Eligible criteria

The lists of source that was processed to manual search

Table S1. PRISMA NMA Checklist

Table S2. Electronic Search Strategies.

Table S3. Basic characteristics of included trials.

Table S4. Assessment of loop inconsistency in networks.

Table S5. Assessment of global inconsistency in network using the ‘design-by-treatment’ interaction model.

Table S6. Assessment of inconsistency in network using node-splitting method.

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

Figure S2. Surface under the cumulative ranking probabilities of PCSK9 inhibitors, statins, and ezetimibe for (A) LDL cholesterol, (B) HDL cholesterol, (C) total cholesterol level. PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease.

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

Figure S4. Surface under the cumulative ranking probabilities of statins, ezetimibe, PCSK9 inhibitors for cardiovascular events. PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease.

Figure S5. Surface under the cumulative ranking probabilities of statins, ezetimibe, PCSK9 inhibitors for (A) all-cause mortality and (B) cardiovascular mortality. PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease.

Figure S6. Surface under the cumulative ranking probabilities of statins, ezetimibe, PCSK9 inhibitors for (A) serious adverse events and (B) neurocognitive events. PCSK9 = proprotein convertase subtilisin-kexin type 9 serine protease.
**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. |
| 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 |
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 bias). | 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). |
| --- | --- | --- |

**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. |
| --- | --- | --- |
| **Presentation of network structure** | **S3** | Provide a network graph of the included studies to enable visualization of the geometry of the treatment network. |
| **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. |
| 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. |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment. |
| 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.* |
| 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.* |
| **Exploration for inconsistency** | **S5** | Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency |
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. |
|-----------------------------|----|----------------------------------------------------------------------------------------------------|
| 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). |

**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). |
|---------------------|----|------------------------------------------------------------------------------------------------------------------------------------|
| 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). |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. |

**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. |
|---------|----|------------------------------------------------------------------------------------------------------------------------------------|

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.
| 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 rosvastatin: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 #16 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 | #23 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 |
'hypercholesterolaemia':ab,ti
'hypercholesteremia':ab,ti
'hyperlipidaemia':ab,ti
'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]
| 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 |
|---------------------------|---------|--------------------------|-----------------|-----------------|------------|-------------|------|---------------|-------------|-------------|-------------|---------------------------------|
| 2000, SCAT¹               | Multi-center | Simvastatin | 460             | 4               | 61         | 36          | 11   | 100           | 130         | 38          | 160         | Diet therapies                  |
| 2000, GISSI Prevention²   | 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, FAST⁴              | Single center | Pravastatin | 164             | 2               | 66.1       | 40          | 56   | NR            | 166         | 57          | 150         | Diet therapies                  |
| 2002, ALLHAT-LLT⁵         | Multi-center | Pravastatin | 10,355          | 6               | 66.4       | 100         | 35.1 | 14.2          | 146         | 48          | 150         | Usual care                      |
| 2002, GREACE⁶             | 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/BHF⁸            | Multi-center | Simvastatin | 20,536          | 5               | NR         | 41          | 19.4 | 80.6          | 132         | 41          | 280         | NR                               |
| 2002, PROSPECT³           | Multi-center | Pravastatin | 5,804           | 3.2             | 75.3       | 61.9        | 10.7 | NR            | 147         | 50          | 120         | NR                               |
| Year | Study        | Design       | Drug(s)                  | N  | LDL (%) | HDL (%) | TC (%) | HDL (%) | TG (%) | Lower Lipid Diet (%) | Lower Lipid Diet (%) | Diet Therapies | Low Lipid Diet | Statins were prescribed both in experimental and control group. | Additional Lipid-lowering treatment on the top of study drug was allowed |
|------|--------------|--------------|--------------------------|----|---------|---------|--------|---------|--------|----------------------|----------------------|-----------------|----------------|-------------------------------------------------|---------------------------------------------------------------|
| 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 |  |
| 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. |  |
| Year   | Study      | Design   | Statin(s)                           | Participants | Follow-up | HDL | LDL | TC  | TG  | LDL-CH | HDL-C | TC  | LDL-CH | HDL-C | Compliance | Notes                                                                 |
|--------|------------|----------|-------------------------------------|--------------|-----------|-----|-----|-----|-----|--------|-------|-----|--------|-------|-------------|----------------------------------------------------------------------|
| 2005   | TNT        | 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      | 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     | Single-center | Cerivastatin                       | 250          | 2         | 58.5| 50.4| 100 | 0   | 132    | 48    | 162 | NR                                              |                                                                       |
| 2005   | COMETS     | Multi-center | Rosuvastatin, Atorvastatin         | 397          | 0.1       | 57.7| NR  | 0   | 0   | 169    | 60    | 115 | Diet therapies                                                      |
| 2005   | MARS       | Multi-center | Lovastatin                          | 270          | 2         | 58  | 0   | NR  | 100 | 153    | 43    | 180 | Diet therapies                                                      |
| 2005   | AHEROMA    | Multi-center | Pravastatin                         | 361          | 3         | 59.3| 42  | 18.8| 100 | 143    | 50    | 165 | Diet therapies                                                      |
| 2006   | ASPEN      | Multi-center | Atorvastatin                        | 2,410        | 4         | 61.1| 55  | 100 | NR  | 114    | 47    | 165 | Diet therapies                                                      |
| 2007   | HYRIM      | Single-center | Fluvastatin                         | 568          | 4         | 57.2| 100 | NR  | NR  | 150    | 49    | 155 | Intensive lifestyle intervention or usual care                      |
| 2008   | JUPITER    | Multi-center | Rosuvastatin                        | 17,802       | 1.9       | 66  | 57.3| 0   | 11.5| 108    | 49    | 145 | NR                                              |                                                                       |
| 2009   | RCASS      | Multi-center | Simvastatin                         | 227          | 2         | 63  | 69.2| 91.2| 100 | 151    | 45    | 165 | NR                                              |                                                                       |
| Year       | Study Name     | Design          | Drug(s)          | n   | Mean Age | HDL   | LDL   | Triglycerides | HDL Change | LDL Change | Triglycerides Change | Treatment |
|------------|----------------|-----------------|------------------|-----|----------|-------|-------|---------------|------------|------------|-----------------------|-----------|
| 2009       | MEGA29         | Multi-center    | Pravastatin      | 3,277 | 5        | 58.5  | 100   | 20.5          | 0          | 159        | 58                   | Diet therapies |
| 2010       | SEARCH30       | Multi-center    | Simvastatin      | 12,064 | 6.7      | 64.2  | 42    | 11            | 100        | 97         | 40                   | Statins were prescribed both in experimental and control group. |
| 2010       | ASTRONOMER31   | Multi-center    | Rosuvastatin     | 269  | 3.5      | 58    | 28    | 0             | 0          | 122        | 61                   | NR        |
| 2010       | METEOR32       | Multi-center    | Rosuvastatin     | 984  | 2        | 57    | 19.9  | NR            | 10         | 155        | 50                   | NR        |
| 2016       | HOPE33         | Multi-center    | Rosuvastatin     | 12,705 | 5.6      | 65.8  | 37.9  | 5.8           | 0          | 128        | 45                   | Individualized structured lifestyle advice was provided to the participants |

**Ezetimibe-related trials**

| Year       | Study Name     | Design          | Drug(s)          | n   | Mean Age | HDL   | LDL   | Triglycerides | HDL Change | LDL Change | Triglycerides Change | Treatment |
|------------|----------------|-----------------|------------------|-----|----------|-------|-------|---------------|------------|------------|-----------------------|-----------|
| 2002       | Davidson MH et al. 34 | Multi-center    | Ezetimibe, Simvastatin | 394  | 0.2      | 57.4  | NR    | 4.6           | NR         | 179        | 51                   | Diet therapies |
| 2002       | Dujovne et al. 35  | Multi-center    | Ezetimibe        | 892  | 0.2      | 58    | 33.3  | NR            | NR         | 167        | 52                   | Diet therapies |
| 2003       | Ballantyne et al. 36 | Multi-center    | Ezetimibe, Atorvastatin | 373  | 0.2      | 57.5  | 34    | 3.5           | 9          | 180        | 53                   | Diet therapies |
| 2003       | Kerzner et      | Multi-center    | Ezetimibe        | 356  | 0.2      | 56.2  | 30.9  | 6.5           | 7          | 179        | 52                   | Diet therapies |
| Year       | Authors                  | Setting       | Type           | Study Code | Mean Age (y) | HDL (mg/dL) | LDL (mg/dL) | Non-HDL (mg/dL) | Triglycerides (mg/dL) | TG/HDL | Diet therapies | Lipid-lowering therapies |
|------------|--------------------------|---------------|----------------|-------------|--------------|-------------|-------------|---------------------|------------------------|---------|----------------|--------------------------|
| 2000       | al.37                    | Multi-center  | Lovastatin     |             |              |             |             |                     |                        |         |                | Diet therapies           |
| 2003       | Knopp et al.38           | Multi-center  | Ezetimibe      | 827         | 0.2          | 58.1        | 34.7        | 5.7                | 6.8                    | 157     | 52             | 200                      |
| 2003       | Melani et al.39          | Multi-center  | Ezetimibe, Pravastatin | 334       | 0.2          | 54.2        | 29.6        | 5.1                | 6                      | 178     | 50             | 180                      |
| 2004       | Bays et al.40            | Multi-center  | Ezetimibe, Simvastatin | 919       | 0.2          | 55.2        | 36.7        | 5.7                | 14.5                   | 178     | 52             | 160                      |
| 2004       | Feldman et al.41         | Multi-center  | Ezetimibe      | 362         | 0.4          | 63          | NR          | 47.8               | 52.2                   | 172     | 46             | 180                      |
| 2004       | Goldberg et al.42        | Multi-center  | Ezetimibe, Simvastatin | 534       | 0.2          | NR          | 31.2        | 5.6                | 6.8                    | 175     | 50             | 170                      |
| 2005       | Cruz-Fernandez et al.43  | Multi-center  | Ezetimibe      | 450         | 0.2          | 63.2        | 55.8        | 17.5               | 100                    | 122     | 52             | 150                      |
| 2005       | Masana et al.44          | Multi-center  | Ezetimibe      | 433         | 1            | 59.4        | NR          | NR                 | NR                     | 136     | 50             | 145                      |
| 2006       | Patel et al.45           | Multi-center  | Ezetimibe      | 152         | 0.1          | 65.4        | 45.4        | 3.9                | 100                    | 169     | 54             | 40                       |
| 2006       | UK-HARP-II46             | Multi-center  | Ezetimibe, Simvastatin | 203       | 0.5          | 60.0        | NR          | 10.8               | NR                     | 119     | 40             | 190                      |
| 2007       | Shankar et al.47         | Multi-center  | Ezetimibe      | 230         | 0.2          | 51.9        | 33.9        | NR                 | 73.9                   | 128     | 42             | 460                      |
| 2008       | ENHANCE48                | Multi-center  | Ezetimibe      | 720         | 1            | 45.9        | 16.4        | 1.8                | NR                     | 318     | 47             | 175                      |
| 2008       | Strony et al.49          | Multi-center  | Ezetimibe      | 109         | 1            | 57.3        | 29.4        | 5.5                | NR                     | 178     | 49             | 180                      |
| Year       | Study Type | Study Name       | Treatment                          | N     | BMI  | LDL-C | HDL-C | TG    | CR     | LDL-C  | HDL-C  | CR     | LDL-C  | HDL-C  | CR     | Setting | Lipid-lowering therapies   |
|------------|------------|------------------|------------------------------------|-------|------|-------|-------|-------|--------|--------|--------|--------|--------|--------|--------|---------|---------------------------|
| 2012       | Single     | Arimura          | Atorvastatin, Ezetimibe            | 50    | 0.5  | 68    | 75    | 30    | NR     | 100    | 50     | 150    |        |        |         |          | Lipid-lowering therapies  |
| 2015       | Multi      | IMPROVE-IT       | Ezetimibe, Simvastatin             | 18,144| 6    | 63.6  | 61.4  | 27.2  | 100    | 94     | NR     | NR     |        |        |         |          | Lipid-lowering therapies  |
| 2015       | Single     | Masuda           | Rosuvastatin, Ezetimibe             | 51    | 0.5  | 67.1  | 75    | 47.5  | 40     | 127    | 50     | 110    |        |        |         |          | Lipid-lowering therapies  |
| 2015       | Multi      | PRECISE - IVUS   | Atorvastatin, Ezetimibe             | 202   | 1    | 66.5  | 70.3  | 29.7  | 49     | 109    | 41     | 125    |        |        |         |          | Lipid-lowering therapies  |
| 2016       | Single     | Wang             | Rosuvastatin, Ezetimibe             | 98    | 1    | 64    | 49    | 35.7  | 56.1   | 137    | 44     | 70     |        |        |         |          | Lipid-lowering therapies  |
| 2016       | Multi      | HIJ-PROPER       | Ezetimibe, Pitavastatin            | 1,734 | 3.9  | 65.6  | NR    | NR    | 100    | 135    | NR     | NR     |        |        |         |          | Lipid-lowering therapies  |

**PCSK9 inhibitors-related trials**

| Year       | Study Type | Study Name       | Treatment                          | N     | BMI  | LDL-C | HDL-C | TG    | CR     | LDL-C  | HDL-C  | CR     | LDL-C  | HDL-C  | CR     | Setting | Lipid-lowering therapies   |
|------------|------------|------------------|------------------------------------|-------|------|-------|-------|-------|--------|--------|--------|--------|--------|--------|--------|---------|---------------------------|
| 2012       | Multi      | LAPLACE-TIMI 57   | Evolocumab                         | 315   | 0.2  | 63    | 70.2  | 17    | 32     | 122    | 54     | 125    |        |        |         |          | Lipid-lowering therapies  |
| 2012       | Multi      | MENDEL 57        | Evolocumab                         | 225   | 0.2  | 51    | 32.9  | 0     | NR     | 143    | 53     | 125    |        |        |         |          | Without lipid-lowering therapies |
| 2012       | Multi      | McKenney et al.  | Alirocumab                         | 62    | 0.2  | 56.6  | 48.4  | 6.5   | 6.5    | 127    | 51     | 140    |        |        |         |          | Lipid-lowering therapies  |
| 2012       | Multi      | RUTHERFORD 59    | Evolocumab                         | 112   | 0.2  | 50.6  | NR    | NR    | 21.5   | 156    | 50     | 110    |        |        |         |          | Lipid-lowering therapies  |
| 2012       | Multi      | Roth et al. 60   | Alirocumab                         | 61    | 0.2  | 56.9  | 49.2  | 16.4  | 1.5    | 123    | 55     | 125    |        |        |         |          | Lipid-lowering therapies  |
| Year          | Study Name       | Therapy                        | Dose | LDL Initial | LDL at Baseline | HDL | Triglycerides | Lp(a) | Body Mass | Therapies       |
|--------------|------------------|--------------------------------|------|-------------|----------------|-----|--------------|-------|-----------|----------------|
| 2012, Stein et al.\(^61\) | Multi-center     | Alirocumab                     | 31   | 0.2         | 54             | NR  | 0            | 35.5  | 146       | Lipid-lowering therapies |
| 2012, GAUSS\(^62\)    | Multi-center     | Evolocumab                     | 65   | 0.2         | 61             | NR  | NR           | NR    | 194       | Lipid-lowering therapies |
| 2014, DESCARTES\(^63\) | Multi-center     | Evolocumab                     | 901  | 1           | 56             | 48.6| 11.5         | 15.1  | 104       | Lipid-lowering therapies |
| 2014, YUKAWA\(^64\)  | Multi-center     | Evolocumab                     | 207  | 0.2         | 61             | 72.9| 35           | 27    | 139       | Lipid-lowering therapies |
| 2014, MENDEL-\(^2\)\(^65\) | Multi-center    | Evolocumab                     | 614  | 0.2         | 53             | 28.7| 0            | 0     | 143       | Without lipid-lowering therapies |
| 2014, LAPLACE-\(^2\)\(^66\) | Multi-center    | Evolocumab, Ezetimibe          | 1,897| 0.2         | 60             | NR  | 15           | 23    | 109       | Lipid-lowering therapies |
| 2014, GAUSS-\(^2\)\(^67\) | Multi-center     | Evolocumab                     | 307  | 0.2         | 62             | 59  | 20           | 29    | 193       | Lipid-lowering therapies |
| 2015, ODYSSEY OPTIONS I\(^68\) | Multi-center    | Alirocumab, Ezetimibe          | 206  | 0.2         | 64             | 78.6| NR           | NR    | 104       | Lipid-lowering therapies |
| 2015, ODYSSEY COMBO II\(^69\) | Multi-center    | Alirocumab, Ezetimibe          | 720  | 1           | 62             | NR  | 31           | 90    | 107       | Lipid-lowering therapies |
| 2015, ODYSSEY FHI and FHII\(^70\) | Multi-center    | Alirocumab                     | 735  | 1.5         | 52.4           | 39.6| 8.2          | 42.6  | 139       | Lipid-lowering therapies |
| 2015, ODYSSEY COMBO I\(^71\) | Multi-center     | Alirocumab                     | 316  | 1           | 63             | NR  | 43.1         | 78.2  | 102       | Lipid-lowering therapies |
| 2015, ODYSSEY       | Multi-center     | Alirocumab                     | 314  | 0.5         | 63.5           | 62.7| 23.9         | 47    | 192       | Without lipid-lowering therapies |
| Study Name | Study Type | Treatment | N | TD | LDL | HDL | Triglycerides | HDL | LDL | Triglycerides | Baseline | Follow-up | Change | Lipid-lowering therapies |
|------------|------------|-----------|---|----|-----|-----|---------------|-----|-----|---------------|----------|-----------|--------|----------------------------|
| ALTERNATIVE 2 | Multi-center | Ezetimibe | Evolocumab | 331 | 0.2 | 51.2 | NR | NR | 31.3 | 155 | 50 | 106 | lowering therapies |
| 2015, RUTHERFORD-2 | Multi-center | Ezetimibe | Evolocumab | 2,341 | 1.5 | 63.5 | NR | 23.9 | 47 | 122 | 50 | NR | Lipid-lowering therapies |
| 2015, ODYSSEY LONG TERM | Multi-center | Ezetimibe | Evolocumab | 103 | 0.5 | 60.2 | NR | 3.9 | NR | 140 | 57 | 130 | Without lipid-lowering therapies |
| 2015, ODYSSEY MONO | Multi-center | Ezetimibe | Evolocumab | 4,465 | 1 | 58 | 52 | 13 | 20 | 120 | 51 | 160 | Without lipid-lowering therapies |
| 2016, ODYSSEY OPTIONS II | Multi-center | Ezetimibe | Ezetimibe | 204 | 0.5 | 60.9 | 71.1 | 39.7 | 56.9 | 112 | 51 | 129 | Lipid-lowering therapies |
| 2016, YUKAWA-2 | Multi-center | Ezetimibe | Evolocumab | 404 | 0.2 | 61.5 | 73.5 | 48.8 | 12.9 | 106 | 57 | 123 | Lipid-lowering therapies |
| 2016, GAUSS-3 | Multi-center | Ezetimibe | Evolocumab | 218 | 0.5 | 58.8 | 51.4 | 11.9 | 31.7 | 220 | 50 | 185 | Without lipid-lowering therapies |
| 2016, ODYSSEY HIGH FH | Multi-center | Ezetimibe | Evolocumab | 107 | 0.5 | 50.6 | 57 | 14 | 49.5 | 198 | 48 | 140 | Lipid-lowering therapies |
| 2016, GLAGOV | Multi-center | Ezetimibe | Statins | 968 | 1.5 | 59.8 | 83 | 20.9 | NR | 93 | 46 | 125 | Lipid-lowering therapies |
| Year          | Study Name          | Study Type | Combination Description                  | N   | LDL (mg/dL) | HDL (mg/dL) | TRIG (mg/dL) | HDL-C (mg/dL) | HDL-C (%) | HDL-C (mg/dL) | LDL (mg/dL) | HDL-C (%) | LDL (mg/dL) | HDL-C (%) | Notes                                      |
|--------------|---------------------|------------|------------------------------------------|-----|-------------|-------------|-------------|---------------|-----------|---------------|-------------|-----------|-------------|-----------|------------------------------------------------|
| 2017, SPIRE83 | Multi-center        | Bococizumab, statins combination       | 4,449 | 1           | 61.3        | 78.3        | 53.3        | NR            | 122        | 48            | 160         | 96%       | 96%         | 96%       | 96% were receiving statin therapy at the time of enrollment |
| 2017, FOURIER84 | Multi-center       | Evolocumab, statins combination        | 27,564 | 2.2         | 62.5        | 80.1        | 36.6        | 100           | 92         | 44            | 135         | Lipid-lowering therapies                     |
| 2018, ODYSSEY OUTCOMES85 | Multi-center       | Alirocumab, 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                   | Tau²       | Outcome type (all pharmacological versus pharmacological) | Predictive distributions for Tau² | 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     |                                                           |                                   | Low                        |
| Neurocognitive events      | 0.0390     | Subjective outcomes                                       | Median=0.096; 95% Range=(0.004–2.31) | 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 |
| Side   | Direct |   | Indirect |   | Difference |   | P>|z|   |
|--------|--------|---|----------|---|------------|---|------|
|        | MD     | SE |          | MD | SE         | MD | SE   |
| 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 | 0.037616 | 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 | 1.30322 | 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 | 0.554569 | 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    | CD    | AB    | AC    | AD    | CD    | SE   | MD   | 0.491 |
|----|-------|-------|-------|-------|-------|-------|------|------|-------|
| Neurocognitive events |       |       |       |       |       |       |      |      |       |
| AB | 0.721613 | 1.242356 | -0.13848 | 0.138019 | 0.860093 | 1.248887 | 0.491 |       |       |
| AC | 0.062572 | 0.154995 | 0.285296 | 0.241511 | -0.22272 | 0.277683 | 0.423 |       |       |
| AD* | 3.475959 | 1.350241 | 0.657826 | 0.707907 | 2.818132 | 1.614286 | 0.081 |       |       |
| CD* | -1.02464 | 0.591761 | -3.39186 | 3.070773 | 2.367215 | 3.168005 | 0.455 |       |       |
| New-onset diabetes |       |       |       |       |       |       |      |      |       |
| AB | 0.687638 | 2.008324 | -1.44769 | 2.599645 | 2.135328 | 3.281716 | 0.515 |       |       |
| AC* | 0.422086 | 1.63214 | -1.71324 | 3.279906 | 2.135328 | 3.281716 | 0.515 |       |       |
| AD | 0.194735 | 0.219185 | 4.634044 | 2.307107 | -4.43931 | 2.305992 | 0.054 |       |       |
| CD* | -0.04308 | 0.356107 | 0.017 | 0.297976 | -0.06008 | 0.462232 | 0.897 |       |       |
| 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.
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 $y$. $\mu_{xy}$ 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 $y$. $\mu_{xy}$ is the comparison-specific summary estimate for $x$ versus $y$. 
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 $y$. $\mu_{xy}$ is the comparison-specific summary estimate for $x$ versus $y$. 
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