 OR #37 **#39** #23 AND #31 AND #38 AND ("2000/01/01"[PDAT] : "2017/04/01"[PDAT]) AND "humans"[MeSH Terms]	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 **#24** MeSH descriptor: [Hypercholesterolemia] explode all trees **#25** hypercholesterolemia:ti,ab,kw **#26** hypercholesterolaemia:ti,ab,kw **#27** hypercholesteremia:ti,ab,kw **#28** hyperlipidaemia:ti,ab,kw **#29** dyslipidaemia:ti,ab,kw **#30** elevated cholesterol:ti,ab,kw **#31** #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 **#32** randomized controlled trial:pt **#33** controlled clinical trial:pt **#34** RCT:pt **#35** #32 OR #33 OR #34 **#36** #23 AND #31 AND #35

Table S3. Basic characteristics of included trials.

Publication year, Study ID	Setting	Lipid-lowering therapies	No. of patients	Follow-up (year)	Age (mean)	HP history %	DM %	CAD history %	LDL (mg/dL)	HDL (mg/dL)	TG (mg/dL)	Baseline lipid-lowering therapies
Statins-related trials												
2000, SCAT[1]	Multi-center	Simvastatin	460	4	61	36	11	100	130	38	160	Diet therapies
2000, GISSI Prevention[2]	Multi-center	Pravastatin	4,271	2	60	37	14	100	152	46	155	Diet therapies
2002, LIPS [3]	Multi-center	Fluvastatin	1,677	3.9	60	39	12	100	132	38	150	Dietary and lifestyle counseling
2002, FAST[4]	Single center	Pravastatin	164	2	66.1	40	56	NR	166	57	150	Diet therapies
2002, ALLHAT-LLT[5]	Multi-center	Pravastatin	10,355	6	66.4	100	35.1	14.2	146	48	150	Usual care
2002, GREACE[6]	Multi-center	Atorvastatin	1,600	3	58.5	43	19.5	100	180	41	181	Usual care included life-style
2002, Davidson et al.[7]	Multi-center	Rosuvastatin, Atorvastatin	516	0.2	57	NR	NR	NR	186	50	190	Diet therapies
2002, MRC/BHF[8]	Multi-center	Simvastatin	20,536	5	NR	41	19.4	80.6	132	41	280	NR
2002, PROSPER[9]	Multi-	Pravastatin	5,804	3.2	75.3	61.9	10.7	NR	147	50	120	NR

	center											
2003, ASCOT-LLA[10]	Multi-center	Atorvastatin	19,342	3.3	63.1	100	13.1	9.9	132	50	155	NR
2003, Bruckert et al. [11]	Multi-center	Fluvastatin	1,229	0.5	75.5	56	7	NR	200	53	140	Diet therapies
2004, PREVEND IT[12]	Single center	Pravastatin	864	4	51.3	NR	2.5	NR	155	39	155	NR
2004, ALLIANCE[13]	Multi-center	Atorvastatin	2,442	4.3	61.2	NR	22.2	100	147	41	190	Usual care included life-style
2004, JUST[14]	Multi-center	Simvastatin	299	2	58.7	54.8	43.5	100	154	45	165	Diet therapies
2004, PHYLLIS[15]	Multi-center	Pravastatin	508	2.6	58.4	100	NR	100	181	53	140	Low lipid diet
2004, CARDS[16]	Multi-center	Atorvastatin	2,838	3.9	61.7	84	100	0	117	55	175	Additional lipid-lowering treatment on the top of study drug was allowed
2004, PROVE-IT[17]	Multi-center	Pravastatin, Atorvastatin	4,162	2	58.2	50.2	16.7	100	106	39	180	Statins were prescribed both in experimental and control group.
2004, A to Z[18]	Multi-center	Simvastatin	4,497	2	61	49.7	23.8	100	112	39	170	Statins were prescribed both in experimental and control group.

2005, TNT[19]	Multi-center	Atorvastatin	10,001	4.9	61	54.1	15	100	98	47	150	Statins were prescribed both in experimental and control group.
2005, IDEAL[20]	Multi-center	Atorvastatin, Simvastatin	8,888	4.8	61.7	33	12	100	122	46	140	Statins were prescribed both in experimental and control group.
2005, CERDIA[21]	Single center	Cerivastatin	250	2	58.5	50.4	100	0	132	48	162	NR
2005, COMETS[22]	Multi-center	Rosuvastatin, Atorvastatin	397	0.1	57.7	NR	0	0	169	60	115	Diet therapies
2005, MARS[23]	Multi-center	Lovastatin	270	2	58	0	NR	100	153	43	180	Diet therapies
2005, ATHEROMA[24]	Multi-center	Pravastatin	361	3	59.3	42	18.8	100	143	50	165	Diet therapies
2006, ASPEN[25]	Multi-center	Atorvastatin	2,410	4	61.1	55	100	NR	114	47	165	Diet therapies
2007, HYRIM[26]	Single center	Fluvastatin	568	4	57.2	100	NR	NR	150	49	155	Intensive lifestyle intervention or usual care
2008, JUPITER[27]	Multi-center	Rosuvastatin	17,802	1.9	66	57.3	0	11.5	108	49	145	NR
2009, RCASS[28]	Multi-	Simvastatin	227	2	63	69.2	91.2	100	151	45	165	NR

	center											
2009, MEGA[29]	Multi-center	Pravastatin	3,277	5	58.5	100	20.5	0	159	58	135	Diet therapies
2010, SEARCH[30]	Multi-center	Simvastatin	12,064	6.7	64.2	42	11	100	97	40	335	Statins were prescribed both in experimental and control group.
2010,ASTRONOMER[31]	Multi-center	Rosuvastatin	269	3.5	58	28	0	0	122	61	110	NR
2010, METEOR[32]	Multi-center	Rosuvastatin	984	2	57	19.9	NR	10	155	50	120	NR
2016, HOPE3[33]	Multi-center	Rosuvastatin	12,705	5.6	65.8	37.9	5.8	0	128	45	140	Individualized structured lifestyle advice was provided to the participants
Ezetimibe-related trials												
2002, Davidson MH et al.[34]	Multi-center	Ezetimibe, Simvastatin	394	0.2	57.4	NR	4.6	NR	179	51	175	Diet therapies
2002, Dujovne et al.[35]	Multi-center	Ezetimibe	892	0.2	58	33.3	NR	NR	167	52	170	Diet therapies
2003, Ballantyne et al.[36]	Multi-center	Ezetimibe, Atorvastatin	373	0.2	57.5	34	3.5	9	180	53	170	Diet therapies
2003, Kerzner et	Multi-	Ezetimibe,	356	0.2	56.2	30.9	6.5	7	179	52	170	Diet therapies

al.[37]	center	Lovastatin										
2003, Knopp et al.[38]	Multi-center	Ezetimibe	827	0.2	58.1	34.7	5.7	6.8	157	52	200	Diet therapies
2003, Melani et al.[39]	Multi-center	Ezetimibe, Pravastatin	334	0.2	54.2	29.6	5.1	6	178	50	180	Diet therapies
2004, Bays et al.[40]	Multi-center	Ezetimibe, Simvastatin	919	0.2	55.2	36.7	5.7	14.5	178	52	160	Diet therapies
2004, Feldman et al.[41]	Multi-center	Ezetimibe	362	0.4	63	NR	47.8	52.2	172	46	180	Lipid-lowering therapies
2004, Goldberg et al.[42]	Multi-center	Ezetimibe, Simvastatin	534	0.2	NR	31.2	5.6	6.8	175	50	170	Diet therapies
2005, Cruz-Fernandez et al.[43]	Multi-center	Ezetimibe	450	0.2	63.2	55.8	17.5	100	122	52	150	Lipid-lowering therapies
2005, Masana et al.[44]	Multi-center	Ezetimibe	433	1	59.4	NR	NR	NR	136	50	145	Lipid-lowering therapies
2006, Patel et al.[45]	Multi-center	Ezetimibe	152	0.1	65.4	45.4	3.9	100	169	54	40	Lipid-lowering therapies
2006, UK-HARP-II[46]	Multi-center	Ezetimibe, Simvastatin	203	0.5	60.0	NR	10.8	NR	119	40	190	Lipid-lowering therapies
2007, Shankar et al.[47]	Multi-center	Ezetimibe	230	0.2	51.9	33.9	NR	73.9	128	42	460	Lipid-lowering therapies
2008, ENHANCE[48]	Multi-center	Ezetimibe	720	1	45.9	16.4	1.8	NR	318	47	175	Lipid-lowering therapies
2008, Strony et al.[49]	Multi-center	Ezetimibe	109	1	57.3	29.4	5.5	NR	178	49	180	Lipid-lowering therapies

2012, Arimura[50]	Single center	Atorvastatin, Ezetimibe	50	0.5	68	75	30	NR	100	50	150	Lipid-lowering therapies
2015, IMPROVE-IT[51]	Multi-center	Ezetimibe, Simvastatin	18,144	6	63.6	61.4	27.2	100	94	NR	NR	Lipid-lowering therapies
2015, Masuda[52]	Single center	Rosuvastatin, Ezetimibe	51	0.5	67.1	75	47.5	40	127	50	110	Lipid-lowering therapies
2015, PRECISE‐IVUS[53]	Multi-center	Atorvastatin, Ezetimibe	202	1	66.5	70.3	29.7	49	109	41	125	Lipid-lowering therapies
2016, Wang[54]	Single center	Rosuvastatin, Ezetimibe	98	1	64	49	35.7	56.1	137	44	70	Lipid-lowering therapies
2016, HIJ-PROPER[55]	Multi-center	Ezetimibe, pitavastatin	1,734	3.9	65.6	NR	NR	100	135	NR	NR	Lipid-lowering therapies
PCSK9 inhibitors-related trials												
2012, LAPLACE-TIMI 57[56]	Multi-center	Evolocumab	315	0.2	63	70.2	17	32	122	54	125	Lipid-lowering therapies
2012, MENDEL[57]	Multi-center	Evolocumab	225	0.2	51	32.9	0	NR	143	53	125	Without lipid-lowering therapies
2012, McKenney et al.[58]	Multi-center	Alirocumab	62	0.2	56.6	48.4	6.5	6.5	127	51	140	Lipid-lowering therapies
2012, RUTHERFORD[59]	Multi-center	Evolocumab	112	0.2	50.6	NR	NR	21.5	156	50	110	Lipid-lowering therapies
2012, Roth et al.[60]	Multi-	Alirocumab	61	0.2	56.9	49.2	16.4	1.5	123	55	125	Lipid-lowering

	center											therapies
2012, Stein et al.[61]	Multi-center	Alirocumab	31	0.2	54	NR	0	35.5	146	52	135	Lipid-lowering therapies
2012, GAUSS[62]	Multi-center	Evolocumab	65	0.2	61	NR	NR	NR	194	57	155	Lipid-lowering therapies
2014, DESCARTES[63]	Multi-center	Evolocumab	901	1	56	48.6	11.5	15.1	104	53	105	Lipid-lowering therapies
2014, YUKAWA[64]	Multi-center	Evolocumab	207	0.2	61	72.9	35	27	139	54	145	Lipid-lowering therapies
2014, MENDEL-2[65]	Multi-center	Evolocumab	614	0.2	53	28.7	0.2	0	143	55	115	Without lipid-lowering therapies
2014, LAPLACE-2[66]	Multi-center	Evolocumab, Ezetimibe	1,897	0.2	60	NR	15	23	109	54	130	Lipid-lowering therapies
2014, GAUSS-2[67]	Multi-center	Evolocumab	307	0.2	62	59	20	29	193	52	NR	Lipid-lowering therapies
2015, ODYSSEY OPTIONS I[68]	Multi-center	Alirocumab, Ezetimibe	206	0.2	64	78.6	NR	NR	104	NR	NR	Lipid-lowering therapies
2015, ODYSSEY COMBO II[69]	Multi-center	Alirocumab, Ezetimibe	720	1	62	NR	31	90	107	46	160	Lipid-lowering therapies
2015, ODYSSEY FHI and FHII[70]	Multi-center	Alirocumab	735	1.5	52.4	39.6	8.2	42.6	139	NR	NR	Lipid-lowering therapies
2015, ODYSSEY COMBO I[71]	Multi-center	Alirocumab	316	1	63	NR	43.1	78.2	102	48	NR	Lipid-lowering therapies
2015, ODYSSEY	Multi-	Alirocumab	314	0.5	63.5	62.7	23.9	47	192	50	153	Without lipid-

ALTERNATIVE[72]	center	, Ezetimibe										lowering therapies
2015, RUTHERFORD-2[73]	Multi-center	Evolocumab	331	0.2	51.2	NR	NR	31.3	155	50	106	Lipid-lowering therapies
2015, ODYSSEY LONG TERM[74]	Multi-center	Alirocumab	2,341	1.5	63.5	NR	23.9	47	122	50	NR	Lipid-lowering therapies
2015, ODYSSEY MONO[75]	Multi-center	Alirocumab, Ezetimibe	103	0.5	60.2	NR	3.9	NR	140	57	130	Without lipid-lowering therapies
2015, OSLER-1 (OSLER-1 extension)[76]and OSLER-2[77]	Multi-center	Evolocumab	4,465	1	58	52	13	20	120	51	160	Without lipid-lowering therapies
2016, ODYSSEY OPTIONS II[78]	Multi-center	Alirocumab, Ezetimibe	204	0.5	60.9	71.1	39.7	56.9	112	51	129	Lipid-lowering therapies
2016, YUKAWA-2[79]	Multi-center	Evolocumab	404	0.2	61.5	73.5	48.8	12.9	106	57	123	Lipid-lowering therapies
2016, GAUSS-3[80]	Multi-center	Evolocumab, Ezetimibe	218	0.5	58.8	51.4	11.9	31.7	220	50	185	Without lipid-lowering therapies
2016, ODYSSEY HIGH FH[81]	Multi-center	Alirocumab	107	0.5	50.6	57	14	49.5	198	48	140	Lipid-lowering therapies
2016, GLAGOV[82]	Multi-center	Evolocumab, statins	968	1.5	59.8	83	20.9	NR	93	46	125	Lipid-lowering therapies

		combination										
2017, SPIRE[83]	Multi-center	Bococizumab, statins combination	4,449	1	61.3	78.3	53.3	NR	122	48	160	96% were receiving statin therapy at the time of enrollment
2017, FOURIER[84]	Multi-center	Evolocumab, statins combination	27,564	2.2	62.5	80.1	36.6	100	92	44	135	Lipid-lowering therapies
2018, ODYSSEY OUTCOMES[85]	Multi-center	Alirocuma, statins combination	18,924	2.8	NA	NA	NA	100	87	NA	NA	Lipid-lowering therapies

Table S4. The tau values for the network meta-analyses for each outcome

Outcomes	Tau^2	Outcome type (all pharmacological versus pharmacological)	Predictive distributions for Tau^2	The extent of heterogeneity
LDL Cholesterol	1.7432	Biological marker	Median = 0.033; 95% Range = 0.0001–10.2; N = 401	Moderate
HDL Cholesterol	0.0707			Moderate
Total Cholesterol	0.6027			Moderate
All-cause mortality	0.0000	All-cause mortality	Median=0.014; 95% Range=(0.0008 –0.25)	Low
Cardiovascular events	0.0094	Semi-objective outcomes	Median=0.040; 95% Range=(0.001–1.58)	Low
Cardiovascular mortality	0.0028			Low
Serious adverse events	0.0000	Subjective outcomes	Median=0.096; 95% Range=(0.004–2.31)	Low
Neurocognitive events	0.0390			Moderate
New-onset diabetes	0.0000			Low
Alanine aminotransferase	0.0801			Moderate
Creatine kinase	0.0894			Moderate

Table S5. Assessment of loop inconsistency in networks

Closed triangular of quadratic loop of evidence	Inconsistency factor (95% confidence interval)	Loop heterogeneity tau2
LDL-C Cholesterol		
Placebo- statin - Ezetimibe	0.33 (0.00,1.34)	0.735
Placebo - Ezetimibe - PCSK9 inhibitor	0.31 (0.00,1.86)	1.421
HDL Cholesterol		
Placebo- statin - Ezetimibe	0.12 (0.00,0.39)	0.042
Placebo - Ezetimibe - PCSK9 inhibitor	0.02 (0.00,0.36)	0.050
TC Cholesterol		
Placebo- statin - Ezetimibe	0.39 (0.00,1.38)	0.673
Placebo - Ezetimibe - PCSK9 inhibitor	0.51 (0.00,2.23)	0.374
All-cause Mortality		
Placebo - Ezetimibe - PCSK9 inhibitor	1.41 (0.00, 2.97)	0.032
Cardiovascular Events		
Placebo - Ezetimibe - PCSK9 inhibitor	0.27 (0.00, 0.86)	0.000
Cardiovascular Mortality		
Placebo - Ezetimibe - PCSK9 inhibitor	0.83 (0.00, 2.51)	0.000
Serious adverse events		
Placebo- statin - Ezetimibe	0.68 (0.00,3.90)	0.000
Placebo - Ezetimibe - PCSK9 inhibitor	0.30 (0.00,0.81)	0.000
Neurocognitive events		
Placebo - Ezetimibe - PCSK9 inhibitor	1.70 (0.00,5.23)	0.167
Alanine aminotransferase		
Placebo- statin - Ezetimibe	0.38 (0.00,1.93)	0.161
Placebo - Ezetimibe - PCSK9 inhibitor	0.09 (0.00,1.08)	0.000
Creatine kinase		
Placebo- statin - Ezetimibe	0.82 (0.00,2.54)	0.131
Placebo - Ezetimibe - PCSK9 inhibitor	0.03 (0.00,0.79)	0.000
Loop inconsistency is these 95% confidence interval of IF do not include zero. PCSK9 = proprotein convertase subtilisin/kexin type 9.		

Table S6. Assessment of global inconsistency in network using the 'design-by-treatment' interaction model

Network outcomes	X^2	*p*
LDL-C Cholesterol	1.06	0.9580
HDL Cholesterol	4.70	0.4531
TC Cholesterol	2.40	0.4944
All-cause Mortality	6.16	0.2910
Cardiovascular Events	4.88	0.4308
Cardiovascular Mortality	3.55	0.6154
Serious adverse events	2.72	0.7431
Neurocognitive events	3.70	0.1573
Diabetes mellitus	0.42	0.5153
Alanine aminotransferase	5.87	0.3192
Creatine kinase	5.37	0.3729

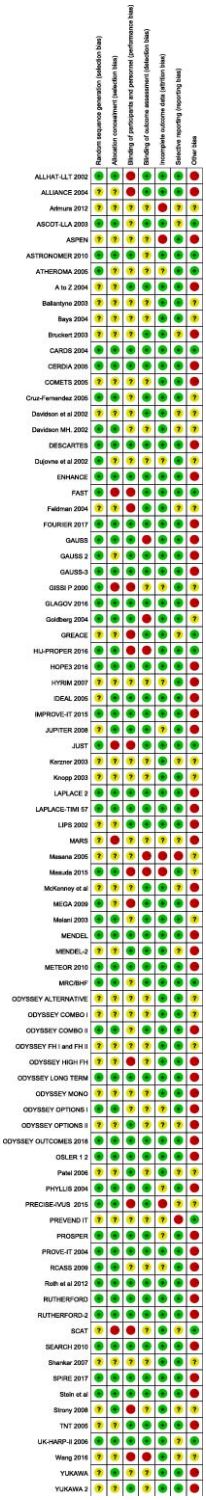
Table S7. Assessment of inconsistency in network using node-splitting method

Side	Direct		Indirect		Difference		
	MD	SE	MD	SE	MD	SE	*P*>z
LDL-C Cholesterol							
AB *	-34.25191	5.598098	-32.35565	15.24308	-1.896263	16.25099	0.907
AC	-18.98119	4.20185	-17.79963	7.445088	-1.181552	8.549083	0.89
AD	-51.2717	4.471976	-49.26347	7.661502	-2.008235	8.871485	0.821
BC	15.3439	7.234701	15.30719	9.107439	0.036716	11.63768	0.997
CD	-32.61689	5.675222	-31.34708	6.47908	-1.269805	8.613301	0.883
HDL Cholesterol							
AB *	4.439886	0.761344	2.076081	2.290125	2.363805	2.453188	0.335
AC	2.645776	0.634813	1.613645	1.221601	1.032132	1.374759	0.453
AD	6.904214	0.740043	8.63683	1.233247	-1.73262	1.443118	0.230
BC	-1.38092	1.017874	-2.34124	1.303222	0.960323	1.673548	0.566
CD	5.859438	0.937287	3.864463	1.011478	1.994975	1.384029	0.149
TC Cholesterol							
AB *	-24.788	2.146922	-24.4767	6.14591	-0.31126	6.524142	0.962
AC	-12.7974	1.704555	-17.2585	3.263156	4.461104	3.681609	0.226
AD	-37.8391	2.338783	-32.1902	3.122321	-5.64881	3.901138	0.148
BC	11.20461	2.781255	10.64914	3.656018	0.555469	4.600281	0.904
CD	-19.4522	2.649189	-25.0964	2.863959	5.644162	3.901269	0.148
Cardiovascular Events							
AB *	-0.21804	0.028664	-1.45239	1.563152	1.234348	1.563417	0.430
AC	-0.05635	0.081754	-0.38582	0.330919	0.329468	0.341036	0.334
AD	-0.21195	0.069484	0.170727	0.345231	-0.38268	0.352676	0.278
BC	1.298057	0.897185	0.133345	0.083234	1.164712	0.901032	0.196
CD	0.194331	0.311056	-0.15921	0.108637	0.353543	0.329324	0.283
All-cause Mortality							
AB *	-0.09795	0.029551	-1.36645	1.560542	1.268499	1.560595	0.416
AC	-0.05133	0.070296	1.11689	0.513526	-1.16822	0.516949	0.024**
AD	-0.01984	0.088838	-0.94225	0.541053	0.922414	0.546892	0.092
BC	1.298189	0.89672	0.056773	0.072834	1.241416	0.899669	0.168
CD	-0.9139	0.502238	0.032899	0.107065	-0.94679	0.513529	0.065
Cardiovascular Mortality							
AB *	-0.19162	0.051864	-1.28293	1.580433	1.091303	1.581302	0.490
AC	-0.02655	0.13371	0.799517	0.552804	-0.82606	0.567995	0.146
AD	-0.04988	0.14932	-0.55238	0.587372	0.502495	0.605455	0.407
BC	1.29814	0.898631	0.184336	0.14233	1.113804	0.909819	0.221
CD	-0.61459	0.529311	-0.02341	0.200817	-0.59118	0.566136	0.296
Serious adverse events							
AB *	-0.01293	0.022852	-1.1608	2.356139	1.147868	2.356311	0.626
AC	-0.35672	0.233058	-0.04506	0.160089	-0.31166	0.27508	0.257
AD	-0.01531	0.024535	-0.34316	0.303407	0.327845	0.304375	0.281

BC	0.721613	1.242356	-0.13848	0.138019	0.860093	1.248887	0.491
CD	0.062572	0.154995	0.285296	0.241511	-0.22272	0.277683	0.423
Neurocognitive events							
AB	.	.	.	.	.	.	.
AC	3.475959	1.350241	0.657826	0.707907	2.818132	1.614286	0.081
AD*	0.194735	0.219185	4.634044	2.307107	-4.43931	2.305992	0.054
CD*	-1.02464	0.591761	-3.39186	3.070773	2.367215	3.168005	0.455
New-onset diabetes							
AB	.	.	.	.	.	.	.
AC*	0.687638	2.008324	-1.44769	2.599645	2.135328	3.281716	0.515
AD	.	.	.	.	.	.	.
CD*	0.422086	1.643214	-1.71324	3.279906	2.135328	3.281716	0.515
Alanine aminotransferase							
AB *	0.652469	0.148128	-0.17051	1.344088	0.822975	1.359409	0.545
AC	0.056679	0.249533	0.516735	0.5289045	-0.46006	0.577567	0.426
AD	-0.13413	0.197245	0.502289	0.6512191	-0.63642	0.679713	0.349
BC	0.128723	0.637262	-0.6262	0.2911915	0.754918	0.695728	0.278
CD	-0.27959	0.462524	-0.18656	0.3378483	-0.09303	0.571831	0.871
Creatine kinase							
AB *	0.382736	0.145379	-0.56896	1.391608	0.951699	1.399991	0.497
AC	-0.40333	0.254204	0.057914	0.382013	-0.46124	0.451402	0.307
AD	-0.28232	0.158216	-0.22269	0.458323	-0.05963	0.482339	0.902
BC	0.455567	0.676592	-0.79068	0.25777	1.246252	0.718214	0.083
CD	-0.04308	0.356107	0.017	0.297976	-0.06008	0.462232	0.897

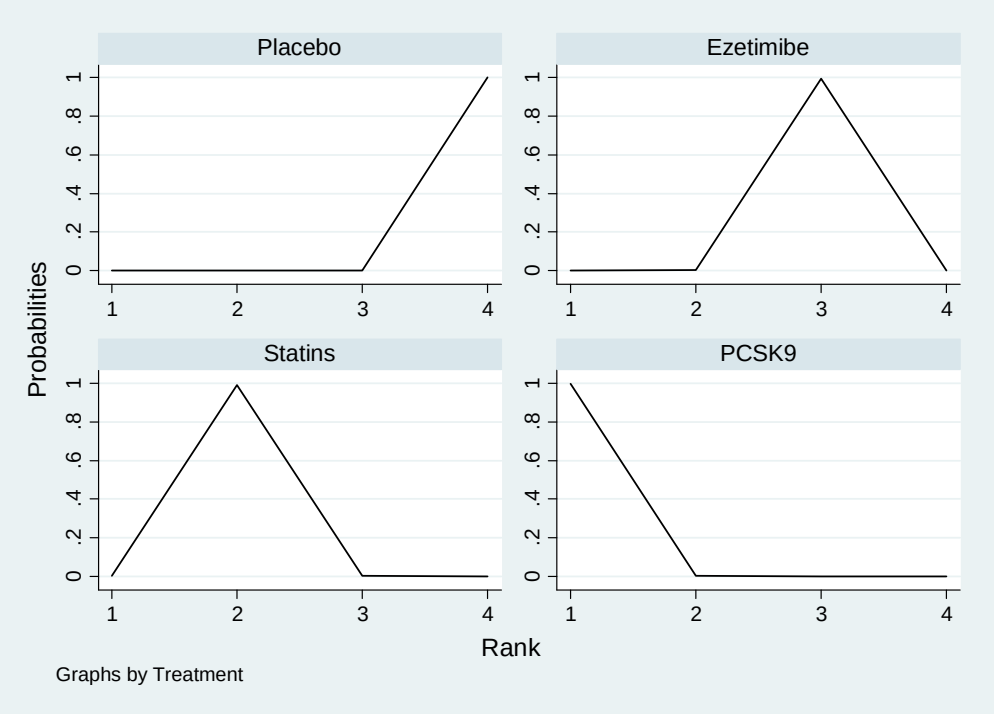
*Warning: all the evidence about these contrasts comes from the trials which directly compare them. No inconsistency was found for all efficacy and safety outcomes. **Inconsistency was detected between direct and indirect evidences. A = Placebo, B = Statins, C = Ezetimibe, D = proprotein convertase subtilisin/kexin type 9 inhibitors. SE = standard error, MD = mean difference.

Figure S1. The summarized quality of included studies as assessed by tool recommended in Cochrane Collaboration guidelines.



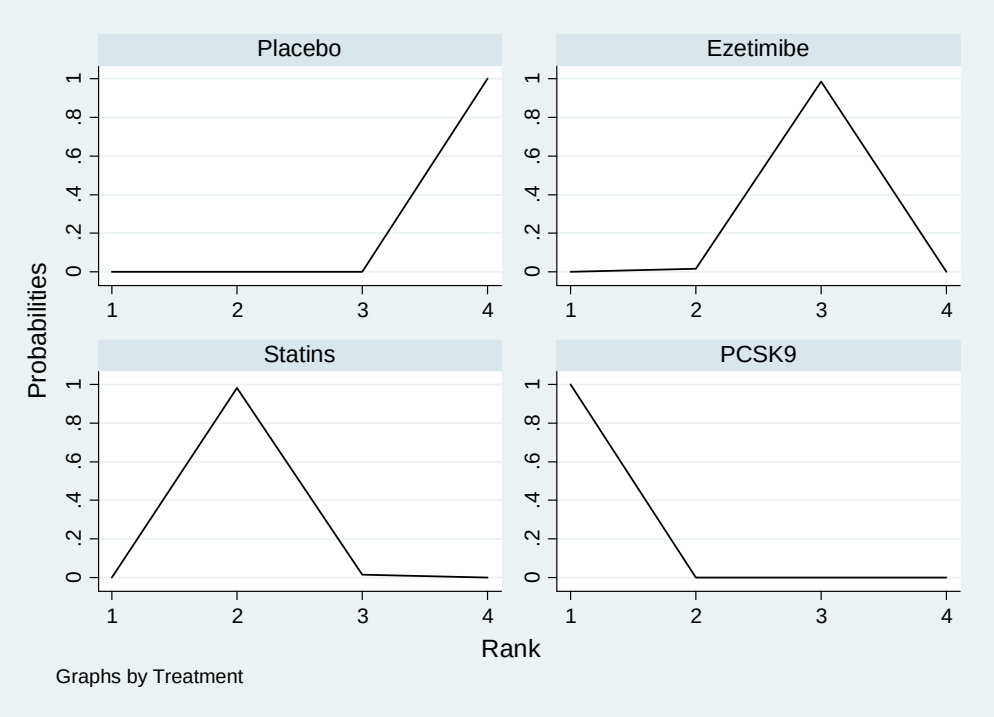
The judgment (Low, Unclear, and High) of each risk of bias item was based on the recommended tool in Cochrane review.

Figure S2A: Ranking of the effects of statins, ezetimibe, PCSK9 inhibitors for improving LDL-C cholesterol level. PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease.



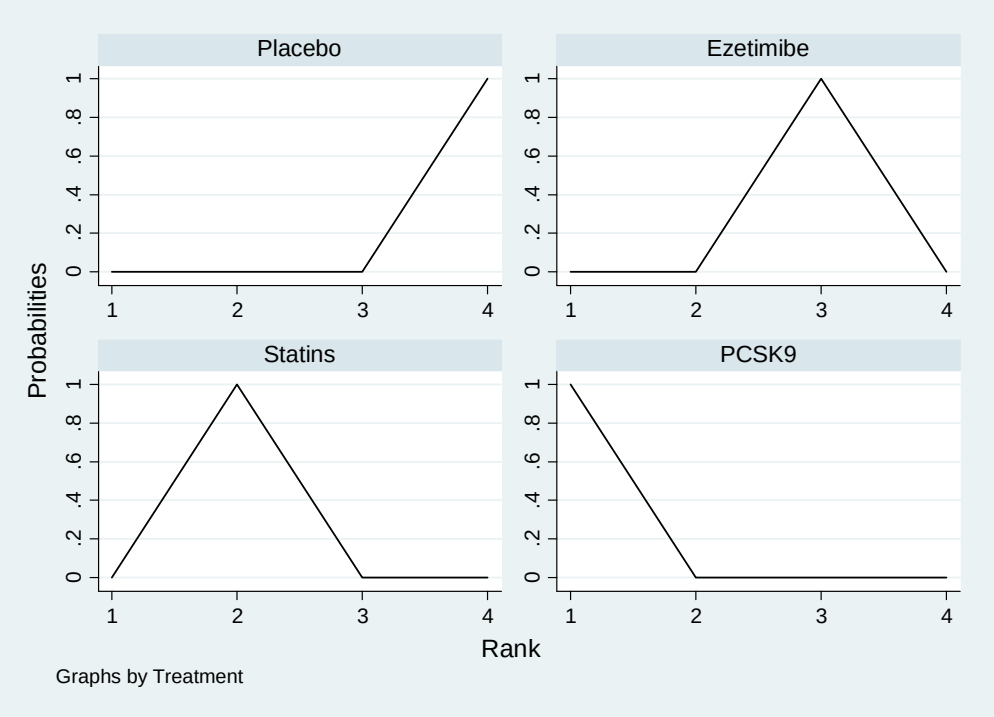
Treatment	SUCRA	PrBest	MeanRank
Placebo	0.0	0.0	4.0
Statin	66.7	0.2	2.0
Ezetimibe	33.4	0.0	3.0
PCSK9 inhibitor	99.9	99.8	1.0

Figure S2B: Rankogram of statins, ezetimibe, PCSK9 inhibitors for HDL cholesterol level. PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease.



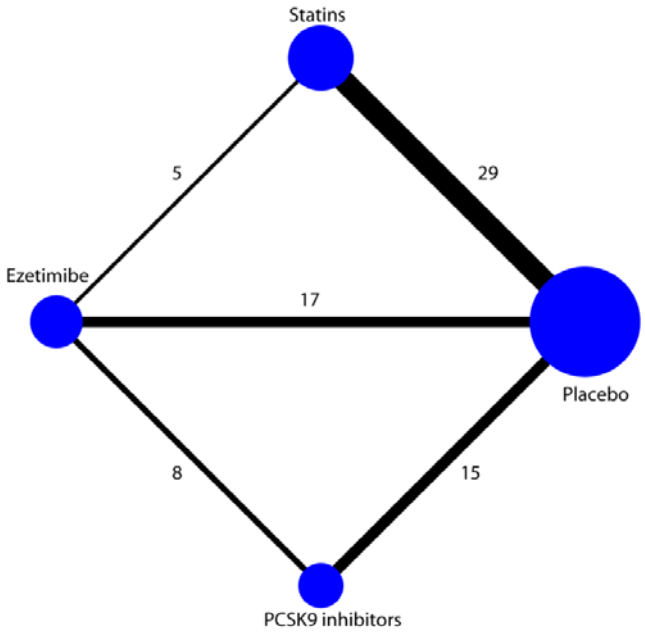
Treatment	SUCRA	PrBest	MeanRank
Placebo	0.0	0.0	4.0
Statin	66.2	0.0	2.0
Ezetimibe	33.8	0.0	3.0
PCSK9 inhibitor	100.0	100.0	1.0

Figure S2C: Rankogram of statins, ezetimibe, PCSK9 inhibitors for TC cholesterol level. PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease.



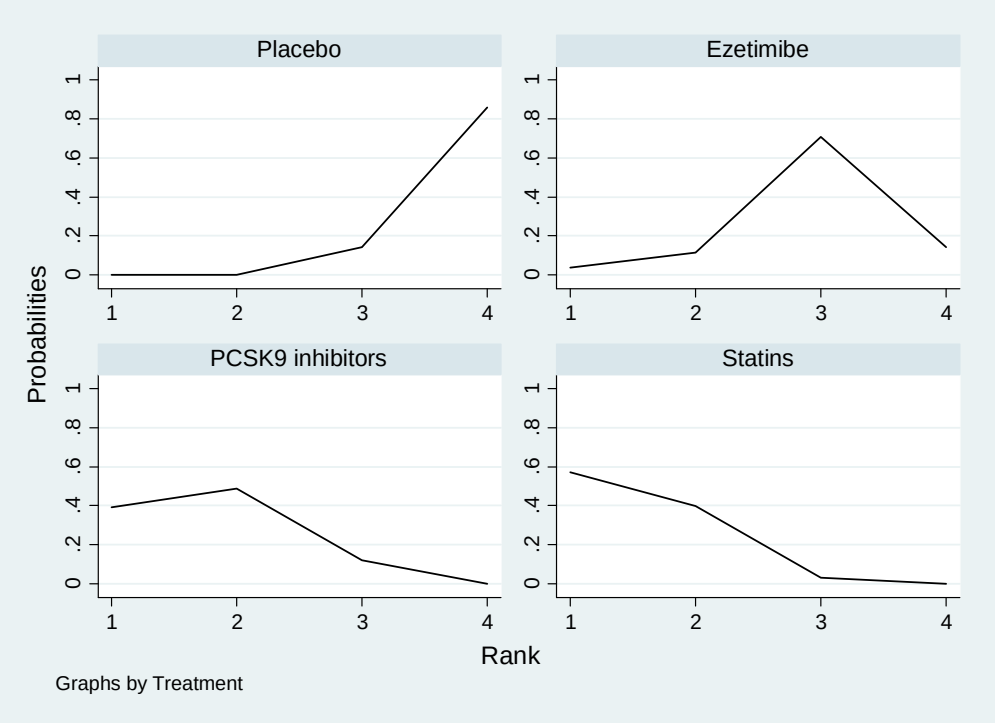
Treatment	SUCRA	PrBest	MeanRank
Placebo	0.0	0.0	4.0
Statin	66.2	0.0	2.0
Ezetimibe	33.3	0.0	3.0
PCSK9 inhibitor	100.0	100.0	1.0

Figure S3: Network comparison among statins, ezetimibe, and PCSK9 inhibitors for cardiovascular events in patients with hypercholesterolemia.



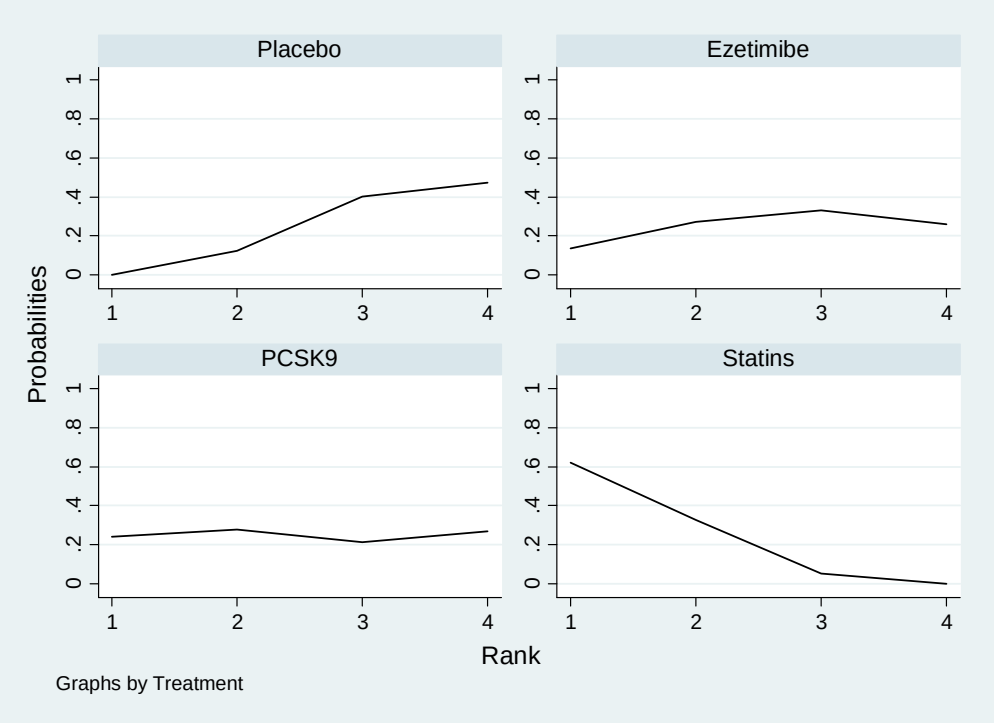
The size of the nodes (navy blue circles) is proportional to the number of trials that randomised to corresponding treatment and the thickness of lines to the number of trials that evaluated the comparison. Numbers next the line which connect two interventions refer to the number of studies that compared the interventions. PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease.

Figure S4: Rankogram of statins, ezetimibe, PCSK9 inhibitors for cardiovascular events. PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease.



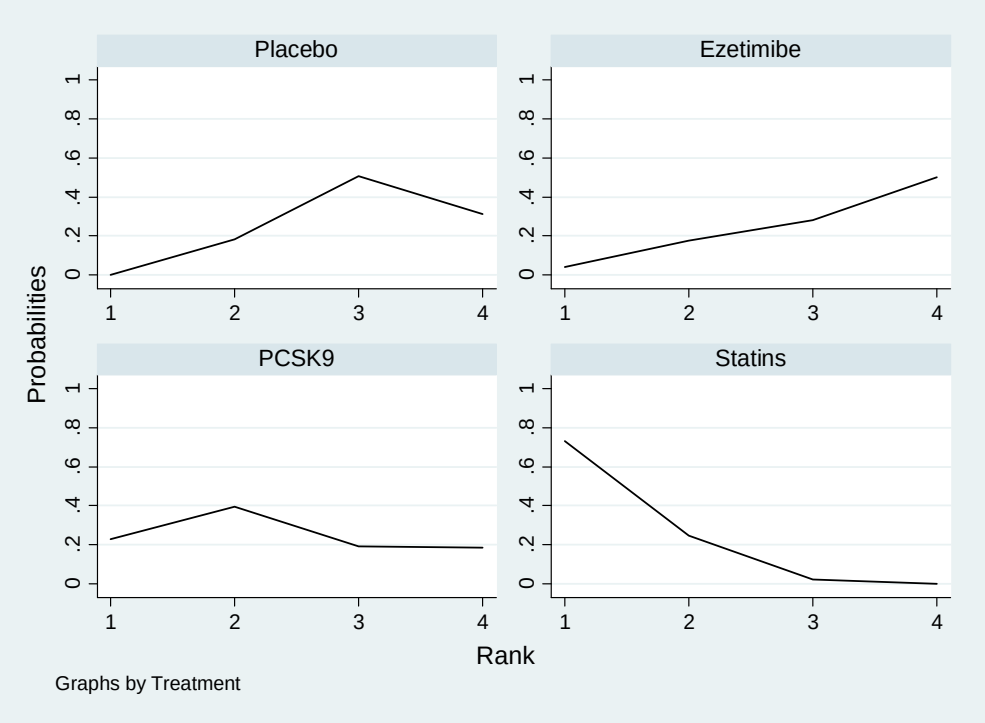
Treatment	SUCRA	PrBest	MeanRank
Placebo	4.2	0.0	3.9
Statin	85.3	59.4	1.4
Ezetimibe	35.3	3.3	2.9
PCSK9 inhibitor	75.2	37.3	1.7

Figure S5A: Rankogram of statins, ezetimibe, PCSK9 inhibitors for all-cause mortality. PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease.



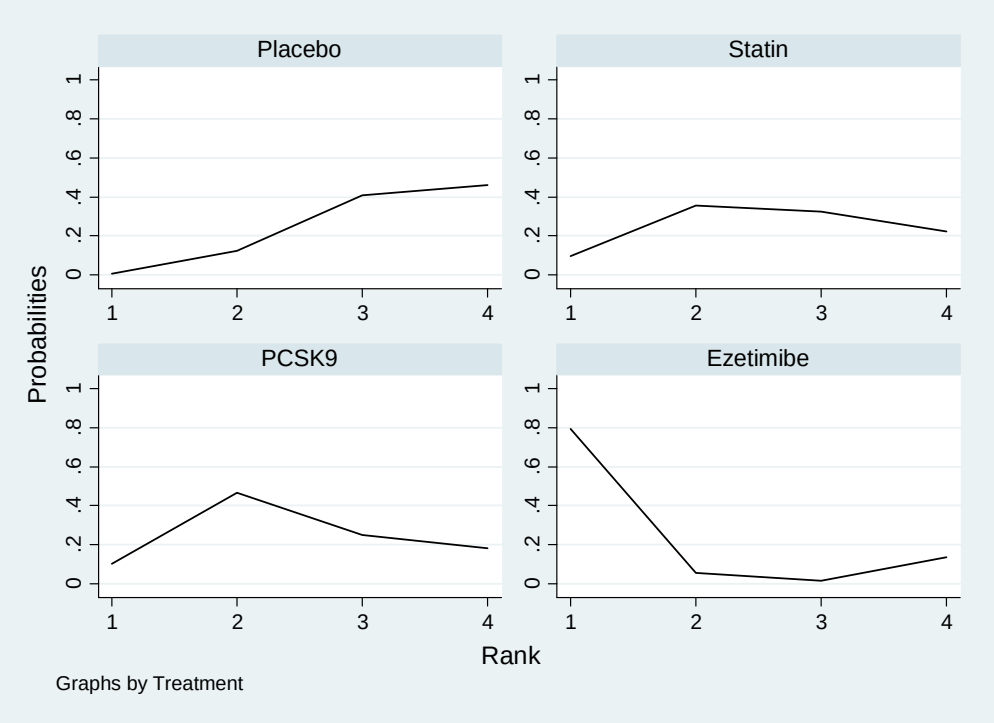
Treatment	SUCRA	PrBest	MeanRank
Placebo	21.6	0.0	3.4
Statin	85.4	62.0	1.4
Ezetimibe	42.7	12.5	2.7
PCSK9 inhibitor	50.3	25.5	2.5

Figure S5B: Rankogram of statins, ezetimibe, PCSK9 inhibitors for cardiovascular mortality. PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease.



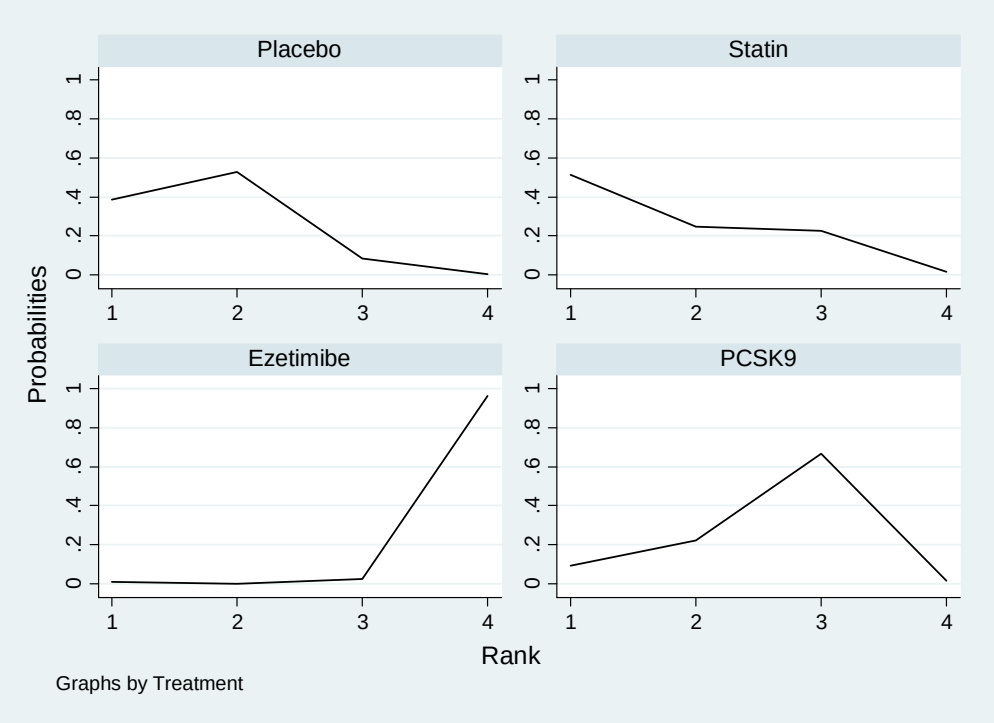
Treatment	SUCRA	PrBest	MeanRank
Placebo	30.1	0.1	3.1
Statin	91.2	75.8	1.3
Ezetimibe	25.2	4.1	3.2
PCSK9 inhibitor	53.5	20.0	2.4

Figure S6A: Rankogram of statins, ezetimibe, PCSK9 inhibitors for serious adverse events. PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease.



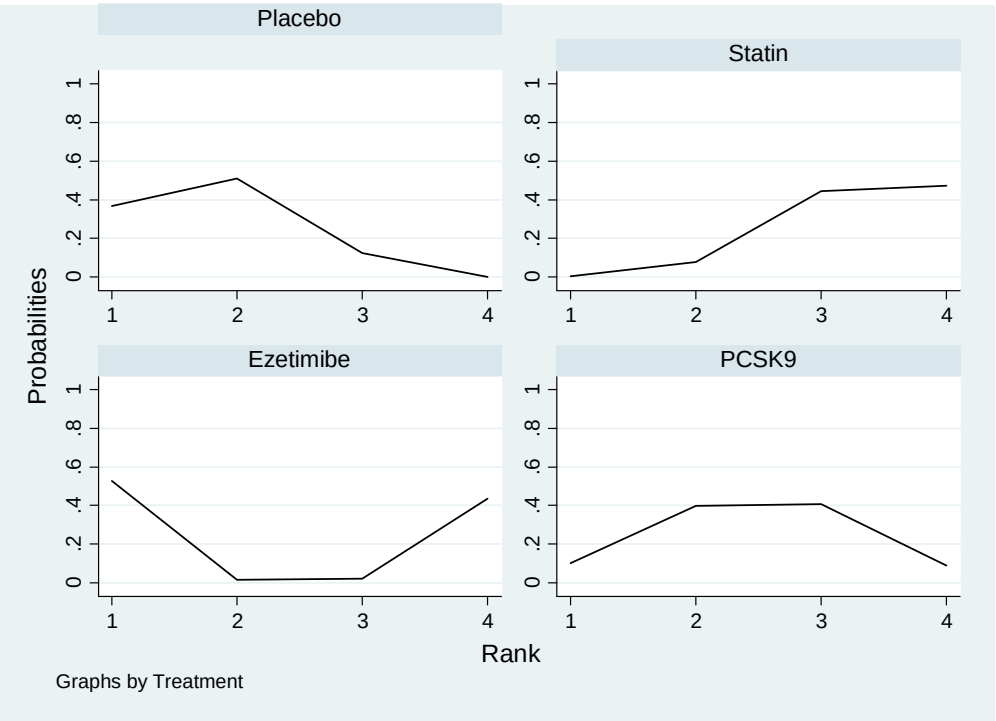
Treatment	SUCRA	PrBest	MeanRank
Placebo	22.3	1.0	3.3
Statin	43.3	9.1	2.7
Ezetimibe	83.3	79.5	1.5
PCSK9 inhibitor	51.2	10.4	2.5

Figure S6B: Rankogram of statins, ezetimibe, PCSK9 inhibitors for neurocognitive events. PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease.



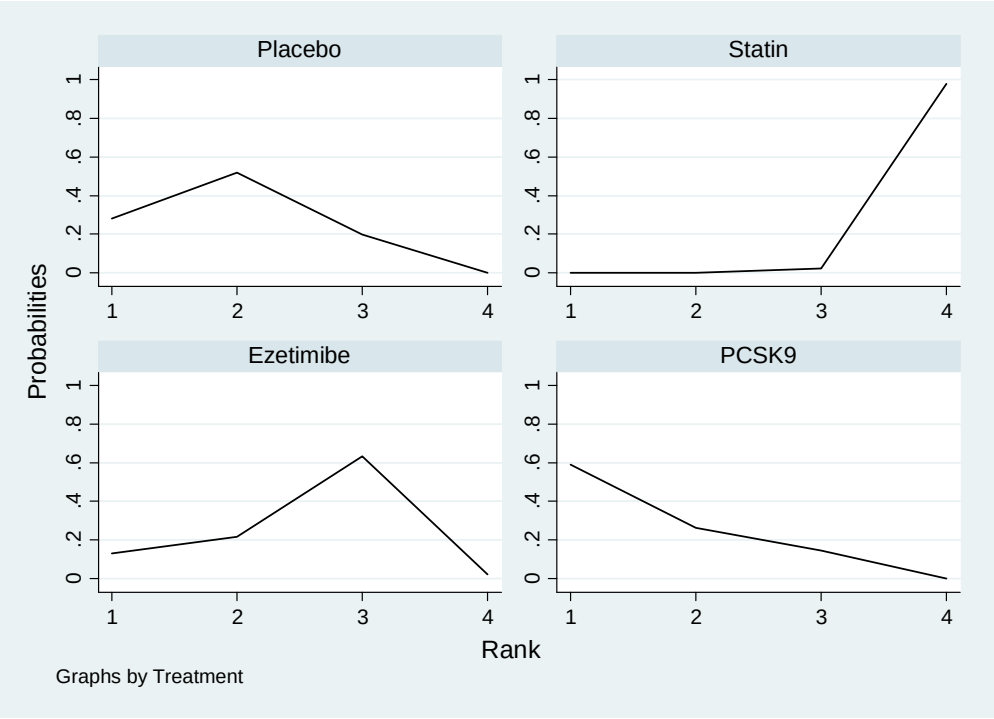
Treatment	SUCRA	PrBest	MeanRank
Placebo	75.9	38.3	1.7
Statin	75.2	51.4	1.7
Ezetimibe	2.3	0.6	3.9
PCSK9 inhibitor	46.5	9.7	2.6

Figure S7A: Rankogram of statins, ezetimibe, PCSK9 inhibitors for new-onset diabetes. PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease.



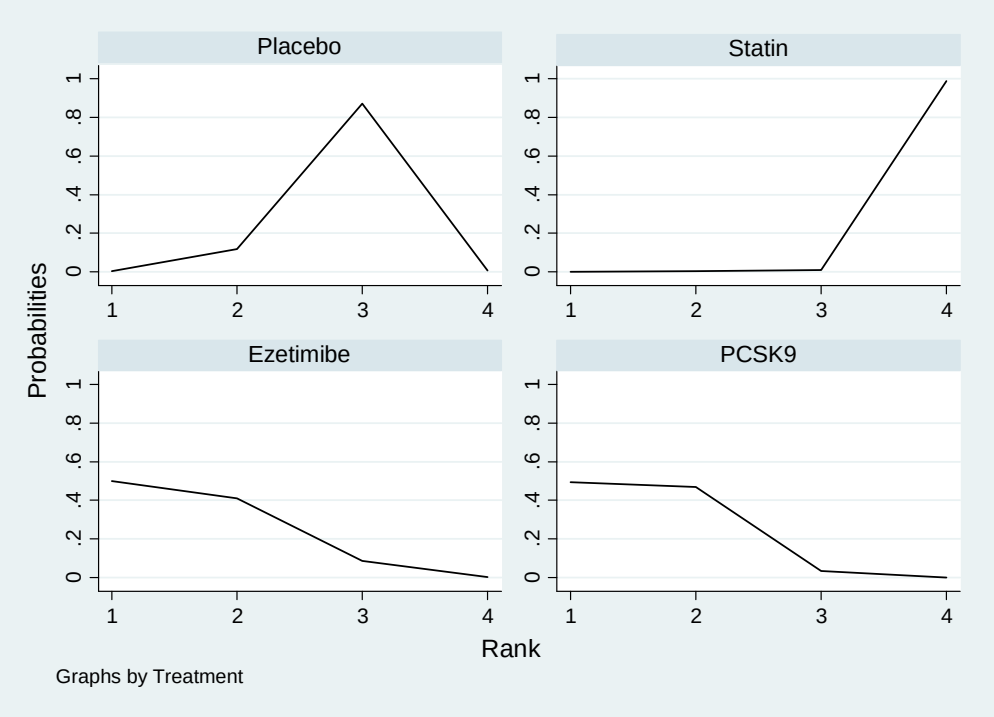
Treatment	SUCRA	PrBest	MeanRank
Placebo	62.7	20.9	2.1
Statin	15.4	0.5	3.5
Ezetimibe	56.2	54.7	2.3
PCSK9 inhibitor	65.7	23.9	2.0

Figure S7B: Rankogram of statins, ezetimibe, PCSK9 inhibitors for alanine aminotransferase. PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease.



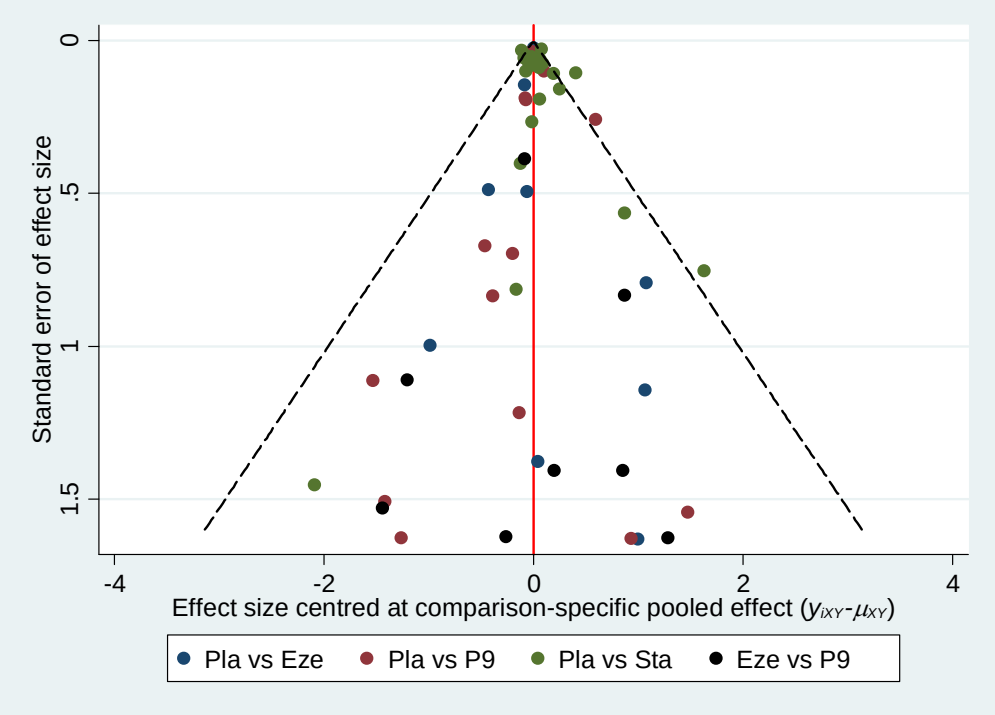
Treatment	SUCRA	PrBest	MeanRank
Placebo	68.6	25.4	1.9
Statin	0.8	0.0	4.0
Ezetimibe	48.5	15.3	2.5
PCSK9 inhibitor	82.1	59.3	1.5

Figure S7C: Rankogram of statins, ezetimibe, PCSK9 inhibitors for creatine kinase. PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease.



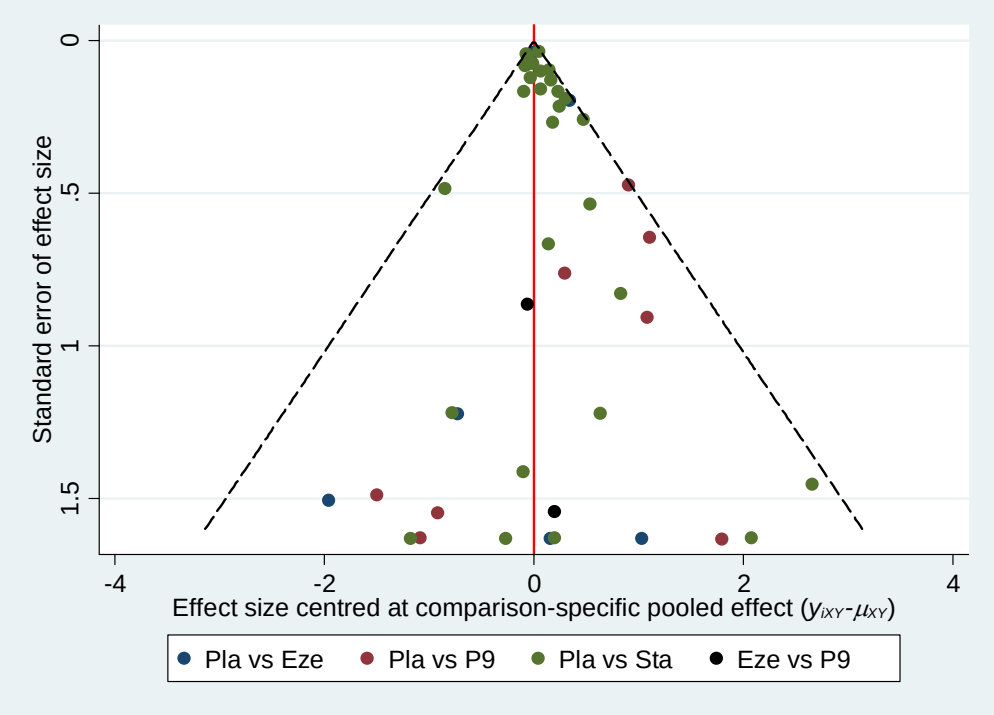
Treatment	SUCRA	PrBest	MeanRank
Placebo	37.9	1.1	2.9
Statin	0.2	0.0	4.0
Ezetimibe	79.6	48.4	1.6
PCSK9 inhibitor	82.3	50.5	1.5

Figure S8A: Comparison-adjusted funnel plot for the network of cardiovascular events. Pla = placebo, Sta = Statins, Eze = Ezetimibe, P9 = proprotein convertase subtilisin-kexin type 9 serine protease.



The red solid line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. The two black dashed lines represent a 95% CI for the difference between study-specific effect sizes and comparison-specific summary estimates. y_{ixy} is the noted effect size in study i that compares x with y. μ_{xy} is the comparison-specific summary estimate for x versus y.

Figure S8B: Comparison-adjusted funnel plot for the network of all-cause mortality. Pla = placebo, Sta = Statins, Eze = Ezetimibe, P9 = proprotein convertase subtilisin-kexin type 9 serine protease.



The red solid line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. The two black dashed lines represent a 95% CI for the difference between study-specific effect sizes and comparison-specific summary estimates. y_{ixy} is the noted effect size in study i that compares x with y. μ_{xy} is the comparison-specific summary estimate for x versus y.

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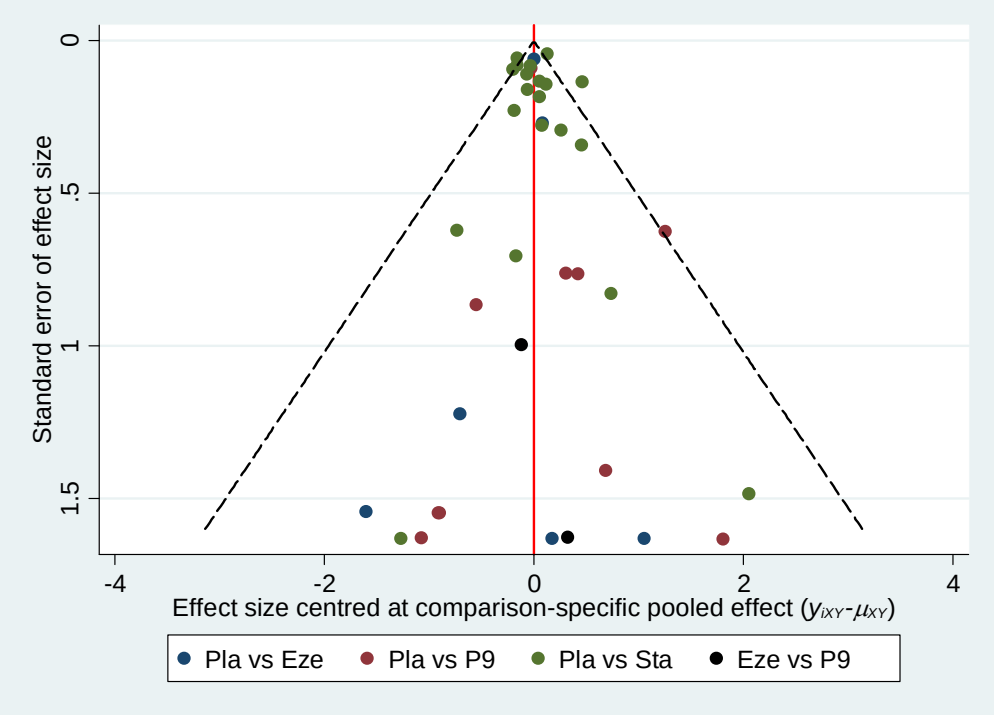
Figure S8C: Comparison-adjusted funnel plot for the network of cardiovascular mortality. Pla = placebo, Sta = Statins, Eze = Ezetimibe, P9 = proprotein convertase subtilisin-kexin type 9 serine protease.



The red solid line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. The two black dashed lines represent a 95% CI for the difference between study-specific effect sizes and comparison-specific summary estimates. y_{ixy} is the noted effect size in study i that compares x with y. μ_{xy} is the comparison-specific summary estimate for x versus y.

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