Safety of ezetimibe: A systematic review and meta-analysis

Appendix Figures and Tables

CONTENTS

Figure S1 Risk of bias graph for randomized controlled trials

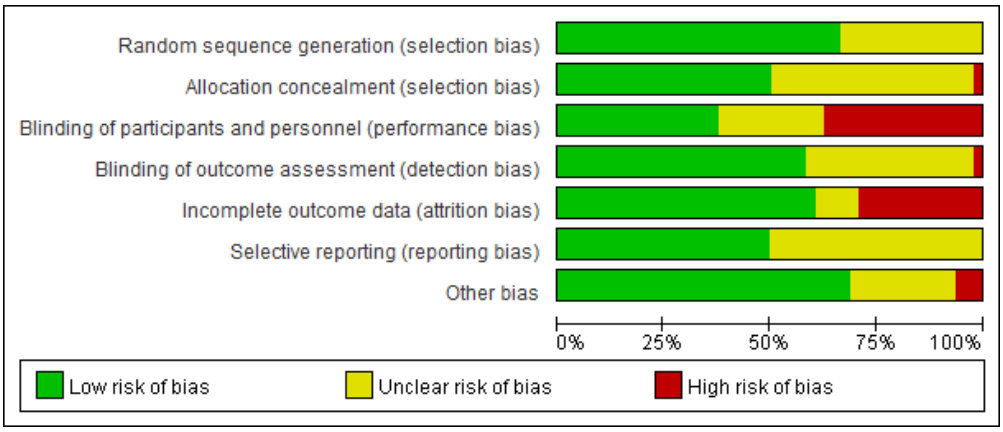


Figure S2 Risk of bias summary for randomized controlled trials

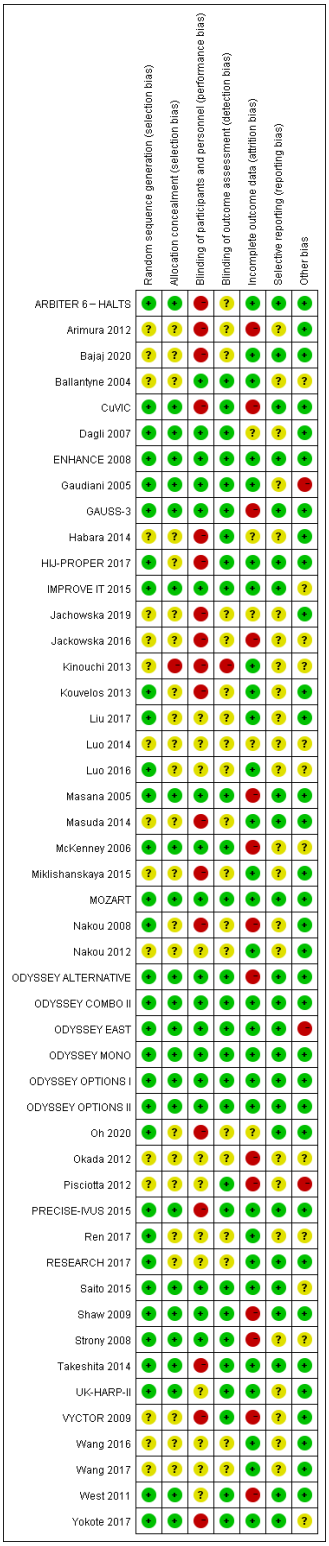
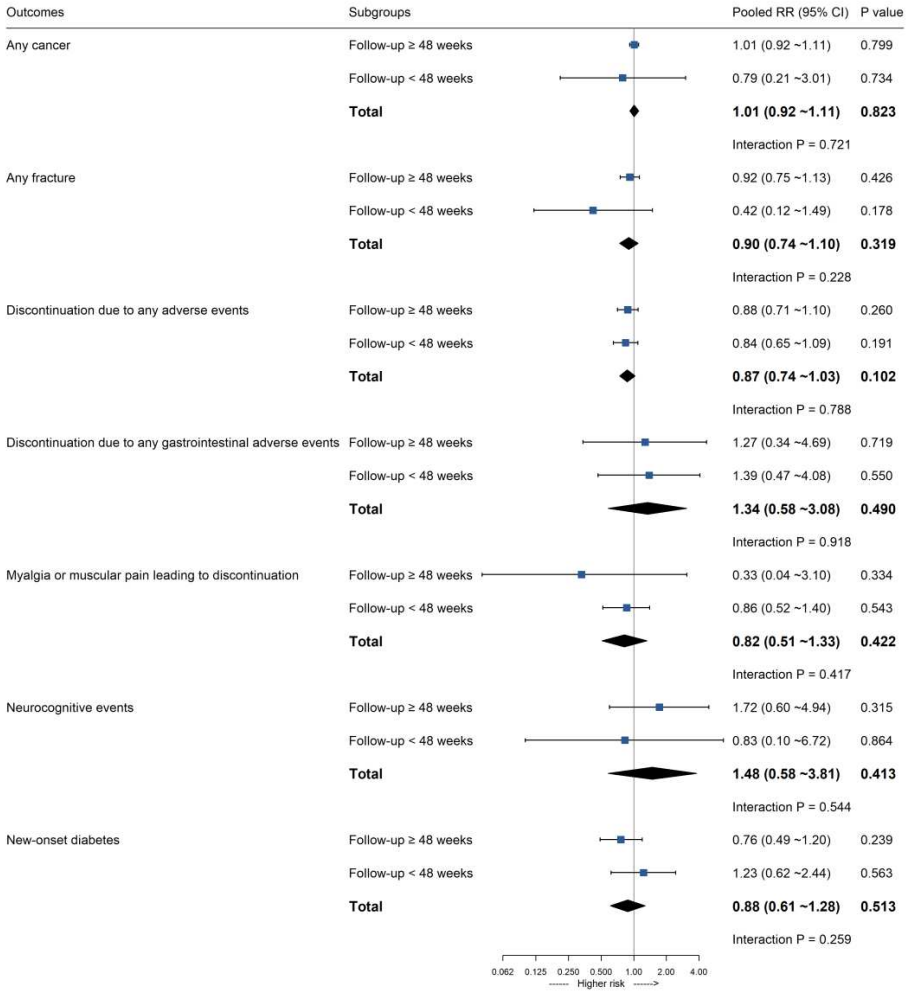
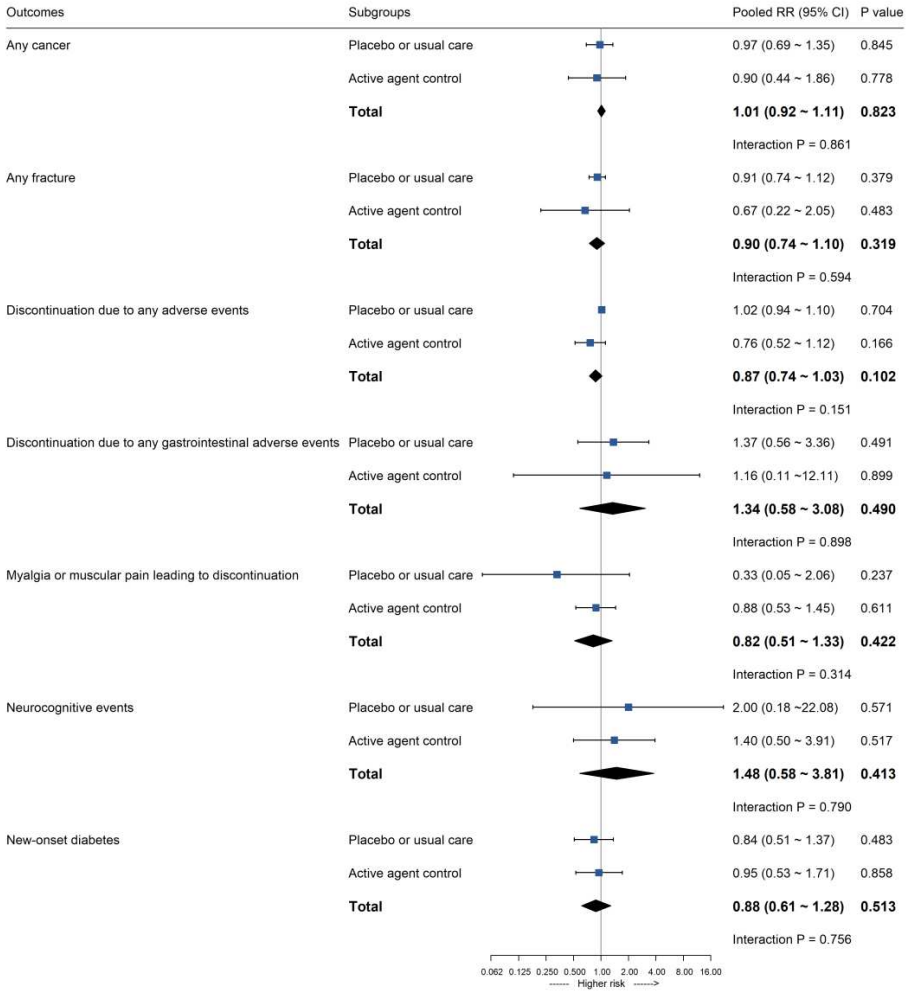


Figure S3 Subgroup analyses based on follow-up duration



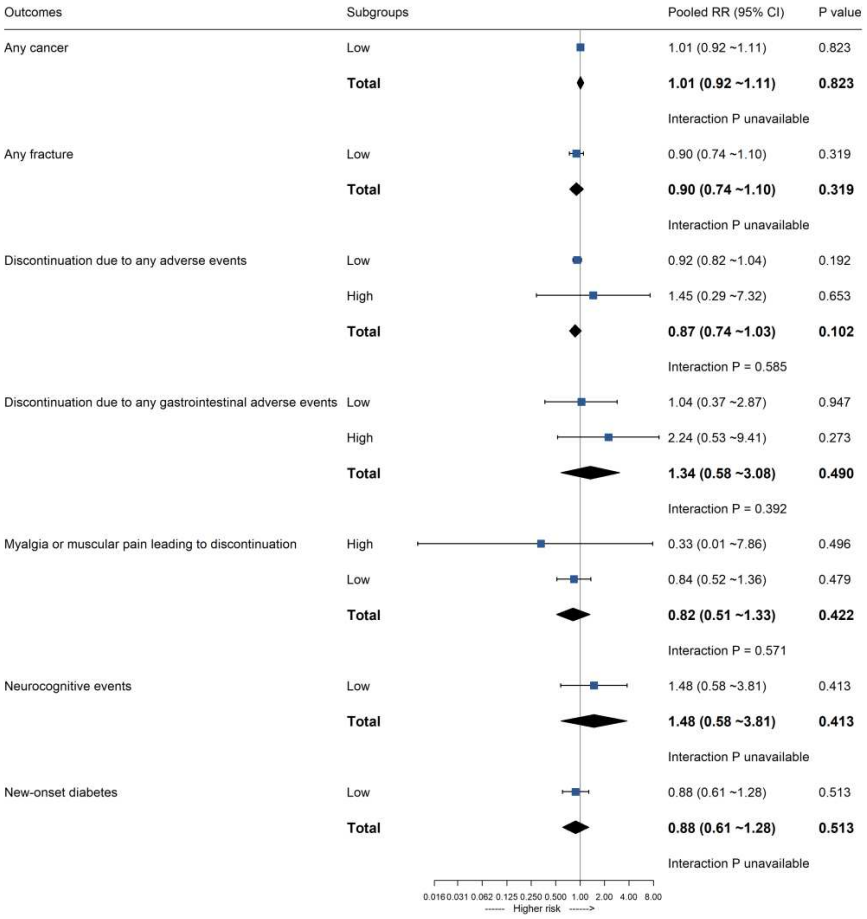
Abbreviations: CI, confidence interval; RR, relative ratio; DM, diabetes mellitus

Figure S4 Subgroup analyses based on type of control



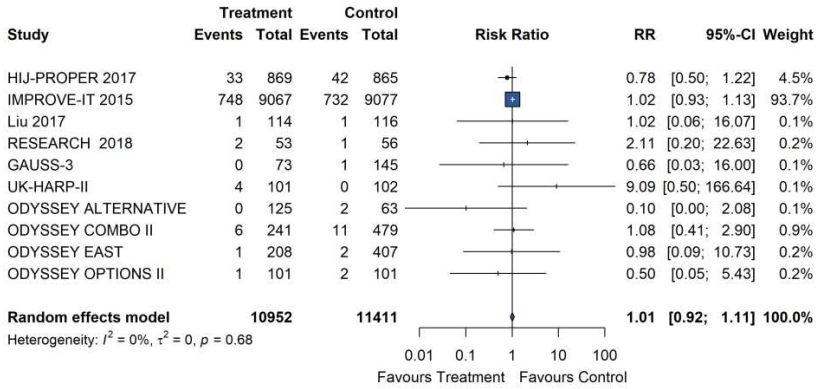
Abbreviations: CI, confidence interval; RR, relative ratio; DM, diabetes mellitus

Figure S5 Subgroup analyses based on risk of bias



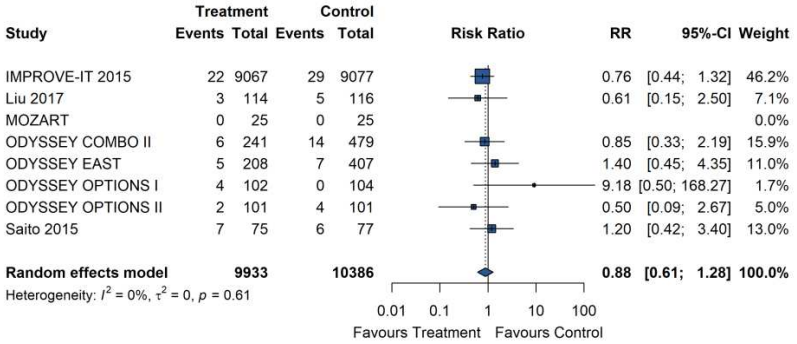
Abbreviations: CI, confidence interval; RR, relative ratio; DM, diabetes mellitus

Figure S6 Effect of ezetimibe on any cancer in randomized controlled trials



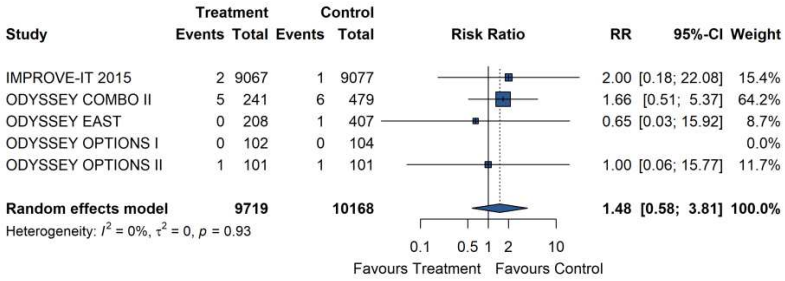
Abbreviations: CI, confidence interval; RR, relative ratio

Figure S7 Effect of ezetimibe on new-onset diabetes mellitus in randomized controlled trials



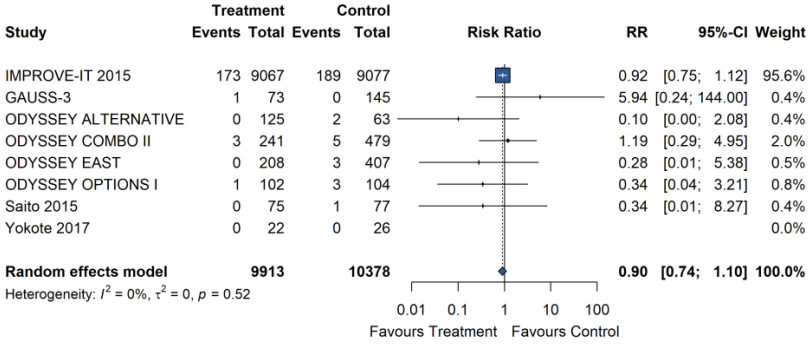
Abbreviations: CI, confidence interval; RR, relative ratio

Figure S8 Effect of ezetimibe on neurocognitive events in randomized controlled trials



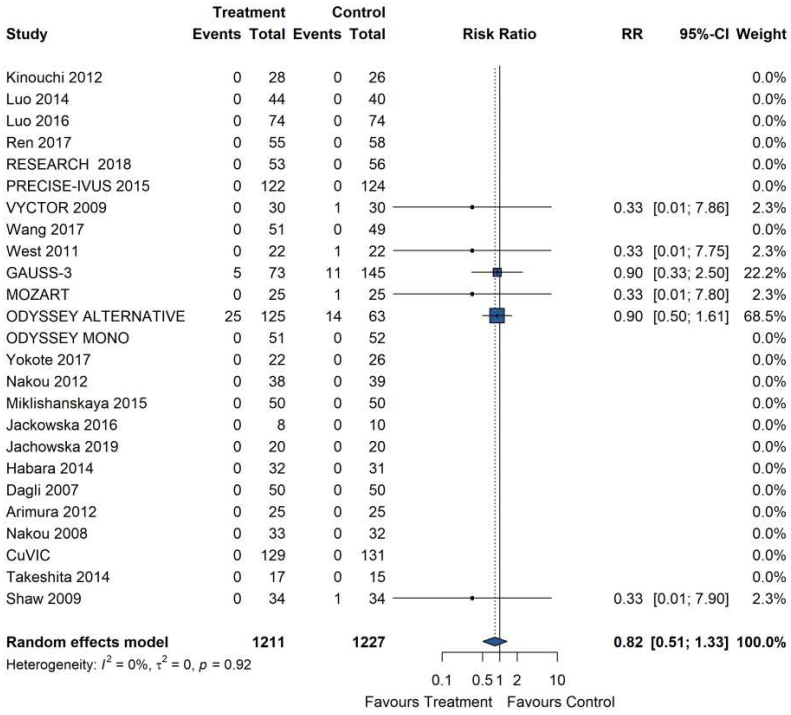
Abbreviations: CI, confidence interval; RR, relative ratio

Figure S9 Effect of ezetimibe on any fracture in randomized controlled trials



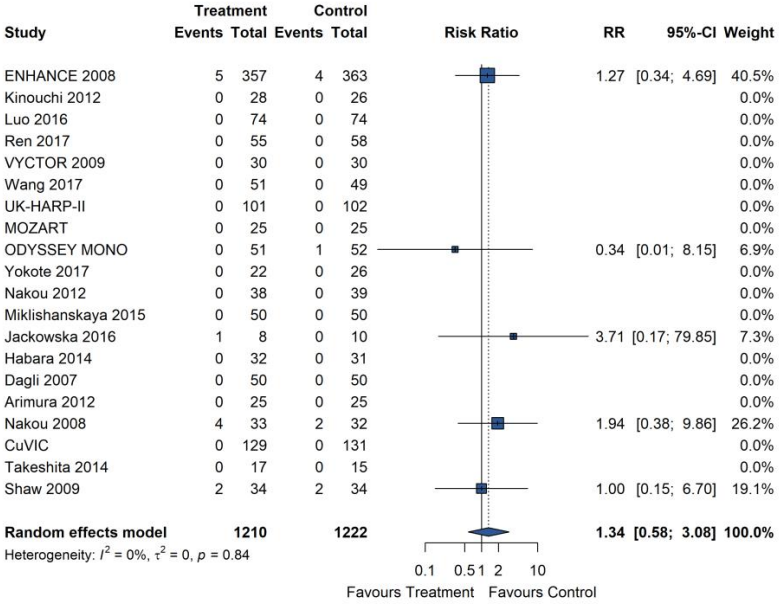
Abbreviations: CI, confidence interval; RR, relative ratio

Figure S10 Effect of ezetimibe on myalgia or muscular pain leading to discontinuation



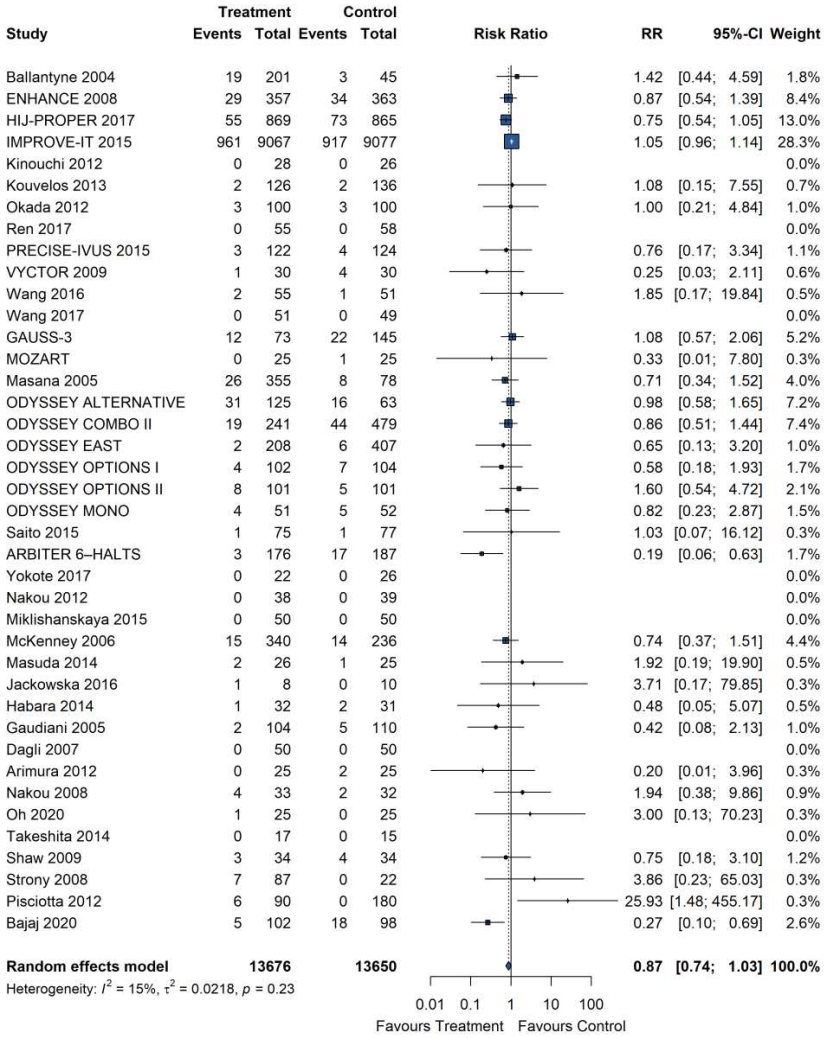
Abbreviations: CI, confidence interval; RR, relative ratio

Figure S11 Effect of ezetimibe on discontinuation due to any gastrointestinal adverse events in randomized controlled trials



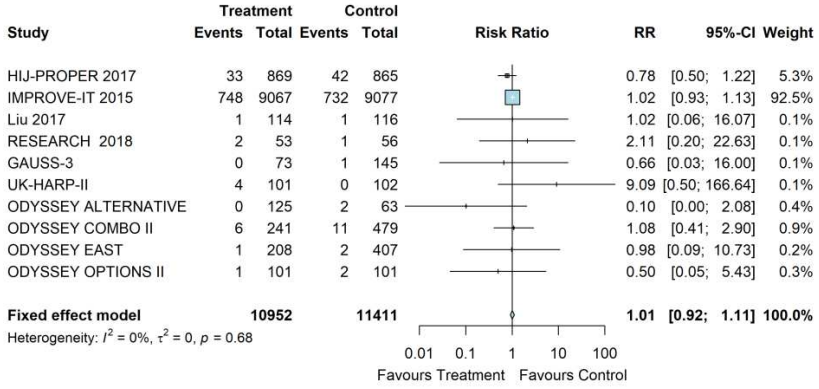
Abbreviations: CI, confidence interval; RR, relative ratio

Figure S12 Effect of ezetimibe on discontinuation due to any adverse effect in randomized controlled trials



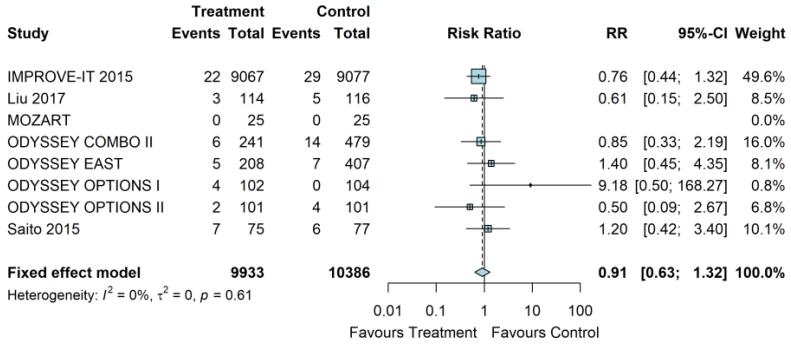
Abbreviations: CI, confidence interval; RR, relative ratio

Figure S13 Sensitivity analysis using the fixed-effect model in any cancer in randomized controlled trials



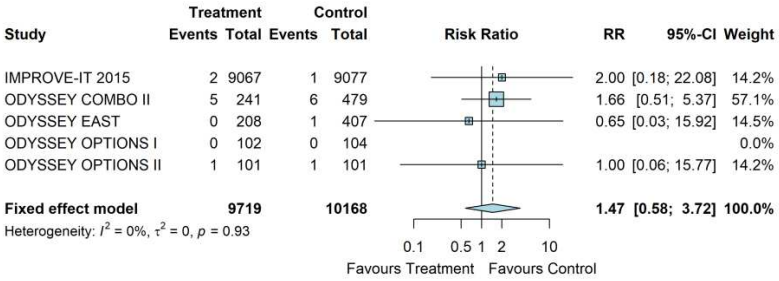
Abbreviations: CI, confidence interval; RR, relative ratio

Figure S14 Sensitivity analysis using the fixed-effect model in new-onset diabetes mellitus in randomized controlled trials



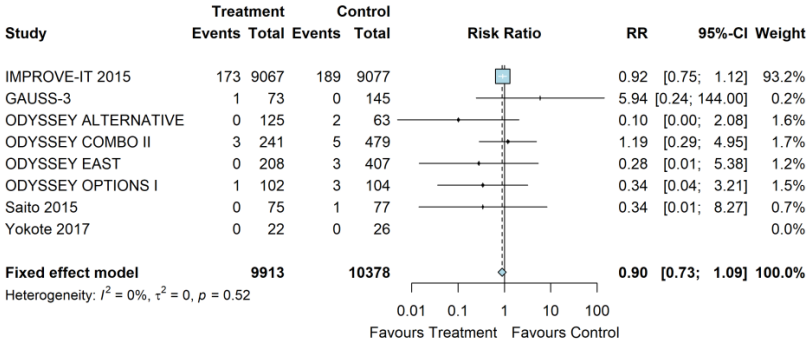
Abbreviations: CI, confidence interval; RR, relative ratio

Figure S15 Sensitivity analysis using the fixed-effect model in neurocognitive events in randomized controlled trials



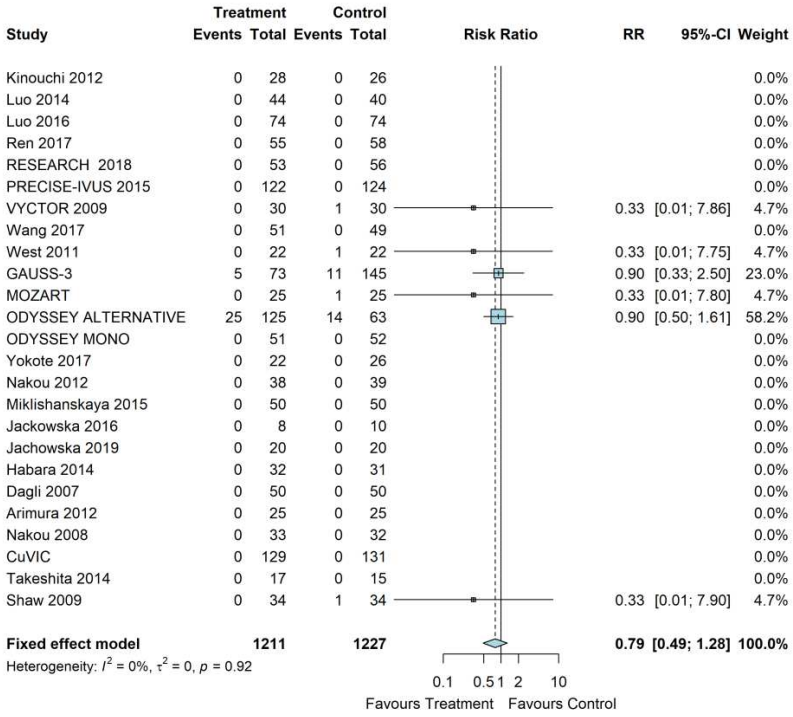
Abbreviations: CI, confidence interval; RR, relative ratio

Figure S16 Sensitivity analysis using the fixed-effect model in any fracture in randomized controlled trials



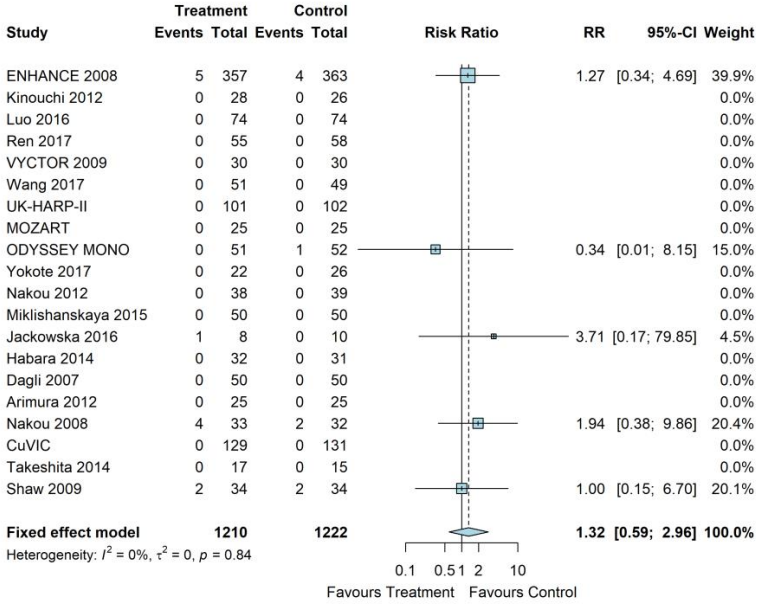
Abbreviations: CI, confidence interval; RR, relative ratio

Figure S17 Sensitivity analysis using the fixed-effect model in myalgia or muscular pain leading to discontinuation in randomized controlled trials



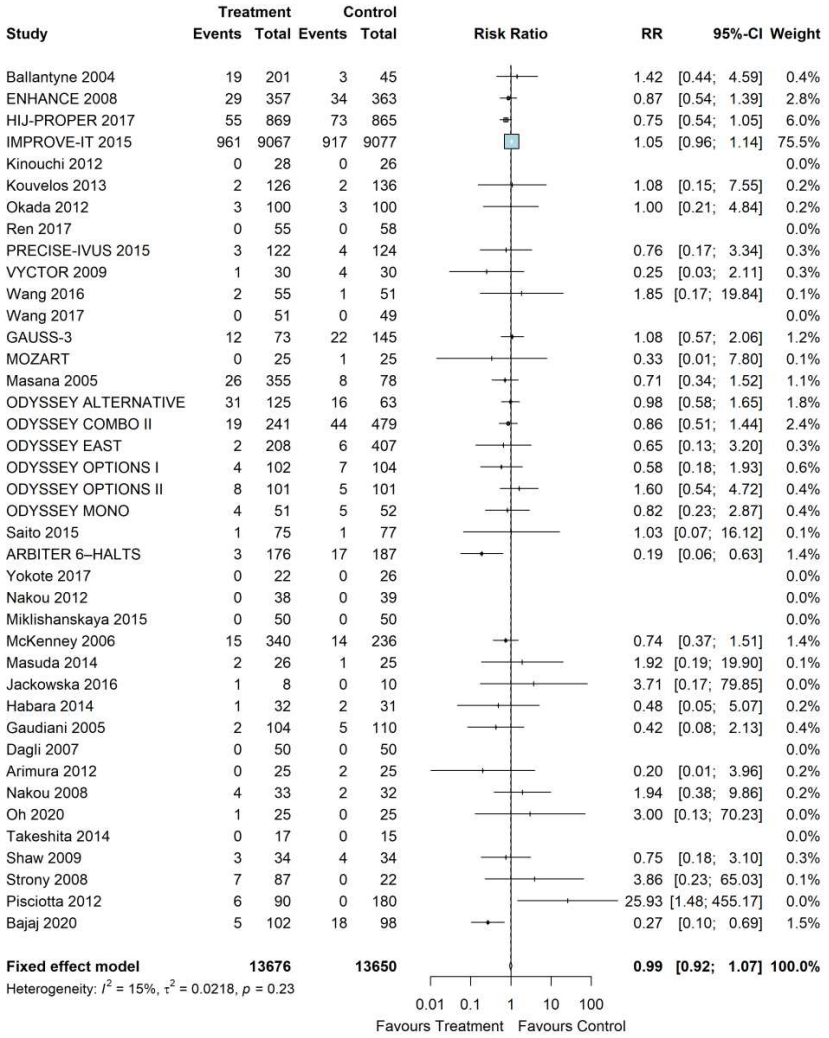
Abbreviations: CI, confidence interval; RR, relative ratio

Figure S18 Sensitivity analysis using the fixed-effect model in discontinuation due to any gastrointestinal adverse events in randomized controlled trials



Abbreviations: CI, confidence interval; RR, relative ratio

Figure S19 Sensitivity analysis using the fixed-effect model in discontinuation due to any adverse effect in randomized controlled trials



Abbreviations: CI, confidence interval; RR, relative ratio

Table S1 PRISMA checklist

Section/topic	#	Checklist item	Reported on page
TITLE			Page 1
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			Page 3
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 3
INTRODUCTION			Page 5
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 5
METHODS			Page 5-9
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 6
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.	Page 6-7
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.	Page 6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 6
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).	Page 6-7
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.	Page 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 7
Risk of bias in 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.	Page 7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 8

RESULTS			Page 9-11
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.	Page 9
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.	Page 9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 9-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 10-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page11
DISCUSSION			Page11-13
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).	Page11-12
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).	Page12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page13
FUNDING			Page13
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.	Page13

Table S2 MOOSE Checklist

#	Checklist item	Reported on Page
Reporting of background should include		
1	Problem definition	Page 5
2	Hypothesis statement	Page 5
3	Description of study outcome(s)	Page 5
4	Type of exposure or intervention used	Page 5
5	Type of study designs used	Page 5
6	Study population	Page 5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	Page 5-6
8	Search strategy, including time period included in the synthesis and keywords	Page 5-6
9	Effort to include all available studies, including contact with authors	Page 5-6
10	Databases and registries searched	Page 5-6
11	Search software used, name and version, including special features used (eg, explosion)	Page 5-6
12	Use of hand searching (eg, reference lists of obtained articles)	Page 5-6
13	List of citations located and those excluded, including justification	Page 5-6
14	Method of addressing articles published in languages other than English	Page 5-6
15	Method of handling abstracts and unpublished studies	Page 5-6
16	Description of any contact with authors	Page 5-6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Page 5-6
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Page 5-6
19	Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Page 5-6
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Page 5-6
21	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Page 5-6
22	Assessment of heterogeneity	Page 7-8
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Page 7-8
24	Provision of appropriate tables and graphics	Page 7-8
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 2
26	Table giving descriptive information for each study included	Table1
27	Results of sensitivity testing (eg, subgroup analysis)	Figure S13-19, Table S8
28	Indication of statistical uncertainty of findings	Page 9-11
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	Page 11-13
30	Justification for exclusion (eg, exclusion of non–English-language citations)	Page 11-13
31	Assessment of quality of included studies	Page 11-13
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	Page 13
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Page 13
34	Guidelines for future research	Page 13

Table S3 Search strategy for randomized controlled trials

CENTRAL (Last searching date: 9 July, 2021)

#1	MeSH descriptor: [Ezetimibe] explode all trees
#2	(ezetimibe or ezetimib)
#3	ezetrol
#4	zetia
#5	vytorin
#6	inegy
#7	SCH-58235
#8	SCH 58235
#9	SCH58235
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

MEDLINE Ovid (1946 to July 08, 2021)

1.	exp ezetimibe/
2.	(ezetimibe or ezetimib).tw.
3.	ezetrol.tw.
4.	zetia.tw.
5.	vytorin.tw.
6.	inegy.tw.
7.	SCH-58235.tw.
8.	SCH 58235.tw.
9.	SCH58235.tw.
10.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11.	randomized controlled trial.pt.
12.	controlled clinical trial.pt.
13.	randomized.ab.
14.	placebo.ab.
15.	drug therapy.fs.
16.	randomly.ab.
17.	trial.ab.
18.	groups.ab.
19.	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20.	exp animals/ not humans.sh.
21.	19 not 20
22.	10 and 21

Embase Ovid (1974 to 2021 July 08)

1.	exp ezetimibe/
2.	(ezetimibe or ezetimib).tw.
3.	ezetrol.tw.
4.	zetia.tw.
5.	vytorin.tw.
6.	inegy.tw.
7.	SCH-58235.tw.

8.	SCH 58235.tw.
9.	SCH58235.tw.
10.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11.	random$.tw.
12.	factorial$.tw.
13.	crossover$.tw.
14.	cross over$.tw.
15.	cross-over$.tw.
16.	placebo$.tw.
17.	(doubl$ adj blind$).tw.
18.	(singl$ adj blind$).tw.
19.	assign$.tw.
20.	allocat$.tw.
21.	volunteer$.tw.
22.	crossover procedure/
23.	double blind procedure/
24.	randomized controlled trial/
25.	single blind procedure/
26.	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27.	(animal/ or nonhuman/) not human/
28.	26 not 27
29.	10 and 28

ClinicalTrials.gov (Last searching date: 12 July, 2021)

Intervention:	ezetimibe
Condition:	cardiovascular OR hyperlipidemia OR dyslipidemia
Study type:	Intervention studies

Table S4 Search strategy for observational studies

MEDLINE Ovid (1946 to July 15, 2021)

1.	exp ezetimibe/
2.	(ezetimibe or ezetimib).tw.
3.	ezetrol.tw.
4.	zetia.tw.
5.	vytorin.tw.
6.	inegy.tw.
7.	SCH-58235.tw.
8.	SCH 58235.tw.
9.	SCH58235.tw.
10.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11.	exp Cohort Studies/ or cohort*.mp.
12.	exp Longitudinal Studies/ or longitudinal.mp.
13.	exp Prospective Studies/ or prospective.mp.
14.	exp Retrospective Studies/ or retrospective.mp.
15.	observational.mp. or exp Observational Study/
16.	exp Follow-up Studies/ or follow-up.mp.
17.	population-base*.mp.
18.	11 or 12 or 13 or 14 or 15 or 16 or 17
19.	10 and 18

Embase Ovid (1974 to 2021 July 15)

1.	exp ezetimibe/
2.	(ezetimibe or ezetimib).tw.
3.	ezetrol.tw.
4.	zetia.tw.
5.	vytorin.tw.
6.	inegy.tw.
7.	SCH-58235.tw.
8.	SCH 58235.tw.
9.	SCH58235.tw.
10.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11.	exp cohort analysis/ or cohort*.mp.
12.	longitudinal.mp. or exp longitudinal study/
13.	exp prospective study/ or prospective.mp.
14.	exp retrospective study/ or retrospective.mp.
15.	exp observational study/ or exp observational method/ or observational.mp.
16.	follow-up.mp. or exp follow up/
17.	population-base*.mp.
18.	11 or 12 or 13 or 14 or 15 or 16 or 17
19.	10 and 18

Table S5 Rational of excluding studies during the full-text screening of randomized controlled trials

Title	Reason for exclusion
Ezetimibe add-on to statin therapy for effectiveness trial (EASE)[1]	Follow-up duration is less than 24 weeks.
More news from IMPROVE-IT (Improved reduction of outcomes: vytorin efficacy international trial)[2]	It's an editorial.
Changes in lipoprotein lipase and endothelial lipase mass in familial hypercholesterolemia during three-drug lipid-lowering combination therapy[3]	The comparison is not eligible.
Response by takase and matoba to letter regarding article, "ezetimibe in combination with statins ameliorates endothelial dysfunction in coronary arteries after stenting: the cuvic trial (effect of cholesterol absorption inhibitor usage on target vessel dysfunction after coronary stenting), a multicenter randomized controlled trial"[4]	It's a reply.
Rationale and design of a randomized trial of automated hovering for post-myocardial infarction patients: the HeartStrong program[5]	The comparison is not eligible.
Letter by westerink and visseren regarding article, "ezetimibe in combination with statins ameliorates endothelial dysfunction in coronary arteries after stenting: the cuvic trial (effect of cholesterol absorption inhibitor usage on target vessel dysfunction after coronary stenting), a multicenter randomized controlled trial"[6]	It's a comment.
Letter by Koh Regarding Article, "Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus: results From IMPROVE-IT (Improved Reduction of Outcomes: vytorin Efficacy International Trial)"[7]	It's a comment.
Letter by Donzelli et al Regarding Article, "Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus: results From IMPROVE-IT (Improved Reduction of Outcomes: vytorin Efficacy International Trial)"[8]	It's a comment.
Letter by del pinto et al regarding article, "prevention of stroke with the addition of ezetimibe to statin therapy in patients with acute coronary syndrome in IMPROVE-IT (Improved Reduction of Outcomes: vytorin Efficacy International Trial)"[9]	It's a comment.
Letter by thomopoulos and michalopoulou regarding article, "prevention of stroke with the addition of ezetimibe to statin therapy in patients with acute coronary syndrome in IMPROVE-IT (Improved reduction of outcomes: vytorin efficacy international trial)"[10]	It's a comment.
Letter by koh regarding article, "prevention of stroke with the addition of ezetimibe to statin therapy in patients with acute coronary syndrome in IMPROVE-IT (Improved Reduction of Outcomes: vytorin Efficacy International Trial)"[11]	It's a comment.

Letter by cordero et al regarding article, "prevention of stroke with the addition of ezetimibe to statin therapy in patients with acute coronary syndrome in IMPROVE-IT (Improved reduction of outcomes: vytorin efficacy international trial)"[12]	It's a comment.
If the IMPROVE-IT Trial Was Positive, as Reported, Why Did the FDA Denied Expanded Approval for Ezetimibe and Simvastatin? An Explanation of the Tipping Point Analysis[13]	It's an editorial.
Effect of simvastatin and ezetimibe on suPAR levels and outcomes[14]	The comparison is not eligible.
Early combination therapy pays off[15]	It's not written in English.
Application of a novel UPLC-MS/MS method for the pharmacokinetic/bioequivalence determination of atorvastatin and ezetimibe in human plasma[16]	The comparison is not eligible.
Effects of lipid-lowering treatment on platelet reactivity and platelet-leukocyte aggregation in diabetic patients without and with chronic kidney disease: a randomized trial[17]	Follow-up duration is less than 24 weeks.
Effects of lipid-lowering treatment on circulating microparticles in patients with diabetes mellitus and chronic kidney disease[18]	Follow-up duration is less than 24 weeks.
Pleiotropic effects with equivalent low-density lipoprotein cholesterol reduction: comparative study between simvastatin and simvastatin/ezetimibe coadministration[19]	Follow-up duration is less than 24 weeks.
Impact of pressure recovery on echocardiographic assessment of asymptomatic aortic stenosis: a SEAS substudy[20]	The comparison is not eligible.
Goal-RCT: results from the first randomized trial comparing colesevelam vs. ezetimibe in type 2 diabetes[21]	It's a conference abstract.
Application of one-step liquid chromatography-electrospray tandem MS/MS and collision-induced dissociation to quantification of ezetimibe and identification of its glucuronated metabolite in human serum: a pharmacokinetic study[22]	The comparison is not eligible.
Efficacy of co-administered ezetimibe plus simvastatin versus atorvastatin alone in adults with hypercholesterolemia[23]	It's a conference abstract.
Efficacy and Safety of Bempedoic Acid + Ezetimibe Fixed-Dose Combination in Patients at High CVD Risk and with Elevated LDL-C Receiving Maximally Tolerated Statin Therapy[24]	It's a conference abstract.
Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial[25]	Follow-up duration is less than 24 weeks.
Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy[26]	Follow-up duration is less than 24 weeks.
Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study)[27]	Follow-up duration is less than 24 weeks.
Effects of ezetimibe on markers of synthesis and absorption of cholesterol in high-risk patients with elevated C-reactive protein[28]	Follow-up duration is less than 24 weeks.

Ezetimibe + simvastatin versus doubling the dose of simvastatin in high cardiovascular risk diabetics: a multicenter, randomized trial (the LEAD study)[29]	Follow-up duration is less than 24 weeks.
Are post-treatment low-density lipoprotein subclass pattern analyses potentially misleading?[30]	Follow-up duration is less than 24 weeks.
Efficacy and safety of ezetimibe added to atorvastatin versus atorvastatin uptitration or switching to rosuvastatin in patients with primary hypercholesterolemia[31]	Follow-up duration is less than 24 weeks.
A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia[32]	Follow-up duration is less than 24 weeks.
Effects of coadministered ezetimibe plus fenofibrate in mixed dyslipidemic patients with metabolic syndrome[33]	Follow-up duration is less than 24 weeks.
Rosuvastatin for Reduction of Myocardial Damage during Coronary Angioplasty - the Remedy Trial[34]	Follow-up duration is less than 24 weeks.
LDL-C goal attainment with the addition of ezetimibe to ongoing simvastatin treatment in coronary heart disease patients with hypercholesterolemia[35]	Follow-up duration is less than 24 weeks.
Does ENHANCE diminish confidence in lowering LDL or in ezetimibe?[36]	It's a comment.
Efficacy of ezetimibe/simvastatin 10/40 mg compared to doubling the dose of low-, medium- and high-potency statin monotherapy in patients with a recent coronary event[37]	Follow-up duration is less than 24 weeks.
Ezetimibe plus a statin after acute coronary syndromes[38]	It's a comment.
Efficacy of cholesterol uptake inhibition added to statin therapy among subjects following a low-carbohydrate diet: a randomized controlled trial[39]	Follow-up duration is less than 24 weeks.
Design and rationale of the GAUSS-2 study trial: a double-blind, ezetimibe-controlled phase 3 study of the efficacy and tolerability of evolocumab (AMG 145) in subjects with hypercholesterolemia who are intolerant of statin therapy[40]	Follow-up duration is less than 24 weeks.
Ezetimibe effectively decreases LDL-cholesterol in HIV-infected patients[41]	Follow-up duration is less than 24 weeks.
Ezetimibe: clinical and scientific meaning of the IMPROVE-IT study[42]	It's a comment.
Ezetimibe plus a statin after acute coronary syndromes[43]	It's a comment.
Efficacy and safety of ezetimibe coadministered with statins: randomised, placebo-controlled, blinded experience in 2382 patients with primary hypercholesterolemia[44]	Follow-up duration is less than 24 weeks.
Inhibition of intestinal cholesterol absorption with ezetimibe increases components of reverse cholesterol transport in humans[45]	Follow-up duration is less than 24 weeks.
A randomised placebo-controlled double-blind trial to evaluate lipid-lowering pharmacotherapy on proteolysis and inflammation in abdominal aortic aneurysms[46]	Follow-up duration is less than 24 weeks.
Ezetimibe added to ongoing statin therapy improves LDL-C goal attainment and lipid profile in patients with diabetes or metabolic syndrome[47]	Follow-up duration is less than 24 weeks.

Cholesterol lowering and ezetimibe[48]	It's an editorial.
Open-label therapy with alirocumab in patients with heterozygous familial hypercholesterolemia: results from three years of treatment[49]	The comparison is not eligible.
Ezetimibe plus a statin after acute coronary syndromes[50]	It's a comment.
Safety and efficacy of ezetimibe monotherapy in 1624 primary hypercholesterolaemic patients for up to 2 years[51]	The comparison is not eligible.
Effect of Combination Therapy of Ezetimibe and Atorvastatin on Remnant Lipoprotein Versus Double Atorvastatin Dose in Egyptian Diabetic Patients[52]	Follow-up duration is less than 24 weeks.
Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals[53]	Follow-up duration is less than 24 weeks.
Effects of four antiplatelet/statin combined strategies on immune and inflammatory responses in patients with acute myocardial infarction undergoing pharmacoinvasive strategy: design and rationale of the B and T Types of Lymphocytes Evaluation in Acute Myocardial Infarction (BATTLE-AMI) study: study protocol for a randomized controlled trial[54]	The comparison is not eligible.
Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia[55]	Follow-up duration is less than 24 weeks.
Efficacy and safety of ezetimibe co-administered with ongoing atorvastatin therapy in achieving low-density lipoprotein goal in patients with hypercholesterolemia and coronary heart disease[56]	Follow-up duration is less than 24 weeks.
A randomized placebo-controlled double-blind trial to evaluate ezetimibe combination therapy on abdominal aortic aneurysm wall proteolysis and inflammation[57]	It's a conference abstract.
Endothelial Effect of Statin Therapy at a High Dose Versus Low Dose Associated with Ezetimibe[58]	Follow-up duration is less than 24 weeks.
Statin Therapy with Ezetimibe or Niacin in High-Risk Patients[59]	It's an editorial.
Vascular and metabolic effects of ezetimibe combined with simvastatin in patients with hypercholesterolemia[60]	Follow-up duration is less than 24 weeks.
Pathologic Intimal Thickening Plaque Phenotype: not as Innocent as Previously Thought. A Serial 3D Intravascular Ultrasound Virtual Histology Study[61]	It's not a RCT.
Treatment of alopecia areata with simvastatin/ezetimibe[62]	It's not a RCT.
Effect of Switching From Statin Monotherapy to Ezetimibe/Simvastatin Combination Therapy Compared With Other Intensified Lipid-Lowering Strategies on Lipoprotein Subclasses in Diabetic Patients With Symptomatic Cardiovascular Disease[63]	Follow-up duration is less than 24 weeks.
The effects of low-dose simvastatin and ezetimibe compared to high-dose simvastatin alone on post-fat load endothelial function in patients with metabolic syndrome: a randomized double-blind crossover trial[64]	Follow-up duration is less than 24 weeks.

Pharmacokinetic and pharmacodynamic interactions between the immunosuppressant sirolimus and the lipid-lowering drug ezetimibe in healthy volunteers[65]	Follow-up duration is less than 24 weeks.
Drug interactions between the immunosuppressant tacrolimus and the cholesterol absorption inhibitor ezetimibe in healthy volunteers[66]	Follow-up duration is less than 24 weeks.
Pharmacokinetic bioequivalence crossover study of branded generic and innovator formulations of the cholesterol lowering agent ezetimibe[67]	The comparison is not eligible.
Ezetimibe plus a statin after acute coronary syndromes[68]	It's a comment.
A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial[69]	Follow-up duration is less than 24 weeks.
Attainment of LDL-cholesterol treatment goals in patients with familial hypercholesterolemia: 5-year SAFEHEART registry follow-up[70]	It's a cohort study.
Long-term treatment with evolocumab added to conventional drug therapy, with or without apheresis, in patients with homozygous familial hypercholesterolaemia: an interim subset analysis of the open-label TAUSSIG study[71]	It's a non-randomised trial.
Relationship Between Low-Density Lipoprotein Cholesterol, Free Proprotein Convertase Subtilisin/Kexin Type 9, and Alirocumab Levels After Different Lipid-Lowering Strategies[72]	Follow-up duration is less than 24 weeks.
Ezetimibe plus a statin after acute coronary syndromes[73]	It's a comment.
The efficacy of statin monotherapy uptitration versus switching to ezetimibe/simvastatin: results of the EASEGO study[74]	Follow-up duration is less than 24 weeks.
A comparison of efficacy and safety of an ezetimibe/simvastatin combination compared with other intensified lipid-lowering treatment strategies in diabetic patients with symptomatic cardiovascular disease[75]	Follow-up duration is less than 24 weeks.
Effects of combined ezetimibe and simvastatin therapy as compared with simvastatin alone in patients with type 2 diabetes: a prospective randomized double-blind clinical trial[76]	Follow-up duration is less than 24 weeks.
Effects of combined ezetimibe and simvastatin therapy as compared with simvastatin alone in patients with type 2 diabetes: a prospective randomized double-blind clinical trial[77]	It's a comment.
Ezetimibe plus a statin after acute coronary syndromes[78]	It's a comment.
Development of a joint population pharmacokinetic model of ezetimibe and its conjugated metabolite[79]	Follow-up duration is less than 24 weeks.
Tolerability and effects on lipids of ezetimibe coadministered with pravastatin or simvastatin for twelve months: results from two open-label extension studies in hypercholesterolemic patients[80]	The comparison is not eligible.
Treatment with ETC-1002 alone and in combination with ezetimibe lowers LDL cholesterol in hypercholesterolemic patients with or without statin intolerance[81]	Follow-up duration is less than 24 weeks.

Ezetimibe provides incremental reduction in risk for cardiovascular events and need for revascularisation following an acute coronary syndrome[82]	It's a comment.
Priority Paper Evaluation: are antibodies against PCSK9 the statins of the 21st century?[83]	It's a comment.
Ezetimibe/simvastatin or atorvastatin for the treatment of hypercholesterolemia in patients with the metabolic syndrome: the VYMET study[84]	It's a comment.
Letter by Weingärtner et al regarding article, "combined effects of ezetimibe and phytosterols on cholesterol metabolism: a randomized, controlled feeding study in humans"[85]	It's a comment.
Endothelial progenitor cell levels in obese men with the metabolic syndrome and the effect of simvastatin monotherapy vs. simvastatin/ezetimibe combination therapy[86]	Follow-up duration is less than 24 weeks.
Ezetimibe alone reduces low-density lipoprotein cholesterol in HIV-infected patients receiving combination antiretroviral therapy[87]	Follow-up duration is less than 24 weeks.
Comparison of statin plus ezetimibe with double-dose statin on lipid profiles and inflammation markers[88]	Follow-up duration is less than 24 weeks.
Lack of pharmacokinetic interaction of mipomersen sodium (ISIS 301012), a 2′-O-methoxyethyl modified antisense oligonucleotide targeting apolipoprotein B-100 messenger RNA, with simvastatin and ezetimibe[89]	Follow-up duration is less than 24 weeks.
Colesevelam HCl and ezetimibe combination therapy provides effective lipid-lowering in difficult-to-treat patients with hypercholesterolemia[90]	Follow-up duration is less than 24 weeks.
Lack of pharmacokinetic interaction of mipomersen sodium (ISIS 301012), a 2'-O-methoxyethyl modified antisense oligonucleotide targeting apolipoprotein B-100 messenger RNA, with simvastatin and ezetimibe[91]	Follow-up duration is less than 24 weeks.
Pharmacokinetics and exploratory efficacy biomarkers of bococizumab, an anti-PCSK9 monoclonal antibody, in hypercholesterolemic Japanese subjects[92]	Follow-up duration is less than 24 weeks.
Fenofibric acid: In combination therapy in the treatment of mixed dyslipidemia[93]	It's not a RCT.
Comparison of statin plus ezetimibe with double-dose statin on lipid profiles and inflammation markers 11 Medical and Health Sciences 1103 Clinical Sciences[94]	Follow-up duration is less than 24 weeks.
Letter by Weingartner et al Regarding Article, "ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): A Randomized, Controlled Trial"[95]	It's a comment.
Closing the remaining evidence gap randomized controlled trial data to support statin therapy for low-Density lipoprotein >=190 mg/dL[96]	It's a comment.
The potential of mipomersen, an ApoB synthesis inhibitor, to reduce necessity for LDL-apheresis in patients with heterozygous familial hypercholesterolemia and coronary artery disease[97]	The comparison is not eligible.

Variation in Lipid-Lowering Therapy Use in Patients With Low-Density Lipoprotein Cholesterol >=190 mg/dL: Insights From the National Cardiovascular Data Registry-Practice Innovation and Clinical Excellence Registry[98]	It's a cohort study.
Relationship between "LDL-C" estimated true LDL-C, apolipoprotein B-100, and PCSK9 levels following lipoprotein(a) lowering with an antisense oligonucleotide[99]	The comparison is not eligible.
One year perspective on COURAGE[100]	It's a comment.
Regions with higher medicare Part D spending show better drug adherence, but not lower medicare costs for two diseases[101]	It's not a RCT.
Efficacy of ezetimibe is associated with gender and baseline lipid levels in patients with type 2 diabetes[102]	It's a single-arm study.
Low-density lipoprotein lowering therapy: An analysis of the options[103]	It's a comment.
Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis[104]	The comparison is not eligible.
Acute Effects of Statin Therapy on Coronary Atherosclerosis Following an Acute Coronary Syndrome[105]	The comparison is not eligible.
Effect of 1 or 2 Doses of Inclisiran on Low-Density Lipoprotein Cholesterol Levels: One-Year Follow-up of the ORION-1 Randomized Clinical Trial[106]	The comparison is not eligible.
Balancing randomized trials with anecdote[107]	It's an editorial.
Pleiotropic effects of ezetimibe/simvastatin vs. high dose simvastatin[108]	Follow-up duration is less than 24 weeks.
Changes in muscle strength in individuals with statin-induced myopathy: A summary of 3 investigations[109]	The comparison is not eligible.
The effects of low-dose simvastatin and ezetimibe compared to high-dose simvastatin alone on post-fat load endothelial function in patients with metabolic syndrome: A randomized double-blind crossover trial[110]	Follow-up duration is less than 24 weeks.
The gravity of JUPITER (justification for the use of statins in primary prevention: An Intervention Trial Evaluating Rosuvastatin)[111]	The comparison is not eligible.
Statins and familial hypercholesterolaemia[112]	It's an editorial.
Endoplasmic reticulum stress effector CCAAT/enhancer-binding protein homologous protein (CHOP) regulates chronic kidney disease-induced vascular calcification[113]	The comparison is not eligible.
Rescued by randomization (Clinical and Mendelian)[114]	It's a comment.
LDL-C goal attainment with ezetimibe plus simvastatin coadministration vs atorvastatin or simvastatin monotherapy in patients at high risk of CHD[115]	Follow-up duration is less than 24 weeks.
Impact of an Initial Strategy of Medical Therapy Without Percutaneous Coronary Intervention in High-Risk Patients From the Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation (COURAGE) Trial[116]	The comparison is not eligible.

Longitudinal assessment of carotid plaque texture in three-dimensional ultrasound images based on semi-supervised graph-based dimensionality reduction and feature selection[117]	The comparison is not eligible.
Effect of switching from statin monotherapy to ezetimibe/simvastatin combination therapy compared with other intensified lipid-lowering strategies on lipoprotein subclasses in diabetic patients with symptomatic cardiovascular disease[118]	Follow-up duration is less than 24 weeks.
Pharmacodynamic interaction between the new selective cholesterol absorption inhibitor ezetimibe and simvastatin[119]	Follow-up duration is less than 24 weeks.
Effects of atorvastatin on renal function in patients with dyslipidemia and chronic kidney disease: assessment of clinical usefulness in CKD patients with atorvastatin (ASUCA) trial[120]	The comparison is not eligible.
Effect of fixed-dose combinations of ezetimibe plus rosuvastatin in patients with primary hypercholesterolemia: MRS-ROZE (Multicenter Randomized Study of ROsuvastatin and eZEtimibe)[121]	Follow-up duration is less than 24 weeks.
Inhibition of cholesterol absorption by the combination of dietary plant sterols and ezetimibe: Effects on plasma lipid levels[122]	Follow-up duration is less than 24 weeks.
Crossing family histories of diabetes and cardiovascular disease leads to unexpected outcomes in diabetic offspring[123]	It's a cross-sectional study.
Serum cholesterol and statin use predict virological response to peginterferon and ribavirin therapy[124]	The comparison is not eligible.
After ENHANCE: The cholesterol hypothesis is alive and well[125]	It's an editorial.
Evolution of the Lipid Trial Protocol of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial[126]	The comparison is not eligible.
Safety of the combination of intensive cholesterol-lowering therapy with oral anticoagulation medication in elderly patients with atrial fibrillation: A randomized, double-blind, placebo-controlled study[127]	The comparison is not eligible.
Individualized low-density lipoprotein cholesterol reduction with alirocumab titration strategy in heterozygous familial hypercholesterolemia: Results from an open-label extension of the ODYSSEY LONG TERM trial[128]	It's a single-arm study.
Utilization patterns of extended-release niacin in Canada: Analysis of an administrative claims database[129]	It's not a RCT.
Projected coronary heart disease risk benefit with ezetimibe[130]	Follow-up duration is less than 24 weeks.
Expanding the understanding of the treatment of chronic angina: A 21st century approach - Part II[131]	It's an editorial.
Efficacy and safety of coadministration of fenofibrate and ezetimibe compared with each as monotherapy in patients with type IIb dyslipidemia and features of the metabolic syndrome: A prospective, randomized, double-blind, three-parallel arm, multicenter, comparative study[132]	Follow-up duration is less than 24 weeks.

Effects of lipid-lowering treatment on platelet reactivity and plateletleukocyte aggregation in diabetic patients without and with chronic kidney disease: A randomized trial[133]	Follow-up duration is less than 24 weeks.
Effect of ezetimibe-simvastatine over endothelial dysfunction in dyslipidemic patients: Assessment by ¹³N-ammonia positron emission tomography[134]	It's a case control study.
Is combined lipid-regulating therapy safe and feasible for the very old patients with mixed dyslipidemia?[135]	It's not a randomised controlled trial.
Intensive lipid-lowering therapy: obvious benefits, possible risks[136]	It's a case report.
Induction of microsomal triglyceride transfer protein expression is a candidate mechanism by which ezetimibe therapy might exert beneficial effects in patients with nonalcoholic steatohepatitis[137]	It's a comment.
Heterozygous Ldlr-Deficient Hamster as a Model to Evaluate the Efficacy of PCSK9 Antibody in Hyperlipidemia and Atherosclerosis[138]	Follow-up duration is less than 24 weeks.
Rapid Regression of Multiple-Site Xanthomas in an Adult With Homozygous Familial Hypercholesterolemia by Triple Lipid-Lowering Drugs[139]	It's a case report.
Effect on Fasting Serum Glucose Levels of Adding Ezetimibe to Statins in Patients With Nondiabetic Hypercholesterolemia[140]	It's a pooled analysis.
Cardiovascular Screening and Management Among Kidney Transplant Candidates in Hungary[141]	It's not a RCT.
The antilipidemic effects of ezetimibe in patients with diabetes[142]	Follow-up duration is less than 24 weeks.
Treatment of symptomatic HyperLp(a)lipoproteinemia with LDL-apheresis: a multicentre study[143]	It's not a RCT.
Use of ezetimibe during HIV infection[144]	Follow-up duration is less than 24 weeks.
Asymptomatic carotid stenosis[145]	It's a case report.
Letter to the Editor: The ezetimibe 'controversy' is a misunderstanding[146]	It's a comment.
Is carotid intima-media thickness a reliable clinical predictor?[147]	It's a review.
Hepatitis C RNA clearance after treatment with ezetimibe[148]	It's a case report.
New lipid-lowering combo proves successful[149]	It's a comment.
Making sense of ENHANCE: ezetimibe (Zetia) lowers LDL cholesterol but doesn't decrease carotid intima-media thickness[150]	It's a comment.
Inhibition of PCSK9 in familial hypercholesterolaemia[151]	It's a comment.
Letter by Settergren et al regarding article, "Evidence for statin pleiotropy in humans: differential effects of statins and ezetimibe on rho-associated coiled-coil containing protein kinase activity, endothelial function, and inflammation"[152]	It's a comment.
Differential effect of hypolipidemic drugs on lipoprotein-associated phospholipase A2[153]	It's not a RCT.
Two more drugs for dyslipidemia[154]	It's an editorial.

Colesevelam hydrochloride-ezetimibe combination lipid-lowering therapy in patients with diabetes or metabolic syndrome and a history of statin intolerance[155]	It's not a RCT.
Effects of Statins on the Development of Cataract-the Long Standing Debate[156]	It's a comment.
Effect of ezetimibe coadministered with statins in genotype-confirmed heterozygous FH patients[157]	It's not a RCT.
Reduction of ischemic events in Improved Reduction of Outcomes: Vytorin Efficacy International Trial: Intensive cholesterol lowering or ezetimibe antithrombotic effects?[158]	It's an editorial.
Biomarkers and surrogate endpoints in cardiovascular therapeutics research: under scrutiny following results of the ENHANCE Study[159]	It's a comment.
Atorvastatin in combination with ezetimibe and carotid atherosclerosis[160]	It's a comment.
Clinical usefulness of additional treatment with ezetimibe in patients with coronary artery disease on statin therapy. - From the viewpoint of cholesterol metabolism[161]	Follow-up duration is less than 24 weeks.
Ezetimibe in heart transplantation: initial experience[162]	It's a single-arm study.
Effect of ezetimibe in HCV viral load after liver transplantation[163]	It's a single-arm study.
SPG5 siblings with different phenotypes showing reduction of 27-hydroxycholesterol after simvastatin-ezetimibe treatment[164]	It's a case series.
Evaluating Statin Versus Statin Plus Ezetimibe for Coronary Plaque Regression[165]	It's a comment.
IMPROVE-IT clinical implications. Should the "high-intensity cholesterol-lowering therapy" strategy replace the "high-intensity statin therapy"[166]	It's a comment.
Treatment with ezetimibe in kidney transplant recipients with uncontrolled dyslipidemia[167]	It's a single-arm study.
Alopecia areata (AA) and treatment with simvastatin/ezetimibe: Experience of 20 patients[168]	It's a single-arm study.
Combination therapy analysis of ezetimibe and statins in Chinese patients with acute coronary syndrome and type 2 diabetes[169]	It's not a RCT.
The Effect of Ezetimibe/Statin Combination and High-Dose Statin Therapy on Thyroid Autoimmunity in Women with Hashimoto's Thyroiditis and Cardiovascular Disease: A Pilot Study[170]	It's not a RCT.
Ezetimibe - a new approach in hypercholesterolemia management[171]	It's a comment.
Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab[172]	Follow-up duration is less than 24 weeks.
Intriguing Off-Target Effects of Ezetimibe[173]	It's a comment.
Access to Nonstatin Lipid-Lowering Therapies in Patients at High Risk of Atherosclerotic Cardiovascular Disease[174]	It's not a RCT.
Low-density lipoprotein cholesterol lowering therapy and established atherosclerosis[175]	It's an editorial.
Efficacy and safety of long-term ezetimibe/simvastatin treatment in patients with familial hypercholesterolemia[176]	It's a single-arm study.
Getting there: statin plus ezetimibe for low-density lipoprotein cholesterol goals[177]	It's a comment.
Flutamide-induced photoleukomelanoderma[178]	It's a case report.

Evolocumab for the treatment of heterozygous familial hypercholesterolemia in end-stage chronic kidney disease and dialysis[179]	It's a case report.
Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) Study[180]	Follow-up duration is less than 24 weeks.
Ezetimibe, oxidized low density lipoprotein, Lp (a), and dyslipidemia[181]	It's a comment.
High-intensity statin monotherapy versus moderate-intensity statin plus ezetimibe therapy: effects on vascular biomarkers[182]	Follow-up duration is less than 24 weeks.
Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals[183]	Follow-up duration is less than 24 weeks.
Ptosis, diplopia and statins: an association?[184]	It's a case report.
Ezetimibe-induced hyperlipidaemia[185]	It's a case report.
Clinical role of a fixed combination of standardized Berberis aristata and Silybum marianum extracts in diabetic and hypercholesterolemic patients intolerant to statins[186]	It's not a RCT.
Efficacy and safety of ezetimibe/simvastatin association on non-diabetic and diabetic patients with polygenic hypercholesterolemia or combined hyperlipidemia and previously intolerant to standard statin treatment[187]	It's not a RCT.
Available oral lipid-lowering agents could bring most high-risk patients to target: an estimate based on the Dyslipidemia International Study II-Italy[188]	It's an observational study.
Modulation of adhesion molecules by cholesterol-lowering therapy in mononuclear cells from hypercholesterolemic patients[189]	It's not a RCT.
Atherosclerosis: cell biology and lipoproteins: cholesterol absorption inhibitors: gateway therapy for hypercholesterolaemia[190]	It’s an editorial.
Consistency in efficacy and safety of ezetimibe coadministered with statins for treatment of hypercholesterolemia in women and men[191]	Follow-up duration is less than 24 weeks.
Comparison of Renal Effects of Ezetimibe-Statin Combination versus Statin Monotherapy: A Propensity-Score-Matched Analysis[192]	It's a cohort study.
Safety and efficacy of combined ezetimibe/simvastatin treatment and simvastatin monotherapy in patients with non-alcoholic fatty liver disease[193]	It's not a RCT.
The effects of ezetimibe on the LDL-cholesterol particle number[194]	It's a case series.
Benefit of Targeting a LDL (Low-Density Lipoprotein) Cholesterol <70 mg/dL During 5 Years After Ischemic Stroke[195]	The comparison is not eligible.
Efficacy and Safety of Long-term Coadministration of Fenofibrate and Ezetimibe in Patients with Combined Hyperlipidemia: Results of the EFECTL Study[196]	There is no safety outcome of interest.

Influence of ezetimibe in addition to high-dose atorvastatin therapy on plaque composition in patients with ST-segment elevation myocardial infarction assessed by serial: intravascular ultrasound with iMap: the OCTIVUS trial[197]	There is no safety outcome of interest.
Effects of Ezetimibe-Statin Combination Therapy on Coronary Atherosclerosis in Acute Coronary Syndrome[198]	There is no safety outcome of interest.
Comparative efficacy and adverse effects of the addition of ezetimibe to statin versus statin titration in chronic kidney disease patients[199]	There is no safety outcome of interest.
Oxidative stress improvement is associated with increased levels of taurine in CKD patients undergoing lipid-lowering therapy[200]	There is no safety outcome of interest.
Add-on ezetimibe treatment to low-dose statins vs medium-intensity statin monotherapy in coronary artery disease patients with poorly controlled dyslipidemia[201]	Follow-up duration is less than 24 weeks.
Short-term ezetimibe is well tolerated and effective in combination with statin therapy to treat elevated LDL cholesterol in HIV-infected patients[202]	Follow-up duration is less than 24 weeks.
Ezetimibe increases intestinal expression of the LDL receptor gene in dyslipidaemic men with insulin resistance[203]	Follow-up duration is less than 24 weeks.
Effects of atorvastatin and ezetimibe on endothelial function in dyslipidemic patients with chronic kidney disease[204]	Follow-up duration is less than 24 weeks.
A multi-center, open label, crossover designed prospective study evaluating the effects of lipid lowering treatment on steroid synthesis in patients with Type 2 diabetes (MODEST Study)[205]	Follow-up duration is less than 24 weeks.
Effects of non-statin antilipemic drugs on vascular endothelial function in patients with type 2 diabetes with hypercholesterolemia[206]	Follow-up duration is less than 24 weeks.
Indices of Cholesterol Metabolism and Relative Responsiveness to Ezetimibe and Simvastatin[207]	Follow-up duration is less than 24 weeks.
Coadministration of ezetimibe with pegylated interferon plus ribavirin could improve early virological response in chronic hepatitis C obese Egyptian patients[208]	There is no safety outcome of interest.
Influence of ezetimibe on plaque morphology in patients with ST Elevation Myocardial Infarction assessed by Optical Coherence Tomography: An OCTIVUS sub-study[209]	Sub-study report of an included study, and no more interested outcome was reported.
Efficacy of Combination Therapy of Rosuvastatin and Ezetimibe vs Rosuvastatin Monotherapy on Lipid Profile of Patients with Coronary Artery Disease[210]	There is no safety outcome of interest.
Virtual histology evaluation of atherosclerosis regression during atorvastatin and ezetimibe administration: HEAVEN study[211]	The comparison is not eligible.
Plant sterol supplementation on top of lipid-lowering therapies in familial hypercholesterolemia[212]	There is no safety outcome of interest.

Usefulness of Low-Dose Statin Plus Ezetimibe and/or Nutraceuticals in Patients With Coronary Artery Disease Intolerant to High-Dose Statin Treatment[213]	The comparison is not eligible.
Usefulness of Nutraceuticals (Armolipid Plus) Versus Ezetimibe and Combination in Statin-Intolerant Patients With Dyslipidemia With Coronary Heart Disease[214]	The comparison is not eligible.
Efficacy and safety of ezetimibe 40 mg vs. ezetimibe 10 mg in the treatment of patients with homozygous sitosterolaemia[215]	There is no safety outcome of interest.
Co-administration of ezetimibe enhances proteinuria-lowering effects of pitavastatin in chronic kidney disease patients partly via a cholesterol-independent manner[216]	There is no safety outcome of interest.
A comparison of the efficacy of combined ezetimibe and statin therapy with doubling of statin dose in patients with remnant lipoproteinemia on previous statin therapy[217]	There is no safety outcome of interest.
A multi-centre, randomised, double-blind 14-week extension study examining the long-term safety and efficacy profile of the ezetimibe/simvastatin combination tablet[218]	The comparison is not eligible.
Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): a Randomized, Controlled Trial[219]	There is no safety outcome of interest.
Effect of intensive lipid-lowering therapies on cholinesterase activity in patients with coronary artery disease[220]	There is no safety outcome of interest.
Intensive statin therapy, used alone or in combination with ezetimibe, improves homocysteine level and lipid peroxidation to a similar degree in patients with coronary artery diseases[221]	There is no safety outcome of interest.
A pilot study of ezetimibe vs. atorvastatin for improving peripheral microvascular endothelial function in stable patients with type 2 diabetes mellitus[222]	There is no safety outcome of interest.
Effects of ezetimibe on visceral fat in the metabolic syndrome: a randomised controlled study[223]	There is no safety outcome of interest.
Effectiveness and safety of combinational therapy compared with intensified statin monotherapy in patients with coronary heart disease[224]	There is no safety outcome of interest.
Changes in cholesterol absorption and cholesterol synthesis caused by ezetimibe and/or simvastatin in men[225]	Follow-up duration is less than 24 weeks.
Effects of ezetimibe and simvastatin on apolipoprotein B metabolism in males with mixed hyperlipidemia[226]	Follow-up duration is less than 24 weeks.
Atorvastatin 10 mg plus ezetimibe 10 mg compared with atorvastatin 20 mg: Impact on the lipid profile in Japanese patients with abnormal glucose tolerance and coronary artery disease[227]	Follow-up duration is less than 24 weeks.
Long-term (48-week) safety of ezetimibe 10 mg/day coadministered with simvastatin compared to simvastatin alone in patients with primary hypercholesterolemia[228]	This two-phase study didn't report outcomes in each group clearly.

Table S6 Rational of excluding studies during the full-text screening of observational studies

Title	Reason for exclusion

Statins in primary biliary cirrhosis: are they safe?[229]	The comparison is ineligible.
LDL-cholesterol target attainment according to the 2011 and 2016 ESC/EAS dyslipidaemia guidelines in patients with a recent myocardial infarction - nationwide cohort study, 2013-2017.[230]	No outcome of interest was reported.
Epidemiological characteristics, management and early outcomes of acute coronary syndromes in Greece: The PHAETHON study.[231]	The comparison is ineligible.
Short-term outcome and attainment of secondary prevention goals in patients with acute coronary syndrome-Results from the countrywide TARGET study.[232]	The comparison is ineligible.
Application of the 2019 ESC/EAS dyslipidaemia guidelines to nationwide data of patients with a recent myocardial infarction: a simulation study.[233]	No outcome of interest was reported.
Use and misuse of ezetimibe: Analysis of use and cost in Saskatchewan, a Canadian jurisdiction with broad access.[234]	The comparison is ineligible.
Attainment of normal lipid levels among patients on lipid-modifying therapy in Hong Kong.[235]	The comparison is ineligible.
Diagnosis, management and prognosis of familial hypercholesterolaemia in a UK tertiary cardiac centre.[236]	The comparison is ineligible.
Statin utilization and lipid goal attainment in high or very-high cardiovascular risk patients: Insights from Italian general practice.[237]	The comparison is ineligible.
Prediction of individual life-years gained without cardiovascular events from lipid, blood pressure, glucose, and aspirin treatment based on data of more than 500 000 patients with Type 2 diabetes mellitus.[238]	The comparison is ineligible.
Prevalence and Determinants of the Use of Lipid-Lowering Agents in a Population of Older Hospitalized Patients: the Findings from the REPOSI (REgistro POliterapie Societa Italiana di Medicina Interna) Study.[239]	The comparison is ineligible.
Low-density lipoprotein cholesterol goal achievement in patients with familial hypercholesterolemia in countries outside Western Europe: The International ChoLesterol management Practice Study.[240]	No outcome of interest was reported.
Statin Discontinuation, Reinitiation, and Persistence Patterns among Medicare Beneficiaries after Myocardial Infarction: A Cohort Study.[241]	The comparison is ineligible.
Statins and other lipid-lowering therapy and pregnancy outcomes in homozygous familial hypercholesterolaemia: A retrospective review of 39 pregnancies.[242]	The comparison is ineligible.
Suboptimal control of lipid levels: Results from the non-interventional Centralized Pan-Russian Survey of the Undertreatment of Hypercholesterolemia II (CEPHEUS II).[243]	The comparison is ineligible.
The Effect of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibition on Sterol Absorption Markers in a Cohort of Real-World Patients.[244]	No outcome of interest was reported.
An innovative lipid-lowering approach to enhance attainment of low-density lipoprotein cholesterol goals.[245]	The comparison is ineligible.
Low-Density Lipoprotein Cholesterol Target Attainment in Patients Surviving an Acute Coronary Syndrome in Thailand: Results From the Dyslipidaemia International Study (DYSIS) II.[246]	The comparison is ineligible.
The association between achieving low-density lipoprotein cholesterol (LDL-C) goal and statin treatment in an employee population.[247]	The comparison is ineligible.
Longitudinal treatment patterns among US patients with atherosclerotic cardiovascular disease or familial hypercholesterolemia initiating lipid-lowering pharmacotherapy.[248]	No outcome of interest was reported.
Simulation of lipid-lowering therapy intensification in a population with atherosclerotic cardiovascular disease.[249]	No outcome of interest was reported.
Treatment and Low-Density Lipoprotein Cholesterol Management in Patients Diagnosed With Clinical Atherosclerotic Cardiovascular Disease in Alberta.[250]	The comparison is ineligible.
Contemporary use of lipid-lowering therapy for secondary prevention in Korean patients with atherosclerotic cardiovascular diseases.[251]	No outcome of interest was reported.
Ezetimibe reduces low-density lipoprotein cholesterol (LDL-C) in renal transplant patients resistant to HMG-CoA reductase inhibitors.[252]	The comparison is ineligible.
Improvement in arterial stiffness after short-term treatment with PCSK9 inhibitors.[253]	It's a case series.

Ezetimibe prescriptions in older Canadian adults after an acute myocardial infarction: A population-based cohort study.[254]	The comparison is ineligible.
Clinical Implications of Switching Lipid Lowering Treatment from Rosuvastatin to Other Agents in Primary Care.[255]	The comparison is ineligible.
Lipid Lowering Treatment and Eligibility for PCSK9 Inhibition in Post-Myocardial Infarction Patients in Italy: Insights from Two Contemporary Nationwide Registries.[256]	No outcome of interest was reported.
Statins for primary prevention and rhabdomyolysis: A nationwide cohort study in France.[257]	The comparison is ineligible.
Risk of hospitalized rhabdomyolysis associated with lipid-lowering drugs in a real-world clinical setting.[258]	No outcome of interest was reported.
Management of lipid-lowering therapy in patients with cardiovascular events in the UK: A retrospective cohort study.[259]	The comparison is ineligible.
Available oral lipid-lowering agents could bring most high-risk patients to target: an estimate based on the Dyslipidemia International Study II-Italy.[188]	The comparison is ineligible.
Waist circumference as an independent risk factor for NODAT.[260]	The comparison is ineligible.
Treatment gaps in adults with heterozygous familial hypercholesterolemia in the United States.[261]	The comparison is ineligible.
Under-prescription of statins in patients with non-alcoholic fatty liver disease.[262]	The comparison is ineligible.
Are lipid-lowering drugs associated with a risk of cataract? A pharmacovigilance study.[263]	No outcome of interest was reported.
Retrospective analysis of the effects of a highly standardized mixture of Berberis aristata, Silybum marianum, and monacolins K and KA in patients with dyslipidemia.[264]	The comparison is ineligible.
A real-world experience of clinical, biochemical and genetic assessment of patients with homozygous familial hypercholesterolemia.[265]	The comparison is ineligible.
Utilization patterns of extended-release niacin in Canada: Analysis of an administrative claims database.[129]	The comparison is ineligible.
Longitudinal low density lipoprotein cholesterol goal achievement and cardiovascular outcomes among adult patients with familial hypercholesterolemia: The CASCADE FH registry.[266]	The comparison is ineligible.
Characteristics of lipid profile and effectiveness of management of dyslipidaemia in patients with acute coronary syndromes - Data from the TERCET registry with 19,287 patients.[267]	The comparison is ineligible.
Clinical use and effectiveness of lipid lowering therapies in diabetes mellitus-an observational study from the Swedish National diabetes Register.[268]	No outcome of interest was reported.
Effect of lipid-lowering treatment on natural history of heterozygous familial hypercholesterolemia in past three decades.[269]	The comparison is ineligible.
Secondary prevention advices after cardiovascular index event: From drug prescription to risk factors control in real world practice.[270]	The comparison is ineligible.
Lipid-lowering Therapy and Goal Achievement in High-risk Patients From French General Practice.[271]	The comparison is ineligible.
Effectiveness of ezetimibe monotherapy in patients with hypercholesterolemia.[272]	The comparison is ineligible.
Cardiovascular risk in patients with familial hypercholesterolemia using optimal lipid-lowering therapy.[273]	The comparison is ineligible.
Current lipid management and low cholesterol goal attainment in common daily practice in Spain: The REALITY study.[274]	The comparison is ineligible.
SAFEHEART risk-equation and cholesterol-year-score are powerful predictors of cardiovascular events in French patients with familial hypercholesterolemia.[275]	The comparison is ineligible.
Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: Results from the Dyslipidemia International Study II.[276]	The comparison is ineligible.
Contemporary data on treatment practices for low-density lipoprotein cholesterol in 6794 patients with stable coronary heart disease across the world.[277]	The comparison is ineligible.
Safety and efficacy of combined ezetimibe/simvastatin treatment and simvastatin monotherapy in patients with non-alcoholic fatty liver disease.[193]	No outcome of interest was reported.
Comparison of renal effects of ezetimibe-statin combination versus statin monotherapy: A propensity-score-matched analysis.[278]	No outcome of interest was reported.

Attainment of multifactorial treatment targets among the elderly in a lipid clinic.[279]	No outcome of interest was reported.
How effective are the ESC/EAS and 2013 ACC/AHA guidelines in treating dyslipidemia? Lessons from a lipid clinic.[280]	No outcome of interest was reported.
Prior experience with cardiovascular medicines predicted longer persistence in people initiated to combinations of antihypertensive and lipid-lowering therapies: Findings from two australian cohorts.[281]	No outcome of interest was reported.
Demographic And Clinical Characteristics Of Patients Prescribed Proprotein Convertase Subtilisin/kexin Type 9 Inhibitor Therapy And Patients Whose Current Lipid-Lowering Therapy Was Modified.[282]	The comparison is ineligible.
Real-world data to assess changes in low-density lipoprotein cholesterol and predicted cardiovascular risk after ezetimibe discontinuation post reporting of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression trial.[283]	No outcome of interest was reported.
Simvastatin-ezetimibe combination therapy is associated with a lower rate of major adverse cardiac events in type 2 diabetics than high potency statins alone: A population-based dynamic cohort study.[284]	No outcome of interest was reported.
Low-density lipoprotein cholesterol outcomes post-non-PCSK9i lipid-lowering therapies in atherosclerotic cardiovascular disease and probable heterozygous familial hypercholesterolemia patients.[285]	No outcome of interest was reported.
Treatment patterns of lipid-lowering therapies and possible statin intolerance among statin users with clinical atherosclerotic cardiovascular disease (ASCVD) or diabetes mellitus (DM) in Taiwan.[286]	No outcome of interest was reported.
Impact of combination therapy with statin and ezetimibe on secondary prevention for post-acute myocardial infarction patients in the statin era.[287]	No outcome of interest was reported.
Long-term safety and efficacy of triple combination ezetimibe/simvastatin plus extended-release niacin in patients with hyperlipidemia.[288]	The comparison is ineligible.
Model-observational bridging study on the effectiveness of ezetimibe on cardiovascular morbidity and mortality in France: A population-based study.[289]	No outcome of interest was reported.
Changes in LDL-C levels and goal attainment associated with addition of ezetimibe to simvastatin, atorvastatin, or rosuvastatin compared with titrating statin monotherapy.[290]	No outcome of interest was reported.
Changes in LDL-C levels and goal attainment associated with addition of ezetimibe to simvastatin, atorvastatin, or rosuvastatin compared with titrating statin monotherapy.[291]	No outcome of interest was reported.
Combination Therapy With Ezetimibe/Simvastatin Versus Statin Monotherapy for Low-Density Lipoprotein Cholesterol Reduction and Goal Attainment in a Real-World Clinical Setting.[292]	No outcome of interest was reported.
Statin myopathy: A lipid clinic experience on the tolerability of statin Rechallenge.[293]	No outcome of interest was reported.
Effectiveness of adherence to lipid lowering therapy on LDL-cholesterol in patients with very high cardiovascular risk: A real-world evidence study in primary care.[294]	No outcome of interest was reported.
Observational study of ezetimibe discontinuation in primary care practices in the UK.[295]	The comparison is ineligible.
Target-attainment rates of low-density lipoprotein cholesterol using lipid-lowering drugs one year after acute myocardial infarction in Sweden.[296]	The comparison is ineligible.
Prevalence of familial hypercholesterolemia in patients with acute coronary syndrome in Japan: Results of the EXPLORE-J study.[297]	The comparison is ineligible.
Clinical and laboratory phenotype of patients experiencing statin intolerance attributable to myalgia.[298]	The comparison is ineligible.
Unmet Patient Need in Statin Intolerance: the Clinical Characteristics and Management.[299]	The comparison is ineligible.
Lipid attainment among patients newly treated with lipid-altering drugs.[300]	The comparison is ineligible.
Determinants for achieving the LDL-C target of lipid control for secondary prevention of cardiovascular events in Taiwan.[301]	The comparison is ineligible.
The use of primary care electronic health records for research: Lipid medications and mortality in elderly patients.[302]	The comparison is ineligible.

Use of ezetimibe in the United States and Canada.[303]	No outcome of interest was reported.
Impact of lipid-lowering therapy on the prevalence of dyslipidaemia in patients at high-risk of cardiovascular events in UK primary care - A retrospective database study.[304]	The comparison is ineligible.
Clinical characteristics and lipid lowering treatment of patients initiated on proprotein convertase subtilisin-kexin type 9 inhibitors: A nationwide cohort study.[305]	The comparison is ineligible.
Statins and All-Cause Mortality in Patients Undergoing Hemodialysis.[306]	The comparison is ineligible.
Discontinuation of Lipid Modifying Drugs Among Commercially Insured United States Patients in Recent Clinical Practice.[307]	No outcome of interest was reported.
Use of lipid-lowering medications and the likelihood of achieving optimal LDL-cholesterol goals in coronary artery disease patients.[308]	No outcome of interest was reported.
Non-statin lipid-lowering therapy over time in very-high-risk patients: effectiveness of fixed-dose statin/ezetimibe compared to separate pill combination on LDL-C.[309]	The comparison is ineligible.
Use of a treatment optimization algorithm involving statin-ezetimibe combination aids in achievement of guideline-based low-density lipoprotein targets in patients with dyslipidemia at high vascular risk Guideline-based Undertaking to Improve Dyslipidemia Management in Canada (GUIDANC).[310]	The comparison is ineligible.
Impact of combined lipid lowering and blood pressure control on coronary plaque: myocardial ischemia treated by percutaneous coronary intervention and plaque regression by lipid lowering and blood pressure controlling assessed by intravascular ultrasonography (MILLION) study.[311]	The comparison is ineligible.
Comparison of different statin therapy to change low-density lipoprotein cholesterol and high-density lipoprotein cholesterol level in Korean patients with and without diabetes.[312]	No outcome of interest was reported.
Utilization Patterns of Lipid-lowering Therapies in Patients With Atherosclerotic Cardiovascular Disease or Diabetes: A Population-based Study in South Korea.[313]	No outcome of interest was reported.
Persistence with statin therapy in Hungary.[314]	No outcome of interest was reported.
Low-density lipoprotein cholesterol target achievement in patients at high risk for coronary heart disease.[315]	No outcome of interest was reported.
Use of Lipid-modifying Therapy and LDL-C Goal Attainment in a High-Cardiovascular-Risk Population in the Netherlands.[316]	No outcome of interest was reported.
Latvian registry of familial hypercholesterolemia: The first report of three-year results.[317]	The comparison is ineligible.
Prevalence and extent of atherosclerotic coronary artery disease and related outcome based on coronary computed tomographic angiography in asymptomatic elderly patients: Retrospective cohort study.[318]	The comparison is ineligible.
Lipid testing trends in the us before and after the release of the 2013 cholesterol treatment guidelines.[319]	No outcome of interest was reported.
A prospective study of statin use and mortality among 67,385 blacks and whites in the southeastern United States.[320]	The comparison is ineligible.
Predictors of adverse outcome in a diabetic population following acute coronary syndromes.[321]	The comparison is ineligible.
Managing dyslipidemia in primary care with restricted access to lipid-modifying therapy.[322]	The comparison is ineligible.
Association of glycaemia with lipids in adults with type 1 diabetes: Modification by dyslipidaemia medication.[323]	The comparison is ineligible.
Use of lipid lowering drugs in patients at very high risk of cardiovascular events: An analysis on nearly 3,000,000 Italian subjects of the ARNO Observatory.[324]	No outcome of interest was reported.
Remnant lipoprotein cholesterol and mortality after acute myocardial infarction: Further evidence for a hypercholesterolemia paradox from the TRIUMPH registry.[325]	The comparison is ineligible.
Utilization of lipid-modifying therapy and low-density lipoprotein cholesterol goal attainment in patients at high and very-high cardiovascular risk: Real-world evidence from Germany.[326]	The comparison is ineligible.

Ezetimibe use and LDL-C Goal achievement: A retrospective database analysis of patients with clinical atherosclerotic cardiovascular disease or probable heterozygous familial hypercholesterolemia.[327]	The comparison is ineligible.
Vascular age derived from coronary artery calcium score on the risk stratification of individuals with heterozygous familial hypercholesterolaemia.[328]	The comparison is ineligible.
One-Year Outcomes of Patients With Established Coronary Artery Disease Presenting With Acute Coronary Syndromes.[329]	The comparison is ineligible.
Room for manoeuvre when prescribing statins to dyslipidaemic patients on antiretroviral therapy.[330]	The comparison is ineligible.
Treatment patterns, statin intolerance, and subsequent cardiovascular events among Japanese patients with high cardiovascular risk initiating statin therapy.[331]	The comparison is ineligible.
Investigation into lipid management in acute coronary syndrome patients from the EXPLORE-J study.[332]	The comparison is ineligible.
The clinical relevance of dysfunctional HDL in patients with coronary artery disease: A 3-year follow-up study.[333]	The comparison is ineligible.
Lipid-lowering treatment in hypercholesterolaemic patients: The CEPHEUS Pan-Asian survey.[334]	It's a cross-sectional study.
Long term follow-up of genetically confirmed patients with familial hypercholesterolemia treated with first and second-generation statins and then with PCSK9 monoclonal antibodies.[335]	The comparison is ineligible.
Residual inflammatory risk in coronary heart disease: incidence of elevated high-sensitive CRP in a real-world cohort.[336]	The comparison is ineligible.
Attainment of LDL-cholesterol treatment goals in patients with familial hypercholesterolemia: 5-year SAFEHEART registry follow-up.[337]	No outcome of interest was reported.
Effect of lipid-lowering treatment in cardiovascular disease prevalence in familial hypercholesterolemia.[338]	It's a case-control study.
Clinical Management of High and Very High Risk Patients with Hyperlipidaemia in Central and Eastern Europe: An Observational Study.[339]	The comparison is ineligible.
Management of High and Very High-Risk Subjects with Familial Hypercholesterolemia: Results from an Observational Study in Bulgaria.[340]	The comparison is ineligible.
Effect of ezetimibe coadministered with statins in genotype-confirmed heterozygous FH patients.[157]	No outcome of interest was reported.
Baseline glucose homeostasis predicts the new onset of diabetes during statin therapy: A retrospective study in real life.[341]	The comparison is ineligible.
Dyslipidemia and lipid-lowering treatment in a hematopoietic stem cell transplant cohort: 25 years of follow-up data.[342]	The comparison is ineligible.
Lipid-lowering treatment modifications among patients with hyperlipidemia and a prior cardiovascular event: a US retrospective cohort study.[343]	The comparison is ineligible.
Attainment of optional low-density lipoprotein cholesterol goal of less than 70 mg/dl and impact on prognosis of very high risk stable coronary patients: A 3-year follow-up.[344]	The comparison is ineligible.
Attainment of Recommended Lipid Targets in Patients With Familial Hypercholesterolemia: Real-World Experience With PCSK9 Inhibitors.[345]	The comparison is ineligible.
Effects of lifestyle counseling and combination lipid-modifying therapy on lipoprotein-associated phospholipase A2 mass concentration.[346]	The comparison is ineligible.
Improvement of low-density lipoprotein cholesterol target achievement rates through cardiac rehabilitation for patients after ST elevation myocardial infarction or non-ST elevation myocardial infarction in Germany: Results of the PATIENT CARE registry.[347]	It's a cross-sectional study.
The antilipidemic effects of ezetimibe in patients with diabetes.[348]	The comparison is ineligible.
Estimation of Eligibility for Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors and Associated Costs Based on the FOURIER Trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk): Insights from the Department of Veterans Affairs.[349]	No outcome of interest was reported.
Very High-Risk ASCVD and Eligibility for Nonstatin Therapies Based on the 2018 AHA/ACC Cholesterol Guidelines.[350]	No outcome of interest was reported.
Effect of ezetimibe on major atherosclerotic disease events and all-cause mortality.[351]	No outcome of interest was

	reported.
Efficacy and safety of ezetimibe in combination with atorvastatin for acute coronary syndrome patients accompanied with type 2 diabetes: A Single-Center, Non-randomized Cohort Study.[352]	No outcome of interest was reported.
Retrospective, observation study: Quantitative and qualitative effect of ezetimibe and HMG-CoA reductase inhibitors on LDL-cholesterol: Are there disappearance thresholds for small, dense LDL and IDL?[353]	The comparison is ineligible.
Clinical outcome of statin plus ezetimibe versus high-intensity statin therapy in patients with acute myocardial infarction propensity-score matching analysis.[354]	No outcome of interest was reported.
Differential association of ezetimibe-simvastatin combination with major adverse cardiovascular events in patients with or without diabetes: a retrospective propensity score-matched cohort study.[355]	No outcome of interest was reported.
Retrospective study on antihyperlipidemic efficacy and safety of simvastatin, ezetimibe and their combination in Korean adults.[356]	Follow-up duration is less than 24 weeks.
Impact of ezetimibe coadministered with statins on cardiovascular events following acute coronary syndrome: a 3-year population-based retrospective cohort study in Taiwan.[357]	No outcome of interest was reported.
Effectiveness of a combination of ezetimibe and statins in patients with acute coronary syndrome and multiple comorbidities: A 6-year population-based cohort study.[358]	No outcome of interest was reported.
Effectiveness and safety of combinational therapy compared with intensified statin monotherapy in patients with coronary heart disease.[359]	No outcome of interest was reported.
Ezetimibe-simvastatin therapy reduce recurrent ischemic stroke risks in type 2 diabetic patients.[360]	No outcome of interest was reported.
Arterial stiffness improvement after adding on PCSK9 inhibitors or ezetimibe to high-intensity statins in patients with familial hypercholesterolemia: A Two-Lipid Center Real-World Experience.[361]	No outcome of interest was reported.
Intensive statin versus low-dose statin + ezetimibe treatment for fibrous cap thickness of coronary vulnerable plaques.[362]	No outcome of interest was reported.
Ezetimibe in combination with a statin does not reduce all-cause mortality.[363]	No outcome of interest was reported.
High-potency statin and ezetimibe use and mortality in survivors of an acute myocardial infarction: a population-based study.[364]	No outcome of interest was reported.
Cholesterol Treatment Patterns and Cardiovascular Clinical Outcomes Associated with Colesevelam HCl and Ezetimibe.[365]	No outcome of interest was reported.
Statin use and lower extremity amputation risk in nonelderly diabetic patients.[366]	The comparison is ineligible.
The value of surrogate markers to monitor cholesterol absorption, synthesis and bioconversion to bile acids under lipid lowering therapies.[367]	No outcome of interest was reported.
Disease modifying therapies modulate cardiovascular risk factors in patients with multiple sclerosis.[368]	The comparison is ineligible.
Cardiovascular event rates and trajectories of LDL-cholesterol levels and lipid-lowering therapy in patients with atherosclerotic cardiovascular disease: A population-based cohort study.[369]	The comparison is ineligible.
Colesevelam, Ezetimibe, and Patients With Type 2 Diabetes Mellitus: Characteristics and Clinical Outcomes From a Health Care Database.[370]	No outcome of interest was reported.
Familial Hypercholesterolaemia in a Bulgarian Population of Patients with Dyslipidaemia and Diabetes: An Observational Study.[371]	The comparison is ineligible.
Usefulness of statin-ezetimibe combination to reduce the care gap in dyslipidemia management in patients with a high risk of atherosclerotic disease.[372]	The comparison is ineligible.
Therapeutic practice patterns related to statin potency and ezetimibe/simvastatin combination therapies in lowering LDL-C in patients with high-risk cardiovascular disease.[373]	No outcome of interest was reported.
LDL-cholesterol target achievement in patients with heterozygous familial hypercholesterolemia at Groote Schuur	The comparison is ineligible.

Hospital: Minority at target despite large reductions in LDL-C.[374]	
Predictors and outcomes of increases in creatine phosphokinase concentrations or rhabdomyolysis risk during statin treatment.[375]	The comparison is ineligible.
Adherence To Lipid-Lowering Therapy In Patients With Coronary Heart Disease From The State Of Saxony-Anhalt, Germany.[376]	No outcome of interest was reported.
First-line treatment patterns and lipid target levels attainment in very high cardiovascular risk outpatients.[377]	No outcome of interest was reported.
New fibrate use and acute renal outcomes in elderly adults a population-based study.[378]	No outcome of interest was reported.
Statin-ezetimibe versus statin lipid-lowering therapy in patients with acute coronary syndromes undergoing percutaneous coronary intervention.[379]	Only one-month and three-month side effects were reported.

Table S7 Baseline Characteristics of each included randomized controlled trial

Trial	Location	Centers	Randomized (I/C)	Follow-up	duration of study treatment	prevention type	Treatment	Control	background treatment
Ballantyne 2004[380]	United States (multi-continent)	Multi-center	201/45	12 months	12 months	primary	ezetimibe10 mg/d	placebo	atorvastatin 10 mg/d + NCEP Step I or stricter diet
ENHANCE 2008[381]	Netherlands (multi-continent)	Multi-center	357/363	24 months	24 months	unspecific	ezetimibe 10 mg/d	placebo	simvastatin 80 mg/d
HIJ-PROPER 2017[382]	Japan	Multi-center	869/865	3.86 years	3.86 years	secondary	ezetimibe 10mg/d	/	pitavastatin
IMPROVE-IT 2015[383]	United States (multi-continent)	Multi-center	9067/9077	6 years	6 years	secondary	Ezetimibe 10mg/d	placebo	Simvastatin 40mg/d
Kinouchi 2012[384]	Japan	Single-center	28/26	12 months	12 months	unspecific	ezetimibe 10 mg/d	/	fluvastatin 20 mg/d
Kouvelos 2013[385]	Greece	Single-center	126/136	12 months	12 months	secondary	Ezetimibe 10 mg/d	/	rosuvastatin 10 mg/d
Liu 2017[386]	China	Single-center	114/116	12 months	12 months	secondary	atorvastatin 10 mg/d +ezetimibe10 mg/d	atorvastatin 20 mg/d	/
Luo 2014[387]	China	Single-center	44/40	12 months	12 months	secondary	ezetimibe 10 mg/d	/	atorvastatin 20 mg/d
Luo 2016[388]	China	Single-center	74/74	12 months	12 months	secondary	ezetimibe 10 mg/d	/	atorvastatin 20 mg/d
Okada 2012[389]	Japan	Multi-center	100/100	52 weeks	52 weeks	secondary	Statin (atorvastatin 10 mg/d or rosuvastatin 2.5 mg/d) + ezetimibe10 mg/d	Statin (atorvastatin 20 mg/d or rosuvastatin 5 mg/d)	/
Ren 2017[390]	China	Single-center	55/58	12 months	12 months	secondary	Ezetimibe 10 mg/d	/	rosuvastatin 10 mg/d
RESEARCH 2017[391]	Japan	Multi-center	53/56	52 weeks	52 weeks	primary	statin(atorvastatin 10 mg/d or pitavastatin 1 mg/d)+ezetimibe10 mg/d	Statin (atorvastatin 20 mg/d or pitavastatin 2 mg/d)	/
PRECISE-IVUS 2015[392]	Japan	Multi-center	122/124	12 months	9-12 months	secondary	ezetimibe 10 mg/d	/	atorvastatin

VYCTOR 2009[393]	Mexico	Single-center	30/30	12 months	12 months	unspecific	simvastatin 20/up to 40mg/d + ezetimibe 10mg/d	simvastatin 40/up to 80mg/d	/
Wang 2016[394]	China	Single-center	55/51	12 months	12 months	secondary	Ezetimibe 10 mg/d	/	Rosuvastatin 10 mg/d + lifestyle change
Wang 2017[395]	China	Single-center	51/49	12 months	12 months	secondary	ezetimibe 10 mg/d	/	atorvastatin 20 mg/d
West 2011[396]	United States	Single-center	22/22	2 years	2 years	secondary	ezetimibe 10 mg/d	/	simvastatin 40 mg
GAUSS-3[397]	multi-continent	Multi-center	73/145	24 weeks	24 weeks	unspecific	ezetimibe 10mg/d + injection placebo	evolocumab 420mg QM + oral placebo	/
UK-HARP-II[398]	United Kingdom	Multi-center	101/102	6 months	6 months	primary	simvastatin 20 mg/d + ezetimibe 10 mg/d	simvastatin 20 mg/d + placebo	/
MOZART[399]	United States	Multi-center	25/25	24 weeks	24 weeks	unspecific	ezetimibe 10 mg/d	placebo	/
Masana 2005[400]	multi-continent	Multi-center	355/78	48 weeks	48 weeks	unspecific	ezetimibe 10 mg/d	placebo	simvastatin
ODYSSEY ALTERNATIVE[401]	multi-continent	Multi-center	125/63	24 weeks	24 weeks	unspecific	alirocumab subcutaneous placebo Q2W + oral ezetimibe 10 mg/d	alirocumab subcutaneous placebo Q2W + oral atorvastatin 20 mg/d	diet (NCEP-ATP III TLC or equivalent) and background lipid-modifying therapy (other than ezetimibe, statins, red yeast rice, and fibrates [other than fenofibrate])
ODYSSEY COMBO II[402]	multi-continent	Multi-center	241/479	112 weeks	104 weeks	secondary	injection placebo SC Q2W + ezetimibe 10 mg/d + statin	alirocumab 75 mg SC Q2W + placebo PO daily + statin	NCEP-ATP III TLC or equivalent diet + statin at maximal tolerated daily dose
ODYSSEY EAST[403]	multi-continent	Multi-center	208/407	32 weeks	24 weeks	secondary	placebo Q2W SC + ezetimibe 10 mg/d + statin	alirocumab 75 mg/up to 150 mg Q2W SC + placebo PO daily + statin	/
ODYSSEY OPTIONS I[404]	multi-continent	Multi-center	102/104	32 weeks	24 weeks	unspecific	ezetimibe 10mg/d + injection placebo	Alirocumab 75/up to 150 mg Q2W + oral placebo	atorvastatin 20/40 mg/d

ODYSSEY OPTIONS II[405]	multi-continent	Multi-center	101/101	32 weeks	24 weeks	secondary	ezetimibe 10 mg/d + rosuvastatin 10/20 mg/d	double-dose (20/40 mg/d) rosuvastatin + oral placebo	injection placebo
ODYSSEY MONO[406]	multi-continent	Multi-center	51/52	32 weeks	24 weeks	primary	Ezetimibe 10 mg/d + injection placebo	Alirocumab 75/up to 150 mg Q2W + oral placebo	NCEP-ATPIII therapeutic lifestyle changes or equivalent diet
Saito 2015[407]	Japan	Multi-center	75/77	24 weeks	24 weeks	primary	ezetimibe 10 mg/d	placebo	/
ARBITER 6–HALTS[408]	United States	Multi-center	176/187	14 months	14 months	secondary	ezetimibe 10 mg/d	extended-release niacin 500 mg/up to 2000 mg/d	statin
Yokote 2017[409]	Japan	Multi-cencer	22/26	24 weeks	16 weeks	primary	ezetimibe 10mg/d	placebo	atorvastatin
McKenney 2006[410]	NR	Multi-center	340/236	48 weeks	48 weeks	primary	ezetimibe 10 mg/d	placebo	fenofibrate 160 mg/d
Masuda 2014[411]	Japan	Single-center	26/25	6 months	6 months	secondary	ezetimibe 10 mg/d	/	rosuvastatin 5mg/d
Jackowska 2016[412]	Poland	NR	8/10	6 months	6 months	secondary	ezetimibe 10 mg/d + atorvastatin 10 mg/d	atorvastatin 40 mg/d	/
Jachowska 2019[413]	Poland	NR	20/20	6 months	6 months	secondary	ezetimibe 10 mg/d + atorvastatin 10 mg/d	atorvastatin 40 mg/d	/
Habara 2014[414]	Japan	Single-center	32/31	9 months	9 months	secondary	ezetimibe 10 mg/d	/	Fluvastatin 30 mg/d
Gaudiani 2005[415]	United states	Multi-center	104/110	24 weeks	24 weeks	unspecific	ezetimibe 10 mg/d	simvastatin 20 mg/d	simvastatin 20 mg/d
Dagli 2007[416]	Turkey	Single-center	50/50	6 months	6 months	unspecific	ezetimibe 10 mg/d + pravastatin 10 mg/d	pravastatin 40 mg/d	/
Arimura 2012[417]	Japan	Single-center	25/25	6-8 months	6-8 months	secondary	ezetimibe 10 mg/d + atorvastatin 10 mg/d	atorvastatin 10 mg/d	aspirin and ticlopidine or clopidogrel
Nakou 2008[418]	Greece	Single-center	33/32	6 months	6 months	primary	ezetimibe 10 mg/d	/	orlistat 120mg tid + individualized low-fat diet
Pisciotta 2012[419]	Italy	Single-center	90/180	6 months	6 months	primary	ezetimibe 10 mg/d	a nutraceutical-combined pill (containing berberine 500 mg, policosanol 10 mg and red yeast rice 200 mg)	/
CuVIC[420]	Japan	Multi-center	129/131	6-8 months	6-8 months	secondary	ezetimibe 10 mg/d	/	statin

Oh 2020[421]	South Korea	Two-center	25/25	6 months	6 months	secondary	ezetimibe 10 mg/d + rosuvastatin 5 mg/d	rosuvastatin 20 mg/d	/
Takeshita 2014[422]	Japan	Single-center	17/15	6 months	6 months	unspecific	ezetimibe 10 mg/d	/	nutritional and exercise counselling
Shaw 2009[423]	United Kingdom	Single-center	34/34	6 months	6 months	unspecific	ezetimibe 10 mg/d	placebo	usual treatment
Strony 2008[424]	United states	Multi-center	87/22	12 months	12 months	primary	ezetimibe 10 mg/d	placebo	simvastatin
Nakou 2012[425]	Greece	Single-center	38/39	6 months	6 months	primary	ezetimibe 10 mg/d	simvastatin 40 mg/d	usual lifestyle recommendations
Miklishanskaya 2015[426]	Russia	NR	50/50	6 months	6 months	secondary	ezetimibe 10 mg/d	/	simvastatin
Bajaj 2020[427]	Canada	Multi-center	102/98	24 weeks	24 weeks	primary	ezetimibe 10 mg/d	colesevelam 3.75 g/d	/

Abbreviations: I/C, intervention/control; NR, not reported; Q2W, once per two weeks; QM, once per month; PO, per os; SC, subcutaneous; tid, three times a day.

Trial	**Age (ezetimibe group)**	**Age (control group)**	**Male% (ezetimibe group)**	**Male% (control group)**	**BMI (ezetimibe group)**	**BMI (control group)**	**LDL-C concentration (mg/dl) (ezetimibe group)**	**LDL-C concentration (mg/dl) (control group)**	**HDL-C concentration (mg/dl) (ezetimibe group)**	**HDL-C concentration (mg/dl) (control group)**	**triglycerides concentration (mg/dl) (ezetimibe group)**	**triglycerides concentration (mg/dl) (control group)**
Ballantyne 2004[380]	57.6±10	58.5±7	39	51	NR	NR	181.75±23.20	185.61±23.20	54.14±15.47	50.27±11.60	165.63±65.54	159.43±65.54
ENHANCE 2008[381]	46.1±9.0	45.7±10.0	53.5	49.3	27.4±4.6	26.7±4.4	319.0±65.0	317.8±66.1	46.7±11.3	47.4±13.2	162.33±77.04	167.00±83.70
HIJ-PROPER 2017[382]	65.7±11.7	65.5±11.9	74.0	77.1	24.3±3.5	24.3±3.6	134.8± 29.3	135.6 ± 30.0	49.0 ± 12.5	48.3 ± 12.3	129.1± 69.3	132.5 ± 72.8
IMPROVE-IT 2015[383]	63.6±9.7	63.6±9.8	75.5	75.9	28.3±5.2	28.3±5.2	93.8±22.96	93.8±23.11	42.1±11.85	42.2±11.85	137.6±64.44	137.5±64.44
Kinouchi 2012[384]	55.2±12.0	53.4±11.4	71.4	61.5	24.7±2.5	24.9±7.2	159±21	156±20	54±12	54±16	146.67±103.70	155.00±81.48

Kouvelos 2013[385]	70±8	72±7	89.7	89.7	NR	NR	148.2±58.1	143±54.1	40.9±12.8	41.3±11	159 (median)	160.2 (median)
Liu 2017[386]	84.2±2.9	84.0±1.8	52.6	50.9	25.6±3.5	25.4±3.9	85.07±23.20	88.94±30.94	46.40±11.60	50.27±11.60	132.86±88.57	141.72±132.86
Luo 2014[387]	67.21±6.40	66.31±5.82	55	50	24.43±4.61	24.72±4.42	126.45±13.92	128.00±17.79	45.24±14.69	45.63±17.79	201.95±42.52	208.15±56.69
Luo 2016[388]	60.76±11.56	61.55±9.72	54.1	59.5	25.23±4.67	24.68±5.42	138.05±14.69	136.12±17.79	45.24±15.47	46.02±17.79	219.66±38.97	226.75±56.69
Okada 2012[389]	65.7±10.1	65.9±8.7	73.1	73.6	25.1±3.0	25.3±3.8	111.9±22.6	109.3±23.2	51.4±11.4	51.3±12.2	142.83±78.15	135.60±61.26
Ren 2017[390]	57.3±1.5	60.7±1.3	87.3	79.3	NR	NR	116.01±37.12	113.30±39.44	40.22±10.05	40.99±8.89	170.06±100.97	156.78±92.12
RESEARCH 2017[391]	61.7±11.1	62.6±9.5	58.5	57.1	NR	NR	130.6±19.2	135.2±22.6	56.7±15.2	54.7±9.6	146.7±95.2	161.9±88.3
PRECISE-IVUS 2015[392]	66±10	67±10	78	78	24.8±3.4	24.9±3.1	109.8±25.4	108.3±26.3	41.1±9.5	40.0±10.3	117.67±57.04	122.33±49.63
VYCTOR 2009[393]	58±9	57±8	47.5	38.7	29±6	29±4	131±39	130±33	46±11	45±9	195±82	198±86
Wang 2016[394]	63±10	65±12	72	73	NR	NR	139.98±45.63	134.57±48.72	43.70±8.12	43.70±8.51	174.49±59.34	168.29±57.57
Wang 2017[395]	58±10	58±9	60.8	61.2	NR	NR	136.50±33.64	133.41±29.00	NR	NR	305.58±66.43	169.18±18.60
West 2011[396]	62±8	59±10	56	69	28±6	30±7	118±9	118±10	48±4	45±4	130±21	227±47
GAUSS-3[397]	58.5±9.4	59.0±11.1	46.6	53.8	28.5±5.9	27.8±4.4	221.9±70.2	218.8±73.1	50.2±15.5	49.7±15.4	173.50±77.04	179.17±78.15
UK-HARP-II[398]	60±15	60±14	70	69	27.1±6.4	27.5±5.5	121	117	40	40	167	188
MOZART[399]	49.0±14.9	49.5±13.7	44	32	33.8±5.2	32.9±5.1	100.0±32.0	90.0±50.5	NR	NR	152.0±58.0	149.0±104.0
Masana 2005[400]	59±10.33	61±9.16	57	55	29.2±5.2	29.6±6.1	136.6±47.3	131.4±45.6	50.1±11.9	51.0±13.4	131.0±4.1	128.0±8.4
ODYSSEY ALTERNATIVE[401]	62.8±10.1	63.4±8.9	53.6	55.6	28.4±4.9	29.7±5.4	193.5±70.9	187.3±59.5	50.7±14.1	51.1±12.5	151.00±91.11	174.33±94.07

ODYSSEY COMBO II[402]	61.3±9.2	61.7±9.4	70.5	75.2	30.3±5.1	30.0±5.4	104.41±34.80	108.28±34.80	46.40±15.47	46.40±11.60	150.58±71.74	141.72±71.74
ODYSSEY EAST[403]	58.3±11.2	58.8±10.7	70.2	77.4	25.2±3.0	25.6±3.7	111.2±49.8	110.7±48.5	43.2±11.3	43.7±11.4	134.77±61.11	130.83±58.59
ODYSSEY OPTIONS I[404]	64.87±9.61	63.10±10.18	65.69	61.54	31.23±5.94	31.12±6.83	99.71±29.23	109.55±36.41	47.79±11.49	48.15±13.26	124.7±58.53	134.33±57.23
ODYSSEY OPTIONS II[405]	61.82±10.33	61.03±10.54	56.43	70.30	31.10±6.41	31.74±6.44	111.11±45.75	109.57±39.96	51.63±13.32	47.66±13.84	135.94±63.69	144.31±72.04
ODYSSEY MONO[406]	59.6±5.3	60.8±4.6	52.9	53.8	28.4±6.7	30.1±5.9	138.3±24.5	141.1±27.1	59.9±19.2	54.3±16.1	119.33±49.63	120.33±47.41
Saito 2015[407]	59.3±10.8	60.0±9.7	61.3	62.3	26.2±5.3	25.7±3.9	138.6±11.2	139.4±10.4	55.0±13.5	53.7±12.8	119.6±57.3	129.5±63.8
ARBITER 6–HALTS[408]	65±11	64±11	82	78	31.0±5.4	30.8±6.7	83.7±19.9	80.5±17.2	43.3±8.5	42.5±8.6	123.67±55.56	127.67±51.11
Yokote 2017[409]	58.2±10.7	58.2±11.2	54.5	50.0	24.7±2.6	25.6±3.3	135.36±24.75	135.90±24.70	56.98±9.61	58.54±14.68	147.75±49.63	140.00±58.89
McKenney 2006[410]	54.1±9.5	52.9±10.4	56.5	58.9	29.5±4.6	29.3±4.4	159.7±27.7	164.1±27.9	41.7±8.8	41.9±9.5	275.0±101.6	277.0±86.5
Masuda 2014[411]	64.0±7.9	70.2±7.6	90.5	84.2	24.7±4.3	23.8±2.0	131.8±25.6	123.0±27.0	53.1±11.8	47.1±12.5	129.7±5.1	144.9±4.8
Jackowska 2016[412]	NR	NR	NR	NR	NR	NR	104±35	101±15	50±10	46±7	144±52	167±73
Jachowska 2019[413]	63.65±7.39	61.80±7.10	80	90	25.76±2.18	26.66±2.60	110.70±30.49	111.85±20.22	53.49±9.32	52.70±12.42	131.80±57.77	130.95±55.40
Habara 2014[414]	69.8±7.8	68.8±7.8	65	83	24.5±3.0	23.5±4.0	122.5±33.6	109.1±30.2	49.9±13.0	48.1±10.2	126.0±50.4	113.0±60.6
Gaudiani 2005[415]	57.8±7.5	58.3±6.83	59.6	55.5	32.5±5.9	33.7±6.8	93.97±28.62	91.65±24.36	47.56±10.83	49.11±10.83	149.69±115.15 (median)	151.46±110.72 (median)
Dagli 2007[416]	53.2±12.2	57.1±11.1	46	52	25.7 ± 3.7	26.9 ± 3.4	158.1±47.5	165.7±29.7	43.7±11	46.3±10.25	270.3±158.9	243.5±96.8
Arimura 2012[417]	69±9	69±8	73	68	23.6±2.4	22.5±2.9	103.6±29.9	104.1±31.8	50.2±11.2	51.0±14.6	131.6±40.7	123.1±68.3

Nakou 2008[418]	55±10	54±9	31	24.1	35.5±6.1	35.7±6.7	172±32	164±38	53±7	52±9	162.50±28.00	175.25±46.83
Pisciotta 2012[419]	58.3±12.3	57.3±12.1	40.8	40.8	23.5±2.8	23.9±2.9	207.27±20.11	207.27±18.56	60.71±13.15	59.94±13.53	148.80±29.23	135.52±57.57
CuVIC[420]	66±11	67±9	83	73	25±4	24±4	96±31	99±36	44±12	46±12	135±71	144±74
Oh 2020[421]	59.6±9.9	59.2±9.7	84	92	NR	NR	127.5±32.8	123.6±40.3	45.0±11.0	46.1±13.9	121.0±70.5	128.0±78.7
Takeshita 2014[422]	50.4±12.0	55.5±11.6	64.7	64.3	30.5±4.9	27.7±6.6	NR	NR	52.59±12.76	54.14±11.99	126.66±39.86	118.69±40.74
Shaw 2009[423]	52±14	57±10	82	85	NR	NR	112.14±38.67	108.28±46.40	58.00±15.47	65.74±23.20	194.86±115.15	186.01±97.43
Strony 2008[424]	56.4±11.9	60.7±8.4	51	36	28.9±5.1	29.8±5.3	178.1±23.8	176.2±23.9	48.6±11.8	52.4±10.3	178.7±68.4	177.0±59.9
Nakou 2012[425]	54±5		43		NR	NR	170.8±20.1	178.7±34.2	55.0±11.6	55.8±14.6	163.2±88.59	178.4±90.37
Miklishanskaya 2015[426]	62.25±2.17	60.25±1.83	74	78	28.00±0.83	26.75±0.83	157.39±40.22	138.82±31.32	43.31±11.60	48.72±8.51	139.06±52.26	132.86±52.26
Bajaj 2020[427]	59.0±10.3	59.9±10.2	51	45.9	29.9±7.2	29.7±6.1	96.7±21.3	97.8±24.3	45.24±10.44	46.02±11.99	134.63±62.89	143.49±63.77

Abbreviations: BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NR, not reported.

Table S8 Summary of subgroup analyses

Outcome	Subgroup	RR	P value	Interaction Q	Interaction P
Prevention type					
Any cancer	Secondary prevention	1.01 (0.92 to 1.11)	0.84	3.58	0.17
	Primary prevention	3.78 (0.60 to 23.77)	0.16		
	Unspecific	0.25 (0.03 to 2.20)	0.21		
Any fracture	Secondary prevention	0.92 (0.75 to 1.12)	0.39	0.62	0.74
	Unspecific	0.53 (0.06 to 4.45)	0.56		
	Primary prevention	0.34 (0.01 to 8.27)	0.51		
Discontinuation due to any adverse events	Primary prevention	1.03 (0.50 to 2.12)	0.94	0.40	0.82
	Unspecific	0.85 (0.65 to 1.10)	0.21		
	Secondary prevention	0.92 (0.76 to 1.12)	0.40		
Discontinuation due to any gastrointestinal adverse events	Unspecific	1.18 (0.40 to 3.45)	0.77	0.48	0.79
	Secondary prevention	3.71 (0.17 to 79.85)	0.40		
	Primary prevention	1.35 (0.32 to 5.75)	0.68		
Myalgia or muscular pain leading to discontinuation	Unspecific	0.84 (0.52 to 1.36)	0.48	0.32	0.57
	Secondary prevention	0.33 (0.01 to 7.75)	0.49		
	Primary prevention	NA	NA		
Neurocognitive events	Secondary prevention	1.48 (0.58 to 3.81)	0.41	0.00	NA
	Unspecific	NA	NA		
New-onset DM	Secondary prevention	0.80 (0.53 to 1.21)	0.29	3.02	0.22
	Unspecific	9.18 (0.50 to 168.27)	0.14		
	Primary prevention	1.20 (0.42 to 3.40)	0.73		
Type of control					
Any cancer	Placebo or usual care	0.97 (0.69 to 1.35)	0.84	0.03	0.86
	Active agent control	0.90 (0.44 to 1.86)	0.78		
Any fracture	Placebo or usual care	0.91 (0.74 to 1.12)	0.38	0.28	0.59
	Active agent control	0.67 (0.22 to 2.05)	0.48		
Discontinuation due to any adverse events	Placebo or usual care	1.02 (0.94 to 1.10)	0.70	2.06	0.15
	Active agent control	0.76 (0.52 to 1.12)	0.17		
Discontinuation due to any gastrointestinal adverse events	Placebo or usual care	1.37 (0.56 to 3.36)	0.49	0.02	0.90
	Active agent control	1.16 (0.11 to 12.11)	0.90		

Myalgia or muscular pain leading to discontinuation	Placebo or usual care	0.33 (0.05 to 2.06)	0.24	1.01	0.31
	Active agent control	0.88 (0.53 to 1.45)	0.61		
Neurocognitive events	Placebo or usual care	2.00 (0.18 to 22.08)	0.57	0.07	0.79
	Active agent control	1.40 (0.50 to 3.91)	0.52		
New-onset DM	Placebo or usual care	0.84 (0.51 to 1.37)	0.48	0.10	0.76
	Active agent control	0.95 (0.53 to 1.71)	0.86		
Risk of bias					
Discontinuation due to any adverse events	Low	0.92 (0.82 to 1.04)	0.19	0.30	0.58
	High	1.45 (0.29 to 7.32)	0.65		
Discontinuation due to any gastrointestinal adverse events	Low	1.04 (0.37 to 2.87)	0.95	0.73	0.39
	High	2.24 (0.53 to 9.41)	0.27		
Myalgia or muscular pain leading to discontinuation	High	0.33 (0.01 to 7.86)	0.50	0.32	0.57
	Low	0.84 (0.52 to 1.36)	0.48		
Follow-up duration					
Any cancer	Follow-up ≥48 weeks	1.01 (0.92 to 1.11)	0.80	0.13	0.72
	Follow-up <48 weeks	0.79 (0.21 to 3.01)	0.73		
Any fracture	Follow-up ≥48 weeks	0.92 (0.75 to 1.13)	0.43	1.45	0.23
	Follow-up <48 weeks	0.42 (0.12 to 1.49)	0.18		
Discontinuation due to any adverse events	Follow-up ≥48 weeks	0.87 (0.72 to 1.05)	0.16	0.00	1.00
	Follow-up <48 weeks	0.87 (0.63 to 1.21)	0.42		
Discontinuation due to any gastrointestinal adverse events	Follow-up ≥48 weeks	1.27 (0.34 to 4.69)	0.72	0.01	0.92
	Follow-up <48 weeks	1.39 (0.47 to 4.08)	0.55		
Myalgia or muscular pain leading to discontinuation	Follow-up ≥48 weeks	0.33 (0.04 to 3.10)	0.33	0.66	0.42
	Follow-up <48 weeks	0.86 (0.52 to 1.40)	0.54		
Neurocognitive events	Follow-up ≥48 weeks	1.72 (0.60 to 4.94)	0.32	0.37	0.54
	Follow-up <48 weeks	0.83 (0.10 to 6.72)	0.86		
New-onset DM	Follow-up ≥48 weeks	0.76 (0.49 to 1.20)	0.24	1.28	0.26
	Follow-up <48 weeks	1.23 (0.62 to 2.44)	0.56		

Abbreviations: RR, relative ratio; DM, diabetes mellitus; NA, not available

Table S9 Summary of Begg's rank correlation test and Egger's linear regression test

Outcomes	t for Begg	P for Begg	Z for Egger	P for Egger
Any cancer	-0.63	0.53	-0.41	0.69
Discontinuation due to any adverse events	1.35	0.18	-1.44	0.16

Table S10 Baseline characteristics of the included observational studies

Study	% of patients receiving statin at baseline	Mean age (ezetimibe group)	Mean age (control group)	Male% (ezetimibe group)	Male% (control group)	Mean BMI (ezetimibe group)	Mean BMI (control group)	Mean LDL-C (mg/dl) (ezetimibe group)	Mean LDL-C (mg/dl) (control group)	Mean HDL-C (mg/dl) (ezetimibe group)	Mean HDL-C (mg/dl) (control group)	Mean TG (mg/dl) (ezetimibe group)	Mean TG (mg/dl) (control group)
Barkas 2016	16*	52.33†	56.67†	45	43	26.83†	27.40†	201.67†	170.67†	54.67†	52.67†	120.33†	142.33†
Kim 2017	0	64.17	64.05	29.9	27.1	24.02	24.04	NR	NR	NR	NR	NR	NR
Kłosiewicz-Latoszek 2018	NR	NR	NR	NR	NR	NR	NR	259.09†	230.86†	NR	NR	NR	NR
Rivers 2007	100	62.5‡		50‡		31.4‡		166‡		57‡		240‡	

*Data in specific sub-population of interest were not available, so data in overall population were presented.

†Mean was estimated from median and IQR.

‡Data were not reported in each group respectively, only data in overall population were presented.

Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides, NR, not reported

Table S11 Risk of bias of included observational studies

Study	Representativeness of the Exposed Cohort (0-1)	Selection of the Non-Exposed Cohort (0-1)	Ascertainment of Exposure (0-1)	Demonstration That Outcome of Interest Was Not Present at Start of Study (0-1)	Comparability of Cohorts on the Basis of the Design or Analysis (0-2)	Assessment of Outcome (0-1)	Was Follow-Up Long Enough for Outcomes to Occur (0-1)	Adequacy of Follow Up of Cohorts (0-1)	Other Concerns (0-1)	Total score
Barkas 2016	0*	1	1	1	2	0#	1	1	0‡	7
Kim 2017	0*	1	1	1	1§	1	1	1	0**	7
Kłosiewicz-Latoszek 2018	1	1	0#	1	0†	1	1	0#	1	6
Rivers 2007	0*	1	1	1	0†	1	1	1	0##	6

* Potential selection bias in exclusion criteria.

No explicit statement.

§ Adjusted effect estimate was presented without specifying adjusted covariates.

† Only raw event data were reported without matching or adjustment.

‡ It's a post-hoc analysis.

** Indirect comparison.

Incomplete data reporting.

Table S12 Summary of previously published meta-analyses on the effects of ezetimibe on safety outcomes

Study	Key Findings
Battaggia 2015[428]	The study included 7 studies and showed a non-significant tendency with ezetimibe towards damage for cancer (RR, 2.14; 95%CI, 0.07–64.24).
Savarese 2015[429]	The study included 7 studies and showed ezetimibe was not associated with cancer (RR, 1.040; 95% CI, 0.965–1.120).
Zhao 2019[430]	The study included 84 studies and showed ezetimibe was not associated with new-onset DM (Network OR, 0.90; 95%CI, 0.04–20.25). But ezetimibe was associated with increased rate of neurocognitive adverse events (Network OR, 3.94; 95%CI, 1.18–13.12).
Chaiyasothi 2019[431]	The study included 67 studies and suggested ezetimibe was not associated with discontinuation due to any adverse events (RR, 0.90; 95%CI, 0.74–1.11).
Davidson 2005[432]	The study included 17 studies and showed that the incidence of myalgia or muscular pain leading to discontinuation was no more common in patients taking ezetimibe/simvastatin (18/4558, 0.4%) than in those taking simvastatin alone (9/2563, 0.4%).
Pandor 2008[433]	The study included 8 studies and showed that the incidence of discontinuation due to any adverse events in patients taking ezetimibe (69/1791, 3.85%) was similar to that in those taking placebo (31/931, 3.33%).

Abbreviations: CI, confidence interval; RR, relative ratio; OR, odds ratio; DM, diabetes mellitus

Table S13 Meta-regression according to different baseline LDL-c levels

Outcome	Coefficient	95% CI	P value
Discontinuation due to any adverse events	0.0013	(-0.0015, 0.0041)	0.3536
Discontinuation due to any gastrointestinal adverse events	-0.0003	(-0.0094, 0.0089)	0.9543
Any cancer	-0.0065	(-0.0159, 0.0030)	0.1785
New-onset Diabetes mellitus	0.0115	(-0.0130, 0.0359)	0.3569
Neurocognitive events	-0.0376	(-0.2166, 0.1414)	0.6804
Any fracture	-0.0024	(-0.0210, 0.0162)	0.7992
Myalgia or muscular pain leading to discontinuation	0.0094	(-0.0081, 0.0268)	0.2916

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