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Efficacy and Safety of Aliskiren Combination Therapy: A Protocol for An Umbrella Review

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ABSTRACT

Introduction

Efficacy of aliskiren combination therapy with other antihypertensive has been evaluated in the treatment of patients with hypertension in recent systematic reviews. However, most previous reviews only focused on one single health outcome or one setting, none of them made a full summary that assessed the impact of aliskiren combination treatment comprehensively. As such, this umbrella review is aimed to synthesize the evidences on efficacy, safety and tolerability of aliskiren-based therapy for hypertension and related comorbid patients.

Methods and analysis

A comprehensive search of PubMed, EMBASE, Cochrane Library, CNKI published from inception to August 2020 will be conducted. The selected articles are systematic reviews which evaluated efficacy, safety and tolerability of aliskiren combination therapy. Two reviewers will screen eligible articles, extract data and evaluate quality independently. Any disputes will be resolved by discussion or the arbitration of a third person. The quality of reporting evidence will be assessed using the AMSTAR2 tool. We will take a mixed-methods approach to synthesizing the review literatures, reporting summary of findings tables and iteratively mapping the results.

Ethics and dissemination

Ethical approval is not required for the study, as we would only collect data from available published materials. This umbrella review will be also submitted to a peer-reviewed journal for publication after completion.

Trial Registration

Our study has been registered in PROSPERO (CRD42020192131)

Keywords: Aliskiren; combination therapy; clinical outcome

Strengths and limitations of this study

- This will be the first study that systematically summarizes the effectiveness, safety and tolerability of aliskiren combination therapy.
- When sufficient data are available, we will compare clinical outcomes of different aliskiren combination therapies.
- If the included reviews in our study are not of high quality, we will re-analyze each outcome using the random effects model.
- The methodological quality of the eligible reviews will be evaluated using AMSTAR2 for assessing risk of bias.
- The results of this umbrella review are an asset to patients, clinicians and researchers, help them to better acknowledge the scientific value of aliskien combined use.

INTRODUCTION

Aliskiren is the first in a new class of oral, non-peptide, low molecular weight direct renin inhibitor (DRI).It has been approved by the US Food and Drug Administration (FDA) for the management of hypertension in2007[1]. As studies revealed, aliskirenis effective in controlling blood pressure as monotherapy[2,3]. Furthermore, researchers found that aliskiren could provide more anti-hypertension efficacy when combined with other kinds of blood pressure medicines [4-8]. An increasing number of clinical trials and systematic reviews have assessed the anti-hypertension efficacy and tolerability of aliskiren combination therapies [4,9,10]. However, there has yet to be a comprehensive evidence map that summarizes the wide array of health benefits and safety of aliskiren combination treatments. As noted above, existing systematic reviews on aliskiren combination treatments focused on single health outcomes, and most reviews evaluated only one type of combination treatment rather than exploring the multiple combination treatments. In addition, due to the diversity in settings, types and outcomes of aliskiren combination treatments, the quality of these reviews were varied. Umbrella reviews can systematically appraise evidence in the published literature by evaluating meta-analyses of multiple combination treatment on multiple outcomes[11].We would perform an umbrella review of systematic reviews to holistically evaluate and summarize existing systematic reviews that assess the efficacy, safety and tolerability of aliskiren combination therapy.

METHODS

Protocol development

This umbrella review protocol follows the Joanna Briggs Institute Methodology for Umbrella Reviews [12]. This protocol was also developed to align with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 statement [13] and has been registered with the PROSPERO database for systematic reviews (CRD42020192131).

Eligibility criteria

We used the population, intervention, comparator, outcomes and study design structure in formulating the scope of this umbrella review.

Population: This umbrella review will include systematic reviews that include hypertension patients and related comorbid populations.

Intervention: This umbrella review will include systematic reviews that focus on aliskiren combination with other anti-hypertension medicine, such as ARBs, ACEIs, HCTZs.

Comparators: Aliskiren monotherapy or aliskiren combined with another medicine.

Outcomes

We will assess the following outcomes: The primary efficacy outcomes were cardiovascular outcomes such as mortality rate, the composite of death and major adverse events, the incidence of stroke and myocardial infarction. Secondary efficacy outcomes were rates of therapeutic response and BP control, reduction from baseline to the end of treatment in mean clinical SBP (ΔmSBP) and DBP (ΔmDBP). The safety of drug was assessed by incidence of some adverse events such as hyperkalaemia, acute kidney injury. The tolerability of the drug was assessed by considering overall rates of any adverse events and withdrawal from a study due to adverse events. Reviews with any of the above outcomes will be included.

Type of studies: Systematic reviews, meta-analyses or pooled analyses

The reviews that were out of date will be excluded. Meta-analyses that did not provide specific study data (number of incident events, number of study population, follow-up period, relative risks and 95% confidence intervals (CI)) and in which the missing data was not retrievable from the original studies will be excluded.

Search Strategy

We will search the following databases from inception of databases to August 2020: Pubmed, Embase, Cochrane Library and CNKI. Additionally, we will manually search all reference lists of the included studies to identify additional reviews of relevance.

We developed this search strategy using keywords, MeSH (Medical Subject Headings) terms and text words, which will be searched in combination (aliskiren OR direct renin inhibitor OR renin-angiotensin inhibition OR spp100 OR takturna) AND (systematic review OR meta-analysis OR pooled analysis). We will modify the database-specific controlled vocabulary and key terms to suit the above mentioned databases.

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Electronic search results will be down loaded into Endnote software, and duplicates will be removed automatically and manually based on an exact match of the title, date, author and result. Two reviewers will independently screen titles and abstracts of retrieved articles according to the inclusion and exclusion criteria. When the reviewers cannot decide the eligibility of a study through title or abstract screening, full-texts will be screened. Disagreements between reviewers will be resolved using consensus, and by a third reviewer if necessary. The outline of the study selection procedure will be shown in a flow chart (Figure 1).

Data Extraction

Standardized abstraction forms will be established in Microsoft EXCEL, and the data from each eligible systematic review will be extracted by two reviewers independently. Ambiguities related to data extraction will be resolved by discussion or by a third reviewer if the reviewers are unable to achieve consensus. The following information will be extracted: characteristics of included reviews (e.g. first author, publication year, number and type of studies included in each review, total sample size), population (disease conditions), intervention and control (medicine of intervention or control, sample size of each group and details of treatment, follow-up period) and outcomes (name and definition of outcome, summary effect size and its related 95% CI and the number of participants included in the outcome assessment). When the data are only provided through plots, we will use Ycasd to determine the effect size and its 95% CI [14]. We will contact the corresponding authors to ask for data, when necessary data were not provided in the article.

Assessment of methodological quality of included reviews

The quality of the included studies will be appraised by using the Assessment of Multiple Systematic Reviews 2 tool (AMSTAR2, an updated version of AMSTAR), which is updated to allow for both randomized and observational studies. Unlike its predecessor, AMSTAR 2 has the capacity to identify critical weaknesses that reduce confidence in the findings of a review [15]. AMSTAR 2 consists of 16 items with the following response options: Yes, Partial Yes and No. Two reviewers will independently rate the quality of each systematic review as high, moderate, low and critically low based on the overall score of the AMSTAR2. Any

disagreements between reviewers will be resolved among themselves through discussion and by a third reviewer if being unable to achieve consensus.

Data synthesis and statistical analysis

Statistical analysis will be conducted using RevManV.5.3 software and StataV.14.0 software. In our analysis, when possible, we will stratify the comparisons into several groups according to the characteristics of our targeted population. We will divide patients into three groups: simple hypertension patients, patients with hypertension and diabetes; and patients who are suffering from hypertension, diabetes and nephropathy or albuminuria at the same time. When evaluating antihypertensive effects, we will divide patients into three groups: young patients (<50years), early elderly patients (50-70years), elderly patients (>70years).

For each outcome, if the random model was already used, we will extract the pooled effect sizes of included systematic review. If not, we will extract original data and reanalyze them with the random effect methods to get the pooled effect size and its related 95% CI. We will also estimate the 95% prediction interval (95% PI) for the summary estimate based on the random-effect model, to represent the range in which the effect estimates of future studies will lie. The Q and I^2 test statistics will be calculated to determine the degree of heterogeneity. For the Q statistic, $p<0.05$will be considered significant. We will classify the degree of heterogeneity into substantial heterogeneity ($I^2>50\%$) and considerable heterogeneity ($I^2>75\%$).We will conduct a Bayesian network meta-analysis to estimate relative combination therapy effects based on a synthesis of direct and indirect evidence.

Where no quantitative pooling of effect sizes was reported or where outcomes were reported descriptively by single studies, we will provide these results by using standardized

language indicating direction of effect and statistical significance.

If an outcome is examined at least 3 articles, we will use Egger's test (conducted using StataV.14.0) to evaluate if the reporting bias exists. Values of $p<0.1$ will be interpreted as statistically significant [16].

All included systematic reviews and meta-analyses will be screened for over lapping of included original studies. We will explore this through the use of The Cochrane Handbook's template for mapping individual primary studies contained within included systematic reviews [17]. If reviews are reporting the same outcomes from the same study, we will highlight this overlap. To assess the degree of overlap, we will calculate the corrected covered area (CCA)[18]. A CCA score of 0-5 indicates slight overlap, 6-10 moderate, 11-15 high and >15 very high. We will consider overlap when interpreting results of the overview.

Patient and public involvement

Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. The results of this work will be disseminated to the public via conferences, publications and presentations.

DISCUSSION

Aliskiren is an orally administered, direct renin inhibitor approved in numerous countries, including the US and the EU for the management of hypertension. The clinical efficacy and tolerability of aliskiren-based therapy in hypertension have been previously reviewed by many systematic reviews, while the evidence about aliskiren combination therapy has not been appraised holistically. Umbrella review is a review of systematic reviews and meta-analyses, which is viewed as one of the four next-generation

meta-analyses[19].

For this umbrella review, we will (1) identify and synthesize existing review and meta-analysis studies on aliskiren combination therapies; (2) critically evaluate the available evidence both narrative and quantitative; and (3) identify the most prominent aliskiren combination treatment used to manage hypertension. We will use qualitative methods and quantitative methods to synthesizing the review literatures. We plan to evaluate the credibility of included evidences. We will create the summary of findings tables and report a summary of findings from all included reviews based on data synthesis, presenting a comprehensive overview of what is known in the literatures about the efficacy, safety and tolerability of different aliskiren combination therapies.

This is the first umbrella review about aliskiren combination therapy. Summarizing these evidences will be an asset to clinicians and researchers aiming to improve the scientific of aliskien combine use. Anticipated limitations of our study are the heterogeneity and quality of the included reviews. To address the limitations, we will reanalyze each outcome using the random effects model and evaluate the quality of included studies. Furthermore, these two factors will be carefully considered when interpreting the results. Another limitation of this overview will be the potential for study overlap across reviews. Considering this potential bias, we will examine and report on any overlap in the overview. Despite anticipated limitations, this umbrella review will be conducted using the most systematic procedures available at this time. Adhering to these guidelines helps ensure that we produce a high-quality umbrella review, which will be a useful and trustworthy resource for interested parties.

Ethics and dissemination

Ethical approval is not required for the study, as we only collected data from available materials. This umbrella review will be also submitted to a peer-reviewed journal for publication.

Authors' contributors

Jiantong Shen and Wenming Fen carried on the conception and construction of this protocol. Yike Wang developed the search strategy. Qiyuan Zhao and Jingya Lu compared and found the best tools for assessing possible bias and evaluating quality of included reviews. Jiantong Shen wrote the protocol. BILLONG Laura Flavorta added grammar editing and conceptual clarification. All authors read and approved of the final manuscript.

Funding statement

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Competing interests

None declared

Patient and public involvement

No patients and public are involved in developing plans for project and implementation of this study. None of them are asked to advise on interpretation of results. The results will be disseminated to the general population through public presentations by the authors.

REFERENCES

1. Duggan ST, Chwieduk CM, Curran MP. Aliskiren: a review of its use as monotherapy and as combination therapy in the management of hypertension. *Drugs* 2010; 70:2011-49.

2. Zhao QY, Shen JT, Lu JY, et al. Clinical efficacy, safety and tolerability of Aliskiren Monotherapy (AM): an umbrella review of systematic reviews. *BMC Cardiovasc Disord* 2020; 20:179.

3. Musini VM, Lawrence KA, Fortin PM, et al. Blood pressure lowering efficacy of renin inhibitors for primary hypertension. *Cochrane Database Syst Rev* 2017; 4:CD007066.

4. Liu Y, Chen K, Kou X, et al. Aliskiren and Amlodipine in the Management of Essential Hypertension: Meta-Analysis of Randomized Controlled Trials. *PLoS ONE* 2013; 8: e70111

5. Miyoshi T, Murakami T, Sakuragi S, et al. Comparable effect of aliskiren or a diuretic added on an angiotensin II receptor blocker on augmentation index in hypertension: a multicentre, prospective, randomised study. *Open Heart* 2017;4:e000591.

6. Abdel Kawy HS. Aliskiren and valsartan in combination is a promising therapy for hypertensive renal injury in rats. *Clin Exp Hypertens* 2018; 40:560-8.

7. Oparil S, Yarows SA, Patel S, et al. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. *Lancet* 2007; 370: 221-9.

8. Littlejohn TW 3rd, Trenkwalder P, Hollanders G, et al. Long-term safety, tolerability and efficacy of combination therapy with aliskiren and amlodipine in patients with hypertension. *Curr Med Res Opin* 2009; 25:951-9.

9. Liu Y, Yan R, Song A, et al. Aliskiren/amlodipine vs. aliskiren/hydrochlorothiazide in hypertension: indirect meta-analysis of trials comparing the two combinations vs. monotherapy. *Am J Hypertens* 2014; 27:268-78.

10. Zhang JT, Chen KP, Guan T, et al. Effect of aliskiren on cardiovascular outcomes in patients with prehypertension: a meta-analysis of randomized controlled trials. *Drug Des Devel Ther* 2015;9:1963-71.

11. Aromataris E, Fernandez R, Godfrey CM, et al. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc* 2015; 13:132-40.

12. Aromataris E, Fernandez RS, Godfrey C, et al. *Methodology for JBI Umbrella Reviews*. The Joanna Briggs Institute; 2014.

13. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.

14. Gross A, Schirm S, Scholz M. Ycasd - a tool for capturing and scaling data from graphical representations. *BMC Bioinformatics* 2014; 15:219.

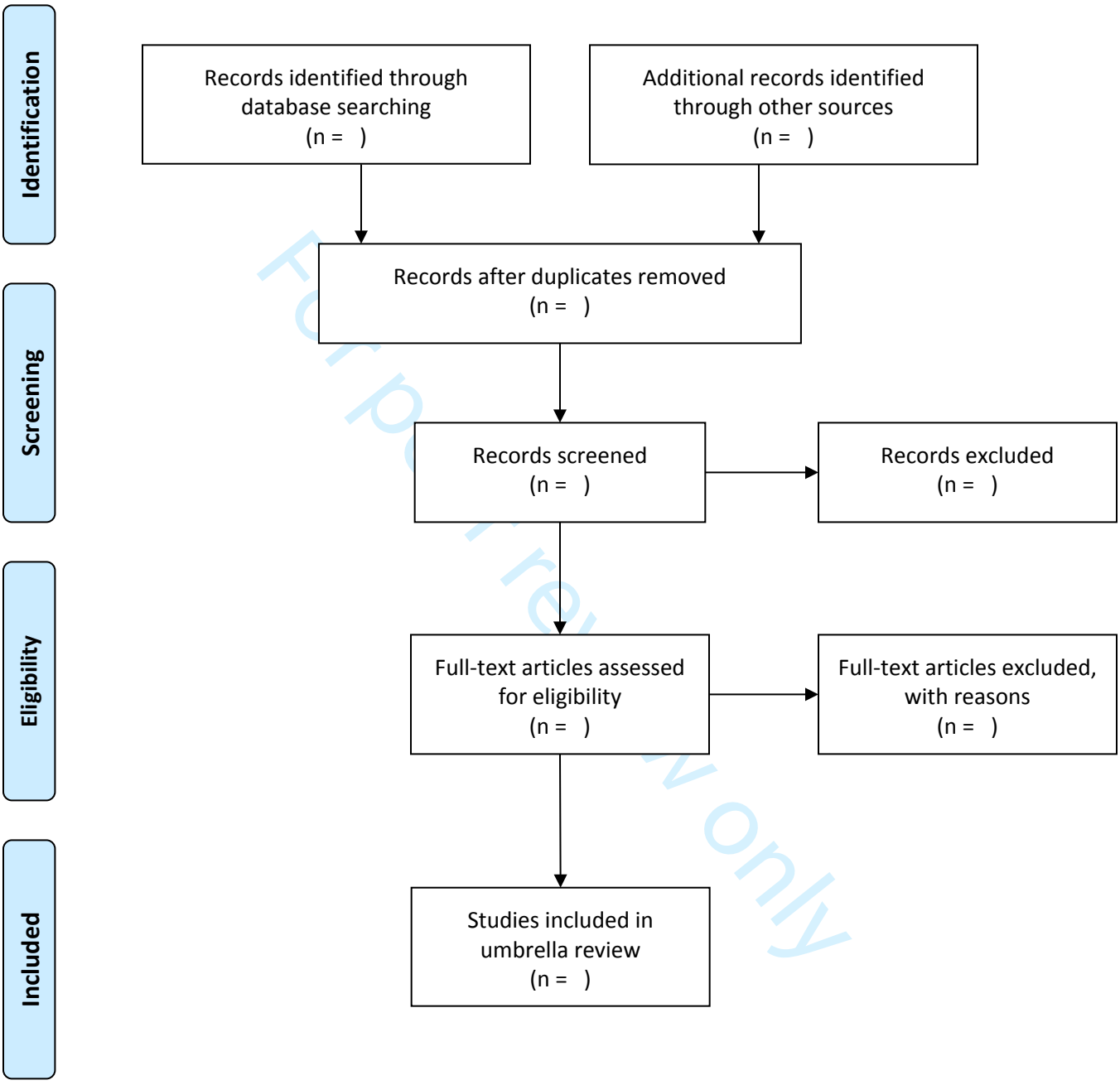
15. Shea BJ, Reeves BC, Wells G, et al. AMSTAR2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017; 358:1-8.

16. Poole R, Kennedy OJ, Roderick P, et al. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ* 2017; 359:j5024-18.

17. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*. Cochrane, 2019. Available from www.training.cochrane.org/handbook.

18. Pieper D, Antoine S-L, Mathes T, et al. Systematic review finds overlapping reviews were not mentioned in every other overview. *J Clin Epidemiol* 2014; 67:368-75.

19. Ioannidis J. Next-generation systematic reviews: prospective meta-analysis, individual-level data, networks and umbrella reviews. *Br J Sports Med* 2017; 51:1456-8.



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Assessment of methodological quality of included reviews

The quality of the included studies will be appraised by using the Assessment of Multiple Systematic Reviews 2 tool (AMSTAR2, an updated version of AMSTAR), which is updated to allow for both randomized and observational studies. Unlike its predecessor, AMSTAR 2 has the capacity to identify critical weaknesses that reduce confidence in the findings of a

review [15]. AMSTAR 2 consists of 16 items with the following response options: Yes, Partial Yes and No. Two reviewers will independently rate the quality of each systematic review as high, moderate, low and critically low based on the overall score of the AMSTAR2. Any disagreements between reviewers will be resolved among themselves through discussion and by a third reviewer if being unable to achieve consensus.

Data synthesis and statistical analysis

Statistical analysis will be conducted using RevManV.5.3 software and StataV.14.0 software. In our analysis, when possible, we will stratify the comparisons into several groups according to the characteristics of our targeted population. We will divide patients into three groups: simple hypertension patients, patients with hypertension and diabetes; and patients who are suffering from hypertension, diabetes and nephropathy or albuminuria (an eGFR < 60 mL/min/1.73 m2 or The Kidney Disease Improving Global Outcomes (KDIGO) GFR stages 3 to 5) at the same time. In order to be consistent with changes in the classification and diagnostic criteria for diabetes over the years, the diagnosis should be established using the standard criteria valid at the time of the trial commencing (for example ADA 2003; ADA 2008; WHO 1998). Ideally, the diagnostic criteria should have been described. We will use the trial authors' definition of diabetes mellitus if necessary. We plan to subject diagnostic criteria to a sensitivity analysis. When evaluating antihypertensive effects, we will divide patients into three groups: young patients (<50years), early elderly patients (50-70years), elderly patients (>70years).

For each outcome, if the random model was already used, we will extract the pooled effect sizes of included systematic review. If not, we will extract original data and reanalyze

them with the random effect methods to get the pooled effect size and its related 95% CI. We will also estimate the 95% prediction interval (95% PI) for the summary estimate based on the random-effect model, to represent the range in which the effect estimates of future studies will lie. The Q and I^2 test statistics will be calculated to determine the degree of heterogeneity. For the Q statistic, $p<0.05$will be considered significant. We will classify the degree of heterogeneity into substantial heterogeneity ($I^2>50\%$) and considerable heterogeneity ($I^2>75\%$). We will conduct a Bayesian network meta-analysis to estimate relative combination therapy effects based on a synthesis of direct and indirect evidence.

Where no quantitative pooling of effect sizes was reported or where outcomes were reported descriptively by single studies, we will provide these results by using standardized language indicating direction of effect and statistical significance.

If an outcome is examined at least 3 articles, we will use Egger's test (conducted using StataV.14.0) to evaluate if the reporting bias exists. Values of $p<0.1$ will be interpreted as statistically significant [16].

All included systematic reviews and meta-analyses will be screened for over lapping of included original studies. We will explore this through the use of The Cochrane Handbook's template for mapping individual primary studies contained within included systematic reviews [17]. If reviews are reporting the same outcomes from the same study, we will highlight this overlap. To assess the degree of overlap, we will calculate the corrected covered area (CCA)[18]. A CCA score of 0-5 indicates slight overlap, 6-10 moderate, 11-15 high and >15 very high. We will consider overlap and do sensitivity analyses when interpreting results of the overview.

Patient and public involvement

No patients and public are involved in developing plans for project and implementation of this study. None of them are asked to advise on interpretation of results. The results will be disseminated to the general population through public presentations by the authors.

DISCUSSION

Aliskiren is an orally administered, direct renin inhibitor approved in numerous countries, including the US and the EU for the management of hypertension. The clinical efficacy and tolerability of aliskiren-based therapy in hypertension have been previously reviewed by many systematic reviews, while the evidence about aliskiren combination therapy has not been appraised holistically. Umbrella review is a review of systematic reviews and meta-analyses, which is viewed as one of the four next-generation meta-analyses [19].

For this umbrella review, we will (1) identify and synthesize existing review and meta-analysis studies on aliskiren combination therapies; (2) critically evaluate the available evidence both narrative and quantitative; and (3) identify the most prominent aliskiren combination treatment used to manage hypertension. We will use qualitative methods and quantitative methods to synthesizing the review literatures. We plan to evaluate the credibility of included evidences. We will create the summary of findings tables and report a summary of findings from all included reviews based on data synthesis, presenting a comprehensive overview of what is known in the literatures about the efficacy, safety and tolerability of different aliskiren combination therapies.

This is the first umbrella review about aliskiren combination therapy. Summarizing

these evidences will be an asset to clinicians and researchers aiming to improve the scientific of aliskien combine use. Anticipated limitations of our study are the heterogeneity and quality of the included reviews. To address the limitations, we will reanalyze each outcome using the random effects model and evaluate the quality of included studies. Furthermore, these two factors will be carefully considered when interpreting the results. Another limitation of this overview will be the potential for study overlap across reviews. Considering this potential bias, we will examine and report on any overlap in the overview. Despite anticipated limitations, this umbrella review will be conducted using the most systematic procedures available at this time. Adhering to these guidelines helps ensure that we produce a high-quality umbrella review, which will be a useful and trustworthy resource for interested parties.

Ethics and dissemination

Ethical approval is not required for the study, as we only collected data from available materials. This umbrella review will be also submitted to a peer-reviewed journal for publication.

Authors' contributors

Jiantong Shen and Wenming Feng carried on the conception and construction of this protocol. Yike Wang developed the search strategy. Qiyuan Zhao and Jingya Lu compared and found the best tools for assessing possible bias and evaluating quality of included reviews. Jiantong Shen wrote the protocol. BILLONG Laura Flavorta added grammar editing and conceptual clarification. All authors read and approved of the final manuscript.

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Competing interests

None declared**REFERENCES**

1. Duggan ST, Chwieduk CM, Curran MP. Aliskiren: a review of its use as monotherapy and as combination therapy in the management of hypertension. *Drugs* 2010; 70:2011-49.

2. Zhao QY, Shen JT, Lu JY, et al. Clinical efficacy, safety and tolerability of Aliskiren Monotherapy (AM): an umbrella review of systematic reviews. *BMC Cardiovasc Disord* 2020; 20:179.

3. Musini VM, Lawrence KA, Fortin PM, et al. Blood pressure lowering efficacy of renin inhibitors for primary hypertension. *Cochrane Database Syst Rev* 2017; 4:CD007066.

4. Liu Y, Chen K, Kou X, et al. Aliskiren and Amlodipine in the Management of Essential Hypertension: Meta-Analysis of Randomized Controlled Trials. *PLoS ONE* 2013; 8: e70111

5. Miyoshi T, Murakami T, Sakuragi S, et al. Comparable effect of aliskiren or a diuretic added on an angiotensin II receptor blocker on augmentation index in hypertension: a multicentre, prospective, randomised study. *Open Heart* 2017;4:e000591.

6. Abdel Kawy HS. Aliskiren and valsartan in combination is a promising therapy for hypertensive renal injury in rats. *Clin Exp Hypertens* 2018; 40:560-8.

7. Oparil S, Yarows SA, Patel S, et al. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. *Lancet* 2007; 370: 221-9.

8. Littlejohn TW 3rd, Trenkwalder P, Hollanders G, et al. Long-term safety, tolerability and efficacy of combination therapy with aliskiren and amlodipine in patients with hypertension. *Curr Med Res Opin* 2009; 25:951-9.

9. Liu Y, Yan R, Song A, et al. Aliskiren/amlodipine vs. aliskiren/hydrochlorothiazide in hypertension: indirect meta-analysis of trials comparing the two combinations vs. monotherapy. *Am J Hypertens* 2014; 27:268-78.

10. Zhang JT, Chen KP, Guan T, et al. Effect of aliskiren on cardiovascular outcomes in patients with prehypertension: a meta-analysis of randomized controlled trials. *Drug Des Devel Ther* 2015;9:1963-71.

11. Aromataris E, Fernandez R, Godfrey CM, et al. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc* 2015; 13:132-40.

12. Aromataris E, Fernandez RS, Godfrey C, et al. *Methodology for JBI Umbrella Reviews*. The Joanna Briggs Institute; 2014.

13. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.

14. Gross A, Schirm S, Scholz M. Ycasd - a tool for capturing and scaling data from graphical representations. *BMC Bioinformatics* 2014; 15:219.

15. Shea BJ, Reeves BC, Wells G, et al. AMSTAR2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017; 358:1-8.

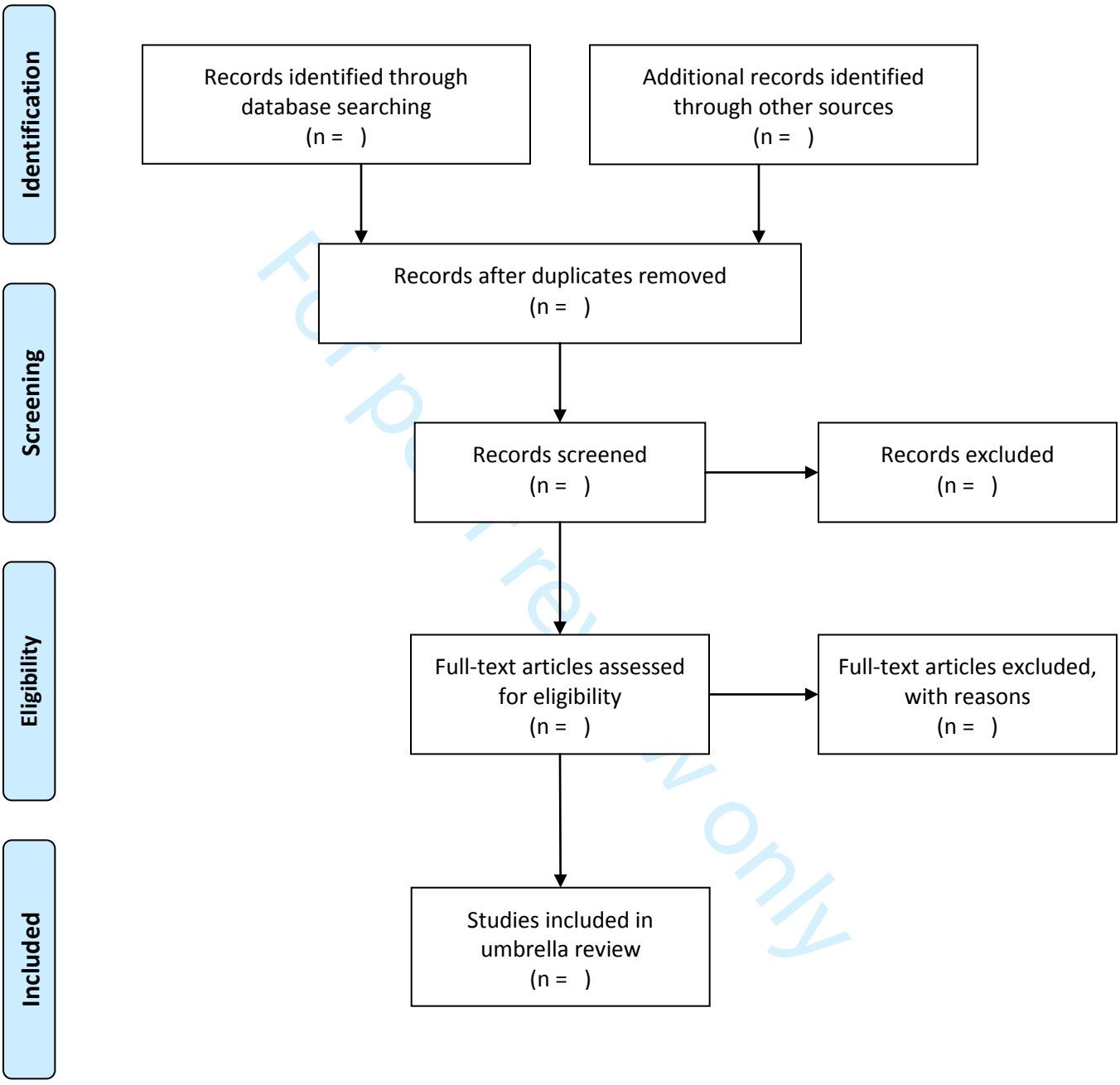
16. Poole R, Kennedy OJ, Roderick P, et al. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ* 2017; 359:j5024-18.

17. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*. Cochrane, 2019. Available from www.training.cochrane.org/handbook.

18. Pieper D, Antoine S-L, Mathes T, et al. Systematic review finds overlapping reviews were not mentioned in every other overview. *J Clin Epidemiol* 2014; 67:368-75.

19. Ioannidis J. Next-generation systematic reviews: prospective meta-analysis, individual-level data, networks and umbrella reviews. *Br J Sports Med* 2017; 51:1456-8.

305 Figure 1 Flow diagram of study selection process



Supplementary 1

Search Pubmed

#1 "aliskiren"[Supplementary Concept]
#2 "Rasilez"[Title/Abstract]
#3 "tekturna"[Title/Abstract]
#4 "spp100"[Title/Abstract]
#5 "renin angiotensin inhibition"[Title/Abstract]
#6 "direct renin inhibitor"[Title/Abstract]
#7 "aliskiren"[Title/Abstract]
#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
Filters: Meta-Analysis, Systematic Review