PCSK9 inhibitors and ezetimibe with or without statin therapy for cardiovascular risk reduction: a systematic review and network meta-analysis

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ABSTRACT

OBJECTIVE

To compare the impact of ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors on cardiovascular outcomes in adults taking maximally tolerated statin therapy or who are statin intolerant.

DESIGN

Network meta-analysis.

DATA SOURCES

Medline, EMBASE, and Cochrane Library up to 31 December 2020.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Randomised controlled trials of ezetimibe and PCSK9 inhibitors with ≥500 patients and follow-up of ≥6 months.

MAIN OUTCOME MEASURES

We performed frequentist fixed-effects network meta-analysis and GRADE (grading of recommendations, assessment, development, and evaluation) to assess certainty of evidence. Results included relative risks (RR) and absolute risks per 1000 patients treated for five years for non-fatal myocardial infarction (MI), non-fatal stroke, all-cause mortality, and cardiovascular mortality. We estimated absolute risk differences assuming constant RR (estimated from network meta-analysis) across different baseline therapies and cardiovascular risk thresholds; the PREDICT risk calculator estimated cardiovascular risk in primary and secondary prevention. Patients were categorised at low to very high cardiovascular risk. A guideline panel and systematic review authors established the minimal important differences (MID) of 12 per 1000 for MI and 10 per 1000 for stroke.

RESULTS

We identified 14 trials assessing ezetimibe and PCSK9 inhibitors among 83 660 adults using statins. Adding ezetimibe to statins reduced MI (RR 0.87 (95% confidence interval 0.80 to 0.94)) and stroke (RR 0.82 (0.71 to 0.96)) but not all-cause mortality (RR 0.99 (0.92 to 1.06)) or cardiovascular mortality (RR 0.97 (0.87 to 1.09)). Similarly, adding PCSK9 inhibitor to statins reduced MI (0.81 (0.76 to 0.87)) and stroke (0.74 (0.64 to 0.85)) but not all-cause (0.95 (0.87 to 1.03)) or cardiovascular mortality (0.95 (0.87 to 1.03)). Among adults with very high cardiovascular risk, adding PCSK9 inhibitor was likely to reduce MI (16 per 1000) and stroke (21 per 1000) (moderate to high certainty); whereas adding ezetimibe was likely to reduce stroke (14 per 1000), but the reduction of MI (11 per 1000) (moderate certainty) did not reach MID. Adding ezetimibe to PCSK9 inhibitor and statin may reduce stroke (11 per 1000), but the reduction of MI (9 per 1000) (low certainty) did not reach MID. Adding PCSK9 inhibitors to statins and ezetimibe may reduce MI (14 per 1000) and stroke (17 per 1000) (low certainty). Among adults with high cardiovascular risk, adding PCSK9 inhibitor probably reduced MI (12 per 1000) and stroke (16 per 1000) (moderate certainty); adding ezetimibe probably reduced stroke (11 per 1000), but the reduction in MI did not achieve MID (8 per 1000) (moderate certainty). Adding ezetimibe to PCSK9 inhibitor and statins did not reduce outcomes beyond MID, while adding PCSK9 inhibitor to ezetimibe and statins may reduce stroke (13 per 1000). These effects were consistent in statin-intolerant patients. Among moderate and low cardiovascular risk groups, adding PCSK9 inhibitor or ezetimibe to statins yielded little or no benefit for MI and stroke.

CONCLUSIONS

Ezetimibe or PCSK9 inhibitors may reduce non-fatal MI and stroke in adults at very high or high cardiovascular risk who are receiving maximally tolerated statin therapy or are statin-intolerant, but not in those with moderate and low cardiovascular risk.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Statins are recommended as first-line drugs for cardiovascular risk reduction; ezetimibe and proprotein convertase subtilisn/kexin type 9 (PCSK9) inhibitors are recommended as add-on therapies if patients require further cardiovascular risk reduction

The absolute effects of ezetimibe and PCSK9 inhibitors, separately or in combination, on cardiovascular outcomes based on baseline cardiovascular risks of the individuals taking the maximally tolerated dose of statins or who are statin-intolerant are uncertain

WHAT THIS STUDY ADDS

Ezetimibe or PCSK9 inhibitors may reduce non-fatal myocardial infarction and stroke in adults at very high or high cardiovascular risk who are taking the maximally tolerated dose of statins or who are statin-intolerant. However, these benefits were not shown in those with moderate and low cardiovascular risk

Adding ezetimibe or PCSK9 inhibitor as add-on therapies or in statin-intolerant adults had no significant effect on all-cause or cardiovascular mortality

Prescribing these lipid-lowering agents should be considered among appropriate candidates at very high or high cardiovascular risk to achieve desired cardiovascular benefits, as reflected in the risk-stratified BMJ Rapid Recommendations informed by this systematic review

Introduction

Therapies have shown promising efficacy in reducing low density lipoprotein cholesterol (LDL-C) levels and cardiovascular risk by (*a*) interfering with cholesterol synthesis (statins),[1] (*b*) blocking the absorption of cholesterol molecules by the small intestine (ezetimibe),[2] or (*c*) neutralising the effects of proprotein convertase subtilisn/kexin type 9 (PCSK9) protein, either by inhibiting the circulating fraction of protein by monoclonal antibodies (such as alirocumab or evolocumab)[3 4] or inhibiting the hepatic synthesis of protein by small interfering RNA (siRNA) therapeutic agents (such as inclisiran).[5] Both the American Heart Association/American College of Cardiology (AHA/ACC) guidelines[6] and the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines[7 8] recommend statins as first-line drugs for cardiovascular risk reduction; ezetimibe as the second-line therapy in patients who are either statin intolerant or unable to achieve desired LDL-C lowering despite being on maximally tolerated statin therapy. If further lowering in LDL-C is required, a step-up approach using PCSK9 inhibitors is recommended.[6]

These recommendations for ezetimibe were derived from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial),[2] in which ezetimibe and simvastatin generated an incremental reduction in LDL-C compared with up-titration of simvastatin alone (from 40 mg to 80 mg per day), resulting in a significant reduction in cardiovascular outcomes in patients with acute coronary syndrome. The recommendations for PCSK9 inhibitors relied on the results of the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk)[3] and ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab)[4] trials. Both trials showed that PCSK9 inhibitors produced an impressive reduction in LDL-C levels and cardiovascular outcomes when added to statin therapy (with or without ezetimibe) in patients with recent acute coronary syndrome.[3 4] However, the high cost of PCSK9 inhibitors have raised concerns about their actual net worth. Cost-effectiveness analyses demonstrated that the drugs' cost is considerably higher than their clinical value.[9]

The absolute cardiovascular benefits of the therapies depend on individuals' baseline cardiovascular risk.[10 11] However, to our knowledge, no large trial or meta-analysis has assessed the potential absolute incremental effects of ezetimibe and PCSK9 inhibitors, separately or in combination, by estimating the extent of absolute cardiovascular risk reductions with these therapies in individuals who are using the maximally tolerated statins or are statin-intolerant across different cardiovascular risk groups. We performed a systematic review and network meta-analysis to investigate this issue to fill this knowledge gap. This review quantitatively informed the effects of ezetimibe and PCSK9 inhibitors on cardiovascular outcomes for a parallel clinical practice guideline with risk-stratified recommendations for the two lipid-lowering drugs.[12] This guideline representing the *BMJ* Rapid Recommendations is a collaborative initiative from the MAGIC Evidence Ecosystem Foundation (www.magicproject.org) and the *BMJ* (see box 1 for details of the linked articles).

Box 1: Linked resources 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/#/guideline/jz7rXL)
  - Expanded version of results with multi-layered recommendations, evidence summaries and decision aids for use on all devices

Methods

This network meta-analysis was conducted following the Cochrane Collaboration guidelines and was reported in accordance to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).[13 14]

Guideline panel and patient involvement

The multi-professional *BMJ* Rapid Recommendations panel that included cardiologists, general practitioners, general internists, endocrinologists, a geriatrician, methodologists, and three patient partners (already taking statins or intolerant to statins) provided oversight over the steps of this review. Patient partners received personal training and individual support in the methods used throughout the guideline development process. The panel assisted in framing the study question, defining the interventions and comparisons, prioritising outcome measures (rated from 1 to 9 on the importance to individual patients, with 9 being most important),[12] proposing subgroup analyses, determining thresholds of important benefits (to rate imprecision in cardiovascular outcomes), and performing baseline risk calculations (see appendix on bmj.com). The panel selected four effective critical outcomes: non-fatal myocardial infarction, non-fatal stroke, all-cause mortality, and cardiovascular mortality. Two separate reviews in company addressed adverse outcomes.[15 16] The safety outcomes of PCSK9 inhibitors included new-onset diabetes, injection site reaction leading to discontinuation of treatment,

flu-like symptoms leading to discontinuation, myalgia or muscular pain leading to discontinuation, any adverse events leading to discontinuation, neurocognitive events, cataract, and gastrointestinal haemorrhage.[15] The safety outcomes of ezetimibe included cancer of any type, new-onset diabetes, neurocognitive events, fractures, myalgia or muscular pain leading to discontinuation, discontinuation due to gastrointestinal adverse events, or discontinuation due to any adverse effect.[16]

Data sources and searches

A detailed literature search was performed without language restriction using electronic databases of Medline, EMBASE, Cochrane library, and ClinicalTrials.gov up to 31 December 2020. Additional online sources included websites of major cardiovascular and medical journals (www.nejm.org; https://www.thelancet.com/; https://jamanetwork.com; https://academic.oup.com/eurheartj; www.onlinejacc.org; https://annals.org/aim; and www.ahajournals.org/journal/circ), and bibliographies of relevant studies and meta-analyses. The search strategy included a combination of the following broad search terms: "lipid," LDL," "cholesterol," "statin," "ezetimibe," and "proprotein convertase subtilisin/kexin type 9 inhibitor" (appendix table 1).

Study selection

The pre-determined inclusion criteria were: randomised controlled trials in which patients at median baseline LDL-C values ≥70 mg/dL (≥1.8 mmol/L) seeking cardiovascular risk reduction regardless of baseline cardiovascular risk were randomised to receive PCSK9 inhibitors versus control, ezetimibe *v* control, or PCSK9 inhibitors *v* ezetimibe; sample size of ≥500 patients and follow-up of ≥6 months to generate reliable estimates; and trials needed to report specified outcomes of interests. We excluded trials in which the intervention arm (PCSK 9 inhibitors or ezetimibe) systematically received different statin doses than the control arm.[17]

PCSK9 inhibitors included therapies that reduce circulating levels of PCSK9 through monoclonal antibodies (evolocumab and alirocumab)[3 4] and those which control the production of PCSK9 protein via siRNA (inclisiran).[5] Two trials of bococizumab (SPIRE 1 and 2)[18] also met the study selection criteria. However, production of bococizumab was discontinued since the drug showed higher levels of immunogenicity and higher rate of injection site reactions.[19] The guideline panel decided to exclude SPIRE trials[18] since bococizumab is no longer a therapeutic option. That said, while we decided to focus on drugs available to patients, exclusion of these trials would have raised selection bias concerns. Therefore, we decided to report results of network meta-analysis by including SPIRE 1 and 2 trials[18] separately in a sensitivity analysis.

We removed the duplicates and, following the study selection criteria, we screened the remaining articles at the title and abstract level and then at the full-text level (appendix fig 1). The process of study search and selection was performed independently by two reviewers (SUK and SHY). Any conflicts were resolved by discussion and mutual consensus.

Data extraction

Two reviewers (SUK and SHY) independently extracted the data on pre-specified collection forms, appraised the accuracy of data, and resolved any discrepancies by consensus after discussion. We abstracted data on characteristics of trials and participants (age, sex, comorbidities, treatment arms with doses, control arms, baseline LDL-C and achieved LDL-C values (mg/dL)), crude point estimates, numbers of events, sample sizes, and follow-up duration. We abstracted data on the intention-to-treat principle. We contacted the authors of the trials in case of missing data in the original publication.

Risk of bias within individual studies

We used a modified Cochrane tool for assessing the risk of bias in randomised trials (RoB 1.0).[20] Risk of bias assessment was done across the following domains: bias due to randomisation process; bias due to deviation from the intended intervention; bias due to missing outcome data; bias in the measurement of the outcome; bias in the selection of the reported results, including divergence from the registered protocol; and bias owing to early termination for benefit. Trials were rated as at low risk of bias, some concerns—probably low risk of bias, some concerns—probably high risk of bias, or high risk of bias. Trials were rated at high risk of bias overall if one or more domains were rated as probably high risk of bias or as high risk of bias; trials were rated at low risk of bias if all domains were rated as probably low risk of bias or low risk of bias. Two reviewers (SUK and SHY) independently appraised the potential risks of bias, and discrepancies were resolved by discussion or adjudication by a third party (appendix table 2).

Data synthesis and summary measures

We performed a network meta-analysis using a frequentist framework for all patients, regardless of drug doses. We preferred the frequentist over the Bayesian approach since the latter can inflate between-comparison heterogeneity when using vague priors in sparse networks. Outcomes were estimated as risk ratios with 95% confidence intervals. However, to facilitate interpretation of the results, we calculated absolute effects for outcomes from risk ratios using baseline cardiovascular risk. Since risk ratios generally usually remain similar across risk categories, we estimated absolute risk differences assuming constant risk ratios across different baseline therapies (dose and duration) and different cardiovascular risk thresholds.

We adopted the risk calculator derived from PREDICT[21] to estimate patients' cardiovascular risks, reporting the incidence of MACE, in all cardiovascular risk groups, both in primary and secondary prevention, which is not the case with most other risk scores. Clinical trials provide average treatment effects across participants

with variable cardiovascular risk. However, since some of the participants would have qualified as high or very high cardiovascular risk patients, measuring the absolute effects of therapy in these trials would overestimate effects in patients with lower risk. In contrast, our approach allowed the guideline panel to judge the absolute effects of the different drugs for patients with a similar cardiovascular risk rather than using only the risk category for participants included in trials.

We estimated risks for individual outcomes (non-fatal myocardial infarction, non-fatal stroke, all-cause mortality, and cardiovascular mortality) over five years for primary and secondary prevention and defined four broad risk categories ranging from low to very high risk. We used medians of the risk within each risk category from the PREDICT cohort[21 22] as the baseline risk estimates. The risk categories were defined as low risk patient with one or two cardiovascular risk factors (risk of MACE over five years is 0-5%, median 2%); moderate risk, patients with three or four cardiovascular risk factors (risk of MACE over five years is 5-15%, median 7%); high cardiovascular risk, patients with five or more additional cardiovascular risk factors or hereditary or familial lipid disorder without any cardiovascular risk factors (the risk of MACE over five years is >15%, median 18%); and very high risk, patients with established cardiovascular disease or hereditary or familial lipid disorder (median risk of MACE over 5 years is 24%). Further details are provided in the appendix.

Treatment nodes

Treatments were grouped into common nodes based on drugs and not on dose or duration. We generated nodes for ezetimibe, PCSK9 inhibitors, and control (appendix fig 2). PCSK9 inhibitor node comprises anti-PCSK9 monoclonal antibodies (evolocumab, alirocumab) and anti-PCSK9 siRNA therapeutic agent (inclisiran). The control node was composed of a placebo or ezetimibe with or without statin. We generated network plots using the netgraph command of the netmeta package of R Project for Statistical Computing version 4.9-4 with the thickness of lines between nodes and the size of nodes based on a number of component studies of the network.

Statistical analysis

We performed network meta-analysis using a fixed-effects model. We preferred the fixed-effects model over the random-effects model because heterogeneity estimation in random-effects in the sparse network can generate unreliable results[23] (appendix). Statistical heterogeneity was interpreted by the τ^2 and I^2 statistic (values of <25%, 25-50%, and >50% representing low, moderate, and high heterogeneity degrees, respectively) (appendix table 3). The node-splitting method examined the consistency between direct and indirect sources of evidence. The 95% confidence intervals that did not cross 1 were considered statistically significant. We used the netmeta package of R Project for Statistical Computing version 4.9-4 for all analyses. Funnel plots with Egger's regression test for evidence of small-study effects in analyses including 10 or more studies were generated (appendix figs 3-6). We planned subgroup analysis if sufficient data were available for follow-up duration (<1 or ≥1 year), risk of bias (low *v* high), familial hypercholesteraemia or not, and focus of trials (cardiovascular outcomes *v* non-cardiovascular outcomes (LDL-C or adverse events)) (see appendix figs 7-10). Finally, to assess the consistency of results, we performed sensitivity analyses by adding SPIRE trials and excluding inclisiran trials (owing to a different mechanism of action than anti-PCSK9 monoclonal antibodies).

Certainty of the evidence

We evaluated the certainty of evidence using the grading of recommendations assessment, development, and evaluation (GRADE) approach for network meta-analysis.[24] Two reviewers (QH and SL) rated each domain for each comparison separately and resolved discrepancies by consensus. We rated the certainty for each comparison and endpoint as high, moderate, low, or very low, based on the risk of bias, inconsistency, indirectness, publication bias, intransitivity, and incoherence (the difference between direct and indirect effects), and imprecision. A guideline panel with whom systematic review authors collaborated established the minimal important differences (MID) for rating imprecision. If the 95% confidence interval included the MID value, we rated it down for imprecision. Accordingly, the panel chose the medians of the survey results for each outcome as the best estimate of the MID: a reduction of 12 per 1000 for non-fatal myocardial infarction, 10 per 1000 for non-fatal stroke, and 8 per 1000 for all-cause or cardiovascular mortality for five years. We created a summary of findings tables in the MAGIC authoring and publication platform (www.magicapp.org) to provide user-friendly formats for clinicians and patients and to allow re-use in the context of clinical practice guidelines (appendix table 4).

Patient and public involvement

Patients were involved in populations, interventions, and outcomes of interest identification, the interpretation of results, and the generation of parallel recommendations as part of the *BMJ* Rapid Recommendations initiative.

Results

Description of included studies

A total of 582 articles were assessed for eligibility after the removal of duplicates and screening at the title and abstract level. Further, 566 articles were removed based on a priori study selection criteria. Ultimately, 16 trials encompassing 111 098 patients were selected, of which 14 trials (83 660 individuals) were included in the primary analyses, and two trials (SPIRE 1 and 2)[18] were added in the sensitivity analyses. The characteristics of the participants and trials are reported in table 1. Of the 14 trials in the primary

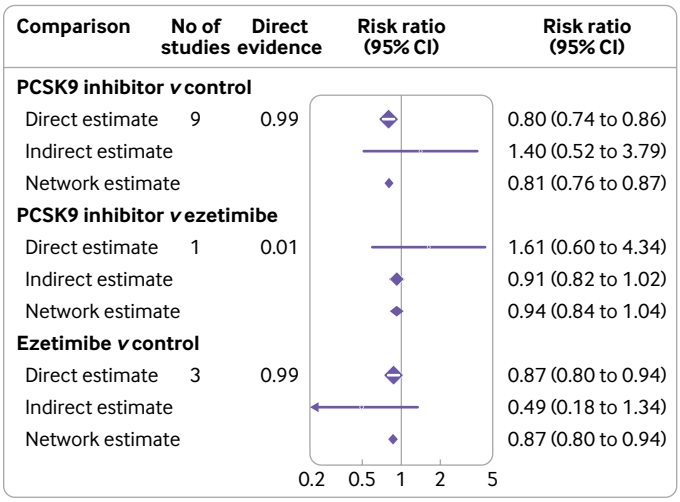

Fig 1 | Forest plot showing node-split analysis for non-fatal myocardial infarction. Number of studies represent number of component trials in each comparison. Direct evidence reports proportion of direct evidence in summary estimates. PCSK9 = proprotein convertase subtilisn/kexin type 9

analyses, one trial compared PCSK9 inhibitor with ezetimibe,[26] 10 trials compared PCSK9 inhibitor with control,[3-5 25 27-30 32] and three trials compared ezetimibe with control.[2 31 33] The median age across the trials was 61 years (interquartile range (IQR) 60-65 years), and the median LDL-C concentration was 105 mg/dL (IQR 94-122 mg/dL). The median follow-up duration across the trials was two years (IQR 1-3 years).

Statistical heterogeneity for each comparison and outcome was non-significant (P>0.05). Subgroup analyses showed no significant interaction (P>0.05) for cardiovascular outcomes and mortality among PCSK9 inhibitor trials focused on cardiovascular outcomes compared with those focused on non-cardiovascular outcomes. We could not perform subgroup analyses for ezetimibe since all trials focused on cardiovascular outcomes.

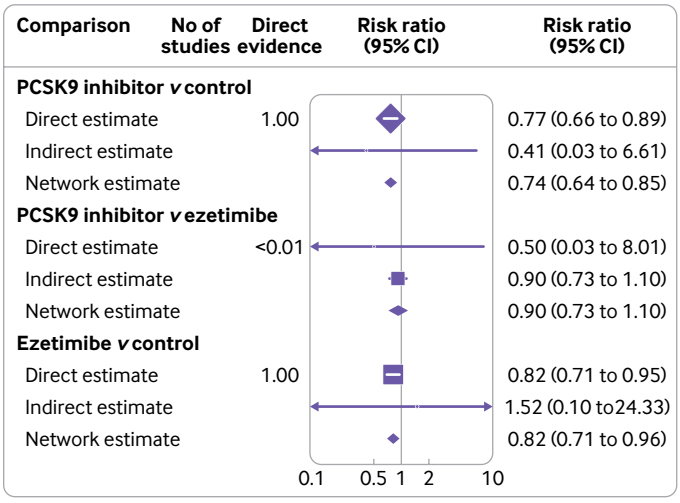

Fig 2 | Forest plot showing node-split analysis for non-fatal stroke. Number of studies represent number of component trials in each comparison. Direct evidence reports proportion of direct evidence in summary estimates. PCSK9 = proprotein convertase subtilisn/kexin type 9

The relative and absolute estimates per 1000 patients over a five year period are reported in tables 2 and 3. For all the endpoints, we considered consistent relative risk reductions in cardiovascular events across all the baseline cardiovascular risk categories for PCSK9 inhibitors or ezetimibe. However, the absolute effects of these drugs depend on individual patients' baseline cardiovascular risk.

Adults receiving maximally tolerated statin therapy (table 2)

Non-fatal myocardial infarction and stroke

Figures 1 and 2 illustrate the contribution of direct and indirect evidence in generating summary estimates for non-fatal myocardial infarction (MI) and stroke, respectively. Compared with control, ezetimibe reduced MI (risk ratio 0.87 (95% CI 0.80 to 0.94)) and stroke (0.82 (0.71 to 0.96)), as did PCSK9 inhibitors (0.81 (0.76 to 0.87) for MI, 0.74 (0.64 to 0.85) for stroke). The relative estimates were consistent in sensitivity analyses using SPIRE trials or exclusion of ORION trials (appendix tables 5 and 6).

In patients with very high cardiovascular risk, adding PCSK9 inhibitors to a statin is likely to reduce MI (16 per 1000) and stroke (21 per 1000) (moderate to high certainty); adding ezetimibe to statin probably reduced stroke (14 per 1000), but the reduction of MI (11 per 1000) (moderate certainty) did not reach the minimal important difference (MID) (see table 2). Adding ezetimibe to PCSK9 inhibitor and statin may reduce stroke (11 per 1000), but the reduction of MI (9 per 1000) (low certainty) did not reach MID. Finally, adding PCSK9 inhibitors to statin and ezetimibe therapy may reduce MI (14 per 1000) and stroke (17 per 1000) (low certainty).

In patients with high cardiovascular risk, adding PCSK9 inhibitor to statin is likely to reduce MI (12 per 1000) and stroke (16 per 1000) (moderate certainty); adding ezetimibe probably reduced stroke (11 per 1000), but the reduction in MI did not achieve MID (8 per 1000) (moderate certainty). Adding ezetimibe to PCSK9 inhibitor and statin therapy did not reduce outcomes beyond MID (moderate to low certainty), whereas adding PCSK9 inhibitor to ezetimibe and statin may reduce stroke (13 per 1000) (low certainty).

In patients with moderate to low cardiovascular risk, adding ezetimibe or PCSK9 inhibitor to background lipid-lowering therapy yielded little or no benefits on reducing MI and stroke (moderate to low certainty). There was no variability in summary estimates when trials were grouped by their primary focus of analysis (appendix figs 7-10).

All-cause and cardiovascular mortality

Appendix figures 11 and 12 illustrate the contribution of direct and indirect evidence in generating summary estimates for all-cause and cardiovascular mortality respectively. Compared with control, ezetimibe had no significant effect on all-cause mortality in all cardiovascular risk groups (risk ratio 0.99 (95% CI 0.92 to 1.06)), nor did PCSK9 inhibitors (0.95 (0.87 to

Table 1 | Baseline characteristics of trials and participants

Study	Participants at baseline						Intervention		Control		Background therapy (%)	Outcome focus*	Median follow-up (years)
	No	Mean LDL-C (mg/dL)	Mean age (years)	No (%) women	No (%) CAD	No (%) diabetes	Agent	No	Agent	No			
Trials included in primary analysis													
DESCARTES 2014[25]	901	104.2	56.3	471 (52)	136 (15)	104 (12)	Evolocumab 420 mg	599	Placebo	392	Statin (88))/ ezetimibe (21)	LDL-C	0.9
ODYSSEY COMBO II 2014[26]	720	106	61.5	190 (26)	649 (90.1)	90 (12)	Alirocumab 75 mg	479	Ezetimibe 10 mg	241	Statin (100)	LDL-C	0.9
IMPROVE IT 2015[2]	18 144	93.8	63.6	4416 (24)	18144 (100)	4933 (27)	Simvastatin 40-80 mg + ezetimibe 10 mg	9067	Simvastatin 40-80 mg + placebo	9077	Statin (100)	CV outcome	6.0
ODYSSEY LONGTERM 2015[27]	2341	122	60.5	884 (38)	1607 (69)	809 (35)	Alirocumab 150 mg	1553	Placebo	788	Statin (100)/ ezetimibe (15)	LDL-C	1.5
OSLER 2015[28]	4465	120	58.0	2210 (49)	896 (20.1)	599 (13)	Evolocumab 140- 420 mg	2976	Standard therapy	1489	Statin (71)/ ezetimibe (14)	Adverse events	0.9
GLAGOV 2016[29]	968	92	59.8	269 (28)	340 (35.1)	202 (21)	Evolocumab 420 mg	484	Placebo	484	Statin (99)/ ezetimibe (2)	Percent atheroma volume	1.4
ODYSSEY CHOICE I 2016[30]	803	127.5	60.3	341 (42)	0	217 (27)	Alirocumab 75-300 mg	573	Placebo	230	Statin (68)/ ezetimibe (12)	LDL-C	1.1
HIJ-PROPER 2017[31]	1721	135	65.5	421 (24)	1,721 (100)	520 (30)	Pitavastatin 10 mg + ezetimibe 10 mg	864	Pitavastatin 10 mg	857	Statin (100)	CV outcome	3.8
ODYSSEY DM-INSULIN 2017[32]	517	108 to 128	60.3	232 (45)	165 (32)	517 (100)	Alirocumab 75-150 mg	345	Placebo	167	Statin (75)/ ezetimibe (12)	LDL-C	0.5
FOURIER 2017[3]	27 564	92	62.5	6769 (25)	22 351 (81)	10081 (37)	Evolocumab 140 or 420 mg	13784	Placebo	13780	Statin (100)/ ezetimibe (5)	CV outcome	2.2
ODYSSEY OUTCOMES 2018[4]	18 924	92	58.5	4762 (25)	18 924 (100)	5444 (29)	Alirocumab 75-150 mg	9462	Placebo	9462	Statin (98)/ ezetimibe (3)	CV outcome	2.8
EWTOPIA 75 2019[33]	3411	161	80.6	2539 (74.5)	0	867 (25)	Ezetimibe 10 mg	1716	Dietary counselling	1695	Statin (‹5)	CV outcome	4.1
ORION 10 2020[5]	1561	105	66.1	478 (31)	1561 (100)	702 (44.9)	Inclisiran 284 mg	781	Placebo	781	Statin (89)/ ezetimibe (10)	LDL-C	1.5
ORION 11 2020[5]	1620	105	64.8	460 (28)	1414 (87)	562 (35)	Inclisiran 284 mg	801	Placebo	807	Statin (95)/ ezetimibe (7)	LDL-C	1.5
Trials included in sensitivity analysis													
SPIRE-1 2017[18]	16 817	93.7	63.3	4439 (26)	–	8047 (48)	Bococizumab 150 mg	8408	Placebo	8409	Statin (99)/ ezetimibe (8)	CV outcome	0.6
SPIRE-2 2017[18]	10 621	133.6	62.4	3675 (35)	–	4986 (47)	Bococizumab 150 mg	5312	Placebo	5309	Statin (83)/ ezetimibe (13)	CV outcome	1.0

CAD = coronary artery disease; CV = cardiovascular; LDL-C = low density lipoprotein cholesterol.
*For studies where primary outcome not cardiovascular events, risk of bias during ascertainment was considered high, as CV outcomes were collected as safety outcomes, without a systematic regular ascertainment.

1.03)). Similarly, ezetimibe had no significant effect on cardiovascular mortality compared with control (0.97 (0.92 to 1.06)), nor did PCSK9 inhibitors (0.95 (0.87 to 1.03)). Accordingly, both ezetimibe and PCSK9 inhibitors yielded no benefits across all baseline risk categories (moderate to high certainty evidence). These results were consistent in sensitivity analyses.

Outcomes in statin-intolerant patients (table 3)

Non-fatal myocardial infarction and stroke

In patients with very high cardiovascular risk, ezetimibe monotherapy probably reduced non-fatal MI (16 fewer per 1000) and stroke (17 fewer per 1000) (moderate certainty); PCSK9 inhibitor monotherapy also reduced non-fatal MI (23 fewer per 1000) and stroke (24 fewer per 1000) (high certainty). Adding PCSK9 inhibitor to ezetimibe therapy probably reduced non-fatal MI (20 fewer per 1000) and stroke (20 fewer per 1000) (moderate certainty). On the same note, adding ezetimibe to PCSK9 inhibitor may reduce non-fatal MI and stroke (both 13 fewer per 1000, low certainty).

In patients with high cardiovascular risk, ezetimibe monotherapy likely reduced non-fatal MI (12 fewer per 1000) and stroke (13 fewer per 1000) (moderate certainty); PCSK9 inhibitor monotherapy also reduced non-fatal MI (17 fewer per 1000) and stroke (18 fewer per 1000) (high certainty). Adding PCSK9 inhibitors to ezetimibe may reduce non-fatal MI (15 fewer per 1000) and stroke (15 fewer per 1000) (low certainty). However, adding ezetimibe to PCSK9 inhibitors did not reach MID for non-fatal MI and stroke.

In patients with moderate to low cardiovascular risk, ezetimibe or PCSK9 inhibitor yielded slight or no reductions in non-fatal MI or stroke (moderate to low certainty evidence).

Table 2 | Effects of ezetimibe and PCSK9 inhibitor on cardiovascular outcomes in patients taking maximally tolerated statin therapy

	Ezetimibe versus		PCSK9 inhibitor versus		
	Statin	PCSK9 inhibitor and statin	Statin	Ezetimibe	Ezetimibe and statin
Non-fatal myocardial infarction					
Risk ratio (95% CI)	0.87 (0.80 to 0.94)		0.81 (0.76 to 0.87)	0.94 (0.84 to 1.04)	0.81 (0.76 to 0.87)
Absolute difference (95% CI)*:					
Very high risk†	*11 fewer (17 fewer to 5 fewer)*‡ ⊕⊕⊕§	*9 fewer (14 fewer to 4 more)*‡ ⊕⊕§	16 fewer (20 fewer to 11 fewer) ⊕⊕⊕§	*4 fewer (12 fewer to 3 more)*‡ ⊕⊕§	14 fewer (18 fewer to 9 fewer) ⊕⊕§
High risk†	*8 fewer (13 fewer to 4 more)*‡ ⊕⊕⊕§	*7 fewer (10 fewer to 3 fewer)*‡ ⊕⊕⊕§	12 fewer (15 fewer to 8 fewer) ⊕⊕⊕§	*3 fewer (9 fewer to 2 more)*‡ ⊕⊕⊕§	*10 fewer (13 fewer to 7 fewer)*‡ ⊕⊕§
Moderate risk†	*4 fewer (5 fewer to 1 fewer)*‡ ⊕⊕⊕§	*3 fewer (4 fewer to 1 fewer)*‡ ⊕⊕§	*5 fewer (6 fewer to 3 fewer)*‡ ⊕⊕⊕§	*1 fewer (4 fewer to 1 more)*‡ ⊕⊕§	*4 fewer (5 fewer to 3 fewer)*‡ ⊕⊕§
Low risk†	*1 fewer (1 fewer to 0 fewer)*‡ ⊕⊕⊕§	*1 fewer (1 fewer to 0 fewer)*‡ ⊕⊕§	*1 fewer (2 fewer to 1 fewer)*‡ ⊕⊕⊕§	*0 fewer (1 fewer to 0 fewer)*‡ ⊕⊕§	*1 fewer (1 fewer to 0 fewer)*‡ ⊕⊕§
Non-fatal stroke					
Risk ratio (95% CI)	0.82 (0.71 to 0.96)		0.74 (0.64 to 0.85)	0.90 (0.73 to 1.10)	0.74 (0.64 to 0.85)
Absolute difference (95% CI)*:					
Very high risk†	14 fewer (23 fewer to 3 fewer) ⊕⊕⊕§	11 fewer (17 fewer to 2 fewer) ⊕⊕§	21 fewer (29 fewer to 12 fewer) ⊕⊕⊕⊕§	*7 fewer (18 fewer to 7 more)*‡ ⊕⊕§	17 fewer (24 fewer to 10 fewer) ⊕⊕⊕§
High risk†	11 fewer (17 fewer to 2 fewer) ⊕⊕⊕§	*8 fewer (13 fewer to 2 fewer)*‡ ⊕⊕§	16 fewer (22 fewer to 9 fewer) ⊕⊕⊕§	*5 fewer (13 fewer to 5 more)*‡ ⊕⊕§	13 fewer (18 fewer to 7 fewer) ⊕⊕§
Moderate risk†	*4 fewer (7 fewer to 1 fewer)*‡ ⊕⊕⊕§	*3 fewer (5 fewer to 1 fewer)*‡ ⊕⊕§	*6 fewer (8 fewer to 3 fewer)*‡ ⊕⊕⊕§	*2 fewer (5 fewer to 2 more)*‡ ⊕⊕§	*5 fewer (7 fewer to 3 fewer)*‡ ⊕⊕§
Low risk†	*1 fewer (2 fewer to 0 fewer)*‡ ⊕⊕⊕§	*1 fewer (1 fewer to 0 fewer)*‡ ⊕⊕§	*2 fewer (3 fewer to 1 fewer)*‡ ⊕⊕⊕§	*1 fewer (2 fewer to 1 more)*‡ ⊕⊕§	*2 fewer (2 fewer to 1 fewer)*‡ ⊕⊕§
All-cause mortality					
Risk ratio (95% CI)	0.99 (0.92 to 1.06)		0.95 (0.87 to 1.03)	0.96 (0.86 to 1.07)	0.95 (0.87 to 1.03)
Absolute difference (95% CI)*:					
Very high risk†	*0 fewer (3 fewer to 2 more)*‡ ⊕⊕⊕⊕§	*0 fewer (2 fewer to 2 more)*‡ ⊕⊕⊕§	*2 fewer (4 fewer to 1 more)*‡ ⊕⊕⊕⊕§	*1 fewer (4 fewer to 2 more)*‡ ⊕⊕⊕§	*2 fewer (4 fewer to 1 more)*‡ ⊕⊕⊕§
High risk†	*0 fewer (2 fewer to 1 more)*‡ ⊕⊕⊕⊕§	*0 fewer (2 fewer to 1 more)*‡ ⊕⊕⊕§	*1 fewer (3 fewer to 1 more)*‡ ⊕⊕⊕⊕§	*1 fewer (3 fewer to 2 more)*‡ ⊕⊕⊕§	*1 fewer (3 fewer to 1 more)*‡ ⊕⊕⊕§
Moderate risk†	*0 fewer (1 fewer to 1 more)*‡ ⊕⊕⊕§	*0 fewer (1 fewer to 1 more)*‡ ⊕⊕§	*0 fewer (1 fewer to 0 fewer)*‡ ⊕⊕⊕§	*0 fewer (1 fewer to 1 more)*‡ ⊕⊕§	*0 fewer (1 fewer to 0 fewer)*‡ ⊕⊕§
Low risk†	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕⊕§	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕§	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕⊕§	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕§	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕§
Cardiovascular mortality					
Risk ratio (95% CI)	0.97 (0.87 to 1.09)		0.95 (0.85 to 1.07)	0.98 (0.84 to 1.15)	0.95 (0.85 to 1.07)
Absolute difference (95% CI)*:					
Very high risk†	*1 fewer (2 fewer to 2 more)*‡ ⊕⊕⊕⊕§	*1 fewer (2 fewer to 2 more)*‡ ⊕⊕⊕§	*1 fewer (3 fewer to 1 more)*‡ ⊕⊕⊕⊕§	*0 fewer (3 fewer to 3 more)*‡ ⊕⊕⊕§	*1 fewer (3 fewer to 1 more)*‡ ⊕⊕⊕§
High risk†	*0 fewer (2 fewer to 1 more)*‡ ⊕⊕⊕⊕§	*0 fewer (2 fewer to 1 more)*‡ ⊕⊕⊕§	*1 fewer (2 fewer to 1 more)*‡ ⊕⊕⊕⊕§	*0 fewer (2 fewer to 2 more)*‡ ⊕⊕⊕§	*1 fewer (2 fewer to 1 more)*‡ ⊕⊕⊕§
Moderate risk†	*0 fewer (1 fewer to 1 more)*‡ ⊕⊕⊕§	*0 fewer (1 fewer to 1 more)*‡ ⊕⊕§	*0 fewer (1 fewer to 0 fewer)*‡ ⊕⊕⊕§	*0 fewer (1 fewer to 1 more)*‡ ⊕⊕§	*0 fewer (1 fewer to 0 fewer)*‡ ⊕⊕§
Low risk†	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕⊕§	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕§	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕⊕§	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕§	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕§

PCSK9=Proprotein convertase subtilisn/kexin type 9.
*Absolute difference per 1000 persons over five years. Minimal important difference designated as 12 per 1000 reductions for non-fatal myocardial infarction, 10 per 1000 for non-fatal stroke, 8 per 1000 for all-cause or cardiovascular mortality.
†Risk categories: very high risk, patients with established cardiovascular risk or hereditary or familial lipid disorder; high risk, patients with ≥5 cardiovascular risk factors or with hereditary or familial lipid disorder without any cardiovascular risk factors; moderate risk, patients with 3-4 cardiovascular risk factors; low risk, patients with 1-2 cardiovascular risk factors.
‡Italicised results show where the 95% CI of the absolute difference included the minimal important difference value, in which case quality was rated down for imprecision.
§Certainty of the evidence: high ⊕⊕⊕⊕; moderate ⊕⊕⊕; low ⊕⊕; very low ⊕.

All-cause and cardiovascular mortality

When used as monotherapy or combined, ezetimibe or PCSK9 inhibitor therapy had no impact on all-cause and cardiovascular mortality (table 3).

Discussion

Principal findings

In this network meta-analysis of 83 660 individuals receiving maximal statin therapy or intolerant to statin therapy, ezetimibe or PCSK9 inhibitor may reduce non-fatal myocardial infarction and stroke in adults at very high or high cardiovascular risk, but not in those with moderate and low cardiovascular risk. Adding ezetimibe or PCSK9 inhibitor to the background lipid-lowering therapy had no significant effect on all-cause or cardiovascular mortality. Thus, patients with the most significant cardiovascular risk may gain maximum benefits, whereas those with moderate to low cardiovascular risk achieve trivial absolute reductions in non-fatal myocardial infarction

Table 3 Effects of ezetimibe and PCSK9 inhibitor on cardiovascular outcomes in patient intolerant to statin therapy

	Ezetimibe versus		PCSK9 inhibitor versus	
	No lipid-lowering therapy	PCSK9 inhibitor	No lipid-lowering therapy	Ezetimibe
Non-fatal myocardial infarction				
Risk ratio (95% CI)	0.87 (0.80 to 0.94)		0.81 (0.76 to 0.87)	0.94 (0.84 to 1.04)
Absolute difference (95% CI)*:				
Very high risk†	16 fewer (24 fewer to 7 fewer) ⊕⊕⊕§	13 fewer (20 fewer to 6 fewer) ⊕⊕§	23 fewer (29 fewer to 16 fewer) ⊕⊕⊕⊕§	20 fewer (25 fewer to 14 fewer) ⊕⊕⊕§
High risk†	12 fewer (18 fewer to 6 fewer) ⊕⊕⊕§	*10 fewer (15 fewer to 4 fewer)*‡ ⊕⊕§	17 fewer (22 fewer to 12 fewer) ⊕⊕⊕⊕§	15 fewer (19 fewer to 10 fewer) ⊕⊕§
Moderate risk†	*5 fewer (7 fewer to 2 fewer)*‡ ⊕⊕⊕§	*4 fewer (6 fewer to 2 fewer)*‡ ⊕⊕§	*7 fewer (9 fewer to 5 fewer)*‡ ⊕⊕⊕§	*6 fewer (7 fewer to 4 fewer)*‡ ⊕⊕§
Low risk†	*1 fewer (2 fewer to 0 fewer)*‡ ⊕⊕⊕§	*1 fewer (2 fewer to 0 fewer)*‡ ⊕⊕§	*2 fewer (2 fewer to 1 fewer)*‡ ⊕⊕⊕§	*2 fewer (2 fewer to 1 fewer)*‡ ⊕⊕§
Non-fatal stroke				
Risk ratio (95% CI)	0.82 (0.71 to 0.96)		0.74 (0.64 to 0.85)	0.90 (0.73 to 1.10)
Absolute difference (95% CI)*:				
Very high risk†	17 fewer (27 fewer to 4 fewer) ⊕⊕⊕§	13 fewer (20 fewer to 3 fewer) ⊕⊕§	24 fewer (34 fewer to 14 fewer) ⊕⊕⊕⊕§	20 fewer (28 fewer to 12 fewer) ⊕⊕⊕§
High risk†	13 fewer (20 fewer to 3 fewer) ⊕⊕⊕§	*9 fewer (15 fewer to 2 fewer)*‡ ⊕⊕§	18 fewer (25 fewer to 10 fewer) ⊕⊕⊕⊕§	15 fewer (21 fewer to 9 fewer) ⊕⊕§
Moderate risk†	*5 fewer (8 fewer to 1 fewer)*‡ ⊕⊕⊕§	*4 fewer (6 fewer to 1 fewer)*‡ ⊕⊕§	*7 fewer (10 fewer to 4 fewer)*‡ ⊕⊕§	*6 fewer (8 fewer to 3 fewer)*‡ ⊕⊕§
Low risk†	*1 fewer (2 fewer to 0 fewer)*‡ ⊕⊕⊕§	*1 fewer (2 fewer to 0 fewer)*‡ ⊕⊕§	*2 fewer (3 fewer to 1 fewer)*‡ ⊕⊕⊕§	*2 fewer (3 fewer to 1 fewer)*‡ ⊕⊕§
All-cause mortality				
Risk ratio (95% CI)	0.99 (0.92 to 1.06)		0.95 (0.87 to 1.03)	0.96 (0.86 to 1.07)
Absolute difference (95% CI)*:				
Very high risk†	*0 fewer (3 fewer to 2 more)*‡ ⊕⊕⊕⊕§	*0 fewer (3 fewer to 2 more)*‡ ⊕⊕⊕§	*2 fewer (5 fewer to 1 more)*‡ ⊕⊕⊕⊕§	*2 fewer (5 fewer to 1 more)*‡ ⊕⊕⊕§
High risk†	*0 fewer (2 fewer to 2 more)*‡ ⊕⊕⊕⊕§	*0 fewer (2 fewer to 2 more)*‡ ⊕⊕⊕§	*1 fewer (4 fewer to 1 more)*‡ ⊕⊕⊕⊕§	*1 fewer (4 fewer to 1 more)*‡ ⊕⊕⊕§
Moderate risk†	*0 fewer (1 fewer to 1 more)*‡ ⊕⊕⊕§	*0 fewer (1 fewer to 1 more)*‡ ⊕⊕§	*1 fewer (1 fewer to 0 fewer)*‡ ⊕⊕⊕§	*1 fewer (1 fewer to 0 fewer)*‡ ⊕⊕§
Low risk†	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕⊕§	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕§	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕⊕§	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕§
Cardiovascular mortality				
Risk ratio (95% CI)	0.97 (0.87 to 1.09)		0.95 (0.85 to 1.07)	0.98 (0.84 to 1.15)
Absolute difference (95% CI)*:				
Very high risk†	*1 fewer (3 fewer to 2 more)*‡ ⊕⊕⊕⊕§	*1 fewer (3 fewer to 2 more)*‡ ⊕⊕⊕§	*1 fewer (4 fewer to 2 more)*‡ ⊕⊕⊕⊕§	*1 fewer (3 fewer to 2 more)*‡ ⊕⊕⊕§
High risk†	*1 fewer (2 fewer to 2 more)*‡ ⊕⊕⊕⊕§	*1 fewer (2 fewer to 2 more)*‡ ⊕⊕⊕§	*1 fewer (3 fewer to 1 more)*‡ ⊕⊕⊕⊕§	*1 fewer (3 fewer to 1 more)*‡ ⊕⊕⊕§
Moderate risk†	*0 fewer (1 fewer to 1 more)*‡ ⊕⊕⊕§	*0 fewer (1 fewer to 1 more)*‡ ⊕⊕§	*0 fewer (1 fewer to 0 fewer)*‡ ⊕⊕⊕§	*0 fewer (1 fewer to 0 fewer)*‡ ⊕⊕§
Low risk†	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕⊕§	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕§	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕⊕§	*0 fewer (0 fewer to 0 fewer)*‡ ⊕⊕§

PCSK9=Proprotein convertase subtilisn/kexin type 9.
*Absolute difference per 1000 persons over five years. Minimal important difference designated as 12 per 1000 reductions for non-fatal myocardial infarction, 10 per 1000 for non-fatal stroke, 8 per 1000 for all-cause or cardiovascular mortality.
†Risk categories: very high risk, patients with established cardiovascular risk or hereditary or familial lipid disorder; high risk, patients with ≥5 cardiovascular risk factors or with hereditary or familial lipid disorder without any cardiovascular risk factors; moderate risk, patients with 3-4 cardiovascular risk factors; low risk, patients with 1-2 cardiovascular risk factors.
‡Italicised results show where the 95% CI of the absolute difference included the minimal important difference value, in which case quality was rated down for imprecision.
§Certainty of the evidence: high ⊕⊕⊕⊕; moderate ⊕⊕⊕; low ⊕⊕; very low ⊕.

and stroke. Similarly, ezetimibe or PCSK9 inhibitors in statin-intolerant patients may reduce myocardial infarction and stroke among patients with very high and high cardiovascular risk. Overall, PCSK9 inhibitors seemed to have the highest absolute reductions in myocardial infarctions and strokes when added to background therapy, followed by ezetimibe.

Strength and limitations of this study

Our study is unique since we focused on the absolute benefits of lipid-lowering therapies based on a risk-based approach, facilitating physicians to allocate precise treatment strategies instead of merely focusing on LDL-cholesterol targets. In contrast with previous reports,[34-36] this study draws strengths from close collaboration with an international multidisciplinary panel,[12] a comprehensive literature search to identify eligible trials, estimation of absolute event reduction over a five-year timeframe based on baseline cardiovascular risk of participants, and assessment of the certainty of evidence using the GRADE to inform clinical practice.

However, this study has certain limitations. Global consistency in direct and indirect comparison could not be evaluated since summary estimates relied predominantly on direct or indirect evidence. Estimates for statin-intolerant patients were derived from trials conducted mainly in patients taking statin therapy,

as we found no trial with a cardiovascular endpoint for statin-intolerant patients. Evidence for PCSK9 inhibitors versus ezetimibe was mainly driven from indirect comparison, with no trial directly comparing ezetimibe and PCSK9 inhibitor on risk of myocardial infarction and stroke as primary outcomes. There is also little direct evidence on adding one of these drugs to the other, and very little direct evidence in moderate and low risk individuals.

In addition to these issues, various other aspects were also considered in rating the evidence, including heterogeneous study populations in terms of baseline cardiovascular risks and limited follow-up duration of trials (median of 2 years). While cardiovascular outcome data in trials assessing non-cardiovascular events may have risk of bias during ascertainment, subgroup analysis did not demonstrate significant interaction among trials focused on cardiovascular outcomes versus those with non-cardiovascular outcome focus.

The PREDICT estimator was developed based on cohorts from New Zealand, and other populations may have somewhat different levels of risk determination than PREDICT. We included trials of inclisiran, the efficacy of which on cardiovascular outcomes is yet to be established.[5] However, inclisiran has shown a remarkable ~50% reduction in LDL-cholesterol levels, with a pattern of fewer cardiovascular outcomes favouring the drug. Moreover, our findings were consistent in sensitivity analyses excluding inclisiran trials.

We did not stratify the analyses based on LDL-cholesterol values, follow-up duration, diabetes, or familial hypercholesteremia versus non-familial hypercholesteremia because of the paucity of data. Current data are also limited to older adults (median age of population included was 61 years). We could not calculate individual cardiovascular risk given the lack of the baseline variables of individual participants. Finally, this study did not incorporate cost analyses but focused on the therapeutic efficacy of the treatment strategies.

Comparisons with other studies

Our results are consistent with prior evidence on lipid-lowering therapies. For instance, a network meta-analysis by Ma et al showed larger relative risk reduction in cardiovascular outcomes by addition of PCSK9 inhibitor on statin than ezetimibe.[37] Ezetimibe has been shown to reduce risk of non-fatal myocardial infarction and stroke, but not mortality (moderate to high certainty).[34 35] Another Bayesian network meta-analysis[38] demonstrated that—although statins had the highest probability of achieving the lowest all-cause mortality, followed by PCSK9 inhibitors and ezetimibe and statins—PCSK9 inhibitors were ranked best for preventing myocardial infarction and stroke, followed by ezetimibe and statin therapy. Toyota et al found that risk reduction in cardiovascular outcomes differs across intensive strategies for lowering LDL-cholesterol with relatively minor relative risk reductions with ezetimibe compared with PCSK9 inhibitors.[36] On the same note, PCSK9 inhibitors generated greater lowering of LDL-cholesterol than ezetimibe in statin-intolerant patients.[39] Therefore, it is conceivable that the absolute risk reduction with PCSK9 inhibition would be greater than that conferred by ezetimibe, given the considerably larger reduction in LDL-cholesterol achieved with PCSK9 inhibitors (50-60%).[40]

Clinical uncertainties

Both ezetimibe and PCSK9 inhibitors failed to achieve mortality benefits despite intensive lowering of LDL-cholesterol levels. The survival advantage relies on several factors, including the efficacy of the drug, competing risks, off-target effects, baseline cardiovascular risk, and follow-up duration of the study.[10 11 41] In a prior meta-analysis[10] reductions in all-cause and cardiovascular mortality were limited to trials with baseline LDL-cholesterol levels of ≥100 mg/dL. However, these subgroup analyses should be interpreted with caution due to the potential ecological fallacy.[42] Another critical consideration is the limited length of follow-up of PCSK9 trials compared with those of statin therapy.[3 4] A comparative analysis of the Cholesterol Treatment Trialists (CTT) Collaboration meta-analysis of statin therapy and PCSK9 inhibitor trials showed that the degree of cardiovascular risk reduction achieved by PCSK9 inhibitors for up to two years was comparable to what has been found for statins over two years.[40]

Policy implications

This systematic review informs decision makers about the benefits of PCSK9 inhibitors and ezetimibe on important cardiovascular outcomes and mortality in adults who are taking the maximum tolerated statin therapy or who are statin-intolerant and need further cardiovascular risk reduction. The key observations are that moderate to high certainty evidence favours PCSK9 inhibitors or ezetimibe for reducing non-fatal myocardial infarction and stroke in patients with very high or high cardiovascular risk, but not among patients with moderate and low cardiovascular risk. Furthermore, these agents lead to no reduction on all-cause or cardiovascular mortality. Our findings were the basis for the rapid recommendation on this topic.

Conclusions

In adults receiving maximally tolerated statin therapy or who are statin-intolerant, ezetimibe and PCSK9 inhibitor may reduce non-fatal myocardial infarction and stroke in adults at very high or high cardiovascular risk, but not in those with moderate and low cardiovascular risk. Therefore, prescribing these lipid-lowering agents should be considered among appropriate candidates with very high or high cardiovascular risk patients to achieve desired cardiovascular benefits.

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Contributors: SUK, QH, GG, ND, GEB, POV, IBR, SL, BA, NR conceived the study. SUK and SHY designed the search strategy. ANL performed the literature search; SUK, SHY, ANL screened studies for eligibility; SHY and ANL assessed the risk of bias; and SUK and SHY performed data extraction. UK, SHY, ANL, QH, GG, ND, GEB, POV, IBR, SL, BA, NR interpreted the data analysis; QH, GG, ND, GEB, POV, IBR, SL, BA, NR assessed the certainty of the evidence; SUK wrote the first draft of the manuscript; and all other authors revised the manuscript. SUK and NR are guarantors. 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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Dissemination to participants and related patient and public communities: The paper informs the *BMJ* Rapid Recommendation (https://www.bmj.com/rapid-recommendations) on the use of PCSK9 inhibitors and ezetimibe, also available in MAGICapp (https://www.magicapp.org/) for organisations to reuse or adapt for their own materials and purposes.

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