




Safety of ezetimibe in lipid-lowering treatment: systematic review and meta-analysis of randomised controlled trials and cohort studies

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ABSTRACT

OBJECTIVE To determine the harms of ezetimibe in people who need lipid-lowering treatment.

DESIGN Systematic review and meta-analysis.

DATA SOURCES Randomised controlled trials and cohort studies.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES Studies comparing ezetimibe with placebo, standard care, or other lipid-lowering agents in people who need lipid-lowering treatment with a follow-up duration of at least six months (or 24 weeks). The relative effects for potential harms of ezetimibe were pooled by use of random effect pairwise meta-analyses for randomised controlled trials and the evidence from observational studies was narratively summarised. The certainty of evidence was assessed using the Grading of Recommendation Assessment, Development, and Evaluation.

RESULTS 48 randomised controlled trials with 28 444 participants (median follow-up 34 weeks, range 24–312 weeks) and four observational studies with 1667 participants (median follow-up 282 weeks, range 72–400 weeks) were included. The meta-analyses of randomised trials showed moderate to high certainty that ezetimibe was not associated with cancer (relative risk 1.01; 95% confidence interval 0.92 to 1.11), fractures (0.90; 0.74 to 1.10), discontinuation due to any adverse event (0.87; 0.74 to 1.03), gastrointestinal adverse events leading to discontinuation (1.34; 0.58 to 3.08), myalgia or muscular pain leading to discontinuation (0.82; 0.51 to 1.33), neurocognitive events (1.48; 0.58 to 3.81), or new-onset diabetes

(0.88; 0.61 to 1.28). The narrative analysis of observational studies provided consistent findings. No credible subgroup effects were identified for the harm outcomes, including shorter versus longer follow-up duration of trials.

CONCLUSIONS Ezetimibe results in little to no difference in adverse events or other undesirable effects compared with placebo, usual care or other lipid-lowering agents.

REVIEW REGISTRATION PROSPERO CRD42020187437.

Introduction

Cardiovascular disease is one of the leading causes of death and disability worldwide.^{1–3} Statins are first line cholesterol-lowering drugs for the reduction of cardiovascular risk but can cause adverse effects such as myalgia, muscular pain, and new-onset diabetes.^{4 5} Ezetimibe, an oral cholesterol-lowering drug taken after statins, which inhibits intestinal cholesterol absorption and decreases biliary cholesterol secretion, lowers low density lipoprotein cholesterol (LDL-C) by 20%.^{6–9} Clinical trials and systematic reviews have established that ezetimibe can reduce cardiovascular events.^{10–13} Guidelines from the European Society of Cardiology¹⁴ and American Heart Association¹⁵ recommend ezetimibe as a second lipid-lowering drug in addition to treatment with statins when LDL-C treatment goals are not met, or as a single drug in case of statin-intolerance. The number of prescriptions of ezetimibe doubled in North America from 2003 to 2006 for the primary and secondary prevention of cardiovascular diseases.¹⁶

Although ezetimibe is well tolerated in clinical practice, some studies suggest concerns regarding potential harms such as cancer, neurocognitive events, fractures, gastrointestinal adverse events, myalgia, muscular pain, and new-onset diabetes.^{4 17–22} The cause and magnitude of adverse events or undesirable effects of ezetimibe remain unclear. Therefore, we conducted a pairwise systematic review and meta-analysis of randomised controlled trials and observational studies to evaluate the safety of ezetimibe in people who need lipid-lowering treatment. This systematic review quantitatively informed the potential harms of ezetimibe for a

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Ezetimibe lowers low density lipoprotein cholesterol and reduces cardiovascular risks by blocking the gastrointestinal absorption of dietary cholesterol
- ⇒ Although ezetimibe is generally safe, there are concerns about its potential harms including cancer, neurocognitive events, fractures, gastrointestinal adverse events, myalgia, muscular pain, and new-onset diabetes

WHAT THIS STUDY ADDS

- ⇒ Adding ezetimibe results in little to no difference in adverse events or other undesirable effects in people who need lipid-lowering treatment

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

- ⇒ When deciding to add ezetimibe to statins for lipid-lowering treatment, clinicians can have confidence in the evidence that adverse events are rare

parallel clinical practice guideline with risk-stratified recommendations for ezetimibe and PCSK9 inhibitors.²³ This guideline forms part of a *BMJ* Rapid Recommendation and is a collaborative effort by the MAGIC Evidence Ecosystem Foundation (<https://magicevidence.org>) and *The BMJ* (box 1).²⁴ For the visual abstract of this paper, see figure 1.

Methods

Study design

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (known as PRISMA) statement and the Meta-analysis of Observational Studies in Epidemiology (known as MOOSE) statement (checklists in online supplemental tables S1 and S2).^{25 26} We registered the protocol in PROSPERO (CRD42020187437).

Guideline panel and patient involvement

The *BMJ* Rapid Recommendation panel,²⁴ including clinicians, methodologists, and patients provided critical oversight over the steps of this review. The panel included cardiologists, general practitioners, general internists, endocrinologists, a geriatrician, methodologists, and three patient partners. Patient partners received personal training and individual support in the methods used throughout the

BOX 1 | LINKED ARTICLES IN THIS *BMJ* RAPID RECOMMENDATIONS CLUSTER

- ⇒ Hao Q, Aertgeerts B, Guyatt G, et al. PCSK9 inhibitors and ezetimibe for the reduction of cardiovascular events: a clinical practice guideline with risk-stratified recommendations. *BMJ* 2022;377:e069066, doi:10.1136/bmj-2021-069066
 - Summary of the results from the Rapid Recommendation process
- ⇒ Khan SU, Yedlapati SH, Lone AN, et al. Anti-PCSK9 agents and ezetimibe for cardiovascular risk reduction: a systematic review and network meta-analysis. *BMJ* 2022;377:e069116, doi:10.1136/bmj-2021-069116
 - Review and network meta-analysis of all available randomised trials that assessed effects of PCSK9 inhibitors and ezetimibe with or without statin therapy for cardiovascular risk reduction
- ⇒ Harm reviews
 - Wang Y, Zhan S, Du H, et al. Safety of ezetimibe in lipid-lowering treatment: systematic review and meta-analysis of randomised controlled trials and cohort studies. *BMJ MED* 2022;1. doi:10.1136/bmjmed-2022-000134
 - Li J, Du H, Wang Y, et al. Safety of proprotein convertase subtilisin/kexin 9 inhibitors: a systematic review and meta-analysis. *Heart* 2022; doi:10.1136/heartjnl-2021-320556
- ⇒ MAGICApp (<https://app.magicapp.org>)
 - Expanded version of results with multi-layered recommendations, evidence summaries, and decision aids for use on all devices

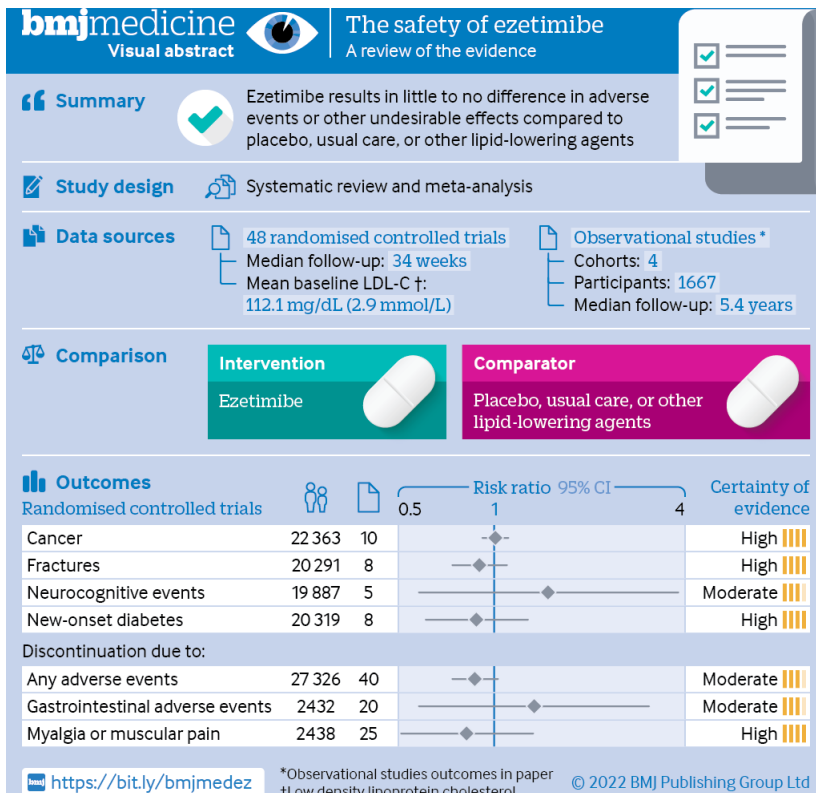


Figure 1 | Visual abstract

guideline development process. The panel assisted in framing the study question, defining the interventions and comparisons, prioritising outcome measures, and proposing subgroup analyses. Three patient partners were members of the guideline panel that contributed to this systematic review and the associated *BMJ* Rapid Recommendation.

Data sources

We searched Medline, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to July 2021. We also searched ClinicalTrials.gov for completed unpublished registered trials with results. The search strategy is shown in online supplemental tables S3 and S4.

Paired reviewers (YW and HD) searched the literature and selected studies through screening titles and abstracts. Potentially eligible papers

were screened in full text. In case of conflict, a third reviewer (SL) arbitrated disagreement by discussion. We crosschecked the study inclusion with a previously published systematic review.¹³

We included randomised controlled trials and cohort studies that compared ezetimibe with placebo, standard care, or other lipid-lowering agents with at least six months (or 24 weeks) follow-up duration. We included studies explicitly reporting data for at least one outcome of interest, including cancer (any type), new-onset diabetes mellitus, neurocognitive events, fractures, myalgia or muscular pain leading to discontinuation, discontinuation due to gastrointestinal adverse events, or discontinuation due to any adverse effect. The longest follow-up duration or the largest population study was included when studies reported on the same or overlapping populations. Only studies published in English were included.

Data were collected in a predefined collection form incorporating study characteristics (eg, first author name, year of publication, study design, sample size, follow-up duration, prevention type, the intervention of control, and background treatment); baseline characteristics (eg, age, sex, body mass index, LDL-C, high density lipoprotein cholesterol, and triglycerides); intervention characteristics (eg, drug dose, treatment duration); and safety outcomes (eg, number of events and patients of each outcome) for randomised controlled trials. If a published trial did not report the outcome information, while the corresponding ClinicalTrials.gov reported relevant data, we collected data from the registry report. When the data in publication and ClinicalTrials.gov conflicted, we used the data from the publication. For observational studies, additional data were collected, including prospective or retrospective design, exposure, data source, and methods for comparability (that is, matching or adjusting for confounding variables). Adjusted effect estimates (that is, relative risks or odds ratios) and corresponding 95% confidence intervals were preferred to raw data of adverse events in observational studies. Paired reviewers (YW and HD) performed the data extraction and a third reviewer (SL) judged the discrepancies if any.

Paired reviewers (YW and HD) assessed the risk of bias for randomised controlled trials using the Cochrane Collaboration's risk-of-bias assessment tool²⁷ and that for observational studies with the modified Newcastle-Ottawa quality assessment scale.²⁸ We added one item, which we named "other concerns" because some concerns could not be classified into any of the existing eight items in the scale. A third reviewer (SL) was involved in the discussion if any discrepancy occurred.

Statistical analysis

For the included randomised controlled trials, we pooled relative risks and their 95% confidence intervals using the random effects model for all meta-analyses.

Statistical heterogeneity was assessed by χ^2 and I^2 tests with significance defined by $\chi^2 P < 0.1$ or $I^2 > 50\%$. We used baseline risks for each outcome based on the pooled event rates of included control groups and calculated absolute effects for each outcome at both five years and two years. As a result of limited data reported and low certainty of evidence, we did not pool outcome data quantitatively in the analysis of observational studies but instead conducted a narrative summary of the included studies.

We analysed three subgroup analyses to explore the potentially hypothetical heterogeneity. Firstly, the follow-up duration (<48 v ≥ 48 weeks) in particular, potential affects of larger relative effects in studies with longer follow-up duration. Secondly, risk of bias (low v high risk), focusing on larger relative effects in studies with high risk. A high risk of bias is defined if at least two high risk items from the Cochrane Collaboration Risk of Bias Tool are noted. Finally, type of control (placebo or usual care v active agents) with larger relative effects in studies with placebo or usual care.

As recommended by reviewers, we exploratorily performed a meta-regression according to different baseline LDL-C concentrations. When the included number of non-zero-event trials surpassed 10, funnel plots, Begg's rank correlations, and Egger's linear regression were applied in evaluating publication bias. We used the fixed effects model to pool the data for each outcome as the sensitivity analysis. All data analyses were done using RStudio (R Pack Version 3.6.1).

To evaluate the certainty of evidence, we used the Grading of Recommendation Assessment, Development, and Evaluation (known as GRADE) framework²⁹ and assessed the credibility of subgroup analyses based on the literature.³⁰

Patient and public involvement

Three patient partners were involved in the design of this research.

Results

Included studies

Of 6881 citations of randomised controlled trials, we included 48 with a total of 28 444 participants (figure 2, table 1, and online supplemental tables S6 and S7).¹¹ Follow-up durations ranged from 24 to 312 weeks (median 34 weeks). The mean age of participants was 62.6 years, 71.9% were male, the mean baseline LDL-C was 112.1 mg/dL (2.9 mmol/L), and the mean proportion of individuals using statins at admission was 39.6% (table 1). Of 25 multicentre trials, treatment regimens included ezetimibe in monotherapy (663 participants in 11 trials), ezetimibe plus statin (13 230 participants in 36 trials), and ezetimibe plus fibrate (340 participants in one trial).

Of 3625 citations of observational studies, we included four cohort retrospective cohorts with 1667 participants in our narrative summary (figure 2, table 2, and online supplemental table S10).³¹⁻³⁴

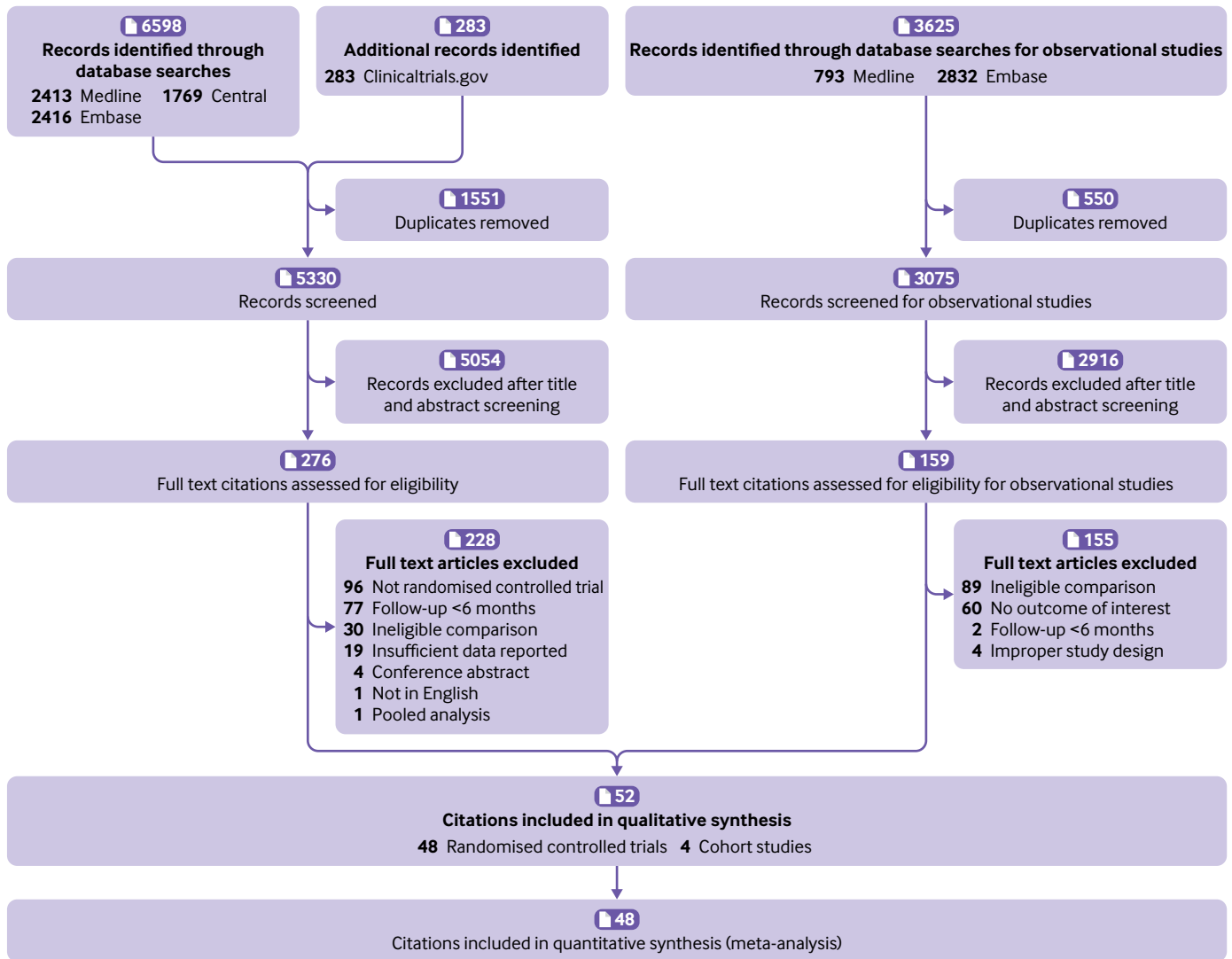


Figure 2 | PRISMA flow diagram

Follow-up durations ranged from 72 to 400 weeks (that is, 1.38-7.70 years; median 282 weeks (that is, 5.42 years)). The population from two studies were identified from electronic health records.^{32 34} The mean age of the participants was 59.5 years, 35.6% were male, the mean baseline LDL-C was 191.0 mg/dL (4.9 mmol/L), and 9.7% of participants were using statins at admission. Three studies compared ezetimibe plus statin versus statin alone, and one other compared ezetimibe versus colesevlam.

Risk of bias

We rated the overall risk of bias as low across all 48 included trials; 29 trials raised concerns (online supplemental file 1). We rated 14 (29%) studies as high risk of bias because the number of missing participants was higher than 20% or the analysis was not done by an intention-to-treat protocol. We rated 18 (38%) trials as high risk of bias owing to inadequate masking of participants and personnel, 14 (29%) trials owing to an open label design, and four (8%)

trials because the trial design did not have a matching placebo. The overall scores of the Newcastle-Ottawa quality assessment scale were six to seven among the included observational studies, indicating some risks of bias (table 3; online supplemental table S11).

Meta-analyses of randomised controlled trials

As shown in figure 3, moderate to high certainty evidence indicated that ezetimibe has little to no effect on the risks of cancer (relative risk 1.01; 95% confidence interval 0.92 to 1.11), fractures (0.90; 0.74 to 1.10), discontinuation due to any adverse events (0.87; 0.74 to 1.03), discontinuation due to gastrointestinal adverse events (1.34; 0.58 to 3.08), myalgia or muscular pain leading to discontinuation (0.82; 0.51 to 1.33), neurocognitive events (1.48; 0.58 to 3.81), or new-onset diabetes (0.88; 0.61 to 1.28). We downgraded the certainty of the evidence to moderate for discontinuation due to any adverse events for indirectness because of the composite nature of the outcome. We also

Table 1 | Baseline characteristics of included trials

Characteristics	No (%)	Interquartile range	Range
Eligible studies:			
Total No of trials	48	—	—
Median trial size	131	65-246	18-18 144
Median follow-up (weeks)	34	24-52	24-312
No of studies funded by pharmaceutical companies	26 (54.2)	—	—
No of studies that were phase 2/3	12 (25.0)	—	—
No of studies that were not phase 2/3	36 (75.0)	—	—
Participants:			
Mean age (years)	62.6	57.7-64.0	45.9-84.1
Male sex (%)	71.9	51.9-75.3	27.6-89.7
Mean LDL-C (mg/dL) at baseline	112.1	109.92-150.47	82.05-318.40
Mean proportion (%) of patients receiving statin at baseline	39.6	0-100	0-100
Region:			
World	12 (25.0)	—	—
Europe*	9 (18.8)	—	—
Asia†	20 (41.7)	—	—
America	7 (14.6)	—	—
Prevention type:			
Primary prevention	12 (25.0)	—	—
Secondary prevention	24 (50.0)	—	—
Unspecific prevention	12 (25.0)	—	—

LDL-C=low density lipoprotein cholesterol (1 mg/dL=0.0259 mmol/L).
 *One study conducted in Russia was included in this category.
 †One study conducted in Turkey was included in this category.

downgraded the certainty of evidence of discontinuation due to any gastrointestinal adverse events and neurodegenerative events for imprecision because of wide 95% confidence intervals, which could not support clinical decision making.

Subgroups and sensitivity analysis

None of the subgroup analyses identified potential subgroup effects in different trials with different follow-up durations, risk of bias, and type of control (online supplemental table S8 and figures S3–S5). For example, the cancer risk did not show heterogeneity across the subgroups of <48 weeks follow-up

(relative risk 0.79; 95% confidence interval 0.21 to 3.01) and ≥48 weeks follow-up (1.01; 0.92 to 1.11) with the interaction P value being 0.72. The meta-regression did not identify any association between baseline LDL-C concentrations and outcomes (online supplemental table S13).

The sensitivity analyses supported the robustness of the pooled results using the fixed effects model (online supplemental figures S7–S19). Neither funnel plots nor Begg’s and Egger’s tests for the outcomes of cancer and discontinuation due to any adverse events did not identify signals of publication bias (online supplemental table S9).

Table 2 | Characteristics of the included observational studies

Study	Study design	Data sources	Funding	Location	No of centres	No of participants	Median follow-up duration	Mean LDL-C (mg/dL) at baseline	Prevention type
Barkas et al ³¹	Retrospective cohort study	NR	Not funded	Greece	Single centre	796	6.84 years*	177.8	Primary
Kim et al ³²	Retrospective cohort study	Electronic medical records	Ministry of Health and Welfare, Republic of Korea	Korea	Single centre	665	4 years	NR	NR
Kłosiewicz-Latoszek et al ³³	Retrospective cohort study	NR	Sanofi	Poland	Single centre	190	7.70 yearst	239.8	Primary†
Rivers et al ³⁴	Retrospective cohort study	Electronic medical records	Sankyo Pharma	US	Single centre	16	Phase 1: 305 days; phase 2: 199 days	166	NR

LDL-C=low density lipoprotein cholesterol (1 mg/dL=0.0259 mmol/L); NR=not reported.
 *Mean was estimated from median and interquartile range.
 †Data in specific subpopulation of interest were not available, so data in overall population were presented.

Table 3 | Treatments, outcomes, and risk of bias of included observational studies

Outcome	Study	Treatment of interest	Control group	Summary of findings	NOS score (0-10)
New-onset diabetes	Barkas et al ³¹	Ezetimibe+statin	Statin	Ezetimibe did not increase the risk of new-onset diabetes (adjusted OR 1.01; 95% CI 0.51 to 1.99). OR was adjusted for the log-transformed baseline fasting glucose levels and follow-up duration, the presence of metabolic syndrome, and family history of diabetes.	7
	Kim et al ³²	Simvastatin (20 mg) with ezetimibe (10 or 20 mg) complex	Simvastatin (20 and 40 mg)	Ezetimibe did not increase the risk of new-onset diabetes (adjusted OR via indirect comparison* 1.24; 95% CI 0.65 to 2.39). OR was adjusted for baseline variables, which were not reported explicitly.	7
Myalgia or muscular pain leading to discontinuation	Kłosiewicz-Latoszek et al ³³	Ezetimibe+statin	Statin	No case of myalgia or muscular pain leading to discontinuation was reported in each group.	6
	Rivers et al ³⁴	Phase 1: ezetimibe; phase 2: ezetimibe+colesevelam	Phase 1: colesevelam; phase 2: ezetimibe+colesevelam	No case of myalgia or muscular pain leading to discontinuation was reported in each group.	6
Discontinuation due to any gastrointestinal adverse events	Rivers et al ³⁴	Phase 1: ezetimibe; phase 2: ezetimibe+colesevelam	Phase 1: colesevelam; phase 2: ezetimibe+colesevelam	No case of discontinuation due to any gastrointestinal adverse events was reported in each group.	6
Discontinuation due to any adverse events	Rivers et al ³⁴	Phase 1: ezetimibe; phase 2: ezetimibe+colesevelam	Phase 1: colesevelam; phase 2: ezetimibe+colesevelam	No case of discontinuation due to any adverse events was reported in each group.	6

CI=confidence interval; NOS=Newcastle-Ottawa quality assessment scale; OR=odds ratio.

*The comparison was indirect because the OR and 95% CI of simvastatin and ezetimibe versus imvastatin were calculated from the ORs and 95% CIs of simvastatin versus atorvastatin and of simvastatin and ezetimibe versus atorvastatin.

Narrative summary of observational studies

Two retrospective studies^{31 32} suggested that ezetimibe was not associated with an increased risk of new-onset diabetes (adjusted odds ratio 1.01, 95% confidence interval 0.51 to 1.99; adjusted odds ratio via indirect comparison 1.24, 0.65 to 2.39) during the four to six year follow-up duration (table 3). Two studies reported no instances of myalgia or muscular pain during the follow-up duration.^{33 34} One study with 16 participants reported no cases of discontinuation due to any adverse events including gastrointestinal effects in a 10 month follow-up duration.³⁴ We consider these findings to be very low certainty evidence due to high risk of bias (new-onset diabetes, myalgia or muscular pain leading to discontinuation, discontinuation due to any gastrointestinal adverse events and discontinuation due to any adverse events), indirectness (new-onset diabetes and discontinuation due to any adverse events) and imprecision (myalgia or muscular pain leading to discontinuation, discontinuation due to any gastrointestinal adverse events and discontinuation due to any adverse events).

Discussion

Main findings

Moderate to high certainty evidence shows that ezetimibe has little to no effect on adverse events (compared with no ezetimibe), including cancer, new-onset diabetes, neurocognitive events, fractures, myalgia or muscular pain leading to discontinuation, or discontinuation due to gastrointestinal adverse events or any adverse events.

Drugs that do not cause adverse events are rare in clinical practice.³⁵ Unlike the pleiotropy of targets for other lipid-lowering drugs, ezetimibe lowers LDL-C

concentration by blocking the Niemann-Pick C1 Like 1 (NPC1L1) protein, which inhibits intestinal cholesterol absorption, thus mimicking a low cholesterol diet.^{36 37} Ezetimibe does not directly interact with the lipid metabolism in the liver and other organs and is biologically safe, except for the potential harms of very low cholesterol intake, which remains open to debate.³⁸

Compared with the previous studies

We identified six previous meta-analyses investigating the safety concerns of ezetimibe.³⁹⁻⁴⁴ Results for these studies were consistent with our findings, except that Zhao and colleagues⁴⁴ significantly linked ezetimibe to increased neurocognitive events in their network meta-analysis (network odds ratio 3.94, 95% confidence interval 1.18 to 13.12).

Neurocognitive safety is one of the most important concerns followed by very low LDL-C concentrations.⁴⁵ Nevertheless, the findings from our meta-analysis of randomised controlled trials did not show an effect of neurodegenerative events in people treated with ezetimibe, nor did the findings from the observational studies. Our study did not show an effect on cancer, a concern that was raised by the SEAS trial.²² We did not note an association with fractures or gastrointestinal effects, events that could be linked to the limited absorption of lipids in intestines.^{5 20 21} However, discontinuation due to any gastrointestinal adverse events and neurodegenerative events were downgraded to moderate certainty due to wide 95% confidence intervals. New evidence could change our confidence in these effects.^{46 47}

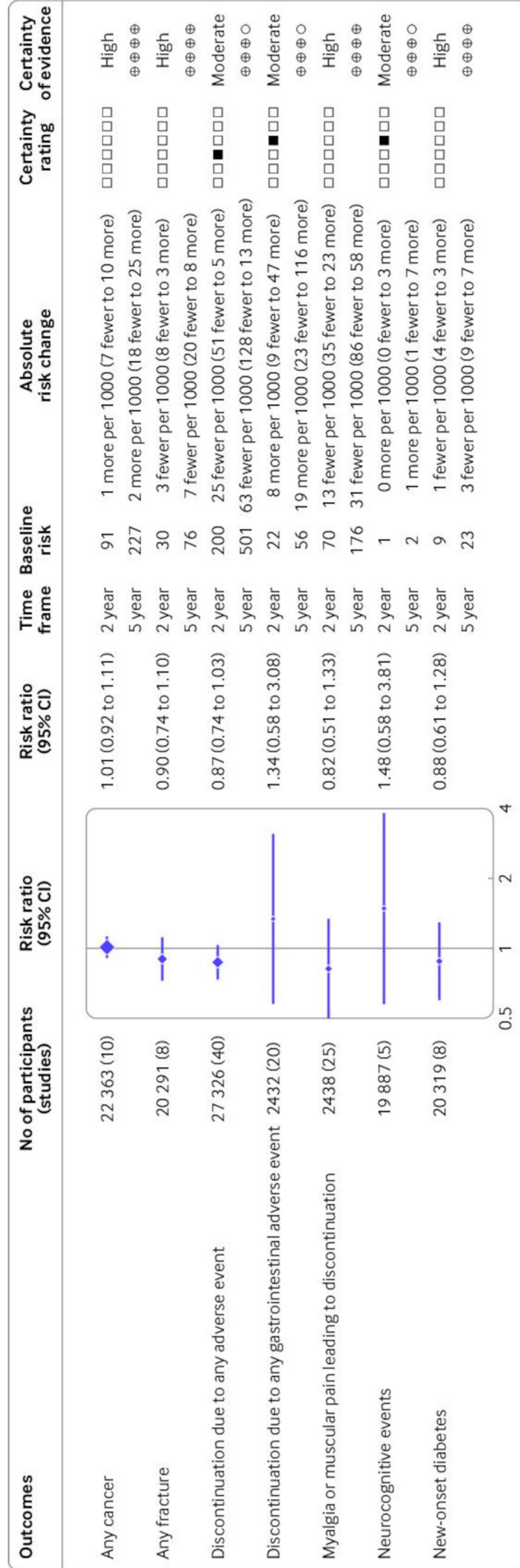


Figure 3 | Summary of findings for relative and absolute risks of the safety outcomes of ezetimibe. Hollow squares in the certainty rating column represent six rating domains listed in order from left to right including risk of bias, inconsistency, indirectness, imprecision, publication bias, and other concerns. Black squares means that the certainty was downgraded because of that domain. CI=confidence interval

Strengths and limitations

Our study systematically reviewed all ezetimibe trials and cohort studies from literature and ClinicalTrials.gov and engaged a multidisciplinary panel to contextualise our findings into clinical practice. The GRADE approach based on the absolute effects facilitates the application in clinical practice. In trials, we did not identify credible subgroup effects for any of the harm outcomes regarding different follow-up durations. With the support from observational studies with a median follow-up duration of up to 7.7 years, our study supports the long term safety of the drug. Nevertheless, long term surveillance remains necessary.

The key limitation of this study is that the number of some events (that is, gastrointestinal and neuro-cognitive events) is rare and therefore findings for these events could be imprecise. Unfortunately, the included observational studies to supplement the trial evidence overall provided very low certainty evidence and were not powered to improve precision for these or other harm outcomes. A large scale, population based study could be helpful in the future. However, such rare events might not alter clinical decision making because of the very low absolute baseline risk. The systematic review did not provide direct evidence for people with characteristics that were not represented by the study population (eg, low LDL-C concentration before treatment). People who might not be represented, therefore, should use when considering the direct evidence.

Conclusion

In this systematic review, moderate to high certainty evidence show that treatment with ezetimibe has little to no effect on adverse events compared with no ezetimibe. Nevertheless, the clinical practice warrants long term surveillance of rare events, especially in unrepresented populations from previous studies.

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Contributors SL, HT, POV, IR, ND, GB, GG, BA, QH, and SUK conceived the study, YW performed the literature search; YW and JL screened studies for eligibility; YW, SZ, LL, and SL assessed the risk of bias; YW and JL performed data extraction; SL, BA, GG, POV, and NS interpreted the data analysis; SL, BA, GG, QH, ND, and HD assessed the certainty of the evidence; HD wrote the draft of the manuscript; and all other authors revised the manuscript. SL is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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REFERENCES

- Laslett LJ, Alagona P, Clark BA, *et al*. The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of cardiology. *J Am Coll Cardiol* 2012;60:S1–49. doi:10.1016/j.jacc.2012.11.002
- GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the global burden of disease study 2013. *Lancet* 2015;385:117–71. doi:10.1016/S0140-6736(14)61682-2
- Roth GA, Huffman MD, Moran AE, *et al*. Global and regional patterns in cardiovascular mortality from 1990 to 2013. *Circulation* 2015;132:1667–78. doi:10.1161/CIRCULATIONAHA.114.008720
- Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;289:1681–90. doi:10.1001/jama.289.13.1681
- Wang Z, Li Y, Zhou F, *et al*. Effects of statins on bone mineral density and fracture risk: a PRISMA-compliant systematic review and meta-analysis. *Medicine* 2016;95:e3042. doi:10.1097/MD.0000000000003042

- 6 Wang HH, Portincasa P, Mendez-Sanchez N, *et al.* Effect of ezetimibe on the prevention and dissolution of cholesterol gallstones. *Gastroenterology* 2008;134:2101–10. doi:10.1053/j.gastro.2008.03.011
- 7 Feingold KR, Anawalt B, Boyce A. *Cholesterol Lowering Drugs. Endotext [Internet]: MDText. com, Inc.*, 2021.
- 8 Dujovne CA, Ettinger MP, McNeer JF, *et al.* Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. *Am J Cardiol* 2002;90:1092–7. doi:10.1016/S0002-9149(02)02798-4
- 9 Sudhop T, Lütjohann D, Kodal A, *et al.* Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation* 2002;106:1943–8. doi:10.1161/01.CIR.0000034044.95911.DC
- 10 Baigent C, Landray MJ, Reith C, *et al.* The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (study of heart and renal protection): a randomised placebo-controlled trial. *Lancet* 2011;377:2181–92. doi:10.1016/S0140-6736(11)60739-3
- 11 Cannon CP, Blazing MA, Giugliano RP, *et al.* Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;372:2387–97. doi:10.1056/NEJMoa1410489
- 12 Ouchi Y, Sasaki J, Arai H, *et al.* Ezetimibe lipid-lowering trial on prevention of atherosclerotic cardiovascular disease in 75 or older (EWTOPIA 75): a randomized, controlled trial. *Circulation* 2019;140:992–1003. doi:10.1161/CIRCULATIONAHA.118.039415
- 13 Zhan S, Tang M, Liu F, *et al.* Ezetimibe for the prevention of cardiovascular disease and all-cause mortality events. *Cochrane Database Syst Rev* 2018;11:CD012502. doi:10.1002/14651858.CD012502.pub2
- 14 Mach F, Baigent C, Catapano AL, *et al.* 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111–88. doi:10.1093/eurheartj/ehz455
- 15 Grundy SM, Stone NJ, Bailey AL, *et al.* 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019;73:3168–209. doi:10.1016/j.jacc.2018.11.002
- 16 Jackevicius CA, Tu JV, Ross JS, *et al.* Use of ezetimibe in the United States and Canada. *N Engl J Med* 2008;358:1819–28. doi:10.1056/NEJMsao801461
- 17 Navarese EP, Buffon A, Andreotti F, *et al.* Meta-Analysis of impact of different types and doses of statins on new-onset diabetes mellitus. *Am J Cardiol* 2013;111:1123–30. doi:10.1016/j.amjcard.2012.12.037
- 18 Feingold KR, Grunfeld C. *Cholesterol lowering drugs. Endotext [Internet]: MDText. com, Inc.*, 2018.
- 19 Banach M, Rizzo M, Nikolic D, *et al.* Intensive LDL-cholesterol lowering therapy and neurocognitive function. *Pharmacol Ther* 2017;170:181–91. doi:10.1016/j.pharmthera.2016.11.001
- 20 Martinez AI, Freeman PR, Moga DC. Statin use and gastrointestinal hemorrhage: a large retrospective cohort study. *Am J Cardiovasc Drugs* 2019;19:65–74. doi:10.1007/s40256-018-0301-4
- 21 Yamauchi M, Yamaguchi T, Nawata K, *et al.* Increased low-density lipoprotein cholesterol level is associated with non-vertebral fractures in postmenopausal women. *Endocrine* 2015;48:279–86. doi:10.1007/s12020-014-0292-0
- 22 Rossebø AB, Pedersen TR, Boman K, *et al.* Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008;359:1343–56. doi:10.1056/NEJMoa0804602
- 23 Hao Q, Aertgeerts B, Guyatt G. PCSK9 inhibitors and ezetimibe for the reduction of cardiovascular events: clinical practice guideline with risk stratified recommendations. *BMJ* 2022;377:e069066. doi:10.1136/bmj-2021-069066
- 24 Siemieniuk RA, Agoritsas T, Macdonald H, *et al.* Introduction to BMJ rapid recommendations. *BMJ* 2016;354:i5191. doi:10.1136/bmj.i5191
- 25 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097. doi:10.1371/journal.pmed.1000097
- 26 Stroup DF, Berlin JA, Morton SC, *et al.* Meta-Analysis of observational studies in epidemiology: a proposal for reporting. meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA* 2000;283:2008–12. doi:10.1001/jama.283.15.2008
- 27 Higgins JPT, Altman DG, Gøtzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928. doi:10.1136/bmj.d5928
- 28 Wells GA, Shea B, O'Connell D. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Oxford, 2000. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
- 29 Guyatt GH, Oxman AD, Vist GE, *et al.* Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6. doi:10.1136/bmj.39489.470347.AD
- 30 Sun X, Briel M, Busse JW, *et al.* Credibility of claims of subgroup effects in randomised controlled trials: systematic review. *BMJ* 2012;344:e1553. doi:10.1136/bmj.e1553
- 31 Barkas F, Elisaf M, Liberopoulos E, *et al.* Statin therapy with or without ezetimibe and the progression to diabetes. *J Clin Lipidol* 2016;10:306–13. doi:10.1016/j.jacl.2015.11.015
- 32 Kim TM, Kim H, Jeong Y, *et al.* The differences in the incidence of diabetes mellitus and prediabetes according to the type of HMG-CoA reductase inhibitors prescribed in Korean patients. *Pharmacoepidemiol Drug Saf* 2017;26:1156–63. doi:10.1002/pds.4237
- 33 Ktosiewicz-Latoszek L, Cybulska B, Białobrzeska-Paluszkiwicz J, *et al.* Clinical management of heterozygous familial hypercholesterolemia in a Polish outpatient metabolic clinic: a retrospective observational study. *Arch Med Sci* 2018;14:962–70. doi:10.5114/aoms.2017.1855
- 34 Rivers SM, Kane MP, Busch RS, *et al.* Colesevelam hydrochloride-ezetimibe combination lipid-lowering therapy in patients with diabetes or metabolic syndrome and a history of statin intolerance. *Endocr Pract* 2007;13:11–16. doi:10.4158/EP13.11
- 35 Angamo MT, Chalmers L, Curtain CM, *et al.* Adverse-drug-reaction-related hospitalisations in developed and developing countries: a review of prevalence and contributing factors. *Drug Saf* 2016;39:847–57. doi:10.1007/s40264-016-0444-7
- 36 Altmann SW, Davis HR, Zhu L-J, L-j Z, *et al.* Niemann-Pick C1 like 1 protein is critical for intestinal cholesterol absorption. *Science* 2004;303:1201–4. doi:10.1126/science.1093131
- 37 Temel RE, Tang W, Ma Y, *et al.* Hepatic Niemann-Pick C1-like 1 regulates biliary cholesterol concentration and is a target of ezetimibe. *J Clin Invest* 2007;117:1968–78. doi:10.1172/JCI30060
- 38 Kosoglou T, Statkevich P, Johnson-Levonas AO, *et al.* Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2005;44:467–94. doi:10.2165/00003088-200544050-00002
- 39 Battaggia A, Donzelli A, Font M, *et al.* Clinical efficacy and safety of ezetimibe on major cardiovascular endpoints: systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2015;10:e0124587. doi:10.1371/journal.pone.0124587
- 40 Savarese G, De Ferrari GM, Rosano GMC, *et al.* Safety and efficacy of ezetimibe: a meta-analysis. *Int J Cardiol* 2015;201:247–52. doi:10.1016/j.ijcard.2015.08.103
- 41 Chaiyasothi T, Nathisuwan S, Dilokthornsakul P, *et al.* Effects of Non-statin Lipid-Modifying agents on cardiovascular morbidity and mortality among statin-treated patients: a systematic review and network meta-analysis. *Front Pharmacol* 2019;10:547. doi:10.3389/fphar.2019.00547
- 42 Davidson MH, MacCubbin D, Stepanavage M, *et al.* Striated muscle safety of ezetimibe/simvastatin (Vytorin). *Am J Cardiol* 2006;97:223–8. doi:10.1016/j.amjcard.2005.08.038
- 43 Pandor A, Ara RM, Tumor I, *et al.* Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. *J Intern Med* 2009;265:568–80. doi:10.1111/j.1365-2796.2008.02062.x
- 44 Zhao Z, Du S, Shen S, *et al.* Comparative efficacy and safety of lipid-lowering agents in patients with hypercholesterolemia: a frequentist network meta-analysis. *Medicine* 2019;98:e14400. doi:10.1097/MD.00000000000014400
- 45 Olsson AG, Angelin B, Assmann G, *et al.* Can LDL cholesterol be too low? possible risks of extremely low levels. *J Intern Med* 2017;281:534–53. doi:10.1111/joim.12614
- 46 Revicki D, Hays RD, Cella D, *et al.* Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *J Clin Epidemiol* 2008;61:102–9. doi:10.1016/j.jclinepi.2007.03.012
- 47 King MT. A point of minimal important difference (mid): a critique of terminology and methods. *Expert Rev Pharmacoecon Outcomes Res* 2011;11:171–84. doi:10.1586/erp.119

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bmjmed-2022-000134>).

Safety of ezetimibe: A systematic review and meta-analysis**Appendix Figures and Tables****CONTENTS**

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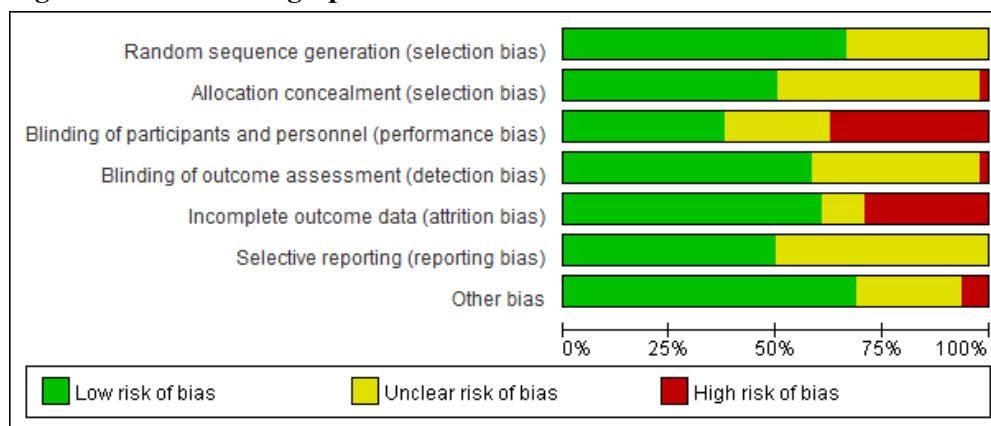
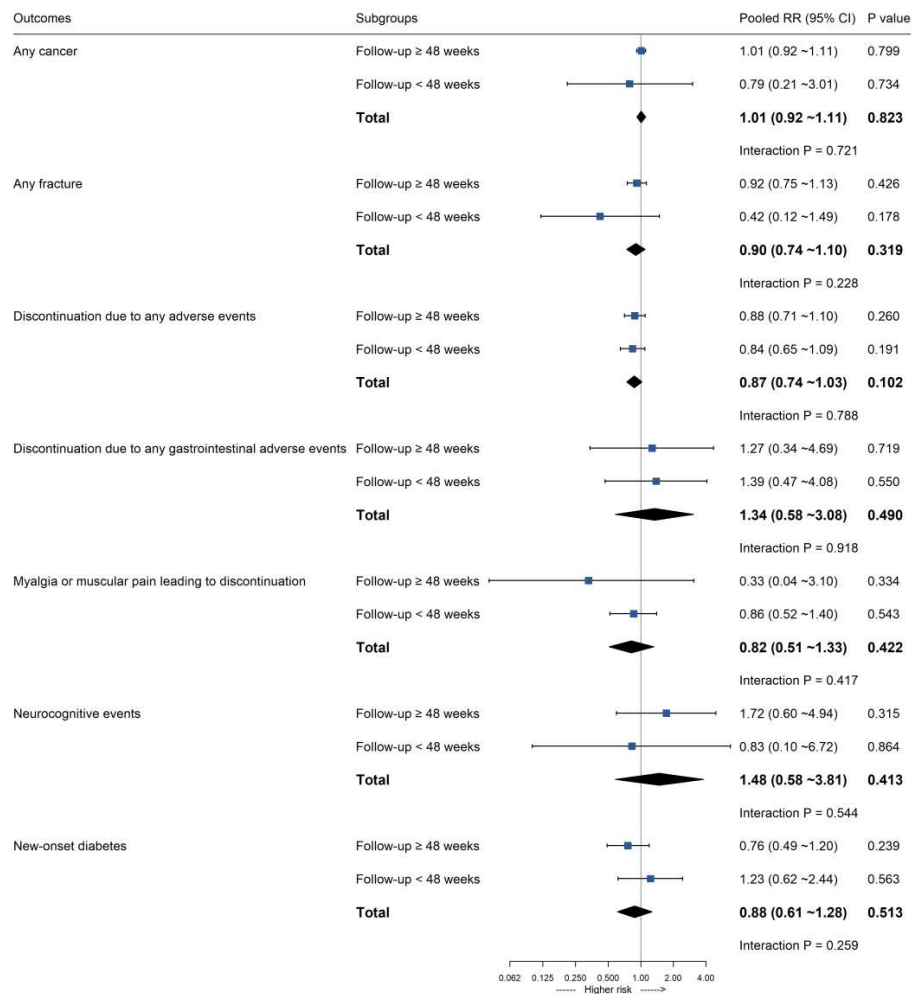
Figure S1 Risk of bias graph for randomized controlled trials

Figure S2 Risk of bias summary for randomized controlled trials

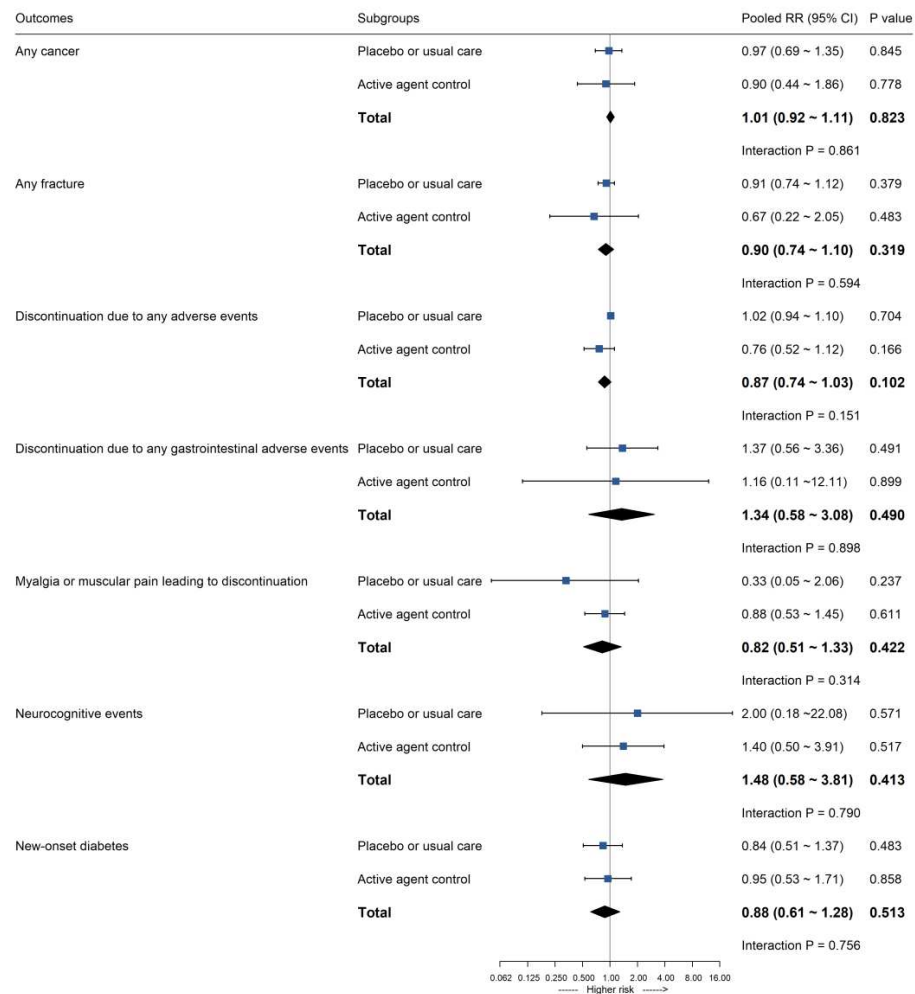
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
ARBITER 6 – HALTS	●	●	●	?	●	●	●
Arimura 2012	?	?	●	?	●	?	●
Bajaj 2020	?	?	●	?	●	●	●
Baillanlyne 2004	?	?	●	●	●	?	?
CuVIC	●	●	●	●	●	●	●
Dagli 2007	●	●	●	?	?	●	●
ENHANCE 2008	●	●	●	●	●	●	●
Gaudiani 2005	●	●	●	●	?	●	●
GAUSS-3	●	●	●	●	●	●	●
Habara 2014	?	?	●	?	?	?	●
HU-PROPER 2017	●	?	●	●	●	●	●
IMPROVE IT 2015	●	●	●	●	●	?	●
Jachowska 2019	?	?	?	?	?	?	●
Jackowska 2016	?	?	●	?	?	?	?
Kinouchi 2013	?	●	●	●	?	?	?
Kouvelos 2013	●	?	●	?	●	?	●
Liu 2017	●	?	?	?	●	?	●
Luo 2014	?	?	?	?	?	?	?
Luo 2016	●	?	?	?	?	?	?
Masana 2005	●	●	●	●	●	●	●
Masuda 2014	?	?	●	?	●	●	●
McKenney 2006	●	●	●	●	●	?	?
Mikhailanskaya 2015	?	?	●	?	?	?	●
MOZART	●	●	●	●	●	●	●
Nakou 2008	●	?	●	?	?	?	●
Nakou 2012	?	?	?	?	?	?	●
ODYSSEY ALTERNATIVE	●	●	●	●	●	●	●
ODYSSEY COMBO II	●	●	●	●	●	●	●
ODYSSEY EAST	●	●	●	●	●	●	●
ODYSSEY MONO	●	●	●	●	●	●	●
ODYSSEY OPTIONS I	●	●	●	●	●	●	●
ODYSSEY OPTIONS II	●	●	●	●	●	●	●
Oh 2020	●	?	●	?	?	?	●
Okada 2012	?	?	?	?	?	?	?
Pisciotta 2012	?	?	?	?	?	?	?
PRECISE-IVUS 2015	●	●	●	●	●	●	●
Ren 2017	●	?	?	?	?	?	?
RESEARCH 2017	●	?	?	?	?	?	?
Saito 2015	●	●	●	●	●	?	?
Shaw 2009	●	●	●	●	●	●	●
Strony 2008	●	●	●	●	●	?	?
Takeshita 2014	●	●	●	●	●	●	●
UK-HARP-II	●	●	?	●	?	?	●
VYCTOR 2009	?	?	●	●	?	?	●
Wang 2016	?	?	?	?	?	?	●
Wang 2017	?	?	?	?	?	?	●
West 2011	●	●	?	●	●	●	●
Yokole 2017	●	●	●	●	●	?	?

Figure S3 Subgroup analyses based on follow-up duration



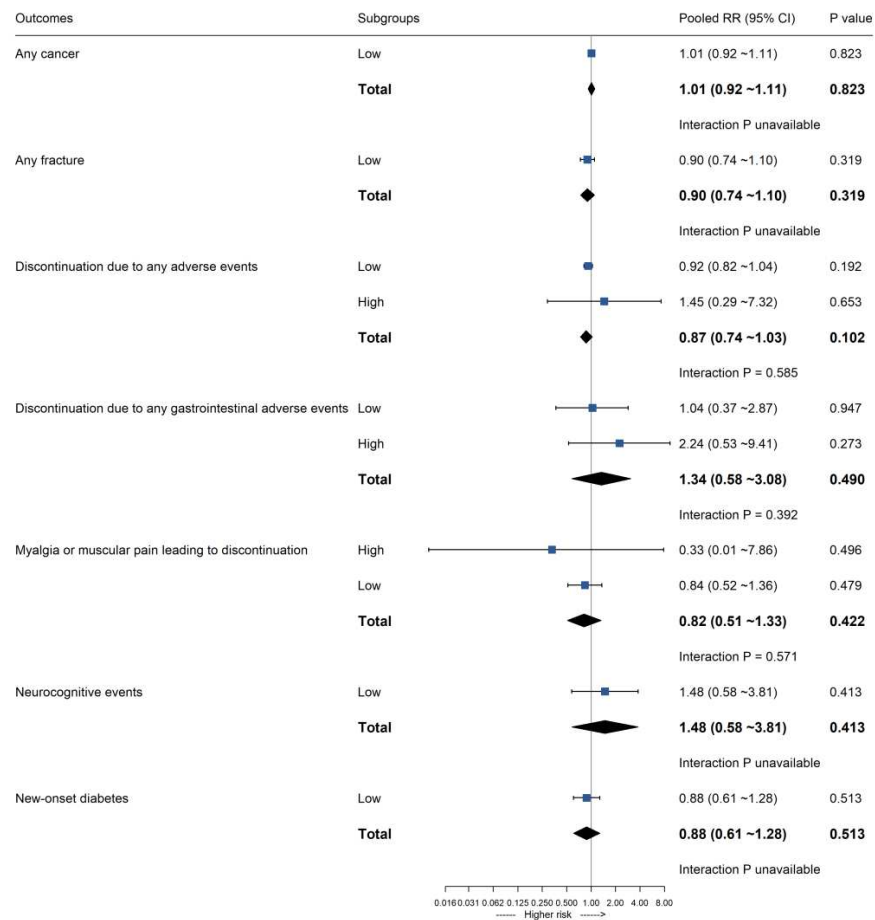
Abbreviations: CI, confidence interval; RR, relative ratio; DM, diabetes mellitus

Figure S4 Subgroup analyses based on type of control

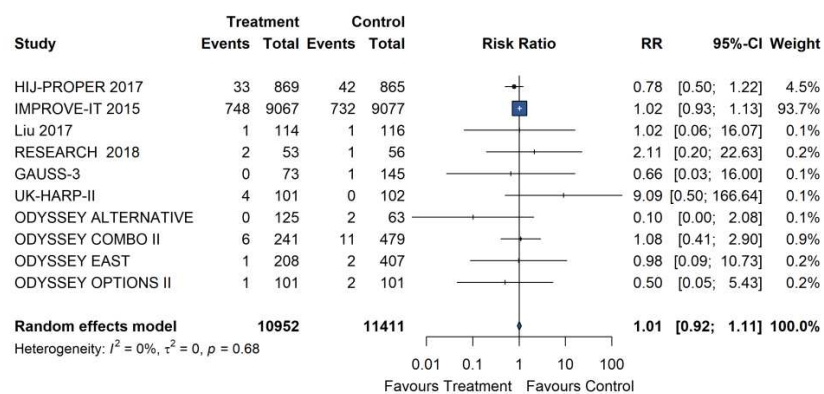


Abbreviations: CI, confidence interval; RR, relative ratio; DM, diabetes mellitus

Figure S5 Subgroup analyses based on risk of bias

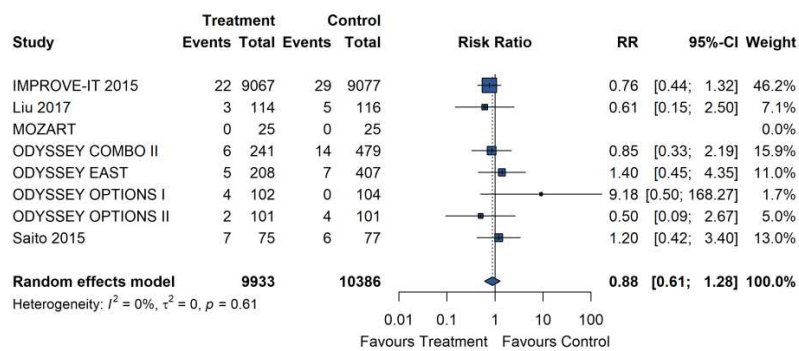


Abbreviations: CI, confidence interval; RR, relative ratio; DM, diabetes mellitus

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

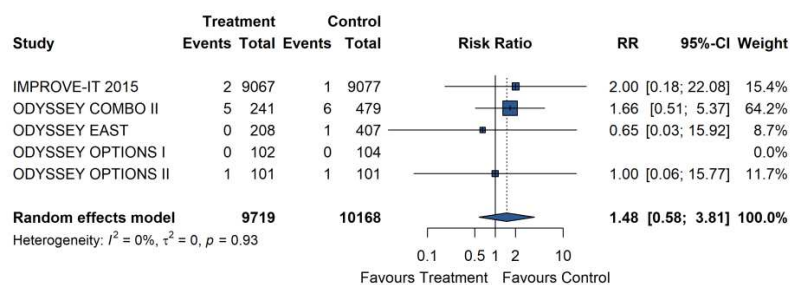
Abbreviations: CI, confidence interval; RR, relative ratio

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

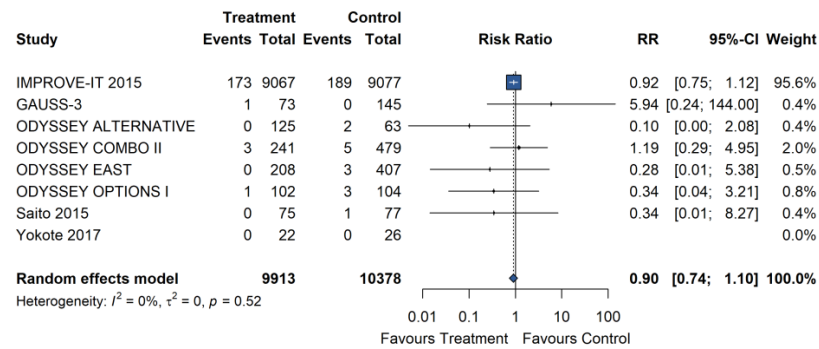


Abbreviations: CI, confidence interval; RR, relative ratio

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

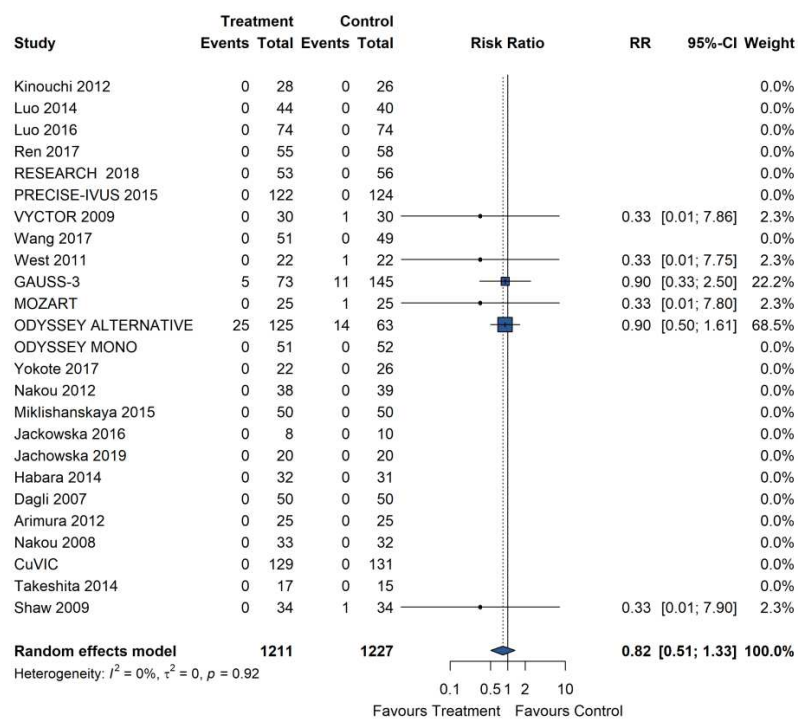


Abbreviations: CI, confidence interval; RR, relative ratio

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

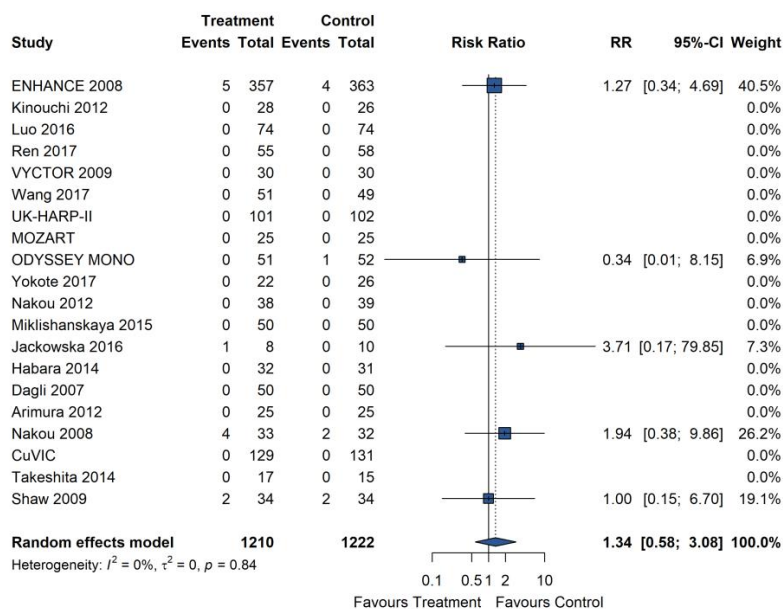
Abbreviations: CI, confidence interval; RR, relative ratio

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



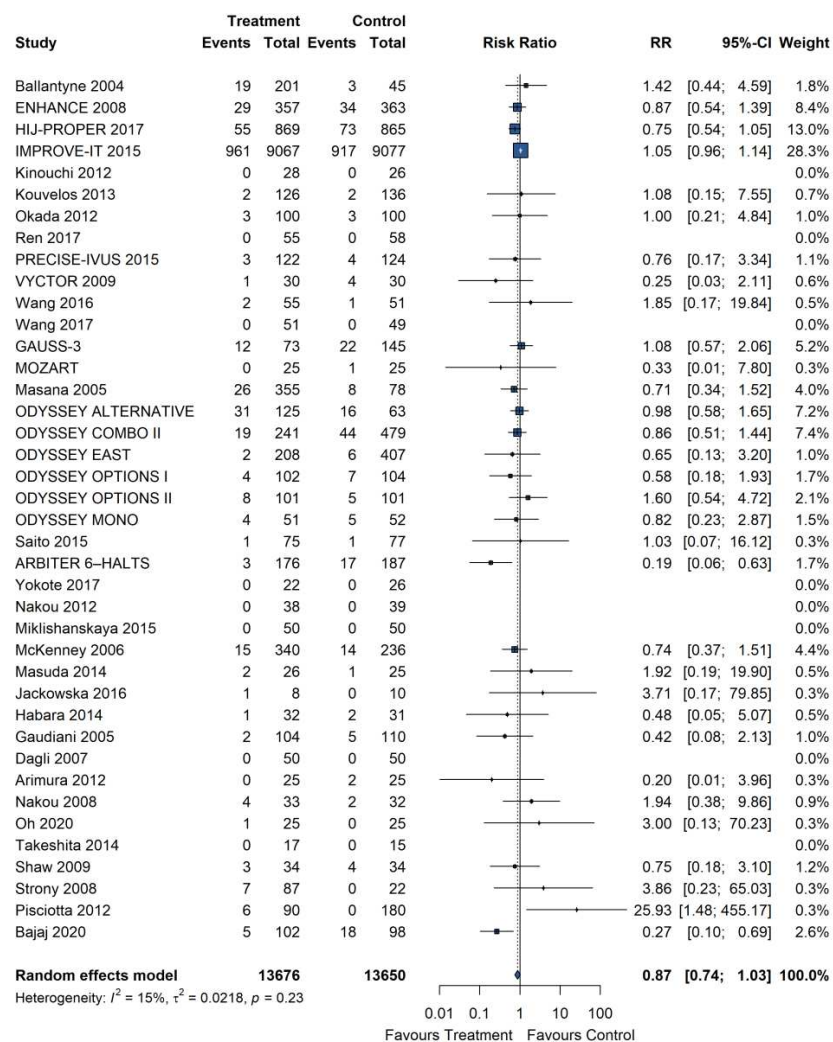
Abbreviations: CI, confidence interval; RR, relative ratio

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



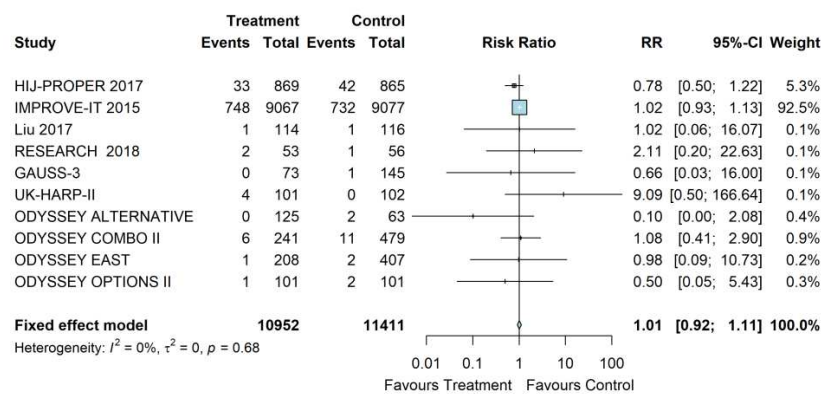
Abbreviations: CI, confidence interval; RR, relative ratio

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



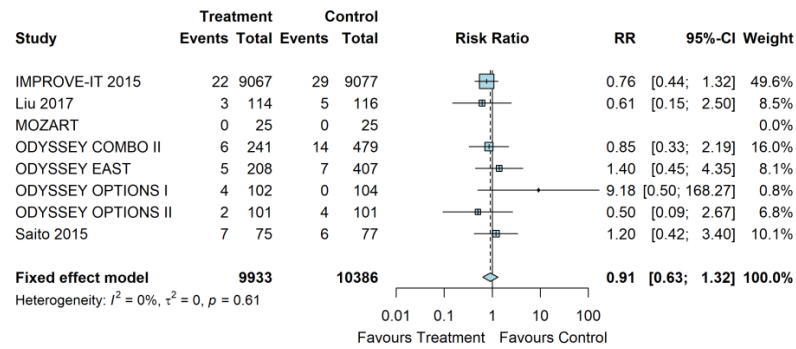
Abbreviations: CI, confidence interval; RR, relative ratio

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



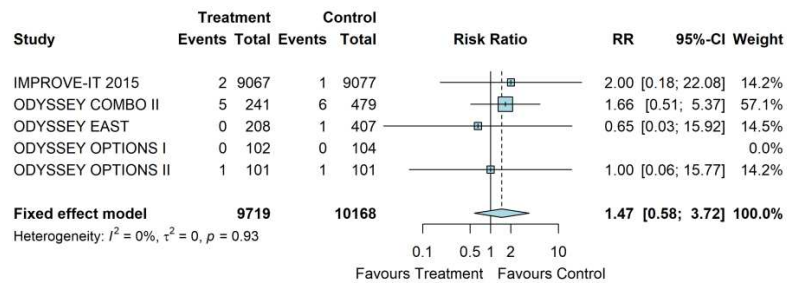
Abbreviations: CI, confidence interval; RR, relative ratio

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



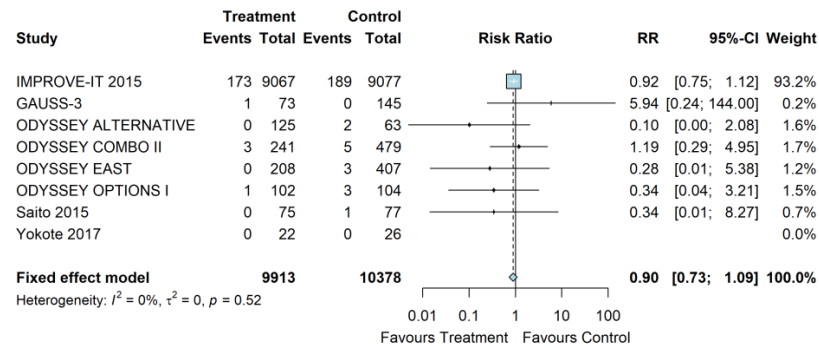
Abbreviations: CI, confidence interval; RR, relative ratio

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



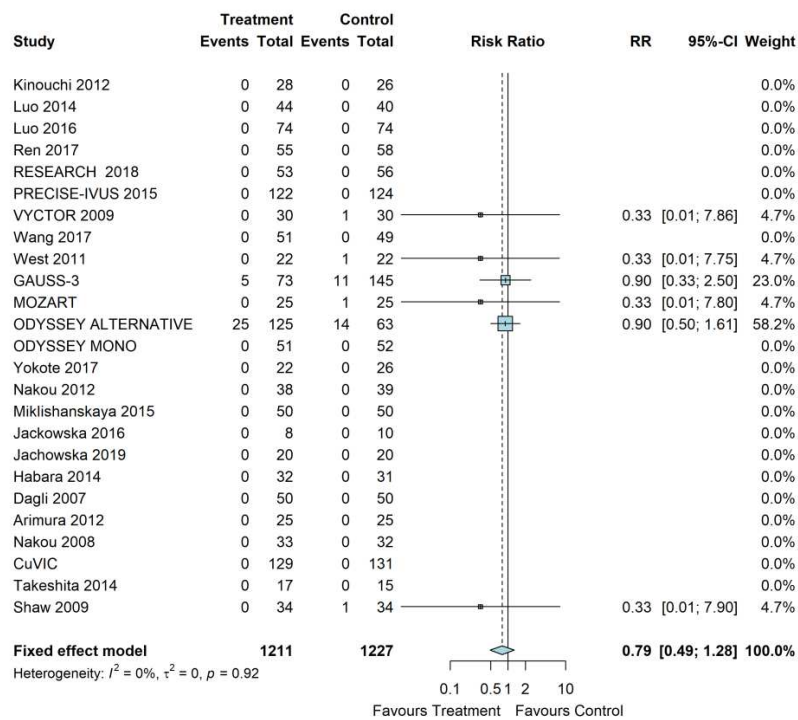
Abbreviations: CI, confidence interval; RR, relative ratio

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



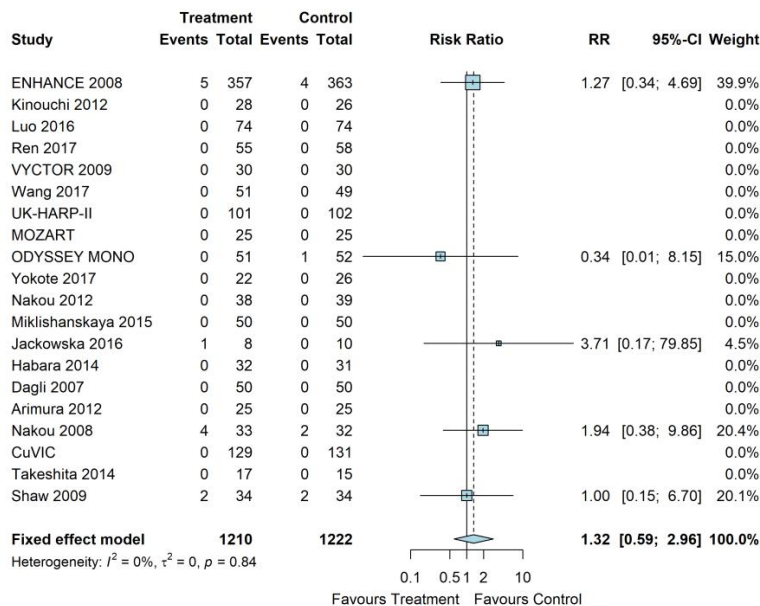
Abbreviations: CI, confidence interval; RR, relative ratio

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



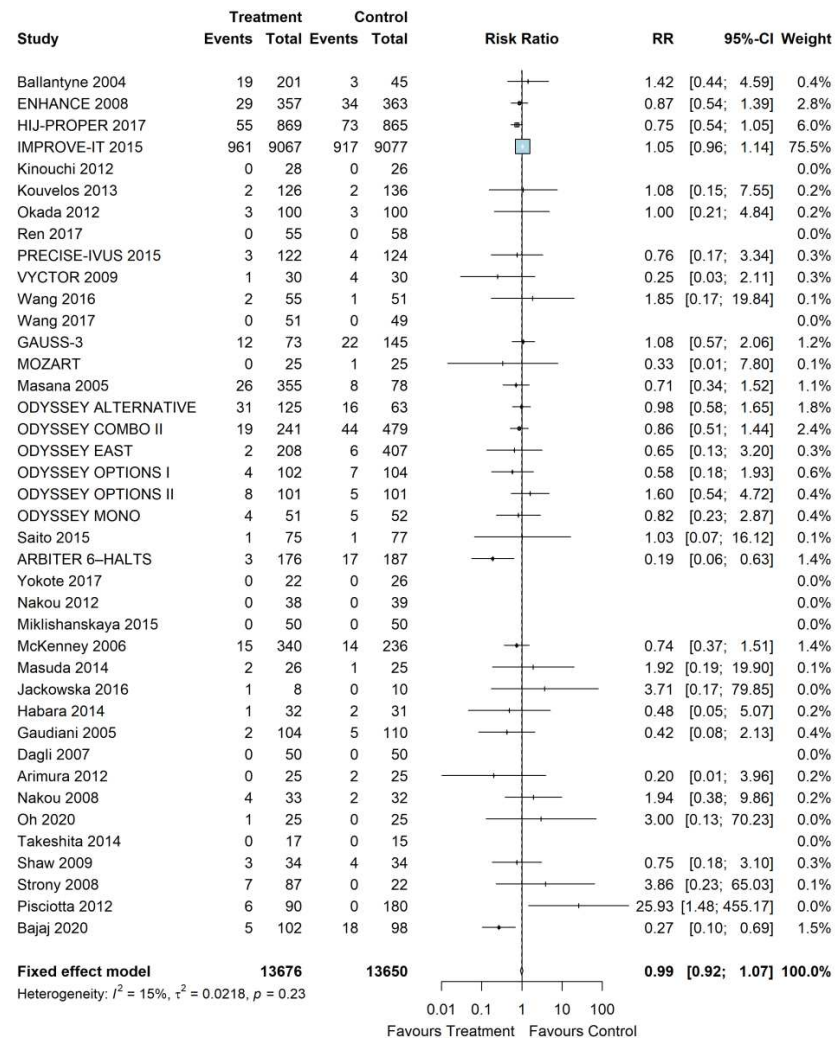
Abbreviations: CI, confidence interval; RR, relative ratio

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]).	Page 11
DISCUSSION			Page 11-13
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).	Page 11-12
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).	Page 12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 13
FUNDING			Page 13
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.	Page 13

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	Table 1
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

35	Disclosure of funding source	Page 13
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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 ¹³ N-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 photoleukoderma 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 (Armolid 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
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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.

	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	ezetimibe 10 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
HU-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-center	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
HJ-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 \geq 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 \geq 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 \geq 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 \geq 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 \geq 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 \geq 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 \geq 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
Battaglia 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

Reference

1. Anonymous. Ezetimibe add-on to statin therapy for effectiveness trial (EASE). *ACC Current Journal Review* 2004;13(7):14-15. doi: <http://dx.doi.org/10.1016/j.accreview.2004.07.001>
2. Katsiki N, Athyros VG, Mikhailidis DP. More news from IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial). *Hormones* 2016;15(1):5-7. doi: <https://dx.doi.org/10.14310/horm.2002.1658>
3. Tada H, Kobayashi J, Kawashiri MA, et al. Changes in lipoprotein lipase and endothelial lipase mass in familial hypercholesterolemia during three-drug lipid-lowering combination therapy. *Lipids in health and disease* 2016;15:66. doi: 10.1186/s12944-016-0238-z
4. Takase S, Matoba T. 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". *Arteriosclerosis, Thrombosis, and Vascular Biology* 2017;37(5):e54. doi: <http://dx.doi.org/10.1161/ATVBAHA.117.309301>
5. Troxel AB, Asch DA, Mehta SJ, et al. Rationale and design of a randomized trial of automated hovering for post-myocardial infarction patients: The HeartStrong program. *American Heart Journal* 2016;179:166-74. doi: <http://dx.doi.org/10.1016/j.ahj.2016.06.006>
6. Westerink J, Visseren F. 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". *Arteriosclerosis, Thrombosis, and Vascular Biology* 2017;37(5):e53. doi: <http://dx.doi.org/10.1161/ATVBAHA.117.309295>
7. 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)". *Circulation* 2018;138(17):1914-15. doi: 10.1161/CIRCULATIONAHA.118.035512
8. 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)". *Circulation* 2018;138(17):1912-13. doi: 10.1161/CIRCULATIONAHA.118.034068
9. 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)". *Circulation* 2018;137(24):2654-55. doi: 10.1161/CIRCULATIONAHA.117.032448

10. 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)". *Circulation* 2018;137(24):2656-57. doi: 10.1161/CIRCULATIONAHA.117.032249
11. 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)". *Circulation* 2018;137(24):2660-61. doi: 10.1161/CIRCULATIONAHA.118.033569
12. 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)". *Circulation* 2018;137(24):2658-59. doi: 10.1161/CIRCULATIONAHA.118.033559
13. 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. *Journal of general internal medicine* 2018;1-2. doi: 10.1007/s11606-018-4498-3
14. Hodges GW, Bang CN, Forman JL, et al. Effect of simvastatin and ezetimibe on suPAR levels and outcomes. *Atherosclerosis* 2018;272:129-36. doi: 10.1016/j.atherosclerosis.2018.03.030
15. Early combination therapy pays off. *MMW fortschritte der medizin* 158 (11) (pp 76), 2016 Date of publication: 09 jun 2016 2016 doi: 10.1007/s15006-016-8390-y
16. Abdelbary G, Nebsen M. Application of a novel UPLC-MS/MS method for the pharmacokinetic/bioequivalence determination of atorvastatin and ezetimibe in human plasma. *Journal of pharmacy research* 2013;7(1):24-32. doi: 10.1016/j.jopr.2013.01.010
17. Almquist T, Jacobson SH, Lins PE, et al. Effects of lipid-lowering treatment on platelet reactivity and platelet-leukocyte aggregation in diabetic patients without and with chronic kidney disease: a randomized trial. *Nephrology, dialysis, transplantation* 2012;27(9):3540-46. doi: 10.1093/ndt/gfs183
18. Almquist T, Mobarrez F, Jacobson SH, et al. Effects of lipid-lowering treatment on circulating microparticles in patients with diabetes mellitus and chronic kidney disease. *Nephrology, dialysis, transplantation* 2016;31(6):944-52. doi: 10.1093/ndt/gfv337
19. Araujo DB, Bertolami MC, Ferreira WP, et al. Pleiotropic effects with equivalent low-density lipoprotein cholesterol reduction: comparative study between simvastatin and simvastatin/ezetimibe coadministration. *Journal of cardiovascular pharmacology* 2010;55(1):1-5. doi: 10.1097/FJC.0b013e3181bfb1a2
20. Bahlmann E, Cramariuc D, Gerds E, et al. Impact of pressure recovery on echocardiographic assessment of asymptomatic aortic stenosis: a SEAS substudy. *JACC Cardiovascular imaging* 2010;3(6):555-62. doi: 10.1016/j.jcmg.2009.11.019

21. Bajaj HS, Brown RE, Jiandani DS, et al. Goal-RCT: results from the first randomized trial comparing colesevelam vs. ezetimibe in type 2 diabetes. *Circulation* 2017;136
22. Bahrami G, Mohammadi B, Khatabi PM, et al. 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. *Journal of chromatography B, analytical technologies in the biomedical and life sciences* 2010;878(28):2789-95. doi: 10.1016/j.jchromb.2010.08.023
23. Ballantyne C, Blazing M, King T, et al. Efficacy of co-administered ezetimibe plus simvastatin versus atorvastatin alone in adults with hypercholesterolemia. *Atherosclerosis Supplements* 2004;5(1):105.
24. Ballantyne C, Laufs U, Ray KK, et al. 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. *Atherosclerosis* 2019;287:e7-e8. doi: 10.1016/j.atherosclerosis.2019.06.020
25. Ballantyne CM, Hourii J, Notarbartolo A, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. *Circulation* 2003;107(19):2409-15. doi: 10.1161/01.CIR.0000068312.21969.C8
26. Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *European journal of preventive cardiology* 2019 doi: 10.1177/2047487319864671
27. Ballantyne CM, Weiss R, Moccetti T, et al. 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). *American Journal of Cardiology* 2007;99(5):673-80.
28. Izar MC, Barbosa SP, Lins LC, et al. Effects of ezetimibe on markers of synthesis and absorption of cholesterol in high-risk patients with elevated C-reactive protein. *European heart journal* 2013;34:768-69.
29. Bardini G, Giorda CB, Pontiroli AE, et al. Ezetimibe + simvastatin versus doubling the dose of simvastatin in high cardiovascular risk diabetics: a multicenter, randomized trial (the LEAD study). *Cardiovascular diabetology* 2010;9:20. doi: 10.1186/1475-2840-9-20
30. Bays H, Conard S, Leiter LA, et al. Are post-treatment low-density lipoprotein subclass pattern analyses potentially misleading? *Lipids in health and disease* 2010;9:136. doi: 10.1186/1476-511X-9-136
31. Bays HE, Averna M, Majul C, et al. Efficacy and safety of ezetimibe added to atorvastatin versus atorvastatin uptitration or switching to rosuvastatin in patients with primary hypercholesterolemia. *American journal of cardiology* 2013;112(12):1885-95. doi: 10.1016/j.amjcard.2013.08.031

32. Bays HE, Ose L, Fraser N, et al. 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. *Clinical therapeutics* 2004;26(11):1758-73. doi: 10.1016/j.clinthera.2004.11.016
33. Bays HE, Shah A, Macdonell G, et al. Effects of coadministered ezetimibe plus fenofibrate in mixed dyslipidemic patients with metabolic syndrome. *Metabolic syndrome and related disorders* 2011;9(2):135-42. doi: 10.1089/met.2010.0068
34. Briguori C, Madonna R, Zimarino M, et al. Rosuvastatin for Reduction of Myocardial Damage during Coronary Angioplasty - the Remedy Trial. *Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy* 2016;30(5):465-72. doi: 10.1007/s10557-016-6672-3
35. Brohet C, Banai S, Alings AM, et al. LDL-C goal attainment with the addition of ezetimibe to ongoing simvastatin treatment in coronary heart disease patients with hypercholesterolemia. *Current medical research and opinion* 2005;21(4):571-78. doi: 10.1185/030079905X382004
36. Brown BG, Taylor AJ. Does ENHANCE diminish confidence in lowering LDL or in ezetimibe? *New england journal of medicine* 2008;358(14):1504-07.
37. Brudi P, Reckless JP, Henry DP, et al. 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. *Cardiology* 2009;113(2):89-97. doi: 10.1159/000172795
38. Richard T, Lelubre C, Vanhaeverbeek M. Ezetimibe plus a statin after acute coronary syndromes. *New England journal of medicine* 2015;373(15):1475.
39. Chirinos JA, Williams MM, Bregman DB, et al. Efficacy of cholesterol uptake inhibition added to statin therapy among subjects following a low-carbohydrate diet: a randomized controlled trial. *American heart journal* 2010;159(5):918.e1-6. doi: 10.1016/j.ahj.2010.02.010
40. Cho L, Rocco M, Colquhoun D, et al. 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. *Clinical cardiology* 2014;37(3):131-39. doi: 10.1002/clc.22248
41. Coll B, Aragonés G, Parra S, et al. Ezetimibe effectively decreases LDL-cholesterol in HIV-infected patients. *AIDS (london, england)* 2006;20(12):1675-77. doi: 10.1097/01.aids.0000238418.43937.3b
42. Correia LC. Ezetimibe: clinical and scientific meaning of the IMPROVE-IT study. *Arquivos brasileiros de cardiologia* 2016;106(3):247-49.
43. Silbernagel G, Baumgartner I, Marz W. Ezetimibe plus a statin after acute coronary syndromes. *New England journal of medicine* 2015;373(15):1473.

44. Davidson MH, Ballantyne CM, Kerzner B, et al. Efficacy and safety of ezetimibe coadministered with statins: randomised, placebo-controlled, blinded experience in 2382 patients with primary hypercholesterolemia. *International journal of clinical practice* 2004;58(8):746-55. doi: 10.1111/j.1368-5031.2004.00289.x
45. Davidson MH, Voogt J, Luchoomun J, et al. Inhibition of intestinal cholesterol absorption with ezetimibe increases components of reverse cholesterol transport in humans. *Atherosclerosis* 2013;230(2):322-29. doi: 10.1016/j.atherosclerosis.2013.08.006
46. Dawson JA, Choke E, Loftus IM, et al. A randomised placebo-controlled double-blind trial to evaluate lipid-lowering pharmacotherapy on proteolysis and inflammation in abdominal aortic aneurysms. *European journal of vascular and endovascular surgery* 2011;41(1):28-35. doi: 10.1016/j.ejvs.2010.08.023
47. Denke M, Pearson T, McBride P, et al. Ezetimibe added to ongoing statin therapy improves LDL-C goal attainment and lipid profile in patients with diabetes or metabolic syndrome. *Diabetes & vascular disease research* 2006;3(2):93-102. doi: 10.3132/dvdr.2006.020
48. Drazen JM, Jarcho JA, Morrissey S, et al. Cholesterol lowering and ezetimibe. *New england journal of medicine* 2008;358(14):1507-08.
49. Dufour R, Bergeron J, Gaudet D, et al. Open-label therapy with alirocumab in patients with heterozygous familial hypercholesterolemia: results from three years of treatment. *International journal of cardiology* 2017;228:754-60. doi: 10.1016/j.ijcard.2016.11.046
50. Singh JS, Struthers AD, Lang CC. Ezetimibe plus a statin after acute coronary syndromes. *New England journal of medicine* 2015;373(15):1476.
51. Dujovne CA, Suresh R, McCrary Sisk C, et al. Safety and efficacy of ezetimibe monotherapy in 1624 primary hypercholesterolaemic patients for up to 2 years. *International journal of clinical practice* 2008;62(9):1332-36. doi: 10.1111/j.1742-1241.2008.01798.x
52. El-Tamalawy MM, Ibrahim OM, Hassan TM, et al. Effect of Combination Therapy of Ezetimibe and Atorvastatin on Remnant Lipoprotein Versus Double Atorvastatin Dose in Egyptian Diabetic Patients. *Journal of clinical pharmacology* 2018;58(1):34-41. doi: 10.1002/jcph.976
53. Feldman T, Koren M, Insull W, et al. 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. *American journal of cardiology* 2004;93(12):1481-86. doi: 10.1016/j.amjcard.2004.02.059
54. Fonseca FAH, Izar MC, Maugeri IML, et al. 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. *Trials* 2017;18(1) doi: <http://dx.doi.org/10.1186/s13063-017-2361-1>
55. Gagné C, Bays HE, Weiss SR, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *American journal of cardiology* 2002;90(10):1084-91. doi: 10.1016/s0002-9149(02)02774-1
56. Cruz-Fernández JM, Bedarida GV, Adgey J, et al. 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. *International journal of clinical practice* 2005;59(6):619-27. doi: 10.1111/j.1368-5031.2005.00565.x
57. Dawson J, Choke E, Cockerill G, et al. A randomized placebo-controlled double-blind trial to evaluate ezetimibe combination therapy on abdominal aortic aneurysm wall proteolysis and inflammation. *The vascular society of great britain & ireland yearbook, 2007* 2007:91.
58. Garcia MM, Varela CG, Silva PF, et al. Endothelial Effect of Statin Therapy at a High Dose Versus Low Dose Associated with Ezetimibe. *Arquivos brasileiros de cardiologia* 2016;106(4):279-88. doi: 10.5935/abc.20160048
59. Kastelein JJP, Bots ML. Statin Therapy with Ezetimibe or Niacin in High-Risk Patients. *New england journal of medicine* 2009;361(22):2180-83.
60. Koh KK, Oh PC, Sakuma I, et al. Vascular and metabolic effects of ezetimibe combined with simvastatin in patients with hypercholesterolemia. *International journal of cardiology* 2015;199:126-31. doi: 10.1016/j.ijcard.2015.07.016
61. Kovarnik T, Chen Z, Wahle A, et al. Pathologic Intimal Thickening Plaque Phenotype: not as Innocent as Previously Thought. A Serial 3D Intravascular Ultrasound Virtual Histology Study. *Revista espanola de cardiologia (english ed)* 2017;70(1):25-33. doi: 10.1016/j.rec.2016.04.058
62. Lattouf C, Jimenez JJ, Tosti A, et al. Treatment of alopecia areata with simvastatin/ezetimibe. *Journal of the american academy of dermatology* 2015;72(2):359-61. doi: 10.1016/j.jaad.2014.11.006
63. Le NA, Tomassini JE, Tershakovec AM, et al. 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. *Journal of the American Heart Association* 2015;4(10) doi: <http://dx.doi.org/10.1161/JAHA.114.001675>
64. Olijhoek JK, Hajer GR, Graaf YVD, et al. 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. *Journal of Cardiovascular Pharmacology* 2008;52(2):145-50. doi: <http://dx.doi.org/10.1097/FJC.0b013e31817ffe76>
65. Oswald S, Nassif A, Modest C, et al. Pharmacokinetic and pharmacodynamic interactions between the immunosuppressant sirolimus and the lipid-lowering drug

- ezetimibe in healthy volunteers. *Clinical pharmacology and therapeutics* 2010;87(6):663-67. doi: 10.1038/clpt.2009.266
66. Oswald S, Nassif A, Modess C, et al. Drug interactions between the immunosuppressant tacrolimus and the cholesterol absorption inhibitor ezetimibe in healthy volunteers. *Clinical pharmacology and therapeutics* 2011;89(4):524-28. doi: 10.1038/clpt.2011.4
67. Palmer JL, Kunihitlu A, Costantini A, et al. Pharmacokinetic bioequivalence crossover study of branded generic and innovator formulations of the cholesterol lowering agent ezetimibe. *Clinical pharmacology in drug development* 2014;3(3):242-48. doi: 10.1002/cpdd.80
68. Nunes JP. Ezetimibe plus a statin after acute coronary syndromes. *New England journal of medicine* 2015;373(15):1475.
69. Pearson TA, Denke MA, McBride PE, et al. 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. *Mayo clinic proceedings* 2005;80(5):587-95. doi: 10.4065/80.5.587
70. Perez De Isla L, Alonso R, Watts GF, et al. Attainment of LDL-cholesterol treatment goals in patients with familial hypercholesterolemia: 5-year SAFEHEART registry follow-up. *Journal of the american college of cardiology* 2016;67(11):1278-85. doi: 10.1016/j.jacc.2016.01.008
71. Raal FJ, Hovingh GK, Blom D, et al. 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. *The lancet diabetes and endocrinology* 2017;(no pagination) doi: 10.1016/S2213-8587%2817%2930044-X
72. Rey J, Poitiers F, Paehler T, et al. Relationship Between Low-Density Lipoprotein Cholesterol, Free Proprotein Convertase Subtilisin/Kexin Type 9, and Alirocumab Levels After Different Lipid-Lowering Strategies. *Journal of the american heart association* 2016;5(6) doi: 10.1161/JAHA.116.003323
73. Egom EE. Ezetimibe plus a statin after acute coronary syndromes. *New England journal of medicine* 2015;373(15):1474.
74. Roeters van Lennep HW, Liem AH, Dunselman PH, et al. The efficacy of statin monotherapy uptitration versus switching to ezetimibe/simvastatin: results of the EASEGO study. *Current medical research and opinion* 2008;24(3):685-94. doi: 10.1185/030079908X273273
75. Rosen JB, Jimenez JG, Pirags V, et al. 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. *Diabetes & vascular disease research* 2013;10(3):277-86. doi: 10.1177/1479164112465212
76. Ruggenti P, Cattaneo D, Rota S, et al. 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. *Diabetes care* 2010;33(9):1954-56. doi: 10.2337/dc10-0320
77. Sarigianni M, Katsiki N, Mikhailidis DP. 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. *Diabetes care* 2010;33(10):e132. doi: 10.2337/dc10-1250
78. Couture P, Durand M, Laskine M. Ezetimibe plus a statin after acute coronary syndromes. *New England journal of medicine* 2015;373(15):1473-74.
79. Soulele K, Karalis V. Development of a joint population pharmacokinetic model of ezetimibe and its conjugated metabolite. *European journal of pharmaceutical sciences* 2019;128:18-26. doi: 10.1016/j.ejps.2018.11.018
80. Strony J, Hoffman R, Hanson M, et al. 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. *Clinical therapeutics* 2008;30(12):2280-97. doi: 10.1016/j.clinthera.2008.12.008
81. Thompson PD, MacDougall DE, Newton RS, et al. Treatment with ETC-1002 alone and in combination with ezetimibe lowers LDL cholesterol in hypercholesterolemic patients with or without statin intolerance. *Journal of clinical lipidology* 2016;10(3):556-67. doi: 10.1016/j.jacl.2015.12.025
82. Toth PP. Ezetimibe provides incremental reduction in risk for cardiovascular events and need for revascularisation following an acute coronary syndrome. *Evidence-based medicine* 2015;20(5):176.
83. Tziomalos K, Athyros VG. Priority Paper Evaluation: are antibodies against PCSK9 the statins of the 21st century? *Clinical lipidology* 2014;9(2):141-44. doi: 10.2217/clp.14.1
84. Villa J, Pratley RE. Ezetimibe/simvastatin or atorvastatin for the treatment of hypercholesterolemia in patients with the metabolic syndrome: the VYMET study. *Current diabetes reports* 2010;10(3):173-75.
85. Weingartner O, Bohm M, Laufs U. Letter by Weingärtner et al regarding article, "combined effects of ezetimibe and phytosterols on cholesterol metabolism: a randomized, controlled feeding study in humans". *Circulation* 2012;125(10):e456. doi: 10.1161/CIRCULATIONAHA.111.060806
86. Westerweel PE, Visseren FL, Hajer GR, et al. Endothelial progenitor cell levels in obese men with the metabolic syndrome and the effect of simvastatin monotherapy vs. simvastatin/ezetimibe combination therapy. *European heart journal* 2008;29(22):2808-17. doi: 10.1093/eurheartj/ehn431
87. Wohl DA, Waters D, Simpson RJ, et al. Ezetimibe alone reduces low-density lipoprotein cholesterol in HIV-infected patients receiving combination antiretroviral therapy. *Clinical infectious diseases* 2008;47(8):1105-08. doi: 10.1086/592116
88. Wu NQ, Guo YL, Zhu CG, et al. Comparison of statin plus ezetimibe with double-dose statin on lipid profiles and inflammation markers. *Lipids in health and disease* 2018;17(1):265. doi: 10.1186/s12944-018-0909-z

89. Yu RZ, Geary RS, Flaim JD, et al. 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. *Clinical pharmacokinetics* 2009;48(1):39-50. doi: 10.2165/0003088-200948010-00003
90. Zema MJ. Colesevelam HCl and ezetimibe combination therapy provides effective lipid-lowering in difficult-to-treat patients with hypercholesterolemia. *American journal of therapeutics* 2005;12(4):306-10. doi: 10.1097/01.mjt.0000155109.69831.a3
91. Yu RZ, Geary RS, Flaim JD, et al. 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. *Clinical Pharmacokinetics* 2009;48(1):39-50. doi: <http://dx.doi.org/10.2165/0003088-200948010-00003>
92. Yokote K, Suzuki A, Li Y, et al. Pharmacokinetics and exploratory efficacy biomarkers of bococizumab, an anti-PCSK9 monoclonal antibody, in hypercholesterolemic Japanese subjects *International journal of clinical pharmacology and therapeutics* 2019;57(12):575-89. doi: 10.5414/CP203418
93. Yang LPH, Keating GM. Fenofibric acid: In combination therapy in the treatment of mixed dyslipidemia. *American Journal of Cardiovascular Drugs* 2009;9(6):401-09. doi: <http://dx.doi.org/10.2165/11203920-000000000-00000>
94. Wu NQ, Guo YL, Zhu CG, et al. Comparison of statin plus ezetimibe with double-dose statin on lipid profiles and inflammation markers 11 Medical and Health Sciences 1103 Clinical Sciences. *Lipids in Health and Disease* 2018;17(1) doi: <http://dx.doi.org/10.1186/s12944-018-0909-z>
95. Weingartner O, Sijbrands E, Lutjohann D. 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". *Circulation* 2020:E65-E66. doi: <http://dx.doi.org/10.1161/CIRCULATIONAHA.119.043726>
96. Watson KE, Fonarow GC. Closing the remaining evidence gap randomized controlled trial data to support statin therapy for low-Density lipoprotein ≥ 190 mg/dL. *Circulation* 2017;136(20):1892-94. doi: <http://dx.doi.org/10.1161/CIRCULATIONAHA.117.030989>
97. Vogt A, Parhofer KG. The potential of mipomersen, an ApoB synthesis inhibitor, to reduce necessity for LDL-apheresis in patients with heterozygous familial hypercholesterolemia and coronary artery disease. *Expert Opinion on Pharmacotherapy* 2013;14(6):691-97. doi: <http://dx.doi.org/10.1517/14656566.2013.779253>
98. Virani SS, Kennedy KF, Akeroyd JM, et al. 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. *Circulation* 2018;Cardiovascular quality and outcomes. 11(5):e004652. doi: <http://dx.doi.org/10.1161/CIRCOUTCOMES.118.004652>
99. Viney NJ, Yeang C, Yang X, et al. Relationship between "LDL-C" estimated true LDL-C, apolipoprotein B-100, and PCSK9 levels following lipoprotein(a) lowering with an antisense oligonucleotide. *Journal of Clinical Lipidology* 2018;12(3):702-10. doi: <http://dx.doi.org/10.1016/j.jacl.2018.02.014>
100. Tommaso CL. One year perspective on COURAGE. *Catheterization and Cardiovascular Interventions* 2008;72(3):426-29. doi: <http://dx.doi.org/10.1002/ccd.21642>
101. Stuart B, Samantha Shoemaker J, Dai M, et al. Regions with higher medicare Part D spending show better drug adherence, but not lower medicare costs for two diseases. *Health Affairs* 2013;32(1):120-26. doi: <http://dx.doi.org/10.1377/hlthaff.2011.0727>
102. Shigematsu E, Yamakawa T, Taguri M, et al. Efficacy of ezetimibe is associated with gender and baseline lipid levels in patients with type 2 diabetes. *Journal of Atherosclerosis and Thrombosis* 2012;19(9):846-53. doi: <http://dx.doi.org/10.5551/jat.12799>
103. Sacks FM. Low-density lipoprotein lowering therapy: An analysis of the options. *Journal of the American College of Cardiology* 2002;40(12):2135-38. doi: <http://dx.doi.org/10.1016/S0735-1097%2802%2902609-8>
104. Rossebo AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *New England Journal of Medicine* 2008;359(13):1343-56. doi: <https://dx.doi.org/10.1056/NEJMoa0804602>
105. Rodes-Cabau J, Tardif JC, Cossette M, et al. Acute Effects of Statin Therapy on Coronary Atherosclerosis Following an Acute Coronary Syndrome. *American Journal of Cardiology* 2009;104(6):750-57. doi: <http://dx.doi.org/10.1016/j.amjcard.2009.05.009>
106. Ray KK, Stoekenbroek RM, Kallend D, et al. 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. *JAMA Cardiology* 2019;4(11):1067-75. doi: <http://dx.doi.org/10.1001/jamacardio.2019.3502>
107. Phillips PS. Balancing randomized trials with anecdote. *Annals of Internal Medicine* 2009;150(12):885-86. doi: <http://dx.doi.org/10.7326/0003-4819-150-12-200906160-00014>
108. Pesaro AE, Serrano CV, Fernandes JL, et al. Pleiotropic effects of ezetimibe/simvastatin vs. high dose simvastatin. *International journal of cardiology* 2012;158(3):400-04. doi: 10.1016/j.ijcard.2011.01.062
109. Panza GA, Taylor BA, Dada MR, et al. Changes in muscle strength in individuals with statin-induced myopathy: A summary of 3 investigations. *Journal of Clinical Lipidology* 2015;9(3):351-56. doi: <http://dx.doi.org/10.1016/j.jacl.2015.01.004>

110. Olijhoek JK, Hajer GR, van der Graaf Y, et al. 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. *Journal of cardiovascular pharmacology* 2008;52(2):145-50. doi: 10.1097/FJC.0b013e31817ffe76
111. O'Keefe JH, Carter MD, Lavie CJ, et al. The gravity of JUPITER (justification for the use of statins in primary prevention: An Intervention Trial Evaluating Rosuvastatin). *Postgraduate Medicine* 2009;121(3):113-18. doi: <http://dx.doi.org/10.3810/pgm.2009.05.2010>
112. Neil A, Humphries SE. Statins and familial hypercholesterolaemia. *BMJ (Online)* 2009;338(7688):185-86. doi: <http://dx.doi.org/10.1136/bmj.a3041>
113. Miyazaki-Anzai S, Masuda M, Demos-Davies KM, et al. Endoplasmic reticulum stress effector CCAAT/enhancer-binding protein homologous protein (CHOP) regulates chronic kidney disease-induced vascular calcification. *Journal of the American Heart Association* 2014;3(3) doi: <http://dx.doi.org/10.1161/JAHA.114.000949>
114. McPherson R, Hegele RA. Rescued by randomization (Clinical and Mendelian). *Arteriosclerosis, Thrombosis, and Vascular Biology* 2015;35(3):e13-e15. doi: <http://dx.doi.org/10.1161/ATVBAHA.114.305012>
115. McKenney J, Ballantyne CM, Feldman TA, et al. LDL-C goal attainment with ezetimibe plus simvastatin coadministration vs atorvastatin or simvastatin monotherapy in patients at high risk of CHD. *Medgenmed : medscape general medicine* 2005;7(3):3.
116. Maron DJ, Spertus JA, Mancini GBJ, et al. 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. *American Journal of Cardiology* 2009;104(8):1055-62. doi: <http://dx.doi.org/10.1016/j.amjcard.2009.05.056>
117. Lin M, Cui H, Chen W, et al. Longitudinal assessment of carotid plaque texture in three-dimensional ultrasound images based on semi-supervised graph-based dimensionality reduction and feature selection. *Computers in Biology and Medicine* 2020;116 (no pagination) doi: <http://dx.doi.org/10.1016/j.compbiomed.2019.103586>
118. Le NA, Tomassini JE, Tershakovec AM, et al. 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. *Journal of the american heart association* 2015;4(10):e001675. doi: 10.1161/JAHA.114.001675
119. Kosoglou T, Meyer I, Veltri EP, et al. Pharmacodynamic interaction between the new selective cholesterol absorption inhibitor ezetimibe and simvastatin. *British journal of clinical pharmacology* 2002;54(3):309-19. doi: 10.1046/j.1365-2125.2002.01633.x

120. Kimura G, Kasahara M, Ueshima K, et al. 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. *Clinical and Experimental Nephrology* 2017;21(3):417-24. doi: <http://dx.doi.org/10.1007/s10157-016-1304-6>
121. Kim KJ, Kim SH, Yoon YW, et al. Effect of fixed-dose combinations of ezetimibe plus rosuvastatin in patients with primary hypercholesterolemia: mRS-ROZE (Multicenter Randomized Study of ROsuvastatin and eZetimibe). *Cardiovascular therapeutics* 2016;34(5):371-82. doi: 10.1111/1755-5922.12213
122. Jakulj L, Trip MD, Sudhop T, et al. Inhibition of cholesterol absorption by the combination of dietary plant sterols and ezetimibe: effects on plasma lipid levels. *Journal of lipid research* 2005;46(12):2692-98. doi: 10.1194/jlr.M500260-JLR200
123. Hermans MP, Ahn SA, Rousseau MF. Crossing family histories of diabetes and cardiovascular disease leads to unexpected outcomes in diabetic offspring. *Journal of Diabetes* 2019;11(4):301-08. doi: <http://dx.doi.org/10.1111/1753-0407.12840>
124. Harrison SA, Rossaro L, Hu KQ, et al. Serum cholesterol and statin use predict virological response to peginterferon and ribavirin therapy. *Hepatology* 2010;52(3):864-74. doi: <http://dx.doi.org/10.1002/hep.23787>
125. Hamilton-Craig IR. After ENHANCE: The cholesterol hypothesis is alive and well. *Medical Journal of Australia* 2008;189(6):303-04.
126. Ginsberg HN, Bonds DE, Lovato LC, et al. Evolution of the Lipid Trial Protocol of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial. *American Journal of Cardiology* 2007;99(12 SUPPL.):S56-S67. doi: <http://dx.doi.org/10.1016/j.amjcard.2007.03.024>
127. Enajat M, Teerenstra S, Van Kuilenburg JT, et al. 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. *Drugs and Aging* 2009;26(7):585-93. doi: <http://dx.doi.org/10.2165/10558450-000000000-00000>
128. Dufour R, Hovingh GK, Guyton JR, et al. 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. *Journal of Clinical Lipidology* 2019;13(1):138-47. doi: <http://dx.doi.org/10.1016/j.jacl.2018.11.007>
129. Dorais M, Chirovsky D, Ambegaonkar B, et al. Utilization patterns of extended-release niacin in Canada: Analysis of an administrative claims database. *Canadian Journal of Cardiology* 2010;26(7):e229-e35. doi: [http://dx.doi.org/10.1016/S0828-282X\(10\)70413-X](http://dx.doi.org/10.1016/S0828-282X(10)70413-X)
130. Davies GM, Cook JR, Erbey J, et al. Projected coronary heart disease risk benefit with ezetimibe. *Atherosclerosis* 2005;179(2):375-78. doi: <http://dx.doi.org/10.1016/j.atherosclerosis.2004.10.030>

131. Conti CR. Expanding the understanding of the treatment of chronic angina: A 21st century approach - Part II. *Clinical Cardiology* 2008;31(7):295-96. doi: <http://dx.doi.org/10.1002/clc.20406>
132. Ansquer JC, Bekaert I, Guy M, et al. 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. *American journal of cardiovascular drugs* 2009;9(2):91-101. doi: 10.1007/bf03256580
133. Almquist T, Jacobson SH, Lins PE, et al. Effects of lipid-lowering treatment on platelet reactivity and plateletleukocyte aggregation in diabetic patients without and with chronic kidney disease: A randomized trial. *Nephrology Dialysis Transplantation* 2012;27(9):3540-46. doi: <http://dx.doi.org/10.1093/ndt/gfs183>
134. Alexanderson E, Garcia-Rojas L, Jimenez M, et al. Effect of ezetimibe-simvastatine over endothelial dysfunction in dyslipidemic patients: Assessment by ¹³N-ammonia positron emission tomography. *Journal of Nuclear Cardiology* 2010;17(6):1015-22. doi: <http://dx.doi.org/10.1007/s12350-010-9273-8>
135. Zou X, Si QJ. Is combined lipid-regulating therapy safe and feasible for the very old patients with mixed dyslipidemia? *Journal of Geriatric Cardiology* 2013;10(4):349-54. doi: <https://dx.doi.org/10.3969/j.issn.1671-5411.2013.04.014>
136. Zimlichman E, Szyper-Kravitz M, Katz U, et al. Intensive lipid-lowering therapy: obvious benefits, possible risks. *Isr Med Assoc J* 2006;8(12):890-1.
137. Yoneda M, Fujita K, Imajo K, et al. Induction of microsomal triglyceride transfer protein expression is a candidate mechanism by which ezetimibe therapy might exert beneficial effects in patients with nonalcoholic steatohepatitis. *J Gastroenterol* 2011;46(3):415-6; author reply 17. doi: <https://dx.doi.org/10.1007/s00535-010-0356-8>
138. Wu Y, Xu MJ, Cao Z, et al. Heterozygous Ldlr-Deficient Hamster as a Model to Evaluate the Efficacy of PCSK9 Antibody in Hyperlipidemia and Atherosclerosis. *International Journal of Molecular Sciences* 2019;20(23):26. doi: <https://dx.doi.org/10.3390/ijms20235936>
139. Wu NQ, Guo YL, Zhu CG, et al. Rapid Regression of Multiple-Site Xanthomas in an Adult With Homozygous Familial Hypercholesterolemia by Triple Lipid-Lowering Drugs. *American Journal of Therapeutics* 2019;26(6):e775-e77. doi: <https://dx.doi.org/10.1097/MJT.0000000000000868>
140. Toth PP, Catapano AL, Farnier M, et al. Effect on Fasting Serum Glucose Levels of Adding Ezetimibe to Statins in Patients With Nondiabetic Hypercholesterolemia. *American Journal of Cardiology* 2016;118(12):1812-20. doi: <https://dx.doi.org/10.1016/j.amjcard.2016.08.071>
141. Szabo RP, Varga I, Balla J, et al. Cardiovascular Screening and Management Among Kidney Transplant Candidates in Hungary. *Transplantation Proceedings* 2015;47(7):2192-5. doi: <https://dx.doi.org/10.1016/j.transproceed.2015.07.018>
142. Stroup JS, Kane MP, Busch RS. The antilipidemic effects of ezetimibe in patients with diabetes. *Diabetes Care* 2003;26(10):2958-9.

143. Stefanutti C, D'Alessandri G, Russi G, et al. Treatment of symptomatic HyperLp(a)lipoproteinemia with LDL-apheresis: a multicentre study. *Atherosclerosis Supplements* 2009;10(5):89-94. doi: [https://dx.doi.org/10.1016/S1567-5688\(09\)71819-7](https://dx.doi.org/10.1016/S1567-5688(09)71819-7)
144. Stebbing J, Asghar AK, Holmes P, et al. Use of ezetimibe during HIV infection. *Journal of Antimicrobial Chemotherapy* 2009;63(1):218-20. doi: <https://dx.doi.org/10.1093/jac/dkn440>
145. Spence JD. Asymptomatic carotid stenosis. *Circulation* 2013;127(6):739-42. doi: <https://dx.doi.org/10.1161/CIRCULATIONAHA.112.153734>
146. Spence JD. Letter to the Editor: The ezetimibe 'controversy' is a misunderstanding. *Expert Opinion on Pharmacotherapy* 2012;13(17):2579-80; author reply 80. doi: <https://dx.doi.org/10.1517/14712598.2012.727618>
147. Spence JD. Is carotid intima-media thickness a reliable clinical predictor? *Mayo Clinic Proceedings* 2008;83(11):1299-300; author reply 300-1. doi: <https://dx.doi.org/10.4065/83.11.1299>
148. Soza A. Hepatitis C RNA clearance after treatment with ezetimibe. *Liver Int* 2012;32(8):1323-4. doi: <https://dx.doi.org/10.1111/j.1478-3231.2012.02848.x>
149. SoRelle R. New lipid-lowering combo proves successful. *Circulation* 2003;107(19):e9043-4.
150. Smith D. Making sense of ENHANCE: ezetimibe (Zetia) lowers LDL cholesterol but doesn't decrease carotid intima-media thickness. *Mt Sinai J Med* 2008;75(2):143-7. doi: <https://dx.doi.org/10.1002/msj.20031>
151. Sijbrands EJ. Inhibition of PCSK9 in familial hypercholesterolaemia. *Lancet* 2012;380(9836):6-7. doi: [https://dx.doi.org/10.1016/S0140-6736\(12\)60814-9](https://dx.doi.org/10.1016/S0140-6736(12)60814-9)
152. Settegren M, Ryden L, Pernow J. Letter by Settegren 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". *Circulation* 2009;120(9):e68; author reply e69-70. doi: <https://dx.doi.org/10.1161/CIRCULATIONAHA.109.854315>
153. Saougos VG, Tambaki AP, Kalogirou M, et al. Differential effect of hypolipidemic drugs on lipoprotein-associated phospholipase A2. *Arterioscler Thromb Vasc Biol* 2007;27(10):2236-43.
154. Roberts WC. Two more drugs for dyslipidemia. *American Journal of Cardiology* 2004;93(6):809-11.
155. Rivers SM, Kane MP, Busch RS, et al. Colesevelam hydrochloride-ezetimibe combination lipid-lowering therapy in patients with diabetes or metabolic syndrome and a history of statin intolerance. *Endocrine Practice* 2007;13(1):11-6.
156. Pourafkari L, Mahdavi-Fard A, Nader ND. Effects of Statins on the Development of Cataract-the Long Standing Debate. *American Journal of Cardiology* 2016;117(3):489-90. doi: <https://dx.doi.org/10.1016/j.amjcard.2015.11.053>

157. Pisciotta L, Fasano T, Bellocchio A, et al. Effect of ezetimibe coadministered with statins in genotype-confirmed heterozygous FH patients. *Atherosclerosis* 2007;194(2):e116-22.
158. Pesaro AE, Granger CB, Lopes RD. Reduction of ischemic events in Improved Reduction of Outcomes: Vytorin Efficacy International Trial: Intensive cholesterol lowering or ezetimibe antithrombotic effects? *American Heart Journal* 2016;172:42-4. doi: <https://dx.doi.org/10.1016/j.ahj.2015.11.001>
159. Pauriah M, Struthers AD, Lang CC. Biomarkers and surrogate endpoints in cardiovascular therapeutics research: under scrutiny following results of the ENHANCE Study. *Cardiovascular therapeutics* 2008;26(2):85-8. doi: <https://dx.doi.org/10.1111/j.1527-3466.2008.00048.x>
160. Paraskevas KI, Mikhailidis DP, Giannoukas AD. Atorvastatin in combination with ezetimibe and carotid atherosclerosis. *Genet Mol Res* 2014;13(3):4805-7. doi: <https://dx.doi.org/10.4238/2014.July.2.10>
161. Okada K, Kimura K, Iwahashi N, et al. Clinical usefulness of additional treatment with ezetimibe in patients with coronary artery disease on statin therapy. - From the viewpoint of cholesterol metabolism. *Circulation journal* 2011;75(10):2496-504. doi: 10.1253/circj.cj-11-0391
162. Moro J, Almenar L, Martinez-Dolz L, et al. Ezetimibe in heart transplantation: initial experience. *Transplantation Proceedings* 2007;39(7):2389-92.
163. Monrroy-Bravo H, Angulo J, Pino K, et al. Effect of ezetimibe in HCV viral load after liver transplantation. *Ann Hepatol* 2016;15(5):803-5. doi: <https://dx.doi.org/10.5604/16652681.1212623>
164. Mignarri A, Carecchio M, Del Puppo M, et al. SPG5 siblings with different phenotypes showing reduction of 27-hydroxycholesterol after simvastatin-ezetimibe treatment. *J Neurol Sci* 2017;383:39-41. doi: <https://dx.doi.org/10.1016/j.jns.2017.10.022>
165. Mascitelli L, Goldstein MR. Evaluating Statin Versus Statin Plus Ezetimibe for Coronary Plaque Regression. *Journal of the American College of Cardiology* 2015;66(25):2916. doi: <https://dx.doi.org/10.1016/j.jacc.2015.08.1131>
166. Masana L, Pedro-Botet J, Civeira F. IMPROVE-IT clinical implications. Should the "high-intensity cholesterol-lowering therapy" strategy replace the "high-intensity statin therapy"? *Atherosclerosis* 2015;240(1):161-2. doi: <https://dx.doi.org/10.1016/j.atherosclerosis.2015.03.002>
167. Lopez V, Gutierrez C, Gutierrez E, et al. Treatment with ezetimibe in kidney transplant recipients with uncontrolled dyslipidemia. *Transplantation Proceedings* 2008;40(9):2925-6. doi: <https://dx.doi.org/10.1016/j.transproceed.2008.09.046>
168. Loi C, Starace M, Piraccini BM. Alopecia areata (AA) and treatment with simvastatin/ezetimibe: Experience of 20 patients. *Journal of the American Academy of Dermatology* 2016;74(5):e99-e100. doi: <https://dx.doi.org/10.1016/j.jaad.2015.09.071>

169. Li L, Zhang M, Su F, et al. Combination therapy analysis of ezetimibe and statins in Chinese patients with acute coronary syndrome and type 2 diabetes. *Lipids health dis* 2015;14:10. doi: <https://dx.doi.org/10.1186/s12944-015-0004-7>
170. Krysiak R, Szkrobka W, Okopien B. 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. *Exp Clin Endocrinol Diabetes* 2016;124(9):577-81.
171. Kostapanos MS, Elisaf MS, Mikhailidis DP. Ezetimibe - a new approach in hypercholesterolemia management. *Pharmacol Rep* 2012;64(4):997-8.
172. Koren MJ, Lundqvist P, Bolognese M, et al. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. *Journal of the American College of Cardiology* 2014;63(23):2531-40. doi: 10.1016/j.jacc.2014.03.018
173. Koh KK. Intriguing Off-Target Effects of Ezetimibe. *Journal of the American College of Cardiology* 2015;66(24):2808. doi: <https://dx.doi.org/10.1016/j.jacc.2015.08.1130>
174. Knowles JW, Howard WB, Karayan L, et al. Access to Nonstatin Lipid-Lowering Therapies in Patients at High Risk of Atherosclerotic Cardiovascular Disease. *Circulation* 2017;135(22):2204-06. doi: <https://dx.doi.org/10.1161/CIRCULATIONAHA.117.027705>
175. Kawaguchi R. Low-density lipoprotein cholesterol lowering therapy and established atherosclerosis. *Circulation Journal* 2012;76(1):49-50.
176. Avellone G, Di Garbo V, Guarnotta V, et al. Efficacy and safety of long-term ezetimibe/simvastatin treatment in patients with familial hypercholesterolemia. *International Angiology* 2010;29(6):514-24.
177. Hurley DL, Isley WL. Getting there: statin plus ezetimibe for low-density lipoprotein cholesterol goals. *Mayo Clinic Proceedings* 2005;80(5):585-6.
178. Higashiyama A, Yokoyama T, Omoto Y, et al. Flutamide-induced photoleukomelanoderma. *J Dermatol* 2016;43(9):1105-6. doi: <https://dx.doi.org/10.1111/1346-8138.13340>
179. Gonzalez Sanchidrian S, Labrador Gomez PJ, Aguilar Aguilar JC, et al. Evolocumab for the treatment of heterozygous familial hypercholesterolemia in end-stage chronic kidney disease and dialysis. *Nefrologia* 2019;39(2):218-20. doi: <https://dx.doi.org/10.1016/j.nefro.2018.09.005>
180. Ballantyne CM, Abate N, Yuan Z, et al. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) study. *American heart journal* 2005;149(3):464-73.
181. Fonseca HA, Izar MC, Bianco HT, et al. Ezetimibe, oxidized low density lipoprotein, Lp (a), and dyslipidemia. *J Atheroscler Thromb* 2010;17(8):888.
182. Ferreira CES, Franca CN, Izar MCO, et al. High-intensity statin monotherapy versus moderate-intensity statin plus ezetimibe therapy: effects on vascular

- biomarkers. *International journal of cardiology* 2015;180:78-79. doi: 10.1016/j.ijcard.2014.11.177
183. Feldman T, Koren M, Insull Jr W, et al. 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. *American Journal of Cardiology* 2004;93(12):1481-86. doi: <http://dx.doi.org/10.1016/j.amjcard.2004.02.059>
184. Elsaies A, Lund C, Kerty E. Ptosis, diplopia and statins: an association? *Eur J Neurol* 2008;15(10):e92-3. doi: <https://dx.doi.org/10.1111/j.1468-1331.2008.02234.x>
185. Doherty E, Lumb PJ, Chik G, et al. Ezetimibe-induced hyperlipidaemia. *International Journal of Clinical Practice* 2005;Supplement.(147):3-5.
186. Di Pierro F, Bellone I, Rapacioli G, et al. Clinical role of a fixed combination of standardized Berberis aristata and Silybum marianum extracts in diabetic and hypercholesterolemic patients intolerant to statins. *Diabetes Metab Syndr Obes* 2015;8:89-96. doi: <https://dx.doi.org/10.2147/DMSO.S78877>
187. Derosa G, D'Angelo A, Franzetti IG, et al. 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. *J Clin Pharm Ther* 2009;34(3):267-76.
188. De Ferrari GM, Perna GP, Nicosia A, et al. Available oral lipid-lowering agents could bring most high-risk patients to target: an estimate based on the Dyslipidemia International Study II-Italy. *Journal of Cardiovascular Medicine* 2018;19(9):485-90. doi: <https://dx.doi.org/10.2459/JCM.0000000000000680>
189. Cerda A, Rodrigues AC, Alves C, et al. Modulation of adhesion molecules by cholesterol-lowering therapy in mononuclear cells from hypercholesterolemic patients. *Cardiovascular therapeutics* 2015;33(4):168-76. doi: <https://dx.doi.org/10.1111/1755-5922.12126>
190. Brown AJ. Atherosclerosis: cell biology and lipoproteins: cholesterol absorption inhibitors: gateway therapy for hypercholesterolaemia. *Current Opinion in Lipidology* 2002;13(6):701-3.
191. Bennett S, Sager P, Lipka L, et al. Consistency in efficacy and safety of ezetimibe coadministered with statins for treatment of hypercholesterolemia in women and men. *Journal of women's health* 2004;13(10):1101-07.
192. Bae J, Hong N, Lee BW, et al. Comparison of Renal Effects of Ezetimibe-Statin Combination versus Statin Monotherapy: A Propensity-Score-Matched Analysis. *J* 2020;9(3):15. doi: <https://dx.doi.org/10.3390/jcm9030798>
193. Abel T, Feher J, Dinya E, et al. Safety and efficacy of combined ezetimibe/simvastatin treatment and simvastatin monotherapy in patients with non-alcoholic fatty liver disease. *Medical Science Monitor* 2009;15(12):MS6-11.
194. Al-Shaer MH. The effects of ezetimibe on the LDL-cholesterol particle number. *Cardiovasc Drugs Ther* 2004;18(4):327-8.

195. Amarenco P, Kim JS, Labreuche J, et al. Benefit of Targeting a LDL (Low-Density Lipoprotein) Cholesterol <70 mg/dL During 5 Years After Ischemic Stroke. *Stroke* 2020;51(4):1231-39. doi: <http://dx.doi.org/10.1161/STROKEAHA.119.028718>
196. Oikawa S, Yamashita S, Nakaya N, et al. Efficacy and Safety of Long-term Coadministration of Fenofibrate and Ezetimibe in Patients with Combined Hyperlipidemia: results of the EFECTL Study. *Journal of atherosclerosis and thrombosis* 2017;24(1):77-94. doi: 10.5551/jat.35626
197. Hougaard M, Hansen HS, Thayssen P, et al. 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. *Cardiovascular revascularization medicine* 2017;18(2):110-17. doi: 10.1016/j.carrev.2016.11.010
198. Hibi K, Sonoda S, Kawasaki M, et al. Effects of Ezetimibe-Statin Combination Therapy on Coronary Atherosclerosis in Acute Coronary Syndrome. *Circulation journal* 2018;82(3):757-66. doi: 10.1253/circj.CJ-17-0598
199. Suzuki H, Watanabe Y, Kumagai H, et al. Comparative efficacy and adverse effects of the addition of ezetimibe to statin versus statin titration in chronic kidney disease patients. *Therapeutic advances in cardiovascular disease* 2013;7(6):306-15. doi: 10.1177/1753944713513222
200. Zinellu A, Sotgia S, Loriga G, et al. Oxidative stress improvement is associated with increased levels of taurine in CKD patients undergoing lipid-lowering therapy. *Amino acids* 2012;43(4):1499-507. doi: 10.1007/s00726-012-1223-0
201. Sakuma M, Toyoda S, Hashimoto R, et al. Add-on ezetimibe treatment to low-dose statins vs medium-intensity statin monotherapy in coronary artery disease patients with poorly controlled dyslipidemia. *Hypertension Research* 2019;42(12):1923-31. doi: <http://dx.doi.org/10.1038/s41440-019-0308-5>
202. Chow D, Chen H, Glesby MJ, et al. Short-term ezetimibe is well tolerated and effective in combination with statin therapy to treat elevated LDL cholesterol in HIV-infected patients. *AIDS (london, england)* 2009;23(16):2133-41. doi: 10.1097/QAD.0b013e32833068e3
203. Drouin-Chartier JP, Tremblay AJ, Lemelin V, et al. Ezetimibe increases intestinal expression of the LDL receptor gene in dyslipidaemic men with insulin resistance. *Diabetes, obesity & metabolism* 2016;18(12):1226-35. doi: 10.1111/dom.12749
204. Ishimitsu T, Ohno E, Ueno Y, et al. Effects of atorvastatin and ezetimibe on endothelial function in dyslipidemic patients with chronic kidney disease. *Clinical and experimental nephrology* 2014;18(5):704-10. doi: 10.1007/s10157-013-0904-7
205. Kanat M, Serin E, Tunckale A, et al. 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). *Journal of endocrinological investigation* 2009;32(10):852-56. doi: 10.1007/BF03345757
206. Koie M, Kondo Y, Santou T, et al. Effects of non-statin antilipemic drugs on vascular endothelial function in patients with type 2 diabetes with

- hypercholesterolemia. *Diabetology international* 2013;5(3):175-80. doi: 10.1007/s13340-013-0152-9
207. Lakoski SG, Xu F, Vega GL, et al. Indices of cholesterol metabolism and relative responsiveness to ezetimibe and simvastatin. *Journal of clinical endocrinology and metabolism* 2010;95(2):800-09. doi: 10.1210/jc.2009-1952
208. Helal GK, Gad MA, Abd-Allah MF, et al. Coadministration of ezetimibe with pegylated interferon plus ribavirin could improve early virological response in chronic hepatitis C obese Egyptian patients. *European journal of gastroenterology & hepatology* 2016;28(5):553-57. doi: 10.1097/MEG.0000000000000587
209. Hougaard M, Hansen HS, Thayssen P, et al. Influence of ezetimibe on plaque morphology in patients with ST Elevation Myocardial Infarction assessed by Optical Coherence Tomography: an OCTIVUS sub-study. *Cardiovascular revascularization medicine* 2019 doi: 10.1016/j.carrev.2019.04.021
210. Joshi S, Sharma R, Rao HK, et al. Efficacy of combination therapy of rosuvastatin and ezetimibe vs rosuvastatin monotherapy on lipid profile of patients with coronary artery disease. *Journal of clinical and diagnostic research* 2017;11(12):OC28-OC31. doi: 10.7860/JCDR/2017/30458.11004
211. Kovarnik T, Mintz GS, Skalicka H, et al. Virtual histology evaluation of atherosclerosis regression during atorvastatin and ezetimibe administration: HEAVEN study. *Circulation journal* 2012;76(1):176-83. doi: 10.1253/circj.cj-11-0730
212. Izar MC, Machado VA, Fonseca HA, et al. Plant sterol supplementation on top of lipid-lowering therapies in familial hypercholesterolemia. *European Heart Journal* 2015;36:285. doi: <http://dx.doi.org/10.1093/eurheartj/ehv399>
213. Marazzi G, Campolongo G, Pelliccia F, et al. Usefulness of Low-Dose Statin Plus Ezetimibe and/or Nutraceuticals in Patients With Coronary Artery Disease Intolerant to High-Dose Statin Treatment. *American journal of cardiology* 2019;123(2):233-38. doi: 10.1016/j.amjcard.2018.09.041
214. Marazzi G, Pelliccia F, Campolongo G, et al. Usefulness of Nutraceuticals (Armolid Plus) Versus Ezetimibe and Combination in Statin-Intolerant Patients With Dyslipidemia With Coronary Heart Disease. *American journal of cardiology* 2015;116(12):1798-801. doi: 10.1016/j.amjcard.2015.09.023
215. Musliner T, Cselovszky D, Sirah W, et al. Efficacy and safety of ezetimibe 40 mg vs. ezetimibe 10 mg in the treatment of patients with homozygous sitosterolaemia. *International journal of clinical practice* 2008;62(7):995-1000. doi: 10.1111/j.1742-1241.2008.01786.x
216. Nakamura T, Sato E, Fujiwara N, et al. Co-administration of ezetimibe enhances proteinuria-lowering effects of pitavastatin in chronic kidney disease patients partly via a cholesterol-independent manner. *Pharmacological research* 2010;61(1):58-61. doi: 10.1016/j.phrs.2009.07.011
217. Nakamura T, Hirano M, Kitta Y, et al. 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. *Journal of cardiology* 2012;60(1):12-17. doi: 10.1016/j.jjcc.2012.02.005
218. Ose L, Johnson-Levonas A, Reyes R, et al. A multi-centre, randomised, double-blind 14-week extension study examining the long-term safety and efficacy profile of the ezetimibe/simvastatin combination tablet. *International journal of clinical practice* 2007;61(9):1469-80. doi: 10.1111/j.1742-1241.2007.01402.x
219. Ouchi Y, Sasaki J, Arai H, et al. Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): a Randomized, Controlled Trial. *Circulation* 2019;140(12):992-1003. doi: 10.1161/CIRCULATIONAHA.118.039415
220. Pytel E, Bukowska B, Koter-Michalak M, et al. Effect of intensive lipid-lowering therapies on cholinesterase activity in patients with coronary artery disease. *Pharmacological reports : PR* 2017;69(1):150-55. doi: 10.1016/j.pharep.2016.09.016
221. Pytel E, Jackowska P, Chwatko G, et al. 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. *Pharmacological reports : PR* 2016;68(2):344-48. doi: 10.1016/j.pharep.2015.08.019
222. Sugiyama S, Jinnouchi H, Hieshima K, et al. A pilot study of ezetimibe vs. atorvastatin for improving peripheral microvascular endothelial function in stable patients with type 2 diabetes mellitus. *Lipids in health and disease* 2015;14:37. doi: 10.1186/s12944-015-0028-z
223. Takase H, Dohi Y, Okado T, et al. Effects of ezetimibe on visceral fat in the metabolic syndrome: a randomised controlled study. *European journal of clinical investigation* 2012;42(12):1287-94. doi: 10.1111/eci.12000
224. Liu C, Liu Q, Xiao X. Effectiveness and safety of combinational therapy compared with intensified statin monotherapy in patients with coronary heart disease. *Experimental Ther* 2018;15(6):4683-88. doi: <https://dx.doi.org/10.3892/etm.2018.6024>
225. Sudhop T, Reber M, Tribble D, et al. Changes in cholesterol absorption and cholesterol synthesis caused by ezetimibe and/or simvastatin in men. *Journal of lipid research* 2009;50(10):2117-23. doi: 10.1194/jlr.P900004-JLR200
226. Tremblay AJ, Lamarche B, Hogue JC, et al. Effects of ezetimibe and simvastatin on apolipoprotein B metabolism in males with mixed hyperlipidemia. *Journal of lipid research* 2009;50(7):1463-71. doi: 10.1194/jlr.P800061-JLR200
227. Uemura Y, Watarai M, Ishii H, et al. 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. *Journal of Cardiology* doi: <http://dx.doi.org/10.1016/j.jjcc.2011.09.001>
228. Bays H, Sapre A, Taggart W, et al. Long-term (48-week) safety of ezetimibe 10 mg/day coadministered with simvastatin compared to simvastatin alone in patients with primary hypercholesterolemia. *Curr Med Res Opin* 2008;24(10):2953-66. doi: <https://dx.doi.org/10.1185/03007990802365094>

229. Abu Rajab M, Kaplan MM. Statins in primary biliary cirrhosis: are they safe? *Dig Dis Sci* 2010;55(7):2086-8. doi: <https://dx.doi.org/10.1007/s10620-009-0988-9>
230. Allahyari A, Jernberg T, Lautsch D, et al. 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. *European heart journal Quality of care & clinical outcomes* 2020;06 doi: <http://dx.doi.org/10.1093/ehjqcco/qcaa016>
231. Andrikopoulos G, Terentes-Printzios D, Tzeis S, et al. Epidemiological characteristics, management and early outcomes of acute coronary syndromes in Greece: The PHAETHON study. *Hellenic Journal of Cardiology* 2016;57(3):157-66. doi: <http://dx.doi.org/10.1016/j.hjc.2016.06.003>
232. Andrikopoulos G, Tzeis S, Nikas N, et al. Short-term outcome and attainment of secondary prevention goals in patients with acute coronary syndrome-Results from the countrywide TARGET study. *International Journal of Cardiology* 2013;168(2):922-27. doi: <http://dx.doi.org/10.1016/j.ijcard.2012.10.049>
233. Allahyari A, Jernberg T, Hagstrom E, et al. Application of the 2019 ESC/EAS dyslipidaemia guidelines to nationwide data of patients with a recent myocardial infarction: a simulation study. *European heart journal* 2020;18 doi: <http://dx.doi.org/10.1093/eurheartj/ehaa034>
234. Alsabbagh WM, Dagenais J, Yan L, et al. Use and misuse of ezetimibe: Analysis of use and cost in Saskatchewan, a Canadian jurisdiction with broad access. *Canadian Journal of Cardiology* 2014;30(2):237-43. doi: <http://dx.doi.org/10.1016/j.cjca.2013.11.031>
235. Ambegaonkar B, Chirovsky D, Tse HF, et al. Attainment of normal lipid levels among patients on lipid-modifying therapy in Hong Kong. *Advances in Therapy* 2012;29(5):427-41. doi: <http://dx.doi.org/10.1007/s12325-012-0017-9>
236. Barbir M, Breen J, Neves E, et al. Diagnosis, management and prognosis of familial hypercholesterolaemia in a UK tertiary cardiac centre. *Clinical Lipidology and Metabolic Disorders* 2019;14(1):1-10. doi: <http://dx.doi.org/10.1080/17584299.2019.1587877>
237. Arca M, Ansell D, Aversa M, et al. Statin utilization and lipid goal attainment in high or very-high cardiovascular risk patients: Insights from Italian general practice. *Atherosclerosis* 2018;271:120-27. doi: <http://dx.doi.org/10.1016/j.atherosclerosis.2018.02.024>
238. Berkelmans GFN, Gudbjornsdottir S, Visseren FLJ, et al. 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. *European Heart Journal* 2019;40(34):2899-906. doi: <http://dx.doi.org/10.1093/eurheartj/ehy839>
239. Bertolotti M, Franchi C, Rocchi MBL, et al. 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. *Drugs and Aging* 2017;34(4):311-19. doi: <http://dx.doi.org/10.1007/s40266-017-0448-8>
240. Blom DJ, Almahmeed W, Al-Rasadi K, et al. Low-density lipoprotein cholesterol goal achievement in patients with familial hypercholesterolemia in countries outside Western Europe: The International ChoLesterol management Practice Study. *Journal of Clinical Lipidology* 2019;13(4):594-600. doi: <http://dx.doi.org/10.1016/j.jacl.2019.05.004>
241. Booth JN, Colantonio LD, Chen L, et al. Statin Discontinuation, Reinitiation, and Persistence Patterns among Medicare Beneficiaries after Myocardial Infarction: A Cohort Study. *Circulation: Cardiovascular Quality and Outcomes* 2017;10(10) doi: <http://dx.doi.org/10.1161/CIRCOUTCOMES.117.003626>
242. Botha TC, Pilcher GJ, Wolmarans K, et al. Statins and other lipid-lowering therapy and pregnancy outcomes in homozygous familial hypercholesterolaemia: A retrospective review of 39 pregnancies. *Atherosclerosis* 2018;277:502-07. doi: <http://dx.doi.org/10.1016/j.atherosclerosis.2018.05.038>
243. Boytsov S, Logunova N, Khomitskaya Y, et al. Suboptimal control of lipid levels: Results from the non-interventional Centralized Pan-Russian Survey of the Undertreatment of Hypercholesterolemia II (CEPHEUS II). *Cardiovascular Diabetology* 2017;16(1) doi: <http://dx.doi.org/10.1186/s12933-017-0641-4>
244. Brandt EJ, Benes LB, Lee L, et al. The Effect of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibition on Sterol Absorption Markers in a Cohort of Real-World Patients. *Journal of Cardiovascular Pharmacology and Therapeutics* 2019;24(1):54-61. doi: <http://dx.doi.org/10.1177/1074248418780733>
245. Buonvino C, Chopard R, Guillon B, et al. An innovative lipid-lowering approach to enhance attainment of low-density lipoprotein cholesterol goals. *European Heart Journal: Acute Cardiovascular Care* 2020 doi: <http://dx.doi.org/10.1177/2048872620912639>
246. Buddhari W, Uerojanaungkul P, Sriratanasathavorn C, et al. Low-Density Lipoprotein Cholesterol Target Attainment in Patients Surviving an Acute Coronary Syndrome in Thailand: Results From the Dyslipidaemia International Study (DYSIS) II. *Heart Lung and Circulation* 2020;29(3):405-13. doi: <http://dx.doi.org/10.1016/j.hlc.2019.02.193>
247. Burton WN, Chen CY, Schultz AB, et al. The association between achieving low-density lipoprotein cholesterol (LDL-C) goal and statin treatment in an employee population. *Population Health Management* 2010;13(1):1-8. doi: <http://dx.doi.org/10.1089/pop.2009.0020>
248. Burke JP, Simpson RJ, Paoli CJ, et al. Longitudinal treatment patterns among US patients with atherosclerotic cardiovascular disease or familial hypercholesterolemia initiating lipid-lowering pharmacotherapy. *Journal of Clinical Lipidology* 2016;10(6):1470-80.e3. doi: <http://dx.doi.org/10.1016/j.jacl.2016.09.002>

249. Cannon CP, Khan I, Klimchak AC, et al. Simulation of Lipid-Lowering Therapy Intensification in a Population With Atherosclerotic Cardiovascular Disease. *JAMA Cardiology* 2017;2(9):959-66. doi: <https://dx.doi.org/10.1001/jamacardio.2017.2289>
250. Chen G, Farris MS, Cowling T, et al. Treatment and Low-Density Lipoprotein Cholesterol Management in Patients Diagnosed With Clinical Atherosclerotic Cardiovascular Disease in Alberta. *Canadian Journal of Cardiology* 2019;35(7):884-91. doi: <http://dx.doi.org/10.1016/j.cjca.2019.04.008>
251. Choi SY, Yang BR, Kang HJ, et al. Contemporary use of lipid-lowering therapy for secondary prevention in Korean patients with atherosclerotic cardiovascular diseases. *Korean Journal of Internal Medicine* 2020;35(3):593-604. doi: <http://dx.doi.org/10.3904/kjim.2018.312>
252. Chuang P, Langone AJ. Ezetimibe reduces low-density lipoprotein cholesterol (LDL-C) in renal transplant patients resistant to HMG-CoA reductase inhibitors. *American Journal of Therapeutics* 2007;14(5):438-41. doi: <http://dx.doi.org/10.1097/01.mjt.0000209693.83065.a6>
253. Cicero AFG, Toth PP, Fogacci F, et al. Improvement in arterial stiffness after short-term treatment with PCSK9 inhibitors. *Nutrition, Metabolism and Cardiovascular Diseases* 2019;29(5):527-29. doi: <http://dx.doi.org/10.1016/j.numecd.2019.01.010>
254. Clemens KK, Shariff SZ, McArthur E, et al. Ezetimibe prescriptions in older Canadian adults after an acute myocardial infarction: A population-based cohort study. *Lipids in Health and Disease* 2018;17(1) doi: <http://dx.doi.org/10.1186/s12944-017-0649-5>
255. Colivicchi F, Gulizia MM, Franzini L, et al. Clinical Implications of Switching Lipid Lowering Treatment from Rosuvastatin to Other Agents in Primary Care. *Adv Ther* 2016;33(11):2049-58.
256. Colivicchi F, Massimo Gulizia M, Arca M, et al. Lipid Lowering Treatment and Eligibility for PCSK9 Inhibition in Post-Myocardial Infarction Patients in Italy: Insights from Two Contemporary Nationwide Registries. *Cardiovascular Therapeutics* 2020;2020 (no pagination) doi: <http://dx.doi.org/10.1155/2020/3856242>
257. Coste J, Billionnet C, Rudnichi A, et al. Statins for primary prevention and rhabdomyolysis: A nationwide cohort study in France. *European Journal of Preventive Cardiology* 2019;26(5):512-21. doi: <http://dx.doi.org/10.1177/2047487318776831>
258. Cziraky MJ, Willey VJ, McKenney JM, et al. Risk of hospitalized rhabdomyolysis associated with lipid-lowering drugs in a real-world clinical setting. *Journal of Clinical Lipidology* 2013;7(2):102-08. doi: <http://dx.doi.org/10.1016/j.jacl.2012.06.006>
259. Danese MD, Gleeson M, Kutikova L, et al. Management of lipid-lowering therapy in patients with cardiovascular events in the UK: A retrospective cohort study. *BMJ Open* 2017;7(5) doi: <http://dx.doi.org/10.1136/bmjopen-2016-013851>

260. Dedinska I, Laca L, Miklusica J, et al. Waist circumference as an independent risk factor for NODAT. *Annals of Transplantation* 2015;20:154-59. doi: <http://dx.doi.org/10.12659/AOT.892067>
261. Degoma EM, Ahmad ZS, O'Brien EC, et al. Treatment gaps in adults with heterozygous familial hypercholesterolemia in the United States. *Circulation: Cardiovascular Genetics* 2016;9(3):240-49. doi: <http://dx.doi.org/10.1161/CIRCGENETICS.116.001381>
262. Del Ben M, Baratta F, Polimeni L, et al. Under-prescription of statins in patients with non-alcoholic fatty liver disease. *Nutrition, Metabolism and Cardiovascular Diseases* 2017;27(2):161-67. doi: <http://dx.doi.org/10.1016/j.numecd.2016.09.011>
263. Despas F, Rousseau V, Lafaurie M, et al. Are lipid-lowering drugs associated with a risk of cataract? A pharmacovigilance study. *Fundamental and Clinical Pharmacology* 2019;33(6):695-702. doi: <http://dx.doi.org/10.1111/fcp.12496>
264. Di Pierro F, Putignano P, Ferrara T, et al. Retrospective analysis of the effects of a highly standardized mixture of Berberis aristata, Silybum marianum, and monacolins K and KA in patients with dyslipidemia. *Clinical Pharmacology: Advances and Applications* 2017;9(no pagination) doi: <http://dx.doi.org/10.2147/CPAA.S120032>
265. Di Taranto MD, Giacobbe C, Buonaiuto A, et al. A real-world experience of clinical, biochemical and genetic assessment of patients with homozygous familial hypercholesterolemia. *Journal of Clinical Medicine* 2020;9(1) doi: <http://dx.doi.org/10.3390/jcm9010219>
266. Duell PB, Gidding SS, Andersen RL, et al. Longitudinal low density lipoprotein cholesterol goal achievement and cardiovascular outcomes among adult patients with familial hypercholesterolemia: The CASCADE FH registry. *Atherosclerosis* 2019;289:85-93. doi: <http://dx.doi.org/10.1016/j.atherosclerosis.2019.08.007>
267. Dyrbus K, Gasior M, Desperak P, et al. 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. *Pharmacological Research* 2019;139:460-66. doi: <http://dx.doi.org/10.1016/j.phrs.2018.12.002>
268. Eliasson B, Svensson AM, Miftaraj M, et al. Clinical use and effectiveness of lipid lowering therapies in diabetes mellitus-an observational study from the Swedish National diabetes Register. *PLoS ONE* 2011;6(4) doi: <http://dx.doi.org/10.1371/journal.pone.0018744>
269. Elis A, Zhou R, Stein EA. Effect of lipid-lowering treatment on natural history of heterozygous familial hypercholesterolemia in past three decades. *American Journal of Cardiology* 2011;108(2):223-26. doi: <http://dx.doi.org/10.1016/j.amjcard.2011.03.027>
270. Faggiano P, Fattirolli F, Frisinghelli A, et al. Secondary prevention advices after cardiovascular index event: From drug prescription to risk factors control in real world practice. *Monaldi Archives for Chest Disease* 2019;89(2):143-50. doi: <http://dx.doi.org/10.4081/monaldi.2019.1040>

271. Ferrieres J, Gorcyca K, Iorga R, et al. Lipid-lowering Therapy and Goal Achievement in High-risk Patients From French General Practice. *Clinical Therapeutics* 2018;40(9):1484-95.e22. doi: <http://dx.doi.org/10.1016/j.clinthera.2018.07.008>
272. Friedman HS, Rajagopalan S, Barnes JP, et al. Effectiveness of ezetimibe monotherapy in patients with hypercholesterolemia. *American Journal of Pharmacy Benefits* 2010;2(4):267-74.
273. Galema-Boers AM, Lenzen MJ, Engelkes SR, et al. Cardiovascular risk in patients with familial hypercholesterolemia using optimal lipid-lowering therapy. *Journal of Clinical Lipidology* 2018;12(2):409-16. doi: <http://dx.doi.org/10.1016/j.jacl.2017.12.014>
274. Garcia Ruiz FJ, Marin Ibanez A, Perez-Jimenez F, et al. Current lipid management and low cholesterol goal attainment in common daily practice in Spain: The REALITY study. *Pharmacoeconomics* 2004;22(SUPPL. 3):1-12.
275. Gallo A, Vimont A, Chapman MJ, et al. SAFEHEART risk-equation and cholesterol-year-score are powerful predictors of cardiovascular events in French patients with familial hypercholesterolemia. *Atherosclerosis* 2020;306:41-49. doi: <http://dx.doi.org/10.1016/j.atherosclerosis.2020.06.011>
276. Gitt AK, Lautsch D, Ferrieres J, et al. Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: Results from the Dyslipidemia International Study II. *Atherosclerosis* 2017;266:158-66. doi: <http://dx.doi.org/10.1016/j.atherosclerosis.2017.08.013>
277. Gitt AK, Lautsch D, Ferrieres J, et al. Contemporary data on treatment practices for low-density lipoprotein cholesterol in 6794 patients with stable coronary heart disease across the world. *Data Brief* 2018;18:1937-40. doi: <https://dx.doi.org/10.1016/j.dib.2018.04.092>
278. Bae J, Hong N, Lee BW, et al. Comparison of renal effects of ezetimibe-statin combination versus statin monotherapy: A propensity-score-matched analysis. *Journal of Clinical Medicine* 2020;9(3) doi: <http://dx.doi.org/10.3390/jcm9030798>
279. Barkas F, Liberopoulos E, Klouras E, et al. Attainment of multifactorial treatment targets among the elderly in a lipid clinic. *Journal of Geriatric Cardiology* 2015;12(3):239-45. doi: <http://dx.doi.org/10.11909/j.issn.1671-5411.2015.03.004>
280. Barkas F, Milionis H, Kostapanos MS, et al. How effective are the ESC/EAS and 2013 ACC/AHA guidelines in treating dyslipidemia? Lessons from a lipid clinic. *Current Medical Research and Opinion* 2015;31(2):221-28. doi: <http://dx.doi.org/10.1185/03007995.2014.982751>
281. Bartlett LE, Pratt NL, Roughead EE. Prior experience with cardiovascular medicines predicted longer persistence in people initiated to combinations of antihypertensive and lipid-lowering therapies: Findings from two australian cohorts. *Patient Preference and Adherence* 2018;12:835-43. doi: <http://dx.doi.org/10.2147/PPA.S150142>

282. Baum SJ, Wade RL, Xiang P, et al. Demographic And Clinical Characteristics Of Patients Prescribed Proprotein Convertase Subtilisin/kexin Type 9 Inhibitor Therapy And Patients Whose Current Lipid-Lowering Therapy Was Modified. *Ther Clin Risk Manag* 2019;15:1325-32. doi: <https://dx.doi.org/10.2147/TCRM.S216606>
283. Bays HE, Patel MD, Mavros P, et al. 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. *Journal of Clinical Lipidology* 2017;11(4):929-37. doi: <https://dx.doi.org/10.1016/j.jacl.2017.04.121>
284. Chang SH, Wu LS, Lee CH, et al. 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. *International Journal of Cardiology* 2015;190(1):20-25. doi: <http://dx.doi.org/10.1016/j.ijcard.2015.04.121>
285. Chen CC, Rane PB, Hines DM, et al. Low-density lipoprotein cholesterol outcomes post-non-PCSK9i lipid-lowering therapies in atherosclerotic cardiovascular disease and probable heterozygous familial hypercholesterolemia patients. *Therapeutics and Clinical Risk Management* 2018;14:2425-35. doi: <http://dx.doi.org/10.2147/TCRM.S180783>
286. Chen WJ, Wen YC, Fox KM, et al. 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. *Journal of Evaluation in Clinical Practice* 2020;26(4):1171-80. doi: <http://dx.doi.org/10.1111/jep.13286>
287. Ebisawa S, Izawa A, Ueki Y, et al. Impact of combination therapy with statin and ezetimibe on secondary prevention for post-acute myocardial infarction patients in the statin era. *IJC Heart and Vasculature* 2015;8:154-60. doi: <http://dx.doi.org/10.1016/j.ijcha.2015.07.007>
288. Fazio S, Guyton JR, Polis AB, et al. Long-term safety and efficacy of triple combination ezetimibe/simvastatin plus extended-release niacin in patients with hyperlipidemia. *American Journal of Cardiology* 2010;105(4):487-94. doi: <https://dx.doi.org/10.1016/j.amjcard.2009.10.001>
289. Ferrieres J, Dallongeville J, Rossignol M, et al. Model-observational bridging study on the effectiveness of ezetimibe on cardiovascular morbidity and mortality in France: A population-based study. *Journal of Clinical Lipidology* 2016;10(6):1379-88. doi: <https://dx.doi.org/10.1016/j.jacl.2016.08.015>
290. Foody JAM, Toth PP, Tomassini JE, et al. Changes in LDL-C levels and goal attainment associated with addition of ezetimibe to simvastatin, atorvastatin, or rosuvastatin compared with titrating statin monotherapy. *Vascular Health and Risk Management* 2013;9(1):719-27. doi: <http://dx.doi.org/10.2147/VHRM.S49840>
291. Foody JM, Toth PP, Tomassini JE, et al. Changes in LDL-C levels and goal attainment associated with addition of ezetimibe to simvastatin, atorvastatin, or

- rosuvastatin compared with titrating statin monotherapy. *Vasc Health Risk Manag* 2013;9:719-27. doi: <https://dx.doi.org/10.2147/VHRM.S49840>
292. Friedman HS, Rajagopalan S, Barnes JP, et al. Combination Therapy With Ezetimibe/Simvastatin Versus Statin Monotherapy for Low-Density Lipoprotein Cholesterol Reduction and Goal Attainment in a Real-World Clinical Setting. *Clinical Therapeutics* 2011;33(2):212-24. doi: <http://dx.doi.org/10.1016/j.clinthera.2011.02.011>
293. Fung EC, Crook MA. Statin myopathy: A lipid clinic experience on the tolerability of statin Rechallenge. *Cardiovascular Therapeutics* 2012;30(5):e212-e18. doi: <http://dx.doi.org/10.1111/j.1755-5922.2011.00267.x>
294. Guglielmi V, Bellia A, Pecchioli S, et al. 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. *Atherosclerosis* 2017;263:36-41. doi: <https://dx.doi.org/10.1016/j.atherosclerosis.2017.05.018>
295. Hall GC, Amber V, O'Regan C, et al. Observational study of ezetimibe discontinuation in primary care practices in the UK. *Current Medical Research and Opinion* 2013;29(12):1737-45. doi: <http://dx.doi.org/10.1185/03007995.2013.842164>
296. Hambraeus K, Lindhagen L, Tyden P, et al. Target-attainment rates of low-density lipoprotein cholesterol using lipid-lowering drugs one year after acute myocardial infarction in Sweden. *American Journal of Cardiology* 2014;113(1):17-22. doi: <https://dx.doi.org/10.1016/j.amjcard.2013.09.007>
297. Harada-Shiba M, Ako J, Arai H, et al. Prevalence of familial hypercholesterolemia in patients with acute coronary syndrome in Japan: Results of the EXPLORE-J study. *Atherosclerosis* 2018;277:362-68. doi: <http://dx.doi.org/10.1016/j.atherosclerosis.2018.06.856>
298. Harris LJ, Thapa R, Brown M, et al. Clinical and laboratory phenotype of patients experiencing statin intolerance attributable to myalgia. *Journal of Clinical Lipidology* 2011;5(4):299-307. doi: <http://dx.doi.org/10.1016/j.jacl.2011.05.005>
299. Harrison TN, Hsu JWY, Rosenson RS, et al. Unmet Patient Need in Statin Intolerance: the Clinical Characteristics and Management. *Cardiovascular Drugs and Therapy* 2018;32(1):29-36. doi: <http://dx.doi.org/10.1007/s10557-018-6775-0>
300. Hess G, Chang CL, Chung K. Lipid attainment among patients newly treated with lipid-altering drugs. *Current Medical Research and Opinion* 2014;30(9):1743-56. doi: <http://dx.doi.org/10.1185/03007995.2014.925436>
301. Ho LT, Yin WH, Chuang SY, et al. Determinants for achieving the LDL-C target of lipid control for secondary prevention of cardiovascular events in Taiwan. *PLoS ONE* 2015;10(3) doi: <http://dx.doi.org/10.1371/journal.pone.0116513>
302. Hodgkins AJ, Mullan J, Mayne DJ, et al. The use of primary care electronic health records for research: Lipid medications and mortality in elderly patients. *Pharmacy* 2019;7(3) doi: <http://dx.doi.org/10.3390/pharmacy7030134>

303. Jackevicius CA, Tu JV, Ross JS, et al. Use of ezetimibe in the United States and Canada. *New England Journal of Medicine* 2008;358(17):1819-28. doi: <http://dx.doi.org/10.1056/NEJMsa0801461>
304. Jameson K, Amber V, D'Oca K, et al. 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. *International Journal of Clinical Practice* 2013;67(12):1228-37. doi: <http://dx.doi.org/10.1111/ijcp.12238>
305. Jensen JS, Weeke PE, Bang LE, et al. Clinical characteristics and lipid lowering treatment of patients initiated on proprotein convertase subtilisin-kexin type 9 inhibitors: A nationwide cohort study. *BMJ Open* 2019;9(4) doi: <http://dx.doi.org/10.1136/bmjopen-2018-022702>
306. Jung J, Bae GH, Kang M, et al. Statins and All-Cause Mortality in Patients Undergoing Hemodialysis. *Journal of the American Heart Association* 2020;9(5):e014840. doi: <http://dx.doi.org/10.1161/JAHA.119.014840>
307. Kamal-Bahl SJ, Burke T, Watson D, et al. Discontinuation of Lipid Modifying Drugs Among Commercially Insured United States Patients in Recent Clinical Practice. *American Journal of Cardiology* 2007;99(4):530-34. doi: <http://dx.doi.org/10.1016/j.amjcard.2006.08.063>
308. Karalis DG, Victor B, Ahedor L, et al. Use of lipid-lowering medications and the likelihood of achieving optimal LDL-cholesterol goals in coronary artery disease patients. *Cholesterol* 2012;2012 (no pagination) doi: <http://dx.doi.org/10.1155/2012/861924>
309. Katzmann JL, Sorio-Vilela F, Dornstauder E, et al. 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. *Clinical Research in Cardiology* 2020 doi: <http://dx.doi.org/10.1007/s00392-020-01740-8>
310. Katz PM, Mendelsohn AA, Goodman SG, et al. 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). *Canadian Journal of Cardiology* 2011;27(2):138-45. doi: <https://dx.doi.org/10.1016/j.cjca.2010.12.010>
311. Kawashiri MA, Sakata K, Hayashi K, et al. 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. *Heart and Vessels* 2017;32(5):539-48. doi: <http://dx.doi.org/10.1007/s00380-016-0910-2>
312. Khang AR, Song YS, Kim KM, et al. Comparison of different statin therapy to change low-density lipoprotein cholesterol and high-density lipoprotein cholesterol level in Korean patients with and without diabetes. *Journal of Clinical Lipidology* 2016;10(3):528-37.e3. doi: <https://dx.doi.org/10.1016/j.jacl.2015.12.013>

313. Kim S, Kim H, Kim E, et al. Utilization Patterns of Lipid-lowering Therapies in Patients With Atherosclerotic Cardiovascular Disease or Diabetes: A Population-based Study in South Korea. *Clinical Therapeutics* 2018;40(6):940-51.e7. doi: <https://dx.doi.org/10.1016/j.clinthera.2018.04.007>
314. Kiss Z, Nagy L, Reiber I, et al. Persistence with statin therapy in Hungary. *Archives of Medical Science* 2013;9(3):409-17. doi: <http://dx.doi.org/10.5114/aoms.2013.35327>
315. Kitkungvan D, Fillipon NML, Dani SS, et al. Low-density lipoprotein cholesterol target achievement in patients at high risk for coronary heart disease. *Journal of Clinical Lipidology* 2010;4(4):293-97. doi: <http://dx.doi.org/10.1016/j.jacl.2010.06.003>
316. Kuiper JG, Sanchez RJ, Houben E, et al. Use of Lipid-modifying Therapy and LDL-C Goal Attainment in a High-Cardiovascular-Risk Population in the Netherlands. *Clinical Therapeutics* 2017;39(4):819-27.e1. doi: <http://dx.doi.org/10.1016/j.clinthera.2017.03.001>
317. Latkovskis G, Saripo V, Gilis D, et al. Latvian registry of familial hypercholesterolemia: The first report of three-year results. *Atherosclerosis* 2018;277:347-54. doi: <http://dx.doi.org/10.1016/j.atherosclerosis.2018.06.011>
318. Lee HJ, Kim YJ, Hur J, et al. Prevalence and extent of atherosclerotic coronary artery disease and related outcome based on coronary computed tomographic angiography in asymptomatic elderly patients: Retrospective cohort study. *International Journal of Cardiovascular Imaging* 2014;30(3):669-76. doi: <http://dx.doi.org/10.1007/s10554-014-0366-3>
319. Levintow SN, Reading SR, Saul BC, et al. Lipid testing trends in the us before and after the release of the 2013 cholesterol treatment guidelines. *Clinical Epidemiology* 2020;12:835-45. doi: <http://dx.doi.org/10.2147/CLEP.S259757>
320. Lipworth L, Fazio S, Kabagambe EK, et al. A prospective study of statin use and mortality among 67,385 blacks and whites in the southeastern United States. *Clinical Epidemiology* 2014;6(1):15-25. doi: <http://dx.doi.org/10.2147/clep.s53492>
321. Lourenco C, Antonio N, Teixeira R, et al. Predictors of adverse outcome in a diabetic population following acute coronary syndromes. *Revista Portuguesa de Cardiologia* 2011;30(3):263-75.
322. Lynch JT, Cooke CE, Rosen J, et al. Managing dyslipidemia in primary care with restricted access to lipid-modifying therapy. *American Health and Drug Benefits* 2010;3(5):340-48.
323. Maahs DM, Ogden LG, Dabelea D, et al. Association of glycaemia with lipids in adults with type 1 diabetes: Modification by dyslipidaemia medication. *Diabetologia* 2010;53(12):2518-25. doi: <http://dx.doi.org/10.1007/s00125-010-1886-6>
324. Maggioni AP, Calabria S, Rossi E, et al. 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. *International Journal of Cardiology* 2017;246:62-67. doi: <http://dx.doi.org/10.1016/j.ijcard.2017.02.108>

325. Martin SS, Faridi KF, Joshi PH, et al. Remnant lipoprotein cholesterol and mortality after acute myocardial infarction: Further evidence for a hypercholesterolemia paradox from the TRIUMPH registry. *Clinical Cardiology* 2015;38(11):660-67. doi: <http://dx.doi.org/10.1002/clc.22470>
326. Marz W, Dippel FW, Theobald K, et al. 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. *Atherosclerosis* 2018;268:99-107. doi: <http://dx.doi.org/10.1016/j.atherosclerosis.2017.11.020>
327. Menzin J, Aggarwal J, Boatman B, et al. Ezetimibe use and LDL-C Goal achievement: A retrospective database analysis of patients with clinical atherosclerotic cardiovascular disease or probable heterozygous familial hypercholesterolemia. *Journal of Managed Care and Specialty Pharmacy* 2017;23(12):1270-76b. doi: <http://dx.doi.org/10.18553/jmcp.2017.16414>
328. Miname MH, Bittencourt MS, Pereira AC, et al. Vascular age derived from coronary artery calcium score on the risk stratification of individuals with heterozygous familial hypercholesterolaemia. *European Heart Journal Cardiovascular Imaging* 2020;21(3):251-57. doi: <http://dx.doi.org/10.1093/ehjci/jez280>
329. Murphy A, Hamilton G, Andrianopoulos N, et al. One-Year Outcomes of Patients With Established Coronary Artery Disease Presenting With Acute Coronary Syndromes. *American Journal of Cardiology* 2019;123(9):1387-92. doi: <http://dx.doi.org/10.1016/j.amjcard.2019.01.037>
330. Myers J, Rayment M, Sonecha S, et al. Room for manoeuvre when prescribing statins to dyslipidaemic patients on antiretroviral therapy. *HIV Medicine* 2012;13(3):190-92. doi: <http://dx.doi.org/10.1111/j.1468-1293.2011.00957.x>
331. Nagar SP, Rane PP, Fox KM, et al. Treatment patterns, statin intolerance, and subsequent cardiovascular events among Japanese patients with high cardiovascular risk initiating statin therapy. *Circulation Journal* 2018;82(4):1008-16. doi: <http://dx.doi.org/10.1253/circj.CJ-17-0811>
332. Nakamura M, Ako J, Arai H, et al. Investigation into lipid management in acute coronary syndrome patients from the EXPLORE-J study. *Journal of Atherosclerosis and Thrombosis* 2019;26(6):559-72. doi: <http://dx.doi.org/10.5551/jat.45583>
333. Paneni F, Cosentino F, Marrara F, et al. The clinical relevance of dysfunctional HDL in patients with coronary artery disease: A 3-year follow-up study. *International Journal of Cardiology* 2012;158(1):158-60. doi: <http://dx.doi.org/10.1016/j.ijcard.2012.04.032>
334. Park JE, Chiang CE, Munawar M, et al. Lipid-lowering treatment in hypercholesterolaemic patients: The CEPHEUS Pan-Asian survey. *European Journal of Preventive Cardiology* 2012;19(4):781-94. doi: <http://dx.doi.org/10.1177/1741826710397100>
335. Pasta A, Cremonini AL, Formisano E, et al. Long term follow-up of genetically confirmed patients with familial hypercholesterolemia treated with first and second-

- generation statins and then with PCSK9 monoclonal antibodies. *Atherosclerosis* 2020;308:6-14. doi: <https://dx.doi.org/10.1016/j.atherosclerosis.2020.07.006>
336. Peikert A, Kaier K, Merz J, et al. Residual inflammatory risk in coronary heart disease: incidence of elevated high-sensitive CRP in a real-world cohort. *Clinical Research in Cardiology* 2020;109(3):315-23. doi: <https://dx.doi.org/10.1007/s00392-019-01511-0>
337. Perez De Isla L, Alonso R, Watts GF, et al. Attainment of LDL-cholesterol treatment goals in patients with familial hypercholesterolemia: 5-year SAFEHEART registry follow-up. *Journal of the American College of Cardiology* 2016;67(11):1278-85. doi: <http://dx.doi.org/10.1016/j.jacc.2016.01.008>
338. Perez-Calahorra S, Laclaustra M, Marco-Benedi V, et al. Effect of lipid-lowering treatment in cardiovascular disease prevalence in familial hypercholesterolemia. *Atherosclerosis* 2019;284:245-52. doi: <http://dx.doi.org/10.1016/j.atherosclerosis.2019.02.003>
339. Petrov I, Dumitrescu A, Snejdrlava M, et al. Clinical Management of High and Very High Risk Patients with Hyperlipidaemia in Central and Eastern Europe: An Observational Study. *Advances in Therapy* 2019;36(3):608-20. doi: <http://dx.doi.org/10.1007/s12325-019-0879-1>
340. Petrov IS, Postadzhiyan AS, Tokmakova MP, et al. Management of High and Very High-Risk Subjects with Familial Hypercholesterolemia: Results from an Observational Study in Bulgaria. *Folia medica* 2018;60(3):389-96. doi: <http://dx.doi.org/10.2478/foimed-2018-0020>
341. Ponziani MC, Karamouzis I, Mele C, et al. Baseline glucose homeostasis predicts the new onset of diabetes during statin therapy: A retrospective study in real life. *Hormones* 2017;16(4):396-404. doi: <http://dx.doi.org/10.14310/horm.2002.1760>
342. Premstaller M, Perren M, Kocack K, et al. Dyslipidemia and lipid-lowering treatment in a hematopoietic stem cell transplant cohort: 25 years of follow-up data. *Journal of Clinical Lipidology* 2018;12(2):464-80.e3. doi: <http://dx.doi.org/10.1016/j.jacl.2017.11.008>
343. Punekar RS, Fox KM, Paoli CJ, et al. Lipid-lowering treatment modifications among patients with hyperlipidemia and a prior cardiovascular event: a US retrospective cohort study. *Current Medical Research and Opinion* 2017;33(5):869-76. doi: <http://dx.doi.org/10.1080/03007995.2017.1292898>
344. Rallidis LS, Kotakos C, Sourides V, et al. 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. *Expert Opinion on Pharmacotherapy* 2011;12(10):1481-89. doi: <http://dx.doi.org/10.1517/14656566.2011.591379>
345. Razek O, Cermakova L, Armani H, et al. Attainment of Recommended Lipid Targets in Patients With Familial Hypercholesterolemia: Real-World Experience With PCSK9 Inhibitors. *Canadian Journal of Cardiology* 2018;34(8):1004-09. doi: <http://dx.doi.org/10.1016/j.cjca.2018.04.014>

346. Reddy KJ, Singh M, Batsell RR, et al. Effects of lifestyle counseling and combination lipid-modifying therapy on lipoprotein-associated phospholipase A2 mass concentration. *Journal of Clinical Lipidology* 2009;3(4):275-80. doi: <http://dx.doi.org/10.1016/j.jacl.2009.06.004>
347. Schwaab B, Zeymer U, Jannowitz C, et al. 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. *European Journal of Preventive Cardiology* 2019;26(3):249-58. doi: <http://dx.doi.org/10.1177/2047487318817082>
348. Stroup JS, Kane MP, Busch RS. The antilipidemic effects of ezetimibe in patients with diabetes. *Diabetes Care* 2003;26(10):2958-59. doi: <http://dx.doi.org/10.2337/diacare.26.10.2958-a>
349. Virani SS, Akeroyd JM, Nambi V, et al. 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. *Circulation* 2017;135(25):2572-74. doi: <http://dx.doi.org/10.1161/CIRCULATIONAHA.117.028503>
350. Virani SS, Akeroyd JM, Smith SC, et al. Very High-Risk ASCVD and Eligibility for Nonstatin Therapies Based on the 2018 AHA/ACC Cholesterol Guidelines. *Journal of the American College of Cardiology* 2019;74(5):712-14. doi: <http://dx.doi.org/10.1016/j.jacc.2019.05.051>
351. Hayek S, Canepa Escaro F, Sattar A, et al. Effect of ezetimibe on major atherosclerotic disease events and all-cause mortality. *American Journal of Cardiology* 2013;111(4):532-39. doi: <http://dx.doi.org/10.1016/j.amjcard.2012.11.002>
352. Huang Z, Li Q, Ye W, et al. 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. *Chemical and Pharmaceutical Bulletin* 2019;67(5):419-25. doi: <http://dx.doi.org/10.1248/cpb.c18-00685>
353. Inoue I, Awata T, Katayama S. 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? *Recent Patents on Cardiovascular Drug Discovery* 2010;5(2):143-52. doi: <http://dx.doi.org/10.2174/157489010791515386>
354. Ji MS, Jeong MH, Ahn YK, et al. Clinical outcome of statin plus ezetimibe versus high-intensity statin therapy in patients with acute myocardial infarction propensity-score matching analysis. *International Journal of Cardiology* 2016;225:50-59. doi: <http://dx.doi.org/10.1016/j.ijcard.2016.09.082>
355. Lee YH, Hong N, Lee CJ, et al. Differential association of ezetimibe-simvastatin combination with major adverse cardiovascular events in patients with or without

- diabetes: a retrospective propensity score-matched cohort study. *Scientific Reports* 2018;8(1):11925. doi: <https://dx.doi.org/10.1038/s41598-018-30409-6>
356. Lee YH, Kim MJ, Choi CI, et al. Retrospective study on antihyperlipidemic efficacy and safety of simvastatin, ezetimibe and their combination in Korean adults. *Archives of Pharmacal Research* 2011;34(8):1331-37. doi: <http://dx.doi.org/10.1007/s12272-011-0813-9>
357. Lin CF, Gau CS, Wu FL, et al. Impact of ezetimibe coadministered with statins on cardiovascular events following acute coronary syndrome: a 3-year population-based retrospective cohort study in Taiwan. *Clinical Therapeutics* 2011;33(9):1120-31. doi: <https://dx.doi.org/10.1016/j.clinthera.2011.08.002>
358. Lin Wu FL, Wang J, Ho W, et al. Effectiveness of a combination of ezetimibe and statins in patients with acute coronary syndrome and multiple comorbidities: A 6-year population-based cohort study. *International Journal of Cardiology* 2017;233:43-51. doi: <https://dx.doi.org/10.1016/j.ijcard.2017.02.006>
359. Liu C, Liu Q, Xiao X. Effectiveness and safety of combinational therapy compared with intensified statin monotherapy in patients with coronary heart disease. *Experimental and Therapeutic Medicine* 2018;15(6):4683-88. doi: <http://dx.doi.org/10.3892/etm.2018.6024>
360. Liu CH, Chen TH, Lin MS, et al. Ezetimibe-simvastatin therapy reduce recurrent ischemic stroke risks in type 2 diabetic patients. *Journal of Clinical Endocrinology and Metabolism* 2016;101(8):2994-3001. doi: <http://dx.doi.org/10.1210/jc.2016-1831>
361. Mandraffino G, Scicali R, Rodriguez-Carrio J, et al. 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. *Journal of Clinical Lipidology* 2020;14(2):231-40. doi: <https://dx.doi.org/10.1016/j.jacl.2020.01.015>
362. Meng PN, Yin DL, Lu WQ, et al. Intensive statin versus low-dose statin + ezetimibe treatment for fibrous cap thickness of coronary vulnerable plaques. *Chinese medical journal* 2020;03 doi: <http://dx.doi.org/10.1097/CM9.0000000000001067>
363. Patel AY, Pillarisetti J, Marr J, et al. Ezetimibe in combination with a statin does not reduce all-cause mortality. *J Clin Med Res* 2013;5(4):275-80. doi: <https://dx.doi.org/10.4021/jocmr1371w>
364. Pauriah M, Elder DH, Ogston S, et al. High-potency statin and ezetimibe use and mortality in survivors of an acute myocardial infarction: a population-based study. *Heart* 2014;100(11):867-72. doi: <https://dx.doi.org/10.1136/heartjnl-2013-304678>
365. Schwab P, Louder A, Li Y, et al. Cholesterol Treatment Patterns and Cardiovascular Clinical Outcomes Associated with Colesevelam HCl and Ezetimibe. *Drugs and Aging* 2014;31(9):683-94. doi: <http://dx.doi.org/10.1007/s40266-014-0200-6>
366. Sohn MW, Meadows JL, Oh EH, et al. Statin use and lower extremity amputation risk in nonelderly diabetic patients. *Journal of Vascular Surgery* 2013;58(6):1578-85.e1. doi: <http://dx.doi.org/10.1016/j.jvs.2013.06.069>

367. Stellaard F, von Bergmann K, Sudhop T, et al. The value of surrogate markers to monitor cholesterol absorption, synthesis and bioconversion to bile acids under lipid lowering therapies. *J Steroid Biochem Mol Biol* 2017;169:111-22. doi: <https://dx.doi.org/10.1016/j.jsbmb.2016.03.030>
368. Sternberg Z, Leung C, Sternberg D, et al. Disease modifying therapies modulate cardiovascular risk factors in patients with multiple sclerosis. *Cardiovascular Therapeutics* 2014;32(2):33-39. doi: <http://dx.doi.org/10.1111/1755-5922.12049>
369. Sundboll J, Larsen AP, Veres K, et al. Cardiovascular event rates and trajectories of LDL-cholesterol levels and lipid-lowering therapy in patients with atherosclerotic cardiovascular disease: A population-based cohort study. *Thromb Res* 2019;183:124-30. doi: <https://dx.doi.org/10.1016/j.thromres.2019.09.034>
370. Swindle JP, Ye X, Mallick R, et al. Colesevelam, Ezetimibe, and Patients With Type 2 Diabetes Mellitus: Characteristics and Clinical Outcomes From a Health Care Database. *Annals of Pharmacotherapy* 2014;48(7):847-55. doi: <http://dx.doi.org/10.1177/1060028014531737>
371. Tankova T, Elenkova A, Robeva R, et al. Familial Hypercholesterolaemia in a Bulgarian Population of Patients with Dyslipidaemia and Diabetes: An Observational Study. *Diabetes Therapy* 2020;11(2):453-65. doi: <http://dx.doi.org/10.1007/s13300-019-00748-2>
372. Teoh H, Mendelsohn AA, Goodman SG, et al. Usefulness of statin-ezetimibe combination to reduce the care gap in dyslipidemia management in patients with a high risk of atherosclerotic disease. *American Journal of Cardiology* 2009;104(6):798-804. doi: <https://dx.doi.org/10.1016/j.amjcard.2009.05.019>
373. Toth PP, Foody JM, Tomassini JE, et al. Therapeutic practice patterns related to statin potency and ezetimibe/simvastatin combination therapies in lowering LDL-C in patients with high-risk cardiovascular disease. *Journal of Clinical Lipidology* 2014;8(1):107-16. doi: <http://dx.doi.org/10.1016/j.jacl.2013.09.009>
374. van Delden XM, Huijgen R, Wolmarans KH, et al. LDL-cholesterol target achievement in patients with heterozygous familial hypercholesterolemia at Groote Schuur Hospital: Minority at target despite large reductions in LDL-C. *Atherosclerosis* 2018;277:327-33. doi: <https://dx.doi.org/10.1016/j.atherosclerosis.2018.06.820>
375. Van Staa TP, Carr DF, O'Meara H, et al. Predictors and outcomes of increases in creatine phosphokinase concentrations or rhabdomyolysis risk during statin treatment. *British Journal of Clinical Pharmacology* 2014;78(3):649-59. doi: <http://dx.doi.org/10.1111/bcp.12367>
376. Wasmuth S, Rohe K, Noack F, et al. Adherence To Lipid-Lowering Therapy In Patients With Coronary Heart Disease From The State Of Saxony-Anhalt, Germany. *Vasc Health Risk Manag* 2019;15:477-83. doi: <https://dx.doi.org/10.2147/VHRM.S197089>

377. Xanthopoulou I, Davlouros P, Siahos S, et al. First-line treatment patterns and lipid target levels attainment in very high cardiovascular risk outpatients. *Lipids in Health and Disease* 2013;12(1) doi: <http://dx.doi.org/10.1186/1476-511X-12-170>
378. Zhao YY, Weir MA, Manno M, et al. New fibrate use and acute renal outcomes in elderly adults a population-based study. *Annals of Internal Medicine* 2012;156(8):560-69. doi: <http://dx.doi.org/10.7326/0003-4819-156-8-201204170-00401>
379. Dai YY, Zhang HS, Zhang XG, et al. Statin-ezetimibe versus statin lipid-lowering therapy in patients with acute coronary syndromes undergoing percutaneous coronary intervention. *Journal of Thoracic Disease* 2017;9(5):1345-52. doi: <http://dx.doi.org/10.21037/jtd.2017.05.46>
380. Ballantyne CM, Lipka LJ, Sager PT, et al. Long-term safety and tolerability profile of ezetimibe and atorvastatin coadministration therapy in patients with primary hypercholesterolaemia. *International journal of clinical practice* 2004;58(7):653-58. doi: 10.1111/j.1368-5031.2004.00278.x
381. Kastelein JJ, Akdim F, Stroes ES, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *New England journal of medicine* 2008;358(14):1431-43. doi: 10.1056/NEJMoa0800742
382. Hagiwara N, Kawada-Watanabe E, Koyanagi R, et al. Low-density lipoprotein cholesterol targeting with pitavastatin + ezetimibe for patients with acute coronary syndrome and dyslipidaemia: the HIJ-PROPER study, a prospective, open-label, randomized trial. *European Heart Journal* 2017;38(29):2264-76. doi: <https://dx.doi.org/10.1093/eurheartj/ehx162>
383. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *New England Journal of Medicine* 2015;372(25):2387-97. doi: <https://dx.doi.org/10.1056/NEJMoa1410489>
384. Kinouchi K, Ichihara A, Bokuda K, et al. Effects of adding ezetimibe to fluvastatin on kidney function in patients with hypercholesterolemia: a randomized control trial. *Journal of atherosclerosis and thrombosis* 2013;20(3):245-56. doi: 10.5551/jat.14860
385. Kouvelos GN, Arnaoutoglou EM, Matsagkas MI, et al. Effects of rosuvastatin with or without ezetimibe on clinical outcomes in patients undergoing elective vascular surgery: results of a pilot study. *Journal of cardiovascular pharmacology and therapeutics* 2013;18(1):5-12. doi: 10.1177/1074248412445506
386. Liu Z, Hao H, Yin C, et al. Therapeutic effects of atorvastatin and ezetimibe compared with double-dose atorvastatin in very elderly patients with acute coronary syndrome. *Oncotarget* 2017;8(25):41582-89. doi: 10.18632/oncotarget.15078
387. Luo P, Li L, Wang LX, et al. Effects of atorvastatin in combination with ezetimibe on carotid atherosclerosis in elderly patients with hypercholesterolemia. *Genet Mol Res* 2014;13(2):2377-84. doi: <https://dx.doi.org/10.4238/2014.April.3.10>

388. Luo P, Wang L, Zhu H, et al. Impact of atorvastatin combined with ezetimibe for the treatment of carotid atherosclerosis in patients with coronary heart disease. *Acta cardiologica sinica* 2016;32(5):578-85. doi: 10.6515/ACS20151013H
389. Okada K, Iwahashi N, Endo T, et al. Long-term effects of ezetimibe-plus-statin therapy on low-density lipoprotein cholesterol levels as compared with double-dose statin therapy in patients with coronary artery disease. *Atherosclerosis* 2012;224(2):454-56. doi: 10.1016/j.atherosclerosis.2012.07.036
390. Ren Y, Zhu H, Fan Z, et al. Comparison of the effect of rosuvastatin versus rosuvastatin/ezetimibe on markers of inflammation in patients with acute myocardial infarction. *Experimental and therapeutic medicine* 2017;14(5):4942-50. doi: 10.3892/etm.2017.5175
391. Sakamoto K, Kawamura M, Watanabe T, et al. Effect of ezetimibe add-on therapy over 52 weeks extension analysis of prospective randomized trial (RESEARCH study) in type 2 diabetes subjects. *Lipids in health and disease* 2017;16(1):122. doi: 10.1186/s12944-017-0508-4
392. Tsujita K, Sugiyama S, Sumida H, et al. Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention: the Multicenter Randomized Controlled PRECISE-IVUS Trial. *Journal of the American College of Cardiology* 2015;66(5):495-507. doi: 10.1016/j.jacc.2015.05.065
393. Meaney A, Ceballos G, Asbun J, et al. The VYtorin on Carotid intima-media thickness and overall arterial rigidity (VYCTOR) study. *Journal of clinical pharmacology* 2009;49(7):838-47. doi: 10.1177/0091270009337011
394. Wang X, Zhao X, Li L, et al. Effects of Combination of Ezetimibe and Rosuvastatin on Coronary Artery Plaque in Patients with Coronary Heart Disease. *Heart, lung & circulation* 2016;25(5):459-65. doi: 10.1016/j.hlc.2015.10.012
395. Wang J, Ai XB, Wang F, et al. Efficacy of ezetimibe combined with atorvastatin in the treatment of carotid artery plaque in patients with type 2 diabetes mellitus complicated with coronary heart disease. *International angiology* 2017;36(5):467-73. doi: 10.23736/S0392-9590.17.03818-4
396. West AM, Anderson JD, Meyer CH, et al. The effect of ezetimibe on peripheral arterial atherosclerosis depends upon statin use at baseline. *Atherosclerosis* 2011;218(1):156-62. doi: <http://dx.doi.org/10.1016/j.atherosclerosis.2011.04.005>
397. Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: the GAUSS-3 Randomized Clinical Trial. *JAMA* 2016;315(15):1580-90. doi: 10.1001/jama.2016.3608
398. Landray M, Baigent C, Leaper C, et al. The second United Kingdom Heart and Renal Protection (UK-HARP-II) study: A randomized controlled study of the biochemical safety and efficacy of adding ezetimibe to simvastatin as initial therapy among patients with CKD. *American Journal of Kidney Diseases* 2006;47(3):385-95. doi: <http://dx.doi.org/10.1053/j.ajkd.2005.11.018>

399. Loomba R, Sirlin CB, Ang B, et al. Ezetimibe for the treatment of nonalcoholic steatohepatitis: assessment by novel magnetic resonance imaging and magnetic resonance elastography in a randomized trial (MOZART trial). *Hepatology* 2015;61(4):1239-50. doi: <https://dx.doi.org/10.1002/hep.27647>
400. Masana L, Mata P, Gagne C, et al. Long-term safety and, tolerability profiles and lipid-modifying efficacy of ezetimibe coadministered with ongoing simvastatin treatment: a multicenter, randomized, double-blind, placebo-controlled, 48-week extension study. *Clinical Therapeutics* 2005;27(2):174-84.
401. Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the ODYSSEY ALTERNATIVE randomized trial. *Journal of clinical lipidology* 2015;9(6):758-69. doi: 10.1016/j.jacl.2015.08.006
402. Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. *European Heart Journal* 2015;36(19):1186-94. doi: <https://dx.doi.org/10.1093/eurheartj/ehv028>
403. Han Y, Chen J, Chopra VK, et al. ODYSSEY EAST: Alirocumab efficacy and safety vs ezetimibe in high cardiovascular risk patients with hypercholesterolemia and on maximally tolerated statin in China, India, and Thailand. *Journal of Clinical Lipidology* 2020;14(1):98-108.e8. doi: <http://dx.doi.org/10.1016/j.jacl.2019.10.015>
404. Bays H, Gaudet D, Weiss R, et al. Alirocumab as Add-On to Atorvastatin Versus Other Lipid Treatment Strategies: ODYSSEY OPTIONS I Randomized Trial. *Journal of clinical endocrinology and metabolism* 2015;100(8):3140-48. doi: 10.1210/jc.2015-1520
405. Farnier M, Jones P, Severance R, et al. Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: the ODYSSEY OPTIONS II randomized trial. *Atherosclerosis* 2016;244:138-46. doi: 10.1016/j.atherosclerosis.2015.11.010
406. Roth EM, Taskinen MR, Ginsberg HN, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized Phase 3 trial. *International journal of cardiology* 2014;176(1):55-61. doi: 10.1016/j.ijcard.2014.06.049
407. Saito I, Azuma K, Kakikawa T, et al. A randomized, double-blind, placebo-controlled study of the effect of ezetimibe on glucose metabolism in subjects with type 2 diabetes mellitus and hypercholesterolemia. *Lipids in health and disease* 2015;14:40. doi: 10.1186/s12944-015-0036-z
408. Taylor AJ, Villines TC, Stanek EJ, et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. *New England journal of medicine* 2009;361(22):2113-22. doi: 10.1056/NEJMoa0907569
409. Yokote K, Kanada S, Matsuoka O, et al. Efficacy and safety of bococizumab (RN316/PF-04950615), a monoclonal antibody against proprotein convertase

- subtilisin/kexin type 9, in hypercholesterolemic Japanese subjects receiving a stable dose of atorvastatin or treatment-naïve: Results from a randomized, placebo-controlled, dose-ranging study. *Circulation Journal* 2017;81(10):1496-505. doi: <http://dx.doi.org/10.1253/circj.CJ-16-1310>
410. McKenney JM, Farnier M, Lo KW, et al. Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. *Journal of the american college of cardiology* 2006;47(8):1584-87. doi: 10.1016/j.jacc.2005.11.072
411. Masuda J, Tanigawa T, Yamada T, et al. Effect of combination therapy of ezetimibe and rosuvastatin on regression of coronary atherosclerosis in patients with coronary artery disease. *International heart journal* 2015;56(3):278-85. doi: 10.1536/ihj.14-311
412. Jackowska P, Pytel E, Koter-Michalak M, et al. The Effect of Combined Ezetimibe/Atorvastatin Therapy vs. Atorvastatin Monotherapy on the Erythrocyte Membrane Structure in Patients with Coronary Artery Disease: a Pilot Study. *Advances in clinical and experimental medicine : official organ wroclaw medical university* 2016;25(3):433-39. doi: 10.17219/acem/34791
413. Jackowska P, Chałubiński M, Łuczak E, et al. The influence of statin monotherapy and statin-ezetimibe combined therapy on FoxP3 and IL 10 mRNA expression in patients with coronary artery disease. *Advances in clinical and experimental medicine : official organ wroclaw medical university* 2019;28(9):1243-48. doi: 10.17219/acem/108627
414. Habara M, Nasu K, Terashima M, et al. Impact on optical coherence tomographic coronary findings of fluvastatin alone versus fluvastatin + ezetimibe. *American journal of cardiology* 2014;113(4):580-87. doi: 10.1016/j.amjcard.2013.10.038
415. Gaudiani LM, Lewin A, Meneghini L, et al. Efficacy and safety of ezetimibe co-administered with simvastatin in thiazolidinedione-treated type 2 diabetic patients. *Diabetes, obesity & metabolism* 2005;7(1):88-97. doi: 10.1111/j.1463-1326.2004.00420.x
416. Dagli N, Yavuzkir M, Karaca I. The effects of high dose pravastatin and low dose pravastatin and ezetimibe combination therapy on lipid, glucose metabolism and inflammation. *Inflammation* 2007;30(6):230-35. doi: 10.1007/s10753-007-9041-3
417. Arimura T, Miura S, Ike A, et al. Comparison of the efficacy and safety of statin and statin/ezetimibe therapy after coronary stent implantation in patients with stable angina. *Journal of cardiology* 2012;60(2):111-18. doi: 10.1016/j.jjcc.2012.03.002
418. Nakou ES, Filippatos TD, Georgoula M, et al. The effect of orlistat and ezetimibe, alone or in combination, on serum LDL and small dense LDL cholesterol levels in overweight and obese patients with hypercholesterolaemia. *Current medical research and opinion* 2008;24(7):1919-29. doi: 10.1185/03007990802177150
419. Pisciotta L, Bellocchio A, Bertolini S. Nutraceutical pill containing berberine versus ezetimibe on plasma lipid pattern in hypercholesterolemic subjects and its

- additive effect in patients with familial hypercholesterolemia on stable cholesterol-lowering treatment. *Lipids in health and disease* 2012;11:123. doi: 10.1186/1476-511X-11-123
420. Takase S, Matoba T, Nakashiro S, et al. 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. *Arteriosclerosis, thrombosis, and vascular biology* 2017;37(2):350-58. doi: 10.1161/ATVBAHA.116.308388
421. Oh M, Kim H, Shin EW, et al. Comparison of High-Dose Rosuvastatin Versus Low-Dose Rosuvastatin Plus Ezetimibe on Carotid Atherosclerotic Plaque Inflammation in Patients with Acute Coronary Syndrome. *J Cardiovasc Transl Res* 2020;04:04. doi: <https://dx.doi.org/10.1007/s12265-020-10009-4>
422. Takeshita Y, Takamura T, Honda M, et al. The effects of ezetimibe on non-alcoholic fatty liver disease and glucose metabolism: a randomised controlled trial. *Diabetologia* 2014;57(5):878-90. doi: 10.1007/s00125-013-3149-9
423. Shaw SM, Chaggar P, Ritchie J, et al. The efficacy and tolerability of ezetimibe in cardiac transplant recipients taking cyclosporin. *Transplantation* 2009;87(5):771-75. doi: 10.1097/TP.0b013e318198d7d0
424. Strony J, Yang B, Hanson ME, et al. Long-term safety and tolerability of ezetimibe coadministered with simvastatin in hypercholesterolemic patients: a randomized, 12-month double-blind extension study. *Current medical research and opinion* 2008;24(11):3149-57. doi: 10.1185/03007990802426581
425. Nakou E, Babageorgakas P, Bouchliou I, et al. Statin-induced immunomodulation alters peripheral invariant natural killer T-cell prevalence in hyperlipidemic patients. *Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy* 2012;26(4):293-99. doi: 10.1007/s10557-012-6387-z
426. Miklishanskaya SV, Vlasik TN, Kheimets GI, et al. The possibility of reducing the Lp-PLA2 mass level using simvastatin monotherapy and combination therapy with ezetimibe. *Cor ET vasa* 2015;57(4):e257-e64. doi: 10.1016/j.crvasa.2015.03.012
427. Bajaj HS, Brown RE, Jiandani D, et al. Goal achievement of HbA1c and LDL-cholesterol in a randomized trial comparing colesevelam with ezetimibe: GOAL-RCT. *Diabetes, Obesity & Metabolism* 2020;22(10):1722-28. doi: <https://dx.doi.org/10.1111/dom.14084>
428. Battaggia A, Donzelli A, Font M, et al. Clinical efficacy and safety of Ezetimibe on major cardiovascular endpoints: systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2015;10(4):e0124587. doi: 10.1371/journal.pone.0124587 [published Online First: 2015/04/29]
429. Savarese G, De Ferrari GM, Rosano GM, et al. Safety and efficacy of ezetimibe: A meta-analysis. *Int J Cardiol* 2015;201:247-52. doi: 10.1016/j.ijcard.2015.08.103 [published Online First: 2015/08/25]

430. Zhao Z, Du S, Shen S, et al. Comparative efficacy and safety of lipid-lowering agents in patients with hypercholesterolemia: A frequentist network meta-analysis. *Medicine (Baltimore)* 2019;98(6):e14400. doi: 10.1097/md.00000000000014400 [published Online First: 2019/02/09]
431. Chaiyasothi T, Nathisuwan S, Dilokthornsakul P, et al. Effects of Non-statin Lipid-Modifying Agents on Cardiovascular Morbidity and Mortality Among Statin-Treated Patients: A Systematic Review and Network Meta-Analysis. *Front Pharmacol* 2019;10:547. doi: 10.3389/fphar.2019.00547 [published Online First: 2019/06/14]
432. Davidson MH, Maccubbin D, Stepanavage M, et al. Striated muscle safety of ezetimibe/simvastatin (Vytorin). *Am J Cardiol* 2006;97(2):223-8. doi: 10.1016/j.amjcard.2005.08.038 [published Online First: 2006/01/31]
433. Pandor A, Ara RM, Tumur I, et al. Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. *J Intern Med* 2009;265(5):568-80. doi: 10.1111/j.1365-2796.2008.02062.x [published Online First: 2009/01/15]