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Combined antihypertensive and statin therapy for the prevention of cardiovascular events in patients with hypertension without complications: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction High blood pressure (BP) affects over 40% of adults over the age of 25 worldwide and is the leading global risk factor for death or disability. Hypertension is also the most important risk factor for endovascular atherosclerosis, which, when combined with other cardiovascular risk factors, leads to atherosclerotic cardiovascular disease (ASCVD). Statins are one of the most widely used drugs for the prevention of ASCVD. The recently announced study of Heart Outcomes Prevention Evaluation-3 suggests that cholesterol-lowering agents combined with antihypertensive therapy can prevent cardiovascular events and reduce the combined endpoint. We plan to conduct a systematic review and meta-analysis to evaluate whether combined antihypertensive and statin therapy is more beneficial than antihypertensive therapy alone in patients with hypertension without complications.
Methods and analysis We will perform a comprehensive search for randomised controlled trials evaluating combined antihypertensive and statin therapy for the treatment of patients with hypertension. The following English electronic databases will be searched: The Cochrane Library, EMBASE and PubMed. Outcomes will be categorised as short-term (≤6 months) or long-term (>6 months). When evaluating the effects of combined antihypertensive and statin therapy, a short-term outcome is usually defined as a change in BP or lipid levels, while a long-term outcome is usually defined as cardiovascular benefits or risks. The data screening and extraction will be conducted by two different reviewers. The quality of the RCTs will be assessed according to the Cochrane handbook risk of bias tool.
Ethics and dissemination This review does not require ethics approval and the results of the meta-analysis will be submitted to a peer-review journal.
PROSPERO registration number CRD42017071935.

INTRODUCTION

High blood pressure (BP) affects over 40% of adults over the age of 25 worldwide and is the leading global risk factor for death or disability.[1–3] In 2009, the American Society of Hypertension (ASH) collaboration group defined hypertension as a progressive vascular syndrome caused by a series of complex and intervening causes[4] that are not only evidenced by an increase in blood pressure. Hypertension is also the most important risk factor for endovascular atherosclerosis, which, when combined with other cardiovascular risk factors, leads to atherosclerotic cardiovascular disease (ASCVD).[5–8] Statins are one of the most widely used drugs for the prevention of ASCVD.[9] Previously, the primary indication for prescribing statins for patients with hypertension was elevated lipid levels. However, recent studies have found that patients with hypertension should be started on combined therapy of antihypertensives and statins as soon as possible to prevent the development of ASCVD.[7] The recently announced results from the study of Heart Outcomes Prevention Evaluation-3 (HOPE-3) suggests that cholesterol-lowering agents combined with antihypertensive therapy can prevent cardiovascular events and reduce the combined endpoint by approximately 30% in the CVD stratification of moderate risk people (only 37.9% of all participants had high blood pressure, with an average BP of 138.1/91.9 mm Hg).[10 11] However, the other two large trials that assessed the effect of adding a statin to an antihypertensive treatment regimen reached different conclusions. In the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm, when compared with placebo, adding a statin to the treatment regimen of patients with hypertension was associated with a 36% decrease in non-fatal myocardial infarction and fatal coronary heart disease (CHD), and a 27% decrease in the incidence

of fatal and non-fatal stroke for patients with hypertension who were at high risk.[12–14] Conversely, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Trial, the addition of pravastatin 40 mg did not lead to a significant difference in all-cause mortality and CHD events when compared with usual care.[15 16]

Therefore, while statins are often considered along with blood pressure-lowering therapy in the treatment of patients with grade 1 hypertension who are at moderate risk (irrespective of cholesterol levels), the real benefit of this therapeutic regimen is unknown.[3 17] The current guidelines recommend that patients with hypertension in the moderate risk category be treated with statins.[3] Further, before starting antihypertensive treatments, these patients should first be encouraged to adopt lifestyle intervention strategies to improve blood pressure levels and also begin statin therapy.[17] In light of these recommendations, we plan to conduct a systematic review and meta-analysis to evaluate whether combined antihypertensive and statin therapy is more beneficial than antihypertensive therapy alone in patients with hypertension without complications.

METHODS AND ANALYSIS
Registration
The study protocol has been registered with the international prospective register of systematic reviews (PROSPERO). The registration number is CRD42017071935. The procedure for this protocol will be conducted

according to the guidance provided by the Preferred Reporting Item for Systematic Review and Meta-analysis Protocols.

Criteria for considering studies for this review
Types of studies
All published randomised controlled trials (RCTs) with a parallel, cluster or crossover design will be included. We will exclude quasi-randomised trials (such as randomisation according to odd and even hospital numbers or admission time).

Types of participants
The participants of interest must have a diagnosis of hypertension (based on the Sixth and Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI/VII) guidelines) and be at risk for cardiovascular disease (risk stratification according to the definition provided in the original study), without settings, age or gender limitations. The participants must not have any medical complications at baseline such as stroke, cardiac and kidney diseases or peripheral artery disease (table 1).

Types of interventions
Interventions
Interventions will include any combination of antihypertensive and statin therapy (either in single pill form or separate pills, excluding traditional Chinese

Table 1	Criteria for considering studies	
	Inclusion criteria	**Exclusion criteria**
Population	1. Age ≥18, gender is not limited. 2. Hypertension diagnosis established. 3. Accompanied by dyslipidaemia, hyperuricaemia, smoking and other cardiovascular risk factors. 4. Voluntary signing of informed consent.	1. Patients with cardiogenic shock, heart failure, severe valvular disease or other short-term prognosis for cardiac disease that are expected to be poor. 2. Patients with chronic renal insufficiency (estimated glomerular filtration rate <30 mL/min) and previous strokes.
Intervention	Any combination of antihypertensive and statin therapy.	Any additional treatment that was not evenly distributed between experimental and control groups.
Comparison	Antihypertensive therapy alone	1. Studies that only use placebo. 2. Studies comparing different dosages or types of antihypertensives or cholesterol lowering drugs.
Outcome	Primary outcomes: 1. Composite endpoint (long term). 2. Total cardiovascular events (long term). 3. Primary control rate after the intervention (short term). Secondary outcomes: 1. Each specific cardiovascular event included in primary outcomes (long term). 2. All-cause mortality (long term). 3. Participants experiencing any adverse event (short term). 4. Termination of use of the intervention (short term). 5. The mean change from baseline to the end of each phase in blood pressure and lipid indexes (short term). 6. The mean change from baseline to the end of each phase in global risk factor scores (short term).	

medicine). Any other add-on therapies referred to as 'other therapies' must be equally assigned between the experimental and control groups.

Comparisons
The following comparisons will be conducted:
► Combined antihypertensive and statin therapy versus antihypertensive therapy alone.
► Combined antihypertensive and statin therapy in single pill form versus a combination of blood pressure and cholesterol lowering agents with separate pills.

Studies that use only placebo as a control will be excluded. We will also exclude studies comparing different dosages or types of antihypertensives or cholesterol-lowering drugs.

Types of outcome measures
Outcomes will be categorised as short term (≤6 months) or long term (>6 months). When evaluating the effects of combined antihypertensive and statin therapy, a short-term outcome is usually defined as a change in BP or lipid levels, while a long-term outcome is usually defined as cardiovascular benefits or risks.

Primary outcomes
► Composite endpoint (long term): non-fatal myocardial infarction plus fatal CHD.
► Total cardiovascular events (long term): death from cardiovascular causes, intractable angina, peripheral vessel reconstruction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, fatal or non-fatal stroke, heart failure.
► Primary control rate after the intervention (short term)
  – The percentage of participants who reached their recommended BP goals (based on the Sixth and Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI/VII) guidelines).
  – The percentage of participants who reached their recommended lipid goals (based on the National Cholesterol Education Programme Adult Treatment Panel III guidelines);
  – The percentage of participants who reached both BP and lipid goals.

Secondary outcomes
► Each specific cardiovascular event included in the primary outcomes (long term).
► All-cause mortality (long term).
► Participants experiencing any adverse event (short term).
► Termination of use of the intervention (short term).
► The mean change from baseline to the end of each phase in BP and lipid indexes (short term).
► The mean change from baseline to the end of each phase in global risk factor scores (short term).

Search methods for identification of studies
Electronic searches
We plan to search all published RCTs without limitations regarding language or publication year. The following English electronic databases will be searched: The Cochrane Library, EMBASE and PubMed. The search strategy to be used in PubMed is presented in the online Supplementary appendix 1.

Searching other resources
We will crosscheck the reference lists of relevant systematic reviews to identify any potentially eligible RCTs.

Data collection and analysis
Selection of studies
Two authors (YW and SJF) will first screen the search results independently according to the title and abstract and then screen the potentially relevant references at a full text level. Any disagreements will be solved by discussion with a third author (LJ). We will exclude the references still containing unclear information after full-text screening and after contacting the author. Finally, a study screening flow diagram will be presented that clearly outlines the steps used in the selection process.

Data extraction and management
A structured and standardised data extraction form will be used to extract the relevant information. For cases in which information from a potentially included study is lacking, the study authors will be contacted in an attempt to obtain the relevant information. A pilot and revised version of the data extraction form will include:
► Identification of the study (first authors and year of publication).
► Methods of study design (location, settings, multicenter or single centre, methods of randomisation and blinding, follow-up).
► Participant information (sample size, diagnosis, age, sex, baseline characteristics, inclusion and exclusion criteria).
► Interventions information (content of intervention and control group; dosage, duration and frequency of treatment).
► Outcomes data (prespecified outcomes in our protocol; other outcomes reported by included studies; drop-outs).

We will extract primary endpoint data and will only use change data if the former are not available.

Two authors (YW and SJF) will independently perform data extraction. A third author (LJ) will crosscheck all entries and arbitrate any discordance. Finally, the data will be entered into Review Manager V.5.3 for further analysis.[18]

Assessment of risk of bias in included studies
Two authors (YW and SJF) will independently assess the risk of bias for all included RCTs at the study level based on the standard criteria outlined by the Cochrane Collaboration,[19] which contains six domains: random sequence

generation and allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Disagreements will be resolved by discussion with a third author (LJ).

Finally, a 'risk of bias graph' and a 'risk of bias summary' will be generated. Green will denote 'low risk', yellow 'unclear risk' and 'high risk' will be shown in red.

Measures of treatment effect

For dichotomous data, we will present the effect by estimating the risk ratios (RR) with 95% CIs. For continuous data, we will present the effect using summarised mean differences with 95% CIs. We will convert the unit to the commonly used one (eg, mmol/L) when different units of measurement (eg, mg/dL or mmol/L) are employed.

Unit of analysis issues
Cluster trials

When the data from cluster-randomised studies is to be added into the quantitative synthesis, adjustments will be made to address the effect of clustering using the methods described in the Cochrane Handbook.[19] A determination will be made about whether the clustering effect had been taken into account in the original analysis. The intracluster correlation coefficient (ICC) of the trial will be obtained, and the effective sample size calculated.[20–22] If the ICC cannot be obtained from the original studies or other similar studies, the data will not be pooled into other individual data, and the studies' results will be presented in a descriptive fashion.

Crossover trials

The results of the crossover designed trials may be influenced by lag effects of the interventions. We intend to use the first phase of the study (pre-crossover) only. In cases in which the first phase results are not reported, we will also use the final study data. According to the Cochrane handbook, we will exam whether the crossover trials did an appropriate analysis (paired t-test) for two period data to be incorporated in the meta-analysis when using the full study data. If the trials could not be pooled in the meta-analysis, we will only describe the results of these trials.

Studies with multiple treatment groups

When a study involves more than two treatment arms, if relevant, the additional treatment arms will be presented in the comparisons. If all interventions are combined in the same meta-analysis, we will divide the sample size in the control group to combine the data.[19] Data will not be reported when the additional treatment arms were not relevant.

Dealing with missing data

Only available data from the original studies in which the attrition rate is less than 50% will be analysed. Otherwise, the data will not be used because a high attrition bias will likely influence the credibility of the results.[23] The potential impact of missing data on the findings of the review will be addressed in the discussion section.

Assessment of heterogeneity

Clinical and methodological heterogeneity will be considered and fully discussed before data synthesis. Different comparisons will be conducted or priori subgroup analyses will be performed based on the factors that may induce heterogeneity (subgroup analysis and investigation of heterogeneity). I^2 and χ^2 statistics will be employed to evaluate statistical heterogeneity.[19] Heterogeneity will be considered significant when I^2 is more than 50% with a p value of the χ^2 test of less than 0.1. Data will be pooled using a random-effects model when the source of heterogeneity is not found.

In addition, we will not pool data in the meta-analysis when a particular outcome has high I^2, and we will not include studies with sparse data. We will make descriptive results for these studies respectively.

Assessment of reporting biases

The reporting biases will be assessed using funnel plots only if there are sufficient studies (10 or more) under the outcomes section in the meta-analysis.[19]

Data synthesis

Review Manager V.5.3 will be used to carry out the meta-analysis. For all analyses, data will be pooled using a fixed-effects model. Where a significant statistical heterogeneity is found, data analysis will be performed using a random-effects model. If the outcome data is from a single study, the treatment effect will be calculated, and the results presented in an additional table.

Subgroup analysis and investigation of heterogeneity
Priori subgroup analysis

A subgroup analysis will be conducted for primary outcomes according to the risk stratification of participants at baseline, including the three subgroups as follows:

► Moderate risk.
► High risk.
► Extreme risk.

Furthermore, when evaluating combined blood pressure and cholesterol-lowering therapy versus antihypertensive therapy alone, a subgroup analysis will be performed according to the types of blood pressure and cholesterol-lowering therapies used (single pill form versus combination of two separate pills).

Investigation of heterogeneity

We will consider the other potential clinical factors that may cause heterogeneity except for the two factors in the priori subgroup analysis. For cases in which heterogeneity is significant, we plan to perform subgroup analyses and meta-regression (for outcomes that included more than 10 studies) using the following characteristics: (1) intensity of lipid-lowering drugs, (2) definition of hypertension or outcome measures, (3) dosing schedule, (4)

age of participants, (5) severity of illness and (6) drug manufacturers.[19]

Sensitivity analysis

A sensitivity analysis of primary outcomes will be conducted to evaluate the effect of excluding RCTs with a high risk of allocation bias, performance bias or detection bias.

'Summary of findings' table

The Grading of Recommendations, Assessment, Development and Evaluations system will be used to evaluate the overall quality of the evidence for outcomes reported in the review considering the within-study risk of bias, directness of evidence, heterogeneity, precision of effect estimate and risk of publication bias if the data is sufficient.[19 24 25] The following outcomes will be included in the 'Summary of findings' table:

Composite endpoint (long term).

► Total cardiovascular events (long term).
► The percentage of participants who reached their recommended BP goals (short term).
► The percentage of participants who reached their recommended lipid goals (short term).
► The percentage of participants who reached both BP and lipid goals (short term).
► Fatal or non-fatal stroke (long term).
► Participants experiencing any adverse event (short term).

DISCUSSION

It is well established that statins can be effective in preventing ASCVD events in patients with coronary heart disease. Currently, combined antihypertensive and statin therapy has been thought to reduce the incidence of cardiovascular and cerebrovascular disease in patients with hypertension. A previous meta-analysis showed that cardiovascular events were further reduced by 45% if the blood pressure and blood lipid levels were both reduced by 10%.[14] Furthermore, the HOPE-3 study has provided evidence that initiating statin therapy in a moderate risk population of patients with hypertension offers a significant benefit.[11] Blood pressure control in patients with hypertension when combined with attention that is simultaneously focused on cholesterol-lowering treatment for the prevention of cardiovascular disease is of great significance.[26] This systematic review will be the first review to compare antihypertensive and statin therapy versus antihypertensive therapy alone in the treatment of patients with hypertension. We hope that the results of this review will provide useful recommendations for clinical practitioners in treating patients with hypertension without complications and will promote the practice of evidence-based clinical medicine.

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