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Impact of conventional lipid-lowering therapy on circulating levels of PCSK9: protocol for a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Introduction Conventional lipid-lowering agents, including statins, ezetimibe, fibrates, bile acid sequestrants, nicotinic acid, bempedoic acid and Omega-3, are essential to the management of dyslipidaemia. However, these agents have been shown to increase the level of plasma proprotein convertase subtilisin/kexin 9 (PCSK9), a serine protease associated with increased cardiovascular risk. This review aims to investigate the impact of commonly available conventional lipid-lowering agents on circulating PCSK9 levels and lipid profiles.

Methods and analysis This protocol is conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines. A systematic search will be conducted in the following databases: MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, Web of Science, SCOPUS and ScienceDirect. Additional information will be retrieved from clinical trial registries or from reference list searches. Published and peer-reviewed randomised controlled trials with adults receiving statin, ezetimibe, fibrate, bile acid sequestrant, nicotinic acid, bempedoic acid or Omega-3 monotherapy or in combination for at least 2 weeks, with availability of plasma PCSK9 at the beginning and end of treatment or the net changes in values, will be included. Study selection, data extraction and assessment of the risk of bias will be independently conducted by two investigators. Continuous data will be presented as a standardised mean difference with 95% confidence interval (CI) and dichotomous data as risk ratios with 95% CI. Subgroup analysis and sensitivity analysis will be performed when sufficient studies are included. Publication bias will be assessed with a funnel plot and Egger's test.

Ethics and dissemination Ethics approval is not required as this review will only include data from published sources. The results will be published in a peer-reviewed journal.

Patient and public involvement No patient or members of the general public are involved.

PROSPERO registration number CRD42022297942.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review and meta-analysis will synthesise high-quality evidence from randomised controlled trials (RCTs) and quasi-RCTs.
⇒ Variation of the availability of agents among countries and regions is a potential source of bias and heterogeneity.
⇒ Variation of agents and doses among included studies will produce heterogeneity that complicates data synthesis and analysis.

INTRODUCTION

Lipid-lowering therapy is an essential part of the primary and secondary prevention of cardiovascular disease (CVD) in patients with dyslipidaemia, which is defined by the presence of hypercholesterolemia and/or hypertriglyceridemia.[1–3] The 2019 European Society of Cardiology and European Atherosclerosis Society guidelines recommended a treat-to-target approach with more intensive plasma low-density lipoprotein cholesterol (LDL-C) goals, which ranges from 3.0 mmol/L to 1.4 mmol/L for individuals of low to very high cardiovascular (CV) risk categories, respectively.[2] The guidelines recognised the need for a more comprehensive approach in the management of dyslipidaemia, involving both conventional lipid-lowering drugs, represented by statins, ezetimibe, fibrates, bile acid sequestrants, nicotinic acid, bempedoic acid, omega-3 and novel agents represented by proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Statins are competitive inhibitors of 3-hydroxy-3-methyl-glutaryl-CoA reductase, inhibiting cholesterol production at the rate-limiting step.[4] Reduced hepatic cholesterol

synthesis leads to increased turnover of LDL receptors in hepatocytes and enhanced LDL clearance. Ezetimibe is a cholesterol absorption inhibitor that interacts with Niemann-Pick C1-like proteins 1 on the intestinal brush border. Ezetimibe further lowers plasma LDL-C by upregulating LDL receptors on the hepatocyte membrane, which is the hepatic response to lowered cholesterol uptake.[5] Fibrates are nuclear receptor peroxisome proliferator-activated receptor α agonists and can simulate triglyceride degradation, lower LDL-C levels and raise high-density lipoprotein cholesterol (HDL-C) levels in the bloodstream.[6] Bile acid sequestrants like cholestyramine and cholestipol bind to bile acids in the intestine and prevent their reabsorption.[7 8] Nicotinic acid reduces hepatic synthesis of very low-density lipoprotein particles and raises HDL-C levels in the blood.[9] Bempedoic acid is an adenosine triphosphate-citrate lyase inhibitor and can decrease cholesterol biosynthesis and increase LDL receptor expression.[10] Omega-3 polyunsaturated fatty acids from fish or plants have been suggested to improve blood fat composition and reduce the risk of CV mortality.[11] PCSK9 inhibitors are novel lipid-lowering agents that have been primarily approved for the treatment of individuals with inadequately controlled LDL-C with conventional lipid-lowing therapies.[2 12]

PCSK9 is a serine protease that binds to the LDL receptors on the cellular membrane of hepatocytes, inhibiting LDL receptor recycling and promoting its lysosomal degradation, which results in elevated plasma LDL-C as well as promotes vascular remodelling and atheroma development.[13] Accumulating evidence has demonstrated that elevated circulating PCSK9 level has been associated with increased CVD risk.[14] Although multiple randomised controlled trials (RCTs) and meta-analyses have demonstrated the efficacy of PCSK9 inhibitors in treating dyslipidaemia, several studies have reported that conventional lipid-lowering therapies could lead to increased circulating PCSK9 levels.[15–20] On the other hand, it has been reported that statin treatment raises PCSK9 in primarily the inactivated form.[21] Additionally, PCSK9 expression is controlled by the circadian rhythm and is influenced by multiple hormonal and nutritional factors, which further complicates the quantification of its plasma concentration.[22 23] Even though conventional lipid-lowering drugs are commonly used in clinical practice, it is rare to investigate the change in plasma PCSK9 levels when treating with these drugs. In light of this, it is necessary to further clarify the effect of conventional lipid-lowering drugs on the circulating activity of PCSK9.

Previous systematic reviews and meta-analyses have evaluated the effect of statins and fibrates on circulating PCSK9 levels.[24 25] However, the availability of recently published evidence, including several RCTs of high quality, underlines the need to reconduct those reviews.[19 26] Furthermore, previous reviews have not considered the effect of other commonly prescribed therapeutics, including ezetimibe, bile acid sequestrants, nicotinic acid, bempedoic acid and omega-3 on the level of circulating PCSK9. This systematic review and meta-analysis will identify the effects of commonly available conventional lipid-lowering drugs on circulating PSCK9 levels and lipid profiles in adults, to better understand the cause of PCSK9 changes and guide the clinical application of PCSK9 inhibitions when lipid-lowering therapy is combined with conventional drugs.

Box 1 Eligibility criteria of the systematic review and meta-analysis.

Inclusion criteria

1. Randomised controlled trials (RCTs) or quasi-RCTs (non-blinded or interrupted time series) with parallel or cross-over designs.
2. At least one kind of statin, ezetimibe, fibrates, bile acid sequestrants, nicotinic acid, bempedoic acid or omega-3, is used in the intervention arm.
3. Treatment duration of at least 2 weeks.
4. Availability of plasma proprotein convertase subtilisin/kexin 9 (PCSK9) levels at the begin and end of treatment period, or the net changes in values.

Exclusion criteria

1. Studies not of RCT or quasi-RCT designs.
2. Studies that recruited subjects already receiving stable statin therapy.
3. Studies that did not provide mean (or median) plasma levels of PCSK9 at baseline and end of trial, or the net changes in values.

METHODS AND ANALYSIS

Registration

This protocol of systematic review and meta-analysis has been registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/). This protocol is in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines (see online supplemental file 1, PRISMA-P checklist).[27] The completed systematic review and meta-analysis will be reported following the PRISMA guidelines.[28]

Study design

This systematic review and meta-analysis will consider published and peer-reviewed RCTs or quasi-RCTs of parallel or cross-over designs. Details of the eligibility criteria are listed in box 1. The study is expected to begin on 1 August 2022, and complete by 1 October 2022.

Participants

This systematic review and meta-analysis will include data from adults of at least 18 years of age, treated with any kind of statins, ezetimibe, fibrates, bile acid sequestrants, nicotinic acid, bempedoic acid or omega-3 monotherapy or in combination for at least 2 weeks, in isolation or in comparison with placebo, diet, no intervention or another type of lipid-lowering therapy.

Outcomes

The primary outcome is the mean difference in plasma PCSK9 levels. The secondary outcomes are the differences in lipid profile between baseline and the completion of

the lipid-lowing intervention. The lipid profiles include total cholesterol, LDL-C, HDL-C, triglycerides, apolipoprotein A1, apolipoprotein B and lipoprotein[a].

Search strategy

Relevant studies will be identified through a systematic search in online databases, using search strategies developed with the assistance of information specialists. Electronic bibliographic databases, including MEDLINE, CENTRAL, EMBASE, Web of Science (Science and Social Science Citation Index), SCOPUS and ScienceDirect will be searched. ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform will be searched for relevant RCTs. Further information will be retrieved from published sources by accessing the grey literature sources or contacting the original authors when necessary. The reference lists of related review and articles will be reviewed to identify trials missed during the searches. Additionally, we also will search the grey databases such as preprinted database for unpublished literature. A filter designed for retrieval of RCTs with maximised sensitivity will be applied.[29] The search will be limited to studies published from 1 January 2003, to the formal search date. The search strategy for MEDLINE (Ovid) is presented in online supplemental file 2. Search strategies for other databases will be adapted accordingly. The searches will be rerun just before the final analyses and further studies retrieved for inclusion. Reference lists and citations of identified trials will be further examined for inclusion.

Study selection and data extraction

The primary selection of potentially eligible studies will be conducted independently by two authors (JL and TH) by reviewing the titles and abstracts of publications identified in the electronic searches. The same two authors will independently assess the full manuscripts (if available) against the eligibility criteria, and, where necessary, resolve any disagreement with discussion or the involvement of the third author (TW).

Primary and secondary outcome data will be independently extracted by the same two authors. Apart from the primary and secondary outcomes, further information intended to be extracted includes (1) general information: title, journal, authors, country or region, year of publication, (2) trial characteristics: study design, target condition, duration of follow-up, allocation concealment and method, randomisation and method, blinding (outcome assessors), checking of blinding, intention-to-treat analysis, (3) intervention: loading dose, dosage, duration of treatment, (4) participants: total number and number in comparison, age, gender, diet, hormone levels, time of blood sample collection, the similarity of groups at baseline, withdrawals/losses to follow-up or any other related demographic or clinical information. Disagreement will be resolved either by discussion or by the involvement of the third investigator (TW). If necessary, the authors of the included studies will be contacted via email for the key missing data.

Quality assessment

Two authors (XZ and XW) will independently assess the risk of bias, with any disagreement resolved either by discussion or by the involvement of the third author (TW). The risk of bias of individual RCTs will be assessed using the Cochrane Risk of Bias V.2.0 assessment tool, and the individual items will be graded as of 'low', 'unclear' or 'high' risk of bias.[30] The items include: (1) random sequence generation, (2) allocation concealment, (3) intervention blinding, (4) outcome blinding, (5) missing outcome data, (6) selective reporting, (7) other biases.

Data synthesis and analysis

Data management and synthesis

We will use EndNote X V.9 software to manage the literature and Microsoft Excel to synthesise the extracted data. RevMan V.5.4 will be used for data integration.[31] Continuous data will be presented as standardised mean difference with 95% CI, and dichotomous data will be presented as risk ratios with 95% CI.

Assessment of heterogeneity

For trials with statistically significant heterogeneity (p value <0.1), a random-effects model will be applied to calculate the pooled estimates of the treatment effect. If a significant level of heterogeneity is not identified, the pooled estimates of the treatment effect for each outcome will be calculated with Mantel-Haenszel fixed-effect model. The findings will be presented as forest plots. Clinical heterogeneity will be assessed by examining differences in study designs, participant characteristics, the direction of treatment effect and overlap of CI on forest plots. Statistical heterogeneity among studies will be calculated using the I^2 statistic and τ^2, the latter calculated from random-effects model. The results will be classified as mild (<40%), moderate (40–60%) or substantial (>60%) heterogeneity. Where substantial heterogeneity is present between studies, subgroup and sensitivity analyses will be performed to further identify potential sources of heterogeneity. If substantial heterogeneity persists after these analyses, the narrative review will be performed.

Subgroup analysis

Subgroup analysis is planned when a sufficient number of studies can be included and such analysis is deemed appropriate by heterogeneity analysis. Meta-regression will be conducted to explore whether treatment effects differ between study baseline characteristics on a continuous scale. Subgroup analysis will be planned based on the following items: gender, age, ethnicity, types of lipid-lowering therapy, monotherapy or combined therapy, dose, duration of treatment and the measurement methods of PCSK9.

Sensitivity analysis

Sensitivity analysis will be used to assess the validity and robustness of the review's findings by excluding studies with a high risk of bias in one or more domains and

comparing the direction and magnitude of results of the sensitivity analysis to that of the primary analysis.

Assessment of reporting biases

If equal or more than 10 studies can be included in the systematic review, funnel plot analysis and Egger's test will be performed to assess whether this review is subjected to publication bias.[32]

Grading the quality of evidence

The quality of evidence for outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation system. Evidence will be examined based on criteria of study design, risk of bias, imprecision, inconsistency, indirectness and magnitude of effect.[33]

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research. Patient consent for publication is not required.

DISCUSSION

The current systematic review and meta-analysis will assess the effect of the conventional lipid-lowing agents such as statins, ezetimibe, fibrates, bile acid sequestrants, nicotinic acid, bempedoic acid and omega-3 on plasma PCSK9 levels. Plasma PCSK9, binding to LDL receptors on hepatic cell membranes, can prevent LDL receptors from recycling to the cellular surface and increase its lysosomal degradation.[34] LDL-C absorption is highly reliant on the LDL receptor level. Elevated plasma PCSK9 levels will impair the lowing-lipid effect of conventional agents.[35 36] Therefore, it is necessary to determine the effect of conventional lipid-lowing agents on plasma PCSK9 levels for the management of dyslipidaemia and atherosclerotic CVDs.

This systematic review and meta-analysis has some limitations. First, some agents, for instance, nicotinic acid, are not globally available. This variation in availability may be a potential source of bias and heterogeneity. In addition, differences in agents and doses between studies could add to the heterogeneity of the analysis. However, subgroup and sensitivity analyses will be used when appropriate to explore the sources of heterogeneity and the effects of heterogeneity on the results. Furthermore, the current study will only include RCTs and quasi-RCTs with high-quality evidence, improving the reliability of the review's findings and providing a solid conclusion for the assessment of the effect of conventional lipid-lowing agents on plasma PCSK9 levels.

Ethics and dissemination

Ethics approval is not required for this study as only published information will be included. Findings of this systematic review and meta-analysis will be published in a peer-reviewed journal after completion.

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Contributors LJ and TW contributed to the conception of the study. The systematic review protocol was drafted by TH and was reviewed by JL and TW. The search strategy was developed by RX and XW and will be performed by YY, LL and XZ. YZ, YJ, JW and HY will independently screen the potential studies, extract data from the included studies, assess the risk of bias, and complete the data synthesis. YM and BY will arbitrate in cases of disagreement and ensure the absence of errors. All authors reviewed and approved the publication of the protocol.

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Competing interests None declared.

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Data availability statement Not applicable, as no datasets are generated for this protocol.

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